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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014004
Article Type:	Research
Date Submitted by the Author:	24-Aug-2016
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Paediatrics

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Keywords:	obesity, puberty, EPIDEMIOLOGY, PUBLIC HEALTH, PAEDIATRICS

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Investigating the association between precocious puberty and obesity: a cross-sectional study in Shanghai city of China

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ABSTRACT

Objectives: Obesity is reported closely relevant to early sexual development in girls but the relationship between sexual precocity and obesity or central obesity is still inconsistent especially in boys. We aimed to investigate the relationship between precocious puberty and obesity as well as central obesity.

Design: A large population-based cross-sectional study study using multistage, stratified cluster random sampling.

Setting: Data from the Shanghai Children's Health, Education and Lifestyle Evaluation (SCHEDULE) study in June 2014.

Participants: 17,620 Chinese children aged 6–12 years.

Primary and secondary outcome measures: Obesity was defined according to the WHO Child Growth Standards. Central obesity was defined by sex-specific waist-to-height ratio (WHtR) cut-offs (WHtR ≥ 0.48 for boys, WHtR ≥ 0.46 for girls). Precocious puberty was identified by Tanner stage of breast, pubic hair and testicle. A chi-square test was performed to compare rates. Odds ratios (ORs) with 95% confident interval (CI) were calculated to assess the association between precocious puberty and General Obesity and central obesity. Probit analysis was used for estimating the median age at entry into Tanner stage 2 or greater for breast, pubic hair and testicle development.

Results: 25.98% and 38.58% precocious boys were accompanied with obesity (OR = 2.15, 95%CI = 1.31–3.50) and central obesity (OR = 2.10, 95%CI = 1.46–3.03) separately, meanwhile, 13.86% and 29.42% precocious girls with obesity (OR = 9.00, 95%CI = 5.60–14.46) and central obesity (OR = 2.00, 95%CI = 1.66–2.40). The median ages of breast, pubic hair and testicle

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development decreased with BMI increased and median ages of thelarche and testicular rather than pubarche were earlier in children with central obesity

Conclusions: Earlier pubertal development was positively associated with obesity and central obesity in Chinese children.

Strengths and limitations of this study:

- This study is a large population-based cross-sectional study and the subjects were representative of the general population for Shanghai.
- Early pubertal development was found to be associated with obesity and central obesity which is of relevance to the current public health concern about the risk factors associated with the declining of puberty.
- Longitudinal investigations are still needed to determine the causal direction between obesity and precocious puberty.
- Imaging diagnosis of breast and testicle development such as B-ultrasonic scan, may help to reduce false positives in future research.

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INTRODUCTION

Puberty is an essential and complex process with wide physiologic variation and maturation. Mechanisms controlling the onset of puberty and tempo of development are complicated and involve genetic, nutritional, and environmental interactions.[1] Increasing numbers of countries are experiencing earlier development of secondary sexual characteristics in children.[2-4] Earlier puberty has been reported to be associated with a higher risk of psychological problems, reproductive tract cancers and the development of metabolic syndrome features later in life.[5]

Recent data suggest that earlier timing or faster progression of puberty development is related to higher body mass index (BMI) and greater risk of overweight in later adolescence and adulthood. [6 7] Those who develop earlier tend to be more obese with a trunk-oriented distribution pattern from adolescence to adulthood.[8] Also, children with overweight and obesity appear to sexually develop earlier than lean children.[9] The underlying biological mechanisms like insulin resistance with compensatory hyperinsulinemia, endocrine disruptors and androgens in girls may contribute to the sexual characteristic changes.[10] In addition, a central or abdominal distribution of body fat was reported to be related to adverse health outcomes compared with peripheral fat which implied body fat patterning may also influence sexual maturation.[7 11]

The relationship between sexual precocity and obesity or central obesity is still inconsistent especially in boys. The purpose of this study is to evaluate the relationship between the timing of sexual maturation and body mass, as well as the effect of central obesity on precocious puberty.

METHODS

Participants and sampling

Informed consent was obtained from the participant children and their parents and the study was approved by the Institutional Review Boards of the Shanghai Children's Medical Center. The

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participants were selected from the Shanghai Children's Health, Education and Lifestyle Evaluation (SCHEDULE) study. This cross-sectional study was conducted in June 2014 by multistage and stratified cluster random sampling. Nineteen districts of Shanghai were stratified into central urban area, suburb and outer suburb according to the 2005 Shanghai census report [12] and seven districts were randomly chosen including Jing'an, Changning, Zhabei, Jiading, Jinshan, Pudong, Chongming. From these, 26 general primary schools were randomly sampled from school lists and students in grades 1 to 5 were recruited (**Figure 1**). Children with medication which could cause precocious puberty were excluded from the study. Trained teachers handed out questionnaires to the recruited students, asking them to take the questionnaires home and their parents to fill in the questionnaires on family, social and environmental issues as well as on dietary habits. Then teachers collected the completed questionnaires and returned it to the investigators. Data were analysed in 2016.

Physical Examination

Sexual development of children was jointly evaluated by professional pediatric endocrinology physicians and pediatric care physicians. The pubertal assessments of breast development used inspection combined with palpation and as for obese girls, we paid close attention to the palpation of nodule in breast. Testicular volume was determined by palpation and testicular meter, i.e. palpated and compared the testicle with the most similar bead in orchidometer. Tanner staging method was adopted to assess sexual development in children. The pubertal stages of breast and pubic hair development were graded from 1 (prepubertal) to 5 (fully mature) and delineated by Marshall and Tanner.[13 14] Precocious puberty was considered as being under 8 years for Tanner stage 2 or above for breast (B_2) or pubic hair development (PH_2) and 10 years for menstruation in girls, and under 9 years for Tanner stage 2 or above for pubic hair or testicle development (T_2) (testicular volume, TV $\geq$ 4 ml) in boys.[15-17]

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Height measurement was performed without shoes and standing upright by wall-mounted stadiometer to the nearest 0.1 cm. Participants wore light clothes and were barefoot when weight was measured by research assistants using a standardized digital scale to the nearest 0.1 kg; Waist circumference (WC) determination was at midpoint of the horizontal line between the lower rib margin and the superior border of ilium while standing with an inelastic measuring tape at the end of normal expiration to the nearest 0.1 cm. Calculation of BMI was weight (kg) divided by the square of height (m^2) and classified into severe thinness, thinness, overweight and obesity categories according to the WHO Child Growth Standards (http://www.who.int/growthref/en/), i.e., severe thinness is BMI < -3 standard deviation (SD), thinness is BMI < -2 SD, overweight is BMI ≥1 SD and obesity is BMI ≥2 SD.[18 19] The overweight category excludes obesity and thinness excludes severe thinness. Waist-to-height ratio (WHtR) was calculated as WC (cm) divided by height (cm) and central obesity was defined as WHtR ≥ 0.48 in boys and WHtR ≥ 0.46 in girls.[20] All physical data were collected at school settings.

Statistical analysis

All data were recorded and proofread using EpiData 3.1 (EpiData Association, Odense, Denmark) by two groups of researchers. The detection rate of precocious puberty was directly calculated and the chi-square test was performed to compare rates. Odds ratios (ORs) with 95% confident interval (CI) were calculated to assess the association between precocious puberty and General Obesity and central obesity. Probit analysis was used for estimating the median age at entry into Tanner stage 2 or greater for breast, pubic hair and testicle development. All the raw data were analysed using IBM SPSS Statistic package version 21 (IBM Corp., Armonk, NY, USA) with two-sided and the *P* value < 0.05 was considered statistically significant.

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RESULTS

Sample

A total of 17,620 parents of recruited children completed the questionnaires, and 17,368 (98.57%) were valid. The number of 6-12-year-old children who completed the physical examination was 16,958 (96.24%). After eliminating missing (845), extreme and invalid data (176) of age, sex and key physical parameters including height and weight, a total of 15,937 (90.45%) children including 8,546 (53.62%) boys and 7,391 (46.48%) girls aged range from 6 to 12 years constituted the final sample.

Subject characteristics

Boys had obviously higher levels of weight, height, WC (7 missing), BMI and WHtR than the girls ($P < 0.005$). Moreover, the prevalence of both obesity and central obesity was relative higher in boys than girls (The prevalence of obesity was 18.61% for boys and 5.63% for girls; of central obesity was 28.65% for boys and 13.09% for girls) (P <0.001). 4221 boys aged 6-9-year, 2000 girls aged 6-8 years and girls with menstruation aged blow 10 years could be estimated precocious puberty whether or not because of the age-specific definition. The overall detection rate of precocious puberty was 9.53% (596 cases) and girls (469 cases, 23.07%)had significantly higher rate than boys (127 cases, 3.01%) (P <0.001). (**Table** 1)

Associations between different types of obesity and the risk of precocious puberty

The prevalence of obesity and central obesity was relatively high and had an obvious influence on precocious children in both gender. **Table** 2 showed the results, 25.98% precocious boys and 13.86% precocious girls accompanied with obesity. Childhood obesity increased the risk of precocious puberty and the risk was obviously higher in girls than boys (OR = 2.15, (95% CI = 1.31–3.50) for boys; OR = 9.00 (95% CI = 5.60–14.46) for girls). Besides, 38.58% precocious boys and 29.42% precocious girls accompanied with central obesity. However, central obesity

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had relatively similar effect on both gender (boys: OR = 2.10, 95% CI = 1.46–3.03; girls: OR = 2.00, (95% CI = 51.66–2.40). The status of obesity using either BMI or WHtR was significantly associated with precocious puberty.

Attaining median age of pubertal stages

We estimated the median age of both girls and boys and the 95% CI for attainment of Tanner stage 2 for breast, pubic hair and testicle development according to probit analysis (**Table** 3).

As for girls, the median ages of B_2 decreased from 10.86 in severe thinness group, 9.88 in thinness group, 8.85 in normal weight group, 7.68 in overweight group and 7.14 in obesity group. The same trend was observed in the median ages of PH_2 from 12.56, 11.13, 10.73, 10.22 decreased to 10.18 years within increased BMI group. For boys, median ages of PH_2 and T_2 decreased slightly within increased BMI group except for a lower median age of PH_2 in severe thinness group. The median ages of B_2, PH_2 and T_2 showed a negative association with BMI. It demonstrated a significant downward trend in median age of thelarche, pubarche and testicular development with an increase of BMI in 6 to 12-year-old children.

The median ages of B_2 and PH_2 were 8.69 (95% CI = 8.64–8.74) and 10.62 (95% CI = 10.53–10.72) years for non-centrally obese girls, 7.20 (95% CI = 6.97–7.44) and 10.60 (95% CI = 10.26–10.96) years for centrally obese girls. The median age of B_2 was lower in the central obesity group but tiny lower for PH_2. For boys, the median ages of PH_2 and T_2 were 13.78 (95% CI = 13.34–14.35) and 10.52 (95% CI = 10.28–10.80) years for non-centrally obese boys, and 14.00 (95% CI = 13.47–14.65) and 10.33 (95% CI = 9.95–10.74) years for centrally obese boys. The median age of T_2 was slightly lower and of PH_2 was a little higher in the centrally obese boys than in the non-centrally obese boys.

DISCUSSION

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This is a large-scale population-based cross-sectional survey of children pubertal growth and development in Shanghai, China. The total detection rate of precocious puberty was 9.53% (3.01% for boys, 23.07% for girls) in the present study.

Increasing evidence suggests that obesity is closely relevant to early sexual development in girls.[7 9 21-24] Atay *et al.*[23] found a strong association between different levels of BMI SD scores and the occurrence of premature thelarche but not with premature pubarche among 4–8-year-old girls in Istanbul. Kaplowitz *et al.*[22] observed that greater BMI is associated with an increased likelihood of early appearance of pubic hair and breast development in American girls aged 3–12 years. In addition, Rosenfield *et al.*[24] reported that girls with excessive BMI had a significantly higher prevalence of thelarche from ages 8.0 to 9.6 years and pubarche from ages 8.0 to 10.2 years. Our results are consistent with most studies.

In boys, there are limited studies that have evaluated the association between early sexual maturation and obesity. Wang [21] reported that early sexual maturation was negatively associated with overweight and obesity in boys aged 8–14 years in a population-based cross-sectional study in the United States in 1988 - 1994. And the prevalence of overweight was 23% in boys and 34% in girls with precocious puberty, and prevalence of obesity was 7% for boys and 16% for girls with precocious puberty. The subjects were mainly non-Hispanic white (25%), non-Hispanic black (36%) and Mexican American (35%). While in our study, prevalence of obesity was 25.98% for boys and 13.86% for girls with precocious puberty. Additionally, Sorensen *et al.*[25] reported in a combined cross-sectional and longitudinal study in Denmark that BMI was negatively associated with testicular growth and pubic hair development, indicating that higher BMI results in an older age for pubertal onset in Caucasian boys aged 5.8 to 19.8 years. However, in a longitudinal population-based study, Lee *et al.*[26] provided further evidence that higher BMI during early childhood is not associated with earlier pubertal onset in American

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boys. These boys were aged 2 to 11.5 years and their ethnicities were white (79.5%) and nonwhite (20.5%); and 12.2% of the boys were prepubertal at age 11.5 years according to Tanner genitalia staging. In contrast to these studies, Lee HS *et al.*[27] conducted a hospital-based gonadotropin-releasing hormone (GnRH) stimulation test involving Korean boys with a mean age of 8.7 years and reported that excess adiposity may influence the hypothalamic-pituitary-gonadal axis in boys, suggesting that obese boys enter puberty at an earlier age than normal weight boys. Dai *et al.*[28] described in a Chinese cross-sectional study that early sexual maturation was positively associated with obesity in boys only by the indicator of testicular volume. Our study was consistent with the positive results and further provided evidence of the relation between pubic hair development and obesity. The discrepancy of these findings might be explained by ethnic background differences, variation in the assessment criteria of pubertal stage and obesity, sample size, time factor, social culture, etc. Characteristics of our study and other related literatures were attached in Supplemental **Table S1** online.

More and more researches explored the linkage between precocious puberty and obesity, but the potential mechanisms remain unclear. Longitudinal epidemiologic evidence suggests that obesity has an important effect on precocious puberty.[9 21 27] The effect of obesity is likely to be related to leptin, a hormone secreted by adipocytes, which affect pubertal onset through activation of permissive hypothalamic GnRH secreting neurons.[29] As a consequence of obesity, insulin resistance plays an important role in the timing of puberty by interfering with leptin signaling and causing additional weight gain.[29] Additionally, premature adrenarche is also reported to be associated with obesity, but the potential mechanisms remain unknown.[30]

Research is lacking on the effect of fat distribution on pubertal development based on a large representative population. Biro *et al.*[30] suggested both adrenarche pathway for pubic hair development and thelarche pathway for breast development were influence by body fat and BMI.

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Even though there is an overlap between central obesity and obesity defined by BMI, BMI measurement is not effective for providing information on fat distribution. WHtR, which is described using WC and height, is reported easily to determine fat distribution and less affected by gender and ethnicity compared with BMI.[31] David *et al*.[11] emphasized the importance of obtaining information on fat distribution and, particularly, waist circumference in children. They found that a relative excess of adipose tissue in abdominal or central region was related to adverse concentrations of insulin, which was independent of weight and height. Our study further clearly revealed a relatively higher rate of precocious puberty and earlier median age of thelarche and testicular development rather than pubarche in children with central obesity.

Strengths and limitations of this study

This study is a large population-based cross-sectional study and the subjects were representative of the general population for Shanghai. Early pubertal development was found to be associated with obesity and central obesity which is of relevance to the current public health concern about the risk factors associated with the declining of puberty. However, some limitations should be acknowledged. First, though the sample size is large, the results cannot determine the causality or the speed of the consecutive pubertal stages because sexual development and obesity are measured at the same time point. Therefore, longitudinal investigations are needed to determine the causal direction, as to whether obesity has an impact on precocious puberty during childhood is a long-term consequence. Second, it would be desirable if more accurate assessment of breast development were available in overweight or obese children in a field survey. Discriminating between glandular breast and fat tissue is a critical concern, and inspection or palpation may lead to errors in estimating precocious puberty in obese children with excessive subcutaneous fat in the chest. It was rather difficult to employed imaging diagnosis in a large scale of children taking part in the physical examination, so we only adopted inspection combined with palpation as the

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method often used in population epidemiological studies: Rosenfield *et al.*[24] used inspection to ascertain pubertal signs of breast in 8- through 18-year-old children of the Third National Health and Nutrition Examination Survey (NHANES III); A cohort study of breast development, a part of the National Institute of Environmental Health Sciences/National Cancer Institute Breast Cancer and the Environment Research Program (BCERP), described that breast development was assessed through both observation and palpation, which limited misclassification of fat tissue deposited in the chest area.[32] Bias may also have existed in distinguishing testicular development from hydrocele or cysts, etc. It was relatively objective that the testicle volume was measured with Prader testicular meter and imaging diagnosis such as B-ultrasonic scan, may help to reduce false positives in future research.

CONCLUSIONS

Early pubertal development was found to be positively associated with obesity and central obesity. We observed the pubertal timing of breast, pubic hair, and testicular volume decreased with BMI increased but earlier median age of thelarche and testicular development rather than pubarche in children with central obesity. Children with obesity are more vulnerable to psychological problems beyond physical influence while early puberty undoubtedly strengthen these problems. Further, obesity children may need special attention of puberty knowledge and mental health in school education. We hope our results will serve as a reference for future research investigating the mechanism and causal effect between precocious puberty and obesity for the development of appropriate approaches to consider precocious puberty in clinical settings.

Contributors Professor Fan Jiang (MD, PhD) and Mrs. Yunting Zhang (PhD) designed the research; Yunting Zhang (PhD), Wanqi Sun (MS), Yao Chen (MS), Yanrui Jiang (MS), Yuanjin

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Song (MS), Qinmin Lin (MS), Lixia Zhu (MS), Qi Zhu (BS), performed the study; Miss Chang Chen (MS) and Dr. Shijian Liu (PhD) drafted the manuscript and performed statistical analyses; Dr. Shijian Liu and Mrs. Xiumin Wang (MD, PhD) contributed to interpretation of the results and critically reviewed the manuscript; Professor Shijian Liu had primary responsibility for final content. All authors read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work. No financial disclosures were reported by the authors of this paper.

Funding This work was supported by Chinese National Natural Science Foundation [81422040, 81172685]; MOE New Century Excellent Talents [NCET-13-0362], Shanghai Science and Technology Commission [12411950405, 14441904004, 13QH1401800]; The fourth round of Three-Year Public Health Action Plan (2015-2017) [GWIV-36]; Shanghai Municipal Education Commission [D1502]; The Ministry of Science and Technology [2010CB535000].

Competing interests None declared.

Ethics approval The study was approved by the Institutional Review Boards of the Shanghai Children's Medical Center.

Data sharing statement No additional data are available.

REFERENCES

1. Clarkson J, Han SK, Liu X, et al. Neurobiological mechanisms underlying kisspeptin activation of gonadotropin-releasing hormone (GnRH) neurons at puberty. Molecular and cellular endocrinology 2010;**324**(1-2):45-50.
2. Ma HM, Du ML, Luo XP, et al. Onset of breast and pubic hair development and menses in urban chinese girls. Pediatrics 2009;**124**(2):e269-77.
3. Jaruratanasirikul S, Chanpong A, Tassanakijpanich N, et al. Declining age of puberty of school girls in southern Thailand. World journal of pediatrics : WJP 2014;**10**(3):256-61.
4. Rubin C, Maisonet M, Kieszak S, et al. Timing of maturation and predictors of menarche in girls enrolled in a contemporary British cohort. Paediatric and perinatal epidemiology 2009;**23**(5):492-504.
5. Golub MS, Collman GW, Foster PM, et al. Public health implications of altered puberty timing. Pediatrics 2008;**121 Suppl 3**:S218-30.
6. Adair LS, Gordon-Larsen P. Maturational timing and overweight prevalence in US adolescent girls. American

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journal of public health 2001;**91**(4):642-4.
7. Bratberg GH, Nilsen TI, Holmen TL, et al. Early sexual maturation, central adiposity and subsequent overweight in late adolescence. a four-year follow-up of 1605 adolescent Norwegian boys and girls: the Young HUNT study. BMC public health 2007;**7**:54.
8. van Lenthe FJ, Kemper HC, van Mechelen W, et al. Biological maturation and the distribution of subcutaneous fat from adolescence into adulthood: the Amsterdam Growth and Health Study. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 1996;**20**(2):121-9.
9. Davison KK, Susman EJ, Birch LL. Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. Pediatrics 2003;**111**(4 Pt 1):815-21.
10. Burt Solorzano CM, McCartney CR. Obesity and the pubertal transition in girls and boys. Reproduction (Cambridge, England) 2010;**140**(3):399-410.
11. Freedman DS, Serdula MK, Srinivasan SR, et al. Relation of circumferences and skinfold thicknesses to lipid and insulin concentrations in children and adolescents: the Bogalusa Heart Study. The American journal of clinical nutrition 1999;**69**(2):308-17.
12. Tanita M, Matsunaga J, Miyamura Y, et al. Polymorphic sequences of the tyrosinase gene: allele analysis on 16 OCA1 patients in Japan indicate that three polymorphic sequences in the tyrosinase gene promoter could be powerful markers for indirect gene diagnosis. Journal of human genetics 2002;**47**(1):1-6.
13. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child-Fetal 1969;**44**(235):291-303.
14. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child-Fetal 1970;**45**(239):13-23.
15. Bridges NA, Christopher JA, Hindmarsh PC, et al. Sexual precocity: sex incidence and aetiology. Archives of disease in childhood 1994;**70**(2):116-8.
16. Lebrethon MC, Bourguignon JP. Management of central isosexual precocity: diagnosis, treatment, outcome. Current opinion in pediatrics 2000;**12**(4):394-9.
17. Klein KO. Precocious puberty: who has it? Who should be treated? The Journal of clinical endocrinology and metabolism 1999;**84**(2):411-4.
18. de Onis M, Onyango AW, Borghi E, et al. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;**85**(9):660-7.
19. de Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity 2010;**5**(6):458-60.
20. Subspecialty Group of Endocrinologic H, Metabolic Diseases TSoPCMA, Subspecialty Group of Cardiology TSoPCMA, et al. [The definition of metabolic syndrome and prophylaxis and treatment proposal in Chinese children and adolescents]. Zhonghua er ke za zhi Chinese journal of pediatrics 2012;**50**(6):420-2.
21. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics 2002;**110**(5):903-10.
22. Kaplowitz PB, Slora EJ, Wasserman RC, et al. Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics 2001;**108**(2):347-53.
23. Atay Z, Turan S, Guran T, et al. The prevalence and risk factors of premature thelarche and pubarche in 4- to 8-year-old girls. Acta paediatrica 2012;**101**(2):e71-5.
24. Rosenfield RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics 2009;**123**(1):84-8.
25. Sorensen K, Aksglaede L, Petersen JH, et al. Recent changes in pubertal timing in healthy Danish boys: associations with body mass index. The Journal of clinical endocrinology and metabolism 2010;**95**(1):263-70.
26. Lee JM, Kaciroti N, Appugliese D, et al. Body mass index and timing of pubertal initiation in boys. Archives of pediatrics & adolescent medicine 2010;**164**(2):139-44.
27. Lee HS, Park HK, Ko JH, et al. Impact of body mass index on luteinizing hormone secretion in gonadotropin-releasing hormone stimulation tests of boys experiencing precocious puberty. Neuroendocrinology 2013;**97**(3):225-31.
28. Dai YL, Fu JF, Liang L, et al. Association between obesity and sexual maturation in Chinese children: a

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muticenter study. International journal of obesity 2014;**38**(10):1312-6.
29. Roemmich JN, Rogol AD. Role of leptin during childhood growth and development. Endocrinology and metabolism clinics of North America 1999;**28**(4):749-64, viii.
30. Biro FM, Lucky AW, Simbartl LA, et al. Pubertal maturation in girls and the relationship to anthropometric changes: pathways through puberty. The Journal of pediatrics 2003;**142**(6):643-6.
31. Daniels SR, Khoury PR, Morrison JA. Utility of different measures of body fat distribution in children and adolescents. American journal of epidemiology 2000;**152**(12):1179-84.
32. Biro FM, Greenspan LC, Galvez MP, et al. Onset of breast development in a longitudinal cohort. Pediatrics 2013;**132**(6):1019-27.

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Table 1 Basic characteristics of the subjects

Variables	Total (N=15937)	Boys (N=8546)	Girls (N=7391)	x^2/T	P#
Age (y)				5.54	0.354
6	856 (5.37)	469 (5.49)	387 (5.24)		
7	3549 (22.27)	1936 (22.65)	1613 (21.82)		
8	3341 (20.96)	1816 (21.25)	1525 (20.63)		
9	3318 (20.82)	1731 (20.26)	1587 (21.47)		
10	2758 (17.31)	1467 (17.17)	1291 (17.47)		
11	2115 (13.27)	1127 (13.19)	988 (13.37)		
Weight (Kg)	32.94 ± 9.87	34.02 ± 0.36	31.68 ± 9.11	15.18	<0.001
Height (Cm)	136.56 ± 10.52	136.78 ± 10.18	136.31 ± 10.90	2.76	0.006
WC (cm)	59.64 ± 9.37	62.24 ± 10.26	56.63 ± 7.13	40.50	<0.001
BMI (Kg/m^2)	17.33 ± 3.22	17.84 ± 3.44	16.74 ± 2.83	22.08	<0.001
WHtR	0.44 ± 0.05	0.45 ± 0.06	0.42 ± 0.04	48.69	<0.001
General Obesity Category[a]				731.88	<0.001
Severe Thinness	60 (0.38)	37 (0.43)	23 (0.31)		
Thinness	420 (2.64)	183 (2.14)	237 (3.21)		
Normal	10681 (67.02)	5098 (59.65)	5583 (75.54)		
Overweight	2770 (17.38)	1638 (19.17)	1132 (15.32)		
Obesity	2006 (12.59)	1590 (18.61)	416 (5.63)		
Central Obesity Category[b]				569.44	<0.001
Normal	12515 (78.56)	6096 (71.35)	6419 (86.91)		
Central Obesity	3415 (21.44)	2448 (28.65)	967 (13.09)		
Puberty[c]				640.46	<0.001
Normal	5658 (90.47)	4094 (96.99)	1564 (76.93)		
Precocious	596 (9.53)	127 (3.01)	469 (23.07)		

WC, waist circumference; BMI, body mass index; WHtR, waist to height ratio.

All qualitative are expressed as frequency (%)， all quantitative data are expressed as mean ± standard deviation.

[#] *P* for t-tests or x^2-tests.

[a] Defined as severe thinness (BMI-for-age < -3 SD); thinness (-3 SD ≤ BMI-for-age < -2 SD); normal (-2 SD ≤ BMI-for-age ≤ 1 SD); overweight (1 SD < BMI-for-age ≤ 2 SD); obesity (BMI-for-age > 2 SD).

[b] Defined as central obesity (WHtR ≥ 0.48 in boys or WHtR ≥ 0.46 in girls); normal (WHtR <0.48 in boys or WHtR <0.46 in girls).

[c] Defined as under 8 years for Tanner stage 2 or above for breast or pubic hair development and 10 years for menstruation in girls, and under 9 years for Tanner stage 2 or above for pubic hair or testicle development in boys.

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Table 2 Associations between different types of obesity and the risk of precocious puberty

Puberty	General Obesity			Central Obesity		
	Normal, N(%)	Obesity, N(%)	OR (95% CI)	Normal, N(%)	Obesity, N(%)	OR (95% CI)
Boy						
Normal	2692 (65.75)	647 (15.80)	Reference	3151 (76.99)	942 (61.42)	Reference
Precocious	64 (50.39)	33 (25.98)	2.15 (1.31-3.50)	78 (23.01)	49 (38.58)	2.10 (1.46-3.03)
Girl						
Normal	1352 (86.45)	37 (2.37)	Reference	1451 (92.83)	112 (7.17)	Reference
Precocious	264 (56.29)	65 (13.86)	9.00 (5.60-14.46)	331 (70.58)	138 (29.42)	2.00 (1.66-2.40)

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Table 3 Median age (95% CI) of attainment different pubertal stages according to probit analysis in Shanghai children

General Obesity Category	Girls		Boys	
	B_2	PH_2	PH_2	T_2
Severe Thinness	10.86 (9.77-12.08)	12.56 (10.64-14.86)	13.56 (11.31-16.40)	11.72 (8.35-16.59)
Thinness	9.88 (9.58-10.18)	11.13 (10.69-11.60)	14.50 (13.00-16.34)	11.28 (9.74-13.15)
Normal Weight	8.85 (8.79-8.91)	10.73 (10.62-10.84)	13.96 (13.46-14.60)	10.57 (10.31-10.88)
Overweight	7.68 (7.55-7.80)	10.22 (10.04-10.40)	13.82 (13.28-14.49)	10.32 (9.93-10.74)
Obesity	7.14 (6.93-7.35)	10.18 (9.89-10.48)	13.66 (13.13-14.32)	10.27 (9.87-10.70)
Total	8.62 (8.57-8.67)	10.62 (10.53-10.71)	13.84 (13.40-14.40)	10.46 (10.21-10.78)

B_2, Tanner stage 2 for breast development; PH_2, Tanner stage 2 for pubic hair development; T_2, Tanner stage 2 for testicle development with testicular volume ≥ 4 ml.

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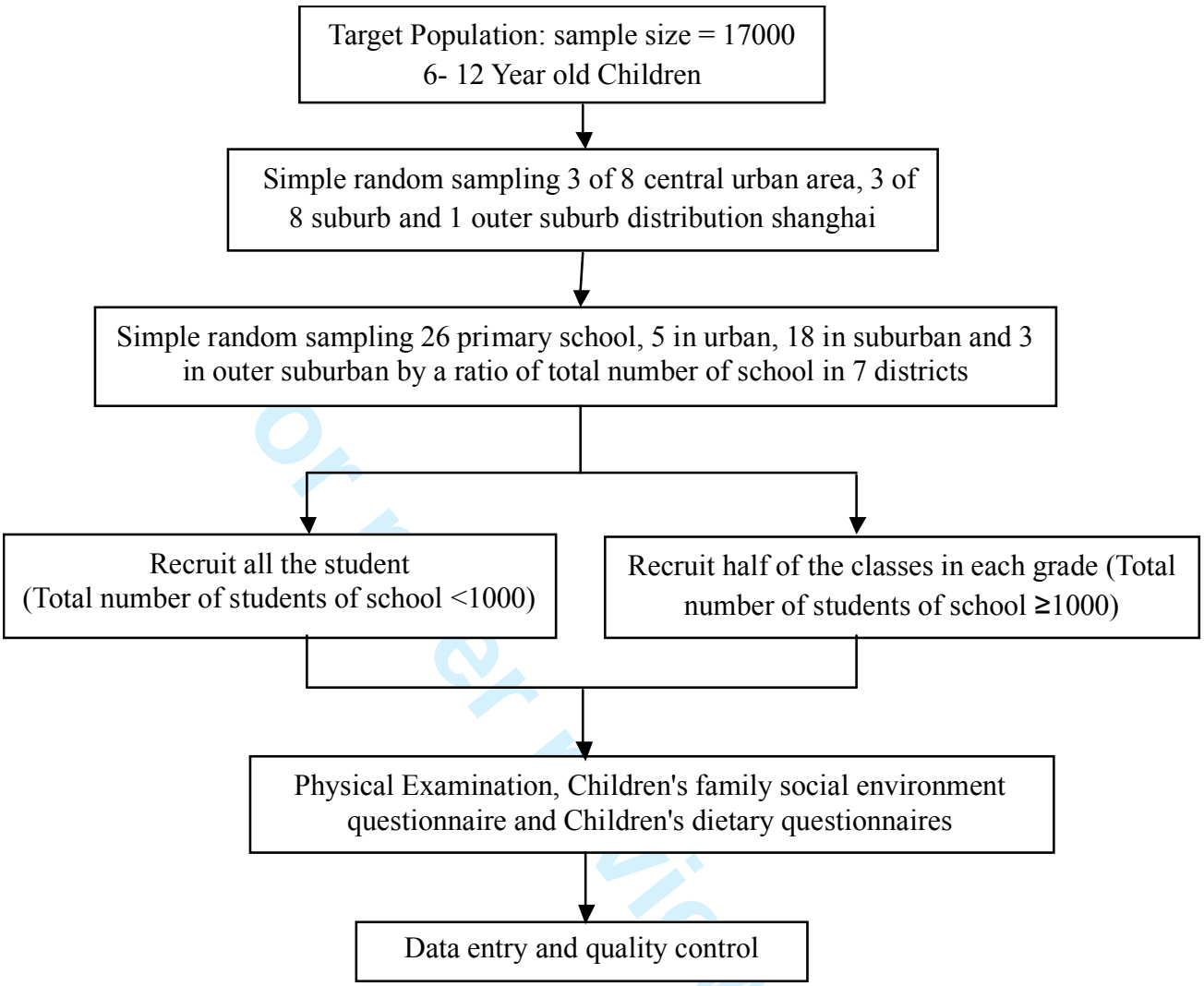

Figure 1 Sampling scheme of the study

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Table S1 Characters of literature between overweight/obesity and precocious puberty

Author	Year	Sample size	Age	Ethnic	Design	Country	Definition of overweight/obesity	Definition of precocious puberty/early puberty	Association of obesity and precocious puberty
Current study	2014	17620	6-12 years	Chinese	Cross-sectional study	China	WHO Overweight: BMI ≥ 1SD, Obesity: BMI ≥ 2SD	Girls: breast Tanner stage 2 or above before 8 year old; Boys: Testicular volume ≥ 4 ml before 9 year old;	Prevalence of precocious puberty in 4.17% boys and 48.54% girls with overweight; 4.85% boys and 61.86% girls with obesity; Prevalence of overweight in 22.05% boys and 26.01% girls with precocious puberty; 25.98% boys and 13.76% girls for obesity with precocious puberty
Adair LS *et al.*	1988-1991	6507 girls	12-17 years	54.8% non-Hispanic White,21.1% non-Hispanic Black,17.0% Hispanic,7.1% Asian;	Longitudinal study	America	Overweight: BMI≥85th percentile;	Age at menarche: maturing early (younger than 11 years average); maturing late (11–13); maturing late (14 years or older);	Prevalence of overweight was 41.5%, 25% and 18.7% in early, average and late maturing girls respectively.

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Atay Z *et al.*	2009	820 girls	4-8 years	-	Cross-sectional study	Turkey	BMI standard deviation scores(SDS)	Premature thelarche (PT);Premature pubarche (PP)	56.1% girls were PT with BMI SDS values above 1 in the PT group; 31.4% girls were PP with BMI SDS values above 1 in the PT group;
Dai YL *et al.*	2009-2010	8895 girls 9812 boys	6-18 years	Chinese	Cross-sectional study	China	Chinese Working Group on Obesity，Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	tertiles on the timing of breast and testicular Tanner stage 2 or more (early-maturing group: earliest tertile; non-early-maturing: average and late maturers)	Median age of B2 was 9.69 years; Median age of G2 was 11.25 years; OR and 95% CIs for overweight were 1.48 (1.22–1.79) for boys and 2.64 (2.16–3.23) for girls, and for obesities were 1.61 (1.22–2.11) and 3.49 (2.59–4.70), respectively
Davison KK *et al.*	-	181 girls	5-9 years	-	Longitudinal study	America	American 2000 CDC criteria: BMI percentiles	At 9 years: estradiol levels; breast Tanner stage 3; pubertal Development Scale	BMI percentile was 79.6 and 59.4 in earlier puberty and later puberty girls
Lee HS *et al.*	2003-2010	104 boys	Mean age of 8.7 years	Korean	Cohort study	Korea	Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	Testicular volume > 4 ml; advanced bone age > 1 year above chronological age; pubertal LH peak values; serum testosterone levels;	Testicular volume was 6.8 ml (normal weight), 5.9 ml (overweight) and 6.1 ml (obesity)

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Lee JM *et al.*	1991	401 boys	2-11.5 years	White (79.5%); Nonwhite (20.5%)	Longitudinal study	America	Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	Genitalia Tanner stage 2 before age 11.5 years	49 boys (12.2%) were prepubertal at age 11.5 years by Tanner genitalia staging
Rosenfield RL *et al.*	1988-1994	-	8- 18 years	Non-Hispanic white, non-Hispanic black, Mexican American	Cross-sectional study	America	normal BMI (10th–84th per-centile); excessive BMI (85th per-centile)	Thelarche stage 2; pubarche stge3; menarche	The median age were 10.81 and 9.79 of breast stage 2, 11.57 and 11.39 of pubarche stage 3, 12.57 and 12.06 of menarche in normal and excessive BMI group respectively;
Sorensen K *et al.*	1991–1993; 2006–2008;	1528 boys	5.8-19.8 years	Caucasian origin	Cross-Sectional study; Longitudinal study	Denmark	American 2000 CDC criteria, Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	Testicular volume > 3 ml; genital stages 2 (G2);pubic hair stages 2 (PH2)	Median age of G2 was 11.83 years in 1991 and 11.59 years in 2006; Median age of PH2 was 11.89 years in 1991 and 12.38 years in 2006; Median age of TV was 11.92 years in 1991 and 11.66 years in 2006
Wang Y *et al.*	1988-1994	1501 girls;	8-14 years	Non-Hispanic white	Cross-sectional	America	American 2000 CDC criteria,	Girls: breast Tanner stage 2;	Prevalence of overweight in 23% boys and 34% girls with early

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		(25%), non-Hispanic black (36%), Mexican American (35%)	study	Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	Boys: genitalia stage 3, earlier than the median age for that stage.	mature; 7% boys and 16% girls for obesity with early mature;
1520 boys						

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

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
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	7,8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7,20
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	8
Results			

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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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	20
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,17
		(b) Indicate number of participants with missing data for each variable of interest	9,17
Outcome data	15*	Report numbers of outcome events or summary measures	9
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	9,10
		(*b*) Report category boundaries when continuous variables were categorized	9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12,13
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	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
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	15

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

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

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Investigating the relationship between precocious puberty and obesity: a cross-sectional study in Shanghai, China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014004.R1
Article Type:	Research
Date Submitted by the Author:	09-Mar-2017
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Paediatrics
Keywords:	EPIDEMIOLOGY, PAEDIATRICS, Obesity, Puberty

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Investigating the relationship between precocious puberty and obesity: a cross-sectional study in Shanghai city of China

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ABSTRACT

Objectives: Obesity is reported closely relevant to early sexual development but the relationship between sexual precocity and obesity or central obesity is still inconsistent, especially in boys. We aimed to investigate the relationship between precocious puberty and obesity as well as central obesity.

Design: A large population-based cross-sectional study using multistage, stratified cluster random sampling.

Setting: Data from the Shanghai Children's Health, Education and Lifestyle Evaluation (SCHEDULE) study in June 2014.

Participants: 17,620 Chinese children aged 6–12 years.

Primary and secondary outcome measures: Obesity was defined by WHO Child Growth Standards. Central obesity was defined by sex-specific waist-to-height ratio (WHtR) cut-offs (WHtR ≥ 0.48 for boys, WHtR ≥ 0.46 for girls). Precocious puberty was identified by Tanner stage of breast, pubic hair and testicle. A chi-square test was performed to compare rates. Odds ratios (ORs) with 95% confident interval (CI) were calculated to assess the association between precocious puberty and general obesity and central obesity. Probit analysis was used for estimating the median age at entry into Tanner stage 2 or greater for breast, pubic hair and testicle development. Linear regression was utilized to compare the effects of WHtR and BMI on sex development indicators.

Results: 25.98% and 38.58% precocious boys were respectively accompanied by obesity (OR = 2.15, 95%CI = 1.31–3.50) or central obesity (OR = 2.10, 95%CI = 1.46–3.03); meanwhile, 13.86% and 29.42% precocious girls were respectively accompanied by obesity (OR = 9.00, 95%CI = 5.60–14.46) or central obesity (OR = 5.40, 95%CI = 4.10–7.12). The median ages of

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breast, pubic hair and testicle development decreased with BMI increased and median ages of thelarche and testicular rather than pubarche were earlier in children with central obesity.

Conclusions: Earlier pubertal development was positively associated with obesity and central obesity in Chinese children.

Strengths and limitations of this study:

- This study is a large population-based cross-sectional study and the subjects were representative of the general population for Shanghai.
- Early pubertal development was found to be associated with obesity and central obesity which is of relevance to the current public health concern about the risk factors associated with the earlier onset of puberty.
- Longitudinal investigations are still needed to determine the causal direction between obesity and precocious puberty.
- Imaging diagnosis of breast and testicle development such as B-ultrasonic scan, may help to reduce false positives in future research.

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INTRODUCTION

Puberty is an essential and complex process with wide physiologic variation and maturation. Mechanisms controlling the onset of puberty and tempo of development are complicated and involve genetic, nutritional, and environmental interactions.[1] Increasing numbers of countries are experiencing earlier development of secondary sexual characteristics in children.[2-4] Earlier puberty has been reported to be associated with a higher risk of psychological problems, reproductive tract cancers and the development of metabolic syndrome features later in life.[5]

Recent data suggest that earlier timing or faster progression of pubertal development is related to higher body mass index (BMI) and greater risk of overweight in later adolescence and adulthood. [6 7] Those who develop earlier tend to be more obese with a trunk-oriented distribution pattern from adolescence to adulthood.[8] Also, children with overweight and obesity appear to sexually develop earlier than lean children.[9] The underlying biological mechanisms like insulin resistance with compensatory hyperinsulinemia, endocrine disruptors and androgens in girls may contribute to the sexual characteristic changes.[10] In addition, a central or abdominal distribution of body fat was reported to be related to adverse health outcomes compared with peripheral fat which implied body fat patterning may also influence sexual maturation.[7 11]

The relationship between sexual precocity and obesity or central obesity is still inconsistent, especially in boys. The purpose of this study is to evaluate the relationship between the timing of sexual maturation and body mass, as well as the effect of central obesity on precocious puberty.

METHODS

Participants and sampling

Informed consent was obtained from the participant children and their parents and the study was approved by the Institutional Review Boards of the Shanghai Children's Medical Center. The

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participants were selected from the Shanghai Children's Health, Education and Lifestyle Evaluation (SCHEDULE) study. This cross-sectional study was conducted in June 2014 by multistage and stratified cluster random sampling. Nineteen districts of Shanghai were stratified into central urban area, suburb and outer suburb according to the 2005 Shanghai census report [12] and seven districts were randomly chosen including Jing'an, Changning, Zhabei, Jiading, Jinshan, Pudong, Chongming. From these, 26 general primary schools were randomly sampled from school lists and students in grades 1 to 5 were recruited (**Figure 1**). Children who had been diagnosed with organic disease (such as ovarian tumor, hamartoma, etc.), chronic diseases (such as chronic kidney disease, asthma, epilepsy, etc.), genital abnormalities (such as cryptorchidism, hypospadias, etc.), and children with medication (such as glucocorticoid) which could cause precocious puberty were excluded from the study. Trained teachers handed out questionnaires to the recruited students, asking them to take the questionnaires home and their parents to complete the questionnaires concerning family, social and environmental issues as well as dietary habits. Then teachers collected the completed questionnaires and returned it to the investigators. Data were analyzed in 2016.

Physical Examination

Sexual development of children was jointly evaluated by professional pediatric endocrinology physicians and pediatric care physicians. The pubertal assessments of breast development used inspection combined with palpation. For obese girls, we paid close attention to the palpation of nodules in breast. Testicular volume was determined by palpation and testicular meter, i.e. palpated and compared the testicle with the most similar bead in orchidometer. Tanner staging method was adopted to assess sexual development in children. The pubertal stages of breast and pubic hair development were graded from 1 (prepubertal) to 5 (fully mature) and delineated by Marshall and Tanner.[13 14] Precocious puberty was considered as being under 8 years for Tanner

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stage 2 or above for breast (B_2) or pubic hair development (PH_2) and 10 years for menstruation in girls as well as under 9 years for Tanner stage 2 or above for pubic hair or testicle development (T_2) (testicular volume, TV ≥ 4 ml) in boys.[15-17]

Height measurement was performed without shoes and standing upright by a wall-mounted stadiometer to the nearest 0.1 cm. Participants wore light clothes and were barefoot when weight was measured by research assistants using a standardized digital scale to the nearest 0.1 kg; Waist circumference (WC) determination was obtained to the nearest 0.1 cm at the midpoint of the horizontal line between the lower rib margin and the superior iliac border while standing with an inelastic measuring tape at the end of normal expiration. Calculation of BMI was weight (kg) divided by the square of height (m^2). Subjects were classified into severe thinness, thinness, overweight and obesity categories according to the WHO Child Growth Standards (http://www.who.int/growthref/en/), i.e., severe thinness is BMI < -3 standard deviation (SD), thinness is BMI < -2 SD, overweight is BMI ≥1 SD and obesity is BMI ≥2 SD.[18 19] The overweight category excludes obesity and thinness excludes severe thinness. BMI was converted to BMI Z-scores based on the mean and the SD of the children at same age group and gender. Waist-to-height ratio (WHtR) was calculated as WC (cm) divided by height (cm) and central obesity was defined as WHtR ≥ 0.48 in boys and WHtR ≥ 0.46 in girls.[20] All physical data were collected at school settings.

Statistical analysis

All data were recorded and proofread using EpiData 3.1 (EpiData Association, Odense, Denmark) by two groups of researchers. The detection rate of precocious puberty was directly calculated and the chi-square test was performed to compare rates. Odds ratios (ORs) with 95% confident interval (CI) were calculated to assess the association between precocious puberty,

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general obesity and central obesity. Probit analysis was used for estimating the median age of the population at entry into Tanner stage 2 or greater for breast, pubic hair and testicular development. Linear regression was applied to evaluate the relationship between WHtR, BMI Z-score and sexual maturation among children detected as Tanner stage 2 of breast, pubic hair or testicle development. All the raw data were analysed using IBM SPSS Statistic package version 21 (IBM Corp., Armonk, NY, USA) with two-sided and the *P* value < 0.05 was considered statistically significant.

RESULTS

Sample

A total of 17,620 parents of recruited children completed the questionnaires, and 17,368 (98.57%) were valid. The number of 6-12 year-old children who completed the physical examination was 16,958 (96.24%). After eliminating missing (845), extreme and invalid data (176) for age, sex and key physical parameters including height and weight, a total of 15,937 (90.45%) children including 8,546 (53.62%) boys and 7,391 (46.48%) girls age range from 6 to 12 years constituted the final sample.

Subject characteristics

Boys had obviously higher levels of weight, height, WC (7 missing), BMI and WHtR than the girls (P < 0.005). Moreover, the prevalence of both obesity and central obesity was relative higher in boys than girls (The prevalence of obesity was 18.61% for boys and 5.63% for girls; of central obesity was 28.65% for boys and 13.09% for girls) (*P* <0.001). 4221 boys aged 6-9-year, 2000 girls aged 6-8-year and girls with menstruation aged below 10 years were diagnosed with or without precocious puberty according to the age-specific definition. The overall detection rate of

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precocious puberty of boys was 9.53% (596 cases). Girls (469 cases, 23.07%) had a significantly higher rate than boys (127 cases, 3.01%) (P <0.001). (**Table** 1)

Relationship between different types of obesity and the risk of precocious puberty

The prevalence of obesity and central obesity was relatively high and had an obvious influence on precocious puberty in both genders. **Table** 2 showed the results, 25.98% precocious boys and 13.86% precocious girls were obese. Childhood obesity increased the risk of precocious puberty and the risk was obviously higher in girls than boys (OR = 2.15, (95% CI = 1.31–3.50); for boys, OR = 9.00 (95% CI = 5.60–14.46) for girls). Moreover, 38.58% precocious boys and 29.42% precocious girls had central obesity. Central obesity had a relatively similar effect on obesity (boys: OR = 2.10, 95% CI = 1.46–3.03; girls: OR = 5.40, (95% CI = 4.10–7.12). The status of obesity using either BMI or WHtR was significantly associated with precocious puberty.

Attaining median age of pubertal stages

We estimated the median age of both girls and boys and the 95% CI for attainment of Tanner stage 2 for breast, pubic hair and testicle development according to probit analysis (**Table** 3).

For girls, the median ages of B_2 decreased from 10.86 in severe thinness group, 9.88 in thinness group, 8.85 in normal weight group, 7.68 in overweight group to 7.14 in obesity group. The same trend was observed in the median ages of PH_2 from 12.56, 11.13, 10.73, 10.22 decreased to 10.18 years within increased BMI group. For boys, median ages of PH_2 and T_2 decreased slightly within increased BMI group except for a lower median age of PH_2 in severe thinness group. The median ages of B_2, PH_2 and T_2 showed a negative association with BMI. It demonstrated a significant downward trend in median age of thelarche, pubarche and testicular development with an increase of BMI in 6 to 12-year-old children.

The median ages of B_2 and PH_2 were 8.69 (95% CI = 8.64–8.74) and 10.62 (95% CI = 10.53–10.72) years for non-centrally obese girls, 7.20 (95% CI = 6.97–7.44) and 10.60 (95% CI =

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10.26–10.96) years for centrally obese girls. The median age of B_2 was slightly lower than that of PH_2 in the central obesity group. For boys, the median ages of PH_2 and T_2 were 13.78 (95% CI = 13.34–14.35) and 10.52 (95% CI = 10.28–10.80) years for non-centrally obese boys, and 14.00 (95% CI = 13.47–14.65) and 10.33 (95% CI = 9.95–10.74) years for centrally obese boys. The median age of T_2 was slightly lower and of PH_2 was a little higher in the centrally obese boys than in the non-centrally obese boys.

Relationship between WHtR, BMI Z-score and sexual maturation

Using linear regression analysis, we analyzed the relationship between WHtR, BMI Z-score and sexual maturation (**Table** 4). The age of physical examination was estimated as the time of pubertal onset. For girls, both WHtR and BMI were negatively and statistically significantly related to the age of B_2 and PH_2. Higher WHtR was correlated to the earlier age of breast and pubic hair development, the similar change was observed in BMI Z-score. For boys, both WHtR and BMI were positively related to the age of PH_2 but negatively corrected to T_2. However, statistical significance only existed in the correlation between BMI Z-score and age of T_2. In addition, WHtR had greater impact on the age of PH_2 while BMI Z-score influenced more on the age of T_2.

DISCUSSION

This is a large-scale population-based cross-sectional survey of children pubertal growth and development in Shanghai, China. The total detection rate of precocious puberty was 9.53% (3.01% for boys, 23.07% for girls) in the present study.

Increasing evidence suggests that obesity is closely relevant to early sexual development in girls.[7 9 21-24] Atay *et al.*[23] found a strong association between different levels of BMI SD scores and the occurrence of premature thelarche but not with premature pubarche among 4–8-year-old

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girls in Istanbul. Kaplowitz *et al.*[22] observed that greater BMI is associated with an increased likelihood of early appearance of pubic hair and breast development in American girls aged 3–12 years. In addition, Rosenfield *et al.*[24] reported that girls with excessive BMI had a significantly higher prevalence of thelarche from ages 8.0 to 9.6 years and pubarche from ages 8.0 to 10.2 years. Our results are consistent with most studies that obesity was a significant risk factor for precocious puberty. We observed that the median age of both thelarche and pubarche decreased with BMI increased. The estimated age of B_2 and PH_2 were also negatively related to BMI Z-score.

In boys, there are limited studies that have evaluated the association between early sexual maturation and obesity. Wang [21] reported that early sexual maturation was negatively associated with overweight and obesity in boys aged 8–14 years in the United States in 1988 - 1994. In this population-based cross-sectional study, the prevalence of overweight was 23% and obesity 7% for boys with precocious puberty. The subjects were mainly non-Hispanic white (25%), non-Hispanic black (36%) and Mexican American (35%). Additionally, Sorensen *et al*.[25] reported in a combined cross-sectional and longitudinal study in Denmark that BMI was negatively associated with testicular growth and pubic hair development, indicating that higher BMI results in a later age for pubertal onset in Caucasian boys aged 5.8 to 19.8 years. However, in a longitudinal population-based study, Lee *et al.*[26] provided further evidence that higher BMI during early childhood is not associated with earlier pubertal onset in American boys. These boys were aged 2 to 11.5 years and their ethnicities were white (79.5%) and nonwhite (20.5%); and 12.2% of the boys were prepubertal at age 11.5 years according to Tanner genitalia staging. In contrast to these studies, Lee HS *et al.*[27] conducted a hospital-based gonadotropin-releasing hormone (GnRH) stimulation test involving Korean boys with a mean age of 8.7 years and reported that excess adiposity may influence the hypothalamic-pituitary-gonadal axis in boys,

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suggesting that obese boys enter puberty at an earlier age than normal weight boys. Dai *et al.*[28] described in a Chinese cross-sectional study that early sexual maturation was positively associated with obesity in boys only by the indicator of testicular volume. Our study was consistent with the positive results and further provided evidence of the relation between pubic hair development and obesity. The discrepancy of these findings might be explained by ethnic background differences, variation in the assessment criteria of pubertal stage and obesity, sample size, time factor, social culture, etc. Characteristics of ourstudy and other related literatures were attached in Supplemental **Table S1** online. Our study also further provided evidence of the relation between pubic hair, testicular development and obesity. Timing of testicular development was decreased with increasing BMI and negatively related to BMI Z-score. For pubic hair, the median age of PH_2 was slightly decreased with increased BMI, but the youngest age demonstrated a wide range of 95%CI in the severe thinness group and might be related to the small sample size. Though the estimated age of T_2 was positively related to BMI Z-score, it showed no statistical significance. The result of pubic hair was inconsistent; one possible reason might be the analysis of BMI Z-score excluded boys with T3 or greater Tanner stage who were more likely to be obese. Obesity had little or no effect on pubic hair development, it mainly influenced testicle development.

More and more researchers have explored the linkage between precocious puberty and obesity, but the potential mechanisms remain unclear. Longitudinal epidemiologic evidence suggests that obesity has an important effect on precocious puberty.[9 21 27] The effect of obesity is likely to be related to leptin, a hormone secreted by adipocytes, which affect pubertal onset through activation of permissive hypothalamic GnRH secreting neurons.[29] As a consequence of obesity, insulin resistance plays an important role in the timing of puberty by interfering with

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leptin signaling and causing additional weight gain.[29] Additionally, premature adrenarche is also reported to be associated with obesity, but the potential mechanisms remain unknown.[30]

Research is lacking on the effect of fat distribution on pubertal development based on a large representative population. Biro *et al.*[30] suggested both the adrenarche pathway for pubic hair development and the thelarche pathway for breast development were influenced by body fat and BMI. Even though there is an overlap between central obesity and obesity defined by BMI, BMI measurement is not effective for providing information on fat distribution. WHtR, which is calculated using WC and height, is reported easily to influence fat distribution and is less affected by gender and ethnicity compared with BMI.[31] David *et al.*[11] emphasized the importance of obtaining information on fat distribution and, particularly, waist circumference in children. They found that a relative excess of adipose tissue in the abdominal or central region was related to adverse concentrations of insulin, which was independent of weight and height. Our study further clearly revealed a relatively higher rate of precocious puberty and earlier median age of thelarche and testicular development rather than pubarche in children with central obesity. Furthermore, we revealed an earlier median age of thelarche and pubarche development among central obesity girls. Also, higher WHtR was correlated to earlier age of estimated timing of B_2 and PH_2, but the influence of WHtR was weaker than BMI. For boys, central obesity varied the effect. The timing of testicular development was earlier in central obesity boys, WHtR affected the timing of testicular development more than BMI, but pubarche development demonstrated a totally opposite outcome. That is, the timing was later in boys with central obesity and positively related to WHtR. But BMI had greater influence than WHtR. These findings hinted that the different effects of WHtR on sex development indicated with different extents and mechanisms.

Strengths and limitations of this study

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This study is a large population-based cross-sectional study and the subjects were representative of the general population for Shanghai. Early pubertal development was found to be associated with obesity and central obesity, which is of relevance to the current public health concern about the risk factors associated with the declining timing of puberty. However, some limitations should be acknowledged. First, though the sample size is large, the results cannot determine the causality or the speed of the consecutive pubertal stages because sexual development and obesity are measured at the same time point. In addition, our cross-sectional study couldn't measure the timing of pubertal onset exactly. Therefore, longitudinal investigations are needed to more accurately evaluate timing of pubertal onset and determine the causal direction, as to whether obesity has an impact on precocious puberty during childhood.

Second, we were unable to characterize the parents' pubertal development especially a history of precocious puberty, which may influence the pubertal development of the next generation. Since precocious puberty was idiopathic, we will take parents' pubertal information into consideration in the follow-up study.

Third, it would be desirable if more accurate assessment of breast development were available in overweight or obese children field survey. Discriminating between glandular breast and fat tissue is a critical concern, and inspection or palpation may lead to errors in estimating precocious puberty in obese children with excessive subcutaneous fat in the chest. It was rather difficult to employed imaging diagnosis in a large-scale of children taking part in the physical examination, so we only adopted inspection combined with palpation as the method often used in population epidemiological studies: Rosenfield *et al.*[24] used inspection to ascertain pubertal signs of the breast in 8- 18-year-old children in the Third National Health and Nutrition Examination Survey (NHANES III. A cohort study of breast development sponsored by the National Institute of Environmental Health Sciences/National Cancer Institute Breast Cancer and the Environment

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Research Program (BCERP), indicated that breast development was assessed through both observation and palpation, which limited misclassification of fat tissue deposited in the chest area.[32] Bias may exist in distinguishing testicular development from hydrocele or cysts, etc. We didn't assess bone age because it was difficult to apply x-ray detection in large-scale population-based study. We will apply bone age diagnosis and improve the research methods by imaging diagnosis, such as B-ultrasonic scan in our further study.

CONCLUSIONS

Early pubertal development was found to be positively associated with obesity and central obesity. We observed the pubertal timing of breast and pubic hair decreased with BMI as WHtR increased in girls, and testicular volume decreased but pubic hair increased as BMI and WHtR increased in boys. Earlier median age of thelarche and testicular development rather than pubarche in children with central obesity. Children with obesity are more vulnerable to psychological problems beyond physical influence while early puberty undoubtedly strengthen these problems. Further, obesity children may need special attention of puberty knowledge and mental health in school education. We hope our findings will serve as a reference for future research investigating the mechanism and causal effect between precocious puberty and obesity leading to the development of appropriate approaches to consider precocious puberty in clinical settings.

Contributors Professor Fan Jiang (MD, PhD) and Mrs. Yunting Zhang (PhD) designed the research; Yunting Zhang (PhD), Wanqi Sun (MS), Yao Chen (MS), Yanrui Jiang (MS), Yuanjin Song (MS), Qinmin Lin (MS), Lixia Zhu (MS), Qi Zhu (BS), performed the study; Miss Chang Chen (MS) and Dr. Shijian Liu (PhD) drafted the manuscript and performed statistical analyses;

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Dr. Shijian Liu and Mrs. Xiumin Wang (MD, PhD) contributed to interpretation of the results and critically reviewed the manuscript; Professor Shijian Liu had primary responsibility for final content. All authors read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work. No financial disclosures were reported by the authors of this paper.

Funding This work was supported by Chinese National Natural Science Foundation [81172685, 81602868, 81601162, 81602870]; MOE New Century Excellent Talents [NCET-13-0362]; Shanghai Science and Technology Commission [14441904004]; The fourth round of Three-Year Public Health Action Plan (2015-2017) [GWIV-36] ;Shanghai Municipal Education Commission [D1502].

Competing interests None declared.

Ethics approval The study was approved by the Institutional Review Boards of the Shanghai Children's Medical Center.

Data sharing statement No additional data are available.

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REFERENCES

1. Clarkson J, Han SK, Liu X, et al. Neurobiological mechanisms underlying kisspeptin activation of gonadotropin releasing hormone (GnRH) neurons at puberty. *Mol Cell Endocrinol* 2010;324:45-50.
2. Ma HM, Du ML, Luo XP, et al. Onset of breast and pubic hair development and menses in urban chinese girls. *Pediatrics* 2009;124:e269-77.
3. Jaruratanasirikul S, Chanpong A, Tassanakijpanich N, et al. Declining age of puberty of school girls in southern Thailand. *World J Pediatr* 2014;10:256-61.
4. Rubin C, Maisonet M, Kieszak S, et al. Timing of maturation and predictors of menarche in girls enrolled in a contemporary British cohort. *Paediatr Perinat Epidemiol* 2009;23:492-504.
5. Golub MS, Collman GW, Foster PM, et al. Public health implications of altered puberty timing. *Pediatrics* 2008;121 Suppl 3:S218-30.
6. Adair LS, Gordon-Larsen P. Maturational timing and overweight prevalence in US adolescent girls. *Am J Public Health* 2001;91:642-4.
7. Bratberg GH, Nilsen TI, Holmen TL, et al. Early sexual maturation, central adiposity and subsequent overweight in late adolescence. a four-year follow-up of 1605 adolescent Norwegian boys and girls: the Young HUNT study. *BMC Public Health* 2007;7:54.
8. van Lenthe FJ, Kemper HC, van Mechelen W, et al. Biological maturation and the distribution of subcutaneous fat from adolescence into adulthood: the Amsterdam Growth and Health Study. *Int J Obes Relat Metab Disord* 1996;20:121-9.
9. Davison KK, Susman EJ, Birch LL. Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. *Pediatrics* 2003;111:815-21.
10. Burt Solorzano CM, McCartney CR. Obesity and the pubertal transition in girls and boys. *Reproduction* 2010;140:399-410.
11. Freedman DS, Serdula MK, Srinivasan SR, et al. Relation of circumferences and skinfold thicknesses to lipid and insulin concentrations in children and adolescents: the Bogalusa Heart Study. *Am J Clin Nutr* 1999;69:308-17.
12. Tanita M, Matsunaga J, Miyamura Y, et al. Polymorphic sequences of the tyrosinase gene: allele analysis on 16 OCA1 patients in Japan indicate that three polymorphic sequences in the tyrosinase gene promoter could be powerful markers for indirect gene diagnosis. *J Hum Genet* 2002;47:1-6.
13. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291-303.
14. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13-23.
15. Bridges NA, Christopher JA, Hindmarsh PC, et al. Sexual precocity: sex incidence and aetiology. *Arch Dis Child* 1994;70:116-8.
16. Lebrethon MC, Bourguignon JP. Management of central isosexual precocity: diagnosis, treatment, outcome.

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Curr Opin Pediatr 2000;12:394-9.

17. Klein KO. Precocious puberty: who has it? Who should be treated? *J Clin Endocrinol Metab* 1999;84:411-4.
18. de Onis M, Onyango AW, Borghi E, et al. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007;85:660-7.
19. de Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? *Int J Pediatr Obes* 2010;5:458-60.
20. Subspecialty Group of Endocrinologic Hereditary, Metabolic Diseases, Subspecialty Group of Cardiology, Subspecialty Groups of Child Health Care, the Society of Pediatrics Chinese Medical Association. The definition of metabolic syndrome and prophylaxis and treatment proposal in Chinese children and adolescents. *Zhonghua Er Ke Za Zhi* 2012;50:420-2.
21. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. *Pediatrics* 2002;110:903-10.
22. Kaplowitz PB, Slora EJ, Wasserman RC, et al. Earlier onset of puberty in girls: relation to increased body mass index and race. *Pediatrics* 2001;108:347-53.
23. Atay Z, Turan S, Guran T, et al. The prevalence and risk factors of premature thelarche and pubarche in 4- to 8-year-old girls. *Acta Paediatr* 2012;101:e71-5.
24. Rosenfield RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. *Pediatrics* 2009;123:84-8.
25. Sorensen K, Aksglaede L, Petersen JH, et al. Recent changes in pubertal timing in healthy Danish boys: associations with body mass index. *J Clin Endocrinol Metab* 2010;95:263-70.
26. Lee JM, Kaciroti N, Appugliese D, et al. Body mass index and timing of pubertal initiation in boys. *Arch Pediatr Adolesc Med* 2010;164:139-44.
27. Lee HS, Park HK, Ko JH, et al. Impact of body mass index on luteinizing hormone secretion in gonadotropin-releasing hormone stimulation tests of boys experiencing precocious puberty. *Neuroendocrinology* 2013;97:225-31.
28. Dai YL, Fu JF, Liang L, et al. Association between obesity and sexual maturation in Chinese children: a muticenter study. *Int J Obes (Lond)* 2014;38:1312-6.
29. Roemmich JN, Rogol AD. Role of leptin during childhood growth and development. *Endocrinol Metab Clin North Am* 1999;28:749-64, viii.
30. Biro FM, Lucky AW, Simbartl LA, et al. Pubertal maturation in girls and the relationship to anthropometric changes: pathways through puberty. *J Pediatr* 2003;142:643-6.
31. Daniels SR, Khoury PR, Morrison JA. Utility of different measures of body fat distribution in children and adolescents. *Am J Epidemiol* 2000;152:1179-84.
32. Biro FM, Greenspan LC, Galvez MP, et al. Onset of breast development in a longitudinal cohort. *Pediatrics* 2013;**132**:1019-27.

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Figure legend

Figure 1 Sampling theme of the study

This study was conducted by multistage and stratified cluster random sampling. Seven districts were randomly chosen, 26 general primary schools were randomly sampled were recruited.

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Table 1 Basic characteristics of the subjects

Variables	Total N=15937	Boys N=8546	Girls N=7391	χ^2/t	*P* value[#]
Age (y)				5.54	0.354
6	856 (5.37)	469 (5.49)	387 (5.24)		
7	3549 (22.27)	1936 (22.65)	1613 (21.82)		
8	3341 (20.96)	1816 (21.25)	1525 (20.63)		
9	3318 (20.82)	1731 (20.26)	1587 (21.47)		
10	2758 (17.31)	1467 (17.17)	1291 (17.47)		
11	2115 (13.27)	1127 (13.19)	988 (13.37)		
Weight (Kg)	32.94 ± 9.87	34.02 ± 0.36	31.68 ± 9.11	15.18	<0.001
Height (Cm)	136.56 ± 10.52	136.78 ± 10.18	136.31 ± 10.90	2.76	0.006
WC (cm)	59.64 ± 9.37	62.24 ± 10.26	56.63 ± 7.13	40.50	<0.001
BMI (Kg/m^2)	17.33 ± 3.22	17.84 ± 3.44	16.74 ± 2.83	22.08	<0.001
WHtR	0.44 ± 0.05	0.45 ± 0.06	0.42 ± 0.04	48.69	<0.001
General Obesity Category[a]				731.88	<0.001
Severe Thinness	60 (0.38)	37 (0.43)	23 (0.31)		
Thinness	420 (2.64)	183 (2.14)	237 (3.21)		
Normal	10681 (67.02)	5098 (59.65)	5583 (75.54)		
Overweight	2770 (17.38)	1638 (19.17)	1132 (15.32)		
Obesity	2006 (12.59)	1590 (18.61)	416 (5.63)		
Central Obesity Category[b]				569.44	<0.001
Normal	12515 (78.56)	6096 (71.35)	6419 (86.91)		
Central Obesity	3415 (21.44)	2448 (28.65)	967 (13.09)		
Puberty[c]				640.46	<0.001
Normal	5658 (90.47)	4094 (96.99)	1564 (76.93)		
Precocious	596 (9.53)	127 (3.01)	469 (23.07)		

WC, waist circumference; BMI, body mass index; WHtR, waist to height ratio.

All qualitative are expressed as frequency (%)，all quantitative data are expressed as mean ± standard deviation.

[#] *P* for t-test or χ^2-test.

[a] Defined as severe thinness (BMI-for-age < -3 SD); thinness (-3 SD ≤ BMI-for-age < -2 SD); normal (-2 SD ≤ BMI-for-age ≤ 1 SD); overweight (1 SD < BMI-for-age ≤ 2 SD); obesity (BMI-for-age > 2 SD).

[b] Defined as central obesity (WHtR ≥ 0.48 in boys or WHtR ≥ 0.46 in girls); normal (WHtR <0.48 in boys or WHtR <0.46 in girls).

[c] Defined as under 8 years for Tanner stage 2 or above for breast or pubic hair development and 10 years for menstruation in girls, and under 9 years for Tanner stage 2 or above for pubic hair or testicle development in boys.

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Table 2 Associations between different types of obesity and the risk of precocious puberty

Puberty	General Obesity			Central Obesity		
	Normal, N(%)	Obesity, N(%)	OR (95% CI)	Normal, N(%)	Obesity, N(%)	OR (95% CI)
Boy						
Normal	2692 (65.75)	647 (15.80)	Reference	3151 (76.99)	942 (61.42)	Reference
Precocious	64 (50.39)	33 (25.98)	2.15 (1.31-3.50)	78 (23.01)	49 (38.58)	2.10 (1.46-3.03)
Girl						
Normal	1352 (86.45)	37 (2.37)	Reference	1451 (92.83)	112 (7.17)	Reference
Precocious	264 (56.29)	65 (13.86)	9.00 (5.60-14.46)	331 (70.58)	138 (29.42)	5.40 (4.10-7.12)

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Table 3 Median age (95% CI) of attainment different pubertal stages according to probit analysis in Shanghai children

General Obesity Category	Girls		Boys	
	B_2	PH_2	PH_2	T_2
Severe Thinness	10.86 (9.77-12.08)	12.56 (10.64-14.86)	13.56 (11.31-16.40)	11.72 (8.35-16.59)
Thinness	9.88 (9.58-10.18)	11.13 (10.69-11.60)	14.50 (13.00-16.34)	11.28 (9.74-13.15)
Normal Weight	8.85 (8.79-8.91)	10.73 (10.62-10.84)	13.96 (13.46-14.60)	10.57 (10.31-10.88)
Overweight	7.68 (7.55-7.80)	10.22 (10.04-10.40)	13.82 (13.28-14.49)	10.32 (9.93-10.74)
Obesity	7.14 (6.93-7.35)	10.18 (9.89-10.48)	13.66 (13.13-14.32)	10.27 (9.87-10.70)
Total	8.62 (8.57-8.67)	10.62 (10.53-10.71)	13.84 (13.40-14.40)	10.46 (10.21-10.78)

B_2, Tanner stage 2 for breast development; PH_2, Tanner stage 2 for pubic hair development; T_2, Tanner stage 2 for testicle development with testicular volume ≥ 4 ml.

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Table 4 The relationship between age of Tanner 2 and WHtR and BMI by linear regression

Index	N	Coefficient B_0 (95% CI)	Standard Error	Standardized Coefficients B_1	t	*P*
B_2 for girls						
WHtR	2256	-8.89 (-9.97, -7.80)	0.55	-0.32	-16.06	<0.001
BMI Z-score	2258	-0.44 (-0.48, -0.39)	0.02	-0.37	-18.81	<0.001
PH_2 for girls						
WHtR	1093	-1.90 (-3.41, -0.40)	0.77	-0.08	-2.49	0.013
BMI Z-score	1093	-0.14 (-0.20, -0.07)	0.03	-0.12	-4.16	<0.001
PH_2 for boys						
WHtR	356	0.65 (-1.25, 2.55)	0.96	0.04	0.67	0.501
BMI Z-score	356	0.02 (-0.10, 0.13)	0.06	0.01	0.26	0.795
T_2 for boys						
WHtR	708	-0.65 (-1.77, 0.46)	0.57	-0.04	-1.15	0.251
BMI Z-score	708	-0.13 (-0.20, -0.06)	0.03	-0.14	-3.75	<0.001

B_2, Tanner stage 2 for breast development; PH_2, Tanner stage 2 for pubic hair development; T_2, Tanner stage 2 for testicle development with testicular volume $\geqslant$ 4

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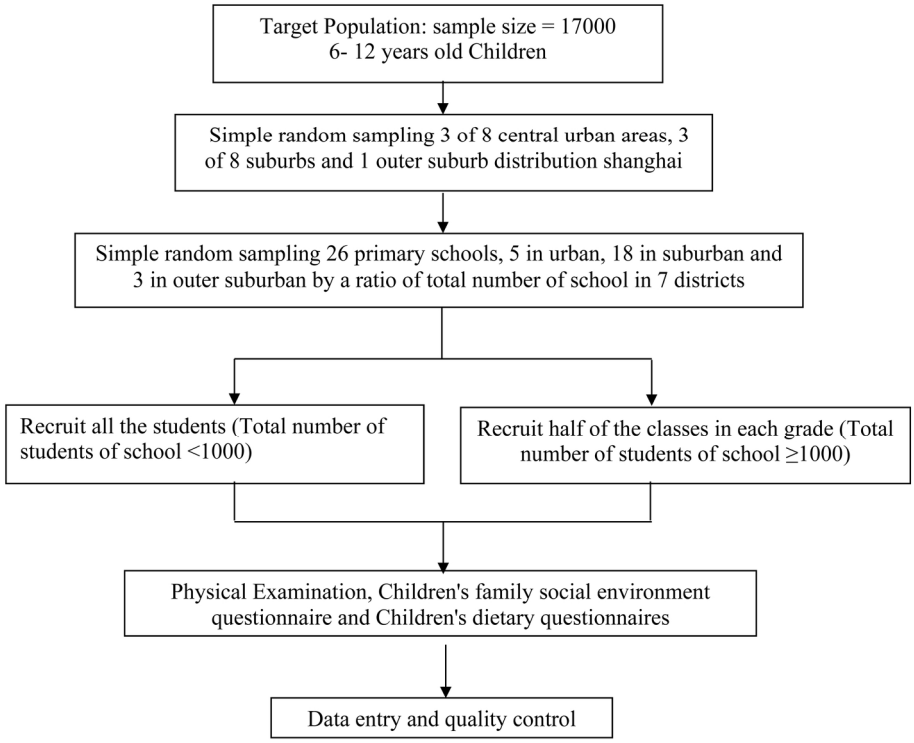

Figure 1 Sampling theme of the study

181x179mm (300 x 300 DPI)

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Table S1 Characters of literature between overweight/obesity and precocious puberty

Author	Year	Sample size	Age	Ethnic	Design	Country	Definition of overweight/obesity	Definition of precocious puberty/early puberty	Association of obesity and precocious puberty
Current study	2014	17620	6-12 years	Chinese	Cross-sectional study	China	WHO Overweight: BMI ≥ 1SD, Obesity: BMI ≥ 2SD	Girls: breast Tanner stage 2 or above before 8 year old; Boys: Testicular volume ≥ 4 ml before 9 year old;	Prevalence of precocious puberty in 4.17% boys and 48.54% girls with overweight; 4.85% boys and 61.86% girls with obesity; Prevalence of overweight in 22.05% boys and 26.01% girls with precocious puberty; 25.98% boys and 13.76% girls for obesity with precocious puberty
Adair LS *et al.*	1988-1991	6507 girls	12-17 years	54.8% non-Hispanic White,21.1% non-Hispanic Black,17.0% Hispanic,7.1 % Asian;	Longitudinal study	America	Overweight: BMI≥85th percentile;	Age at menarche: maturing early (younger than 11 years average); maturing late (11–13); maturing late (14 years or older);	Prevalence of overweight was 41.5%, 25% and 18.7% in early, average and late maturing girls respectively.
Atay Z *et al.*	2009	820 girls	4-8 years	-	Cross-sectional study	Turkey	BMI standard deviation scores(SDS)	Premature thelarche (PT);Premature pubarche (PP)	56.1% girls were PT with BMI SDS values above 1 in the PT group; 31.4% girls were PP with BMI SDS values above 1 in the PT group;

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Dai YL *et al.*	2009-2010	8895 girls 9812 boys	6-18 years	Chinese	Cross-sectional study	China	Chinese Working Group on Obesity，Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	tertiles on the timing of breast and testicular Tanner stage 2 or more (early-maturing group: earliest tertile; non-early-maturing: average and late maturers)	Median age of B2 was 9.69 years; Median age of G2 was 11.25 years; OR and 95% CIs for overweight were 1.48 (1.22–1.79) for boys and 2.64 (2.16–3.23) for girls, and for obesities were 1.61 (1.22–2.11) and 3.49 (2.59–4.70), respectively
Davison KK *et al.*	-	181 girls	5-9 years	-	Longitudinal study	America	American 2000 CDC criteria: BMI percentiles	At 9 years: estradiol levels; breast Tanner stage 3; pubertal Development Scale	BMI percentile was 79.6 and 59.4 in earlier puberty and later puberty girls
Lee HS *et al.*	2003-2010	104 boys	Mean age of 8.7 years	Korean	Cohort study	Korea	Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	Testicular volume > 4 ml; advanced bone age > 1 year above chronological age; pubertal LH peak values; serum testosterone levels;	Testicular volume was 6.8 ml (normal weight), 5.9 ml (overweight) and 6.1 ml (obesity)
Lee JM *et al.*	1991	401 boys	2-11.5 years	White (79.5%); Nonwhite (20.5%)	Longitudinal study	America	Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	Genitalia Tanner stage 2 before age 11.5 years	49 boys (12.2%) were prepubertal at age 11.5 years by Tanner genitalia staging

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Rosenfield RL *et al.*	1988-1994	-	8- 18 years	Non-Hispanic white, non-Hispanic black, Mexican American	Cross-sectional study	America	normal BMI (10th–84th per-centile); excessive BMI (85th per-centile)	Thelarche stage 2; pubarche stge3; menarche	The median age were 10.81 and 9.79 of breast stage 2, 11.57 and 11.39 of pubarche stage 3, 12.57 and 12.06 of menarche in normal and excessive BMI group respectively;
Sorensen K *et al.*	1991–1993; 2006–2008;	1528 boys	5.8-19.8 years	Caucasian origin	Cross-Sectional study; Longitudinal study	Denmark	American 2000 CDC criteria, Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	Testicular volume > 3 ml; genital stages 2 (G2);pubic hair stages 2 (PH2)	Median age of G2 was 11.83 years in 1991 and 11.59 years in 2006; Median age of PH2 was 11.89 years in 1991 and 12.38 years in 2006; Median age of TV was 11.92 years in 1991 and 11.66 years in 2006
Wang Y *et al.*	1988-1994	1501 girls; 1520 boys	8-14 years	Non-Hispanic white (25%), non-Hispanic black (36%), Mexican American (35%)	Cross-sectional study	America	American 2000 CDC criteria, Overweight: BMI≥85th percentile; Obesity: BMI≥95th percentile	Girls: breast Tanner stage 2; Boys: genitalia stage 3, earlier than the median age for that stage.	Prevalence of overweight in 23% boys and 34% girls with early mature; 7% boys and 16% girls for obesity with early mature;

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

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
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	7,8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7,20
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	8
Results			

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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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	20
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,17
		(b) Indicate number of participants with missing data for each variable of interest	9,17
Outcome data	15*	Report numbers of outcome events or summary measures	9
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	9,10
		(*b*) Report category boundaries when continuous variables were categorized	9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12,13
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	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
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	15

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

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

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Corrections: Investigating the relationship between precocious puberty and obesity: a cross-sectional study in Shanghai, China

Chen C, Zhang Y, Sun W, *et al*. Investigating the relationship between precocious puberty and obesity: a cross-sectional study in Shanghai, China. *BMJ Open* 2017;7:e014004. doi: 10.1136/bmjopen-2016-014004

This article has been corrected since it first published. Both Liu Shijian and Jiang Fan are listed a corresponding authors for this paper.

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BMJ Open 2017;**7**:e016427corr1. doi:10.1136/bmjopen-2016-014004corr1