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Genetic and Environmental Effects on Weight, Height, and BMI Under 18 Years in a Chinese Population-Based Twin Sample

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This study examined the genetic and environmental effects on variances in weight, height, and body mass index (BMI) under 18 years in a population-based sample from China. We selected 6,644 monozygotic and 5,969 dizygotic twin pairs from the Chinese National Twin Registry (CNTR) aged under 18 years ($n = 12{,}613$). Classic twin analyses with sex limitation were used to estimate the genetic and environmental components of weight, height, and BMI in six age groups. Sex-limitation of genetic and shared environmental effects was observed, especially when puberty begins. Heritability for weight, height, and BMI was low at 0–2 years old (less than 20% for both sexes) but increased over time, accounting for half or more of the variance in the 15–17 year age group for boys. For girls, heritabilities for weight, height and BMI was maintained at approximately 30% after puberty. Common environmental effects on all body measures were high for girls (59–87%) and presented a small peak during puberty. Genetics appear to play an increasingly important role in explaining the variation in weight, height, and BMI from early childhood to late adolescence, particularly in boys. Common environmental factors exert their strongest and most independent influence specifically in the pre-adolescent period and more significantly in girls. These findings emphasize the need to target family and social environmental interventions in early childhood years, especially for females. Further studies about puberty-related genes and social environment are needed to clarify the mechanism of sex differences.

■ **Keywords:** height, weight, BMI, heritability, twin study

Childhood obesity is one of the most serious public health challenges in the 21st century, and its prevalence has increased at an alarming rate in developing countries (Gupta et al., 2012). Overweight and obese children are more likely to become or stay obese into adulthood and to develop non-communicable diseases at an early age, such as hypertension, type 2 diabetes, and cardiovascular disease (World Health Organization, 2014). Obesity is a complex disease caused by many genetic and environmental factors (Salsberry & Reagan, 2010), such as excessive energy intake, physical inactivity and sedentary lifestyle (Prentice-Dunn & Prentice-Dunn, 2012).

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Twin studies are able to quantify the relative importance of genetic and environmental factors as they provide valuable information, with heritability estimates of BMI ranging from 40 to 70%. However, growth is a complex process, and genetic control of BMI as well as body size and mass throughout childhood involves the turning on and off of various genes at different points in the growth process (den Hoed et al., 2010; Haworth et al., 2008; Rutters et al., 2011; Silventoinen et al., 2007b). Recent studies have rarely considered longitudinal changes in the genetic variance across childhood and adolescence (Lajunen et al., 2009; Silventoinen et al., 2007b). Thus, a pattern for the relative contribution of genetic and environmental influences affecting variation in body measures from infancy to adulthood has not been established, which may help in making intervention strategies for preventing or treating children with obesity at specific ages.

Additionally, genetics of childhood obesity is distinct from genetics of adult obesity (Haberstick et al., 2010). The effects of genes and environment are affected by sex-limited effects (Schousboe et al., 2003). Although a few studies have detected sex differences in the heritability of obesity, they remain controversial. One study found marginal significant sex-limitation of genetic effects at 5 mon (Dubois et al., 2007); others detected inconsistent results, in which sex is more strongly influenced by genetic factors between 16–25 years (Harris et al., 1995; Pietiläinen et al., 1999). Heritability of BMI from a sample of 116 twin pairs in the Chinese Han population observed a non-significant disparity between sexes among children aged 6–12 years (Wu et al., 2005). Another two Chinese twin studies of 588 twin pairs reported mild to moderate heritability of BMI. However, the sex in which a higher genetic effect was detected remained controversial among children aged 8–12 and 13–17 years old in the studies (Ji et al., 2014; Ning et al., 2013). The varied estimates may be due to differences in sample sizes, races, and age groups. Further large-scale studies in Chinese population are needed to help clarify the inconsistency.

Using large-scale, population-based data from the CNTR, the present study examined the genetic and environmental influences on variances in these body measures from 0–17 years; sex heterogeneity of genetic and environmental effects was explored at each age group.

Materials and Methods

Participants

The CNTR is a population-based twin registry that started in 2001 and has been previously described (Li et al., 2013). Briefly, the CNTR recruited participants from nine selected areas in China, which geographically covered western (Qinghai and Sichuan), eastern (Qingdao, Jiangsu, Shanghai, and Zhejiang), northern (Heilongjiang), and southern areas (Shanghai and Zhejiang). A total number of 31,840 participants aged under 18 years were enrolled in the survey. Twins were asked to provide their demographic information, parents' names, contact details, birth weight, current weight, current height, medical history of obesity, hypertension, diabetes, asthma, and genetic disease history. All participants or their parents provided informed consent, and the Ethics Committee at Peking University Health Science Center approved the study protocol.

Measures

Height and weight was self- or parent-reported height (in meters) and weight (in kilograms) within 3 mon of baseline survey. BMI was defined as weight/height^2 (in kg/m^2). To detect whether the genetic determination of the analyzed traits fluctuated through a growth period, the sample was divided into six subgroups based on children's age: 0–2 years, 3–5 years, 6–8 years, 9–11 years, 12–14 years, and 15–17 years. The age group 0–2 years corresponds to 0.00–2.99 years, 3–5 years to 3.00–5.99 years, and so on.

Zygosity was determined by well-validated items on similarity and confusability of appearance in the self-report questionnaire (Gao et al., 2006). Twins were asked the following question: 'During childhood, were you and your twin partner are alike?' with three possible answers: (1) 'We were as alike as two peas in a pod and were frequently mistaken for one another by strangers', (2) 'We were not more alike than siblings in general' and (3) 'Hard to say'. If the answer was (1) and the twin pairs were same-sex, they were considered to be MZ; if the answer was (2) or the twins were opposite-sex, then they were considered to be DZ. Zygosity of twin pairs with the answer (3) is considered to be uncertain.

We excluded 410 participants who were triplets and those where only one of the twin pairs was collected, as well as 1,968 pairs whose zygosity were uncertain. We also excluded 558 twin pairs whose height and weight were missing, or extreme outliers (the 3rd and 97th percentile of the age and sex specific height and weight was considered as the cut off-point for extreme outliers). We further excluded 288 twins with under -3 or over 3 z score of $\log_e$-transformed age and sex-specific BMI, who were below 9 kg/m^2 or over 34 kg/m^2 respectively.

Statistical Analyses

We used $\log_e$-transformed BMI values in the analyses to reduce positive skewness of the BMI distribution. Intra-class correlations of height, weight and BMI were computed for the total number of MZ and DZ twin pairs included in the study and five zygosity-by-sex groups (MZ-boys, MZ-girls, DZ-boys, DZ-girls, DZ-opposite-sex) respectively. Then, classical twin models were used to test for different models and to quantify the magnitude of the genetic and environmental influences on variations in the body measures using the OpenMx package (Boker et al., 2011) in the R software (http://www.r-project.org; Ihaka & Gentleman, 1996). However, three important assumptions were made: (1) trait

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relevant environments are similar to the same extent in MZ and DZ twin pairs; (2) mating occurs randomly in the population; and (3) no interaction or correlation between genes and environment (Elston, 2012).

Classical biometrical model-fitting methods (Elston et al., 2012; Neale & Cardon, 1992) were used to decompose the total phenotypic variance into four sources of variance: (1) additive genetic (A) effect, the sum of the effect of all alleles on a specific trait over all loci; (2) non-additive genetic (D) effect with the inclusion of dominant genetic, caused by interactions between alleles in the same locus, and epistatic effect, caused by interactions between alleles at different loci; (3) common environmental (C) factors shared by co-twins, which is assumed to be 1.0 in both MZ and DZ twins' correlation if they are reared together; and (4) unique environmental (E) effect, which consists of environmental factors that are unique to each individual, and measurement error. However, when analyzing information on twins reared together, the C and D components cannot be estimated simultaneously, so only one of these parameters can be estimated in a model (Grayson, 1989; Hewitt, 1989). Given the data in the present study, we have chosen to focus primarily on ACE (instead of ADE) models because the magnitude of the MZ and DZ same-sex intra-class correlation ratios tends to satisfy $2r_{DZ} > r_{MZ} > r_{DZ}$ at different age groups. A lower intra-class correlation in opposite-sex pairs than in same-sex DZ pairs suggests that some of the genetic effects are not fully shared between boys and girls, which means a sex-specific genetic effect exists.

To explore the heterogeneity between sex, we first fitted general heterogeneity (sex-limitation) model (Eley, 2005), boys and girls have genetic (A_f, A_m) and environmental (C_f, C_m/E_f, E_m) components that are not constrained to be equal, allowing magnitudes of these effects to differ between the sexes. Including DZOS twins in the analyses not only increases power, but allows one to estimate an additional male or female specific additive genetic (A'_m/A'_f) or common environmental (C'_m/C'_f) component that does not correlate with the genetic or environmental effects on the female (or male) phenotype. Then, subsequent models were compared in the order of qualitative model, quantitative model and homogeneity (without sex difference) model using Akaike information criterion (AIC). Significant estimates of the qualitative model mean that the specific genes affecting the body measures might not be equal between boys and girls. The quantitative model only suggests a difference in the magnitude of the genetic effects, while the homogeneity model suggests that boys and girls are not significantly different in the magnitude of the effects. Models were compared using a likelihood ratio test and AIC, which also considers both goodness-of-fit and parsimony in a model's explanatory value. Age (as a continuous variable) and regions (as seven dummy variables) were adjusted as covariates in the mean structure of the model.

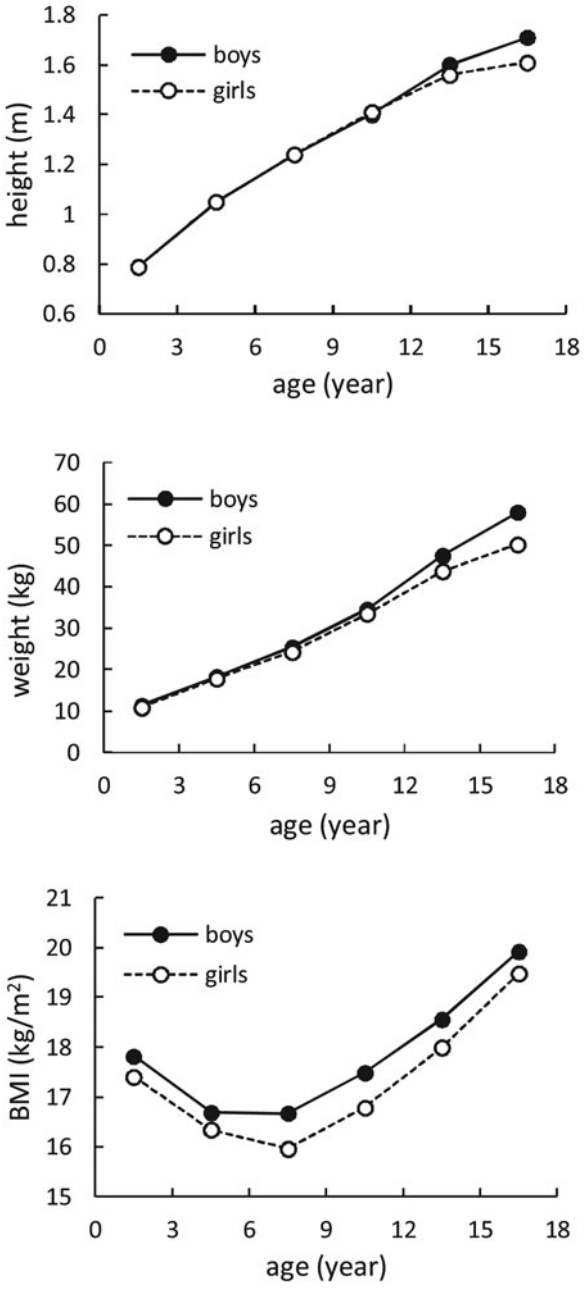

FIGURE 1

Mean height (m), weight (kg), and BMI (kg/m²) in boys and girls for each age group.

Results

A total of 25,226 participants consisting of 3,380 MZ boys, 3,264 MZ girls, 1,711 DZ boys, 1,453 DZ girls and 2,805 DZ opposite-sex twin pairs were included in the present study. The basic features of the participants are presented in Table 1. Boys accounted for 62.60% in all participants.

Figure 1 showed that over all age groups, boys and girls maintained similar patterns of growth in mean weight, height, and BMI. Height and weight increased steadily with

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TABLE 1

Basic Features of 25,226 Participants Aged Under 18 Years in the Chinese National Twin Registry

	MZ			DZ				All twins
Age group	Boys	Girls	Total	Boys	Girls	Opposite sex	Total	Total
0–2	1,458 (50.35)	1,438 (49.65)	2,896 (100)	942 (28.67)	712 (21.67)	1,632 (49.66)	3,286 (100)	6,182
3–5	1,468 (51.91)	1,360 (48.09)	2,828 (100)	722 (28.92)	602 (24.12)	1,172 (46.96)	2,496 (100)	5,324
6–8	1,098 (49.73)	1,110 (50.27)	2,208 (100)	514 (27.78)	450 (24.32)	886 (47.90)	1,850 (100)	4,058
9–11	946 (51.47)	892 (48.53)	1,838 (100)	436 (28.42)	378 (24.64)	720 (46.94)	1,534 (100)	3,372
12–14	876 (51.23)	834 (48.77)	1,710 (100)	390 (27.98)	388 (27.83)	616 (44.19)	1,394 (100)	3,104
15–17	914 (50.55)	894 (49.45)	1,808 (100)	418 (30.33)	376 (27.29)	584 (42.38)	1,378 (100)	3,186
Total	6,760 (50.87)	6,528 (49.13)	13,288 (100)	3,422 (28.66)	2,906 (24.34)	5,610 (47.00)	11,938 (100)	25,226

age but there were slight differences between sexes during 13–17 years. With the increase of age, BMI first decreased and then increased. The 6–8 years age group achieved the lowest mean BMI value (see Figure 1). There were no significant differences between MZ and DZ (same- and opposite-sex) twin pairs for mean height, weight, and BMI (see Supplementary Table S1).

When intra-class correlations between MZ and DZ twins were examined (see Figure 2), MZ twin correlations were consistently greater than those of DZ twins for weight, height, and BMI, and the difference between MZ and DZ correlations increased with age. While MZ twins maintained a correlation of approximately 0.9 or greater in weight, height, and BMI for each age group, DZ twin correlations reduced from around 0.9 to close to 0.4–0.6 over those same years, indicating the presence of strong genetic effects. At all age groups examined, and for all measures except for age group 6–8 years, there was a lower intra-class correlation in OS pairs than in same-sex DZ pairs, suggesting possible sex limitation in the heritability of these body measures (see Supplementary Table S2).

The heterogeneous ACE model was the best-fitting model for height, weight and BMI for all age groups. Quantitative heterogeneity was observed in almost all variables of all age groups, while qualitative sex-limitation was observed in the 3–5 and 15–17 years age groups for BMI, the 6–8 and 12–14 years age groups for height and the 3–5 and 15–17 years age groups for weight (see Supplementary Table S3). The proportion of variance in weight and height explained by genetic influence was greater in boys than in girls; the difference became obvious from age group 12–14 years for height and weight (see Table 2). This sex difference was significant, but less apparent for BMI. For girls, the effect of the common environment played a more important role, particularly in explaining the variability in weight and height. For boys, heritability in variances for body weight, height, and BMI was low at age group 0–2 — between 13–28% in all measures, but this greatly increased over time (see Figure 3).

Genetic effects accounted for 20% or less of the variance in height, weight, and BMI at age group 0–2 years in both sexes, while the effect of the common environment in all body measures was high at birth, between 63–83% in all measures for boys and between 75–87% in all measures for girls, but this reduced markedly over time. For all three measures, the effect of the common environment maintained a greater influence over a longer period during early childhood (from birth up to age group 9–11 years). The effect of the unique environment generally remained stable for both sexes across all body measures and for all age groups, accounting for less than 12% (ACE models) of the variance in weight, height, and BMI for each age group.

Discussion

Using anthropometric information from the CNTR, our study showed that heritability of height, weight, and BMI increased with age in the Chinese population aged under 18 years, and a difference observed between boys and girls, while common environmental factors decreased dramatically in the older age group. This finding indicated that variability in the three body measures among Chinese is strongly influenced by common environment factors in both sexes in early childhood, while genetic variance plays a more important role in mid and late adolescence, especially for boys.

Corresponding to the present study's findings, the heritability of BMI from Finnish twin pairs was estimated to be 0.58 among boys aged 11–14 years and 0.83 among boys aged 17 years (Lajunen et al., 2009; Silventoinen et al., 2007a). However, the results were different for girls. A study in Qingdao, China estimated genetic variance for BMI was 0.69 (95% CI: 0.27–0.79) for 8–12 years and 0.71 (95% CI: 0.44–0.89) for 13–17 years (Ning et al., 2013). The inconsistency between Ning's study and ours might be due to the sample sizes and large differences between regions in China. Additionally, the increasing heritability in the different age groups observed in the present study is generally in agreement with results from other large twin studies (Dubois et al., 2012; Salsberry & Reagan, 2010; Silventoinen et al., 2007a; 2007b). But the rising trends of heritability for height, weight, and BMI in this study are much slower than results from an international study of twin pairs, which reported a dramatic increase for heritability to almost 70% at 5 mon (Dubois et al., 2012). The incongruence with previous European studies may be mainly explained by genetic differences and feeding practices (Birch & Davison, 2001;

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TABLE 2

Heterogeneity (Qualitative and Quantitative) and Homogeneity Model Results for BMI, Height and Weight for Each Age Group, and the Proportion of Variance Explained By Additive Genetic (a^2), Common Environmental (c^2), and Unique Environmental (e^2) Influences

		Model 1: Qualitative ACE model						Model 2: Quantitative ACE model								
		Girls			Boys			Girls			Boys			Model 3: Homogeneity ACE model		
	Age group (year)	a^2	c^2	e^2	a^2	c^2	e^2	a^2	c^2	e^2	a^2	c^2	e^2	a^2	c^2	e^2
BMI (kg/m^2)	0–2	0.07	0.82	0.11	0.15	0.76	0.09	**0.07**	**0.82**	**0.11**	**0.15**	**0.76**	**0.09**	0.13	0.77	0.10
	3–5	**0.25**	**0.68**	**0.08**	**0.17**	**0.72**	**0.10**	0.19	0.73	0.08	0.13	0.76	0.11	0.19	0.72	0.09
	6–8	0.26	0.69	0.06	0.17	0.75	0.08	**0.26**	**0.69**	**0.06**	**0.17**	**0.75**	**0.08**	0.25	0.68	0.07
	9–11	0.16	0.78	0.06	0.27	0.67	0.06	**0.16**	**0.78**	**0.06**	**0.27**	**0.67**	**0.06**	0.26	0.68	0.06
	12–14	0.27	0.65	0.09	0.48	0.44	0.08	**0.14**	**0.86**	**0.00**	**0.58**	**0.34**	**0.08**	0.45	0.47	0.08
	15–17	**0.30**	**0.61**	**0.08**	**0.40**	**0.47**	**0.12**	0.29	0.63	0.08	0.61	0.27	0.12	0.54	0.35	0.11
Height (m)	0–2	0.08	0.86	0.05	0.14	0.81	0.05	**0.07**	**0.87**	**0.05**	**0.13**	**0.83**	**0.05**	0.12	0.83	0.05
	3–5	0.20	0.75	0.05	0.22	0.71	0.07	**0.18**	**0.76**	**0.05**	**0.20**	**0.74**	**0.07**	0.22	0.72	0.06
	6–8	**0.32**	**0.63**	**0.05**	**0.37**	**0.59**	**0.03**	0.22	0.73	0.05	0.27	0.69	0.03	0.29	0.67	0.04
	9–11	0.21	0.75	0.04	0.20	0.77	0.03	**0.19**	**0.76**	**0.04**	**0.19**	**0.78**	**0.03**	0.22	0.74	0.04
	12–14	**0.25**	**0.70**	**0.05**	**0.40**	**0.55**	**0.04**	0.25	0.69	0.05	0.56	0.40	0.04	0.48	0.47	0.05
	15–17	0.19	0.78	0.03	0.72	0.25	0.02	**0.19**	**0.78**	**0.03**	**0.72**	**0.25**	**0.02**	0.87	0.11	0.03
Weight (kg)	0–2	0.13	0.75	0.12	0.28	0.63	0.08	**0.13**	**0.75**	**0.12**	**0.28**	**0.63**	**0.08**	0.26	0.65	0.10
	3–5	**0.34**	**0.58**	**0.08**	**0.33**	**0.55**	**0.12**	0.29	0.63	0.08	0.28	0.61	0.12	0.33	0.57	0.10
	6–8	0.40	0.54	0.06	0.40	0.51	0.09	**0.35**	**0.59**	**0.06**	**0.34**	**0.57**	**0.09**	0.40	0.52	0.08
	9–11	0.26	0.68	0.06	0.37	0.56	0.08	**0.26**	**0.68**	**0.06**	**0.37**	**0.56**	**0.08**	0.37	0.56	0.07
	12–14	0.34	0.59	0.07	0.63	0.31	0.07	**0.34**	**0.59**	**0.07**	**0.63**	**0.31**	**0.07**	0.58	0.35	0.07
	15–17	**0.25**	**0.70**	**0.05**	**0.63**	**0.29**	**0.09**	0.25	0.67	0.08	0.91	0.03	0.06	0.66	0.27	0.07

Note: Note: Best fitting and most parsimonious models are displayed in bold. AE model excluded as it did not provide the best fit.

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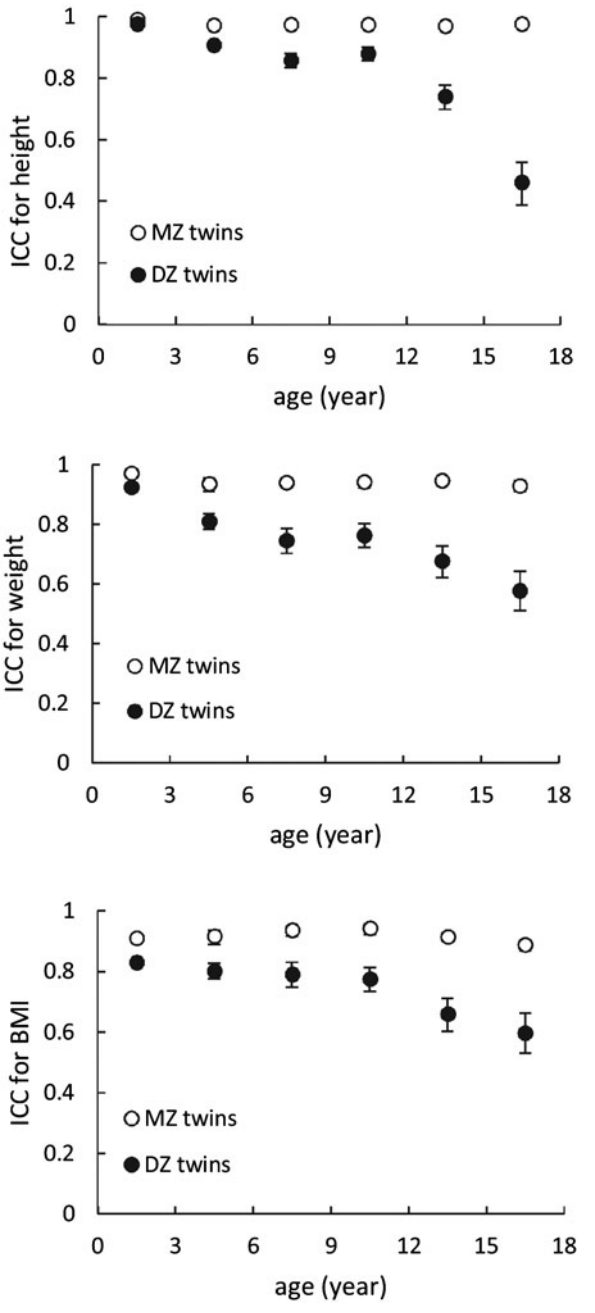

FIGURE 2

Intra-class correlations (with 95% confidence intervals) between MZ and DZ twin pairs for BMI (kg/m^2), height (m), and weight (kg).

Spruijt-Metz et al., 2002), cultural differences (Blissett & Bennett, 2013), early childhood education (Cheah et al., 2013) and ethnic differences (Cardel et al., 2012; Crawford et al., 2001) between Chinese and Caucasian populations. Interestingly, we also examined a sharp increase of genetic contribution for BMI during puberty. This may be due to changes in age-dependent gene expressions or the cumulative effect of shared familial effects. For example, a number of studies indicated that expression of FTO and MC4R may become stronger throughout childhood (den Hoed et al., 2010; Elks et al., 2012; Haworth et al., 2008; Kaakinen et al., 2010; Rutters et al., 2011; Rzehak et al., 2010). It may also be attributed in part to gene-environment interaction and gene-environment correlation because both interaction between A and C and correlation between A and E act like A. Further studies on the association between obesity with early life environmental factors in Chinese are necessary.

Our study identified significant sex-limited genetic effects in the dynamic picture of genetic expression for height, weight, and BMI from puberty to late adolescence. Consistent with some studies, the effect of genes contributing to BMI variation are not identical between sexes. Heritability of height, weight, and BMI for boys are much higher than girls aged from 9–11 years (Salsberry & Reagan, 2010; Schousboe et al., 2003). Another study using a sibling-based sample from the US-based National Longitudinal Survey (Salsberry & Reagan, 2010) found similar genetically driven growth patterns across sex as our study. Although the present study found more significant difference between sex than other studies (Dubois et al., 2012; Silventoinen et al., 2007a; 2007b), it was not able to identify any qualitative sex difference using the current biometric model. However, considering there was enough power provided by large sample in our study, this may have been due to the magnitude of the genetic effect between sexes, indicating a similar set of genetic mechanisms are operating in males and females (Eley, 2005).

In addition, our study showed that genetic effects of height, weight, and BMI become evidently discrepant when puberty begins (i.e., girls begin from 9 to 12 years old and boys from 10 to 13 years old). The reasons behind these are intricate. On the one hand, some features of the metabolic syndrome (Poulsen et al., 2001) and leptin levels (Souren et al., 2007) that mediate fat mass distribution and hormonal milieu have been shown to be more heritable in males than in females, which may lead to differentiation between the two genders around puberty. On the other hand, girls are more susceptible to social and school environment than boys. Compared to boys, environmental factors exert greater influences on girls, such as parental education level, fast food advertizing and exposure to negative life events (Noll et al., 2007; Silberg et al., 2001), which are associate with obesity-related practices. Further studies about hormonal regulation and social environment are needed to clarify the mechanism of sex differences by using gene-environment interaction method.

Our study included a large population-based sample of twins from eight areas in China. We detected a sex limitation profile of the genetic and environmental contributions on weight, height, and BMI over childhood and adolescence for the Chinese population. However, this should be interpreted in light of a number of limitations. First, the data in our study were obtained from cross-sectional baseline

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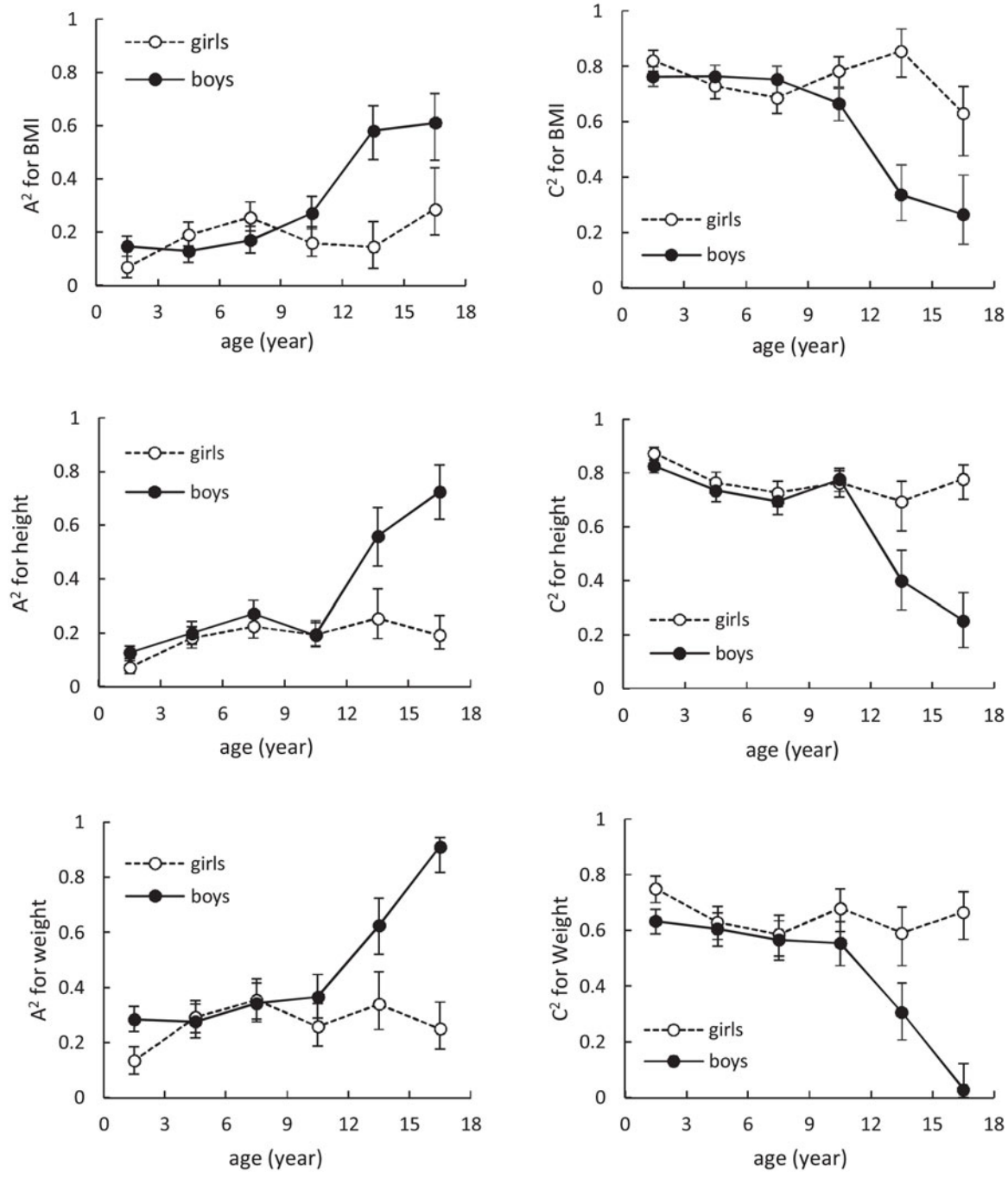

FIGURE 3

Proportion of the variance (with 95% confidence intervals) in BMI (kg/m^2), height (m), and weight (kg), explained by A^2 and C^2 in boys and girls separately, for each age group (Quantitative ACE models assumed).

information from the CNTR, and the results of genetic and environmental changes were confined to groups of people of different ages rather than individuals from birth toward adulthood. As reported previously, the prevalence of overweight and obesity has facilitated an obesogenic environment in the recent years (Neovius et al., 2008). Therefore, we cannot exclude the impact of birth cohort effect (i.e., changes of common environmental factors related to obesity for younger age groups in the present study may slow down the truly sharp increasing heritability). Second, we used self- or parent-reported weights and heights for the study. These might underestimate overweight prevalence and be biased by sex and weight status (Sherry et al., 2007; Tokmakidis et al., 2007). Girls tend to under-report their

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weight to a much larger extent than boys, especially in opposite DZ twin pairs. Parents tend to report similar measurement values for twins, which can lead to recall bias. This might also contribute to large DZ correlations in early childhood and a lower intra-class correlation and inflated sex limitation of weight and BMI. Third, zygosity determination for twin pairs in the present study was based on self-reported information. This may lead to a loss in accuracy in early childhood in comparison with older ones because parents might have difficulties deciding whether their children are alike when they are very young (Liu et al., 2015). However, for convenience, assessing the extent to which co-twins look like each other using questionnaires is one of the most widely used methods for zygosity classification, especially in large sample studies like ours (Gao et al., 2006; Jackson et al., 2001). Many twin studies have shown that questionnaire-based zygosity diagnosis can achieve accuracy of around 93% (Rietveld et al., 2000).

In conclusion, using a large population-based sample of twins from eight provinces/cities in China, this study provided an overall profile of the genetic and environmental contributions on weight, height, and BMI. Our analysis also suggested that a growing discrepancy of heritability values across sex from 9 to 11 years in most of the anthropometric phenotypes reflects some gender-related genes. These findings may have both theoretical and practical perspectives. Identification of the gender-related genes, and understanding their physiological pathways and potential interactions with environmental factors, may shed light on appropriate prevention strategies for childhood and adolescent obesity targeting boys and girls respectively, and contribute to a better understanding of how and why obesity develops later in life.

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Supplementary Material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/thg.2015.63.

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