Association of infant growth and pubertal adiposity: implications for future cardiovascular health and immunological benefits

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KEY MESSAGES

1. In the Children of 1997 birth cohort, faster infant growth was associated with higher body mass index (BMI) and waist circumference, but not waist-to-hip ratio at age 13 years.
2. Higher BMI among adolescence with faster infant growth may partially be attributed to a heavier frame and greater muscle mass rather than greater fat mass.
3. Fast growth in the first year of life was not associated with a lower risk of infectious morbidity.

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Introduction

Cardiovascular diseases are the leading cause of death in the world. Infancy is a key window of developmental plasticity and intervention, but the role of foetal and infant growth in cardiovascular disease remains controversial. We have reported a positive association of infant growth with body mass index (BMI) at age 7 years,[1] in the Children of 1997 birth cohort in Hong Kong.[2] Nonetheless, BMI in childhood may not track into adulthood and represents an unknown combination of muscle mass and fat mass. This study aimed to use the same birth cohort to clarify the association of infant growth with adiposity in adolescence in terms of both BMI and waist ratios, and to assess the association of infant growth and hospital use due to infections.

Methods

Children of 1997 birth cohort

The Children of 1997 birth cohort[2] is a population-representative Chinese birth cohort (n=8327) that covered 88% of all births in Hong Kong from 1 April 1997 to 31 May 1997. Families were recruited at their first postnatal visit to the 49 maternal and child health centres (MCHCs). Baseline characteristics including parental socio-economic position, birth characteristics, infant feeding, and second-hand smoke exposure were obtained using a self-administered questionnaire in Chinese. Passive follow-up via record linkage was instituted since 2005 to obtain: (1) weight and height from birth to age 5 years from the MCHCs; (2) weight and height, pubertal status, physiological well-being, and blood pressure from the Student Health Service; (3) hospital discharge records from the Hospital Authority; and (4) death records from the Death Registry. Surveys I and II concerning family history and psychological well-being, respectively, were implemented during 2008/9 and 2009/10. Survey III was sent to cohort families in 2011/12 with a measuring tape to collect self-measured waist and hip circumferences, weight, and height. In the end, 78% (n=5950) of the contactable cohort families responded to Survey III, from which 60% were telephone interviewed.

The study was approved by the University of Hong Kong-Hospital Authority Hong Kong West Cluster Joint Institutional Review Board and the Ethics Committee of the Department of Health, Government of the Hong Kong SAR, People's Republic of China.

Exposure

The main exposures were foetal and infant growth in terms of all 9 combinations of tertiles of birth weight for gestational age and infant growth. Birth weight for gestational age was calculated as the sex- and gestational age-specific birth weight z-score, relative to standards for contemporary Hong Kong Chinese infants interpolated onto a scale from 0.5 kg to 5.2 kg for each gestational week from 24 to 42 weeks using the Akima package in R. Infant growth was calculated as the change in weight z-score, ie standard deviation score, from birth to age 3 or 12 months. Weight z-score was calculated relative to the 2006 World Health Organization (WHO) growth standards. We used the Akima package in R (version 2.3.1) to interpolate the WHO standards onto a daily scale, so that all weight z-scores were calculated at exact daily ages.

Outcome measures

The primary outcome measure was BMI and central adiposity at age 13 years. We used age- (in days) and sex-specific z-scores for BMI and height relative to the 2007 WHO growth standards. Central adiposity was proxied by waist circumference, z-scores for waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR). Waist and hip circumferences were reported by the participants. The waist circumference was measured at the narrowest part of the waist (at the umbilicus if unavailable) and the hip circumference was over the trochanters. A validity study of 172 randomly selected participants found a mean overestimation of 0.24 (95% confidence interval [CI], -0.84 to 0.37) cm on waist circumference and a mean underestimation of 0.85 (95% CI, 0.41 to 1.29) cm on hip circumference. The bias was not varied by weight status or parental education.

The secondary outcome measure was infection, proxied by the number of hospital admissions for respiratory infections or any infection during infancy, childhood, and adolescence. To check for any uncontrolled confounding by socio-economic position, we also considered admissions for accidents. Those without any record of hospital admission were assumed to have had no admission.

Statistical analysis

Multivariable linear regression was used to assess the association of foetal and infant growth with adiposity. Whether infant growth had different associations with adiposity by sex or birth weight for gestational age was assessed by comparing the Akaike information criterion (AIC) of models with and without the interaction terms. A smaller AIC indicates a better fitting model.

Potential confounders included sex, parity, obstetric conditions, early infant feeding practise, parental place of birth, parental education, parental BMI, and parental height. We additionally analysed the type of birth hospital and self-reported private hospital use on infections. We used multiple imputation for weight at ages 3 months (8.2% missing) and 12 months (10% missing). The results from ten imputed datasets were summarised into single estimates with CIs adjusted for missing data uncertainty.

Results

Participant characteristics

As of 30 April 2012, 8242 of 8327 participants were alive and had not withdrawn, of whom 7768 were term births. We further excluded 95 with birth defects and one with sex unknown, thus 7673 were analysed. Faster infant growth was more common among infants with lower birth weight for gestational age, shorter gestational age, or with more educated parents or being born in a private hospital (Table 1).

Infant growth and adiposity at age 13 years

At age 13 years, BMI of 6861 participants and waist and hip circumference of 5476 participants were measured. Waist circumference, WHR, and WHtR were positively related to BMI at age 13 years in both sexes, although this positive trend was less apparent in adolescents with a lower BMI (Fig). There was some evidence that the association of infant growth with adiposity at age 13 years differed by birth weight for gestational age and/or by sex. Table 1 shows that both foetal and infant growth at ages 0-3 months or 0-12 months were positively associated with BMI z-score and waist circumference at age 13 years after adjusting for place of birth, education, and body size of parents. The association of infant growth with BMI z-score was somewhat less among those born big. Those born big who grew fast in infancy had the greatest BMI and waist circumference at age 13 years. Foetal and infant growth were positively associated with WHtR among boys but not girls, but had little association with WHR. Results were unchanged when pubertal timing or height at age 13 years were included in the models.

Infant growth and hospital admission due to infection

A total of 3303 term births had at least one admission to a public hospital during 1-13.9 years. Admission was higher among boys, adolescents born lighter, and those born in public hospitals. The private hospital use due to infection after age 5 years was obtained from 50% of the cohort members, with 93% reporting no such admission. Growth rate was unrelated to admission due to respiratory infections, any infections, or accidents in infancy, childhood, or adolescence, after adjusting for confounders (Table 2). There was no interaction by sex or birth weight for gestational age.

Discussion

In the Children of 1997 birth cohort, faster foetal and infant growth were associated with greater BMI and greater waist circumference at age 13 years in both boys and girls. Nonetheless, foetal and infant growth had little association with WHR at age 13 years, and were only associated with WHtR among boys.

There are some limitations in this study. First, cohort members who were excluded due to missing adiposity information had relatively higher-educated parents. Nonetheless, the association of infant

TABLE 1. Changes in body mass index (BMI) z-score, waist circumference, waist-to-hip ratio (WHR) z-score, and waist-to-height ratio (WHtR) z-score at age 13 years for birth weight tertile groups by growth rate tertiles at ages 0-3 months and 0-12 months*

Growth rate tertile	Birth weight tertile (β [95% CI])					
	Boys			Girls		
	1st tertile	2nd tertile	3rd tertile	1st tertile	2nd tertile	3rd tertile
BMI z-score						
Age 0-3 months						
1st tertile	Ref	0.24 (0.02, 0.46)	0.48 (0.26, 0.69)	Ref	0.11 (-0.09, 0.31)	0.38 (0.20, 0.57)
2nd tertile	0.14 (-0.08, 0.36)	0.42 (0.20, 0.65)	0.61 (0.39, 0.83)	0.23 (0.03, 0.42)	0.34 (0.14, 0.53)	0.53 (0.33, 0.73)
3rd tertile	0.42 (0.21, 0.63)	0.69 (0.46, 0.91)	0.74 (0.49, 0.99)	0.33 (0.14, 0.52)	0.54 (0.34, 0.74)	0.61 (0.37, 0.85)
Age 0-12 months						
1st tertile	Ref	0.26 (0.04, 0.47)	0.45 (0.25, 0.65)	Ref	0.22 (0.00, 0.44)	0.47 (0.26, 0.67)
2nd tertile	0.19 (-0.02, 0.41)	0.47 (0.26, 0.68)	0.74 (0.51, 0.97)	0.29 (0.07, 0.51)	0.41 (0.20, 0.63)	0.69 (0.47, 0.91)
3rd tertile	0.44 (0.23, 0.64)	0.72 (0.50, 0.95)	0.84 (0.58, 1.10)	0.48 (0.27, 0.68)	0.66 (0.45, 0.88)	0.74 (0.49, 0.99)
Waist circumference (cm)						
Age 0-3 months						
1st tertile	Ref	1.95 (0.20, 3.69)	3.49 (1.79, 5.20)	Ref	0.10 (-1.53, 1.72)	1.92 (0.39, 3.45)
2nd tertile	1.03 (-0.76, 2.82)	3.21 (1.40, 5.03)	4.36 (2.58, 6.14)	0.25 (-1.36, 1.86)	1.60 (0.03, 3.17)	2.94 (1.30, 4.59)
3rd tertile	2.89 (1.20, 4.57)	5.47 (3.63, 7.31)	5.74 (3.63, 7.85)	1.35 (-0.16, 2.86)	2.05 (0.43, 3.68)	3.68 (1.72, 5.64)
Age 0-12 months						
1st tertile	Ref	1.61 (-0.10, 3.32)	3.06 (1.45, 4.67)	Ref	0.90 (-0.84, 2.64)	2.48 (0.87, 4.10)
2nd tertile	1.12 (-0.59, 2.84)	3.61 (1.91, 5.30)	5.58 (3.74, 7.41)	1.53 (-0.18, 3.24)	1.86 (0.21, 3.51)	4.06 (2.32, 5.79)
3rd tertile	3.02 (1.37, 4.68)	5.78 (3.97, 7.59)	6.29 (4.15, 8.42)	1.93 (0.31, 3.55)	3.22 (1.51, 4.92)	4.47 (2.48, 6.46)
WHR z-score						
Age 0-3 months						
1st tertile	Ref	0.05 (-0.14, 0.23)	0.04 (-0.14, 0.22)	Ref	-0.04 (-0.26, 0.18)	-0.02 (-0.22, 0.19)
2nd tertile	-0.04 (-0.23, 0.15)	0.01 (-0.18, 0.20)	0.10 (-0.10, 0.30)	-0.19 (-0.41, 0.03)	-0.07 (-0.28, 0.14)	-0.02 (-0.23, 0.21)
3rd tertile	0.07 (-0.11, 0.25)	0.10 (-0.09, 0.29)	0.07 (-0.15, 0.29)	-0.06 (-0.27, 0.14)	-0.04 (-0.26, 0.18)	0.07 (-0.18, 0.33)
Age 0-12 months						
1st tertile	Ref	0.00 (-0.19, 0.19)	0.07 (-0.11, 0.25)	Ref	0.05 (-0.18, 0.29)	-0.01 (-0.22, 0.21)
2nd tertile	0.03 (-0.16, 0.22)	0.04 (-0.14, 0.23)	0.09 (-0.11, 0.29)	-0.04 (-0.27, 0.19)	-0.04 (-0.26, 0.18)	0.09 (-0.14, 0.33)
3rd tertile	0.05 (-0.13, 0.22)	0.16 (-0.04, 0.36)	0.06 (-0.18, 0.30)	-0.08 (-0.30, 0.14)	-0.04 (-0.27, 0.19)	0.05 (-0.22, 0.31)
WHtR z-score						
Age 0-3 months						
1st tertile	Ref	0.12 (-0.07, 0.30)	0.20 (0.03, 0.38)	Ref	-0.10 (-0.31, 0.12)	0.08 (-0.12, 0.28)
2nd tertile	0.01 (-0.17, 0.20)	0.19 (0.00, 0.38)	0.21 (0.02, 0.40)	-0.06 (-0.27, 0.16)	0.04 (-0.16, 0.25)	0.10 (-0.12, 0.32)
3rd tertile	0.15 (-0.02, 0.33)	0.30 (0.11, 0.49)	0.31 (0.09, 0.52)	0.03 (-0.17, 0.23)	0.03 (-0.18, 0.25)	0.19 (-0.08, 0.45)
Age 0-12 months						
1st tertile	Ref	0.09 (-0.09, 0.27)	0.15 (-0.02, 0.32)	Ref	0.00 (-0.23, 0.23)	0.10 (-0.11, 0.31)
2nd tertile	-0.02 (-0.19, 0.17)	0.16 (-0.02, 0.34)	0.29 (0.10, 0.48)	0.07 (-0.16, 0.30)	0.00 (-0.22, 0.22)	0.20 (-0.03, 0.42)
3rd tertile	0.13 (-0.05, 0.30)	0.30 (0.11, 0.48)	0.23 (0.01, 0.45)	0.03 (-0.19, 0.24)	0.11 (-0.11, 0.34)	0.19 (-0.08, 0.45)

* Adjusted for gestational age, highest parental education, parental BMI, parental height, and parental place of birth

growth with adiposity did not differ by parental education. Second, the change in infant weight over time may be subjected to the regression to the mean, but this was avoided by using categorical exposure groups considering all possible combinations of infant growth and birth size. Third, self-measured waist and hip circumferences may incur error, but the validation study confirmed good agreement between self- and assessor-measured values.

In the same cohort, higher birth weight and

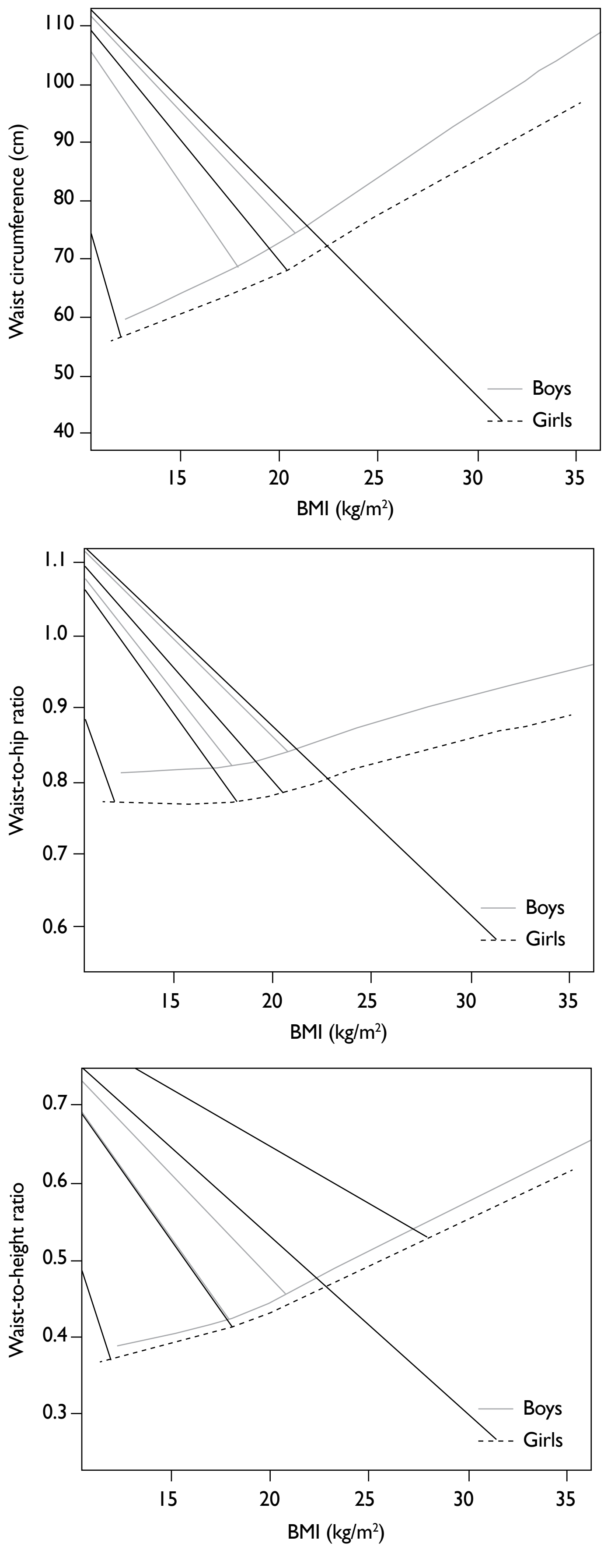

FIG. Waist circumference, waist-to-hip ratio, and waist-to-height ratio by body mass index (BMI) z-score at age 13 years

faster infant growth was associated with higher BMI at age 7 years,[1] with no immunological benefit.[3] At age 13 years, there was also no immunological benefit of infant growth, and faster foetal or infant growth was associated with greater BMI and waist circumference, which is consistent with another study.[4] Nonetheless, faster foetal or infant growth was not positively associated with central adiposity, as proxied by WHR in both sexes, or with WHtR among girls. There are several possible explanations for the differences in the associations of foetal and infant growth with measures of general and central obesity. First, foetal and/or infant growth may promote development of muscle mass, hence a higher BMI without substantially greater fat mass, as reflected by WHR. This possibility could not be examined further because of a lack of detailed measures of body composition for this cohort. Second, cohort members who grow faster in infancy have earlier pubertal onset and greater height,[5] hence higher BMI but possibly not higher WHR due to the redistribution of fat at puberty to more gynoid shapes among girls and android shapes among boys. Nonetheless, the associations were largely unchanged by additionally adjusting for pubertal status. Moreover, such a process might have been expected to generate different associations by sex, although it is possible that the influence of pubertal growth may not be fully expressed in boys who were at a relatively earlier stage of puberty than girls. Third, factors enabling faster growth during the mini-puberty of infancy could also enable a more intense puberty, and more pronounced pubertal development with differences by sex. We have previously suggested that up-regulation of the axis controlling growth over generations of improving living conditions would result in larger size, faster growth, and more sexually dimorphic body shapes,[2] including a more android body shape among men. In this case faster infant growth would be associated with higher levels of sex-steroids at puberty and more sexually dimorphic shapes at puberty. We do not currently have measures of pubertal sex-steroids for this cohort, so we cannot examine this possibility further.

Conclusion

Growing fast during infancy was positively associated with BMI and waist circumference, but not with WHR at age 13 years in both boys and girls or with WHtR among girls. Fast infant growth was not associated with any immunological benefits. Fast infant growth had different associations with different measures of adiposity. As such this may reflect differential sex-specific effects of infant growth, or its drivers, on different aspects of body composition, such as fat mass and muscle mass, or on body shape.

TABLE 2. Incident rate ratios (IRR) for hospital admissions due to respiratory infection, any infection, or accidents during infancy, childhood, and adolescence by growth rate tertiles at ages 0-3 months and 0-12 months*

Growth rate tertile	IRR (95% CI)		
	Respiratory infection	Any infection	Accident
Infancy			
Age 0-3 months			
1st tertile	1.00	1.00	1.00
2nd tertile	0.88 (0.70, 1.10)	0.86 (0.71, 1.03)	0.93 (0.57, 1.51)
3rd tertile	0.94 (0.74, 1.20)	0.94 (0.78, 1.14)	0.94 (0.56, 1.59)
Age 0-12 months			
1st tertile	1.00	1.00	1.00
2nd tertile	0.82 (0.65, 1.03)	0.90 (0.74, 1.08)	0.96 (0.56, 1.62)
3rd tertile	0.96 (0.75, 1.23)	1.01 (0.83, 1.22)	0.83 (0.48, 1.44)
Childhood			
Age 0-3 months			
1st tertile	1.00	1.00	1.00
2nd tertile	1.10 (0.93, 1.31)	0.99 (0.86, 1.14)	1.00 (0.76, 1.31)
3rd tertile	1.02 (0.84, 1.24)	1.00 (0.86, 1.16)	0.97 (0.73, 1.30)
Age 0-12 months			
1st tertile	1.00	1.00	1.00
2nd tertile	1.00 (0.84, 1.19)	0.93 (0.81, 1.07)	1.01 (0.77, 1.32)
3rd tertile	1.03 (0.85, 1.24)	0.98 (0.84, 1.14)	0.84 (0.62, 1.13)
Adolescence			
Age 0-3 months			
1st tertile	1.00	1.00	1.00
2nd tertile	0.89 (0.63, 1.25)	0.78 (0.59, 1.04)	1.41 (0.98, 2.02)
3rd tertile	0.97 (0.67, 1.40)	0.88 (0.65, 1.18)	1.20 (0.81, 1.78)
Age 0-12 months			
1st tertile	1.00	1.00	1.00
2nd tertile	0.81 (0.58, 1.15)	0.90 (0.74, 1.09)	1.31 (0.92, 1.88)
3rd tertile	0.85 (0.59, 1.22)	1.00 (0.82, 1.22)	1.28 (0.86, 1.91)

* Adjusted for birth weight for gestational age, gestational age, highest parental education, type of birth hospital, parental place of birth, and private hospital use since age 5 years due to infections

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