The predictive-adaptive response paradigm postulates that slow fetal growth advances puberty as a life-history strategy for reproductive success, when constraints on postnatal growth are minimal. The authors examined the association of birth weight for gestational age and small for gestational age (SGA) status (birth weight for gestational age <10th percentile, 6.9%) with clinically assessed age at onset of Tanner stage II in a non-Western developed population using interval-censored regression in 7,366 children (89% follow-up) from a population-representative Chinese birth cohort, “Children of 1997” in Hong Kong. Neither SGA status nor birth weight z score for gestational age was associated with age at onset of puberty, adjusted for sex, mother’s place of birth, parental height, income, and parental education. Greater childhood height and linear growth were associated with younger age at onset of puberty. SGA status was associated with earlier puberty after adjustment for childhood height (time ratio = 0.984, 95% confidence interval: 0.972, 0.995) but later puberty after adjustment for linear growth (time ratio = 1.017, 95% confidence interval: 1.005, 1.030). In this developed city of China, SGA status was not associated with timing of puberty. However, the observation may be contextually specific depending on how other attributes, such as childhood growth, differ between SGA and other children.

Chinese; growth; infant, small for gestational age; puberty

Abbreviations: AGA, appropriate for gestational age; SGA, small for gestational age; WHO, World Health Organization.
studies (35–37) from non-Western populations reported similar observations, while there were null associations in studies from Turkey (38), Jamaica (39), India (40), and the Phillipines (41, 42) and some larger studies from developed Western countries (43–45). These contrasting observations suggest that the associations could be contextually specific rather than biologically based. The association is also less clear among boys where most studies report no association (25, 35, 38, 40), but one study found birth weight adjusted for postnatal growth rates associated with earlier puberty (42) and another with later puberty (26). Whether fetal growth has the same associations with the timing of puberty among boys and girls is unclear (13, 26). Moreover, it is also unclear whether postnatal growth should be considered as a proxy for other unmeasured confounders (46), a related factor that also determines the timing of puberty, in which case growth rate might be important, or a factor on the causal pathway. Few studies have reported whether the association of birth size with pubertal timing varies with childhood growth and either did not formally test for differences (15) or found no differences (33, 46).

We used a large, population-representative birth cohort from a non-Western developed population, where there is minimal social patterning of birth weight, to clarify the association of fetal growth with age at onset of puberty, to identify any differences by sex, and to assess the role of postnatal growth. To illustrate the issues with allowing for postnatal growth when considering the role of birth weight in age of puberty, we also explicitly considered the role of allowing for either postnatal prepubertal linear growth status or growth rate, summarized by height at 7 years and linear postnatal growth rate to 7 years, because we have previously shown that height at 7 years is strongly associated with timing of puberty (22).

MATERIALS AND METHODS

The “Children of 1997” birth cohort

The Hong Kong Children of 1997 birth cohort is a population-representative Chinese birth cohort (n = 8,327) that covered 88% of all births from April 1, 1997, to May 31, 1997. The study was initially established to investigate the impact of secondhand smoke exposure on infant health (47, 48). Families were recruited at their 1997. The study was initially established to investigate the impact of secondhand smoke exposure on infant health (47, 48). Families were recruited at their Maternal and Child Health Centers (96% success); 2) hospital discharge records from the Hospital Authority that manages all public hospitals; and 4) death records from the Death Registry. Active follow-up via direct contact was instituted in 2007. A postal survey (Survey I), including questions on family history, was sent in July 2008 and then re-sent a second and third time as necessary to nonrespondents over the following 9 months (27). With each wave of data collection, missing baseline data were updated, and discrepancies between waves were reconciled.

The study was reviewed by and received approval from the University of Hong Kong-Hospital Authority Hong Kong West Cluster Joint Institutional Review Board.

Birth weight for gestational age

We used a sex- and gestational age-specific birth weight z score, because prematurity is associated with age at onset of puberty (21), and birth weight relative to standards for contemporary Hong Kong Chinese infants (50) interpolated onto a scale from 0.5 kg to 5.2 kg for each gestational week from 24 to 42 weeks using the “Akima” (51) package in R (R Foundation for Statistical Computing, Vienna, Austria). We also categorized children as SGA (sex- and gestational age-specific birth weight z score: <10th percentile) or appropriate for gestational age (AGA). To assess nonlinear associations, we used 4 sex- and gestational age-specific birth weight z score groups: ≥90th, 50th–<90th, 10th–<50th, and <10th percentile.

Childhood height and linear growth rate

We obtained sex- and age-specific childhood height z scores relative to the 2007 World Health Organization (WHO) growth standards at 7 years (proxied by the closest measurement to 7 years between 5.5 and 9.0 years) using the “Akima” (51) package in R to interpolate the WHO standards onto a daily scale. Because birth length is unavailable, linear growth rate to 7 years was defined as the difference between height z score at approximately 7 years and birth weight z score relative to the 2006 WHO growth standards, consistent with a previous study (30).

Timing of onset of puberty

The main outcome was age at onset of puberty, that is, the earliest age of Tanner stage II for breast or genitalia development. Pubertal stage was clinically assessed by physicians at the Student Health Service Centers, according to the criteria of Marshall and Tanner (52), in grades 1, 3, 5, and 7, that is, usually at age 6–7 years, 8–9 years, 10–11 years, and 12–13 years. We excluded children with infeasible sequences of pubertal stages, such as pubertal stage II before pubertal stage I (32 boys and 22 girls).

Statistical analysis

We used multivariable interval-censored survival analyses to examine the adjusted association of birth weight $z$ score and SGA status with clinically assessed age at onset of puberty, from which we report time ratios, giving the ratio of estimated age at onset of puberty between groups. A time ratio greater than 1 indicates older age at onset of puberty compared with the reference group, whereas a time ratio less than 1 indicates younger age at onset of puberty. For example, a time ratio of 1.05 compared with a reference group with age at onset of puberty at 10.0 years indicates age at onset of puberty 6 months later at 10.5 years. Whether there were different associations with age at onset of puberty by sex, height at 7 years, or linear growth rate to 7 years was assessed from heterogeneity across strata and the significance of interaction terms. To illustrate the association of childhood height with age at onset of puberty by birth weight for gestational age, we plotted smoothed heights against age from 5.5 to 13 years by the 4 birth weight groups using the LOWESS program (53).

The potential confounders considered were sex, birth order, highest parental educational level, household income, mother’s place of birth, mother’s age of menarche, maternal smoking during pregnancy, and parental height, categorized as shown in Table 1. As illustrations of the lack of confounding, model 0 adjusted for sex, and model 1 additionally adjusted for highest parental education, household income, mother’s place of birth, mother’s age at menarche, and parental height. Model 2 additionally adjusted for height $z$ score at 7 years, and model 3 additionally adjusted for linear growth rate to 7 years instead of height.

We used multiple imputation to predict missing confounders and birth weight based on a flexible additive regression model with predictive mean matching (54) incorporating data on sex, birth weight, gestational age, parity, breastfeeding, secondhand smoking, parental ages, parental height, mother’s age at menarche, mother’s place of birth, education, occupation, household income, type of hospital at birth, infant weight, childhood height, and body mass index, as well as area of residence during the early postnatal period, maximum age at Tanner stage I, and minimum age at Tanner stage II (55). Parental height and mother’s age at menarche were imputed for 56%–59%, household income for 11%, and mother’s place of birth for 8%, while birth weight, maternal smoking during pregnancy, parity, and parental education were imputed for <5%.

We summarized the results from 10 imputed data sets into complete case analysis as a sensitivity analysis. Statistical analyses were performed by using Stata, version 9 (Stata Corp, College Station, Texas), and R, version 2.3.1 (R Development Core Team, Vienna, Austria).

RESULTS

Of the original 8,327 cohort members, as of June 30, 2010, 7,933 were alive, had not withdrawn (22 withdrawn), and were living in Hong Kong, of whom 7,366 had information concerning age at onset of puberty. Participants included were similar to those excluded ($n=939$) in birth weight for gestational age; however, parents of the excluded were more educated. Most included cohort members (90%) had at least 2 records of pubertal stage. Almost all were Tanner stage I before 7.5 years. About 21% of girls were Tanner stage II when assessed at 7.6–9.5 years, while boys were almost all Tanner stage I; 86% of girls and 24% of boys were Tanner stage II at 9.6–11.5 years. The estimated mean age at onset of puberty (Tanner stage II) was 9.6 years in girls, 2.1 years earlier than boys, similar to the mean age at Tanner stage II for girls (9.8 years) and boys (11.7 years) among Hong Kong Chinese adolescents in the 1990s (56, 57). Both greater height at and more linear growth to 7 years were associated with earlier onset of puberty (Figure 1).

Consistent with previous observations on the lack of social patterning of birth weight in Hong Kong (58), SGA children (280 or 7.6% of boys and 232 or 7.3% of girls) did not differ from AGA children by parental education or mother’s place of birth (Table 1). Maternal smoking during pregnancy was associated with a lower birth weight $z$ score of $-0.13$ (95% confidence interval: $-0.24$, $-0.02$) but not with SGA status, most likely because of low power. As would be expected, SGA children were more likely to be firstborn and had more linear growth to 7 years, but they were shorter and thinner at 7 years than AGA children. Children with lower birth weight for gestational age were shorter at 7 years and started puberty at a shorter height (Figure 2).

Use of 4 birth weight groups had a worse fit (higher Akaike Information Criterion) than use of the birth weight $z$ score for gestational age, indicating no nonlinear associations. Table 2 shows that neither birth weight $z$ score for gestational age nor SGA status was associated with age at onset of puberty, with or without adjustment for mother’s place of birth, parental height, mother’s age at menarche, household income, and highest parental education (models 1 and 0). However, after adjustment for height at 7 years (model 2), the higher birth weight $z$ score for gestational age was associated with older age at the onset of puberty, because children with lower birth weight tended to be shorter at 7 years and at onset of puberty. Conversely, after adjustment for linear growth rate to 7 years (model 3), the higher birth weight $z$ score for gestational age was associated with younger age at onset of puberty, because children with lower birth weight tended to have faster linear growth, which was also associated with earlier puberty. There was no evidence of differences by sex.

There was no evidence that the association of birth weight $z$ score for gestational age with age at onset of puberty varied with height at 7 years or with linear growth rate to 7 years. However, the association of SGA status with the onset of puberty varied with both height at 7 years and linear growth rate to 7 years, because SGA children have different linear growth rates and childhood height from AGA children (Table 1); thus, the SGA/AGA categorization introduces confounding by childhood height and linear growth rate. To illustrate, Table 3 shows the joint
associations of SGA status and childhood height with age at onset of puberty. SGA children who were tall at 7 years had the greatest linear growth rate and had the earliest onset of puberty. Conversely, shorter SGA children who had grown at the same rate as the tall AGA children had later onset of puberty than those tall AGA children. However, shorter SGA children, who had also grown faster than shorter AGA children, had a similar age at onset of puberty as shorter AGA children, despite a faster linear growth rate. A complete case analysis obtained similar results (data not shown).

**DISCUSSION**

In this large, prospective population-representative Chinese birth cohort from a developed setting, with little social patterning of birth weight, we found neither birth weight for gestational age nor SGA status to be associated with age at onset of puberty, with no differences by sex. As in previous studies (15, 24, 33), SGA children who had grown tall into childhood had earlier onset of puberty. Our findings are consistent with the previous observation in this cohort that faster infant growth was associated with earlier onset of puberty, mediated by greater childhood height (22). Our study adds by demonstrating the role of the childhood linear growth rate, or its drivers, in the onset of puberty.
puberty, as well as its potential relevance to varying observations about the timing of puberty in SGA children.

Many studies in other settings have observed higher birth weight associated with later age at menarche (15, 28, 34) or SGA status associated with earlier onset of breast development (25, 35), peak height velocity (26), or age at menarche (15, 30, 33, 37). Our study differs from these studies in contextual factors and methodology. Unlike in Western populations, in our population birth weight and SGA status are not confounded by socioeconomic position. Many previous studies reporting an association between limited fetal growth and earlier menarche did not control for gestational age (15, 25–28, 30–32, 34), whereas we used birth weight for gestational age. We also considered age at onset of puberty rather than age at menarche, which is a composite of the timing and progression of puberty (31). In addition, we considered the association of both linear growth rate and height with age at onset of puberty, which inevitably differs between SGA and AGA children. We also used clinically assessed pubertal stage rather than self-report.

This study has several caveats. First, attending the Student Health Service for regular health checks provided by the Hong Kong government is voluntary. However, 89% of the eligible birth cohort members were included. Second, less than 10% of the birth cohort members were SGA according to the Hong Kong reference. Some SGA children may not have been recruited probably because of hospitalization during early infancy, most likely due to extremely low birth weight, prematurity, or poor health, all of which could reduce early infant and later growth. We might have missed short SGA children with probably late puberty, so that we are more confident in our observed null association between SGA status and early onset of puberty. Third, we used the z score for birth weight instead of birth length to estimate linear growth to approximately 7 years, which may overestimate for children born long and which may underestimate for those born short. Although this may overestimate the time ratio for age at onset of puberty of SGA children after adjustment for linear growth rate (Table 2, model 3), it should not affect the null association.

### Table 2. Adjusted Associations of Birth Weight z Score for Gestational Age and SGA Status With Age at Onset of Puberty in 7,366 Children From the Hong Kong “Children of 1997” Birth Cohort

<table>
<thead>
<tr>
<th>Time Ratio Per Unit Birth Weight z Score for Gestational Age</th>
<th>Time Ratio SGA Compared With AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Ratio 95% CI</td>
<td>Time Ratio 95% CI</td>
</tr>
<tr>
<td>Model&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.000 0.996, 1.003 0.998 0.986, 1.010</td>
</tr>
<tr>
<td>1</td>
<td>1.001 0.997, 1.004 0.996 0.984, 1.008</td>
</tr>
<tr>
<td>2</td>
<td>1.007 1.004, 1.011 0.984 0.972, 0.995</td>
</tr>
<tr>
<td>3</td>
<td>0.987 0.983, 0.991 1.017 1.005, 1.030</td>
</tr>
<tr>
<td>P&lt;sub&gt;interaction with&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.28 0.96</td>
</tr>
<tr>
<td>Height z score at 7 years</td>
<td>0.51 0.01</td>
</tr>
<tr>
<td>Linear growth rate to 7 years</td>
<td>0.71 0.01</td>
</tr>
</tbody>
</table>

Abbreviations: AGA, appropriate for gestational age; CI, confidence interval; SGA, small for gestational age.

<sup>a</sup> Model 0: adjusted for sex; model 1: adjusted for sex, mother's place of birth, parental height, mother's age at menarche, household income, and highest parental education; model 2: adjusted for sex, mother's place of birth, parental height, mother's age at menarche, household income, highest parental education, and height z score at 7 years; model 3: adjusted for sex, mother's place of birth, parental height, mother's age at menarche, household income, highest parental education, and linear growth rate to 7 years.
between SGA and age at onset of puberty (models 0 and 1). Fourth, the closest measurement between 5.5 years and 9.0 years was used to proxy height at 7 years. However, we calculated z scores for height at exact ages in days. Finally, overweight girls may be more likely to be misclassified with puberty onset by use of visual assessment (59). However, SGA girls were shorter and thinner, suggesting that such misclassification would make our reported null association between SGA and timing of puberty conservative.

The factors triggering the onset of puberty are not clearly understood. Given that rapid linear growth was associated with earlier puberty, the linear growth rate may be an overlooked factor relevant to the age at onset of puberty. As such, the linear growth rate may confound comparisons between SGA and AGA children, as the categorization inevitably creates groups that differ in linear growth. Moreover, rapid linear growth is often more common and more marked among SGA children, particularly in developed settings, and hence, the association of SGA status with earlier puberty, as commonly observed in such settings, particularly among those who have grown tall in childhood (15, 24, 33). Similar factors driving or enabling both rapid linear growth and earlier puberty in children born small would also be consistent with the older age at puberty in very limited conditions, such as mid-20th century China (60), where both economic hardship and undernutrition were common, and fetal growth (61) and postnatal growth (62) were slow. Consideration of the role of childhood conditions and their biologic effects, as indicated by linear growth, may provide a mechanism explaining contextually specific observations of SGA status with timing of puberty. The null association in this study could be the result of a specific combination of slow and fast growing children in both the SGA and AGA groups. Whether there is an additional role of reaching a predetermined height in the onset of puberty is difficult to isolate with current analytic methods, as linear growth and height are perfectly collinear. SGA children grew more, but they were shorter throughout childhood and at the onset of puberty. If all children have the same height potential, earlier onset of puberty among SGA children after adjustment for height is consistent with a trade-off between earlier reproduction and less growth in the allocation of resources as an adaptation to adverse fetal conditions (1, 17). However, SGA children may be genetically or epigenetically shorter. Adjustment for childhood height is essentially comparing fast growing SGA children with slower growing AGA children, while adjustment for linear growth rate compares short SGA children with tall AGA children. Either comparison is invalid and may induce biased (63) or artifactual associations (64). Nevertheless, our study suggests that a factor that promotes or is associated with rapid linear growth could be relevant to the age at onset of puberty. The most obvious candidate is upregulation of the somatotropic axis and growth hormone, which is associated with earlier puberty (65–67), but there are also other candidates, such as insulin resistance (68, 69), or upregulation of the gonadotropic axis at the minipuberty of infancy (70).

From a practical perspective, our study illustrates the difficulty of studying arbitrarily defined subgroups and the risk of these definitions creating potentially misleading confounding by categorization. From a public health perspective, our findings suggest that very rapid postnatal growth may not be beneficial for SGA infants, because it may promote earlier puberty, which carries long-term health risks. However, children with poor linear growth before puberty tend to have later puberty and more pubertal growth (26), which is also associated with cardiovascular risk factors (71). In addition, there may be other benefits of rapid growth in SGA children, such as better cognition or mental health.

In a large, population-representative non-Western birth cohort in the most developed and Westernized city in China, there was no evidence that birth weight for gestational age or SGA status was associated with age at onset of puberty in girls or boys. Instead, SGA children were shorter at the onset of puberty, consistent with either a trade-off between linear growth and maturation or simply with less growth potential. Both linear growth rate and height appeared to be related to the timing of puberty, which may generate contextually specific associations between SGA status and timing of puberty, depending on the specific growth rates in SGA compared with AGA children. Whether SGA status is related to the progression of puberty and advances the timing of later pubertal stages remains to be determined.
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Conflict of interest: none declared.

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