



<b>Title</b>	<b>Associations of birth order with early adolescent growth, pubertal onset, blood pressure and size: Evidence from Hong Kong's "Children of 1997" birth cohort</b>
<b>Author(s)</b>	<b>Kwok, MK; Leung, GM; Schooling, CM</b>
<b>Citation</b>	<b>PLoS One, 2016, v. 11 n. 4, p. e0153787</b>
<b>Issued Date</b>	<b>2016</b>
<b>URL</b>	<b><a href="http://hdl.handle.net/10722/235697">http://hdl.handle.net/10722/235697</a></b>
<b>Rights</b>	<b>This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.</b>

RESEARCH ARTICLE

# Associations of Birth Order with Early Adolescent Growth, Pubertal Onset, Blood Pressure and Size: Evidence from Hong Kong's "Children of 1997" Birth Cohort

Man Ki Kwok<sup>1</sup>, Gabriel M. Leung<sup>1</sup>, C. Mary Schooling<sup>1,2\*</sup>

**1** School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China, **2** City University of New York School of Public Health and Hunter College, New York, NY, United States of America

\* [cms1@hku.hk](mailto:cms1@hku.hk)



OPEN ACCESS

**Citation:** Kwok MK, Leung GM, Schooling CM (2016) Associations of Birth Order with Early Adolescent Growth, Pubertal Onset, Blood Pressure and Size: Evidence from Hong Kong's "Children of 1997" Birth Cohort. PLoS ONE 11(4): e0153787. doi:10.1371/journal.pone.0153787

**Editor:** Andrew Wolfe, John Hopkins University School of Medicine, UNITED STATES

**Received:** December 27, 2015

**Accepted:** April 4, 2016

**Published:** April 18, 2016

**Copyright:** © 2016 Kwok et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** Data are available upon request from the "Children of 1997" data access committee: [aprmay97@hku.hk](mailto:aprmay97@hku.hk). The volume and complexity of the data collected precludes public data deposition, because the participants could be identifiable from such extensive data which would comprise participant privacy.

**Funding:** This work is a sub-study of the "Children of 1997" birth cohort which was initially supported by the Health Care and Promotion Fund, Health and Welfare Bureau, Government of the Hong Kong SAR [HCPF Grant # 216106] and re-established in 2005 funded

## Abstract

### Background

Birth order has been proposed as a cardiovascular risk factor, because the lower birth weight and greater infant weight gain typical of firstborns could programme metabolism detrimentally.

### Methods

We examined the associations of birth order (firstborn or laterborn) with birth weight-for-gestational age, length/height and body mass index (BMI) z-scores during infancy, childhood, and puberty using generalized estimating equations, with age at pubertal onset using interval-censored regression and with age-, sex- and height-standardized blood pressure, height and BMI z-scores at 13 years using linear regression in a population-representative Chinese birth cohort: "Children of 1997" (n = 8,327).

### Results

Compared with laterborns, firstborns had lower birth weight-for-gestational age (mean difference = -0.18 z-score, 95% confidence interval (CI) -0.23, -0.14), lower infant BMI (-0.09 z-score, 95% CI -0.14, -0.04), greater childhood height (0.10 z-score, 95% CI 0.05, 0.14) and BMI (0.08 z-score, 95% CI 0.03, 0.14), but not greater pubertal BMI (0.05 z-score, 95% CI -0.02, 0.11), adjusted for sex, parental age, birthplace, education and income. Firstborns had earlier onset of pubic hair (time ratio = 0.988, 95% CI 0.980, 0.996), but not breast or genitalia, development. Firstborns had greater BMI (0.07 z-score, 95% CI 0.002, 0.15), but not height (0.05 z-score, 95% CI -0.01, 0.11), at 13 years, but similar blood pressure.

by the Health and Health Services Research Fund [HHSRF Grant # 03040771] and the University Research Committee Strategic Research Theme (SRT) of Public Health, The University of Hong Kong. This sub-study was funded by the Health and Health Services Research Fund [HHSRF Grants # 07080841, # 07080751, # 08090761 and # 09101061], Government of the Hong Kong SAR. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing Interests:** The authors have declared that no competing interests exist.

## Conclusions

Differences by birth order continue into early adolescence with firstborns being heavier with earlier pubic hair development, which could indicate long-term cardiovascular risk.

## Introduction

Differences between groups in cardiovascular disease (CVD) rates at the same level of well-established adult risk factors suggest etiologic gaps, which could be exploited to develop more focused and effective interventions.[1] The World Health Organization (WHO) has endorsed birth weight as an additional CVD risk factor.[2] Nevertheless, the fetal origins hypothesis remains controversial because experimental evidence in humans is limited and the observational evidence appears to be contextually specific, for example less evident in developing populations.[3]

In this situation, examining the effects of other naturally occurring drivers of birth weight and subsequent growth, such as birth order, may help elucidate the role of birth weight and infant growth. Firstborns are different from laterborns in having lower birth weight,[4–6] possibly related to physiological changes in maternal uterine arteries during the first pregnancy facilitating nutrient flow to laterborns,[7] and faster infant growth.[8, 9] They also tend to be taller and/or heavier in early childhood in many settings, including Brazil,[10] the Philippines,[11] Taiwan,[12] New Zealand[13] and Poland,[14] although null associations have been observed in Japan,[15] Denmark[16] and the UK.[17] Given different factors drive growth at different stages (fetal, infant, childhood and puberty),[18] different growth patterns between firstborns and laterborns might be expected to have different long-term consequences.[19] Firstborns tend to have higher blood pressure in childhood and early adolescence as observed in Australia[20] and in older, but not younger, cohorts from Brazil[10, 17] and the UK.[21] They have also been observed to have earlier pubertal onset in a Brazilian cohort.[10] These differences and all subsequent health effects may be the consequences of fetal and infant growth programming metabolism for life,[22, 23] or of childhood growth which may play a larger role in CVD risk factor.[24, 25] Alternatively, these differences in growth could also be a reflection of contextually-specific parenting attitudes, rearing practices, resource sharing and family roles. A decision to have more than one child may be associated with parents' age, education, income and birthplace. These parental characteristics and the related behaviors may affect the child's diet, lifestyle, medical care and environmental exposures, thereby generating the observed differences, although a common set of exposures that results in lower birth weight but faster subsequent growth requires somewhat complex explanation. Given worldwide declining trends in fertility, an increasing proportion of the global population are firstborns accentuating the need for understanding its public health implications. Specifically, firstborns represent a particular growth pattern of lower birth weight with faster infant growth. Differences in growth and CVD risk factors between firstborns and laterborns would suggest birth weight and/or infant growth as potentially causal factors of CVD and inform optimal growth patterns for the prevention of CVD. Here, we hypothesized that firstborns are smaller at birth followed by faster subsequent growth and earlier pubertal development, and attain greater current size and higher blood pressure, which might predispose firstborns to higher CVD risks than laterborns.

Most previous studies of parity and CVD risk mainly examined size at a single time point and only one study examined pubertal development. Collating snapshots of growth at different

ages from various settings and birth years may not fully reveal growth and development across life-course by birth order, particularly in the presence of sociocultural influences. Hong Kong provides a contrasting, economically developed, non-Western setting to clarify how firstborns differ from laterborns. In Hong Kong, families usually have one to two children with firstborns tending to have younger more educated parents,[26] whereas in more commonly studied Western countries, firstborns have younger but similarly educated parents as laterborns.[27] Intriguingly, children with migrant mothers, mainly from the neighbouring ethnically homogeneous Southern Chinese province, have higher birthweight than those with Hong Kong born mothers,[28] perhaps due to parental self-selection, the healthy migrant effect[29] or gestational diabetes,[30] whereas children with migrant mothers of different ethnicity tend to have lower birthweight than those with native born Caucasian mothers in Western countries.[31] We examined the associations of birth order with length/height and body mass index (BMI) growth at different growth phases, with age at pubertal onset and with blood pressure, height and BMI in early adolescence in a large, population representative Chinese birth cohort, “Children of 1997”.

## Materials and Methods

### Data Source

Hong Kong’s “Children of 1997” birth cohort is a population representative Chinese birth cohort ( $n = 8,327$ ) that covered 88.0% of all births in Hong Kong from April 1, 1997 to May 31, 1997, described in detail elsewhere.[32] The study was initially established to investigate the effect of second-hand smoke exposure on infant health. Families were recruited at the first postnatal visit to any of the 49 Maternal and Child Health Centers in Hong Kong, which parents of all newborns are strongly encouraged to attend for free vaccinations and well-baby checks. Characteristics obtained using a self-administered questionnaire in Chinese at recruitment and subsequent routine visits include maternal and birth characteristics and socioeconomic position. Passive follow-up via record linkage was instituted in 2005 to obtain weight and height from birth to 5 years from the Maternal and Child Health Centers ( $n = 7,999$ , 96% successful matching); and annual weight and height and bi-annual pubertal status (grade 1 (age 6–7 years) onwards) and blood pressure (grade 5 (age 10–11 years) onwards) from the Student Health Service, Department of Health, which provides free annual check-ups for all school students ( $n = 7,809$ , 94% successful matching). At the Student Health Service, height without shoes was measured by stadiometer to the nearest 0.1 centimetre and weight without shoes and outer clothing was measured by digital scale to the nearest 0.1 kilogram. BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured by nurses on the right arm in a seated position after more than 10 minutes of rest with an age and size appropriate cuff size using an automated oscillometric device. Initial systolic or diastolic blood pressure more than the 90<sup>th</sup> percentile for sex, age and height was double checked by physicians with a sphygmomanometer after 15 minutes of rest and this second measurement was recorded. Pubertal status was visually assessed by physicians for breast (girls) or genitalia (boys) and pubic hair (both sexes) development according to the criteria of Marshall and Tanner.

### Exposure

Information on birth order was obtained from self-administered questionnaires completed mainly by mothers at recruitment (generally shortly after birth) at the Maternal and Child Health Centers. Birth order was categorized as “firstborns” or “laterborns”, because relatively few families had more than two children (11.0%).

## Outcomes

The outcomes were birth weight-for-gestational age z-score, length/height and BMI z-scores (standard deviation scores) at different growth phases, age at pubertal onset, and blood pressure, height and BMI z-scores in early adolescence as previously defined.[33–35] Since we do not have birth length, we used birth weight-for-gestational age z-score relative to sex- and gestational age-specific contemporary Hong Kong Chinese infants to proxy fetal growth.[36] Gestational age was calculated from the actual and expected dates of delivery, reported by the mothers or primary caregivers at baseline. The reported expected date of delivery could be based on the date of the last menstrual period and any dating scans. We used length/height or BMI z-scores during 3 to 9 months for infancy (birth-<2 years), 3 to 7 years for childhood (2-<8 years) and 8 to 13 years for puberty (8-<14 years).[37] Each cohort member had up to 11 length/height or BMI measurements taken at about 3 and 9 months for infancy, at 3, 6 and 7 years for childhood, and at 8, 9, 10, 11, 12 and 13 years for puberty. All length/height and BMI measurements were considered as age- and sex-standardized z-scores relative to the 2005 WHO growth standards for 0–5 years[38] and the 2007 WHO growth references for 5–19 years.[39] Age at pubertal onset was defined, as the earliest age when Tanner stage II for breast (girls) or genitalia (boys) and that for pubic hair (both) was recorded. Children with infeasible sequences of pubertal stages, such as pubertal stage II before pubertal stage I (25 girls and 34 boys) were excluded. Systolic and diastolic blood pressure at ~13 years (12-<15 years) z-scores was calculated relative to age-, sex- and height-standardized blood pressure standards from the United States National High Blood Pressure Education Group in 2004.[40] Finally, we considered height and BMI z-score at ~13 years (12-<15 years).

## Statistical analysis

We used multivariable linear regression to assess the adjusted associations of birth order with birth weight-for-gestational age z-score, blood pressure, height and BMI z-scores at ~13 years and multivariable generalized estimating equations with an exchangeable working correlation structure to assess the adjusted associations with height or BMI z-scores during infancy, childhood and puberty, from which mean differences in birth weight-for-gestational age, blood pressure, length/height or BMI z-scores with 95% confidence intervals (CI) are presented. We used multivariable interval-censored regression,[41] with a log-normal distribution, to examine the adjusted associations of birth order with age at pubertal onset, from which time ratios with 95% CI are presented. A time ratio gives the comparison of ages at pubertal onset between groups, so a time ratio greater than 1 indicates older age at pubertal onset, while a time ratio less than 1 indicates younger age at pubertal onset. We also plotted smoothed length/height and BMI from birth to 14 years by birth order using the LOWESS program.

Confounders included were sex, mother's and father's age at birth, mother's and father's birthplace, highest parental education and household income per head, as categorized in [Table 1](#). We used multiple imputation for missing exposures (among 8,260 cohort members studied, birth order imputed for 3.6%) and confounders (mother's age for 2.4%, father's age for 2.5%, mother's birthplace for 5.4%, father's birthplace for 4.6%, highest parental education for 2.3% and household income per head for 12.5%) based on a flexible additive regression model with predictive mean matching[42] incorporating data on sex, birth order, mother's and father's age, parental height, mother's and father's birthplace, highest parental education, household income per head, birth weight-for-gestational age z-score, height, BMI and blood pressure z-scores and maximum age at Tanner stage I and minimum age at Tanner stage II. [43] We summarized the results from 20 imputed datasets into single estimated beta-coefficients or time ratios with CIs adjusted for missing data uncertainty.[44] We also performed an

**Table 1. Baseline characteristics by birth order for 8,260 adolescents from Hong Kong’s “Children of 1997” birth cohort, Hong Kong, China, 1997–2010.**

Characteristics	No.	%	Birth order		P-value
			Firstborns	Laterborns	
			(n = 3,899)	(n = 4,361)	
			%	%	
Child’s sex					0.06
Female	3913	50.7	51.6	49.9	
Male	4347	56.3	54.8	57.6	
Mother’s age at birth (years)					<0.001
≤24	1036	13.4	21.2	6.4	
25–29	2574	33.3	40.0	27.3	
30–34	3148	40.8	34.9	46.0	
≥35	1503	19.5	10.3	27.8	
Father’s age at birth (years)					<0.001
≤24	317	4.1	7.0	1.5	
25–29	1135	14.7	21.1	8.9	
30–34	2770	35.9	40.8	31.4	
≥35	4038	52.3	37.5	65.7	
Mother’s birthplace					<0.001
Mainland China or elsewhere	3243	42.0	35.4	48.0	
Hong Kong	5017	65.0	71.0	59.6	
Father’s birthplace					<0.001
Mainland China or elsewhere	2538	32.9	24.5	40.4	
Hong Kong	5722	74.1	81.8	67.1	
Parent’s education at recruitment					<0.001
Grade 9 or below	2537	32.9	25.0	40.0	
Grade 10–11	3518	45.6	47.9	43.4	
Grade 12 or above	2206	28.6	33.5	24.1	
Household income per head at recruitment <sup>a</sup>					<0.001
1 <sup>st</sup> quintile	1676	21.7	14.4	28.3	
2 <sup>nd</sup> quintile	1733	22.4	18.4	26.1	
3 <sup>rd</sup> quintile	1633	21.1	19.2	22.9	
4 <sup>th</sup> quintile	1591	20.6	25.9	15.9	
5 <sup>th</sup> quintile	1627	21.1	28.4	14.4	

<sup>a</sup> Mean (standard deviation) for household income per head at recruitment in quintiles (in Hong Kong dollar; pegged at a rate of 7.8 dollar = 1 U.S. dollar) were 1<sup>st</sup> quintile: \$1,740 (416), 2<sup>nd</sup> quintile: \$2,848 (327), 3<sup>rd</sup> quintile: \$4,365 (557), 4<sup>th</sup> quintile: \$6,812 (874) and 5<sup>th</sup> quintile: \$14,994 (16,341).

doi:10.1371/journal.pone.0153787.t001

available case analysis, i.e., deleting cases with missing data on variables on an analysis-by-analysis basis, for comparison. Statistical analyses were performed using Stata version 10 (Stata Corp, College station, Texas, USA) and R version 3.0.1 (R Development Core Team, Vienna, Austria).

### Ethics approval

Since our participants are children, informed consent was obtained from the parents, next of kin, caretakers or guardians (informants) on behalf of the participants by completing the



questionnaire at enrollment as approved by The University of Hong Kong Medical Faculty Ethics Committee. Ethical approval for further studies was obtained from the University of Hong Kong-Hospital Authority Hong Kong West Cluster Joint Institutional Review Board and/or the Ethics Committee of the Department of Health, Government of the Hong Kong Special Administrative Region as appropriate.

## Results

Of the original 8,327 cohort members, as of December, 2013, 26 had permanently withdrawn. Among the 8,260 adolescents with at least one measurement of birth weight-for-gestational age, length/height, BMI, blood pressure and pubertal onset, 47.5% were firstborns. [Table 1](#) shows that parents of firstborns were younger, more educated and more likely to be born in Hong Kong and had higher household income per head at recruitment than those of laterborns.

[Table 2](#) shows that compared with laterborns, firstborns had lower birth weight-for-gestational age, after adjusting for sex, parental age, birthplace, education and household income. During infancy, firstborns had lower BMI z-score. During childhood, firstborns had greater height and BMI z-scores. During puberty, firstborns had greater height, but not BMI, z-score. Compared with laterborns, firstborns had earlier age at onset of pubic hair development, but not age at onset of breast or genitalia development, after adjusting for sex, parental age, birthplace, education and household income. At ~13 years, firstborns had greater BMI, but not height, z-score, and similar systolic or diastolic blood pressure z-score. The available case analysis produced similar patterns, except the association of birth order with BMI z-scores at 13 years was not statistically significant ([S1 Table](#)). [Fig 1](#) shows compared with laterborns, firstborns had similar length/height from early infancy, but lower BMI until about ~3 years after which they had higher BMI than laterborns.

## Discussion

In this economically-developed non-Western setting, firstborns had lower birth weight-for-gestational age, lower infant BMI, greater childhood height and BMI, but not greater BMI during puberty than laterborns. By 13 years, firstborns had higher BMI than, but similar height as, laterborns. As a result firstborns had a different trajectory of BMI and height that laterborns with lower BMI in infancy but higher BMI into puberty, they also had somewhat greater childhood and pubertal height which was transient. Firstborns also had earlier age at onset of pubic hair, but not breast or genitalia, development than laterborns. At ~13 years firstborns had similar age-, sex- and height-standardized blood pressure to laterborns.

Several limitations of this study exist. First, we do not have birth length or head circumference as a proxy of fetal growth. Second, pubertal stage was assessed by different physicians. However, a standard guideline for staging and an orchimeter were available and, with our large sample, statistical power is unlikely to have been compromised. Third, using a single blood pressure measurement may slightly overestimate average blood pressure,[\[45\]](#) but systematic overestimation is unlikely to bias the associations of growth with blood pressure. Fourth, we are limited by the latest available measures of growth and blood pressure. However, we considered growth in biologically distinct phases and assessed the role of growth in three of the four growth phases. Fifth, follow-up of our cohort was high, but not complete, so selection bias is possible, although inclusion of adolescents with particular combinations of birth weight, postnatal growth, pubertal development and blood pressure was unlikely. Sixth, unmeasured confounding such as by maternal or fetal outcomes of pregnancy, by family pressure or by infant temperament might affect the child's growth and parental decisions about having a

**Table 2. Adjusted<sup>a</sup> association of birth order with birth weight-for-gestational age z-score for growth during fetal phase, height and body mass index (BMI) z-scores during infancy, childhood and pubertal phases, age at onset of breast or genitalia or pubic hair development (Tanner stage II) and blood pressure, height and BMI z-scores at 13 years in the Hong Kong's "Children of 1997" birth cohort, Hong Kong, China, 1997–2010.**

Age	Outcomes	Birth order	n	Mean difference <sup>b</sup>	95% CI
Fetal	Birth weight-for-gestational age z-score	Firstborns	3,878	-0.18	-0.23, -0.14
		Laterborns	4,361	Reference	
Infancy	Length z-score	Firstborns	3,136	0.002	-0.05, 0.05
		Laterborns	3,374	Reference	
	BMI z-score	Firstborns	3,136	-0.09	-0.14, -0.04
		Laterborns	3,374	Reference	
Childhood	Height z-score	Firstborns	3,544	0.10	0.05, 0.14
		Laterborns	3,868	Reference	
	BMI z-score	Firstborns	3,544	0.08	0.03, 0.14
		Laterborns	3,868	Reference	
Puberty	Height z-score	Firstborns	3,592	0.09	0.05, 0.14
		Laterborns	3,994	Reference	
	BMI z-score	Firstborns	3,592	0.05	-0.02, 0.11
		Laterborns	3,994	Reference	
			n	Time ratio	95% CI
	Age at onset of breast or genitalia development	Firstborns	3,558	0.995	0.987, 1.002
		Laterborns	3,965	1.000	
	Age at onset of pubic hair development	Firstborns	3,577	0.988	0.980, 0.996
		Laterborns	3,980	1.000	
			n	Mean difference <sup>b</sup>	95% CI
13 years	Systolic blood pressure z-score	Firstborns	2,827	0.02	-0.04, 0.08
		Laterborns	2,726	Reference	
	Diastolic blood pressure z-score	Firstborns	2,827	-0.01	-0.04, 0.03
		Laterborns	2,726	Reference	
	Height z-score	Firstborns	2,989	0.05	-0.01, 0.11
		Laterborns	2,979	Reference	
	BMI z-score	Firstborns	2,989	0.07	0.002, 0.15
		Laterborns	2,979	Reference	

<sup>a</sup> Adjusted for sex, parental age at birth, parental birthplace, highest parental education and household income per head at recruitment

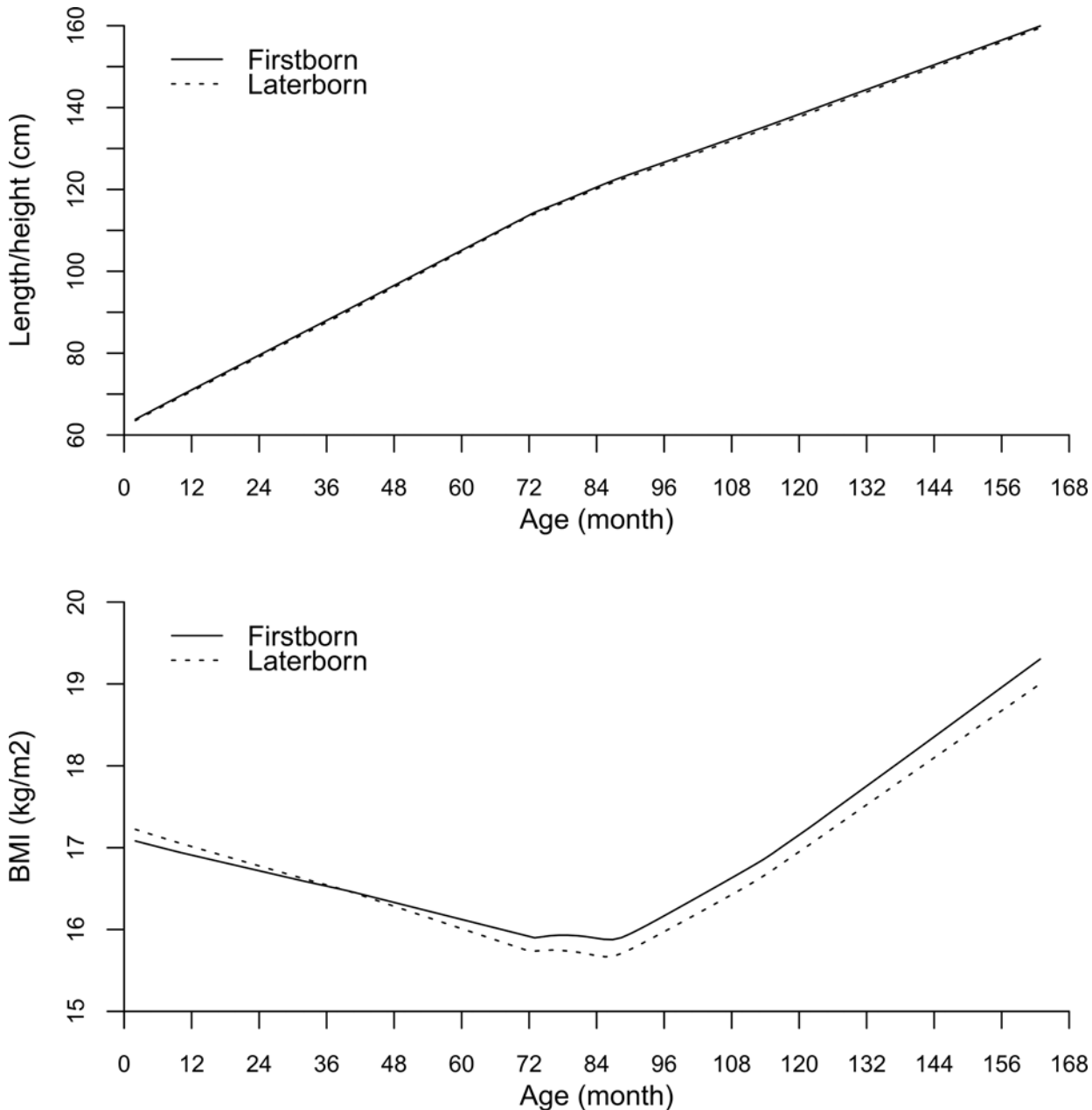
<sup>b</sup> Mean difference in z-score: 1 unit change in birth weight-for-gestational age z-score is approximated to 370 grams; 1 unit change in height z-score is approximated to 2.3 cm at 9 months, 5.6 cm at 7 years and 7.4 cm at 13 years; 1 unit change in body mass index z-score is approximated to 1.5 kg/m<sup>2</sup> at 9 months, 1.9 kg/m<sup>2</sup> at 7 years and 2.7 kg/m<sup>2</sup> at 13 years; 1 unit change in systolic blood pressure z-score is approximated to 10.6 mmHg and 1 unit change in diastolic blood pressure z-score is approximated to 11.3 mmHg.

doi:10.1371/journal.pone.0153787.t002

second child. However, to what extent these unmeasured factors explain the observed differences are unknown. Finally, we lack information on total number of children by the same mother and cannot adjust for family size, although Hong Kong families usually have one to two children.

The finding that firstborns have distinctive growth patterns at different phases across the early life course from laterborns is broadly consistent with previous studies focusing on size at particular ages. Firstborns were lighter at birth adjusted for gestational age.[4–6] They had lower infant BMI, but similar length, unlike infants from rural Gambia[8] or the UK[9] with greater weight. Firstborns had greater childhood height and BMI as seen in Brazil[10] and Philippines,[11] although the greater BMI is not always seen, i.e., in New Zealand,[13] Japan,[15]





**Fig 1. Length/height and body mass index (BMI) growth curves from birth to 14 years by birth order in the Hong Kong's "Children of 1997" birth cohort, Hong Kong, China, 1997–2010.**

doi:10.1371/journal.pone.0153787.g001

Denmark,[16] and in younger cohorts of Brazil and the UK.[17] Our findings could indicate that firstborns had greater BMI, but not height, in early adolescence because firstborns start off smaller, any compensatory growth is mainly for BMI occurring in childhood and persists into adolescence.

Our findings of earlier onset of pubic hair, but not breast or genitalia, development among firstborns are similar to the only previous study (from Brazil) that examined pubertal onset, [10] although the two signs of pubertal development were not distinguished. The association of fast infant weight growth with earlier puberty was mediated by childhood height in this birth

cohort.[46] Given growth hormone has been associated with earlier puberty,[47] up-regulation of the somatotrophic axis controlling growth together with androgens, rather than estradiol,[48] might underlie our observation of greater childhood height and BMI growth together with earlier onset of pubic hair among firstborns. Firstborns in Western settings have earlier age at menarche,[49, 50] consistent with the higher breast cancer incidence among firstborns.[51]

The lack of association of birth order with age-, sex- and height-standardized blood pressure in early adolescence are less consistent with a positive association in Brazilian adolescents[10] and British children[21] or a J-shaped association in Australian children,[20] where blood pressure was not adjusted for height, but are more consistent with no association in Swedish conscripts[52] and Brazilian adults.[53] Our findings suggest birth weight and infant growth play little role in early adolescent blood pressure, inconsistent with fetal and infant metabolic programming,[22, 23] but more consistent with other growth phases playing a larger role.[24] Life history theory posits that resources are partitioned between growth, maturation and maintenance to maximize reproductive success,[54] with any metabolic effects as a by-product; no particular reason suggests firstborns pursue a different strategy from laterborns.

Alternatively, parents may pay more attention to firstborns and feed or raise them differently from laterborns. Many firstborns may be only children, whilst laterborns are not. A difference in intelligent quotient between first-borns and laterborns appears to be socially rather than biologically driven, because second-borns whose older sibling dies in infancy have similar intelligent quotient as firstborns.[55] In this cohort, mothers of firstborns were more likely to initiate breastfeeding. Differences in early growth patterns between firstborns and laterborns might reflect family resource allocation. Firstborns naturally have their parents' undivided attention at least in the first year and will obtain more resources. With the birth of other siblings, it is theorized that parents may still preferentially allocate resources to firstborns over laterborns in favourable conditions, perhaps due to earlier reproductive maturity.[24] In Hong Kong, preferences for longer intervals between births[25] could have allowed longer period of undivided attention for firstborns. Moreover, domestic helpers and grandparents are the main caregivers, particularly among higher income families in Hong Kong;[26] such informal child care (compared with parental care) was positively associated with childhood adiposity.[27] Firstborns might tend to have greater adiposity in our setting in view of the socio-cultural childrearing practice, although this unlikely explain our findings of lower birth weight and lower infant BMI among firstborns. Alternatively, migrant mothers may exert different child-rearing practice from Hong Kong born mothers, as shown by the opposite socioeconomic patterning of childhood adiposity.[56] However, in this study, laterborns were more common in families with migrant mothers and thus would be expected to have greater adiposity,[56] which was opposite to our observed association. Moreover, we adjusted for parents' age, birth-place, education and income, hence our observed greater adiposity and earlier pubic hair development in firstborns are unlikely explained by different rearing attitudes or practice by migrant status. Nonetheless, such non-salient differences could be open to unmeasured or residual socioeconomic confounding. However, our specific associations of birth order might suggest some degree of biological plausibility and distinguish a causal hypothesis from a non-causal hypothesis because residual confounding would be expected to generate systematic associations.

## Conclusions

Firstborns were heavier into early adolescence. They also had earlier pubic hair, but not breast or genitalia, development, perhaps due to biological factors that underlie growth and pubic hair development and are more common in firstborns. Whether these differences extend into

adulthood and affect cardiovascular risk remains to be elucidated in a range of settings with different confounding structures. Our study highlights the importance of replicating observations in different settings that allows thorough investigation of the underlying biological mechanism to presage any consequences in populations with increasing proportion of firstborns. Equally important, our findings showed very modest differences in birth weight (-0.18 z-score, equivalent to ~67 grams) or BMI z-scores between firstborns and laterborns until adolescence (e.g. for BMI at 13 years, 0.07 z-score, equivalent to ~0.19 kg/m<sup>2</sup>). Based on 1 kilogram higher birth weight is associated with 16% lower risk of ischemic heart disease[57] and 1 kilogram higher adult BMI is associated with 4–5% higher risk of coronary heart disease,[58] our estimates could translate to ~1% lower risk of CVD. Given CVD is the leading cause of morbidity and mortality,[59] these are important at a population level, particularly as firstborns are forming an increasing proportion of the population in developed or rapidly developing settings where family size is falling with improved living conditions. These associations also add etiological insights for more complete understanding of the life course development of CVD, implying that the typical growth pattern of firstborns (lower birth weight and greater subsequent adiposity) may be suboptimal for the prevention of CVD.

## Supporting Information

**S1 Table. Available case analysis for adjusted association of birth order with birth weight-for-gestational age z-score for growth during fetal phase, length/height and body mass index (BMI) z-scores during infancy, childhood and pubertal phases, age at onset of breast or genitalia or pubic hair development (Tanner stage II) and blood pressure, height and BMI z-scores at 13 years in the Hong Kong's "Children of 1997" birth cohort, Hong Kong, China, 1997–2010.**

(DOC)

## Acknowledgments

The authors thank colleagues at the Student Health Service and Family Health Service of the Department of Health for their assistance and collaboration. They thank Dr. Connie Hui for her assistance with the record linkage and the late Dr. Connie O for coordinating the project and all the fieldwork for the initial study in 1997–8.

## Author Contributions

Conceived and designed the experiments: CMS. Performed the experiments: MKK. Analyzed the data: MKK. Contributed reagents/materials/analysis tools: CMS GML MKK. Wrote the paper: MKK CMS GML. Reviewed/edited the manuscript: MKK CMS GML.

## References

1. Aboderin I KA, Ben-Shlomo Y, Lynch JW, Yajnik CS, Kuh D, Yach D. Life course perspectives on coronary heart disease, stroke and diabetes: key issues and implications for policy and research. Geneva: World Health Organization, 2002.
2. World Health Organization (WHO). Strategic priorities of the WHO Cardiovascular Disease programme 2013 [9 July 2013]. Available from: [http://www.who.int/cardiovascular\\_diseases/priorities/en/](http://www.who.int/cardiovascular_diseases/priorities/en/).
3. Adair LS, Fall CHD, Osmond C, Stein AD, Martorell R, Ramirez-Zea M, et al. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. *Lancet*. 2013. Epub 26 Mar 2013. [http://dx.doi.org/10.1016/S0140-6736\(13\)60103-8](http://dx.doi.org/10.1016/S0140-6736(13)60103-8).
4. Wilcox MA, Chang AM, Johnson IR. The effects of parity on birthweight using successive pregnancies. *Acta Obstet Gynecol Scand*. 1996; 75(5):459–3. Epub 1996/05/01. PMID: [8677771](https://pubmed.ncbi.nlm.nih.gov/8677771/).

5. Pang MW, Leung TN, Sahota DS, Lau TK, Chang AM. Development of a customised birthweight standard for ethnic Chinese subjects. *Aust N Z J Obstet Gynaecol.* 2000; 40(2):161–4. Epub 2000/08/05. PMID: [10925902](#).
6. Mathai M, Jacob S, Karthikeyan NG. Birthweight standards for south Indian babies. *Indian pediatrics.* 1996; 33(3):203–9. Epub 1996/03/01. PMID: [8772839](#).
7. Khong TY, Adema ED, Erwich JJ. On an anatomical basis for the increase in birth weight in second and subsequent born children. *Placenta.* 2003; 24(4):348–53. Epub 2003/03/27. S0143400402909227 [pii]. PMID: [12657508](#).
8. Prentice A, Cole TJ, Whitehead RG. Impaired growth in infants born to mothers of very high parity. *Hum Nutr Clin Nutr.* 1987; 41(5):319–25. Epub 1987/09/01. PMID: [3692906](#).
9. Ong KK, Preece MA, Emmett PM, Ahmed ML, Dunger DB. Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. *Pediatr Res.* 2002; 52(6):863–7. Epub 2002/11/20. doi: [10.1203/00006450-200212000-00009](#) PMID: [12438662](#).
10. Wells JC, Hallal PC, Reichert FF, Dumith SC, Menezes AM, Victora CG. Associations of birth order with early growth and adolescent height, body composition, and blood pressure: prospective birth cohort from Brazil. *American journal of epidemiology.* 2011; 174(9):1028–35. Epub 2011/09/24. kwr232 [pii] doi: [10.1093/aje/kwr232](#) PMID: [21940799](#).
11. Adair LS. Filipino children exhibit catch-up growth from age 2 to 12 years. *J Nutr.* 1999; 129(6):1140–8. PMID: [10356078](#)
12. Floyd B. Heights and weights of Da-an boys: did sisters really make a difference? *Journal of biosocial science.* 2005; 37(3):287–300. Epub 2005/05/24. PMID: [15906885](#).
13. Savage T, Derraik JGB, Miles HL, Mouat F, Cutfield WS, Hofman PL. Birth order progressively affects childhood height. *Clinical Endocrinology.* 2013; 79(3):379–85. doi: [10.1111/cen.12156](#) PMID: [23347499](#)
14. Koziel S, Kolodziej H. Birth order and BMI in teenage girls. *Collegium antropologicum.* 2001; 25(2):555–60. Epub 2002/01/29. PMID: [11811286](#).
15. Ochiai H, Shirasawa T, Ohtsu T, Nishimura R, Morimoto A, Obuchi R, et al. Number of siblings, birth order, and childhood overweight: a population-based cross-sectional study in Japan. *BMC public health.* 2012; 12:766. Epub 2012/09/13. doi: [10.1186/1471-2458-12-766](#) [pii]. PMID: [22966779](#); PubMed Central PMCID: PMC3509397.
16. Haugaard LK, Ajslev TA, Zimmermann E, Angquist L, Sorensen TI. Being an only or last-born child increases later risk of obesity. *PLoS One.* 2013; 8(2):e56357. Epub 2013/02/26. doi: [10.1371/journal.pone.0056357](#) PONE-D-12-31085 [pii]. PMID: [23437116](#); PubMed Central PMCID: PMC3577826.
17. Howe LD, Hallal PC, Matijasevich A, Wells JC, Santos IS, Barros AJ, et al. The association of birth order with later body mass index and blood pressure: a comparison between prospective cohort studies from the United Kingdom and Brazil. *Int J Obes (Lond).* 2013. Epub 2013/10/08. doi: [10.1038/ijo.2013.189](#) [pii]. PMID: [24097298](#).
18. Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. *Acta Paediatr Scand Suppl.* 1989; 350:70–94. PMID: [2801108](#)
19. Schooling CM, Leung GM. A socio-biological explanation for social disparities in non-communicable chronic diseases: the product of history? *J Epidemiol Community Health.* 2010; 64:941–9. Epub 2010/06/03. jech.2008.086553 [pii] doi: [10.1136/jech.2008.086553](#) PMID: [20515893](#).
20. Lawlor DA, Najman JM, Sterne J, Williams GM, Ebrahim S, Smith GD. Associations of parental, birth, and early life characteristics with systolic blood pressure at 5 years of age: findings from the Mater-University Study of Pregnancy and its Outcomes. *Circulation.* 2004; 110(16):2417–23. doi: [10.1161/01.cir.0000145165.80130.b5](#) PMID: [15477400](#)
21. Whincup PH, Cook DG, Shaper AG. Early influences on blood pressure: a study of children aged 5–7 years. *BMJ.* 1989; 299(6699):587–91. PMID: [2508814](#).
22. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet.* 2004; 363(9421):1642–5. doi: [10.1016/S0140-6736\(04\)16210-7](#) PMID: [15145640](#).
23. Barker DJ. Fetal nutrition and cardiovascular disease in later life. *Br Med Bull.* 1997; 53(1):96–108. Epub 1997/01/01. PMID: [9158287](#).
24. Kwok MK, Freeman G, Lin SL, Lam TH, Schooling CM. Simulated growth trajectories and blood pressure in adolescence: Hong Kong's Chinese Birth Cohort. *J Hypertens.* 2013; 31(9):1785–97. Epub 2013/06/12. doi: [10.1097/HJH.0b013e3283622ea0](#) PMID: [23751966](#).
25. Tu YK, Woolston A, Baxter PD, Gilthorpe MS. Assessing the impact of body size in childhood and adolescence on blood pressure: an application of partial least squares regression. *Epidemiology.* 2010; 21(4):440–8. doi: [10.1097/EDE.0b013e3181d62123](#) PMID: [20234316](#).

26. Frejka T, Jones GW, Sardon JP. East Asian childbearing patterns and policy developments. *Population and Development Review*. 2010; 36(3):579–606. PMID: [20882707](#)
27. Whiting S. Socio-demographic comparison between those UK families with up to two children and those with three or more. *Population Matters*. 2011.
28. Cheung YB, Yip PS. Social patterns of birth weight in Hong Kong, 1984–1997. *Social science & medicine*. 2001; 52(7):1135–41. PMID: [11266055](#).
29. Verropoulou G, Basten S. Very low, low and heavy weight births in Hong Kong SAR: how important is socioeconomic and migrant status? *Journal of biosocial science*. 2014; 46(3):316–31. doi: [10.1017/S0021932013000321](#) PMID: [23790003](#).
30. Wong KC, Wang Z. Prevalence of type 2 diabetes mellitus of Chinese populations in Mainland China, Hong Kong, and Taiwan. *Diabetes research and clinical practice*. 2006; 73(2):126–34. doi: [10.1016/j.diabres.2006.01.007](#) PMID: [16563548](#).
31. Urquia ML, Glazier RH, Blondel B, Zeitlin J, Gissler M, Macfarlane A, et al. International migration and adverse birth outcomes: role of ethnicity, region of origin and destination. *Journal of epidemiology and community health*. 2010; 64(3):243–51. doi: [10.1136/jech.2008.083535](#) PMID: [19692737](#); PubMed Central PMCID: PMC2922721.
32. Schooling CM, Hui LL, Ho LM, Lam TH, Leung GM. Cohort Profile: 'Children of 1997': a Hong Kong Chinese birth cohort. *Int J Epidemiol*. 2011; 41(3):611–20. Epub 2011/01/13. doi: [10.1093/ije/dyq243](#) PMID: [21224275](#).
33. Kwok MK, Leung GM, Lam TH, Leung SS, Schooling CM. Grandparental education, parental education and child height: evidence from Hong Kong's "Children of 1997" birth cohort. *Ann Epidemiol*. 2013; 23(8):475–84. Epub 2013/07/31. doi: [10.1016/j.annepidem.2013.05.016](#) S1047-2797(13)00154-3 [pii]. PMID: [23889857](#).
34. Kwok MK, Leung GM, Lam TH, Schooling CM. Breastfeeding, childhood milk consumption and onset of puberty: Hong Kong's "Children of 1997" birth cohort. *Pediatrics*. 2012; 130(3):e631–9. [published online ahead of print August 20, 2012] (doi: [10.1542/peds.2011-3697](#)) PMID: [22908108](#)
35. Kwok MK, Leung GM, Schooling CM. Breastfeeding and adolescent blood pressure: evidence from Hong Kong's "Children of 1997" Birth Cohort. *Am J Epidemiol*. 2013; 178(6):928–36. Epub 2013/07/17. doi: [10.1093/aje/kwt076](#) PMID: [23857775](#).
36. Fok T, So H, Wong E, Ng P, Chang A, Lau J, et al. Updated gestational age specific birth weight, crown-heel length, and head circumference of Chinese newborns. *Arch Dis Child Fetal Neonatal Ed*. 2003; 88(3):F229–36. PMID: [12719398](#)
37. Luo ZC, Low LC, Karlberg J. Critical growth phases for adult shortness in Hong Kong Chinese. *Journal of pediatric endocrinology & metabolism: JPEM*. 2001; 14(6):757–65. PMID: [11453526](#).
38. World Health Organization. WHO child growth standards. Geneva, Switzerland: World Health Organization, 2005.
39. World Health Organization (WHO). WHO growth reference 5–19 years. Geneva: WHO, 2007.
40. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood -pressure in children and adolescents. *Pediatrics*. 2004; 114(Supplement 2):555–76.
41. Peto R. Experimental survival curves for interval-censored data. *Journal of the Royal Statistical Society Series C (Applied Statistics)*. 1973; 22(1):86–91.
42. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer Verlag; 2001.
43. Moons KG, Donders RA, Stijnen T, Harrell FE Jr. Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol*. 2006; 59(10):1092–101. Epub 2006/09/19. doi: [10.1016/j.jclinepi.2006.01.009](#) PMID: [16980150](#).
44. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res*. 1999; 8:3–15. PMID: [10347857](#)
45. Wong SN, Tz Sung RY, Leung LCK. Validation of three oscillometric blood pressure devices against auscultatory mercury sphygmomanometer in children. *Blood Pressure Monitoring*. 2006; 11(5):281–91. PMID: [16932037](#)
46. Hui LL, Wong M-Y, Lam TH, Leung GM, Schooling CM. Infant growth and onset of puberty: prospective observations from Hong Kong's "Children of 1997" Birth Cohort. *Annals of Epidemiology*. 2012; 22(1):43–50. doi: [10.1016/j.annepidem.2011.10.003](#) PMID: [22056481](#)
47. Kamp GA, Waelkens JJ, de Muinck Keizer-Schrama SM, Delemarre-Van de Waal HA, Verhoeven-Wind L, Zwinderman AH, et al. High dose growth hormone treatment induces acceleration of skeletal maturation and an earlier onset of puberty in children with idiopathic short stature. *Arch Dis Child*. 2002; 87(3):215–20. Epub 2002/08/24. PMID: [12193430](#); PubMed Central PMCID: PMC1719235.

48. Euling SY, Herman-Giddens ME, Lee PA, Selevan SG, Juul A, Sorensen TIA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics*. 2008; 121(Suppl 3):S172–91. doi: [10.1542/peds.2007-1813D](https://doi.org/10.1542/peds.2007-1813D) PMID: [18245511](https://pubmed.ncbi.nlm.nih.gov/18245511/)
49. D'Aloisio AA, DeRoo LA, Baird DD, Weinberg CR, Sandler DP. Prenatal and infant exposures and age at menarche. *Epidemiology*. 2013; 24(2):277–84. Epub 2013/01/26. doi: [10.1097/EDE.0b013e31828062b7](https://doi.org/10.1097/EDE.0b013e31828062b7) PMID: [23348069](https://pubmed.ncbi.nlm.nih.gov/23348069/); PubMed Central PMCID: PMC3563843.
50. Apraiz AG. Influence of family size and birth order on menarcheal age of girls from Bilbao city (Biscay, Basque country). *Am J Hum Biol*. 1999; 11(6):779–83. Epub 2001/09/05. 10.1002/(SICI)1520-6300(199911/12)11:6<779::AID-AJHB8>3.0.CO;2-7 [pii] doi: [10.1002/\(SICI\)1520-6300\(199911/12\)11:6<779::AID-AJHB8>3.0.CO;2-7](https://doi.org/10.1002/(SICI)1520-6300(199911/12)11:6<779::AID-AJHB8>3.0.CO;2-7) PMID: [11533994](https://pubmed.ncbi.nlm.nih.gov/11533994/).
51. Hemminki K, Mutanen P. Birth order, family size, and the risk of cancer in young and middle-aged adults. *Br J Cancer*. 2001; 84(11):1466–71. Epub 2001/06/01. doi: [10.1054/bjoc.2001.1811](https://doi.org/10.1054/bjoc.2001.1811) [pii]. PMID: [11384095](https://pubmed.ncbi.nlm.nih.gov/11384095/); PubMed Central PMCID: PMC2363659.
52. Jelenkovic A, Silventoinen K, Tynelius P, Myrskylä M, Rasmussen F. Association of birth order with cardiovascular disease risk factors in young adulthood: a study of one million Swedish men. *PLoS One*. 2013; 8(5):e63361. Epub 2013/05/23. doi: [10.1371/journal.pone.0063361](https://doi.org/10.1371/journal.pone.0063361) PONE-D-13-03301 [pii]. PMID: [23696817](https://pubmed.ncbi.nlm.nih.gov/23696817/); PubMed Central PMCID: PMC3656047.
53. Siervo M, Horta BL, Stephan BCM, Victora CG, Wells JCK. First-borns carry a higher metabolic risk in early adulthood: evidence from a prospective cohort study. *PLoS One*. 2010; 5(11):e13907. doi: [10.1371/journal.pone.0013907](https://doi.org/10.1371/journal.pone.0013907) PMID: [21085691](https://pubmed.ncbi.nlm.nih.gov/21085691/)
54. Worthman CM, Kuzara J. Life history and the early origins of health differentials. *American Journal of Human Biology*. 2005; 17(1):95–112. PMID: [15611966](https://pubmed.ncbi.nlm.nih.gov/15611966/)
55. Kristensen P, Bjerkedal T. Explaining the relation between birth order and intelligence. *Science*. 2007; 316(5832):1717. Epub 2007/06/26. 316/5832/1717 [pii] doi: [10.1126/science.1141493](https://doi.org/10.1126/science.1141493) PMID: [17588924](https://pubmed.ncbi.nlm.nih.gov/17588924/).
56. Schooling CM, Yau C, Cowling BJ, Lam TH, Leung GM. Socio-economic disparities of childhood body mass index in a newly developed population: evidence from Hong Kong's 'Children of 1997' birth cohort. *Archives of disease in childhood*. 2010; 95(6):437–43. doi: [10.1136/adc.2009.168542](https://doi.org/10.1136/adc.2009.168542) PMID: [20418337](https://pubmed.ncbi.nlm.nih.gov/20418337/).
57. Huxley R, Owen CG, Whincup PH, Cook DG, Rich-Edwards J, Smith GD, et al. Is birth weight a risk factor for ischemic heart disease in later life? *The American journal of clinical nutrition*. 2007; 85(5):1244–50. PMID: [17490959](https://pubmed.ncbi.nlm.nih.gov/17490959/).
58. Mongraw-Chaffin ML, Peters SA, Huxley RR, Woodward M. The sex-specific association between BMI and coronary heart disease: a systematic review and meta-analysis of 95 cohorts with 1.2 million participants. *The lancet Diabetes & endocrinology*. 2015; 3(6):437–49. doi: [10.1016/S2213-8587\(15\)00086-8](https://doi.org/10.1016/S2213-8587(15)00086-8) PMID: [25960160](https://pubmed.ncbi.nlm.nih.gov/25960160/); PubMed Central PMCID: PMC4470268.
59. World Health Organization (WHO). Cardiovascular diseases (CVDs) 2015. Available from: <http://www.who.int/mediacentre/factsheets/fs317/en/>.