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REGULAR ARTICLE

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Stunting, recovery from stunting and puberty development in the MINIMat cohort, Bangladesh

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Abstract

Aim: This paper aimed to analyse the association between small for size at birth, stunting, recovery from stunting and pubertal development in a rural Bangladeshi cohort.

Methods: The participants were 994 girls and 987 boys whose mothers participated in the Maternal and Infant Nutrition Interventions in Matlab trial. The birth cohort was followed from birth to puberty 2001-2017. Pubertal development according to Tanner was self-assessed. Age at menarche was determined and in boys, consecutive height measurements were used to ascertain whether pubertal growth spurt had started. The exposures and outcomes were modelled by Cox's proportional hazards analyses and logistic regression.

Results: There was no difference in age at menarche between girls that were small or appropriate for gestational age at birth. Boys born small for gestational age entered their pubertal growth spurt later than those with appropriate weight. Children who were stunted had later pubertal development, age at menarche and onset of growth spurt than non-stunted children. Children who recovered from infant or early childhood stunting had similar pubertal development as non-stunted children.

Conclusion: Infant and childhood stunting was associated with a later pubertal development. Recovery from stunting was not associated with earlier puberty in comparison with non-stunted children.

KEYWORDS
stunting, catch-up growth, developmental origin of health and disease, menarche, puberty

Abbreviations: AGA, appropriate for gestational age; BMI, body mass index; HAZ, height-for-age z-scores; icddr,b, International centre for diarrheal disease research, Bangladesh; SD, standard deviation; SGA, small for gestational age; WHO, World Health Organisation.

1 | INTRODUCTION

Stunting, defined as height measurements below minus two standard deviations of the World Health Organization (WHO) growth reference median, reflects chronic exposure to a deficient environment and undernutrition. Stunting in early life is linked to a wide range of adverse consequences for the individual and the formation of human capital.[1] Stunted children have increased risks of morbidity and mortality and are more likely to have a lower educational achievement and to become short adults. Also, growing evidence supports the hypothesis that undernutrition during early development might increase chronic disease risks later in life. Recovery from stunting may prevent several of these negative consequences for short- and long-term health and is hence desirable.[1] Paradoxically, there is also evidence that catch-up growth, following early life undernutrition, might increase the risk of adult non-communicable diseases.

The onset of puberty is an intermediate factor that is associated with early life nutrition as well as future health outcomes. Nutritional status is a well-known determinant of pubertal development. Younger age at menarche has been reported to be a risk indicator of adult chronic diseases in low-, middle- and high-income countries,[2,3] including Bangladesh.[4] The mechanisms behind these associations seem, however, to differentiate between these contexts. In low-resource settings with widespread undernutrition pubertal development and menarche usually take place at an older age.[5] Epidemiological and adoption studies have indicated that intrauterine growth restriction and early life undernutrition that are followed by rapid post-natal weight gain and subsequent height gain may result in early puberty and younger age at menarche.[6,7] In light of this recent evidence of adverse outcomes of so-called catch-up growth, concerns have been raised on the potential long-term effects of recovery from stunting. Further, the association is poorly understood between recovery from early growth restriction in children who remain in a low-resource setting and their pubertal development. This study aimed to analyse the association between being born small for gestational age (SGA), infancy and childhood stunting, recovery from stunting, and pubertal development, assessed by self-reported Tanner stages, age at menarche and start of puberty growth spurt, in a rural Bangladeshi cohort.

Key notes

- We examined the consequences of stunting and recovery from stunting for pubertal development in children in rural Bangladesh.
- Girls that were stunted in infancy and childhood had a later menarche and boys started their growth spurt later, as compared to non-stunted children.
- No unfavourable association between recovery from stunting in infancy or childhood and early puberty was found.

2 | METHODS

The study area, Matlab, is a rural sub-district 57 km southeast of the capital Dhaka where relatively widespread child and maternal undernutrition still prevail. The International Center for Diarrhoeal Disease Research, Bangladesh (icddr,b) runs a Health and Demographic Surveillance System in the area. Community health workers visit all households and collect demographic and health information on a monthly basis.

The participants in this study were children born to women participating in the Maternal and Infant Nutrition Interventions in Matlab (MINIMat, isrctn.org identifier: ISRCTN16581394). MINIMat was a factorial randomised trial, which provided early prenatal food and micronutrient supplementation to pregnant women. The primary outcomes were maternal haemoglobin, size at birth and infant mortality. There were several short- and long-term secondary outcomes that have motivated a follow-up of the MINIMat birth cohort. From November 2001 to October 2003 all women within in the icddr,b service area who reported to a community health worker that their menstruation was overdue or that they were pregnant were offered a pregnancy test and invited to participate in the MINIMat trial. In total, 4436 pregnant women participated, resulting in 3625 live births. The children whose mothers participated in the initial prenatal intervention study have so far been followed up from the time of their birth until the typical age of puberty onset. The data collection for the puberty assessment was carried out at two time points with a 6-month interval. The first round of data collection was carried out from July 2016 to February 2017 and the second round from January to July 2017.

At enrolment, trained community health workers collected information on household socioeconomic characteristics, parental education and pregnancy history in the respondents' homes. Anthropometry and puberty assessments were done at clinic visits at local sub-centres run by the icddr,b in the Matlab area.

The children's weight, length or height were measured at birth, every month up to 1 year, every 3 months up to 24 months, during follow-up surveys at 4.5 and 10 years, and two times at puberty follow-up in the age interval 12-15 years. Most birth anthropometry was measured within 72 hours after birth. Measurements taken up to 30 days after birth were adjusted using a standard deviation score transformation, based on the assumption that infants remain in the same relative position in the anthropometric distribution during this period. The recumbent length at birth and during infancy (until 1.5 years) was measured with a locally manufactured, collapsible length board with a precision of 0.1 cm. Maternal weight and height were measured at around 8 weeks of pregnancy and at follow-ups. Uniscale beam scales or SECA electronic scales (UNICEF,

USA; SECA Gmbh & Co), with a precision of 0.01 kg were used when measuring children's weight. Height was measured to the nearest 0.1 cm, using a freestanding stadiometer. Height-for-age *z*-scores (HAZ) were calculated from the measured length and height data using the programme WHOAnthro, from birth to 4.5 years and AnthroPlus at puberty using WHO growth references for 0-5 and 5-19 years, respectively. Being stunted was defined as having a HAZ below minus two, and not being stunted was defined as having a HAZ at or above minus two, respectively. The SGA variable is based on weight for gestational age.[8] HAZ at birth was not adjusted for gestational age.

During puberty follow-up, anthropometry and puberty assessment was done at sub-centres run by the icddr,b. This was done separately for girls and boys by teams of female and male nurses and doctors. Guided by pictures, participants self-assessed pubertal development; breast, genital and pubic hair development as appropriate, according to Tanner.[9] The female staff interviewed the girls about whether they had had their first menstruation and the date at menarche was noted. When needed, the interview was supported by the mother and by use of a local events calendar. Refresher training on data collection methods including standardization of anthropometric measurements was conducted periodically for the staff.

Written and oral informed consent was obtained from all participating women in the MINIMat trial and from the parents of the participating children. The Ethical Review Committee at icddr,b in Bangladesh, approved the original trial, and the Ethical Review Committee at icddr,b in Bangladesh and the Regional Ethical Review Board at Uppsala University, Sweden, approved each follow-up.

2.1 | Statistical analysis

An initial dataset was created with children who had height measurements at birth and at 12, 24 and 54 months of age (n = 1930). For descriptive purposes, self-reported pubertal stages according to Tanner from the second follow-up was reported. For the exposure analyses, the outcomes of interest were age at menarche for girls and onset of the puberty growth spurt for boys, as the validity of self-reported pubertal development is typically low.

For three of the girls, the year but not the month of menarche was known and month June was imputed. In cases (n = 362) when the month but not the date was known, the value 15 was imputed. For girls who were not participating in the second pubertal data collection (n = 43), the information on menarche from the first round was used. Stage of pubertal development from the second data collection was used. For descriptive purposes, pubertal stages with less than 15 individuals were merged with the next pubertal stage. Median age at menarche was calculated with the Kaplan Meier method. Boys with height assessments at 4.5 and 10 years, and two height measurements in the puberty follow-up were included in an assessment regarding whether they were pre-pubertal, or had started or completed their growth spurt. The height velocities between 4.5 and 10 years and between the two pubertal measurements were calculated (cm/y) and compared. Boys with a height velocity higher than the velocity from 4.5 to 10 years between the two follow-ups during puberty were classified as having started the growth spurt. Boys with a height velocity not different from the pre-pubertal velocity and having genital development less than stage four pubertal. Boys with no height increase or a height velocity below the pre-pubertal speed and who had reached genital development stage four to five were considered to already have passed the growth spurt. Lastly, these three groups were re-classified into two groups: not having started the growth spurt or, having started or already passed the growth spurt.

The exposure variables were SGA or appropriate for gestational age (AGA), stunting, and recovery from stunting at and between the following ages: birth, 12, 24 and 54 months. Children with a height-for-age *Z*-score (HAZ) below minus two SD were classified as stunted. Children who had been stunted at birth, 12, 24 and 54 months but were not stunted, that is had a HAZ at or above minus two SD, at the following age were categorised as recovered from stunting.

Differences between population characteristics of included, excluded and non-participating mothers and children were tested by the chi-square test. The chi-square test was also used to test the differences in distribution of background characteristics and the adolescents' pubertal stage and age. The Cox' proportional hazards regression model was used to examine the relationship between SGA, stunting at birth, at 12, 24 and 54 months of age and recovery from stunting on age at menarche. The start of study time was birth. Girs who had not had the event (menarche) were censored at the time of last examination. Logistic regression was used to model the same exposure variables and the binary outcome of whether the boy was pre-pubertal or pubertal, that is had started or already completed the growth spurt. Both crude and adjusted hazards ratios and odds ratios were calculated. In the crude analyses, each predictor was included one-by-one. In the adjusted model, the variables of maternal education, maternal body mass index (BMI) at recruitment, around gestational week 8, socioeconomic status of the household represented by tertiles of asset scores, parity and preterm birth were included. All analyses were performed using the R statistical software, version 3.2.4[10] and the packages 'Epi'[11]and 'survival'[12].

3 | RESULTS

3.1 | General characteristics

From 2002 to 2004, there were 3625 children born to the 4436 women enrolled in the MINIMat trial (Figure 1). A total of 845 women were lost during follow-up before delivery, mainly due to outmigration, foetal loss or withdrawal of consent. Puberty data were collected from 2307 adolescents. Reasons for losses from follow-up after birth up to puberty included outmigration, refusal to participate and death. Out of the children assessed for pubertal development, 377 were excluded due to missing height measurements at birth, 12, 24 or 54 months resulting in a final sample of 1930 adolescents. A total of 474 boys had height measurements at

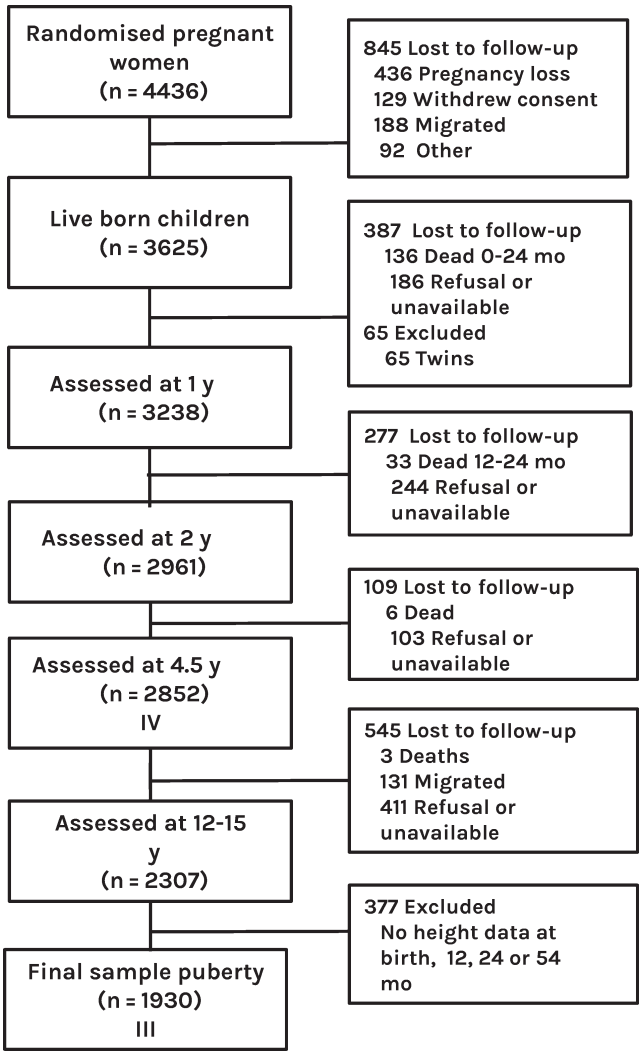

FIGURE 1 Flow chart of children participating in the MINIMat trial from birth to puberty

4.5 and 10 years and two times, 6 months apart, during the pubertal follow-up. The major limiting factor was the 10-year follow-up, which included only one of the two-calendar-year MINIMat cohort. There were 54 boys with some of these assessments with obvious errors, resulting in 420 boys included in the analysis of pre-pubertal or pubertal growth spurt status.

The randomized prenatal interventions were not associated with any of the determinants of growth included in the analysis (data not shown). Among mothers of the children not participating in the puberty follow-up, there were a slightly higher proportion of young (<20 years), first-time mothers, with more than 6 years of education, and mothers from households belonging to the lowest socioeconomic tertile (data not shown). Out of these, only socioeconomic status was associated with the outcomes (data not shown). At birth, non-participating children were stunted more frequently when compared to participating children (19.2% and 16.3%, respectively, P = <0.05). Other background characteristics did not differ between participating and non-participating children.

TABLE 1 Baseline characteristics of mothers at 8wk of gestation and households participating in the MINIMat trial, Bangladesh

Characteristics	n/n (%)
Maternal age	
<20	274/1930 (14.2%)
20-29	567/1930 (29.4%)
≥30	1089/1930 (56.4%)
Maternal BMI	
<18.5	564/1922 (29.3%)
≥18.5	1358/1922 (70.7%)
Maternal education	
No education	652/1930 (33.8%)
Formal education	1278/1930 (66.2%)
Parityat enrolment	
0	524/1930 (27.2%)
1	534/1930 (27.7%)
2 or more	871/1930 (45.2%)
Perceived income-expenditure status	
Surplus	490/1929 (25.4%)
Breakeven	1050/1929 (54.4%)
Occasional deficit	325/1929 (16.8%)
Constant deficit	57/1929 (3.0%)
Don't know	71/1929 (0.4%)

The characteristics of the households, mothers and children at birth are presented in Table 1. The participating mothers were short and slender at recruitment with an average height and weight of 151 cm (SD 5.3 cm) and 48 kg (SD 4.7 kg), respectively, corresponding to an average BMI of 20.1 (SD 2.6). Average weight gain from pregnancy week 8 to 30 was 5.4 kg (SD 2.5 kg).

Approximately one-third of the women were illiterate, and half of them had more than two children from before.

3.2 | Birth characteristics and linear growth

At birth, HAZ was low (mean −0.94), 16% were stunted, and more than half of the children (62%) were born SGA. HAZ declined rapidly up to 24 months of age, resulting in a mean HAZ at 12 and 24 months of −1.6 and −2.0 and a stunting prevalence of 35% and 50%, respectively (Table 2, Figure 2). Few children recovered from stunting during infancy (Figure 2). From 24 to 54 months, HAZ increased (mean HAZ at 54 months -1.6) and the prevalence of stunting decreased to 34% at 54 months of age. At 12 months of age, boys had a higher prevalence of stunting than girls. Later in childhood, the pattern was reversed; fewer girls recovered from stunting from 24 to 54 months and at 54 months girls had a higher prevalence of stunting than boys (girls 34.8% and boys 29.1%, P < 0.01). The mean HAZ change for children who recovered from stunting was 1.1 HAZ 0-12 months, 0.62 HAZ 12-24 months, and 0.85 HAZ in the age interval 24-54 months.

3.3 | Pubertal development

The girls were between 12.4 and 14.5 years of age at the first puberty follow-up (mean age 13.3, SD 0.49), and between 12.9 and 15.0 (mean age 13.9, SD 0.49) years at the second round. The boys were between 12.3 and 14.4 years of age at the first puberty follow-up (mean age 13.4, SD 0.47), and between 12.8 and 15.0 (mean age 13.9, SD 0.47) years at the second round. The age of the participating adolescents did not differ across the baseline characteristics or predictor variables (data not shown). No differences in puberty characteristics or age at menarche were found when comparing the participants and the 377 excluded children who were missing some of the previous anthropometry measurements.

TABLE 2 Anthropometric characteristics of girls and boys participating in the MINIMat trial from birth to puberty follow-up

	Girls (n = 987)	Boys (n = 987)
	Mean (SD)	Mean (SD)
Birth weight, g	2654 (374)	2746 (413)
Birth length, cm	47.5 (2.04)	48.1 (2.2)
HAZ[a] at birth	−0.92 (1.1)	−0.95 (1.2)
HAZ at 12 mo	−1.60 (0.96)	−1.68 (1.0)
HAZ at 24 mo	−2.03 (0.95)	−2.03 (1.03)
HAZ at 54 mo	−1.67 (0.86)	−1.47 (0.91)
Height at 10 y (cm)[b]	129.4 (6.9)	129.4 (5.9)
Height at 12 y (cm)	147 (5.92)	146 (8.29)
Height at 13 y (cm)	149 (5.57)	150 (8.48)
Height at 14 y (cm)	151 (5.90)	155 (8.48)
BMI at 12 y	16.91 (2.71)	16.03 (2.41)
BMI at 13 y	17.72 (3.07)	16.40 (2.63)
BMI at 14 y	18.32 (2.76)	16.96 (2.40)

[a]Height-for-age Z-score.
[b]Only half of the cohort was followed at 10 y, n girls464, boys = 466.

Table 3 illustrates puberty development at the second round of data collection, baseline characteristics and stunting status for girls, and Table 4 for boys. All girls had reached Tanner stage two or higher in breast development, with a majority of girls being at stage three (68.5%). For pubic hair development, only two girls were still prepubertal (0.2%, stage one), most girls were at stage two (42.5%) or three (49.8%) and none had reached stage five in breast or pubic hair development. Most boys were at genital stage three (27.1%) or four (72.3%), and 0.6% had reached stage five. Only 0.7% of the boys had not developed any pubic hair, no boys were at stage two, 47.7% had reached stage three, 51.4% stage four, and only 0.2% stage five. Adolescents, who had reached a later stage of puberty, were characterised by more frequently having mothers with higher education, a higher BMI, and belonging to a higher socioeconomic group (Tables 3 and 4).

The median age at menarche was 13.0 years. A total of 61.8% of the girls had reached menarche in the first round and 76.2% in the second round of data collection. Girls with later menarche were characterised by more frequently being stunted and having mothers from a lower socioeconomic group, with less education, and a low BMI. The mean recall time, that is time between menarche and data collection, was 0.9 years, range 0-3.6 years.

There was no difference in pubertal development or age at menarche between SGA and AGA girls (Tables 3 and 5). Boys who were born SGA, however, came into their pubertal growth spurt later than

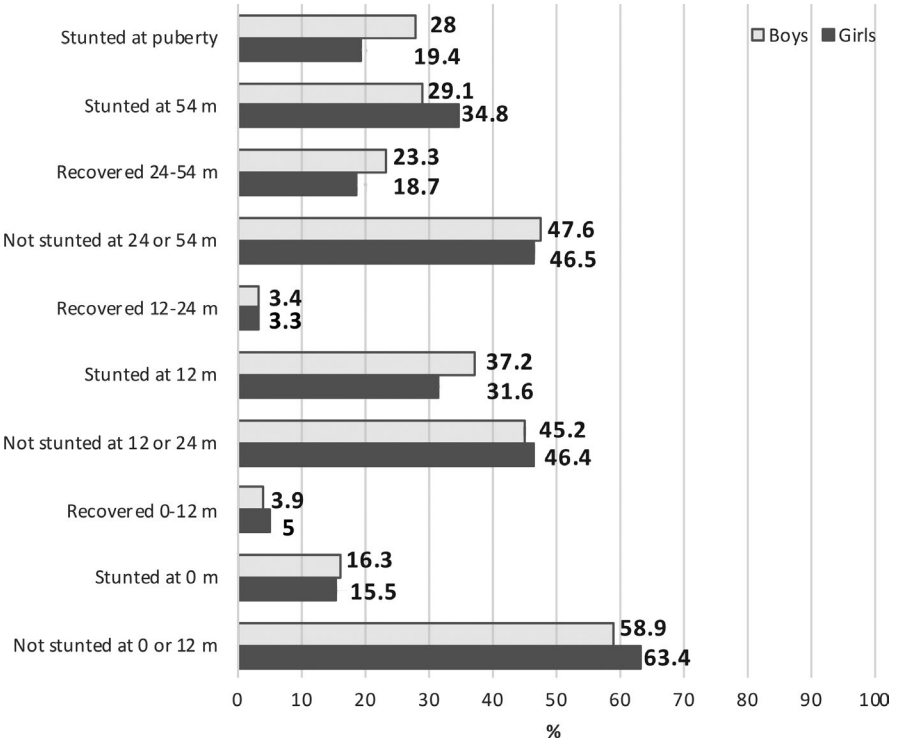

FIGURE 2 Stunting prevalence and recovery from stunting in girls and boys from birth to adolescence in the MINIMat cohort

TABLE 3 Age at menarche and self-reported pubertal development stages according to maternal characteristics, birth size, stunting and recovery from stunting among girls in the MINIMat cohort

	Girls								
		Breast development				Pubic hair development			
	Age at menarche[a] Median (CI)	2 128/943 (13.6%)	3 646/943 (68.5%)	4 169/943 (17.9%)	*P*	1 and 2[b] 421/943 (42.7%)	3 492/943 (49.8%)	4 30/943 (3.0%)	*P*
Maternal education									
No education	13.3 (13.1-13.4)	51/128 (39.8%)	224/646 (34,7%)	43/169 (25.4%)	0.02	169/421 (40.1%)	145/492 (29.5%)	4/30 (13.3%)	<0.01
Formal education	13.0 (12.9-13.1)	77/128 (60.2%)	422/646 (65.3%)	126/169 (74.6%)		252/421 (59.9%)	347/492 (70.5%)	26/30 (86.7%)	
Wealth index tertiles									
Lowest	13.3 (13.1-13.4)	58/128 (45.3%)	250/646 (38.7%)	42/169 (24.9%)	<0.01	181/421 (43.0%)	166/492 (33.7%)	3/30 (10.0%)	<0.01
Middle	13.1 (13.0-13.3)	55/128 (43.0%)	210/646 (32.5%)	55/169 (32.5%)		146/421 (34.7%)	166/419 (33.7%)	10/30 (33.3%)	
Highest	12.7 (12.6-12.9)	15/128 (11.7%)	186/646 (28.8%)	72/169 (42.6%)		98/421 (23.3%)	160/492 (32.5%)	17/30 (56.7%)	
Maternal BMI									
<18.5	13.3 (13.1-13.5)	44/128 (34.4%)	201/646 (31.2%)	39/169 (23.2%)	0.07	144/421 (34.2%)	138/492 (28.2%)	4/30 (13.3%)	0.02
≥18.5	13.0 (12.9-13.1)	84/128 (65.6%)	443/646 (68.8%)	129/169 (76.8%)		278/421 (66.0%)	352/492 (71.8%)	26/30 (86.7%)	
Birth size									
SGA	13.1 (13.0-13.2)	80/128 (62.5%)	388/646 (60.0%)	94/169 (55.6%)	0.44	252/419 (60.1%)	296/492 (60.1%)	15/30 (50.0%)	0.24
AGA	13.1 (13.0-13.2	48/128 (37.5%)	258/646 (39.9%)	75/169 (44.4%)		170/419 (40.6%)	196/492 (39.8%)	15/30 (50.0%)	
Stunted at birth	13.1 (13.0-13.3)	27/128 (21.1%)	107/646 (16.6%)	15/169 (8.9%)	0.01	75/421 (17.8%)	71/492 (14.4%)	3/30 (10.0%)	0.25
Not stunted at birth	13.1 (13.0-13.1	101/128 (78.9%)	539/646 (83.4%)	154/169 (91.1%)		346/421 (82.2%)	421/492 (85.6%)	27/30 (90.0%)	
Reached menarche									
No		96/128 (75.0%)	116/646 (18.0%)	2/169 (1.2%)	<0.01	172/421 (40.1%)	41/492 (91.7%)	29/30 (96.7%)	<0.01
Yes		32/128 (25.0%)	530/646 (82.0%)	167/169 (98.8%)		249/421 (59.1%)	451/492 (8.3%)	1/30 (3.3%)	
Stunting and recovery from stunting 0-12 mo									
Not stunted at 0 or 12 mo	13.0 (12.9-13.1)	59/128 (46.1%)	406/646 (62.8%)	130/169 (76.9%)	<0.01	244/421 (158.0%)	328/492 (66.7%)	23/30 (76.7%)	<0.01
Recovered 0-12 mo	12.9 (12.6-13.4)	4/128 (3.1%)	36/646 (5.6%)	9/169 (5.3%)		15/421 (3.6%)	32/492 (6.5%)	2/30 (6.7%)	
Stunted at 12 mo	13.3 (13.1-13.5)	65/128 (50.8%)	204/646 (31.6%)	30/169 (17.8%)		162/421 (38.5%)	132/492 (26.8%)	5/30 (1.7%)	
Stunting and recovery from stunting 12-24 mo									
Not stunted at 12 or 24 mo	12.9 (12.8-13.0)	32/128 (25.0%)	290/646 (44.9%)	110/169 (65.1%)	<0.01	158/421 (37.5%)	251/492 (51.0%)	23/30 (76.7%)	<0.01
Recovered 12-24 mo	12.8 (12.6-13.5)	5/128 (3.9%)	23/646 (3.6%)	4/169 (2.4%)		12/421 (2.9%)	20/492 (4.1%)	0/30 (0%)	
Stunted at 24 mo	13.3 (13.1-13.4)	91/128 (71.0%)	333/646 (51.6%)	55/169 (32.5%)		252/421 (59.6%)	221/492 (44.9%)	7/30 (23.3%)	

(Continues)

TABLE 3 (Continued)

	Girls								
		Breast development				Pubic hair development			
	Age at menarche[a] Median (CI)	2 128/943 (13.6%)	3 646/943 (68.5%)	4 169/943 (17.9%)	*P*	1 and 2[b] 421/943 (42.7%)	3 492/943 (49.8%)	4 30/943 (3.0%)	*P*
Stunting and recovery from stunting 24-54 mo									
Not stunted at 24 or 54 mo	12.8 (12.7-13.0)	31/128 (24.2%)	293/646 (45.4%)	108/169 (63.9%)	<0.01	154/421 (36.6%)	255/492 (51.8%)	23/30 (76.7%)	<0.01
Recovered 24-54 mo	13.0 (12.9-13.1)	20/128 (715.6%)	133/646 (20.6%)	26/169 (15.4%)		79/421 (18.8%)	98/492 (19.9%)	2/30 (6.7%)	
Stunted at 54 mo	13.5 (13.3-13.6)	220/128 (34.1%)	220/646 (34.1%)	35/169 (20.7%)		188/421 (44.7%)	139/492 (28.3%)	5/30 (16.7%)	

Abbreviations: AGA, Appropriate for Gestational Age at birth; SGA, Small for Gestational Age at birth.
[a]Calculated by time-to-event analysis according to Kaplan-Meier.
[b]Stage 1 (2/943, 0.2%), Stage 2 (419/943, 42.5%).

those with an appropriate weight at birth (Table 6). Girls and boys who were stunted at 12, 24 and 54 months were less likely to be in a higher Tanner stage (Tables 3 and 4) and reach menarche (Table 5) or enter pubertal growth spurt (Table 6). There was no tendency among adolescents who recovered from stunting between 0-12, 12-24 or 24-54 months to experience an earlier menarche or pubertal growth spurt than adolescents who never had been stunted (Tables 5 and 6).

4 | DISCUSSION

In this study, we followed a birth cohort from rural Bangladesh and examined the association between longitudinal growth restriction, assessed as stunting, recovery from stunting and pubertal development. A difference in pubertal maturation between children who were born small or AGA was seen only in boys, where boys born small were less likely to have entered the puberty growth spurt. As expected, children who were stunted in infancy and childhood had later pubertal development, that is girls had later menarche and boys had started their growth spurt later as compared to non-stunted children. Children who recovered from stunting, however, had a similar puberty development as their peers who never had been stunted, independently of when during infancy or childhood the recovery had occurred.

The MINIMat cohort study was implemented in an area with a health and demographic surveillance system and a well-developed research infrastructure. This setting made it possible to run a complex cohort study over long time. Experienced field workers, study nurses and medical doctors collected data during pregnancy, at birth, and in the follow-up periods during infancy, childhood and adolescence. The data collectors received frequent refresher training, including anthropometry standardization exercises.

There were small and statistically significant differences in background characteristics between participating and non-participating children. Younger, more educated women may spend time out of the study area more frequently, for example in their maternal home. The household wealth classification reflects partly other conditions than maternal education, and the observed slight over-representation of a lower socioeconomic group among non-participants was not contradictory. Of the background characteristics that differed between participating and non-participating children, only socioeconomic status was associated with puberty development and therefore potentially a confounding factor. The differences were small, adjustments were done in the analyses, and it is therefore unlikely that they influenced the main findings. There were small but significant differences in the occurrence of stunting at birth, but not later, between non-participating and participating children. There were no differences in background characteristics or linear growth between girls with a complete menarche date and those with missing information on exact day.

The date of menarche was collected by self-reported date of onset at two time points, increasing the probability of collecting the information close to the event. The accuracy of recall of menarche

TABLE 4 Self-reported pubertal development stages in relation to maternal characteristics, birth size, previous stunting and recovery from stunting among boys in the MINIMat cohort, Bangladesh

	Boys					
	Genital development			Pubic hair development		
All	3 239/882 (27.1%)	4 and 5[a] 643/882 (72.9%)	*P*	2 and 3[b] 427/882 (48.4%)	4 and 5[c] 455/882 (51.6%)	*P*
Maternal education						
No education	94/239 (39.3)	200/643 (31.1%)	0.02	145/427 (31.9%)	149/455 (34.9%)	0.34
Formal education	145/239 (60.7%)	443/643 (68.9%)		310/427 (68.1%)	278/455 (65.1%)	
Wealth index tertiles						
Lowest	97/239 (40.6%)	200/643 (31.1%)	<0.01	156/427 (36.5%)	141/455 (31.0%)	<0.01
Middle	99/239 (41.4%)	236/643 (36.7%)		174/427 (40.7%)	161/455 (35.4%)	
Highest	43/239 (18.0%)	207/643 (32.2%)		97/427 (22.7%)	152/455 (33.6%)	
Maternal BMI						
<18.5	89/239 (37.2%)	166/643 (26.0%)	<0.01	143/427 (33.6%)	112/455 (24.8%)	<0.01
≥18.5	150/239 (62.8%)	473/643 (74.0%)		283/427 (66.4%)	340455 (75.2%)	
Birth size						
SGA	154/239 (64.4%)	349/642 (54.3%)	<0.01	263/427 (61.6%)	240/455 (52.7%)	<0.01
AGA	85/239 (35.6%)	294/642 (45.7%)		164/427 (38.4%)	215/455 (47.3%)	
Stunted at birth	44/239 (18.4%)	93/642 (14.5%)	0.15	80/427(18.7%)	57/455 (12.5%)	0.01
Not stunted at birth	195/239 (81.6%)	550/643 (85.5%)		347/427 (81.3%)	398/455 (87.5%)	
Stunting and recovery from stunting 0-12 mo						
Not stunted at 0 or 12 mo	108/239 (45.2%)	424/642 (65.9%)	<0.01	214/427 (50.1%)	318/455 (69.9%)	<0.01
Recovered 0-12 mo	6/239 (2.5%)	28/642 (4.4%)		16/427 (3.7%)	18/455 (4.0%)	
Stunted at 12 mo	125/239 (52.3%)	191/642 (29.7%)		197/427 (46.1%)	119/455 (26.2%)	
Stunting and recovery from stunting 12-24m						
Not stunted at 12 or 24 mo	74/239 (30.9%)	336/642 (54.3%)	<0.01	158/427 (37.0%)	252/455 (55.4%)	<0.01
Recovered 12-24 mo	10/239 (4.2%)	19/642 (3.0%)		11/427(2.6%)	18/455 (4.0%)	
Stunted at 24 mo	155/239 (64.9%)	288/642 (44.8%)		258/427 (60.4%)	185/455 (40.7%)	
Stunting and recovery from stunting 24-54 mo						
Not stunted at 24 or 54 mo	80/239 (33.5%)	350/642 (54.4%)	<0.01	164/427 (38.4%)	266/455 (58.5%)	<0.01
Recovered 24-54 mo	55/239 (23.0%)	153/642 (23.8%)		106/427 (24.8%)	102/455 (22.4%)	
Stunted at 54 mo	104/239 (43.5%)	140/642 (21.8%)		157/427 (36.8%)	87/455 (19.1%)	

Abbreviations: AGA, Appropriate for Gestational Age at birth; SGA, Small for Gestational Age at birth.
[a]Stage 4 (638/882, 72.3%), Stage 5 (5/882, 0.6%).
[b]Stage 2 (6/882, 0.68 %), Stage 3 (421/882, 47.7%).
[c]Stage 4 (453/882, 51.4%), Stage 5 (2/882, 0.2%).

date depends mainly on the interval of recall, that is the time between the date of menarche and the time of data collection.[13] In our study, the mean interval of recall was 0.9 years, thus the recall errors were probably low. The time-to-event analyses employed are appropriate for this kind of data, where some girls have not yet had their first menstruation.

The analysis of start of growth spurt was done only in the subset of boys, who had anthropometric measurement at 10 years of age. The 10-year follow-up was carried out in one of the two-calendar-year birth cohort. The selection should therefore not suffer from any selection bias related to the exposures of interest in this analysis. The classification of boys in relation to pubertal growth spurt was mainly based on the height measurements and did therefore not suffer from the reporting bias that influences the self-assessment of pubertal stage.

Studies on the reliability of self-assessment of pubertal have found reasonable agreement between self-assessment and examination by a trained clinician in some studies,[14] whereas others have

TABLE 5 Size at birth, stunting and recovery from stunting in relation to the hazards ratios for girls having reached menarche in the MINIMat cohort. Crude and adjusted Cox's proportional hazard analyses n = 987

	Crude[a]		Adjusted[b]	
	HR	95% CI	HR	95% CI
Size at birth				
AGA	ref		ref	
SGA	1.00	0.87-1.16	1.06	0.90-1.23
Stunted at birth				
Not stunted at birth	ref		ref	
Stunted at birth	0.93	0.77- 1.14	0.94	0.76-1.27
Stunting and recovery from stunting 0-12 mo				
Not stunted at 0 or 12 mo	ref		ref	
Recovered 0-12 mo	1.05	0.77- 1.44	1.08	0.79-1.49
Stunted at 12 mo	0.70	0.60-0.83	0.71	0.60-0.84
Stunting and recovery from stunting 12-24 mo				
Not stunted at 12 or 24 mo	ref		ref	
Recovered 12-24 mo	0.92	0.62-1.39	0.97	0.64- 1.46
Stunted at 24 mo	0.68	0.59-0.79	0.75	0.64-0.88
Stunting and recovery from stunting 24-54 mo				
Not stunted at 24 or 54 mo	ref		ref	
Recovered 24-54 mo	1.00	0.83-1.20	1.06	0.87-1.29
Stunted at 54 mo	0.54	0.46-0.64	0.54	0.45-0.64

Abbreviation: AGA, Appropriate weight for Gestational Age at birth; SGA, Small for Gestational Age

[a]Bivariable analysis of each row characteristic separately

[b]Analysis for each row characteristic with adjustments made for preterm birth, maternal parity, height, BMI, education and socioeconomic status when giving birth.

found considerable inconsistencies.[15] There seems to be an agreement that self-assessment is appropriate in larger epidemiological studies in order to examine the relative distribution of being in an earlier or later pubertal development stage. Studies on the reliability of self-assessment have also reported that girls, especially younger girls, tend to underestimate their development stage, whereas boys, especially older boys, tend to overestimate. This could possibly be due to expectations to be in a similar puberty stage as their peers.[15] These biases were most probably also present in our study, where boys generally reported being in a later puberty stage than girls, despite the fact that girls generally enter puberty at a younger age than boys. On average, girls start to develop secondary sexual characteristics about 1 year before boys[9] and their pubertal growth spurt starts 2 years ahead of boys: Growth velocity during puberty is at its highest in girls at breast stage three and in boys at genital stage four. Due to the fact that it is probable that boys overestimated their pubertal stage, height measurements from the follow-ups were used to estimate pubertal development.

The research question 'Does recovery from stunting come with any adverse future effects?' inspired the analysis in this paper. The terminology regarding recovery from stunting and catch-up growth is problematic, as there are no commonly accepted definitions. Similar studies in high-income settings have used the terminology 'catch-up', describing children with rapid linear growth, with velocities above normal after a period of slow growth. This type of 'catch-up growth' was not prevalent in our cohort. Recovery from stunting was in this paper defined as having a HAZ score above minus two, with no extra criteria. However, the children that were classified as 'recovered' from stunting did display a substantial increase in HAZ.

The median age at menarche in our sample was 13.0 years, which was substantially lower than a previous estimate of 15.8 years in Bangladesh in 1976[16], but the same as in a study from 1996 (median age 13.0)[17] and slightly higher than the estimate in a study from 2009 (median age 12.8 years)[18]. These assessments were all carried out in rural areas. The median age at menarche of 13.0 years from our study does not differ much from age at menarche in several high-income countries, such as Canada, 12.9 years,[19]and Sweden, 13.2 years[5]. During the last century, age at menarche has decreased in most high-income countries and the same downward secular trend is now also observed in low- and middle-income countries. As the decline in age at menarche mainly has been attributed to general improvements in nutrition and health, the relatively low age at menarche reported in our and other studies from rural Bangladesh is not fully explained, considering the large proportion of adolescents that still is affected by undernutrition.

In our cohort, more than 60% of the children were born SGA, and length for age at birth was almost one standard deviation below the median of the WHO growth reference. Linear growth faltered dramatically up to 24 months of age when half of the children were stunted. Very few recovered from stunting during infancy. About one-fifth of the children recovered from stunting after 2 years, but at 4.5 years one-third of the children were still stunted. This growth pattern is consistent with established growth trajectories in South Asia and reported patterns of stunting and recovery from stunting from both Africa and Asia.[20,21]

The prevalence of stunting differed significantly between girls and boys. Boys had a higher stunting prevalence during infancy and at puberty, whereas girls had a higher prevalence of stunting at 4.5 years. This may be explained by factors such as differences in foetal growth,[22] variation in susceptibility to exposures during early development[23] as well as gender inequalities in the society starting already in childhood.[24] Another factor to be considered is a different timing of puberty growth spurt onset among girls and boys in our study sample as compared to the WHO reference population.

TABLE 6 Size at birth, stunting and recovery from stunting in relation to the odds ratios for boys having started the growth spurt in the MINIMat cohort. Crude and adjusted logistic regression analyses

		Started spurt?		Crude[a]		Adjusted[b]	
Characteristic	**Mean age**	**No**	**Yes**	**OR**	**95% CI**	**OR**	**95% CI**
Size at birth							
AGA	13.8	22	153	ref		ref	
SGA	13.9	58	187	0.46	0.27-0.79	0.47	0.24-0.92
Stunted at birth							
Not stunted at birth	13.8	59	289	ref		ref	
Stunted at birth	13.9	21	50	0.49	0.27-0.87	0.31	0.13-0.74
Stunting and recovery from stunting 0-12 mo							
Not stunted at 0 or 12 mo	13.8	36	201	ref		ref	
Recovered 0-12 mo	13.9	5	14	0.50	0.17-1.48	0.28	0.07-1.15
Stunted at 12 mo	13.9	38	121	0.57	0.34-0.95	0.45	0.23-0.89
Stunting and recovery from stunting 12-24 mo							
Not stunted at 12 or 24 mo	13.8	22	144	ref		ref	
Recovered 12-24 mo	13.9	2	13	0.99	0.21-4.70	1.19	0.13-11.0
Stunted at 24 mo	13.9	50	158	0.48	0.28-0.84	0.54	0.27-1.05
Stunting and recovery from stunting 24-54 mo							
Not stunted at 24 or 54 mo	13.9	23	155	ref		ref	
Recovered 24-54 mo	13.8	17	70	0.61	0.31-1.22	0.91	0.40-2.07
Stunted at 54 mo	13.9	34	98	0.43	0.24-0.77	0.36	0.17-0.78

Abbreviations: AGA, Appropriate weight for Gestational Age at birth; SGA, Small for Gestational Age.

[a]Bivariable analysis of each row characteristic separately.

[b]Analysis for each row characteristic with adjustments made for preterm birth, maternal parity, height, BMI, education and socioeconomic status when giving birth.

Age at puberty onset and linear growth restriction can be viewed as two outcomes of nutritional cues, an older age at puberty onset prolongs the childhood growth phase and results in a taller height at the start of puberty. As expected, children who were stunted in childhood had reached a lower pubertal stage and had an older age at menarche.

Earlier epidemiological and adoption studies have reported associations of being born SGA with a younger age at puberty onset, especially in girls.[25,26]

In our sample, we found evidence that SGA boys differed in pubertal development as compared to AGA boys. We did not, however, find any association of being born SGA and early puberty in girls. The reasons of the discrepancy between our findings and earlier evidence might be that the causes of intrauterine growth restriction and low birthweight are complex and vary between different contexts. High-income settings, where most studies on SGA and puberty have been carried out, have a prevalence of SGA from 4% to 8% and smoking is the most prominent risk factor.[27] In our setting, we had an almost tenfold higher prevalence of SGA, and smoking was extremely rare among women. Another important factor that distinguishes the South Asian context is the relatively small maternal size, contributing to small size at birth.[28]

There were gender differences infant and child growth trajectories, occurrence of stunting and recovery from stunting. The observed gender differences in the association between SGA and pubertal development may therefore reflect the gender-specific growth trajectories after birth. Another explanation can be the different outcomes representing puberty development for girls and boys, as these occur at different stages of the pubertal development, menarche (relatively late) and growth spurt (very early).

Many studies that have reported associations between prenatal growth, post-natal growth during infancy and childhood and puberty.[26,29] In an adoption study from Sweden, the girls with the most pronounced stunting and fastest weight gain and catch-up growth had the lowest age at menarche.[29] In our analysis, children who recovered from stunting had a similar puberty development as children who were never stunted, irrespective of when during infancy or childhood the recovery occurred. That is, we did not find any evidence of adverse effects of recovery from stunting in infancy or childhood in terms of very early pubertal development. In contrast to most of the above-mentioned epidemiological and adoption studies, the adolescents in this cohort were born into and remained in an underprivileged setting. The nutrition transition, characterised by increased access to highly processed foods and sugar-sweetened beverages and less physical activity, which rapidly takes place in many low- to middle-income settings, is not yet fully present in our rural study area, as reflected by the low occurrence of overweight in our sample.[30] Thus, the results of our study are mainly representative for other rural areas in Bangladesh and neighbouring countries in South Asia where children are born small and become and stay short and light.

The reported associations of puberty onset with adult chronic diseases do not necessarily reflect causal pathways.[2] Puberty onset and adult chronic risk may, however, share common developmental origins. Age at puberty may therefore be seen as an early indicator for the interactions of genetics and environmental conditions possibly affecting future adult health.

5 | CONCLUSION

In this study, a birth cohort from rural Bangladesh with children having substantial prenatal, infancy and childhood growth restriction was followed into puberty. Stunted children were less biologically mature than their non-stunted peers. In contrast to earlier studies in high-income settings or on children adopted to high-income countries, we could not demonstrate any unfavourable association between recovery from stunting in infancy or childhood and very early puberty development. Those recovering from stunting in this context had similar puberty development as children who had never been stunted. Considering stunting's devastating consequences for the individual and society, the prevention and treatment of stunting should be highly prioritized in national and global public health agendas.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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