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ORIGINAL ARTICLE

Impaired head circumference growth and behavioural problems in childhood: Longitudinal findings from the MINA-Brazil birth cohort

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A commentary based on this article appears on pages 81-83.

Abstract

Background: Previous evidence on the relation between early head circumference (HC) growth and behavioural outcomes in preschoolers has been inconsistent.

Objective: We aimed to investigate whether HC growth from birth to 5 years of age was related to internalising or externalising behavioural problems at 5 years of age in a sex-specific manner.

Methods: Among 303 girls and 318 boys from the MINA-Brazil birth cohort, we examined the associations between changes in HC from birth to 5 years of age and internalising and externalising behaviour problem scores at 5 years according to the Strengths and Difficulties Questionnaire for parents. HC values were transformed into sex- and age-specific z-scores (HCZ) using World Health Organisation standards, and the differences between values at 5 years of age and birth were classified into quintiles. We estimated adjusted mean differences with 95% confidence intervals in behavioural problem scores between HCZ change quintiles using multivariable linear regression by sex. To examine nonlinear associations, we included cubic spline terms.

Results: Head circumference growth from birth to 5 years of age was inversely and nonlinearly associated with internalising problems in girls. Compared with girls at the lowest quintile of HC growth, those above had an adjusted 1.27 (95% confidence interval 0.28, 2.27) points lower mean internalising problems score. This association was mostly driven by HC growth during the first 2 years. We found no association between HC growth and externalising behaviour in either sex.

Conclusions: Impaired HC growth was related to higher mean internalising problem scores at 5 years of age in girls but not in boys. HC growth was not associated with externalising problems.

KEYWORDS
behaviour, birth cohort, cephalometry, longitudinal study, preschool children, problem behaviour

1 | BACKGROUND

There is strong evidence of life-course associations between behaviour problems and the development of psychiatric disorders in adults[1]; yet, the role of infant factors in behavioural outcomes in early childhood is still poorly understood.

Mental health problems in early childhood include both internalising behaviours, such as introspective, depressive, and anxious demeanours, and externalising behaviours, such as aggressive, inattentive, and rule-breaking attitudes. Some infant factors have been related to the development of these problems, including neglect and abuse experiences[2,3] as well as reduced prefrontal and limbic grey matter volume.[4] However, the role of objectively measurable indicators of brain development in predicting behavioural problems remains unclear.

Head circumference (HC) is positively correlated with intracranial and brain volume from birth to approximately 6 years of age.[5] In addition, HC growth is a validated estimate of grey and white matter volumes in early life.[6,7] Whether HC growth predicts the development of behavioural problems later in life is an intriguing possibility; notwithstanding, studies addressing this question have yielded inconsistent results. In Belarus, birth HC was not independently related to behavioural problems at age 6.5 years.[8,9] Similarly, HC growth trajectories during the first 2 years of life among Chinese children were not related to internalising or externalising behavioural outcomes in early adolescence.[10] In contrast, faster head growth from 20 to 56 months among late preterm children in Finland was related to fewer internalising problems at 24–26 years of age.[11]

Although there is evidence of sex differences in child behaviour and its determinants,[12] few studies examining the associations between HC growth and internalising and externalising problems have explored this aspect.[13] Thus, the association between early life HC growth and behaviour may be nonlinear or sex-specific. In addition, a prescriptive approach to HC growth using international standards may contribute to our understanding of this association; hence, we aimed to investigate whether HC growth from birth to 5 years of age was related to internalising or externalising behavioural problems at 5 years of age in a sex-specific manner.

Synopsis

Study question

Is head circumference growth during infancy associated with childhood behavioural problems?

What is already known

Head circumference (HC) is correlated with brain intracranial volume in young children. Results from previous studies of HC growth and behaviour problems among preschoolers are inconsistent; sex-specific and nonlinear associations have not been evaluated.

What this study adds

Impaired HC growth from birth to 5 years of age is nonlinearly associated with higher internalising behaviour problems at 5 years of age in girls only. HC growth was not related to externalising problems in girls or boys.

2 | METHODS

2.1 | Study population

This study was conducted using data from the Maternal and Child Health and Nutrition in Acre, Brazil (MINA-Brazil Study), a prospective population-based birth cohort in the city of Cruzeiro do Sul, Acre State, Western Brazilian Amazon.[14] The study design has been previously described in detail elsewhere.[14] Briefly, between July 2015 and June 2016, we enrolled 1246 mothers with live births at the city's maternity hospital. At baseline, participants provided socioeconomic and demographic information. Face-to-face follow-up assessments of children's anthropometry, feeding practices, and behaviour were performed at 1, 2, and 5 years after birth.

2.2 | Main exposure

The primary exposure was HC growth from birth to 5 years of age, defined as the difference in HC z-score (HCZ) values at the 5-year follow-up and at birth. Secondary exposures included HC growth from birth to 2 years and from 2 to 5 years. We considered HC growth both in quintiles of sex- and age-specific distributions and as a continuous variable. At each follow-up assessment (at 1, 2, and 5 years of age), the children's HC was measured without hairstyles or headdresses. With the child's head fixed, HC was measured with an inelastic tape accurate to 1 mm (SECA, model 218) wrapped around the head and positioned firmly over the maximal occipital prominence and eyebrow arch. All measurements were obtained in duplicate, and the maximum difference allowed between the measurements was 2 mm. We generated HCZ for sex and age using World Health Organisation (WHO) standards.[15,16] For children older than 60 months (80.4%; age range 61.02–71.90 months), we used the reference values at 60 months, assuming that HC growth after this age is negligible. We excluded implausible HCZ values (<−4SD or >+4SD) which accounted for less than 1%.

2.3 | Outcomes

At the 5-year follow-up visit, trained interviewers administered the Portuguese version of the Strengths and Difficulties Questionnaire (SDQ) to each child's parent or caregiver. The SDQ screens for behavioural problems in children aged 2–17 years[17,18] and has been validated in Brazilian populations.[19,20] We used the SDQ internalising and externalising problem scales, each consisting of 10 questions on

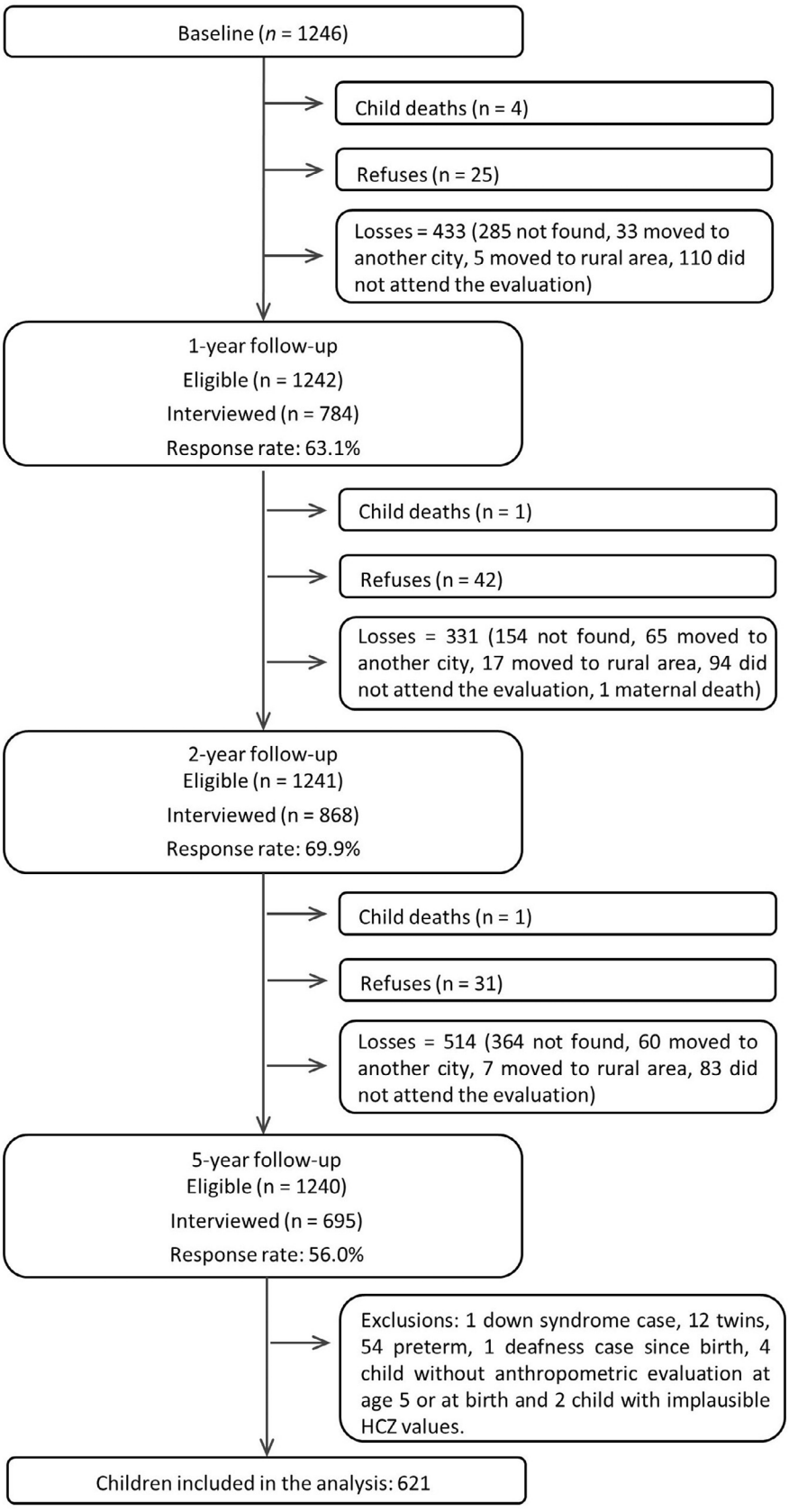


FIGURE 1 Flowchart of the MINA-Brazil cohort participants.

inward and outward behaviours, respectively.[21] Possible responses to the questions were 'Not True', 'Somewhat True', or 'Certainly True'. The answers were coded as 0, 1, or 2,[18] generating a final severity score ranging from 0 to 20 for each scale. The raw scores of the internalising and externalising scales were considered as continuous outcomes, each ranging from 0 to 20 points. We also defined the

TABLE 1 Behaviour problems scores at the 5-year follow-up visit according to participant characteristics in the MINA-Brazil Study.

	Internalising problems[a]				Externalising problems[a]			
	Girls ($n=303$)		Boys ($n=318$)		Girls ($n=303$)		Boys ($n=318$)	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Household characteristics at birth								
Wealth index (tertile)								
1st (poorest)	40	5.1 (3.2)	57	5.4 (3.7)	40	5.9 (3.5)	57	7.9 (4.7)
2nd	111	4.9 (3.2)	116	4.8 (3.4)	111	6.7 (3.9)	116	7.2 (4.7)
3rd (wealthiest)	145	4.6 (3.1)	140	4.1 (2.7)	145	5.6 (3.7)	140	6.5 (3.6)
Beneficiary of the Bolsa Família program								
No	190	4.8 (3.1)	197	4.2 (2.7)	190	5.9 (3.8)	197	6.7 (4.2)
Yes	106	4.8 (3.3)	116	5.3 (3.6)	106	6.3 (3.6)	116	7.6 (4.3)
Maternal characteristics at child's birth								
Age								
<19 years	44	5.3 (3.2)	51	5.5 (3.5)	44	6.8 (4.0)	51	7.4 (4.6)
19 |-| 34 years	218	4.8 (3.2)	235	4.4 (2.9)	218	5.9 (3.7)	235	7.0 (4.2)
≥35 years	41	3.9 (2.8)	32	4.8 (3.5)	41	5.7 (3.8)	32	7.0 (4.6)
Schooling								
≤9 years	78	5.3 (3.7)	80	5.5 (3.7)	78	6.3 (3.6)	80	8.0 (4.6)
10 |–| 12 years	153	4.7 (2.7)	161	4.4 (2.7)	153	6.2 (3.8)	161	7.0 (4.4)
>12 years	65	4.3 (3.3)	71	4.0 (3.1)	65	5.3 (3.8)	71	6.1 (3.5)
Responsible for the household								
No	252	5.0 (3.1)	264	4.6 (3.0)	252	6.1 (3.8)	264	6.8 (4.2)
Yes	44	3.5 (2.8)	49	4.7 (3.6)	44	5.3 (3.5)	49	7.9 (4.6)
Having a paid job								
No	186	5.0 (3.0)	298	4.9 (3.2)	186	6.1 (3.8)	298	7.2 (4.3)
Yes	110	4.5 (3.3)	115	4.1 (3.0)	110	5.8 (3.6)	115	6.7 (4.2)
Depression 3 months after child's birth[b]								
No	223	4.6 (3.2)	218	4.5 (3.0)	223	6.0 (3.7)	218	7.0 (4.4)
Yes	30	6.2 (2.5)	30	5.6 (3.0)	30	6.5 (4.2)	30	7.7 (3.5)
Pregnancy and delivery								
Number of prenatal health visits								
<6	48	6.0 (3.2)	47	4.3 (3.3)	48	6.5 (3.6)	47	7.6 (5.1)
≥6	254	4.6 (3.1)	270	4.6 (3.0)	254	5.9 (3.8)	270	6.9 (4.1)
Planned pregnancy								
No	172	5.2 (3.2)	185	4.6 (3.3)	172	5.2 (3.2)	185	4.6 (3.3)
Yes	124	4.3 (3.0)	128	4.6 (2.9)	124	4.3 (3.0)	128	4.6 (2.9)
Smoking during pregnancy								
No	283	4.8 (3.1)	303	4.6 (3.1)	283	6.0 (3.8)	303	6.9 (4.2)
Yes	13	5.5 (4.6)	10	5.0 (3.4)	13	6.9 (3.8)	10	10.9 (4.0)
Neonatal characteristics								
Birth weight, z score[c]								
Small-for-gestational age	23	5.0 (3.8)	25	4.5 (3.6)	23	6.8 (3.1)	25	8.0 (4.6)
Adequate-for-gestational age	234	4.7 (3.1)	253	4.7 (3.1)	234	5.9 (3.8)	253	6.8 (4.2)
Large-for-gestational age	46	4.8 (3.1)	40	4.5 (2.9)	46	6.0 (3.7)	40	7.9 (4.7)
Birth length, z score[c]								
Small-for-gestational age	21	5.2 (3.5)	27	5.7 (4.1)	21	7.1 (4.2)	27	9.1 (4.5)
Adequate-for-gestational age	241	4.7 (3.2)	259	4.6 (3.1)	241	5.8 (3.7)	259	6.9 (4.3)
Large-for-gestational age	41	4.9 (2.8)	32	4.0 (2.5)	41	6.4 (4.0)	32	6.5 (3.9)

(Continues)

TABLE 1 (Continued)

	Internalising problems[a]				Externalising problems[a]			
	Girls (*n* = 303)		Boys (*n* = 318)		Girls (*n* = 303)		Boys (*n* = 318)	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
HC at birth, z score[c]								
Small-for-gestational age	44	5.5 (3.2)	38	4.7 (3.2)	44	6.5 (3.3)	38	7.0 (4.2)
Adequate-for-gestational age	180	4.4 (3.1)	195	4.5 (3.1)	180	5.7 (3.6)	195	7.0 (4.2)
Large-for-gestational age	79	5.1 (3.1)	85	4.8 (3.1)	79	6.4 (4.3)	85	7.2 (4.7)
Exclusive breast feeding in the first 90 days								
No	184	4.8 (3.1)	177	4.9 (3.2)	184	5.9 (4.0)	177	7.6 (4.6)
Yes	103	4.9 (3.3)	105	4.4 (3.0)	103	5.9 (3.4)	105	6.2 (3.8)
Breast feeding for at least 90 days								
No	23	3.0 (1.8)	32	5.6 (3.6)	23	4.3 (2.6)	32	7.2 (5.0)
Yes	272	4.9 (3.2)	278	4.5 (3.1)	272	6.2 (3.8)	278	7.0 (4.2)

Note: Totals differ due to missing values.

Abbreviation: SD, standard derivation.

[a]Internalising and externalising symptoms scores ranged from 0 to 20 points and were assessed per the Strengths and Difficulties Questionnaire ta the 5-year follow-up.

[b]Maternal depressive symptoms were assessed using the validated Brazilian version of the Edinburgh Postnatal Depression Scale.

[c]Birth anthropometric measures for sex and age in z-score using the INTERGROWTH^{21st} references.

presence of behaviour problems as a categorical outcome, considering scores in the top 20% of their corresponding distributions (≥7 and ≥9 for the internalising and externalising scales, respectively).

2.4 | Covariates

At enrolment, mothers provided information on age (<19, 19–34, or >34 years), schooling (≤9, 10–12, or > 12 years), whether the pregnancy was planned (yes or no), if they had a paid job (yes or no), and if they were beneficiaries of the *Bolsa Família* conditional cash transfer program[22] (yes or no). An asset-based wealth index was calculated using principal component analysis as a proxy for socioeconomic status[23] and was categorised into tertiles. Maternal depressive symptoms were assessed using the validated Brazilian version of the Edinburgh Postnatal Depression Scale (EPDS), a self-administered 10-item scale. Each item has four possible responses (0–3), resulting in a final score ranging from 0 to 30.[24,25] Mothers with an EPDS score ≥ 13 were classified as depressed. Maternal smoking during pregnancy was self-reported as smoking ≥1 cigarette per day every day for ≥3 months during pregnancy (yes or no). The total number of prenatal visits was assessed using the mother's pregnancy health card and categorised into ≤6 or >6 visits according to the Brazilian Ministry of Health recommendations.[26] Hospital records were used to obtain neonatal data, including the child's sex (girl or boy) and type of delivery (vaginal or Caesarean section). We estimated gestational age from either the reported date of the last menstrual period (LMP) or the ultrasound examination (46%). The LMP was considered for women with regular menses cycles, without use of oral contraceptive, and when the agreement between LMP and ultrasonography was ≤7 days.[27] Birth weight was transformed into z-scores according to the INTERGROWTH-21st curve[28] and categorised into small for gestational age (SGA, <10th percentile), adequate for gestational age (AGA, 10th to 90th percentile), or large for gestational age (LGA, >90th percentile). Birth length for gestational age and HC were defined analogously. Throughout all follow-ups, mothers reported whether the child was still receiving breast milk (yes or no) and, if not, when weaning occurred.

2.5 | Statistical analysis

We estimated the adjusted mean differences with 95% confidence intervals (CI) using multivariable linear regression. The adjustment covariates in these models included the following known independent predictors of behaviour outcomes that were related to exposure without being in the causal pathway: maternal education, planned pregnancy (yes/no), wealth index, type of birth, birth weight and birth HC for gestational age, and child's age in months at the 5 year follow-up. Although breast feeding for 90 days or more occurs after birth, it was included in the model based on evidence that it may affect both HC[29,30] and behaviour in childhood.[31] The first HC growth quintile was used as reference. To examine nonlinear associations, we included cubic spline terms[32] for HC growth in the models and estimated differences in behavioural problem scores between the given values of HC growth and the median value of the first quintile. Then, we compared the prevalence of behaviour problems between HC growth quintiles and estimated the adjusted prevalence ratios with 95% CI using Poisson regression. Robust variances were specified in all the models. All analyses

were stratified by sex, and the significance level was set at 5%. Analyses were performed using Stata (version 17.0; StataCorp) and SAS version 9.4 (SAS Institute).

2.6 | Missing data

Of the 1246 children enrolled in the cohort, 695 completed the SDQ at the 5-year follow-up (56% of the original cohort), with 621 included in the analysis (Figure 1). Due to the non-random loss of over 40% of participants, the available information for accurate imputations is limited. In the multiple adjusted models, participants with missing values in categorical covariates (<5%) were maintained in the model by creating a new missing-value category. Participants lost to follow-up were from families with lower wealth indices, less educated and more adolescent mothers (Table S1). We implemented inverse probability of selection weighting (IPSW) to account for selection bias due to children lost to follow-up. Multivariable linear regressions for behaviour problem scores were weighted by the inverse probability of participation at the end of follow-up; variables used to predict participation included HCZ at birth, maternal education, wealth index, planned pregnancy, type of delivery, and birth weight z-scores (Table S2).

2.7 | Ethics approval

The study was conducted according to the principles of the Declaration of Helsinki and approved by the institutional review board of the School of Public Health at the University of São Paulo, Brazil (#872.613, 2014; #2.358.129, 2017). All mothers or caregivers who participated in the study provided written informed consent.

3 | RESULTS

Of the 1246 mother-infant dyads recruited, 695 completed all postnatal follow-up assessments at 1, 2, and 5 years of age. For this analysis, we excluded 12 twins, 54 infants born preterm (<37 weeks), one child with Down syndrome, one child with deafness from birth, four children without anthropometric evaluation at age 5 or at birth, and two children with implausible HCZ values (Figure 1). The final sample consisted of 621 children (303 girls and 318 boys). Compared with the children included in the analysis, those excluded were more likely to be from poorer households and have less educated and younger mothers (Table S1). The participants' mean age at the time of behaviour assessment was 63.43 ± 2.70 months; 48.8% were girls. Birth through Caesarean section, birth weight, length, and HC were inversely related to HC growth in the first 5 years of life (Table S3).

3.1 | Internalising behaviour problems

The mean internalising problem scores were 4.76 ± 3.13 in girls and 4.62 ± 3.12 in boys. Table 1 presents the mean scores for behavioural problems at the 5-year follow-up visit, adjusted for potential confounders. Girls whose mothers were younger, less educated, primary household providers, had fewer than six prenatal visits, experienced an unplanned pregnancy, breast feeding for less than 90 days, or had postpartum depression showed higher mean scores for internalising problems (Table 1). Boys from the poorest families, beneficiaries of *Bolsa Familia*, with mothers who were less educated, without a paid job, had shorter birth lengths, or had postpartum depression showed higher mean scores for internalising problems (Table 1).

Head circumference growth from birth to 5 years of age was inversely and nonlinearly associated with the mean internalising problem scores in girls (Table 2 and Figure 2). Compared with girls at the lowest quintile of HC growth, those above had an adjusted 1.27 (95% CI 0.24, 2.24) points lower mean internalising problems scores. This association did not vary according to the mode of delivery (P, interaction: 0.93) (Figure S1). HC growth from birth to 2 years was similarly associated with internalising problems among girls, but no association was observed for HC growth from 2 to 5 years (Table S4 and Figure S2). Consistent with these results, the prevalence of internalising behaviour problems was higher in girls in the first HC growth quintile than in those above (Table S5).

In boys, HC growth from birth to 5 years of age was not associated with internalising behaviour (Figure 2, Table 2, and Table S5) or within the narrower periods considered (Table S4 and Figure S2). For both sexes, interpretation of the associations between HC growth and internalising behaviour remained unchanged after accounting for potential selection bias (Table S2).

3.2 | Externalising behaviour problems

The mean externalising problem scores were 6.00 ± 3.77 in girls and 7.06 ± 4.30 in boys. Girls whose mothers had unplanned pregnancies and breast feeding for 90 or more days had higher scores of externalising problems. Boys from the poorest families, beneficiaries of Bolsa Familia, with mothers who were less educated or smoked during pregnancy and with shorter birth lengths had higher scores of externalising problems (Table 1).

Head circumference growth from birth to 5 years of age was not associated with externalising behaviour overall (Figure 2, Table 2, and Table S5), and results were similar in models weighted by the inverse probability of participation (Table S2). No associations were observed within the narrower periods considered (Table S4 and Figure S2).

TABLE 2 Head circumference (HCZ) growth and behaviour problem scores at the 5-year follow-up visit in the MINA-Brazil Study.

HCZ growth[b] quintiles from birth to 5 years (median, girls/boys)	Internalising behaviour problems[a]					
	Girls ($n = 303$)			Boys ($n = 318$)		
	Mean (SD)	Mean difference (95% CI)[c]	Adjusted mean difference (95% CI)[d]	Mean (SD)	Mean difference (95% CI)[c]	Adjusted mean difference (95% CI)[d]
1st (−1.59/−1.46)	5.38 (3.09)	0.00 (Reference)	0.00 (Reference)	5.17 (3.44)	0.00 (Reference)	0.00 (Reference)
2nd (−0.46/−0.39)	4.48 (3.15)	−0.90 (−2.01, 0.21)	−1.06 (−2.17, 0.06)	4.53 (2.70)	−0.64 (−1.72, 0.44)	−0.63 (−1.71, 0.45)
3rd (0.26/0.36)	4.30 (2.98)	−1.08 (−2.16, 0.01)	−1.57 (−2.87, −0.27)	4.65 (2.96)	−0.52 (−1.64, 0.60)	−0.36 (−1.63, 0.90)
4th (1.08/1.06)	4.67 (3.40)	−0.70 (−1.86, 0.45)	−1.35 (−2.65, −0.04)	4.25 (3.35)	−0.92 (−2.10, 0.26)	−0.63 (−1.91, 0.65)
5th (2.12/2.05)	4.98 (2.99)	−0.39 (−1.48, 0.69)	−1.17 (−2.67, 0.33)	4.52 (3.09)	−0.65 (−1.79, 0.49)	−0.38 (−1.80, 1.03)

Abbreviations: CI, confidence interval; HCZ, Head circumference-for-sex and age in z-score using the World Health Organisation standards; Ref, reference group; SD, standard derivation.

[a]Internalsing and externalising symptoms scores ranged from 0 to 20 points and were assessed per the Strengths and Difficulties Questionnaire at the 5-year follow-up.

[b]Difference in HCZ values at the 5-year follow-up and birth.

[c]Mean internalising/externalising problems score differences were estimated with use of multivariable linear regression.

[d]Mean internalising/externalising problems score differences were estimated with use of multivariable linear regression adjusted by: maternal education (<9, 10–12, >12 years); planned pregnancy (yes or no); wealth index in tertiles; type of birth (vaginal or Caesarean); head circumference at birth and birth weight-for-sex and age in z-score using the INTERGROWTH^{21st} references, continuous; breast feeding for at least 90 days (yes or no); child's age in months at the 5 years follow-up, continuous.

3.3 | Comment

3.3.1 | Principal findings

In this prospective study of Amazonian preschool children, impaired HC growth was associated with more internalising problems in girls. This association was primarily due to HC growth during the first 2 years of life. HC growth was not related to internalising problems in boys or to externalising problems in either sex.

3.3.2 | Strengths of the study

This study has several strengths. First, we used longitudinal measures of exposure to account for changes in HC according to a prescriptive approach during different periods of early childhood. Second, the analyses were stratified according to sex and adjusted for several potential confounding variables. Finally, we used a validated instrument to ascertain internalising and externalising problems in children.

3.3.3 | Limitations of the data

This study has some important limitations. First, the attrition rate up to 5 years of age was high (~40%) and loss to follow-up was not random, as it differed with respect to predictors of exposure and outcome, which could have compromised the external validity of our findings. We used IPSW to correct for selection bias due to measured covariates including HCZ at birth; however, we lacked information on HC growth in children lost to follow-up, as this was calculated from birth to age 5 years. If HC growth predicts participation, some residual bias would be unaccounted for by the IPSW procedure. Second, the identification of behavioural problems by maternal report is subjective and prone to recall bias. Third, as there are no validated cut-off points for the internalising and externalising scales, we defined the presence of behaviour problems categorically, identifying scores in the top 20% of their respective distributions. Although this specific cut-off lacks validation, our rationale for this decision was informed by methodologies used in establishing the original SDQ cut-offs. In a population-based UK survey, the original banding proposed by SDQ authors aimed to set cut-points so that 80% of children scored 'normal', 10% 'borderline', and 10% 'abnormal'. Therefore, we employed a similar approach in our study. Fourth, residual confounding cannot be ruled out. Finally, the limited sample size may have compromised the detection of associations specific to sex.

3.3.4 | Interpretation

Previous studies have reported inconsistent results on the association between HC growth and behaviour problems among pre-schoolers. In this study, no association between HC growth and externalising behaviour in either sex was observed. However, there was a small association between impaired HC growth and behaviour problems in girls (1.27 points lower mean scores; 95% CI 0.28, 2.27). Similar findings were also reported in a study conducted with late preterm finish children, in which faster head growth from 20 to 56 months showed a small and linear association with lower internalising and total behaviour problems scores at 24–26 years of age (effect sizes −0.30 and −0.33 SD, respectively, for every one SD faster growth; 95% CI's −0.66 to −0.004).[11] In contrast, HC growth trajectories

Externalising behaviour problems[a]					
Girls ($n = 303$)			Boys ($n = 318$)		
Mean (SD)	Mean difference (95% CI)[c]	Adjusted mean difference (95% CI)[d]	Mean (SD)	Mean difference (95% CI)[c]	Adjusted mean difference (95% CI)[d]
6.57 (4.17)	0.00 (Reference)	0.00 (Reference)	7.45 (4.39)	0.00 (Reference)	0.00 (Reference)
5.87 (3.83)	−0.70 (−2.13, 0.72)	−0.74 (−2.23, 0.76)	6.70 (4.61)	−0.75 (−2.32, 0.82)	−0.83 (−2.45, 0.81)
5.82 (3.66)	−0.76 (−2.16, 0.64)	−1.04 (−2.62, 0.54)	7.17 (4.24)	−0.28 (−1.78, 1.23)	−0.31 (−2.19, 1.57)
6.13 (3.73)	−0.44 (−1.85, 0.97)	−0.94 (−2.64, 0.76)	7.19 (3.77)	−0.27 (−1.69, 1.16)	−0.25 (−1.93, 1.44)
5.63 (3.45)	−0.94 (−2.31, 0.43)	−1.31 (−3.18, 0.56)	6.76 (4.54)	−0.69 (−2.25, 0.87)	−0.64 (−2.70, 1.41)

during the first 2 years of life among Chinese children had no association with internalising or externalising behavioural outcomes in early adolescence.[10]

A possible explanation for the sex differences observed in the present study is that internalising symptoms develop distinctly in females and males, as they respond to stressors in distinct ways. A study of 1364 children in the United States reported the development of internalising symptoms between 2 and 11 years of age. Using the latent growth mixture method, the authors identified three different trajectories for each sex: low-stable, decreasing/increasing, and elevated-stable. Although there were no sex differences in the low-stable trajectory, nearly twice as many girls showed elevated-stable internalising symptoms as boys, and nearly twice as many boys showed decreasing/increasing internalising symptoms. There were also sex differences in the associations between postpartum maternal depression or anxiety and the trajectories of internalising symptoms.[12]

Additionally, differences in behavioural problem determinants between boys and girls have been reported in previous studies, suggesting that factors influencing mental health operate through different mechanisms across the sexes. In the aforementioned study,[12] sex differences in maternal covariates affected the trajectories of internalising symptoms. A prospective study of 274 preschool-aged children and their primary caregivers found that the indirect effects of adversity on behaviour problems through temperament varied across sexes. For example, anger mediated the associations between lifetime stress and behaviour problems for the full sample, but inhibitory control and appropriate attentional allocation were intermediary mechanisms of lifetime stress only for boys.[33] Furthermore, in a prospective cohort of 260 children from the United States, higher microbiome diversity at 6 weeks of age was associated with better internalising problems at the age of 3 years in boys but not in girls.[34]

The association between impaired HC growth and higher mean internalising problem scores in girls is in line with current evidence on the role of abnormally slow or fast head size growth in childhood in a range of neurodevelopmental disorders that comprise socio-emotional impairments. A meta-analysis of 27 studies showed that brain overgrowth, resulting in a larger HC and brain size during early childhood was positively associated with autism.[35] Similarly, a study of four Spanish birth cohorts showed that a larger HCZ from birth to 4 years of age was associated with improved cognitive function and fewer attention deficit hyperactivity disorder symptoms at 5 years of age.[36]

In this study, the association between HC growth and internalising problems in girls was driven by HC growth in the first 2 years of life. This lifespan represents a particularly sensitive period for neurodevelopment, when brain formation is particularly active and vulnerable. The brain doubles in size during the first year of life, reaching 80% of its maximum size after 2 years.[37] Thus, accelerated intracranial volume growth occurs during this period, particularly in the grey matter,[37] which is strongly correlated with HC in young children.

Additionally, HC growth was not associated with externalising behaviours in our study. This is in contrast with a study of 756 Canadian children in which HC growth during the first year of life predicted the temperamental traits of surgency and effortful control at 24 months of age in boys but not in girls.[13]

We considered relevant factors for the adjustment of our analysis, including household wealth, maternal education, and prenatal care, as predictors of behaviour outcomes during preschool age. The importance of similar prenatal health and psychosocial risk factors, such as maternal smoking during pregnancy, maternal anxiety, and

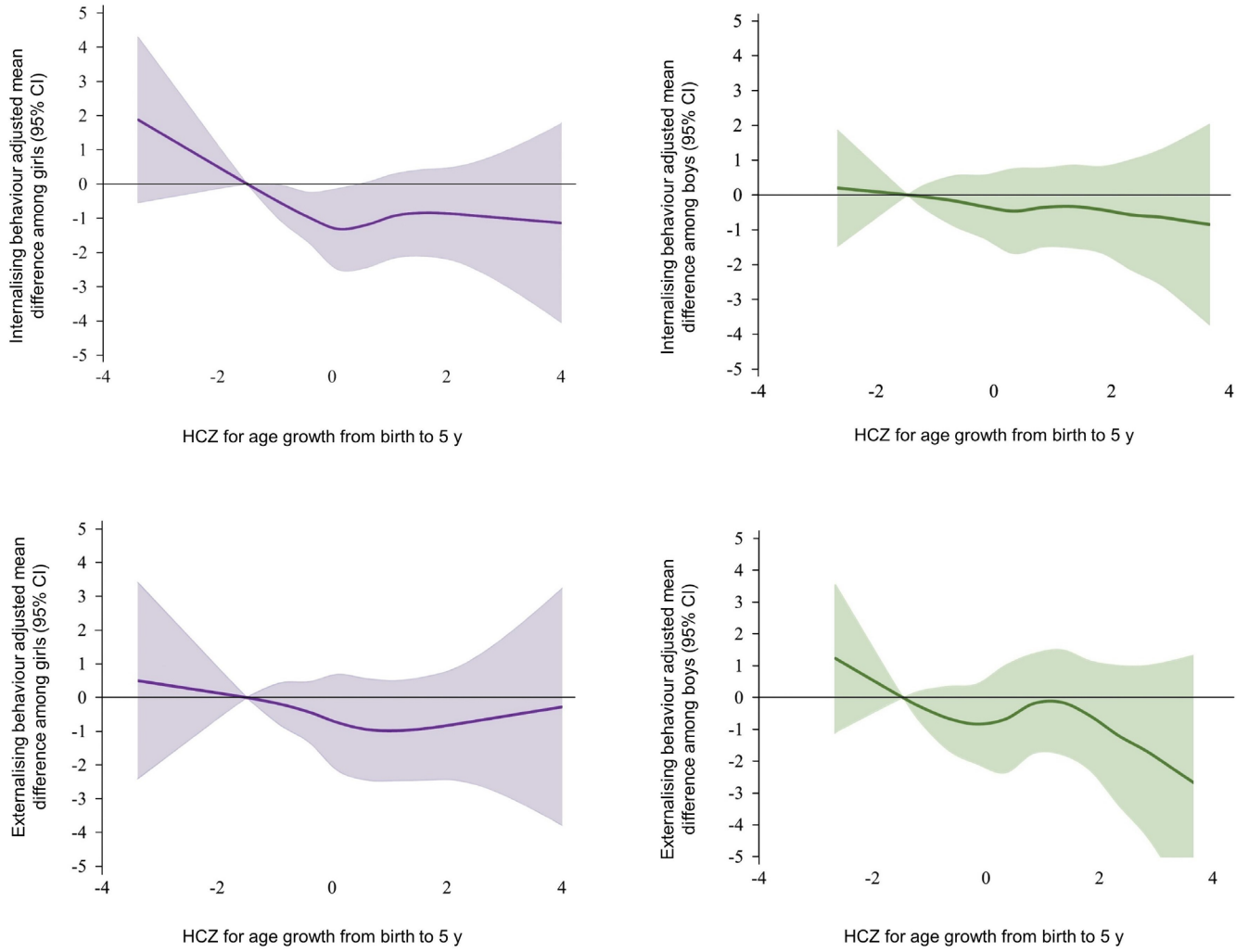


FIGURE 2 Head circumference growth and adjusted mean differences in behaviour scores at the 5-year follow-up visit stratified by sex in the MINA-Brazil Study. The dark line represents adjusted mean differences in the internalising and externalising behaviour scores between the head circumference-for-sex and age in z-score (HCZ) using the World Health Organisation standards at the 10th percentile. The shaded areas represent 95% confidence intervals. Estimates are from linear regression models using robust variance with internalising and externalising behaviour scores and HC growth as continuous outcome and exposure, respectively. The models were adjusted by maternal education (<9, 10–12, >12 years); planned pregnancy (yes or no); wealth index in tertiles; type of birth (vaginal or Caesarean); head circumference at birth and birth weight-for-sex and age in z-score using the INTERGROWTH21st references, continuous; breast feeding for at least 90 days (yes or no); child's age in months at the 5 years follow-up, continuous.

depression in the development of childhood internalising/externalising behaviours has been highlighted in the literature.[38]

4 | CONCLUSIONS

Impaired growth during infancy and early childhood was associated with internalising problems at 5 years of age in girls. The etiological pathways linking head growth and mental health outcomes may be sex-specific. Future studies are warranted to elucidate the possible pathways linking HC and internalising behaviour. Our results highlight the importance of monitoring child growth, advancing research on non-invasive early predictors of mental health, and providing comprehensive care for mental health early in life.

AUTHOR CONTRIBUTIONS

IG: conceptualisation, methodology, formal analysis, data curation, and writing—original draft. EV: conceptualisation, methodology, and writing—review and editing. BHL: methodology, data curation, writing—review and editing. MZ: methodology, writing—review. ALS: methodology, writing—review. AM: methodology, writing—review and editing. MAC: conceptualisation, methodology, supervision, writing—review and editing, funding acquisition, guarantor.

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CONFLICT OF INTEREST STATEMENT

None to declare.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available on reasonable request from the corresponding author, MAC. The data are not publicly available as they contain information that compromises the privacy of the research participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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