Relative effects of postnatal rapid growth and maternal factors on early childhood growth trajectories

Miaobing Zheng[1*], Steven J. Bowe[2], Kylie D Hesketh[1], Kristy Bolton[3], Rachel Laws[1], Peter Kremer[3], Ken K. Ong[4,5], Sandrine Lioret[6,7], Elizabeth Denney-Wilson[8], Karen J Campbell[1]

[1]Deakin University, Geelong, Australia, Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences

[2] Deakin University, Geelong, Australia, Biostatistics Unit, Faculty of Health

[3]Deakin University, Geelong, Australia, Centre for Sport Research, School of Exercise and Nutrition Sciences

[4]Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, UK.

[5]Department of Paediatrics, University of Cambridge, Cambridge, UK

[6]INSERM, U1153 Epidemiology and Biostatistics Sorbonne Paris Cité Research Center (CRESS), Early Origin of the Child's Health and Development ORCHAD team, Villejuif, France

[7]Paris Descartes University, Paris, France

[8] Sydney University Faculty of Medicine and Health, and Sydney Local Health District, New South Wales, Australia

*Corresponding author

Miaobing Zheng

Mailing address: 221 Burwood Highway, Burwood, Victoria, 3125

Telephone number: 613 9248502

Fax number: 613 9244 6017

Email: j.zheng@deakin.edu.au

Short title: Determinants of growth in early childhood

Conflict of interest: Authors declare no conflict of interest.

Abstract

Background: A range of postnatal and maternal factors influences childhood obesity, but their relative importance remains unclear. This study aimed to assess the relative impact of postnatal rapid growth and maternal factors on early childhood growth trajectories.

Subjects: Secondary longitudinal analysis of pooled data from the Melbourne Infant Feeding Activity and Nutrition Trial (InFANT) Program and the InFANT Extend Program (n=977) were performed. Children's height and weight were collected at birth, 3, 9, 18, and 36/42 months. Body mass index-for-age and height for-age z-scores (BAZ, HAZ) were computed using WHO growth standards. Mixed effect polynomial regression models were fitted to examine BAZ and HAZ trajectories and their determinants.

Results: Rapid growth from birth to 3 months, maternal country of birth, and pre-pregnancy BMI were each independently associated with BAZ from 3 to 42 months. Children with rapid growth, those whose mothers were Australian-born, and those whose mothers were overweight/obese pre-pregnancy had higher BAZ from 3 to 42 months. Children with rapid growth had an increase in HAZ growth, but their average HAZ from 3 to 42 months was smaller than children without rapid growth. Children of tall mothers (above average height) had higher HAZ than those of short mothers (below average height). Average HAZ from 3 to 42 months did not differ by maternal country of birth.

Conclusion: Children who experienced rapid growth from birth to 3months, whose mothers were Australian-born or whose mothers were overweight/obese pre-pregnancy demonstrated less favorable growth trajectories across early childhood, potentially predispose them for development of future obesity.

Keywords: infant; growth; determinants; maternal; trajectory

Introduction

Infant growth is a sensitive indicator of nutrition and health status. Growth monitoring is a widely promoted strategy worldwide for ensuring optimal health status in early life. Description of early growth trajectories and determinants will provide insights into early influences on later health and can inform design of future interventions and strategies [1].

Child growth and obesity are influence by an array of genetics, environmental, socioeconomic, and behavioural factors [2]. The programming effects of early factors in the first 1000 days from conception to age 2 years in childhood obesity have been widely acknowledged [3]. Understanding the early origins of childhood obesity is imperative to inform polices and interventions to optimise child growth and facilitate the early prevention of childhood obesity [3]. A range of early factors has been associated with childhood obesity. Postnatal rapid growth, defined as upward centile crossing in weight growth charts within the first 2 years of life, has been proposed as a pivotal factor programming later obesity, diabetes, and cardiovascular disease [4-6]. Apart from postnatal rapid growth, a range of maternal factors such as pre-pregnancy overweight/obesity, and education (as proxy for socio-economic position) have been identified as important in the genesis of childhood overweight and obesity [7]. However, the influence of these factors on longitudinal growth trajectories in early childhood and their relative importance remains unclear. The preponderance of studies on child growth have utilized a cross-sectional approach that does not permit evaluation of longitudinal growth trajectories.

It is conceivable that both postnatal rapid growth and maternal factors play a crucial and potentially synergistic role in child growth and obesity. Postnatal rapid growth may influence hormones that regulate body composition, food intake and metabolism, that could in turn affect growth and later health outcomes [8]. Maternal factors contribute to complex genetic, biological, social and environmental pathways of child growth and development. Maternal overweight/obesity may contribute to an over-nutrition environment in-utero that promotes excess fetal and postnatal growth via higher circulating insulin and other hormones through both metabolic and genetic pathways [9]. Maternal education as a proxy for socioeconomic status (SES), is associated with feeding styles and family environment that may, in turn, affect child growth [10]. Examining the relative importance of postnatal rapid growth and maternal factors will inform future research priorities for intervention.

Previous scholars highlight the lack of longitudinal research seeking to explain the relative contribution of postnatal versus maternal factors on child growth and obesity [3, 11]. Therefore, in this study we aim to assess the relative effects of early postnatal rapid growth and maternal factors on longitudinal trajectories of both standardized BMI and height in early childhood within two cohorts of infants in the state of Victoria, Australia. The findings of this study will

Subjects and Methods

Study participants

Data from the Melbourne Infant Feeding Activity and Nutrition Trial (InFANT) Program (n=542) and the InFANT Extend Program (n=514) were used. The InFANT program was registered with Current Controlled Trials (ISRCTN81847050) and the InFANT Extend program was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR 12611000386932). Ethical approval for both studies was granted by the Deakin University Human Research Ethics Committee, the Victorian Office for Children and the Department of Education and Early Childhood Development (Victoria, Australia). Details of these studies have been reported previously [12-14]. In brief, the Melbourne InFANT Program was a 15-month parent-focused intervention aiming to reduce infant obesity risk behaviors with subsequent follow-up until age five years to test sustainability of intervention effects (June 2008 to December 2013). First-time parent groups were recruited from 14 representative local government areas of Melbourne, Australia during standard group meetings at Maternal and Child Health Centers and randomized to intervention or control conditions. Intervention strategies included six dietitian-delivered group education sessions that included information on infant feeding, physical activity and sedentary behaviors. The control group received usual care. The InFANT Extend Program was an extension of the Melbourne InFANT Program that was conducted from June 2011 to October 2015 that utilized the same study design, in a different cohort, with an additional post and online intervention delivered until the child was three years of age. Previous analyses documented that there were no intervention effects on growth and weight outcomes in either trial [15], and thus data from intervention and control groups across both studies were pooled and utilized in the present analyses.

Assessment of child anthropometrics

In both studies, children's height/length and weight were reported by parents at birth and were measured by trained staff at four time points when children's mean age was approximately 3 (T1), 9 (T2), 18 (T3), and 36 (InFANT Extend) or 42 (InFANT) months (T4). Height/length was measured to the nearest 0.1 cm using a calibrated measuring mat or portable stadiometer and weight (in light clothes) was measured to the nearest 10 grams using calibrated infant digital scales [12, 14]. Both height/length and weight were measured twice, and the average was used for analysis. Height/length-for-age z-score (HAZ), weight-for-age z-score (WAZ) and BMI-for-age z-score (BAZ) were computed using World Health Organization (WHO) gender-specific growth standards [16]. BAZ and HAZ were used to describe growth in the current cohort. Although WHO recommends the weight-for-height z-scores (WHZ) to classify overweight and obesity in young children [16], BAZ was chosen over WHZ to allow better comparison with research studies that mostly report on BAZ and also enables tracking of growth beyond the age of 5 years. Evidence has also shown high agreement of BAZ and WHZ in growth monitoring in young children [17].

Early postnatal rapid growth

Early postnatal rapid growth was defined as an increase in WAZ>0.67 between birth and 3 months; this is clinically equivalent to crossing the centile lines in a growth chart and is a widely accepted definition of rapid growth [5].

Maternal factors

Data on maternal country of birth, education level, height, pre-pregnancy weight, and gestational age were assessed using a self-administered questionnaire completed at baseline. Country of birth was classified as Australia or Not Australia. Maternal education level was classified as either high (university degree and higher) or low (certificate/diploma/apprenticeship/high school). Maternal pre-pregnancy body mass index (BMI) (kg/m^2) was calculated using self-reported weight and height, and categorized into healthy-weight ($<25kg/m^2$), and overweight/obese ($\geq 25kg/m^2$). Maternal height (average ±SD 164.5 ± 7.0 cm) was classified into short (height ≤ average) or tall (height >average). Gestational age was reported in weeks.

Statistical analysis

Descriptive analyses of child and maternal characteristics by study cohort were performed and independent t-tests or Pearson's Chi-squared tests were used to compare characteristics by study cohort. Mixed effect polynomial regression models (also known as multilevel growth curve models) with both fixed and random effects, were used to construct the longitudinal growth trajectories of BAZ and HAZ from 3 to 42 months [18, 19]. This method has been widely used to elucidate longitudinal child growth trajectories [19], allowing modelling of nonlinear growth trajectories and assessment of determinants. It mitigates within-subject correlations and unequal variances over time through use of the covariance structure. Furthermore, it permits modeling of growth using unbalanced longitudinal data and does not exclude participants with missing measurements. Inclusion of random intercepts and slopes allows individual variations in growth trajectory. The basic model included repeated measures of BAZ and HAZ as the dependent variable; age and age^2 as fixed effects; age and parent groups as random effects with an unstructured covariance structure. The random effects take account of the cluster-based nature of the sample and the correlation between individual repeated measures. The estimate of age represents rate of growth (increase $+\beta$ or decrease $-\beta$) and estimate of age^2 represents acceleration ($+\beta$) or deceleration ($-\beta$) of growth, which determines the curvilinear shape of the growth trajectory. Parameters in the model were estimated through restricted maximum likelihood methods. To explore if growth trajectories differed for early postnatal rapid growth and maternal factors (country of birth, education, and pre-pregnancy BMI), these variables were included in the model as fixed effects. Interactions of individual factors with age and age^2 were also included in the model to allow rate of change in BAZ/HAZ to vary by these factors. Only interactions associated with BAZ or HAZ with $P<0.05$ were retained in the model. Multivariable analyses including all individual factors simultaneously in the same model with adjustment for child sex, intervention group, study cohort, gestational age, and BAZ or HAZ at birth were conducted to assess respective effects on outcomes. Multicollinearity of all independent variables was assessed and no variables were highly correlated[20], therefore, all variables were included in the same model. Interactions among predictor variables were performed to test potential synergistic effects, and no interaction effects were found. Average BAZ and HAZ trajectories by child or maternal factors were plotted by predicted means at each time point, and the difference in predicted means were tested using analysis of variance models specifying a Bonferroni correction for multiple comparison. Stratified analysis by intervention group was also conducted, the effect of rapid growth and maternal factors on growth trajectories did not differ (Supplementary Table 3). All analyses were conducted using Stata 15.0 [21].

Sensitivity analysis

To account for missing data, we conducted a sensitivity analysis using multiple imputation (MI). The number of observations available in the mixed effects analysis was 3065 (for outcome and covariates). There are a number of MI approaches available and our preference was MI by chained equations (MICE) due to its flexibly in determining imputation models [22, 23]. The chained equation approach used separate conditional univariate imputation models specified for each variable with missing data (i.e. logistic regressions for binary variables and linear regressions for continuous variables) [24]. Multiple imputation using chained equations with 50 imputations and 10 burn-in iterations were fit simultaneously for both outcomes as well as covariates considered in the mixed models.

Results

Sample characteristics

Of 1056 children, a total of 977 children (93% of total sample) with complete anthropometric measures at ≥2 time points from birth to 36/42 months were included in the longitudinal analyses. Children with anthropometric measures < 2 time points contribute no information about change in BAZ/HAZ, and were thus excluded from analysis. A further 68 children was excluded due to missing data on child or maternal factors, resulting a final sample of 909 children being included in the multivariable analysis (Figure 1). Comparison of children who were included and excluded from analyses indicated no difference in any of the variables (Supplementary Table 1). Descriptive statistics for child and maternal characteristics, number of children at each follow-up, and outcome measurements at each time point by study cohort are shown in Table 1. There were no differences on percentage of children who experienced rapid growth from birth to three months, maternal country of birth, pre-pregnancy BMI, or education level between the two cohorts. Compared with the InFANT Extend cohort, the InFANT cohort included more tall mothers and gestational age was lower.

Determinants of BAZ trajectories

With adjustment for all covariates, results from the multivariable mixed effects models showed that early postnatal rapid growth from birth to 3 months, maternal country of birth and pre-pregnancy BMI, but not maternal education, were independently associated with BAZ trajectory from 3 to 42 months (Table 2). Average BAZ trajectory had a sharp increase from 3 to 18 months followed by a plateau from 18 to 42 months (Figure 1). The BAZ trajectory curve differed by early postnatal rapid growth and country of birth as indicated by significant age and age^2 interactions (Table 2). Children with rapid growth in general had greater BAZ than children without rapid growth (Figure 2). The mean difference in average BAZ from 3 to 42 months was 0.61 (95% CI 0.56, 0.66). Children of Australian born mothers (black lines) also had higher average BAZ than did children of not Australian born mothers (grey lines) (mean difference 0.15 95% CI 0.10, 0.20). BAZ of children whose mothers were overweight/obese pre-pregnancy was also higher than children of healthy-weight mothers (round versus triangle markers, mean difference 0.23 95% CI 0.19, 0.29). Moreover, children with rapid growth, whose mothers were Australian born and overweight/obese pre-pregnancy had the highest BAZ from age 3 to 42 months; whereas, children without rapid growth, whose mothers were not Australian born and healthy-weight pre-pregnancy had the lowest BAZ (Figure 2). The mean difference of average BAZ between these two groups was 1.07 (95% CI 0.97, 1.18).

Determinants of HAZ trajectories

Results of multivariable mixed models for HAZ demonstrated that early postnatal rapid growth from birth to 3 months, maternal country of birth and height, but not maternal education, were associated with HAZ trajectory from 3 to 42 months (Table 2). The HAZ trajectory curve differed by rapid growth and maternal country of birth as indicated by significant age and age^2 interactions ($P < 0.001$). From 3 to 18 months, HAZ of children with rapid growth increased or remained stable, but all children without rapid growth had a sharp decrease in HAZ (Figure 3). This was followed by a slight increase or plateau from 18 to 42 months in all children. The average HAZ at 3 months of children with rapid growth was 0.48 (95% CI -0.67, -0.29) smaller than children without rapid growth, but no difference was found in average HAZ from 9 to 42 months between the two groups. Despite the slopes of HAZ trajectory curve differing by maternal country of birth (black versus grey lines, Figure 3), the average HAZ from 3 to 42 months was not different at all ages (data not shown). Children whose mothers were tall (round markers) were in general taller than children of short mothers (triangle markers) at all ages from 3 to 42 months (mean difference: 0.46 95% CI 0.39, 0.52). At 42 months, children with rapid growth and whose mothers were Australian born and tall had the highest HAZ, whereas, children with rapid growth whose mothers were not Australian born and short had the lowest HAZ (mean difference 0.75 95% CI 0.04 1.47). No difference was found between maternal pre-pregnancy BMI and HAZ trajectory (data not shown).

Comparisons of mixed effects models with multiple imputation models

Overall, analyses with the combined summary estimates from the multiple imputation revealed similar results to the primary mixed models (Supplementary Tables 3). Wider 95% confidence intervals were observed for some estimates. This was expected since the multiple imputation process is designed to build additional uncertainty into the parameter (β) estimates [22, 25].

Comment

Principle findings

In two cohorts of Australian children, the present study found early postnatal rapid growth from birth to 3 months and maternal factors had independent effects on trajectories of both BAZ and HAZ in early childhood.

Strengths of the study

This study has a number of important strengths. Our study has a large sample size. The repeated measures of height and weight by trained staff enabled the use of mixed effect polynomial models to evaluate longitudinal trajectories of both BAZ and HAZ, and their determinants. Moreover, multiple imputation was used to address missing data. Our findings on relative effects of maternal factors and postnatal rapid growth on both BAZ and HAZ trajectories are novel and extend the current understanding of growth in early childhood.

Limitations of the data

Our study also has several limitations. While the cohort included mothers and children across the socioeconomic spectrum, highly educated mothers were overly represented and clearly this may have implications for generalizability. We were unable to examine the influence of specific maternal country of birth other than Australia on growth due to the large number of international countries reported and limited number of participants from each country. Despite the inclusion of many known covariates, unmeasured variables and residual confounding may limit our findings. Maternal anthropometrics were self-reported after birth, thus recall bias and potential misreporting cannot be ruled out. Evidence has shown that females tend to underreport their body weight [26], thus bias the association towards null, but we were still able to find a differential effect for maternal pre-pregnancy BMI on child BAZ trajectory. We studied the early determinants of child growth and obesity, other predictors of growth and obesity such as infant feeding patterns, dietary intake and physical activity were not examined in the present study.

Interpretation

Our findings suggest children demonstrating postnatal rapid growth as early as by 3 months of age had higher BAZ after controlling for BAZ at birth and gestational age. Consistent with our findings, two German studies in term children with an appropriate-for-gestational age birth weight have reported that rapid growth from birth to 2 years predicted higher subsequent BAZ and fat mass to age 6 [27] and 7 year [28], respectively, after adjusting for BAZ at birth. The proposed mechanisms by which postnatal rapid growth programs later obesity remains unclear. It is hypothesized that rapid growth is more likely to occur among children with in-utero growth restriction. However, in line with our findings, numerous studies report the association between rapid growth and later obesity occurs independent of birth weight and is evident among children without in-utero growth restriction [5, 27, 28].

We also found that having a mother born in Australia and/or one who was overweight/obese pre-pregnancy increased the susceptibility of children with rapid growth to higher BAZ. A small number of studies have utilized a longitudinal approach to examine the relative effects of postnatal rapid growth and maternal factors on child growth [27]. Findings from a cohort of German children (n=370) demonstrated that postnatal rapid growth along with maternal overweight predicted greatest change in fat mass from ages 2 to 6 years [27]. Other studies have examined the effects of maternal BMI alone or with other maternal factors on BMI trajectories[29]. In a cohort of European children, maternal BMI was found to be a strong determinant of offspring BAZ from age two to three years [30]. A large US study (n = 10700) found maternal overweight/obesity along with diabetes and excessive gestational weight gain were associated with the highest BAZ from 9 to 48 months [31]. The influence of maternal BMI on child BAZ is likely attributable to complex interactions of genetics and metabolic pathways. Overweight/obese mothers may have a higher risk of metabolic dysfunction that may impact on both fetal and postnatal child growth potentially through effects of higher circulating insulin [9] Additionally, overweight/obese mothers may be more likely to have obesity promoting dietary and lifestyle habits that may influence their children lifestyle behaviours and in turn weight trajectories across early life. Evidence suggests that overweight/obese mothers are prone to overfeeding practices [32].

To date few studies have evaluated the factors associated with early childhood height trajectories. In the current study, we found early postnatal rapid growth, maternal country of birth, and maternal height were determinants of HAZ trajectories from 3 to 42months. While one previous study reported that HAZ trajectory did not differ substantially by maternal overweight/obesity, diabetes, or excessive gestational weight gain among a US cohort [31], there have been no studies reporting the longitudinal effect of early postnatal rapid growth on height trajectory in early childhood. Our finding that children with rapid growth showed an increase in HAZ growth after the period of rapid growth is likely a result of higher insulin-like growth factors-1[33]. It has to be noted that despite the initial increase in HAZ growth among children with rapid growth, their average HAZ from 9 to 42 months remained similar to those who did not show rapid growth. However, children with rapid growth had higher average BAZ than children without rapid growth at all ages from 3 to 42 months, highlighting that children with rapid growth may at higher risk of developing future obesity. Faster HAZ growth may not necessarily offset future obesity risk, but it may be a precursor to earlier puberty[34]. With respect to maternal country of birth and height, it is plausible that they determine height growth through genetics and/or the cultural difference in dietary and lifestyle pattern.

There is a scarcity of research regarding associations between maternal education or socioeconomic position and children's growth trajectories [35]. The null finding for maternal education and growth trajectories in our study is not unexpected. Given postnatal rapid growth and pre-pregnancy BMI are possible underlying mediators of the association between maternal education and BAZ, the adjustment for these factors could potentially attenuate any direct association. Indeed, in univariable analysis without adjusting for postnatal rapid growth and other maternal factors, low maternal education was associated with higher BAZ (β=0.11, P=0.04). Similar findings were also documented in a Dutch cohort showing that low maternal education was associated with child weight-for-length gain, but the association attenuated after adjusting for other maternal factors [36]. In contrast, an Australian study demonstrated differential effects of socioeconomic status on BMI trajectory among Aboriginal boys (mean age: 11 year olds) with 8 years follow-up [37]. It has to be noted that that study only adjusted for recruitment phase, birth weight and Aboriginal status.

Our study findings have important public health implications. Children with early rapid growth, and whose mothers were both Australian-born and overweight/obese pre-pregnancy demonstrated the highest BAZ trajectory, but the average BAZ at 42 months was below 2 z-scores (the WHO cut-off for overweight/obesity).[16] It would be desirable to monitor the growth of these children into later childhood to test the latent effects of these early determinants. We cannot modify maternal country of birth. However, early postnatal rapid growth and maternal pre-pregnancy overweight/obesity, as independent modifiable determinants of child BAZ, provide important targets for early childhood obesity prevention. Public health campaigns should focus on prevention of rapid growth in infancy and support mothers to achieve a healthy body weight. This may be particularly important in the pre-conception and pregnancy period. Future obesity prevention interventions should target children with rapid growth during infancy and children of mothers who were overweight/obese pre-pregnancy as at highest risk.

Conclusions

In conclusion, the present study showed early postnatal rapid growth, maternal country of birth, maternal pre-pregnancy BMI or height are each associated with growth trajectories in early childhood. Children who experienced early rapid growth, those whose mothers were Australian born, and those whose mothers were overweight/obese pre-pregnancy had higher BAZ in early childhood. The findings underscore the importance of targeting these children for obesity prevention.

Acknowledgements

We would like to acknowledge all parents and children who participated in the Melbourne Infant Feeding Activity and Nutrition Trial (InFANT) Program and the InFANT Extend Program.

Conflict of interests

MZ is funded by NHMRC Early Career Fellowship. KDH is supported by an Australian Research Council Future Fellowship and an Honorary National Heart Foundation of Australia Future Leader Fellowship. All authors declare no conflict of interest.

References

1. Chrestani MA, Santos IS, Horta BL, Dumith SC, de Oliveira Dode MA. Associated factors for accelerated growth in childhood: a systematic review. *Matern Child Health J*. 2013; 17:512-519.

2. Hill JO, Melanson EL. Overview of the determinants of overweight and obesity: current evidence and research issues. *Med Sci Sports Exerc*. 1999; 31:S515-521.

3. Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk Factors for Childhood Obesity in the First 1,000 Days: A Systematic Review. *Am J Prev Med*. 2016; 50:761-779.

4. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life--a systematic review. *Obes Rev*. 2005; 6:143-154.

5. Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr*. 2006; 95:904-908.

6. Zheng M, Lamb KE, Grimes C, Laws R, Bolton K, Ong KK, et al. Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. *Obes Rev*. 2018; 19:321-332.

7. Williams CB, Mackenzie KC, Gahagan S. The effect of maternal obesity on the offspring. *Clin Obstet Gynecol*. 2014; 57:508-515.

8. Stettler N, Iotova V. Early growth patterns and long-term obesity risk. *Curr Opin Clin Nutr Metab Care*. 2010; 13:294-299.

9. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis.

PLoS One. 2013; 8:e61627.

10. Newton S, Braithwaite D, Akinyemiju TF. Socio-economic status over the life course and obesity: Systematic review and meta-analysis. *PLoS One*. 2017; 12:e0177151.

11. Russell CG, Russell A. Biological and Psychosocial Processes in the Development of Children's Appetitive Traits: Insights from Developmental Theory and Research. *Nutrients*. 2018; 10.

12. Campbell K, Hesketh K, Crawford D, Salmon J, Ball K, McCallum Z. The Infant Feeding Activity and Nutrition Trial (INFANT) an early intervention to prevent childhood obesity: cluster-randomised controlled trial. *BMC Public Health*. 2008; 8:103.

13. Hesketh KD, Campbell K, Salmon J, McNaughton SA, McCallum Z, Cameron A, et al. The Melbourne Infant Feeding, Activity and Nutrition Trial (InFANT) Program follow-up. *Contemp Clin Trials*. 2013; 34:145-151.

14. Campbell KJ, Hesketh KD, McNaughton SA, Ball K, McCallum Z, Lynch J, et al. The extended Infant Feeding, Activity and Nutrition Trial (InFANT Extend) Program: a cluster-randomized controlled trial of an early intervention to prevent childhood obesity. *BMC Public Health*. 2016; 16:166.

15. Campbell KJ, Lioret S, McNaughton SA, Crawford DA, Salmon J, Ball K, et al. A parent-focused intervention to reduce infant obesity risk behaviors: a randomized trial. *Pediatrics*. 2013; 131:652-660.

16. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. . Geneva: World Health Organization; 2006.

17. Furlong KR, Anderson LN, Kang H, Lebovic G, Parkin PC, Maguire JL, et al. BMI-for-Age and Weight-for-Length in Children 0 to 2 Years. *Pediatrics*. 2016; 138.

18. Tilling K, Macdonald-Wallis C, Lawlor DA, Hughes RA, Howe LD. Modelling childhood growth using fractional polynomials and linear splines. *Ann Nutr Metab*. 2014; 65:129-138.

19. Johnson W, Balakrishna N, Griffiths PL. Modeling physical growth using mixed effects models. *Am J Phys Anthropol*. 2013; 150:58-67.

20. Katz M. *Multivariable Analysis: A practical guide for clinicians.* New York: Cambridge University Press; 1999.

21. StataCorp. *Stata Statistical Software: Release 14*. College Station: TX: StataCorp LLC 2015.

22. Hayati Rezvan P, Lee KJ, Simpson JA. The rise of multiple imputation: a review of the reporting and implementation of the method in medical research. *BMC Med Res Methodol*. 2015; 15:30.

23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011; 30:377-399.

24. Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. *Am J Epidemiol*. 2010; 171:624-632.

25. Little R, Rubin D. *Statistical analysis with missing data*. Second Edition ed.: John Wiley & Sons, Inc. ; 2002.

26. Villanueva EV. The validity of self-reported weight in US adults: a population based cross-sectional study. *BMC Public Health*. 2001; 1:11.

27. Karaolis-Danckert N, Buyken AE, Kulig M, Kroke A, Forster J, Kamin W, et al. How pre-

and postnatal risk factors modify the effect of rapid weight gain in infancy and early childhood on subsequent fat mass development: results from the Multicenter Allergy Study 90. *Am J Clin Nutr*. 2008; 87:1356-1364.

28. Karaolis-Danckert N, Buyken AE, Bolzenius K, Perim de Faria C, Lentze MJ, Kroke A. Rapid growth among term children whose birth weight was appropriate for gestational age has a longer lasting effect on body fat percentage than on body mass index. *Am J Clin Nutr*. 2006; 84:1449-1455.

29. Pryor LE, Tremblay RE, Boivin M, Touchette E, Dubois L, Genolini C, et al. Developmental trajectories of body mass index in early childhood and their risk factors: an 8-year longitudinal study. *Arch Pediatr Adolesc Med*. 2011; 165:906-912.

30. Linabery AM, Nahhas RW, Johnson W, Choh AC, Towne B, Odegaard AO, et al. Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels Longitudinal Study. *Pediatr Obes*. 2013; 8:159-169.

31. Xie C, Wang Y, Li X, Wen X. Childhood Growth Trajectories of Etiological Subgroups of Large for Gestational Age Newborns. *J Pediatr*. 2016; 170:60-66 e61-65.

32. Imdad A, Yakoob MY, Bhutta ZA. Impact of maternal education about complementary feeding and provision of complementary foods on child growth in developing countries. *BMC Public Health*. 2011; 11 Suppl 3:S25.

33. Sharma D, Shastri S, Sharma P. Intrauterine Growth Restriction: Antenatal and Postnatal Aspects. *Clin Med Insights Pediatr*. 2016; 10:67-83.

34. Ibanez L, Ferrer A, Marcos MV, Hierro FR, de Zegher F. Early puberty: rapid progression and reduced final height in girls with low birth weight. *Pediatrics*. 2000; 106:E72.

35. Howe LD, Tilling K, Galobardes B, Smith GD, Gunnell D, Lawlor DA. Socioeconomic differences in childhood growth trajectories: at what age do height inequalities emerge? *J Epidemiol Community Health*. 2012; 66:143-148.

36. Van Den Berg G, Van Eijsden M, Galindo-Garre F, Vrijkotte T, Gemke R. Low maternal education is associated with increased growth velocity in the first year of life and in early childhood: the ABCD study. *Eur J Pediatr*. 2013; 172:1451-1457.

37. Kim S, Macaskill P, Baur LA, Hodson EM, Daylight J, Williams R, et al. The differential effect of socio-economic status, birth weight and gender on body mass index in Australian Aboriginal Children. *Int J Obes (Lond)*. 2016; 40:1089-1095.

Table 1. Summary of maternal and child characteristics by study cohorts

Characteristics	InFANT	InFANT Extend
Total sample (n)	527	450
Intervention (%)	49.9	52.4
Maternal characteristics		
Country of birth		
Australian born (%)	78.9	75.8
Overseas born (%)	20.9	23.1
Missing (%)	0.2	1.1
Education		
Low (%)	45.9	41.3
High (%)	54.1	57.3
Missing (%)	0.0	1.3
Pre-pregnancy BMI		
Healthy weight (% ≤25kg/m^2)	63.8	58.5
Overweight/Obese (% >25kg/m^2)	35.3	35.1
Missing (%)	0.9	6.4
Height		
Short (%≤ average)	46.1	51.1
Tall (%> average)	53.7	43.3
Missing (%)	0.2	5.6
Gestational age (weeks)	38.8(2.4)	39.1(1.9)
Child characteristics		
Boys (%)	53.1	53.8
Birth weight (kg)	3.4(0.6)	3.4(0.6)
Birth height (cm)	50.0(2.7)	50.3(2.6)
Rapid weight gain from birth to 3 months		
Rapid weight gain (%)	14.4	13.8
Number of children at each follow-up		
T1 (3 months)	527	450
T2 (9months)	518	386
T3 (18months)	469	356
T4 (36/42months)	361	344
Number of BAZ/HAZ measurement		
2	9	41
3	37	39
4	144	103
5	337	267

**Maternal height average: 164.5cm*

Table 2 Mixed effect polynomial model between association of early postnatal rapid growth, maternal factors, and trajectories of body mass index for age z-score (BAZ) and height for age z-score (HAZ) from ages 3 to 42 months (n=3065 observations).

	BAZ	HAZ
	β(95%CI)	β(95%CI)
Age	0.15(0.13,0.16)	-0.07(-0.08,-0.05)
Age^2	-0.002(-0.003,-0.002)	0.001(0.001,0.002)
Maternal education (low)	0.03(-0.07,0.13)	0.09(-0.02,0.19)
Maternal pre-pregnancy OW/OB	0.17(0.07,0.28)	-
Maternal height (>average)	-	0.34(0.23,0.44)
Maternal country of birth (Australia)	-0.05(-0.23,0.12)	-0.23(-0.41,-0.05)
Maternal country of birth (Australia) x Age	0.02(0.004,0.04)	0.03(0.01,0.05)
Maternal country of birth (Australia) x Age^2	-0.0004(-0.001,-0.00002)	-0.001(-0.001,-0.0002)
Rapid growth	1.53(1.31,1.75)	-0.01(-0.24,0.21)
Rapid growth x Age	-0.07(-0.09,-0.05)	0.07(0.05,0.09)
Rapid growth x Age^2	0.001(0.001,0.002)	-0.001(-0.002,-0.001)
Constant	-0.62(-1.74,0.51)	-0.07(-1.18,1.32)

OW/OB (overweight/obese): body mass index >25kg/m^2; Maternal height average: 164.5cm. The reference categories are maternal high education, maternal healthy weight, maternal height ≤ average, maternal not Australian born, and children without rapid growth. All variables were included in the same model as fixed effects and the model adjusted for child sex, intervention group, study cohorts, gestational age, and BAZ or HAZ at birth and included parent group and age as random effects. The β of age represents rate of growth (increase +β, decrease -β) and β of age^2 represents acceleration (+β) or deceleration (-β) of growth, which determines the curvilinear shape of the growth trajectory. Interaction terms with age and age^2 allows rate of change in BAZ to vary this factor. Maternal education and OW/OB or height with age and age^2 interactions were not associated with the outcome, thus excluded from the model

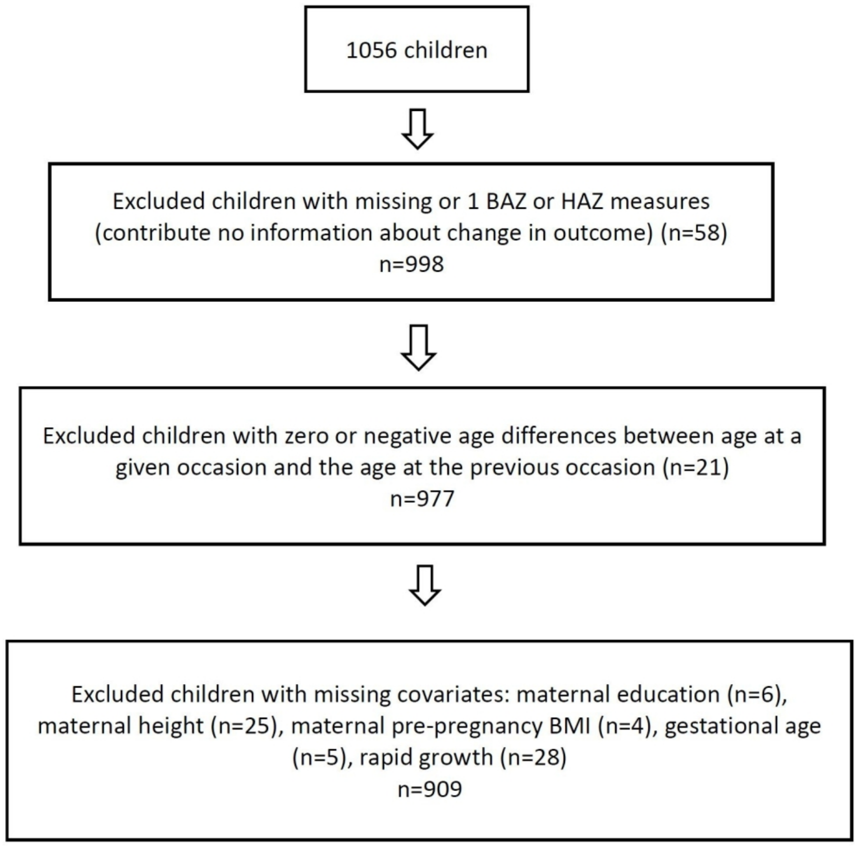

Figure 1 Flow chart showing the number participants included in the final analysis.

205x174mm (216 x 216 DPI)

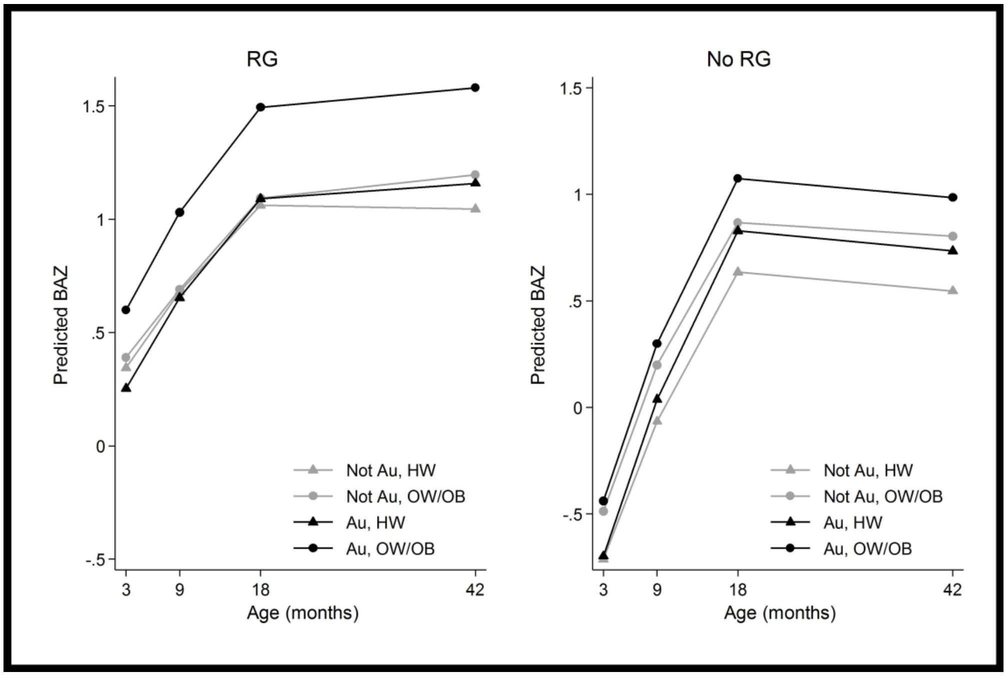

Figure 2 Predicted mean body mass index for age z-score (BAZ) trajectory from 3 to 42 months by maternal country of birth (Au: Australia, Not Au: Not Australia), maternal pre-pregnancy BMI (HW: healthy weight; OW/OB: overweight/obesity), RG (rapid growth) from multivariable mixed effect polynomial model with adjustment for child sex, intervention group, study cohorts, gestational age and BAZ at birth.

430x288mm (216 x 216 DPI)

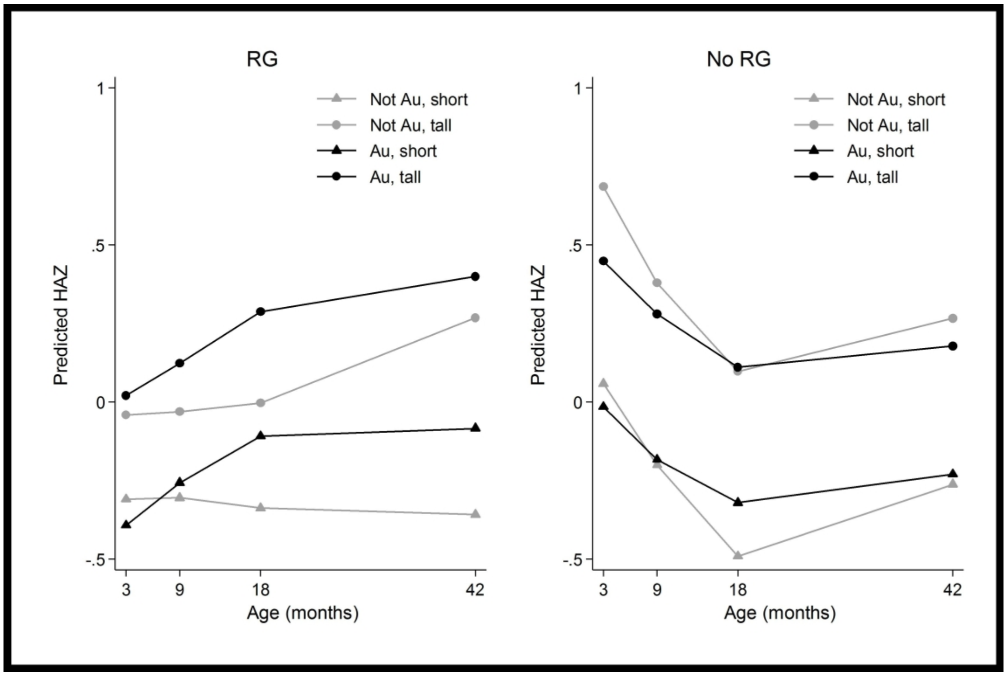

Figure 3 Predicted mean height for age z-score (HAZ) trajectory from 3 to 42 months by maternal country of birth (Au: Australia, Not Au: Not Australia), maternal height (Short ≤ average height 164.5cm; Tall >average height 164.5cm), RG (rapid growth) from multivariable mixed effect polynomial model with adjustment for child sex, intervention group, study cohorts, gestational age and HAZ at birth.

430x288mm (216 x 216 DPI)

Supplementary Table 1. Comparison of excluded vs included in the analysis*

Characteristics	Included	Excluded
Intervention (%)	51.1	46.2
Maternal characteristics		
Country of birth		
Australian born (%)	78.22	72.92
Overseas born (%)	21.8	27.1
Education		
Low (%)	43.8	48.4
High (%)	56.2	51.6
Pre-pregnancy BMI		
Healthy weight (% ≤25kg/m^2)	63.2	74.6
Overweight/Obese (% >25kg/m^2)	36.8	25.4
Height		
Short (%≤ average)	49.3	57.0
Tall (%> average)	50.7	43.0
Gestational age (weeks)	38.9 (2.1)	38.7 (3.0)
Child characteristics		
Boys (%)	53.0	47.8
Birth weight (kg)	3.4(0.6)	3.3(0.5)
Birth height (cm)	50.1(2.7)	50.1(25)
Rapid weight gain from birth to 3 months		
Rapid weight gain (%)	15.0	11.5

*n ranged from 63 to 147 for those excluded from the analysis.

*n =909 for those included in the analysis

Supplementary Table 2 Sensitivity analysis of mixed effect polynomial model between association of early postnatal rapid growth, maternal factors, and body mass index for age z-score (BAZ) trajectories from ages 3 to 42 months using multiple imputation with 50 imputations (n=3912 observations).

	BAZ	HAZ
	β(95%CI)	β(95%CI)
Age	0.15(0.13,0.16)	-0.07(-0.08,-0.05)
Age^2	-0.003(-0.003,-0.002)	0.001(0.001,0.002)
Maternal education (low)	0.03(-0.07,0.13)	0.08(-0.02,0.18)
Maternal pre-pregnancy OW/OB	0.2(0.09,0.30)	-
Maternal height (>average)	-	0.39(0.29,0.50)
Maternal country of birth (Australia)	-0.03(-0.19,0.14)	-0.27(-0.44,-0.10)
Maternal country of birth (Australia) x Age	0.02(0.003,0.04)	0.03(0.01,0.04)
Maternal country of birth (Australia) x Age^2	-0.0004(-0.001,-0.00002)	-0.001(-0.001,-0.0002)
Rapid growth	1.48(1.27,1.70)	-0.02(-0.24,0.21)
Rapid growth x Age	-0.07(-0.09,-0.05)	0.06(0.04,0.08)
Rapid growth x Age^2	0.001(0.001,0.002)	-0.001(-0.002,-0.001)
Constant	-0.79(-1.84,0.27)	-0.19(-1.42,1.04)

OW/OB (overweight/obese): body mass index >25kg/m^2; Maternal height average: 164.5cm. The reference categories are maternal high education, maternal healthy weight, maternal height ≤ average, maternal not Australian born, and children without rapid growth. All variables were included in the same model as fixed effects and the model adjusted for child sex, intervention group, study cohorts, gestational age, and BAZ or HAZ at birth and included parent group and age as random effects. Maternal education and OW/OB or height with age and age^2 interactions were not associated with the outcome, thus excluded from the model.

Supplementary Table 3: Mixed effect polynomial model between associations of early postnatal rapid growth, maternal factors, and trajectories of body mass index for age z-score (BAZ) and height for age z-score (HAZ) from ages 3 to 42 months by intervention group.

	BAZ		HAZ	
	Control β(95%CI)	Intervention β(95%CI)	Control β(95%CI)	Intervention β(95%CI)
Age	0.16(0.13,0.18)	0.14(0.12,0.16)	-0.07(-0.09,-0.05)	-0.06(-0.08,-0.04)
Age^2	-0.003(-0.003,-0.002)	-0.002(-0.003,-0.002)	0.001(0.001,0.002)	0.001(0.001,0.002)
Maternal education (low)	0.02(-0.02,0.27)	0.05(-0.18,0.09)	0.07(-0.09,0.23)	0.08(-0.07,0.23)
Maternal pre-pregnancy OW/OB	0.19(0.04,0.34)	0.18(0.04,0.33)	-	-
Maternal height (>average)	-	-	0.4(0.24,0.55)	0.3(0.15,0.45)
Maternal Australia born	-0.06(-0.21,0.31)	-0.05(-0.40,0.10)	-0.34(-0.6,-0.07)	-0.14(-0.39,0.11)
Maternal Australia born x Age	0.01(-0.02,0.04)	0.03(0.01,0.06)	0.03(0.01,0.06)	0.02(-0.0003,0.05)
Maternal Australia born x Age^2	-0.0002(-0.0007,0.0004)	-0.0006(-0.0011,-0.0001)	-0.001(-0.001,-0.0001)	-0.0005(-0.001,0.00005)
Rapid growth	1.63(1.27,2)	1.44(1.15,1.73)	-0.07(-0.44,0.29)	-0.01(-0.3,0.29)
Rapid growth x Age	-0.06(-0.1,-0.02)	-0.07(-0.1,-0.05)	0.06(0.02,0.09)	0.07(0.05,0.1)
Rapid growth x Age^2	0.001(0.0003,0.002)	0.001(0.001,0.002)	-0.001(-0.002,-0.0002)	-0.001(-0.002,-0.001)

OW/OB (overweight/obese): body mass index >25kg/m2; Maternal height average: 164.5cm. The reference categories are maternal high education, maternal healthy weight, maternal height ≤ average, maternal not Australian born, and children without rapid growth. All variables were included in the same model as fixed effects and the model adjusted for child sex, intervention group, study cohorts, gestational age, and BAZ or HAZ at birth and included parent group and age as random effects.