Title Page

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Title: Longitudinal Growth and Undernutrition Burden among Term Low Birth Weight Newborns reared in adverse socio-economic conditions in Delhi, India

Running Title: Term LBW growth in urban poor

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Author contributions

The DIVIDS Cohort study was designed and initiated by GTK (Principal Investigator), HSS and SF, and was supervised by GTK. HSS conceptualized the research question in this manuscript. MK was involved in data collection. SS did the primary analyses and interpretation under the supervision of CO and HSS. MK and HSS drafted the initial manuscript. All authors provided critical inputs into revision of the article and approved the finalized draft. and are willing to be accountable for all aspects of the study.

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Competing interest: None for all authors.

Ethical considerations: The DIVIDS-1 study was approved by the ethical committees of Institute of Home Economics (University of Delhi), Safdarjung Hospital, Sitaram Bhartia Institute of Science and Research, and the London School of Hygiene and Tropical Medicine. The DIVIDS-2 study was approved by the ethical committees of Institute of Home Economics (University of Delhi), Sitaram Bhartia Institute of Science and Research, and the London School of Hygiene and Tropical Medicine. Parents provided written or thumbprint informed consent for their child's participation. Children were seen by a medical doctor and provided with treatments or referrals as required. Names and addresses were removed from datasets prior to analysis. Authors declare that the study procedures conform to the principles laid down in the Declaration of Helsinki.

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Abstract

Background: There is limited data in term Low Birth Weight (LBW) from urban poor settings on the incidence of and recovery from undernutrition and co-existence of its different forms, under conditions of appropriate health and nutrition care counselling.

Aim: Determine the longitudinal growth and undernutrition burden among term LBW newborns reared in adverse socio-economic conditions, but with appropriate counselling in Delhi, India.

Methods: 2079 term LBW (1800-2499 grams) newborns from an urban poor setting were followed-up for growth from 0 to 26 weeks (n=1282) and at 2.8-6.8 years (n=912). Using Cole's LMS approach, age- and sex-specific internal Z-scores were computed and subsequently adjusted for the effect of a vitamin D intervention and potential bias due to attrition. Back-transformed measurements were then used to compute WHO Z-scores for height-for-age (HAZ), weight-for-age (WAZ), and BMI-for-age (BMIZ).

Results: HAZ remained fairly stable: mean changes from birth till 6 weeks, 26 weeks and 3-7 years were 0.07, 0.04 and 0.2 SD, respectively. BMIZ and WAZ showed considerable catch-up; 0.69, 1.84 and 1.38 SD for BMIZ and 0.25, 0.89 and 0.60 SD for WAZ, respectively. Still, 60%-92% had at least one form of undernutrition and co-existence was frequent. Half the children remained stunted till 5 years while underweight and wasting declined considerably from 0-6 months.

Conclusion: With appropriate counselling of parents, term LBW infants reared under adverse socio-economic conditions show substantial catch-up growth in BMIZ and WAZ but not in HAZ. The long-term consequences of this excess weight over length gain, needs urgent evaluation.

Keywords: Catch-up growth, Low birth weight, Small for gestational age, Term, Undernutrition

Undernutrition is a major contributor to global disease burden in under five children, especially in low- and middle-income countries (LMICs). The burden is estimated to be highest in South-central Asia [1]. India has a particularly high burden as per the latest national estimates; 35.5%, 32.1% and 19.3% are stunted, underweight and wasted, respectively [2]. Several determinants contribute to childhood undernutrition. A conceptual framework categorizes these determinants into segments including political, socio-economic, and environmental conditions; access to and use of health services; infectious diseases; feeding and caregiving resources and practices; food security, breastfeeding, and nutrient-rich foods [1]. The individual contribution of these factors is debatable and probably varies across different time periods and settings.

Small for gestational age (SGA) or low birth weight (LBW; birth weight <2500g) are recognized as important predictors of undernutrition in LMICs [3,4]. Pooled data from 19 cohorts showed that term, SGA children were at increased risk of being stunted (1.7 to 2.1 times), wasted (1.4 to 2.6 times) and underweight (1.7 to 2.4 times) between 12-60 months of age [4]. India has one of the highest burdens of LBW infants (21.4% in 2017) [5]. The majority (77%-90%) of these LBW are full term but SGA [6,7]. In a national database, 18.2% of term births had weights between 1800 and 2499 grams [8]. It is, therefore conceivable that a substantial proportion of under-five undernutrition in India is attributable to these undersized newborns.

Reanalysis of the WHO Multi-Centre Growth Reference Study indicated that children born to short mothers can achieve near normal post-natal growth, if reared in favorable socio-economic conditions with adherence to internationally prescribed health and nutrition care recommendations [9]. Similarly, partial catch-up growth may be feasible with appropriate health and nutrition care under sub-optimal socio-economic conditions, even in SGA or term LBW babies. The first six months are particularly important because of increased vulnerability of rapid growth to nutritional and illness related insults and the potential for such anthropometric deficits to persist in childhood. A better understanding of this capability for catch-up growth and its facilitating factors will help optimize post-natal management in situations where women cannot be reached with appropriate interventions during pregnancy or where, even if they are reached, fail to benefit from the interventions.

A few studies on large LMICs cohorts of term LBW have evaluated the longitudinal growth and burden of undernutrition [10], but not for all three anthropometric classifications. Further, there is

 limited data in urban poor on the incidence of and recovery from undernutrition and co-existence of its different forms, when health and nutrition care counselling approximate international recommendations. We report on these aspects from a prospective cohort of term LBW infants at periodic intervals from birth to 6 months of age and once later during childhood (2.8 to 6.8 years). We have previously analysed the patterns of early growth in the same cohort and their influence on later anthropometry and bone density [11]; here we focus on how the children moved in and out of the conditions of stunting, wasting and underweight.

Methods

The Delhi Infant Vitamin D Supplementation Study (DIVIDS-1) was a double blinded, randomized controlled trial of weekly vitamin D3 supplementation among term LBW Indian infants from birth to 6 months of age [12]. The trial was registered at ClinicalTrials.gov (NCT00415402). The primary outcome was infants' morbidity or mortality, whereas growth and vitamin D status at 6 months were secondary outcomes. 2079 singleton term LBW (>37 weeks gestation; birth weight between 1800 and 2499 grams), aged less than 48 hours; and whose parents consented to participate and were living within 15 km radius of Safdarjung Hospital, New Delhi were enrolled between March 2007 and July 2010. Infants with any severe congenital abnormalities, acute severe morbidity, or intention to move outside the catchment area before 6 months of age were excluded. At recruitment, anthropometry of the infant and socio-demographic profile of the family were recorded. Recruited infants were randomized either to receive weekly vitamin D3 supplements (1400 IU or 35µg/week; n=1039) or identical looking and tasting placebo (n=1040) from first week till 6 months of age (maximum 25 doses) mixed in expressed breast milk. Anthropometric and clinical evaluation were performed at ages 6, 10, 14, 18, 22 and 26 weeks during scheduled visits to the hospital (n=1282) or at home for defaulters (n=207). During these visits, appropriate health care and nutrition counseling was done, primarily repeated advice on exclusive breastfeeding till 6 months age, complementary feeding, hygienic behavior, and ageappropriate immunizations. The parents were encouraged and facilitated to bring their infants to Safdarjung Hospital, whenever ill. Infants' anthropometry (in duplicate) was performed according to standard operating procedures [13]. Body weight was measured in minimal clothing, using an electronic weighing scale (sensitivity=0.01 kg). For measuring length, an infantometer was used

(sensitivity=0.1 cm). A total of 1489 infants (Vitamin D group n=744; Placebo n=745) completed 6 months supplementation (Figure 1).

We followed-up 912 participants from November 2012 to January 2014, between 2.8 and 6.8 years of age, during the DIVIDS-2 phase to investigate their anthropometry (in triplicate), bone and muscular strength, body composition and vitamin D status; these results are published elsewhere [11,14]. Weight was measured using digital scales (sensitivity=0.01 kg) and height using a wall mounted stadiometer (sensitivity=0.1 cm). Technical errors of measurements were within acceptable ranges [15].

Statistical Analysis

Data was double entered in Microsoft Access and converted to SPSS ver. 20 for statistical analysis. Data integrity and distributions were checked and appropriate transformations were done. Ageand sex-specific internal Z-scores were computed for serial anthropometric measurements (length and weight) by LMS Chartmaker Light (Ver. 2.54, Medical Research Council, UK) [16]. Age intervals at various time points were defined as follows: 6 weeks: 27 to 57 days; 10 weeks: 58 to 85 days; 14 weeks: 86 to 113 days; 18 weeks: 114 to 141 days; 22 weeks: 142 to 169 days and 26 weeks: 170 to 232 days. Mixed modeling was used to explore the interaction of intervention effect with age and sex. As the intervention and age interaction term was significant (p<0.005), average estimated effect sizes were subtracted from internal Z-scores for treatment group of respective age interval. These adjusted Z-scores were back-transformed to compute weight and length. This adjustment was unnecessary for DIVIDS-2 because an intervention effect was not evident. WHO length (or height)-for-age (HAZ), weight-for-age (WAZ), BMI-for-age (BMIZ) and weight-forlength (or height) (WHZ) Z-scores were computed through SPSS user written program till 5 years of age [17]. Similarly, WHO Z scores were computed for above 5 years of age except for weightfor-height for which no reference exists. We computed the prevalence of undernutrition (HAZ/WAZ/WHZ<-2 SD) and severe undernutrition (HAZ/WAZ/WHZ<-3SD) at each time point. We determined the incidence of undernutrition (for example, the proportion of children who were not stunted at an earlier time point but who were stunted later), as well as the incidence of recovery (the proportion of children who were stunted at an earlier time point but who were not stunted later). To estimate the likely bias in subjects' size due to loss to follow-up in a time interval, we adopted the approach detailed in Web Appendix 1.

These studies were approved by respective Institutional Ethics Committees for both phases and written informed consent was taken prior to recruitment.

Results

Pertinent information on population characteristics detailed earlier [12] is summarized below. The mean (SD) maternal age at delivery was 23.5 (3.4) years. The population was predominantly Hindu (88%), fairly poor, with low incomes and low education (51% fathers and 67% mothers only till middle school). The mothers were homemakers (97%) while fathers were employed (97%; only 1% as professionals). They were mostly residing in permanent ("pukka") dwellings (87%), in a joint or extended family system (55%), with substantial crowding (mean 6 family members). Only 39% had access to water supply through a private tap while just 13% households owned a flush latrine. Participants not followed-up at the end of both phases were significantly more likely to be from poorer, smaller, and nuclear families and have less educated fathers and mothers [12,14]. These children also had significantly lower WHO Z scores at earlier time points; 0.06 to 0.29 SD for HAZ, 0.01 to 0.3 SD for WAZ and 0.25 SD for BMIZ at only 6 weeks of age.

The incidence rates (per child year) during the first six months of follow-up were: death 0.046 (95% CI: 0.034 to 0.065) and any severe morbidity 0.44 (95% CI: 0.39 to 0.49) [12]. Breastfeeding was almost universal; the median durations of exclusive and predominant breastfeeding were 15 and 20 weeks, respectively. At 26 weeks of age, exclusive breastfeeding was reported by 27% and predominant breastfeeding by 35% mothers. Predominant breastfeeding was defined [12] if breastmilk was the predominant source of nourishment; however, the infant may have received limited quantities of liquids (water and water-based drinks, fruit, juice, oral rehydration solution), ritual fluids, and drops or syrups (vitamins, minerals, medicines). Nearly all (96%) infants were completely immunized for age as per government programme.

Boys were significantly heavier and taller than girls (Web Table I). In general, WHO Z scores were significantly different in boys till 26 weeks of age; 0.19 to 0.4 SD lower for HAZ, 0.1 to 0.36 SD lower for WAZ, and for WHZ 0.27 and 0.19 SD higher at 6 weeks and 10 weeks, respectively but 0.18 to 0.24 SD lower from 18 to 26 weeks.

Figure 2 and Web Table II compare the observed and bias (due to loss to follow-up) corrected WHO anthropometric Z scores for boys and girls combined. There was evidence of minimal bias;

in the worst-case scenario, the observed values were higher by 0 to 0.08 SD only. Among the anthropometric indices, HAZ was the most stable; bias corrected mean change from birth till 6 weeks, 26 weeks and later childhood was 0.07, 0.04 and 0.2 SD, respectively. However, both BMIZ and WAZ showed considerable increase in Z scores; the corresponding values were 0.69, 1.84 and 1.38 SD for BMIZ and 0.25, 0.89 and 0.60 SD for WAZ, respectively. For both these indices, the maximal catch-up had occurred at 26 weeks with some growth faltering thereafter (-0.46 SD for BMIZ and -0.29 SD for WAZ). Overall, BMIZ had a greater catch-up than WAZ (0.44 to 0.95 SD more). WHZ trajectory paralleled BMIZ but the catch-up was lower till 5 years (1.0 SD at 6 weeks, 0.25 SD at 26 weeks, and 0.19 SD later). The maximal transition in individual Z scores for all anthropometric indices occurred between birth and 6 weeks in comparison to any two other successive time points later. Pearson correlation coefficients between birth and 6 weeks were 0.628 for HAZ, 0.463 for WAZ, 0.321 for BMIZ and 0.355 for WHZ (P<0.001 for all).

Figure 3 depicts the overall and sex stratified prevalence of undernutrition (<-2 SD) for available participants. Stunting and underweight were more prevalent in boys while wasting was comparable in both sexes. The overall prevalence of stunting (~50%) remained unchanged from birth till 5 years. There was a progressive decline in prevalence of underweight (89% to 34%) and wasting (43% to 7%) from birth till 26 weeks; the decrease was most steep (~28%) from birth to 6 weeks. After this, the prevalence increased in later childhood; from 34% to 48% for underweight and 7% to 15% for wasting. Similar sex differences were evident for severe undernutrition (<-3 SD). Overall prevalence of severe stunting was relatively stable till 5 years (14% - 17%). Severe underweight progressively declined from 21% at 6 weeks to 8% at 26 weeks and increased to 12% in later childhood. Severe wasting (severe acute malnutrition) prevalence declined substantially from birth (9.4%) to 6 weeks (3.5%) and thereafter ranged between 2.3% and 0.8%.

Figure 4 illustrates sequential incidence and recovery rates from undernutrition. Both rates were equivalent for stunting till 5 years while recovery was greater than incidence for wasting and underweight throughout except in later childhood for underweight. Viewed from another perspective (Web Figure 1), from 6 weeks till 26 weeks, roughly a quarter of children each were either never or always stunted while half were either stunted or normal at different time points. The corresponding proportions for underweight were one-third never, one-fifth always and half sometimes, and for wasted were three-fourths never, 1% always and one-quarter sometimes. For

all three indices, in children not undernourished after 6 weeks, the maximal increase in mean Z scores had occurred between birth and 6 weeks.

The potential combinations of undernutrition (stunting, underweight and wasting) in an individual child are summarized in Table 1. A vast majority had at least one form of undernutrition; the proportion declined from 92% at birth to 67% at 14 weeks and stabilized around 60% thereafter. Three-fourths had co-existence of any two forms of undernutrition at birth; the proportion progressively declined to half at 6 weeks to a quarter at 26 weeks and again rose to 43% in later childhood. Stunting and underweight was the most common combination (24% to 49%), followed by underweight and wasting (41% at birth and 7% to 15% thereafter) whereas stunting and wasting was most infrequent (3% to 11%). Between 3% and 11% had all three forms of undernutrition.

Discussion

Term LBW newborns reared in an unfavorable socio-economic *milieu* exhibited considerable improvement in weight-for-age, BMI-for-age and weight-for-height, and a slight increase in height-for-age until 5 years of age. Still, 60%-92% had at least one form of anthropometric undernutrition and co-existence was frequent, with stunting and underweight being most common. One-half remained stunted till 5 years while underweight and wasting declined considerably from 0-6 months.

This cohort study from an urban poor setting in South Asia was conducted on a large sample size with a community follow-up, employing robust methodology and a strict quality control. It therefore provides confident programmatic expectations for subsequent growth and undernutrition burden among term LBW children living in adverse socio-economic conditions while their parents received intense counselling on health and nutrition care for the first 6 months. The relatively lower mortality and serious morbidity rates, almost universal immunization and good predominant or exclusive breastfeeding status till 6 months provide evidence of successful counseling and logistic support.

These catch-up growth patterns are contradictory to analyses from demographic surveys in 54 LMICs, wherein substantial faltering was observed for WAZ and HAZ (0.75Z and 1.5Z at 24 months) and slight decline for WHZ (\sim 0.25Z) till 9 months age [18]. The differences relate to the cross-sectional nature of demographic surveys in which small-, appropriate- and large-for-

gestational age participants are all included, thereby masking the heterogenous growth patterns. However, in conformity with the earlier reports [4,10], this study reaffirms that term LBW is an important predictor of undernutrition.

Studies from Europe and Americas have predominantly focused on height, employing heterogenous definitions of SGA and catch-up. Most term SGA births experienced catch-up growth to achieve a height >-2Z; this was typically an early (~80% by 6 months) postnatal process, which was usually completed by 2 years [19-22]. In case-control reports based on 10-85 SGA children only, at 1-3 years, the average catch-up in WAZ (0.3-2.2Z) and BMIZ (~2Z in one study) was greater than LAZ (0.15-1.1Z) [23-27]. The postulated reasons for the observed faster postnatal growth include regression to the mean, genetic factors [28], intrauterine restraint of fetal growth [29], and optimal health and nutrition care.

Paucity of comparable analyses from South Asia precludes robust external validation of disproportionately faster growth in weight and BMI in comparison to length, in similar adverse settings with appropriate counselling. A recent study, conducted in two Districts of Haryana, India reported only on linear growth trajectories till 6 months of age in a cohort (n=8360) of infants weighing 1500-2250 grams at birth of any gestational age [10]. The small for gestational age low birth weight (SGA-LBW) infants had lower average increase in HAZ (0.77Z) in comparison to those who were appropriate for gestational (AGA-LBW; 0.88Z). At 6 months of age, among the SGA-LBW, 55% (1908/3477) showed catch-up growth, defined as an increase of HAZ >0.67Z. The independent predictors of poor catch-up growth included poverty, home delivery, higher order birth (>4), boys, term gestation, non-exclusive breastfeeding at 3 months, and past episodes of pneumonia. A tertiary care center in Delhi, in a follow-up of 34 term LBW (1500-2500 grams) at 7.2 months mean age, also documented a disproportionately greater increase in WAZ (0.8Z) and WHZ (1.2Z) in comparison to HAZ (0.3Z) [30]. Similar findings were observed during the followup of 100 asymmetric SGA from upper socio-economic strata in Chandigarh at 6 months (WAZ 1.38, LAZ 0.52) and at one-year (WAZ 1.51, LAZ 0.24). However, the increase in these indices was lower and comparable in symmetric SGA at 6 months (WAZ 0.82, LAZ 0.76) and at one-year (WAZ 0.87, LAZ 0.85) [31]. The comparatively lower catch-up in length at 6 months age in our study could thus reflect poorer socio-economic status, higher birth weight (1800-2500 grams), term gestation and morbidity profile.

The following limitations merit consideration. First, after 6 months of age, there was no provision for logistic support, counseling (particularly for optimal complementary feeding) and periodic data collection on morbidity, immunization, and dietary intake. Nevertheless, the available growth data provide valuable insight into the residual effect of counseling in later childhood. Second, predictably there was substantial attrition with age in this setting (~38% at 6 months and ~56% later), predominantly due to outmigration. However, we adjusted for the small potential bias (0.0 to 0.08 SD) due to attrition on longitudinal growth. The undernutrition prevalence was slightly underestimated as it was based on available participants only.

Are there any public health implications of these findings in this era of rapid nutrition transition? First, 60-70% of term LBW have at least one anthropometric deficit between 6 months to 5 years of age; thus, caregivers also need to consider low birth size as an important contributor to cross-sectionally detected undernutrition in under-five children. Second, disproportionately faster growth in weight or BMI has been linked with increased adiposity, liver fat, and adverse cardiometabolic biomarkers in childhood and later life [28,32,33]. There is thus an urgent need to create relevant and contextual evidence to inform public health guidelines for ensuring that intervention(s) to address anthropometric undernutrition do not inadvertently result in adverse cardio-metabolic consequences in later life. Finally, the finding of maximal transition in individual Z scores between birth and 6 weeks needs external validation and exploration, for example, to determine if it applies only to LBW infants who may catch up rapidly after being released from factors which constrained their growth in utero. If this early catch-up is seen widely, it could be a tool to aid clinical and public health decisions.

In conclusion, appropriately counselled, term LBW infants reared under adverse socio-economic conditions show substantial catch-up growth in BMIZ and WAZ but not in HAZ. The long-term consequences of this excess weight over length gain, need urgent evaluation.

WHAT IS ALREADY KNOWN?

- Term Low Birth Weight (LBW) children contribute substantially to undernutrition burden in children below five years of age in India.
- There is limited data on longitudinal growth and undernutrition burden in term LBW from urban poor settings, where there is appropriate health and nutrition care counselling.

WHAT THIS STUDY ADDS?

• With appropriately counselled parents, term LBW infants reared under adverse socioeconomic conditions showed substantial catch-up growth in Body Mass Index for age Zscores and Weight-for-age Z-scores but not in Height-for-age Z-scores.

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Table I: Co-existence of different forms of under-nutrition from birth to childhood

Age	V	Any one	V	ny two	Stunted	and Wasted	Under	rweight and	Stu	inted and	Stun	ted and
							-	Wasted	Une	lerweight	Underv W	veight and asted
	Z	%	N	%	Z	%	N	%	Z	%	N	%
		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)
Birth	2078	92.4	2074	72.4	1498*	8.7	1498*	40.7	2074	49.3	1498*	8.7
		(91.2, 93.5)		(70.4, 74.2)		(7.4, 10.2)		(38.1, 43.1)		(47.1, 51.4)		(7.4, 10.2)
6 weeks	1674	71.1	1657	48.2	1656	4.6	1656	11.4	1657	41.4	1656	3.7
		(68.9, 73.2)		(45.7, 50.5)		(3.6, 5.7)		(9.9, 12.9)		(39.0, 43.7)		(2.9, 4.7)
10 weeks	1609	67.9	1590	44.2	1590	2.8	1590	9.5	1590	37.5	1590	2.8
		(65.5, 70.1)		(41.7, 46.6)		(2.1, 3.7)		(8.1, 11.0)		(35.2, 39.9)		(2.1, 3.7)
14 weeks	1537	66.6	1516	40.2	1516	3.1	1516	8.7	1516	34.6	1516	3.1
		(64.2, 68.9)		(37.8, 42.7)		(2.3, 4.1)		(7.3, 10.2)		(32.2, 37.0)		(2.3, 4.1)
18 weeks	1440	61.2	1421	34.5	1421	2.7	1421	7.6	1421	29.6	1421	2.7
		(58.6, 63.6)		(32.0, 36.9)		(2.0, 3.7)		(6.3, 9.1)		(27.3, 32.0)		(2.0, 3.7)
22 weeks	1356	61.7	1339	33.5	1339	3.0	1339	8.2	1339	28.2	1339	3.0
		(59.1, 64.2)		(30.9, 36.0)		(2.2, 4.0)		(6.8, 9.8)		(25.8, 30.7)		(2.2, 4.0)
26 weeks	1270	57.5	1253	28.4	1253	3.0	1253	0°L	1253	24.4	1253	3.0
		(54.7, 60.1)		(25.9, 30.9)		(2.2, 4.1)		(5.7, 8.5)		(22.1, 26.8)		(2.2, 4.1)
2.5 -5 years	475	9.09	474	42.6	474	11.0	474	14.6	474	39.0	474	11.0
		(56.1, 64.9)		(38.2, 47.1)		(8.4, 14.1)		(11.6, 18.0)		(34.7, 43.4)		(8.4, 14.1)

Table I: Co-existence of different forms of under-nutrition from birth to childhood

* Birth length for 576 infants ranged between 40 - 44.9 cm, which was below the lowest stated value in the publicly available WHO reference [17] for computing weight-for-length Z-score. Thus, their wasting status could not be determined.







