Healthy Infant Growth: What Are the Trade-Offs in the Developed World?

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Abstract

More rapid infant weight gain is associated with long-term benefits, such as better neurodevelopmental outcomes for some infants, but also with harms, such as an increased risk of later obesity and higher blood pressure. Determining the optimal rate of infant weight gain requires balancing these benefits and risks, the magnitude of which appears to differ for specific populations of infants. Among healthy full-term infants, gain in weight-for-length is associated with obesity and adverse cardiometabolic outcomes, with no substantial benefit to neurodevelopment. Preterm infants derive substantial neurodevelopmental benefit from gain in weight-for-length during the neonatal intensive care unit stay, and possibly from linear growth thereafter; excess weight-for-length gain may predict adverse cardiometabolic outcomes. Among full-term SGA infants, evidence is limited; excess weight-for-length gain in infancy may predict later cardiometabolic risk, but does not appear to modify neurodevelopmental outcomes. Future research should consider not just the magnitude but also the value of the various outcomes in each population. More work is also needed to identify shared determinants of rapid early weight gain, cardiometabolic risk, and neurodevelopment, and to differentiate effects of weight gain that is proportional to linear growth from weight gain that is excessive.

Overview of Trade-Offs

Early infancy is a period of rapid fat accumulation, linear and brain growth, and cognitive, motor, and social development. More rapid infant weight gain has been associated with long-term benefits, such as better neurodevelopmental...
outcomes for undernourished and preterm infants, but also with harms such as an increased risk of later obesity and higher blood pressure. Determining the optimal rate of infant weight gain requires balancing these benefits and risks. Additionally, the balance of benefits and risks may differ for specific population of infants, for example infants born full term vs. preterm or appropriate vs. small for gestational age (SGA). Here, we review our current understanding of the risks and benefits associated with rapid infant weight gain in these distinct populations.

Trade-Offs for Full-Term Infants

As reviewed in a recent Nestlé Nutrition Institute workshop [1], extensive evidence now exists that rapid infant weight gain is associated with later increased adiposity. In one of several systematic reviews, Ong and Loos [2] identified 21 studies, all of which reported positive associations of infant weight gain with later obesity risk. For each 0.67 standard deviation (SD) excess weight gain from birth to 4–24 months of age in the different studies, obesity risk increased 1.26- to 4.55-fold. Other studies have linked rapid weight gain in infancy with cardiovascular risk factors such as higher blood pressure [3]. In one study, more rapid infant weight gain from birth to 6 months was also linked with a higher metabolic risk score, consisting of waist circumference, systolic and diastolic blood pressure, and fasting glucose, insulin, triglycerides, and high-density lipoprotein cholesterol, assessed at age 17 years (fig. 1) [4]. The association of more rapid weight gain with later blood pressure appears to be strongest for infants who were thinnest at birth [5], whereas the association with obesity may not be modified by birth size [6].

With strong epidemiologic evidence that obesity and cardiometabolic risk in general has roots in early rapid weight gain, it is reasonable to consider intervening in some way to moderate early weight gain to prevent later cardiometabolic disease. However, given the rapid brain growth and steep developmental trajectory of early infancy, potential neurodevelopmental harms of such a strategy must be considered.

A body of research focused on ‘weight faltering’ or failure to thrive (FTT), has provided some evidence that particularly slow weight gain early in infancy may lead to poorer cognitive outcomes. However, most studies are limited by poor generalizability and failure to account for size at birth, gestational age, and other confounding variables [7]. One study [8] that examined a regional cohort and defined FTT based on weight gain found that, after adjustment for maternal IQ and organic vs. non-organic etiology of the FTT, the IQ at age 8 years of children with FTT was only 1.7 points lower (95% confidence interval, CI: –5.2, 1.9) than children without FTT. Reading scores were 1.5 points higher (95% CI: –2.1, 5.3) in the children with FTT.
Literature on FTT can provide clues to outcomes among children with extreme weight faltering, but given the strong link between more rapid infant weight gain and later obesity, examining the entire spectrum of infant weight gain with respect to later cognition is more relevant than examining FTT alone. A recent systematic review [9] identified 5 relevant studies of contemporary, full-term cohorts in developed countries. The studies included appropriate for gestational age (AGA) children. Two UK studies [7, 10] found small (<1/10 SD in outcome per 1 SD in weight gain) but statistically significant associations of early weight gain with school age IQ and educational test scores. In one of those studies [10], only early (birth to 8 weeks) but not later (8 weeks to 9 months) weight gain was associated with later scores, and the effect size was small (0.8 IQ points per SD change in weight). Similarly, a Finnish study [11] of full-term infants found that more rapid BMI gain from birth to 5 months was associated with small improvements in general reasoning (1 point per SD BMI gain, 95% CI: 0.2, 1.8) and visual motor integration (2.2 points per SD BMI gain, 95% CI: 1.3, 3.1) at 4 years, but there was no association of BMI or weight gain from birth to 5 months with verbal competence or language comprehension, nor was there an appreciable association of linear growth from birth to 5 months with any of the cognitive outcomes. Those authors also noted a small association of linear growth – but not BMI gain – from 5 to 20 months with visual motor integration. They identified an inverted U-shaped relationship in which both smaller and larger BMI at 20 months were associated with lower visual motor integration scores.

Other studies have found no association of early weight gain with later cognition. For example, in a US cohort [12], we found that neither weight gain from

![Fig. 1. Association of rapid (>0.67 SD), average (no change), and slow (<0.67 SD) weight gain from birth to 6 months with metabolic risk score at 17 years. The metabolic risk score was highest in participants with rapid weight gain and lowest in participants with slow weight gain. From Ekelund et al. [4].](image-url)
birth to 8 weeks nor from 8 weeks to 6 months was related to cognition at age 3 years (fig. 2) or at 7 years [Belfort et al., unpubl. data]; findings were similar in a UK cohort [9]. In a Dutch study that compared postnatal weight gain and IQ adolescence in twins, the twin with greater weight gain from birth to 2 years had an IQ 3.2 points lower (p = 0.002) than the twin with less weight gain, although the authors did not account for confounding by birthweight or gestational age, and only 60% of the cohort was born full term. Thus, in healthy populations in developed countries, there is only inconsistent evidence for a small effect of early weight gain on later cognition.

In sum, among healthy full-term infants, ample data support a strong association of rapid infant weight gain with later obesity as well as limited evidence regarding other cardiometabolic disease risk factors. In contrast, studies of early weight gain and later neurodevelopmental outcomes have generally shown small or no associations.

Trade-Offs for Preterm Infants

Preterm infants, particularly those born very low birthweight (<1,500 g), often experience poor weight gain and linear growth after birth. Of almost 24,000 preterm infants discharged from a large network of US neonatal intensive care units (NICUs), approximately one third were at less than the 10th percentile for weight and length for age at the time of discharge; the proportion was higher for less mature infants [13]. By school age, most preterm children have attained a weight and height similar to their full-term peers, although males born SGA may remain lighter and shorter into early adulthood [14].

Children born preterm also experience substantial motor, cognitive, and behavioral deficits. On average, at school age, performance on motor testing is

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Fig. 2. Estimated Peabody Picture Vocabulary Test (PPVT) score at age 3 and standard error within deciles of infant weight z score at 8 weeks and 6 months. Estimates are adjusted for birthweight z score and other maternal and infant factors. No association between infant weight gain and later PPVT score is seen. Data from 872 participants in Project Viva. From Belfort et al. [12].
nearly 1 SD lower for preterm compared with full-term children [15], and IQ is 11 points lower [16], with differences more pronounced for children born at lower gestational ages.

An important determinant of neurodevelopmental outcome for preterm infants is weight gain during the NICU hospitalization. In a multicenter US study of 495 infants born at <1,000 g and assessed at 18–22 months of age, being in the highest versus lowest quartile of weight gain from birth to ‘status’ (discharge, transfer, 120 days of age, or 2 kg) was associated with higher Bayley cognitive (2.3 points, 95% CI: 1.0, 4.9) and motor (1.9 points, 95% CI: 0.9, 4.3) scores, an 8-fold reduction in cerebral palsy, and a 2.5-fold reduction in neurodevelopmental impairment [17]. That study did not examine the role of BMI gain or linear growth. In an Australian cohort of preterm infants <33 weeks’ gestation that also measured Bayley scores at 18 months, we found that BMI gain through term (40 weeks’ postmenstrual age) was associated with better motor (2.5 points per z score weight gain, 95% CI: 1.2, 3.9) and cognitive (1.7 points, 95% CI: 0.4, 3.1) scores at 18 months (table 1) [18].

Combined results from parallel randomized trials of a protein-, calorie-, and mineral-enriched preterm formula either as the sole diet (trial A) or as a supplement to mother’s milk (trial B) also support the importance of NICU growth for optimizing brain development. As compared with children who received a standard term formula, children who received the preterm formula had faster NICU weight gain (15.8 vs. 13.3 g/kg per day, p < 0.001) and better neurodevelopmental outcomes at 18 months (2.6 Bayley cognitive points, 95% CI: −1.7, 6.9; 6.2 Bayley motor points, 95% CI: 2.4, 10.0, and 4.5 social quotient points, 95% CI: 1.3, 7.7) [19]. Follow-up of the cohort to school age revealed a persistent cognitive benefit of the preterm formula, with a stronger effect in boys (6.5 IQ points, 95% CI: 0.5, 12.5) versus girls (1.3 points, 95% CI: −4.3, 6.9) [20], and in a subset of original trial participants followed to adolescence, larger caudate and hippocampus volumes on MRI [21]. Based on this evidence, use of preterm formulas and nutrient enrichment of human milk are routine practices in contemporary NICUs.

While the importance of NICU growth for later neurodevelopment is well documented, relatively few studies have examined the importance of infant growth after NICU discharge, and even fewer have separated effects of growth after discharge from growth during the NICU hospitalization. In our analysis of a multicenter US cohort of preterm (<37 weeks), low birthweight (<2,500 g) infants born in the 1980s, greater weight gain (2.1 points per SD, 95% CI: 1.1, 3.1) and linear growth (2.4 points per SD, 95% CI: 1.3, 3.5) from term to 4 months corrected age – but not from 4 to 12 months of age – were associated with higher IQ scores at age 8 years [22]. Similarly, in a contemporary Australian cohort born between 2001 and 2005, we found that greater weight gain and linear growth from term to 4 months were associated with better motor scores at 18 months (table 1) [18]. In neither of those studies was infant gain in
weight-for-length from term to 4 months associated with later neurodevelopmental outcome, suggesting that in the earliest months after NICU discharge – which typically occurs around term – linear growth is beneficial, but weight gain out of proportion to linear growth is not. These post-discharge observations contrast with findings during the NICU hospitalization, during which excess weight gain does appear to benefit later neurodevelopment. Later infancy (4–12 months) gain in weight-for-length was associated with better outcomes in one of those studies [22] but not the other [18].

Observational studies support modest benefits of more rapid post-discharge linear growth, but results from a UK randomized trial [23] do not. At 9 months of age, preterm infants who had been randomized at discharge to receive a post-discharge formula enriched with protein, calories, and minerals were 0.36 kg heavier (95% CI: 0.04, 0.69) and 1.1 cm longer (95% CI: 0.31, 1.89) compared with infants who received a standard term formula, but at 18 months there were no measurable differences in weight or length, or in cognitive or motor function. That trial did not report results of growth in terms of weight-for-length, but a different UK study [24] reported that feeding a similar post-discharge formula led to increased lean mass and decreased fat mass percent measured by dual energy X-ray absorptiometry in male preterm infants, with no differences observed among females.

While interest in neurodevelopmental outcomes in preterm infants is long-standing, more recently, researchers have begun to focus on their cardiometabolic health, and emerging evidence suggests that preterm infants may be at

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**Table 1. Adjusted associations of infant growth with 18-month Bayley scores**

<table>
<thead>
<tr>
<th></th>
<th>Week 1 to term (n = 561)</th>
<th>Term to 4 months (n = 550)</th>
<th>4–12 months (n = 432)</th>
</tr>
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<tbody>
<tr>
<td><strong>MDI</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Weight gain</td>
<td>2.4 (0.8, 3.9)</td>
<td>−0.4 (−1.9, 1.1)</td>
<td>0.3 (−1.7, 2.3)</td>
</tr>
<tr>
<td>Linear growth</td>
<td>0.3 (−1.0, 1.7)</td>
<td>0.4 (−1.2, 1.9)</td>
<td>−0.9 (−2.5, 0.6)</td>
</tr>
<tr>
<td>BMI gain</td>
<td>1.7 (0.4, 3.1)</td>
<td>−0.1 (−1.5, 1.3)</td>
<td>0.8 (−0.8, 2.4)</td>
</tr>
<tr>
<td>Head growth</td>
<td>1.4 (−0.0, 2.8)</td>
<td>−0.5 (−2.2, 1.1)</td>
<td>−0.0 (−1.7, 1.6)</td>
</tr>
<tr>
<td><strong>PDI</strong></td>
<td></td>
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<tr>
<td>Weight gain</td>
<td>2.7 (1.2, 4.2)</td>
<td>1.7 (0.2, 3.1)</td>
<td>0.1 (−1.9, 2.0)</td>
</tr>
<tr>
<td>Linear growth</td>
<td>0.8 (−0.5, 2.1)</td>
<td>2.0 (0.7, 2.3)</td>
<td>0.3 (−1.1, 1.6)</td>
</tr>
<tr>
<td>BMI gain</td>
<td>2.5 (1.2, 3.9)</td>
<td>1.2 (−0.2, 2.5)</td>
<td>0.9 (−0.8, 2.6)</td>
</tr>
<tr>
<td>Head growth</td>
<td>2.5 (1.2, 3.9)</td>
<td>0.2 (−1.3, 1.8)</td>
<td>0.6 (−0.9, 2.1)</td>
</tr>
</tbody>
</table>

Figures represent linear regression estimate of points per z score increment (95% CI). MDI = Mental development index; PDI = psychomotor development index. Term is 40 weeks’ postmenstrual age. Other ages are corrected for prematurity. Estimates adjusted for child and parental factors. From Belfort et al., in press.
increased risk for cardiovascular disease in adulthood. In adolescence and young adulthood, our meta-analysis of observational studies shows that former preterm infants have approximately 2.5 mm Hg higher systolic blood pressure than full-term infants (fig. 3) [25], and are about twice as likely to be hypertensive as adults [26]. Finnish, Dutch, and New Zealand groups have reported greater insulin resistance in preterm compared with full-term adolescents and young adults [27–29], and preterm infants appear to be at about 60% higher risk to develop type II diabetes later in adulthood [30]. Fat mass in childhood appears to be lower and lean mass higher in preterm versus full-term infants, but truncal fat relative to arm fat deposition is greater [31].

While promoting more rapid infant weight gain, at least during the NICU hospitalization, is clearly beneficial to neurodevelopment, it is also possible that promoting more rapid weight gain could harm cardiometabolic health. Some experimental evidence supports this concern. For example, a subset of preterm children randomized in 2 parallel trials to receive a protein-, calorie-, and mineral-enriched preterm formula from birth through hospital discharge had higher fasting levels of 32–33 split proinsulin in adolescence, which may indicate greater insulin resistance, as compared with children who received banked donor breast milk or standard formula [32]. Additionally, children who received the preterm formula had higher diastolic (but not systolic) blood pressure versus children who received banked donor breast milk (3.2 mm Hg, 95% CI: 0.6,
5.8) but not versus children who received the standard formula [33]. In terms of body fat, in a different UK trial of a post-discharge protein, calorie, and mineral enriched vs. standard formula, boys (but not girls) who received the enriched formula for 6 months demonstrated faster weight gain and had greater lean mass as measured by DXA at 12 months, compared with boys who received the standard formula.

Observational studies have provided inconsistent evidence that early rapid weight gain is associated with later cardiometabolic risk in preterm infants. In terms of blood pressure, in 2 studies [34, 35] that included infants born <32 weeks, there was no association of infant weight or weight gain with blood pressure at school age or in late adolescence. We found a small (~1 mm Hg per SD weight gain) association of weight gain and linear growth from term to 4 months with systolic blood pressure at 6.5 years, and of gain in weight-for-length from 4 to 12 months with later systolic blood pressure [22]; the associations of weight gain and linear growth with later BP were seen only in the more mature (>32 weeks’ gestation) infants. A study [27] of preterm infants <28 weeks’ gestation found that those in the highest quartile of systolic BP at age 21 years had been heavier and longer in infancy than those in the lowest BP quartile, suggesting that more rapid weight gain was associated with higher blood pressure, although this finding may be confounded by birth size and/or gestational age.

In terms of insulin resistance, a Dutch study of 345 infants <32 weeks and/or <1,500 g reported a weak association of weight gain through 3 months of age with the log insulin concentration on fasting blood specimen at age 19 years, but no association with c-peptide or log HOMA-IR levels [36]. Further study of a subset (n = 37) of the same cohort at age 21 years revealed that children in the lowest quartile of insulin sensitivity – measured by the euglycemic-hyperinsulinemic clamp method – had been longer at 12 months and heavier at 24 months, but not earlier in infancy, compared with children in the highest quartile of insulin sensitivity, although these results reflect birth weight as well as weight gained after birth. More rapid infant weight gain in preterm infants has also been linked with obesity at age 8 years (odds ratio 2.7, 95% CI: 1.9, 3.9) per 100 g additional weight gain in the first year) [37], and with higher BMI (0.2 SD per SD additional weight gain from birth to 3 months) and greater body fat and abdominal fat percentage as measured by DXA at age 19 years [38].

Thus, among preterm infants – particularly very low birthweight infants most vulnerable to neurodevelopmental impairments – the rationale is strong during the NICU hospitalization to promote rapid weight gain, even out of proportion to linear growth, in the interest of optimizing neurodevelopmental outcomes. In contrast, limited evidence suggests that after term, excess weight gain out of proportion to linear growth does not have substantial neurodevelopmental advantages, and may contribute to cardiometabolic risk later in life.
In contrast to preterm infants who show slow early postnatal weight gain, full-term SGA infants tend to experience rapid gains in length (and weight) in the first months after birth, typically catching up to their AGA peers by 6–12 months of age [39]. Similar to preterm infants, infants born at term but SGA appear to have poorer neurodevelopmental outcomes than those born AGA [40, 41], although effect sizes are much smaller. While numerous studies have identified associations of lower birthweight with later cardiovascular disease risk factors, relatively few have specifically examined populations of full-term SGA infants. In the few studies that have, full-term SGA infants appear to be more prone than AGA infants to hypertension [42] and insulin resistance [43] in childhood, suggesting an increased risk for cardiovascular disease risk later in life.

In terms of the link between infant weight gain and later cardiometabolic disease among full-term SGA babies, in the Collaborative Perinatal Project cohort in the US, increasing weight z score by at least 1 from birth to 4 months and 4 months to 1 year predicted a higher incidence of high blood pressure at age 7 years [44]. Another [45] study found a linear association of faster weight gain from birth to 16 weeks with higher BMI at school age. More rapid early infant weight gain has also been linked to insulin resistance in adolescence [46].

Two randomized trials in the UK aimed to promote more rapid infant weight gain by feeding full-term SGA infants a protein-, calorie-, and mineral-enriched formula; the trials differed by inclusion criteria (study 1, birthweight <10th vs. study 2, <20th percentile) and length of the intervention (study 1, 9 months vs. study 2, 6 months). Combined follow-up of a subset of participants revealed that by school age, as compared with children who received the standard formula, children who received the enriched formula had similar BMI but greater fat mass index as measured by bioelectrical impedance (measured in study 1 participants only; 36%, 95% CI: 10, 68), although not as measured by deuterium dilution (measured in study 2 participants only; 0.6%, 0.1, 1.4) [47]. Children in study 1 who received the enriched formula also had higher diastolic blood pressure (3.5 mm Hg, 95% CI: 0.7, 6.2), and systolic blood pressure was also higher, but not statistically significant (2.0 mm Hg, −1.3, 5.3) [48].

Given the potential cardiometabolic harms of more rapid early postnatal weight gain, it is also important to examine the potential benefits of rapid weight gain to later neurodevelopment. Most studies of SGA infants have focused on preterm children, or combined full-term and preterm children, despite the fact that benefits of early growth to later neurodevelopment may differ for full-term and preterm infants. We could identify only one observational study of neurodevelopment in full-term SGA infants that isolated effects of early infant weight gain from weight gain later in childhood, and also accounted for size at birth. In an analysis of data, the Collaborative Perinatal Project, both slower and more rapid weight gain from birth to 16 weeks (inverted J-shaped relationship) were
associated with lower IQ score at age 7 years (fig. 4) [45]. A randomized trial in the UK demonstrated that feeding full-term, SGA infants a protein-, calorie-, and mineral-enriched formula for 9 months led to improved linear growth that was sustained to 18 months [49], as compared with feeding infants a standard term formula. However, neurodevelopmental outcomes at age 9 months were slightly poorer among infants who had received the enriched formula, and no different at 18 months [50].

In summary, full-term SGA infants appear to be at increased risk relative to AGA infants both for neurodevelopmental deficits and for cardiometabolic disease later in life. Limited evidence suggests that more rapid weight gain may increase the risk for insulin resistance, high blood pressure, and increased fat mass, but not improve neurodevelopmental outcomes.

Conclusions and Recommendations for Future Research

Defining the optimal rate of infant weight gain requires balancing its risks, primarily later obesity and related cardiometabolic consequences, with its potential benefits, chiefly healthy brain growth and neurodevelopment. Current evidence suggests that the magnitude of benefit versus harm differs for healthy full-term, preterm, and SGA populations. Among full-term infants, gain in weight-for-length is associated with obesity and adverse cardiometabolic outcomes, with no substantial benefit on neurodevelopment. Preterm infants derive neurodevelopmental benefit from gain in weight-for-length during the NICU stay, and

Fig. 4. In full-term SGA children, both slower and more rapid weight gain from birth to 16 months of age were associated with lower IQ at 7 years. From Pylipow et al. [45].
possibly from linear growth thereafter. Although based on less evidence, excess weight-for-length gain may predict adverse cardiometabolic outcomes. Among full-term SGA infants, evidence is even more limited; excess weight-for-length gain in infancy may predict later cardiometabolic risk, but does not appear to modify neurodevelopmental outcomes (table 2).

Future research should consider not just the magnitude but also the value of the various outcomes of more rapid weight gain. For example, for preterm infants, children and their families may value improved neurodevelopmental outcomes more highly than preventing high blood pressure, thus favoring more rapid early weight gain despite cardiometabolic harms. Educational and health care costs incurred by society in caring for children with these sequelae should also be considered. Decision analysis provides a quantitative framework by which to incorporate data from many sources to analyze these risks and benefits, and will be useful in defining ‘healthy’ growth for various populations of infants.

Prior to considering interventions to moderate infant weight gain, one must first identify its determinants, with a particular focus on shared determinants of early weight gain and later neurodevelopment and cardiometabolic outcomes. Some are likely to be modifiable, for example infant diet and parental feeding practices. Others, such as genetic and hormonal influences, will be less so. The ability to alter patterns of early weight gain and linear growth may be greater for preterm infants, whose intake is strictly controlled during the NICU hospitalization, than for healthy full-term infants. Weight gain accounts both for linear growth and for weight attributable to adiposity. Future work should attempt to differentiate effects of weight gain that is proportional to linear growth from weight gain that is excessive. Timing of growth also impacts potential

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<th>Healthy full-term AGA</th>
<th>Preterm</th>
<th>Full-term SGA</th>
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<tbody>
<tr>
<td></td>
<td>linear growth</td>
<td>gain in weight-for-length</td>
<td>linear growth</td>
</tr>
<tr>
<td>Neurodevelopment</td>
<td>↔ ↔</td>
<td>+</td>
<td>+/↔¹</td>
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<tr>
<td>Obesity/cardio-metabolic risk</td>
<td>? +</td>
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<td>? +</td>
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↔ ↔ No association; + = positive association; ? = insufficient evidence.
¹ Gain in weight-for-length during NICU hospitalization associated with better neurodevelopment; weight-for-length gain after NICU discharge appears less important.
interventions; future studies of infant weight gain should attempt to identify narrow windows of time that are most sensitive to later neurodevelopmental and cardiometabolic effects.

References


