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COMMENT

Post-discharge nutrition and growth : relationship to later cognition

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The long-standing concept that early undernutrition or, indeed, malnutrition impacts adversely on long-term cognitive development has had a frustratingly difficult history in terms of proof of causation. Smart[1] cited 165 animal studies on malnutrition, many showing later effects on learning and behaviour. However, a concern was the extent to which this vast body of animal work, based on species that had different timings of the critical brain growth spurt to that in humans, could in any case be extrapolated to human intellect. More disturbing was the recognition of major flaws in the numerous studies relating malnutrition in infants from developing countries to impaired later cognition. Indeed, these epidemiological investigations left major doubt as to whether the cognitive deficits related to prior nutrition at all but rather to associated poor social circumstances, poverty, and lack of stimulation. In 1986 John Dobbing, a pioneer in defining vulnerable periods of development for undernutrition, convened a meeting of experts to review available evidence, subsequently published in a book "Early nutrition and later achievement" (1987). One contributor, Richardson, summarised the state of play expressed by this expert group as follows: **"**there is still no clear evidence that malnutrition has any demonstrated long-term irreversible effects on intellectual or social development"[2].

Following this "low point" in the development of the field more convincing evidence emerged, notably in preterm infants. Thus, in babies born in the second and third trimesters, randomised controlled trials (RCTs) of enhanced nutrition in the NICU favourably affected cognition in childhood.[3] These nutritional effects persisted into adolescence[4] when MRI studies showed an impact on the underlying structure of the brain.[5] These RCTs are backed by observational studies showing that early growth in weight and head circumference are positively related to later cognition.[6]

The new paper by Embleton et al.:[7] "Early diet in preterm infants and later cognition: 10-year follow-up of a randomised controlled trial"—explores the vulnerability to undernutrition during a further window in time, the post-discharge period when the infant is beyond full-term equivalent. This follow-up at 10 years of 92 subjects included data on key aspects of cognitive function based on a short version of the Weschler Intelligence Scale for Children (WISC-III). The study compares non-breast-fed babies randomised up to 6-month corrected age to a nutrient-enriched preterm formula versus standard term formula. A smaller "crossover" group changed from preterm to term formula at term-equivalent age. An important further observational analysis related faster weight gain and head growth in infancy to significantly higher cognitive performance at 10 years.

Most but not all RCTs fail to establish a link between post-discharge nutritional supplementation in formula-fed babies and later development, largely using Bayley scales up to 24 months.[8] The importance of the new study is providing data from the more sensitive WISC-III at 10 years. When findings were analysed as randomised the cognitive area of most interest was the processing speed index (PSI) of major importance to cognition. There was a significant 10-point advantage for the preterm formula group versus the crossover group, and a trend to a 5 point higher score for preterm formula versus term formula. However, statistical under-powering is a major issue in post-discharge trials of formulas. Nevertheless, in 2 of 11 post-discharge trials reviewed in 2015[8] there were significant benefits of nutrient supplemented formula on later development. Some studies show trends to higher scores in the supplemented limb. In the largest developmental follow-up, 181 formula-fed post-discharge infants were tested at 18 months.[9] Those randomised to a nutrient-enriched post-discharge formula versus a term formula, had ~3 point advantage in Bayley psychomotor development index at 18 months—insufficient to establish a relationship. Yet, educationalists recognise that even small effects have importance for populations. However, this difference would have required around 800 subjects to explore. In the study by Embleton et al.[7], after adjusting for confounders, effect sizes for PSI were large: with an advantage for the preterm formula group of 6.2 points versus term formula and 7.7 points versus the crossover group. In both cases P was >0.05, so this could have been due to chance, but as recognised by the authors, the study was not powered to explore this with 37 subjects in each of the two main groups and 18 in the crossover group.

Meta-analyses of post-discharge formula trials have not detected overall developmental or cognitive impact of nutritional supplementation.[8] However, considerable heterogeneity across studies is a major barrier for detecting effective interventions. The interventions have different timings; differ in the infant's maturity at birth (Embleton et al. inferred that their historic cohort comprising larger, well babies might be less prone to cognitive effects of nutrition); and the age and sophistication of outcome testing varies. Within each category of formula used—"term", "post-discharge" and "preterm"—composition differs greatly. Outcome effects could be blunted by variable timing of the introduction of weaning foods which reduce intake of the trial diets. Another area of heterogeneity is the possible impact of the composition of the trial diets on the infant's volume intake. Historic studies by Fomon et al.[10] suggested that ad libitum-fed infants regulated volume milk intake according to their energy

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intake. This phenomenon has now been shown in several post-discharge nutrition studies.[8] However, volume regulation may not occur with alteration in protein intake.[11] In our trial[9] the nutrient-enriched post-discharge formula was principally protein supplemented, with a similar energy content to that in the term formula-fed control group (just 6% difference). This resulted in no difference in volume intake between the two groups.[11] In the current study the enriched preterm formula had ~20% more energy than the term formula. Figure 2 in Cooke's original paper[12]—the basis for this study—provides an excellent physiological demonstration of feed volume regulation. Infants regulated their milk volume intake such that the energy intake in the two main groups was the same and the consequent reduction in the difference in volume intake between the randomised groups will have correspondingly reduced the advantage of the higher protein content in the preterm formula group. Thus, use of relatively high-energy post-discharge feeds could diminish the differential protein intake between groups and hence the potential for achieving a cognitive benefit in the supplemented group.

Thus, RCTs of post-discharge nutrition in formula-fed babies are underpowered. Indeed, in the 2015 review, half of the trials had less than 50 subjects. This together with the major heterogeneity could potentially obscure effects of nutrient supplementation on neurodevelopment. Whether more robust and targeted trials will be performed to further explore the impact of nutrient fortification on cognition is unknown. All supplementation trials pose the ethical issue of equipoise and whether subjects can be randomised to a control group potentially providing suboptimal nutrition.

Suboptimal nutrition in post-discharged preterm infants was a neglected area until studies began around 30 years ago. Even with good care, many preterm infants are discharged home with significant deficits in body protein and energy—as shown by Embleton et al.[13] Growth deficits may persist well into childhood. These babies may leave hospital with under-mineralised bones and depleted stores of a several specific nutrients. Nutritionally enriched feeds can improve growth and nutritional status,[8] but a key question has been whether this ultimately affects outcome. Neurodevelopment has been a logical focus because in preterm neonates in the NICU, early growth is linked to better cognition[6], and indeed RCTs of growth-promoting diets have shown, as expected, improved cognitive scores.[3,4]

The gold standard for exploring the equivalent value of post-discharge nutrition may remain RCTs, but firm conclusions from these are limited by factors discussed in this commentary. Therefore, other types of evidence to support current practice must also be considered. It is notable that use of mother's own milk for preterm infants both pre- and post-discharge is rightly unchallenged even though all the supportive evidence is observational and not one RCT has been performed for obvious ethical reasons. A key aspect of the study by Embleton et al., supported by work of others, is the strong positive relationship between weight gain in early infancy or head growth throughout infancy and cognitive outcomes a decade later, even after adjusting for multiple confounders. Regarding safety, reassuringly preliminary data from our own RCT showed randomisation of preterm infants to a growth-promoting post-discharge formula did not increase later fat mass or blood pressure at 5–8 years;[14] this area needs further work. Despite the uncertainties of RCT evidence and a recognition of the limitations of observational data, Embleton et al. sensibly conclude: "The strong associations between infant growth and later cognition are important and suggest that nutritional exposures and growth in the first year of life require closer attention". Their study supports the concern expressed 30 years ago, that this large population of often sub-optimally nourished babies indeed merits our closer attention notably in relation to their cognitive potential.

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ADDITIONAL INFORMATION

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