

REVIEW ARTICLE

Postnatal growth in preterm infants and later health outcomes: a systematic review

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INTRODUCTION

Developmental plasticity refers to the capacity of an organism to adjust its phenotypic development in response to environmental cues to maximise its reproductive fitness, possibly through epigenetic, metabolic and/or anatomical mechanisms (1). Mismatch arises when the predicted conditions do not correspond to the actual environment and this can adversely impact long-term health and longevity. Initial evidence that early exposure to environmental cues can alter the risk of developing metabolic diseases in humans came from associations between low birthweight and higher incidence of coronary heart disease or glucose intolerance (2). Low birthweight can result from intrauterine growth restriction and/or prematurity and, when followed by adequate postnatal nutrition, rapid ('catch-up') growth typically occurs during infancy. While this confers potential advantages for preterm infants in terms of short-term survival and later cognitive outcome, rapid catch-up growth may increase the risk of metabolic disease later in life. The relative importance of prenatal undernutrition versus postnatal

ABSTRACT

In preterm infants, poor postnatal growth is associated with adverse neurocognitive outcomes; conversely, rapid postnatal growth is supposedly harmful for future development of metabolic diseases.

Conclusion: In this systematic review, observational studies reported consistent positive associations between postnatal weight or head growth and neurocognitive outcomes; however, there was limited evidence from the few intervention studies. Evidence linking postnatal weight gain to later adiposity and other cardiovascular disease risk factors in preterm infants was also limited.

rapid growth to these outcomes is still unresolved. In contemporary birth cohorts, postnatal rapid growth occurs more often in infants who were subjected to intrauterine growth restriction, but also reflects the infant's genetic potential, and can be induced in the general population by excessive infancy nutrition, including higher protein intake. Human growth is regulated by

Key Notes

- We aimed to identify sensitive periods of postnatal growth in preterm infants associated with neurodevelopmental and metabolic outcomes.
- The dissonance between findings of intervention and observational studies raises the possibility of confounding by diseases or other factors that affect both growth and cognition.
- Future nutritional intervention studies in preterm and term infants should report effects on weight gain and growth, as well as later body composition and neurocognitive outcomes.

genetic, epigenetic, nutritional and endocrine signals orchestrated in a timely fashion, and each of these mechanisms may be involved in long-term metabolic programming (3).

There is a wealth of supportive evidence for developmental programming from experimental animal models. These have demonstrated causal effects of nutritionally induced accelerated growth, with or without low birth-weight, on long-term risks of metabolic dysfunction. Initial studies in rats over 50 years ago demonstrated the detrimental effects of excess nutrition during lactation by manipulation of litter size (4). Rats that were reared in small litters where there was little competition for the mother's milk gained more weight during lactation and remained fatter and heavier throughout life, even when weaned onto a healthy low-fat diet, compared with animals reared in larger litters. Strikingly, raising rodent pups in large litters to reduce the plane of nutrition during lactation protects genetically prone animals from becoming obese (5). Manipulation of nutritional content during lactation has similar effects (6). When mouse or rat offspring of normally nourished mothers are suckled by dams fed a low-protein diet, pups grow slowly and remain permanently smaller and leaner than controls. Furthermore, these animals exposed to maternal low-protein diet during lactation are resistant to diet-induced obesity. These findings highlight the importance of nutrition during lactation in determining long-term risk of obesity. Studies in rodent models have also shown the association between low birthweight followed by postnatal catch-up growth and increased risks of obesity, cardiovascular disease, insulin resistance and glucose intolerance. This has been demonstrated in a range of different models where foetal growth has been restricted including those employing maternal caloric restriction, maternal protein restriction and intrauterine artery ligation (6). Mice that were growth restricted *in utero* by maternal protein restriction and that then underwent accelerated growth through suckling a normally fed dam are more susceptible to diet-induced obesity. The mechanisms underlying these programming effects remain to be fully established but may involve permanent structural changes, epigenetic changes and accelerated cellular ageing (6).

It has been suggested that avoidance of excessive rates of early growth could have a role in the prevention of cardiovascular disease (7); however, the benefits and risks of this approach must be carefully weighed in high-risk low birth-weight groups. Preterm infants are considered to be particularly susceptible to developmental programming of adverse health outcomes because of their abnormal *ex-utero* growth patterns; the majority exhibit poor growth and weight gain during the initial postnatal period between preterm birth to full-term gestational age but subsequently most show spontaneous rapid catch-up growth back to their genetic trajectory. Some studies suggest that in preterm infants, poor early growth is associated with adverse neurodevelopmental outcomes; thus, current nutritional strategies aim to enhance their nutrient intake to promote rapid growth and brain

development despite the potential long-term metabolic costs (8). The objective of the present review was to summarise the available evidence on postnatal growth in preterm infants in relation to the potential neurodevelopmental benefits and adverse metabolic outcomes and attempt to identify critical postnatal windows during which growth might influence these outcomes.

METHODS

We extracted reports published before 2003 from the review by Baird et al. (9). That extensive review included literature on term infants (AGA+SGA) and a number of outcomes not relevant to our review here (i.e. mental health, sudden infant death), so only references that referred to i) preterm infants, ii) early growth (rather than size during infancy) and iii) developmental or metabolic outcomes that were predefined were extracted for the current review. Seven relevant papers were identified, all reported neurocognitive or developmental outcomes, and these are marked in Table 1a,b.

We performed a systematic search of electronic databases (Medline (PubMed), EMBASE and Google Scholar) to identify studies published between 2003 and May 2013 reporting associations between postnatal growth and later neurocognitive or metabolic outcomes in preterm infants. MeSH terms and search words representing the following categories were combined: i) the population (e.g. preterm infants), ii) postnatal growth (e.g. early weight gain; failure to thrive) and iii) outcome related to neurocognitive development (e.g. IQ; neurological impairment) or to metabolic disease (e.g. percentage body fat). One investigator (KK) carried out the search and hand-searched the reference lists of identified papers for further relevant papers. Abstracts were read, and if thought to be relevant, the full report was read and relevant data were extracted; 120 full papers published in 2003 or later were reviewed in this way (Fig. 1).

Inclusion criteria:

Population

Definitions that were considered for this search were as follows: 'preterm infants; premature infants; preemie births; low-birthweight infants; very low-birthweight infants; extremely low birthweights; and preterm/premature SGA/IUGR infants'. Studies of populations that also included term infants were included if the findings for the preterm infants were presented separately.

Exposure

A measure of postnatal growth velocity that could be compared between groups was identified. Care was taken to use a definition that considered *gains* in weight and/or head circumference between at least two time points (e.g. between birth to age six weeks) rather than only measurements of body size at one specific age. Growth was accepted if reported as an absolute velocity or as a change in SD scores; in the case of the latter, we required the growth

Table 1 Postnatal growth in a) weight (WT) and b) head circumference (HC) in preterm born infants related to later neurocognitive outcomes. Reports are ordered by study design and age at outcome assessment. Variables used for adjusted analyses: G – general; N – neonatal; S – social; IQ – maternal IQ

	Design	Timing of exposure	N	Age at outcome	Summary result	Comments	Adjustment
(a)WT gain Biasini (10)	int	b-discharge	61	3 & 12 months (GMDS)	++ (3 months only)	Milk fortifier increased HC, WT and length gains	Nil
Cooke (11)	int	discharge-6 months	113	18 months (BSID)	0	Enriched preterm formula increased HC, WT and length gains in boys only	Nil
Aimone (12)	int	Discharge-12 weeks	39	18 months (BSID)	0	Human milk fortifier increased WT and length gains (but not HC)	G
Lucas (13)	int	Discharge-9 months	229	18 months (BSID)	0	Enriched postdischarge formula increased WT gain (but not HC)	Nil
Lucas (14)	int	b-discharge	422	18 months (BSID)	0	Enriched preterm formula increased WT & HC gains vs. banked breast milk	Nil
Lucas (15)	int	b-discharge	360	7-8 years (WISC)	++ (Boys only*)	Enriched preterm formula increased WT & HC gains. *Only in boys who received no human milk or had the highest intakes of the trial diet.	Nil
O'Connor (16)	obs	in NICU	463	12 months (BSID)	0	Nonrandomised infants on preterm formula were 500 g heavier at 12 months than breast-fed	G,N,S (IQ)
Tudhope* (18)	obs	b-12 months	162	12 months (GMDS)	++ (AGA only)	Poor WT gain in preterm-AGA infants (n = 131) was associated with lower scores	Nil
Cooke (19)	obs	b-28 day, 28 day -18 months	108	18 months (BSID)	++	Preterm-SCA infants with catch-up WT gain did better than those who remained small	Nil
Belfort (20)	obs	b-term, term-4 months, 4-12 months	613	18 months (BSID)	++	Positive associations with WT gain between b-term, and with post-term WT gain only if proportionate to length gain	G,N,S
Sices (21)	obs	term-4 months, 4-8 months, 8-20 months	154	20 months (BSID, CP)	++	Poor outcomes associated with poor WT gain between term-4 months and 8-20 months	G,S
Ehrenkranz (22)	obs	b-discharge (or 2 kg or 120 day)	695	20 months (BSID, CP)	++	Similar associations with HC gain	G,N,S
Latal-Hajnal* (23)	obs	b-2 years	219	24 months (BSID)	++	Infants categorised as WT above/below the 10th centile	G,N
Ma (24)	obs	b-2 years	76	24 months (BSID)	0	Infants categorised as WT above/below the 10th centile	G,N,S
Shah (25)	obs	b-3.6 week gestation	?	24 months (BSID)	++	Growth failure between b-3.6 wk associated with poorer psychomotor development (but not mental development)	?
Nash (26)	obs	b-18/24 months	289	24 months (BSID)	++	Poor WT gain associated with poor outcomes, but rapid WT gain not associated with better outcomes	G,N

Table 1 (Continued)

	Design	Timing of exposure	N	Age at outcome	Summary result	Comments	Adjustment
Kelleher* (27)	obs	?	180	24 & 36 months (BSID)	++	Poor growth defined as WT <5th centile on 2 or more occasions	G,N,S
Powers (28)	obs	6-36 months	135	36 months (BSID)	++	Similar associations with HC gain	G,N,S
Huang (17)	obs	b-4to7 years	654	4 to 7 years (WYCSI-C)	0	Positive associations were seen in full-term (n = 7735) but not preterm infants	G,N,S,IQ
Franz (29)	obs	b-discharge disch-5.4 years	219	5.4 years (KABC, CP)	++ (b-discharge only)	Similar associations with HC gain	G,N,S
Claas (30)	obs	b-5.5 years	101	5.5 years (WPPSI, M-ABC)	++	Preterm-AGA infants who remained > -2 SDs had better outcomes	Nil
Casey (31)	obs	4-36 months	985	8 years (WISC)	++	Poor WT gain was associated with poor outcomes in both SGA and AGA preterms	G,S
Kan (32)	obs	b-2 years, 2-8years	179	8 years (WISC, WRAT, M-ABC)	0	No association with WT gain adjusted for HC growth	G,N,S
Belfort (33)	obs	Term-12 months	905	8 years (WISC)	++	Positive association with adjusted WT gain between term-12 months (or term-4 months)	G,S,IQ
Weisglas (34)	obs	b-3 months	562	19 years (MCT-M)	++	Poor outcomes in preterm-AGA with poor WT gain and in preterm-SGA without catch-up	G,N,S
(b)HC growth							
Biasini (10)	int	b-discharge	61	3 & 12 months (GMDS)	++ (3 months only)	Milk fortifier increased HC, WT and length gains	Nil
Cooke (11)	int	discharge-6 months	113	18 months (BSID)	0	Enriched preterm formula increased HC, WT and length gains in boys only	Nil
Lucas (14)	Int	b-discharge	422	18 months (BSID)	0	Enriched preterm formula increased WT & HC gains vs. banked breast milk	Nil
Lucas (15)	int	b-discharge	360	7-8 years (WISC)	++ (Boys only*)	Enriched preterm formula increased WT & HC gains. *Only in boys who received no human milk or had the highest intakes of the trial diet.	Nil
O'Connor (16)	obs	b-12 months	463	12 months (BSID)	0	Nonrandomised infants on preterm formula were 500 g heavier at 12 months than breast-fed groups	G,N,S
Simon* (35)	obs	0-12 months	48	12 months (BSID)	++	Compared catch-up (defined as HC recovering to >5th centile) to no-catch-up group	Nil
Ehrenkranz (22)	obs	b-discharge (or 2 kg or 200 day)	695	22 months (BSID)	++	Positive associations also with WT gain	G,N,S
Ford* (36)	obs	b-2 year	83	24 months (BSID)	0		?
Kuban (37)	obs	b-2 year	1200	24 months (BSID)	++		G,N
Wood (38)	obs	b-term, term-30 months	283	30 months (BSID, CP, NDI)	0		G,N,S

Table 1 (Continued)

	Design	Timing of exposure	N	Age at outcome	Summary result	Comments	Adjustment
Hack* (39)	obs	8 months, 8-20 months	139	30 months (SB)	++ (8 months only)	Positive association with HC at 8 months, but not HC growth 8-20 months	G,N,S
Powers (28)	obs	6-12, 12-18, 18-24, 24-30, 30-36 months	135	36 months (BSID, NDI)	++ (NDI only)	Positive associations also with WT gain	G,N,S
Franz (29)	obs	b-disch, disch-5.4 years	219	5.4 years (KABC, NDI)	++ (NDI only)	Positive associations also with WT gain	G,N,S
Claas (30)	obs	b-5.5 years	101	5.5 years (WPPSI, M-ABC)	++	Positive associations with HC growth in both SGA and ACA preterm infants	Nil
Stathis* (40)	obs	b-4 months, 4-8 months	87	6 years (RWM)	++ (b-4 months only)	Positive association with HC growth b-4 months, but not 4-8 months	G,N,S
Brandt (41)	obs	b-12 months	51	72 months (SB) adult (MIT)	++	Preterm-SGA infants. Compared catch-up HC growth to no-catch-up group	G,N,S
Cooke (42)	obs	b-7 years	280	7 years (M-ABC, VMI)	++ (VMI only)		G,N
Cooke (43)	obs	b-disch, disch-4 years, 4-15 years	194	8 years (WISC + MMI)	++ (MMI only)	HC growth between birth discharge associated with MMI. HC at 4 and 15y was associated with IQ	G,N,S
Kan (32)	obs	b-2 years, 2-8 years	179	8 years (WISC, WRAT, M-ABC)	++ (0-2 years only)	HC growth only between 0 and 2y was associated with IQ, reading & spelling (but not maths & motor ability).	G,N,S
Belfort (33)	obs	term-12 months	905	8 years (WISC)	++	Positive associations with HC growth between term-12 months (or 4-12 months)	G,S,IQ

'++' statistically significant positive association; '+' nonsignificant positive trend; '0' no association; '-' non-significant inverse trend; '-' significant inverse association; '?' unstated adjustment factors.

*Reference extracted from the review of Baird et al., 2003 (9).

Cognitive tests used: BSID = Bayleys scale of infant development; CP = Assessment for cerebral palsy; GMDS = Griffiths mental development scale; KABC = Kaufman assessment battery for children; M-ABC = Movement assessment battery for children; MCT-M: Multicentre capacity test intermediate level; MIT = Adult Mannheim intelligence test; MMI = Minor motor impairment assessment; NDI = Neurodevelopmental impairment; RWM = Reading, writing and maths assessments; SB = Stanford Binet Intelligence Test; VMI = Visual motor integration; WISC = Wechsler intelligence scale for children; WPPSI = Wechsler preschool and primary scale of intelligence; WRAT = Wide range achievement test; WYCSI-C = Chinese Wechsler young children scale of intelligence.

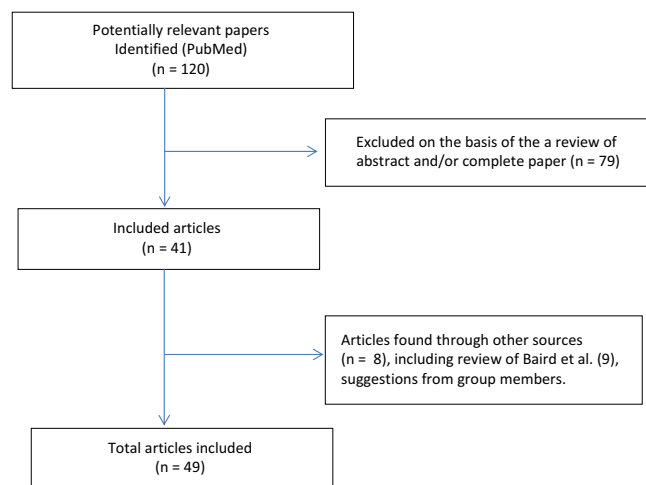


Figure 1 Flow chart for systematic review of literature on the effects of postnatal growth in preterm infants and later health outcomes.

reference used to be reported. Papers were accepted if the outcome (see below) was assessed at the same age as the second growth measurement, or later.

Outcomes

Neurocognitive development. Measures related to neurocognitive outcomes included: ‘neurodevelopment; intelligence; IQ; behaviour; motor and neurological impairment’. We applied no limit regarding the age at outcome assessment; the earliest was at the age of 12 months and the oldest was in young adults (21 years).

Metabolic. Outcomes were included related to body composition (e.g. overweight and obesity; percentage fat), insulin resistance, glucose control or cardiovascular risk factors (e.g. lipid profile; blood pressure).

Study design

Both intervention and observational studies were accepted. We considered as ‘intervention studies’ those where the intervention had an influence on postnatal growth and the study also assessed one of our review outcomes above. Some papers reported cohort analyses of interventional studies (particularly where the intervention did not influence early growth); these were labelled as ‘observational’ evidence.

Exclusion criteria

We excluded animal studies and also studies where body size at only one time point was reported. Queries about the eligibility of specific studies were resolved by discussions with MF and KO, or with all authors in cases of uncertainty. Further studies suggested by co-authors for possible inclusion were considered, but no new eligible studies were identified in this way.

Data extraction and interpretation

KK was responsible for the data extraction, tabulation and preliminary interpretation. Only published data were considered, and no further data were sought from authors. Forty-nine individual reports were used (34 examining early growth and later developmental outcomes and 15 examining metabolic outcomes); however, 20 (41%) of these papers were used more than once, as they reported more than one outcome of interest.

For each identified study, KK extracted information on the following: study design, timing and nature of the exposure, number of participants, and age at follow-up measurements. All authors agreed on the generation of a summary result indicator attributed to each study to show whether it reported a positive effect/association between postnatal growth and the outcome measure (‘+++’ statistically significant positive association; ‘+’ nonsignificant positive trend; ‘0’ no association; ‘-’ nonsignificant inverse trend; and ‘---’ significant inverse association). Due to wide heterogeneity between studies in the measurement and/or categorisation of the exposure and outcome variables, quantitative summary by meta-analysis was deemed not possible.

RESULTS

Neurocognitive outcomes

Neurocognitive outcomes were assessed in six clinical trials that promoted faster postnatal growth using a nutritional intervention (Table 1a; Fig. 2) (10–15). Of these, only one trial reported an overall benefit on neurodevelopment, but only at the age of three months and not at the age of 12 months (10) and one trial reported a benefit only in subgroups of boys, but not in girls at the age of 7–8 year (15). Both of these trials, and a third trial that showed no benefit at 18 months (14), tested interventions given during the prehospital discharge age period. The other three trials tested posthospital discharge interventions: one promoted faster gains in weight, length and HC in boys (11); and two promoted faster gains in weight and length, but not HC (12,13); however, none had any benefit for neurodevelopment, assessed at the age of 18 months in all three trials.

In observational studies, weight gain ($n = 19$ studies) showed generally consistent positive associations with neurocognitive outcomes at ages ranging from 12 months to 19 year old (Table 1a; Fig. 2) (16–34). Outcomes were measured using a variety of assessment tools across different studies, largely reflecting the relevance of each tool to specific age ranges. The timing of the postnatal weight gain tested as the exposure also varied widely between studies, from as early as birth-to-full-term age or hospital discharge, to weight gain up to mid-childhood. No obvious period(s) of postnatal weight gain was more consistently associated with later neurocognitive outcomes. Whilst some of these studies included adjustment for potential neonatal or social confounders, only three included adjustment for maternal IQ.

Influence of weight gain on later cognition

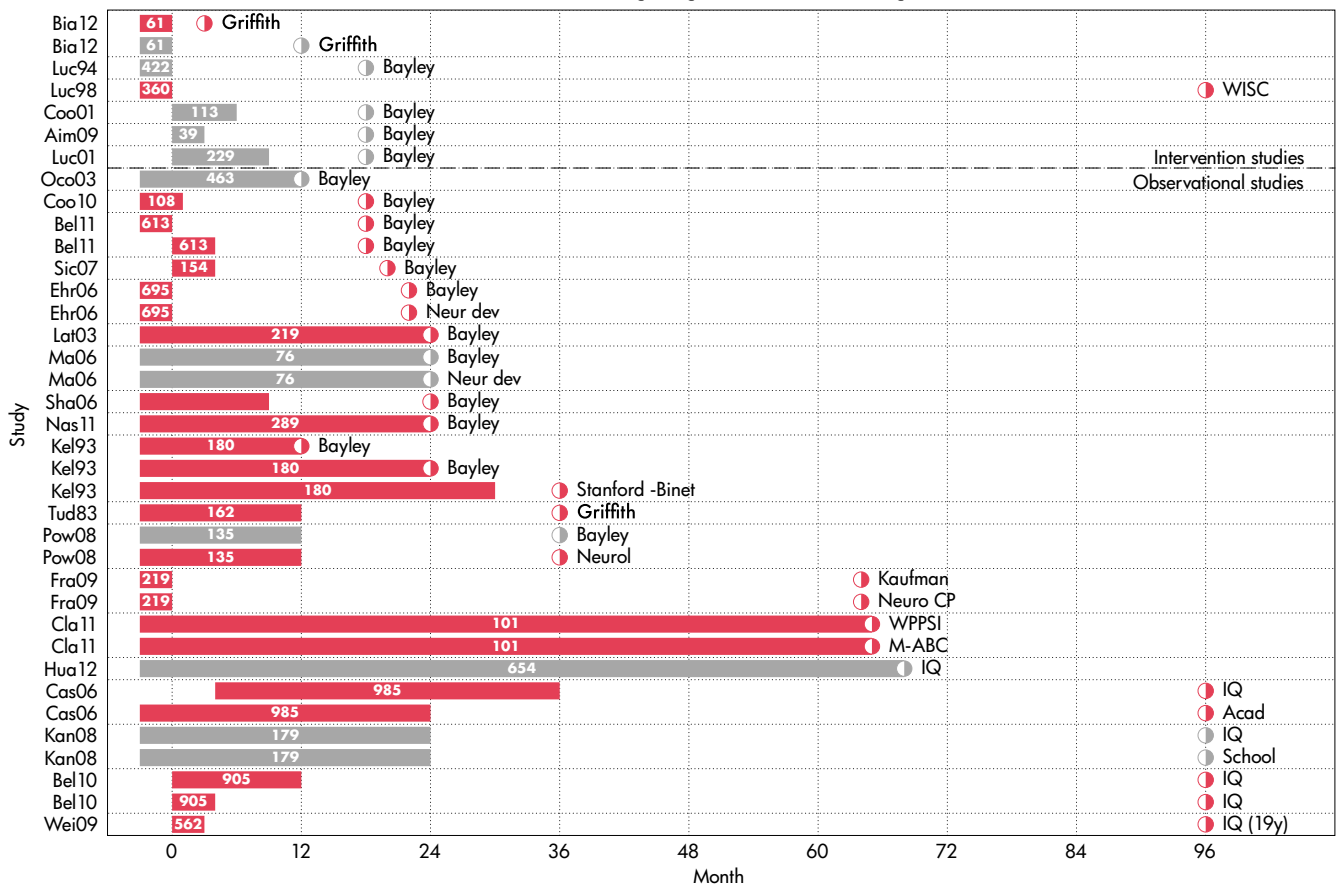


Figure 2 Gain-outcome graph of weight gain and cognition. Each row indicates a study result. The label on the vertical axis is the name of the study. Age is on the horizontal axis. The bar in each row codes the period in which weight gain occurred. The half-open circle indicates the age at which the outcome was measured, and the label describes the type of outcome. The number of children in the study is printed in the bar. A red bar indicates a significant positive association. A grey bar indicates no significant association.

Similarly, 16 observational studies reported on the association between postnatal head growth and neurocognitive outcomes (Table 1b; Fig. 3) (16,22,28–30,32,33,35–43). Postnatal head growth showed generally consistent positive associations with neurocognitive outcomes measured at ages ranging from 12 months old to adulthood, although the benefits for neurodevelopment outcomes were more consistent than for cognition. As for postnatal weight gain, no obvious period(s) of postnatal head growth was more consistently associated with later neurocognitive outcomes.

Percentage body fat

Percentage body fat was assessed as an outcome in three clinical trials that altered postnatal growth using a nutritional intervention (Table 2a; Fig. S1) (12,44,45). In all three trials, percentage body fat was assessed at the age of 12 months by DXA scans. In two trials (12,45), the posthospital discharge intervention promoted faster weight gain, but neither had any effect on percentage body fat. In the third trial (44), surprisingly the enriched formula milk

intervention given from full enteral feeding to age 12 months led to lower weight gain (the authors suggested this was due to lower milk intake, although this was not measured) and also lower percentage body fat, consistent with a positive relationship between weight gain and adiposity.

Four observational studies reported on the association between postnatal weight gain and percentage body fat (Table 2a; Fig. S1) (46–49). The two larger studies reported positive associations with percentage body fat in young adults (48,49); both studies reported stronger effects of weight gain during earlier (between birth to three months corrected age) versus later infancy (between 3–12 months). The two smaller studies reported no or variable associations between postnatal weight gain and percentage body fat at the ages of two year and 14 year (46,47).

Insulin resistance

Insulin resistance was assessed in only one clinical trial that promoted faster postnatal growth using a nutritional intervention (Table 2b; Fig. S2) (50). The nutrient-enhanced

Influence of head circumference gain on later cognition

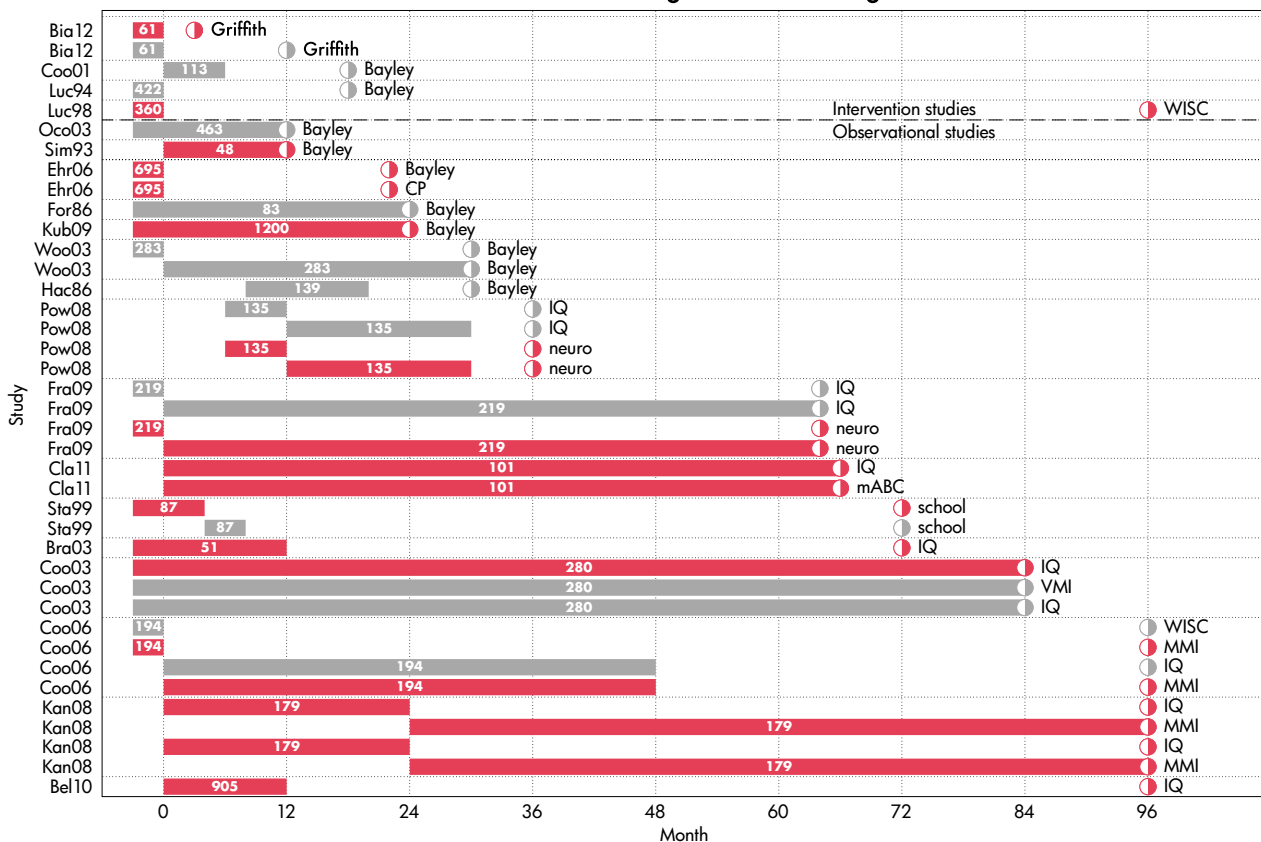


Figure 3 Gain-outcome graph of head circumference and cognition. Each row indicates a study result. The label on the vertical axis is the name of the study. Age is on the horizontal axis. The bar in each row codes the period in which head circumference growth occurred. The half-open circle indicates the age at which the outcome was measured, and the label describes the type of outcome. A red bar indicates a significant positive association. A grey bar indicates no significant association.

preterm formula milk given in the first four weeks of postnatal life increased postnatal weight gain and also increased fasting 32–33 split proinsulin levels at the age of 15 year, independent of BMI, although levels were similar to those in healthy term-born individuals.

Of the four observational studies (49,51–53), three reported positive associations between postnatal weight gain and insulin resistance at the ages of 10 to 22 year (Table 2b; Fig. S2) (51–53). However, there were inconsistent findings between studies, including the timing of weight gain related to insulin resistance [e.g. birth to three month post-term (52); from 18 months only (51)], and whether associations were only seen in subgroups [within preterm-SGA but not preterm-AGA infants (53)]. Furthermore, only one observational study showed that the association with insulin resistance was independent of body composition (53).

Other cardiovascular risk factors

Associations between postnatal weight gain and various later CVD risk factors were reported by eight observational studies; most had sample sizes >160 and had long follow-up, to ages ranging from six to 21 year old (Table 2c; Fig. S3) (33,47,49,54–58). Positive associations were vari-

ably and/or sparsely reported with arterial blood pressure (two of five studies); total cholesterol levels (one of three studies); flow mediated dilatation (one study); and carotid artery intima-media thickness (one of one study). Furthermore, most of the studies that reported positive associations did not include adjustment for body size at the time of outcome assessment.

DISCUSSION

This systematic review of growth in preterm infants in relation to later outcomes found only a few intervention studies and a greater number of observational studies with information on later neurocognitive, adiposity and insulin resistance/cardiovascular risk factor outcomes. In relation to neurocognitive outcomes, intervention studies that aimed to promote postnatal growth in preterm infants, whether during hospital stay or postdischarge, produced little consistent evidence for beneficial effects of faster early growth. The observational studies reviewed showed generally consistent positive associations between postnatal weight gain and head growth (n = 18 and 15 studies, respectively) and neurocognitive outcomes at ages ranging from one year to adulthood, with no obvious period(s) of

Table 2 Postnatal weight gain in preterm born infants related to a) adiposity (% body fat); b) insulin resistance; c) other cardiovascular markers. Reports are ordered by study design and age at outcome assessment

	Design	Timing of exposure (nature)	N	Age at outcome	Summary result	Comments
(a)Adiposity						
Koo (44)	int	41 day -12 months (Enriched formula)	89	12 months	++	Intervention group surprisingly grew slower and had lower %BF
Aimone (12)	int	discharge-3 months (HMF)	39	12 months	0	Intervention increased WT and length gains, but not %BF
Cooke (45)	int	discharge-6 months (Preterm formula)	129	12 months	+	Intervention increased WT gain and both fat and lean mass; nonsignificant increase in %BF
Hernandez (46)	obs	(b-2 weeks) b-4 weeks (WT gain)	26	24 months	(-) ++	Surprisingly, the effect of WT gain between b-2 weeks was opposite to that for WT gain b-4 week
Ludwig-Auser (47)	obs	b-14 days (Energy intake)	61	14.5 years	0	Infants with intakes >70 vs. < 70 kcal/kg/days were taller and heavier at the age of 14 years
Euser (48)	obs	b-3 months, 3-12 months (WT gain)	403	19 years	++	Stronger effect of early vs. later WT gain on BMI & %FM. Findings persisted when adjusted for height
Kerkhof (49)	obs	b-term, term-3 months (WT gain, adj. length)	162	21 years	++	Compared rapid (>0.67 SD) vs. slow (<0.67 SD) catch-up infancy WT gain. Stronger effect of early vs. later catch-up
(b)Insulin resistance						
Singhal (50)	int	b-4 weeks (Preterm formula)	216	15 years	++	Higher nutrient diet increased fasting 32-33 proinsulin levels at 13-16 years (adjusted for BMI)
Fewtrell (51)	obs	b-18 months, 18 months-9 to 12 years (WT gain)	385	10 years	++ (18 months -9 to 12 year only)	WT gain 18 months -9/12 years associated with higher fasting, split, proinsulin and 30 minutes insulin (adjusted for HT & WT)
Finken (52)	obs	b-3 months (WT gain)	346	19 years	++	WT gain b-3 months associated with higher fasting insulin resistance
Kerkhof (49)	obs	b-term, term-3 months (WT gain, adj. length)	162	21 years	0	Insulin sensitivity was not associated with WT gain during any period between b-12 months
Hovi (53)	obs	b-term (WT gain)	100	22 years	++ (only in SGA, not AGA)	WT gain b-term associated with higher fasting and 2 hour insulin levels; only in SGA subgroup (n = 31) (adjusted for BMI)
(c)CVD risk factors						
Bracewell (54)	obs	b-term, term-30 months, term-6 years (WT gain)	241	6 years	0 (BP)	WT gain in any period was unrelated to BP at 6 year (adjusted for BMI)
Belfort (33)	obs	term-12 months (WT gain)	666	6 years	++ (BP)	WT gain term-12 months associated with modestly higher BP (in adjusted model, SBP was 0.7 mm Hg higher vs. slower growing infants).
Ludwig-Auser (47)	obs	b-14 days (Energy intake)	61	14 years	0 (BP)	Infants with intakes >70 vs. < 70 kcal/kg/day were taller and heavier at the age of 14 years
Keijzer-Veen (55)	obs	b-5 years (WT gain)	588	19 years	++ (BP)	Also positive association with childhood height growth
Mortaz (57)	obs	b-discharge; 18 months (WT gain)	412	11 years	0 (Lipids)	WT gain to 18 months was unrelated to various cholesterol metabolism parameters (adjusted for current size)
Kerkhof (49)	obs	term-3 months, 9-12 months (WT gain)	162	21 years	++ (Lipids) - (BP)	WT gain term-3 months -> higher TChol & LDL. WT gain 9-12 months -> higher TChol, LDL & ApoB. No associations with BP
Singhal (58)	obs	b-4 weeks (WT gain)	216	15 years	++ (FMD)	FMD was 4% lower in adolescents with high vs. low WT gain (adjusted for HT & WT)
Finken (56)	obs	3-12 months (WT gain)	346	19 years	++ (CIMT) - (Lipids)	WT gain 3-12 months -> greater CIMT (but not when adjusted for height). No associations with lipid profile

'++' statistically significant positive association; '+' nonsignificant positive trend; '0' no association; '-' nonsignificant inverse trend; '-/' significant inverse association.

weight gain or head growth more consistently associated with later outcomes. The dissonance between findings of intervention and observational studies raises the possibility of confounding in the latter by other factors, such as neonatal morbidities that could directly affect both growth and neurocognitive outcomes, although the paucity of intervention studies limits conclusions.

In relation to later adiposity, our review of intervention studies to promote postnatal growth in preterm infants found no studies that assessed adiposity at ages older than one year; of three trials, two promoted weight gain without increasing percentage body fat, while in the third, the enriched formula milk intervention led to lower weight gain, perhaps as a result of lower milk intake. Among

observational studies with data on later adiposity, the two larger studies found that greater weight gain from birth to three months corrected age was associated with a higher percentage body fat in young adulthood, with a weaker effect of weight gain from age 3–12 months; smaller studies reported no or variable associations between postnatal weight gain and percentage body fat at the ages of two year and 14 year. For insulin resistance, one intervention study that promoted faster postnatal growth led to normalised fasting 32–33 split proinsulin levels at the age of 15 year relative to children born at term, whereas those who grew more slowly in hospital had reduced proinsulin levels in adolescence. Findings were inconsistent among the four observational studies and only one reported an association between faster growth and later insulin resistance independent of body composition. No study in preterm infants examined relations between nutritional intervention to promote growth and other cardiovascular risk factors. While observational studies variably reported some positive associations between faster early growth and arterial blood pressure, total cholesterol levels, flow mediated dilatation and carotid intima-media thickness, most did not include adjustment for body size at the time of outcome assessment.

An important limitation of this review was the inability to perform quantitative summaries and to consider effect sizes arising from the paucity of studies, the variability in which these were reported and the inconsistency of adjustment for generally agreed potentially confounding influences, most notably current body size. A further limitation is that the data available did not allow us to consider growth conditional on the infant's size at birth; this is important as a previous systematic review found that larger size at birth is associated with a higher risk of later obesity (59), and postnatal growth patterns differ in small and large infants (60). Potential sources of bias widely prevalent in the studies considered included: insufficient description of participants, high attrition rates in both the intervention and observational studies, and inadequate consideration of confounding factors. Publication bias may be a further source of error and was not formally analysed in our review due to the absence of quantitative summaries.

It is important to recognise that these findings in preterm infants may not be applicable to term-SGA infants; focused studies in this group are needed to determine whether developmental adaptations induced before birth in term-SGA infants result in their responses to nutritional interventions to promote growth being different to those of preterm infants. In this respect, a previous systematic review concluded that term infants who grow rapidly during infancy are at increased risk of subsequent obesity, but did not consider neurocognitive outcomes (59).

Prematurity has a high and increasing prevalence worldwide. It is widely recognised that the growth of preterm infants is frequently suboptimal, with many being discharged at lower percentiles for weight, head circumference and length than those at which they were born (61). Moreover, preterm infants are particularly susceptible to developmental programming of adverse neurodevelopmental

tal, body composition and metabolic outcomes. Despite some evidence that the prevalence of childhood overweight and obesity is no longer rising in a number of populations the prevalence remains at an unacceptably high level. This high prevalence has major implications for the global burden of ill health and disease and preterm infants are an important group in which to optimise early nutrition and later outcomes. Having common outcome measures for infant nutrition trials in both preterm and term infants would lead to a strengthened evidence base for nutritional interventions to improve growth and long-term outcomes during this important period of development. A recent systematic review found that early parenteral nutrition in preterm infants improves short-term growth outcomes (62). Among very preterm infants nutrition is often suboptimal (63), and while there is yet no evidence linking progressive advancement of enteral milk feeds to risk of adverse short-term outcomes, such as necrotising enterocolitis and late-onset infection, the need for further trials is recognised (64).

In summary, only a few predischARGE intervention studies to promote growth in preterm infants have information on later neurocognitive, adiposity and insulin resistance/cardiovascular risk factor outcomes. While there is abundant and consistent evidence from observational studies linking faster postnatal growth to better neurocognitive outcomes in preterm infants, these studies show no obvious windows of association and there is a high risk of confounding by other factors/disease processes that affect both growth and cognition. Where associations are reported in observational studies linking faster postnatal growth to adverse cardiovascular risk markers in preterm infants, the findings have often not been adjusted for body size at the time of the outcome measurements. Moreover, comparisons were often not made to the normal ranges of these outcome parameters in unselected populations. Further research is needed to determine the optimal growth in preterm infants to achieve neurocognitive benefits while minimising the longer-term risk of chronic disease. We therefore strongly support the recommendation of the COMMENT initiative (65) that all nutritional intervention studies in preterm and term infants should report effects on weight gain and growth, as well as later body composition and neurocognitive outcomes.

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AUTHOR CONTRIBUTIONS

KK and KKO had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in study concept and design. KK participated in acquisition of data. KK participated in statistical analysis. All authors participated in analysis and interpretation of data. All authors participated in drafting of the manuscript. All authors participated in critical revision of the manuscript.

CONFLICT OF INTEREST DISCLOSURES

All authors have completed and submitted the journal's Form for Disclosure of Potential Conflicts of Interest and none were reported.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Gain-outcome graph of weight gain and adiposity.

Figure S2 Gain-outcome graph of weight gain and insulin levels.

Figure S3 Gain-outcome graph of weight gain and CVD risk.