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.

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 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 birthweight, 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 birthweight 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; premmie 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

| 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 | | | | | | |
| Basini (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) |
| Tudehope* (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-SGA 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-36 week gestation | ? | 24 months (BSID) | ++ | Growth failure between b-36 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 |
| 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,NS |
| Powers (28) | obs | 6-36 months | 135 | 36 months (BSID) | ++ | Similar associations with HC gain | G,NS |
| 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,NS,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,NS |
| Glaas (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,NS |
| 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,NS |
| 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,SIQ |
| 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,NS |
| 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,NS |
| 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,NS |
| Ford* (36) | obs | b-2 year | 83 | 24 months (BSID) | 0 | ? | G,N |
| Kuban (37) | obs | b-2 year | 1200 | 24 months (BSID) | ++ | | G,NS |
| Wood (38) | obs | b-term, term-30 months | 283 | 30 months (BSID, CP, NDI) | 0 | | |
| Design       | Timing of exposure | N                    | Age at outcome | Summary result | Comments | Adjustment |
|--------------|-------------------|----------------------|----------------|----------------|----------|------------|
| Hack* (39)   | obs               | 139                  | 30 months (SB)| ++ (8 months)  | Positive association with HC at 8 months, but not HC growth 8-20 months | G,N,S     |
|             |                   |                      |                |                |          |            |
| Powers (28)  | obs               | 135                  | 56 months (NDI)| ++ (NDI only)  | Positive associations also with WI growth in both SGA and AGA preterm infants | G,N,S     |
|             |                   |                      |                |                |          |            |
| Franz (29)   | obs               | 219                  | 5.4 years (KABC, NDI) | ++ (NDI only)  | Positive association with HC growth in both SGA and AGA preterm infants. Compared catch-up HC growth to no-catch-up group | G,N,S     |
|             |                   |                      |                |                |          |            |
| Claas (30)   | obs               | 101                  | 5.5 years (WPPSI, M-ABC) | ++            | Positive associations with HC growth in both SGA and AGA preterm infants. Compared catch-up HC growth to no-catch-up group | G,N,S     |
|             |                   |                      |                |                |          |            |
| Stathis* (40)| obs               | 87                   | 6 years (RWM)  | ++ (b-4 months only) | Positive association with HC growth in both SGA and AGA preterm infants. Compared catch-up HC growth to no-catch-up group | G,N,S     |
|             |                   |                      |                |                |          |            |
| Brandt (41)  | obs               | 51                   | 72 months (SB) | ++ (WMI only)  | Positive associations also with WI growth in both SGA and AGA preterm infants. Compared catch-up HC growth to no-catch-up group | G,N,S     |
|             |                   |                      |                |                |          |            |
| Cooke (42)   | obs               | 280                  | 8 years (M-ABC, WI) | ++ (MMI only)  | Positive associations also with WI growth in both SGA and AGA preterm infants. Compared catch-up HC growth to no-catch-up group | G,N,S     |
|             |                   |                      |                |                |          |            |
| Cooke (43)   | obs               | 194                  | 8 years (WISC, WRAT, M-ABC) | ++ (MMI only)  | Positive associations also with WI growth in both SGA and AGA preterm infants. Compared catch-up HC growth to no-catch-up group | G,N,S     |
|             |                   |                      |                |                |          |            |
| Kan (32)     | obs               | 179                  | 8 years (WISC, WRAT, M-ABC) | ++ (MMI only)  | Positive associations also with WI growth in both SGA and AGA preterm infants. Compared catch-up HC growth to no-catch-up group | G,N,S     |
|             |                   |                      |                |                |          |            |
| Belfort (33) | obs               | 905                  | 8 years (WISC, WRAT, M-ABC) | ++ (MMI only)  | Positive associations also with WI growth in both SGA and AGA preterm infants. Compared catch-up HC growth to no-catch-up group | G,N,S     |
|             |                   |                      |                |                |          |            |

‘++’ statistically significant positive association; ‘+’ nonsignificant positive trend; ‘0’ no association; ‘−’ nonsignificant 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 = Comprehensive preschool and primary scale of intelligence; GMDS = Griffiths mental development scale; KABC = Kaufman assessment battery for children; M-ABC = Movement assessment battery for children; PABCL = Peabody assessment of basic concepts and language; PPVT = Peabody picture vocabulary test; SB = Stanford Binet Intelligence Test; SB-III = Stanford-Binet Intelligence Scale – Third Edition; SB-IV = Stanford-Binet Intelligence Scale – Fourth Edition; SB-5 = Stanford-Binet Intelligence Scale – Fifth Edition; SB-6 = Stanford-Binet Intelligence Scale – Sixth Edition; SB-7 = Stanford-Binet Intelligence Scale – Seventh Edition; 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.
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.
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 head 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
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 variably 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...
weight gain may be associated with the risk for overweight and obesity in later life. However, the evidence from intervention studies is inconsistent and limited, with some studies reporting increased weight gain and others reporting no significant association. The reason for these discrepancies may be due to differences in study design, population characteristics, and the timing of the intervention. Furthermore, the long-term outcomes for these children remain unclear, and more research is needed to understand the relationship between early weight gain and later health outcomes.

In conclusion, the long-term effects of early weight gain are still uncertain, and further research is needed to better understand the relationship between early growth and later health outcomes. It is important to continue monitoring and assessing the growth of preterm infants to identify those at risk for long-term health problems and to develop effective intervention strategies to promote healthy growth patterns.

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**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**

| Study | Design | Timing of exposure (nature) | N  | Age at outcome | Summary result | Comments |
|-------|--------|-----------------------------|----|----------------|----------------|----------|
| Kerkhof (49) | obs | b-term, term-3 months (WT gain, adj. length) | 162 | 21 years | ++ | Intervention increased WT gain and both fat and lean mass; Stronger effect of early vs. later WT gain on BMI & %FM. Findings persisted when adjusted for height. Compared rapid (<0.67 SD) vs. slow (<0.67 SD) catch-up infancy WT gain. Stronger effect of early vs. later catch-up growth. |
| Ludwig-Auser (47) | obs | b-14 days (Energy intake) | 61 | 14.5 years | 0 | Infants with intake >70 vs. < 70 kcal/kg/day 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) | 162 | 21 years | ++ | Intervention increased WT gain and both fat and lean mass; Stronger effect of early vs. later WT gain on BMI & %FM. Findings persisted when adjusted for height. Compared rapid (<0.67 SD) vs. slow (<0.67 SD) catch-up infancy WT gain. Stronger effect of early vs. later catch-up growth. |
| Singhal (50) | int | b-4 weeks (Preterm formula) | 216 | 15 years | ++ | Higher nutrient diet increased fasting 33-34 proinsulin levels at 13–16 years (adjusted for BMI). WT gain 18 months -9/12 years associated with higher fasting, split, proinsulin and 30 minutes insulin (adjusted for HT & WT). |
| Fewtrell (51) | obs | b-18 months, 18 months-9 to 12 years (WT gain) | 385 | 10 years | ++ (18 months-9 to 12 years only) | Intervention increased WT gain and both fat and lean mass; Stronger effect of early vs. later WT gain on BMI & %FM. Findings persisted when adjusted for height. Compared rapid (<0.67 SD) vs. slow (<0.67 SD) catch-up infancy WT gain. Stronger effect of early vs. later catch-up growth. |
| Finken (52) | obs | b-3 months (WT gain) | 346 | 19 years | ++ | Intervention increased WT gain and both fat and lean mass; Stronger effect of early vs. later WT gain on BMI & %FM. Findings persisted when adjusted for height. Compared rapid (<0.67 SD) vs. slow (<0.67 SD) catch-up infancy WT gain. Stronger effect of early vs. later catch-up growth. |
| 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. |
| Howi (53) | obs | b-term (WT gain) | 100 | 22 years | ++ (only in SGA, not AGA) | Intervention increased WT gain and both fat and lean mass; Stronger effect of early vs. later WT gain on BMI & %FM. Findings persisted when adjusted for height. Compared rapid (<0.67 SD) vs. slow (<0.67 SD) catch-up infancy WT gain. Stronger effect of early vs. later catch-up growth. |
| Bracewell (54) | obs | b-term, term-30 months, term-6 months (WT gain) | 241 | 6 years | 0 (BP) | Adjustment for BMI. WT gain in any period was unrelated to BP at 6 year (adjusted for BMI). WT gain term-12 months associated with modestly higher BP (in adjusted model, SBP was 0.7 mm Hg higher vs. slower growing infants). Infants with intake >70 vs. < 70 kcal/kg/day were taller and heavier at the age of 14 years. |
| Belfort (33) | obs | term-12 months (WT gain) | 666 | 6 years | ++ (BP) | Adjustment for BMI. WT gain in any period was unrelated to BP at 6 year (adjusted for BMI). WT gain term-12 months associated with modestly higher BP (in adjusted model, SBP was 0.7 mm Hg higher vs. slower growing infants). Infants with intake >70 vs. < 70 kcal/kg/day were taller and heavier at the age of 14 years. |
| Ludwig-Auser (47) | obs | b-14 days (Energy intake) | 61 | 14 years | 0 (BP) | Adjustment for BMI. WT gain in any period was unrelated to BP at 6 year (adjusted for BMI). WT gain term-12 months associated with modestly higher BP (in adjusted model, SBP was 0.7 mm Hg higher vs. slower growing infants). Infants with intake >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) | Adjustment for BMI. WT gain in any period was unrelated to BP at 6 year (adjusted for BMI). WT gain term-12 months associated with modestly higher BP (in adjusted model, SBP was 0.7 mm Hg higher vs. slower growing infants). Infants with intake >70 vs. < 70 kcal/kg/day were taller and heavier at the age of 14 years. |
| Mortaz (57) | obs | b-discharge; 18 months (WT gain) | 412 | 11 years | 0 (Lipids) | Adjustment for BMI. WT gain in any period was unrelated to BP at 6 year (adjusted for BMI). WT gain term-12 months associated with modestly higher BP (in adjusted model, SBP was 0.7 mm Hg higher vs. slower growing infants). Infants with intake >70 vs. < 70 kcal/kg/day were taller and heavier at the age of 14 years. |
| Kerkhof (49) | obs | term-3 months, 9–12 months (WT gain) | 162 | 21 years | ++ (Lipids) | Adjustment for BMI. WT gain in any period was unrelated to BP at 6 year (adjusted for BMI). WT gain term-12 months associated with modestly higher BP (in adjusted model, SBP was 0.7 mm Hg higher vs. slower growing infants). Infants with intake >70 vs. < 70 kcal/kg/day were taller and heavier at the age of 14 years. |
| Singhal (58) | obs | b-4 weeks (WT gain) | 216 | 15 years | ++ (FMD) | Adjustment for BMI. WT gain in any period was unrelated to BP at 6 year (adjusted for BMI). WT gain term-12 months associated with modestly higher BP (in adjusted model, SBP was 0.7 mm Hg higher vs. slower growing infants). Infants with intake >70 vs. < 70 kcal/kg/day were taller and heavier at the age of 14 years. |
| Finken (56) | obs | 3–12 months (WT gain) | 346 | 19 years | ++ (CIMT) | Adjustment for BMI. WT gain in any period was unrelated to BP at 6 year (adjusted for BMI). WT gain term-12 months associated with modestly higher BP (in adjusted model, SBP was 0.7 mm Hg higher vs. slower growing infants). Infants with intake >70 vs. < 70 kcal/kg/day were taller and heavier at the age of 14 years. |

*++* statistically significant positive association; *+* nonsignificant positive trend; *0* no association; *−* nonsignificant inverse trend; *−−* significant inverse association.
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, 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.

ACKNOWLEDGEMENTS

This work was conducted by an expert group of the European branch of the International Life Sciences Institute (ILSI Europe). The Metabolic Imprinting Task Force members of ILSI Europe nominated renowned scientists based on their expertise within the chosen scientific area of the study to create the expert advisory group. Expert groups comprise of at least 50% scientists from academia and the public sector and up to 50% industry scientists. The expert group carried out the work, that is collecting/analysing data/information and writing the scientific paper independently of the task force. Experts are not paid for the time spent on this work; however, the nonindustry members within the expert group received travel support from the
Metabolic Imprinting Task Force to attend meetings to discuss the review. Industry members of this task force are listed on the ILSI Europe website at www.ilsi.eu and the institute has a transparency policy whereby all of this information is freely available on the website. The authors would like to thank Dr Florence Rochat who was a former member of this expert group for their active contribution to this work. This publication was coordinated by Dr Pratima Rao Jasti and Dr Jackie Whyte, Scientific Project Managers at ILSI Europe. For further information about ILSI Europe, please email info@ilsi.europe.be or call +32 2 771 00 14. The opinions expressed herein and the conclusions of this publication are those of the authors and do not necessarily represent the views of ILSI Europe nor those of its member companies.

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.

FUNDING/SUPPORT
The expert group received funding from the ILSI Europe Metabolic Imprinting Task Force (please see acknowledgments for further information). Industry members of this task force are listed on the ILSI Europe website at www.ilsi.eu. KMG is supported by the National Institute for Health Research through the NIHR Southampton Biomedical Research Centre and by the European Union’s Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition under grant agreement no 289346.

ROLE OF SPONSOR
The funding organisations had no role in the design, collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

References
1. Godfrey KM, Gluckman PD, Hanson MA. Developmental origins of metabolic disease: life course and intergenerational perspectives. Trends Endocrinol Metab 2010; 21: 199-205.
2. Osmond C, Barker DJ. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environ Health Perspect 2000; 108 (Suppl. 3): 545–53.
3. Wells JC, Chomtho S, Fewtrell MS. Programming of body composition by early growth and nutrition. Proc Nutr Soc 2007; 66: 423–34.
4. Widdowson EM, McCance RA. The effect of finite periods of undernutrition at different ages on the composition and subsequent development of the rat. Proc R Soc Lond B Biol Sci 1965; 158: 529–42.
5. Patterson CM, Bouret SG, Park S, Irani BG, Dunn-Meynell AA, Levin BE. Large litter rearing enhances leptin sensitivity and protects selectively bred diet-induced obese rats from becoming obese. Endocrinology 2010; 151: 4270–9.
6. Terry-Adkins JL, Ozanne SE. Mechanisms of early life programming: current knowledge and future directions. Am J Clin Nutr 2011; 94: 1765S–71S.
7. Lanigan J, Singhal A. Early nutrition and long-term health: a practical approach. Proc Nutr Soc 2009; 68: 422–9.
8. Embleton ND. Early nutrition and later outcomes in preterm infants. World Rev Nutr Diet 2013; 106: 26–32.
9. Baird J, Lucas P, Kleijnen J, Fisher D, Roberts H, Law C. Defining optimal infant growth for lifetime health: a systematic review of lay and scientific literature. Available from URL http://www.mrc.soton.ac.uk/systematic-review/2005.
10. Biasini A, Marvulli L, Neri E, China M, Stella M, Monti F. Growth and neurological outcome in ELBW preterms fed with human milk and extra-protein supplementation as routine practice: do we need further evidence? J Matern Fetal Neonatal Med 2012; 25(Suppl. 4): 72–4.
11. Cooke RJ, Embleton ND, Griffin IJ, Wells JC, McCormick KP. Feeding preterm infants after hospital discharge: growth and development at 18 months of age. Pediatr Res 2001; 49: 719–22.
12. Aimone A, Rovet J, Ward W, Jefferies A, Campbell DM, Asztalos E, et al. Growth and body composition of human milk-fed premature infants provided with extra energy and nutrients early after hospital discharge: 1-year follow-up. J Pediatr Gastroenterol Nutr 2009; 49: 456–66.
13. Lucas A, Fewtrell MS, Morley R, Singhal A, Abbott RA, Isaacs E, et al. Randomized trial of nutrient-enriched formula versus standard formula for postdischarge preterm infants. Pediatrics 2001; 108: 705–11.
14. Lucas A, Morley R, Cole TJ, Gore SM. A randomised multicentre study of human milk versus formula and later development in preterm infants. Arch Dis Child Fetal Neonatal Ed 1994; 70: F141–6.
15. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ 1998; 317: 1481–7.
16. O’Connor DL, Jacobs J, Hall R, Adamkin D, Auestad N, Castillo M, et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula. J Pediatr Gastroenterol Nutr 2003; 37: 437–46.
17. Huang C, Martorell R, Ren A, Li Z. Cognition and behavioural development in early childhood: the role of birth weight and postnatal growth. Int J Epidemiol 2013; 42: 160–71.
18. Tudehope DI, Burns Y, O’Callaghan M, Mohay H, Silcock A. The relationship between intrauterine and postnatal growth on the subsequent psychomotor development of very low birthweight (VLBW) infants. Aust Paediatr J 1983; 19: 3–8.
Ong et al.

Postnatal growth in preterm infants and later health

19. Cooke RJ. Postnatal growth and development in the preterm and small for gestational age infant. Nestle Nutr Workshop Ser Pediatr Program 2010; 65: 85–95; discussion 6-8.

20. Belfort MB, Rifas-Shiman SL, Sullivan T, Collins CT, McPhee AJ, Ryan P, et al. Infant growth before and after term: effects on neurodevelopment in preterm infants. Pediatrics 2011; 128: e899–906.

21. Sices L, Wilson-Costello D, Minich N, Friedman H, Hack M. Postdischarge growth failure among extremely low birth weight infants: correlates and consequences. Paediatr Child Health 2007; 12: 22–8.

22. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006; 117: 1253–61.

23. Latal-Hajnal B, von Siebenthal K, Kovari H, Buczeri HU, Largo 32. Kan E, Roberts G, Anderson PJ, Doyle LW. Victorian Infant
24. Franz AR, Pohlandt F, Bode H, Mihatsch WA, Sander S, Kron 30. Claas MJ, de Vries LS, Koopman C, Uniken Venema MM,
25. Shah PS, Wong KY, Merko S, Bishara R, Dunn M, Asztalos E, 33. Weisglas-Kuperus N, Hille ET, Duivenvoorden HJ, Finken MJ,
26. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, 34. Koo WW, Hockman EM. Posthospital discharge feeding for
27. Kelleher KJ, Casey PH, Brady NR, Stafford RL. Catch-up head growth and motor performance in very-low-birthweight infants. Clin 35. Simon NP, Brady NR, Stafford RL. Catch-up head growth and
28. Ford G, Rickards A, Kitchen WH, Ryan MM, Lissenden JV. Relationship of growth and psychoneurologic status of 2-year-old children of birthweight 500-999 g. Early Hum Dev 1986; 13: 529–37.

29. Kuban KC, Allred EN, O’Shea TM, Paneth N, Westra S, Miller C, et al. Developmental correlates of head circumference at birth and two years in a cohort of extremely low gestational age newborns. J Pediatr 2009; 155: 344–9 e13.

30. Wood NS, Costeole K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR, et al. The EPIcure study: growth and associated problems in children born at 25 weeks of gestational age or less. Arch Dis Child Fetal Neonatal Ed 2003; 88: F492–500.

31. Hack M, Breslau N. Very low birth weight infants: effects of brain growth during infancy on intelligence quotient at 3 years of age. Pediatrics 1986; 77: 196–202.

32. Stathis SL, O’Callaghan M, Harvey J, Rogers Y. Head circumference in ELBW babies is associated with learning difficulties and cognition but not ADHD in the school-aged child. Dev Med Child Neurol 1999; 41: 375–80.

33. Brandt I, Sticker EJ, Lentze MJ. Catch-up growth of head circumference of very low birth weight, small for gestational age preterm infants and mental development to adulthood. J Pediatr 2003; 142: 465–8.

34. Cooke RW, Foulader-Hughes L. Growth impairment in the very preterm and cognitive and motor performance at 7 years. Arch Dis Child 2003; 88: 482–7.

35. Cooke RW. Are there critical periods for brain growth in children born preterm? Arch Dis Child Fetal Neonatal Ed 2006; 91: F17–20.

36. Koo WW, Hockman EM. Posthospital discharge feeding for preterm infants: effects of standard compared with enriched milk formula on growth, bone mass, and body composition. Am J Clin Nutr 2006; 84: 1357–64.

37. Cooke RJ, McCormick K, Griffin IJ, Embleton N, Faulkner K, Wells JC, et al. Feeding preterm infants after hospital discharge: effect of diet on body composition. Pediatr Res 1999; 46: 461–4.

38. Hernandez MI, Rossel K, Pena V, Cavada G, Avila A, Iniguez G, et al. Leptin and IGF-I/II during the first weeks of life in ELBW newborns. J Pediatr 2009; 155: 344–9 e13.

39. Kerkhof GF, Willemsen RH, Leunissen RW, Breukhoven PE, Dekker FW, et al. Associations between prenatal and infancy growth and neurodevelopment in very low birth weight. Early Hum Dev 2008; 84: 409–16.

40. Belfort MB, Martin CR, Smith VC, Gillman MW, McCormick MC. Infant weight gain and school-age blood pressure and cognition in former preterm infants. Pediatrics 2010; 125: e1399–408.

41. Eyer JS, Simonsick EM, Johnson KA, Cauley JA, Kritchevsky SB, Salive ME. Physical activity and long-term adult survival in a community-dwelling population of older adults. J Gerontol A Biol Sci Med Sci 2006; 61: 351–5.

42. Kwiterovich PO, Pearson TA, Mosca L. Identification and treatment of children for primary and secondary prevention of cardiovascular disease. Pediatrics 2006; 117: 568–81.

43. Rosenblatt DL, Fung MH, Brown SA, Jeffery RW, Popkin BM. Trends in energy and macronutrient intake among men and women in the United States, 1980–2000. J Am Diet Assoc 2004; 104: 1169–78.

44. Cole TJ, Bellisle E, Homoet J-P, Lobstein T. Obesity in children and young people: a brief review of its definition, prevalence, and consequences. Arch Dis Child Fetal Neonatal Ed 2007; 92: F1–11.

45. Koo WW, Hockman EM. Posthospital discharge feeding for preterm infants: effects of standard compared with enriched milk formula on growth, bone mass, and body composition. Am J Clin Nutr 2006; 84: 1357–64.

46. Cooke RW, Foulader-Hughes L. Growth impairment in the very preterm and cognitive and motor performance at 7 years. Arch Dis Child 2003; 88: 482–7.

47. Ludwig-Auser H, Sherar LB, Erlandson MC, Baxter-Jones AD, Jackowski SA, Arnold C, et al. Influence of nutrition provision during the first two weeks of life in premature infants on adolescent body composition and blood pressure. Zhongguo Dang Dai Er Ke Za Zhi 2013; 15: 161–70.

48. Eyer JS, Simonsick EM, Johnson KA, Cauley JA, Kritchevsky SB, Salive ME. Physical activity and long-term adult survival in a community-dwelling population of older adults. J Gerontol A Biol Sci Med Sci 2006; 61: 351–5.

49. Kerkhof GF, Willemsen RH, Leunissen RW, Breukhoven PE, Dekker FW, et al. Associations between prenatal and infancy growth and neurodevelopment in very low birth weight. Early Hum Dev 2008; 84: 409–16.

50. Belfort MB, Martin CR, Smith VC, Gillman MW, McCormick MC. Infant weight gain and school-age blood pressure and cognition in former preterm infants. Pediatrics 2010; 125: e1419–26.

51. Weisglas-Kuperus N, Hille ET, Duivenvoorden HJ, Finken MJ, Wit JM, van Buuren S, et al. Intelligence of very preterm or very low birthweight infants in young adulthood. Arch Dis Child Fetal Neonatal Ed 2009; 94: F196–200.
52. Finken MJ, Keijzer-Veen MG, Dekker FW, Frolich M, Hille ET, Romijn JA, et al. Preterm birth and later insulin resistance: effects of birth weight and postnatal growth in a population based longitudinal study from birth into adult life. *Diabetologia* 2006; 49: 478–85.

53. Hovi P, Andersson S, Eriksson JG, Jarvenpaa AL, Strang-Karlsson S, Makitie O, et al. Glucose regulation in young adults with very low birth weight. *N Engl J Med* 2007; 356: 2053–63.

54. Bracewell MA, Hennessy EM, Wolke D, Marlow N. The EPICure study: growth and blood pressure at 6 years of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2008; 93: F108–14.

55. Keijzer-Veen MG, Finken MJ, Nauta J, Dekker FW, Hille ET, Frolich M, et al. Is blood pressure increased 19 years after intrauterine growth restriction and preterm birth? A prospective follow-up study in The Netherlands. *Pediatrics* 2005; 116: 725–31.

56. Finken MJ, Inderson A, Van Montfoort N, Keijzer-Veen MG, van Weert AW, Carfil N, et al. Lipid profile and carotid intima-media thickness in a prospective cohort of very preterm subjects at age 19 years: effects of early growth and current body composition. *Pediatr Res* 2006; 59: 604–9.

57. Mortaz M, Fewtrell MS, Cole TJ, Lucas A. Birth weight, subsequent growth, and cholesterol metabolism in children 8-12 years old born preterm. *Arch Dis Child* 2001; 84: 212–7.

58. Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? *Circulation* 2004; 109: 1108–13.

59. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ* 2005; 331: 929.

60. Ong KK. Catch-up growth in small for gestational age babies: good or bad? *Curr Opin Endocrinol Diabetes Obes* 2007; 14: 30–4.

61. Johnson MJ, Wootton SA, Leaf AA, Jackson AA. Preterm birth and body composition at term equivalent age: a systematic review and meta-analysis. *Pediatrics* 2012; 130: e640–9.

62. Moyes HE, Johnson MJ, Leaf AA, Cornelius VR. Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. *Am J Clin Nutr* 2013; 97: 816–26.

63. Westin V, Stoltz Sjostrom E, Ablsson F, Domellof M, Norman M. Perioperative nutrition in extremely preterm infants undergoing surgical treatment for patent ductus arteriosus is suboptimal. *Acta Paediatr* 2014; 103: 282–8.

64. SIFT Investigators Group. Early enteral feeding strategies for very preterm infants: current evidence from Cochrane reviews. *Arch Dis Child Fetal Neonatal Ed* 2013; 98: F470–2.

65. Koletzko B, Szajewska H, Ashwell M, Shamir R, Aggett P, Baerlocher K, et al. Documentation of functional and clinical effects of infant nutrition: setting the scene for COMMENT. *Ann Nutr Metab* 2012; 60: 222–32.

**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.