Early Infancy as a Critical Period for Development of Obesity and Related Conditions

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Abstract
The current obesity epidemic has affected even the youngest children in our societies, including those in the first months of life. Animal experiments suggest that the early postnatal period may be critical to development of healthful energy homeostasis and thus prevention of obesity. In humans, observational studies and follow-up of randomized feeding trials show that rapid weight gain in the first half of infancy predicts later obesity and higher blood pressure. Despite the mounting consistency of results, several questions remain to be answered before clinical or public health implications are clear. These include the need for body composition data in infancy and data from the developing world to identify modifiable determinants of gain in adiposity in the early weeks of life, to mount interventions to modify these determinants, to examine tradeoffs of more vs. less rapid weight gain for different outcomes, and to incorporate any interventions that prove to be efficacious into clinical and public health practice in a cost-effective manner.

Obesity is now the most burdensome and costly nutritional condition worldwide. Childhood obesity not only presages adult obesity, diabetes, and heart disease, but it is also harmful to the child [1]. Overweight and obese children are at higher risk for developing asthma and orthopedic problems, they have worse cardiometabolic risk profiles, and they suffer psychosocial adversity. Once obesity is present, tenacious physiological processes resist weight loss [2]. By age 5 years, childhood obesity is fairly resistant to change throughout the remainder of childhood [3]. For these reasons, early childhood prevention of obesity is a key to avoiding myriad health problems. But how early in childhood?
Infancy is a period of rapid growth in stature and in neurocognitive, motor, and social development. Weight gain in the first 6 months is primarily gain in fat, whereas fat-free mass accumulates preferentially after that age [4]. Organs and systems are in developmentally plastic stages in which they may be particularly sensitive to perturbations. For example, in rat experiments from almost half a century ago, modification of energy intake in the first weeks of life had lifelong effects on weight gain even if normal energy intake was restored afterwards [5]. In contrast, energy reduction later in life had only a transient effect on weight gain. In a more recent rat model, administration of leptin postnatally abolished the otherwise permanent offspring metabolic effects of prenatal maternal energy restriction [6]. These and other animal experiments raise the possibility that the early postnatal period may be critical to development of healthful energy homeostasis and thus prevention of obesity and related conditions.

These issues are brought into sharper focus by the fact that the current obesity epidemic has affected even the youngest children in our societies. In a large study from a US-managed care population, from the early 1980s to the early 21st century the prevalence of overweight and obesity among 0- to 6-month-old infants rose from 10.4% to 17.0% [7]. Increases in older infants and preschoolers were more modest. Thus, questions naturally arise about infancy as a key period for development of obesity and its consequences.

Several studies now address the role of growth during infancy as a predictor of later adiposity. In 2005, for example, Baird et al. [8] published a systematic review of 10 studies that assessed the relation of infant weight gain with subsequent obesity. Relative risks of later obesity ranged from 1.17 to 5.70 among infants with more rapid weight gain in the first year of life. Associations were consistent for obesity at different ages and for people born over a period from 1927 to 1994.

Since 2005, more observational studies have appeared, some with measured adiposity outcomes, not just body mass index (BMI). Yliharsila et al. [9] measured body composition with an 8-polar bioimpedance system among almost 2,000 Finnish adult men and women whose weights and heights were available from child welfare and school records. Gain in BMI from birth to age 1 year, or 1 to 2, was associated with later lean, but not fat, mass. The authors did not subdivide the first year of life further, but inspection of the published figures in Barker et al. [10] from the same cohort gives the impression that the BMI of Finnish men who eventually developed coronary heart disease increased in the first ~3 months before decreasing (fig. 1).

Among several hundred French boys and girls, Botton et al. [11] showed that weight gain velocity after the age of 3 years predicts fat and fat-free mass in adolescence, as measured by a foot-to-foot bioimpedance device. In that study, weight gain velocity at 3 and 6 months predicted adolescent fat mass better than weight gain velocity at 1 or 2 years. The data from the French
cohort agree that weight gain velocity at age 1 or 2 years is a poor predictor of later fat mass.

Earlier data from the Finns [10] suggest that increasing BMI over the entire period from birth to 2 years does not predict higher (and may actually predict lower) risk of coronary heart disease as an adult, and data from Delhi on risk of impaired glucose intolerance appear to agree [12].

However, as in the Finnish cohort, early infancy in the Delhi cohort appeared to be a special period: gain in BMI in the first 6 months was related to both BMI and sum of skinfolds in adulthood [13].

Among 234 British 4- to 20-year-olds, Chomtho et al. [14] examined associations of early weight gain with fat mass and fat-free mass measured by the gold standard four-compartment model. They found that weight gain in the first 3 months of life predicted both fat mass and fat-free mass, weight gain from 3 to 6 months predicted fat mass only, and weight gain from 6 to 12 months predicted neither. Weight gain in the early months also predicted centrally deposited fat as indicated by waist circumference and (less so) by trunk fat mass estimated from dual X-ray absorptiometry.

Some data are emerging on relations of infant weight gain with cardiometabolic risk factors. In the US cohort study Project Viva, gain in weight-for-length from 0 to 6 months predicted not only higher BMI and sum of skinfolds, but
also blood pressure at age 3 years [15]. In a recent study from the UK's Barry Caerphilly cohort, a steeper trajectory of weight gain in the first 5 months of life predicted higher blood pressure in adulthood [16]. In both of these studies, birthweight was inversely related to blood pressure level, in agreement with many other studies [17]. In the Viva cohort, the effect of infant growth on 3-year blood pressure was more pronounced in infants born small-for-dates (fig. 2), but no similar effect modification by fetal growth was evident for BMI and skinfold outcomes. In the SWEDES study, weight gain from 0 to 6 months predicted not only adiposity but also a metabolic risk score at age 17. Gain from 3 to 6 years did not predict this cluster of metabolic risk factors [18].

Some other studies also indicate that weight gain in the first half of infancy is more predictive of later obesity than is weight gain later in infancy or childhood. For example, in a formula-only fed population, Stettler et al. [19] showed that weight gain in the 1st week of life was directly associated with overweight in adulthood. In a cohort culled from electronic medical records of well-child visits in a managed care organization, we recently observed that upward crossing of 2 major weight-for-length centiles in the first 6 months was both common and predicted a high risk of obesity 5 years later. Upward crossing from 6 to 12, 12 to 18, or 18 to 24 months was less common and less predictive (fig. 3).

As reported elsewhere in this volume, Lucas and Singhal have published a series of observational follow-up studies of a subset of participants in feeding trials of premature infants. The findings suggest that weight gain in the first few weeks is directly associated with adolescent blood pressure and plasma

![Fig. 2. Predicted difference in systolic blood pressure at age 3 years according to quartile of weight-for-length z score at birth and age 6 months, adjusted for child age, sex, height, and blood pressure measurement conditions, and maternal income, education, race, ethnicity, and smoking status. Reproduced with permission from Belfort et al. [15].](image-url)
insulin and leptin [20]. In more recent trials, term small-for-gestational age infants randomized to energy-enriched formula had more rapid weight gain from 0 to 9 months and higher fat mass and diastolic blood pressure at age 6–8 years [21].

Thus mounting evidence suggests that the first few months are critical for development of obesity and its related health conditions. This observation reveals a number of research imperatives:

1. The need for longitudinal body composition measures during infancy (the exposure period). Most studies have employed only weight measurements. Using weight-for-length is an improvement if length is measured by research standards [22]. Even the addition of length, however, is suboptimal. While weight and length are relevant for clinical decision making, relying on these as exposures in research studies does not provide sufficient information to investigate mechanism and determinants. For example, part of weight gain during infancy comprises lean mass rather than fat mass. Whether rapid increase in lean mass predicts adverse outcomes as well as fat mass is not known. Also in most of the existing literature, representation from developing countries, where stunting and wasting are still prevalent, is limited. The same is true for lower-income and racial/ethnic minority populations in western societies. More data are required to determine if, and why, associations differ across these and other populations.

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**Fig. 3.** Prevalence of obesity for boys at age 5 years (BMI >95th percentile) predicted by crossing upwards two major percentile lines on the CDC growth charts from 1 to 6, 6 to 12, 12 to 18, and 18 to 24 months of age. Unpublished data from HMO Nutrition Surveillance System.
The need to identify the modifiable determinants of gain in adiposity in the early weeks of life that also underlie long-term risks of obesity-related sequelae. Some determinants of infancy weight gain may predict later obesity, others not. Often we assume that mode of infant feeding must explain any association of infant weight gain with later obesity, but this assumption is not necessarily true. In Project Viva, while longer breastfeeding duration was associated with lower prevalence of obesity at age 3, this effect did not appear to be mediated by weight gain in the first 6 months (unpubl.). Also, in a seeming paradox, breastfeeding results in faster weight gain in the first few months than formula feeding; only later in infancy do breastfed infants have lower weights [23]. Perhaps overfeeding due to lack of responsiveness to infants’ satiety cues is more germane than just breast vs. bottle. It is also plausible that prenatal factors could play a role, factors such as maternal smoking, gestational weight gain, alterations in glucose-insulin homeostasis, or other nutrient-hormonal adaptations in the maternal-placental-fetal unit [24]. A preliminary analysis from Project Viva shows that gestational diabetes, as well as umbilical cord blood leptin concentration, is associated with less rapid gain in weight-for-length from birth to 6 months [25].

Once determinants are identified, the need to mount interventions to modify these determinants. As the nutritional, hormonal or other pathways that lead to harmful levels of weight gain are likely to be complex, so must any interventions to modify them take these complexities into account. In addition, interventions that improve some health outcomes may not do the same for others (see next section).

The need to examine tradeoffs of more vs. less rapid weight gain for different outcomes. At least among infants born preterm, more rapid weight gain in early infancy predicts better neurocognitive outcomes in childhood [26, 27]. Whether this same situation holds with term infants is less clear [28]. Thus, the amount of weight gain that optimizes both neurocognitive and cardiometabolic risk may differ by gestational age.

The need to educate clinicians, policy makers, and parents about the findings from these studies. It will not be enough to have pediatric clinicians identify rapid gainers from the usual growth charts, because the proper response is not yet known. For example, attempting to modify energy intake or expenditure among infants who are entrained by prenatal hormonal or genetic pathways to gain weight on a certain trajectory may cause at least as much harm as good. Should effective interventions be identified, a further challenge will be to incorporate such interventions into clinical and public health practice in a cost-effective manner.

‘How big should my baby be?’ is a question on the mind of most parents. Researchers, clinicians, and the public health community need to be able
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to answer that question. But they also need to address the follow-up challenge of how to achieve this optimal size for each infant. The answers to these questions hold great promise for prevention of obesity and related health outcomes.

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**References**

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Discussion

Dr. Sunga: In the Philippines, we also have an increasing incidence of obesity, and we have produced cross-sectional studies which looked at the association between cardiovascular risk factors and outcomes. Can you please define early growth or steep weight gain so that we would know when to intervene? Does this correspond to a weight of >2 standard deviations?

Dr. Gillman: In the US, there are typical ways the clinicians will flag excessive weight gain. They look at the growth charts and they look at the number of percentile lines that children cross. My point about the early infancy is that we are still in a stage of discovery rather than clinical application. We found that upward centile crossing in the first months of life does predict later obesity and other obesity-related consequences, but that doesn't tell us what to do about it. We need to find out more about the determinants of this phenomenon and the modifiable determinants of them before we can say what to do because I am a little concerned about clinicians finding babies who are crossing centiles and doing something to prevent that, which may do them more harm than good.

Dr. Islam: Is it possible to define the critical level of rapid weight gain in early infancy that can be a predictor of risk factors in later life.

Dr. Gillman: When we translate population epidemiologic findings into clinical decision making, there are whole series of steps we really should go through before we get to a point where we are sure about a clinical decision. So the first step is translating relative risks to absolute risks, and that's part of what we did here, so these are actually probabilities, not relative risks, because we make clinical decisions on absolute risks, not on relative risks. But then, the second thing would be what can
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we do about it, how effective are those interventions, what are the risks and benefits and how cost effective are the interventions, and I think we are only two steps into that whole clinical decision making round, and that's why I don't think there should be a grand statement or an authoritative organization saying what we should do about upper crossing in early infancy. I am glad to hear the counter argument to that, but I tend to be rather cautious clinically until things are proven.

Dr. Mobarak: Concerning your studies on early infantile growth which implicates cardiovascular disease. I was wondering whether you have taken into account potential confounding factors such as obesity, genetics, diet, parents' education and home environment. Did you do a control study for these things? Could you say that there is an effect of modification?

Dr. Gillman: In all the observational studies I have shown, the investigators have taken into account potential confounding factors. A confounding factor would be some third factor underlying both the infant growth and the later outcome that actually explains why the two are related, a noncausal explanation. In our studies in Project Viva, we always take account of the maternal and the paternal BMI; we take account of the demographic factors and the socioeconomic factors, as well as try to take account of some of the things that happen between birth and say 3 years of age like the diet and the physical activity of the child him or herself. In those particular studies that I showed you from Project Viva, taking account of these factors actually didn't change the estimates very much. Still, in observational studies we are left with the concern of residual confounding. In other words, did we not measure something that really accounts for this relationship, and that's why it's important to combine the data of observational studies with randomized control trials and with animal data to get the totality of the evidence and our best evidence of causation. Each of these study designs has strengths and weaknesses, and the totality of them gives us the best answer. Your other question is about effect modification; that question would be, is the relationship of infant weight gain and later obesity different in different subgroups, for example a higher or lower socioeconomic group, a different race or ethnicity, or for example if the mother is less or more obese. We haven't done those studies yet, but we are in the process of doing them.

Dr. Mehta: How can we alter infant feeding to change the trajectory of growth?

Dr. Gillman: I showed the slides on breastfeeding and how breastfeeders gain more weight in the early months of life just to raise the question about whether this is all a feeding phenomenon or whether it's really entrained by prenatal factors like the hormonal milieu. I want to point out that we need to raise new questions about what the determinants of growth are, and if it's something about maternal placental fetal hormonal factors that is entraining the weight or even the adiposity gain in the first 6 months of life, that leads us to new questions and possibly new interventions.

Dr. Davies: Could you make some comments about the apparent protective effect of prolonged breastfeeding on the development of overweight obesity in children?

Dr. Gillman: I think the state of the evidence is actually murky. Most observational studies, meta-analyses and systematic reviews of observational studies suggest that there is a protective effect of breastfeeding, either initiating, duration or exclusivity, on the incidence or prevalence of obesity later in life. The evidence that we have from the biggest randomized control trial, the one in Belarus, suggests that that's not true, and there is one meta-analysis of observational studies that suggests when you take all the confounding into account, maybe you don't have any effect. I don't know of any studies that suggest that breastfeeding promotes obesity, so I think at the end of the day there is probably going to be some small to moderate relationship between duration of exclusive breastfeeding and protection against later obesity.
**Dr. Makrides:** I have a question that relates to the interaction between the hormonal and feeding milieu. You mentioned that leptin levels in cord blood weren't related to nutritional factors that you measured during pregnancy. After birth, leptin does appear in breast milk. Can you comment on the variability of leptin in breast milk and whether we need to consider hormonal feeding interactions in the post-birth period?

**Dr. Gillman:** One of the hypotheses about how breastfeeding, especially breast milk, could protect against later obesity, is through active hormones within the breast milk, one of which might be leptin, and leptin is contained in breast milk. One of my endocrinologist colleagues says that the leptin molecule in breast milk is too big to be absorbed by term infants, and so I think there is a question out there about whether the immature gut actually could let some of the leptin in, and maybe it's different in premature and term babies. I think there are some very interesting questions out there about the bioavailability of leptin in breast milk and whether it could actually be a mediator of breastfeeding effect on later growth and obesity rates.

**Dr. Lucas:** I feel I need to respond to a rather provocative remark that you made about the limitation of infant nutrition to modify health outcomes or particularly you are talking about obesity. When you look at the experimental studies in both primate models and rodent models, strict experimental interventions that only involve postnatal nutrition have dramatic effects on long-term cardiovascular disease risk and obesity, and those studies that have been done in an experimental fashion in humans, both in preterm and term infants, admittedly much more limited number of studies than in animals, have shown exactly the same things. Now it is to say that randomized manipulation of early nutrition has produced changes in cardiovascular and fatness if you like risk profiles. So how do you match that with the epidemiological data?

**Dr. Gillman:** It’s entirely possible for infant feeding and breastfeeding or breast milk in particular to have an impact on later cardiovascular risk without being mediated through weight gain in the first 6 months. Today, we are talking about early growth and its prediction of later obesity and cardiovascular disease, and maybe the determinants of this phenomenon are different from infant feeding. It’s possible that infant feeding does good things later but this isn’t the way it does it. In terms of the evidence from randomized control trials, my own reading is that it’s mixed because the trials that you and Atul have done suggest that there is some benefit both in term SGA and preterm on adiposity and cardiovascular disease outcomes, whereas the breastfeeding promotion trial in Belarus does not, and there are certainly differences among those trials. Michael Kramer’s Byelorussian trial is a cluster randomized trial in a large population in a country that wasn’t quite westernized in the 1980s. It resulted in further large differences in duration and exclusivity of breastfeeding, but everyone breastfed, there wasn’t a formula-fed comparison group. So different trials answer different questions and we try to put all the evidence together.

**Dr. Lucas:** The animal studies which you quote show major differences in growth, like the Mecan study with major differences in later outcome. One may attempt to extricate growth and nutrition, but growth was an important part of the short-term response to nutrition as well as the long-term one. So it is difficult just to eliminate all that evidence if you like on growth as well as nutrition.

**Dr. Gillman:** The first thing is, I don’t want to eliminate the evidence, the second thing is I was provocative on purpose, the third thing is that rats are not humans, and oftentimes the magnitude of the intervention we do on animal studies is a lot more than the natural variability in humans.

**Dr. Haschke:** Upward crossing of percentiles is associated with higher probability of later obesity. You used the CDC charts. Have you made the effort to use the WHO
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charts? The 90th and 95th percentiles are quite different from the respective CDC charts. Therefore, the outcome might be different.

**Dr. Gillman:** We're just actually starting to do this in the same data set, and what we've shown so far is that using the 95th on the CDC charts or the 97th on the WHO charts or using weight-for-length or BMI in WHO, you get almost the same prediction of age 5 obesity. That's a static measure within infancy; we haven't yet done the crossing percentiles analysis but we should do in the near future.

**Dr. Ke:** What should the clinician be monitoring, is it weight, length, weight-for-length or BMI? And how useful is BMI before the age of 2 years because the IUDF cutoffs are all from 2 years onwards.

**Dr. Gillman:** The new WHO growth standards do have BMI before the age of 2 and I think the question is, what are the relationships between these growth parameters in the first 2 years of life and later outcomes, using either BMI or weight-for-length or this growth standard or that growth standard. So far, in our preliminary data it looks like using BMI or weight-for-length in the WHO standards gives you about the same prediction of obesity later, so it may very well turn out that using BMI before age 2 is a reasonable thing to do. People have argued about what the superscript on length should be in the denominator of measures of body mass before the age of 2, should we look for some exponent that makes the term as unrelated to length as possible, that's one way to look at it, and another way to look at it is to see what the prediction of these things for later outcome is. And the question about clinical implications, I think it's true that upward crossing of percentiles shows you who is at greater risk later for obesity-related outcomes, but I am going to stick to my guns here and say that I don't think we know what the clinical implications are yet.

**Dr. Atici:** Sometimes, exclusively breastfed healthy babies overgrow. Do you think that these babies are at an increased risk for cardiovascular diseases or any metabolic disease or obesity?

**Dr. Gillman:** In the randomized control trial in Belarus, the Probit study, the subjects are all breastfeeders. The intervention group had longer duration and exclusivity than the control group, and at least at age 6 there weren't any differences in weight or blood pressure. I am involved in a collaboration to follow up those kids to age 11 to look at better indices of body composition through skinfolds as well as some cardiometabolic markers in blood. One other comment is that we need to have much better information on what we mean by breastfeeding because mother-infant pairs who breastfeed do it in many different ways: there is expressed breast milk vs. nursing, people may tap off any breastfeeding with a formula feed, and they might put something in the bottle. Therefore, a lot of times in epidemiology we don't measure the infant feeding very well and that's another thing we need to do.

**Dr. Singhal:** The original data which showed that a higher nutrient intake could influence growth acceleration and long-term risk of obesity were actually collected from breastfed infants [1, 2]. In all of our studies, the same effects of faster growth are seen in formula-fed and breastfed infants [3]. There are also populations such as those from Iceland, which are almost entirely breastfed and where you see exactly the same phenomena [3]. So, although we don't have any experimental data on breastfed infants, all of the epidemiological findings apply to both formula-fed and breastfed infants.

**References**