

The first months of life: a critical period for development of obesity¹⁻³

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“If life were measured by accomplishments, most of us would die in infancy.”

—AP Gouthey

Perhaps all is not accomplished in infancy, although it is the period of most rapid linear growth. Our organs are still in developmentally plastic stages. We have more fat than any other species, perhaps to keep our prodigious brains functioning during times of famine (1). Every day and every week we make huge leaps in neurocognitive, motor, and social development. Yet we are dependent on someone else to feed us and for locomotion. Thus, it should be no surprise that what happens in the first months of life could be essential to lifelong nutritional status.

Now that obesity is the most burdensome and costly nutritional condition worldwide, questions naturally arise about infancy as a key period for development of obesity and its consequences. Two articles in this issue of the Journal address the role of growth during infancy as a predictor of later adiposity. Ylihärsilä et al (2) measured body composition with an 8-polar bioimpedance system in nearly 2000 Finnish adult men and women whose weights and heights were available from child welfare and school records. Excess weight gain, as determined on the basis of body mass index (BMI), from ages 2 to 11 y is a strong determinant of both fat and lean mass 5–6 decades later. In the second article, Botton et al (3) showed in several hundred French boys and girls that weight gain velocity after the age of 3 y predicts fat and fat-free mass in adolescence, as measured with a foot-to-foot bioimpedance device. Both articles advance the field by measuring adiposity directly, not just BMI, as an outcome. Their results agree with earlier findings from the Finnish cohort, as well as others, which show that excess weight gains in school age and adolescence predict adult obesity, diabetes, and cardiovascular disease (4, 5). We can all agree, then, that obesity prevention starting in preschool or school age is a public health imperative.

What about weight gain at earlier ages? In the Finnish cohort, gain in BMI from birth to age 1 y or to ages 1–2 y was associated with later lean, but not fat, mass. The data from the French cohort agree that weight gain velocity at age 1 or 2 y is a poor predictor of later fat mass. Earlier data from the Finns (6) suggest that increasing BMI from birth to 2 y does not predict a 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 (4).

If these were the only data available regarding the first 1–2 y of life, many might concur with Barker (7) that “...coronary heart disease, type 2 diabetes, stroke and hypertension originate in developmental plasticity, in response to undernutrition during fetal life and infancy.” However, a growing body of literature suggests otherwise. 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 persons born over a period from 1927 to 1994, although representation from developing countries, where stunting and wasting are still prevalent, was limited.

What could explain these discrepancies? Ylihärsilä et al propose some possibilities, including differences in age, ethnicity, and nutritional status of the children; the fact that associations of BMI and adiposity may have changed over time; and the intriguing possibility that the Finnish children’s experience of living through food shortages during World War II could limit applicability to today’s children. It is also possible that associations of weight gain with adiposity differ from those with harder clinical outcomes such as diabetes and coronary heart disease.

Whereas each of these arguments has merit, another explanation is worth considering: that the first few weeks to months of life are a particularly sensitive period for development of obesity and cardiometabolic complications. What epidemiologic evidence supports this assertion?

- 1) Reexamination of published studies. In this issue, Ylihärsilä et al do not subdivide the first year of life further, but if one looks closely at the published figures in Barker et al (6) from the same cohort, it appears that the BMI of Finns who eventually developed coronary heart disease increased in the first ≈3 mo before decreasing. Botton et al, who explicitly examined earlier stages of infancy, found

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that weight gain velocity at 3 and 6 mo predicted adolescent fat mass better than did weight gain velocity at 1 or 2 y. In the Delhi study, gain in BMI in the first 6 mo was related to both BMI and sum of skinfold thicknesses in adulthood (9).

- 2) Interventions in premature and small-for-dates babies. Singhal et al (10, 11) 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 insulin and leptin (11). In a more recent publication, term small-for-gestational age infants randomly assigned to energy-enriched formula had more rapid weight gain from 0 to 9 mo and higher diastolic blood pressure at age 6–8 y (11).
- 3) Newer cohorts of childhood adiposity-related outcomes. In the US cohort study Project Viva, gain in weight-for-length from 0 to 6 mo predicted higher BMI, sum of skinfold thicknesses, and blood pressure at age 3 y (12). A study in the WIC (Women, Infants, and Children) program in New York state confirms the direct associations of 0–6-mo weight gain with BMI-defined obesity at age 4 y (13). 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 mo was both common and predicted a high risk of obesity 5 y later. Upward crossing from 6 to 12, 12 to 18, or 18 to 24 mo was less common and less predictive.
- 4) Cohorts examining adult outcomes. In the SWEDS study, weight gain from 0 to 6 mo predicted not only adiposity but also a metabolic risk score at age 17 y. Weight gain from 3 to 6 y did not predict this cluster of metabolic risk factors (14). 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. In a formula-only fed population, Stettler et al (15) showed that weight gain in the first week of life was directly associated with overweight in adulthood.

In addition to this epidemiologic evidence, auxologic studies tell us that weight gain in the first 6 mo is primarily a gain in fat, whereas fat-free mass accumulates preferentially after that age (16). Classic rat experiments from the 1960s show that modification of energy intake in the first weeks of life has lifelong effects on weight gain, even if normal energy intake is restored afterward (17). In a more recent rat model, administration of leptin postnatally abolished the otherwise permanent offspring metabolic effects of prenatal maternal energy restriction (18). Furthermore, the current obesity epidemic has not spared our youngest children: in our large study from a managed care population, from the early 1980s to the early 21st century, the prevalence of overweight and obesity among 0- to 6-mo-old infants rose from 10.4% to 17.0% (19). Increases in older infants and preschoolers were more modest.

Thus, mounting evidence suggests that the first few months of life are critical for the development of obesity, an inference that raises a number of research imperatives. One is the need for longitudinal body-composition measures during infancy. Whereas weight and length are relevant for clinical decision making, relying on these as exposures in research studies leaves us mechanistically unsatisfied. Second, we 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. Often we assume that the 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, whereas a longer breastfeeding duration was associated with a lower prevalence of obesity at age 3 y, this effect did not appear to be mediated by weight gain in the first 6 mo. Also, in a seeming paradox, breastfeeding results in faster weight gain than does formula feeding in the first few months of life; only later in infancy do breastfed infants have lower weights (20). Perhaps overfeeding due to lack of responsiveness to infants' satiety cues is more germane than just the differences between breastfeeding and bottle feeding. It is also plausible that prenatal factors could play a role, such as maternal smoking, gestational weight gain (21), alterations in glucose-insulin homeostasis, or other nutrient-hormonal adaptations in the maternal-placental-fetal unit (22).

All parents want to know, "How big should my baby be"? Researchers, clinicians, and the public health community need to be able to respond not only to that question, but also to the follow-up challenge of what we can do to ensure that babies are the right size. The answers hold great promise for prevention of obesity.

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