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Infant Growth and Long-term Cardiometabolic Health: a Review of Recent Findings

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Abstract

Purpose of Review Infant weight gain is recognized to increase obesity risk across the lifespan. This review evaluates recent evidence relating growth in infancy to childhood, adolescent and adult body composition, and cardiometabolic risk factors.

Recent Findings Greater weight or BMI gains in infancy increase both fat mass and fat-free mass in later life, but may preferentially contribute to central adiposity. Impacts of infant growth on cardiometabolic health are mixed, and most findings are attenuated after adjusting for current body size.

Summary Infant weight gain, length gain, and BMI changes are important in establishing risk for cardiometabolic health across the lifespan. Infant growth effects on cardiometabolic health may be indirect, acting through changes in obesity risk or body composition.

Keywords Catch-up growth · Infant weight gain · Body composition · Lipids · Insulin · Blood pressure

Abbreviations

ADP	Air-displacement plethysmography (Pea Pod or Bod Pod)
AGA	Appropriate for gestational age
AGEAP	Age at infant BMI peak
AUC	Area under the curve
AUS	Abdominal ultrasound
BIA	Bioelectrical impedance
BMI	Body mass index
BMIAP	BMI at infant BMI peak
CDC	US Centers for Disease Control and Prevention
cIMT	Carotid intima media thickness
DOHaD	Developmental Origins of Health and Disease
DXA	Dual x-ray absorptiometry
FFM	Fat-free mass
FFMI	Fat-free mass index
FM	Fat mass
FMI	Fat mass index
FPIR	First-phase insulin response
IFG	Impaired fasting glucose
LBW	Low birth weight
LV	Left ventricular
MetS	Metabolic syndrome
MRI	Magnetic resonance imaging
NA	Not assessed/not available
PMA	Post-menstrual age
PWV	Pre-peak weight velocity
SAT	Subcutaneous adipose tissue
SDS	Standard deviation score (*z*-score)
SFT	Skinfold thicknesses
SGA	Small for gestational age
SITAR	Superimposition by Translation and Rotation
SST	Sum of skinfold thicknesses
T2DM	Type 2 diabetes
TBW	Total body water, assessed by deuterium excretion
VAT	Visceral adipose tissue
VLBW	Very low birth weight
WBISI	Whole-body insulin sensitivity index
WHO	World Health Organization

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Introduction

It is now widely recognized that many adult chronic conditions have their origins in childhood, infancy, and even in utero development. This concept was first highlighted by Dr. Barker, who identified that adults who experienced in utero growth restriction or low birth weight were at higher risk for developing cardiovascular disease, type 2 diabetes (T2DM) and metabolic syndrome (MetS) as adults [1, 2]. In particular, early studies noted the combination of low birth weight with accelerated growth during childhood (but not infancy) represented the highest risk for cardiovascular disease [3] and T2DM [4] in adulthood, as well as death from ischemic heart disease [5]. Subsequent work in adults implicated both infant (age 0–2 years) and childhood weight or BMI gains with impaired cardiometabolic health in adults [6]. The developmental programming hypothesis (also referred to as the Barker Hypothesis or more recently, the Developmental Origins of Health and Disease, DOHaD) thus posits that early life exposures occurring during sensitive periods of development, during gestation or postnatally, may permanently alter gene expression, tissue development, and biologic processes in a way that is maladaptive or mismatched to exposures encountered later in life [1, 7].

This review will focus on one aspect of the DOHaD hypothesis pertaining to the role of infant growth during the first 24 months in the development of later childhood, adolescent, and adult cardiometabolic health and disease. In particular, given the increasing obesity prevalence, we will focus on recent evidence relating to excess infant growth, rather than growth inadequacy or faltering. Importantly, this review will not focus on the role of birth weight or infant size at specific ages, or predictors of infant growth differences. We will first review the metrics and methods commonly used to evaluate infant growth, particularly infant weight metrics, then will summarize the evidence for how infant growth is related to obesity and body composition, as well as cardiometabolic outcomes at later developmental stages.

Assessment of Infant Growth

Infant growth is not linear, and various aspects of growth are non-linear in differing ways. On average, weight decreases within the first 7–14 days after birth, then increases rapidly to about 6 months of age, and increases at a slower rate thereafter. Length increases quickly in the first few months, then slows thereafter. Body mass index (BMI) increases rapidly to about 6 months of age (the so-called infant BMI peak), before decreasing to a nadir around 3–6 years of age ("BMI rebound"), then increasing more slowly throughout childhood. In addition, the variability of infant weight and length is smaller than at later stages of life, magnifying the impact of even small changes or measurement error. Infant growth, then, is not easily simplified into linear slopes, particularly for studies involving infants of differing ages or time intervals between measurements.

Most studies focusing on longitudinal weight changes in relation to later outcomes do so using metrics designed to identify growth beyond that anticipated from growth charts. One of the most common metrics is change in weight-for-age ≥ 0.67 SD within a given time period, also referred to as "upward percentile crossing," "rapid infant weight gain," or "catch-up growth." The + 0.67 SD change is typically equated with crossing of two centile lines on standard growth charts [8], but it should be noted that this is only true in reference to the UK 1990 growth charts, which display centile lines at exact 0.67 SD intervals [9, 10]. However, the extent of weight gain per month (weight velocity) required to achieve a + 0.67 SD increase in weight-for-age SD score varies significantly by age and interval between measurements. This is an issue when attempting to compare studies using this "standard" + 0.67 SD benchmark, but without standardizing the ages or intervals between measurements, or even which reference growth chart is used. As one paper notes, an "unconditional difference in z-score can be considered a metric of velocity [only] when the interval duration is constant for all children" [11].

One issue with examining changes in SD scores or *z*-scores is that it inherently assumes that most children will not deviate from their initial SD score [8], but will quickly stabilize at a given percentile; therefore, deviation from their original centile is viewed as clinically relevant. However, a recent study found that changes in weight *z*-scores from 1 month to the next exhibit both positive and negative feedback, depending on age [12, 13], suggesting that infants do not "pick a centile," but rather change weight dynamically relative to growth charts, especially during infancy. This is demonstrated within the Avon Longitudinal Study of Parents and Children cohort, where 31% of infants experienced an increase in weight *z*-score > + 0.67 SD between birth and 2 years, while 25% of infants experienced a similar decrease during this time [8], suggesting a roughly normal distribution of weight change in infancy relative to growth curves. In infancy, there is also a tendency for growth to regress toward the mean, such that higher weight or length at one time point is negatively related to the change in weight or length over a subsequent period [14]. This leads to the concept of "catch up" or "catch down" growth in infancy, characterized by the extent of centile crossing as described above, which has also been highlighted as a concern for later obesity or cardiometabolic risk. A reasonable question, given these two phenomena, is at what point is centile crossing normative, relating to regression toward the mean or normal changes in infant centiles, versus problematic, relating to increased risk for later outcomes? At this point, little information is available to address these questions.

In addition to two-point change analyses, trajectory analyses are common, particularly with BMI, permitting the incorporation of multiple assessments of growth per infant. Because BMI increases in infancy and then decreases, modeling of individuals' BMI values using non-linear regressions or splines allow the estimation of the magnitude of infant peak BMI (BMI at peak, or BMIAP), age at BMI peak (AGEAP), and weight velocity prior to the peak (pre-peak weight velocity, or PWV). These parameters have then been examined as potential alternate metrics of infant growth in relation to outcomes. Shape invariant techniques, such as Superimposition by Translation and Rotation (SITAR) modeling [15], assume that individuals in a population share a common "average" growth trajectory, from which each person deviates in specific, estimable ways (vertical deviation or size; horizontal deviation or tempo; and expanding or contracting the time axis, or velocity). These deviation parameters can then be modeled in relation to outcomes. Some studies employ conditional growth metrics, whereby the growth in one period is adjusted for growth in previous time periods, to allow for independent assessment of each time frame.

Finally, when assessing infant growth, it is important to recognize that relationships between infant growth and later outcomes may differ depending on which aspects of growth are considered (e.g., length, weight, or an index of the two such as weight-for-length or BMI). Research regarding length growth parameters, BMI or weight-for-length SD, or *z*-score changes may provide additional information regarding body proportionality, beyond weight gain.

How Does Infant Weight Growth Affect Obesity Risk and Body Composition Later in Life?

Considerable previous literature has demonstrated clear links between weight gain velocity in infancy and obesity risk in later childhood, adolescence, and adulthood. Three systematic reviews were conducted on studies published before 2006, each including between 10 and 21 studies [16–18], which identified that "rapid infant weight gain," often defined as change in weight-for-age SD score ≥ + 0.67, carries a significant and consistent 2–3-fold increased risk for later obesity, particularly when the infant exposure window is extended to age 2; the obesity outcome is assessed at a younger age, and adjustments are not made for confounding factors [16]. A formal meta-analysis was not possible at that time because of differences in exposure and outcome definitions, as "rapid" weight gain was defined over variable time frames, from a period of weeks to years [16], and with some studies evaluating outcomes (e.g., obesity) at ages young enough to be included in the exposure windows of other studies. A later systematic review [19], a 2012 meta-analysis of 10 large cohort studies including risk prediction models [20], and a very recent meta-analysis of 16 studies conducted after 2006 [21••] confirm these earlier conclusions. The 2018 meta-analysis estimated that rapid weight gain ≥ + 0.67 SD is associated with a 3.66-fold increased risk for overweight or obesity (95% CI 2.59–5.17), which is higher when considering childhood rather than adult obesity or for infant weight gain limited to 0–12 months of age, rather than 0–24 months [21••]. The 2012 prediction equation for childhood obesity included change in weight SDS from birth to 12 months, birth weight SDS, and mother's BMI and sex, with an AUC of 77% and reasonably high sensitivity and specificity [20].

Given that early infant weight gain is widely accepted to be associated with later obesity status, more recent investigations have focused on two related lines of inquiry. First, does rapid versus slow infant weight gain differentially impact the deposition of fat mass versus lean mass, or the distribution of fat mass to visceral or subcutaneous depots? Table 1 presents a summary of findings from 39 studies published between 2003 and 2018 evaluating early infant weight growth and later body composition parameters [22–60]. While not a systematic review, these studies are nearly unanimous in their findings that greater infant weight gain between birth and 24 months tends to increase both fat mass (represented as either absolute fat mass (FM) or fat mass index (e.g., fat mass (kg)/height (m) [2]; FMI)), as well as fat-free (lean) mass (as either absolute amount (FFM) or fat-free mass index (FFMI)) in children, adolescents, and adults. Only three studies reported negative findings [49, 50, 53]. The overwhelming evidence thus supports that infant weight gain is associated with both FM and FFM accretion, across a wide range of ages (from 6 months to 46 years of age) and methods of body composition assessment (including dual x-ray absorptiometry [DXA], bioelectrical impedance [BIA], skinfold thicknesses [SFT], air-displacement plethysmography [ADP], and abdominal ultrasound [AUS]), suggesting a robust effect of infant weight gain on overall body size rather than body composition.

It has been suggested the relationship of infant weight gain with FFM is stronger than with FM in developing countries [23, 28, 61, 62]; and currently, studies in developing countries present a mixed picture of positive and negative results [39, 40, 42, 44, 45, 49, 52, 55, 57, 60]. However, most studies in developed countries find that percent body fat is increased with greater infant weight gain, and that fat gains are seen preferentially in the abdominal region. Only one study to our knowledge has reported on visceral versus subcutaneous fat distribution, with no difference between these depots among those with high-versus-low infant weight gain among middle-aged adults [32]. This may indicate that while both FM and FFM are impacted by infant weight gain, the effects may be somewhat stronger for FM, resulting in higher percent body fat and central adiposity, highlighting the importance of infant weight gain to later adiposity risk.

Table 1 Studies reporting on the association between infant weight growth and later body composition

			Infant growth		Body composition outcome		Associations			
Reference	*N*	Population	Infant age range (months)	Growth metric (method or growth chart)	Age (years)	Body composition measurement	FM or FMI	FFM or FFMI	Body fat % or SST	Abdominal adiposity[a]
Cameron [22]	193	South Africa	0–24	Δ weight SDS ≥ + 0.67 (UK)	9	DXA, SFT	+	+	+	+
Wells [23]	172 boys	Brazil	0–6	Δ weight SDS (UK)	9	BIA	0	+	NA	NA
Euser [24]	403 very preterm	Netherlands	0–3	Δ weight SDS (Swedish)	19	SFT, waist	+	+	+/0	+
Ekelund [25]	248	Sweden	0–6	Δ weight SDS ≥ + 0.67 (Swedish)	17	ADP, waist	+	+	+	+
Ibanez [26]	29 SGA and 22 AGA	Spain	0–24	Weight gain, kg	4	DXA	NA	NA	+	+
Karaolis-Danckert [27]	249	Germany	0–24	Δ weight SDS ≥ + 0.67 (German)	5	SFT	NA	NA	+[c]/+	NA
Joglekar [28][b]	698	India	0–6, 6–12, 12–24	Conditional weight SDS (WHO, CDC)	6	DXA	+	+	NA	NA
Chomtho [29]	234	UK	0–3, 3–6	Δ weight SDS (UK)	11	DXA, TBW, ADP, waist	+	+ (0–3 months)	NA	+ (0–3 months)
Botton [30][b]	468	France	0–3	Weight velocity (instantaneous)	8–17	SFT, BIA, waist	+	+[c]	+	+
Botton [30][b]	468	France	0–6	Weight velocity (instantaneous)	8–17	SFT, BIA, waist	+	0	+[d]	+[d]
Karaolis-Danckert [31]	370	Germany	0–24	Δ weight SDS ≥ + 0.67 (German)	6	SFT	NA	NA	+	NA
Demerath [32]	233	US	0–24	Δ weight SDS ≥ + 0.67 (cohort-specific)	46	DXA, waist, abdominal MRI	+	+	+	+
Holzhauer [33]	909	Netherlands	0–6	Δ weight SDS ≥ + 0.67 (Dutch)	0.5 (6 months)	SFT	NA	NA	+	+
Ong [34]	2715	UK	0–2	Δ weight SDS (UK)	10	DXA	+	+	+	NA
Leunissen [35]	217	Netherlands	0–3	Weight gain (kg)	18–24	DXA, waist	NA	NA	0	+/0
Lamkjaer [36]	95	Denmark	0–3, 0–6, 0–9	Δ weight SDS (WHO)	17	DXA, waist	NA	NA	+	+/0
Durmus [37]	481	Netherlands	0–24	Δ weight SDS (ref not indicated)	2	AUS	NA	NA	NA	+
Singhal [38][b]	153 SGA	UK	0–6, 0–9	Δ weight SDS (UK)	7	BIA, SFT, TBW	+	+/0	+	NA
Wells [39][b]	425	Brazil	0–6, 6–12	Conditional weight velocity tertiles	14	TBW, waist	+[d] (6 months) +[c] (12 months)	+	+[d] (6 months) +[c] (12 months)	+[d] (6 months) +[c] (12 months)
Kuzawa [40]	3432	Brazil, Guatemala, India, Philippines, South Africa	0–12, 12–24	Conditional weight gain	Adult	BIA (Brazil); abdominal circ (Guatemala); SFT (India, Philippines); DXA (South Africa)	+	+	+	NA
Wright [41]	561	UK	0–12	Conditional weight *z*-score change	7–8	BIA, adiposity index (internal factor)	NA	+	+[d]	NA
Sacco [42]	98	Brazil	0–12	Δ weight SDS ≥ + 0.67 (WHO)	5	BIA, waist	NA	NA	+	+
Gomez-Lopez [43][b]	423	Canada	0–24	Weight *z*-score slope (WHO)	9.5	DXA (total and trunk), waist	+	+	+	+
Khandelwal [44]	54 LBW	India	0–3, 0–7.2	Δ weight *z*-score	0.6 (7.2 months)	DXA	NA	NA	+	NA
Vieira [45]	257	Brazil	0–6	Weight gain (g/d)	4–7	DXA (abdomen), waist	NA	NA	+	+

Table 1 (continued)

Reference	*N*	Population	Infant growth		Body composition outcome		Associations			
			Infant age range (months)	Growth metric (method or growth chart)	Age (years)	Body composition measurement	FM or FMI	FFM or FFMI	Body fat % or SST	Abdominal adiposity[a]
Bann [46]	1558	UK	0–24	Conditional weight velocity *z*-score (cohort-specific)	60–64	DXA	+[c]	+	NA	+
Ejlerskov [47]	167	Denmark	0–5	Δ weight *z*-score (WHO)	3	BIA	+[e]	+	+	NA
Cheng [48]	548	Germany	0–24	Weight velocity (SITAR)	18–25	SFT	+[d]	+[d]	NA	NA
Salgin [49]	2352	South Africa	0–12	Δ weight SDS ≥ + 0.67 (cohort-specific)	8, 18	DXA, SFT	0	−/0	0	NA
Fonseca [50]	717	Portugal	0–0.13 (96 h)	% Δ weight	4, 7	BIA	0	0	NA	0
De Beer [51][b]	2227	Netherlands	0–1, 1–3, 3–6, 6–12	Conditional relative weight *z*-score	5–6	BIA	+	+	NA	NA
Musa [52]	1935	South Africa	0–24	Conditional relative weight gain	18	DXA	+	NA	NA	NA
Embleton [53]	153 preterm	UK	0–3, 3–12	Δ weight SDS (UK)	11.5	DXA	0	0	NA	0
Gishti [54][b]	6464	Netherlands	0–6, 6–12, 12–24	Δ weight SDS (Dutch)	6	DXA, AUS	+	–	NA	+
Kolle [55]	1874	Brazil	0–24	Conditional relative weight gain *z*-score	30	ADP, AUS	+	NA	NA	0
Perng [56][b]	706	USA	0–5	Δ weight *z*-score (WHO)	0.42 (5 months)	ADP (Δ FM and Δ FFM)	+	+	NA	NA
Antonisamy [57]	907	India	0–3	Conditional relative weight gain	28	Waist	NA	NA	NA	+
Saenz de Pipaon [58]	95 VLBW	Spain	36 weeks PMA - 6 months	Δ weight SDS (WHO)	0.5–3	DXA	+	0	+	NA
Woo [59][b]	322	USA	0–24	Weight velocity (SITAR)	3 and 7	DXA	+ (3 years)	+	+ (3 years)	NA
Prioreschi [60][b]	266	South Africa	0–24	Conditional weight gain	22	DXA	+	+	NA	+ (VAT and SAT)[d]

FM, fat mass; *FMI*, fat mass index; *FFM*, fat-free mass; *FFMI*, fat-free mass index; *SST*, sum of skinfold thicknesses; *SDS*, standard deviation score (*z*-score); *NA*, not assessed/not available; *CDC*, US Centers for Disease Control and Prevention; *WHO*, World Health Organization; *SGA*, small for gestational age; *AGA*, appropriate for gestational age; *LBW*, low birth weight; *VLBW*, very low birth weight; *PMA*, post-menstrual age; *DXA*, dual x-ray absorptiometry; *SFT*, skinfold thicknesses; *BIA*, bioelectrical impedance; *TBW*, total body water, assessed by deuterium excretion; *AUS*, abdominal ultrasound; *ADP*, air-displacement plethysmography (Pea Pod or Bod Pod); *MRI*, magnetic resonance imaging; *SITAR*, Superimposition by Translation and Rotation; *VAT*, visceral adipose tissue; *SAT*, subcutaneous adipose tissue

[a] Abdominal adiposity metrics included waist circumference; waist to hip ratio; % trunk fat SFT ((subscapular SFT + suprailiac SFT)/(biceps SFT + triceps SFT)); % trunk fat DXA; and preperitoneal fat (AUS)

[b] Results from different analyses from the same report

[c] Association in males only

[d] Association in females only

[e] Association in non-breastfed individuals only

How Do Infant Length, BMI, and Body Composition Changes Relate to Later Obesity Risk and Body Composition?

Some of the most interesting recent data have come from investigations of infant growth using length or BMI changes, rather than weight gain alone. Length growth in infancy is less commonly evaluated (Table 2), and unfortunately the results from the 11 studies identified are highly mixed with respect to associations with later body composition [28, 30, 38, 39, 51, 54, 56, 59, 60, 64] or obesity risk [30, 38, 51, 54, 57, 59, 63, 64]. While some studies note that longer length (but not necessarily length gain) is associated with greater lean mass [59, 60] or height at a later age [57], it is not clear that length growth in infancy has a consistent impact on later obesity risk or body composition.

The use of BMI metrics in studies of infant growth is relatively recent, as BMI is not typically measured in clinical practice, and the WHO growth charts for infant BMI were first published in 2006. Particularly since 2013, several groups have evaluated infant BMI trajectories and *z*-scores in relation to childhood obesity (Table 2). Both BMI *z*-score change in infancy [43, 61, 63] and higher BMIAP and later AGEAP [65, 66, 68, 69, 71, 72] are consistently associated with higher obesity risk or higher BMI, assessed from age 2 to 29 years. When considering body composition, a higher infant BMIAP and a higher infant PWV are associated with higher FM [67, 72], FFM [67], percent body fat [66, 69, 72], and abdominal obesity [66, 69, 70••]. Associations of AGEAP with body composition are mixed, with a later AGEAP associated with lower FM and FFM at age 3 in one study [67], associated with higher percent body fat and abdominal adiposity in two others [66, 69], and not associated with body composition in a final study [72]. BMI *z*-score change in infancy is generally associated with both higher FM and FFM [43, 59, 61], and higher percent body fat and abdominal adiposity [43, 61], similar to findings of weight-for-age SD change.

Very few studies have presented data regarding changes in infant body composition and later outcomes (Table 2), mostly because assessment of body composition in large numbers of infants is difficult and expensive. In one study of 314 Ethiopian children, FM accretion during the first 4 months of life was associated with higher FMI at age 4 years, while FFM accretion from 0 to 6 months was positively associated with both FMI and FFMI [75•]. Accretion of FFM, but not FM, in infancy in this cohort is also related to length at 1 year of age [76]. A small study of children from the USA found that FM gains between 0 and 4 or 0–8 months, but not FFM gains, were associated with higher odds of overweight/obesity at age 9 [73]. And a third study from the Netherlands found that gain in percent body fat in the first 3 months of life was associated with greater visceral fat at 3 months of age and with greater percent body fat at 6 months [74]. Further research in other populations and larger sample sizes is needed to validate and extend these results.

How Does Infant Growth Affect Cardiometabolic Structure or Function in Later Life?

Given the early findings regarding retrospective associations between birth weight and early growth patterns with cardiovascular disease [1, 3], T2DM [2], and MetS [6], several studies have prospectively examined the relationship between infant growth patterns and later cardiometabolic risk factors, as well as assessing whether these relationships are independent of concurrent BMI or other measures.

Blood Pressure and Circulating Lipids

With respect to blood pressure, higher BMIAP or greater BMI *z*-score or weight changes in infancy are associated with higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) in childhood, adolescence, or adulthood [28, 66, 72, 77, 78••, 79–82]. However, several of these associations do not account for [72, 77], or are not significant after adjusting for [66, 78••, 79–81], concurrent BMI, suggesting associations between high infant weight gain and later BP may be largely mediated by the impact of early weight gain on obesity itself. Negative findings are also reported [35, 83, 84]. One study noted that greater length growth between birth and 3 months of age is associated with higher DBP in women adjusting for adult size [57]. From a retrospective analysis, adults with elevated blood pressure (≥ 130/85 mmHg or treatment for hypertension) did not experience different BMI trajectories from normotensive adults at any point during childhood [70••].

Relationships between infant weight gain and later lipid profiles are weak. Many studies identified no relationships with total cholesterol [35, 78••, 83, 85, 86], or with HDL or LDL cholesterol [35, 57, 78••, 83, 85, 86]. Several others have identified adverse associations (e.g., higher total or LDL cholesterol, higher TG, or lower HDL cholesterol) that are either not corrected for [35, 87–89], or are attenuated [57] upon adjustment by concurrent body size. However, one study noted that later AGEAP in infancy was associated with lower TG at age 6, particularly in boys, even after adjusting for concurrent fat mass and lean mass [78••]. Linear growth between birth and 3 months is also reported to be associated with higher cholesterol and TG in men, adjusted for adult size [57]. A retrospective study of adults with and without MetS identified that BMI trajectories of those with high-versus-low TG did not diverge until after age 1.5 years, while BMI trajectories of those with high-versus-low HDL did not diverge across childhood [70••].

Insulin Resistance and Sensitivity

With respect to insulin sensitivity, findings differ somewhat depending on whether infants were born preterm/small for gestational age (SGA), or not. Among term infants, an early study in a population of middle-aged men from Herfordshire, England, noted that the prevalence of impaired glucose tolerance and plasma insulin concentrations were lower with higher birth weight or higher weight at 1 year, implicating low weight through infancy with adult insulin resistance, particularly when coupled with higher adult BMI [4]. More recent prospective studies have reported associations between faster infant weight gain and lower insulin sensitivity [28, 35] and acute insulin response [35], but these results are not adjusted for later body size. Null findings are also reported [36, 57, 78••]. One study noted that both weight growth and height growth between 6 and 12 months of age were associated with lower insulin sensitivity after adjusting for concurrent fat and lean mass [28]. However, one study of children with obesity found that greater infant weight gain between birth and 24 months was associated with higher whole-body insulin sensitivity index (WBISI) at age 10, correcting for birth weight and concurrent height and percent body fat [90]; however, weight gain after age 4 in this group was associated with lower WBISI. A similar finding was noted in 6511 young adults from low-income countries, where greater weight gain between birth and 24 months was protective against impaired fasting glucose/type 2 diabetes (IGF/T2DM) adjusting for adult waist circumference; by contrast, weight gain after age 4 was associated with lower insulin sensitivity and risk of IFG/T2DM [91]. A retrospective study of adults noted that adults with MetS versus without MetS similarly did not demonstrate different BMI trajectories until after age 4 [70••]. Thus, the complexity of these findings suggests that while higher infant weight gain is often associated with lower insulin sensitivity, it may be beneficial in some circumstances, and weight gains in later childhood may be more important in this relationship.

Significantly more research has been conducted regarding infant weight gain and later insulin resistance among preterm, low birth weight (LBW), and/or SGA infants. Among preterm or SGA infants, relationships between infant growth and insulin resistance are somewhat stronger and more consistent [35, 92, 93], with some of these findings also reviewed recently [94]. In particular, among infants born small or early, greater infant weight growth between 0 and 3 months [35, 95] or 6–12 months [93] appears to be related to lower insulin sensitivity in young adulthood and early childhood, respectively, although not adjusted for concurrent body size. In more detailed analyses, markers of insulin resistance (fasting 32–33 split proinsulin and intact proinsulin) were higher among adolescents born preterm with greater weight gain in the first 2 weeks, but *not* growth at later ages, accounting for concurrent body size [87]. Weight gain from birth to term age in very low birth weight (VLBW) infants also born SGA was also associated with higher fasting and 2-h insulin levels in young adults, but this was not seen in appropriate for gestational age (AGA) VLBW infants [96]. Young adults born preterm with the highest quartile of weight SD gain between birth and term age had lower insulin sensitivity, higher acute insulin response, and higher disposition index compared with lower quartiles; however, this finding was not adjusted for concurrent body size [88]. Conversely, in a study of 9–12-year-olds born preterm, growth in the first 18 months, but *not* between birth and term age, was associated with *lower* insulin, 32–33 split proinsulin, intact proinsulin, and postload insulin, accounting for current weight [97], suggesting improved insulin sensitivity. Length growth in small infants may also play a role. At age 1 year, SGA infants with greater length SD gain between birth and 1 year had higher postload insulin secretion, assessed by insulin area under the curve (AUC) or first-phase insulin response (FPIR) [92]; greater length growth in early infancy has also been associated with greater beta cell function (HOMA-%β) at age 4 [93]. Null findings are reported in this population, as well [53, 58, 92]. From these studies, it appears that preterm or SGA infants may experience a closer link between infant weight and length growth and later insulin resistance, but a critical period for this growth is not consistent among studies.

Circulating Hormones

Few studies have examined the relationship of infant growth with circulating hormones related to growth, insulin sensitivity, or cardiometabolic function. One study noted that weight gain from 0 to 3 or 0–9 months was associated with higher ghrelin and adiponectin (both corrected for body fat), but not with leptin, at age 17 [36]. At age 13–16, leptin was also not associated with birth weight or discharge weight *z*-scores in adolescents born preterm [98]. Greater weight gain between 0 and 18 months was associated with higher high-sensitivity C-reactive protein at age 8, but not after adjusting for concurrent body size [80]. No differences in insulin-like growth factor binding protein-1, sex hormone binding globulin, or cortisol at age 1 year were seen in SGA infants with versus without catch-up growth [92]. In addition, no significant associations were detected between weight growth between 0 and 3 months and the liver markers γ-glutamyltransferase, alanine aminotransferase, or aspartate aminotransferase in young adults [89]. Thus, overall, there is little evidence to support an association between infant growth rate and circulating hormones related to later obesity or cardiometabolic risk.

Cardiac and Vascular Structure and Function

Cardiac and vascular structure and function parameters may, however, have an independent relationship with greater early

Table 2 Associations of infant length growth, BMI change, or body composition changes on later obesity risk and body composition

			Infant growth		Anthropometry or body composition outcome		Associations				
Reference	*N*	Population	Infant age range (months)	Growth metric (method or growth chart)	Age (years)	Anthropometry or body composition measurement	FM or FMI	FFM or FFMI	Body fat % or SST	Abdominal adiposity[a]	BMI/obesity risk
Length growth											
Joglekar [28][b]	698	India	0–6, 6–12, 12–24	Conditional length SDS (WHO, CDC)	6	DXA	+/0	+	NA	NA	NA
Botton [30][b]	468	France	0–6	Length velocity (instantaneous)	8–17	SFT, BIA, waist	0	0	0	0	0
Singhal [38][b]	153 SGA	UK	0–6, 0–9	Δ length SDS (UK)	7	BIA, SFT, TBW	+/0	+/0	+/0	NA	+/0
Wells [39][b]	425	Brazil	0–6, 6–12	Conditional length velocity	14	TBW	+[c] (0–6 months)	+ (0–6 months)	NA	NA	NA
Belfort [63][b]	945 preterm LBW	USA	0–4, 4–12, 12–18	Δ length *z*-score (WHO)	8, 18	Overweight/obesity	NA	NA	NA	NA	+ (Δ 0–4 months with age 8)
Alves [64]	79 VLBW	Brazil	0–12	Δ length *z*-score > 2 (WHO)	3	AUS	0	NA	NA	0	0
De Beer [51][b]	2227	Netherlands	0–1, 1–3, 3–6, 6–12	Conditional relative length *z*-score	5–6	BIA	+	+	NA	NA	+ (6–12 months)
Gishti [54][b]	6464	Netherlands	0–6, 6–12, 12–24	Δ length SDS (Dutch)	6	DXA, AUS	− (12–24 months)	+ (12–24 months)	NA	− (12–24 months)	+ (6–12, 12–24 months)
Perng [56][b]	706	USA	0–5	Δ length *z*-score (WHO)	0.42 (5 months)	ADP (Δ FM and Δ FFM)	+	+	NA	NA	NA
Antonisamy [57]	907	India	0–3	Conditional length	28	Waist	NA	NA	NA	+	NA
Woo [59][b]	322	USA	0–24	Length velocity (SITAR)	3 and 7	DXA	0	+ (3 years)	0	NA	0
Poreschi [60][b]	267	South Africa	0–24	Conditional length growth	22	DXA	0	+	NA	0	NA
BMI growth											
Sachdev [61]	957	India	0–12	Δ BMI SDS (cohort-specific)	29	SFT	+/0	+	+/0	+	+
Silverwood [65]	1162	Sweden	0–36	AGEAP, BMIAP	5–13	BMI *z*-score (Sweden)	NA	NA	NA	NA	+
Hof [66]	2809	Netherlands	0–48	AGEAP, BMIAP	5–6	BIA, waist/ht., BMI	NA	NA	+	+	+
Gomez-Lopez [43][b]	423	Canada	0–24	BMI *z*-score slope (WHO)	9.5	DXA, waist	+	+	+	+	+
Belfort [63][b]	945 preterm LBW	USA	0–4, 4–12, 12–18	Δ BMI *z*-score (WHO)	8, 18	Overweight/obesity	NA	NA	NA	NA	+
Jensen [67]	311	Denmark	0–19	PWV, AGEAP, BMIAP	3	BIA, BMI	+ (PWV, BMIAP) − (AGEAP)	+ (PWV, BMIAP) − (AGEAP)	NA	NA	NA
Roy [68]	1075	USA	0–30	PWV, AGEAP, BMIAP	4	BMI *z*-score (CDC)	NA	NA	NA	NA	+ (BMIAP, AGEAP)
Kruithof [69]	5126	Netherlands	0–36	PWV, AGEAP, BMIAP	6	DXA, AUS	NA	NA	+ (PWV, BMIAP) + (AGEAP) [d]	+ (PWV, BMIAP) + (AGEAP)[d]	+
Giudici [70••]	1919	France	0–12	BMI trajectory	31	Waist	NA	NA	NA	+	NA
Sun [71]	2073	China	0–14	PWV, AGEAP, BMIAP	2	Overweight/obesity	NA	NA	NA	NA	+ (BMIAP, AGEAP)

Table 2 (continued)

			Infant growth		Anthropometry or body composition outcome		Associations				
Reference	*N*	Population	Infant age range (months)	Growth metric (method or growth chart)	Age (years)	Anthropometry or body composition measurement	FM or FMI	FFM or FFMI	Body fat % or SST	Abdominal adiposity[a]	BMI/obesity risk
Aris [72]	1020	Singapore	0–18	PWV, AGEAP, BMIAP	4	SFT, FMI, overweight/obesity	+ (PWV, BMIAP)	NA	+ (PWV, BMIAP)	NA	+ (BMIAP, AGEAP)
Perng [56][b]	706	USA	0–5	Δ BMI *z*-score (WHO)	0.42 (5 months)	ADP (Δ FM and Δ FFM)	+	+	NA	NA	NA
Body composition growth											
Koontz [73]	53	USA	0–4, 0–8, 0–12	FM and FFM gain (100 g/month; TOBEC)	9	Overweight/obesity	NA	NA	NA	NA	+ (Δ FM 0–4 and 0–8 months)
Breij [74]	300	Netherlands	0–3	Δ FM% (ADP)	0.33 (3 months) and 0.5 (6 months)	ADP, AUS (VAT and SAT)	NA	NA	+ (6 months)	+ (3 months VAT)	NA
Admassu [75•]	314	Ethiopia	0–4, 0–6	Δ FFM 0–6, Δ FM 0–4 months (ADP)	4	ADP	+	+ (Δ FFM 0–6)	NA	NA	NA

FM, fat mass; *FMI*, fat mass index; *FFM*, fat-free mass; *FFMI*, fat-free mass index; *SST*, sum of skinfold thicknesses; *SDS*, standard deviation score (*z*-score); *NA*, not assessed/not available; *CDC*, US Centers for Disease Control and Prevention; *WHO*, World Health Organization; *SGA*, small for gestational age; *LBW*, low birth weight; *VLBW*, very low birth weight; *DXA*, dual x-ray absorptiometry; *SFT*, skinfold thicknesses; *BIA*, bioelectrical impedance; *TBW*, total body water, assessed by deuterium excretion; *AUS*, abdominal ultrasound; *ADP*, air-displacement plethysmography (Pea Pod or Bod Pod); *SITAR*, Superimposition by Translation and Rotation; *AGEAP*, age at infant adiposity peak; *BMIAP*, body mass index at infant adiposity peak; *PWV*, peak infant weight velocity; *TOBEC*, total body electrical conductivity; *VAT*, visceral adipose tissue; *SAT*, subcutaneous adipose tissue

[a] Abdominal adiposity metrics included waist circumference; waist to hip ratio; % trunk fat SFT ((subscapular SFT + suprailiac SFT)/(biceps SFT + triceps SFT)); % trunk fat DXA; and preperitoneal fat (AUS)

[b] Results from different analyses from the same report

[c] Association in males only

[d] Association in females only

infant growth. Although few studies exist, those that do suggest that higher infant weight gain is associated with lower left ventricular (LV) mass at age 6 years [78••], higher carotid intima media thickness (cIMT) at 8 years [80], lower flow-mediated dilation at 13–16 years [99], and higher carotid-radial pulse wave velocity at age 16–20 years [100], all of which, except lower LV mass, are risk factors for adverse cardiovascular events, and all but the last finding adjusted for concurrent body size. The contrary finding of lower LV mass with greater infant PWV [78••] is unexpected, and may require additional research to place this finding in context. Another study of young adults born preterm found no association between late infancy weight gain (3–12 months) and cIMT after adjustment for adult height SDS [85]. These studies suggest that greater weight gain in infancy may be related to subclinical atherosclerosis, endothelial dysfunction, and vascular stiffness, independent of obesity development.

Conclusions

Weight gain in infancy has been strongly shown to be associated with higher obesity risks in a variety of populations across the life course. This review newly highlights that a substantial body of literature also supports an association of greater infant weight gain or greater BMI gain with both greater fat mass *and* lean mass, suggesting an impact on larger overall body size. Greater infant weight gain may also result in higher percent body fat and greater central fat deposition.

Infant weight gain is also associated with worse cardiometabolic profiles in later childhood through young adulthood, although much of these associations appears to be indirect, through the impact on increased obesity and adiposity. This indirect pathway may make sense developmentally, as late gestation and infancy are periods of rapid growth and accumulation of both fat and fat-free tissue, but development of organs important in cardiometabolic health, including the heart and pancreas, has largely already been completed in utero. Indeed, the original Barker work noted that birth weight and later childhood growth were both critical periods in establishment of risk for T2DM and cardiovascular disease, but that infancy was not [2, 3]. The impact of later childhood growth on risk development is supported by other findings noted in this review, particularly in relation to insulin resistance and MetS risk. Although not fully reviewed here, mid-childhood weight gains may be the first postnatal developmental stage with independent associations with several later metabolic comorbidities.

From both a clinical and public health standpoint, monitoring infant weight and length gain velocity and BMI trajectories, especially in relation to standard growth charts, is important in understanding future risk of obesity, and for developing potential strategies to prevent obesity development during childhood and beyond. In particular, it is important to monitor growth among preterm and small for gestational age infants to ensure balance between these infants' additional energy requirements to prevent inadequate growth, while avoiding overnutrition and excessive growth rates to prevent obesity. Additional research is needed to fully understand the mechanisms, critical windows of development, and vulnerable populations involved in the direct versus indirect pathways between infant growth and later cardiometabolic risk.

Compliance with Ethical Standards

Conflict of Interest Jessica G. Woo declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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