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Is growth in early childhood a window of opportunity for programming long-term health?

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Running title: Growth in preschool children and later health

Abstract *(247 words)*

Background: Rapid growth characterises early childhood, with the highest weight gain in early infancy and continued relatively high gains during preschool years. **Summary:** Subnormal weight and length gain from birth to about 2 years of age predict increased childhood wasting and stunting, whereas excessive weight gain in infancy and early childhood is associated with increased later obesity. Breastfeeding attenuates the risk of high early weight gain and later obesity, adding another reason for promoting, protecting and supporting breastfeeding. Avoiding high infant protein intakes from infant formula and complementary foods is strongly recommended since it markedly reduces later obesity and adiposity. This can be achieved by avoiding cows' and other animal milks as a drink in infancy and choosing infant formula with a low protein content, more similar to breastmilk, for infants not (fully) breastfed. High weight gain in toddlers is also associated with increased later obesity, predicted by overfeeding, high intakes of sugary foods and beverages, and high intakes of protein, particularly animal protein. In an ongoing controlled trial in Germany and Spain, we randomised 1,618 toddlers to milk drinks in the second year of life providing protein contents either similar to cows' milk or more similar to human milk. First results show high protein milk inducing high weight and length gains deviating from normal growth trajectories, whereas reduced protein intakes support weight and length growth matching WHO growth standards. Follow-up until early school age is ongoing to explore a potential impact on later growth and overweight risk. **Key messages:** Avoiding rapid weight gain in infancy and toddlerhood can reduce later obesity risk. Promoting, protecting and supporting breastfeeding and avoidance of high animal protein intakes in early childhood can contribute to reaching this goal.

Key words:

Early metabolic programming of later health, Early protein hypothesis, Growth trajectories, Milk drinks for young children, Weight gain velocity

Abbreviations:

BCAA - branched-chain amino acids

BMI – Body Mass Index

CHOP Trial - European Childhood Obesity Project Trial

CI – Confidence Interval

EFSA - European Food Safety Authority

HUMIS - Norwegian Human Milk Study

OR – Odds Ratio

PreventCD study - Prevention of Coeliac Disease study

ToMI trial - Toddler Milk Intervention trial

WHO - World Health Organisation

WMD – Weighted mean difference

Introduction: Early childhood growth and later health

Infancy and early childhood are characterised by rapid growth and development. Early growth trajectories are associated with numerous later outcomes, such as final height, body mass index (BMI), obesity risk and adiposity (body fatness) in childhood, adolescence and adult age, asthma risk, behavioural and cognitive outcomes, and others (1-3). Although growth velocity is highest in early infancy, length and weight gain velocities continue to be relatively high during the preschool years (4), along with high nutrient needs per kg bodyweight (5). This points to the potential of health promoting interventions applied from infancy through to the preschool age.

For a long time the focus of paediatric clinicians and researchers was directed to the causes and consequences of malnutrition, underweight and stunting. These continue to be a major health burden in populations around the world. With respect to the development of underweight and stunting, the critical importance of infancy and early childhood has been well established. For example, Victora et al. documented the key role of growth trajectories from birth to about 2 years of age in the development of stunting and underweight when analysing data of national anthropometric surveys from as many as 54 countries (6). They found that mean weight for age declined from a z-score close to 0 after birth to about -1 z at age 2 years and remained rather stable thereafter (**Figure 1**). Mean length/height for age also showed a z-score close to 0 at birth but faltered dramatically until age 2 years, with only a slight increase thereafter, even though there were noticeable bumps just after 2, 3, and 4 years of age. Matching results evolved from the analysis of pooled data of 860,351 children from 94 countries, showing a rising prevalence of stunting until the ages of about 28 months when it started to slowly decline. A similar lasting impact of slow growth in the first two years of life was detected in a prospective cohort study from a high-income country, Canada, with inclusion of almost 6,000 children (7). Healthy urban children exhibiting underweight in the first 2 years showed at age 10 years a mean weight 1.6 kg (girls) and 0.9 kg (boys) lower, respectively, than in children without underweight during the first two years. Children with both underweight and a lower length during the first 2 years were on average 2.0 kg lighter and 0.8 cm shorter at age 10 years (7). Together, these findings underline the great importance of environmental cues including nutrition during the about first two years of life, energy expenditure, and certain infections, for shaping later height and weight as well as the risk of stunting. Attention to preventive interventions is required, given that stunting in childhood is linked to numerous later health outcomes including physical and cognitive performance, disease risk, quality of life, and income.

Over the last three to four decades, the prevalence of childhood waisting has decreased, while there has been a much lesser decrease of the prevalence of stunting (8). The Global Nutrition Report states that 150.8 million children worldwide are stunted, and 50.5 million are waisted (9). However, during the same period the prevalence of childhood obesity has markedly increased and now exceeds that of underweight (9). A recent analysis including 3663 population based studies with data on 222 million adults and children from around 130 countries showed a higher prevalence of obesity than thinness in school aged children and adolescents in 2022, while thinness was more prevalent than obesity only in 26% and 34% of all countries in girls and boys, respectively (10). From 1990 to 2022, obesity prevalence of girls increased in 93% of all countries, and that of boys in 98% of all countries. although the burden of stunting and underweight remains high, especially in south and southeast Asia and parts of Africa where food insecurity persists, a clear shift from underweight-dominated to obesity-dominated disease burden occurred, with the largest rise in some low-income and middle-income countries.

Similar to the early origins of later stunting and underweight, early childhood has also been shown to be a critical time window for modulating the development of obesity in later childhood and adult age (11, 12). Rapid weight gain in infancy and the preschool age was identified as a strong risk predictor for later obesity in more than 30 studies (1, 2, 13-15). Children with rapid weight gain during the first two years of life, defined as a weight gain of at least two thirds of a standard deviation above the average weight gain of the population, have an almost doubled obesity risk (adjusted for confounders) in later childhood, adolescence and adulthood (16).

Rapid early weight gain also predicts increased body fat deposition (adiposity), a key risk factor for the development of insulin resistance and related adverse metabolic dysregulation associated with increased risk of developing non-communicable diseases. In a meta-analysis of 17 observational studies including 4,473 children, Chen et al. confirmed rapid early weight gain, in most studies in infancy and early childhood, as a risk predictor for an increased BMI at later ages (pooled WMD of 0.582, 95% CI 0.348 to 0.816, P<0.001) (17). In a pooled analysis with 11 studies the authors also found rapid weight gain associated with a higher body fat percentage at later ages (WMD 1.057, 95%CI 0.768 to 1.345, P <0.001), whereas rapid length gain was not predictive. Children who showed rapid gain for durations lasting longer than 2 years had a greater effect size on later BMI and body fat.

Further insights into the critical role of early childhood BMI gain were obtained from the analysis of a large population based sample of more than 51,000 children with sequential anthropometric measurements (18). High gains in BMI during the preschool years, but not during the school years, predicted a 1.4-fold higher risk of overweight or obesity in adolescence, compared to those with a stable BMI z-score in the preschool years.

We studied the patterns of early growth trajectories and their relation to later outcomes using data from four longitudinal cohort studies (West Australian Pregnancy Cohort, RAINE; European Childhood Obesity Project Trial, CHOP; Norwegian Human Milk Study, HUMIS, and Prevention of Coeliac Disease study, PreventCD), enrolling a total of 6,708 children after birth in 11 high-income countries (19). Applying longitudinal growth mixture modelling, we identified three BMI derived growth patterns (**Figure 2**). Some 55% of children showed a pattern we consider as “normative growth”, with a BMI z-score staying close to 0 from birth to age 6 years, i.e. an ideal BMI evolution based on the WHO child growth reference standards (20). Another 40% of children showed an “early rapid growth” pattern, with a BMI increase of about 1 standard deviation (SD) from birth to age 2 years. In this group, BMI z-scores subsequently decreased to plus 0.42 SD above the normative trajectory class at age 6 years, indicating that an early BMI increase predicts a persistent risk increase for later obesity. About 5 % of children were grouped in the “persistent rapid growth” cluster characterized by accelerating and persistent rapid gain in BMI above the growth standards during early childhood, with a continuous increase of BMI z-scores from about 0 at birth to 2.8 at 6 years. Children in this group have an extremely high obesity risk. In a subgroup followed to the age of 20 years, early childhood BMI trajectories also predicted anthropometric measurements in young adulthood. Children in either of the two rapid BMI-trajectory classes had significantly higher BMI and fat mass values in adulthood compared those following a normative trajectory class (**Figure 3**), as well as higher fat mass index values (19). We believe a likely underlying mechanism is that high weight gain in early childhood induces predominantly fat deposition and not lean body mass accretion, with high body fat inducing insulin resistance, metabolic disruption and metabolic syndrome, and an increased later risk of non-communicable diseases such as diabetes mellitus type 2, cardiovascular diseases (e.g. ischemic heart disease and stroke), some forms of cancer, and other disorders (21).

Together, the available evidence points to lasting and grave adverse health effects of rapid weight gain in infancy and the preschool years. However, the available evidence is largely based on observational studies where results may have been influenced by confounding, or by residual confounding if the date were adjusted for some confounders that could be assessed while others may have been missed. Thus, strengthing the evidence base through randomised controlled intervention trials in early childhood with longer-term follow-up of the participating children is highly desirable. Nonetheless, when the monitoring child growth in clinical care it appears prudent to pay close attention not only to the evolution of growth faltering, but also to upward deviations of weight centiles or z-scores. The predictive power of rapid weight gain trajectories might be even enhanced in the future by the combination with further data from the medical history, clinical findings, or biomarkers, which should be further explores. In any case, health care professionals should offer advice to families on adequate infant and young child feeding that can support normative growth.

Nutrition in infancy, early weight gain, and later risk of obesity and associated diseases

In our analysis on BMI trajectory patterns cited above, infant feeding was significantly related to the pattern of BMI evolution (22). In a model adjusted for gestational age, birth weight, maternal age at delivery, maternal pre-pregnancy BMI, maternal education, and maternal smoking during pregnancy, we found a significant association of full breastfeeding for less than 3 months, compared with breastfeeding for 3 months or longer, with increased odds of being in both the persistent rapid-growth trajectory (OR: 2.66; 95% CI 1.48, 4.79) and the early rapid growth trajectory (OR: 1.96; 95% CI 1.51, 2.55) compared with the normative growth pattern. Thus, no or a short duration of full breastfeeding was a predictor for rapid-weight gain patterns in early childhood, predisposing to adiposity (high body fat mass) and adverse health outcomes such as insulin resistance, diabetes mellitus, cardiovascular diseases, and other non-communicable diseases.

This observation is in line with previous studies associating breastfeeding in infancy with a reduced later risk of obesity. In the first large study published on this question, we evaluated routine measurements of height and weight of 9,357 children aged 5 and 6 years who participated in the obligatory health examination at the time of school entry in the German state of Bavaria (23). We found a higher prevalence of obesity in children who had never been breast fed (4.5%) compared to those ever breast-fed (2.8%). We also described a clear dose-response effect: longer duration of breastfeeding was associated with a lower obesity prevalence (3.8% for 2 months breast feeding, 2.3% for 3-5 months, 1.7% for 6-12 months, and 0.8% for <12 months). After adjusting for potential confounding factors, breastfeeding remained a significant protective factor against the later development of overweight (OR 0.79, 05% CI 0.68 to 0.93) and obesity (odds ratio 0.75, 95% CI 0.57 to 0.98).

The relation between mode of infant feeding and later obesity risk has subsequently been explored in numerous cohort studies. A recent meta-analysis including as many as 159 studies reported breastfeeding associated with a reduced pooled odds ratio for obesity risk of 0.76 (95% CI 0.69 to 0.83) (24). Although causality cannot be inferred since the data are gathered from observational studies with a wide variability of study quality (25), a causal protective effect of breastfeeding is biologically plausible. Breastfeeding is associated with a lower weight gain from birth to age 1 year, compared to bottle feeding of conventional infant formula (26, 27), which could explain the risk reduction for later obesity. The lesser weight gain in breastfed infants was proposed to be due to lower levels of both

insulin and insulin like growth factor 1 (IGF-1) in response to a different substrate supply, when compared to babies fed conventional infant formula (28, 29).

We hypothesized that the protective effect of breastfeeding against obesity development is mediated - at least in part - through the lower protein content of human milk relative to conventional infant formula (30). Milk protein supply in childhood is a strong predictor of insulin and IGF1 levels (31), which are key modulating factors of early growth. Earlier work showed normal infant growth with reducing the historically high protein levels in infant formula (32), whereas high protein intakes during the complementary feeding period had been associated with later adiposity development (33). We performed a large double-blind randomized clinical trial enrolling more than 1,600 infants and demonstrated that a lowered protein content of infant and follow-on formula fed during the first year of life markedly reduced obesity prevalence in early school age by more than 2.5 times (34, 35), along with reduced body fatness (36) and lasting beneficial effects until early adolescence (37). These impressive effect sizes of improved infant feeding regarding reduced later obesity risk are much greater than those of other evaluated obesity prevention strategies in childhood (12). In a later systematic review, we identified 12 randomized clinical trials in children aged 0 to 3 years fed cows' milk based formulas with variations in protein concentration (38). While the data show no safety concerns with reduced formula protein intakes and lower mean weight and weight z scores from 6 to 12 months of age, the studies were rather heterogeneous, and most studies had a relatively small sample size and no long-term follow up. However, it is encouraging that supported by the strong data from the CHOP trial, the concept of reducing dairy protein supply in infancy has been rapidly adopted by manufacturers of respective products as well as in regulatory standards (39-41).

Nutrition in the toddler and preschool age to support adequate weight gain and better health

Weight gain in the toddler and preschool age continues to depend on the balance between energy expenditure, composed primarily of resting energy expenditure and energy expenditure for physical activity, and the energy intake from food and beverages. Overfeeding with excessive calorie intake, due to inappropriate feeding and eating behaviours and/or regular consumption of high energy density foods and drinks (i.e. a high amount of calories per unit weight), is the dominant risk factor for excessive weight gain and subsequent development of obesity. Regular consumption of sugar containing beverages such as soft drinks, fruit juices and sweetened teas has been consistently identified as an independent risk factor for obesity development (42, 43). Even only a single daily serving of fruit juice taken regularly was shown to have a significant effect on increasing BMI (42).

The preschool age offers particular opportunities for the promotion of healthy eating and drinking behaviours, because habits learned and consolidated in this age period tend to persist over decades. Families have a very strong influence on the behaviours of their preschool children and often are highly motivated to support health promoting habits. Therefore, informing families about good child nutrition, providing advice on practical implementation, and offering motivating and encouraging messages is a worthwhile investment, with indications of obesity-preventive effects in preschool and school-age children (44).

Setting-based interventions at day care and kindergarten settings offer particular opportunities to reach children from most if not all populations groups, with establishment of health promoting behaviours as a daily routine. One example is the TigerKids programme widely implemented by the Stiftung Kindergesundheit (Child Health Foundation) in day care settings in Germany and Austria

(https://www.tigerkids.de/). With this programme children learn to drink water instead of sugared beverages and to eat fresh vegetables and fruit as a snack instead of energy dense processed foods (45). A cluster-randomized evaluation of the programme effects after one kindergarten year, i.e. after 9 months attendance of a kindergarten with or without the TigerKids programme, showed that TigerKids achieved a sustained increase of the proportion of children with a high vegetable and fruit consumption at home, both after 6 months (adjusted odds ratio 1.59, 95% CI 1.26 to 2. 01) and after 18 months (adj. OR 1.48. 95% CI 1.08 to 2.03) (46). Consistent beneficial effects were also found in subgroups with higher risk related to pre-existing overweight or disadvantaged families. The results indicate that simple setting-based interventions aimed at establishing behaviour change in the preschool age can have considerable beneficial effects.

In addition, societal standards aiming at reducing the consumption of foods and drinks can contribute to protecting child health. For example, a systematic Cochrane review indicated that traffic-light labelling of food products, taxation and limiting availability in school settings has beneficial effects on sales and consumption of sugar sweetened beverages (47).

Dairy protein intakes in toddlers and weight development

Considering the large benefit of limiting dairy protein supply in infancy on later obesity risk reported above, the question arises whether limiting dairy protein intake after the age of one year might also have beneficial effects on body weight and obesity development. If confirmed, this strategy could present a great opportunity for practical prevention, because toddlers and preschool children around the world tend to consume protein intakes that are much higher than their metabolic needs. The European Food Safety Authority (EFSA) reviewed dietary intakes of young children in the European Union and concluded that their intakes tend to be low for the omega-3 fatty acids alpha-linolenic and docosahexaenoic acids as well as for iron, vitamin D, and in some European countries also for iodine. In contrast, the mean and median protein intakes of young children are clearly above both average requirements and population reference intakes in all surveys. Actual protein intakes range from 12 to 19 % of energy intakes, whereas the protein needs are only in the range of 4.5 to 6.2 % of energy intakes between 1 and 3 years of age (48). Thus protein intakes in young children tend to be 2-4 times higher than population reference intakes, which should meet the needs of basically all individuals in a population (49). Similar results were found in a review of nutrient intakes of young children aged 12–36 months around the world. Intakes were found to be often inadequate for the vitamins A, D, B12, C and folate, and for calcium, iron, iodine and zinc, whereas protein intakes clearly exceeded recommended intakes in all countries, except for Bangladesh where reported protein intakes were just close to recommendations (50).

The rather high protein intake of preschool children could be very relevant for health outcomes. Several cohort studies reported dietary protein intakes at the ages of 9 months to 24 months to be a positively associated with the occurrence of later overweight and adiposity (51-54). The effects of protein supply during the second year of life on higher weight gain as well as obesity risk later in childhood were specifically addressed in a systematic review (55). Based on the data of ten studies with a total of 46,170 children, we found moderate-quality evidence for an association of protein intake during the second year of life with fat mass at 2 years and at 7 years (55). However, effects on BMI and obesity risk were inconclusive due to both heterogeneity and low evidence. A more recent systematic review examined the evidence for associations between the dietary protein intake in children from Western populations between the ages of 4 months and 5 years with respect to both

growth measures and the risk of overweight or obesity up to the age of 18 years (56). Twentyone studies from 27 publications were included. The meta-analysis showed a positive relationship between total protein intake and BMI, with a pooled effect estimate of 0.06 (95% CI 0.03, 0.1) kg/m^2 BMI per one E% increment in total protein (I^2 = 15.5). The authors concluded that there is a probable causal relationship between a high-protein intake in early childhood (≤ 18 months of age) and higher BMI later in childhood, with consistent findings across cohort studies. They also report indications for a particularly decisive role of the intake of proteins from animal origin. Regarding underlying mechanisms, we and others have proposed that a higher protein intake will increase the blood and tissue concentrations of indispensable amino acids and particularly of branched-chain amino acids (BCAA), which enhance the secretion of insulin and IGF-I that are known growth stimulators through the mammalian target of rapamycin signalling pathway (29, 57-59). The BCAA leucine is a particularly powerful stimulator of insulin and IGF-I secretion, therefore, limiting the dietary intake of leucine rich proteins such as cows' milk protein may be particularly relevant (59). In fact, we demonstrated such effects of protein content of cows' milk based infant formula on BCAA, insulin and IGF-1 levels in the double-blind randomised CHOP trial (57, 60).

To test possible effects of modified protein intakes in young children, we designed an investigator-initiated trial examining the role of milk protein intake during the second year of life on child growth and later obesity risk (Trial registration NCT02907502) (61). The Toddler Milk Intervention trial (ToMI trial) is a two-arm, parallel, randomised, double blind controlled trial that enrols healthy children aged 1 year and evaluate the effect of young child formula with different protein contents on growth in the second year of life. The control milk contains 2.95 g protein/100 mL (6.15 g/100 kcal) and is comparable to standard cows' milk with 2% fat content. The intervention milk formula contains 0.72 g protein/100 mL (1.5 g/100 kcal), similar to the typical protein content of human milk in advanced lactation, with a fat content of 4.25 g/100 kcal. Both milks have similar contents of energy, carbohydrates, vitamins and minerals. The study is conducted at university hospitals in Munich, Germany and in Tarragona and Reus, Spain. The primary endpoint is the BMI-for-age z-score (based on the WHO Multicentre Growth Reference Study) at the age of 24 months, adjusted for BMI-for-age z-score at age 12 months. Secondary endpoints include BMI-for-age z-score at 72 months, the percentage of children with overweight and obesity at 24 months and 72 of age, and at different time points anthropometric measures (z-scores for weight, length and head, waist and arm circumference and hip circumference), subcutaneous fat distribution, total body fat and lean mass, blood pressure, child development, as well as various metabolic and endocrine markers. Recruitment has been completed, with 1,618 children enrolled in the trial. All children have reached the age of 2 years. First data evaluations indicate that children randomised to the intervention group have a lower BMI than children in the control group at the age of 18 months but not at 24 months (62). The intervention group shows relatively stable z-scores for length and weight from 12 to 24 months of age, whereas children in the higher protein group show a marked upward deviation of both the z-scores for length and weight away from the reference of the WHO growth standard. It appears that high cows' milk protein intakes can induce abnormally high length and weight gains that differ from normal growth patterns the second year of life. Based on the available data indciating possible adverse effects of high protein intakes in early life both from the several observational studies cited above and from the first results of our ongoing randomized clilnical trials, it appears prudent to avoid very high intakes of animal protein both in infancy and toddlerhood. Accordingly, the recent recommendations in the WHO's Guideline on Complementary Feeding (63) to provide unmodified animal milks to infants aged 6 months and older and only unmodified animal milks but no formula in the second year of life, both based on "low certainty evidence", does not fully reflect

the currently available evidence, and while it may be an acceptable option under precarious conditions when no other options are feasible, is not supported as a recommended for all populations worldwide (64). Further follow-up of the children participating in our ongoing randomized trial until early school age 6 years is being performed to explore potential effects at later ages.

Conclusions:

- The burden of stunting and underweight remains high, especially in South and Southeast Asia and parts of Africa where food insecurity persists.
- Over the last 3 to 4 decades, a shift from underweight-dominated to obesity-dominated disease burden has occurred, with the largest rise in some low-income and middle-income countries.
- Rapid weight gain in infancy and the preschool years points to lasting and grave adverse health effects.
- Monitoring of child growth in clinical care should pay close attention not only to the evolution of growth faltering, but also to prevention of upward deviation of weight centiles or z-scores.
- Breastfeeding is associated with lower weight gain from birth to age 1 year, and with childhood obesity prevention, compared to bottle feeding of conventional infant formula, and should be proactively protected, promoted and supported.
- Lower protein content of infant formulas provided during the first year of life reduce both excessive weight gain and later obesity risk.
- Also in the second year of life, high intakes of cows' milk protein appear to induce supranormal length and weight gains that differ from normal growth patterns.
- The preschool age offers particular opportunities for the promotion of healthy eating and drinking behaviours.

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Figure 1: The analysis of child growth patterns in 54 countries (z-scores relative to WHO growth standards) suggests that growth during the first 2 years of life predicts later body size. Drawn from data of (6).

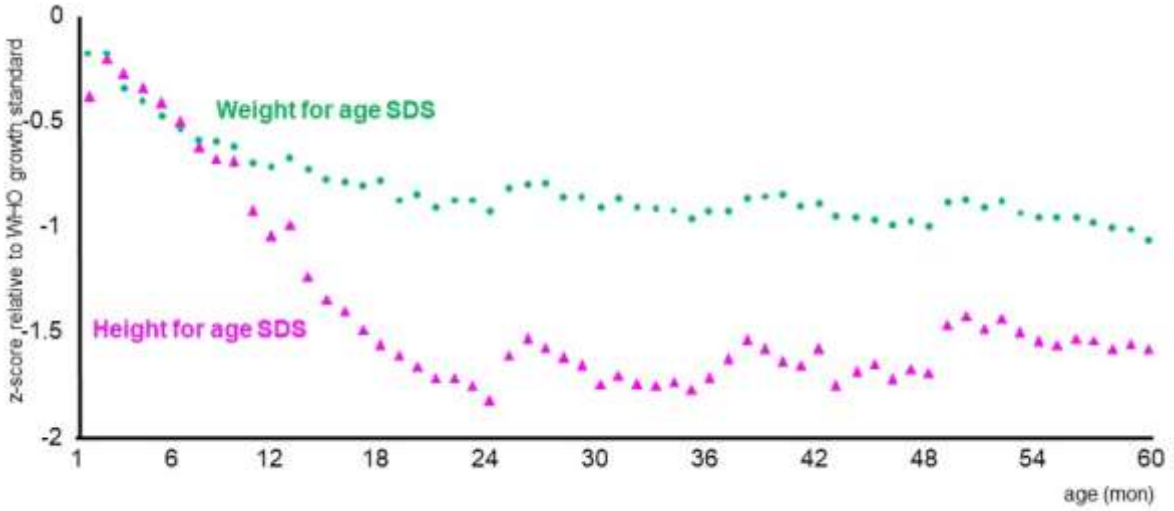

Figure 2: : Latent growth mixture modeling analyses identified three classes of BMI-SDS development from birth to age 6 years in 6708 children from four pooled cohorts. Drawn from data of (19).

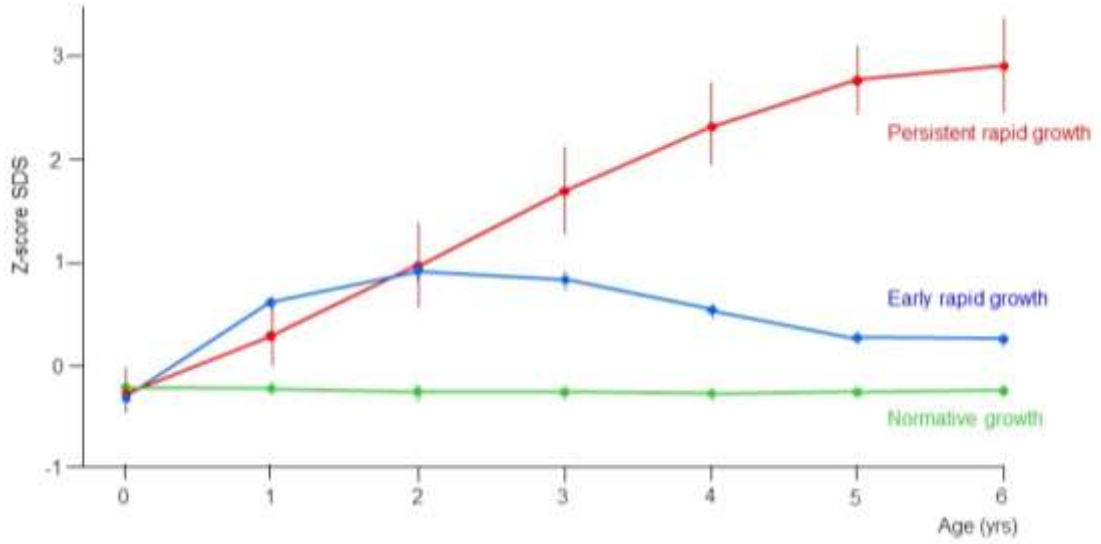

Figure 3: Early childhood trajectories of BMI gain predict BMI and body fat mass at the age of 20 years. Drawn from date of (19).