Adolescent Nutrition 1

Nutrition in adolescent growth and development

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During adolescence, growth and development are transformative and have profound consequences on an individual's health in later life, as well as the health of any potential children. The current generation of adolescents is growing up at a time of unprecedented change in food environments, whereby nutritional problems of micronutrient deficiency and food insecurity persist, and overweight and obesity are burgeoning. In a context of pervasive policy neglect, research on nutrition during adolescence specifically has been underinvested, compared with such research in other age groups, which has inhibited the development of adolescent-responsive nutritional policies. One consequence has been the absence of an integrated perspective on adolescent growth and development, and the role that nutrition plays. Through late childhood and early adolescence, nutrition has a formative role in the timing and pattern of puberty, with consequences for adult height, muscle, and fat mass accrual, as well as risk of non-communicable diseases in later life. Nutritional effects in adolescent development extend beyond musculoskeletal growth, to cardiorespiratory fitness, neurodevelopment, and immunity. High rates of early adolescent pregnancy in many countries continue to jeopardise the growth and nutrition of female adolescents, with consequences that extend to the next generation. Adolescence is a nutrition-sensitive phase for growth, in which the benefits of good nutrition extend to many other physiological systems.

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This is the first in a **Series** of three papers on adolescent nutrition

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Introduction

Adolescence is a transformative life phase, with growth and maturation of all organs and physiological systems. On average, 10–19 year olds gain 20% of their final adult height and 50% of adult weight during this phase, with a considerable remodelling of the skeleton and an increase in bone mass of up to 40%.[1] Inevitably, the link between nutrition and adolescent development is strong. For example, particularly in girls, iron requirements increase sharply during adolescence to meet additional needs relating to menstruation. Iron deficiency in adolescents results in compromised growth, decreased cognitive function, and depressed immune function.[2] Despite this understanding, iron deficiency anaemia remains prevalent worldwide, showing little reduction over three decades, and is the third most important cause of lost disability-adjusted life-years in adolescents.[3]

Not only are there more adolescents nowadays than at any other timepoint in human history but they are also growing up at a time of momentous shift—ie, rapid urbanisation, climate change, food systems shifting towards foods with an increased caloric and decreased nutritional value, the COVID-19 pandemic, and growing socioeconomic inequality. The consequences of these changing contexts have profound impacts on adolescent nutrition and development. Figure 1 presents data from 54 million children and adolescents (aged 5–19 years) and shows the effects that varying nutrition and living conditions can have on height and adiposity (ie, body-mass index [BMI]) over age and time, and across countries. There is a difference of at least 20 cm in the mean height of individuals aged 19 years between the tallest and shortest populations. The data highlight that, for many countries, linear growth in children and adolescents still falls below the WHO reference. Despite this evidence of persisting undernutrition, overweight and obesity are now widespread. Since height and BMI have been considered together over the past two decades, the unhealthiest changes of gaining too little height, too much weight, or both, have been prevalent in both high-income countries and low-income and middle-income countries (LMICs).[4] Consequences include an increased risk of non-communicable diseases (NCDs) and a suboptimal start to life in the next generation.[5]

Understanding adolescent biology and its relationship to nutrition is essential for identifying the best timing and form of action, and for avoiding potentially negative consequences. Therefore, this first Series paper synthesises our understanding of adolescent biological development and its relationship with nutrition.

Pubertal maturation

The adolescent growth phase starts with puberty, which drives linear growth; accrual of bone, muscle, and fat mass; and maturation of biological systems. The onset and

Search strategy and selection criteria

For this narrative review, we searched Pubmed, MEDLINE, Google Scholar, and Embase, without date or language restrictions, from Jan 31, 2020, to March 30, 2021, for literature pertaining to the general domains of puberty, physical growth, body composition, neurodevelopment, cardiorespiratory fitness, immune development, and adolescent pregnancy and intergenerational consequences. We also sought longitudinal studies to illustrate further effects of nutrition on adolescent growth and development.

Key messages

- Adolescence is a time of transformative growth when both undernutrition and obesity affect the maturation of multiple physiological systems
- Adolescent malnutrition is multiplicative in that, if any one physiological system is affected, the development of other systems will also be compromised
- Nutrition in childhood and early adolescence affects the timing and form of puberty with consequences on linear growth, body composition, and maturation of other physiological systems
- Although some catch-up growth in height can occur in late childhood and early adolescence, it rarely happens if the adverse nutritional environment of early life persists into adolescence
- Across late childhood and early adolescence, the pubertal transition offers a nutrition-sensitive window to promote healthy growth and reduce risk of obesity in later life
- Given that nutrition is a cornerstone of investments in human capital, scaling up research into the effects of nutrition on adolescent growth and development is a pressing need

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duration of puberty differ markedly between adolescents living in environments with varying childhood nutrition.[6] Pubertal timing, as indicated by the late pubertal event of menstruation (menarche) in girls, has decreased by 1·0 year in high-income countries over time, from a mean of 13·5 years for births before 1930 to 12·6 years for births between 1970 and 1984.[7] Among healthy girls in LMICs during 2009–17, mean age at menarche was estimated to be 12·3 years.[8] In some LMIC populations, where nutrition has improved to a lesser extent than typical LMIC populations, the mean age of menarche is significantly later; for example, 15·1 years in rural parts of The Gambia.

Adiposity is associated with pubertal form. For girls, the mean age of thelarche (ie, breast budding)—an early indicator of gonadal maturation—is 10·2 years for individuals with underweight, 10·4 years for individuals with normal weight, and 8·4 years for individuals with overweight.[8] In boys, mean age of puberty onset—indicated by the scrotum becoming pendulous—is 11·3 years for individuals with underweight, 11·0 years for individuals with normal weight, and 10·3 years for individuals with overweight.[8] Nutritional status not only affects onset of puberty but also its duration.[9] In Australian children aged 8–9 years, high androgen concentrations, reflecting adrenal maturation as the earliest pubertal change, were associated with an increased BMI and waist circumference.[10] In turn, pubertal form has implications for obesity in later life, with early onset and short duration predicting increased adiposity in adulthood (aged ≥40 years).[11,12]

Furthermore, previous parental and childhood nutrition influences pubertal form. For example, maternal obesity before conception predicts early pubertal onset in offspring.[13] Children who were breastfed for 6 months or longer have a later onset of pubertal development than do those who were not breastfed or were breastfed for less than 6 months, perhaps in part reflecting different growth patterns in infancy.[14] A high intake of animal protein in children at age 5–6 years and 12 years predicted an earlier onset of the pubertal growth spurt, whereas a high intake of vegetable protein predicted a later onset.[15–17] A high dietary intake of carbohydrates and fats in girls aged 8 years predicted earlier gonadal maturation and menarche, and faster pubertal tempo than did a high intake of protein.[18] Consumption of sugar-sweetened beverages advances onset of menarche in girls.[19] Given the extent to which pubertal form is a marker of growth, development, and NCD risk in later life, there is a need for research to develop a comprehensive lifecourse understanding of its nutritional and other, potentially modifiable, determinants.

Linear growth

Adolescent linear growth has the highest velocity after infancy and occurs at the growth plate in a two-step cellular process. First, bone elongation cells—chondrocytes—sequentially proliferate, secrete matrix, and undergo hypertrophy, hydraulically propelling bone elongation and producing a protein model of the lengthened bone. Second, bone-secreting cells—osteoblasts—secrete a mineral matrix on the newly created protein model to consolidate the new growth into bone.[20–22] Without the first step, linear growth cannot occur; without the second step, new growth is lost, and the protein model is resorbed. Mechanisms underlying progress across the phases of the chondrocytic lifecycle, from stem cells to hypertrophic transition, involve prompts and inhibitions from complex networks of regulatory proteins[23,24] and endocrine signals.[25] Many nutrients are important for chondrocytic function and for ensuring mineral consolidation.[26–29] Any nutritional intervention to ameliorate retardation in linear growth should consider both of these steps, with the added challenge that the underlying cause originates from past conditions in which the child lived and might be neither evident nor reparable due to missed opportunity, epigenetic effects, or both. Albeit incomplete, some restoration of lost linear growth can occur; however, this can only happen if the intervention substantially improves socioeconomic and living conditions, such as through adoption. Nutrition-specific interventions alone are not likely to restore lost growth.[30]

Height has increased in all populations over decades.[31,32] In high-income countries, this trend is modest in children aged 6 years and largest in adolescents aged 10–14 years; in LMICs, trends vary.[33] Preschool children (aged <60 months) living in conditions conducive to good health and development grow similarly. For preadolescent children in favourable conditions, height across global populations differs by 3–5 cm,[34] and Asian populations are slightly shorter.[31] Both nutrition and living conditions contribute to attained height.[35] South Asian children living in the Netherlands grew taller between 1992 and 2010, but remained shorter than their Dutch peers at each age, with greater divergence during

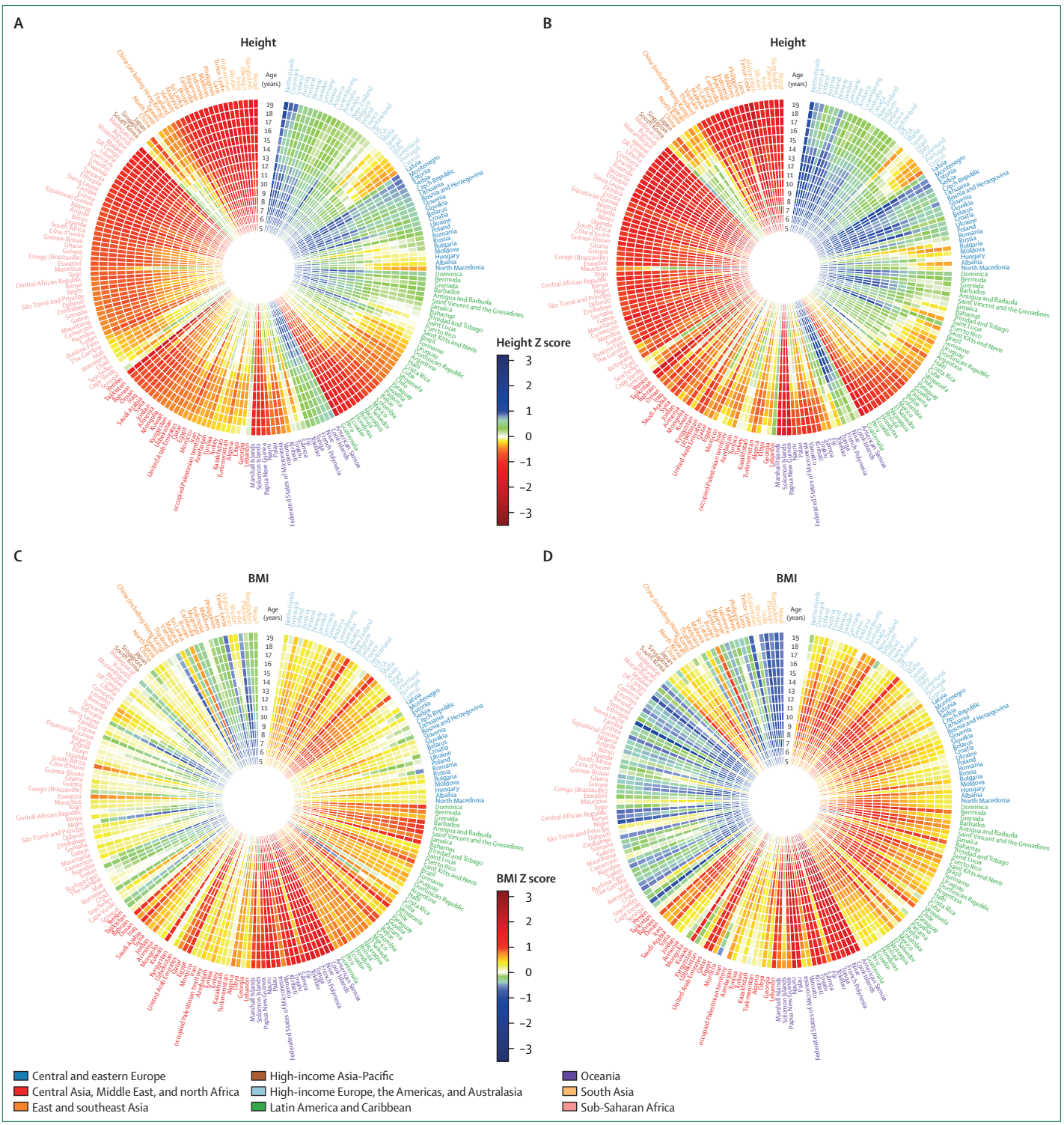

Figure 1: **Z scores for mean height and BMI of 54 million children and adolescents globally**

Z scores for mean height of girls (A) and boys (B). Z scores for mean BMI for girls (C) and boys (D). Individuals were born in 2000 and data were collected every year from age 5 years to 19 years. Each cell represents the Z score, derived from the WHO growth reference for a given age. Countries are ordered by region. For height, the heat map represents Z scores ranging from up to −3 (dark red) to above 3 (dark blue). For many countries, children and adolescents are shorter (stunted <2 Z score) than the WHO standard, as seen through the proliferation of red across the dial. For BMI, the heat map represents Z scores ranging from up to −3 (dark blue) to above 3 (dark red). For an increasing number of countries, children and adolescents are becoming overweight or obese (>1 Z score). BMI=body-mass index.

***Panel 1*: Long-term effects of calcium supplementation on pubertal timing and skeletal growth**

Most studies on calcium supplementation have been done in populations with adequate habitual calcium intakes. Therefore, in populations with extremely low calcium intake, interventions might be beneficial to skeletal development. Although most studies reported an initial increase in bone mineral density or size-adjusted bone mineral content (BMC), after a period of follow-up, the differences between intervention and control groups were attenuated.[47-49] To date, the study with the longest period of follow-up following supplementation is the 11-year follow-up study in The Gambia, in which calcium intakes were, on average, 300 mg/day. Pre-pubertal children aged 8–11 years were given 1000 mg of calcium or placebo for 5 days per week over 1 year.[49] The participants were then followed up until the end of growth, approximately 12 years later. At the end of the trial and 1 year and 2 years after supplementation, the calcium group had higher size-adjusted BMC at the midshaft radius than did the placebo group; the mean difference in size-adjusted BMC at the end of the trial was 4·6% (SE 0·9), reduced to 2·5% (1·3) by 2 years after supplementation. After modelling longitudinal growth for the entire follow-up period, group differences in pubertal timing, the velocity of growth, and final size were found, split by sex. In girls, no significant differences were found between the intervention groups in the amount of bone accrued or in the timing of puberty. In boys, pubertal timing (age at peak height velocity) was brought forward by approximately 7 months in participants in the calcium group and, although they transitioned through puberty at the same velocity as the placebo group, they stopped growing earlier (figure 2). Consequently, the boys in the calcium group were taller and had greater BMC in mid-adolescence compared with their counterparts in the placebo group; however, on average, they were 3·5 cm shorter at the end of the follow-up period. There were no significant group differences in bone outcomes at the end of growth, which could suggest that the supplementation had a negative effect on longitudinal growth with no direct benefit on bone mineralisation.

See Online for appendix

adolescence.[36] Economic hardship during preadolescent and adolescent periods is associated with short adult height.[37] Preference to have boys in China is associated with greater sex differences in height during childhood and adolescence than in the Philippines, where preference for boys exists to a lesser extent.[38] In Japan, day length predicts a regional gradient in height in late adolescence.[39] This mechanism might relate to regional gradients in photoperiod (ie, day length), which affects secretion of melatonin, inhibiting sexual and skeletal maturation, and inducing an increase in height.

In preschool children from Belarus and the USA, high BMI was associated with an increased velocity of upper body length and height in the following 4–5 years and with decreased height velocity during the next 5-year period.[40] Higher BMI in middle childhood (aged 6–8 years) was associated with earlier puberty and increased standing height and trunk length in adolescence. Data for the roles of specific nutrients or foods in adolescent height are scarce. In a cohort study of children aged 2–17 years in Iowa, USA, a high dietary intake of milk throughout childhood and adolescence (adjusted for nutrient adequacy, energy intake, and baseline socioeconomic status) was associated with greater height in adulthood than a low intake of milk.[41] Whether this association is specifically due to milk or to other attributes of the family or child is not known. Exposure to the Dutch famine of 1944–45 in young children during gestation or aged 1–2 years was associated with 3–4 cm deficits in adult height; however, inconsistent, smaller associations were seen for exposure at older ages (2–15 years).[42] Exposure to famines in Nigeria and Cambodia during adolescence reduced adult height more than exposure during younger ages (aged <12 years).[43,44] In Alabama (USA), early undernourishment delayed skeletal growth and menarche, and prolonged the period of growth in girls, with no difference in final adult height.[45] In Guatemala, receipt of a high protein-energy supplement improved nutrition, resulting in increased growth during the preschool period.[46] At adolescence, these children had greater height, muscle, and bone mass than did adolescents who had not received the supplement and, for boys only, skeletal maturation had advanced by 0·5 months.[46] A follow-up study in The Gambia explored the effect of calcium supplementation on the timing of puberty in children, and found a negative effect on attained height (panel 1).

Data from three decades of research in China suggest the interplay between socioeconomic context and the prevalence of stunting, thinness, and overweight or obesity over time. These findings highlight that linear growth restriction is reduced when environmental constraints are lifted (appendix p 1). These same environmental transitions have a substantial effect on the prevalence of overweight and obesity among adolescents. Given the consequences of undernourishment on health, such as an increased risk of NCDs (eg, diabetes and hypertension), as well as the rising incidence of overweight and obesity, achieving a balance between optimising linear growth and avoiding the negative consequences of excessive weight gain is needed to reduce the burden of NCDs.

Body composition

During adolescence, changes in the proportions and distribution of bone, muscle, and fat form the foundation of metabolic and musculoskeletal health.[50] The timing of onset, duration, and velocity of these indicators of body composition are important for nutrition-sensitive interventions to optimise body composition trajectories. Body composition is commonly calculated with dual-energy x-ray absorptiometry measures of total body fat mass, fat free mass, and bone mineral content (BMC), which is a marker of bone strength and fracture risk. Lean mass is used as a surrogate of muscle mass and is derived by fat free mass minus BMC.[51] According to data from high-income countries, girls reach peak height velocity (PHV)—ie, the period of time with the fastest upward growth (8·3 cm/year for girls and 9·5 cm/year for boys)—at an average age of 11·8 years, which is earlier than boys. By contrast, boys reach PHV at an average age of 13·5 years.[1,52] Additionally, girls have lower total body

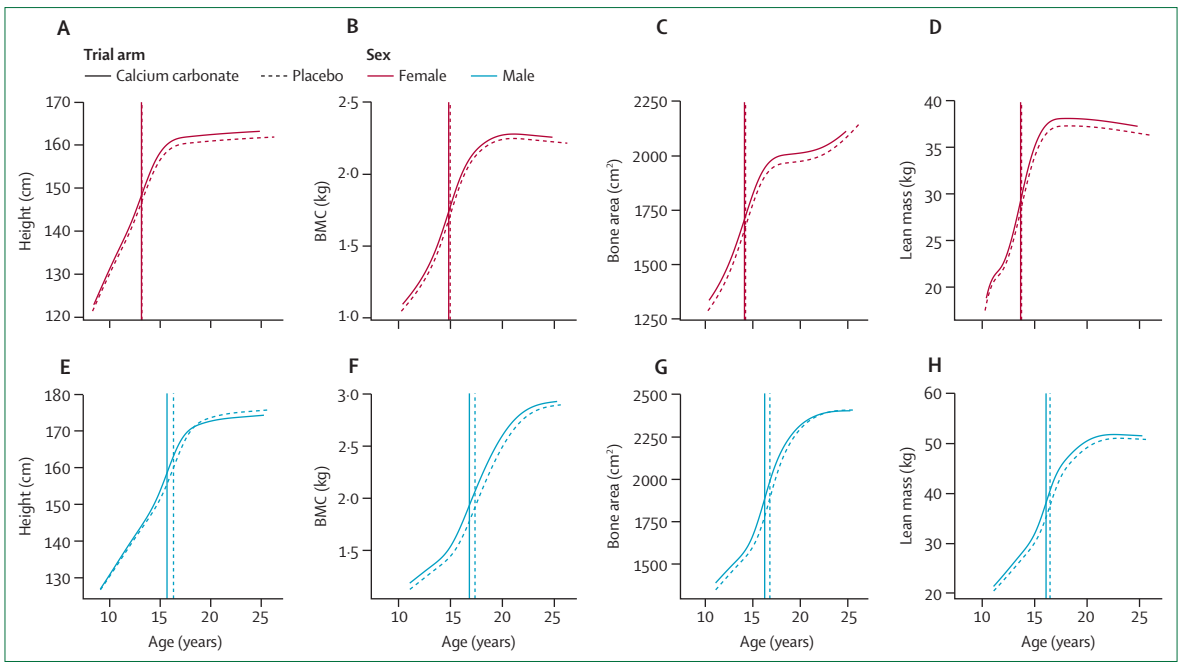

Figure 2: **Effect of calcium supplementation on distance curves for linear, bone, and muscle growth in adolescents from The Gambia**
Distance curves per year plotted for peak height (A), whole-body BMC (B), whole-body bone area (C), and lean mass (D) in female participants, and peak height (E), whole-body BMC (F), whole-body bone area (G), and lean mass (H) in male participants. The vertical line indicates age at peak accrual. Order of growth is height, lean mass, bone area, and BMC in both sexes. Male adolescents appear to continue accruing bone mineral after age 25 years. For more detail on this study, see panel 1. BMC=bone mineral content.

lean mass but greater fat mass than do boys.[1,52] Alongside greater lean mass, boys exhibit less total fat mass but similar (or greater in some cases) central fat mass than do girls.[52] These generalised values do not apply to all populations; for example, the age of PHV in The Gambia is approximately 16 years for boys and 13 years for girls (panel 1; figures 2, 3).

As height increases in girls and boys (for approximately 3 years after reaching PHV), there are corresponding increases in bone area and BMC.[1] Patterns of bone acquisition are relatively consistent between girls and boys; however, final BMC is higher[1,53] and reaches its plateau approximately 2 years later (at an average age of 18 years in girls and 20 years in boys) in boys than in girls.[1] Furthermore, ethnic differences are evident, with data suggesting that African American children have a higher BMC than do White children, despite similarities in height.[53] The onset and duration of puberty and nutrition can affect peak bone mass. A late onset of puberty has been associated with 10% decrease in bone mineral density and an increased risk of hip fracture in later life.[54,55]

Lean mass increases in girls and boys during adolescence; however, the rate of lean mass acquisition is higher in boys.[54] On average, girls attain stable, adult levels of lean mass at approximately 15–16 years of age.[45,54] In boys, steady acquisition of lean mass occurs from approximately 8–18 years of age, with more rapid increases at 12–15 years.[50,56] Independent of chronological age, puberty is associated with an average 1·14 kg/year increase in absolute fat mass in girls.[56,57] In boys, absolute fat mass is relatively stable over the pubertal period, which results in a decrease in body fat percentage during adolescence as a result of rapid increases in lean mass.[56] There are no significant sex differences in peripheral fat mass in the upper body compartments (ie, arm and torso), suggesting that differences in lower body (ie, legs) fat mass are the primary contributor to the sexual dimorphism in adiposity.[52] In general, boys have been shown to have higher amounts of visceral fat mass in later adolescence than do girls.[52] Panel 2 and figure 4 detail the trajectories of body composition in adolescents from South Africa, and show the altered trajectories of fat mass in individuals who have obesity as young adults. These results suggest that efforts to prevent obesity need to start earlier in adolescence (age 9–11 years). Furthermore, given the variations in timing and duration of puberty between girls and boys, interventions should be tailored by sex.

Cardiorespiratory fitness

High cardiorespiratory fitness (ie, reduced oxygen uptake during exercise, as measured by a maximal oxygen consumption test) attained during adolescence might decrease risk of cardiovascular disease in adulthood. A 2018 review concluded that, regardless of sex, cardiorespiratory fitness in childhood and

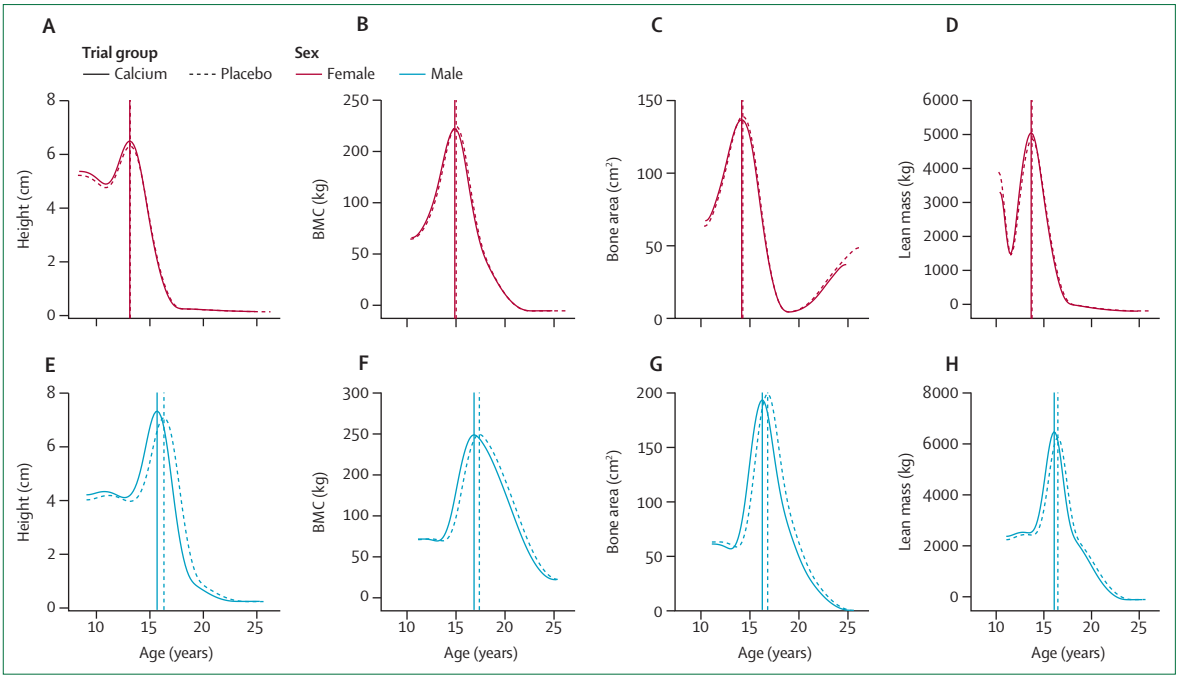

Figure 3: **Effect of calcium supplementation on velocity curves for linear, bone, and muscle growth in adolescents from The Gambia**
Measurement velocity curves per year plotted for peak height (A), whole-body BMC (B), whole-body bone area (C), and lean mass (D) in female participants, and peak height (E), whole-body BMC (F), whole-body bone area (G), and lean mass (H) in male participants. Velocity curves show the offset in peak velocity for each measure. The vertical line indicates age at peak accrual. Order of growth is height, lean mass, bone area, and BMC in both sexes. Age at peak height velocity (ie, onset of puberty) was 13·3 years (girls) and 14·4 years (boys) in the calcium group and 13·2 years (girls) and 14·8 years (boys) in the placebo group. For more detail on this study, see panel 1. BMC=bone mineral content.

adolescence was associated with decreased fat mass over time.[58] Additionally, analyses of the Swedish military conscription register indicated that low cardiorespiratory fitness at conscription strongly predicted being on a disability pension in later life due to ischaemic heart disease, cerebrovascular diseases, or heart failure.[59,60] Cardiorespiratory fitness in adolescence predicts a favourable risk factor profile for cardiovascular disease during adulthood, including reduced blood pressure, a favourable lipid profile, and reduced plasma fasting glucose concentrations.[61] Although cardiorespiratory fitness has a strong genetic component, high amounts of moderate-to-vigorous activity during adolescence have been associated with increased cardiorespiratory fitness.[62,63] The beneficial effects of cardiorespiratory fitness on body composition and adiposity, as well as the early establishment of healthy physical activity habits, could be jointly responsible for these health benefits in the long term (appendix pp 2–4).

Neurodevelopment

The brain reaches approximately 90% of its adult size by age 6 years, but the grey and white matter subcomponents continue to undergo dynamic changes throughout adolescence.[5] Considerable brain growth and development occur during adolescence in the construction and strengthening of regional neurocircuitry, with rewiring accomplished through dendritic pruning and myelination. In particular, the prefrontal cortex continually reconstructs, consolidates, and matures.[64] The adolescent brain is characterised by neuroplasticity, which is the ability of neural networks to reorganise in response to different social, learning, and nutritional environments.[65] On one hand, plasticity enables learning and adaptation; on the other hand, it brings a susceptibility to adverse environmental exposures, such as poor nutrition and stressful experiences.[66,67] This susceptibility raises the possibility of lasting changes in neurocircuitry, perhaps one explanation for why many psychiatric disorders first manifest in adolescence.[64]

Adolescent nutrition can have direct and indirect effects on the maturing brain. The severe undernutrition of anorexia nervosa can interrupt pubertal development, with impairment of cognitive flexibility and working memory.[68] Extended undernutrition results in a reduction in grey and white matter of the brain,[68,69] especially the frontoparietal network, with effects on higher executive functions.[68] These changes are also associated with poor emotional regulation, poor processing of social cues, and altered responses to reward.[68,70] Changes in brain structure in people with non-chronic anorexia nervosa seem largely reversible in response to improved nutrition and weight gain, with one study showing that the volume of grey and white matter normalised within 2–8 years of remission;[69] however, there might be less reversibility in chronic disorders.

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Excessive consumption of energy-dense foods can alter self-regulatory processes by affecting brain function.[71] High-fat and high-sugar diets might affect neurodevelopment through alterations in two neurotransmitter systems: dopamine-mediated reward signalling and inhibitory neurotransmission controlled by γ-aminobutyric acid.[71] Consequently, modifications of these two systems during adolescence could lead to dysregulated eating and impulsive behaviours.

Neurodevelopment seems to be linked to the maturation of other biological systems. For example, there appears to be a bidirectional communication between the gut microbiome and the brain. Dysbiosis (ie, change in the gut microbiome composition with metabolic and inflammatory effects) seems to affect neural function in vitro, in vivo, and in human studies, raising the possibility of neurodevelopmental consequences.[72] Additionally, musculoskeletal growth has consequences for neurocognitive development, with absence of the bone-derived hormone, osteocalcin, linked to anxiety and depression, as well as inhibited exploration, spatial learning, and memory.[73,74]

Immune system development

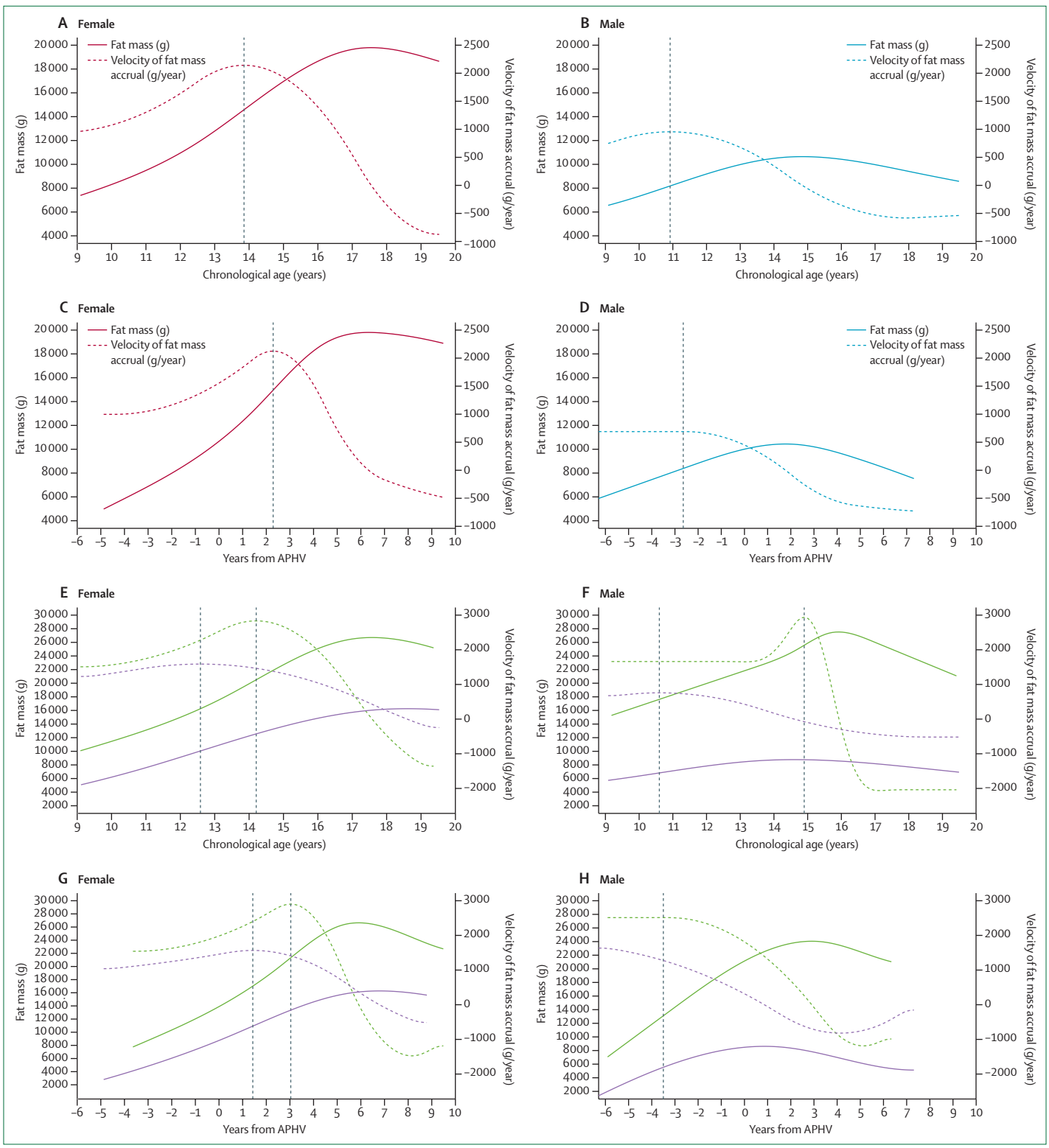
In infancy, passively acquired maternal immunity and breastfeeding provide protection against pathogens. Both innate (eg, neutrophils, monocytes, macrophages, and dendritic cells) and adaptive (eg, B and T lymphocytes) components of the immune system deliver tempered responses to pathogens and commensal microorganisms. In childhood, this pattern changes to provide more robust innate responses to pathogens and to allow for the development of protective immunological memory to pathogens through memory B and T cells, as well as pathogen-specific antibody responses. By late childhood, adult-like innate and adaptive responses are typically observed: the number of memory B and T cells reach adult numbers, and the output of naive T cells by the thymus diminishes substantially as immune memory to childhood infectious diseases has developed.[75] Therefore, adolescents have adult-like innate and adaptive immune responses, with adult-like sex differences in these responses.[76] Although some sex differences result from X-linked immune system genes and are seen throughout life, the differences that develop after puberty are caused primarily by the different actions of androgens and oestrogen on immune cells.[77] Sex can also influence the development of the immune system due to gender-specific differences in behaviour that affect exposure to environmental factors, including diet.[76,78–80]

Thus, nutritional status might affect adolescent health in a sex-specific manner, in which these effects are mediated by immune function. For example, as children, girls have a more robust adaptive immune response to infection than do boys and, consequently, lower mortality rates from infectious disease.[81–83] However, these mortality rates are similar for adolescent girls and boys, and are higher in adult women than in adult men, highlighting the impact of nutrition and social influences on biology (appendix p 4). In populations with a high HIV prevalence in adolescents, infection exacerbates undernutrition, which can further impair immunity. Dietary deficiencies in both macronutrients (eg, too little dietary protein) and micronutrients (eg, deficiencies in vitamins B12, C, and D) can impair most aspects of immune function, including compromising epithelial barriers (particularly relevant in HIV and other sexually transmitted infections) and impairing the development and function of innate and adaptive immune cells, with the predictable result of increasing the severity of common infectious diseases. For example, in adolescents with a dietary deficiency, macrophages and neutrophils have a diminished ability to

Panel 2: Body composition of adolescents from Soweto, South Africa

As part of the Birth to Twenty Plus Birth Cohort, longitudinal sub-cohort data on the body composition of children born in 1990 in Soweto, Johannesburg, South Africa, were derived from dual-energy x-ray absorptiometry. Data from 3067 scans, performed in 174 girls and 196 boys annually from age 9 years to 18 years, highlighted variation in timing and development of body composition between the sexes (figure 3). The peak velocity for bone mineral content (BMC) and fat-free soft-tissue mass (surrogate for lean mass) in boys occurred significantly later than in girls (BMC 14·6 years *vs* 12·2 years; fat-free soft-tissue mass 14·3 years *vs* 11·4 years). By contrast, peak velocity for fat mass occurred earlier in boys (10·9 years *vs* 13·9 years), although the magnitude of the mass and velocity for fat is significantly less in boys than in girls. However, after standardising for puberty, similar patterns for bone mass accrual were evident in boys and girls, and occurred approximately 1 year following peak height velocity (PHV), with boys having greater bone mass accrual. This finding was similar for lean mass, but not for fat mass. The peak fat mass velocity in boys occurred approximately 2·0 years before PHV, whereas for girls it was 2·5 years after, with significant differences in fat mass accrual between the sexes. This result aligns with the deposition of post-menarche fat mass in female adolescents in preparation for pregnancy. We know from longitudinal data that over 40% of female participants and 15% of male participants in the Birth to Twenty Plus Birth Cohort had overweight or obesity by adulthood. Using body-mass index in young adulthood (aged 20 years) to classify overweight or obesity, we examined the adolescent profile of fat mass accrual in young adults with or without overweight or obesity (figure 3). Unlike in adolescents without overweight, male adolescents with overweight or obesity have similar profiles to female adolescents with or without overweight or obesity in terms of peak fat mass velocity occurring after PHV. These data suggest that prevention should start in early adolescence to minimise excess accumulation of fat mass.

take up and kill pathogenic bacteria, lymphocyte cell counts in the spleen and lymph nodes are reduced, and development of memory T and B cells is impaired.[84] One example is seen with protein-energy malnutrition, which particularly impairs the T-cell arm of adaptive immunity by diminishing thymic function to reduce the supply of



naive T cells to peripheral lymphoid tissue. Therefore, this reduction might impair development of immunological memory, leading to an increased risk of death from infectious disease in childhood.[84] Nevertheless, studies in adolescence are scarce. Nutritional interventions that support resistance to infectious disease could benefit girls and boys.

Chronic inflammation caused by activation of the immune system during adolescence can decrease linear growth, partly due to the activity of proinflammatory cytokines (including IL-1β, TNFα, and IL-6) on the growth plate of long bones.[85] Obesity in adolescence stimulates chronic inflammation that increases the risk of various NCDs during adulthood, including fatty liver disease, type 2 diabetes (also in adolescence; appendix pp 2–4), and cardiovascular disease.[86] The cause of inflammation in obesity is complex, probably involving activation of innate immune cells in adipose tissue depots because of metabolic or cellular stress. The mechanism might involve diet-induced disruption of the intestinal barrier, perhaps initially causing changes to the intestinal microbiome that lead to increased exposure to microbial products (eg, bacterial lipopolysaccharides), which trigger systemic or local inflammation in abdominal adipose tissue.[87] During adolescence, the inflammation observed in obesity is associated with increased risk of chronic inflammatory diseases, including asthma.[88] Thus, preventing or treating obesity in adolescence could have clinically significant benefits by preventing immune-mediated exacerbations of infectious or chronic inflammatory diseases.

Adolescent pregnancy, nutrition, and intergenerational effects

Sexual maturation and relationships during adolescence set the scene for future parenthood. Reproductive success and optimal upbringing of children are best achieved after parents have largely completed the physical, mental, social, and emotional development of adolescence. Nevertheless, WHO estimates that around 16 million adolescent girls become mothers every year in LMICs.[89] Although the rate of adolescent pregnancy has decreased globally, an increasing number of adolescents overall means that the absolute number of adolescent pregnancies is increasing, particularly in settings with the greatest nutritional disadvantage.

The occurrence of adolescent pregnancies varies greatly across regions and within countries, but the number tends to be high in groups facing nutritional disadvantage, including rural and Indigenous populations.[90] These pregnancies occur more frequently in socioeconomically disadvantaged populations and among girls with unstable relationships and financial resources.[89] Adolescent pregnancy compounds disadvantages for girls by leaving education, limiting life chances (eg, employment), and perpetuating the cycle of poverty.[91] Neonates of adolescent mothers in LMICs are at increased risk of low birthweight and short birth length, at least partly because of maternal stunting and competition for nutrients between the mother and fetus during pregnancy.[92,93] Neonates of adolescent mothers are also at increased risk of preterm delivery,[94,95] with heightened risks for poor childhood growth and nutritional status, low educational attainment, and increased fasting glucose concentrations in adulthood.[94,95] These risks are most pronounced among children of the youngest adolescent mothers (figure 5),[95] and are likely to result from the biological immaturity of their mothers and their socioeconomic context.[94] Even though there are almost no data available from LMICs, scarce evidence suggests that adolescent fathers have similar offspring outcomes to adolescent mothers in terms of low birthweight, increased risk of preterm birth and infant mortality, and poor childhood health overall.[97]

When considered in the context of pregnancy and parenthood, the growing burden of adolescent malnutrition is of concern.[98] Undernutrition, food insecurity, and poor quality, monotonous diets remain common, especially in sub-Saharan Africa and south Asia. Gender inequality in nutrition often emerges in adolescence.[99] Both undernutrition and overweight or obesity in mothers before conception or during pregnancy predict altered growth and health in their offspring. Maternal height is positively associated with birthweight, adult stature, and educational attainment and income in the offspring.[100] Low maternal folate, vitamin B12, and vitamin D status in pregnancy have been associated with reduced cognitive function and changes in glucose and insulin concentrations in offspring, which indicate an increased future risk of diabetes.[101–103] Mothers with overweight or obesity are at an increased risk of developing gestational diabetes.[104] In turn, gestational glucose intolerance risks congenital malformations in the fetus, increasing the child's risk of increased adiposity and insulin resistance, elevated blood pressure, and early onset type 2 diabetes.[105,106] Although none of these associations are specific to adolescent pregnancy, stunting, micronutrient deficiencies, and overweight or obesity among adolescents all persist into later pregnancies, and shape fetal programming, development in early life, and cardiometabolic health of the offspring in the long term.

Figure 4: **Longitudinal modelling of fat mass and velocity of fat mass accrual by chronological age and APHV**

Whole-body fat mass (solid line) and velocity of fat mass accrual (dashed line) in female and male adolescents by chronological age (A, B) and by years from APHV (C, D) from the Birth to Twenty Plus Birth Cohort in South Africa. Longitudinal modelling of whole-body fat mass and velocity of fat mass accrual in female and male adolescents by chronological age (E, F) and years from APHV (G, H), stratified by individuals with (green) or without (purple) overweight or obesity at age 20 years. Unlike in adolescents with healthy weight, overweight and obesity in male adolescents have similar profiles to female adolescents, with peak velocity of fat mass accrual occurring after peak height velocity. In individuals with overweight or obesity, fat mass accrues early in adolescence and continues to increase until late adolescence. For more detail on this study, see panel 2. APHV=age at peak height velocity.

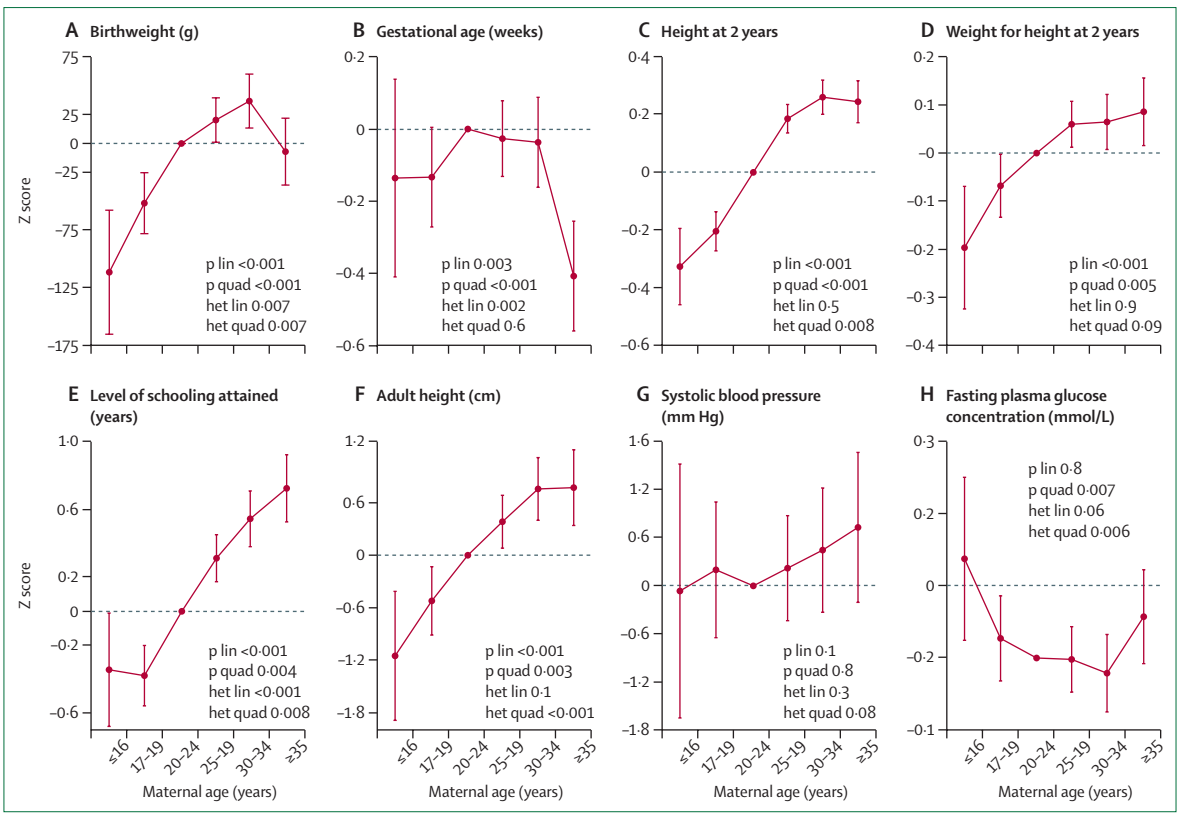


Figure 5: **Associations between maternal age and outcomes in offspring**
Z scores provided for birthweight, gestational age, height at 2 years, weight for height at 2 years, years of schooling attained, adult height, adult systolic blood pressure, and adult fasting plasma glucose concentration. Data taken from the COHORTS collaboration of five birth cohorts from low-income and middle-income countries.[96] For each maternal age group, the amount (95% CI) by which the outcome differs from offspring of mothers aged 20–24 years was obtained using linear regression of a pooled dataset from 19 403 women from five cohorts in Brazil, Guatemala, India, the Philippines, and South Africa, adjusted for offspring sex, maternal height, parity, marital status, schooling, wealth, race (Brazil and South Africa), urbanicity (the Philippines), breastfeeding duration (postnatal outcomes only), and offspring age (adult outcomes only). p values were derived using maternal age as a continuous variable. p lin is the p value from a test for linear trends in the outcome with maternal age; p quad is the p value from a test for quadratic trends; het lin is the F test p value for heterogeneity in the linear trends between the five cohorts; and het quad is the p value for heterogeneity in the quadratic trends.

There is growing research interest into whether paternal nutritional status has similar intergenerational effects through epigenetic changes in sperm, although most available evidence currently comes from animal studies.[107,108] In rodents, changes in paternal diet or exposure to stress between weaning and sexual maturity have been shown to alter the metabolism of offspring (ie, glucose tolerance and lipid metabolism), stress responsiveness, and mood. Although other epigenetic mechanisms could be involved, micro RNAs carried in sperm are strong candidates for messengers that link paternal nutritional state before conception to offspring phenotype.[107]

Conclusion

Biological development during adolescence involves a finely tuned orchestration of maturation of different physiological systems, with varying onsets and durations. Furthermore, this orchestration differs between girls and boys. Although undernutrition and overnutrition have diverse and different effects on biological development during adolescence, research has been scarce and there is still much to learn, particularly around adolescent growth and development in LMICs. Future studies into adolescent growth and nutrition should move beyond a focus on a single physiological system, towards integrated system-wide approaches over the lifecourse. Such research should include a better understanding of the relationships between pubertal development and nutrition, physical activity, and metabolic state, which could give rise to strategies that optimise growth and prevent diseases (eg, type 2 diabetes, osteoporosis and other musculoskeletal disorders, and cardiovascular disease) in later life. At a time when a rapid nutrition transition is shifting diets for most young people globally, improving adolescent nutrition provides an opportunity to shape the health and wellbeing of this generation and the next.

Contributors
SAN, EAF, and GCP conceptualised and coordinated the paper, and incorporated all revisions until submission. SAN, YD, CF, AP, and KAW

contributed figures to the paper. All authors contributed to writing designated sections of the paper and editing the paper and have reviewed and approved the final version of the manuscript.

Declaration of interests

AP declares grants from Medical Research Council (UK) during the conduct of The Gambia study. KAW declares personal fees from Abbott Laboratories, Pfizer Consumer Healthcare, and *Journal of Bone and Mineral Research*, outside of the submitted work. All other authors declare no competing interests.

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