Socioeconomic circumstances and childhood growth: a study in the birth cohort Generation XXI

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Aos meus pais, por serem a minha casa.

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“Quando eu nasci, as frases que hão-de salvar a humanidade já estavam todas escritas, só faltava uma coisa - salvar a humanidade.”

— José de Almada Negreiros, A Invenção do Dia Claro

TABLE OF CONTENTS

ABSTRACT

Childhood is the most important period of development during life-course, highly sensitive to external influences and with a profound impact on children's lives.

Studies have demonstrated that children exposed to material deprivation or psychosocial stressful events, are likely to experience negative long-term outcomes in the adult life, including chronic illness and premature death. Reducing health inequalities and improving child health are international policy goals. Understanding how socioeconomic circumstances influence growth from the evidence of longitudinal data is an important first step in revealing the mechanism by which the intergenerational transmission of poverty takes place and evolves.

Therefore, to guarantee a solid and steady economic and human development, each country must use all tools available to diminish the existent gap between the poorest and the richest proportion of the children population, by providing a better start for a better life of those in the bottom end of the society, and consequently to achieve a future with a more equal and just society.

Taking advantage of an established Portuguese population-based birth cohort, this thesis aims to understand how socioeconomic circumstances impact childhood growth by assessing how childhood growth trajectories vary between different socioeconomic groups.

To achieve this objective a manuscript was produced.

RESUMO

A infância é o período de desenvolvimento mais importante durante o decorrer da vida, altamente sensível às influências externas e com um impacto profundo na vida das crianças.

Estudos demonstraram que crianças expostas a privações materiais ou eventos psicossociais adversos estão em risco de ter problemas de saúde a longo prazo, na vida adulta, incluindo doenças crónicas e morte prematura. Reduzir as desigualdades na saúde e melhorar a saúde infantil são objetivos políticos internacionais. Compreender de que forma as circunstâncias socioeconómicas influenciam o crescimento a partir de dados longitudinais é um primeiro passo para revelar o mecanismo pelo qual a transmissão intergeracional da pobreza ocorre e evolui.

Assim, para garantir um desenvolvimento económico e humano sólido e estável, cada país deve usar todas as ferramentas disponíveis para diminuir a desigualdade existente entre os estratos mais pobres e mais ricos da população infantil, proporcionando “um começo melhor para uma vida melhor” para as crianças que vivem na base da sociedade e, consequentemente, alcançar um futuro com uma sociedade mais igualitária e justa.

Aproveitando uma coorte de nascimentos de base populacional portuguesa já estabelecida, esta tese visa compreender de que forma as circunstâncias socioeconómicas impactam o crescimento infantil, avaliando de que forma as trajetórias de crescimento infantil variam entre os diferentes grupos socioeconómicos.

Para atingir esse objetivo, foi produzido um manuscrito.

1. INTRODUCTION

Childhood is the most important period of development during life-course, highly sensitive to external influences and with a profound impact on children's lives.[1,2] During this period, the foundations for every individual's physical and mental health capacities and attainment are laid, influencing growth, development and well-being in adolescence and adulthood.

Retrospective studies have demonstrated that children exposed to material deprivation or psychosocial stressful events, are likely to experience negative long-term outcomes in the adult life, including chronic illness[3–6] and premature death.[7,8] Therefore, examining these stressors in childhood is of particular relevance in life-course epidemiology for understanding the production of health inequalities.

Reducing health inequalities and improving child health are international policy goals. Poverty and social inequality harm children's health and limit children's potential and development, leading to poor health and life chances in adulthood. It is known that socioeconomic circumstances during childhood shape later developmental opportunities. Understanding how socioeconomic circumstances influence growth from the evidence of longitudinal data is an important first step in revealing the mechanism by which the intergenerational transmission of poverty takes place and evolves.

Therefore, to guarantee a solid and steady economic and human development, each country must use all tools available to diminish the existent gap between the poorest and the richest proportion of the children population,[9] by providing a better start for a better life of those in the bottom end of the society, and consequently to achieve a future with a more equal and just society.

1.1 HUMAN GROWTH AND THE GROWTH CURVE

Human growth refers to the physiological increase in size, due to the proliferation of tissues. In the case of height, specifically, growth refers to the process from fertilization to the fusion of epiphyses and metastases of the long bones, through which an individual reaches his final adult height.[10] This process is highly complex and regulated through both genetic and environmental factors.[11]

Prenatal growth refers to the fastest period of growth, during which an organism develops from a zygote to a 51 cm foetus and includes both the embryogenesis and the foetal phase. Embryogenesis occurs in the first trimester of pregnancy and it's thought to be a rather autonomous period of growth, largely independent from external factors.[12]

Starting at the end of the first trimester, the foetal phase of growth is determined by genetic, nutritional, foetal and placental factors and their complex interactions.[13] During this phase, growth rapidly accelerates reaching a peak in height velocity of 2.5 cm/week, between the 20th and the 24th week of gestation, and decreasing subsequently.[14]

Chromosomal and genetic abnormalities (Down's syndrome, Turner's syndrome, etc.) can impair foetal growth, however, in the absence of genetic errors, foetal growth is mainly determined by foetal growth factors.[15] More specifically, foetal growth is regulated through the foetal IGF system, responsible for organ growth (IGF-I) and cell differentiation (IGF-II), and hormones such as insulin and leptin, and the interaction with placental and maternal hormones.[13]

Nonetheless, this intrauterine endocrine milieu is highly sensitive to environmental factors. Disturbances to the maternal environment include nutritional, behavioural and disease-related factors.[16]

Low calorie intake and macronutrient deficiencies, as well as poor weight pre-pregnancy and poor weight gain during pregnancy, are associated with impaired foetal growth. Additionally, maternal behaviours (e.g. smoking, alcohol consumption and drug use) and diseases (e.g. hypertensive disorders, diabetes, autoimmune diseases and chronic infections) are also important risk factors.[16]

Disturbances to placental function (e.g. abnormal implantation and vascularization of placenta) impact the nutritional and oxygen supply to the foetus and substrate availability and can result in restricted foetal growth.[12]

Towards the end of gestation, growth velocity decreases mainly due to maternal size constraints, causing the foetus to not reach his genetic potential.[12] Male foetus, however, are usually around 0.9 cm larger than female foetus due to high levels of testosterone production near the pregnancy term.[17]

To describe postnatal linear growth, Karlberg proposed the ICP growth model, dividing postnatal growth into three different components: infancy, childhood and puberty.[18]

At birth, infants can be classified as small, appropriate and large for gestational age (SGA, AGA, LGA, respectively) and their size is not strongly correlated with adult height ($r = 0,30$).[16,19] After birth, infants need to adapt to a very complex and rapidly changing environment.[11] Although height velocity is still high in the first year, it rapidly decreases from 20 cm/year to around 10-12 cm/year at the end of the first year.[10]

Throughout infancy, the maternal factors do not remain the main determinants of growth. Instead, growth genes are activated and become increasingly influential.[10] Children often change percentiles on growth charts to reach their genetically determined centile, in a process called canalization. For infants diagnosed as SGA or LGA, catch-up or catch-down growth, respectively, occurs within the 6^{th} and 18^{th} month of age. Despite the great influence of genes, this first phase of postnatal development is highly dependent on nutrition.[11]

At the end of the 24-month period, children grow to approximately 50% of their final height and their height is strongly correlated with their adult height ($r = 0,80$).[19]

Childhood, the second phase of postnatal growth, is characterized by a gradual decrease in height velocity. Height velocity lowers to 7.5 cm/year in the second year and to 5-6 cm/year from the third year to the onset of puberty. This steady decrease can be explained by the mixed effects of both the infancy and the childhood component in the first three years of postnatal life.[10,18]

During this phase, the growth hormone is the main determinant of growth and its influence is increasingly greater.[11] Disturbances in the GH-IGF-I axis and abnormal thyroid hormone levels are the main cause of impaired growth, with conditions usually being diagnosed during this period.[17]

A mid-childhood growth spurt around 7-8 years of age has been described in several studies and was thought to be related to increased level of adrenal androgen secretions, in adrenarche.[18,20,21] However, more recent evidence disputes the association between the two events.[22]

The third component of Karlberg's model is puberty (P).[18] Right before the pubertal growth spurt, height velocity might decrease to as little as 2 cm/year. Puberty refers to the development of secondary sexual characteristics through which an individual becomes sexually mature. At the onset of puberty (signalled by breast budding in girls and testicular enlargement in boys), the hypothalamic-gonadotropin axis is no longer supressed, and its activity leads to the increase in secretion of sex hormones.[10,17] Furthermore, increases in the levels of insulin, GH and IGF-I and the normal functioning of the thyroid are crucial to the pubertal growth spurt.[10,23]

The timing and tempo of puberty differs between populational groups and sexes.[24] Nonetheless, the pubertal growth spurt occurs around 11 years of biological age for girls, and 13 years for boys. For girls, the pubertal growth spurt occurs at an earlier phase of puberty, peak height velocity is 9 cm/year at around 12 years of age and the height gain is of around 25 cm. For boys, however, this growth spurt occurs at a later stage of puberty, leading to a longer period of prepubertal growth. Peak height velocity is 10.3 cm/year and the height gain is of 28 cm.[17,25]

Higher peak height velocity and the 2 extra years of prepubertal growth in males culminate in a 13 cm difference in adult height, between males and females. At the end of puberty, oestrogen causes epiphyseal and metaphyseal plates to fuse and growth is terminated, usually around 15 years of age for girls and 17 years for boys.[23,25]

Although growth has been thought to be a continuous linear process, studies of shorter interval measurements (weekly, biweekly and daily) found growth to be non-linear and discontinuous.[26]

Lampl and colleagues proposed the model of Saltation and Stasis to describe the pattern of growth that includes intermittent periods of time-constrained growth (saltations), separated by times of no measurable growth accrual (stasis). Timing and amplitude of saltations is thought to be specific to each individual and occur at aperiodic, non-random intervals.[27] Shorter periods of stasis are characteristic of growth spurts periods (i.e., infancy and puberty). Notwithstanding, saltation episodes occur across all ages, usually in minutes to hours periods.[28,29]

Saltations have been hypothesized to be a product of cellular proliferation and expansion in the endochondral growth plate of the long bones. Bone elongation is driven by hypertrophic chondrocytes, in the final period of cell maturation. Each period of chondrocytes' life cycle presents a critical point during which dietary inadequacies can

lead to decreased saltation amplitude or loss of the saltatory event. Thus, resources shortages cause reduced skeletal growth and shorter stature.[28]

1.2 HEALTH/BIOLOGICAL AND SOCIAL CONSEQUENCES OF ADULT HEIGHT

Shorter stature has both biologic and social consequences.[30] Adult height has been associated with various health outcomes and diseases. In 1988, Waaler studied the association between height and weight and total mortality and found height to be negatively associated with all-cause mortality.[31] Several studies have since corroborated Waaler's findings,[32–34] even when socioeconomic determinants are accounted for.[35]

The association between height and cause-specific mortality and morbidity is however heterogenous.[32,36] Wormser et al. analysed data from over 1 million participants in population-based studies and conclude that higher baseline height was negatively associated with coronary disease, ischaemic stroke, haemorrhagic stroke, subarachnoid haemorrhage, unclassified stroke and death from heart failure. Oppositely, data showed height to be positively associated with pulmonary embolism and ruptured aortic aneurysm. When adjusting for age, sex, birth year and common risk factors, the hazard ratios were not significantly altered.[36] On a different study, height was found to be positively associated with atrial fibrillation, vasculitis and venous thromboembolism.[37]

Furthermore, Wormser and colleagues found height to be associated with total cancer mortality, in both men and women, even when adjusting for common chronic diseases' risk factors.[36] This finding is supported by more recent studies, such as the Million Women Study whose findings suggest cancer incidence increases with increasing adult height in all-sites and the association is maintained after adjustment for socioeconomic status.[38] A Mendelian randomisation study in the UK Biobank reached the same conclusions, i.e. taller people are at higher risk of being diagnosed and dying from all types of cancer, although the effect is stronger for women.[39]

Focusing on non-European populations, a study of almost 23 million Korean participants found height to be positively associated with risk of all site-combined cancers and cancer in the oral cavity, larynx, lung, stomach, colorectum, liver, pancreas, biliary tract and gallbladder, breast, ovary, cervix and corpus uteri, prostate, testes, kidney, bladder, central nervous system, thyroid, skin, and lymphatic and haematopoietic systems. Only the association with malignancy in the oesophagus was non-significant.

Again, the association was shown to be stronger for women and non-smokers.[40] Nonetheless, for pancreatic, oesophagus and stomach malignancies, evidence is still conflicting, as different studies show either no interaction or a negative association with height.[41]

Height has been negatively associated with other diseases, such as Chronic Obstructive Pulmonary Disease, oesophageal reflux disease, diaphragmatic hernia[42] and death from liver disease, pneumonia and mental disorders.[36] On the contrary, height was positively associated with intervertebral disc disorder and hip fracture.[37]

Furthermore, a study on the association between height and health in six different emerging economies found height to be positively associated with good self-reported health, lung function, grip function, and no difficulties with activities of daily living or instrumental activities of daily living.[43] Height has also been positively associated with general well-being, cognitive function, and IQ.[44,45]

The social impact of adult height is connected to the fact that tall stature is socially desirable, as taller people are attributed traits as intelligence, employability, and leadership. Furthermore, height is associated with wealth, income, education, happiness and success. [46] Taller individuals have been shown to be more socially upwardly mobile, earn more and achieve higher education levels. [30,44]

A special concern is how inequalities during childhood can alter biologic processes and increase the risk for future generations. Additionally, decreased social mobility for shorter individuals can perpetuate social inequalities in height. These combined risk factors can become intergenerational, leading to systematic inequalities in health.[30]

1.3 DETERMINANTS OF GROWTH AND HEIGHT

Height has been found to be a product of both genetic and environmental factors. For western populations, it is estimated that 80% of height variability is due to heritability, whereas 20% is a result of environmental factors.[47]

Additionally, variability due to heritability has been demonstrated to be lower in infancy, increasing from childhood to adolescence and early adulthood. On the contrary, environmental factors have more influence in the early stages of life, with greater impacts in infancy and early childhood.[48,49]

The ability to reach the genetically determined stature is related to the extent to which a person experiences environmental hazards that cause decreased growth velocity and, consequently, shortened attained height.[32]

The secular trend in height, i.e. the documented 0.3 to 5 cm/decade increase in final height described since mid-19 century, is deeply connected to improvements in environmental factors, being positively associated with income, education and social status while being negatively affected by infectious diseases.[50]

A variety of environmental factors can impact height. Of all, net nutrition (i.e. the difference between intake and losses due to activity and disease) is the most important. [51] When nutritional supply is limited at the cellular levels, essential metabolic functions are prioritized despite growth, causing growth retardation, and shortened final height. Nonetheless, nutritional shortages affect growth differently during the pregnancy and the postnatal growth period.[44]

Malnutrition during the prenatal phase is associated with growth retardation in utero and poor foetal brain development, especially when occurring at an early stage of gestation.[52] Among SGA babies who do not experience catch-up growth during infancy and early childhood, malnutrition in the prenatal stage of development, and consequently low birth size, is associated with shortened adult height.[53]

Evidence on the impact of foetal malnutritional, however, is still poorly consolidated. Studies of intrauterine starvation during the siege of Leningrad and the Dutch Famine found no evidence on the impact of prenatal exposure to malnutrition on adult height.[54] On the contrary, different studies found growth failure in utero to be associated with shortness in adulthood.[53,55]

Both deficient energy and protein intake are determinants of growth retardation in the postnatal period.[44,54] Periods of undernutrition lead to increased levels of GH and decreased levels of IGF-I (GH resistance), as well as slowed metabolic rate, as an adaptive response to slow growth and balance nutritional demands.[56–58]

Protein is the most important nutrient, with the consumption ratio between high quality protein intake (milk, pork, fish) from animal sources and low-quality protein (wheat) currently explaining most differences in height between European countries.[59]

Nonetheless, deficiencies of vitamins A and D and minerals, such as calcium, phosphorus, magnesium, zinc and iron, can also impact linear growth, although interventions of nutrient supplementation have only shown small benefits.[60–62]

Disease also constitutes an important cause of growth failure, with an estimated third of all linear growth failure being attributed to illness.[63] Additionally, disease and nutrition are deeply interconnected.

On one hand, a malnourished child (specially with protein-energy malnutrition) has both acquired immunity and innate host defence mechanisms affected, leading to nutritionally acquired immunodeficiency and higher risk of contracting acute and chronic infections.[44]

Additionally, acute infections (mainly those causing diarrhoea), chronic infections (e.g., HIV and tuberculosis) and intestinal parasites can cause decreased food intake, malabsorption and impaired nutrient transport to tissues, as well as increase metabolic requirements and catabolic losses of nutrients, ultimately hindering bone growth and diminishing immunity, leading to a vicious cycle of malnutrition and disease. High rates of infections can also prevent catch-up growth that would allow the child to return to her genetically determined growth trajectory.[64–66]

Chronic diseases (e.g. celiac disease, asthma and cystic fibrosis) and some treatments (corticosteroids) can also lead to impaired growth.[67–72] Nonetheless, the association between disease and growth failure is weaker in developed countries, when compared with developing countries where the rates of communicable diseases are higher.[54]

Chronic exposure to psychosocial stress and emotional deprivation has been found to impact the hypothalamo-pituitary-growth axis causing reversible GH deficiency and low serum levels of IGF-I.[73] The syndrome first described by Powell *et al.* and commonly known as Psychosocial Short Stature (PSS) is found in children with GH deficiency, normal BMI and poor responses to GH treatment.[74,75]

Although the pathophysiology of stress-related short stature is still not completely understood, removal of the child from the abusive environment results in increased levels of both GH and IGF-I, and subsequent catch-up growth.[76] Nonetheless, full catch-up growth to the genetic potential might not be achieved.[73]

1.4 THE CHILD GROWTH AND THE ROLE OF SOCIOECONOMIC CIRCUMSTANCES

Growth involves not only the length and weight of a body, but also includes internal growth and development. Normal growth is usually characterized in a range used by paediatricians to gauge how a child is growing, and there are some average ranges of weight and height based on growth charts.[77]

During infancy and childhood, children gain weight and grow more rapidly than at any other time in life. Therefore, we should focus on the weight gain in the early period of life to be able to understand the trajectories of growth in children. However, some children do not gain weight at a normal rate, either because of expected variations related to genes, or because of being born prematurely, or because of undernutrition, which may occur for a variety of reasons namely the exposure to early low socioeconomic circumstances.[11,78]

It is important to recognize and treat children who are not gaining weight normally because it may be a sign of undernutrition or an underlying medical problem that requires treatment. These conditions will impact the normal growth of the child. On the other hand, a rapid weight gain during infancy will affect normal growth and predisposes a person to the development of a later cardiometabolic risk.[79]

Socioeconomic circumstances are an important determinant of height. Differences in adult height by socioeconomic position have been described extensively both at the individual and group levels. At group level, studies have focused on comparing rural and urban communities, northern and southern European countries, paying and public schools, among others.

At the individual level, differences in height have been found when using parental and personal occupational social class, educational attainment, income, household crowing and number of siblings.[32]

Although some studies have suggested that these differences might be decreasing or even disappearing[80–83] as societies become wealthier, recent studies found that people from lower socioeconomic backgrounds tend to be shorter than their more advantaged peers and that, although narrower, these differences persist today.[44,84,85]

A study conducted by Howe *et al.* found significant differences by socioeconomic groups that were present at birth, with little widening throughout childhood, until 10 years of age.[86] Another study, however, found that although differences were present at birth, different growth rates during childhood explained the widening height inequality to 2 years of age.[87]

Contrarily, a study conducted in the Netherlands in 2012 compared growth in the first 18 months of life and found children of low socioeconomic status to have smaller birth lengths but show accelerated linear growth in infancy leading to an overcompensation of the original height deficit.[88] More recently, a study on the association between risk of poverty and height-for-age between birth and 730 days of age found the negative effect of the risk of poverty on height to decrease or completely disappear between 6 and 18 months of age, however children at risk of poverty were reported to lag in height development again towards the end of the studied period.[89]

Expanding on these results, a study combining evidence from six European cohorts found evidence of widening socioeconomic differentials during childhood when expressed as the lag in growth relative to the tertiary educated (maternal education). Furthermore, the study demonstrated that the catch-up growth experienced in adolescence was not enough to erase the socioeconomic differentials and those persisted into adulthood. [90] A study by Rocha *et al.* further corroborated these findings, showing that socioeconomic differences in height were present at 13, 17 and 21 years of age.[79]

Contrarily, a study conducted by Galobardes *et al.* found that higher educated mothers had taller children. These socioeconomic differences, although small, still persisted. However, evidence showed that maternal and paternal height explained differences in height by maternal education. It was suggested that further research was needed to detangle the genetic and environmental factors behind health inequalities in high income countries.[91]

1.4.1 Biological embodiment of socioeconomic adversity and its impact on growth/height (potential pathways)

Although the impact of socioeconomic adversity on height is well established, evidence on the pathways through which socioeconomic disadvantage can lead to slower growth and shorter attained adult height is still scarce.

Nonetheless, several conceptual models have been proposed and applied to the subject. The Strachan-Sheikh model of life course functioning identifies two different periods of ageing. The build-up stage begins with conception and lasts until late adolescence, being characterized to high sensitivity to biological and environmental exposures that determine the maximum attained health. Early adulthood marks the beginning of the “decline” stage, when exposures strongly determine the rate at which function is lost, leading to disease, disability, and death.[92]

Since a great percentage of height growth occurs during infancy and early childhood, it can be argued that the social patterning of height reflects the embodiment of environmental and societal exposures during childhood.

The concept of “embodiment” proposed by Nancy Krieger encompasses the process through which socially patterned exposures are biologically incorporated (through pathogenic pathways mediated by physiology, behaviour and gene expression), thus affecting our bodily functions and constitution.[30,93]

Expanding on this concept, Blane *et al.* proposed a conceptual framework to explain how the embodiment of societal conditions can lead to biological changes that translate into the social patterns of health. In his paper, it’s suggested that structural, behavioural, and inter-personal exposures can impact biological (material, epigenetic and CNS-mediated) processes and translate into different health outcomes. In the specific case of growth during childhood, Blane *et al*. proposed the societal exposure to nutritional and emotional deprivation as possible explanations for stunted physical height.[94] For instance, studies have explored the association between household food insecurity and children’s height although results are still inconclusive.[95]

In the case of emotional deprivation, evidence on its association with height is very scarce. Nonetheless, studies have explored the association between low socioeconomic position in childhood and later life disease, through the biological embedding of stress and adversity.[96,97] Prolonged exposure to stress during childhood disrupts the nervous, endocrine, and immune systems causing structural and functional abnormalities in stress-sensitive areas, chronic activation of the hypothalamic–pituitary–adrenal axis and increased inflammation levels, respectively.[98,99]

As discussed previously, growth is highly dependent on the endocrine system, thus disruptions to the HPA axis caused by stress might be part of the pathway between socioeconomic circumstances and shorter height in childhood.

Furthermore, it's important to address the concept of epigenetic modification caused by societal exposures that suggests that exposure to socioeconomic disadvantage during sensitive periods could trigger cellular modifications that could be inherited at birth, thus leading to intergenerational disadvantage. Such is particularly important to consider in a trait with as high hereditability as height.[100]

1.5 PUBLIC HEALTH APPROACH TO SOCIAL INEQUALITIES IN HEALTH

A life course approach to disease epidemiology recognizes that chronic diseases develop over a long period of time and have long latency periods and argues that early life circumstances can act as risk factors for late-life diseases, by initiating disease mechanisms.[101]

Considering this theory, one can argue that the socio-environmental determinants of health during childhood influence the development of chronic diseases, through proximal biologic processes. The biological embedding of socioeconomic disadvantage triggers neurologic, endocrine, and immunological reactions that pose as an obstacle to optimal health and lead to shorter attained height and later life disease.[98]

This theory is supported by recent understanding that most chronic diseases are inter-related, sharing endocrine, immune, and inflammatory processes and risk factors, often with overlapping pathways.[100]

Height, however, is not considered to be a part of the causal pathway in the development of disease, but a proxy for health attainment, as it marks genotype and early life exposure.[90]

Low socioeconomic position throughout the life course is associated with poor ageing trajectories and early death.[100] Additionally, a recent study found socioeconomic circumstances to be associated with differences in healthy ageing scores, with individuals with lower educational and wealth levels scoring lower on baseline healthy ageing assessments. Nonetheless, education and wealth were not found to have significant effect on decreasing rates.[102]

In accordance with these findings, a recent study found early socioeconomic circumstances to be associated with later-life health indicators, even after adjusting for adult-SEC, but not their evolution over time.[103]

Still, socioeconomic circumstances during childhood should be addressed as a significant modifiable risk factor and targeted by global and local strategies to reduce health inequalities over the life course.[103]

Understanding the impact of socioeconomic circumstance on childhood growth trajectories could help clarify if inequalities narrow, widen or are maintained as a child ages, therefore allowing us to assess the critical point at which inequalities start to emerge and better target policies and measures to reduce the impact of said inequalities.

2. AIMS

Taking advantage of an established Portuguese population-based birth cohort, this thesis aims to understand how socioeconomic circumstances impact childhood growth by assessing how childhood growth trajectories vary between different socioeconomic groups.

To achieve this objective a manuscript was produced.

3. PAPER

Association of socioeconomic circumstances with childhood weight gain trajectories: findings from the Generation XXI birth cohort

Abstract

Background: Growth in the first years of life is a key factor of a child's health and development and has a significant impact on health and wellbeing in adult life. There is evidence that the growth patterns of children, in the absence of ill-health or other adverse environmental conditions, are remarkably similar across different countries of the world. However, poor health and nutrition can prevent a child from attaining their genetically determined growth potential. The geographical and social patterning of health and nutritional factors results in growth differences between high-, middle- and low-income countries, as well as generating within-country socioeconomic differentials in growth and final body size. Although some studies have suggested that these differences might be decreasing or even disappearing as societies become wealthier, recent studies found that people from lower socioeconomic backgrounds tend to be shorter than their more advantaged peers and that, although narrower, these differences persist today. Thus, socioeconomic circumstances seem to be an important determinant of growth.

Objective: Using data from a population-based sample of children of the same age, we aim to describe the biological and socioeconomic factors that impact on early child growth and to assess how childhood growth trajectories vary between different socioeconomic groups.

Methods: Data was collected as a part of the prospective Portuguese population-based birth cohort Generation XXI, between 2005 and 2006. Follow-up evaluations occurred at 4 and 7 years of age. Socioeconomic were assessed at baseline, through structured questionnaires. Anthropometric measurements were collected by trained professionals. Four weight trajectories were identified normal mixture modeling for model-based clustering and labeled as 'normal weight gain', 'persistent weight gain', 'weight gain during childhood' and 'weight gain during infancy'. Multinomial regression analysis was conducted to assess the association between socioeconomic factors and the trajectories. The final samples were 5225 children.

Results: Children whose mothers had low and intermediate educational levels were at higher risk of being in the 'persistent weight gain' (low: OR= 2.219, CI: 1.729-2.849; intermediate: OR=1.643, CI: 1.258-2.145) and 'weight gain during childhood' (low: OR=1.633, CI: 1.333-2.002; intermediate: OR=1.261, CI: 1.014-1.568) group when compared with children from highly educated mothers. The same pattern was found for paternal education. Children whose fathers had low or intermediate educational levels were found to be at higher risk of being in the 'persistent weight gain' (low: OR= 1.981,

CI: 1.487-2.638; intermediate: OR=1.403, CI: 1.018-1.934) and ‘weight gain during childhood’ (low: OR=1.759, CI: 1.386-2.233; intermediate: OR=1.502, CI: 1.157-1.950) group when compared with participants’ whose fathers had more than 12 years of formal education (high level). Similar results were found for mother and father occupation. Low household income was significantly associated with weight gain trajectories. Statistical significance was maintained even when assessing for sex, age, fruits and vegetable consumption and exposure to mother’s smoke during pregnancy.

Conclusion: Socioeconomic differences were evident regardless the indicator used. However, the associations seemed to be stronger when maternal conditions were examined. Further research is needed to address the adolescence period and young adulthood, to investigate if differences in weight gain trajectories persist or vanish when children reach adulthood. Policies and health promotion programmes should target early childhood as a critical period in development and aim to attenuate the health inequalities that will lead to poorer health outcomes for adults from disadvantaged backgrounds in later life.

Background

Growth in the first years of life is a key factor of a child's health and development and has a significant impact on health and wellbeing in adult life. In addition, the way a child grow will impact their final adult height.[1,2]

There is evidence that the growth patterns of children, in the absence of ill-health or other adverse environmental conditions, are remarkably similar across different countries of the world, even those with very different levels of economic development. Height has been found to be a product of both genetic and environmental factors. For western populations, it is estimated that 80% of height variability is due to heritability, whereas 20% is a result of environmental factors. However, poor health and nutrition can prevent a child from attaining their genetically determined growth potential. Additionally, variability due to heritability has been demonstrated to be lower in infancy, increasing from childhood to adolescence and early adulthood. On the contrary, environmental factors have more influence in the early stages of life, with greater impacts in infancy and early childhood.[3,4] The ability to reach the genetically determined stature is related to the extent to which a person experiences environmental hazards that cause decreased growth velocity and, consequently, shortened attained height.[1] Additionally, the geographical and social patterning of health and nutritional factors results in growth differences between high-, middle- and low-income countries, as well as generating within-country socioeconomic differentials in growth and final body size.

Although some studies have suggested that these differences might be decreasing or even disappearing[5–8] as societies become wealthier, recent studies found that people from lower socioeconomic backgrounds tend to be shorter than their more advantaged peers and that, although narrower, these differences persist today.[9–11] Thus, socioeconomic circumstances seem to be an important determinant of growth. Also, differences in adult height by socioeconomic position have been described extensively with differences in height being found according to parental and personal occupational social class, educational attainment, income, household crowing and number of siblings.

The social impact of adult height is connected to the fact that tall stature is socially desirable, as taller people are attributed traits as intelligence, employability, and leadership. Furthermore, height is associated with wealth, income, education, happiness, and success.[12] Taller individuals have been shown to be more socially upwardly mobile, earn more and achieve higher education levels.[11,13] Adult height has

been associated with various health outcomes. Several studies have since corroborated Waaler's findings,[1,14,15] even when socioeconomic determinants are accounted for.[16]

Growth involves not only the length and weight of a body, but also includes internal growth and development. Normal growth is usually characterized in a range used by paediatricians to gauge how a child is growing, and there are some average ranges of weight and height based on growth charts.[17]

During infancy and childhood, children gain weight and grow more rapidly than at any other time in life. Therefore, we should focus on the weight gain in the early period of life to be able to understand the trajectories of growth in children. However, some children do not gain weight at a normal rate, either because of expected variations related to genes, or because of being born prematurely, or because of undernutrition, which may occur for a variety of reasons namely the exposure to early low socioeconomic circumstances.[18,19]

It is important to recognize and treat children who are not gaining weight normally because it may be a sign of undernutrition or an underlying medical problem that requires treatment. These conditions will impact the normal growth of the child. On the other hand, a rapid weight gain during infancy will affect normal growth and predisposes a person to the development of a later cardiometabolic risk.[20]

Previous studies exploring the relation between biological factors and SES and growth have described associations in relatively small samples of children, with few measurements, or large samples of children, but with varying age ranges and substantial amounts of missing information.[21,22] Therefore, by using data from a population-based sample of children of the same age, we aim to assess how childhood growth trajectories, considering weight gain trajectories, vary between different socioeconomic groups.

Methods

Study Design

Data was collected as a part of the prospective Portuguese population-based birth cohort Generation XXI, with 8647 newborns recruited from five public maternities in Porto, between 2005 and 2006.[23] Follow-up evaluations were performed when children were aged 4 (2009-2011) and 7 (2012-2014) years of age. The number of participants at each re-evaluation was 7459 and 6889 children, respectively.[24] In all study waves, structured questionnaires on sociodemographic, behavioral, and clinical characteristics were administered by trained interviewers. Physical evaluations using standardized procedures were conducted by trained professionals.[25]

The Generation XXI project was approved by the Ethics Committee of the Hospital São João, registered with the Portuguese Authority of Data Protection and all procedures were carried out in accordance with the principles of the Declaration of Helsinki. Written informed consent obtained for all participating children, signed by their legal guardian at each evaluation.

Participants

From the initial 8647 babies, 1188 children were lost to follow-up in the 4 years old (48 months) evaluation. Additionally, 2234 children were excluded from the sample as their mothers did not bring their medical records to the evaluation or data for weight trajectory assignment was insufficient. The final sample included 5225 children.[26]

The characteristics of the participants included in the study were compared with those who did not meet inclusion criteria. Children included in the study had mothers ($n= 4450$, $p=0.001$) and fathers ($n=3927$, $p<0.001$) with higher education levels, both when assessed individually and combined ($n= 4441$, $p<0.001$) and both mothers ($n=4874$, $p<0.001$) and fathers ($n=3899$, $p=0.028$) had higher occupational positions. Additionally, children included in the study belonged to higher income families ($n=4563$, $p<0.001$), were more likely to have an employed mother ($n=4451$, $p=0.018$) or at least one employed parent ($n=4033$, $p=0.009$), and live with both parents ($n=4473$, $p=0.001$).

Further analysis concluded that children who met the inclusion criteria were born from older mothers ($n=5225$, $p<0.001$) and more likely to be born at term ($n=5221$, $p<0.001$) and with a birthweight higher than 2500 grams ($n=5225$, $p<0.001$). Although mothers from children included in the study were more likely to have drunk during the

pregnancy (n=4926, p<0.001), they were less likely to have smoked in the same period (n=5149, p<0.001).

Socioeconomic factors

Socioeconomic factors (maternal education level and occupation, paternal education level and occupation and income) were assessed at baseline evaluation by trained interviewers, using standardized questionnaires.

Education level of each parent was measured as number of years in formal schooling and then classified as low (≤9 years of formal education), intermediate (10-12 years of formal education) and high (>12 years of formal education) educational level, according to the International Standard Classification of Education 2011 classes.[25,27] A new variable was created to assess the highest education level attained between the two parents and classified as previously described.

Occupation for both parents was classified first by major professional groups according to the National Classification of Occupations and grouped into three categories: low (farmers, skilled and unskilled workers, craftsmen, machine operators and assembly workers); intermediate (administrative and related workers, service, and sales workers); and high (executive civil servants, industrial directors, scientists, middle management, and technicians).[25,28]

Employment status was assessed as whether each parent was unemployed or any of the two. Cohabitation was assessed as whether the child lived with both parents or only one.

Finally, disposable household income was measured as total monthly income of all people living at the house, from salaries and other income sources. Monthly disposable household income was grouped into three categories: low (1000€ or less), intermediate (between 1001€ and 2000€) and high (more than 2000€). The lower class includes participants whose parents both receive at least the minimum national wage (374.70€ in 2005 and 385.90€ in 2006.[25,29]

Anthropometric measurements

Birth length and weight was obtained from clinical records held at the maternity units. Additionally, anthropometric measurements between birth and 70 months of age were performed by health professionals and extracted from every child's National Health Service official health book.[26]

At each follow-up, height was measured to the nearest tenth of a centimeter with a wall stadiometer and weight was measured to the nearest one-tenth of a kilogram with a digital scale, with the child barefoot and in light clothing.[22]

Weight gain trajectories

Patterns in weight trajectories were identified through normal mixture modeling for model-based clustering and four different trajectories were defined. The 'normal weight gain' trajectory approximately matched World Health Organization Child Growth Standards' 50th weight-for-age percentile and comprised most children (62.4%).[26] The 'persistent weight gain' trajectory included children with higher weight than average (11.7%). The 'weight gain during childhood trajectory' described continuous weight gain (16.1%) and, lastly, the 'weight gain during infancy' described children born with low birthweight and catch-up weight gain during infancy (9.7%). These trajectories were adjusted for height and are further described elsewhere.[23]

Other covariates

Maternal and child factors associated with growth such as maternal BMI and age, occurrence of pregnancy complications, smoking and drinking during pregnancy and the child's sex, gestational age and malformations were assessed at baseline and complemented with information from clinical records.

At the 48 months follow-up evaluation the legal guardian reported the occurrence of medical problems (vomiting, diarrhea, gastroenteritis, convulsions, otitis, tonsilitis, pneumonia and urinary infection) during the past 12 months, as well as the need of frequent medical care during the same period.

Lastly, the occurrence of health problems since the age of 3 years old was reported at the 84 months follow-up evaluation. Growth, gastro, muscular, renal, and hepatic problems as well as diabetes were grouped into one single variable due to low number of observations. Only obesity was kept separate.

To assess for healthy eating habits and nutrition, a Food Frequency Questionnaire was used and information about the consumption of fruit and vegetables (in soup, boiled or raw) was extracted. A dichotomic variable was computed for less than five portions of fruit and vegetables and five or more portions per day.[30]

Statistical Analysis

Descriptive analysis was conducted, and contingency tables were created to compare the participants in each one of the four weight trajectories in terms of their

distribution by each socioeconomic variable and covariate. Qualitative variables were described as frequency and percentages (n, %), while quantitative variables were expressed as mean and standard deviation. Statistical significance was set at $\rho<0.05$.

Multinomial logistic regressions were performed to evaluate the crude and adjusted odds ratio (OR) and 95% confidence intervals (CI). The model was adjusted for sex and age (model 1), fruit and vegetables consumption at 84 months (model 2) and exposure to mother's smoke during pregnancy (model 3).

Statistical analysis was performed using the statistical software package IBM SPSS® Statistics vs. 26.0 (IBM Corp. released 2017, IBM Corp., Armonk, NY, USA)

Results

Table 1 shows significant statistical differences between socioeconomic circumstances and weight gain trajectories. Persistent weight gain, weight gain during childhood or during infancy were more frequent among those children from mothers and fathers with low education, unemployed fathers, mothers and fathers with low occupation and low income households. History of mother's unemployment and cohabitation were not significantly different across weight gain trajectories. In addition, in general the weight gain was more frequent among children from mothers who smoked during pregnancy, who had pregnancy complications, and were overweight or obese. Drinking alcohol during pregnancy and mother's age were not significantly different between trajectories. All birth-related circumstances (sex, gestational age, and birthweight) analysed were significantly difference between groups ($\rho<0.001$), except for malformations ($\rho=0.126$). Convulsions, otitis, and pneumonia at 48 months were more prevalent among those who had gain weight during infancy, and medical care at 48 months and obesity at 84 months were more prevalent among those with persistent weight gain. Fruit and vegetables intake were not significantly different between trajectories (Table 1).

Table 2 shows that children whose mothers had low and intermediate educational levels were at higher risk of being in the 'persistent weight gain' (low: OR= 2.219, CI: 1.729-2.849; intermediate: OR=1.643, CI: 1.258-2.145) and 'weight gain during childhood' (low: OR=1.633, CI: 1.333-2.002; intermediate: OR=1.261, CI: 1.014-1.568) group when compared with children from highly educated mothers. The same pattern was found for paternal education. Children whose fathers had low or intermediate educational levels were found to be at higher risk of being in the 'persistent weight gain' (low: OR= 1.981, CI: 1.487-2.638; intermediate: OR=1.403, CI: 1.018-1.934) and 'weight gain during childhood' (low: OR=1.759, CI: 1.386-2.233; intermediate: OR=1.502, CI: 1.157-1.950) group when compared with participants' whose fathers had more than 12 years of formal education (high level). Similar results were found for mother and father occupation. Low household income was significantly associated with weight gain trajectories. Exposure to mother smoke during pregnancy and exposure to pregnancy complications were all significantly associated with weight gain trajectories. Children born preterm were at higher risk of being in the 'weight gain during childhood' and 'weight gain during infancy' trajectories. Contrarily, normal birthweight (≥2500g) was associated with lower risk of 'weight gain during infancy'. Children whose mothers' BMI were in the normal/underweight or overweight categories were at lower risk of being in the 'persistent weight gain' and 'weight gain during childhood' trajectories. Sex (boys) followed the

same pattern. Exposure to convulsions, otitis and pneumonia in the last 12 months preceding the 48 months follow-up evaluation was associated with ‘weight gain during infancy’, and frequent usage of medical care in the same period was associated with both ‘persistent weight gain’ and ‘weight gain during infancy’.

Table 3 shows the adjusted models for the association of early socioeconomic circumstances with weight gain trajectories. After adjustment for sex and age, the association of mother and father education, mother and father occupation, and low income, and ‘persistent weight gain’ and ‘weight gain during childhood’ remains statistically significant.

In the model 2, after adjustment for sex, age, and fruits and vegetables consumption at the 84 months, association of mother and father education, maternal occupation, and low income, and the trajectories ‘persistent weight gain’ and ‘weight gain during childhood’ remains statistically significant. Additionally, the association between low paternal occupation and ‘persistent weight gain’ also remains significant.

Finally, model 3 that was adjusted for sex, age, fruits and vegetables consumption at 84 months and exposure to mother’s smoke during pregnancy, the association of mother and father education, mother occupation, and low income, and ‘persistent weight gain’ and ‘weight gain during childhood’ remains statistically significant.

Discussion

The results show that children from less-advantaged socioeconomic backgrounds are at higher risk of having persistent weight gain. These findings are consistent with studies that found socioeconomic differences in growth from birth until childhood.[22,31,32]

It was established that socioeconomic circumstances affect growth trajectories, even when nutrition and risk factors are accounted for, and that differences by socioeconomic group are evident from early infancy to childhood. This period is part of the build-up stage in Strachan-Sheikh model of life course functioning and it's highly sensitive to environmental and biological exposures. Adverse exposures during this period can lead to a decrease in maximum attained health, through the embodiment of environmental exposures.[33]

Socioeconomic differences were evident regardless the indicator used. However, the associations seemed to be stronger when maternal conditions were examined. These findings are consistent with a study from Erola *et al.* showing that maternal education is more impactful during early childhood, while paternal education affects mostly early adulthood.[34] Maternal education is related with maternal care towards the child, feeding practices, and parenting style, and therefore it can explain the consistency of these results.[17]

Furthermore, when adjusting for sex, age, fruit and vegetables intake and exposure to mother's smoke during pregnancy, the association of socioeconomic circumstances and growth trajectories remained significant, meaning these variables are not able to explain the differences between socioeconomic groups.

Findings suggest that periods of restricted prenatal growth (pregnancy complications, preterm birth, low birth weight) might be followed by a period of rapid catch-up growth, during infancy.[18] This period of rapid growth is found to be associated with cardiovascular diseases in adult life.[35]

The results show that infectious diseases and frequent use of medical care in 12 months preceding the 48 months follow-up evaluation were associated with 'weight gain during infancy'. A study from Katona and Katona-Ape that found recurrent infectious diseases to hinder growth. It is hypothesized that children who have experienced acute infectious in this period might experience rapid catch-up growth afterwards, therefore being placed in the 'weight gain during infancy' trajectory.[36] Although information is not

available on infectious diseases during the first 3 years of life, one could argue that these children are more vulnerable to disease and experience periods of catch-up growth throughout their early childhood.

A life course approach to chronic diseases requires addressing early life risk factors, especially modifiable ones. Socioeconomic factors should be addressed as a significant modifiable risk factor and targeted by global and local strategies to reduce health inequalities over the life course.[37]

Some strengths and limitations of this approach should be acknowledged. On one hand, leveraging the data of an established population-based cohort provides an opportunity to study the associations between socioeconomic circumstances, covariates and growth in a large sample of children, with the same age. The collection of socioeconomic information at baseline and the measurements of anthropometric features by trained professionals also decreased the changes of recall.

On the other hand, although this study found socioeconomic differences in weight gain trajectories from early infancy to 7 years of age, further research is needed to address the adolescence period and young adulthood, to investigate if differences in weight gain trajectories persist or vanish when children reach adulthood.

Nonetheless, this study shows evidence of social differences in childhood growth that will compromise future health. Policies and health promotion programmes should target early childhood as a critical period in development and aim to attenuate the health inequalities that will lead to poorer health outcomes for adults from disadvantaged backgrounds in later life.

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Annexes

Table 1. Sociodemographic factors and health characteristics according growth trajectories

		Normal weight gain	Persistent weight gain	Weight gain during childhood	Weight gain during infancy	p-value
n (%)		3263 (62.4)	610 (11.7)	843 (16.1)	509 (9.7)	
Early socioeconomic circumstances						
Mother's education level						
	Low	999 (35.0)	233 (47.7)	309 (43.9)	168 (41.4)	<0.001
	Intermediate	892 (31.3)	154 (31.6)	213 (30.3)	111 (27.3)	
	High	961 (33.7)	101 (20.7)	182 (25.9)	127 (31.3)	
Father's education level						
	Low	1143 (44.9)	234 (57.1)	327 (53.1)	170 (47.9)	<0.001
	Intermediate	745 (29.3)	108 (26.3)	182 (29.5)	100 (28.2)	
	High	658 (25.8)	68 (16.6)	107 (17.4)	85 (23.9)	
Parents' education level (highest achieved)						
	Low	760 (26.7)	183 (37.4)	237 (33.7)	124 (30.7)	<0.001
	Intermediate	951 (33.4)	169 (34.6)	249 (35.4)	134 (33.2)	
	High	1133 (39.8)	137 (28.0)	218 (31.0)	146 (36.1)	
Mother's employment status						
	Unemployed	507 (17.8)	101 (20.8)	119 (16.9)	72 (17.7)	0.354
	Employed	2348 (82.2)	385 (79.2)	585 (83.1)	334 (82.3)	
Father's employment status						
	Unemployed	246 (9.6)	54 (13.1)	63 (10.1)	50 (13.9)	0.023
	Employed	2305 (90.4)	359 (86.9)	559 (89.9)	309 (86.1)	
Parents' employment status						
	One or both unemployed	496 (19.1)	97 (22.5)	117 (18.3)	73 (20.2)	0.318
	Both non-unemployed	2104 (80.9)	334 (77.5)	524 (81.7)	288 (79.8)	
Cohabitation						
	Both parents	2363 (82.7)	394 (80.1)	587 (82.4)	335 (81.3)	0.519
	Only mother or father	494 (17.3)	98 (19.9)	125 (17.6)	77 (18.7)	
Mother's occupation						
	Low	618 (20.3)	160 (28.6)	188 (23.8)	112 (23.7)	<0.001
	Intermediate	1485 (48.7)	295 (52.7)	403 (51.0)	240 (50.7)	
	High	948 (31.1)	105 (18.8)	199 (25.2)	121 (25.6)	
Father's occupation						
	Low	1046 (42.2)	218 (48.7)	274 (45.0)	166 (45.5)	0.049
	Intermediate	640 (25.8)	121 (27.0)	148 (24.3)	87 (23.8)	
	High	791 (31.9)	109 (24.3)	187 (30.7)	112 (30.7)	
Household Income						
	Low	1018 (31.2)	221 (36.2)	296 (35.1)	188 (36.9)	0.025
	Intermediate	1334 (40.9)	240 (39.3)	337 (40.0)	189 (37.1)	
	High	911 (27.9)	149 (24.4)	210 (24.9)	132 (25.9)	
Prenatal health						
Smoking during pregnancy						
	Never	2595 (80.7)	448 (74.4)	658 (79.3)	380 (75.7)	0.001
	Yes	620 (19.3)	154 (25.6)	172 (20.7)	122 (24.3)	
Drinking alcohol during pregnancy						
	Never	2711 (87.7)	503 (87.2)	682 (87.5)	424 (88.3)	0.951
	Yes	379 (12.3)	74 (12.8)	97 (12.5)	56 (11.7)	
Pregnancy complications						
	No	2654 (81.7)	474 (78.0)	641 (76.8)	383 (75.4)	<0,001
	Yes	593 (18.3)	134 (22.0)	194 (23.2)	125 (24.6)	
Mother's BMI						
	Underweight/Normal	1248 (70.4)	166 (53.2)	289 (61.4)	186 (68.4)	<0.001
	Overweight	393 (22.2)	91 (29.2)	122 (25.9)	65 (23.9)	
	Obese	132 (7.4)	55 (17.6)	60 (12.7)	21 (7.7)	
Mother's age						

	<20	114 (3.5)	24 (3.9)	28 (3.3)	21 (4.1)	0.088
	20-34	2531 (77.6)	491 (81.0)	671 (79.6)	415 (81.5)	
	≥35	618 (18.9)	92 (15.1)	144 (17.1)	73 (14.3)	
Birth circumstances						
Sex						
	Girls	1446 (44.3)	323 (53.0)	576 (68.3)	235 (46.2)	<0.001
	Boys	1817 (55.7)	287 (47.0)	267 (31.7)	274 (53.8)	
Gestational age						
	Term	3133 (96.1)	583 (95.6)	795 (94.5)	342 (67.2)	<0.001
	Preterm	128 (3.9)	27 (4.4)	46 (5.5)	167 (32.8)	
Birthweight						
	≥2500	3121 (95.6)	586 (96.1)	815 (96.7)	334 (65.6)	<0.001
	<2500	142 (4.4)	24 (3.9)	28 (3.3)	175 (34.4)	
Head circumference	(mean [st. deviation])	51.3 (1.53)	52.4 (1.74)	51.5 (1.44)	51.6 (1.55)	
Malformations						
	No	3135 (97.8)	592 (98.3)	812 (98.2)	485 (96.4)	
	Yes/suspected	72 (2.2)	10 (1.7)	15 (1.8)	18 (3.6)	0.126
Health at 48 months						
Health problems since the age of 3						
Vomiting	No	1443 (44.4)	256 (42.2)	331 (39.4)	214 (42.5)	0.066
	Yes	1807 (55.6)	351 (57.8)	509 (60.6)	290 (57.5)	
Diarrhea	No	1360 (41.9)	245 (40.4)	370 (44.3)	190 (37.6)	0.103
	Yes	1882 (58.1)	361 (59.6)	466 (55.7)	315 (62.4)	
Gastroenteritis	No	2227 (69.0)	416 (69.0)	572 (68.8)	333 (66.1)	0.627
	Yes	1002 (31.0)	187 (31.0)	260 (31.3)	171 (33.9)	
Convulsions	No	3178 (97.7)	588 (96.9)	816 (97.1)	480 (95.0)	0.009
	Yes	76 (2.3)	19 (3.1)	24 (2.9)	25 (5.0)	
Otitis	No	2000 (61.6)	378 (62.2)	498 (59.4)	278 (55.2)	0.033
	Yes	1247 (38.4)	230 (37.8)	341 (40.6)	226 (44.8)	
Tonsilitis	No	1881 (58.0)	352 (58.3)	468 (56.0)	277 (55.1)	0.480
	Yes	1362 (42.0)	252 (41.7)	368 (44.0)	226 (44.9)	
Pneumonia	No	3204 (98.5)	598 (98.4)	821 (97.5)	485 (95.8)	0.001
	Yes	50 (1.5)	10 (1.6)	21 (2.5)	21 (4.2)	
Urinary infection	No	3070 (94.4)	558 (92.4)	780 (93.0)	472 (93.3)	0.134
	Yes	181 (5.6)	46 (7.6)	59 (7.6)	34 (6.7)	
Frequent medical care	No	2467 (75.9)	423 (69.3)	633 (75.5)	360 (71.0)	0.001
	Yes	783 (24.1)	187 (30.7)	205 (24.5)	147 (29.0)	
Health at 84 months						
Other health problems	No	2444 (87.2)	432 (89.3)	609 (87.4)	344 (86.4)	0.581
	Yes	359 (12.8)	52 (10.7)	88 (12.6)	54 (13.6)	
Obesity	No	2851 (99.7)	431 (88.0)	694 (97.9)	402 (97.8)	<0.001
	Yes	9 (0.3)	59 (12.0)	15 (2.1)	9 (2.2)	
Daily fruit and vegetable consumption						
	<5	1707 (59.5)	304 (61.5)	427 (59.8)	229 (55.3)	0.275
	≥5	1160 (40.5)	190 (38.5)	287 (40.2)	185 (44.7)	

Table 2. Multinomial logistic regression analysis for the association of socioeconomic factors and health characteristics with growth trajectories

	Persistent weight gain *versus* 'Normal weight gain'		Weight gain during childhood *versus* 'Normal weight gain'		Weight gain during infancy *versus* 'Normal weight gain'	
	OR	95% CI	OR	95% CI	OR	95% CI
Mother's education level						
High (reference)	1		1		1	
Intermediate	1.643	1.258-2.145	1.261	1.014-1.568	0.942	0.718-1.234
Low	2.219	1.729-2.849	1.633	1.333-2.002	1.273	0.994-1.629
Father's education level						
High (reference)	1		1		1	
Intermediate	1.403	1.018-1.934	1.502	1.157-1.950	1.039	0.764-1.413
Low	1.981	1.487-2.638	1.759	1.386-2.233	1.151	0.872-1.520
Mother's occupation						
High (reference)	1		1		1	
Intermediate	1.794	1.415-2.274	1.293	1.071-1.561	1.266	1.003-1.599
Low	2.337	1.791-3.050	1.449	1.159-1.812	1.420	1.077-1.872
Father's occupation						
High (reference)	1		1		1	
Intermediate	1.372	1.038-1.814	0.978	0.770-1.243	0.960	0.712-1.294
Low	1.512	1.181-1.938	1.108	0.900-1.364	1.121	0.867-1.449
Income						
High (reference)	1		1		1	
Intermediate	1.100	0.882-1.372	1.096	0.905-1.328	0.978	0.771-1.240
Low	1.327	1.059-1.664	1.261	1.035-1.538	1.275	1.003-1.620
Smoking during pregnancy						
No (reference)	1		1		1	
Yes	1.439	1.174-1.763	1.094	0.905-1.322	1.344	1.076-1.678
Pregnancy complications						
No (reference)	1		1		1	
Yes	1.265	1.024-1.563	1.355	1.127-1.628	1.461	1.171-1.821
Mother's BMI						
Obese (reference)	1		1		1	
Overweight	0.556	0.377-0.820	0.683	0.473-0.985	1.040	0.612-1.766
Underweight/normal	0.319	0.224-0.455	0.509	0.366-0.709	0.937	0.576-1.522
Children's sex						
Girls (reference)	1		1		1	
Boys	0.707	0.595-0.841	0.369	0.314-0.433	0.928	0.769-1.119
Gestational age						
Term (reference)	1		1		1	
Preterm	1.134	0.742-1.733	1.416	1.002-2.001	11.952	9.254-15.437
Birthweight						
<2500	1		1		1	
≥2500	1.111	0.714-1.727	1.324	0.877-2.001	0.087	0.068-0.111
Convulsions (48 Months)						
No (reference)	1		1		1	
Yes	1.351	0.811-2.251	1.230	0.772-1.959	2.178	1.372-3.457
Otitis (48 Months)						
No (reference)	1		1		1	
Yes	0.976	0.816-1.167	1.098	0.941-1.282	1.304	1.079-1.576
Pneumonia (48 Months)						
No (reference)	1		1		1	
Yes	1.072	0.540-2.125	1.639	0.979-2.744	2.775	1.652-4.660
Frequent medical care (48 Months)						
No (reference)	1		1		1	
Yes	1.393	1.152-1.684	1.020	0.855-1.218	1.287	1.045-1.584

Table 3. Multinomial logistic regression for the association of socioeconomic factors with growth trajectories (Adjusted Odds Ratios and 95% confidence Intervals)

	Model 1 - Adjusted for sex and age		Model 2 - Adjusted for sex, age and 5-a-day		Model 3 - Adjusted for sex, age, 5-a-day and smoking during pregnancy	
	OR	95% CI	OR	95% CI	OR	95% CI
Persistent weight gain						
versus 'normal weight gain'						
Mother's education level						
High (reference)	1		1		1	
Intermediate	1.664	1.746-2.885	1.685	1.284-2.209	1.658	1.261-2.182
Low	2.244	1.273-2.175	2.294	1.776-2.963	2.226	1.718-2.885
Father's education level						
High (reference)	1		1		1	
Intermediate	1.436	1.040-1.984	1.405	1.014-1.947	1.319	0.949-1.834
Low	2.029	1.520-2.709	2.015	1.504-2.700	1.945	1.449-2.609
Mother's occupation						
High (reference)	1		1		1	
Intermediate	1.867	1.442-2.416	1.890	1.456-2.455	1.798	1.381-2.342
Low	2.373	1.771-3.179	2.426	1.803-3.266	2.423	1.797-3.266
Father's occupation						
High (reference)	1		1		1	
Intermediate	1.242	0.915-1.686	1.246	0.916-1.694	1.183	0.868-1.613
Low	1.456	1.114-1.902	1.477	1.127-1.935	1.432	1.092-1.879
Income						
High (reference)	1		1		1	
Intermediate	1.120	0.879-1.428	1.129	0.885-1.440	1.094	0.857-1.398
Low	1.343	1.045-1.726	1.343	1.042-1.730	1.252	0.970-1.616
Weight gain during childhood						
versus 'normal weight gain'						
Mother's education level						
High (reference)	1		1		1	
Intermediate	1.278	1.025-1.594	1.284	1.027-1.605	1.257	1.004-1.574
Low	1.644	1.337-2.022	1.656	1.342-2.044	1.630	1.318-2.015
Father's education level						
High (reference)	1		1		1	
Intermediate	1.549	1.189-2.018	1.575	1.207-2.056	1.554	1.190-2.031
Low	1.805	1.417-2.299	1.842	1.441-2.354	1.808	1.413-2.313
Mother's occupation						
High (reference)	1		1		1	
Intermediate	1.293	1.055-1.585	1.288	1.048-1.583	1.272	1.033-1.565
Low	1.547	1.215-1.969	1.551	1.214-1.982	1.524	1.191-1.951
Father's occupation						
High (reference)	1		1		1	
Intermediate	1.023	0.786-1.331	1.023	0.786-1.332	1.014	0.778-1.322
Low	1.207	0.961-1.516	1.203	0.956-1.513	1.169	0.928-1.474
Income						
High (reference)	1		1		1	
Intermediate	1.109	0.899-1.366	1.112	0.902-1.371	1.095	0.887-1.353
Low	1.269	1.020-1.579	1.270	1.019-1.582	1.238	0.992-1.547
Weight gain during infancy						
versus 'normal weight gain'						
Mother's education level						
High (reference)	1		1		1	
Intermediate	0.945	0.720-1.239	0.981	0.746-1.289	0.966	0.733-1.273
Low	1.269	0.990-1.626	1.326	1.030-1.707	1.294	1.002-1.671
Father's education level						
High (reference)	1		1		1	
Intermediate	1.034	0.759-1.409	1.060	0.776-1.447	1.056	0.771-1.446
Low	1.149	0.869-1.519	1.186	0.893-1.574	1.172	0.879-1.561
Mother's occupation						

High (reference)	1		1		1	
Intermediate	1.152	0.897-1.479	1.192	0.926-1.534	1.163	0.901-1.501
Low	1.348	1.000-1.816	1.404	1.037-1.902	1.394	1.026-1.892
Father's occupation						
High (reference)	1		1		1	
Intermediate	0.927	0.674-1.277	0.947	0.687-1.306	0.921	0.666-1.275
Low	0.994	0.752-1.314	1.018	0.768-1.349	1.026	0.773-1.363
Income						
High (reference)	1		1		1	
Intermediate	0.993	0.768-1.286	1.011	0.781-1.310	1.006	0.775-1.306
Low	1.213	0.929-1.583	1.242	0.950-1.625	1.204	0.918-1.578

4. CONCLUSION

In the present thesis, socioeconomic circumstances were found to be associated with childhood growth trajectories, even when other factors were accounted for. Despite evidence that socioeconomic gradients in adult height might be fading in high income countries, the results show that children from different socioeconomic backgrounds growth differently.

The exposures acting on this highly sensitive period that is infancy and childhood will have consequences in later life, from higher rates of cardiovascular diseases to premature death and lower chances of social mobility. In fact, low socioeconomic position throughout the life course is associated with poor ageing trajectories and early death.

Thus, it is critical that policies to address and close socioeconomic inequalities target infancy and early childhood as an optimal period for action on modifiable risk factors. Only by closing the gap between socioeconomic groups will we ensure that children have access to equal opportunities and a chance at healthy living throughout the lifecourse.

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