



EDITORIAL

**Growth retardation and metabolic programming: implications and consequences for adult health and disease risk** ☆,☆☆



**Retardo do crescimento e programação metabólica: implicações e consequências para a saúde do adulto e o risco de doenças**

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Experiencing poor nutrition *in utero* or during early childhood is associated with chronic diseases later in life, a concept now referred to as the developmental origins of adult health and disease (DOHaD).<sup>1</sup> Given the challenges of studying physiological changes in children, scientists and policy makers often rely on human clinical and/or animal studies to improve their understanding of physical adaptations that may support potential mechanisms of DOHaD. The article by Alves et al.,<sup>2</sup> in this edition of the *Jornal de Pediatria*, is an excellent example of the research needed to advance the field. Still, it is important to place the results presented within a proper methodological and scientific context for a clear understanding of their impact on nutrition science and policy, as well as on pediatric practices.

Growth retardation severe enough to cause stunting (height for age less than two standard deviations of a reference population, HAZ < -2.0) is the primary outcome

of chronic undernutrition and most often occurs *in utero* and/or during the first two years of life, the “critical window” of growth.<sup>3</sup> During the first 30 months of growth and development, specific cells, organs, and systems may be differentially affected by undernutrition, depending on the specific point and extent of nutrient and/or energy restriction. Indeed, the nutritional environment during this “critical window” is the primary determinant of growth, while the nutritional environment after the age of 2 years primarily influences body composition more than parameters of growth and development. Essentially, a child at age 2 years meets a juncture at which energy and nutrients that were previously directed towards growth are now directed toward weight and body composition, thereby creating the dietary environment that will allow potential adaptations from past energy restriction to become manifest.

Studies on the relationship between stunting and chronic diseases began in the mid-1990s, when Popkin et al.<sup>4</sup> reported that adults who were stunted as adolescents were more likely to be overweight than their normal height peers. Data from two longitudinal cohort studies suggest that growth retardation early in life predisposes a child to obesity or overweight later in childhood or in adulthood.<sup>5,6</sup> However, some studies have demonstrated that stunting is not associated with adiposity later in life.<sup>7,8</sup> Despite these apparently contradictory studies, it is important to consider that biological adaptations do not always become manifest

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without some environmental cue, such as increased refined sugar intake or chronic positive energy balance, conditions most often associated with the "nutrition transition" that accompanies economic development.<sup>9</sup> Differences in the level of socio-economic development that give rise to an "obesigenic" environment may limit physiological adaptations to manifest as excess fat mass or obesity. Yet, the lack of a biological mechanism to explain the association between stunting and chronic disease persists.

One potential mechanism, mentioned in the article by Alves et al.,<sup>2</sup> is an adaptation in lipid metabolism. In 2000, we reported that stunted children from shantytowns in São Paulo, Brazil metabolized lipids at a lower rate than normal height children from the same socioeconomic environment, independent of dietary intake and other confounding factors.<sup>10</sup> A similar study, conducted with male subjects from the Hertfordshire Cohort in England, observed that men who had suffered intrauterine growth restriction had a lower rate of lipid oxidation when compared to those born with normal weight.<sup>11</sup> Finally, an elegant study that blended human nutrition and anthropology was conducted with adults from Buryat tribes in Southern Siberia, who suffered seasonal undernutrition after the collapse of the Soviet Union.<sup>12</sup> The repeated bouts of food insecurity and poor physical growth were so severe that the generation born in this period was shorter at adulthood than their parents. Metabolic studies of this generation observed that adults who were significantly shorter than their peers had a lower rate of lipid oxidation, controlling for body composition. Thus, based on these three studies of humans from vastly different geographical and socio-economic areas, a consistent observation is that those who experienced some degree of growth retardation *in utero* or during early development present with a metabolic profile that favors fat accumulation during times of dietary excess. In fact, stunted children with impaired fat oxidation gained more central fat during a four-year follow-up period, independent of total fat mass and pubertal status.<sup>13</sup>

Regarding the relationship between poor growth and other aspects of lipid metabolism, epidemiological studies have reported that adults who experience intrauterine growth retardation are more likely to suffer from atherogenic lipid profiles and cardiovascular disease than those who developed normally.<sup>14,15</sup> Perhaps the most significant finding by Alves et al.<sup>2</sup> was the fact that despite benefiting from an intensive treatment program, the children studied only experienced improvements in their lipid profiles for some, but not all, of the parameters assessed. It was also astutely hypothesized that the increased TG concentrations reported may be the result of low LPL expression. These observations warrant explicit attention and the data presented should be further studied in order to develop a more comprehensive assessment of the nature of the lipid profiles in the subjects, including a comparison with a healthy control group of children and/or including measures of dietary factors that may contribute to plasma lipid concentrations. Florencio et al.<sup>16</sup> observed that short, obese women had significantly greater total cholesterol and low-density lipoprotein (LDL) concentrations compared to normal height, obese women. Recently, we reported that 3 to 4 year-old stunted children from a cohort study of maternal nutrition education had significantly higher total

cholesterol concentrations compared to children who were not stunted. These results were independent of gender, maternal education, maternal BMI, breastfeeding history, and child waist circumference, and persisted even when the cut-off for defining a child as growth retarded was "relaxed" to -1.62 HAZ.<sup>17</sup> Thus, a growing body of literature now points to undernutrition early in life as a condition that may predispose an individual to unhealthy or even atherogenic blood lipid profiles. Considering that the period between conception and 2 years of age is critical for development, a link between poor fetal and childhood growth and cardiovascular disease is certainly plausible.

There are a number of biochemical or epigenetic that may explain the association between growth retardation and adaptations in lipid metabolism. Specifically, data from animal studies suggest that undernutrition during the gestational period causes changes in lipid metabolism and structural changes in the liver.<sup>18-20</sup> Cong et al. found that rat pups of protein-restricted mothers had lower liver weights compared to those born to mothers with adequate nutrition.<sup>18</sup> Perhaps more important, pups born to protein-deficient mothers had genes for 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) that were hypomethylated, a condition that allows for the activation of the transcription of the HMGCR gene, resulting in an overexpression of the protein and enhanced basal cholesterol synthesis. An exceptional study by Sohi et al. observed that rat pups born to protein-deprived mothers were hypercholesterolemic at birth and throughout early development.<sup>19</sup> Epigenetic changes in the same litter of pups included increased histone methylation in the cholesterol 7 $\alpha$ -hydroxylase promoter, resulting in decreased gene expression, allowing for decreased cholesterol decay and hypercholesterolemia. Nonetheless, while some data clearly support the mechanism that nutritional deprivation *in utero* imparts epigenetic changes that cause atherogenic lipid profiles, the sum of the available research is still equivocal.

The research cited provide reasonable evidence that undernutrition early in life is associated with elements of an "unhealthy" lipid profile, but it is essential that future studies are developed to further explore potential mechanisms behind such associations, both at the biochemical and the physiological level, with strict attention to study design and data analysis. There are a number of statistical methods that are easily employed to refine our understanding of data collected through complex designs. For example, it is absolutely imperative that potential confounding factors are identified and addressed in the design phase (through randomization) or in the analysis phase (using linear regression or other advanced analyses). In addition, longitudinal data are particularly difficult to analyze using standard statistical approaches, as the number of participants at specific time points change and key variables, such as hormone concentrations, may change as children age. Therefore, it is important to limit the potential for erroneous results that may arise due to the use of statistical techniques that are less than robust for longitudinal analyses. One potential technique would be the use of "life course" analyses.<sup>21</sup> An important feature of life course techniques is that measures of different variables over a period of time (e.g. birth weight and body composition), as well as repeated measures of the same variables (e.g. body weight, lipid profiles, or height),

are appropriately modeled in the analyses. Simply, factors that are more distant to the outcome (e.g. birth weight) are not treated independently, but rather as modifiers of factors that are close to the outcome (e.g. body composition). Incorporating the collection of additional data and using advanced statistical analyses will ensure that solid conclusions can be made from studies of the kind presented.

The implications of the article by Alves et al.<sup>2</sup> are vast and important, given that approximately 171 million children in the world are stunted.<sup>22</sup> The fact that most stunted children do not recover height is secondary to the observations that stunting is a risk factor for chronic metabolic diseases later in life. This reality is complicated as the initial nutritional, social, and economic factors that influence a child's growth (e.g. inadequate diet, poor maternal education, low income, or poor sanitation) are in turn positively associated with the degree of poor growth (e.g. poor cognition, decreased physical capacity, and continued poverty). This vicious cycle of stunting and poverty is often intergenerational,<sup>23</sup> and may be perceived as a "nutrition trap" from which a person or family cannot escape without broad structural changes that include improved sanitation, real educational opportunities, and comprehensive health care, essentially fundamental human rights. If human rights are not strong enough motivators, then economic productivity should be considered, since the segment of a society most at risk for stunting is also the segment that will serve the growing service and manufacturing sectors of many countries.<sup>24</sup> Thus, for transitional economies, hosting a population of adults who are at risk for chronic and costly diseases is both a health and an economic issue.

In conclusion, scientists who study DOHaD are still far from any real consensus regarding the precise mechanisms that explain the relationship between poor growth and chronic disease. Alves et al.<sup>2</sup> present important data that advances the field by exploring changes in lipid profiles of stunted children following treatment for undernutrition. Moreover, these data complement existing studies by expanding the possible realm in which poor growth may alter normal metabolic processes that increase the risk for chronic diseases later in life. Finally, while the social and scientific implications of the work discussed are important, it is equally important to recognize the validation of the treatment program developed and implemented by the Centros de Recuperação e Educação Nutricional where undernourished children are recovering and potentially escaping the vicious cycle of poor growth and poverty.

## Conflicts of interest

The author has previously published manuscripts and is an active collaborator with one of the co-authors of the article discussed;<sup>2</sup> nonetheless, this article is independent of their past or present collaborations.

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