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Social determinants of health and biological embedding: From the social gradient to epigenetics in the DOHaD context

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ABSTRACT

Current evidence shows that social and environmental conditions present from the earliest stages of life can influence health and disease trajectories. From the perspective of the DOHaD (developmental origins of health and disease) paradigm, the social determinants of health interact with nutritional, environmental, toxic, and psychosocial factors during periods of high biological plasticity, especially during the first 1000 days of life, modulating developmental programming processes.

This view is supported by the social gradient in health, which shows a progressive worsening of morbidity and mortality as socioeconomic status declines. Based on these observations, the biological embedding hypothesis and social epigenetics have helped us understand how early-life experiences can influence human biology, providing evidence of molecular mechanisms linked to changes in DNA methylation patterns.

Keywords: *social determinants of health; epigenetics; DOHaD; DNA methylation; life course.*

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INTRODUCTION

From the DOHaD (developmental origins of health and disease) perspective, health and disease are the result of biological and social trajectories that begin before birth and extend throughout life.[1] In this manuscript, we will focus on understanding why some groups of people follow healthy trajectories, while others become ill at an early age. The answer does not lie solely in individual decisions: the social and environmental circumstances surrounding people from before birth shape biology in ways that science is only now beginning to quantify.[2] Social epidemiology, epigenetics, and developmental neuroscience are now converging to demonstrate, with molecular precision, how the social environment is inscribed in the genome during the stages of greatest cellular plasticity.[3,4]

A narrative literature review was conducted with a conceptual and translational focus on social determinants of health, biological embedding, social epigenetics, and the DOHaD paradigm across the pediatric life course, to synthesize the available evidence on the biological pathways that mediate the impact of early social exposures on health throughout the life course. The literature search was conducted between January and August 2025 in databases such as PubMed/MEDLINE, LILACS, and SciELO. It was supplemented with reference documents from the World Health Organization and the Sociedad Argentina de Pediatría. Publications in English and Spanish were included, with no geographic restrictions, prioritizing review articles, relevant original studies, documents from international organizations, and book chapters with a solid theoretical foundation, largely following the research trajectories of M. Marmot, M. Kobor *et al*., and C. Hertzman.

The eligibility criteria included studies addressing: a) social determinants of health and the social gradient, b) the biological imprint of early-life experiences, c) epigenetic mechanisms (particularly DNA methylation) linked to social adversity, and d) applications to the pediatric field and the DOHaD paradigm. Selection was intentional, based on a review of titles and abstracts, and was supplemented by a manual search of the references in key articles, to construct a more integrative conceptual framework instead of a comprehensive systematic review of all available literature.

DEVELOPMENT

The World Health Organization (WHO) defines the social determinants of health (SDH) as the conditions in which people are born, grow up, work, live, and age, including the set of forces and systems that influence daily life. These forces include economic policies, social norms, systems of governance, and structures that shape the distribution of resources, opportunities for development, access to rights, legislation, and access to essential services, all of which directly and indirectly influence the health trajectories of populations.[5]

In recent decades, evidence from social epidemiology, developmental neuroscience, and epigenetics has provided biological support for this conceptual framework. Various studies have demonstrated associations between early socioeconomic adversity, inflammatory activation, alterations in the hypothalamic-pituitary-adrenal axis, and persistent epigenetic changes, particularly in DNA methylation patterns.[3,4] These findings strengthen the biological plausibility of the SDH and its integration with the DOHaD paradigm.

In 2008, the Commission on Social Determinants of Health, led by Michael Marmot, published *Closing the gap in a generation*, the WHO's first official synthesis of social determinants of health from an equity perspective. This work consolidated various explanatory frameworks aimed at understanding the complexity of social determinants and identifying potential points of health and social intervention.[5]

Among these, the conceptual framework developed by Solar and Irwin for the WHO[6] distinguishes between structural determinants and intermediate determinants of health. Structural determinants include the political and socioeconomic context, as well as the socioeconomic status of individuals (defined by variables such as education, income, gender, occupation, and ethnicity). Intermediate determinants, on the other hand, encompass material living conditions, psychosocial and behavioral factors, biological factors, and the healthcare system.

From this perspective, the structural determinants are particularly significant because they shape the unequal distribution of opportunities, resources, and exposures throughout the life course, indirectly influencing intermediate determinants and, consequently, population health.[6]

Long before the publication of this report, Marmot had begun to systematically study the relationship between social status and health through the Whitehall studies, which were conducted among British civil servants and later considered one of the most significant milestones in modern social epidemiology.[7,8] Although the cohort studied had stable employment, universal health coverage, and guaranteed access to basic needs, the results showed a continuous gradient in morbidity and mortality according to occupational hierarchy. Each step down the occupational ladder was associated with poorer health indicators and higher cardiovascular mortality, regardless of extreme poverty or lack of access to health care.[7]

This finding profoundly altered the traditional understanding of health inequities, demonstrating that the impact of social conditions is not solely a function of a dichotomy between poverty and well-being, but rather follows a continuous gradient observable across the entire socioeconomic spectrum. Subsequent research confirmed the universality of this phenomenon across different countries, healthcare systems, and population groups, giving rise to the concept of the "social gradient in health".[8]

Understanding this association led to a new scientific question: how do social and environmental experiences influence people's biology, altering their developmental trajectories? It was precisely this question that prompted Clyde Hertzman to develop the concept of biological embedding.[9] According to this hypothesis, early experiences, especially during periods of high developmental plasticity, can become biologically embedded through mechanisms capable of influencing physiological functions, learning, behavior, and future health trajectories.[10]

Thus, early environmental exposures lead to relatively stable biological changes that can persist throughout life. It is at this point that the DOHaD paradigm and the study of SDH converge most directly, by proposing that social and environmental factors can influence biological processes from very early stages of development. In this context, epigenetics emerges as a potential bridge between the social environment and biology.[11]

Following in Hertzman's footsteps and delving deeper into the search for mechanisms capable of explaining how early social experiences influence human biology, Michael Kobor and his colleagues began to investigate more specifically the relationship between social adversity and biological regulation. Their early work explored the impact of early socioeconomic status on immune function in adults, observing that individuals exposed to unfavorable socioeconomic conditions during the first years of life exhibited differences in gene expression linked to inflammation and glucocorticoid signaling, regardless of their socioeconomic status in adulthood. Among the most relevant findings were the overexpression of genes related to inflammatory signaling, reduced expression of the glucocorticoid receptor, and increased production of interleukin-6 in response to immunological stimuli.[12] Taken together, these results demonstrated that early experiences of socioeconomic adversity were associated with biological programming characterized by increased inflammatory reactivity, subsequently termed the inflammatory phenotype.

As molecular tools evolved and the post-genomic era unfolded, research shifted from gene expression to the direct study of epigenetic modifications. In this context, Bush *et al.*, under the direction of Kobor, prospectively analyzed DNA methylation patterns in a cohort of preschool-aged children from San Francisco who were followed until age nine. The study assessed various components of socioeconomic status (such as family income, parental education, and family adversity) and found that each was associated with partially distinct sets of CpG sites related to immune function and developmental regulation. These findings demonstrated that the various components of social adversity influenced biological trajectories through partially distinct molecular mechanisms. It was particularly noteworthy that these associations were observed in a cohort composed predominantly of middle- and upper-middle-class families, which reinforces the idea that the influence of the social environment on biology is not limited exclusively to contexts of extreme poverty.[13]

Subsequently, research began to explore even more complex dimensions of early development. While initial interest had focused on socioeconomic conditions, the need gradually emerged to understand how human relationships and family experiences could also be biologically incorporated. In this regard, Merrill *et al.* observed associations between disorganized attachment patterns and epigenetic profiles linked to inflammatory regulation.[14] Complementarily, studies on adverse parental experiences suggested possible associations between early

parental adversity and epigenetic modifications observed in offspring during the first months of life.[15] Although many of the mechanisms involved remain the subject of ongoing research, these findings expanded the field of study to include potential intergenerational processes related to early biological programming, while also incorporating a historically under-explored dimension: the possible contribution of paternal experiences and exposures prior to conception to the health and development of offspring.

At the same time, the development of so-called "epigenetic clocks" ushered in a new era in this field of research by making it possible to estimate biological age based on DNA methylation patterns. The epigenetic clock developed by Horvath represented a fundamental advance in exploring phenomena of biological acceleration associated with disease and mortality (as a general correlation in adults, higher epigenetic age or epigenetic aging relative to biological age is associated with a higher disease burden).[16] Building on this, Austin *et al.*, also in collaboration with Kobor, observed associations between low socioeconomic status during childhood and accelerated epigenetic aging in monocytes, regardless of socioeconomic status achieved in adulthood.[17]

These results reinforced the hypothesis that early exposures represent periods of particular biological sensitivity, the consequences of which can persist for decades. In the pediatric population, the need for tools tailored to the specific characteristics of child development led to a new breakthrough. McEwen *et al.*, who are also members of Kobor's group, developed the PedBE (*Pediatric buccal epigenetic clock*) based on methylation data from buccal cells of children and adolescents aged 0-20 years. This pediatric clock estimates epigenetic age with very low error and, unlike clocks developed for adult populations, is specifically calibrated for the growth and maturation dynamics unique to childhood, opening up new possibilities for studying children's development from a biological perspective and integrated environmental management.[18]

In light of these findings, a central question inevitably arises: if early experiences can influence biological trajectories, is it possible to modify those trajectories through timely interventions? Dozier and colleagues conducted a preliminary randomized clinical trial to assess whether the attachment and biobehavioral catch-up (ABC) intervention, aimed at caregivers of young children who have been maltreated or are at risk, modifies children's DNA methylation at the genomic level. The study provides initial evidence that interventions targeting the caregiver-child bond can modulate epigenetic profiles in early childhood, even in contexts of maltreatment. These results suggest that some of the biological imprints associated with early adversity may be partially reversible through programs that support sensitive caregiving.[19] Complementarily, Moore and colleagues described how the amount of early contact with the caregiver is linked to children's epigenetic patterns years later, suggesting that seemingly "everyday" experiences during the neonatal period can have lasting biological effects on developmental trajectories.[20] Taken together, these findings reinforce the idea that early experiences can not only leave biological imprints but also present an opportunity to intervene, promote protective environments, and foster healthier developmental trajectories.

CONCLUSION

The reviewed evidence shows that social determinants of health can influence biological processes from early stages of life through mechanisms of biological and epigenetic social embedding. The social and the biological, historically treated as separate dimensions, now converge within the same scientific and healthcare framework. The DOHaD paradigm provides an integrative framework for understanding how early environmental and social exposures help shape trajectories of health and disease throughout the life course.

These findings underscore the need to incorporate a life-course perspective into pediatric practice and public policy, promoting early interventions aimed at reducing inequalities and fostering healthy environments from the very beginning of life. ■

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