



Jornal de Pediatria

www.jped.com.br



REVIEW ARTICLE

The formation of citizens: the pediatrician's role[☆]

Dioclécio Campos Júnior^{a,b}

^a Department of Pediatrics, Faculdade de Medicina, Universidade de Brasília, DF, Brazil

^b Executive Committee, Global Pediatric Education Consortium (GPEC)

Received 8 December 2015; accepted 17 December 2015

KEYWORDS

Epigenetics;
Prevention;
Toxic stress

PALAVRAS-CHAVE

Epigenética;
Prevenção;
Estresse tóxico

Abstract

Objective: This review article aims to define the fundamental role of the pediatrician in the formation of citizens in the 21st century.

Source of data: Significant bibliographical contributions produced by neuroscience, ecology, and epigenetics in the early childhood scenario.

Synthesis of data: Many diseases that impair the lives of adults result from severe and often uncontrollable disorders that occur in early childhood, an irreplaceable period for the safe construction of the human brain, personality, and intelligence. There is noteworthy scientific evidence that has become unquestionable, according to which abuse and neglect and other forms of violence to which children are exposed during the course of their lives, are the genesis of many physical ailments and other mental diseases, including depressive morbidity and schizophrenia. Conversely, it is also emphasized that healthy practices such as reading and listening to/playing music are able to intensively contribute to the exercise of cognitive capacity inherent to this period of life, as a prerequisite for the acquisition of learning indispensable to the high educational performance during the schooling period.

Conclusion: In the light of the disclosed scientific evidence, the pediatrician emerges as the most differentiated professional to provide preventive and curative care indispensable to the skilled formation of a healthy citizen.

© 2016 Sociedade Brasileira de Pediatria. Published by Elsevier Editora Ltda. All rights reserved.

A formação do cidadão: papel do pediatra

Resumo

Objetivo: O presente artigo de revisão científica tem por objetivo configurar o papel fundamental do pediatra na formação do cidadão do século XXI.

[☆] Please cite this article as: Campos Júnior D. The formation of citizens: the pediatrician's role. J Pediatr (Rio J). 2016. <http://dx.doi.org/10.1016/j.jped.2015.12.002>

E-mail: dicamposjr@gmail.com

<http://dx.doi.org/10.1016/j.jped.2015.12.002>

0021-7557/© 2016 Sociedade Brasileira de Pediatria. Published by Elsevier Editora Ltda. All rights reserved.

Fontes dos dados: Contribuições bibliográficas importantes produzidas pela neurociência, ecologia e epigenética no âmbito da primeira infância.

Síntese dos dados: Grande número de doenças que desqualificam a vida de pessoas adultas resulta de sérios, e muitas vezes incontroláveis distúrbios, que ocorrem na primeira infância, período insubstituível para a construção segura do cérebro, da personalidade e da inteligência humana. Destaca-se a evidência científica que se tornou inquestionável, segundo a qual os abusos e negligência e outras formas de violência, às quais a criança é exposta durante o ciclo de vida demais complexa dinâmica existencial, estão na gênese de várias enfermidades físicas e outras de natureza mental, inclusive as morbidades depressivas e a própria esquizofrenia. Ressalta, por outro lado, as práticas saudáveis como a leitura e a música, capazes de contribuir intensamente para o exercício da capacidade cognitiva inerente a este período de vida como pré-requisito para aquisição da aprendizagem indispensável à alta performance educacional no período da escolaridade.

Conclusão: À luz das evidências científicas arroladas, o pediatra emerge como o profissional mais diferenciado para a prestação dos cuidados preventivos e curativos indispensáveis à estruturação qualificada de um cidadão saudável.

© 2016 Sociedade Brasileira de Pediatria. Publicado por Elsevier Editora Ltda. Todos os direitos reservados.

Introduction

The concept of citizenship is an important advancement in the history of civilization. It includes rights and duties as attributes of individuals living in society, progressively incorporated according to the different stages of life, during which the individual's physical and mental maturity is consolidated, and he/she starts to exercise the relevant role of citizen.

Brazilian sociologist Gilberto Freyre¹ defined the stages of the citizen's formation. The first stage corresponds to the child who comes into the world as a human being, as it belongs to the *Homo sapiens* species. Then, during childhood, the individual is structured as a result of the continuous awakening of their personality through the emotional bond with their mother and other family members. Due to the interaction developed with other members of society, in all environments he/she experiences, the socialized individual becomes a person. At the next stage, the person becomes a citizen through the maturation of the learning process and awareness, during which he/she reaches the most differentiated level, necessary to live in society.

Inside this evolutionary context, the degree of knowledge corresponding to brain differentiation, the safe environmental conditions and factors on which the adequate expression of the genes that comprise the DNA depend, has allowed for the elucidation of the mechanisms that ensure or inhibit decisive phenomena to construct the phenotype.² Thus, broad transformation perspectives are opened in public health that can contribute to the improvement of the evolutionary pattern on which the citizen's essence depends.

Three scientific production fields have developed in recent decades, providing information capable of contributing to the requirements for quality of human beings' formation since conception. Indeed, ecology, neuroscience,

and epigenetics have significantly developed in research aimed mainly at the real needs of human society.

In the health context, the findings that emerged in all three domains of knowledge reinforce observations that highlight the primary importance of preventive actions against diseases. However, pursuant to the logic of the health systems of several countries, investments in the diagnosis and treatment of diseases that compromise the healthy development of individuals still prevail.

An example is the impact of the health care budget of the United States, showing the absence of the abovementioned priority of preventive practices. In that country, massive investments of health resources persist in the maintenance and supply of network services related to the diagnosis and treatment of diseases. According to a research carried out using mortality reduction as an objective indicator of the impact produced by the different actions of the American health care system, the results are clear: 90% of the resources invested in the healing dynamics result in a reduction of only 11% of mortality in the country; 1.5%, invested in lifestyle changes, lead to a 43% decrease in mortality; 1.6%, aimed at improving the quality of the environment result in a 19% decrease in mortality; and 7.9%, spent on health biology, decrease that indicator by 27%.

There is no bigger proof of the need for change in the operating logic for disease prevention to prevail. This change not only brings a remarkable reduction in the costs of health systems, making them sustainable, but also the expansion of healthy populations, an irreplaceable prerequisite for qualified citizenship exercise.³

Importance of the environmental in the citizen's formation

Health care assistance to a human being that is growing and developing must be in harmony with the broad concept set

forth by the United Nations Conference on the Human Environment, held in Stockholm in 1972: "The environment is the set of physical, chemical, biological and social components capable of having direct or indirect effects, in the short or long term, on living beings and human activities".⁴

The environmental impact on the structures and physiological reactions of the human body bears a dimension of unquestionable scientific evidence. The citizens' physical, mental, and social well-being effectively exist only when there is a healthy balance with environmental factors on which their health depends. This is particularly true in the social scenario in which children and adolescents develop. Ecology has been contributing to elucidate the growing associations between injuries that occur in this age range and the diseases that occur in adulthood.

The emphasis on the social components that constitute the environment reinforces the bases of epigenetics, a science that highlights the vital role of environmental factors for the expression of DNA genes. The knowledge from this new field of research have allowed for the establishment, with a high degree of probability, of the cause and effect relationship between violence against children and adolescents and many of the diseases that are identified in young adults.⁵

The main triggering factor is stress, through which abuse generates morbidities in the anatomic and physiologic universe of the body.⁶ The endogenous substances that originate from this damage, among which cortisol, result in disturbances in synaptic connections, triggering alterations that are at the genesis of difficult-to-control diseases.

The association between exposure to adversities in childhood and adolescence and the different morbid disorders in adulthood has been clearly demonstrated in studies conducted over the past decades. Thus, it becomes very clear the role of an adequate environment for the healthy growth and development of human beings at the different stages that are part of the citizen's formation. Several lines of evidence prove the accuracy of such concept. A classic study in psychology⁷ demonstrates that maternal deprivation in this age group is a predisposing factor for aggressive and violent behaviors in adulthood.

Additionally, it appears that many of the adult diseases arise from disorders and abnormalities of growth and development, the two phenomena that characterize childhood and adolescence; there is growing evidence to support this, and some examples are highly illustrative. A meta-analysis study demonstrated, with high statistical significance, the association between abuse and mistreatment in childhood and a high risk of type II diabetes in adulthood.⁸ The effect of neglect was far more pronounced than that of abuse.

Another meta-analysis study indicated a close association between the adversities faced in childhood – especially physical, sexual, and emotional abuse – and obesity in adulthood.⁹ Another scientific analysis correlated physical and sexual abuse, as well as domestic parental violence, with inflammatory bowel disease, particularly ulcerative colitis. Those authors speculated that epigenetic and neuroendocrine agents could act as a possible physiopathological basis for the described association.¹⁰ The hypothesis of cause and effect association between the damages suffered in childhood and adult diseases was emphasized in a cross-sectional study conducted in the United States using

CDC data, which established a close association between the occurrence of such adversities in the abovementioned age range and asthma in adults.¹¹

The physiopathological mechanisms through which abuse and neglect suffered in childhood determine several morbidities throughout life are not well clarified. For this purpose, the scientific assessments have highlighted the concept of allostasis, understood as a degree of stability achieved through adaptive adjustments, as well as the accumulated stress of life, understood as the allostatic load of McEwen.¹² Both are taken into account so that the nosological effects of childhood on adulthood can be understood.

Contributions from neuroscience

In addition to the full physical growth generated by transformations throughout the body, the full scope of a citizen's formation requires the complex structuring of the brain, an organ whose adequate function is an indispensable prerequisite for quality of life. It corresponds to the foundation that supports the construction of cognitive capacity, the genesis of mental dynamics essential to intelligence that ensures the expression of each individual's originality, their innovative strengths and creative profile.

Brain growth and differentiation occurs in the first six years of life, defined as infancy. Not only brain volume increases significantly in this period, but there is also an exponential increase in the number of established synapses. There are approximately 15,000 of them for each neuron in the first three years of age, with an average of 700 connections per second. Subsequently, the pruning process occurs, which selects and maintains the synapses, establishing the brain profile that persists into adulthood.¹³

The establishment of these synaptic connections presupposes adequate nutrition and emotional stimulation compatible with the specific needs of the personality under construction. It is further proof of the environment's decisive role in the genesis of the individual, the person, and the citizen.¹⁴ It is the embodiment of a social uterus in which the newborn starts growing and developing after overcoming the trauma of birth. It comprises not only the family, which is equivalent to an extrauterine placenta, but all members of society.

Some scientific evidence constitutes an example of the truth of such conceptual formulations. They support the recent hypothesis, based on studies of the brain's white matter microstructure, that the adversities suffered in childhood are a possible physiopathological factor of schizophrenia, which appear to be responsible for alterations in the structural connectivity of the cortical-limbic networks.¹⁵

Conversely, based on the use of neuroimaging, the correlation between adversities experienced in the early years of life and the alterations produced in the brain's gray matter volume was evaluated. The results showed that not only the extreme damages, such as severe neglect and abuse, but also moderate damages during childhood and early adolescence resulted in adverse effects on the developing adolescent brain. They conclude that preventing the child's exposure to the abovementioned abuse can ensure

adequate development and differentiation of the brain, thus reducing the risk of mental diseases in adulthood.¹⁶

As neuroscience expands the clarification of the physiological phenomena that are essential for brain growth and maturation, there is growing scientific evidence that the interaction of a child's body with a safe and stimulating environment is a prerequisite for the biopsychosocial evolution of human beings at all stages of their existence, particularly during early childhood.

Contributions of epigenetics

Scientific discoveries in the field of epigenetics explain the associations between ecological components and the individual's phenotypic expression since intrauterine life. Review studies have consolidated the importance of the epigenetic phenomena underlying adult neuropsychiatric morbidities, such as behavioral alterations, anxiety disorders, and schizophrenia.

These described alterations may reflect a dysfunction in the physiological stress response axis, which remains present after the damages suffered in childhood, as demonstrated by the assessment of responsiveness to stressors throughout life. The results obtained highlight the alterations caused by stressor agents on the genetic elements linked to the functional expression of hypothalamic–pituitary–adrenal axis, as well as in the glucocorticoid receptor genes. Moreover, epigenetic alterations in other gene groups, such as those related to neurotrophic factors and serotonin transporters, also result from exposure to stress in the early years, and become triggers of the adult's susceptibility to the above-mentioned psychiatric disorders.¹⁷

Furthermore, chronic malnutrition, change in social conditions, and adverse experiences in early life can stimulate epigenetic mechanisms capable of modifying gene expression and, consequently, of creating phenotypic profiles that contribute to risk of diseases at later stages of adult life.¹⁸

The aforementioned studies reinforce concepts emerging from scientific evidence, according to which the effect of adversities on exposed children and adolescents can produce long-term pathological consequences. In this sense, the role of toxic stress in childhood has been increasingly identified as a mechanism that produces subsequent morbidities, focusing on psychopathological, cardiovascular, and immune disorders.

A research carried out in the Democratic Republic of Congo has supported the bases of this concept. The research was based on previous work that suggested the association between adverse life experiences in childhood – including the intrauterine life period – and increased risk of later-onset chronic diseases.

It is also based on the assumption that there is a critical stage in the development of the intrauterine plasticity when there the most adapted fetal phenotype to antenatal environment is selected. The main merit of the initiative is that it was the first study to test the idea that extreme psychosocial stressors in pregnant women, as observed in the Democratic Republic of Congo, can modify the specific "locus" of epigenetic markers in the newborn, changing the pattern of their health development. The study showed a cause-and-effect association between prenatal stress level

and the newborn's low birth weight, as well as a high rate of methylation of the NR3C1 glucocorticoid receptor promoter in the newborn, which proportional to the degree of stress during intrauterine life. Therefore, it was observed that the increased methylation may constrain the neuroplasticity at the subsequent gene expression, thus restricting the margin of adaptive response to stress of the affected individuals, predisposing them to the risk of diseases in adulthood.¹⁹

The scientific foundations from this new field of research highlight the results of several experimental, clinical, and epidemiological trials that emphasize the role of epigenetic programming, translated into the mechanisms of DNA methylation and deacetylation, which are capable of altering the expression of genes that reflect on the brain structure and function, with negative repercussions throughout life.

Thus, evidence of the production of concepts and ground rules that will support the profound changes in the exercise of Medicine in the 21st century can be identified on the realm of epigenetic science. There is increasingly more evidence that new preventive strategies are being made available so that the positive expression of genetic potentials can actually occur. New diagnostic tools that will allow for the identification of changes in nucleosome proteins will become part of the routine of professionals working in the health area, ensuring a solid basis for preventive and therapeutic actions, both individually and collectively.

New scientific knowledge indicates the relevance of actions related to environmental quality as the true path so that the impact of toxic stress on childhood can be reduced. Therefore, the role of epigenetics in health prevention and promotion develops solidly. It becomes part of the essential content of the pediatricians' training so that their decisive role in the citizen's formation may unfold adequately.

The child's cognitive ability: the personality's embryo

More recent studies have shown that the child's cognitive ability, in the first stage of extrauterine existence (that is, in the first six years of life), reaches the highest rate of all age groups in human beings. This characteristic reflects the high plasticity of the central nervous system, which favors higher receptiveness to environmental stimuli, which in turn trigger an abundance of synaptic connections.

Thus the development of cognition occurs and the greater the aforementioned plasticity, which is a structural brain feature that gradually declines from birth to adulthood, the higher the development. For this reason, the effort required to establish synaptic connections also increases with the increasing age, and is minimal during infancy. Moreover, it is noteworthy that the brain growth rate reaches its highest levels during the first six months of extrauterine life, gradually decreasing until the sixth year.

The synaptic density of this particular stage of brain development is in the order of thousands of trillions. It reflects the intense physiological activity of brain evolution that provides the child with his/her highest cognitive ability in early life, which, according to objective estimates, is two-fold higher than that of an elementary school-aged child.

As this is a period of high brain plasticity, which will not be repeated later, it is important to recognize and appreciate the importance of this age group in the structuring of personality, interaction with the environment, and learning of activities that are essential for the physical and mental development, as well as the expression of originality, the creative and original capabilities that every newborn brings at birth. It is therefore up to society to ensure appropriate conditions for the exercise of these cognitive skills, which are essential for the evolution of personality, defining each individual's behavioral profile at an early age.

There is increasing scientific evidence that indicate the essential nature of this dynamic cognitive phase. Data demonstrate the uniqueness of a period of life that needs to be handled with the care it deserves, enriched by the affective ingredients of tenderness and love, without which the intricate physiological components of infant cognition do not develop at the appropriate level, causing damage that is often irreparable to the developing mind. A relevant meta-analysis study identified that children aged 6–23 months who were breastfed had significantly higher rates of cognitive development than those who received infant formula.²⁰

A subsequent cohort study showed that breastfeeding was positively associated with good educational performance, expressed as cognitive ability at 15 years of age. Breastfeeding during the infant phase was also significantly associated with good reading skills at 53 years of age, regardless of early social status and educational performance achieved at adulthood, but largely based on the high cognitive ability at age 15. The study allows for the conclusion that the benefits of breastfeeding have a potential long-term impact through its influence on cognition in childhood and on school performance.²¹

Also regarding breastfeeding as a synthesis of affective mother/child relationship, the effects produced by the practice are remarkable. As demonstrated in another study, the longer the duration of exclusive breastfeeding, the greater the cortical thickness of the upper and lower parietal lobes of the child. Additionally, adolescents that had received exclusive breastfeeding for a longer period performed better in tests of intelligence quotient (IQ) assessment than those who had not been breastfed.²²

An important study on the topic of cognitive ability includes the assessment carried out during prenatal development on adult hearing, vision, and cognitive impairment. The evaluation of such functions in the adult is related to the birth weight reported by the members of the assessed sample, which is used as prenatal development indicator, and to adult height, considered an indicator of early childhood development. Visual and auditory acuity were measured, as well as reaction time and the IQ of the assessed adults. The sensory and cognitive performance was reassessed after four years. Both adult height and birth weight showed to be positively associated with sensory and cognitive functions.

It is therefore evident that the possibility of adverse experiences in the prenatal period and infancy poses a risk of low cognitive and sensory function performance, as well as earlier onset of sensory and cognitive impairment in the adult. Considering this important finding, clearly discernible implications are identified regarding the role of preventive

actions to reduce the progressive loss of cognitive and sensory capacity at older ages.²³

In the context of the social components that are associated with child development, one of them is the social competence, i.e., the ability to use cognitive and behavioral resources to achieve personal goals in the context of the groups that a child participates in preschool. A study carried out in Portugal aimed to determine whether that competence acquired in the abovementioned period is associated with the pattern of the subgroups experienced by the child. The characteristics of the subgroups to which each one of the sample members belonged were evaluated by analyzing the social interaction data. Social competence was assessed using observational and sociometric measures appropriate for the study objective. Children who belonged to more cohesive groups with greater proximity and interaction showed higher social competence, while those who were not associated to a group had the lowest levels of this same indicator. Therefore, there is strong indication that the affiliation subgroups may both reflect and support the differences in the search for social skills during early childhood.²⁴

In light of these researches, the progress of scientific knowledge related to the child's brain development confirms the validity of traditional practices that deserve and should be more widely disseminated to contribute to the solid formation of the citizen. One of these clear examples refers to the role of musical practice, which appears to be associated with the development of working memory during childhood and adolescence, an indisputable prerequisite of qualified consolidation of the personality, intelligence, and creative ability of the developing individual. One of the studies aimed to clarify and verify the effect of musical training on the development of cognitive ability during childhood. The study focused on the longitudinal assessment of child development, which allowed for the analysis of the association between musical practice and reasoning performance, intellectual processing speed and working memory. A total of 352 individuals, aged between 6 and 25 years, were assessed through neuropsychological evaluations and neuroimaging in two or three occasions, two years apart. It was demonstrated that musical practice had a broad positive association with working memory, intellectual processing speed, and reasoning.

Additionally, it was verified that children who played a musical instrument had a higher volume of gray matter of the brain, both in the cortex of the temporal-occipital region and in the insular cortex, areas that have already been reported as related to the reading of musical notes. Changes in the working memory were proportional to the number of hours spent weekly in musical practice. In conclusion, the data confirmed the importance of this practice for the development of working memory during childhood and adolescence.²⁵

Another conduct whose scientific value has been identified in the formation of the citizen deserves to be considered: the habit of reading books to children during the preschool years, mainly by parents and other caregivers. It activates, in an early and qualified manner, the learning process that supports brain differentiation; reinforces sensory pathways that can sustain the ability of children to report, understand, and explore the world in which they

live; and, if started in childhood and continued over the years in preschool, it allows for the acquisition of the fundamental tools they need to survive in our culture, namely literacy, mathematics, and research skills.

If book reading is integrated in the daily routine since early childhood, children will benefit from this opportunity to keep the prerequisites for literacy, mathematics, and research skills active. Literacy includes several components, including oral language, comprehension of narrative, and recognition of phonemes and letters. The rich vocabulary acquired in the first three years of life produces the basics of literacy. It starts to bloom when children understand the reading and the writing process, looking for the meaning of the text combined with the course of the story and the language structure, incorporating the idea that the printed work represents the spoken language and thoughts. The child's ability to extract meaning from the printed text is solidified through a greater understanding of the sounds of letters and word recognition.

American pediatricians developed a program called "Reach Out and Read". It consists of three practices integrated with the regular office visits, which comprised guidance on the permitted reading; the opportunity to borrow comic books to be read at home; and the presence of community volunteers who read for the children in the waiting room of the office. The assessments indicated that this program increased the frequency of book reading at home and improved the results of reading skills in the early stages of schooling. The practice is already being employed in other countries.

In Canada, parental follow-up indicates that approximately 60% of them read to their children daily and that the daily reading is lower for children younger than 18 months of life. According to the experiment results, the messages that pediatricians should convey to parents are: (a) emphasize the multiple benefits of reading to their children, from very early ages until the early school years; (b) prescribe daily reading to young children starting from the eighth or ninth month of life, using the pediatrician's usual prescription pattern; and (c) encourage parents to read and those who show reading difficulties should be encouraged to tell stories based on the books' pictures in order to encourage the involvement of children in reading activities.²⁶ In Brazil, similar programs are being developed as a result of partnerships between the Brazilian Society of Pediatrics and Instituto Itaú Social.

The pediatrician's role in the citizen's formation

The evidence from the previously mentioned research related to the citizen's formation in the 21st century outlines the prospect of a solid pediatric basis that can support the growing quality of the human differentiation process. For this purpose, the priority nature of investing in preventive protection of early childhood is an irreplaceable route. A solid construction cannot be built without a foundation. The importance of childcare represents the ideal logic of children's health care during the decisive period on which an appropriately planned citizenship depends.

The role of pediatricians has never been so clearly defined. The uniqueness of their global medical expertise

is unquestionable as a professional truly committed to the complexity of the care to be provided, aiming at improving the health of children and adolescents.

In current pediatrics, epigenetics is an important and innovative scientific field of knowledge to be considered. Fundamentally, it summarizes the alterations in gene expression as a result of exposure to environmental factors, resulting in a broader context for the dysfunctions that are the genesis of most morbidities whose onset occurs in childhood, especially when the child is exposed to social aggressions responsible for significant changes in development. It actually reflects changes in gene expression rather than DNA alterations, although they can be transmitted from one generation to another. That is why knowledge of disorders involving epigenetics is of great importance for the pediatrician, as well as the recording of events during childhood that may affect the epigenetic control of gene expression, and awareness of the new therapies as they become available. To fulfill their fundamental role in the development healthy citizens, pediatricians should be prepared to recognize the important risk factors responsible for triggering a large number of morbidities that persist throughout life.²⁷

Conflicts of interest

The author declares no conflicts of interest.

References

1. Freyre G. *Sociologia da Medicina*. São Paulo É Realizações Ltda.; 2009.
2. Odgers CL, Jaffee SR. Routine versus catastrophic influences on the developing child. *Annu Rev Public Health*. 2013;34:29–48.
3. Alan Dever GE. An epidemiological model for health policy analysis. *Soc Indic Res*. 1976;2:453–66.
4. Campos Júnior D. Violência contra a criança e adolescente – visão do pediatra. *Boletim Científico da Sociedade Mineira de Pediatria*. 2015.
5. Shonkoff JP, Phillips DA. *From neurons to neighborhoods. The science of early childhood development*. Washington (DC): National Academies Press (US); 2000.
6. Shonkoff JP, Garner AS, Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012;129:e232–46.
7. Bowlby J. *Cuidados maternos e saúde mental*. 4th ed. São Paulo: Editora Martins Fontes; 2006.
8. Huang H, Shan Z, Chen S, Li M, Luo C, Gao H, et al. Adverse childhood experiences and risk of type 2 diabetes: a systematic review and meta-analysis. *Metabolism*. 2015;64:1408–18.
9. Hemmingsson E, Johansson K, Reynisdottir S. Effects of childhood abuse on adult obesity: a systematic review and meta-analysis. *Obes Rev*. 2014;15:882–93.
10. Fuller-Thomson E, West KJ, Sulman J, Baird SL. Childhood maltreatment is associated with ulcerative colitis but not crohn's disease: findings from a population-based study. *Inflamm Bowel Dis*. 2015;21:2640–8.
11. Bhan N, Glymour MM, Kawachi I, Subramanian SV. Childhood adversity and asthma prevalence: evidence from 10 US states (2009–2011). *BMJ Open Respir Res*. 2014;1:e000016.

12. Rubin LP. Maternal and pediatric health and disease: integrating biopsychosocial models and epigenetics. *Pediatr Res*. 2015; <http://dx.doi.org/10.1038/pr.2015.203> [Epub ahead of print].
13. Rima Shore Repensando o cérebro, tradução de Iara Regina Brazil. Porto Alegre: Editora Mercado Aberto; 2000.
14. Meaney MJ. Epigenetics and the biological definition of gene \times environment interactions. *Child Dev*. 2010;81:41–79.
15. Poletti S, Mazza E, Bollettini I, Locatelli C, Cavallaro R, Smeraldi E, et al. Adverse childhood experiences influence white matter microstructure in patients with schizophrenia. *Psychiatry Res*. 2015;234:35–43.
16. Walsh ND, Dalglish T, Lombardo MV, Dunn VJ, Van Harmelen AL, Ban M, et al. General and specific effects of early-life psychosocial adversities on adolescent grey matter volume. *Neuroimage Clin*. 2014;4:308–18.
17. Jawahar MC, Murgatroyd C, Harrison EL, Baune BT. Epigenetic alterations following early postnatal stress: a review on novel aetiological mechanisms of common psychiatric disorders. *Clin Epigenet*. 2015;7:122.
18. Langley-Evans SC. Nutrition in early life and the programming of adult disease: a review. *Hum Nutr Diet*. 2015;28:S1–14.
19. Mulligan CJ, D'Errico NC, Stees J, Hughes DA. Methylation changes at NR3C1 in newborns associate with maternal prenatal stress exposure and newborn birth weight. *Epigenetics*. 2012;7:853–7.
20. Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. *Am J Clin Nutr*. 1999;70:525–35.
21. Richards M, Hardy R, Wadsworth ME. Long-term effects of breast-feeding in a national birth cohort: educational attainment and midlife cognitive function. *Public Health Nutr*. 2002;5:631–5.
22. Kafouri S, Kramer M, Leonard G, Perron M, Pike B, Richer L, et al. Breastfeeding and brain structure in adolescence. *J Epidemiol*. 2013;42:150–9.
23. Dawes P, Cruickshanks KJ, Moore DR, Fortnum H, Edmondson Jones M, McCormack A, et al. The effect of prenatal and childhood development on hearing, vision and cognition in adulthood. *PLOS ONE*. 2015;10:e0136590.
24. Daniel JR, Santos AJ, Peceguina I, Vaughn BE. Affiliative structures and social competence in Portuguese preschool children. *Dev Psychol*. 2015;51:905–12.
25. Bergman Nutley S, Darki F, Klingberg T. Music practice is associated with development of working memory during childhood and adolescence. *Front Hum Neurosci*. 2014;7:926.
26. Bertrand J, Williams R, Ford-Jones L. Social paediatrics and early child development – the practical enhancements: Part 2. *Paediatr Child Health*. 2008;13:857–61.
27. Hall JG. Epigenetics: what does it mean for paediatric practice? *Paediatr Child Health*. 2014;19:27–30.