

# Child abuse in public institutions: Adversity genes involved (Review)

ELISAVET DAMASKOPOULOU<sup>1</sup>, ELENI PAPAKONSTANTINO<sup>1</sup>, FLORA BACOPOULOU<sup>2</sup>,  
ELIAS ELIOPOULOS<sup>1</sup>, GEORGE P. CHROUSOS<sup>2,3</sup> and DIMITRIOS VLACHAKIS<sup>1-4</sup>

<sup>1</sup>Laboratory of Genetics, Department of Biotechnology, School of Applied Biology and Biotechnology, Agricultural University of Athens, 11855 Athens; <sup>2</sup>University Research Institute of Maternal and Child Health and Precision Medicine, School of Medicine, National and Kapodistrian University of Athens; <sup>3</sup>Division of Endocrinology and Metabolism, Center of Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of The Academy of Athens, 11527 Athens, Greece; <sup>4</sup>Algorithms and Bioinformatics Group, Informatics Department, Faculty of Natural, Mathematical and Engineering Sciences, King's College London, London WC2R 2LS, UK

Received July 8, 2022; Accepted December 1, 2022

DOI: 10.3892/ije.2022.14

**Abstract.** The physical and mental health of children, as well as the effort to ensure a safe environment for their upbringing, have been the main concern of The United Nations Convention on the Rights of the Child (UNCRC) since 1989; a number of countries worldwide have formed numerous organizations to defend these rights. Child abuse, in all its forms, is a major public health concern, affecting millions of children each year worldwide. A number of studies and research have been performed in order to scientifically determine that early social adversity, as well as the physical, sexual or emotional abuse of a child and neglect, lead to alterations in DNA methylation. The present review article summarizes the epigenetic effects resulting from early-life stressful events, such as child abuse, child maltreatment, institutionalization, neglect, orphanhood and/or abandonment. These stressors can lead to a disruption of physiological biological pathways, and alter the methylation profiles in crucial regulatory pathways, such as glucocorticoid receptor signaling and cytokine signaling in immune cell function.

## 1. Introduction

The first years of a child's life are critical for his physical and mental development. According to The United Nations Convention on the Rights of the Child (1), each child has the right to life, survival and development, and each child has the right to be protected from all forms of physical or psychological violence. Nevertheless, millions of children worldwide become victims or witnesses of physical, sexual and emotional violence on a daily basis, and in some form of abuse in the first years of their lives and beyond, either by their family and close environment or by caregivers during their stay in childcare institutions. Child abuse in any form has been shown to be associated with physical, psychological and emotional problems throughout a child's lifetime, while the effects of child abuse and maltreatment have been shown to be associated with epigenetic effects and consequent lifelong provocation (Fig. 1) (2-5).

## 2. Children living in childcare institutions

According to the Common European Guidelines for the Transition from Institutional Care to Local Community Care, an 'Institution is defined as: any form of housing structure where residents are isolated from the wider local community and/or forced to live together' (6). It has been found that ~8 million children lived in institutions globally and 1 million children lived in care/public institutions according to an overall estimate for 30 European countries, and 4.21-7.52 million children in 191 countries (7,8). In Greece, in 2014, there were 2,850 children in Greek institutions of whom 900 were disabled children and 150 were under the age of 3 years (9).

There are three main reasons which lead to a child being sent to an institution or placed in foster care. The most common reason is for the state to remove the child from its family in the case that the environment and family are deemed unsuitable for its upbringing. The second is when a child has been abandoned by his/her biological parents. In addition, the third

## Contents

1. Introduction
2. Children living in childcare institutions
3. Institutionalized children and epigenetics
4. Conclusions and future directions

---

*Correspondence to:* Dr Dimitrios Vlachakis, Laboratory of Genetics, Department of Biotechnology, School of Applied Biology and Biotechnology, Agricultural University of Athens, 75 Iera Odos, 11855 Athens, Greece  
E-mail: dimvl@aua.gr

**Key words:** child abuse, child maltreatment, institutionalization, methylation profile, epigenetic effects, adversity genes

most common reason is when a child has lost both parents, is an orphan and has no other relatives who are able to be appointed as legal guardians. It is important to emphasize that ~90% of institutionalized children in Europe are not orphans and at least 80% of institutionalized children globally are not orphans (8).

The decision to remove a child from its family due to unfavorable circumstances is usually made by a prosecutor or other government service, authorized to oversee these circumstances. In order for such a decision to be taken, the safety and/or life of the child must be endangered, the living conditions must be defective or dangerous, the child needs to exhibit obvious or non-obvious signs of neglect, abandonment and/or abuse, and these need to be confirmed by a medical examination, the family must have serious socio-economic issues and finally, biological parents need to have a chronic mental illness (10).

Nevertheless, the state has the responsibility to support the effort to reconnect the family and the biological parents with their child, as according to the UN Convention on the Rights of the Child (Article 18), the upbringing of the child belongs primarily to the parents and his/her removal from his/her biological family should be the last resort, and as brief as possible (11).

However, a number of children reside in closed institutions, which are often characterized by unsuitable conditions for the proper upbringing of a child. The following characteristics are recognized in the majority of child-hosting institutions: Depersonalization, strict routines, group treatment, social distancing, dependence, lack of accountability, etc. (7). This results in children exhibiting a reduced levels of physical development, brain development, function and intelligence, and can lead to various issues in learning development and behavior (attention deficits, cognitive issues, hyperactivity and insecure attachment) (12-14).

Often, the time that a child spends in these institutions can last from months to years, and specifically in Greece, in state institutions, the residence time of children is ~3 years and sometimes even 6 years, which is far longer than the recommended duration (6 months) (9,15). The reasons for the long stay of children in institutions are the following: The small number of state institutions (four throughout Greece); the legal obstacles that children usually face due to claims by the biological family or the inability to find the biological family to provide their consent and to proceed with the adoption process; health issues that the children hosted in these places may have; the limited response of the population to adoption programs; and finally, the lack of competent staff to initiate the adoption and adoption processes (15).

Studies have demonstrated that children who remain in care for >6 months may experience autism, low self-esteem, behavioral, social and developmental issues, as well as learning disabilities, such as attention deficit and hyperactivity disorder (12,16). Children residing in childcare institutions are also 10-fold more likely to be involved in adult prostitution, 40-fold more likely to have a criminal record and 500-fold more likely than their peers to commit suicide, and by the age of 25 years, a fifth of these children who had been placed in child care, are convicted of a property offence (17,18). Another study, conducted in institutions in Romania, revealed that

there is a serious delay in the development of the brain of the children growing up there (19,20).

It is critical to reduce or even eliminate the time children spend in institutions, and this has been an ongoing goal of the European Union (EU). There is already a process aimed toward the non-existence of childcare institutions; as an alternative form of care, children can be placed in foster care or to become members of an extended family (7,9,12,21). From January 1, 2014, EU Member States cannot spend money on renovating or building institutions and must spend money on the transition to community-based services (8,22).

The lack of maternal care, neglect and concern in the first period of a child's life (early social deprivation), is considered a significantly negative early experience that in addition to the development of the child, appears to affect the physical and mental health of the child and has long-term outcomes (23). The first evidence of this derived from studies on non-human mammals (such as mice), which demonstrated that the long-term exposure to unpleasant stimuli triggered epigenetic mechanisms, leading to the expression of various genes in the brains of neglected offspring. The unpleasant stimuli that have been studied is maternal neglect in various forms, for example, the artificial absence of the mother in the upbringing of the offspring (24).

In mammalian studies that also involved humans, it appears that the rate of maternal care delivery to a newborn is largely responsible for the epigenetic regulation of genes involved in the control of the hypothalamic-pituitary-adrenal axis (25).

Child maltreatment includes various forms of violence, such as sexual, emotional and physical abuse, and/or emotional and physical neglect (26). The numbers of exposed individuals to some form of abuse in the USA are very high; 35% of the population are exposed to some form of emotional abuse, 16% of them are exposed to physical and 30% of females and 15% males experience some form of sexual violence (27,28).

The World Health Organization reports that worldwide, 23% of children report physical abuse, 36% of children report emotional abuse, 16% of children report neglect, 18% of girls and 8% of boys report sexual abuse, while ~41,000 of children are subjected to domestic violence. It also estimates that up to 1 billion children aged 2-17 years, have experienced physical, sexual, or emotional violence or neglect over the past year (29).

### 3. Institutionalized children and epigenetics

All forms of child abuse, both inside and outside of institutions, are closely linked to adverse outcomes throughout the lifetime of an individual (30). More specifically, studies have demonstrated that the sexual abuse of children in institutions for example, can lead to aggressive behavior, difficulty in interpersonal relationships, low levels of education and income, as well as prone to delinquency and re-victimization, either as children or as adults (31-33).

It is also known from other studies on human samples, that some factors may result in epigenetic alterations in a child's genome (34). Some of these factors are the experienced abuse and maltreatment of a child as an early adverse experience (35), parental stress, particularly in infancy and preschool phases (36), the cesarean section due to the change of the time of delivery and the procedures that precede it (37), or reduced mother-child interactions (38).

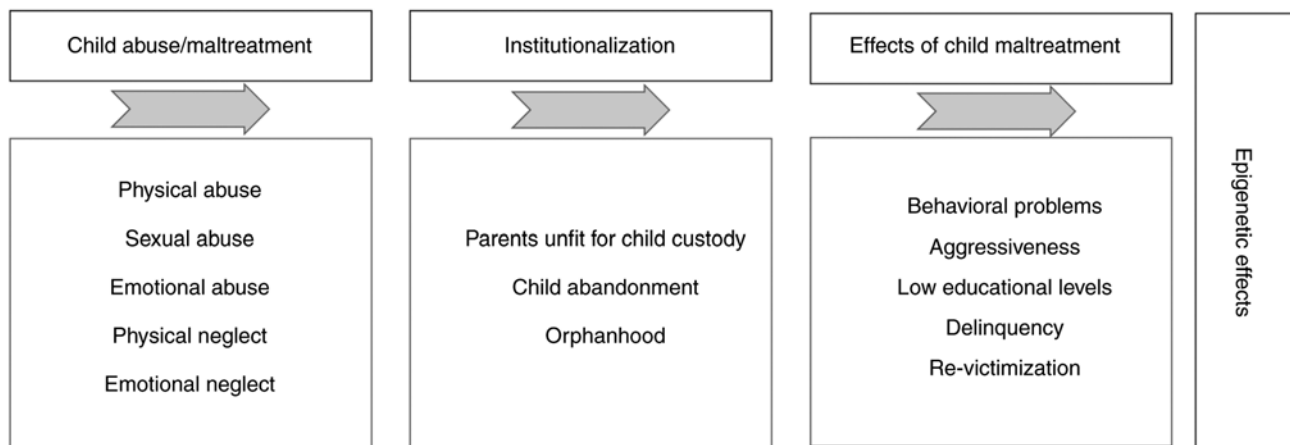


Figure 1. Flow chart of child abuse and institutionalization effects.

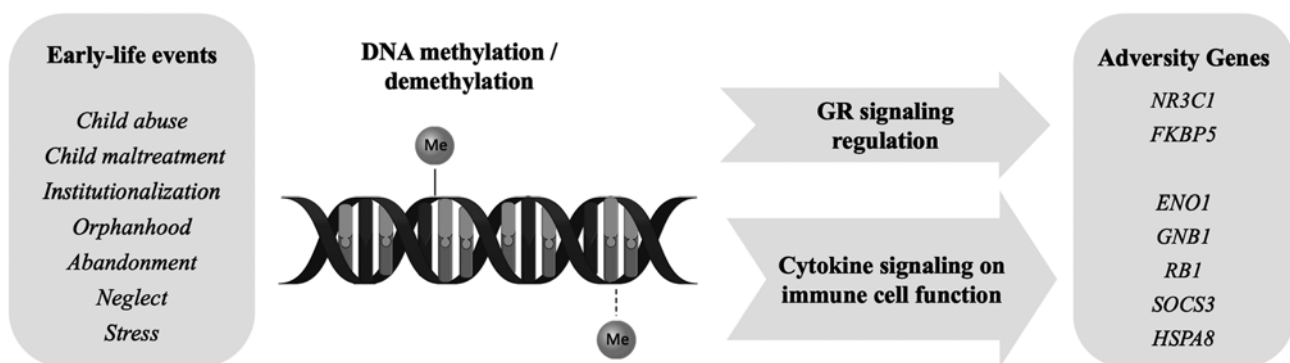


Figure 2. Epigenetic effects of early-life events (child abuse and maltreatment, institutionalization, orphanhood, abandonment, neglect and stress) through DNA methylation and demethylation, and adversity genes for glucocorticoid receptor signaling and cytokine signaling in immune function. GR, glucocorticoid receptor.

In recent years, increasing evidence has indicated that maltreatment is associated with epigenetic alterations that may be associated in the long-term with the onset of chronic mental and organic diseases (36). Early social adversity, as well as the physical, sexual, or emotional abuse of a child and neglect, cause alterations in DNA methylation and this appears to be able to be detected in some tissues and cells, such as brain tissue (35), peripheral lymphocytes (38) and epithelial cells of the buccal cavity (39).

Naumova *et al* (38) reported two possible hypothesis regarding the mechanisms through which early adversity in the epigenome is regulated. According to the first one, simultaneous and independent epigenetic programming occurs in various systems in the body, such as the endocrine system, the nervous system, the immune system and others, when the body undergoes some adversity in early life. On the other hand, a second possible hypothesis is that the organism that undergoes an adversity in its early life, first activates the stress response mechanism and other systems, such as the immune system are subsequently also affected (38).

Environmental factors affect the body through epigenetic processes via leading to chemical modifications, by altering the expression of genes, although at the same time, without changing the DNA sequence (Fig. 2). In their systematic review, Parade *et al* (40), gathered evidence linking child abuse to

changes in DNA methylation in humans. They demonstrated that in the studies that have been carried out thus far (until March, 2020), concerning the connection of child maltreatment and the methylation of candidate genes in children, saliva DNA was mainly used, and in only one sample DNA was obtained from oral cells and in the remaining DNA was tested from blood.

In addition, the most frequently studied genes are those that regulate glucocorticoid signaling, including NR3C1, which encodes the glucocorticoid receptor (GR) and FKBP5, which modulates the sensitivity of the GR (40). A previous study on 29 children who were raised in an institution from infants up to about 4 years of age, and 29 children who were raised with their biological families demonstrated that according to the STRING network, six genes were centrally located in the network, MAPK14, ENO1, GNB1, RB1, SOCS3 and HSPA8. Five of these genes, all apart from MAPK14, were found to be hypomethylated in the group of children raised in the institution. Of note, all of these were involved in the crucial pathways related to immune cell functions with particular emphasis on cytokine signaling (41).

#### 4. Conclusions and future directions

It has been found that the placement of children in an institutional environment from a very young age and for a period

>6 months, leads to changes in the methylation profile of the entire genome of a child. It would be beneficial for all children worldwide, to speed up the process of direct assignment of babies who are born and are unable to be with their biological parents, to foster families or expended families. Even a short time in an institutional setting is harmful to a child.

Further studies on the adverse effects that the living conditions of children being raised in care institutions, may be considered necessary at the level of analysis of the genome involved in epigenetic influences. The evidence provided thus far demonstrates that maltreatment is directly related to the long-term appearance of organic and mental dysfunctions.

### Acknowledgements

Not applicable.

### Funding

The authors would like to acknowledge funding from the following organizations: i) AdjustEBOVGP-Dx (RIA2018EF-2081): Biochemical Adjustments of native EBOV Glycoprotein in Patient Sample to Unmask target Epitopes for Rapid Diagnostic Testing. A European and Developing Countries Clinical Trials Partnership (EDCTP2) under the Horizon 2020 'Research and Innovation Actions' DESCA; and ii) 'MilkSafe: A novel pipeline to enrich formula milk using omics technologies', a research co-financed by the European Regional Development Fund of the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation, under the call RESEARCH-CREATE-INNOVATE (project code: T2EDK-02222).

### Availability of data and materials

Not applicable.

### Authors' contributions

All authors (ED, EP, FB, EE, GPC and DV) contributed to the conceptualization, design, writing, drafting, revising, editing and reviewing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

GPC is the Editor in Chief of the journal, and DV and EE are Editors of the journal. However, they had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

### References

1. The United Nations Convention on the Rights of the Child (UNCRC) (1990), General Assembly of the United Nations. <https://www.ohchr.org/sites/default/files/Documents/ProfessionalInterest/crc.pdf>. Accessed on March 25, 2022.
2. Hébert M, Tremblay-Perreault A and Myre G: The interplay of depression and hostile attributions in the link between PTSD symptoms and peer victimization in child victims of sexual abuse. *Child Psychiatry Hum Dev* 52: 291-300, 2021.
3. Bakermans-Kranenburg MJ, van Ijzendoorn MH and Juffer F: Earlier is better: A meta-analysis of 70 years of intervention improving cognitive development in institutionalized children. *Monogr Soc Res Child Dev* 73: 279-293, 2008.
4. Vorria P, Papaligoura Z, Sarafidou J, Kopakaki M, Dunn J, Van Ijzendoorn MH and Kontopoulou A: The development of adopted children after institutional care: A follow-up study. *J Child Psychol Psychiatry* 47: 1246-1253, 2006.
5. Wolfe DA, Jaffe PG, Jetté JL and Poisson SE: The impact of child abuse in community institutions and organizations: Advancing professional and scientific understanding. *Clin Psychol Sci Practice* 10: 179-191, 2003.
6. European Expert Group on the Transition from Institutional to Community-based Care (2012) Common European Guidelines on the Transition from Institutional to Community-based Care. <https://deinstitutionalisation.com/eeg-publications/>. Accessed on March 23, 2022.
7. AMKE Roots Research Center-<https://www.roots-research-center.gr>. Rots Research Center NGO, 2018.
8. LUMOS: Protecting children providing solutions (2009), Ending the Institutionalisation of Children Globally-the Time is Now, 8 European Commission, Report of the Ad Hoc Expert Group on the Transition from Institutional to Community-based Care, Brussels. <https://www.wearelumos.org/resources/time-now-ending-institutionalisation-children-globally/>
9. Eurochild: Child protection reform in Greece gets new impetus thanks to Eurochild and Martin James Foundation support, 2020.
10. Sutinah and Aminah S: Child abuse and neglect in orphanages in EAST JAVA Province (Study on forms of child abuse, anticipatory efforts developed children and the role of the orphanage). *Children Youth Serv Rev* 93: 24-29, 2018.
11. Varadan S: The Principle of Evolving Capacities under the UN Convention on the Rights of the Child. *Int J Children's Rights* 27: 306-338, 2019.
12. Johnson R, Browne K and Hamilton-Giachritsis C: Young children in institutional care at risk of harm. *Trauma Violence Abuse* 7: 34-60, 2006.
13. Bick J and Nelson CA: Early adverse experiences and the developing brain. *Neuropsychopharmacology* 41: 177-196, 2016.
14. Bick J, Zhu T, Stamoulis C, Fox NA, Zeanah C and Nelson CA: Effect of early institutionalization and foster care on long-term white matter development: A randomized clinical trial. *JAMA Pediatr* 169: 211-219, 2015.
15. Nanou K: The social acceptance of Illegal practices in the Greek domestic adoption system. *Adoption Fostering* 35: 60-67, 2011.
16. Nsabimana E, Rutembesa E, Wilhelm P and Martin-Soelch C: Effects of institutionalization and parental living status on Children's Self-esteem, and externalizing and internalizing problems in Rwanda. *Front Psychiatry* 10: 442, 2019.
17. Côté SM, Orri M, Marttila M and Ristikari T: Out-of-home placement in early childhood and psychiatric diagnoses and criminal convictions in young adulthood: A population-based propensity score-matched study. *Lancet Child Adolesc Health* 2: 647-653, 2018.
18. Lindquist MJ and Santavirta T: Does placing children in foster care increase their adult criminality? *Labour Economics* 31: 72-83, 2014.
19. Humphreys KL, Gleason MM, Drury SS, Miron D, Nelson CA, Fox NA and Zeanah CH: Effects of institutional rearing and foster care on psychopathology at age 12 years in Romania: Follow-up of an open, randomised controlled trial. *Lancet Psychiatry* 2: 625-634, 2015.
20. Beckett C, Castle J, Rutter M and Sonuga-Barke EJ: VI. Institutional deprivation, specific cognitive functions, and scholastic achievement: English and Romanian Adoptee (ERA) study findings. *Monogr Soc Res Child Dev* 75: 125-142, 2010.
21. National Conference of State Legislatures: The Child Welfare Placement Continuum: What's Best for Children? 2019.
22. ENIL 2019 Myth Busters \_EU funds and independent living.pdf., 2019.

23. Naumova OY, Rychkov SY, Kornilov SA, Odintsova VV, Anikina VO, Solodunova MY, Arintcina IA, Zhukova MA, Ovchinnikova IV, Burenkova OV, *et al*: Effects of early social deprivation on epigenetic statuses and adaptive behavior of young children: A study based on a cohort of institutionalized infants and toddlers. *PLoS One* 14: e0214285, 2019.
24. Gonzalez A, Lovic V, Ward GR, Wainwright PE and Fleming AS: Intergenerational effects of complete maternal deprivation and replacement stimulation on maternal behavior and emotionality in female rats. *Dev Psychobiol* 38: 11-32, 2001.
25. Gunnar MR and Quevedo KM: Early care experiences and HPA axis regulation in children: A mechanism for later trauma vulnerability. *Prog Brain Res* 167: 137-149, 2007.
26. Lueger-Schuster B, Knefel M, Glück TM, Jagsch R, Kantor V and Weindl D: Child abuse and neglect in institutional settings, cumulative lifetime traumatization, and psychopathological long-term correlates in adult survivors: The Vienna Institutional Abuse Study. *Child Abuse Negl* 76: 488-501, 2018.
27. Fast Facts: Preventing Child Abuse and Neglect. Centers for Disease Control and Prevention, 2022.
28. Huecker MR, King KC, Jordan GA and Smock W: Domestic violence. In: *StatPearls*. StatPearls Publishing, Treasure Island, FL, 2022.
29. World Health Organization (WHO): Violence Against Children, 2020.
30. Berent D, Szymańska B, Kulczycka-Wojdala D, Macander M, Pawłowska Z and Wojnar M: The role of childhood adversities, FKBP5, BDNF, NR1, and generalized self-efficacy in suicide attempts in alcohol-dependent patients. *Pharmacol Rep* 72: 730-743, 2020.
31. Fisher C, Goldsmith A, Hurcombe R and Soares C: The impacts of child sexual abuse: A rapid evidence assessment. *The Independent Inquiry into Child Sexual Abuse (IICSA)*, July 2017.
32. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP and Marks JS: REPRINT OF: Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The adverse childhood experiences (ACE) study. *Am J Prev Med* 56: 774-786, 2019.
33. Ensink K, Borelli JL, Normandin L, Target M and Fonagy P: Childhood sexual abuse and attachment insecurity: Associations with child psychological difficulties. *Am J Orthopsychiatry* 90: 115-124, 2020.
34. Cecil CAM, Zhang Y and Nolte T: Childhood maltreatment and DNA methylation: A systematic review. *Neurosci Biobehav Rev* 112: 392-409, 2020.
35. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G and Meaney MJ: Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Natu Neurosci* 12: 342-348, 2009.
36. Essex MJ, Thomas Boyce W, Hertzman C, Lam LL, Armstrong JM, Neumann SMA and Kobor MS: Epigenetic vestiges of early developmental adversity: Childhood stress exposure and DNA methylation in adolescence. *Child Dev* 84: 58-75, 2013.
37. Schlinzig T, Johansson S, Gunnar A, Ekström T and Norman M: Epigenetic modulation at birth-altered DNA-methylation in white blood cells after Caesarean section. *Acta Paediatr* 98: 1096-1099, 2009.
38. Naumova OY, Hein S, Suderman M, Barbot B, Lee M, Raefski A, Dobrynin PV, Brown PJ, Szyf M, Luthar SS and Grigorenko EL: Epigenetic patterns modulate the connection between developmental dynamics of parenting and offspring psychosocial adjustment. *Child Dev* 87: 98-110, 2016.
39. Non AL, Hollister BM, Humphreys KL, Childebayeva A, Esteves K, Zeanah CH, Fox NA, Nelson CA and Drury SS: DNA methylation at stress-related genes is associated with exposure to early life institutionalization. *Am J Phys Anthropol* 161: 84-93, 2016.
40. Parade SH, Huffhines L, Daniels TE, Stroud LR, Nugent NR and Tyrka AR: A systematic review of childhood maltreatment and DNA methylation: Candidate gene and epigenome-wide approaches. *Transl Psychiatry* 11: 1-33, 2021.
41. Arintcina IA, Zhukova MA, Ovchinnikova IV, Burenkova OV, Zhukova OV, Muhamedrahimov RJ and Grigorenko EL: Effects of early social deprivation on epigenetic statuses and adaptive behavior of young children: A study based on a cohort of institutionalized infants and toddlers. *PLoS One* 14: 1-29, 2019.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.