JOURNAL OF PSYCHOPATHOLOGY 2020;26:70-76;
doi: 10.36148/2284-0249-369

Review

The biological correlates of childhood trauma in first episode psychosis

Sarah Tosato[1], Simona Tomassi[1]

[1] Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Italy

SUMMARY

Objective

To overview biological mechanisms connecting childhood trauma to the development of psychosis.

Methods

We reviewed the evidence regarding biological correlates associated with childhood trauma in individuals affected by first episode psychosis (FEP) in terms of: 1) Hypothalamic-pituitary-adrenal (HPA) axis & cytokines levels; 2) gene × environment interaction, epigenetic and gene expression modifications and 3) metabolic biomarkers.

Results

Childhood trauma and early psychosis even when explored separately were found associated with several biological correlates. Regarding the immune system activity, in terms of both HPA axis functioning and cytokines levels, FEP patients exposed to childhood trauma showed 1) a less reactive HPA axis, characterized by a blunted cortisol awakening response, and higher serum levels of Tumor necrosis Factor-α (TNF-α) and C-reactive protein (CRP) in comparison with patients without childhood trauma. Genetics and epigenetics were also proven significantly different in traumatized FEP in comparison with non-exposed individuals. Specifically, first 2) the Val/Val genotype at the Val158Met polymorphism in the COMT gene, the A allele at rs4713916 and rs9296158 single nucleotide polymorphisms (SNPs) and the TT homozygosis at rs1360780 SNP in the FKBP5 gene were demonstrated to be risk factors for psychosis in traumatized individuals. Second, childhood trauma in FEP was proven significantly associated with global DNA hypo-methylation and lower BDNF gene expression. Finally, regarding metabolic changes associated with childhood trauma in FEP 3) higher levels of glycated hemoglobin and higher c-peptide and insulin levels were proven in patients exposed to childhood trauma in comparison with those without childhood trauma.

Conclusions

This review has given evidence regarding associations between childhood trauma and its biological correlates in first episode psychosis. Nonetheless, future studies are warranted to investigate putative biological mediators and their temporal sequence in order to elucidate developmental trajectories.

Key words: childhood trauma, first episode psychosis, epigenetic, HPA, cytokines, metabolism

Received: November 30, 2019
Accepted: January 20, 2020

Correspondence
Sarah Tosato
Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, piazzale L.A. Scuro 10, 37134 Verona, Italy

Conflict of interest
The Authors declare no conflict of interest

How to cite this article: Tosato S, Tomassi S. The biological correlates of childhood trauma in first episode psychosis. Journal of Psychopathology 2020;26:70-6. https://doi.org/10.36148/2284-0249-369

© Copyright by Pacini Editore Srl

OPEN ACCESS

This is an open access Journal distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Introduction

Childhood trauma is a complex phenomenon, significantly conditioned by bio-psycho-sociocultural elements. In Italy, almost one children out of 100 (9.5‰) is victim of maltreatments: among them, 6.9 and 4.2% refers physical and sexual abuse respectively, 13.7% reports psychological abuse, while 47.0% relates neglect, both physical and emotional[1]. The effects of childhood trauma can last a lifetime. Adults who were abused or neglected as children have a higher risk of perpetrating or being a victim of violence, becoming obese [2] or developing severe mental disorders, such

as schizophrenia [3,4]. In the general population, individuals recalling a history of childhood trauma show a threefold risk to undergo psychotic like experiences in their adulthood [5]. In turn, individuals affected by psychosis show an increased rate of childhood trauma up to the 47% of cases [4]. Specifically, 26, 39 and 34% of patients affected by psychosis refer sexual, physical and emotional abuse during childhood [6]. Female patients appear to be particularly vulnerable, showing the highest rates of sexual abuse (47.7%), and physical abuse (47.8%)[3]. Moreover, first episode psychosis (FEP) patients showed a two-fold higher prevalence (85.7 *vs* 38.7%) of childhood trauma when compared with healthy controls [7]. Severe sexual abuse was reported in 15.0-18.2% of FEP individuals, while severe physical abuse in 15.2-21.6% [8,9]. Indeed, childhood abuse has been associated with younger age of onset, earlier first admission, double hospitalization rate [4], more severe positive and dissociative symptoms [3], worse cognitive performance, lower quality of life and more deteriorated social-relational functioning [4].

Any reasonable theory that aims to explain how childhood traumatic experiences might favor later on the development of psychosis should account an integrated bio-psycho-social approach. Several paradigms have been developed focusing on diverse elements such as the stress response system, psychological elements, and environmental factors [10]. From a biological point of view, hypothalamic-pituitary-adrenal (HPA) axis functioning and cytokines levels, genetics, epigenetics, and proteomics (including biomarkers related to glucose metabolism) have been investigated to better understand the association between childhood trauma and psychosis.

The main aim of this narrative review is therefore to provide an overview of the potential biological mechanisms connecting the exposure to childhood trauma to the development of psychosis. We thus summarized the evidence related to specific biological correlates associated with childhood trauma in individuals affected by first episode psychosis. Specifically, we reviewed evidence on the role of 1) HPA axis functioning and cytokines levels, 2) gene × environment interaction, epigenetic and gene expression modifications and on 3) the levels of metabolic biomarkers within the association childhood trauma-psychosis.

Results

Hypothalamic-pituitary-adrenal (HPA) axis & cytokines levels

It has been clearly identified a key role for stress in the development and course of many psychiatric disorders, including psychosis. A dysfunctional activation of the immune system may in fact represent a potential biological mechanism connecting childhood trauma to psychopathology [11]. An altered HPA axis functioning has been found significantly associated with both childhood trauma and psychosis. HPA axis is in fact a key element of the body system that modulates the response to stress [12]: in physiological conditions, cortisol, which is the primary hormone released by the HPA axis in response to stress, functions to maintain homeostasis [13]. In case, however, of prolonged or abnormal stimulation this homeostatic mechanism may fail, resulting in increased levels of circulating corticosteroid hormones, due to an altered HPA cortisol-axis negative feedback mechanism and mediated, at least in part, by glucocorticoid receptor resistance. To date, our understanding about HPA axis functioning in FEP patients exposed to childhood trauma is hampered by mixed findings, possibly due to heterogeneous samples, different assay cortisol methodology (saliva or blood), as well as the broad definition of childhood trauma (subtype, timing, duration) [14]. HPA-axis dysfunction was proven associated to first episode psychosis itself. Specifically, HPA-axis hyperactivity, characterized by high cortisol levels in basal condition, and a blunted HPA axis response to stress (hypo-reactivity), have been both found to characterized psychosis [7,15-17]. This basal overactivity of the HPA axis in FEP patients was found in several studies, but not in all [7,15-17]. Moreover, in a recent meta-analysis [18], elevated blood levels of cortisol were demonstrated in individuals with FEP, providing further evidence for abnormal HPA axis function in early psychosis. Both HPA axis hyper- [19-21] and hypo-activation [12] and hyper- [22] and hypo-reactivity to stress [23, 24] have been significantly associated to childhood traumatic experiences. Regarding childhood trauma in FEP, a less reactive HPA axis, characterized by a blunted cortisol awakening response, might represent one of the biological mechanisms involved in the development of psychosis in individuals exposed to severe childhood trauma [25]. However, whether HPA axis dysfunction mediates the childhood trauma-FEP association or represents a trait of illness is still a matter of debate. Nonetheless, several findings [19-21] indicate that abnormalities in the stress response system, and the subsequent increased inflammation, originate in childhood and might be considered a 'biological scar' of the early exposure to high levels of stress [11].

Enhanced peripheral immune activation potentially plays a key role too in the pathogenesis of psychosis. An intricate network of interactions exists between the immune system and the central and peripheral nervous systems [26]. Inflammatory cytokines, including IL-1, IL-6 and TNF-α, represent the main mediators of this network. Cytokines are in fact responsible not only for the

organization of the cellular response to the pathogenic stimulus, but also for the behavioral changes necessary to healing. In physiological conditions, an acute stress activates the secretion of pro-inflammatory cytokines. The physiological cytokine-mediated pro-inflammatory response is temporary and strictly regulated by a balanced anti-inflammatory mechanism. Indeed, under normal conditions a neuro-immuno-endocrine anti-inflammatory response occurs. An adaptive behavioral response also takes place; it is usually temporary and placed under the control of CNS. Thus, a very complex, two-way neuro-immuno-endocrine interaction between the central and peripheral stress system and the immune axis takes place [27-29]. However, if the phlogistic stimulus becomes chronic and/or excessive it can lead to an out-of-control reaction of the inflammatory system, resulting in the development of immune-endocrine disorders (eg excessive production of proinflammatory cytokines and/or HPA axis malfunction) and contributing to the occurrence of non-functional behaviors. They therefore lose their adaptive purpose and sometimes become clinically relevant and attributable to psychiatric syndromes [26]. Cytokines are able to reach the brain through humoral, neural and cellular mechanisms [30], spreading the effect of peripherally produced cytokines on the CNS. Neurons, microglia and astrocytes, are therefore activated and an inflammatory state established. These neural inflammatory subjects, organized in complex systems, seem potentially involved in the development of psychiatric syndromes [31]. A meta-analysis of FEP studies [32] suggests the presence of an inflammatory syndrome in first episode psychosis, characterized by increased levels of IL-1α, IL-6, IL-12, IL-17, sIL-2R, interferon (IFN)-α, TNF-α, (TGF-α). Some cytokines (IL-1α, IL-6, and TGF-α) may represent state markers for acute exacerbations, and others (IL-12, IFN-c, TNF-α, sIL-2R) can be considered trait markers of psychosis [32]. Most interestingly, inflammatory markers were demonstrated particularly higher in those FEP patients who had also experienced childhood trauma [33,34]. Indeed, childhood trauma appears to be an independent risk factor for peripheral immune dysregulation and long-term, low-grade inflammation in adulthood [35]. A state of sustained peripheral inflammation follows exposure to childhood trauma [11], resulting in a chronic immune activation throughout adult life [21]. A recent meta-analysis [11] reported significantly higher levels of CRP, IL-6, and TNF-α in individuals exposed to childhood trauma, when compared with non-exposed controls. Diverse types of traumatic experience impacted differently on inflammatory markers' levels: increased TNF-α and IL-6 were found associated with physical and sexual abuse, while increased CRP levels appeared to be related to parental absence during childhood [11]. Cytokines levels in FEP patients traumatized during childhood were proven to differ significantly from those of both patients without childhood trauma [33,34] and healthy controls [34]. FEP patients with childhood trauma had significantly higher serum levels of TNF-α [33] and CRP [34] when compared with patients without childhood trauma. In particular, the association between childhood trauma and CRP was found to be specific for severe sexual abuse. Specifically, patients who had experienced severe sexual abuse showed higher levels of CRP when compared with both patients without such experience and with healthy controls [34].

Epigenetic modifications/gene expression

It has been demonstrated that childhood traumatic events may interact with genetic vulnerability or shape gene expression via epigenetic mechanisms, contributing to the development of psychiatric disorders [36,37].

Several studies have looked at G × E interactions as a putative missing link between childhood trauma and the development of psychosis. Specifically, several studies have focused on the effects of single nucleotide polymorphisms (SNPs) in the FK506 binding protein 5 (FKBP5) gene, finding that the A allele at two SNPs (rs4713916 and rs9296158) in the FKBP5 gene are a risk factor for psychosis in traumatized individuals [38]. Moreover, individuals who are TT homozygotes at the SNP rs1360780 in the FKBP5 gene and have been exposed to childhood trauma presented higher levels of positive psychotic experiences compared to the CC homozygotes [39]. Regarding the catechol-O-methyltransferase (COMT) gene polymorphism (Val158Met) [40], two studies found that Val/Val homozygotes had significantly higher levels of psychotic experiences after exposure to childhood trauma [41,42].

Epigenetic modifications, like cytosine residues methylation, are known to determine whether a DNA region is compacted and transcriptionally repressed/silent or open and transcriptionally active [43]; they regulate functional expression of genes by decreasing, silencing or increasing gene expression. Epigenetics, has been proven to participate in transducing environmental experiences in both genome and brain structure modifications, potentially underlining the association between childhood trauma and the development of psychosis [44]. Childhood trauma could thus influence gene expression and individuals' capacity of adaptation through epigenetic modifications [45]. Evidence concerning genome-wide methylation and gene expression modifications in FEP [46] shows a global DNA hypo-methylation in FEP patients when compared with controls [47], in line with available knowledge proving global DNA hypo-methylation in schizophrenia [48,49]. Moreover, genes related to transduction, RNA processing, lipid/glucose/protein metabolism, and mitochondrion functioning were prov-

en differently methylated or expressed in FEP patients when compared with healthy controls. In terms of gene expression profile, MPB, NDEL1, AKT1 and DICER1 were found hyper-expressed, while GCH1, DROSHA, COMT, and DISC1 resulted hypo-expressed in FEP patients in comparison with healthy controls. These genes and their proteins are all involved in a variety of CNS functions including neurodevelopment, plasticity and neurotransmission [50,51]. Such alterations could be considered both a direct (expression of a true biological difference) and an indirect (for example related to environmental exposures) manifestation of the psychosis. Childhood trauma per sé has also been proven associated to epigenetic and gene expression modifications in healthy individuals [46]. In terms of genome wide DNA methylation, genes related to central nervous system development [52,53], plasticity and degeneration [52,53], immune system and inflammatory response [53] were found differently methylated in healthy children and adolescents exposed to childhood trauma. When looking at target gene methylation related to childhood trauma in healthy subjects, SLC6A4, NR3C1, KITLG and OXTR [54] promoter regions were found hyper-methylated, while FKBP5 [55,56] and IL-6 [57,58] promoter regions and BDNF gene body [56] were demonstrated hypo-methylated in comparison to controls. Being methylation within promoter regions negatively correlated with gene expression, it is possible to speculate that childhood trauma leads to reduction in SLC6A4, NR3C1, KITLG and OXTR gene expression, favoring a dysfunctional serotonergic system (SLC6A4), an altered stress-reactivity (NR3C1, KITLG) and impaired social behavior and bonding (OXTR). In line with this hypothesis, healthy individuals with childhood trauma had reduced SLC6A4 gene expression [54], while no evidence is available demonstrating a reduction of NR3C1, KITLG or OXTR gene expression in association with childhood trauma. Given the reduced methylation within their promoter regions, it is also possible to hypothesize an increase in FKBP5 and IL-6 gene expression [59] in association with childhood trauma. Both genes encode proteins involved in the stress response system and their hyper-expression could favor a pro-inflammatory, stress-vulnerable phenotype. On the contrary, a gene is less expressed when hypomethylated in its body [60]. As mentioned above, BDNF gene was found significantly hypo-methylated within its body in healthy subjects with childhood trauma [56]; a reduced BDNF gene transcription could thus be a consequence. Despite the known impact of childhood traumatic experiences on FEP individuals [61] and the attention paid recently to epigenetics and gene expression, available studies relating to the epigenetic /gene expression modifications associated with childhood trauma in FEP patients were only three [33,62,63]. Out of them, one study investigated genome wide DNA methylation patterns, while the other two explored gene targets gene expression profile in FEP in relation to childhood trauma [33,63]. As reviewed before [46], the first study [62] indicates that childhood trauma, and specifically emotional abuse and total trauma score, entails global DNA hypo-methylation. However, as mentioned above, similar global DNA hypo-methylation has been also found in FEP patients [47] when compared with controls, not taking into account the presence of childhood trauma. This trauma-associated lower DNA methylation could have a functional relevance to gene regulation and/or be responsible for genomic instability, which has been previously observed in schizophrenia [49]. Further investigations are therefore required to elucidate whether the global hypo-methylation is to be considered as an epigenetic consequence of childhood trauma or a trait of psychosis [46]. The second study [33] found no differences in IL-1α, IL-1β, IL-6, IL-8, MCP-1, VEGF, EGF, INF-γ and TNF-α gene expression between patients with and without childhood trauma, while the third one [63] found a negative correlation between BDNF gene expression and the number of traumatic experiences. Reduced BDNF mRNA levels associated with childhood trauma in FEP [63] could result in altered neuroplasticity, since in this study FEP patients were also characterized by a smaller left hippocampal volume. However, the same study found no association between childhood trauma and BDNF gene expression in healthy controls [63]. Conversely, it was demonstrated that BDNF gene was significantly hypo-methylated within its body, and thus potentially reduced in its expression, also in healthy subjects with a history of childhood trauma [56]. Evidence on the topic appears inconsistent and it stands unclear whether the reduced BDNF gene expression is to be ascribable to a specific effect of childhood trauma per sé, independently from the presence of psychosis. Notably, there are not available replicated findings for methylation and childhood trauma neither in FEP, nor for gene expression and childhood trauma in both FEP and healthy individuals [46]. Large, well-designed case-control studies enrolling FEP subjects both with and without childhood trauma are warranted.

Metabolic dysregulation

Confirming the long-term effects of early life stress on the body, several studies [19] have linked childhood trauma to detrimental changes in physiological functions, including metabolism.

It is in fact worth mentioning that the stress system is closely interconnected with metabolism. HPA axis interacts with glucose metabolism hormones, like insulin, glucagon, gastric-inhibitor-peptide (GIP) and glucagon-like peptide-1 (GLP-1) [64] increasing the likelihood to develop metabolic dysfunctions. Insulin has an in-

hibitory activity on HPA axis, while glucagon, GIP and GLP-1 have an enhancing one, inducing the release of corticotrophin release hormone (CRH)/adrenocorticotrophic hormone (ACTH) [64]. Moreover, glucocorticoid hormones such as cortisol, stimulate gluconeogenesis and facilitate insulin-resistance, whereby chronic HPA axis activation might be at the bottom of the development of alterations in glycemic control [65]. In turn, an increase of fat mass due to glucocorticoids worsens insulin-resistance and glycemic control, triggering a vicious circle consisting of hyper-glycaemia, hyper-lipidemia and insulin-resistance [65]. The activation of the HPA axis activation may also induce alterations in the inflammatory response, which themselves could influence glucose metabolism. Individuals with schizophrenia are at higher risk of developing type 2 diabetes which is twice that of the general population [66]. Controversial results concerning insulin resistance have been reported in drug-naïve individuals with first-episode psychosis: some studies reported higher levels of insulin [67,68], insulin-resistance [67-69], increased levels of insulin-related peptides [70] as c-peptide [71] when compared to controls. In a large cohort of FEP patients recruited by our group decreased levels of glucagon and GLP-1 in compared to controls [72] have been found. Since visceral obesity can contribute to insulin resistance [73], several studies have investigated the role of appetite regulating hormones in FEP [74] reporting lower levels of leptin in drug-naïve FEP patients compared to controls. Taken together, this evidence suggests that other factors, a part from antipsychotic medications, can play a role in the metabolic alterations observed at psychosis onset. Among these, a possible role in the genesis of metabolic alterations could be covered by childhood trauma since it increases the risk for the onset of both psychosis and metabolic dysfunctions [5,75]. Individuals exposed to child sexual and physical abuse are in fact more likely to be obese or to show three or even more symptoms of metabolic syndrome when compared with non-victims [75]. Evidence suggests that individuals who reported an exposure of childhood trauma had an increased risk of the 32% to develop later in life type 2 diabetes [76] and of the 20-50% to develop obesity [77]. Furthermore, individuals with childhood trauma have decreased HDL and increased LDL levels with lower HDL/LDL ratio [78,79], higher triglyceride levels [80], reduced T3 levels and abnormal metabolism of thyroid hormones [81], and higher prevalence of metabolic syndrome [78,82] in later life. To date, evidence whether childhood trauma is involved in the development of abnormal glucose metabolism in FEP is very limited. Only two studies [83,84] have so far explored this relationship. The first one found [83] higher levels of glycated hemoglobin in FEP patients who were physically abused during childhood compared to those were not. The second one found that c-peptide and insulin levels are higher in patients exposed to childhood trauma, suggesting that hyperinsulinemia occurs early in the course of psychosis [84]. These findings underline the importance of monitoring metabolic alterations from the onset, especially in those patients who report childhood trauma, in order to carry out therapeutic interventions aimed at recovering from the negative outcomes of both hyperinsulinemia and trauma. It is still unclear to date whether markers related to glucose metabolism may be used to prevent treatment-induced weight gain in FEP patients [85].

Conclusions

Although evidence highlights a causal relation between childhood trauma and biological maladjustment in later life, the precise developmental trajectories and their temporal coincidence have not been elucidated yet[14].

References

1. Autorità Garante per l'Infanzia e l'Adolescenza - CISMAI - Fondazione Terre des Hommes Italia. Maltrattamento sui bambini: quante le vittime in Italia? Prima Indagine nazionale quali-quantitativa sul maltrattamento a danno di bambini - 2015.
2. World Health Organization. Bridging the gap. Geneva 2015.
3. Read J, van Os J, Morrison AP, et al. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. Acta Psychiatr Scand 2005;112:330-50.
4. Alvarez MJ, Roura P, Oses A, Foguet Q, Sola J, Arrufat FX. Prevalence and clinical impact of childhood trauma in patients with severe mental disorders. J Nerv Ment Dis Mar 2011;199:156-61.
5. Varese F, Smeets F, Drukker M, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull 2012;38:661-71.
6. Bonoldi I, Simeone E, Rocchetti M, et al. Prevalence of self-reported childhood abuse in psychosis: a meta-analysis of retrospective studies. Psychiatry Res 2013;210:8-15.
7. Mondelli V, Dazzan P, Hepgul N, et al. Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: the role of stress and of antipsychotic treatment. Schizophr Res 2010;116:234-42.
8. Neria Y, Bromet EJ, Marshall R. The relationship between trauma exposure, posttraumatic stress disorder (PTSD) and depression. Psychol Med 2002;32:1479-80; author reply 1480-3.
9. Fisher HL, Jones PB, Fearon P, et al. The varying impact of type, timing and frequency of exposure to childhood adversity on its association with adult psychotic disorder. Psychol Med 2010;40:1967-78.
10. Larkin W, Read J. Childhood trauma and psychosis: evidence, pathways, and implications. J Postgrad Med 2008;54:287-93.
11. Baumeister D, Akhtar R, Ciufolini S, et al. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. Mol Psychiatry 2016;21:642-9.

12 Lupien SJ, McEwen BS, Gunnar MR, et al. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 2009;10:434-45.

13 Peters A, Conrad M, Hubold C, et al. The principle of homeostasis in the hypothalamus-pituitary-adrenal system: new insight from positive feedback. Am J Physiol Regul Integr Comp Physiol 2007;293:R83-98.

14 Agorastos A, Pervanidou P, Chrousos GP, et al. Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. Front Psychiatry 2019;10:118.

15 Mondelli V, Pariante CM, Navari S, et al. Higher cortisol levels are associated with smaller left hippocampal volume in first-episode psychosis. Schizophr Res 2010;119:75-8.

16 Walsh P, Spelman L, Sharifi N, et al. Male patients with paranoid schizophrenia have greater ACTH and cortisol secretion in response to metoclopramide-induced AVP release. Psychoneuroendocrinology 2005;30:431-7.

17 Ryan MC, Sharifi N, Condren R, et al. Evidence of basal pituitary-adrenal overactivity in first episode, drug naive patients with schizophrenia. Psychoneuroendocrinology 2004;29:1065-70.

18 Hubbard DB, Miller BJ. Meta-analysis of blood cortisol levels in individuals with first-episode psychosis. Psychoneuroendocrinology 2019;104:269-75.

19 Danese A, Moffitt TE, Harrington H, et al. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med 2009;163:1135-43.

20 Danese A, Moffitt TE, Pariante CM, et al. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch Gen Psychiatry 2008;65:409-15.

21 Danese A, Pariante CM, Caspi A, et al. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci USA 2007;104:1319-24.

22 Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 2000;284:592-7.

23 Klaassens ER, van Noorden MS, Giltay EJ, et al. Effects of childhood trauma on HPA-axis reactivity in women free of lifetime psychopathology. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:889-94.

24 Carpenter LL, Carvalho JP, Tyrka AR, et al. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. Biol Psychiatry 2007;62:1080-7.

25 Ciufolini S, Gayer-Anderson C, Fisher HL, et al. Cortisol awakening response is decreased in patients with first-episode psychosis and increased in healthy controls with a history of severe childhood abuse. Schizophr Res 2019;205:38-44.

26 Krishnadas R, Cavanagh J. Depression: an inflammatory illness? J Neurol Neurosurg Psychiatry May 2012;83:495-502.

27 Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol 2017;17:233-47.

28 Pace TW, Heim CM. A short review on the psychoneuroimmunology of posttraumatic stress disorder: from risk factors to medical comorbidities. Brain Behav Immun 2011;25:6-13.

29 Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behav Immun 2007;21:9-19.

30 Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther 2011;130:226-38.

31 Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 2009;65:732-41.

32 Miller BJ, Buckley P, Seabolt W, et al. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011;70:663-71.

33 Di Nicola M, Cattaneo A, Hepgul N, et al. Serum and gene expression profile of cytokines in first-episode psychosis. Brain Behav Immun 2013;31:90-5.

34 Hepgul N, Pariante CM, Dipasquale S, et al. Childhood maltreatment is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients. Psychol Med 2012;42:1893-901.

35 Misiak B, Krefft M, Bielawski T, et al. Toward a unified theory of childhood trauma and psychosis: a comprehensive review of epidemiological, clinical, neuropsychological and biological findings. Neurosci Biobehav Rev 2017;75:393-406.

36 Babenko O, Kovalchuk I, Metz GA. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. Neurosci Biobehav Rev 2015;48:70-91.

37 Brietzke E, Mansur RB, Soczynska J, et al. A theoretical framework informing research about the role of stress in the pathophysiology of bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2012;39:1-8.

38 Collip D, Myin-Germeys I, Wichers M, et al. FKBP5 as a possible moderator of the psychosis-inducing effects of childhood trauma. Br J Psychiatry 2013;202:261-8.

39 Alemany S, Moya J, Ibanez MI, et al. Research Letter: Childhood trauma and the rs1360780 SNP of *FKBP5* gene in psychosis: a replication in two general population samples. Psychol Med 2016;46:221-3.

40 Ira E, Zanoni M, Ruggeri M, et al. COMT, neuropsychological function and brain structure in schizophrenia: a systematic review and neurobiological interpretation. J Psychiatry Neurosci 2013;38:366-80.

41 Ramsay H, Kelleher I, Flannery P, et al. Relationship between the COMT-Val158Met and BDNF-Val66Met polymorphisms, childhood trauma and psychotic experiences in an adolescent general population sample. PLoS One 2013;8:e79741.

42 Vinkers CH, Van Gastel WA, Schubart CD, et al. The effect of childhood maltreatment and cannabis use on adult psychotic symptoms is modified by the COMT Val(1)(5)(8)Met polymorphism. Schizophr Res 2013;150:303-11.

43 Chuang JC, Jones PA. Epigenetics and microRNAs. Pediatr Res May 2007;61:24R-9.

44 Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry 2001;49:1023-39.

45 Korosi A, Naninck EF, Oomen CA, et al. Early-life stress mediated modulation of adult neurogenesis and behavior. Behav Brain Res 2012;227:400-9.

46 Tomassi S, Tosato S. Epigenetics and gene expression profile in first-episode psychosis: the role of childhood trauma. Neurosci Biobehav Rev 2017;83:226-37.

47 Nishioka M, Bundo M, Koike S, et al. Comprehensive DNA methylation analysis of peripheral blood cells derived from patients with first-episode schizophrenia. J Hum Genet 2013;58:91-7.

48 Melas PA, Rogdaki M, Osby U, et al. Epigenetic aberrations in leukocytes of patients with schizophrenia: association of global DNA methylation with antipsychotic drug treatment and disease onset. FASEB J 2012;26:2712-8.

49 Shimabukuro M, Sasaki T, Imamura A, et al. Global hypomethylation of peripheral leukocyte DNA in male patients with schizophrenia: a potential link between epigenetics and schizophrenia. J Psychiatr Res 2007;41:1042-6.

50 Gouvea ES, Ota VK, Noto C, et al. Gene expression alterations related to mania and psychosis in peripheral blood of patients with a first episode of psychosis. Transl Psychiatry 2016;6:e908.

51 Noto C, Ota VK, Santoro ML, et al. Depression, cytokine, and cytokine by treatment interactions modulate gene expression in antipsychotic naive first episode psychosis. Mol Neurobiol 2016;53:5701-9.

52 Cecil CA, Smith RG, Walton E, et al. Epigenetic signatures of childhood abuse and neglect: Implications for psychiatric vulnerability. J Psychiatr Res 2016;83:184-94.

53 Naumova OY, Lee M, Koposov R, et al. Differential patterns of whole-genome DNA methylation in institutionalized children and children raised by their biological parents. Dev Psychopathol 2012;24:143-55.

54 Wankerl M, Miller R, Kirschbaum C, et al. Effects of genetic and early environmental risk factors for depression on serotonin transporter expression and methylation profiles. Transl Psychiatry 2014;4:e402.

55 Klengel T, Mehta D, Anacker C, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci 2013;16:33-41.

56 Weder N, Zhang H, Jensen K, et al. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. J Am Acad Child Adolesc Psychiatry 2014;53:417-24.e5.

57 Janusek LW, Tell D, Gaylord-Harden N, et al. Relationship of childhood adversity and neighborhood violence to a proinflammatory phenotype in emerging adult African American men: an epigenetic link. Brain Behav Immun 2017;60:126-35.

58 Provencal N, Suderman MJ, Caramaschi D, et al. Differential DNA methylation regions in cytokine and transcription factor genomic loci associate with childhood physical aggression. PLoS One 2013;8:e71691.

59 Schubeler D. Function and information content of DNA methylation. Nature 2015;517:321-6.

60 Portela A, Esteller M. Epigenetic modifications and human disease. Nat Biotechnol 2010;28:1057-68.

61 Tomassi S, Tosato S, Mondelli V, et al. Influence of childhood trauma on diagnosis and substance use in first-episode psychosis. Br J Psychiatry 2017;211:151-6.

62 Misiak B, Szmida E, Karpinski P, et al. Lower LINE-1 methylation in first-episode schizophrenia patients with the history of childhood trauma. Epigenomics 2015;7:1275-85.

63 Mondelli V, Cattaneo A, Belvederi-Murri M, et al. Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume. J Clin Psychiatry 2011;72:1677-84.

64 Nussdorfer GG, Bahcelioglu M, Neri G, et al. Secretin, glucagon, gastric inhibitory polypeptide, parathyroid hormone, and related peptides in the regulation of the hypothalamus- pituitary-adrenal axis. Peptides 2000;21:309-24.

65 Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol 2005;67:259-84.

66 Stubbs B, Vancampfort D, De Hert M, et al. The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. Acta Psychiatr Scand 2015;132:144-57.

67 Pillinger T, Beck K, Gobjila C, et al. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry 2017;74:261-9.

68 Chen S, Broqueres-You D, Yang G, et al. Relationship between insulin resistance, dyslipidaemia and positive symptom in Chinese antipsychotic-naive first-episode patients with schizophrenia. Psychiatry Res 2013;210:825-9.

69 Zhang XY, Chen DC, Tan YL, et al. Glucose disturbances in first-episode drug-naive schizophrenia: relationship to psychopathology. Psychoneuroendocrinology 2015;62:376-80.

70 Guest PC, Schwarz E, Krishnamurthy D, et al. Altered levels of circulating insulin and other neuroendocrine hormones associated with the onset of schizophrenia. Psychoneuroendocrinology 2011;36:1092-6.

71 Wu X, Huang Z, Wu R, et al. The comparison of glycometabolism parameters and lipid profiles between drug-naive, first-episode schizophrenia patients and healthy controls. Schizophr Res 2013;150:157-62.

72 Bocchio-Chiavetto L, Zanardini R, Tosato S, et al. Immune and metabolic alterations in first episode psychosis (FEP) patients. Brain Behav Immun 2018;70:315-24.

73 Roberts CK, Little JP, Thyfault JP. Modification of insulin sensitivity and glycemic control by activity and exercise. Med Sci Sports Exerc 2013;45:1868-77.

74 Misiak B, Bartoli F, Stramecki F, et al. Appetite regulating hormones in first-episode psychosis: a systematic review and meta-analysis. Neurosci Biobehav Rev 2019;102:362-70.

75 Danese A, Tan M. Childhood maltreatment and obesity: systematic review and meta-analysis. Mol Psychiatry 2014;19:544-54.

76 Huang H, Yan P, Shan Z, et al. Adverse childhood experiences and risk of type 2 diabetes: a systematic review and meta-analysis. Metabolism 2015;64:1408-18.

77 Thomas C, Hypponen E, Power C. Obesity and type 2 diabetes risk in midadult life: the role of childhood adversity. Pediatrics 2008;121:e1240-9.

78 Misiak B, Kiejna A, Frydecka D. The history of childhood trauma is associated with lipid disturbances and blood pressure in adult first-episode schizophrenia patients. Gen Hosp Psychiatry 2015;37:365-67.

79 Spann SJ, Gillespie CF, Davis JS, et al. The association between childhood trauma and lipid levels in an adult low-income, minority population. Gen Hosp Psychiatry 2014;36:150-5.

80 Pillinger T, Beck K, Stubbs B, Howes OD. Cholesterol and triglyceride levels in first-episode psychosis: systematic review and meta-analysis. Br J Psychiatry Dec 2017;211(6):339-349.

81 Machado TD, Salum GA, Bosa VL, et al. Early life trauma is associated with decreased peripheral levels of thyroid-hormone T3 in adolescents. Int J Dev Neurosci 2015;47:304-8.

82 Lee C, Tsenkova V, Carr D. Childhood trauma and metabolic syndrome in men and women. Soc Sci Med Mar 2014;105:122-30.

83 Veru-Lesmes F, Rho A, King S, et al. Social determinants of health and preclinical glycemic control in newly diagnosed first-episode psychosis patients. Can J Psychiatry 2018;63:547-56.

84 Tosato S, Bonetto C, Tomassi S, et al. Childhood trauma and glucose metabolism in patients with first-episode psychosis. Psychoneuroendocrinology 2019;113:104536.

85 Fond G, d'Albis MA, Jamain S, et al. The promise of biological markers for treatment response in first-episode psychosis: a systematic review. Schizophr Bull 2015;41:559-73.