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The role of DNA methylation in the association between childhood adversity and cardiometabolic disease

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Abstract

Growing evidence suggests that adverse environmental stimuli, especially during sensitive periods in early life, may lead to cardiometabolic disease in later life. However, the underlying biological mechanisms remain a mystery. Recent studies inferred that epigenetic modifications are likely involved. We review recent studies, primarily focused on the findings from human studies, to indicate the role of DNA methylation in the associations between childhood adversity and cardiometabolic disease in adulthood. In particular, we focused on DNA methylation modifications in genes regulating the hypothalamus pituitary adrenal axis as well as the immune system.

Keywords

DNA methylation; childhood adversity; cardiometabolic disease

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Authors' contributions

GH and SS conceived the idea for the manuscript and produced the first draft. NAY and CLD were involved in critical review and also in rewriting of subsequent drafts. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

1. Introduction

Childhood adversity, including verbal, physical, or sexual abuse, neglect, as well as family dysfunction (e.g., an incarcerated, mentally ill, or substance-abusing family member; domestic violence; absence of a parent because of divorce or separation etc.), is a global problem, and exerts substantial burden on the children themselves and on society.[1] A mounting body of evidence suggests that adverse experiences in childhood are associated with cardiometabolic disease in later life.[2, 3] However, little is known about the underlying biological mechanisms. In the past decade, the search for these mechanisms has progressed rapidly and therein found that epigenetic modifications are likely involved. Emerging evidence from human and animal research suggests that early life stress could lead to lasting, broad, and functionally organized signatures in DNA methylation.[4] For example, mice that were exposed to chronic and unpredictable maternal separation from postnatal day 1 to 14 showed differential methylation in several candidate genes.[5] Subsequent studies in humans also identified differential methylation of *NR3C1* gene promoter not only in postmortem hippocampal tissue among adult suicide victims with a history of childhood abuse, but also in peripheral blood from adults with exposure to childhood maltreatment[6–8]. Several reviews have described the association between childhood adversity and DNA methylation,[9, 10] and the association between DNA methylation and cardiometabolic disease.[11, 12] The present review, however, is primarily focused on the findings from human studies to indicate the role of DNA methylation in the relationship between childhood adversity and cardiometabolic disease in adulthood. While cardiometabolic diseases are caused by a combination of genetic and environmental factors, in this review, we focus on childhood adversity.

Epigenetic modifications are molecular mechanisms that regulate gene expression without changing DNA sequences, including DNA methylation, posttranslational histone modification, small RNA signaling and chromatin conformation changes.[13] Previous studies have demonstrated that the epigenetic modifications take place from the early embryo stage, and could persist across the life course, thereby leading to disease in adulthood.[14] DNA methylation is one of best-studied epigenetic modifications and is essential to mammalian development and cell differentiation. The best-known DNA methylation mechanism is the attachment of a methyl group to cytosine, typically at the fifth carbon position. The primary target of cytosine methylation in mammals is the C-phosphate-G (CpG) dinucleotide.[15] These sites are relatively rare in the genome but more common at promoter regions of genes, also referred to as CpG islands. Generally, increased methylation of CpG islands is associated with gene repression.[16] In addition, methylation at enhancers, insulators and gene bodies were also observed, but the mechanisms by which these influence the binding and function of regulatory proteins are not completely understood.[17] Three active DNA methyltransferases (DNMT1, DNMT3A and DNMT3B) that are responsible for methylation deposition and maintenance have been identified in mammals.[18]

Most data concerning DNA methylation of various pathologies have been obtained from animal models. However, comparable human epigenetic studies are still limited. DNA methylation may hold potential to identify new etiology through which childhood adversity becomes biologically embedded and leads to cardiometabolic disease in adulthood. This

knowledge may aid in developing novel prevention and intervention strategies to reduce the burden associated with stress-related health problems. Candidate gene studies and recent preliminary epigenome-wide association studies (EWAS) in early life stress have identified multiple genes involved in the development of obesity, fatty acid synthase, hypothalamus–pituitary–adrenal (HPA) axis, immune system, cellular and neuronal projection *etc*. (Supplementary Table 1).[19–21] In particular, DNA methylation alterations in genes HPA axis as well as the immune system in human studies are of most interest. Here we first review the DNA methylation involved in the HPA axis and immune system caused by childhood adversity, then explore the associations of those genes with cardiometabolic disease. Figure 1 displays the schematic model showing how DNA methylation modifications in some genes related to the HPA axis and immune system could mediate the effect of childhood adversity on cardiometabolic disease in later life.

2. Methods

In the first-stage, we performed a systematic search of PubMed, Embase, and PsycINFO databases through Oct 2017 for relevant studies of the association between childhood adversity and DNA methylation. The following key words were used: (‘child abuse’ OR ‘physical abuse’ OR ‘sexual abuse’ OR ‘psychological abuse’ OR ‘emotional abuse’ OR ‘neglect*’ OR ‘trauma*’ OR ‘advers*’ OR ‘maltreat*’ OR ‘bully*’ OR ‘bullied’ OR ‘victim*’ OR ‘expressed emotion’ OR ‘communication deviance’ OR ‘parental loss’ OR ‘separate*’ OR ‘discrimination’) AND ‘child*’ AND ‘methylation’. The titles, abstracts and full-texts were reviewed respectively. After excluding 242 duplicated records, we initially retrieved 1576 abstracts (517 from PubMed, 1171 from Embase, and 130 form PsycINFO) (Supplementary Figure 1). A majority of those references were excluded after reviewing the abstracts or titles and 42 articles were identified. Of those 33 articles identified genes in the HPA axis or immune system (Supplementary Table 1). The following information from each study is presented in Supplementary Table 1: first author, years of publication, country of origin, definition of childhood adversity, research design, sample size, age of sample size, and main results.

In the second stage, based on the genes identified in the first stage, we searched the databases and identified the genes not only related to childhood adversity, but also associated with cardiometabolic diseases. The following key words for cardiometabolic disease were used: ‘cardiovascular diseases’ OR ‘cardiovascular’ OR ‘coronary artery disease’ OR ‘atherosclerosis’, ‘coronary disease’ OR ‘coronary heart disease’ OR ‘ischemic heart disease’ OR ‘heart failure’, ‘myocardial infarction’ OR ‘stroke’ OR ‘brain vascular accident’ OR ‘hypertension’ OR ‘metabolic syndrome’ OR ‘metabolic cardiovascular syndrome’ OR ‘diabetes type 2’ OR ‘diabetes mellitus’.

3. Results

3.1. Hypothalamus–pituitary–adrenal axis

The HPA axis is a biological system particularly affected by early adverse experiences, such as child abuse and neglect[22] or being reared in harsh early environments.[23] The HPA axis is one of the primary stress response systems.[24] Upon exposure to stress, the

paraventricular nucleus of the hypothalamus activates and secretes corticotrophin-releasing hormone that promotes the release of adrenocorticotropic hormone from the anterior pituitary to the adrenal glands, which finally stimulates the release of glucocorticoids.[25] The activity and regulation of this system are driven by adrenal cortisol release, which via a negative feedback loop, inhibits the HPA axis activity initiated in the hypothalamus and pituitary. The association between adversity and later health outcomes mediated by HPA axis feedback regulation have been observed not only in childhood,[26] but also long after the cessation of the early adverse experience, in adolescence and adulthood.[27, 28]

3.1.1. Childhood adversity and DNA methylation in HPA axis—Changes in methylation levels of stress reactivity genes can be induced by childhood adversity. Candidate or genome-wide epigenetic studies in humans have found many HPA axis related genes were affected by childhood adversity through DNA methylation, such as glucocorticoid receptor gene (*GR*),[7] Serotonin transporter gene (*SLC6A4*),[29] proopiomelanocortin gene (*POMC*, encodes a preproprotein),[30] potassium voltage-gated channel subfamily Q member 2 (*KCNQ2*), Ephrin B1 (*EFNB1*),[31] alsin Rho guanine nucleotide exchange factor (*ALS2*, involved in small GTPase regulation),[32] leucine rich glioma inactivated 1 (*LGI1*),[33] brain-derived neurotrophic factor (*BDNF*, a stress and activity-dependent factor involved in many activities modulated by the HPA axis),[34], Kit ligand gene (*KITLG*, encodes the ligand of the tyrosine-kinase receptor),[30] and FK506-binding protein 5 (*FKBP5*, an important regulator of the stress hormone system) gene.[35] One of the most studied is the *GR* gene, also known as *NR3C1* gene, which codes for the glucocorticoid receptor and is located in the reverse strand of chromosome 5q31. glucocorticoid receptor is a key element involved in several steps of HPA axis modulation.[25] Higher *NR3C1* methylation levels have been associated with a reduced *NR3C1* expression and a flattened cortisol recovery slope, possibly leading to impaired negative feedback regulation of the HPA axis.[36] Chronic perturbations in the HPA axis system can have a widespread effect on long lasting health outcomes.[37]

Epigenetic changes of *NR3C1* gene caused by early adversity have been observed in brain tissues and peripheral blood samples. Methylation levels of CpG sites measured in the exon region of the *NR3C1* gene in leukocyte cells were associated with early adverse experiences in healthy adults [7] and adults with borderline personality disorder.[8] Methylation differences in leukocyte CpG sites located around the nerve growth factor-inducible protein A (*NGFI-A*) binding regions seem to be particularly affected by early adverse experiences.[7, 8] Similar changes were observed in human brain tissue. McGowan and colleagues demonstrated that individuals with histories of child abuse have higher methylation levels at specific CpG sites in the exon 1F of the promoter region of the *NR3C1* gene in a seminal examination of postmortem hippocampal brain tissue of adult suicide victims.[6] Oberlander and colleagues demonstrated the associations between prenatal maternal depression symptoms and site-specific methylation levels of the *NR3C1* gene in mixed mononuclear cells from human cord blood.[38] Meanwhile, this study also found that methylation levels were associated with infants' salivary cortisol levels at 3 months of age. In another study, the authors found that prenatal psychological stress can have an impact on the methylation pattern of the children's *NR3C1* gene, and not due to direct maternal transmission.[39]

These results further suggested the connections between DNA methylation profiles and ongoing HPA axis activity.[38]

3.1.2. DNA methylation and cardiometabolic disease in HPA axis—The associations between polymorphisms of the *NR3C1* gene and cardiometabolic disease have been confirmed in many studies.[40–42] Recently, a study reported a link between the epigenetic modifications of the *NR3C1* promoter, receptor gene, and physiological measures of the stress response.[43] The researchers found clear association between certain epigenetic alternations and blood pressure. In addition, the socially evaluated cold pressor test (completely immerse the hand in ice-cold (2–3 °C) water while watched by a woman and videotaped) induced a strong cardiovascular and HPA axis response.[44] Both cardiovascular systems and HPA axis were affected by functional genetic variants and methylation patterns. In a twin study, Zhao and colleagues observed an association between methylation of the promoter region of the *NR3C1* gene in peripheral blood leukocytes and subclinical atherosclerosis. This association was independent of genetic, early family environmental and other coronary risk factors.[45]

Besides epigenetic alternations of the *NR3C1* gene, an association of *BDNF* genotype and promoter methylation with acute and long-term stroke outcomes was also found in an East Asian cohort.[46] Many studies suggested that *BDNF* plays an important role in regulating energy homeostasis and body weight.[47, 48] Pereira and colleagues found that *FKBP5* gene expression in subcutaneous adipose tissue was correlated to markers of insulin resistance.[49] These studies provide an important illustration that expression of HPA axis related genes altered by an epigenetic mechanism may contribute to susceptibility to cardiometabolic disease, and posit a possible mechanism underlying the link between childhood adversity and cardiometabolic risk. Rooij and colleagues found that variation in methylation status in the *NR3C1* promoter was associated with physical and perceived acute stress responses, and these associations could largely be explained by differences in lifestyle and education in a large population of healthy adults. [50] This result also supported the hypothesis of DNA methylation acting as a mediator between adverse environment and disease to some extent. The HPA axis is also known to interact with the immune system,[51] which is another pivotal mechanism to mediate the relationship between adversity and cardiometabolic disease.

3.2. Immune System

Accumulating research has suggested that childhood adversity may promote states of heightened proinflammatory signaling that may increase risk for cardiometabolic disease.[52] Individuals who experience childhood adversity have been found to show elevated immune system activity. For example, childhood maltreatment may contribute to higher levels of fibrinogen, white blood cell counts.[53], IL-6, and NF-κB.[54, 55] Lifetime stress, trauma, low socioeconomic conditions, and child abuse have all been associated with elevated levels of IL-4, IL-2, and TNF-α in peripheral blood samples.[56] It was reported that early childhood adversity (deprivation and neglect) affected the long-term functioning of the immune system in adolescents, specifically evinced by a secretion of higher levels of herpes simplex virus secretory Ig-A into saliva.[57] Low socioeconomic status, harsh early

environmental circumstances and maltreatment have also been associated with elevated levels of C-reactive protein in adults.[58, 59] In addition to affecting inflammatory markers in peripheral blood and saliva, adversity early in life has been found to affect patterns of gene expression involved in immune system responses. For example, unfavorable socioeconomic circumstances in the early years of life presage the expression of *NR3C1* and toll-like receptor 4 (*TLR-4*) gene expression in adolescence.[60] Further, posttraumatic stress disorder has been shown to have distinct expression patterns in genes involved in immune activation in peripheral blood cells.[61] Individuals exposed to low socioeconomic status early in life showed an up-regulation of genes involved in inflammatory activity, along with a down-regulation of genes involved in glucocorticoid signaling, which plays a critical role in anti-inflammatory activity.[27]

The important role of inflammation in cardiometabolic disease has been noted for several decades.[62] Many previous studies have demonstrated that patients with elevated inflammatory factors are at increased risk of diabetes and cardiovascular disease.[62] A meta-analysis by Wang and colleagues showed that elevated C-reactive protein levels were significantly associated with increased risk of type 2 diabetes based on results of 22 studies, and a significant dose–response association was also observed between the levels of its inducer IL-6 and later occurrence of type 2 diabetes.[63] Kaptoge and colleagues performed a meta-analysis based on 29 studies and found that several different pro-inflammatory cytokines, including IL-6, IL-18, and TNF-α, were each associated with coronary heart disease risk independent of conventional risk factors and in an approximately log-linear manner.[64] In the past few decades, several studies have also strengthened the concept that hypertension has an immunologic basis.[65]

3.2.1. Childhood adversity and DNA methylation in the immune system—

Associations between early-life adversities with many inflammation related genes have been found in candidate or genome-wide epigenetic studies. Uddin and colleagues examined the associations between posttraumatic stress disorder and methylation patterns from DNA extracted from peripheral blood in adults, and found that externally experienced traumatic events induced downstream alterations in immune function by reducing methylation levels of immune-related genes.[66] A study by Janusek et al. showed that reduced methylation of the *IL6* promoter was related to increased exposure to childhood trauma and greater TSST-induced IL-6 levels in African American men.[20] Another prospective cohort study demonstrated a consistent association between psychological factors with higher average leucocyte DNA methylation in the intercellular adhesion molecule-1 (*ICAM-1*) promoter region and in the coagulation factor III (*F3*) promoter region. The authors also found that hostility was positively associated with toll-like receptor 2 (*TLR-2*) promoter methylation, and that life satisfaction was inversely associated with both *TLR-2* and *iNOS* promoter methylation.[67] A case-control study by Misiak and colleagues showed that emotional abuse and total trauma score predicted lower *LINE-1* methylation in first-episode schizophrenia patients.[68] The New York Women's Birth Cohort study demonstrated that growing up in a single parent family was associated with higher Alu methylation after adjusting for other early life factors.[69] A genome-wide methylation study by Prados and colleagues found that early life events were associated with methylation levels of the CpGs

located near the *IL17RA* gene.[31] Methylation of other immune-related genes, such as *TLR8*, tartrate-resistant acid phosphatase (*ACP5*), and neuropeptide FF receptor 2 (*NPFFR2*), were also found to be associated with posttraumatic stress disorder.[56] These emerging studies are interesting in suggesting a link between trauma and adversity, especially in early life, and DNA methylation related to the immune system. However, further studies are needed to replicate these findings.

3.2.2. DNA methylation and cardiometabolic disease in immune system—

Several studies have demonstrated associations between inflammation gene methylation and cardiometabolic risk. Zuo et al. found that hypomethylation of *IL-6* promoter is associated with the increased risk for coronary heart disease, especially for acute myocardial infarction.[70] Studies by Cash et al. and Baccarelli et al. showed that cardiovascular risk factors, including higher serum vascular cell adhesion molecule, higher low-density lipoprotein and lower high-density lipoprotein cholesterol were associated with *LINE-1* methylation.[71, 72] Baccarelli and Lin et al. have demonstrated that *LINE-1* hypomethylation in blood DNA was associated with risk of ischemic heart disease, stroke, and total mortality.[73, 74] Turcot and colleagues found that *LINE-1* hypomethylation in visceral adipose tissue samples from severely obese individuals was associated with higher prevalence of metabolic syndrome, and therefore elevated risk for cardiovascular disease.[75] The Normative Aging Study (NAS) found that increases in the degree of methylation of *Alu* elements were associated with increases in blood pressure. Positive associations between BP and the degree of methylation of the genes for *TLR2* and *iNOS* and negative associations of BP with methylation of the gene for *IFN-γ* were also found in this study.[76] One cross-sectional study by Kim and colleagues examined Alu methylation in relation to myocardial infarction and reported a higher degree of methylation in cases compared to healthy controls.[77]

These studies aforementioned indicate that childhood adversity affects DNA methylation of selected genes involved in inflammatory processes, which are in turn associated with increased risk of cardiometabolic disease. Such epigenetic changes may represent biological pathways that mediate the effects of psychological factors on cardiometabolic disease.

3.3. Methylation of other possible genes related to childhood adversity

Beside HPA axis and immune systems, childhood adversity have also been associated with DNA methylation of Peptidase M20 Domain Containing 1 which is linked with energy homeostasis regulation (*PM20D1*, a bidirectional enzyme that catalyzes both condensation of fatty acids and amino acids to generate N-acyl amino acids and the reverse hydrolytic reaction),[78] Opioid Receptor Kappa 1 (*OPRK1*, encodes an opioid receptor),[79] oxytocin receptor (*OXTR*),[80] cytochrome p450 family 2 subfamily e member 1 (*CYP2E1*, encodes a member of the cytochrome P450 superfamily of enzymes),[81] and protein phosphatase 1 regulatory subunit 3g (*PPP1R3G*, Involved in glucose homeostasis and glycogenesis in the liver)[82] *etc*. (supplementary Table 1) However, the roles of these in cardiometablic diseases remain unclear.

4. Summary and Future Directions

Although childhood adversity has been associated with cardiometabolic disease, the underlying pathways for this associations have yet to be fully elucidated. For the past few years, epigenetic processes, particularly the DNA methylation, have been considered among the crucial mediators of the effects of childhood adversity.[83] However, there is limited direct evidence that early adversity could increase the risk of cardiometabolic disease through DNA methylation. In this review, we focused on DNA methylation modifications in genes regulating the HPA axis as well as the immune system (Table 1). It is likely that more than one biological mechanism is responsible for the poor cardiometabolic outcomes observed among individuals exposed to childhood adversity.

In order to better characterize the role of DNA methylation between childhood adversity and cardiometabolic disease, a few points should be considered in future research.

1. Epigenetics inheritance and preadaptation theory: There is growing evidence in humans that prenatal maternal emotional state, such as depression, anxiety, trauma or stress, is associated with the methylation state and adverse health outcomes in offspring,[39] which suggests that epigenetic information could be transmitted from one generation to the next. However, the fetus may adapt to adverse environmental cues *in utero* with permanent adjustments in homeostatic systems to aid survival.[84] In other words, organisms could “inform” their progeny about prevailing conditions and reprogram the gene expression through epigenetics modifications to preadapt the child to the current environment. Once these adaptations are inconsistent with the postnatal environment, they may ultimately be disadvantageous and result in an increased risk of disease. Therefore, studies including at least two generations are warranted to confirm this theory in humans and to understand the underlying inheritance patterns. Twin studies offer another promising design to explore the mediation effect of DNA methylation between child adversity and cardiometabolic outcomes, as the twins share 100% (for identical twins) or average 50% (for non-identical twins) of genetics and the same familiar environments when grow up together, which could rule out heterogeneity due to genetic and familiar environmental confounding.[85]

2. Methylation changes with age: Mounting evidence from both animal and human studies suggests that the epigenome is in constant drift throughout the lifespan in response to stochastic and environmental factors.[86] DNA methylation and demethylation are likely modified by early-life unfavorable experiences,[83] but yet there is modification that also occurs throughout life. The monozygotic twin design, completely matched for genetics, age, sex, cohort effects, maternal influences and common environment, can be applied in longitudinal studies to explore the age-dependent patterns in genetic and environmental contributions to epigenetic modification and gene activity, which can be linked to aging-related phenotypes.[87]

3. Cause and consequence: Comparing with the stable and the conservative of DNA sequence, epigenetic processes are developmentally dynamic. It is fundamentally important to identify the methylation tags showing corresponding changes to the changes of psychosocial stress. This will not only serve as solid evidence supporting the direct link for the observed associations but also indicate that the reduction in stress may reverse the DNA methylation, a strong statement for public health initiative. On the other hand, because of the plastic nature of DNA methylation, it is difficult to distinguish whether the identified DNA methylation changes are causal or secondary to the cardiometabolic disease. Therefore, a longitudinal study in healthy population with chronic stress, DNA methylation, and preclinical markers of cardiometabolic disease assessed in multiple times is warranted to address these critical issues.

4. Cell and tissue heterogeneity: DNA methylation patterns may vary between cells and tissue types. This may make study design a challenge because relevant tissues may not be accessible from living individuals. Previous studies have found that both brain and blood can respond to certain environmental stimuli through epigenetically-mediated changes and that these changes are indeed to some extent concordant between both tissue types.[88] Some tools have been developed to aid interpretation of blood-based DNA methylation results in the context of brain tissue.[89] In regards to cell subtypes, there have been several approaches well developed to estimate the percentage of major cell compositions based on genome-wide DNA methylation data, and being adjusted for in the subsequent statistical analysis.[90] However, studies focusing on epigenetic signatures of specific cell types rather than measuring methylation in mixed cells may elucidate which cell types are more relevant to early life stress and thus involved in the mechanisms leading to cardio-metabolic disease.

5. Epigenome wide association studies (EWAS): With new technologies and approaches constantly being invented, such as comprehensive DNA methylation microarrays, more opportunities have been granted to explore these intricate mechanisms. Epigenetic research (especially the EWAS and GWAS) leads to complex data structures. This complicated gene-gene, and gene-environment interactions involved in the relationship between child adversity and cardio-metabolic outcomes [91, 92] induce a great challenges to current statistical methods. Therefore, advanced methodologies are needed to address these knotty issues and to reduce the false positive results. In addition, the majority of previous EWAS studies on childhood adversity did not have an independent replication cohort (Supplementary Table 1). Future research should follow the current recommendations with respect to the study design and data analysis for EWAS.[93]

6. Other related factors: Many studies have shown that adverse exposures in early life were associated with higher rates of smoking, alcohol and drug consumption. [94, 95] The effects of unfavorable lifestyle due to adversity are difficult to disentangle from the effects of the adversity *per se*. Therefore, the complex interplay of genetics, lifestyle changes and environment exposures should be

considered when designing future studies to disentangle the relationships among childhood adversity, epigenetic changes and cardiometabolic outcomes. In addition, resilience, defined as the capacity to resist negative consequences resulting from adverse events or to bounce back from adversities, has become an important area of research. Resilient coping may buffer the effects of childhood adversity on long-term health outcomes in adulthood.[96, 97] Therefore, studies on resilience may provide a better understanding of the mechanisms linking childhood adversity and cardiometabolic diseases, and inform approaches to prevent disease in those affected by childhood adversity.

This review summarized the current state of the literature regarding the effect of childhood adversity on DNA methylation status in genes related to the HPA axis and immune system, and the possible mediation effects of DNA methylation in these two pathways on cardiometabolic disease risk. Shared biological pathways suggest that interdisciplinary research may be a promising strategy to uncover the mechanisms through which childhood adversity contributes to the development of cardiometabolic disease. Future research is warranted to directly target these mechanisms with measures of childhood adversity and cardiometabolic outcomes, which may aid in developing novel prevention and intervention strategies to reduce the burden associated with stress-related health problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- DNA methylation involved in the HPA axis and immune system caused by childhood adversity was reviewed.
- The associations of those genes with cardiometabolic disease were explored.
- This narrative system review gives comprehensive view of childhood adversity, DNA methylation, and cardiometabolic disease.

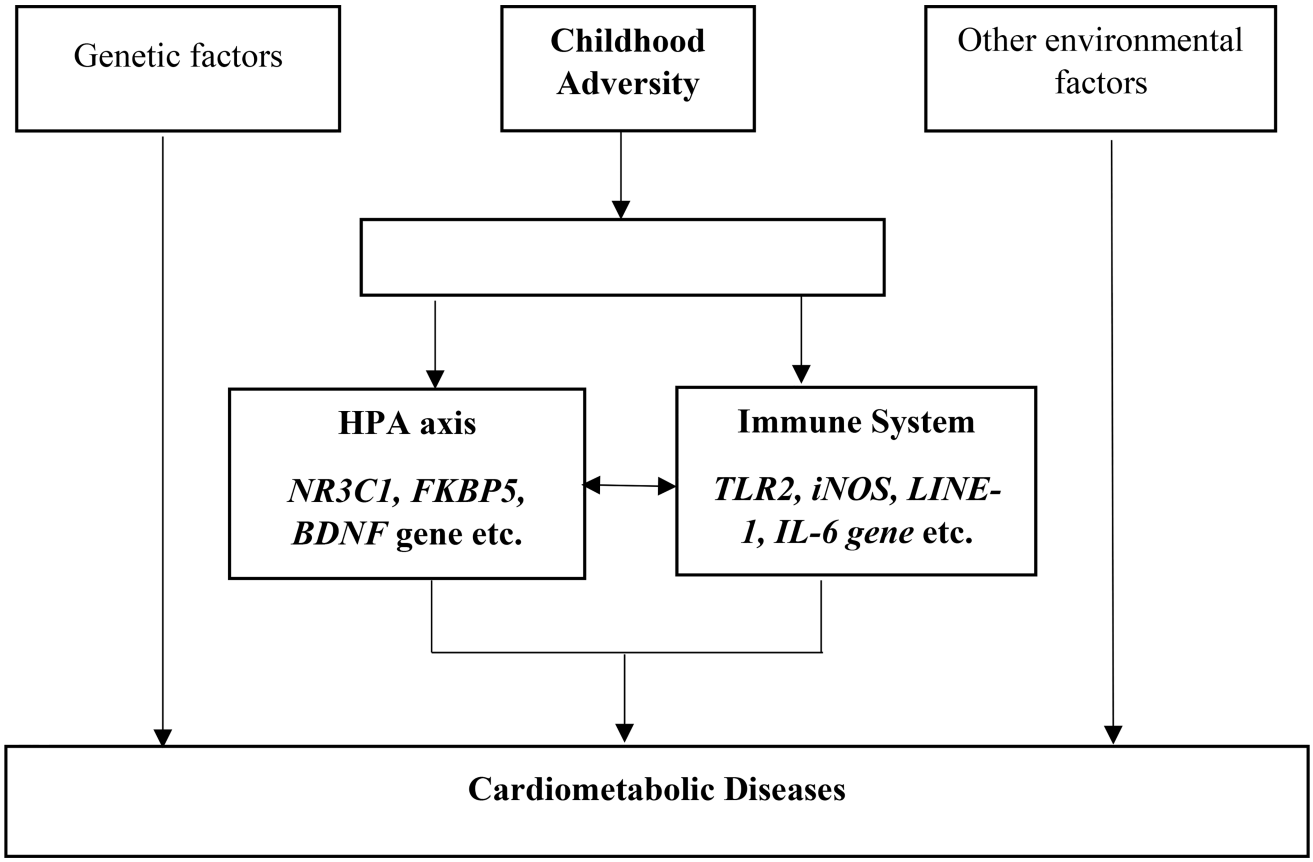

Figure 1.
Childhood adversity associated with later life cardiometabolic disease risk mediated through DNA methylation modifications in HPA axis and immune system.

Table 1

Genes whose methylation may mediate the association between childhood adversities and cardiometabolic disease risk

	Function	Childhood adversity	Methylation status	Cardiometabolic disease
HPA axis				
NR3C1	Located on 5q31, encodes glucocorticoid receptor protein	childhood maltreatment or adversity[7]	↑	Blood pressure,[43] subclinical atherosclerosis[45]
BDNF	Located on 11q13, encodes a member of the nerve growth factor family of proteins	childhood maternal care[98]	↑	Stroke outcome[46]
POMC	Located on 2p23.3, encodes a preproprotein that undergoes extensive, tissue-specific, post-translational processing via cleavage by subtilisin-like enzymes known as prohormone convertases	Maltreatment[30]	↑	Higher triglycerides and higher insulin concentrations[99]
*FKBP5**	Located on 6p21, encodes a member of the immunophilin protein family	Early trauma[100]	↓	Insulin resistance[49]
Immune system				
TLR2#	Located on 4q32, encodes a member of the Toll-like receptor family which plays a fundamental role in pathogen recognition and activation of innate immunity	Negative psychological factors[67]	↑	Blood pressure[76]
iNOS#	Located on 17q11, encodes a nitric oxide synthase which is expressed in liver and is inducible by a combination of lipopolysaccharide and certain cytokines	Negative psychological factors[67]	↓	Blood pressure[76]
LINE-1	Belongs to the group of long interspersed nuclear elements	Emotional abuse and total trauma score[68]	↓	Cardiovascular disease[75]
Alu	A member of the short interspersed repetitive DNA elements family of repetitive elements	Single parent family[69]	↑	Blood pressure[76] [77]
IL6	Located on 7p15.3, encodes a cytokine that functions in inflammation and the maturation of B cells	Childhood trauma [20]	↓	Coronary heart disease[70]

*Only found that higher *FKBP5* gene expression was positively correlated with serum insulin to date.

#Only found that *TLR2 and iNOS* gene methylation were correlated with negative psychological in older population to date.