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REVIEW OPEN ACCESS

Psychosocial Stress, Epigenetics, and Cardiovascular Disease: A Scoping Review of DNA Methylation's Impact on Cardiovascular Disease in African Americans

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Abstract

Introduction: African Americans experience a disproportionate burden of cardiovascular disease by up to 20% due to a combination of social and genetic factors. This paper will examine the potential contributions of DNA methylation to the burden of cardiovascular disease in African Americans in the context of psychosocial stress.

Methods: This scoping review examined peer-reviewed literature published between 1995 and 2025 using databases such as PubMed, Google Scholar, Scopus, and MedLine OVID. Inclusion criteria targeted studies on DNA methylation changes linked to stress and CVD, excluding studies focused on participants with diagnosed psychiatric stress disorders.

Results: Studies indicated that discrimination faced by the African American community correlated to DNA methylation in inflammatory genes such as tumor necrosis factor-α and other proteins implicated in cardiovascular disease pathology. There was a correlation with DNA methylation and altered protein expression potentially exposing an increased risk of cardiovascular disease for African Americans. Additionally, it was found that chronic maternal stress during and before pregnancy can reduce the expression of enzymes critical for oxidizing harmful maternal glucocorticoids. Consequently, the fetus becomes exposed to glucocorticoids such as cortisol and corticosterone that have been demonstrated to cause epigenetic modifications.

Discussion: Psychosocial stress contributes to cardiovascular disease in African American populations through both direct and intergenerational DNA methylation mechanisms. Chronic stress stemming from psychosocial stressors induce DNA methylation alterations in genetic pathways contributing to an increased prevalence of cardiovascular disease. Transgenerationally, chronic maternal stress can alter the expression of protective placental enzymes, potentially modifying the expression of *IGF1* and *IGF2* due to DNA methylation by maternal glucocorticoids. These findings underscore DNA methylation as a mechanism linking racial stress disparities to long-term cardiovascular outcomes.

Conclusion: Stress-induced DNA methylation affects vascular health both directly and transgenerationally, potentially contributing to the development of cardiovascular disease. This highlights a potential route by which African Americans are disproportionately burdened with rates of cardiovascular disease due to psychosocial stressors. The routes proposed here are based on correlational evidence and further directions should aim to highlight causal relationships between DNA methylation, psychosocial stress, and cardiovascular disease.

Keywords: cardiovascular disease; African Americans; psychosocial stress; DNA methylation; epigenetic inheritance

Introduction

Cardiovascular disease (CVD) is a leading global cause of death and disproportionately affects African American (AA) populations [1, 2]. In the United States of America, studies have found that AAs are subject to 20% higher rates of heart disease and upwards of 40% increased rates of stroke [1, 3–5]. Current literature attributes the higher CVD burden in AAs to combined genetic and socioeconomic factors [1, 6–8]. Research suggests that CVD disproportionately affects lower income AAs who also face high psychosocial stress due to financial struggles and discrimination, among other stressors [9–11]. While no definitive mechanism connecting psychosocial stress and CVD has been found, current research highlights potential routes through epigenetic alteration of various cellular pathways [6, 8–14].

Epigenetic modification refers to heritable changes in gene expression that are not due to changes in the nucleotide sequence [5]. These alterations can become

subject to environmental effects and change over a lifetime [5]. These include DNA methylation (DNAm) and acetylation of the histone proteins, among others [15]. This paper will focus on DNAm as the primary method of epigenetic alterations. DNAm occurs through the actions of DNA methyltransferases transferring methyl groups to cytosine-guanine-cytosine (cg) islands [16]. These methyl groups can interfere with the expression of subsequent genes altering their expression [16]. The cg islands often lie in promoter regions, but can also appear intragenically leading to transcript mutagenesis [17]. Hypomethylation can also alter gene expression by reducing DNAm resulting in aberrant expression of affected genes [18].

AAs face psychosocial stressors such as discrimination more often than other groups which may contribute to a disproportionate burden of CVD [19]. Consequently, this can negatively impact hormonal signalling from the amygdala, adrenal gland, and other organs [6, 9]. These changes in signalling are linked to inflammatory responses and diurnal cortisol cycles through a neural-hematopoietic-inflammatory axis that may be implicated in CVD [10]. This suggests that AAs are at risk for epigenetic alterations due to the compounding effects of social stressors on the body [9, 11]. Nevertheless, the current literature requires further research into causal mechanisms solidifying these connections.

Psychosocial stress not only directly impacts our physiology through altered signaling pathways, but also by driving behavioural changes [7]. Individuals often adopt coping behaviours to manage stress, such as tobacco inhalants [7]. Up to 30% of AAs use tobacco, and, as a result, may be subject to increased risk of CVD [20, 21]. This review aims to explore how DNAm may be implicated in mediating this increased risk of CVD. It also aims to examine how other methods of coping may implicate AA's in CVD as a result of faced psychosocial stressors.

Apart from stress within an AAs lifetime, it is possible that they are inheriting DNAm patterns as a result of their parents' experienced psychosocial stress during pregnancy [9]. Previous research into this topic has elucidated that maternal stress is correlated with low birthweight (BW), increased CVD, and cardiometabolic disorder in the child's life [22]. However, the mechanisms by which this occurs are largely unknown and research into potential epigenetic mechanisms is limited [23]. This paper will examine 11β-hydroxysteroid dehydrogenase type 2 (11B-HSD2) as a potential pathway. It works to prevent maternal circulating cortisol from accessing the fetus by degrading it to cortisone [23].

The goal of this article is to examine the current literature on how psychosocial stressors impact CVD through DNAm. This article will examine two routes through which this is possible. The first route is through altered hormonal signalling and behavioural patterns resulting from chronic stress. The second is how psychosocial stress experienced in previous generations results in DNAm implicated in CVD in subsequent generations. Together these may highlight a potential pathway linking the disproportionate burden of CVD that AAs face [1, 3–5].

Methods

This scoping review draws on peer-reviewed articles between the years 1995 and 2025. The review was conducted using PubMed, Google Scholar, Scopus, and MedLine OVID databases to search for peer-reviewed articles. 22 studies were included in this review. PRISMA-ScR guidelines informed this review. To conduct the search, the key terms "DNA Methylation," "Psychosocial Stress," "Cardiovascular Disease," "African-American," "Social Determinants," and "Intergenerational Effect" were used. Articles containing all or a combination of these terms, and their synonyms, were selected.

The inclusion criteria for articles pertaining to intergenerational inheritance of DNAm were articles published no earlier than 1995 and those which discussed the impacts of glucocorticoid exposure on fetal epigenetic programming. For examining direct and indirect impacts of psychosocial stress on DNAm in CVD, the inclusion criteria were articles that contained the keywords above, while also discussing or elucidating a link between stress, DNAm, and CVD. Articles that derived information from subjects with confounding conditions such as clinically diagnosed stress disorders, as defined by the DSM5 criteria, were excluded from the review [24].

Results

The Impact of Psychosocial Stressors on DNAm

Stress has been associated with DNAm of various genes throughout the body [25]. AAs face increased rates of psychosocial stressors due to race and other factors [7]. Zhao et al. found that a higher proportion of AAs experience race-related discrimination at 40.5% compared to their non-hispanic white counterparts at 3.7% [10]. Higher exposure to discrimination in AAs corresponded with altered DNAm at minichromosome maintenance-5 (*MCM5*), NADH:ubiquinone oxidoreductase complex assembly factor 5 (*NDUFS5*), and cardiovascular helix-loop-helix factor 1 (*CHF1*) genes [10]. In both *MCM5* and *CHF1*, DNAm was correlated to differences in protein expression which have a potential to impact CVD and other diseases [10].

Sustained stress from psychosocial stressors have also been found to impact the epigenetic ageing of the body [11]. Ruiz-Narváez et al. found that there was a direct relationship between an individual's experienced racism and two measures of epigenetic ageing: Horvath Pan-Tissue and GrimAge clocks [11]. The potential impact on CVD is highlighted by Ortiz-Whittingham et al., who found a significant correlation between DNAm PhenoAge, another measure of epigenetic ageing, and mean high density lipoprotein size [26].

The Impact of Stress-Induced DNAm on CVD

Stress induced CVD risk may be linked through inflammatory and genetic pathways [6]. Cintron et al. found that social isolation was positively associated with average amygdala activity (AmygA) and household level socioeconomic status was suggestive of negative correlation with left AmygA (L-AmygA) [6]. The study found that maximum AmygA (M-AmygA) was positively correlated to spleen activity and, when adjusted for body mass index (BMI) and atherosclerotic CVD risk, the association remained significant [6]. After multiple testing correction, M-AmygA was associated with DNAm at the nuclear factor kappa B subunit 1 (*NFκB1*) cg07955720 and signal transducer and activator of transcription 3 (*STAT3*) cg19438966 sites [6]. Significant associations between both M-AmygA and spleen activity were found with tumour necrosis factor α (*TNFa*), while L-AmygA was associated with interleukin 1β (*IL-1β*) [6]. *NFκB1*-cg07955720 and *TNFa* were inversely correlated, as well as *STAT3*-cg19438966 and *IL-1β* [6].

Psychosocial stressors were found to be associated with DNAm induced by maladaptive coping mechanisms such as smoking [7]. Brown et al. examined differences in coping strategies based on cumulative stress endured, and found that there was a direct correlation with avoidance coping [7]. Tobacco inhalants are a common form of avoidance coping associated with increased DNAm at SH3-containing guanine nucleotide exchange factor (*SGEF*) and AT-rich interaction domain 5B (*ARID5B*) [7, 21]. Another study associated DNAm at these sites with an increased risk of coronary atherosclerosis, however, a causal link still needs to be established [21]. Tobacco inhalants were also associated with the aryl hydrocarbon receptor repressor DNAm in AAs, which was linked to and acts as a biomarker of atherosclerosis [16]. Sheng et al. found that use of tobacco inhalants was associated with accelerated epigenetic aging [27]. The study also found significant associations of tobacco-use behaviours and DNAm PhenoAge, suggesting that epigenetic age is an important factor implicated in CVD risk [27].

Transgenerational Inheritance of DNAm Induced by Psychosocial Stress

Elements of the prenatal environment have been shown to exert significant and lasting effects on the programming of the fetal hypothalamic-pituitary-adrenal axis [28–31]. Fetal exposure to maternal serum glucocorticoids can induce DNAm and alter physiological stress responses in subsequent generations [32]. Multiple mechanisms regulate fetal exposure to circulating maternal elements, one of which is *11B-HSD2* [22]. This enzyme, found only in the syncytial trophoblast of the placenta, catalyzes the oxidation of human maternal cortisol into its inactive form, cortisone [33, 34]. Down-regulation of *11B-HSD2* has been associated with reduced BW, which in turn correlates with a heightened risk of developing CVD [35, 36]. Critically, reduced expression of this enzyme permits increased fetal exposure to maternal glucocorticoids, with potentially extensive and permanent epigenetic consequences [35, 36]. Vangeel et al. demonstrated a positive correlation between third-trimester maternal cortisol levels and DNAm of the Insulin-like Growth Factor 2 (*IGF2*) gene, at cg33 [37]. At a cortisol area under the curve (AUC) of 100, IGF2-AS cg33 methylation was approximately 5%, rising to about 14% at a cortisol AUC of 375 [37]. Hypermethylation of *IGF2-AS* has been identified as a risk factor for coronary artery disease (CAD) as well as other CVDs [15]. In Wistar rats, elevated circulating corticosterone, the equivalent of cortisol, has been shown to suppress the expression of Insulin-like Growth Factor 1 (*IGF1*) *in utero* [21]. Specifically, caffeine-induced elevations in maternal rat corticosterone were found to reduce both mRNA and protein expression levels of placental *11B-HSD2* [38]. Alongside this reduction, activity within the *IGF1* signaling pathway was also inhibited [22]. Inhibition of *IGF1* via methylation of the gene promoter region has been associated with altered lipid metabolism, muscular atrophy, and limited skeleton growth in Wistar rats [38].

AA newborns have higher *IGF1* methylation patterns resulting in lower BW's when compared to other races [39]. After adjusting for maternal age, parity, and gender, the AA population was still associated with a 7.45% decrease in BW and a 0.62 standard deviation increase in *IGF1* methylation [40]. These observed BW's were reflected in the Center for Disease Control's National Vital Statistics Report in which 14.8% of AA births were found to be low BW while it was 7.04% and 7.92% for White women and Hispanic women, respectively [41]. In AA children and adolescents, lower BW's are predictive of higher blood pressure and elevated cortisol reactivity [42]. These early life pathologies often manifest as end-stage renal disease and other types of CVD [43].

Discussion

Psychosocial Stress Induced DNAm and its Impact on CVD

This paper has found that by altering gene expression through DNAm, psychosocial stress creates changes in inflammatory and CVD pathogenesis that can increase AAs risk of CVD [10]. Through mediating a change in hormonal signalling, psychosocial stress can methylate various genes involved in inflammation [6]. The *NFκB1* and *STAT3* genes are involved in pathways for circulating *TNFa* and *IL-1β* respectively [6]. *NFκB1* experiences supra-activation following hypomethylation which results in increased *TNFa* expression [6, 40]. Consequently, increased *TNFa* creates hypertrophic and apoptotic responses in cardiomyocytes which contribute to developing CVD [40, 44]. *STAT3* supra-activation was correlated with increased circulation of *IL-1β* which is implicated in heart failure, CAD, and multiple arrhythmias [43]. Thus, this highlights a potential path by which

inflammatory responses to psychosocial stressors increase the prevalence of CVD in AA [10].

Gene methylation in non-inflammatory pathways is also a consequence of psychosocial stressors and is implicated in CVD for AAs [7]. *CHF1* encodes for an antihypertrophic protein that directly inhibits the activation of genes implicated in cardiac hypertrophy and was found to have significant methylation in AAs [10, 45]. In response to psychosocial stressors, DNAm of the *CHF1* gene has the ability to alter expression of the protein, influencing its ability to prevent cardiac hypertrophy [45]. However, the study that found DNAm within the *CHF1* gene in response to stress did not find significant changes in the level of protein produced [45]. Regardless, this warrants further study as it presents a potential DNAm pathway that may induce CVD in AAs. Another gene that warrants further study is *NDUFS5*. This gene encodes a subunit of the mitochondrial respiratory chain complex I, and was found to have significant increases in protein expression following stress-induced DNAm [10]. This gene is implicated in the pathophysiology of heart failure and is currently being explored as a biomarker of left ventricular reverse remodelling [46]. Studies have shown that increased expression of the *NDUFS5* protein is correlated with the production of reactive oxygen species and thus by extension heart failure [47]. Although the exact mechanism by which it contributes to CVD pathology is unknown, this represents a potential mechanism that may link DNAm to CVD [46, 47].

Coping with psychosocial stress through smoking has been shown to lead to DNAm and increased risk of CVD [7]. Smoking was associated with DNAm at both *SGEF* and *ARID5B* genes which are both implicated in atherosclerosis risk [14, 48]. It was found that *SGEF* directly plays a role in developing atherosclerosis by encoding an endothelial docking protein promoting the movement of white blood cells into arterial walls enhancing the progression of atherosclerosis [48, 49]. Contrary to *SGEF*, *ARID5B* plays a protective role in atherosclerosis risk as DNAm of the gene has been inversely correlated with protein expression and atherosclerosis [14, 21]. However, increased *ARID5B* expression directly correlates to pro-inflammatory pathways increasing atherosclerotic development [14]. Thus, it can be inferred that *ARID5B* methylation, decreasing protein expression, protects from atherosclerosis by decreasing pro-inflammatory pathways [14]. Although future research is needed to confirm this inference.

In general, psychosocial stressors have contributed to the epigenetic ageing of AAs which increases their risk of CVD [27]. Multiple studies examined in this review found increased epigenetic ageing as a result of chronic stress in the body [12, 27, 49, 50]. The impact of this is a generalized increased risk of CVD that is commonly seen as individuals age [51]. DNAm becomes increasingly implicated in CVD as individuals age through changing expression of receptors, transcription factors, and other proteins [51]. Thus, being faced with psychosocial stressors has the potential to increase the rate of epigenetic ageing, making age associated CVD risk factors prevalent in younger individuals [11].

Maternal Stressors May Cause DNAm of *IGF2 and Potentially IGF1*

This study expands upon proposed mechanistic pathways through which maternal psychosocial stress may induce transgenerational epigenetic alterations, contributing to increased CVD risk in offspring [22, 28–38]. Central to both DNAm of *IGF1* and *IGF2* is the stress-induced down-regulation of placental *11B-HSD2,* which can lead to increased fetal exposure to maternal glucocorticoids [22]. *IGF1* is a major effector for the anabolic effects of growth hormone while *IGF2* is necessary and more active during prenatal development [52]. In the *IGF2* pathway, elevated cortisol exposure is associated with hypermethylation of the antisense region at cg33 [37]. The altered methylation pattern, a consequence of decreased *11B-HSD2* expression in the placenta, has been implicated in CAD as well as other CVDs [15]. Conversely, the mechanism underlying *IGF1* inhibition following fetal glucocorticoid remains less well-characterized [38, 53]. Animal studies have shown that elevations in maternal corticosterone suppress *IGF1* expression and inhibit the signaling pathway in the fetus [54]. These changes are observed alongside decreased placental expression of *11B-HSD2*, mirroring the early steps of the *IGF2* pathway [22]. Given the findings in rats, future studies are warranted to examine if these same epigenetics modifications are present in humans. If so, given the congruency in upstream mechanisms it is plausible that similar epigenetic modifications may also underlie the observed *IGF1* signalling inhibition.

This hypothesis may also offer a compelling explanation for the markedly higher levels of *IGF1* methylation observed in AA newborns [39]. Numerous studies have documented a disproportionately higher prevalence of chronic psychosocial stressors within the AA community [6, 7, 9–11]. Thus, it can be inferred that the expression of placental *11B-HSD2* would be significantly reduced in AA mothers experiencing chronic stress. This down-regulation may impair the placenta's protective enzymatic barrier, thereby increasing fetal exposure to maternal glucocorticoids and risk of developing CVD later in life [22].

Limitations and Future Directions

This review has faced limitations typical of scoping reviews [55]. There was no formal quality assessment of the papers included in the study increasing the risk of bias and reducing the confidence of the findings. Another limitation the review faced is in the methodology of screening papers for inclusion. Articles were only screened once, and thus there is a higher risk of missed studies[55]. The next limitation in our ability to assess the impact of

psychosocial stress on CVD in AA through DNAm was the type of articles included. Many of the articles were correlational in nature rather than providing evidence of causality [6, 7, 10, 15, 26, 27, 32, 35–38]. This limits the confidence in the pathways suggested in this article connecting psychosocial stress to CVD through DNAm, as they have no backing causal data. This presents a direction for the field of research by taking pathways suggested in this article and examining potential causal relationships that may exist. Alternatively, this suggests that future research into psychosocial stress and its ability to create DNAm, requires further causal data and research to elucidate concrete mechanisms through which this happens.

Conclusions

This paper highlights the role of DNAm following psychosocial stress as a contributor to the disproportionate burden of CVD faced by AAs. The DNAm of inflammatory genes such as *TNFa* or structural proteins like *SGEF* following psychosocial stress supports a potential connection between race, ethnicity, and CVD [49].

Importantly, the burden of CVD may also be passed intergenerationally [9]. Maternal stress during pregnancy can down-regulate crucial protective placental enzymes, leaving the fetus exposed to harmful glucocorticoids potentially altering the DNAm of *IGF2* [39, 50, 52]. These epigenetic changes are linked to lower BW and greater lifetime CVD risk in AA populations [3–5, 22].

Although current studies on this topic are largely correlational, they strongly suggest that psychosocial stress may alter gene expression through DNAm, contributing to racial health disparities[8, 23]. Further research should explore causal pathways and identify specific methylation targets, such as the expression of *11B-HSD2* proteins in placentas of AA mothers compared to other races [22]. Addressing these epigenetic effects demands systemic efforts to reduce stressors rooted in racial inequality to ease the burden on AA and marginalized communities.

List of Abbreviations

11B-HSD2: 11β-hydroxysteroid dehydrogenase type 2
AA: African American
AmygA: amygdala activity
ARID5B: at-rich interaction domain 5b
AS: antisense (region)
AUC: area under the curve
BMI: body mass index
BW: birthweight
CAD: coronary artery disease
cg: cytosine-phosphate-guanine
CHF1: cardiovascular helix-loop-helix factor 1
CVD: cardiovascular disease
DNAm: deoxyribonucleic acid methylation
IFNγ: interferon γ
IGF1: insulin-like growth factor
IGF2: insulin-like growth factor 2
IGF2-AS: insulin-like growth factor 2 antisense region
IL-1β: interleukin 1β
L-AmygA: left amygdala activity
M-AmygA: maximum amygdala activity
MCM5: minichromosome maintenance-5
NDUFS5: nadh:ubiquinone oxidoreductase complex assembly factor 5
NFκB1: nuclear factor kappa b subunit 1
SGEF: sh3-containing guanine nucleotide exchange factor
STAT3: signal transducer and activator of transcription 3
TNFa: tumour necrosis factor *a*

Conflicts of Interest

The authors have no conflict of interest to declare.

Ethic Approval/Participant Consent

No participants were included in this study so no consent or ethics approval were necessary.

Authors' Contributions

JL: Contributed to the design of the study, review of DNAm impact on CVD through psychosocial stress, interpretation and analysis of data gathered, drafting of the manuscript, editing of the manuscript, and final approval of the version to be published.
AQA: Performed the research and writing for the intergenerational inheritance of stress section. AQA synthesized and hypothesized the potential mechanism by which maternal psychosocial stressors can act upon the epigenetic programming of the fetus. AQA contributed to the methods, results, and discussion section as well as editing of the manuscript.
LG: Assisted with the research for the psychosocial stressor coping mechanisms. LG uncovered some of the cg sites associated with tobacco inhalants and their relation to cardiovascular risk within African Americans. LG contributed to the introduction and results and editing of the manuscript.

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