



## Full Length Article

## DNA methylation and exposure to violence among African American young adult males



Forough Saadatmand<sup>a,\*</sup>, Katherine Gurdziel<sup>b</sup>, Latifa Jackson<sup>a,c</sup>, Bernard Kwabi-Addo<sup>d</sup>, Douglas M. Ruden<sup>e,f</sup>

<sup>a</sup> Department of Pediatrics, College of Medicine, Howard University, Washington, DC, USA

<sup>b</sup> Office of the Vice President of Research, Wayne State University, Detroit, MI, USA

<sup>c</sup> W. Montague Cobb Research Laboratory, College of Arts and Sciences, Howard University, Washington, DC, USA

<sup>d</sup> Department of Biochemistry and Molecular Biology, College of Medicine, Howard University, Washington, DC, USA

<sup>e</sup> Department of Ob/Gyn, CS Mott Center for Human Growth and Development, Wayne State University School of Medicine, Detroit, MI, USA

<sup>f</sup> Institutes for Environmental Health Science, Wayne State University School of Medicine, Detroit, MI, USA

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## ABSTRACT

Exposure to violence (ETV) has been linked to epigenomics mechanisms such as DNA methylation (DNAm). We used epigenetic profiling of blood collected from 32 African American young adult males who lived in Washington DC to determine if changes in DNAm at CpG sites affiliated with nervous and immune system were associated with exposure to violence. Pathway analysis of differentially methylated regions comparing high and low ETV groups revealed an enrichment of gene sets annotated to nervous system and immune ontologies. Many of these genes are known to interact with each other which suggests DNAm alters gene function in the nervous and immune system in response to ETV. Using data from a unique age group, young African American adult males, we provide evidence that lifetime ETV could impact DNA methylation in genes impacted at Central Nervous System and Immune Function sites.

**Method:** Methylation analysis was performed on DNA collected from the blood of participants classified with either high or low lifetime ETV. Illumina®MethylationEPIC Beadchips (~850k CpG sites) were processed on the iScan System to examine whole-genome methylation differences. Differentially methylated CpG-sites between high (n = 19) and low (n = 13) groups were identified using linear regression with violence and substance abuse as model covariates. Gene ontology analysis was used to identify enrichment categories from probes annotated to the nearest gene.

**Results:** A total of 595 probes (279 hypermethylated; 316 hypomethylated) annotated to 383 genes were considered differentially methylated in association with ETV. Males with high ETV showed elevated methylation in several signaling pathways but were most impacted at Central Nervous System and Immune Function affiliated sites. Eight candidate genes were identified that play important biological roles in stress response to violence with HDAC4 (10%), NR4A3 (11%), NR4A2 (12%), DSCAML1(12%), and ELAVL3 (13%) exhibiting higher levels in the low ETV group and DLGAP1 (10%), SHANK2 (10%), and NRG1(11%) having increased methylation in the high ETV group. These findings suggest that individuals subjected to high ETV may be at risk for poor health outcomes that have not been reported previously.

## 1. Introduction

For many African Americans (AA), experiencing violence, discrimination, and environmentally induced stressors, such as childhood neglect or abuse, are well documented (Jacobs et al., 2014; Pew Research Center, 2016). AAs carry a disproportionate burden of incidence, morbidity, and

mortality from chronic diseases such as hypertension and obesity (Allport et al., 2019; Barendolts et al., 2019; Yang et al., 2019; Li et al., 2019; Faucher et al., 2019; Assari et al., 2019; Nagy et al., 2020; Goode et al., 2017; Go et al., 2014) in addition to exposure to violence (ETV) which has also been shown to have a negative impact on health (Griggs et al., 2019; Goldmann et al., 2011; Woodson et al., 2010; Paranjape and

\* Corresponding author.

E-mail address: [frough.saadatmand@howard.edu](mailto:frough.saadatmand@howard.edu) (F. Saadatmand).

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Kaslow, 2010; Mitchell et al., 2010; Paranjape et al., 2009; McGee et al., 2001; Moffitt and Klaus-Grawe Think, 2013; Olofsson et al., 2012). Therefore, it is worthwhile to examine if lifetime exposure to violence is a contributing factor in AA health disparity. Lifetime ETV is defined in this study as the cumulative effects of ETV during childhood, before age 18, and exposure to community violence after age 18. The key questions we would like to understand in this study is how lifetime exposure to violence, especially during the most vulnerable periods of childhood and adolescence, translates into changes at a molecular level. One possible mechanism is through methylation changes since ETV has been shown to affect the epigenome (Olofsson et al., 2012). Cytosine DNA methylation (DNAm) in humans occurs primarily at CG dinucleotides, which are also called CpG sites (Alberts, 2008). Over half of the promoters in human genes contain CpG islands which are CpG-rich regions that are binding sites for regulatory factors that modulate gene transcription. The most studied type of epigenetic regulation is by DNAm of the promoter regions (Mansell et al., 2019). DNAm generally acts as an On-Off switch that turns genes On when the DNA is not methylated and Off when the DNA is methylated (Alberts, 2008). Cytosine methylation occurs at the 5th position of the base which faces into the major groove of the DNA helix. Since transcription factors bind to the major groove of DNA, DNAm at CpG islands often blocks transcriptional activators from binding to the promoter regions (Alberts, 2008). That is one of the reasons why DNAm usually turns genes off. Another reason why DNAm turns genes off is that methyl-DNA-binding proteins, such as MeCP2, which is mutated in Rett Syndrome patients, binds to methylated cytosines and acts as a transcriptional repressor (Lyst et al., 2013). Blood is usually the surrogate tissue used in humans to DNAm changes caused by environmental or social stressors because other tissues are not generally available in humans (Ebrahimi et al., 2020). In mouse studies, epigenetic changes in the blood often correspond to epigenetic changes in the brain, thus justifying a surrogate tissue approach in humans (McKay et al., 2011). In recent years, contrasting results have been reported about the use of blood to study brain alterations. However, blood can be used to study peripheral rather than central biomarkers.

One remarkable finding over the past couple of decades is that recent epigenetic studies, including those focused on DNAm, have found an association between adverse life experiences (such as exposure to community and family violence, discrimination, and trauma) and modulation of gene regulatory regions that can change behaviors, influence personality, and increase the risk for mental health disorders and psychosocial stressors (Vick and Burris, 2017; Barker et al., 2018; Jovanovic et al., 2017). Other studies have demonstrated the association between DNAm and perceived discrimination among African American women (Barcelona de Mendoza et al., 2018), with the highest rates of perceived discrimination (35%) by African American in comparison to other women (Jacobs et al., 2014). Results from another recent DNAm study in Brazil showed altered gene expression across the lifespan of those who experienced repeated community and domestic violence (Serpeloni et al., 2020). A meta-analysis conducted across five studies exploring the association between DNAm, disadvantaged neighborhoods, and cardiovascular disease risk indicated an association between DNAm changes in expression to the stress- and inflammation-related genes and disadvantaged neighborhoods, and risk of cardiovascular disease (Giurgescu et al., 2019). In a longitudinal study, childhood victimization predicted elevated levels of C-Reactive Protein (CRP) at age 18 with an association that was specific to women (Baldwin et al., 2018). Increased epigenetic aging and heart rate in children ages 6–13 who experienced direct, but not witnessed, violence has also been shown (Jovanovic et al., 2017). Additionally, increased levels of DNAm at CpG sites across the genome have also been associated with socioeconomic status (SES) in a cohort of young adults (McDade et al., 2019). While several studies have investigated the relationship of epigenetic changes and stressful life events, such as exposure to violence, in disadvantage neighborhoods, there is no study that investigate the genomewide changes among African American young adults. To address this issue, we explored the relationship between

DNAm and exposure to different levels of violence, using genome wide DNAm data extracted from whole blood. To our knowledge, there are no published studies that have examined how lifetime exposure to violence is associated with DNAm across the epigenome among AA young adult males. We hypothesized that higher levels of lifetime exposure to violence would result in DNAm changes involved in the immune response in African American young adult males.

## 2. Methods

### 2.1. Participants and procedure

This study selected 32 males who scored in the highest ( $n = 19$ ) and lowest ( $n = 13$ ) 30% of 638 African American males and females (aged 18–25) from economically and socially disadvantaged neighborhoods of Washington DC on a self-reported scale measuring lifetime exposure to violence (Lifetime ETV) for epigenetic profiling. The Lifetime ETV scale combined 34 items measuring ETV during childhood (before age 18) and 35 items on exposure to community violence since adulthood. This study compares the high and low ETV male groups to determine if ETV resulted in changes to DNAm sites affiliated with immune function. This study controlled for drug use in the past 30 days. The IRB was approved by Howard University Office of Regulatory Research Compliance (IRB-13-PED-06).

To qualify for inclusion in the study, respondents had to be between the ages of 18 and 25 as of their most recent birthday, self-identify as African American or Black, screen as HIV negative (to exclude those with HIV compromised immune systems from the larger study on immune function), and currently live in one of the predominantly disadvantaged wards in Washington, DC. The full study entailed a comprehensive survey about participants' ETV before and after the age of 18, adverse life experiences, discrimination, current and childhood socioeconomic characteristics, current health problems and symptoms, current drug use, sleep quality measures, depressive symptom measures, and current HIV risk behaviors.

While mouse epigenetic studies of behavior can involve brain tissues, such tissues are impossible to collect in humans except from human brain banks. Instead, people who study epigenetic regulation of behavior in humans utilize a surrogate tissue such as blood or saliva which can be collected in non-invasive manners (Solomon et al., 2018; Murata et al., 2019). Other tissues have been collected in humans for epigenetic studies, such as fat or muscle biopsies (Taylor et al., 2019), but such collections are much more invasive than collecting blood or saliva and consequently more difficult to collect. Despite the limitation of surrogate tissues in humans, several studies have identified epigenetic biomarkers in genes that correlate with stressful conditions in humans (Sen et al., 2015a, 2015b; Intarasunanont et al., 2012).

### 2.2. Survey of exposure to childhood and community violence

To measure exposure to childhood violence, exposure to community violence as adults, the survey included questions from previously developed and tested instruments. The childhood exposure to violence scale contained 34 questions that asked participants to respond to circumstances that might have happened during their childhood from birth through age 18. The response options were "1 time," "2 times," "3 times," "4 times," "5 times or more," "no times," and "prefer not to answer." This scale has a test-retest reliability coefficient of 0.90 and Cronbach's  $\alpha = 0.85$  (Finkelhor et al., 2010, 2015; Stith and Hamby, 2002; Little and Hamby, 2001). Community exposure to violence as adults was measured by 35 items. Participants were asked to describe the violence that they experienced, saw, or heard about since they turned 18. The responses were "never," "once or twice," "a few times," "many times," or "prefer not to answer." This scale has an internal consistency of 0.85, test-retest reliability of 0.90, and Cronbach's  $\alpha = 0.61, 0.79,$  and  $0.86,$  respectively for violence experienced, seen, and heard (Richters and Saltzman, 1990).

### 2.3. Genomic DNA extraction method

High molecular weight genomic DNA was extracted from 300  $\mu$ L of whole blood from participants using the Qiagen DNAeasy DNA extraction kit for blood and tissue (Qiagen Sciences Inc.) according to the manufacturer's protocol. The concentration and integrity of the DNAs were measured using a NanoDrop 2000c Microvolume Spectrophotometer. The DNA samples (200 ng aliquots) were used in genome-wide DNAm analysis by the Genome Sciences Core at Wayne State University.

### 2.4. Global methylation analysis

Methylation analysis was performed using Illumina®MethylationEPIC Beadchips prepared as described in the Illumina® Infinium® HD Assay Methylation Protocol Guide (15019519 v01) before processing on the Illumina iScan System. Input DNA (250 ng) was bisulfite treated using the Zymo EZ DNA Methylation Kit. Zymo's Human Methylated and Non-methylated DNA controls are treated with samples. Controls are PCR amplified and run on a gel to confirm both methylated and unmethylated bands are present. After bisulfite conversion was confirmed, the bisulfite treated DNA was manually prepared for sequence-specific array-based hybridization using whole-genome amplification (WGA), enzymatic endpoint fragmentation and chemical precipitation. The WGA product was re-suspended and captured by array hybridization. Arrays were then mounted in the Tecan GenePaint automated slide processor on the Tecan Freedom Evo® robotic liquid handling system for primer extension and staining. The amount of fluorescence was measured and used to determine the methylation level of the CpG sites.

### 2.5. Differential methylation analysis

Raw data from the Infinium assays underwent quality control including staining, extension, hybridization, and bisulfite conversion checks (Aryee et al., 2014). After probe correction to remove probes with low intensity and normalization (Triche et al., 2013), differentially methylated CpG-sites (expressed as M values) between high ( $n = 19$ ) and low ( $n = 13$ ) groups were identified using linear regression with violence and substance abuse as model covariates (Ritchie et al., 2015). Substance abuse was calculated by averaging self-reported alcohol, marijuana, cocaine, glue, and heroin use during the thirty-day window prior to the survey. Average Delta  $\beta$  values indicating the differential methylation were calculated by subtracting the average  $\beta$  value of high violence from that of low violence groups. The differentially methylated probes with gene annotation ( $|\Delta\beta| \geq 0.1$ ;  $p$ -value  $\leq 0.05$ ) were further analyzed for significant biological pathways using gene ontology analysis (Huang et al., 2009).

## 3. Results

### 3.1. Descriptive characteristic of participants

Descriptive characteristics and childhood SES variables of participants are summarized in Table 1. The mean age of the participants was  $20.7 \pm 2.4$  and they were all unmarried (1 was engaged). 21.9% did not finish high school and 62.5% reported completing high school or GED. 81.3% made less than \$15,000 a year and 68.8% grew up in families with incomes  $< \$40,000$  a year and 28.1% were unemployed. 72% were exposed to violence during childhood, two-thirds were exposed to community violence during their young adulthood and 78.1% were exposed to both childhood and community violence. 62.5% of participants had at least one drink during their lifetime, 53.1% had ever smoked a cigarette and 68.7% had ever used marijuana. About 47% had restless sleep, and 34.4% felt lonely and fearful in the past week.

The results of genome-wide DNAm analysis of 19 participants with high ETV showed significantly higher DNAm at multiple loci/genes in comparison with the 13 participants with low ETV. Of the 866091 probes on the EPIC Beadchips analyzed, 476292 passed QC across all 32

**Table 1**

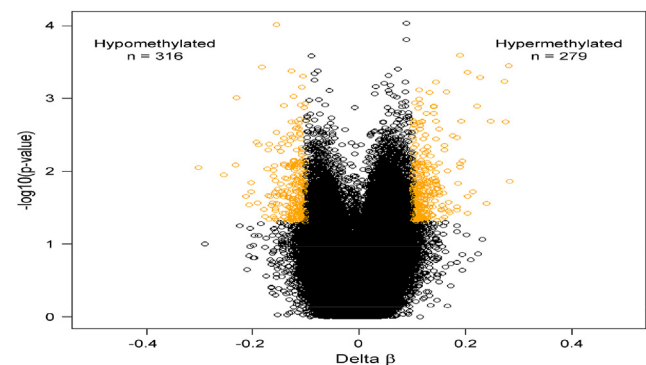
Descriptive characteristic and lifetime exposure to violence of participants ( $N = 32$ ).

Variables	Mean (SD) or percent
Age 18-25	20.7 (2.4)
Income	
< \$14,999	81.3%
\$15,000-\$29,999	12.5%
\$30,000+	6.2%
Education	
Did not finish HS	21.9%
High school or GED	62.5%
Finished vocational or trade school	3.1%
Attend or graduated college	12.5%
Unemployment	28.1%
Source of childhood family income	
People who worked	71.9
Welfare or public assistance	12.5
Worked and welfare	15.5
Childhood Household Income	
< \$14,999	40.6
\$15,000-\$29,999	18.8
\$30,000-\$39,999	9.4
\$40,000-\$49,999	12.5
\$50,000 and more	18.8%
Rented Residence (% yes)	59.4%
Lifetime childhood ETV	72.0%
Lifetime community ETV as adults	75.0%
Lifetime childhood and community ETV	78.1%
Ever drank alcohol (yes)	62.5%
Ever smoked cigarette (yes)	53.1%
Ever used marijuana (yes)	68.7%
Felt lonely past week	34.4%
Restless sleep past week	46.9%
Felt fearful past week	34.4%

samples. Probes that had a greater than 10% change in  $\beta$  ( $p$ -value  $\leq 0.05$ ) between the groups of high and low Lifetime exposure to violence were classified as differentially methylated sites (DMS) (Fig. 1). In total, 595 probes annotated to 383 genes were considered DMS. (See Appendix A. supplementary table showing all 383 genes).

Gene Ontology analysis of genes annotated to DMS (top 30 in Table 2), revealed 85 significant categories ( $FDR \leq 0.05$ ) with several related to the nervous system: nervous system development (GO:0007399), anterograde trans-synaptic signaling (GO:0098916), chemical synaptic transmission (GO:0007268), synaptic signaling (GO:0099536), trans-synaptic signaling (GO:0099537), neurogenesis (GO:0022008) and central nervous system development (GO:0007417). Only one category, inflammatory response to antigenic stimulus (GO:0002437), was related to immune function.

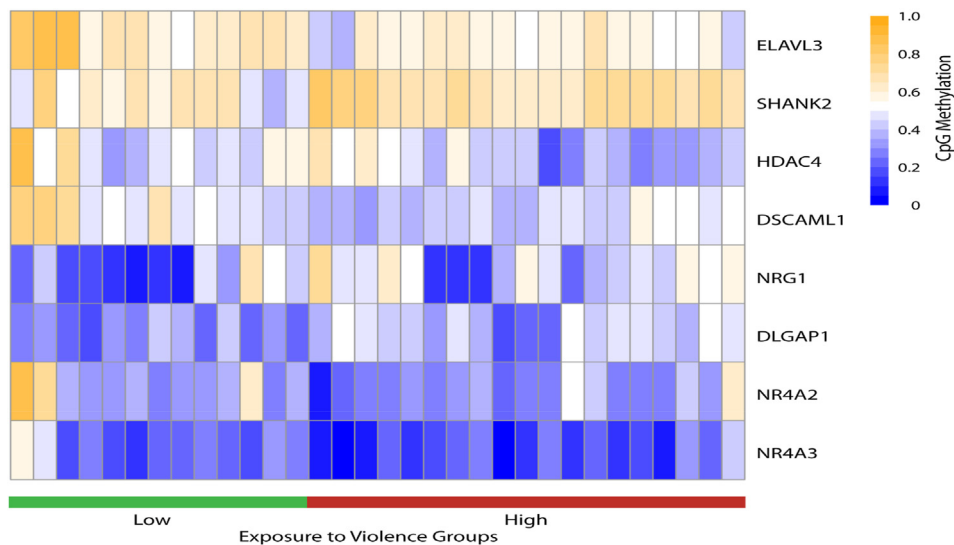
Interaction analysis of the 90 genes categorized as related to the nervous system or immune response revealed interactions between 53



**Fig. 1.** Volcano plot of differentially methylated CpG sites. CpG sites with an absolute Delta  $\beta$  of 10% ( $p$ -value  $\leq 0.05$ ) are depicted in yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)







**Fig. 3.** Heatmap for selected genes showing methylation levels (hypomethylation - blue; hypermethylation - orange) across individual subjects classified into the low (green) and high (red) ETV categories. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

to play important biological roles in stress response to violence (Fig. 3). We observed variable methylation levels within and across the low and high violence groups. Overall, we observed that for NR4A3, NR4A2, DSCAML1, HDAC4, and ELAV3 there was relatively higher methylation in the low violence group compared to high violence group. In contrast, for DLGAP1, NRG1, and SHANK2, there was relatively lower methylation in the low violence when compared to the higher violence exposure.

#### 4. Discussion

There are several environmental determinants associated with health disparities in the USA including exposure to violence. Exposure to violence can directly influence health through biological mechanisms and can be measured as indicator of stressors. The well characterized biological pathway whereby environmental exposure to violence are transmitted through the body to elicit physiological response is via the so-called hypothalamic-pituitary-adrenal axis (HPA axis) system. Signals from the central nervous system in the form of chemical signals or electrical potential are sent to the HPA axis signifying the release of corticotrophin releasing hormone (CRH). The CRH in turn stimulates biosynthesis and release of adrenocorticotrophic hormone that triggers the production of glucocorticoids (cortisol) which are the stress response markers (Welberg et al., 2001).

However, the underlying biological mechanism whereby exposure to violence may alter stressor in the body is unknown. In this study we carried out genome-wide DNAm analysis and found that individuals with high levels of self-reported violence victimization had significant hypermethylation of key CpG sites located in the genes influencing nervous system development, cell adhesion, and cellular signaling as compared to those similarly situated individuals without high violence exposure. Previous studies have shown that experiencing community and domestic violence was associated with gene methylation involved in the neural development in adolescents (Serpeloni et al., 2019), and epigenomic mechanisms possibly associated with risk for health problems later in life in maltreated children. Additionally, increased levels of DNAm at CpG sites across the genome were found to be associated with low socioeconomic status (SES) in a cohort of young adults (McDade et al., 2019).

In our current studies we have observed that high exposure to violence is significantly associated with increased DNAm of genetic networks involved in the central nervous system and the immune system. Several studies suggest that epigenetic mechanisms such as DNAm

changes plays dynamic roles in gene expression throughout the life of neurons and in neurodegenerative diseases including Rett syndrome, fragile X syndrome and Alzheimer's disease (Christopher et al., 2017). Similarly, there are emerging evidence to suggest that aberrant epigenetic DNAm may participate in defects in immune-mediated pathologies (Calle-Fabregat et al., 2020).

In our previous studies we observed that young men and women exposed to violence experienced adverse physical and mental health outcomes including depression, and sleep disturbances (Saadatmand et al., 2017). In women, exposure to violence significantly affected sleep as a result of direct personal violence. In contrast, men exposed to direct personal violence such as gun violence or witnessing violent death had considerably greater impact upon depression and depressive mood. In our more recent study (Saadatmand et al., 2019) we reported that exposure to violence was significantly associated with marijuana use in both men and women. In an exploratory study, Uddin, et al. (Uddin et al., 2013), also suggest that sex differences in DNAm may contribute to sex differences in the prevalence of PTSD and depression.

Thus, our current observation of differential methylation of several genes in the central nervous system and the immune signaling pathway suggests that this is a potential biological mechanism for disrupting normal biological processing including sleeping patterns, depressive moods and drug use with regards to the exposure to violence. In a review of epigenetic findings in both animal and human studies, Lockwood et al. (2015), concluded that epigenetics could play an important role in depression and suicide in humans. A review of previous research concludes that DNAm plays a central role in learning and memory processes and in drug addiction (Bali et al., 2011). Results from a study showed a distinct DNAm pattern in insufficient sleep with differences related to compromised neuroplasticity and neurodegeneration (involving genes, such as ERC2, MAGI2, CAST, and CDK5R1) (Lahtinen et al., 2019).

Naumova et al. (2012), found that children raised in an institution since birth showed greater epigenome-wide DNAm compared with high-poverty children living with their families, particularly in genes related to immune regulation and cellular signaling. More recently, based on a cross-sectional sample of high-risk youth, Cecil, et al. (Cecil et al., 2016), sought to characterize the DNAm 'signatures' of different forms of maltreatment, using an epigenome-wide approach. They found that physical maltreatment showed the strongest associations with DNAm, implicating multiple genes previously associated with psychiatric and physical disorders (e.g., GABBR1, GRIN2D, CACNA2D4, PSEN2).

Of particular interest is the identification of genes including Neuroregulin 1 (NRG1) and nuclear receptor subfamily 4 Group A member 2 (NR4A2) from our GO analysis to be involved in both the nervous system and immune signal pathways. In support of our observation, a recent study by Uddin et al. (2018), identified methylation at 2 CpG sites in an epigenome-wide association studies to be associated with PTSD. One study also found methylation of NRG1 to be associated with inflammation (Song et al., 2016). Taken together, these observations suggests that aberrant methylation of key regulatory genes in the central nervous system and immune signal pathways maybe a potential mechanism for inducing chronic inflammatory changes in various psychiatry disorders including depression, anxiety, and PTSD. Based on their study, Safe et al. (2016), suggest that NR4A2 is important for regulating both inflammation and resolution of inflammatory signaling in activated immune cells and glial cells.

Furthermore, our results showed a gene interaction analysis of the 90 significant genes categorized as related to the nervous system or immune response revealed interactions in 3 clusters. The findings of this study suggest that young African American men who are exposed to high levels of lifetime violence maybe at risk for many health risks and diseases that have not been reported in literature related to this age group. However, we note that no clinical data are available about the participants' psychiatric symptoms. This will be pursued in a future study.

#### 4.1. Study limitations and strengths

The results of this study should be considered in light of several limitations. First, the sample was only from the baseline phase of a longitudinal study and we cannot infer casual associations between exposure to violence and DNAm. Second, this study was based on 32 DNA samples of young African American, living in Washington DC, who were exposed to low and high exposure to violence and might not have enough power analysis. However, given the lack of study on DNAm among young African American, and the high cost associated with the DNAm testing, this study is novel in its approach and the importance of studying the impact of life adversities, such as exposure to violence on DNAm. This study might be a blueprint for a larger study of examining how environmental influences such as exposure to violence become biologically embedded and find causal pathways between DNAm and exposure to violence among young African American males and females.

## 5. Conclusion

While replication is required, this study suggests that overall genes that are differentially methylated are involved in pathways including neurological apoptosis, differentiation and migration, axonal growth, and neurological disorders including autism, Alzheimer's, bipolar disorder, and Parkinson's disease. Future studies will investigate how methylation of these gene network drives health disparities. These analyses lay groundwork for building a portrait of the potential contribution of violence exposure on methylation processes in young African American men.

#### Declaration of competing interest

The authors have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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#### Appendix A. Supplementary data

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