Review Article

Impact of social stress on epigenetics: an updated narrative review

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Background and Objective: Stress is associated with various responses depending on the kind and the intensity of exposure, the number of stressful events and the period of life (age of exposure). Stress modulates the epigenetic machinery, modulating gene expression and impacting health across life. The objective of this narrative review is to identify the impact of social stress on epigenetics and recognise the consequences on mental health.

Methods: This narrative review was performed using PubMed, MEDLINE, Cochrane Library and Google Scholar from January 2015 to June 2025; search terms used to identify relevant publications were: "stress AND epigenetics", "stress and DNA methylation", "stress AND early-life", "stress AND Covid-19", "stress AND work". Language was restricted to English.

Key Content and Findings: This review aims to describe the impact of social stressors (i.e., trauma following abuse, crime, war, workplace stress) during early life, pregnancy and work-related stress on DNA methylation/demethylation at neonatal/child- and adult-age. Social stressors can perturb neuronal development, epigenetic age and adult health by modulation of DNA methylation at selected genes. Furthermore, maternal stress during pregnancy has been observed to perturb the child and mother epigenome, increasing the risk of epigenetic inheritance of these biomarkers in future generations. Work-related stress during coronavirus disease 2019 (COVID-19), with high working hours and reduced sleep time, represents an additional factor that contributes to the development of non-communicable diseases.

Conclusions: Social stressors, in early life and in adulthood age can perturb mental health with long-term effects later in life; preventive strategies to promote epigenetic reversibility at a young age should be considered to avoid stress-induced intergenerational epigenetic inheritance. Actions to counterbalance stress-associated work include scheduling work hours with breaks to improve physical and emotional well-being. Guidelines for training and clinical practice with clear and precise instructions can be helpful to manage stress in healthcare personnel; furthermore, an educational program for people could represent a useful tool for social support.

Keywords: Social stress; epigenetics; early life trauma; mental health; coronavirus disease 2019 work-related stress (COVID-19 work-related stress)

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Introduction

Stress response is individual, and it depends on the extent and the frequency of stressful events (1,2). When stress is mild, it modulates an adaptation process that can promote the resilience of the subject; this is achieved through a complex molecular mechanism of regulation of gene expression involving the adaptation process (2). On the contrary, when the stressful event is traumatic, prolonged and perceived as disturbing, it triggers a series of hormonal and molecular responses with consequences that vary

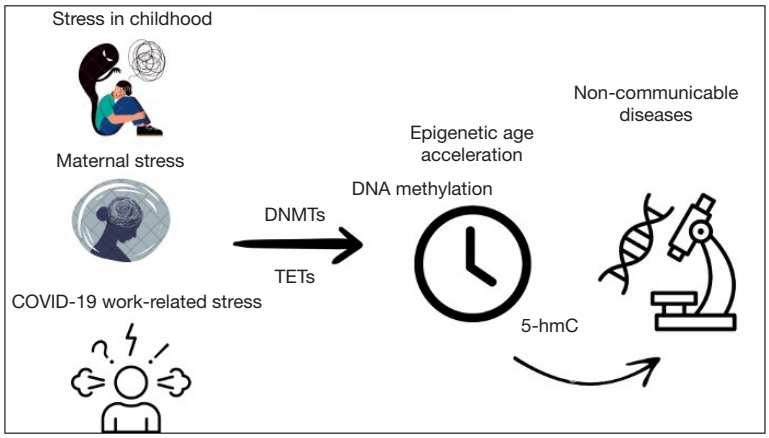

Figure 1 Impact of social stress (i.e., trauma in childhood, maternal stress, COVID-19 work-related stress) on DNMTs and TET dioxygenases proteins, involved in the epigenetic modulation of genes associated with the development of non-communicable diseases (i.e., neurodegeneration, cardiovascular diseases, cancer). 5-hmC, 5-hydroxymethylcytosine; COVID-19, coronavirus disease 2019; DNMTs, DNA methyltransferases; TET, ten-eleven translocation.

from subject to subject. In general, stress activates the hypothalamic-pituitary-adrenal (HPA) axis with secretion of corticotropin by the paraventricular nucleus of the hypothalamus; corticotropin promotes the release of adrenocorticotropic hormone that stimulates the release of cortisol from the adrenal cortex (3). Cortisol is a powerful epigenetic modulator that influences the activity of DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) dioxygenases, enzymes responsible for regulating DNA methylation and demethylation, respectively, involved in the regulation of gene expression following stress. Cortisol production also influences lipid, carbohydrate, protein metabolism and the immune system (4), and prolonged-stress conditions can promote pro-inflammatory cytokines' release and an increased risk of developing low-grade systemic chronic inflammation, which is associated with the development of non-communicable diseases [i.e., neurodegeneration, cardiovascular diseases (CVD), cancer].

Several factors are involved in the activation of stress responses, negatively affecting individuals, animals, or ecosystems. Environmental stress occurs when environmental demands exceed an individual's ability to cope, leading to psychological or physiological strain. Common environmental stressors are physical stressors (i.e., extreme temperatures, loud noises, pollution, overcrowding), social stressors (i.e., crime, war, workplace stress, social isolation), biological stressors (i.e., exposure to pathogens, toxins, or allergens) and climate-related stressors (i.e., natural disasters, droughts, rising sea levels); environmental stress can impact mental health, physical well-being, and ecological stability (5).

The aim of this narrative review is to highlight recent outcomes on the impact of social stress [i.e., stress-associated trauma in early life/childhood, maternal stress, coronavirus disease 2019 work-related stress (COVID-19 work-related stress)] in the modulation of epigenetic machinery and its potential inheritance and link to non-communicable disease risk development (*Figure 1*). Currently, the gaps in the existing research on the association between social stress and epigenetics refer to the difficulty in quantifying the contribution of only social factors, due to the coexistence of multiple causes activating the same pathways, and to the role of individual genetic variability that is responsible for the personalized answer to the same stimulus by people. Thus, this review aims to highlight that social stress represents a significant risk factor for health and that epigenetics can modulate this response, impacting not only the exposed subject but potentially also future generations. For this reason, the present narrative review differs from others that identify the impact of exposome on aging because its main effort is related to the biological consequences of social stress (6,7). Considering the increased extent of social stressors in the world, the goal of this narrative review is to draw attention to the impact of this factor on human health, addressing information useful within a preventive strategy aimed at preserving people's health and promoting educational health policy. I present this article in accordance with the Narrative Review

Table 1 The narrative review search strategy

Items	Specification
Date of search	First search time: August 2024; second search time: June 2025
Databases and other sources searched	PubMed, MEDLINE, Cochrane Library, Google Scholar
Search terms used	Stress, epigenetics, DNA methylation, early-life, COVID-19, work-related stress
Timeframe	January 2015–June 2025
Inclusion criteria	Significant papers and reviews were included. Language was restricted to English
Selection process	The research was conducted by R.G.

COVID-19, coronavirus disease 2019.

reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-25-4/rc).

Methods

This narrative review was performed using PubMed, MEDLINE, Cochrane Library and Google Scholar from January 2015 to June 2025; search terms used to identify relevant publications were: "stress AND epigenetics", "stress AND DNA methylation", "stress AND early-life", "stress AND Covid-19", "stress AND work". Language was restricted to English (*Table 1*).

Stress and epigenetic age acceleration (EAA)

Epidemiological studies show a correlation between psychosocial stress and related psychiatric conditions, such as major depression, post-traumatic stress disorder (PTSD) and increased risk of aging (8). Acute stress disorders (ASDs) can manifest themselves within a month of the traumatic event and if the disorders persist for more than a month, they are diagnosed as PTSD. The number of events capable of inducing biological consequences is important in determining the development of the pathology; a trauma experienced in childhood can lead to consequences on the acceleration of epigenetic age, measurable already at the 20-year-old (9). The acceleration of epigenetic age consists in the measurement of the variation of the biological age of an individual which can differ from the chronological one; an unhealthy lifestyle (i.e., stress, malnutrition, exposure to toxic substances, drugs, inactivity) can accelerate the age of our cells leading to an increased risk of diseases (10). It is possible to measure the acceleration of aging through epigenetic biomarkers, such as variations in DNA methylation in specific regions of our genome, that can also be monitored in white blood cells. DNA methylation consists of the addition of a methyl group to carbon 5 of cytosine (C) located near guanine (G), known as a CpG island; the methylation of CpG sites represents an epigenetic mechanism, that is "above genetics", capable of regulating gene expression without changing the nucleotide sequence (11). This mechanism can promote or reduce the amount of gene expression depending on the area in which the methylation is carried out.

It has been observed that of the over 20 million methylation sites on the human genome, there are several thousand in which the methylation levels are closely related to age; in particular, it is observed that with increasing aging each subject presents, in some positions of the genome, an increase (40%) in the methylation of CpG islands and other ones a decrease (60%) in their methylation. About a quarter of these CpGs are glucocorticoid-responsive elements, indicating a correlation between stress and accelerated aging. The measure of the change in the DNA methylation, "sensitive" to aging, has been used by researchers to build epigenetic clocks capable of evaluating the impact that environmental factors and lifestyle have on our biological aging process. However, other environmental factors like stress, nutrition, environment, drugs, etc., can promote acceleration/deceleration of biological age that can be quantified by specific epigenetic clocks. The first epigenetic clocks were developed by Horvath and Hannum in 2013, using 353 and 71 CpGs on independent tissues, respectively (12). In 2018, Horvath presented another epigenetic clock based on 391 CpGs useful to evaluate the EAA, that is the measure of how much the biological age of a subject is accelerated. Levine proposed an epigenetic clock (PhenoAge) on 513 CpGs able to predict the phenotypic age and the risks associated with mortality; PhenoAge reveals that education, income, physical exercise,

optimal fruit/vegetable consumption and HDL cholesterol are negatively associated with DNA methylation PhenoAge (i.e., a younger epigenetic age) (12). In contrast, C-reactive protein, insulin, glucose, triglyceride levels, body mass index, waist-hip ratio, systolic blood pressure, and smoking have a positive association with DNA methylation PhenoAge. Similarly, Topart *et al.* highlight in their elegant paper that Horvath in 2019 identified a novel epigenetic clock based on 1,030 CpGs that can quantify EAA by comparing biological age and chronological age (12); this clock can predict lifespan but also provide information on the risks of age-related conditions such as coronary heart disease, in relation to a specific lifestyle (12). McEwen identified an epigenetic clock on buccal mucosa cells for newborns, based on 35 CpGs, useful for quantifying the acceleration of biological age in newborns born from mothers at an advanced age and/or in whom an autistic syndrome subsequently developed (12). The key point is that many other epigenetic clocks (more than 50) have been developed to have more precise clocks and, when possible, with a smaller number of CpGs, able to identify the impact of a specific environmental factor on DNA methylation, maintaining the reliability of those with a high number of CpGs. This approach aims to facilitate the translation between research and clinical practice for an easy quantification of specific cues influencing biological age; by evaluation of these epigenetic biomarkers, it is possible to quantify in peripheral white blood cells how a selected factor (i.e., stress, food) can impact our methylome.

Early life stress and epigenetic inheritance

The first 1,000 days of life, represented by the nine months of pregnancy plus the first two years of postnatal life, represent the window of maximum epigenetic plasticity during which adult health is programmed; in this period, the lifestyle and environment in which the mother lives are crucial for the health of the child. Food, stress, smoking, drugs, birth modality and breastfeeding are the factors that can modulate the epigenome and regulate the expression of genes; the mother's stress (experienced during her childhood or in adulthood) has consequences on the epigenome of the child and can also impact that of the offspring through intergenerational epigenetic inheritance of these biomarkers. Furthermore, since epigenetic biomarkers can be acquired across all life when they occur during fertilize period of life can also be transmitted to progenies by epigenetic inheritance.

Epigenetic inheritance can occur following exposure to various risk factors; permanent experience of social stress can modulate the activity of DNMTs and TET proteins, modifying the methylation level. This change can be maintained in somatic and/or germinal cells; if the stimulus responsible for the epigenetic modification is continued, it can induce a change inherited by future generations (intergenerational effect); however, the epigenetic inheritance has also been observed without the maintenance of the risk factor responsible for the observed methylation (transgenerational effect). Moreover, DNA methylation/demethylation can also be repaired because the risk factor that has promoted the epigenetic variation disappears or due to an additional stimulus that can counterbalance the occurred change; this is known as epigenetic reversibility. Intergenerational trauma refers to the impact that traumatic events have on the health, adjustment, and well-being of subsequent generations. Early evidence supporting the concept of intergenerational transmission of trauma comes from studies exploring the impacts of the Holocaust on the children born after World War II (13). However, studies on the intergenerational transmission of Holocaust trauma have yielded varying conclusions; for example, DNA methylation changes in the children of Holocaust survivors and in the sperm of combat veterans with PTSD have been observed. Stress on mothers can also impact a child prenatally; evidence of hormonal and immune alterations during pregnancy in women who experienced childhood trauma has been measured. Intergenerational studies indicate that exposure to stress during pregnancy or early life can lead to epigenetic modifications that affect offspring, influencing their stress response and susceptibility to mental health disorders if reversibility does not occur (14). The impact of stress on the HPA Axis can induce epigenetic changes that alter the function of the HPA axis, which regulates the body's response to stress. This may contribute to increased anxiety and altered cortisol levels in future generations. Furthermore, epigenetic modifications linked to stress exposure have been associated with changes in brain function, immune response, and metabolic health, potentially increasing the risk of conditions like depression and CVD. A substantial body of research, often using animal models and human studies focusing on prenatal or early life adversity, has demonstrated a link between stress exposure and epigenetic inheritance. Genes involved in the HPA axis, the body's main stress response system, are frequently studied in this context, including

the glucocorticoid receptor gene (*NR3C1*), *FKBP5*, and 11β-hydroxysteroid dehydrogenase-2 (*HSD11B2*) (15). The serotonin transporter gene (*SLC6A4*), involved in emotional processing, is another candidate gene frequently examined. These genes show epigenetic sensitivity, particularly DNA methylation changes, in response to prenatal stress (16).

In the brain, changes in DNA methylation and demethylation leading to 5-hydroxymethylcytosine (5-hmC), are involved in neurogenesis, synaptic plasticity and response to neuronal activity (17). 5-hmC interacts with histone markers and chromatin modulating architecture, finally affecting transcriptional regulation; the interaction between 5-hmC and H3K4me3 or H3K27ac has been associated with gene activation, whereas its connection with H3K9me3 or H3K27me3 maintains gene silencing (17). Acute stress, in preclinical studies, has been linked to the development of depressive behaviour where higher 5-hmC levels in the hippocampus and lower 5-hmC in the amygdala have been measured (18). Post-traumatic and social stress have been associated with susceptibility to depression and changes in 5-hmC in mice (19). Furthermore, animal studies demonstrated that alterations in the 5-hmC at the hypothalamus can be measured in adult females affected by anxiety-like behaviour (20).

In the context of the relationship between stress and epigenetic variations, the literature reports a plethora of research; many of these concern stress in neonatal age or the first years of life. This period of life is of particular importance for the modulation of the epigenome as it is characterized by maximum epigenetic plasticity, able to optimize cellular differentiation that allows to obtain more than 300 different types of cells; these, learn the "epigenetic memory" of this differentiation that they transfer to daughter cells during replication, thus allowing the conservation of specific functions throughout life (12). It is in the first years of our life that epigenetics is most sensitive to the environment; studies on three independent cohorts of children (n>300) who have experienced severe stress (trauma) show that the *FKPB5* gene is hypomethylated in subjects who have developed depressive syndrome during their life and who also have high levels of cortisol with advancing age (21). *FKPB5* is a key gene because it modulates not only the activity of the glucocorticoid receptor in response to stress, but also other cellular processes both in the brain and in the periphery; *FKBP5* is regulated through complex interactions between environmental stress, *FKBP5* genetic variants and epigenetic modifications of glucocorticoid-sensitive genomic sites. Children who have suffered stress due to separation from their parents have lower levels of *FKBP5* methylation (21); studies on three independent cohorts show that the decrease in *FKBP5* methylation is related to age/stress and is associated with a history of myocardial infarction in two of the three independent cohorts involved in the longitudinal study (21).

Another study shows that, early life stress during neonatal age and/or pre-puberal age has been associated with release of pro-inflammatory cytokines and stress hormones; they can reach the infant via placenta or breastmilk inducing epigenetic changes which perturb neuronal development and increase the risk to develop autism spectrum disorder and psychiatric disorders like anxiety, mood and psychosis (22) Children with developmental delays have been studied to measure salivary DNA methylation biomarkers associated with inflammation before and after 12 months of internet-based parent-child interaction training program; results show a slower pace of aging and reduced DNA methylation-derived C-reactive protein among children who received the intervention (23).

Change in DNA methylation has been observed with early life adversity; an inverse association between the time spent in institutional care and lower DNA methylation at specific CpG of *FKBP5* and *SLC6A4* genes was measured in children (6 and 31 months old) with developmental delays, suggesting that changes in methylation function is one pathway through which adverse early factors are biologically embedded (24).

Among the risk factors, the COVID-19 pandemic has added a new layer of complexity to prenatal stress experiences and has been linked to epigenetic changes. For instance, studies have investigated the epigenetic signatures of the COVID-19 pandemic lockdown in mothers and infants; findings suggest that maternal exposure to the lockdown during pregnancy was associated with altered methylation patterns in stress-related genes (*NR3C1* and *SLC6A4*) in both mothers and their newborns (25).

The timing of this prenatal exposure to the COVID-19 lockdown appeared to be significant, with greater epigenetic sensitivity observed when the exposure occurred during the second and third trimesters of pregnancy compared to the first. This highlights that major stressful events, like the pandemic, provide opportunities to study the timing effects of adversity on epigenetic regulation. Beyond prenatal exposure, the pandemic's widespread impact and associated stressors are likely to have broader implications for epigenetic regulation in affected individuals across different contexts, though the provided sources focus heavily on the

prenatal link (26).

Maternal stress and epigenetic inheritance

Maternal stress during pregnancy can affect the health of children and of the subsequent generations; sources of stress include malnutrition, alcohol consumption, smoking, exposure to polychlorinated biphenyls, chronic psychosocial stress (e.g., psychiatric disorder, caring for terminally ill relatives or being exposed to domestic violence or living in a war zone), low socioeconomic status and acute traumatic stress (e.g., natural disasters, terrorism or genocide), which can cause the development of PTSD. Common mechanisms are involved in maternal and childhood stress response; maternal and child stress-induced cortisol release, which alters gene expression of important regulators of neurogenesis, synaptogenesis and neuronal health in adulthood. A recent meta-analysis shows an association between maternal prenatal stress and methylation of the *NR3C1* (27). Chronic stress and war trauma alter methylation of HPA axis genes, with significant effects observed at transcription factor binding sites in all target genes tested; in particular, DNA methylation changes have been reported in neonatal cord blood and placenta among the *CRH*, *CRHBP*, *NR3C1* and *FKBP5* genes. Following prenatal exposure to traumatic stress (i.e., war-related), associations differed across tissues and were weaker for chronic stress than trauma and were associated with birth weight changes (28). Low birth weight correlated with different methylation of genes involved in HPA regulation has been observed; in this regard, it is worth mentioning the Baker's study that associates low birth weight with an increased incidence of death from CVD in both males and females (29).

Hjord *et al.* show that severe maternal stress (i.e., sexual violence/torture during the Kosovo war) influences the risk of PTSD during pregnancy in 72% of women, as well as an increase in cortisol levels in their children, where a change in methylation of genes involved in HPA regulation has been measured (30).

Considering that epigenetic biomarkers can be inherited from the mother, the father and even from grandparents, it has been observed that male children born from mothers who suffered childhood abuse showed an increased expression of brain-derived neurotrophic factor (BDNF); furthermore, maternal fear during the mother's life resulting from a trauma experienced, has been associated with a variation in DNA methylation in the BDNF gene with consequent difference of its gene expression in children (31). Maternal stress-induced cortisol release alters BDNF gene expression, an important regulator of neurogenesis and synaptogenesis.

Maternal exposure to traumatic events during childhood, maternal distress during pregnancy (i.e., depressive symptoms, anxiety symptoms, and exposure to childhood trauma) have been associated with alterations in the development of focused attention in childhood and with infants' decreased attention to audiovisual stimuli at 6, 10, and 18 months of age (32).

Sosnowsky *et al.* show an association between maternal adverse childhood experiences (ACEs), restless sleep during pregnancy, and accelerated childhood epigenetic age; only infants whose mothers reported exposure to both ACEs (during the second trimester of pregnancy) and restless sleep demonstrated accelerated epigenetic aging at 7, 9, and 14 years of age (33).

Luo *et al.*, in a study of 4,243 mother-child dyads in Chengdu, China, show that mothers who have ≥2 adverse experiences during their childhood (e.g., physical or emotional abuse, physical or emotional neglect, witnessing domestic violence, substance abuse in the family, mental illness in the family, incarcerated family member, parental separation or divorce, parental death, bullying and community violence), have children with a significantly increased risk of behavioural problems (e.g., conduct problems, learning problems, psychosomatic problems, impulsivity-hyperactivity, anxiety and hyperactivity) (34).

COVID-19 work-related stress and impact on health

The COVID-19 pandemic had a significant and widespread impact on the daily lives of individuals, causing high levels of distress in various adult populations. It has been described as having the potential of being considered a mass traumatic event due to its global scope and impact on all aspects of society, exacerbated by public exposure to information via the internet and social media. The pandemic starkly highlighted and intensified challenges, leading to a surge of burnout and stress across various professions and the general population. The relationship between COVID-19 and stress is significant, as the pandemic has triggered widespread psychological distress. Studies indicate that COVID-19-related stress has led to increased anxiety, depression, and social isolation (35). The World Health Organization reported a 25% rise in anxiety

and depression worldwide due to the pandemic. Factors such as fear of infection, financial instability, and disruptions in daily life contributed to heightened stress levels. Additionally, research suggests that uncertainty and poor sleep quality exacerbate test anxiety among students (36). The COVID-19 pandemic significantly increased and highlighted various forms of stress across different populations, including healthcare professionals, remote workers, working parents, and university students (37). This stress stemmed from factors like high workloads, fear of contagion, lack of resources, moral dilemmas, work-family conflict, social isolation, and financial instability (38).

Furthermore, the COVID-19 pandemic had a significant impact and exacerbated pre-existing stress and burnout in various professional groups. This stress manifested across different contexts, including healthcare settings, academia, and remote work environments. Factors contributing to work-related stress during the pandemic are the sources describe several pandemic-specific factors that contributed to or intensified work-related stress for particular groups; thus, healthcare professionals, were notably vulnerable subjects where factors like high workloads and staff shortages, fear of contagion, lack of resources, moral injury and ethical dilemmas, insufficient communication and support, redeployment to unfamiliar units, especially intensive care units, violence at work, stigma and alienation.

On the other end, a relationship between COVID-19 and epigenetics is an emerging area of research; studies suggest that epigenetic mechanisms, such as DNA methylation and histone modifications, play a role in how the body responds to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Some key findings include epigenetic markers of disease severity, impact on immune response, long-term effects and therapeutic potential. Research has identified specific epigenetic signatures that can predict the severity of COVID-19 outcomes; these markers may help in early diagnosis and personalized treatment strategies (39). Furthermore, epigenetic changes influence immune system function, potentially affecting how individuals respond to the virus and vaccines. This could explain variations in disease progression among patients (40). On the other hand, COVID-19 may induce epigenetic modifications that persist beyond the infection, potentially contributing to long COVID or increased susceptibility to other diseases (41). Finally, understanding epigenetic alterations in COVID-19 patients could lead to new treatments, including epigenetic drugs that modulate gene expression to improve recovery (40).

Even in adulthood, we can influence the responses of our methylome following stress; the pregnant woman and/or mother, and at the same time, workers can be subjected to multiple stressors that can impact her health and that of her child. Research conducted on healthcare workers during the COVID-19 period is a clear example. Pappa *et al.* in their meta-analysis of healthcare workers show that at least one in five healthcare workers report symptoms of depression and anxiety, and four in ten healthcare workers suffer from difficulty sleeping and/or insomnia (42).

Rates of anxiety and depression are higher among female healthcare workers and nurses. In a meta-analysis, Batra *et al.* identified in a sample of 79,437 participants the overall prevalence of anxiety, depression, stress, post-traumatic stress syndrome, insomnia, psychological distress, and burnout of 34.4%, 31.8%, 40.3%, 11.4%, 27.8%, 46.1% and 37.4%, respectively (43). Subgroup analysis indicated a higher prevalence of anxiety and depression among women, nurses and frontline healthcare workers compared to men, physicians and second-line healthcare workers (43).

In another meta-analysis, involving 18,935 nurses, during the COVID period, Galanis *et al.* show that the overall prevalence of emotional exhaustion among staff is 34.1%, depersonalization is 12.6%, and lack of personal accomplishment is 15.2% (44).

In a study of 448 Jordanian nurses (73% women), the majority (64%) suffered from ASD due to stressful conditions during the COVID-19 pandemic and are therefore at risk for PTSD. Over a third of nurses (41%) also suffered from significant psychological distress; younger nurses were more likely to experience psychological distress than older ones (45).

In the cross-sectional observational study conducted 2 months after the lockdown in Argentina on physicians, Appiani *et al.* identified that the prevalence of stress was 93.7%, burnout syndrome 73.5%, anxiety 44%, and depression 21.9%. No association was observed between attendance and medical specialty, while with respect to gender, the frequency of burnout syndrome, anxiety, and depression was significantly higher among residents and physicians working in the emergency department (46).

In another cross-sectional study managed in intensive care and emergency room nurses in 26 public hospitals in Madrid, during the COVID-19 period, 37.5% of staff reported working with the fear of being infected and its consequences, 28.2% described high workloads, inadequate patient-to-nurse ratios, and shifts that did not allow them to disconnect or rest, while taking on greater responsibilities in

the management of COVID-19 patients (23.9%). They also reported deficiencies in communication with management (middle management) (21.2%), inability to provide psychosocial care to patients and families, being emotionally exhausted (53.5%), and having difficulty venting emotions (44.9%) (47).

Resources, measures, and information can be a protective factor to address psychosocial risks of staff, especially during a pandemic; studying the relationships between psychosocial risk and perception of a health emergency is essential to protect and care for nurses, health professionals, and society. In a study during the COVID-19 pandemic, among 92 nurses from two public hospitals in the Valencian Community-Spain (74 women, 79.1%), aged 24 to 63 years [mean (M) =43.37, standard deviation (SD) =11.58] and 325 graduate nurses from the Philippines, resilient nurses and those who perceived greater organizational and social support developed less anxiety related to COVID-19 (48,49).

One key point is to evaluate if work related stress can impact health longer in life; studies on 600,000 men and women from 27 cohort studies in Europe, USA and Japan suggest that work stressors, such as job strain and long working hours, are associated with a moderately elevated risk of CVD and stroke (50). A prospective analysis of 5,651 healthy participants aged 50 years and older, followed for 13 years, assessed the impact of work stress on the incidence of CVD. The results showed that high physical demands [hazard ratio (HR), 1.30] and low reward (HR, 1.19) compared with their counterparts, as well as active physical jobs (HR, 1.41) and high physical effort (HR, 1.45) compared with low physical effort were associated with a higher risk of CVD (51).

A key point is represented by the hours of work; long working hours (>55 hours/week) have been associated with an increased risk of chronic diseases such as stroke or breast cancer; overwork is a risk factor that can reduce hours of sleep and difficulty falling asleep (52).

Stress can induce acceleration of biological age; a study on a Finnish court showed that the association between work stress, effort-reward imbalance and accelerated epigenetic age is about two years (53).

Overall, these studies highlight how work-related stress can be associated with health perturbation as well as an increased risk for health; however, it is not clear yet if it can be identified a gender impact of stress. The data collected is not well defined, in males and females, the impact of stress induced by COVID-19, because outcomes currently available do not permit to have a clear difference.

Conclusions

In conclusion, stress is a key risk factor able to perturb epigenetic mechanisms. Experimental outcomes on early life stress suggest that epigenetic mechanisms, like DNA methylation/demethylation state, are key players in mediating the long-term effects of stress on brain development and vulnerability to neuropsychiatric disorders. Epigenetic alterations induced by stress can influence gene expression and may contribute to altered physiological outcomes, such as stress reactivity and increased risk for psychiatric conditions. For example, changes in *NR3C1* methylation have been linked to altered stress regulation and poorer neurodevelopmental outcomes.

Individual responses to stress vary according to the period and the frequency of exposure; early life trauma, maternal trauma, as well as the long working hours, reduce sleep hours and increase the risk of chronic diseases such as CVD, stroke, and breast cancer. Data from the COVID-19 period has highlighted significant stress-related consequences in women and young healthcare workers. The COVID-19 pandemic was a major catalyst for stress in adults, driven by a multitude of interconnected factors across work, health, and social domains, leading to significant psychological, physical, behavioural and professional/relational consequences. COVID-19 has been associated with various epigenetic changes that could accelerate aging and impact long-term health outcomes; understanding the correlation between stress and epigenetics is crucial for developing effective interventions to support adult well-being during and after such crises.

Strategies to prevent or counterbalance early and maternal stress, maybe associated with the education process, as well as for stress-associated work, scheduling work hours with breaks (e.g., every four hours) can be useful, because this approach could improve physical and emotional well-being.

Guidelines for training and clinical practice with clear and precise instructions can be helpful for some healthcare personnel (e.g., nurses), as well as interventions aimed at providing greater organization and social support can help to manage stress.

The strength of this review is its selected focus on social stress and the key correlation with epigenetics in early life and adulthood; the knowledge on what, when, and how social stress can impact health could help to develop

protective strategies to prevent stress-related diseases.

Limitations in this narrative review are related to the ineffectiveness in identifying the selected impact of the social stress in humans due to the confluence of multiple factors and to individual response associated with genetic variability, which limits the analysis of the consequences of trauma. Another limit is related to the sample collection: DNA methylation is cell/tissue/organ specific, while the main data acquired to develop epigenetic clocks come from white blood cells, so they give indirect information on the methylome (only studies on cancer cells permit an ethical isolation of cells from a specific organ). Another limit related to the use of epigenetic biomarkers as a diagnostic tool is that it is necessary to consider that they are currently used only within research studies, due to the high costs associated with their analysis. Finally, this review considered social stress mainly in women (due to the female role in pregnancy) and does not consider the epigenetic inheritance of social stress in men during their fertile period of life, which, by sperm microRNAs (miRNAs), can contribute to epigenetic inheritance.

Future research needs to screen which individual factors contribute to promoting stress-induce disease to explain why and how the same risk factor (stress) impacts differently each subject.

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None.

Footnote

Reporting Checklist: The author has completed the Narrative Review reporting checklist. Available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-25-4/rc

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Schiele MA, Domschke K. Epigenetics at the crossroads between genes, environment and resilience in anxiety disorders. Genes Brain Behav 2018;17:e12423.
2. Agorastos A, Chrousos GP. The neuroendocrinology of stress: the stress-related continuum of chronic disease development. Mol Psychiatry 2022;27:502-13.
3. Lightman SL, Birnie MT, Conway-Campbell BL. Dynamics of ACTH and Cortisol Secretion and Implications for Disease. Endocr Rev 2020;41:bnaa002.
4. Hewagalamulage SD, Lee TK, Clarke IJ, et al. Stress, cortisol, and obesity: a role for cortisol responsiveness in identifying individuals prone to obesity. Domest Anim Endocrinol 2016;56 Suppl:S112-20.
5. Sundas A, Contreras I, Mujahid O, et al. The Effects of Environmental Factors on General Human Health: A Scoping Review. Healthcare (Basel) 2024;12:2123.
6. Wu Z, Qu J, Zhang W, et al. Stress, epigenetics, and aging: Unraveling the intricate crosstalk. Mol Cell 2024;84:34-54.
7. Zannas AS. Epigenetics as a key link between psychosocial stress and aging: concepts, evidence, mechanisms. Dialogues Clin Neurosci 2019;21:389-96.
8. López-Otín C, Blasco MA, Partridge L, et al. Hallmarks of aging: An expanding universe. Cell 2023;186:243-78.
9. Belsky DW, Caspi A, Corcoran DL, et al. DunedinPACE, a DNA methylation biomarker of the pace of aging. Elife 2022;11:e73420.
10. Duan R, Fu Q, Sun Y, et al. Epigenetic clock: A promising biomarker and practical tool in aging. Ageing Res Rev 2022;81:101743.
11. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet 2003;33 Suppl:245-54.

12. Topart C, Werner E, Arimondo PB. Wandering along the epigenetic timeline. Clin Epigenetics 2020;12:97.
13. Papakonstantinou E, Efthimiou V, Chrousos GP, et al. Genetics and epigenetics of the war child. Int J Epigen 2024;4:2.
14. Nagata DK, Kim JHJ, Gone JP. Intergenerational Transmission of Ethnoracial Historical Trauma in the United States. Annu Rev Clin Psychol 2024;20:175-200.
15. Bakusic J, Ghosh M, Polli A, et al. Role of NR3C1 and SLC6A4 methylation in the HPA axis regulation in burnout. J Affect Disord 2021;295:505-12.
16. Azar N, Booij L. DNA methylation as a mediator in the association between prenatal maternal stress and child mental health outcomes: Current state of knowledge. J Affect Disord 2022;319:142-63.
17. Kang AK, Dhawan U, Mallick BN. Association between epigenetic mark 5-hydroxymethylcytosine and brain pathophysiology. Brain Res 2025. [Epub ahead of print]. doi: 10.1016/j.brainres.2025.149755.
18. Doherty TS, Forster A, Roth TL. Global and gene-specific DNA methylation alterations in the adolescent amygdala and hippocampus in an animal model of caregiver maltreatment. Behav Brain Res 2016;298:55-61.
19. Kuehner JN, Walia NR, Seong R, et al. Social defeat stress induces genome-wide 5mC and 5hmC alterations in the mouse brain. G3: Genes, Genomes, Genetics 2023;13:jkad114.
20. Papale LA, Madrid A, Li S, et al. Early-life stress links 5-hydroxymethylcytosine to anxiety-related behaviors. Epigenetics 2017;12:264-76.
21. Zannas AS, Jia M, Hafner K, et al. Epigenetic upregulation of FKBP5 by aging and stress contributes to NF-κB-driven inflammation and cardiovascular risk. Proc Natl Acad Sci U S A 2019;116:11370-9.
22. Han VX, Patel S, Jones HF, et al. Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. Nat Rev Neurol 2021;17:564-79.
23. Merrill SM, Hogan C, Bozack AK, et al. Telehealth Parenting Program and Salivary Epigenetic Biomarkers in Preschool Children With Developmental Delay: NIMHD Social Epigenomics Program. JAMA Netw Open 2024;7:e2424815.
24. Non AL, Hollister BM, Humphreys KL, et al. DNA methylation at stress-related genes is associated with exposure to early life institutionalization. Am J Phys Anthropol 2016;161:84-93.
25. Nazzari S, Grumi S, Mambretti F, et al. Maternal and infant NR3C1 and SLC6A4 epigenetic signatures of the COVID-19 pandemic lockdown: when timing matters. Transl Psychiatry 2022;12:386.
26. Kundakovic M, Jaric I. The Epigenetic Link between Prenatal Adverse Environments and Neurodevelopmental Disorders. Genes (Basel) 2017;8:104.
27. Palma-Gudiel H, Córdova-Palomera A, Eixarch E, et al. Maternal psychosocial stress during pregnancy alters the epigenetic signature of the glucocorticoid receptor gene promoter in their offspring: a meta-analysis. Epigenetics 2015;10:893-902.
28. Kertes DA, Kamin HS, Hughes DA, et al. Prenatal Maternal Stress Predicts Methylation of Genes Regulating the Hypothalamic-Pituitary-Adrenocortical System in Mothers and Newborns in the Democratic Republic of Congo. Child Dev 2016;87:61-72.
29. Barker DJ. The developmental origins of adult disease. J Am Coll Nutr 2004;23:588S-95S.
30. Hjort L, Rushiti F, Wang SJ, et al. Intergenerational effects of maternal post-traumatic stress disorder on offspring epigenetic patterns and cortisol levels. Epigenomics 2021;13:967-80.
31. Pilkay SR, Combs-Orme T, Tylavsky F, et al. Maternal trauma and fear history predict BDNF methylation and gene expression in newborns. PeerJ 2020;8:e8858.
32. Tu HF, Skalkidou A, Lindskog M, et al. Maternal childhood trauma and perinatal distress are related to infants' focused attention from 6 to 18 months. Sci Rep 2021;11:24190.
33. Sosnowski DW, Rojo-Wissar DM, Peng G, et al. Maternal Childhood Adversity and Infant Epigenetic Aging: Moderation by Restless Sleep During Pregnancy. Dev Psychobiol 2024;66:e22464.
34. Luo S, Chen D, Li C, et al. Maternal adverse childhood experiences and behavioral problems in preschool offspring: the mediation role of parenting styles. Child Adolesc Psychiatry Ment Health 2023;17:95.
35. Wang C, Havewala M, Fan Q, et al. The relations between COVID-19 stress, social connectedness, and mental health: a longitudinal investigation comparing Chinese and American college students. Curr Psychol 2023. [Epub ahead of print]. doi: 10.1007/s12144-023-04290-0.
36. Liu R, Qiu Q, Ye B. The relationship between COVID-19 stress and test anxiety in art students: the chain mediating roles of intolerance of uncertainty and sleep quality. BMC Public Health 2024;24:1163.
37. Tang YL, Raffone A, Wong SYS. Burnout and stress: new insights and interventions. Sci Rep 2025;15:8335.

38. Eugene D, Nöthling J, Tarsitani L, et al. Mental health during the Covid-19 pandemic: An international comparison of gender-related home and work-related responsibilities, and social support. Arch Womens Ment Health 2025;28:359-74.
39. Calzari L, Zanotti L, Inglese E, et al. Role of epigenetics in the clinical evolution of COVID-19 disease. Epigenome-wide association study identifies markers of severe outcome. Eur J Med Res 2023;28:81.
40. Atlante S, Mongelli A, Barbi V, et al. The epigenetic implication in coronavirus infection and therapy. Clin Epigenetics 2020;12:156.
41. Naik N, Patel M, Sen R. Developmental Impacts of Epigenetics and Metabolism in COVID-19. J Dev Biol 2024;12:9.
42. Pappa S, Ntella V, Giannakas T, et al. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis. Brain Behav Immun 2020;88:901-7.
43. Batra K, Singh TP, Sharma M, et al. Investigating the Psychological Impact of COVID-19 among Healthcare Workers: A Meta-Analysis. Int J Environ Res Public Health 2020;17:9096.
44. Galanis P, Vraka I, Fragkou D, et al. Nurses' burnout and associated risk factors during the COVID-19 pandemic: A systematic review and meta-analysis. J Adv Nurs 2021;77:3286-302.
45. Shahrour G, Dardas LA. Acute stress disorder, coping self-efficacy and subsequent psychological distress among nurses amid COVID-19. J Nurs Manag 2020;28:1686-95.
46. Appiani FJ, Rodríguez Cairoli F, Sarotto L, et al. Prevalence of stress, burnout syndrome, anxiety and depression among physicians of a teaching hospital during the COVID-19 pandemic. Arch Argent Pediatr 2021;119:317-24.
47. González-Gil MT, González-Blázquez C, Parro-Moreno AI, et al. Nurses' perceptions and demands regarding COVID-19 care delivery in critical care units and hospital emergency services. Intensive Crit Care Nurs 2021;62:102966.
48. Giménez-Espert MDC, Prado-Gascó V, Soto-Rubio A. Psychosocial Risks, Work Engagement, and Job Satisfaction of Nurses During COVID-19 Pandemic. Front Public Health 2020;8:566896.
49. Labrague LJ, De Los Santos JAA. COVID-19 anxiety among front-line nurses: Predictive role of organisational support, personal resilience and social support. J Nurs Manag 2020;28:1653-61.
50. Kivimäki M, Kawachi I. Work Stress as a Risk Factor for Cardiovascular Disease. Curr Cardiol Rep 2015;17:630.
51. Feng MY, Wang HX, Zhuo LB, et al. Work-Related Stress and Occurrence of Cardiovascular Disease: A 13-Year Prospective Study. J Occup Environ Med 2022;64:927-33.
52. Protsenko E, Wolkowitz OM, Yaffe K. Associations of stress and stress-related psychiatric disorders with GrimAge acceleration: review and suggestions for future work. Transl Psychiatry 2023;13:142.
53. Freni-Sterrantino A, Fiorito G, D'Errico A, et al. Work-related stress and well-being in association with epigenetic age acceleration: A Northern Finland Birth Cohort 1966 Study. Aging (Albany NY) 2022;14:1128-56.

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