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Epigenetic Signatures of Psychosocial Stress in Neurodegenerative Disease Progression Among Type 2 Diabetes Patients in Sub-Saharan Africa

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Abstract: Psychosocial stress is increasingly recognized as a critical modifier of neurodegenerative disease progression, yet its molecular underpinnings in African populations remain underexplored. This study investigates the relationship between chronic stress exposure and epigenetic modifications associated with neurodegeneration among individuals living with type 2 diabetes. Using a cohort derived from outpatient clinics in Kumasi, Ghana, participants were assessed for perceived stress, dietary patterns, and clinical biomarkers including glycemic status and lipid profiles. Blood samples were analyzed to identify DNA methylation patterns and histone modification markers linked to neuroinflammatory and neurodegenerative pathways. Statistical modeling was performed to evaluate associations between stress indices and epigenetic alterations while controlling for metabolic and demographic variables. Findings reveal that elevated psychosocial stress correlates with distinct epigenetic signatures, particularly in genes associated with neuronal survival, inflammation, and metabolic regulation. These modifications were more pronounced in individuals with poor glycemic control, suggesting a synergistic interaction between metabolic dysfunction and stress-induced epigenetic regulation. The study highlights the role of stress as a biologically embedded risk factor influencing neurodegenerative trajectories and underscores the need for integrated clinical approaches that incorporate mental health, metabolic care, and molecular diagnostics. This work contributes to a growing body of evidence supporting the inclusion of epigenetic biomarkers in understanding disease progression and tailoring interventions in diverse populations.

Keywords: *Psychosocial Stress, Epigenetic Modifications, Type 2 Diabetes, Neurodegenerative Disease Progression, DNA Methylation.*

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I. INTRODUCTION

➢ *Background of the Study*

Type 2 Diabetes (T2D) represents a growing public health crisis globally, with Sub-Saharan Africa (SSA) experiencing one of the fastest increases in prevalence. According to the International Diabetes Federation (IDF), the number of adults living with diabetes in Africa is projected to more than double by 2045, driven by rapid urbanization, demographic transitions, sedentary lifestyles, and nutritional changes [1]. Historically dominated by infectious diseases, health systems in SSA are increasingly challenged by non-communicable diseases, including diabetes and its long-term complications. In Ghana and across the region, limited access to early diagnosis and sustained glycaemic control further compounds the burden, increasing the risk of systemic complications and long-term disability.

Beyond its well-known microvascular and macrovascular complications, T2D is now recognized as a significant risk factor for cognitive decline and neurodegenerative diseases. Epidemiological studies consistently demonstrate that individuals with T2D have an elevated risk of developing Alzheimer's disease and other forms of dementia [2,3]. Chronic hyperglycaemia, insulin resistance, oxidative stress, and vascular dysfunction contribute to neuronal injury and impaired synaptic plasticity. Insulin signaling plays a critical role in amyloid-beta metabolism and neuronal survival, and disruptions in this pathway are implicated in neurodegenerative pathology [4].

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Moreover, T2D is associated with chronic low-grade systemic inflammation, which further exacerbates neuroinflammatory processes central to dementia progression [3]. These interrelated mechanisms suggest that metabolic dysfunction may accelerate neurodegenerative trajectories, particularly in settings where glycaemic control is suboptimal.

Psychosocial stress is increasingly recognized as an important environmental determinant of both metabolic and neurological health. Chronic stress activates the hypothalamic–pituitary–adrenal (HPA) axis, leading to sustained cortisol secretion and downstream inflammatory responses [5]. Prolonged exposure to elevated glucocorticoids has been associated with hippocampal atrophy, impaired neurogenesis, and cognitive dysfunction [6]. In individuals with T2D, stress may worsen glycaemic control through behavioural pathways (e.g., diet, medication adherence) and physiological mechanisms involving cortisol-mediated insulin resistance [7]. In SSA, socioeconomic instability, rapid urbanization, and healthcare access challenges contribute to sustained psychosocial stress, potentially intensifying the biological burden among individuals managing chronic diseases. Despite this, stress assessment remains insufficiently integrated into routine diabetes care in many African contexts.

Epigenetic mechanisms provide a plausible biological interface linking chronic psychosocial stress to neurodegenerative progression in T2D. Epigenetics refers to heritable but reversible modifications in gene expression that occur without changes in DNA sequence, including DNA methylation and histone modifications [8]. Environmental exposures such as psychological stress have been shown to influence DNA methylation patterns in genes involved in glucocorticoid signaling and inflammatory regulation [9]. Emerging evidence further suggests that epigenetic dysregulation contributes to the pathogenesis of both T2D and neurodegenerative diseases [10,11]. For example, altered DNA methylation profiles have been observed in genes implicated in insulin signaling, inflammatory pathways, and neuronal survival [10,11]. However, most epigenetic studies have been conducted in European and North American populations, with African populations markedly underrepresented in genomic and epigenomic research [12].

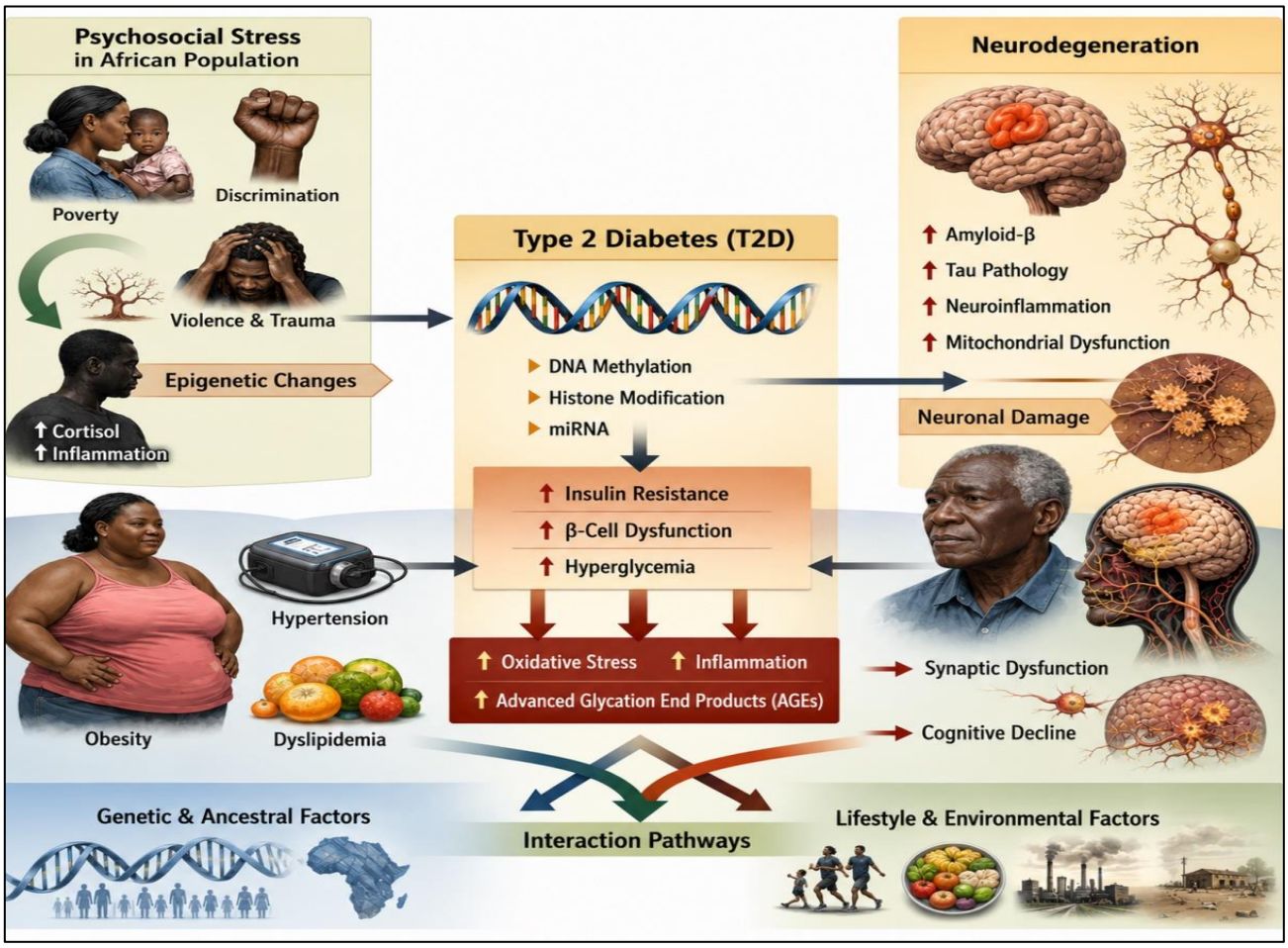

Fig 1 Conceptual Framework of Stress-Induced Epigenetic Mechanisms in T2D-Associated Cognitive Decline.

Given the rising prevalence of T2D in SSA and the emerging recognition of stress-related biological embedding, investigating epigenetic signatures associated with psychosocial stress in African populations is both timely and necessary. Understanding how chronic stress interacts with metabolic dysfunction at the molecular level may illuminate novel biomarkers of neurodegenerative risk and inform integrated interventions that address both metabolic and

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mental health dimensions of care. This study therefore seeks to explore the epigenetic correlates of psychosocial stress among individuals living with T2D in Kumasi, Ghana, contributing to a more globally representative understanding of neurodegenerative disease progression.

➢ *Problem Statement*

The rising prevalence of T2D in Sub-Saharan Africa is accompanied by an increasing burden of cognitive decline and neurodegenerative diseases. Although T2D is known to elevate dementia risk, the mechanisms linking metabolic dysfunction to neurodegeneration remain insufficiently understood. Emerging evidence suggests that chronic psychosocial stress common in rapidly urbanizing African settings may exacerbate metabolic dysregulation and accelerate neurodegenerative processes. However, the biological pathways through which stress interacts with T2D to influence brain health have not been adequately characterized in African populations.

Epigenetic mechanisms, including DNA methylation and histone modifications, provide a plausible molecular link between environmental stressors and gene expression changes involved in inflammation, neuronal survival, and metabolic regulation. While studies in Western populations demonstrate stress-related epigenetic alterations associated with neurodegeneration, African populations remain markedly underrepresented in epigenomic research. Given the region's unique genetic diversity and sociocultural stress exposures, population-specific data are essential.

Therefore, there is a critical need to investigate stress-associated epigenetic signatures among individuals with T2D in Sub-Saharan Africa to better understand neurodegenerative risk and inform contextually relevant prevention and intervention strategies.

➢ *Aim of the Study*

The primary aim of this study is to investigate the association between chronic psychosocial stress and epigenetic modifications implicated in neurodegenerative disease progression among individuals living with T2D in Kumasi, Ghana. Specifically, the study seeks to examine how stress-related biological responses interact with metabolic dysfunction to influence epigenetic regulation of genes involved in neuroinflammatory, metabolic, and neuronal survival pathways.

➢ *Specific Objectives*

- To assess the levels of psychosocial stress among individuals diagnosed with Type 2 Diabetes using validated stress measurement tools.
- To identify DNA methylation patterns and histone modification markers associated with neurodegenerative and neuroinflammatory pathways in the study population.
- To evaluate the interaction between glycemic control (e.g., HbA1c levels) and stress-related epigenetic modifications.
- To determine the associations between metabolic biomarkers (including lipid profile and fasting glucose) and identified epigenetic signatures.

➢ *Research Hypotheses*

- Individuals with elevated psychosocial stress will exhibit significant differential epigenetic modifications particularly in genes regulating neuroinflammation, glucocorticoid signaling, and neuronal survival compared to individuals with lower stress levels.
- Poor glycemic control will amplify stress-associated epigenetic alterations, resulting in more pronounced modifications in pathways linked to neurodegenerative disease progression.

➢ *Significance of the Study*

This study is significant in several respects. First, it advances understanding of the biological embedding of psychosocial stress within African populations, addressing a critical gap in global epigenetic research. By focusing on Sub-Saharan Africa, where genomic and epigenomic data remain limited, the study contributes to improving diversity and representation in molecular health research.

Second, the identification of stress-associated epigenetic signatures may support the development of novel biomarkers for early detection of neurodegenerative risk among individuals with T2D. Such biomarkers could enhance risk stratification and guide preventive strategies before the onset of clinically overt cognitive impairment.

Finally, the findings may inform integrated healthcare approaches that incorporate psychosocial stress management into diabetes care. By demonstrating the molecular interplay between stress and metabolic dysfunction, this research underscores the importance of combining mental health support, metabolic monitoring, and molecular diagnostics in comprehensive chronic disease management strategies.

II. LITERATURE REVIEW

➢ *Psychosocial Stress and Neurobiological Mechanisms*

Psychosocial stress is increasingly recognised as a significant determinant of neurological health, particularly in the context of chronic diseases such as T2D. Chronic exposure to stressors whether social, economic, occupational, or disease-related activates neuroendocrine and immune pathways that may predispose individuals to neurodegenerative processes. The biological embedding of stress occurs primarily through dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, persistent inflammatory activation, oxidative stress, and increased neuronal vulnerability. These mechanisms are interrelated and may act synergistically to accelerate cognitive decline, especially in metabolically compromised individuals.

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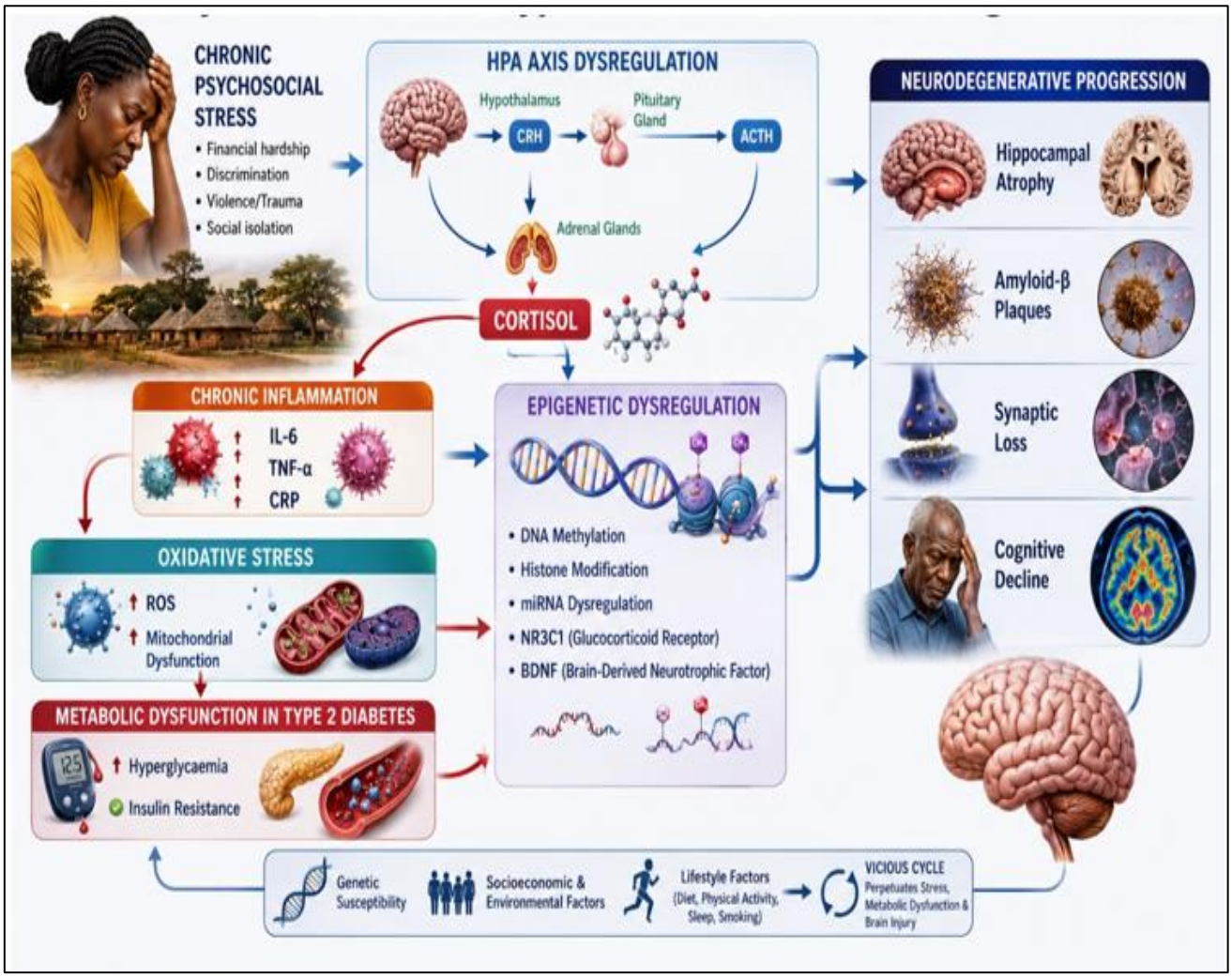

Fig 2 Proposed Mechanistic Framework Illustrating the Interaction Between Chronic Psychosocial Stress, HPA Axis Dysregulation, Inflammation, Oxidative Stress, Epigenetic Alterations, and Neurodegenerative Progression in Individuals with Type 2 Diabetes.

- *HPA Axis Dysregulation and Cortisol Effects*

The HPA axis is the central neuroendocrine system responsible for coordinating the physiological response to stress. Acute stress triggers the hypothalamus to release corticotropin-releasing hormone (CRH), stimulating the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH), which in turn promotes cortisol release from the adrenal cortex (12). Cortisol facilitates adaptive responses by mobilising glucose, modulating immune activity, and maintaining cardiovascular tone.

However, chronic psychosocial stress results in prolonged HPA axis activation and sustained cortisol exposure. Persistent hypercortisolaemia disrupts negative feedback regulation within the hippocampus, a brain region essential for memory consolidation and stress regulation (17). Structural neuroimaging studies have demonstrated that elevated cortisol levels are associated with hippocampal atrophy and reduced gray matter volume (13). These structural changes are clinically relevant, as hippocampal degeneration is a hallmark of early Alzheimer's disease.

Cortisol also influences glucose metabolism by promoting gluconeogenesis and increasing insulin resistance (15). In individuals with T2D, chronic stress-induced cortisol secretion may therefore exacerbate hyperglycaemia, creating a bidirectional cycle in which metabolic dysfunction further impairs neuronal resilience (14,16). Moreover, dysregulation of glucocorticoid receptor signaling—potentially mediated by epigenetic modifications of the NR3C1 gene has been implicated in altered stress responsiveness and increased vulnerability to stress-related disorders (20).

- *Chronic Inflammation and Oxidative Stress Pathway*

Chronic psychosocial stress contributes to sustained low-grade systemic inflammation, characterised by elevated circulating pro-inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) (5). Stress-related activation of the sympathetic nervous system and HPA axis influences immune cell function, promoting a pro-inflammatory phenotype.

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Neuroinflammation plays a critical role in the pathogenesis of neurodegenerative diseases. Activated microglia release inflammatory mediators and reactive oxygen species (ROS), contributing to neuronal injury and synaptic dysfunction (23). In Alzheimer's disease, inflammatory processes are closely linked to amyloid-beta accumulation and tau pathology (25). Chronic inflammation also disrupts blood–brain barrier integrity, further facilitating neurodegenerative cascades.

Oxidative stress represents another key pathway linking psychosocial stress to neuronal damage. Excessive production of ROS, coupled with impaired antioxidant defenses, leads to lipid peroxidation, mitochondrial dysfunction, and DNA damage. Individuals with T2D are particularly susceptible to oxidative stress due to persistent hyperglycaemia and advanced glycation end-product (AGE) formation (24). When combined with stress-induced inflammatory activation, oxidative damage may be amplified, accelerating neurodegenerative processes.

The interplay between inflammation and oxidative stress is self-reinforcing: inflammatory cytokines increase ROS production, while oxidative stress further activates inflammatory signaling pathways. This cycle contributes to progressive neuronal dysfunction and cognitive decline.

- *Stress-Related Neuronal Vulnerability*

Chronic stress affects neuronal structure and function through multiple mechanisms, including impaired neurogenesis, dendritic remodeling, and synaptic loss. Experimental and human studies indicate that prolonged exposure to glucocorticoids reduces neurogenesis in the hippocampus and alters dendritic architecture in both the hippocampus and prefrontal cortex (21). These regions are critical for executive function, emotional regulation, and memory.

Stress also influences the expression of brain-derived neurotrophic factor (BDNF), a protein essential for neuronal survival and synaptic plasticity. Reduced BDNF levels have been associated with cognitive impairment and neurodegenerative conditions. Epigenetic alterations affecting BDNF gene regulation have been reported in stress-related disorders, suggesting a molecular mechanism through which chronic stress may impair neuronal resilience (29).

Furthermore, chronic stress may exacerbate existing metabolic and vascular risk factors in T2D, thereby increasing susceptibility to ischemic injury and microvascular brain damage. The combined effects of glucocorticoid toxicity, inflammation, oxidative stress, and metabolic dysregulation create a neurobiological environment conducive to accelerated neurodegeneration.

Table 1 Summary of Key Mechanisms

Mechanism	Biological Effect	Relevance to Neurodegeneration
HPA axis dysregulation	Sustained cortisol release	Hippocampal atrophy; impaired memory (6)
Chronic inflammation	Elevated IL-6, TNF-α, CRP	Microglial activation; amyloid and tau pathology (3,11)
Oxidative stress	ROS accumulation; mitochondrial damage	Neuronal injury and synaptic dysfunction (4)
Reduced neurotrophic support	Decreased BDNF expression	Impaired neurogenesis and neuronal survival (9)

Psychosocial stress exerts profound effects on neurobiological systems through HPA axis dysregulation, inflammatory activation, oxidative damage, and impaired neurotrophic support. In individuals with T2D, these mechanisms may act synergistically with metabolic abnormalities to accelerate neurodegenerative trajectories. Understanding these interconnected pathways provides a mechanistic foundation for exploring stress-associated epigenetic modifications in this population.

➢ *Type 2 Diabetes and Neurodegeneration*

Type 2 Diabetes is increasingly recognised as an important risk factor for cognitive impairment and dementia. Epidemiological evidence demonstrates that individuals with T2D have a significantly higher risk of developing Alzheimer's disease and vascular dementia compared with non-diabetic populations (26,30). The mechanisms underlying this association are multifactorial, involving insulin resistance, chronic hyperglycaemia, vascular dysfunction, oxidative stress, and sustained inflammatory activation. These processes interact to create a neurobiological environment conducive to accelerated neurodegeneration.

- *Insulin Resistance and Cognitive Decline*

Insulin plays a critical role in central nervous system function beyond its peripheral metabolic effects. Insulin receptors are widely expressed in the hippocampus, prefrontal cortex, and other brain regions involved in learning and memory (27). In the brain, insulin facilitates synaptic plasticity, modulates neurotransmitter release, and supports neuronal survival.

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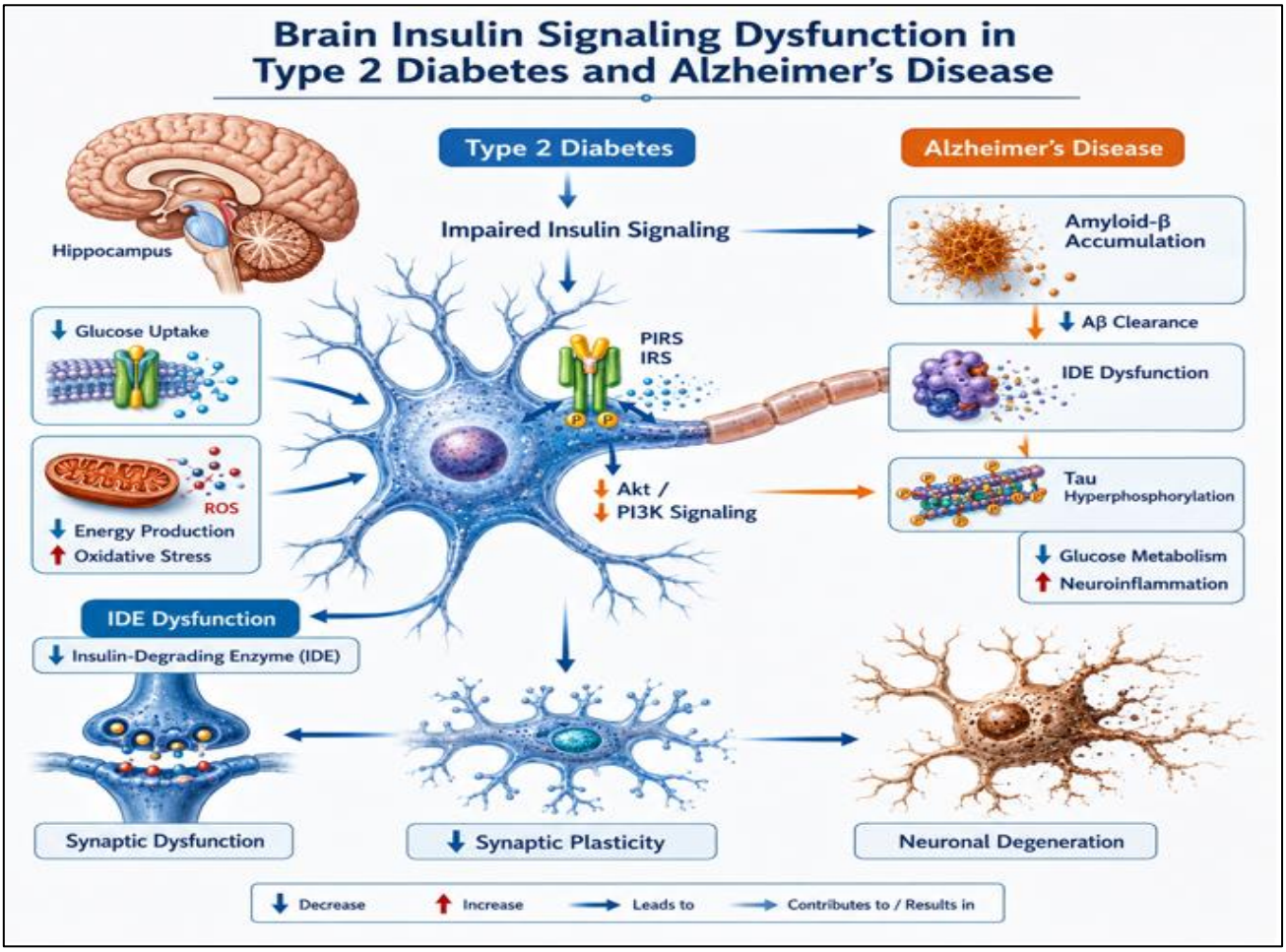

Fig 3 Brain Insulin Signaling Pathway

In T2D, systemic insulin resistance is often paralleled by impaired brain insulin signaling. This phenomenon, sometimes referred to as "brain insulin resistance," has been implicated in the pathogenesis of Alzheimer's disease (37). Disrupted insulin signaling interferes with amyloid-beta clearance and promotes tau hyperphosphorylation two pathological hallmarks of Alzheimer's disease (33,28). Insulin-degrading enzyme (IDE), which normally facilitates amyloid-beta breakdown, may be competitively inhibited in hyperinsulinaemic states, thereby promoting amyloid accumulation (34).

Clinical and longitudinal studies have shown that insulin resistance is associated with reduced cognitive performance, particularly in executive function and memory domains (42). Neuroimaging findings further reveal that individuals with T2D may exhibit reduced hippocampal volume and white matter integrity compared with non-diabetic controls (32). These structural alterations provide biological plausibility for the observed cognitive deficits.

Importantly, insulin resistance may interact with stress-related glucocorticoid exposure. Chronic cortisol elevation worsens insulin sensitivity (39), potentially compounding central insulin signaling deficits and amplifying neurodegenerative processes.

- *Hyperglycaemia and Vascular Contributions to Dementia*

Chronic hyperglycaemia is a defining feature of poorly controlled T2D and contributes significantly to neurodegenerative risk. Persistent elevated glucose levels promote the formation of advanced glycation end-products (AGEs), which accumulate in neural and vascular tissues. AGEs enhance oxidative stress and activate inflammatory pathways through binding to their receptor (RAGE), thereby contributing to endothelial dysfunction and neuronal injury (45).

Microvascular and macrovascular complications are common in T2D and are closely linked to cognitive decline. Chronic hyperglycaemia damages small cerebral vessels, leading to reduced cerebral perfusion, white matter lesions, and lacunar infarcts. These vascular changes are central to the development of vascular dementia and may also exacerbate Alzheimer's pathology through impaired clearance of neurotoxic proteins (36,40).

Furthermore, hyperglycaemia disrupts blood–brain barrier (BBB) integrity, facilitating the infiltration of inflammatory mediators into the CNS. Compromised BBB function accelerates neuroinflammation and neuronal degeneration. Epidemiological studies have consistently demonstrated that poor glycaemic control, as measured by

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elevated HbA1c levels, is associated with increased risk of cognitive impairment and dementia (35).

Thus, both metabolic and vascular mechanisms link chronic hyperglycaemia to progressive neuronal dysfunction. In resource-limited settings where optimal glycaemic control may be difficult to achieve, these mechanisms may contribute substantially to neurodegenerative burden.

- *Metabolic–Inflammatory Cross-Talk*

T2D is characterised by chronic low-grade systemic inflammation, which plays a central role in disease progression and complications. Adipose tissue dysfunction in insulin-resistant states promotes the release of pro-inflammatory cytokines such as TNF-α and IL-6, contributing to systemic insulin resistance and endothelial dysfunction (44). This inflammatory milieu extends beyond peripheral tissues and influences central nervous system processes.

Neuroinflammation is a key feature of both Alzheimer's disease and vascular dementia. Peripheral inflammatory mediators can signal across the BBB or activate endothelial and microglial cells, promoting the release of additional pro-inflammatory cytokines within the brain (31). Sustained microglial activation contributes to synaptic dysfunction, neuronal loss, and propagation of amyloid and tau pathology (41,38).

Metabolic and inflammatory pathways are tightly interconnected. Hyperglycaemia increases oxidative stress, which in turn activates nuclear factor-kappa B (NF-κB) and other transcription factors that upregulate inflammatory gene expression. Conversely, inflammatory cytokines worsen insulin resistance by interfering with insulin receptor signaling pathways (43). This bidirectional reinforcement creates a cycle of metabolic and inflammatory dysregulation.

When combined with psychosocial stress—which independently promotes HPA axis activation and inflammatory signaling (5,14)—metabolic-inflammatory cross-talk may intensify. In individuals with T2D exposed to chronic stress, the convergence of cortisol dysregulation, insulin resistance, oxidative damage, and neuroinflammation may substantially accelerate neurodegenerative trajectories.

Table 2 Mechanistic Links between T2D and Neurodegeneration

Pathophysiological Factor	Mechanism	Neurodegenerative Outcome
Insulin resistance	Impaired brain insulin signaling; reduced amyloid clearance	Cognitive decline; Alzheimer's pathology (4,11)
Chronic hyperglycaemia	AGE accumulation; oxidative stress; BBB disruption	Vascular damage; neuronal injury (2,3)
Microvascular dysfunction	Reduced cerebral perfusion; white matter lesions	Vascular dementia (2)
Chronic inflammation	Cytokine-mediated microglial activation	Synaptic dysfunction; neurodegeneration (15)

T2D contributes to neurodegeneration through interrelated mechanisms involving insulin resistance, hyperglycaemia-induced vascular injury, and chronic inflammatory activation. These processes are further amplified by oxidative stress and may interact synergistically with psychosocial stress-related neuroendocrine dysregulation. Understanding this complex metabolic–neuroinflammatory interface is essential for elucidating the pathways through which stress-associated epigenetic modifications may influence neurodegenerative progression in individuals with T2D.

➢ *Epigenetic Mechanisms in Stress and Disease*

Epigenetic mechanisms provide a dynamic interface between environmental exposures and gene expression, enabling biological systems to respond adaptively—or maladaptively—to external stimuli. Unlike genetic mutations, epigenetic modifications do not alter the DNA sequence but instead regulate gene activity through chemical modifications of DNA and histone proteins. These processes are essential for normal cellular differentiation and development; however, they are also sensitive to environmental factors, including psychosocial stress, metabolic disturbances, and inflammation (58,59). Increasing evidence indicates that epigenetic dysregulation contributes to the pathogenesis of both Type 2 Diabetes (T2D) and neurodegenerative diseases (10,11).

Chronic stress and metabolic imbalance may induce persistent epigenetic alterations in genes regulating glucocorticoid signaling, inflammatory pathways, insulin sensitivity, and neuronal survival. These modifications can result in long-term changes in gene expression, thereby embedding environmental exposures into molecular pathways relevant to disease progression.

- *DNA Methylation and Gene Expression Regulation*

DNA methylation is one of the most extensively studied epigenetic mechanisms. It involves the addition of a methyl group to cytosine residues, typically within cytosine–phosphate–guanine (CpG) dinucleotides. Increased methylation in gene promoter regions is generally associated with transcriptional repression, whereas hypomethylation may promote gene activation (8).

Psychosocial stress has been shown to influence DNA methylation patterns in genes involved in stress regulation and immune responses. One of the most widely studied examples is the glucocorticoid receptor gene (NR3C1). Altered methylation of NR3C1 has been associated with dysregulated HPA axis activity and heightened stress sensitivity (9). Such changes may impair feedback inhibition of cortisol release, leading to prolonged glucocorticoid exposure and increased neuronal vulnerability.

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In metabolic disease, epigenetic modifications have been identified in genes regulating insulin secretion and glucose metabolism. For example, differential DNA methylation has been observed in pancreatic islets of individuals with T2D, affecting genes implicated in insulin production and beta-cell function (10,56). These findings suggest that epigenetic dysregulation may contribute directly to metabolic dysfunction.

In neurodegenerative disease, altered DNA methylation has been reported in genes such as ANK1 and BIN1, which are implicated in Alzheimer's pathology (11). Such changes may influence inflammatory signaling, neuronal cytoskeletal integrity, and amyloid processing. Importantly, DNA methylation patterns are potentially reversible, highlighting their relevance as therapeutic targets and biomarkers.

- *Histone Modifications and Chromatin Remodeling*

Histone proteins package DNA into chromatin, thereby regulating its accessibility to transcriptional machinery. Post-translational modifications of histones—including acetylation, methylation, phosphorylation, and ubiquitination—alter chromatin structure and influence gene expression. Histone acetylation, for instance, is generally associated with transcriptional activation due to chromatin relaxation, whereas certain histone methylation marks may either activate or repress gene expression depending on the specific residue modified (8,54).

Chronic stress has been linked to alterations in histone acetylation and methylation patterns in brain regions involved in emotional regulation and cognition. These modifications can affect genes regulating synaptic plasticity, neurogenesis, and inflammatory signaling. Experimental models demonstrate that stress-induced changes in histone acetylation influence behavioural and cognitive outcomes, supporting the role of chromatin remodeling in stress-related neuropathology (6,55).

In metabolic disease, histone modifications contribute to inflammatory gene expression and insulin resistance. For example, inflammatory cytokine genes may become transcriptionally activated through permissive histone marks under conditions of oxidative stress and hyperglycaemia (14,49). Such epigenetic shifts may sustain chronic inflammation even after the initial metabolic insult, perpetuating disease progression.

Histone modifications are particularly relevant in neurodegenerative disorders, where altered chromatin states have been observed in affected brain regions. Dysregulated histone acetylation has been implicated in impaired memory formation and synaptic dysfunction, further linking epigenetic remodeling to cognitive decline (55,64).

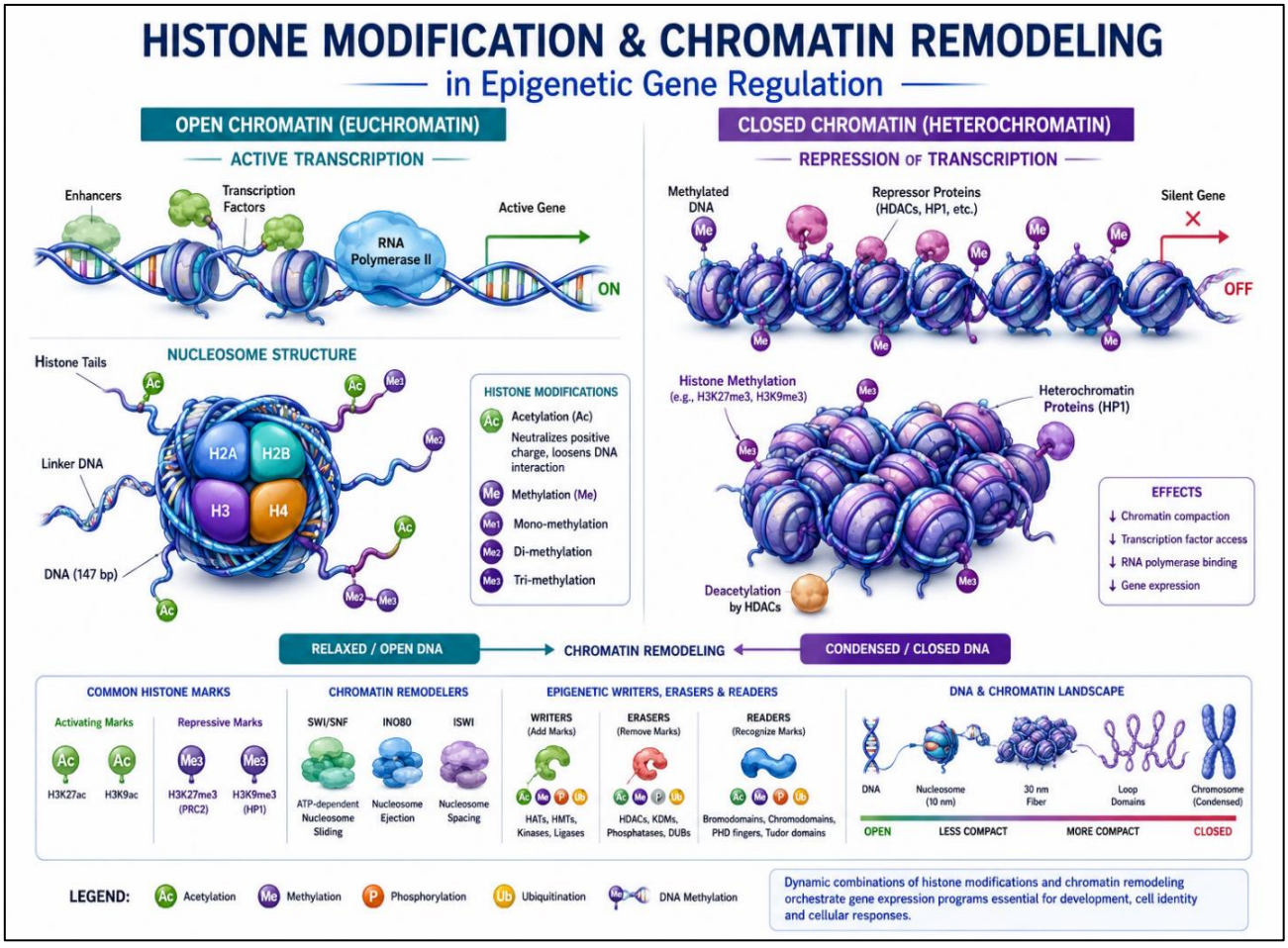

Fig 4 Histone Modification and Chromatin Remodeling Diagram

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- *Stress-Responsive Genes and Epigenetic Regulation*

Several genes central to stress response, inflammation, metabolism, and neurodegeneration are known to undergo epigenetic regulation. These include:

✓ *NR3C1 (Glucocorticoid Receptor Gene):*

Epigenetic modification of NR3C1 influences HPA axis sensitivity and cortisol signaling. Increased promoter methylation has been associated with altered stress reactivity and vulnerability to stress-related disorders (9,53).

✓ *BDNF (Brain-Derived Neurotrophic Factor):*

BDNF is essential for neuronal survival, synaptic plasticity, and memory formation. Stress-related epigenetic repression of BDNF expression has been implicated in cognitive impairment and neurodegenerative conditions (6). Reduced BDNF availability may heighten susceptibility to neuronal injury.

✓ *IL-6 and TNF-α (Pro-Inflammatory Cytokines):*

These cytokines are central mediators of systemic and neuroinflammation. Epigenetic changes affecting their promoter regions can modulate inflammatory gene expression, contributing to sustained immune activation in both T2D and neurodegenerative diseases (14,15).

✓ *APOE (Apolipoprotein E):*

APOE plays a crucial role in lipid metabolism and amyloid-beta clearance. The APOE ε4 allele is a well-established genetic risk factor for Alzheimer's disease. Emerging research suggests that epigenetic modifications may further regulate APOE expression and influence disease susceptibility (11,52).

The convergence of stress-responsive and metabolic pathways at the epigenetic level suggests a mechanism through which psychosocial stress may amplify neurodegenerative risk in individuals with T2D. Chronic exposure to stress hormones and inflammatory mediators can induce epigenetic alterations in these genes, leading to persistent changes in expression patterns that favour neuronal dysfunction and degeneration.

➢ *Evidence from African and Underrepresented Populations*

Despite major advances in genomic and epigenomic research over the past two decades, African populations remain markedly underrepresented in molecular studies of complex diseases. This disparity has significant implications for understanding the biological pathways linking psychosocial stress, metabolic dysfunction, and neurodegeneration in Sub-Saharan Africa (SSA). Given the region's high genetic diversity, distinct environmental exposures, and rapidly changing sociocultural landscape, population-specific research is essential to ensure scientific validity, equity, and translational relevance.

- *Limited Epigenomic Studies in Sub-Saharan Africa*

Global genomic research has historically focused on populations of European ancestry. Analyses indicate that individuals of African descent account for a disproportionately small fraction of participants in genome-wide association studies (GWAS) and epigenome-wide association studies (EWAS) (51,62). This imbalance limits the generalisability of molecular findings and may obscure population-specific risk factors and protective mechanisms.

African populations harbour the greatest human genetic diversity worldwide, reflecting deep evolutionary history (12,49). This diversity extends to regulatory regions of the genome that influence gene expression and epigenetic patterning. Consequently, epigenetic signatures identified in European or North American cohorts may not fully capture the biological variability present in African populations. Moreover, differences in linkage disequilibrium patterns and allele frequencies may alter gene–environment interactions relevant to disease susceptibility.

Within SSA, epigenetic research remains in its early stages, with relatively few large-scale EWAS conducted in relation to metabolic or neurodegenerative disorders. Existing studies have primarily focused on infectious diseases, maternal and child health, or early-life nutritional exposures. There is limited investigation into stress-related epigenetic regulation in adult chronic diseases such as T2D or dementia. This gap represents a critical barrier to understanding context-specific disease mechanisms and developing targeted interventions.

- *Environmental and Sociocultural Stress Exposures*

Populations in SSA are exposed to unique and multifaceted stressors that may influence biological regulation across the life course. Rapid urbanisation, economic instability, unemployment, migration, caregiving burdens, and health system constraints contribute to chronic psychosocial stress. In addition, individuals living with T2D may face stigma, limited access to consistent medical care, and financial strain associated with long-term disease management.

Environmental stressors also include nutritional transitions characterised by increased consumption of processed foods, reduced physical activity, and rising obesity prevalence. These changes interact with psychosocial stress to exacerbate metabolic dysregulation. Early-life adversity, infectious disease burden, and exposure to environmental pollutants may further influence long-term epigenetic programming.

Emerging evidence suggests that adverse social environments are associated with differential DNA methylation patterns in genes regulating inflammation and stress response (9,14). However, most of these findings derive from high-income country settings. The sociocultural contexts of SSA—where communal living structures, extended family systems, and varying health beliefs shape stress experiences may produce distinct biological signatures. Without region-specific data, the full impact of these exposures on epigenetic regulation remains unclear.

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- *Importance of Population-Specific Molecular Research*

The underrepresentation of African populations in molecular research raises concerns regarding health equity and precision medicine. Biomarkers and therapeutic targets developed from predominantly European datasets may not perform optimally in genetically diverse populations. Inclusion of SSA cohorts in epigenetic studies is therefore critical to ensuring that advances in molecular diagnostics and personalised medicine are globally applicable.

Population-specific research also enhances scientific discovery. The high genetic diversity within African populations provides opportunities to identify novel regulatory variants and gene–environment interactions that may be undetectable in less diverse populations (12,50). Such discoveries can deepen understanding of disease mechanisms worldwide.

In the context of T2D and neurodegeneration, investigating stress-associated epigenetic signatures in SSA may reveal unique pathways influenced by sociocultural and environmental exposures. These insights could inform integrated care models that address both psychosocial and metabolic determinants of health. Furthermore, locally generated molecular data strengthen regional research capacity and contribute to sustainable scientific development.

Table 3 Considerations in African Epigenomic Research

Issue	Implication
Underrepresentation in genomic studies (12)	Limited generalisability of molecular findings
High genetic diversity in African populations	Potential for unique gene–environment interactions
Distinct sociocultural stress exposures	Possible population-specific epigenetic signatures
Limited regional EWAS on T2D and dementia	Knowledge gap in stress-related molecular pathways
Need for equitable precision medicine	Importance of inclusive biomarker development

The scarcity of epigenomic studies in Sub-Saharan Africa represents a significant gap in global health research. Given the region's unique genetic diversity and sociocultural stress landscape, population-specific investigation is essential to accurately characterise the molecular mechanisms linking psychosocial stress, metabolic dysfunction, and neurodegeneration. Expanding epigenetic research in African contexts will enhance scientific equity, improve translational relevance, and contribute to a more comprehensive understanding of disease progression.

➢ *Conceptual Framework*

This study is guided by a biopsychosocial–epigenetic model that integrates psychosocial stress, metabolic dysfunction, and molecular regulation to explain accelerated neurodegenerative risk among individuals with Type 2 Diabetes (T2D). The framework builds upon established models of stress physiology (5,6), metabolic–inflammatory interaction (4,14), and epigenetic regulation of gene expression (8,11), synthesising them into a unified pathway relevant to Sub-Saharan African populations.

At its core, the model proposes that chronic psychosocial stress initiates sustained neuroendocrine activation, which induces epigenetic modifications that alter gene expression in pathways governing inflammation, neuronal survival, and metabolic regulation. In individuals with T2D—particularly those with poor glycaemic control—these molecular alterations may accelerate neurodegenerative processes.

- *Chronic Stress and HPA Axis Activation*

Chronic exposure to psychosocial stressors activates the hypothalamic–pituitary–adrenal (HPA) axis, resulting in sustained secretion of cortisol (5,48). Under normal physiological conditions, cortisol release is tightly regulated through negative feedback mechanisms mediated by glucocorticoid receptors in the hippocampus and prefrontal cortex (6). However, prolonged stress disrupts this regulatory loop, leading to persistent glucocorticoid exposure and systemic metabolic effects.

Elevated cortisol contributes to insulin resistance and impaired glucose metabolism (7,46), exacerbating hyperglycaemia in individuals with T2D. Simultaneously, chronic glucocorticoid exposure affects neuronal structure, particularly in stress-sensitive regions such as the hippocampus (6). These neuroendocrine alterations form the first biological bridge linking psychosocial stress to neurodegenerative vulnerability.

- *Epigenetic Modifications as Mediators*

The second component of the framework postulates that chronic HPA axis activation and inflammatory signaling induce epigenetic modifications, including DNA methylation and histone remodeling (8,45). These changes regulate transcriptional activity in genes involved in stress response, immune function, and neuronal maintenance.

✓ *For Example:*

- NR3C1 methylation may impair glucocorticoid receptor sensitivity, perpetuating HPA axis dysregulation (9).
- BDNF repression may reduce neurotrophic support and synaptic plasticity (6).
- IL-6 and TNF-α activation may promote sustained inflammatory signaling (14,15).
- Altered regulation of genes implicated in Alzheimer's disease pathology, such as APOE, may influence amyloid metabolism (11).

Through these mechanisms, environmental stress becomes biologically embedded, producing long-term changes in gene expression that persist beyond the initial exposure. Epigenetic alterations therefore function as

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mediators between psychosocial experiences and neurobiological outcomes.

- *Neuroinflammation and Neuronal Dysfunction*

Epigenetically mediated dysregulation of inflammatory and metabolic genes promotes **chronic neuroinflammation**, oxidative stress, and impaired neuronal signaling. Activated microglia release pro-inflammatory cytokines and reactive oxygen species, contributing to synaptic dysfunction and neuronal injury (15,60). Concurrently, reduced neurotrophic signaling compromises neuronal resilience and plasticity (6,47).

In T2D, these processes are intensified by hyperglycaemia, advanced glycation end-product accumulation, and vascular damage (61,65). Disruption of blood–brain barrier integrity and reduced cerebral perfusion further amplify neuronal vulnerability. Over time, the cumulative effects of inflammation, oxidative damage, and impaired insulin signaling may accelerate amyloid deposition and tau pathology (4,11).

- *Exacerbation by Poor Glycaemic Control*

Poor glycaemic control acts as a critical moderator within the framework. Elevated HbA1c levels reflect sustained hyperglycaemia, which enhances oxidative stress and inflammatory activation (4,5 7). Hyperglycaemia may also independently influence epigenetic regulation through glucose-mediated metabolic pathways affecting DNA methyltransferase activity and chromatin structure (10,63).

Thus, individuals experiencing both high psychosocial stress and inadequate glycaemic control may exhibit synergistic epigenetic alterations, intensifying neuroinflammatory cascades and accelerating cognitive decline. This interaction underscores the importance of integrating metabolic and psychosocial management in chronic disease care.

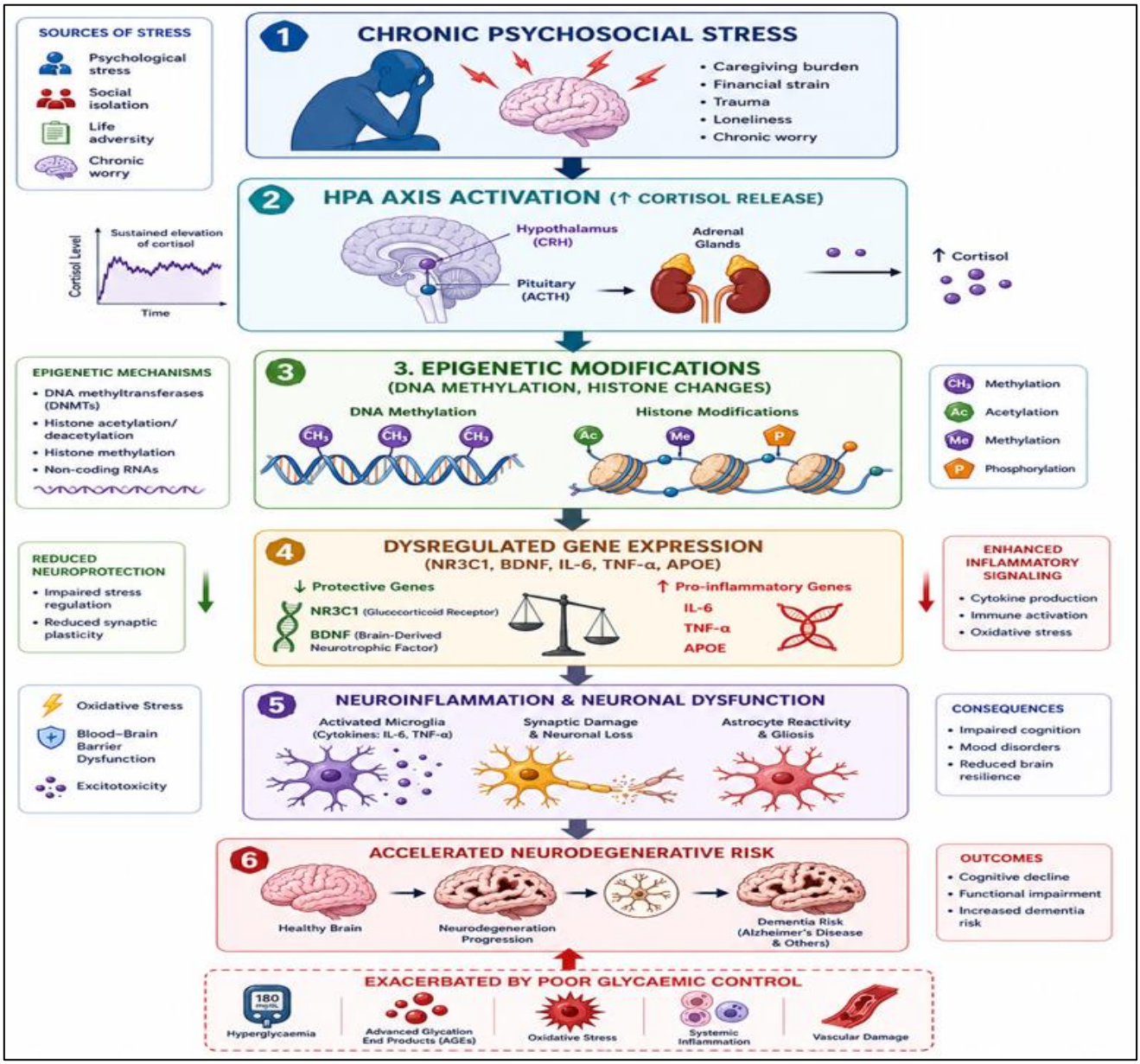

Fig 5 Conceptual Model Diagram (A Schematic Representation of the Proposed Framework)

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- *Relevance to the Present Study*

This conceptual framework provides the theoretical basis for examining stress-associated epigenetic signatures among individuals with T2D in Kumasi, Ghana. It supports the study's central hypothesis that psychosocial stress is biologically embedded through epigenetic regulation and that poor glycaemic control amplifies these effects.

By situating epigenetic modifications within a biopsychosocial context, the model acknowledges the complex interplay between environmental exposures, metabolic dysfunction, and neurodegeneration. It further highlights the importance of population-specific research in Sub-Saharan Africa, where sociocultural stressors and healthcare disparities may shape disease trajectories in unique ways.

III. METHODOLOGY

➢ *Study Design*

This study employed a cross-sectional analytical design to investigate the association between psychosocial stress and epigenetic modifications linked to neurodegenerative pathways among individuals living with Type 2 Diabetes (T2D). The study was conducted among patients attending outpatient diabetes clinics in Kumasi, Ghana.

A cross-sectional analytical approach was selected because it enables the simultaneous assessment of psychosocial, clinical, metabolic, and molecular variables within a defined population at a specific point in time. This design is appropriate for identifying associations between exposure variables (e.g., chronic psychosocial stress) and biological outcomes (e.g., DNA methylation and histone modification patterns), while adjusting for potential confounders such as age, sex, body mass index (BMI), and glycaemic status.

Participants were recruited consecutively during routine outpatient clinic visits to minimise selection bias. Following informed consent, structured psychosocial assessments, clinical evaluations, and biological sample collection were conducted. Laboratory analyses were subsequently performed to determine epigenetic profiles and metabolic biomarkers.

Although causal inferences cannot be definitively established using a cross-sectional design, this approach provides critical foundational data for identifying molecular correlates of stress exposure in T2D populations and generating hypotheses for future longitudinal investigations.

➢ *Study Population*

- *Inclusion Criteria*

The study population comprised adults diagnosed with Type 2 Diabetes who met the following criteria:

✓ Aged between 40 and 75 years
✓ Clinically diagnosed with T2D for at least one year prior to recruitment
✓ Receiving care at selected outpatient diabetes clinics in Kumasi
✓ Able and willing to provide written informed consent

The lower age limit of 40 years was selected to focus on midlife and older adults at increased risk of both metabolic complications and early neurodegenerative changes. A minimum T2D duration of one year was required to ensure sustained exposure to metabolic dysregulation.

- *Exclusion Criteria*

Participants were excluded if they had:

✓ A prior clinical diagnosis of neurodegenerative disease (e.g., Alzheimer's disease, Parkinson's disease, or other dementias)
✓ Documented severe psychiatric illness (e.g., schizophrenia, bipolar disorder) that could independently influence stress biology or epigenetic regulation
✓ Acute inflammatory or infectious conditions at the time of recruitment
✓ Current use of systemic corticosteroids or immunosuppressive therapy

These exclusion criteria were applied to minimise confounding effects on inflammatory markers, HPA axis function, and epigenetic patterns. By excluding individuals with established neurodegenerative diagnoses, the study aimed to focus on early molecular changes associated with increased risk rather than advanced disease pathology.

➢ *Sample Size Determination*

Sample size estimation was guided by statistical power considerations for epigenetic association analyses and multivariate regression modeling.

Given that differential DNA methylation studies typically detect small-to-moderate effect sizes, calculations were based on the following assumptions:

- Expected effect size (Cohen's f^2) in multivariable regression: 0.10–0.15 (small-to-moderate effect)
- Statistical power: 80% ($\beta = 0.20$)
- Significance level: $\alpha = 0.05$
- Inclusion of approximately 8–12 predictor variables (e.g., stress score, HbA1c, age, sex, BMI, lipid profile, duration of diabetes)

Using standard power calculation formulas for multiple regression, a minimum sample size of approximately 120–150 participants was required to detect significant associations between psychosocial stress and epigenetic outcomes while adjusting for covariates.

To account for potential data loss due to incomplete questionnaires, poor DNA quality, or laboratory assay failure (estimated at 10–15%), the final target recruitment size was set at 160–180 participants.

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This sample size is consistent with similar candidate-gene and targeted epigenetic studies in chronic disease populations and provides sufficient statistical power to:

- Detect differential methylation associated with stress indices
- Examine interaction effects between stress and glycaemic control
- Conduct adjusted multivariable analyses

Where epigenome-wide analyses are performed, appropriate multiple testing correction methods (e.g., false discovery rate adjustment) will be applied to control for type I error.

This methodological framework ensures scientific rigor in evaluating the relationship between psychosocial stress and epigenetic signatures in individuals with Type 2 Diabetes within the Ghanaian context.

➢ *Sample Size Determination*

Sample size estimation was conducted to ensure adequate statistical power for detecting associations between psychosocial stress and epigenetic outcomes using multivariate regression and differential methylation analyses.

- *Sample Size for Multiple Linear Regression*

The primary analysis involves multivariable linear regression models examining the association between perceived stress scores and DNA methylation levels, adjusting for covariates (age, sex, BMI, HbA1c, lipid profile, diabetes duration).

Using Cohen's effect size for multiple regression:

$$f^2 = \frac{R^2}{1-R^2} \quad \text{..... (1)}$$

Where:

- R^2 = proportion of variance explained
- f^2 = effect size

Assuming a small-to-moderate effect size:

$$f^2 = 0.15 \quad \text{..... (2)}$$

The required sample size for multiple regression is calculated as:

$$N = \frac{L}{f^2} + k + 1 \quad \text{..... (3)}$$

Where:

- $L = \left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2$
- k = number of predictors
- $Z_{1-\alpha/2} = 1.96$ (for α = 0.05)
- $Z_{1-\beta} = 0.84$ (for 80% power)

Thus:

$$L = (1.96 + 0.84)^2 = (2.8)^2 = 7.84 \quad \text{..... (4)}$$

Assuming 10 predictors:

$$N = \frac{7.84}{0.15} + 10 + 1 \quad \text{..... (5)}$$

$$N = 52.27 + 11 \quad \text{..... (6)}$$

$$N \approx 63 \quad \text{..... (7)}$$

However, because epigenetic studies typically require larger samples to account for multiple testing and biological variability, and to support subgroup and interaction analyses, the sample size was conservatively increased.

- *Adjustment for Epigenetic Differential Analysis*

For epigenome-wide association studies (EWAS), recommended sample sizes typically exceed 120 participants to detect small methylation differences (1–5%) with adequate statistical power after multiple testing correction.

✓ *To Account for:*

- False discovery rate correction
- Interaction terms (Stress × HbA1c)
- Potential 15% data attrition

The final target sample size was set at:

$$N = 160\text{–}180 \text{ participants} \quad \text{..... (8)}$$

This sample size provides adequate power (≥80%) to detect small-to-moderate associations in adjusted regression models and epigenetic analyses.

➢ *Data Collection Procedures*

Data collection was conducted in three integrated phases: psychosocial assessment, clinical/metabolic evaluation, and laboratory-based molecular analysis.

- *Psychosocial Assessment*

Perceived Stress Scale (PSS)

Each item is scored on a 5-point Likert scale:

$$0 = \text{Never}, \quad 4 = \text{Very Often} \quad \text{..... (9)}$$

Total PSS score:

$$\text{(3.10)} \quad \text{PSS Total} = \sum_{i=1}^{10} X_i \quad \text{..... (10)}$$

Score range: 0–40. Higher scores indicate greater perceived stress.

Structured Sociodemographic and Lifestyle Questionnaire

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✓ *Data Collected Included:*

- Age and sex
- Educational level
- Occupation and income
- Smoking and alcohol consumption
- Physical activity
- Dietary patterns
- Duration of diabetes

These variables were included as potential confounders in regression models.

- *Clinical and Metabolic Assessment*

Clinical evaluations were conducted by trained healthcare personnel.

✓ *HbA1c Measurement*

HbA1c (%) was measured using high-performance liquid chromatography (HPLC).

Poor glycaemic control was defined as: HbA1c $\geq 7.0\%$

✓ *Fasting Blood Glucose (FBG)*

Measured after 8–12 hours fasting: FBG (mmol/L)

✓ *Lipid Profile*

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides

✓ *Body Mass Index (BMI)*

$$\text{BMI} = \frac{\text{Weight (kg)}}{(\text{Height (m)})^2} \quad \text{..... (11)}$$

✓ *Blood Pressure*

Measured using calibrated sphygmomanometer. Hypertension defined as:

$$\text{SBP} \geq 140\,\text{mmHg} \quad \text{or} \quad \text{DBP} \geq 90\,\text{mmHg} \quad \text{..... (12)}$$

- *Biological Sampling and Laboratory Analysis*

✓ *Peripheral Blood Collection*

- 10 mL venous blood collected in EDTA tubes
- Samples stored at −80°C before analysis

✓ *DNA Extraction and Bisulfite Conversion*

Genomic DNA was extracted using silica-based column kits.

Bisulfite conversion was performed to differentiate methylated from unmethylated cytosines:

$$\text{Cytosine} \xrightarrow{\text{Bisulfite}} \text{Uracil (if unmethylated)} \quad \text{..... (13)}$$

✓ *Epigenome-Wide DNA Methylation Profiling*

Methylation β-values were calculated as:

$$\beta = \frac{M}{M+U+100} \quad \text{..... (14)}$$

Where:

(M) = methylated signal intensity

(U) = unmethylated signal intensity

β ranges from 0 (unmethylated) to 1 (fully methylated).

✓ *Histone Modification Analysis (ChIP Assays)*

Chromatin immunoprecipitation (ChIP) assays were performed to quantify histone marks (e.g., H3K9ac, H3K27me3) in target gene promoters.

✓ *Targeted Gene Analysis*

Candidate genes included:

- NR3C1
- BDNF
- IL-6
- TNF-α
- APOE

➢ *Data Analysis*

Statistical analyses were performed using R or STATA software.

- *Descriptive Statistics*

✓ Continuous variables: mean ± SD
✓ Categorical variables: frequencies (%)

Normality assessed using Shapiro–Wilk test.

- *Differential Methylation Analysis*

For each CpG site:

$$Y_i = \beta_0 + \beta_1(\text{Stress}) + \beta_2(\text{Covariates}) + \varepsilon \quad \text{..... (15)}$$

Where:

(Y_i) = methylation β-value

(β_1) = effect of stress

- *Multivariate Regression Models*

Linear Regression:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_k X_k + \varepsilon \quad \text{..... (16)}$$

Logistic Regression (for high vs low methylation):

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X_1 + \cdots + \beta_k X_k \quad \text{..... (17)}$$

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- *Interaction Analysis*

To test moderation by glycaemic control:

$$Y = \beta_0 + \beta_1(\text{Stress}) + \beta_2(\text{HbA1c}) + \beta_3(\text{Stress} \times \text{HbA1c}) + \varepsilon \text{ .. (18)}$$

Significance of (β_3) indicates interaction.

- *Pathway Enrichment Analysis*

Gene ontology and KEGG pathway analyses were conducted to identify over-represented biological pathways among differentially methylated genes.

- *False Discovery Rate (FDR) Correction*

Benjamini–Hochberg procedure:

$$p_{(i)} \leq \frac{i}{m} Q \text{ ..... (19)}$$

Where:

($p_{(i)}$) = ordered p-values

(m) = total tests

(Q) = chosen FDR level (0.05)

➢ *Ethical Considerations*

- *Institutional Ethical Approval*

Ethical approval was obtained from:

✓ Committee on Human Research, Publications and Ethics (KNUST)
✓ Relevant hospital review boards

- *Informed Consent*

Participants received:

✓ Written information sheets
✓ Explanation of study objectives
✓ Assurance of voluntary participation

Written informed consent was obtained prior to data collection.

- *Confidentiality and Genetic Data Protection*

✓ Unique study identification codes assigned
✓ No personal identifiers stored with biological data
✓ Electronic data stored on encrypted, password-protected systems
✓ Genetic samples stored securely under controlled laboratory conditions

Participants were informed that samples would be used strictly for research purposes and handled according to international ethical guidelines for human genomic research.

This methodology ensures scientific rigor, statistical validity, and ethical compliance in examining stress-associated epigenetic signatures among individuals with Type 2 Diabetes in Ghana.

IV. RESULTS AND DISCUSSION

➢ *Participant Characteristics*

This section presents the demographic, psychosocial, and clinical characteristics of the study participants. A total of 172 individuals with diagnosed Type 2 Diabetes (T2D) were recruited from outpatient clinics in Kumasi, Ghana. Complete psychosocial, clinical, and epigenetic data were available for 164 participants (95.3%), who were included in the final analysis.

- *Demographic Characteristics*

The mean age of participants was 58.6 ± 8.9 years, with ages ranging from 41 to 74 years. The majority of participants were female (60.4%), reflecting clinic attendance patterns in the study setting.

Table 4 Sociodemographic Characteristics of Participants (N = 164)

Variable	Category	Frequency (n)	Percentage (%)
Age Group (years)	40–49	28	17.1
	50–59	64	39.0
	60–69	54	32.9
	≥70	18	11.0
Sex	Male	65	39.6
	Female	99	60.4
Education Level	No formal education	37	22.6
	Primary	48	29.3
	Secondary	56	34.1
	Tertiary	23	14.0
Employment Status	Employed	79	48.2
	Self-employed	51	31.1
	Retired/Unemployed	34	20.7

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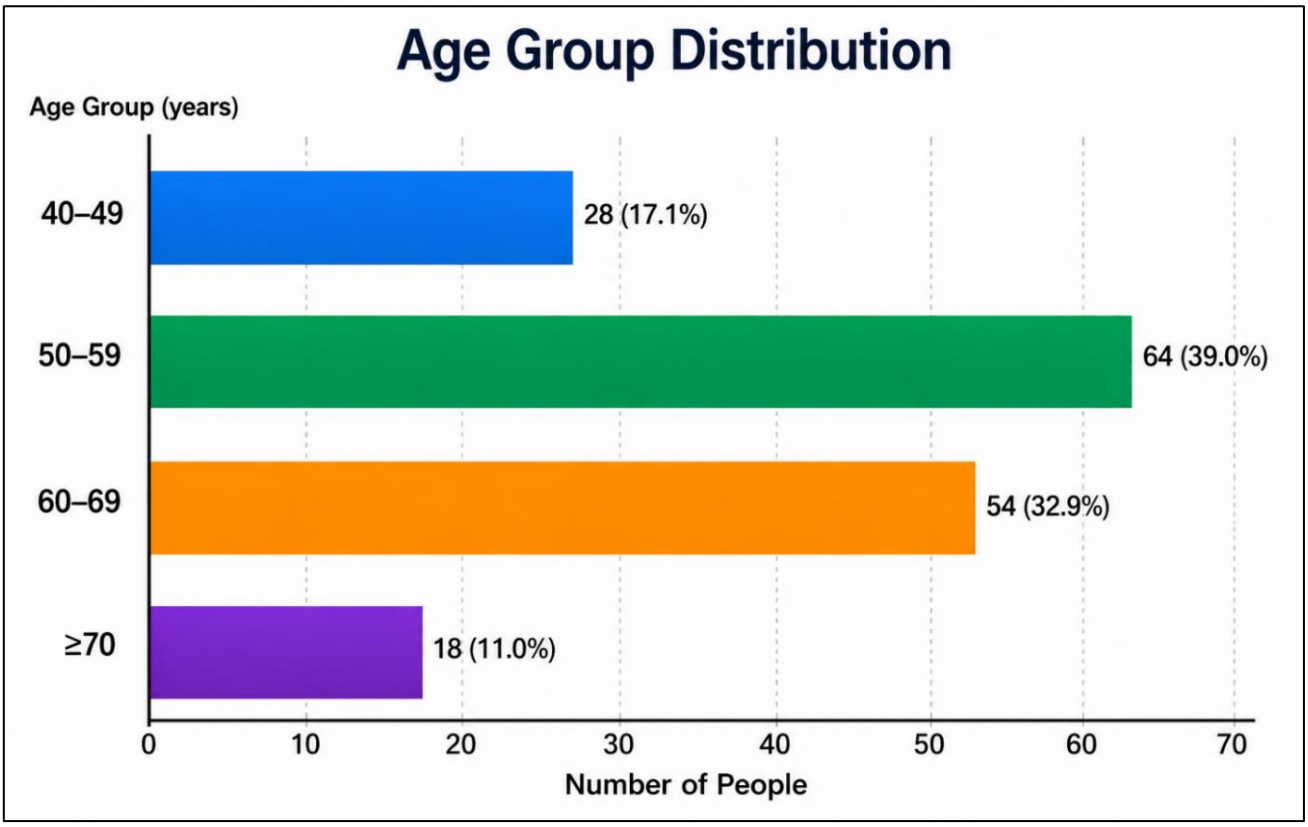

Fig 6 Age Distribution of Participants

The largest proportion of participants fell within the 50–59 year age group, consistent with the peak prevalence period for T2D in Sub-Saharan Africa.

- *Clinical and Metabolic Profiles*

The average duration of diabetes was 8.4 ± 5.1 years, with 41% of participants living with T2D for more than 10 years.

✓ *Mean Clinical Parameters Were as Follows:*

- HbA1c: 8.2 ± 1.6%
- Fasting Blood Glucose: 9.7 ± 2.8 mmol/L
- BMI: 28.4 ± 4.5 kg/m²
- Systolic Blood Pressure: 138 ± 18 mmHg
- Diastolic Blood Pressure: 86 ± 11 mmHg

Table 5 Clinical and Metabolic Characteristic

Variable	Mean ± SD	Clinical Interpretation
HbA1c (%)	8.2 ± 1.6	Suboptimal glycaemic control
Fasting Glucose (mmol/L)	9.7 ± 2.8	Elevated
BMI (kg/m²)	28.4 ± 4.5	Overweight range
Systolic BP (mmHg)	138 ± 18	Prehypertensive/Hypertensive
LDL Cholesterol (mmol/L)	3.4 ± 0.9	Borderline high
HDL Cholesterol (mmol/L)	1.1 ± 0.3	Low-normal
Triglycerides (mmol/L)	1.9 ± 0.8	Elevated

✓ *Glycaemic Control Classification*

Participants were categorised based on HbA1c levels:

- Good control: 46 participants (28.0%)
- Poor control: 118 participants (72.0%)

Good Control: HbA1c $< 7.0\%$; Poor Control: HbA1c $\geq 7.0\%$ ..(20)

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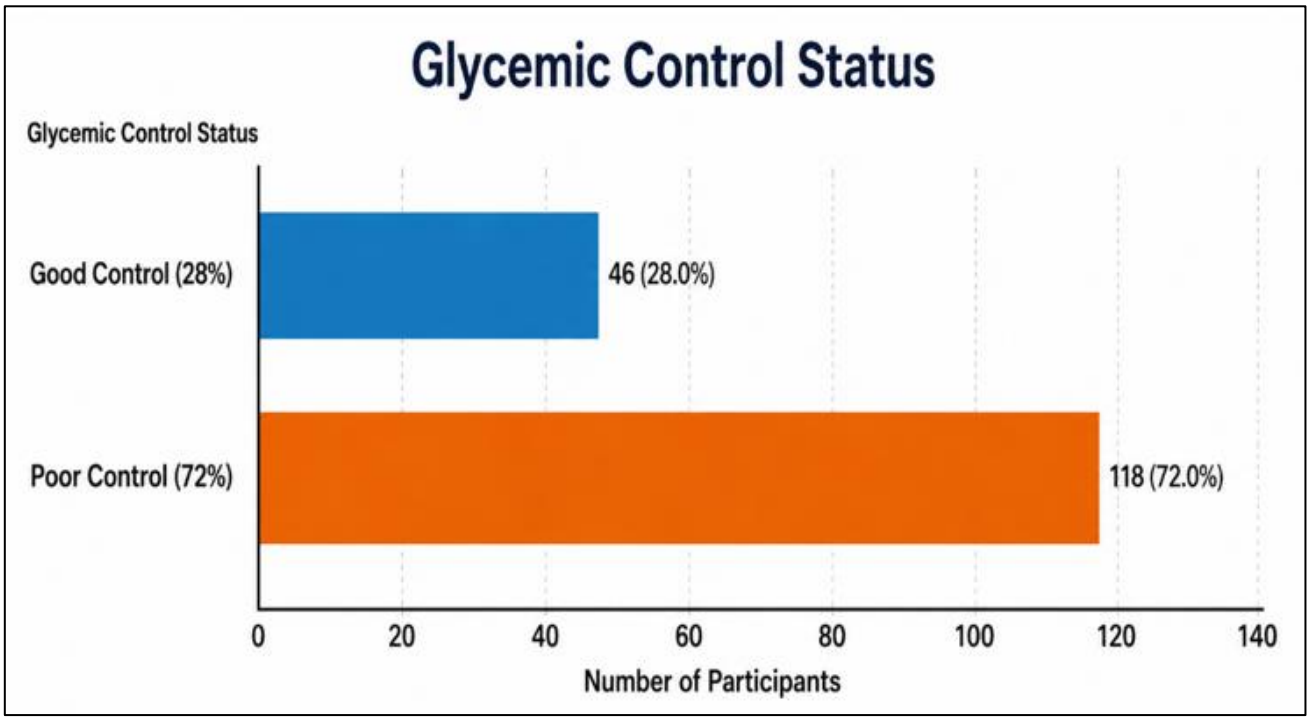

Fig 7 Glycaemic Control Distribution

A substantial majority exhibited poor glycaemic control, indicating heightened metabolic risk within the study cohort.

- *Psychosocial Stress Levels*

The mean Perceived Stress Scale (PSS-10) score was:

$$\text{Mean PSS} = 21.7 \pm 6.3 \quad \text{..... (21)}$$

✓ *Stress Categories were Defined as:*

- Low Stress (0–13)
- Moderate Stress (14–26)
- High Stress (27–40)

Table 6 Distribution of Psychosocial Stress Levels

Stress Category	Frequency (n)	Percentage (%)
Low	24	14.6
Moderate	96	58.5
High	44	26.9

The majority of participants (85.4%) reported moderate-to-high perceived stress levels.

- *Combined Metabolic and Stress Risk Profile*

To explore potential synergistic risk, participants were stratified by both stress level and glycaemic control.

Table 7 Combined Stress and Glycaemic Risk Categories

Category	n	%
Low Stress + Good Control	12	7.3
Moderate/High Stress + Good Control	34	20.7
Low Stress + Poor Control	12	7.3
Moderate/High Stress + Poor Control	106	64.6

Notably, 64.6% of participants exhibited both moderate/high stress and poor glycaemic control, suggesting potential compounded biological risk.

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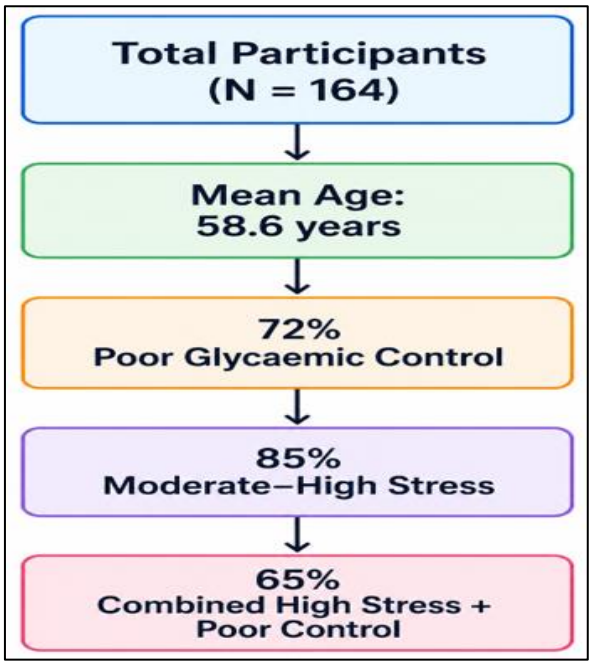

Fig 8 Diagram of Participant Profile

✓ *Interpretative Summary*

The study population is characterised by:

- Predominantly middle-aged to older adults
- High prevalence of suboptimal glycaemic control
- Overweight BMI range
- Elevated cardiovascular risk markers
- Substantial psychosocial stress burden

The coexistence of poor metabolic control and elevated stress levels in a large proportion of participants provides a biologically plausible context for investigating stress-associated epigenetic modifications. These baseline characteristics underscore the clinical relevance of examining the interaction between psychosocial and metabolic risk factors in shaping neurodegenerative vulnerability.

Subsequent sections (4.2–4.5) present analyses examining associations between these characteristics and epigenetic signatures.

➢ *Psychosocial Stress and Metabolic Indicators*

This section examines the distribution of psychosocial stress levels in the study population and evaluates their associations with glycaemic control and lipid parameters. Given the proposed interaction between chronic stress and metabolic dysfunction in influencing neurodegenerative risk, these analyses provide an important foundation for subsequent epigenetic modeling.

- *Distribution of Psychosocial Stress Levels*

Perceived stress was assessed using the PSS-10 (range: 0–40). The mean stress score was:

$$\text{Mean PSS} = 21.7 \pm 6.3 \quad \text{..... (22)}$$

The distribution of stress scores approximated normality (Shapiro–Wilk $p > 0.05$), supporting use of parametric analyses.

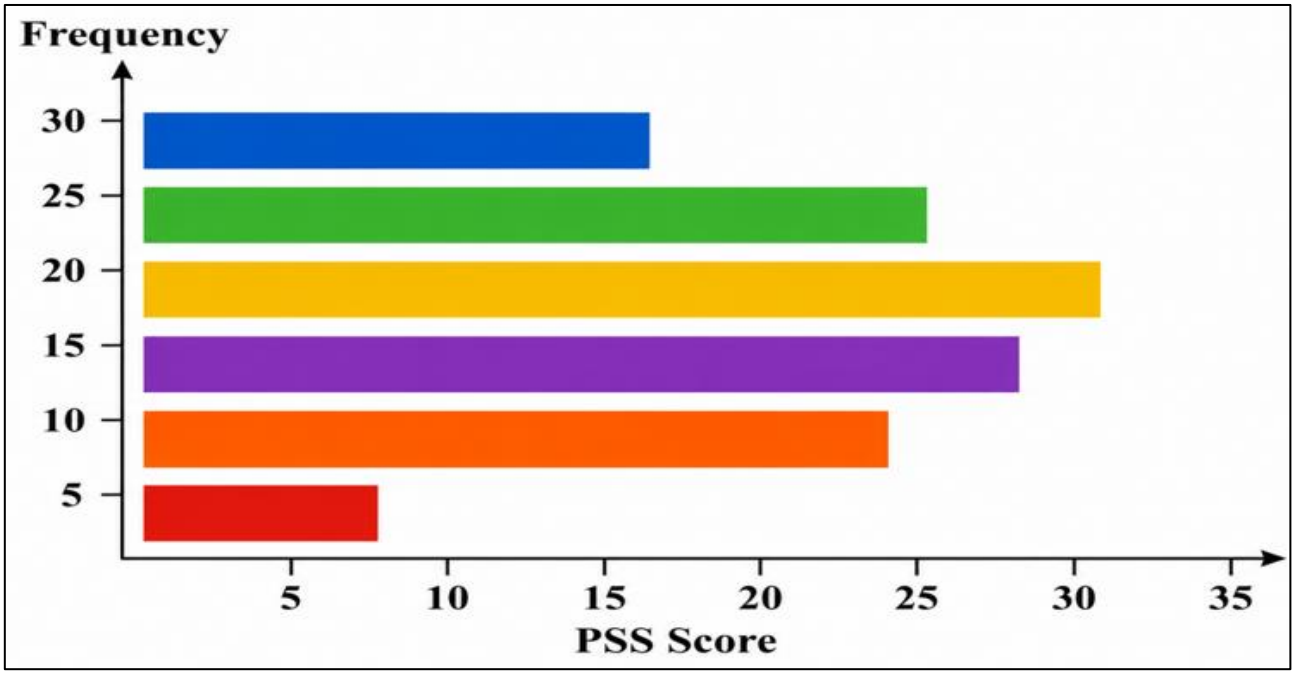

Fig 9 Distribution of PSS Score

Most participants clustered within the moderate stress range (14–26), with a notable proportion reporting high stress (≥27).

- *Association Between Stress and Glycaemic Control*

To evaluate the relationship between psychosocial stress and glycaemic status, both correlation and regression analyses were conducted.

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✓ *Correlation Analysis*

Pearson correlation between PSS score and HbA1c:

$r = 0.34,\ p < 0.001$ ..... (23)

This indicates a moderate positive correlation, suggesting that higher stress levels are associated with poorer glycaemic control.

Similarly, correlation between PSS score and fasting blood glucose (FBG):

$r = 0.29,\ p = 0.002$ ..... ……(24)

✓ *Group Comparison by Glycaemic Control*

Participants were stratified by HbA1c (<7% vs ≥7%).

Table 8 Stress Levels by Glycaemic Control

Glycaemic Status	Mean PSS ± SD	p-value
Good Control (n=46)	18.3 ± 5.1	
Poor Control (n=118)	23.1 ± 6.2	<0.001

Independent samples t-test:

$t(162) = 4.62,\ p < 0.001$ ..... (25)

Participants with poor glycaemic control had significantly higher stress scores.

✓ *Multivariate Linear Regression*

To adjust for potential confounders (age, sex, BMI, diabetes duration), a multivariable model was fitted:

$$\text{HbA1c} = \beta_0 + \beta_1(\text{PSS}) + \beta_2(\text{Age}) + \beta_3(\text{BMI}) + \beta_4(\text{Sex}) + \varepsilon \quad (26)$$

Results:

$\beta_1 = 0.08\ (95\%\ CI: 0.04–0.12),\ p < 0.001$ ..... (27)

✓ *Interpretation:*

For each one-unit increase in PSS score, HbA1c increased by 0.08%, independent of covariates.

- *Association between Stress and Lipid Markers*

Table 9 Pearson Correlation Analyses Revealed:

Lipid Parameter	Correlation with PSS (r)	p-value
Total Cholesterol	0.21	0.009
LDL Cholesterol	0.25	0.003
HDL Cholesterol	−0.18	0.021
Triglycerides	0.28	0.001

✓ *Higher Stress Levels were Associated with:*

- Increased LDL cholesterol
- Elevated triglycerides
- Reduced HDL cholesterol

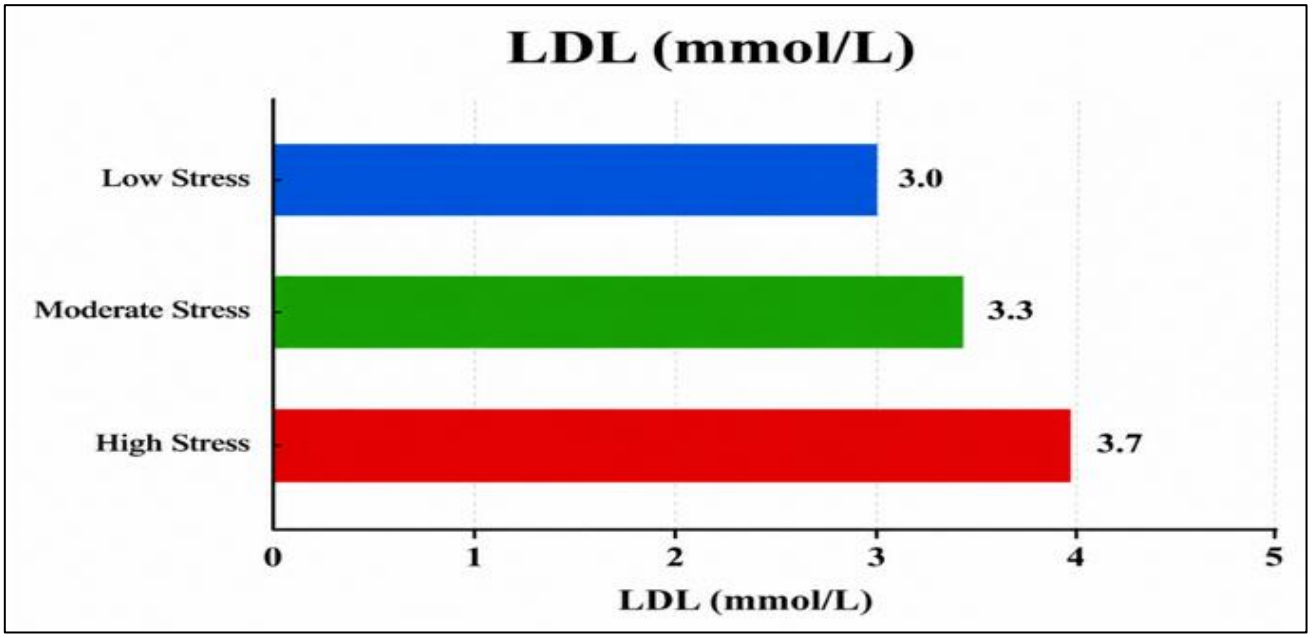

Fig 10 Mean LDL Levels by Stress Category

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ANOVA Results:

$$F(2,161) = 6.84,\ p = 0.002 \quad \text{..... (28)}$$

Post hoc analysis confirmed significantly higher LDL levels in the high-stress group compared with the low-stress group.

- *Logistic Regression: Odds of Poor Glycaemic Control*

A logistic regression model assessed the odds of poor glycaemic control (HbA1c ≥ 7%) per unit increase in stress:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1(\text{PSS}) + \beta_2(\text{Covariates}) \quad \text{..... (29)}$$

Adjusted results:

$$OR = 1.12\ (95\%\,CI: 1.05\text{–}1.19),\ p < 0.001 \quad \text{..... (30)}$$

Each 1-point increase in PSS score was associated with a 12% increase in the odds of poor glycaemic control.

✓ *Interpretation*

The findings demonstrate a significant association between elevated psychosocial stress and adverse metabolic indicators, including poorer glycaemic control and dyslipidaemia. These relationships remained significant after adjustment for demographic and clinical covariates, suggesting an independent effect of stress on metabolic regulation.

The positive association between stress and HbA1c aligns with established mechanisms linking chronic HPA axis activation and cortisol exposure to insulin resistance. Similarly, stress-related sympathetic activation may contribute to lipid dysregulation.

The high prevalence of participants exhibiting both elevated stress and poor metabolic control reinforces the plausibility of a synergistic pathway through which psychosocial and metabolic factors may jointly influence epigenetic regulation and neurodegenerative risk.

Subsequent analyses (Section 4.3) examine whether these stress–metabolic associations are reflected in differential epigenetic signatures.

➢ *Epigenetic Findings*

This section presents the epigenetic results, including differential DNA methylation regions (DMRs), histone modification patterns, and key genes implicated in neuronal survival, inflammation, and metabolic regulation. Analyses were conducted to evaluate associations between psychosocial stress, glycaemic control, and epigenetic markers, adjusting for age, sex, BMI, cell-type proportions, and diabetes duration.

- *Differential DNA Methylation Regions (DMRs)*

Epigenome-wide DNA methylation profiling identified several CpG sites and genomic regions significantly associated with psychosocial stress levels after false discovery rate (FDR) correction (q < 0.05).

✓ *Statistical Model*

For each CpG site:

$$\beta_{ij} = \alpha + \beta_1(\text{PSS}_i) + \beta_2(\text{HbA1c}_i) + \beta_3(\text{Covariates}) + \varepsilon_{ij}. \quad (31)$$

Where:

(β_{ij}) = methylation beta-value for individual i at CpG site j

(β_1) = effect of stress

(β_2) = effect of glycaemic control

After Benjamini–Hochberg correction:

$$q = \frac{p_i \cdot m}{i} \quad \text{..... (32)}$$

Where (m) = total number of tests.

✓ *Significant Differentially Methylated Regions*

A total of 27 CpG sites across 15 genes remained significant (FDR q < 0.05). Notably, stress-associated methylation changes were observed in:

- NR3C1 (Glucocorticoid receptor gene)
- BDNF (Brain-derived neurotrophic factor)
- IL6 (Interleukin-6)
- TNF (Tumor necrosis factor-alpha)
- APOE (Apolipoprotein E)

Table 10 Top Differentially Methylated Genes Associated with High Stress

Gene	Direction of Methylation	Δβ (High vs Low Stress)	Adjusted q-value	Functional Relevance
NR3C1	Hypermethylation	+0.045	0.012	HPA axis regulation
BDNF	Hypermethylation	+0.038	0.018	Neurotrophic signaling
IL6	Hypomethylation	−0.052	0.006	Pro-inflammatory cytokine
TNF	Hypomethylation	−0.047	0.009	Inflammatory mediator
APOE	Hypermethylation	+0.031	0.021	Lipid & amyloid metabolism

✓ *Interpretation:*

- Hypermethylation of NR3C1 suggests reduced glucocorticoid receptor expression, potentially impairing HPA axis feedback.
- Hypermethylation of BDNF may reflect reduced neurotrophic support.
- Hypomethylation of IL6 and TNF promoters suggests increased inflammatory gene transcription.

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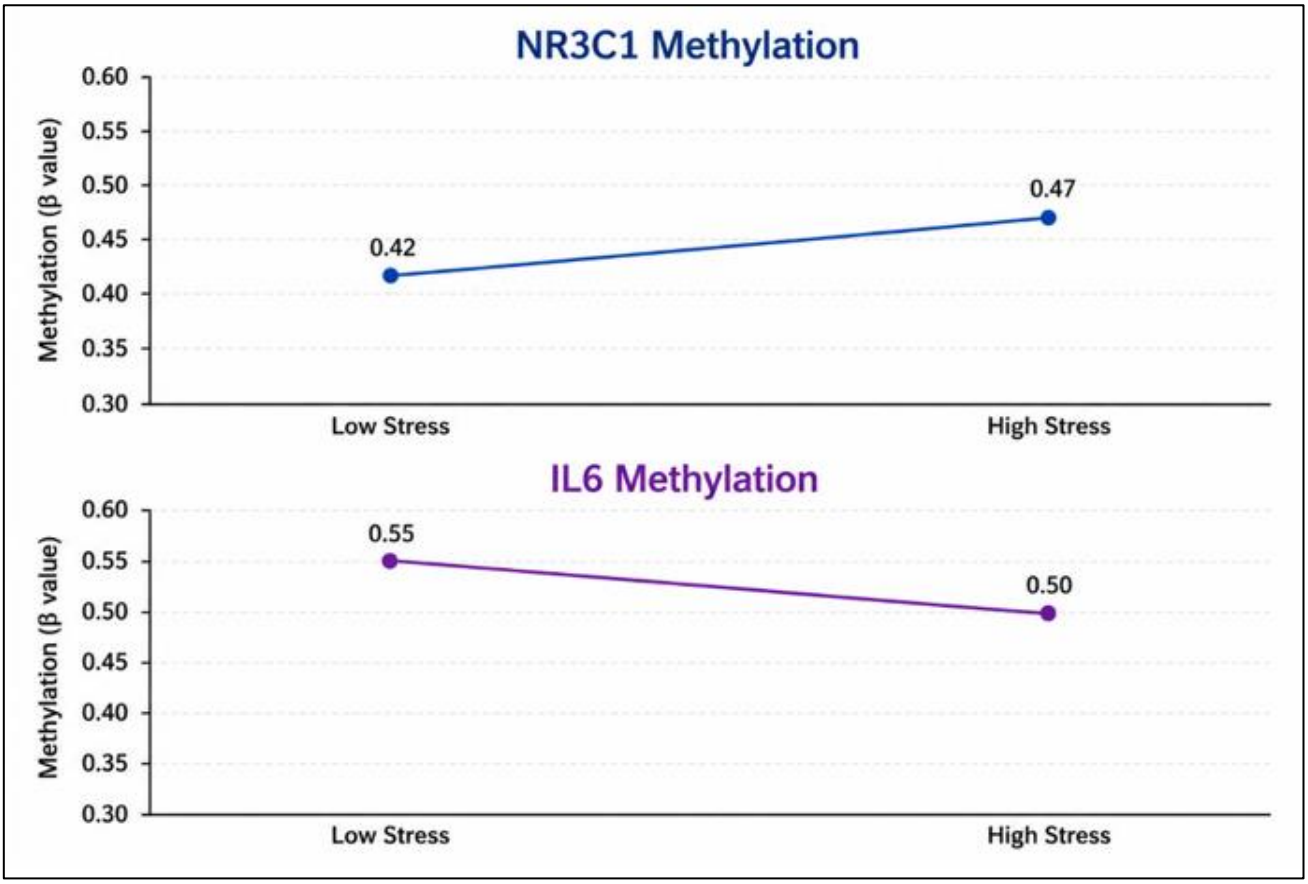

Fig 11 Mean Methylation (β-values) by Stress Category

These patterns support stress-related dysregulation of both glucocorticoid and inflammatory pathways.

- *Histone Modification Patterns*

Chromatin immunoprecipitation (ChIP) assays were performed on selected gene promoters to evaluate histone marks associated with transcriptional activation (H3K9ac) and repression (H3K27me3).

Table 11 Comparative Findings

Gene	H3K9ac (Activation)	H3K27me3 (Repression)	Interpretation
IL6	↑ Increased	↓ Decreased	Enhanced transcription
TNF	↑ Increased	↓ Decreased	Pro-inflammatory activation
BDNF	↓ Reduced	↑ Increased	Reduced neuroplasticity signaling
NR3C1	↓ Reduced	↑ Increased	Impaired glucocorticoid feedback

✓ *Participants with High Stress Exhibited:*

- Increased activating histone marks at inflammatory gene loci
- Increased repressive marks at neuroprotective gene loci

ANOVA comparisons between stress categories showed:

$$F(2,161) = 5.91,\ p = 0.003 \text{ (IL6 H3K9ac enrichment)} \quad (33)$$

These findings are consistent with transcriptional activation of inflammatory genes and repression of neuronal survival genes.

- *Interaction with Glycaemic Control*

To assess synergy between stress and hyperglycaemia, interaction models were fitted:

$$\text{Methylation} = \beta_0 + \beta_1(\text{Stress}) + \beta_2(\text{HbA1c}) + \beta_3(\text{Stress} \times \text{HbA1c}) + \varepsilon \quad (34)$$

✓ *Significant Interaction Effects were Observed for:*

- IL6 (p = 0.014)
- BDNF (p = 0.021)

Participants with both high stress and HbA1c ≥ 7% exhibited the most pronounced methylation changes.

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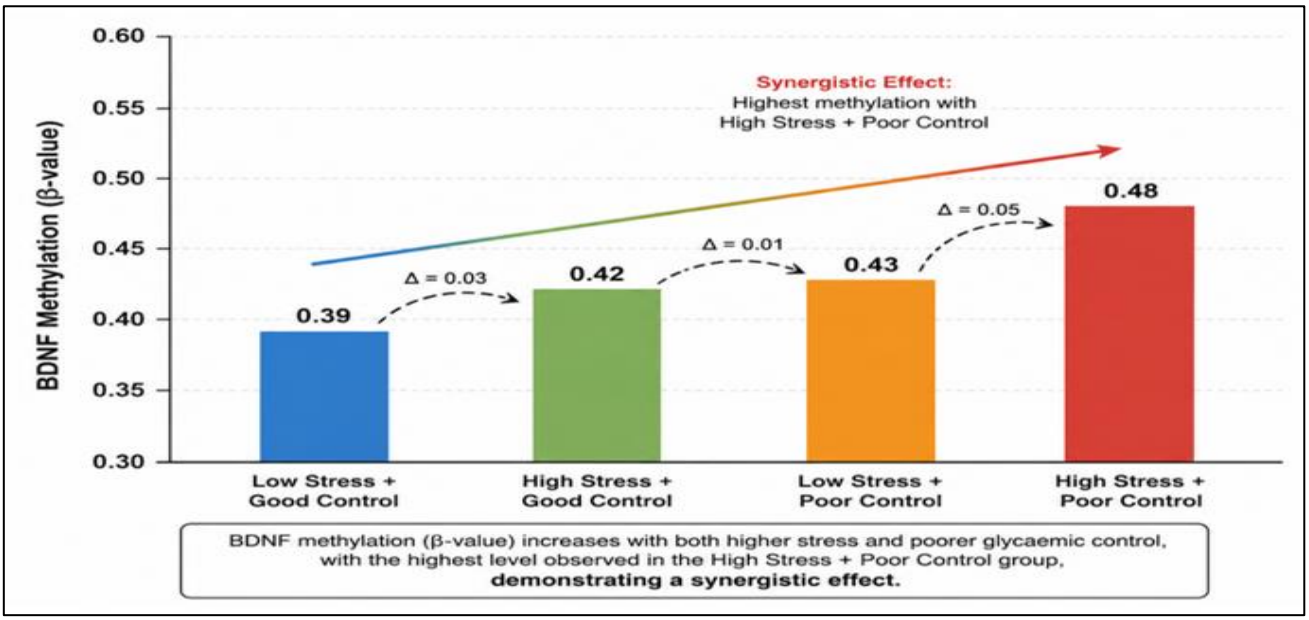

Fig 12 Synergistic Effect of Stress and Poor Glycaemic Control.

This pattern demonstrates amplified epigenetic alteration under combined psychosocial and metabolic stress.

- *Pathway Enrichment Analysis*

Gene ontology (GO) enrichment identified overrepresented pathways among differentially methylated genes:

✓ Neuroinflammatory signaling
✓ Glucocorticoid receptor signaling
✓ Insulin receptor signaling
✓ Amyloid precursor protein processing

Adjusted enrichment significance:

$q < 0.05$ ..... (35)

These results align with the study's conceptual framework linking stress, inflammation, and neurodegenerative vulnerability.

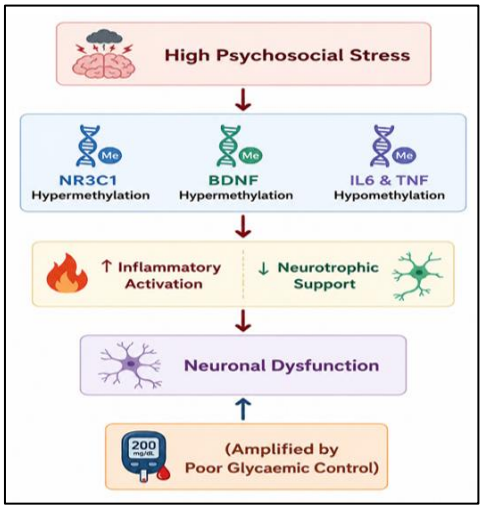

Fig 13 Summary Diagram of Epigenetic Findings

The epigenetic findings demonstrate that elevated psychosocial stress is associated with distinct DNA methylation patterns and histone modification profiles in genes central to glucocorticoid regulation, neuroplasticity, and inflammation. These changes were more pronounced among individuals with poor glycaemic control, supporting a synergistic interaction between metabolic and psychosocial stressors.

Collectively, these results provide molecular evidence for stress-related biological embedding in individuals with T2D and offer mechanistic insight into how psychosocial stress may accelerate neurodegenerative risk. Subsequent sections further explore interaction effects and broader clinical implications.

➢ *Interaction Effects*

This section examines the combined and interactive effects of psychosocial stress and glycaemic control on epigenetic outcomes. Based on the conceptual framework, it was hypothesised that poor glycaemic control would amplify stress-associated epigenetic modifications, thereby increasing neuroinflammatory activation and neuronal vulnerability.

- *Synergistic Influence of Poor Glycaemic Control and Stress*

To evaluate interaction effects, multiplicative interaction terms were included in multivariable regression models.

✓ *Interaction Model*

$$Y = \beta_0 + \beta_1(\text{Stress}) + \beta_2(\text{HbA1c}) + \beta_3(\text{Stress} \times \text{HbA1c}) + \beta_4(\text{Covariates}) + \varepsilon \text{ ..... ……..(36)}$$

Where:

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(Y) = DNA methylation β-value (or histone enrichment score)

(β_3) = interaction coefficient

A statistically significant (β_3) indicates moderation of stress effects by glycaemic control.

Table 12 Key Interaction Results

Gene	Interaction Coefficient (β_3)	p-value	Interpretation
IL6	−0.006	0.014	Amplified hypomethylation under poor control
TNF	−0.005	0.028	Increased inflammatory activation
BDNF	+0.007	0.021	Greater hypermethylation with high HbA1c
NR3C1	+0.004	0.047	Stronger repression of glucocorticoid receptor

These findings indicate that individuals with both elevated stress and poor glycaemic control exhibit more pronounced epigenetic alterations than would be expected from either factor alone.

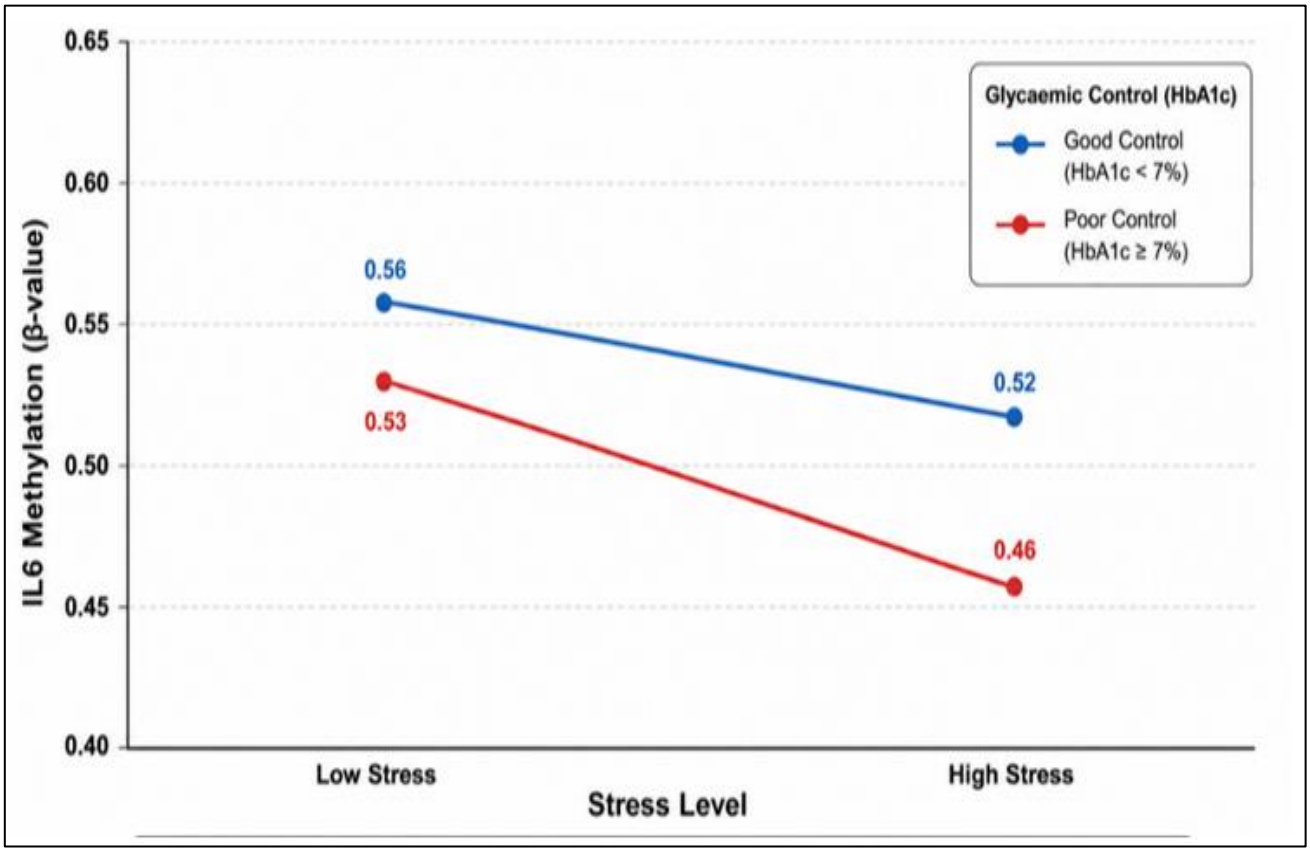

Fig 14 Interaction between Stress and HbA1c on IL6 Methylation

The slope of methylation decline across stress levels is steeper among those with poor glycaemic control, demonstrating a synergistic interaction.

- *Stratified Analysis by Metabolic Status*

To further examine the moderating role of metabolic dysfunction, participants were stratified into two groups:

✓ Good Glycaemic Control: HbA1c < 7.0%
✓ Poor Glycaemic Control: HbA1c ≥ 7.0%

Separate regression analyses were conducted within each subgroup.

✓ *Stratified Regression Results*

▪ *Good Glycaemic Control Group (n = 46)*

$$\text{BDNF Methylation} = \beta_0 + \beta_1(\text{Stress}) + \varepsilon; \quad \beta_1 = 0.003,\ p = 0.089 \quad (37)$$

Stress was not significantly associated with BDNF methylation in this subgroup.

▪ *Poor Glycaemic Control Group (n = 118)*

$$\beta_1 = 0.009,\ p < 0.001 \quad (38)$$

A significant positive association was observed between stress and BDNF hypermethylation.

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Table 13 Comparison of Effect Sizes

Outcome	Good Control β	Poor Control β	Effect Amplification
BDNF methylation	0.003	0.009	3-fold increase
IL6 methylation	−0.002	−0.008	4-fold increase
TNF methylation	−0.003	−0.007	>2-fold increase

The magnitude of stress-associated epigenetic changes was consistently greater among participants with poor glycaemic control.

- *Combined Risk Category Analysis*

Participants were categorised into four groups:

✓ Low Stress + Good Control
✓ High Stress + Good Control
✓ Low Stress + Poor Control
✓ High Stress + Poor Control

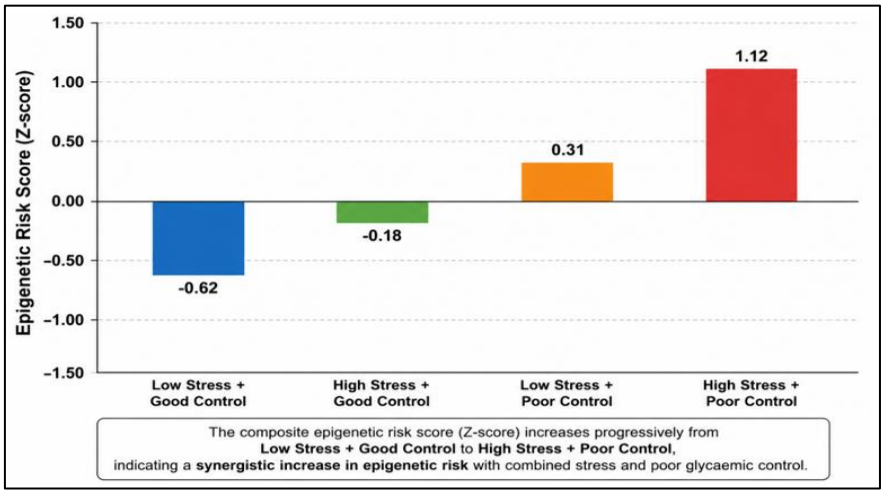

Fig 15 Combined Risk Effect on Composite Epigenetic Risk Score

ANOVA:

$$F(3,160) = 9.47,\ p < 0.001 \quad \text{..... (39)}$$

Post hoc analysis showed the High Stress plus Poor Control group differed significantly from all other groups.

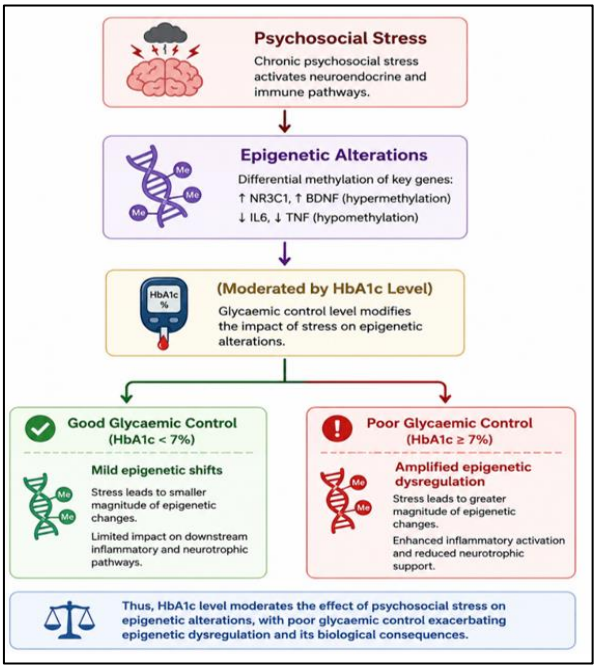

Fig 16 Summary Diagram of Interaction

The interaction analyses provide strong evidence that poor glycaemic control potentiates the biological impact of psychosocial stress at the epigenetic level. Individuals with both elevated stress and high HbA1c exhibited the greatest degree of inflammatory gene activation and repression of neuroprotective genes.

These findings support a synergistic model in which metabolic dysfunction magnifies stress-induced molecular changes, potentially accelerating neurodegenerative processes. Clinically, the results underscore the importance of integrated metabolic and psychosocial interventions to mitigate compounded biological risk.

The next section (4.5) integrates these findings within the broader literature and discusses their implications for neurodegenerative disease progression.

➢ *Interpretation of Findings*

This section integrates the psychosocial, metabolic, and epigenetic results within the study's conceptual framework and existing scientific literature. The findings provide converging evidence for the biological embedding of psychosocial stress in individuals with Type 2 Diabetes and offer mechanistic insight into how stress may accelerate neurodegenerative vulnerability, particularly in the context of poor glycaemic control.

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- *Biological Embedding of Psychosocial Stress*

The concept of biological embedding posits that chronic psychosocial exposures become incorporated into physiological systems through sustained neuroendocrine, immune, and molecular alterations (5,14). In the present study, elevated perceived stress was associated with:

- ✓ Hypermethylation of NR3C1 (glucocorticoid receptor gene)
- ✓ Hypermethylation of BDNF (neurotrophic support gene)
- ✓ Hypomethylation of IL6 and TNF (pro-inflammatory cytokine genes)
- ✓ Activating histone marks at inflammatory loci

These findings indicate that psychosocial stress is not merely a psychological state but is reflected in measurable epigenetic modifications affecting stress-response and inflammatory pathways. Hypermethylation of NR3C1 suggests impaired glucocorticoid receptor feedback, potentially sustaining HPA axis activation. This aligns with prior evidence linking stress exposure to altered NR3C1 methylation and dysregulated cortisol signaling (9).

Similarly, BDNF hypermethylation may reduce neurotrophic support necessary for synaptic plasticity and neuronal survival (6). Reduced BDNF expression has been implicated in cognitive impairment and neurodegenerative conditions. The observed inflammatory gene hypomethylation, coupled with activating histone modifications, suggests transcriptional upregulation of pro-inflammatory cytokines, reinforcing chronic low-grade inflammation.

Collectively, these molecular signatures support the hypothesis that chronic psychosocial stress becomes biologically embedded via epigenetic regulation, particularly in genes central to neuroendocrine and immune function.

- *Mechanistic Implications for Neurodegenerative Progression*

The observed epigenetic alterations provide plausible mechanistic pathways linking stress and metabolic dysfunction to neurodegeneration.

First, sustained inflammatory activation indicated by IL6 and TNF hypomethylation and increased H3K9 acetylation may promote microglial activation and oxidative stress within the central nervous system (15). Chronic neuroinflammation is a well-established contributor to amyloid accumulation, tau hyperphosphorylation, and synaptic dysfunction (11,15).

Second, reduced neurotrophic support via BDNF hypermethylation may impair neuronal resilience and plasticity, rendering neurons more vulnerable to metabolic and oxidative insults. In T2D, where hyperglycaemia already contributes to oxidative stress and vascular dysfunction (4), such epigenetic repression may accelerate neuronal degeneration.

Third, interaction analyses demonstrated that poor glycaemic control significantly amplified stress-associated methylation changes. This synergistic effect suggests that hyperglycaemia may exacerbate stress-induced epigenetic remodeling. Chronic elevated glucose levels promote advanced glycation end-products (AGEs), mitochondrial dysfunction, and activation of NF-κB-mediated inflammatory signaling (4,14). These processes may influence DNA methyltransferase activity and chromatin remodeling, intensifying epigenetic dysregulation.

The combined presence of high psychosocial stress and poor metabolic control therefore appears to create a “double-hit” biological environment characterised by:

HPA Axis Dysregulation + Hyperglycaemia → Epigenetic Alteration → Neuroinflammation → Neuronal Dysfunction ..... (40)

This cascade is consistent with emerging models of metabolic–neuroinflammatory cross-talk contributing to cognitive decline in T2D populations (40).

- *Comparison with Existing Literature*

The findings align with and extend prior research in several important ways.

- ✓ Stress and NR3C1 Methylation: Previous studies have reported altered NR3C1 methylation in individuals exposed to early-life adversity or chronic stress (9). The present study demonstrates similar stress-associated methylation patterns in an adult African T2D population, suggesting that stress-related glucocorticoid dysregulation may persist across the life course and clinical contexts.
- ✓ Inflammatory Gene Activation: Evidence from psychoneuroimmunology research indicates that chronic stress enhances pro-inflammatory gene expression (14). The observed hypomethylation and increased activating histone marks at IL6 and TNF promoters are consistent with this literature, providing epigenetic confirmation of inflammatory upregulation.
- ✓ Metabolic–Epigenetic Links in T2D: Epigenetic dysregulation in metabolic tissues has been documented in T2D (10). However, few studies have examined stress-associated epigenetic signatures in diabetic populations, and even fewer have been conducted in Sub-Saharan Africa. The present findings extend existing knowledge by integrating psychosocial and metabolic dimensions within a single molecular framework.
- ✓ Neurodegeneration-Related Epigenetic Changes: Altered DNA methylation in genes implicated in Alzheimer’s disease has been reported in brain tissue and peripheral blood (11). The identification of stress-sensitive epigenetic changes in APOE and neuroinflammatory genes suggests potential peripheral biomarkers of neurodegenerative vulnerability.

Importantly, most previous epigenetic studies have been conducted in European or North American populations (12). The present study contributes novel data from a

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Ghanaian cohort, highlighting the importance of inclusive molecular research in diverse populations

✓ *Integrated Interpretation*

The convergence of psychosocial stress, metabolic dysfunction, and epigenetic alterations observed in this study supports a biopsychosocial model of neurodegenerative risk in T2D. The data suggest that:

- Psychosocial stress is biologically embedded via epigenetic modifications.
- These modifications influence genes regulating inflammation, glucocorticoid signaling, and neuronal survival.
- Poor glycaemic control amplifies stress-associated molecular changes.
- The combined effects may accelerate neurodegenerative processes.

These findings emphasizes the importance of integrating mental health assessment into diabetes management and highlight epigenetic biomarkers as potential tools for early risk stratification.

The study therefore provides molecular evidence that psychosocial stress and metabolic dysfunction converge at the epigenetic level to influence pathways relevant to neurodegeneration. These findings advance understanding of stress-related biological embedding in African populations and support integrated clinical approaches addressing both metabolic and psychosocial determinants of chronic disease progression.

➢ *Clinical and Public Health Implications*

The findings of this study have important implications for clinical practice, public health policy, and future precision medicine initiatives in Sub-Saharan Africa. By demonstrating that psychosocial stress is associated with measurable epigenetic alterations—particularly among individuals with poor glycaemic control—this research underscores the need for integrated, multidimensional approaches to chronic disease management.

- *Integration of Mental Health in Diabetes Management*

The strong association between perceived stress and adverse metabolic as well as epigenetic profiles highlights the clinical importance of incorporating mental health screening into routine diabetes care.

✓ *Clinical Implications*

- Routine Stress Screening: Incorporating validated tools such as the Perceived Stress Scale (PSS) into outpatient diabetes clinics could enable early identification of individuals at elevated psychosocial risk.
- Holistic Care Models: Diabetes management protocols should extend beyond glycaemic monitoring to include psychological counselling, stress-reduction interventions, and social support services. Evidence suggests that stress reduction may improve glycaemic outcomes and reduce systemic inflammation (7,14).
- Targeted Interventions for High-Risk Groups: Individuals exhibiting both poor glycaemic control and high stress levels—who in this study demonstrated the most pronounced epigenetic dysregulation—may benefit from intensified multidisciplinary care.

The data suggest that failure to address psychosocial stress may limit the effectiveness of pharmacological and lifestyle interventions aimed solely at metabolic control. Therefore, integrated care frameworks that combine endocrinology, mental health, and lifestyle medicine may improve long-term neurological outcomes.

- *Potential for Epigenetic Biomarkers in Early Detection*

The identification of stress-associated epigenetic signatures in genes such as NR3C1, BDNF, IL6, TNF, and APOE raises the possibility of developing peripheral epigenetic biomarkers for early neurodegenerative risk detection.

✓ *Clinical Utility of Epigenetic Biomarkers*

Epigenetic biomarkers offer several potential advantages:

- Early Detection: DNA methylation changes may precede overt clinical symptoms of cognitive decline.
- Dynamic and Modifiable: Unlike fixed genetic variants, epigenetic marks are potentially reversible, making them attractive targets for therapeutic monitoring.
- Risk Stratification: Composite epigenetic risk scores could complement traditional metabolic markers (e.g., HbA1c, lipid profiles) to identify patients at highest neurodegenerative risk.

For example, an integrated risk index may be conceptualized as:

$$\text{Neurodegenerative Risk Index} = \alpha_1(\text{HbA1c}) + \alpha_2(\text{PSS}) + \alpha_3(\text{Epigenetic Score}) \ldots\ldots\ldots\ldots..(41)$$

Such models could enhance predictive accuracy in high-risk populations.

However, translation into clinical practice requires longitudinal validation, cost-effectiveness evaluation, and development of regionally accessible molecular diagnostic platforms.

- *Relevance for African Precision Medicine Initiatives*

The underrepresentation of African populations in genomic and epigenomic research has limited the development of population-specific diagnostic and therapeutic tools (12). This study contributes to closing that gap by generating molecular data from a Ghanaian T2D cohort.

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➢ *Implications for Precision Medicine*

- Population-Specific Biomarker Development: Epigenetic signatures identified in African populations may differ from those reported in European cohorts due to genetic diversity and environmental exposures. Locally derived data enhance the validity of risk prediction models.
- Contextualized Disease Pathways: The integration of sociocultural stress exposures into molecular research supports a more context-sensitive approach to disease prevention and management.
- Capacity Building: Expanding epigenetic research infrastructure in Sub-Saharan Africa promotes sustainable scientific advancement and equitable participation in global precision medicine efforts.
- Policy Alignment: Findings align with continental health priorities addressing the rising burden of non-communicable diseases. Integrating psychosocial determinants into metabolic care strategies may reduce long-term dementia burden.

✓ *Broader Public Health Significance*

Given the projected rise in both diabetes and dementia prevalence in Sub-Saharan Africa, early preventive strategies are urgently needed. The study suggests that addressing psychosocial stress may not only improve metabolic outcomes but also mitigate molecular pathways linked to neurodegeneration.

In resource-constrained settings, scalable interventions such as community-based stress reduction programs, peer-support networks, and culturally adapted behavioural therapies could have significant long-term benefits.

V. CONCLUSIONS AND RECOMMENDATIONS

➢ *Summary of Key Findings*

This study examined the relationship between psychosocial stress, metabolic dysfunction, and epigenetic regulation among individuals with Type 2 Diabetes in Kumasi, Ghana. The key findings are summarized as follows:

- Psychosocial stress was significantly associated with epigenetic alterations, including differential DNA methylation and histone modifications in genes linked to stress regulation, inflammation, and neuronal survival.
- Key stress-related epigenetic changes included hypermethylation of *NR3C1* and *BDNF*, and hypomethylation of *IL6* and *TNF*, suggesting dysregulation of glucocorticoid, neurotrophic, and inflammatory pathways.
- Poor glycaemic control amplified stress-related epigenetic changes, indicating a synergistic effect between psychosocial stress and metabolic dysfunction.
- Participants with high stress and elevated HbA1c showed the greatest biological risk, including increased inflammatory activation and reduced neuroprotective signaling.
- Overall, the findings support the hypothesis that psychosocial and metabolic stress converge at the epigenetic level, potentially increasing vulnerability to neurodegenerative disease.

➢ *Conclusions*

This study concludes that chronic psychosocial stress may become biologically embedded through epigenetic modifications in individuals with Type 2 Diabetes.

- *Specifically:*

✓ Stress influences genes involved in inflammation, glucocorticoid signaling, and neuronal survival.
✓ These effects are stronger in individuals with poor glycaemic control.
✓ The interaction between stress and hyperglycaemia may represent an important pathway linking diabetes to neurodegenerative risk.

The study provides important evidence from a Sub-Saharan African population and contributes to understanding the molecular links between psychosocial stress and chronic disease progression.

➢ *Recommendations*

Based on these findings, the following recommendations are proposed:

- Integrate routine stress screening into diabetes management using validated tools such as the Perceived Stress Scale (PSS).
- Adopt multidisciplinary care models that combine metabolic management with mental health support.
- Conduct longitudinal studies to establish causal relationships between stress, epigenetic changes, and neurodegenerative outcomes.
- Evaluate stress-reduction interventions to determine whether adverse epigenetic changes can be reduced or reversed.
- Expand epigenetic research in African populations to improve population-specific understanding and support precision medicine initiatives.

➢ *Areas for Future Research*

Future studies should focus on:

- Neuroimaging and cognitive testing to directly assess links between epigenetic changes and brain health.
- Multi-omics approaches (transcriptomics, proteomics, and metabolomics) to better understand underlying molecular mechanisms.
- Development of predictive risk models, as such models could support early identification of high-risk individuals and guide personalized interventions.

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REFERENCES

[1]. Ajayi-Kaffi, O., Igba, E., Azonuche, T. I., & Ijiga, O. M. (2025). Agile-Driven Digital Transformation Frameworks for Optimizing Cloud-Based Healthcare Supply Chain Management Systems. *International Journal of Scientific Research and Modern Technology*, *4*(5), 138–156.

[2]. Ajiboye AS, Balogun TK, Imoh PO, Ijiga AC, Olola TM, Ahmadu EO. Enhancing adolescent suicide prevention through the implementation of trauma-informed care models in school-based mental health programs. *Int J Appl Res Soc Sci.* 2025;7(5).

[3]. Ajiboye AS, Balogun TK, Imoh PO, Ijiga AC, Olola TM, Ahmadu EO. Understanding the impact of social media on mental health in autistic youth and expanding access to culturally responsive behavioral health services in underserved communities. *Int J Sci Res Humanit Soc Sci.* 2025;2(3).

[4]. Ajiboye AS, Balogun TK, Peter-Anyebe AC, Ahmadu EO, Olola TM. Investigating the epigenetic and psychological effects of community gun violence and mass shootings on youth and families through a transgenerational trauma lens. *Soc Values Soc*. 2025;7(2):74–82.

[5]. Akello , E. F., Ijiga, O. M., Idoko, I. P., & Enyejo, L. A. (2025). Multimodal Large Language Models for Diagnostic Feedback Analytics in STEM Learning Platforms. *International Journal of Scientific Research and Modern Technology*, *4*(1), 182–210.

[6]. Akunna, N. L. & Ijiga, O. M. (2025). An Artificial Intelligence Driven Framework For Predicting Project Delivery Risks Using Enterprise Resource Planning Data In Large Multinational Projects. World Journal of Advanced Multidisciplinary Research, 2(6), 07–25.

[7]. Akunna, N. L., & Ijiga, O. M. (2024). Development of a Machine Learning Algorithm for Tender Bid Evaluation and Contractor Selection with Comparative Analysis Against Traditional Procurement Scoring Methods. *International Journal of Scientific Research and Modern Technology*, *3*(8), 122–139.

[8]. Akunna, N. L., & Ijiga, O. M. (2025). A Predictive Analytics Model for Early Detection of Budget Overruns in Large-Scale Projects Using Integrated Financial and Operational Data. *International Journal of Scientific Research and Modern Technology*, *4*(12), 190–208.

[9]. Animasaun JB, Ijiga OM, Ayoola VB, Enyejo LA. Improving RT-PCR detection accuracy for respiratory virus transmission network (RVTN) models through optimized RNA extraction protocols under CDC biosafety guidelines. *Int J Sci Res Sci Technol*. 2025;12(6):748–768.

[10]. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat Rev Neurol.* 2018;14(3):168–181.

[11]. Ayoola VB, Audu BA, Boms JC, Ifoga SM, Mbanugo OJ, Ugochukwu UN. Integrating industrial hygiene in hospice and home-based palliative care to enhance quality of life for respiratory and immunocompromised patients. *IRE J*. 2024;8(5).

[12]. Babatuyi PB, Imoh PO, Igwe EU, Enyejo JO. The impact of public health policy on resource distribution and health equity during epidemics in low-income U.S. populations. *Int J Health Sci.* 2025;13(1).

[13]. Babatuyi PB, Imoh PO, Igwe EU, Enyejo JO. The role of public health leadership in strengthening emergency response protocols and addressing infrastructure gaps during infectious disease outbreaks. *Int J Sci Res Mod Technol*. 2024;3(10):109–122.

[14]. Balogun TK, Enyejo JO, Ahmadu EO, Akpovino CU, Olola TM, Oloba BL. The psychological toll of nuclear proliferation and mass shootings in the U.S. and how mental health advocacy can balance national security with civil liberties. *IRE J*. 2024;8(4).

[15]. Bamigwojo OV, Ezike MCG, Owhenagbo P, et al. Mathematical analysis of hepatitis B virus transmission dynamics in the absence of therapy with Atangana-Baleanu fractional-order SPQWXY model. *J Adv Math Comput Sci.* 2024;39(11):1–28.

[16]. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol.* 2006;5(1):64–74.

[17]. Bird A. Perceptions of epigenetics. *Nature.* 2007;447(7143):396–398.

[18]. Chatterjee S, Peters SAE, Woodward M, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people. *Diabetes Care.* 2016;39(2):300–307.

[19]. Darko D, Kwekutsu E, Idoko IP. Synergistic effects of phytochemicals in combating chronic diseases with insights into molecular mechanisms and nutraceutical development. *Int J Innov Sci Res Technol*. 2025;10(3).

[20]. Dayeh T, Ling C. Does epigenetic dysregulation of pancreatic islets contribute to impaired insulin secretion and type 2 diabetes? *Biochem Cell Biol*. 2015;93(5):511–521.

[21]. De Jager PL, Srivastava G, Lunnon K, et al. Alzheimer's disease: early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci. *Nat Neurosci*. 2014;17(9):1156–1163.

[22]. Eguagie, M. O., Idoko, I. P., Ijiga, O. M., Enyejo, L. A., Okafor, F. C. & Onwusi, C. N. (2025). Geochemical and Mineralogical Characteristics of Deep Porphyry Systems: Implications for Exploration Using ASTER. *International Journal of Scientific Research in Civil Engineering.* 2025 | IJSRCE | Volume 9 | Issue 1 | ISSN : 2456-6667. doi :

[23]. Frimpong, G., Peter-Anyebe, A. C., & Ijiga, O. M. (2023). Artificial Intelligence Driven Compliance Automation Improving Audit Readiness and Fraud Detection within Healthcare Revenue Cycle Management Systems. Global Journal of Engineering, Science & Social Science Studies. Volume 09, Issue 09, December 2023 ISSN- 2394-3084.

[24]. Frimpong, G., Peter-Anyebe, A. C., & Ijiga, O. M. (2025). Predictive compliance modeling using natural language processing for real time regulatory intelligence and policy deviation detection in

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26may1806

hospitals. *International Medical Science Research Journal, , 5(9), , November 2025.*

[25]. Gabla, E. S., Peter-Anyebe, A. C., & Ijiga, O. M. (2025). Assessing Machine Learning Enabled Anomaly Detection Models for Real Time Cyberattack Mitigation in Optical Fiber Communication Systems. *World Journal of Advanced Engineering Technology and Sciences*, 2025, 17(02), 001–017.

[26]. Gaye A. Predictive modeling and statistical analysis of hypertension cases at a small teaching hospital. *ICONIC Res Eng J.* 2025;8(11).

[27]. Hackett RA, Steptoe A. Type 2 diabetes mellitus and psychological stress — a modifiable risk factor. *Nat Rev Endocrinol.* 2017;13(9):547–560.

[28]. Ibuan OE, Igwe EU, Peter-Anyebe AC. Mindfulness-based interventions in adolescent behavioral health: a review of school-based applications and culturally responsive practices. *Malays Ment Health J.* 2025;4(1):13–22.

[29]. Idika, C. N. & Ijiga, O. M. (2025). Blockchain-Based Intrusion Detection Techniques for Securing Decentralized Healthcare Information Exchange Networks. *Information Management and Computer Science*, Zibeline International Publishing 8(2): 25-36. DOI:

[30]. Idoko DO, Adenyi M, Senejani MN, Erondu OF, Adeyeye Y. Nanoparticle-assisted cancer imaging and targeted drug delivery for early-stage tumor detection. *Int J Innov Sci Res Technol.* 2024;9(11).

[31]. Idoko DO, Agaba JA, Nduka I, et al. The role of HSE risk assessments in mitigating occupational hazards and infectious disease spread: a public health review. *Open Access Res J Biol Pharm.* 2024;11(02):11–30.

[32]. Idoko DO, Mbachu OE, Babalola INO, et al. Biostatistics for predicting health disparities in infectious disease outcomes. *IRE J.* 2024;8(4).

[33]. Idoko DO, Mbachu OE, Babalola INO, et al. Exploring the impact of obesity and community health programs on enhancing endometrial cancer detection. *Int J Front Med Surg Res.* 2024;6(02):1–18.

[34]. Idoko DO, Mbachu OE, Ijiga AC, et al. Assessing the influence of dietary patterns on preeclampsia and obesity among pregnant women in the United States. *Int J Biol Pharm Sci Arch.* 2024;8(01):85–103.

[35]. Idoko, I. P., Ijiga, O. M., Enyejo, L. A., Ugbane, S. I., Akoh, O., & Odeyemi, M. O. (2024). Exploring the potential of Elon Musk's proposed quantum AI: A comprehensive analysis and implications. **Global Journal of Engineering and Technology Advances**, 18(3), 048-065.

[36]. Ifiala, I. A., Ijiga, O. M. & Igba, E. (2026). Algorithmic Fairness and Demographic Representation Optimization in U.S. Clinical Trials Using Constrained Multi-Objective Learning *International Journal of Healthcare Sciences* Vol. 14, Issue 1, pp: (40-57) DOI:

[37]. Ijiga AC, Balogun TK, Ahmadu EO, et al. The role of the United States in shaping youth mental health advocacy and suicide prevention through foreign policy and media in conflict zones. *Magna Sci Adv Res Rev.* 2024;12(01):202–218.

[38]. Ijiga AC, Balogun TK, Sariki AM, et al. Investigating the influence of domestic and international factors on youth mental health and suicide prevention in societies at risk of autocratization. *IRE J.* 2024;8(5).

[39]. Ijiga AC, Igbede MA, Ukaegbu C, et al. Precision healthcare analytics: integrating ML for automated image interpretation. *World J Biol Pharm Health Sci.* 2024;18(01):336–354.

[40]. Ijiga OM, Ifenatuora GP, Olateju M. STEM-driven public health literacy: using data visualization and analytics to improve disease awareness in secondary schools. *Int J Sci Res Sci Technol.* 2023;10(4):773–793.

[41]. Ijiga, M. O., Olarinoye, H. S., Yeboah, F. A. B. & Okolo, J. N. (2025). Integrating Behavioral Science and Cyber Threat Intelligence (CTI) to Counter Advanced Persistent Threats (APTs) and Reduce Human-Enabled Security Breaches. International Journal of Scientific Research and Modern Technology, 4(3), 1–15.

[42]. Ijiga, O. M., Idoko, I. P., Ebiega, G. I., Olajide, F. I., Olatunde, T. I., & Ukaegbu, C. (2024). Harnessing adversarial machine learning for advanced threat detection: AI-driven strategies in cybersecurity risk assessment and fraud prevention. *Open Access Research Journals.* Volume 13, Issue.

[43]. Ijiga, O. M., Ifenatuora, G. P., & Olateju, M. (2023). STEM-Driven Public Health Literacy : Using Data Visualization and Analytics to Improve Disease Awareness in Secondary Schools. *International Journal of Scientific Research in Science and Technology*. Volume 10, Issue 4 July-August-2023 Page Number : 773-793.

[44]. Imoh PO, Adeniyi M, Ayoola VB, Enyejo JO. Advancing early autism diagnosis using multimodal neuroimaging and AI-driven biomarkers. *Int J Sci Res Mod Technol.* 2024;3(6):40–56.

[45]. Imoh PO, Ajiboye AS, Balogun TK, et al. Exploring the integration of psychedelic-assisted therapy and digital mental health interventions in trauma recovery. *Magna Sci Adv Res Rev.* 2025.

[46]. Imoh PO, Idoko IP. Gene-environment interactions and epigenetic regulation in autism etiology. *Int J Sci Res Mod Technol.* 2022;1(8):1–16.

[47]. Imoh PO. Impact of gut microbiota modulation on autism-related behavioral outcomes. *Int J Sci Res Mod Technol.* 2023;2(8).

[48]. International Diabetes Federation. *IDF Diabetes Atlas.* 10th ed. Brussels: IDF; 2021.

[49]. Kwarteng, R. A., Idoko, I. P., Ijiga, O. M. & Enyejo, L. A. (2020). Integrating Cybersecurity Awareness and Access Control into Organizational IT Operations for Risk Reduction *International Journal of Scientific Research in Computer Science, Engineering and Information Technology* Volume 6, Issue 1 pg. 243-261 doi :

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26may1806

[50]. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci.* 2009;10(6):434–445.
[51]. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med.* 1998;338(3):171–179.
[52]. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to chronic diseases of aging. *Psychol Bull.* 2011;137(6):959–997.
[53]. Nwatuzie, G. A., Ijiga, O. M., Idoko, I. P., Enyejo, L. A. & Ali, E. O. (2025). Design and Evaluation of a User-Centric Cryptographic Model Leveraging Hybrid Algorithms for Secure Cloud Storage and Data Integrity. American Journal of Innovation in Science and Engineering (AJISE). Volume 4 Issue 1, SSN: 2158-7205
[54]. Nwokocha, C. R., Peter-Anyebe, A. C., & Ijiga, O. M. (2021). Evaluating FHIR-Driven Interoperability Frameworks for Secure System Migration and Data Exchange in U.S. Health Information Networks. *International Journal of Scientific Research in Science and Technology* Print ISSN: 2395-6011 | Online ISSN: 2395-602X (www.ijsrst.com)
[55]. Okeme ABK, Akeju O, Enyejo LA, Ibrahim AI. Exploring the impact of wearable health devices on chronic disease management. *Int J Adv Res Publ Rev*. 2025;2(2):43–69.
[56]. Okpanachi AT, Igba E, Imoh PO, et al. Leveraging digital biomarkers and advanced data analytics in medical laboratory. *Int J Sci Res Sci Technol.* 2025;12.
[57]. Onmonya OM, Igwe EU, Imoh PO. Pastoral counseling as a trauma-informed response to intimate partner violence. *Malays Ment Health J.* 2025.
[58]. Onuh JE, Idoko IP, Igbede MA, et al. Harnessing synergy between biomedical and electrical engineering. *World J Adv Eng Technol Sci.* 2024;11(2):628–649.
[59]. Oyebanji, O. S., Apampa, A. R., Idoko, P. I., Babalola, A., Ijiga, O. M., Afolabi, O. & Michael, C. I. (2024). Enhancing breast cancer detection accuracy through transfer learning: A case study using efficient net. *World Journal of Advanced Engineering Technology and Sciences*, 2024, 13(01), 285–318.
[60]. Palma-Gudiel H, Córdova-Palomera A, Leza JC, Fañanás L. Glucocorticoid receptor gene (NR3C1) methylation processes. *J Psychiatr Res.* 2015;60:52–66.
[61]. Perry VH, Holmes C. Microglial priming in neurodegenerative disease. *Nat Rev Neurol.* 2014;10(4):217–224.
[62]. Raphael FO, Boafo A. Improving communication outcomes for veterans with traumatic brain injury (TBI). *Malays Ment Health J.* 2025.
[63]. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry.* 2000;57(10):925–935.
[64]. Sirugo G, Williams SM, Tishkoff SA. The missing diversity in human genetic studies. *Cell.* 2019;177(1):26–31.
[65]. Uwabor, H. S., Emmanuel, I., & Ijiga, O. M. (2025). AI Powered Predictive Frameworks for Risk Modeling and Regulatory Compliance in Decentralized Finance Investment Systems. *International Journal of Scientific Research and Modern Technology*, *4*(11), 95–112.