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Review

Leveraging Artificial Intelligence (AI) in Finding the Interconnected Epidemics and Genetic Predisposition of Obesity and Type 2 Diabetes: A Review

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ABSTRACT

Obesity and Type 2 Diabetes Mellitus (T2DM) are interrelated metabolic disorders that have reached epidemic proportions globally. Both conditions share common etiological factors, including genetic predispositions that significantly influence their pathogenesis. Various studies have shown that there is a significant impact of genetic and environmental factors, but the pathogenesis of obesity and T2DM is still unclear. Obesity contributes to the pathogenesis of type 2 diabetes through mechanisms involving insulin resistance, β-cell dysfunction, chronic inflammation, dysregulated adipokine production and ectopic fat deposition. Addressing obesity through lifestyle modifications, pharmacotherapy or bariatric surgery can significantly reduce the risk and improve the management of T2DM. Research using genetic data has shown exponential growth in these two disorders. In addition to traditional statistical methods for the processing of these data, artificial intelligence (AI) technology has shown obvious advantages in analyzing such complex projects. Furthermore, recent advances in genomic technologies, like NGS have identified several candidate genes associated with obesity and T2DM. This article aims to elucidate the genetic underpinnings of obesity and T2DM, highlighting key genes and their roles in these complex disorders. This review also explores the interplay between these genes and environmental factors, including diet and physical activity, which modulate their expression and impact disease progression. Understanding the genetic landscape of obesity and T2DM provides valuable insights into their pathophysiology and opens avenues for personalized therapeutic strategies. In summary, visceral fat contributes to insulin resistance through inflammatory processes, increased FFAs, dysregulated adipokine production, ectopic fat deposition and its endocrine functions. These mechanisms collectively impair insulin signalling and glucose homeostasis. This review underscores the importance of integrating genetic information with lifestyle interventions to effectively combat these pervasive health challenges.

Keywords: Obesity; Type 2 Diabetes mellitus; Risk factors; Artificial intelligence, Genetic predisposition.

Introduction

Obesity and Type 2 Diabetes Mellitus (T2DM) represent two of the most pressing health challenges globally, often referred to as twin epidemics due to their strong interrelationship. The rising prevalence of these conditions has significant implications for public health, healthcare systems and socio-economic stability. This with article which examines the intricate links between obesity and T2DM, exploring the pathophysiological mechanisms, risk factors and potential intervention strategies. The intersection of genetics with obesity and T2DM underscores the complex etiology of these metabolic disorders. Genetic predisposition plays a crucial role in influencing an individual's risk of developing both obesity and T2DM. This predisposition is mediated through various gene variants that regulate body weight, energy homeostasis and insulin sensitivity.

The Link between Obesity and Type 2 Diabetes

The elaborate connections and sharing of pathophysiological mechanisms between obesity and T2DM are well-established. Both type 2 diabetes and obesity include excess body fat, particularly visceral fat, contributing to insulin resistance and NAFLD (non-alcoholic fatty liver disease) and a constellation of metabolic abnormalities in obese individuals a hallmark of T2DM. However, in some individuals, T2DM can also occur inversely before obesity with inherent insulin resistance resulting in increased hepatic glucose production and elevated insulin levels, which are the actual cause of obesity[1,2]. Genetic and environmental factors play an important role in connecting obesity and T2DM and these factors involved in low insulin secretions from B-cells and peripheral insulin resistance, leading to elevated levels of fatty acids. This causes a decrease in glucose transport into muscle cells, increased fat breakdown and hepatic glucose production. This ectopic fat breakdown interferes with insulin signaling pathways, resulting in insulin resistance, where cells fail to respond effectively to insulin[3]. Further, adipose tissue, particularly in obese individuals, secretes pro-inflammatory cytokines like Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α), interleukin-1β (IL-1β), monocyte chemoattractant protein-1 (MCP-1), IL-6 and others released by activated tissue macrophages and by adipocytes play a significant role. These cytokines provoke important responses in the liver, skeletal muscle, fat tissue and pancreas, resulting in endocrine dysfunction, impaired glucose disposal, impaired β-cell function and reduced suppression of glucose production. In addition to cytokines, adipose tissue produces various adipokines such as leptin and adiponectin. In obesity, an imbalance in these adipokines occurs, with increased leptin (leptin resistance) and decreased adiponectin levels, contributing to the pathogenesis of T2DM. The flow chart (**Figure 1**) depicts the role of Insulin sensitivity leading to obesity and T2DM[4]. Obesity induces ER stress in various tissues, leading to the activation of stress signalling pathways that impair insulin action. This contributes to the development and progression of T2DM (**Figure 1).**

Risk Factors for obesity and T2DM

Several risk factors contribute to the development of obesity and T2DM. Obesity is the primary risk factor since it increases the chance of having T2D by 90 times, and the vast majority of patients are overweight or obese[5]. These include increased age, overweight (especially central obesity)[6], a positive family history, dietary factors such as increased intake of animal fats[7], carbonated drinks and junky foods[8,9]. Ethnic variation in obesity and T2DM is well establish[10]. A history of gestational diabetes, polycystic ovary syndrome, and severe mental illness, comorbidities are also highrisk factors. Cardiovascular disease (CVD) is responsible for 75% of all diabetic-related fatalities, and those with T2D have a higher risk of shorter life spans[11]. Interestingly, longitudinal studies have demonstrated that "psychological stress-related circumstances" (such as stressful working conditions) or mental health problems (such as depression) increase the risk of T2D. Insulin resistance is frequently associated with obesity, which is a pathophysiologic component of type 2 diabetes mellitus (T2DM)[12,13]. Both obesity and T2DM are characterized by high levels of cytokines and fatty acids, and it is believed that both cause insulin resistance, some of the risk factors are listed in (**Table 1**). However, the mechanism by which these impact the disease has yet to be discovered[14,15].

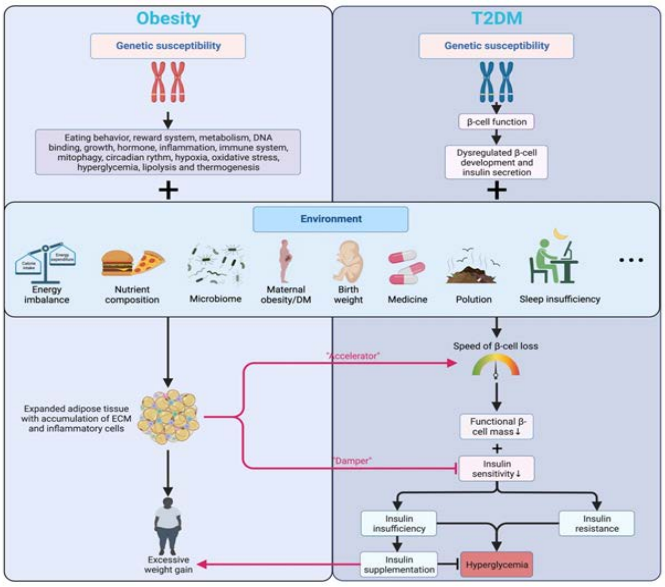

Figure 1: Showing Insulin sensitivity leading to Obesity and T2DM[4].

Role of AI in T2DM and Obesity

In the past years, several studies have been developed involving Information technology (IT) in the healthcare industry to manage patient data and to improve diagnosis and treatment with Artificial Intelligence (AI). This specific area of AI of Computer Science is also a field in science and engineering and it has provided reasoning tools to support clinical decision-making for healthcare professionals[16,17]. Moreover, incorporating AI-based technologies into medical practice is expected to produce substantial changes in many areas of medicine and healthcare[18,19]. AI can help identify risk factors for diabetes development, addressing human limitations and biases when working with massive datasets. Diabetes prevention strategies can be tailored to specific individuals by identifying modifiable risk factors. By incorporating AI analysis a large dataset of demographic details and clinical parameters such as age, gender, BMI, and other socioeconomic status helps in predicting the risk factors of obesity and T2DM. On the other hand, clinical parameter interpretation test results help find accurate and customized treatment plans for patients using AI technology. The development of newer technologies in managing the healthcare system is a potentially significant reduction in the burden of obesity and T2DM treatment which helps in a more proactive and personalized approach[20].

Table 1: The risk factors for obese individuals who may develop Type 2 diabetes mellitus.

Risk Factor	Description
Age	Risk increases with age, particularly after 45 years.
Body Mass Index (BMI)	Higher BMI increases risk; BMI ≥ 25 for most adults.
Over weight	Study shows that ~90% of patients are obese or overweight at T2D diagnosis
Family History	Having a parent or sibling with Type 2 diabetes increases risk.
Diet	High intake of saturated fats, trans fats, and sugary foods.
Carbonated drinks and junky foods	Additional consumption carbonated drinks and junky foods causes Obesity and T2DM
Physical Inactivity	Less than 3 time a week of physical activity.
Non-Alcoholic Fatty Liver Disease	Presence of NAFLD is a significant risk factor.
Gestational Diabetes	History of diabetes during pregnancy.
Ethnicity	Higher risk among African American, Hispanic/ Latino, American Indian, and Asian American populations.
Cardiovascular disease (CVD)	(CVD) is responsible for 75% of all diabetic-related fatalities
Insulin Resistance	Obesity often leads to insulin resistance.
Inflammatory Markers	Elevated levels of proinflammatory cytokines.

Artificial Intelligence and Genomics

After the completion of human Genome projects, the genomes from multiple human populations and diverse primate and non-primate animals have been sequenced and stored in public databases, allowing for key discoveries through DNA sequence comparisons and evaluations of allele frequencies and identifying nucleotide variation in different groups are listed in (**Table 2**)[21,22].

Over the last two decades, significant progress has been achieved in defining protein sequence variation and function (proteomics), as well as RNA transcript isoforms and their expression patterns[23]. Parallel, Artificial intelligence is an essential tool in genetic analysis. Genomic analysis employs Artificial Intelligence (AI) methods such as machine learning (ML) and deep learning (DL) to analyze and understand enormous volumes of genetic data (**Figure 2**). These algorithms may use enormous datasets to identify patterns, predict the outcomes, and categorize genetic variations based on training from large datasets.

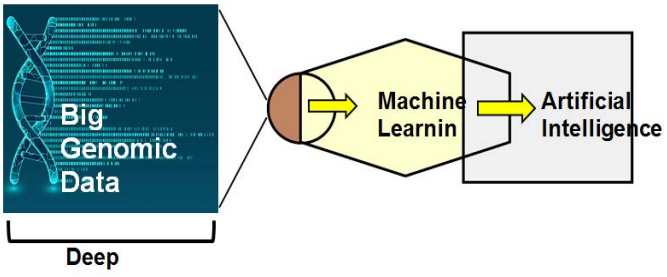

Figure 2: Big Genomic data analysis requires Artificial Intelligence (AI) methods such as machine learning (ML) and deep learning (DL).

Artificial intelligence and their roles in SNPs analysis

As mentioned earlier, the application of artificial intelligence tools to determine which single nucleotide polymorphisms (SNPs) influence disease development is one of the features of medical research, as the use of AI techniques may potentially help physicians to identify the early diagnosis of SNPs related to Type 2 diabetes and obesity and to build a decision support tool for risk prediction. Therefore, the data generated by AI for Genetic predisposition plays a significant role in determining an individual's susceptibility to both obesity and T2DM. Certain gene variants influence body weight regulation and insulin sensitivity. To date, genetic techniques have provided evidence that some genetic variants have a role in obesity and insulin sensitivity in T2DM. Some of them were cohort studies and investigated a large number of loci and SNPs, Some of them are listed in (**Table 3**) and described below. The results of the studies showed a significant association of genetic variants with the major markers of T2D and obesity[24].

Table 2: Artificial Intelligence- power tool for genome sequencing aspects.

Aspects	Description
Accelerated sequencing	AI shortens the time and expense associated with genome sequencing.
Error reduction	AI decreases errors, increasing the accuracy of genome sequencing.
Variant identification	AI swiftly and correctly pinpoints genetic variations related to diseases or traits.
Personalized medicine	AI uses genomic data analysis to personalize medicines based on each patient's genetics.
Population studies	Large-scale datasets are analyzed using AI to provide insights about population-level genetic variants.
Structural variation analysis	Large-scale genomic rearrangements and structural changes can be found with the help of AI.
Data integration	AI combines clinical, environmental, lifestyle, and genomic data to provide thorough insights.
Ethical considerations	Sensitive genomic data storage and dissemination provide ethical difficulties. Aspects Description Accelerated sequencing AI shortens the time and expense associated with genome sequencing. Error reduction AI decreases errors, increasing the accuracy of genome sequencing. Variant identification AI swiftly and correctly pinpoints genetic variations related to diseases or traits. Personalized medicine AI uses genomic data analysis to personalize medicines based on each patient's genetics. Population studies Large-scale datasets are analyzed using AI to provide insights about population-level genetic variants. Structural variation analysis Large-scale genomic rearrangements and structural changes can be found with the help of AI. Data integration AI combines clinical, environmental, lifestyle, and genomic data to provide thorough insights. Ethical considerations Sensitive genomic data storage and dissemination provide ethical difficulties.

Some of genes directly related to obesity and T2DM are described below:

FTO Gene: The fat mass and obesity-associated (FTO) gene is one of the most studied genes linked to obesity and T2DM. Variants in the FTO gene, particularly single nucleotide polymorphisms (SNPs) like rs9939609, are associated with increased body mass index (BMI) and higher fat mass. Individuals with certain FTO variants exhibit a stronger

appetite, reduced satiety and a preference for high-calorie foods, contributing to weight gain and obesity. This gene is also implicated in the regulation of adipocyte function, influencing insulin sensitivity and the risk of T2DM.In a study conducted[25], it was observed that individuals carrying the risk allele (A allele) of the rs9939609 SNP in the FTO gene had 1.67 times higher odds of developing obesity compared to those without the risk allele. Furthermore, another study demonstrated that this variant was associated with increased T2DM risk, independent of BMI, highlighting its direct impact on metabolic pathways[26].

Table 3: Important key genes involved in obesity and Type 2 diabetes mellitus (T2DM)

Gene	Associated Disease	Function/Role
FTO	Obesity, T2DM	Fat mass and obesity-associated gene; influences body mass and fat accumulation.
TCF7L2	T2DM	Transcription factor 7-like 2; involved in insulin secretion and glucose production.
LEP	Obesity	Leptin gene; regulates appetite and energy balance.
LEPR	Obesity	Leptin receptor gene; mediates the effects of leptin
PPARG	Obesity, T2DM	Peroxisome proliferator-activated receptor gamma; regulates fat cell differentiation and glucose metabolism.
KCNJ11	T2DM	Potassium inwardly-rectifying channel, subfamily J, member 11; involved in insulin release.
ABCC8	T2DM	ATP-binding cassette transporter sub-family C member 8; regulates insulin secretion.
MC4R	Obesity	Melanocortin 4 receptor; involved in energy homeostasis and appetite regulation.
IRS1	T2DM	Insulin receptor substrate 1; plays a role in insulin signalling.
ADIPOQ	Obesity, T2DM	Adiponectin gene; involved in glucose regulation and fatty acid breakdown.

TCF7L2 Gene: The transcription factor 7-like 2 (TCF7L2) gene is among the strongest genetic determinants of T2DM. Variants like rs7903146 have been consistently associated with increased T2DM risk, independent of obesity. TCF7L2 influences insulin secretion by affecting the function of pancreatic beta cells. Individuals with high-risk variants of TCF7L2 often exhibit impaired insulin secretion, leading to hyperglycemia and the subsequent development of T2DM.A genome-wide association study (GWAS) identified the TCF7L2 variant rs7903146 as a significant predictor of T2DM[27]. Carriers of this variant had up to a 1.5-fold increased risk of T2DM, with the effect being more pronounced in individuals with a family history of the disease, highlighting the gene's critical role in genetic predisposition.

LEP: Leptin plays an important role in regulating adipose-tissue mass in obese individuals. It has been shown that Leptin is over-expressed at the gene level in the adipose tissue of individuals with obesity[28]. Moreover, other studies showed that strong positive associations exist between plasma leptin levels and body fat percentage[29,30]. The single nucleotide polymorphism (SNP) in the Leptin gene, especially rs7799039 G > A SNP, was implicated in the development of Obesity[31]. A recent report on SNP suggested the association of leptin promoter gene variations i.e., rs72563764C>T and rs7799039G>A with both diabetes and obesity[32]. A few research reports are available on the association between human leptin gene variants and obesity traits in India[33,34]. In vivo, experimental studies confirmed a polymorphism in the ob gene. This confirmation of polymorphism alters the leptin protein function such that mice become morbidly obese[35].

LEPR Gene: Leptin has its physiological action via attaching to the leptin receptor, which is a single transmembrane protein in the class I cytokine receptor family. Upon leptin binding to its leptin receptor, it activates various it activates multiple intracellular signaling pathways, including: including the JAK2/STAT5 pathway, the extracellular signal-regulated kinase (ERK) pathway, and the insulin receptor substrate (IRS)-phosphoinositide 3-kinase (PI3K)/Akt pathway, which diverges to separate downstream signaling [36,37]. The gene LEPR encoding leptin receptor on the chromosomes 1, respectively. The LEPR has been linked to the presence of single-nucleotide polymorphisms (SNPs) that may modulate the circulating concentration of this adipokine[38]. The LEPR genes have been associated with obesity, deregulation of blood pressure levels, and sympathetic hyperactivity[39,40]. The most studied SNPs, rs1137101 (+668A > G) are situated in the exon 6 region of LEPR. A study from Illangasekera et al, demonstrates that the presence of the variant `G allele' of the LEPR Q223R polymorphism is associated with greater BMI and WC measures[41]. Similar results were also reported by Becer et al., where the association between the `G' allele and obesity related anthropometric measures was observed only in obese subjects[42]. Furthermore, a cohort research study identified that an elevated level of LEPR expression is linked to increased neoangiogenesis and metastatic potential in colorectal cancer survival (CRC), whereas low LEPR expression correlates with modest rates of proliferation[43].

PPARG Gene: The peroxisome proliferator-activated receptor gamma (PPARG) gene is critical in adipocyte differentiation and lipid metabolism. The Pro12Ala variant (rs1801282) of the PPARG gene is associated with a reduced risk of T2DM, possibly due to its effects on improving insulin sensitivity[44]. This variant is believed to alter the gene's activity, leading to more favorable fat storage and utilization patterns that protect against insulin resistance and T2DM. The Diabetes Prevention Program (DPP) study examined the role of the PPARG Pro12Ala variant in response to lifestyle interventions and metformin[45]. The study found that individuals with the Ala allele had a lower incidence of T2DM, particularly when combined with lifestyle interventions, suggesting a gene-lifestyle interaction in preventing diabetes onset.

KCNJ11: The synthesis of insulin and secretion is regulated by a family of potassium channels including potassium inwardly rectifying channels, subfamily, member 11(KCNJ11). The KCNJ11 gene, located 4.5 Kb from ABCC8 on chromosome 11p15.1, contains a single exon encoding the 390 amino acid Kir6.2 protein. In KCNJ11 gene several single nucleotide polymorphisms several single nucleotide polymorphisms have been identified, which may alter mRNA and protein expression (rs5219, rs2237892, and rs151290)[46]. A recent study has shown that there is an association of Genetic Variants of KCNJ11 Genes with the Risk of Type 2 Diabetes Mellitus (T2DM) in the Indian Population[47]. Another study suggested that single nucleotide Polymorphism of KCNJ11 (rs5219) gene is associated with glycemic status and insulin resistance and pregnant women with

T allele were at higher risk of developing gestational diabetes mellitus.

ABCC8: The ABCC8 gene, which encodes the sulfonylurea receptor (SUR), is the regulatory subunit of the KATP channel and plays an important role in insulin production[48]. Research in a French adult type 2 diabetes outpatient cohort of 139 individuals discovered two (1.5%) potentially causal ABCC8 mutations[49]. Another investigation in a large cohort of nonobese individuals with a diagnostic age < 40 years and a family history of diabetes showed 8 (8/1564, 0.5%) ABCC8 mutations[50]. In addition, an East Asian investigation discovered one ABCC8 variation (0.9%) among 109 putative monogenic diabetes patients (Park et al., 2019. Various studies estimate the frequency of ABCC8 mutations to be between 0.5% and 1.5%. It implies that the beta-cell protein sulfonylurea receptor (SUR1's) subunit ATP-sensitive potassium (KATP) channel, which encodes the ABCC8 gene, is responsible for a small portion of neonatal diabetes mellitus (NNDM).

MC4R Gene: The melanocortin 4 receptor (MC4R) gene is another critical gene influencing body weight regulation. Mutations in MC4R are the most common genetic cause of monogenic obesity, affecting appetite control and energy expenditure. Individuals with MC4R mutations tend to have severe early-onset obesity and are at a higher risk for T2DM due to the associated insulin resistance[51]. found that MC4R mutations were present in approximately 6% of individuals with severe obesity. These individuals also had a higher incidence of T2DM, illustrating the direct impact of MC4R on both obesity and metabolic dysregulation.

IRS1: Insulin receptor substrate (IRS) molecules are important mediators of insulin signaling. The IRS-1 is the first member of the family to be identified. The IRS-1 gene, located on chromosome 2, has both the 5′-untranslated region and the protein-coding region in a single exon. Several single nucleotide polymorphisms in the IRS genes have been found, but only IRS-1's Gly to Arg 972 alteration appears to have a pathogenic role in the development of type 2 diabetes mellitus[52,53]. Previous studies have shown that the IRS-1 gene's frequent polymorphism (rs 1801278) is a glycine to arginine substitution (GGG ↔ AGG) at codon 972 (G972R), which may contribute to type 2 diabetes through insulin resistance and decreased secretion[54,55]. A recent study by Bedair et al., 2021 suggested that IRS-1 G972R (rs 1801278) polymorphism might be a contributing risk factor for the development of type 2 DM[56]. The study suggested that mutant allele (A) of IRS-1 polymorphism is a risk factor for type 2 diabetes mellitus even in subjects with normal body weight. The increase in body mass index may be an independent risk factor for the development of type 2 diabetes mellitus.

ADIPOQ: Adiponectin is a protein expressed and secreted by adipose tissues. Adiponectin gene (ADIPOQ) locus, 3q27, has been strongly linked to various metabolic disorders like-impaired glucose tolerance, T2D, obesity and dyslipidemia[57]. Genetic research discovered that additive genetic factors might explain 80% of the variation in blood adiponectin levels among nonobese individuals. Recent studies on different ethnic groups have shown a positive association of certain SNPs of the ADIPOQ gene in T2DM[58,59]. Rs266729 is an ADIPOQ gene SNP that is thought to regulate promoter activity. In a study of 1004 adult obese adults, the G allele of rs266729 was linked to decreased blood adiponectin levels and an increased risk of hyperglycemia[60]. Whereas, as a cross-sectional study on Mexican-Mestizo individuals who carry the GG genotype have significantly higher levels of serum adiponectin than individuals who carry the TT or the TG genotypes of the SNP rs2241766 ADIPOQ gene[61].

The key insights gained from the above data, emphasizes how these genes contribute to our understanding of the complex interplay between genetic predisposition and metabolic disorders. The implications of these findings pave the way for future research and point out the potential therapeutic targets, for personalized medicine. Moreover, the limitations of this study is that the gene list is not exhaustive and neither are the pathologies, however, the study suggests areas for further investigation to deepen our understanding of the genetic mechanisms underlying obesity and T2DM. Further, this article does not identify or propose the drugs for these two disorders as treatment options. Insulin a hormone, functions as a chemical messenger that regulates various physiological processes. It exerts its effects by binding to receptors on the cell surface, triggering a cascade of intracellular events through secondary messengers like cAMP. Thus, finding molecules (drugs) for its inhibitory effects to control Diabetes is like altering gene expression which may or may not be as anticipated, especially in cases of comorbidities.

Conclusion

The relationship between obesity and T2DM is complex and multifactorial, involving genetic, environmental, and behavioral factors. Given the global burden of these conditions, an integrated approach that combines individual-level interventions with public health strategies is essential and discussed in this review. Chronic insulin resistance places a higher demand on pancreatic β-cells to produce more insulin. Over time, this can lead to β-cell exhaustion and dysfunction, reducing insulin secretion and contributing to hyperglycemia. Future research should focus on understanding the molecular mechanisms linking the genetic basis of obesity to T2DM, which could lead to the discovery of novel therapeutic targets. The genetic predisposition to obesity and T2DM involves a complex interplay between multiple gene variants, environmental factors and epigenetic modifications. Understanding the specific genetic factors and the demographs of individuals may contribute to these conditions and can form personalized prevention and treatment strategies, particularly in individuals with a strong family history of obesity or T2DM. Research should continue to explore using AI as a tool to unfold the epigenetic mechanisms, as well as their interactions with lifestyle factors, to identify more effective interventions for these interrelated diseases. Addressing these twin epidemics requires a collaborative effort between AI, healthcare providers, policymakers and communities to create environments that promote healthy lifestyles and reduce the incidence of these interrelated conditions.

Declarations

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