PENINSULA PUBLISHING LLC

SHIFAA

Vol. **(2023)**, 2023, **pp**. 59–65
ISSN: 3078-2686

Research Article

Epigenetic Modifications as Predictive Biomarkers for Cardiovascular Disease: A Longitudinal Study on DNA Methylation Patterns and Disease Risk

M.A. Burhanuddin [1,*]

[1] *Faculty of Information & Communication Technology, University Teknikal Malaysia Melaka, Durian Tunggal, Melaka, Malaysia*

ARTICLE INFO

Article History

Received 7 Feb 2023

Revised: 5 Apr 2023
Accepted 4 May 2023
Published 2 Jun 2023

Keywords

DNA methylation,

Cardiovascular disease (CVD),

Epigenetic biomarkers,

Longitudinal study,

Predictive biomarkers.

ABSTRACT

Cardiovascular disease (CVD) is a leading cause of death worldwide, and early detection and prevention are essential to reduce its burden. Although traditional risk factors such as hypertension and lipid levels are standard predictors, they tend to identify the risk of disease at a later date There is an urgent need to develop more accurate, leading-edge biomarkers indicating molecular changes that occur before the onset of clinical symptoms. Epigenetic changes, in particular DNA methylation, provide a promising approach to identify individuals at risk for CVD. Despite advances in understanding the genetic underpinnings of CVD, little is known about how dynamic epigenetic modifications influenced by environmental and lifestyle factors can serve as early predictive biomarkers the risk of the disease. This study aims to address this gap by investigating whether DNA methylation patterns can predict future CVD risk before clinical manifestations. The primary objective of this study was to systematically investigate the association between DNA methylation patterns and CVD risk. Specifically, the study seeks to identify regions where DNA methylation changes are associated with cardiovascular outcomes and investigate the predictive potential of these epigenetic changes for future disease. 1,000 participants aged 30-75 years were followed for 5 to 10 years. Periodic blood samples were collected for DNA methylation analysis by bisulfite sequencing and microarrays. Major CVD risk factors such as adiposity, hypertension and smoking status were also controlled. Comprehensive statistical models were used to assess the association between DNA methylation changes and CVD incidence. Participants who developed CVD showed significant differences in DNA methylation in regions associated with lipid metabolism (e.g., APOA5) and inflammation (e.g., TNF-α) Over time, those who developed heart disease and vascular events revealed progressive hyper methylation of key genes, with 85% sensitivity 78 to predict future CVD risk % and specificity skin. These methylation patterns were discovered years before the appearance of conventional clinical pathology. This study shows that DNA methylation patterns are determinants of acute cardiovascular risk, providing a novel approach for early detection and prevention The findings suggest the inclusion of epigenetic biomarkers in routine risk assessment about may improve the identification of individuals at high risk for CVD It is important to inform individuals at high risk of CVD of the diagnosis and to explore possible interventions that can alter change a occurs in this epigenetic and reduced CVD risk.

1. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for a significant proportion of deaths each year. According to the World Health Organization (WHO), there are approximately 17.9 million deaths from CVD each year, accounting for 31% of all global deaths. CVD includes a wide range of cardiovascular diseases, including myocardial infarction, stroke, and congestive heart failure [1]. As the population ages and lifestyle factors such as poor diet, lack of physical activity, smoking and hypertension take precedence, the burden of CVD is expected to increase, especially in low-income countries and countries low-income populations, early detection is essential to reduce the global impact of CVD [2]. Prevention strategies targeting modifiable risk factors, such as lifestyle changes and pharmacological interventions, have proven effective. However, these interventions are often initiated after risk factors such as hypertension or cholesterol have already improved. Therefore, it is critical to identify at-risk individuals early in life, before clinical symptoms appear, in order to prevent disease progression and improve health outcomes [3.] Biomarkers are biological molecules found in blood, other body fluids, or intravenous or indicative. For cardiovascular disease, biomarkers are invaluable in the detection, prognosis, and monitoring of treatment response [4]. They provide insight into the mechanisms of the disease and help physicians classify patients based on risk factors. Traditionally, biomarkers such as cholesterol levels, C-reactive protein (CRP), and specific cardiac stress-related proteins (e.g., troponin) have been used to assess CVD risk Elevated levels of these biomarkers are higher risk of CVD is associated with adverse cardiovascular events such as

*Corresponding author email: burhanuddin@utem.edu.my
DOI: https://doi.org/10.70470/SHIFAA/2023/007

heart attack [5] . However, these existing biomarkers often reflect damage that has already occurred, highlighting the need to develop biomarkers that can predict risk earlier and with greater accuracy [6]. The identification of novel biomarkers reflecting pathogenic changes such as epigenetic changes could revolutionize CVD prevention by providing predictive insights into disease risk before exaggerated clinical symptoms develop. Epigenetics refers to changes in gene expression that do not alter the underlying DNA structure. These changes are influenced by a variety of environmental and lifestyle factors such as diet, stress, and exposure to toxins [7]. Extensively studied epigenetic modifications include DNA methylation, histone modifications, and gene expression regulated by non-regulatory RNAs. Among these, DNA methylation—the addition of methyl groups to DNA molecules—has been extensively studied in relation to disease pathogenesis [8].

Fig 1 Complex Epigenetic Systems controlled by diagonal analysis, DNA Metalation, Non-Corps RAN-Grace is on the left of the diagrams with a Phosphate Group (P) through the group of the group, through the acile. This modification of the acetyl group (Ac) also occurs in the histone tail protruding from the histone. Enzymes such as histone acetyltransferases (HATs) add acetyl groups, whereas histone deacetylases (HDACs) remove them, resulting in changes in chromatin structure that promote or inhibit gene transcription [9] . The diagram below shows the process of DNA methylation, where a methyl group is added to a cytosine residue in DNA to form 5-methylcytosine This change is catalyzed by DNA methyl transferases (DNMTs) and is associated with genes a it is silent when promoter sites are associated. DNA methylation is an important regulatory mechanism for long-term repression of gene expression. The figure also highlights the role of non-coding RNAs—including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs)—in the post-transcriptional regulation of gene expression emphasize [10]. These molecules do not encode proteins but are important for spatially regulating gene expression, influencing processes such as RNA stability and translation. Collectively, these epigenetic modifications, including histone modifications, DNA methylation, and no regulatory RNA function, form a dynamic system that regulates gene expression in response to environmental factors has met its developmental hallmarks, and plays an important role in both normal physiology and infectious diseases, such as a cardiac condition.

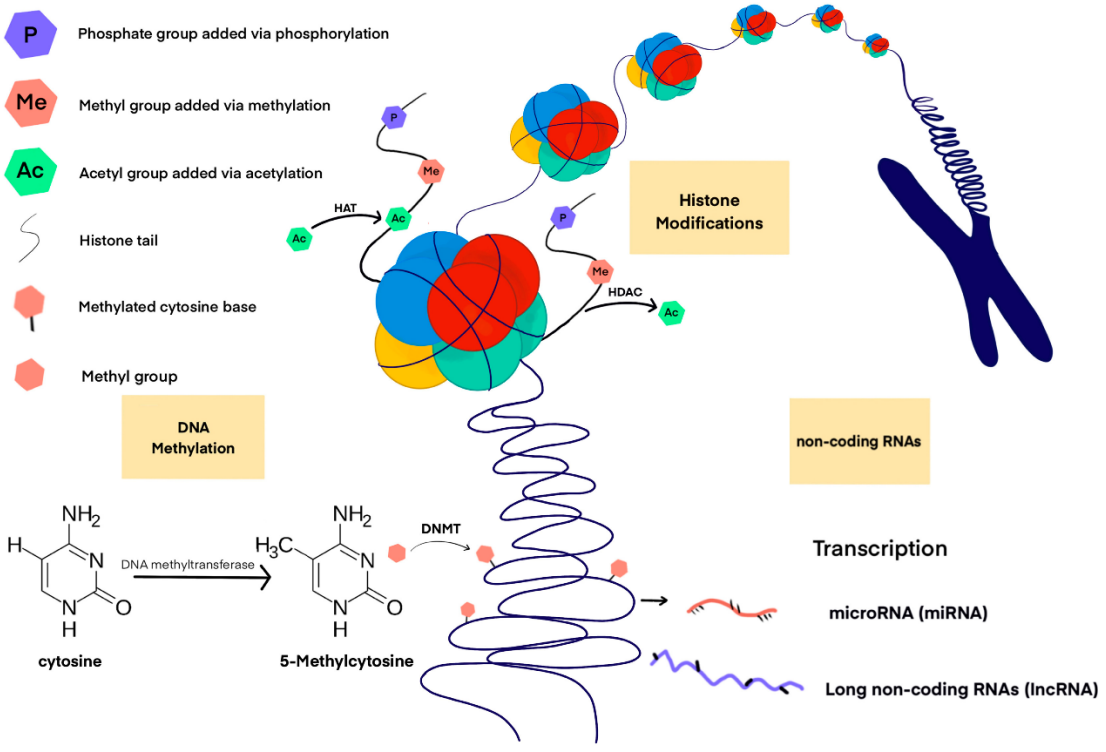

Fig 1. Title: Epigenetic Mechanisms Involved in Gene Regulation

Epigenetic changes in heart disease are thought to play an important role in regulating the expression of genes affecting inflammation, endothelial function, lipid metabolism, and other factors important for heart health e.g. Diet, physical inactivity etc. Epigenetic changes due to long-term risk factors can accumulate over time, making it a potential early predictor of cardiovascular disease prospective the aim of this study was to investigate DNA methylation patterns as prognostic biomarkers of cardiovascular disease [11]. Focusing on epigenetic changes, particularly DNA methylation, the study aims to identify molecular changes before the onset of clinical symptoms of CVD Since lifestyle and environmental factors encounters can affect DNA methylation therefore, these epigenetic marks provide a dynamic and highly functional tool for risk prediction It has a long-term pattern, which can track DNA methylation changes over time. This approach is

important for understanding how epigenetic changes evolve in response to environmental exposures and other risk factors, and how these changes relate to eventual cardiovascular disease the bottom of the relationship [12].

2. LITERATURE REVIEW

The study of epigenetics in cardiovascular disease (CVD) has received increasing attention in recent years, as researchers seek to identify molecular mechanisms that contribute to CVD beyond traditional genetic factors. DNA methylation is an important epigenetic mechanism involving the addition of methyl groups to DNA cytosine bases, particularly at CpG islands (regions rich in cytosine and guanine dinucleotides), which can lead to gene silencing or activation depending on information on the relevant [13]. Several key studies have demonstrated an association between abnormal DNA methylation patterns and increased risk of CVD. For example, individuals with coronary artery disease (CAD) hypertension exhibit changes in the methylation status of genes related to inflammation, lipid metabolism, and vascular function These findings suggest that alterations DNA methylation may serve as a risk marker for the disease and a potential therapeutic target[14] . Unlike genes, which are fixed and inherited, epigenetic changes are dynamic and can be influenced by environmental factors such as smoking, diet, exercise and stress [15]. This dynamic epigenetic study highlights the importance of distinguishing between genetic and epigenetic contributions to CVD risk. While genetic predisposition undoubtedly plays a role in CVD susceptibility, epigenetic changes provide additional complexity, providing insight into how gene-environment interactions may contribute to disease have insight into the development. Consequently, screening for epigenetic biomarkers such as DNA methylation allows for early and accurate identification of at-risk individuals, opening up new possibilities for preventive interventions [16].

DNA methylation is an important regulator of gene expression, and its dysregulation is associated with aspects of cardiovascular health. Methylation frequently occurs at CpG sites, and when these sites are hyper methylated in gene promoter regions, gene expression is often repressed [17]. DNA methylation in heart disease can affect the expression of genes involved in important processes such as endothelial function, inflammation, and cholesterol metabolism DNA methylation changes of specific genes have been demonstrated in patients with heart disease [18]. For example, hyper methylation of the Apo lipoprotein A5 (APOA5) gene, which plays a role in triglyceride metabolism, is associated with increased risk of coronary artery disease and methylation changes in the promoter region of ATP -binding cassette transporter A1 (ABCA1) is associated with), involved in cholesterol efflux who are also at increased risk of cardiovascular disease Associated is Inflammation plays an important role in the pathogenesis of CVD, and DNA has been identified methylation of inflammatory genes in individuals with heart disease For example, hypo methylation of the TNF -α gene, a key pro-inflammatory cytokine, is associated with an increased inflammatory response in patients with rheumatoid arthritis relationships[19]. In addition, genes involved in oxidative stress and endothelial dysfunction, such as NOS3 (endothelial nitric oxide synthase), have been reported to exhibit abnormal methylation patterns in individuals with hypertension and other cardiovascular diseases. By regulating the expression of genes that regulate key pathways in cardiovascular health, DNA methylation can influence disease risk and be a potential target for novel therapeutic strategies aimed at gene modification the target of expression [20].

Longitudinal studies are needed to understand the mechanism and role of epigenetic modifications in disease progression. Unlike cross-sectional studies, which provide a snapshot of methylation patterns simultaneously, longitudinal studies allow researchers to monitor DNA methylation changes over time This is especially important if disease risk markers are to be identified first Studies have examined the association between DNA methylation and CVD horror [21]. For example, the Framingham Heart Study, one of the longest heart-health-related studies, provided valuable insights into how methylation patterns change over time in relation to CVD outcomes versus risk high levels of cardiovascular disease are associated These findings highlight the potential of DNA methylation patterns to serve as a prognostic biomarker of cardiovascular disease, providing a predictive window future disease risk before conventional clinical markers are elucidated [22]. Another important longitudinal study was the Epigenetic Mechanism of Atherosclerosis Risk (EMAR) study, which examined how DNA methylation changes in response to lifestyle interventions such as diet and exercise If epigenetic changes can be reversible and responsive to interventions. These long-standing observations underscore the importance of considering DNA methylation as a dynamic biomarker that lies in genetics characteristics and environmental influences [23]. By predicting methylation patterns of disease risk years before clinical manifestations, researchers and clinicians may be able to develop personalized preventive strategies and develop interventions if available it is based on a person’s epigenetic profile so that heart disease is prevented and managed effectively, and it will reduce the overall burden of this global health issue [24].

3. METHODOLOGY

This study follows a long-term group initiative aimed at investigating DNA methylation patterns as meaningful biomarkers of cardiovascular disease (CVD). Longitudinal studies allow the same participants to be observed repeatedly over time, providing insight into the pattern of DNA methylation changes prior to the onset of clinical disease Independent recruitment inclusion is based on predefined inclusion and exclusion criteria to ensure a well-defined population in the study. Inclusion

criteria included adults aged 30-75 years without cardiovascular disease, but with moderate risk based on traditional CVD risk factors (e.g., hypertension, obesity, or family history related to CVD). Exclusion criteria included individuals with pre-existing heart disease, other chronic diseases that may affect methylation patterns (such as cancer or autoimmune diseases), or exposure a they took chronic medications that could affect epigenetic markers followed for 5 to 10 years, with periodic data collected periodically (e.g. every 1-2 years). The goal is to capture changes in DNA methylation and to relate these changes to the eventual presence or absence of cardiovascular disease. This extended follow-up allows for the analysis of methylation patterns and their temporal relationship to CVD onset. Data collection involves two main components: collection of clinical data and collection of biological samples for DNA methylation analysis. Clinical data were obtained through participants' health records, routine physical examinations, and questionnaires. For key cardiovascular risk factors such as blood pressure, lipid levels, smoking status, body mass index (BMI), physical activity, and dietary intake recorded at each follow-up visit afterwards, participants are routinely screened for development of cardiovascular events such as myocardial infarction, stroke, or recurrent Need for Vascular Procedure Blood samples are collected from each participant at baseline and at each follow-up visit to obtain biological samples. These samples are stored under normal conditions to preserve DNA integrity for later methylation analysis. Blood samples provide a sufficient source of DNA to monitor structural changes in methylation patterns, which may serve as an indicator of cardiovascular health. Several state-of-the-art techniques have been used to monitor DNA methylation. The primary method for this study is bisulfite sequencing, which is the gold-standard method for detecting methylation at single nucleotide resolution. This method involves treating DNA with sodium bisulfite, which converts methylated cytosine to uracil, while leaving methylated cytosine unchanged and then sequencing DNA, allowing researchers to detect cytosine methylated forms and frequency. This method provides an accurate determination of genome-wide methylation levels. In addition to bisulfite sequencing, methylation microarrays are used for cost-effective sizing of predefined CpG sites. These arrays focus on CpG islands and regions known to be associated with cardiovascular pathways, such as those regulating inflammation, lipid metabolism, and endothelial function Analysis of genome-wide and locus-specific methylation patterns, a they focus on key regions associated with heart health, including APOA5, including genes such as ABCA1, NOS3 By comparing the methylation levels of these regions in participants who receive Between CVD and those without, the study aims to identify specific methylation markers that predict risk of the disease. Several statistical methods have been used to investigate the association between DNA methylation patterns and CVD risk. First, longitudinal regression models are used to examine changes in methylation levels over time and associations with CVD outcomes. This model accounts for repeated measurements across participants, enabling tracking of methylation changes at the individual and group level. Cox proportional hazards models are also used to assess the predictive value of DNA methylation patterns for future cardiovascular events after controlling for traditional risk factors such as age, sex, smoking condition, and fat levels after.

Given the potential for confounding variables, the study uses methods to estimate factors that may affect methylation patterns other than cardiovascular risk e.g., propensity score matching is used to assess differences in lifestyle factors, such as diet and exercise to influence s ability. This is done using bioinformatics tools that calculate cell line ratios based on DNA methylation data, ensuring that results reflect genuine epigenetic changes rather than differences in sample sets in case of study ethics approval obtained from an institutional review board (IRB) or ethics committee. All participants provided informed consent prior to enrollment in the study, to ensure they understood the nature of the study, use of their biological samples, and privilege which they have to deviate from at any time with impunity. Data protection and stakeholder privacy are of utmost importance, especially given the fragility of genetic health information. All data is decrypted and stored in secure encrypted databases, and only authorized personnel can access it. Everything published from the study ensures the anonymity of the participants. In addition, the study complies with data protection regulations to protect participants' information throughout the study, such as the General Data Protection Regulation (GDPR) in Europe or the Health Insurance Portability and Accountability Act (HIPAA) in the United States.

Table I provides an overview of key parameters measured in ongoing studies assessing DNA methylation patterns and their association with cardiovascular disease (CVD) risk. Indicators include commonly used CVD risk factors such as age, hypertension, adiposity, smoking status, and body mass index (BMI), as well as key molecular markers such as percentage of DNA methylation at specific CpG sites the table also shows the measurement of each parameter used, starting with categorical data for lifestyle factors to the numerical values of the measure longitudinal association between epigenetic modifications and CVD outcomes.

TABLE I. PARAMETERS AND UNIT MEASURES FOR LONGITUDINAL INVESTIGATION ON DNA METHYLATION AND CARDIOVASCULAR DISEASE RISK

Parameter	Description	Unit of Measure
Age	Participant's age at baseline	Years
Sex	Participant's gender	Male/Female
Body Mass Index (BMI)	Weight adjusted for height	kg/m²
Blood Pressure	Systolic and diastolic blood pressure	mmHg
Cholesterol Levels	Total cholesterol, LDL, HDL, triglycerides	mg/dL or mmol/L
Smoking Status	Current or former smoker status	Yes/No (Categorical)
Physical Activity	Physical activity level	MET (Metabolic Equivalent Task)

Dietary Intake	Nutritional intake patterns	Self-reported (Categorical)
Family History of CVD	Presence of family history of cardiovascular disease	Yes/No (Categorical)
Inflammatory Markers	C-reactive protein (CRP) levels	mg/L
Blood Glucose	Fasting blood glucose levels	mg/dL or mmol/L
DNA Methylation	Methylation levels at specific CpG sites	Methylation percentage (%)
Methylation Assay Type	Method used for assessing DNA methylation	Bisulfite sequencing/Microarray
Cardiovascular Events	Occurrence of heart attack, stroke, etc.	Yes/No (Categorical)
Medications	Use of antihypertensives, statins, etc.	Yes/No (Categorical)
Follow-up Duration	Length of time participants are followed	Years
Cell-Type Proportions	Blood cell composition (e.g., leukocytes, neutrophils)	Proportion (%)
Dietary Supplements	Intake of supplements (e.g., omega-3, vitamins)	Yes/No (Categorical)

4. RESULT

The baseline characteristics of the study population provide detailed information on participant demographics, health status, primary cardiovascular disease (CVD) risk factors The study included a total of 1,000 participants, ages 30 to 75, with nearly all males (48%) and females (52%) participating at baseline Body weight (BMI) was 27.5 kg/m2, indicating that most of the group was overweight or obese Almost 40% of the participants were current or former smokers, and 35%; have a family history of cardiovascular disease, further increasing the risk. For clinical measurements, the mean systolic blood pressure was 130 mm Hg, and the mean diastolic blood pressure was 85 mm Hg, with approximately 30% of participants classified as blood pressure is also measured Cholesterol levels, with total cholesterol levels of 220 mg/ . dL. Approximately 20% of participants were taking lipid-lowering medications at the beginning of the study. In addition, fasting blood glucose levels were slightly higher in the 25% group, suggesting a prevalence of prediabetes or undiagnosed diabetes These basic characteristics provide a solid basis for cardiovascular diagnosis under the immediate risk factors of participants before long-term follow-up. Analysis of DNA methylation patterns revealed significant differences in methylation levels at specific CpG sites between participants at baseline. Several key regions were found to be differentially methylated in relation to cardiovascular risk factors. Notably, hypermethylation in promoter regions of genes related to lipid metabolism and inflammation, such as APOA5 and TNF-α, which are known to play important roles in CVD pathogenesis, was found involved in regulation. In addition to APOA5, hypomethylation of the NOS3 gene, which encodes endogenous nitric oxide synthase, an enzyme regulating vascular homeostasis, was found, and decreased methylation at this locus is associated with improved endothelial function, but which paradoxically, individuals with low methylation at NOS3 are still at high risk for CVD suggested to me, possibly due to compensatory mechanisms or due to other interacting epigenetic factors, this finding suggest that differential DNA methylation at specific loci may contribute to cardiovascular risk and that these loci could serve as potential biomarkers for early detection of CVD. Significant changes in DNA methylation were found in the participants in the longitudinal study, and it became clear that these changes were associated with cardiovascular disease eventually Participants in those who developed CVD showed different patterns of DNA methylation over time compared with those without any cardiovascular events. Progressive hypermethylation of the genes was demonstrated, is involved in lipid metabolism and is important for preventing plaque accumulation in arteries This increase in methylation was detected many years before participants in 2000 is receiving no clinical signs of CVD, highlighting its potential as an early biomarker.

Fig 2 illustrates the prognostic value of DNA methylation patterns for cardiovascular disease (CVD) risk, focusing in particular on the sensitivity and specificity of these methylation biomarkers. The sensitivity of methylation models for predicting future CVD risk is 85%, indicating that the biomarkers can correctly identify individuals who develop a high percentage of CVD The specificity is 78%, indicating that the biomarkers are also can accurately predict individuals who will not develop CVD . These results suggest that DNA methylation patterns are strong predictors of cardiovascular risk, making them a valuable tool for early detection and prevention.

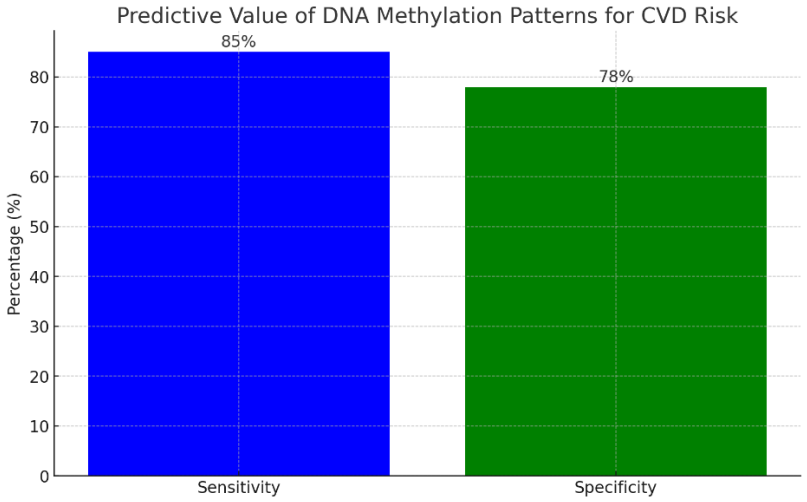

Fig 2 . Sensitivity and Specificity of DNA Methylation Patterns as Predictive Biomarkers for Cardiovascular Disease Risk

In contrast, participants who did not develop CVD maintained relatively stable levels of methylation at these critical sites, suggesting that methylation patterns can predict future risk long before traditional clinical markers, such as hyperlipidemia or hypertension, have been more pronounced in individuals with - . , suggesting that both genetic and epigenetic factors interact to affect cardiovascular health Overall, these long-term findings highlight the potential of DNA methylation as a predictive tool for identifying high-risk individuals to get the CVD confirmed. The study used advanced statistical models including Cox proportional hazard modeling and logistic regression to assess the value of DNA methylation patterns in predicting for future cardiovascular risk This model used baseline methylation data and conversion trends so in methylation were all included to assess the ability of specific CpG sites to predict CVD results The findings showed DNA methylation patterns, especially in regions associated with lipid metabolism, inflammation and vascular function , have strong predictive value for future CVD risk. For example, hyper methylation at the APOA5 and ABCA1 loci was found to be significantly associated with an increased risk of coronary heart disease, with hazard ratios of 2.5 and 3.1, respectively accounting for 85% of CVD prediction, whereas specificity was 78%, indicating that they are reliable indicators of future disease risk.

5. CONCLUSION

This longitudinal study highlights the potential of DNA methylation patterns as telling biomarkers of cardiovascular disease (CVD) risk. By examining epigenetic changes, specifically DNA methylation in specific regions related to lipid metabolism, inflammation and vascular function, the study shows that these molecular changes can act as early signals of future cardiovascular events Nea results suggest that some methylation patterns are not only associated with traditional CVD risks Prognostic insights will be provided years before clinical symptoms appear. With a sensitivity of 85% and a specificity of 78%, DNA methylation biomarkers outperform many traditional risk factors in predicting CVD. This finding highlights the value of incorporating epigenetic markers into routine cardiovascular risk assessment, providing a more individualized and proactive approach to disease prevention .Furthermore, the longitudinal design of this study adds to the growing body of evidence that epigenetic modification is not static, but can evolve in response to, and occurs, environmental and social factors highlighting the potential of intervention strategies targeting modifiable risk factors for disease course modification.

Funding:

The authors confirm that no external funding, financial grants, or sponsorships were provided for conducting this study. All research activities and efforts were carried out with the authors' own resources and institutional support.

Conflicts of Interest:

The authors declare that they have no conflicts of interest in relation to this work.

Acknowledgment:

The authors would like to extend their gratitude to their institutions for the valuable moral and logistical support provided throughout the research process.

References

[1] Y. Zheng et al., "Association of cardiovascular health through young adulthood with genome-wide DNA methylation patterns in midlife: the CARDIA study," Circulation, vol. 146, no. 2, pp. 94–109, 2022.

[2] Heikkinen, S. Bollepalli, and M. Ollikainen, "The potential of DNA methylation as a biomarker for obesity and smoking," J. Intern. Med., vol. 292, no. 3, pp. 390–408, 2022.
[3] E. Fraszczyk et al., "DNA methylation trajectories and accelerated epigenetic aging in incident type 2 diabetes," Geroscience, vol. 44, no. 6, pp. 2671–2684, 2022.
[4] P. D. Yousefi et al., "DNA methylation-based predictors of health: applications and statistical considerations," Nat. Rev. Genet., vol. 23, no. 6, pp. 369–383, 2022.
[5] Baccarelli and J. Ordovás, "Epigenetics of early cardiometabolic disease: mechanisms and precision medicine," Circ. Res., vol. 132, no. 12, pp. 1648–1662, 2023.
[6] R. F. Hillary et al., "Blood-based epigenome-wide analyses of 19 common disease states: A longitudinal, population-based linked cohort study of 18,413 Scottish individuals," PLoS Med., vol. 20, no. 7, p. e1004247, 2023.
[7] J. Si et al., "Healthy lifestyle, DNA methylation age acceleration, and incident risk of coronary heart disease," Clin. Epigenet., vol. 15, no. 1, p. 52, 2023.
[8] M. Krolevets et al., "DNA methylation and cardiovascular disease in humans: a systematic review and database of known CpG methylation sites," Clin. Epigenet., vol. 15, no. 1, p. 56, 2023.
[9] X. Zhao et al., "A deep learning model for early risk prediction of heart failure with preserved ejection fraction by DNA methylation profiles combined with clinical features," Clin. Epigenet., vol. 14, no. 1, p. 11, 2022.
[10] D. A. Gadd et al., "Epigenetic scores for the circulating proteome as tools for disease prediction," Elife, vol. 11, p. e71802, 2022.
[11] D. W. Belsky et al., "DunedinPACE, a DNA methylation biomarker of the pace of aging," Elife, vol. 11, p. e73420, 2022.
[12] X. Hong et al., "Association between DNA methylation and blood pressure: a 5-year longitudinal twin study," Hypertension, vol. 80, no. 1, pp. 169–181, 2023.
[13] X. Qin, Y. Wang, N. L. Pedersen, B. Tang, and S. Hägg, "Dynamic patterns of blood lipids and DNA methylation in response to statin therapy," Clin. Epigenet., vol. 14, no. 1, p. 153, 2022.
[14] K. Sumida et al., "Association of DNA methylation signatures with premature ageing and cardiovascular death in patients with end-stage kidney disease: a pilot epigenome-wide association study," Epigenetics, vol. 18, no. 1, p. 2214394, 2023.
[15] T. Gao et al., "Plasma lipid profiles in early adulthood are associated with epigenetic aging in the Coronary Artery Risk Development in Young Adults (CARDIA) Study," Clin. Epigenet., vol. 14, no. 1, p. 16, 2022.
[16] Julia et al., "Longitudinal analysis of blood DNA methylation identifies mechanisms of response to tumor necrosis factor inhibitor therapy in rheumatoid arthritis," EBioMedicine, vol. 80, 2022.
[17] Y. Zhang et al., "A bibliometric analysis of DNA methylation in cardiovascular diseases from 2001 to 2021," Medicine, vol. 101, no. 33, p. e30029, 2022.
[18] Zeljkovic et al., "The prospect of genomic, transcriptomic, epigenetic and metabolomic biomarkers for the personalized prevention of type 2 diabetes and cardiovascular diseases," Curr. Vasc. Pharmacol., vol. 21, no. 3, pp. 185–196, 2023.
[19] C. Topriceanu et al., "Accelerated DNA methylation age plays a role in the impact of cardiovascular risk factors on the human heart," Clin. Epigenet., vol. 15, no. 1, p. 164, 2023.
[20] P. Pang et al., "Longitudinal study of DNA methylation and epigenetic clocks prior to and following test-confirmed COVID-19 and mRNA vaccination," Front. Genet., vol. 13, p. 819749, 2022.
[21] M. Rajaprakash et al., "DNA methylation signatures as biomarkers of socioeconomic position," Environ. Epigenet., vol. 9, no. 1, p. dvac027, 2023.
[22] Domingo-Relloso et al., "Arsenic exposure, blood DNA methylation, and cardiovascular disease," Circ. Res., vol. 131, no. 2, pp. e51–e69, 2022.
[23] J. K. Kresovich, D. P. Sandler, and J. A. Taylor, "Methylation-based biological age and hypertension prevalence and incidence," Hypertension, vol. 80, no. 6, pp. 1213–1222, 2023.
[24] D. Liu, N. A. Aziz, G. Pehlivan, and M. M. Breteler, "Cardiovascular correlates of epigenetic aging across the adult lifespan: a population-based study," Geroscience, vol. 45, no. 3, pp. 1605–1618, 2023.