JSSF (11) (2) (2025)

Journal of Sport Sciences and Fitness

https://journal.unnes.ac.id/journals/jssf

Physical Exercise And Epigenetic: Molecular Mechanisms

Andi Sri Dewi Anggraeni. M[1*], Arimbi[2], A. Anggriani[3], Kezia Josawel Lesbatta[4], Indriani[5]

[12]Physiotherapy program, Faculty of Sports Science and Health, Universitas Negeri Makassar, Indonesia

[3]Department of Pharmacy, Faculty of Pharmacy, Universitas Hasanuddin, Indonesia

[4]Department of Biomedical Science, Faculty of Science and Technology, Universitas Pattimura, Indonesia

[5]Health Polytechnic Ministry of Health Makassar, Indonesia

Article's Info

Article's History:
Submitted Sept 18, 2025
Revised Oct 10, 2025
Accepted Nov 4, 2025

Keywords:
physical exercise; epigenetics; molecular

DOI:https://doi.org/10.15294/jssf.v11i2.34037

Abstract

Introduction: Physical exercise is associated with an active lifestyle and offers numerous health benefits. Recent research has shown that physical exercise also influences gene expression through epigenetic mechanisms such as DNA methylation, histone modification, mRNA, and microRNA expression. These changes contribute to physiological changes and disease prevention. **Objectives:** This review aims to explain how physical activity can affect a person's epigenetic changes to have an impact on the prevention of chronic diseases. **Method:** This study is a literature review using databases such as PubMed from 2015 to 2025. **Result:** the review revealed that physical activity can cause epigenetic changes at the stage of DNA methylation, histone modification, RNA methylation and MiRNA. Physical activity modulates DNA methylation, affecting genes related to metabolism and immune function. Understanding this pathway is the basis for developing personalized exercise programs as interventions for the prevention and therapy of chronic diseases. Understanding this pathway is the basis for developing personalized exercise programs as interventions for the prevention and therapy of diseases. **Conclusion:** This study reveals the relevance of epigenetic changes to physical activity as an alternative non-pharmacological therapy because it is accompanied by a perspective in choosing the type of physical activity that suits the body's condition as a step in implementing a more precise health pattern.

*Correspondence E-mail: a.sri.dewi.anggraeni@unm.ac.id

PISSN 2252-6528
EISSN 2745-5718

INTRODUCTION

The development of molecular biology has driven the advancement of medical knowledge including in sports. The understanding of complex diseases has significantly changed as a result of advances in molecular-based precision therapy, which integrates genomic data with clinical and environmental information (Vale, 2025). Evidence shows that both physical activity and exercise improves quality of life with little or no safety issues (Posadzki *et al.*, 2020). People who exercise regularly are much lower in risk of breast cancer, colon cancer, diabetes, heart disease, and stroke (Posadzki *et al.*, 2020). Regular physical exercise can help alleviate metabolic disorders in various chronic diseases; however, the molecular mechanisms underlying these effects are still not fully understood (Sailani *et al.*, 2019).

Recently, several studies have shown that physical exercise can affect gene expression through epigenetic changes, which in turn contribute to physiological adaptation and protection against disease (Wu, Zhang and Gao, 2021). Epigenetics is an important layer in transcription regulation, where DNA methylation plays a role as the main form of epigenetic modification that affects chromatin structure and gene expression (Li *et al.*, 2024). Exercise leads to significant changes in the DNA methylation patterns of certain genes and pathways in skeletal muscle (Garcia et al., 2022). Both acute and long-term exercise can cause increases or decreases in CpG methylation at specific sites (Seaborne et al., 2018; Song et al., 2019; Widmann et al., 2019), with some of these changes showing an inverse relationship with gene expression levels (Brown, 2015; Damal Villivalam et al., 2021).

Methylase is an enzyme that adds methyl groups to promote histone methylation in gene promoter regions, while demethylation removes methyl groups, thus influencing gene activity (Li *et al.*, 2024). Previously, the epigenome of organisms was not inherited because it was erased during gametogenesis and embryogenesis. However, it is now accepted that epigenetic modifications are potentially heritable, passed from parents to offspring (Portela & Esteller, 2010; Wu et al., 2021). Post-translational modifications fall under the field of epigenetics. While it do not alter DNA sequence, they can alter expression levels and function (R. Liu et al., 2023). Environmental factors such as nutrition, certain chemicals, emotional states, and physical activity can influence epigenetics. If epigenetic changes are sufficiently stable and involve germ cells, traits can be passed from parent to offspring development (Widmann, Nieß and Munz, 2019).

Epigenetics is one explanation for why cells and organisms with identical DNA can exhibit dramatic phenotypic differences (Hamilton, 2011). This mechanism plays a crucial role in regulating metabolism, muscle function, cellular adaptation, and the risk of chronic disease disease (Farsetti, Illi and Gaetano, 2023). Understanding the molecular mechanisms involved in epigenetic regulation is crucial because it underpins new insights into the role of specific physical activities in genetic changes in individuals with specific health conditions. This

contrasts with previous research on physical exercise, which influences physiological (Dhuha *et al.*, 2024) and biochemical changes (Fajriyah, Sudiana and Wahyuni, 2020), which has been extensively studied, furthermore this research has the potential to be carried out so that more research can be developed in the future, especially that which involves the Indonesian population. This study aims to provide scientific evidence on how physical exercise mechanisms influence epigenetic regulation, ultimately leading to disease prevention and improved quality of life. With this understanding, it is hoped that physical activity will become a viable option for more accessible public health promotion.

METHOD

This study used a systematic review approach to explore the relationship between physical exercise and epigenetic regulation. This approach aims to present conceptual understanding, research developments, and biological implications of previous findings.

The literature search process was carried out online through several scientific databases, namely PubMed. The keywords used include a combination of the terms: physical activity, exercise, epigenetics DNA methylation, histone modification, microRNA. Articles searched were limited to publications in the 2015–2025 period, written in English, and accessible in full-text form. Criteria Inclusion criteria in this review include: Scientific articles discussing the relationship between physical activity and epigenetics, clinical trial and randomized controlled trial which involving humans or animal models Publications presenting data or explanations regarding epigenetic mechanisms (DNA methylation, histone modifications). Although only human studies were included in this systematic analysis, results from non-human studies are also discussed to clarify the possible molecular mechanisms involved.

The literature search was conducted following the PRISMA process. Based on the PubMed database identification, 575 results related to physical activity, exercise, and epigenetics were found. After screening titles and abstracts, 47 journals were screened for eligibility according to the study's inclusion criteria. Of the total, 8 journals met the established criteria.

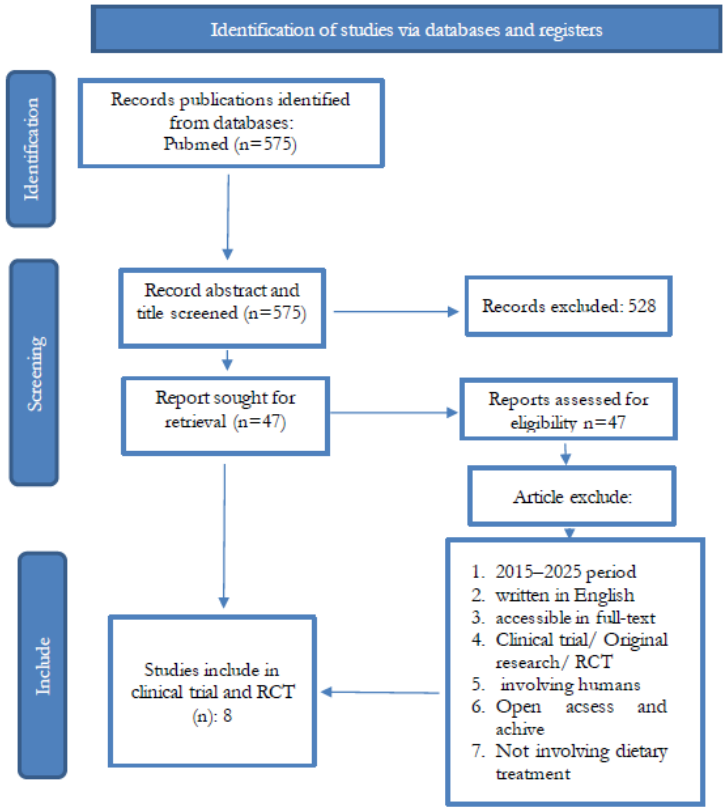

Figure 1. Research topic search flow

RESULT AND DISCUSSION

Result

Table 1. Study findings related to physical exercise and epigenetics

No	Author/ year	Journal title	Type Physical exercise	Research subjects	Main findings	Epigenetic analysis method
1	(Loh *et al.*, 2023)	Exercise and epigenetic ages in older adults with myeloid malignancies	a single-arm pilot study testing a mobile health (mHealth) exercise intervention combining an exercise for cancer patients using mobile app during 2 cycles of chemotherapy.	Patients aged ≥ 60 years with myeloid malignancies undergoing outpatient chemotherapy, able to walk four meters, have a physician-verified Eastern Cooperative Oncology Group (ECOG)	a step (intervention group) increase ≤ median from baseline to post-intervention, patients who experienced a step increase showed a greater decrease in DNA methylation (DNAm) age.	DNA was extracted from whole blood samples and treated with bisulfite. The DNA methylation levels were then analyzed using the Illumina Infinium® microarray platform.
2	(Ferrari *et al.*, 2019)	Effects of Physical Exercise on Endothelial Function	12-week aerobic training program, involving 4r sessions per	Individuals with essential hypertension, along with twenty-four	The gradual increase (intervention group) to post-intervention showed a greater decrease in DNA	DNA methylation was assessed by bisulfite-PCR and pyrosequencing

		and DNA Methylation	week. Session required at 40 minutes of physical activity such as cycling on a bike or jogging with the goal of maintaining the heart rate at the anaerobic threshold (AT).	healthy normotensive controls follow the same exercise training regimen as the patients.	methylation age (DNAm), EDN1 and NOS2 genes. While there are significant increase in ALU methylation after training. NOS3, TLR2, ICAM1, and TNF showed moderate, non-significant increases in methylation.	
3	(Boyne *et al.*, 2018)	Aerobic exercise and DNA methylation in postmenopausal women: An ancillary analysis of the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial	15–20 minutes of aerobic activity Alberta Physical Activity and Breast Cancer Prevention (ALPHA) program, with intensity of 50–60% of maximum heart rate, 3 times per week. Over 3 months, the duration of physical activity was increased to 45 minutes at an intensity of 70–80% of maximum heart rate, 5 times per week for 9 months.	Postmenopausal women aged 50 to 75 who were physically inactive and did not smoke or consume alcohol excessively.	Exercise program did not lead to changes in DNA methylation of LINE-1, ALU, APC, BRCA1, RASSF1, or hTERT genes in healthy, physically inactive postmenopausal women. This suggests that alterations in DNA methylation in these specific genomic areas may not be the pathway linking physical activity to cancer risk reduction in this population.	The level of LINE-1 and Alu methylation was determined through a pyrosequencing method, utilizing the HotStarTaq DNA Polymerase kit and the PyroMark Q24 system.
4	(Sailani *et al.*, 2019)	Lifelong physical activity is associated with promoter hypomethylation of genes involved in metabolism, myogenesis, contractile properties and	The sedentary group, engaging in physical activity no more than once a week throughout their lives, whereas the physically active group exercised more than three times weekly. At	The sedentary group had lived a lifelong sedentary lifestyle with a maximum of one physical activity per week throughout their lives, while the active group had exercised more than three times per week throughout their lives.	Levels of Glycogenin 2 (GYG2), glycogen synthase 1 (GYS1), and the glycogen-degrading enzyme alpha-amylase 2B (AMY2B) higher in active men than inactive men. The promoter region of the gene coding for 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB) showed lower methylation in	DNA read quality was checked using FASTQC in Trim Galore. The percentage of CpG methylation was calculated by performing the analysis at the level of: single CpG. Promoter regions were assessed using Fisher's exact test. CpG

		oxidative stress resistance in aged human skeletal muscle	the time of the research, the active participants consistently performed at least five hours of physical activity per week, despite some variation over the years.		physically active individuals than in inactive ones. Additionally, the promoter of the gene encoding the pyruvate dehydrogenase alpha 1 (PDHA1) subunit was found to be hypomethylated in active subjects. Among physically active participants, 62 Polycomb target gene promoters exhibited reduced methylation levels, suggesting that the Polycomb complex-mediated methylation on histone H3K27Me3 and subsequent gene silencing might occur more slowly in this group.	methylation data were arranged in a matrix (rows = samples, columns = CpG). Identification of muscle tissue-specific histone marks (Epigenomics Roadmap HM ChIP-seq)
5	(Fabre *et al.*, 2018).	Exercise training alters the genomic response to acute exercise in human adipose tissue	a bicycle ergometer with electromagnetic brakes were used for 15-minute exercise session at an intensity equivalent to 80% of predetermined VO_2 max. The procedure was repeated after participants completed a 6-week intensive exercise program (45-minute cycling sessions per day, five days a week, at an intensity of 75–85% of VO_2 max).	Sedentary male participants completed a acute exercise before and after 6-week endurance training program.	DNA methylation levels were lower in 107 and 239 differentially methylated regions (DMRs) before exercise and higher in 112 and 120 DMRs after acute exercise. After narrowing the list to DMRs regulated by exercise, 33 were found to be located near genes, and most were hypomethylated. The genes most affected were CBLB, GPR132, and RELT as well as ADRA2A, FOSL1, METRNL and RARA that involved in adipocyte differentiation and metabolism.	RNA samples collected before and after training for transcriptomic sequencing. Quantitative PCR (qPCR) was performed on pre- and post-training RNA samples to measure the expression of specific transcripts. The resulting cDNA was then used to quantify mRNA expression through real-time qPCR.

6	(Denham *et al.*, 2018)	Small non-coding RNAs are altered by short-term sprint interval training in men	Three times a week on cycle ergometers during 6 week. 4-6 maximal effort with 4 min recovery between sets training for Sprint Interval Training (SIT).	Healthy men recreationally active but did not participate in structured aerobic exercise programs	1,266 of 2,066 small ncRNAs affected after 6 weeks of SIT	RNA prepared with NEBNext, and sequenced on the HiSeq 2500. Data were analyzed in R using Bioconductor tools, with miRNA changes assessed by log fold change and FDR correction. Results were validated by qPCR with TaqMan assays.
7	(Butts *et al.*, 2018)	Effects of Exercise on ASC Methylation and IL-1 Cytokines in Heart Failure	The exercise group followed a progressive moderate-intensity aerobic walking program, starting with 30 minutes at 60% max heart rate (3x/week) for 2 weeks, increasing to 45 minutes at the same intensity for 2 more weeks, and then 45 minutes at 70% for the remaining 8 weeks. The control group received education and light stretching to control for external factors like healthcare attention.	Fifty-four participants from four urban hospitals with heart failure outpatient clinics were randomized to an exercise group or a mindfulness control group for a 3- or 6-month intervention.	IL-18 mRNA levels over time within or between groups showed the same expression, however ASC mRNA expression was significantly different between the exercise and control groups at both 3 and 6 months. iNOS mRNA expression in the exercise group showed significantly increased from baseline to 3 months and remained elevated at 6 months. Higher ASC methylation was linked to reduced iNOS expression, mediated by decreased IL-1β levels. IL-1β was identified as a mediator due to multicollinearity among ASC methylation, iNOS mRNA, and IL-1β.	Genomic DNA from peripheral blood mononuclear cells (PBMCs) was treated with bisulfite, amplified via PCR, and analyzed by pyrosequencing to quantify methylation levels. IL-1β and IL-18 cytokines were measured in duplicates using ELISA kits. mRNA was isolated and converted to cDNA through reverse transcription PCR.
8	(Plaza-Florido *et al.*, 2025)	Integrated analysis of methylome and transcriptome	The exercise intervention was based on international physical activity guidelines and	Children aged 8–11 years with overweight were enrolled Participants were randomly	A total of 485 CpG sites were affected by exercise intervention in boys (306 increases and 179 decreases in methylation levels after	Genomic DNA was extracted, while DNA methylation was assessed. Whole blood genomic

	responses to exercise training in children with overweight/ obesity	lasted 20 weeks. Participants were encouraged to attend the program 5 days per week (90-minute session per day). The exercise intervention sessions were divided into: 1) a warm-up (5–10 minutes) consisting of one to two physical games; 2) an aerobic session (60 minutes) consisting of four to five multi-game games at moderate to vigorous intensity; 3) a resistance training session (20 minutes) consisting of five to ten strength exercises focusing on pushing, pulling, and throwing patterns involving large muscle groups in sets of 10–12 repetitions using body weight, a theraband, and/or a fitball; and 4) a cool-down (5–10 minutes) based	assigned to an exercise group (a 20-week exercise intervention) or a control group that continuing regular activity for 20 weeks). Both groups received a pamphlet at the beginning of the study containing guidance on physical activity and healthy eating.	exercise). While 386 CpG sites were affected by exercise intervention (108 increases and 278 decreases in methylation levels after exercise) in girls group. CpG-annotated gene enrichment analysis showed that exercise enriched gene pathways were related to type 2 diabetes, insulin resistance, fatty acid degradation, NOD-like receptor signaling, and the adipocytokine signaling pathway. In silico data mining detected overlapping genes in boys, include NFKBIA (obesity, inflammation, and cardiovascular disease, PCK2 (obesity and metabolic syndrome), XPA, DNAJB6, TYW3, CALR, FES, MX1, CD6, and GADD45A. In girls, overlapping genes detected in RAC1, CD81, BAG6, PAX5, CCNI, BRD8, ERAL1, and FUCA1 which all of these genes specifically influence the inflammatory, metabolic syndrome, inflammation and cardiovascular disease, obesity, hyperlipidemia and cardiovascular disease.	DNA methylation data are available under Gene Expression Omnibus (GEO). A modified version of the single-cell labeled reverse transcription which was converted to cDNA. Raw sequencing reads were aligned to the hg19 genome and expression levels were quantified using the STRT prep pipeline

	on relaxation and stretching exercises.	

Discussion

Post-translational modifications fall under the field of epigenetics. Post-translational modifications do not change the DNA sequence, but it can alter expression levels and function (R. Liu et al., 2023). Environmental factors such as nutrition, chemical exposure, and physical activity influence these changes, which can lead to disease development (Widmann, Nieß and Munz, 2019).

The following mechanisms of epigenetic changes occur due to exercise including DNA methylation, histone modification, RNA methylation, and non-coding RNA, which affect gene expression without affecting the DNA sequence (Widmann, Nieß and Munz, 2019).

1. DNA methylation

DNA methylation is an important epigenetic mechanism for regulating gene transcription. Methylation in CpG dinucleotides is catalyzed by DNA methyltransferases (DNMTs), which catalyze the addition of a methyl group to the C5 cytosine (Davletgildeeva and Kuznetsov, 2024). Methylation prevents transcription binding that requires interaction with cytosine, which usually results in transcription inhibition (Damal Villivalam *et al.*, 2021). In humans, three canonical isoforms have been identified: DNMT3A, DNMT3B, and DNMT1 (Davletgildeeva and Kuznetsov, 2024). Maintenance of DNA methylation during replication is controlled by DNMT1, while de novo methylation is primarily mediated by DNMT3a and DNMT3b, members of the DNMT family (Plaza-Diaz et al., 2022).

The DNMT1 enzyme maintains the hemimethylated DNA strand as well as the appropriate DNA methylation pattern on the newly synthesized strand through replication, while DNA methyltransferases in particular 3 (DNMT3A and DNMT3B) add methyl groups de novo (Davletgildeeva and Kuznetsov, 2024). De novo DNMTs are highly active in developing embryos compared to adult tissues; however, evidence shows they also contribute to maintaining methylation patterns for instance, simultaneous deletion or inactivation of DNMT1 and DNMT3b leads to a more significant reduction in DNA methylation than when either gene is inactivated alone (Mahmoud & Ali, 2019). Additionally, some studies suggest DNMT1 is also essential for de novo DNA methylation (Mahmoud & Ali, 2019).

Research conducted by (Damal Villivalam *et al.*, 2021) showed that DNMT3A deficiency in skeletal muscle mice experienced muscle fatigue and oxidative stress, which resulted in decreased exercise capacity. This study indicates that DNMT3A in skeletal muscle is essential for supporting mitochondrial function and oxidative capacity, which significantly impact endurance training performance (Damal Villivalam *et al.*, 2021). Excessive reactive oxygen species (ROS) significantly contribute to muscle dysfunction. Transcription of Aldh1l1 was suppressed by DNMT3A by binding to its promoter and modifying its epigenetic state.

Increased expression of ALDH1L1 raises NADPH levels, which promotes excessive ROS production via the NADPH oxidase complex, leading to mitochondrial damage in muscle cells. Therefore, targeting the ALDH1L1 pathway could potentially alleviate oxidative stress and mitochondrial issues caused by Dnmt3a deficiency in muscle fibers. Overall, DNMT3A plays a vital role in skeletal muscle endurance by regulating intracellular oxidative stress (Damal Villivalam *et al.*, 2021).

PGC1-is a regulatory gene for fatty acid oxidation, mitochondrial biogenesis, and skeletal muscle insulin sensitivity (Maasar et al. 2021). The PGC-1 gene is hypomethylated after intense exercise sessions (Maasar et al. 2021). Barrès et al. (2012) performed a biopsy of the vastus lateralis, that found a different methylation state of the promoter of this gene, specifically, 10% less methylation compared to the resting state. The degree of hypomethylation of PGC-1 correlated with an increase in mRNA levels three hours after resistance exercise, confirming that changes in methylation are involved in transcriptional activation (Barres et al. 2012). PGC-1 gene and its control in epigenetic regulation involved in physiological and pathophysiological conditions, including preventing PGC-1 hypermethylation that induced by a high-fat diet in the offspring, and increases PGC-1 levels in regular exercise training pregnant women, thus ameliorating age-related metabolic dysfunction. These reasearch suggest that DNA methylation of PGC-1 may be related to metabolic memory in resistance exercise. Additionally, 4 days of inactivity increased muscle gene expression associated with insulin resistance and increased DNA methylation of PGC-1 in endurance exercise (*Alibegovic* et al. 2010; Plaza-Diaz et al., 2022).

A single session of aerobic endurance exercise in humans temporarily causes hypomethylation in the promoter regions of important mitochondria-related genes (such as PPARGC1A, PDK4, TFAM, and PPARD), which is then followed by an increase in their expression (Barrés et al., 2012; Damal Villivalam et al., 2021). Individuals with a family history of type 2 diabetes (T2D) show reduced PPARGC1A expression in tissues like muscle and fat (Chen et al., 2011; Santos et al., 2020), potentially affecting PGC-1α-regulated genes involved in oxidative phosphorylation. Interestingly, one study suggested that overexpressing PGC-1α in muscle fibers might enhance glucose uptake and improve insulin sensitivity by promoting GLUT4 translocation to the cell membrane (Santos et al., 2020). Normally, the pyruvate dehydrogenase complex (PDC) involves glucose metabolism regulation with converting pyruvate to acetyl-CoA for the citric acid cycle and inhibiting pyruvate dehydrogenase kinase 4 (PDK4). However, reduced methylation of the PDK4 promoter leads to its overexpression when glucose is not properly metabolized, contributing to hyperglycemia and potentially influencing the development of type 2 diabetes (Putra et al., 2023).

Specifically, moderate to high-intensity exercise induced an immediate reduction in the methylation of active promoters, including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), mitochondrial transcription factor A (TFAM), pyruvate

dehydrogenase kinase isoenzyme 4, and MEF2A, and delayed methylation of the peroxisome proliferator-activated receptor δ (PPARδ) promoter 3 hours post-exercise (Serin et al., 2025).

Muscle contraction causes increased oxidative metabolism for ATP production that generates reactive oxygen species (ROS) (Plaza-Diaz et al., 2022). ROS drives DNA that trigger genomic responses. ROS are modulated by members of the carbon metabolism such as S-adenosyl methionine (SAM), which serves as a methyl group donor used in DNA methylation (Kietzmann. 2017). Consequently, modulation of methyl donor availability is how oxidative stress, together with calcium, can be a trigger that controls exercise-induced methylation (Plaza-Diaz et al., 2022).

Studies have shown that exercise induces changes in promoter methylation of genes important for energy and glucose homeostasis, including PGC-1α, pyruvate dehydrogenase kinase kinase isoenzyme 4 (PDK4), and peroxisome proliferator activated receptor δ (PPAR-δ) (Barres et al 2012; Serin et al., 2025).

A number of studies have reported the effects of exercise on genome-wide DNA methylation in various tissues. In skeletal muscle, it is noteworthy that epigenetically modified genes mainly consist of key metabolic genes (Wu et al., 2021). Exercise is responsible for a dose-dependent upregulation of peroxisome proliferator-activated receptor g1a (PPARGC1A, encoding PGC-1a), pyruvate dehydrogenase kinase 4 (PDK4), and PPARd (PPARD, encoding PPARd), consistent with marked hypomethylation of the promoters of these genes (Wu et al., 2021).

DNA methylation changes at 2817 and 7663 genes in skeletal muscle and adipose tissue, respectively. Interestingly, while about three-quarters of the identified genes showed decreased DNA methylation in skeletal muscle, the majority of genes showed increased DNA methylation in adipose tissue in response to exercise, suggesting that epigenetics may have differential effects on the two tissues (Ling and Rönn, 2014).

Modified genes in adipose tissue showed increased methylation and decreased expression, which is in contrast to the expression pattern in skeletal muscle, where most of the identified genes showed decreased methylation and increased expression (Ronn et al. 2013). Ras-like proto-oncogene A-binding protein 1 (RALBP1), a gene involved in the development of metabolic syndrome and impaired glucose transporter 4 (GLUT4), was hypermethylated by exercise in adipose tissue. In addition, exercise modified leukocyte DNA methylation genome-wide after 4 weeks of sprint interval training (Wu et al., 2021). Among the modified genes, genes activated for pathways responsible for cardiovascular fitness including mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3 phosphate kinase/protein kinase B (PI3K/Akt) signaling pathways. Exercise also regulates histone modifications including histone acetylation and methylation (Wu et al., 2021).

Glycogenin 2 (GYG2), glycogen synthase 1 (GYS1), and the glycogen-degrading alpha-amylase 2B (AMY2B) were found to have higher expression capacities for genes involved in

glycogen storage and metabolism in active men compared to inactive men. Promoter hypomethylation was found in key glycolysis and TCA cycle genes, including the gene encoding ADP-dependent glucokinase (ADPGK) that catalyzes the phosphorylation of glucose to glucose-6-phosphate using ADP as a substrate, and muscle-specific pyruvate kinase (PKM), which mediates the final step in glycolysis. The promoter region of the gene encoding the pyruvate dehydrogenase alpha 1 (PDHA1) subunit, which links glycolysis and the TCA cycle, and the rate-limiting enzyme in TCA cycle flux, isocitrate dehydrogenase (IDH3A), was found to be hypomethylated in active subjects compared to inactive subjects (Sailani et a. 2019).

2. Histone Modification

Histones are highly basic proteins, composed of many amino acids with basic side chains (primarily lysine and arginine). Histones package and organize DNA into structural units called nucleosomes and are the main protein components of chromatin (Grazioli *et al.*, 2017). Histones have two important functions, namely to package genomic DNA and regulate gene accessibility (Sokolova, Sarkar and Tan, 2023). Histone modifications are post-translational changes that include acetylation or methylation of certain histone regions, especially histone H3 and H4 and are reversible (Grazioli et al., 2017).

Histone modification enzymes such as HATs, HMTs, HDACs, and HDMs function to regulate gene expression (R. Liu et al., 2023). Histone modifications are generally catalyzed by histone acetyltransferase (HAT) or histone deacetylase (HDAC) enzymes (Richarson 2013; Grazioli et al., 2017). Specifically, acetylation removes the positive charge of histones, thereby reducing interactions with the negatively charged phosphate groups of DNA, resulting in a more relaxed chromatin structure that supports increased gene transcription. This condition can be reversed by HDACs capable of inducing deacetylation, which is associated with reduced transcriptional activity (Grazioli et al., 2017).

Histone modification is an epigenetic mechanism that plays a role in controlling transcriptional activity in the cell nucleus (Lim et al., 2020). This modification pattern varies between fast- and slow-contracting skeletal muscle fibers. In adult mice, transcriptionally active histone markers, such as acetylation and trimethylation of lysine 4 on histone H3 (H3K4me3), are more prevalent in genes highly expressed in fast-contracting muscle fibers, whereas a similar pattern is absent in slow-contracting fibers (Kawano et al., 2015). Consistent with these findings, Masuzawa et al. (2018) reported that acute treadmill exercise triggers increased transcription of PPARGC1A (encoding PGC-1α), primarily in fast-contracting fibers, characterized by increased histone acetylation levels compared to slow-contracting fibers. Meanwhile, Begue et al. (2017) demonstrated that CpG sites of genes typically expressed in myosin heavy chain type I and IIa fibers are hypomethylated in human skeletal muscle. Collectively, these findings suggest that the epigenetic landscape, shaped by muscle fiber type, contributes to differential gene regulation in response to exercise stimuli (Lim et al., 2020).

Recent research has begun to explore exercise induced histone modifications specifically within cardiac tissue. Much of this work has centered on histone acetylation regulated by histone deacetylases (HDACs) in the heart (Wu et al., 2021). Exercise has been shown to influence both histone acetylation and methylation. Initial investigations into histone acetylation highlighted the role of HDACs in modulating the expression of metabolic genes through the transcription factor myocyte enhancer factor 2 (MEF2) following exercise. Several studies have shown that swimming can trigger increased acetylation of histone H3 at lysine residues 9 and 14 (H3K9/14). This increase, or hyperacetylation, is specifically found at the MEF2 binding site in the GLUT4 gene, which in turn strengthens MEF2 interactions and promotes GLUT4 expression (Wu et al., 2021). Physical activity has also been shown to increase H3K4me3 levels at the PGC-1α promoter in skeletal muscle, thereby stimulating PGC-1α protein production and supporting mitochondrial biogenesis (Li *et al.*, 2024).

other findings indicate that exercise can induce the release of HDAC5 from MEF2A, a mechanism that contributes to increased MEF2A expression (Wu et al., 2021). Epigenetic changes in histone modifications have also been associated with a reduced risk of neurological and psychiatric disorders after exercise (Smith et al., 2008). Furthermore, exercise affects the activity of histone acetyltransferase (HAT) enzymes. For example, studies have reported that acute exercise can increase HAT activity, leading to hyperacetylation in the frontal cortex in mice (Wu et al., 2021). However, the specific polycomb repressor complex involved in this mechanism remains unidentified (Wu et al., 2021).

3. mRNA

m6A is one of the most common posttranscriptional RNA modifications in mRNA, another novel epigenetic marker, playing an important role in gene expression regulation (Liu *et al.*, 2022). Through reciprocal interactions with methyltransferases, demethylases, and m6A-binding proteins to balance m6A levels, and to ensure that mRNA transcripts can be properly spliced, transported, transcribed, and degraded (Liu *et al.*, 2022).

As an epigenetic marker, reversible m6A is the most common posttranscriptional regulation of mammalian gene expression (Liu *et al.*, 2022). m6A is abundant in the nervous system, and the cellular dynamics of m6A are associated with neuronal function, neurogenesis, and neuronal survival (S. J. Liu et al., 2022). Dysregulation of m6A is associated with many biological processes, including neurodevelopment and neurodegenerative diseases. Reportedly, upregulation of m6A occurs along with brain maturation, behavioral experience, and memory formation (Liu *et al.*, 2022).

More recently, it has gained significant attention due to its role as an m6A RNA demethylase (Liu *et al.*, 2022). FTO is predominantly expressed in the brain and is thought to participate in various RNA processing mechanisms, including mRNA translation, splicing, and metabolism. The FTO gene has been linked to an increased risk of obesity and type 2 diabetes (Liu *et al.*, 2022). Previous findings indicate that intense physical exercise reduces FTO mRNA

expression in skeletal muscle (Liu *et al*., 2022). In the current study, elevated m6A levels were detected in the hippocampus and hypothalamus of exercised mice. Given that m6A modification is dynamically regulated by methyltransferases, demethylases, and reader proteins, the expression of 13 m6A-related genes including METTL3, ZC3H13, WTAP, RBM15, FTO, ALKBH5, YTHDF1, YTHDF3, YTHDC2, YTHDC1, YTHDF2, METTL14, and HNRNPC was analyzed in these brain regions. Among them, only FTO expression was significantly downregulated in the hippocampus and hypothalamus following exercise (Liu *et al*., 2022).

4. MiRNA

MicroRNAs (miRNAs) primarily function to suppress gene expression at the post-transcriptional level (Shi et al., 2022). Given their involvement in non-homeostatic biological pathways, miRNAs are particularly relevant in the context of exercise physiology (Widmann et al., 2019). A specific group of miRNAs known as myomiRs originating from cardiac and skeletal muscle are enriched in miRNA clusters and play essential roles in muscle function. Currently, seven myomiRs have been identified in skeletal muscle: miR-1, miR-133a, miR-133b, miR-206 (skeletal muscle-specific), miR-208b, miR-486, and miR-499 (Jacques et al., 2019).

The expression of these myomiRs varies depending on the type and duration of physical activity and is closely linked to muscle development, regeneration, and maintenance (Mytidou et al., 2021). Several studies have shown that physical activity can increase the expression of proteins that play a key role in miRNA maturation, including Drosha, Dicer, and Exportin-5. This increase is also accompanied by increased myomiR levels (Li et al., 2022), confirming the close relationship between exercise and miRNA regulation (Mallett, 2025). Recent research reported that acute treadmill exercise can increase muscle-specific RNA Polymerase II (Pol II) activity, which transcriptionally activates miR-451 during PGC-1α activation, indicating the involvement of Pol II in exercise-induced miRNA expression. Furthermore, a single exercise session can promote histone acetylation, which likely facilitates Pol II recruitment and influences miRNA transcription.These miRNAs play a central role in brain development by regulating gene expression related to neuronal growth and survival (Zhang et al., 2025). Several data suggest that exercise plays a role in modulating certain brain miRNAs, such as miR-29, miR-132, miR-133, miR-129-1-3p, miR-144-5p, miR-10b-5p, and miR-708-5p. These miRNAs are known to support neuron development, synaptic function, and neurogenesis by targeting key molecules including BACE1, BDNF, and tyrosine hydroxylase through a transcriptional pathway involving Ptx1. This process also contributes to dopamine synthesis and memory formation (Zhang et al., 2025).

Exercise has also been reported to increase the activity of key components of miRNA biogenesis, namely Drosha, Dicer, and Exportin-5. For example, three hours of moderate-intensity cycling has been shown to significantly increase the activity of these enzymes, thereby increasing miRNA production (Zhang et al., 2025). Furthermore, exercise-induced activation of transcription factors, such as MyoD1 (myoblast determination protein 1) and MEF2

(myocyte enhancer factor 2), can stimulate the expression of specific myomiRs, including miR-129-1-3p, miR-144-5p, miR-10b-5p, and miR-708-5p. Growing evidence indicates that epigenetic mechanisms can mediate the transmission of exercise-induced physiological adaptations across generations. Epigenetic modifications play an essential role in various biological processes, including genomic imprinting and X-chromosome inactivation, and are considered key molecular markers of biological aging. Therefore, epigenetic changes are increasingly recognized as important in the context of development, aging, and disease pathogenesis (Plaza-Diaz et al., 2022).

A limitation of this study is that a formal methodological quality assessment was not conducted. This is related to the study's focus on exploring biomarker studies. However, it is recommended that future research include a quality assessment to strengthen the validity of the results.

CONCLUSION

Exercise affects gene expression without altering DNA sequence. Exercise trigger epigenetic changes through DNA methylation, histone modification, mRNA and miRNA. Exercise influences genetic changes depending on the activity, duration, and condition of a person. Various studies have shown that exercise can be tailored to the body's condition and the potential impacts of the activity. This study examines epigenetic changes in various conditions, which can serve as a guide for more specific exercise tailored to the individual's condition, particularly those related to metabolic diseases and chronic diseases such as chronic kidney disease, cancer, heart failure, and obesity and sedentary habits.

For further research, experimental designs related to measuring specific epigenetic biomarkers in the Indonesian population need to be carried out because differences in demographic and ethnic characteristics may have different impacts from previous research.

REFERENCES

Alibegovic A.C., Sonne M.P., Hojbjerre L., Bork-Jensen J., Jacobsen S., Nilsson E., Faerch K., Hiscock N., Mortensen B., Friedrichsen M., et al. Insulin resistance induced by physical inactivity is associated with multiple transcriptional changes in skeletal muscle in young men. Am. J. Physiol. Endocrinol. Metab. 2010;299:E752–E763. doi: 10.1152/ajpendo.00590.2009.

Barres, R.; Yan, J.; Egan, B.; Treebak, J.T.; Rasmussen, M.; Fritz, T.; Caidahl, K.; Krook, A.; O'Gorman, D.J.; Zierath, J.R. Acute exercise remodels promoter methylation in human skeletal muscle. Cell Metab. 2012, 15, 405–411.

Begue G, Raue U, JemioloB, Trappe S. DNA methylation assessment from human slow- and fast-twitch skeletal muscle fibers. J Appl Physiol. 2017; 122: 952–967. https://doi.org/10.1152/japplphysiol.00867. 2016 PMID: 28057818

Boyne, D.J. et al. (2018) 'Aerobic exercise and DNA methylation in postmenopausal women: An ancillary analysis of the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial', PLoS ONE, 13(6), pp. 1–13. Available at: https://doi.org/10.1371/journal.pone.0198641.

Butts, B. et al. (2018) 'Effects of Exercise on ASC Methylation and IL-1 Cytokines in Heart Failure', Medicine and Science in Sports and Exercise, 50(9), pp. 1757–1766. Available at: https://doi.org/10.1249/MSS.0000000000001641.

Damal Villivalam, S. et al. (2021) 'A necessary role of DNMT3A in endurance exercise by suppressing ALDH1L1-mediated oxidative stress', The EMBO Journal, 40(9). Available at:

https://doi.org/10.15252/embj.2020106491.
Davletgildeeva, A.T. and Kuznetsov, N.A. (2024) 'The Role of DNMT Methyltransferases and TET Dioxygenases in the Maintenance of the DNA Methylation Level', Biomolecules, 14(9), pp. 1–22. Available at: https://doi.org/10.3390/biom14091117.
Denham, J. et al. (2018) 'Small non-coding RNAs are altered by short-term sprint interval training in men', Physiological Reports, 6(7), pp. 1–10. Available at: https://doi.org/10.14814/phy2.13653.
Dhuha, A.A. et al. (2024) 'Pengaruh Interval Training Terhadap Peningkatan Vo2Max Atlet Taekwondo Kota Semarang', Journal of Sport Science and Fitness, 9(2), pp. 122–127. Available at: https://doi.org/10.15294/jssf.v9i2.75264.
Fabre, O. et al. (2018) 'Exercise training alters the genomic response to acute exercise in human adipose tissue', Epigenomics, 10(8), pp. 1033–1050. Available at: https://doi.org/10.2217/epi-2018-0039.
Fajriyah, N., Sudiana, I.K. and Wahyuni, E.D. (2020) 'The Effects from Physical Exercise on the Blood Glucose Levels, HbA1c and Quality of Life of Type 2 Diabetes Mellitus Patients: A Systematic Review', Jurnal Ners, 15(2 Special Issue), pp. 489–496. Available at: https://doi.org/10.20473/jn.v15i2(si).20517.
Farsetti, A., Illi, B. and Gaetano, C. (2023) 'How epigenetics impacts on human diseases', European Journal of Internal Medicine, 114(May), pp. 15–22. Available at: https://doi.org/10.1016/j.ejim.2023.05.036.
Ferrari, L. et al. (2019) 'Effects of physical exercise on endothelial function and DNA methylation', International Journal of Environmental Research and Public Health, 16(14), pp. 1–11. Available at: https://doi.org/10.3390/ijerph16142530.
Grazioli, E. et al. (2017) 'Physical activity in the prevention of human diseases: Role of epigenetic modifications', BMC Genomics, 18(Suppl 8). Available at: https://doi.org/10.1186/s12864-017-4193-5.
Li, J. et al. (2024) 'Endurance exercise-induced histone methylation modification involved in skeletal muscle fiber type transition and mitochondrial biogenesis', Scientific Reports, 14(1), pp. 1–20. Available at: https://doi.org/10.1038/s41598-024-72088-6.
Ling, C. and Rönn, T. (2014) 'Epigenetic adaptation to regular exercise in humans', Drug Discovery Today, 19(7), pp. 1015–1018. Available at: https://doi.org/10.1016/j.drudis.2014.03.006.
Liu, S.J. et al. (2022) 'Long-term exercise training down-regulates m6A RNA demethylase FTO expression in the hippocampus and hypothalamus: an effective intervention for epigenetic modification', BMC Neuroscience, 23(1), pp. 1–13. Available at: https://doi.org/10.1186/s12868-022-00742-8.
Loh, K.P. et al. (2023) 'Exercise and epigenetic ages in older adults with myeloid malignancies', European Journal of Medical Research, 28(1), pp. 1–12. Available at: https://doi.org/10.1186/s40001-023-01145-z.
Plaza-Florido, A. et al. (2025) 'Integrated analysis of methylome and transcriptome responses to exercise training in children with overweight/obesity', Physiological Genomics, 57(2), pp. 91–102. Available at: https://doi.org/10.1152/PHYSIOLGENOMICS.00059.2024.
Posadzki, P. et al. (2020) 'Exercise/physical activity and health outcomes: an overview of Cochrane systematic reviews', BMC Public Health, 20(1), pp. 1–12. Available at: https://doi.org/10.1186/s12889-020-09855-3.
Sailani, M.R. et al. (2019) 'Lifelong physical activity is associated with promoter hypomethylation of genes involved in metabolism, myogenesis, contractile properties and oxidative stress resistance in aged human skeletal muscle', Scientific Reports, 9(1), pp. 1–11. Available at: https://doi.org/10.1038/s41598-018-37895-8.
Sokolova, V., Sarkar, S. and Tan, D. (2023) 'Histone variants and chromatin structure, update of advances', Computational and Structural Biotechnology Journal, 21, pp. 299–311. Available at: https://doi.org/10.1016/j.csbj.2022.12.002.
Vale, N. (2025) 'Special Issue "Molecular Precision Medicine: Unraveling Novel Mechanisms and Delivery Strategies in Complex Diseases"', International Journal of Molecular Sciences, 26(15), pp. 10–13. Available at: https://doi.org/10.3390/ijms26157439.
Widmann, M., Nieß, A.M. and Munz, B. (2019) 'Physical Exercise and Epigenetic Modifications in Skeletal Muscle', Sports Medicine, 49(4), pp. 509–523. Available at: https://doi.org/10.1007/s40279-019-01070-4.
Wu, G., Zhang, X. and Gao, F. (2021) 'The epigenetic landscape of exercise in cardiac health and disease', Journal of Sport and Health Science, 10(6), pp. 648–659. Available at: https://doi.org/10.1016/j.jshs.2020.12.003.