

<https://doi.org/10.47183/mes.2026-467>



INFLUENCE OF PHYSICAL EXERCISE ON EPIGENETIC MODIFICATIONS OF THE GENOME: SIGNIFICANCE FOR SPORTS MEDICINE (A REVIEW)

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Introduction. Physical exercise is one of the most powerful environmental factors modulating epigenetic modifications of the genome. The regulation of gene activity via the chemical modification of DNA, histone alterations, and non-coding RNAs serves as a link between training and the developing athletic phenotype. However, published data remain fragmented and often contradictory due to methodological challenges, heterogeneous cohorts, and a lack of protocol standardization.

Objective. Systematization and synthesis of current data on the influence of physical exercise on epigenetic modifications of the genome, analysis of their contribution to the processes of adaptation, recovery, and formation of the risk of pathological conditions in athletes, as well as assessment of the prospects for the use of epigenetic markers in sports medicine.

Discussion. Physical exercise induces specific changes in the three main components of the epigenome. Acute and chronic loads cause hypomethylation of the promoters of energy metabolism genes (*PPARGC1A*, *PDK4*, *PPARD*), which is accompanied by increased expression and mitochondrial biogenesis. Histone modifications (acetylation, phosphorylation of H3.3-Ser-31, lactylation) alter chromatin packing density. The spectrum of microRNAs depends on the type and duration of training; however, information on individual microRNAs (including miR-1) remains contradictory, largely due to differences in methodology (participant training status, time points, normalization method, sex). Signaling cascades (AMPK, MAPK, IGF-1/Akt, NF-κB, NFE2L2) integrate energetic signals and the epigenetic response. The epigenetic response is tissue-specific and is modulated by sex, age, and ethnicity. Promising directions include the analysis of exerkines, including microRNAs from extracellular vesicles, and nutrigenetics.

Conclusions. Physical exercise consistently induces characteristic epigenetic modifications that participate in adaptation and can be considered as potential biomarkers of an athlete's functional state. Promising areas of application in sports medicine include monitoring recovery through epigenetic clocks, predicting injury and overtraining, personalizing training, and extending the Athlete Biological Passport with epigenetic markers. Implementation of the results into clinical practice requires overcoming methodological limitations and further prospective research.

Keywords: physical exercise; epigenetics; DNA methylation; histone modifications; microRNA; exerkines; sports medicine

For citation: Kadykova A.I., Kopylov E.D., Gladyshev N.S., Deev R.V., Zholinsky A.V. Influence of physical exercise on epigenetic modifications of the genome: significance for sports medicine (a review). *Extreme Medicine*. 2026;28(3):335–345. <https://doi.org/10.47183/mes.2026-467>

Funding. The research was carried out under State Contract No. 107.003.25.14 (20.06.2025) titled "Investigation of Molecular-Genetic Predictors for a Long-Term Sports Career and Epigenetic Genome Modifications in Russian National Team Athletes" (Project Code: "Career-25-27").

Potential conflict of interest. The authors declare no conflict of interest.

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Received: 17 Feb. 2026 **Revised:** 7 May 2026 **Accepted:** 18 May 2026 **Online first:** 24 July 2026

УДК 577.218

ВЛИЯНИЕ ФИЗИЧЕСКИХ НАГРУЗОК НА ЭПИГЕНЕТИЧЕСКИЕ МОДИФИКАЦИИ ГЕНОМА: ЗНАЧЕНИЕ ДЛЯ СПОРТИВНОЙ МЕДИЦИНЫ (ОБЗОР)

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Введение. Физическая нагрузка является одним из наиболее мощных средовых факторов, модулирующих эпигенетические модификации генома. Регуляция активности генов посредством химической модификации ДНК, изменения гистонов и некодирующих РНК выступает связующим звеном между тренировками и формирующимся фенотипом спортсмена. Данные литературы остаются разрозненными и нередко противоречивыми, что обусловлено методологическими сложностями, гетерогенностью исследуемых групп и отсутствием стандартизации протоколов.

Цель. Систематизация и обобщение современных данных о влиянии физических нагрузок на эпигенетические модификации генома, анализ их вклада в процессы адаптации, восстановления и формирования риска патологических состояний у спортсменов, а также оценка перспектив применения эпигенетических маркеров в спортивной медицине.

Обсуждение. Физические упражнения индуцируют специфические изменения в трех основных звеньях эпигенома. Острые и хронические нагрузки вызывают гипометилирование промоторов генов энергетического обмена (*PPARGC1A*, *PDK4*, *PPARD*), что сопровождается усилением экспрессии и митохондриальным биогенезом. Модификации гистонов (ацетилирование, фосфорилирование H3.3-Ser-31, лактирование) изменяют плотность упаковки хроматина. Спектр микроРНК зависит от типа и продолжительности тренировок, однако информация по отдельным микроРНК (в том числе miR-1) остается противоречивой, что в значительной степени определяется различиями в методологии (тренированность участников, временные точки, способ нормализации, пол). Сигнальные каскады (AMPK, MAPK, IGF-1/Akt, NF-κB, NFE2L2) интегрируют энергетические сигналы и эпигенетический ответ. Эпигенетический ответ тканеспецифичен и модулируется полом, возрастом и этнической принадлежностью. Отдельными перспективными направлениями являются анализ экзеркинов, в том числе микроРНК внеклеточных везикул (EVs), и нутриэпигенетика.

Выводы. Физические нагрузки закономерно вызывают характерные эпигенетические модификации, которые участвуют в адаптации, и могут рассматриваться как потенциальные биомаркеры функционального состояния спортсмена. Перспективные

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направления применения в спортивной медицине включают мониторинг восстановления через эпигенетические часы, прогноз травматизма и перетренированности, персонализацию тренировок и расширение «Athlete Biological Passport» (биологического «паспорта» спортсмена) за счет эпигенетических маркеров. Внедрение результатов в клиническую практику требует преодоления методологических ограничений и дальнейших проспективных исследований.

Ключевые слова: физическая нагрузка; эпигенетика; метилирование ДНК; модификации гистонов; микроРНК; экзеркины; спортивная медицина

Для цитирования: Кадыкова А.И., Копылов Е.Д., Гладышев Н.С., Деев Р.В., Жолинский А.В. Влияние физических нагрузок на эпигенетические модификации генома: значение для спортивной медицины (обзор). *Экстремальная биомедицина*. 2026;28(3):335–345. <https://doi.org/10.47183/mes.2026-467>

Финансирование. Научное исследование проведено на основании государственного контракта № 107.003.25.14 от 20.06.2025 «Исследование молекулярно-генетических предикторов длительной спортивной карьеры и эпигенетических модификаций генома спортсменов сборных команд Российской Федерации» (шифр «Карьера-25-27»).

Потенциальный конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

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Статья поступила: 17.02.2026 **После доработки:** 07.05.2026 **Принята к публикации:** 18.05.2026 **Online first:** 24.07.2026

INTRODUCTION

Physical exercise represents a physiological stimulus that triggers adaptive changes in cellular metabolism, signaling cascades, and gene expression in multiple tissues of the body. Along with alterations in the activity of regulatory proteins, the molecular basis of this adaptation involves epigenetic mechanisms — reversible changes in the regulation of gene expression without changes in the DNA sequence [1, 2]. Epigenetic modifications provide the link between the training process and the developing athlete phenotype, determining the characteristics of adaptation to various types of exercise [3, 4].

The primary epigenetic mechanisms include DNA methylation, post-translational histone modifications, and regulation of expression by non-coding RNAs [5], which are sensitive to the influence of external (physical activity, nutrition, sleep, stress) and internal factors [6, 7]. Systematic training induces specific changes in the epigenetic profile of skeletal muscles, myocardium, adipose tissue, and immune cells, affecting the expression of genes involved in mitochondrial biogenesis, oxidative metabolism, muscle hypertrophy, anti-inflammatory and antioxidant responses [8, 9]. The direction and magnitude of changes depend on the type of exercise and its metabolic specificity [10, 11].

Epigenetic modifications induced by exercise can be both protective and adaptive in nature, as well as be associated with an increased risk of diseases, overtraining, and sports injuries [12, 13]. This makes epigenetic markers promising candidates as tools for personalized sports medicine [14, 15]. At the same time, unresolved issues remain regarding the persistence of acquired modifications, the reliability of associations with phenotype, and the clinical applicability of these markers.

The aim of the study is to systematize and synthesize current data on the influence of physical exercise on epigenetic modifications of the genome, analyze their contribution to the processes of adaptation, recovery, and formation of the risk of pathological conditions in athletes, and assess the prospects for the use of epigenetic markers in sports medicine.

The search for scientific publications was conducted for the period 2010–2026 across the PubMed, Scopus, and eLIBRARY databases using keywords in Russian: “epigenetic modifications induced by exercise”, “epigenetic regulation of physical performance”, “epigenetic adaptation to exercise”, “DNA methylation and exercise”, “microRNA and sports training”, “histone modifications and physical activity”, “epigenetic biomarkers in sports”, “exerkines”, “extracellular vesicles in exercise”, “epigenetic clocks and athletes”, “athlete biological passport miRNA”, “epigenetic doping”, “nutri-epigenetics”, as well as equivalent queries in English. Priority was given to original experimental studies, clinical trials, and systematic reviews. Publications without access to full-text versions were excluded from selection. Gene nomenclature follows HUGO guidelines¹. For microRNA identification, the central microRNA nomenclature online database (miRBase)² was used. A detailed glossary of key genes and microRNAs with identifiers is published on the journal's website³.

MAIN BODY

Over the past fifteen years, there have been significant changes in the understanding of how physical exercise affects epigenetic modifications of the genome. Early studies focused on identifying changes in DNA methylation and histone modifications in skeletal muscles. With the development of molecular and bioinformatic methods, integrative multi-omics approaches have been applied, allowing a deeper understanding

¹ Gene Nomenclature Committee. HGNC. www.genenames.org

² Central online database for microRNA nomenclature (miRBase). www.mirbase.org

³ Table 2. Glossary of genes and microRNAs with HGNC / miRBase identifiers. <https://doi.org/10.47183/mes.2026-467-annex>

of the relationships between epigenetic markers and gene expression affecting metabolic health and aging rates [16, 17]. Current research covers a wider range of tissues (skeletal muscle, myocardium, adipose tissue, leukocytes, saliva, spermatozoa) and diverse groups of subjects [18].

Molecular mechanisms of epigenetic regulation during physical exercise

The primary epigenetic changes include DNA methylation, histone modifications, and regulation of gene expression by non-coding RNAs [11]. Epigenetic modifications serve as a molecular “bridge” between genotype and phenotype [19]. A decrease in methylation of promoter regions of genes associated with mitochondrial biogenesis (*PPARGC1A*, *PDK4*, *PPARD*) leads to increased expression and enhanced aerobic endurance [20, 21]. The extent and duration of epigenomic changes range from short-term (minutes to hours) to long-term, providing “epigenetic memory” and sustained adaptation [22]. Table 1 and Figure 1 summarize the three main types of modifications, their molecular essence, and key physiological effects.

DNA methylation

DNA methylation is the most extensively studied epigenetic mechanism [23, 24]. In the work by Barrès

et al., it was shown that global methylation in skeletal muscle decreased after intense exercise, accompanied by a dose-dependent increase in the expression of *PPARGC1A*, *PDK4*, and *PPARD* and marked hypomethylation of their promoters. A similar effect was demonstrated in the soleus muscle of mice 45 min after *ex vivo* contraction [25]. In the study by Seaborne et al., it was found that in healthy men, the genes *GRIK2*, *TRAF1*, *BICC1*, and *STAG1* became hypomethylated after a single resistance exercise session and maintained this state for 22 weeks [26]. A meta-analysis by Etayo-Urtasun et al. also confirmed that both aerobic and resistance training significantly modulate the methylation profile in the skeletal muscle and blood of healthy adults, with the effect depending on the type and duration of training [23].

Histone modifications

Histones are the primary protein components of chromatin. They include five classes (H1, H2A, H2B, H3, H4), each with several subtypes [27]. The key metabolic regulator of acetylation is acetyl-CoA: acetylation “relaxes” chromatin (euchromatin), while deacetylation (HDAC) “condenses” it (heterochromatin) [28]. Physical exercise increases the oxidation of fatty acids and carbohydrates, raising the concentration of acetyl-CoA [29], which creates a substrate basis for hyperacetylation. In the study by Chen et al., it was shown that trichostatin

Table 1. Main epigenetic mechanisms, exercise-induced changes, and physiological effects

Parameter	Type of modification		
	DNA methylation	Histone modifications	Non-coding RNAs (microRNA, lncRNA, circRNA)
Molecular mechanism	Addition of CH ₃ to cytosine in CpG islands; Hypermethylation → repression; Hypomethylation → activation	Acetylation (HAT) ↔ deacetylation (HDAC); Phosphorylation of H3.3 Ser-31; Lactylation of histone lysines	MicroRNAs (18–24 nt) bind to mRNA and cause its degradation or translational blockade; lncRNAs and circRNAs regulate transcription and act as microRNA sponges
Direction of exercise-induced changes	Hypomethylation of promoters of metabolism, mitochondrial biogenesis and hypertrophy genes; Formation of persistent hypomethylation with repeated exercise (“epigenetic memory”)	Increase in acetyl-CoA during exercise → substrate activation of acetylation. HDAC inhibition → hyperacetylation. Phosphorylation of H3.3-Ser-31. Lactylation upon lactate accumulation	Diverse changes in miR-1, miR-133a/b, miR-206 depending on the protocol (resistance or aerobic, acute or chronic, trained or untrained); Increase in miR-21, miR-29b during aerobic exercise
Physiological effects / associated genes	Increased expression of <i>PPARGC1A</i> , <i>PDK4</i> , <i>PPARD</i> → mitochondrial biogenesis; Hypomethylation of <i>GRIK2</i> , <i>TRAF1</i> , <i>BICC1</i> → long-term hypertrophy	Facilitation of transcriptional response, activation of metabolism, regeneration, and hypoxia adaptation genes	Muscle hypertrophy, cardioprotection, lipid metabolism (via PDCD4), post-injury regeneration (miR-206, miR-486), inter-tissue communication via EVs

Table compiled by the authors based on data from references [23, 28, 34]

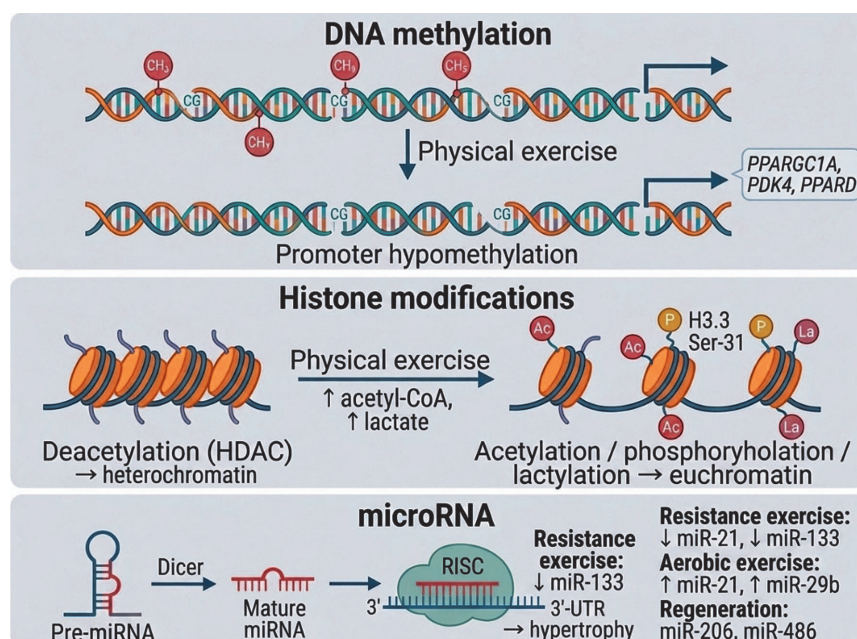


Figure prepared by the authors based on data from [25, 27–32, 34]

Fig. 1. Three levels of epigenetic regulation during physical exercise. RISC — RNA-induced silencing complex; DICER — enzyme complex (ribonuclease III)

A-induced hyperacetylation of myoblasts enhances their fusion and the secretion of extracellular vesicles containing miR-873-3p, which stimulates the osteogenic differentiation of mesenchymal stem cells [30].

Phosphorylation of Ser-31 of histone H3.3 also regulates the muscle response to exercise. Maruyama and Kawano demonstrated that the level of H3.3-Ser-31ph is reduced in the muscles of aged mice; introduction of mutant H3.3 with a serine-to-glutamic acid substitution (H3.3S31E) restored the transcriptional response to exercise [31]. Zhang et al. first established that lactate serves as a substrate for histone lactylation — a novel post-translational modification that modulates the expression of tissue repair and inflammation genes [32]. In the context of physical exercise, elevated lactate levels may contribute to epigenetic regulation through both acetylation and lactylation [33].

Non-coding RNAs: critical analysis of contradictions

MicroRNAs (18–24 nt) regulate gene expression post-transcriptionally by binding to messenger RNA [34]. Physical exercise alters the expression of muscle-specific microRNAs ("myomiRs" — miR-1, miR-133a, miR-133b, miR-206). Resistance training reduces the levels of miR-1 and miR-133, which suppress muscle growth, thereby promoting hypertrophy [34].

Contradictory data on miR-1

In sports medicine, the response of miR-1 to aerobic exercise remains one of the most controversial issues. Nielsen et al. found that in untrained men, a single aerobic

exercise session increased miR-1 expression ($p < 0.05$), but after 12 weeks of training, the baseline level of miR-1 dropped, and acute exercise no longer induced its elevation [35]. Russell et al., in a similar study, demonstrated that miR-1 increased both after acute aerobic exercise and 10 days of training ($p < 0.05$) [36]. Grieb et al. found no significant changes in miR-1 in skeletal muscle after a single submaximal endurance exercise in women [34]. A completely different pattern of changes was observed for circulating microRNAs: plasma miR-1 increased 3 hours after exercise [37], and after a half-marathon, circulating levels of miR-1, miR-133a, and miR-206 significantly increased [38]. The differences between the tissue and circulating pools of miR-1 likely reflect different biological processes.

The discrepancies across studies can be attributed to several methodological factors:

- training status of participants: untrained individuals exhibit inherently higher baseline levels of myomiRs, whereas trained individuals display reduced baseline levels, shifting the magnitude and direction of the response to acute exercise;
- type and intensity of exercise: incorrect comparison of metabolically different exercise protocols (e.g., 70% VO₂ max) based solely on percentage of maximal oxygen consumption without considering their different metabolic specificities [39];
- time points of biopsy collection, including muscle tissue: miR-1 exhibits rapid transient dynamics, and results strongly depend on whether the tissue was collected immediately, 2, 3, or 24 h post-exercise [40];
- sex of participants: most studies have been performed in males; data on females are scarce and demonstrate a different response profile [34];

- normalization method in qPCR: the use of Rnu6, cel-miR-39 as an exogenous control, or other references can significantly alter the results of measuring relative gene expression [41];
- preanalytical factors: plasma hemolysis, RNA isolation method, sample storage conditions can critically distort measurements of circulating microRNAs [42].

Thus, to establish valid epigenetic biomarkers in sports medicine, standardization of protocols is necessary according to the principles being developed by the International Society for Extracellular Vesicles (ISEV) — “Minimal Information for Studies of Extracellular Vesicles (version 2023)” (MISEV2023) [43], and similar initiatives for microRNAs.

In addition to miR-1, other microRNAs involved in the regulation of adaptation include miR-133a (involved in the regulation of hypertrophy and cardioprotection) [44], miR-21 (improvement of lipid metabolism via *PDCD4*) [45–48], miR-29b (adaptation to aerobic exercise), as well as miR-486 (PI3K/AKT via *PTEN*) and miR-206 (responsible for muscle regeneration), which are key for signaling regulation [15]. Current studies are increasingly focusing on the interaction of microRNAs with long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) in the heart: miR-lncRNA and miR-circRNA axes mediate the cardioprotective effect of physical activity, and circular RNA is necessary for exercise-induced myocardial hypertrophy [49].

Signaling cascades and their epigenetic effectors

Physical exercise affects the expression of genes involved in key signaling cascades: AMPK, PGC-1 α (encoded by *PPARGC1A*), MAPK, insulin and IGF-1/Akt pathways, NF- κ B, and the *NFE2L2* (NRF2) antioxidant response [50]. Below, the changes in each of these signaling pathways are briefly presented.

AMP-activated protein kinase (AMPK) is a key energy sensor. During exercise, AMPK stimulates glucose utilization, fatty acid oxidation, and mitochondrial biogenesis [51]. AMPK phosphorylates histone H2B, HDAC4, and HDAC5, which triggers the dephosphorylation of the repressor *MEF2A* and activates the *GLUT4* (SLC2A4) promoter, enhancing muscle glucose uptake [51, 52].

The coactivator PGC-1 α is the primary regulator of mitochondrial biogenesis. In 18-month-old mice, low PGC-1 α levels correlate with hypermethylation of the *PPARGC1A* promoter; exercise training promotes its hypomethylation and increased expression, and different exercise regimens demonstrating comparable efficacy [53].

Mitogen-activated protein kinases (MAPKs) phosphorylate histone H3, altering the accessibility of genes for transcription. The combined activation of AMPK, MAPK, and PGC-1 α after high-intensity exercise enhances mitochondrial biogenesis and oxidative metabolism [54].

The insulin and IGF-1/Akt pathways are associated with muscle hypertrophy [55, 56]. Training in older adults reduces methylation of *IGF1* and improves insulin sensitivity [57]; at the same time, physical activity modulates the methylation of negative regulators of the pathway, including *PTEN* [58]. Moreover, miR-486 directly regulates this cascade through *PTEN* [15].

Inflammation and oxidative stress (NF- κ B and NFE2L2)

Regular physical activity shifts in the immune response toward an anti-inflammatory profile and can modulate the expression of inflammatory response genes through epigenetic mechanisms, including changes in DNA methylation, histone modifications, and microRNA regulation [59, 60]. The cytokine response to exercise depends on intensity, duration, training status, and the time of sample collection [61]. Moderate oxidative stress activates *NFE2L2* (NRF2) — the primary regulator of the antioxidant response — which is accompanied by the demethylation of promoters associated with reactive oxygen species detoxifying enzymes [62].

Specificity of the epigenetic response

The epigenetic response to physical exercise is not uniform across different tissues and cells [9]. Skeletal muscle exhibits the most pronounced shifts in methylation and histone modifications, which affect genes involved in mitochondrial biogenesis, potassium channel regulation, and contractility. In the myocardium, exercise activates specific patterns of miR-1, miR-133, miR-29a, miR-126 and long non-coding and circular RNA axes (lncRNA/circRNA axes) mediated by them, providing cardioprotection [49]. In adipose tissue, after six months of aerobic training in sedentary adults, the methylation level of genes related to glucose metabolism and type 2 diabetes risk is altered [63]. In peripheral blood leukocytes, four weeks of sprint interval training induces demethylation of genes related to the cardiovascular system in 12 healthy men [64]. The leukocyte methylome is convenient for monitoring athlete status; however, its correlation with the muscle methylome is weak and does not allow blood to be used as a surrogate source of epigenomic data. In saliva, analysis of epigenetic clocks (DNAmGrimAge2, DNAmFitAge) is possible [14], and in spermatozoa, physical exercise also alters the methylation and microRNA profile, opening an area for studying possible transgenerational effects [65].

Nature of exercise and sports specialization

Long-term endurance training establishes a distinct DNA methylation pattern in the skeletal muscles of athletes compared to strength-sport athletes and non-athletes [3, 4]. “Endurance” athletes exhibit a lower level of methylation of slow-twitch muscle fiber gene promoters

while simultaneously showing increased methylation of regulatory genes (*FOXO3*, *CREB5*, *PPARGC1A*) [3]. Even within the same type of exercise, different protocols induce different epigenetic changes: when comparing sprinting with turns versus straight-line sprinting, Maasar et al. found more pronounced demethylation of MAPK/AMPK cascade genes, VEGFA, and the insulin pathway during running with turns [66]. In a case-control study, D'Souza et al. demonstrated that microRNA profiles allow distinguishing powerlifters from non-athletes based on five microRNAs (miR-126, miR-23b, miR-16, miR-23a, miR-15a) [67]. Combined programs (aerobic + resistance) also induce specific epigenetic changes: for example, in elderly women with obesity, a 14-week program reduces methylation of lipogenesis genes and improves metabolic parameters [68].

Temporal dynamics of epigenetic changes

Epigenetic changes induced by exercise vary in both intensity and duration. Following intense exercise, the promoters of *PPARGC1A*, *PDK4*, and *PPARD* are hypomethylated, with increased mRNA levels; however, remethylation is observed after 3 h — an example of a dynamic epigenetic response [25]. Using genome-wide methylation analysis (850,000 CpG sites), Seaborne et al. demonstrated that a repeated exercise stimulus induces more pronounced genome-wide hypomethylation (18,816 CpG sites) compared to the initial bout (9,153 CpG sites). A cohort of genes (*AXIN1*, *GRIK2*, *CAMK4*, *TRAF1*) demonstrated maintenance of a hypomethylated status even under detraining conditions with muscle mass returning to baseline levels. Other genes (*UBR5*, *RPL35A*, *HEG1*, *PLAAT3* (formerly known as *PLA2G16*), *SETD3*) also became hypomethylated, but the maximum values and the greatest increase in muscle mass were recorded precisely with repeated exercise — an “epigenetic memory.” The genes *GRIK2*, *TRAF1*, *BICC1*, and *STAG1* became hypomethylated after a single resistance exercise session and maintained this state for 22 weeks [26].

Influence of sex, age, and ethnicity on epigenetic changes

Most studies on the epigenetic effects of exercise have been conducted exclusively in men, substantially limiting their extrapolation to women. Direct comparisons between sexes reveal differences: elite male football players exhibit a higher acceleration of epigenetic aging compared to women [12]. Additionally, Grieb et al. reported that the myomiR response profile to acute exercise in women differs from previously described patterns in men [34]. The influence of menstrual cycle phases, hormonal contraception use, and menopausal status on transcriptional and epigenetic response should also be considered; however, systematic studies on these issues in female athletes are extremely limited [69].

Epigenome plasticity peaks during childhood and adolescence. In elderly individuals, a 14 weeks mixed training program reduces the methylation of lipogenesis genes and improves metabolic parameters [68]; 8 weeks of training in sedentary women reduce epigenetic age by an average of 2 years [57]. Kawamura et al. emphasize that the response to a training stimulus is most pronounced in individuals with an initially high acceleration of biological age [65]. Moreover, epigenetic changes are particularly pronounced in master athletes, whose long-term training experience forms a specific epigenetic “footprint”. Olympic champions demonstrate slower epigenetic aging compared to non-athletes [65].

DNA methylation and microRNA expression patterns may differ between ethnic groups due to both genetic factors (single nucleotide polymorphisms in regulatory regions) and differences in environmental exposures. This implies that reference ranges for epigenetic biomarkers, developed predominantly in European or Asian cohorts, may not be applicable to other populations — an important methodological caveat when attempting to implement epigenetic diagnostics in international sports.

Exerkines and extracellular vesicles

The concept of exerkines (extracellular vesicles, EVs) considers skeletal muscle as an endocrine organ that, upon contraction, secretes peptides, metabolites, and RNAs, including those packaged into extracellular vesicles (exosomes 30–150 nm in size and microvesicles). EVs provide inter-tissue communication in response to exercise, carrying microRNAs, proteins, and lipids to target cells [65, 70]. Frühbeis et al. showed that physical exercise induces a rapid release of small EVs into circulation [71]. Chen et al. noted that HDAC inhibition with trichostatin A enhanced the secretion of myocyte-derived EVs enriched with miR-873-3p, which stimulate osteogenic differentiation of bone marrow mesenchymal stem cells [30]. Lisi et al. demonstrated that EVs isolated from plasma after aerobic exercise exert a cardioprotective effect through the activation of antioxidant pathways [72]. Sex differences also manifest at the EV level: Kargl et al. found that the profile of circulating EVs after 12 weeks of combined training significantly differs between men and women [73]. Recent data have shown that EVs isolated after a training program can partially mimic the effects of physical exercise, accelerating muscle recovery after detraining in mice [74]. It must be emphasized that the correlation between EV-microRNAs and skeletal muscle tissue microRNAs remains weak. In the study by Lamon et al., it was shown that there was no correlation between levels of miR-1, miR-16, miR-23b, and miR-133a/b in EVs and in muscle tissue in men and women after 60 min of cycling at 70% VO_2 peak [75]. This likely confirms that circulating microRNAs in EVs are not a direct “mirror” of muscle

transcription but rather reflect a more complex dynamics of secretion and clearance.

Nutrieigenetics

Nutrition acts as a cofactor in the epigenetic response to training. Polyphenols (resveratrol, curcumin, quercetin, epigallocatechin-3-gallate) modulate the activity of epigenetic enzymes: resveratrol activates SIRT1 (class III HDAC, NAD⁺-dependent), which enhances the suppression of NF- κ B-mediated inflammation, autophagy, and endurance; curcumin and quercetin affect histone acetyltransferases and HDACs, improving redox balance and reducing inflammation [22]. Methyl donors — folates, vitamin B12, betaine, choline, methionine — provide the S-adenosylmethionine pool for DNA and histone methylation reactions. In their deficiency, epigenetic responses to exercise may be impaired. Omega-3 polyunsaturated fatty acids alter inflammation-associated methylation profiles. They may be considered as additional regulators of the epigenetic response to training: as the same exercise protocol can induce different epigenetic effects under different nutritional conditions.

Prospects for the use of epigenetic markers in sports medicine

To date, four key areas of epigenetic marker application can be identified: monitoring recovery and assessing the athlete's biological age, predicting the risk of sports injuries, diagnosing overtraining, and personalizing the training process (Fig. 2).

Biological age biomarkers based on DNA methylation include DNAmGrimAge2, DNAmFitAge, PhenoAge, and DunedinPACE — the so-called epigenetic clocks.

Brooke et al. evaluated professional football players ($n \leq 19$) and identified significant changes in DNA

methylation patterns when comparing samples taken before and after a match. These alterations were accompanied by a marked reduction in biological age estimates derived from epigenetic clocks. For example, estimated age decreased by 32% according to DNAmGrimAge2 ($\beta = -7.07$; $p < 0.001$), and by 18% according to DNAmFitAge ($\beta = -4.76$; $p < 0.001$). Following a rest period, these values returned to baseline. The most pronounced effect was observed in midfielders. The authors also noted a possible association between methylation patterns and injury frequency [14].

Fernández Pérez et al. evaluated 74 elite football players of both sexes, and noted that overall acceleration of epigenetic aging does not directly reflect injury risk; however, specific differentially methylated CpG sites may serve as predictors of individual predisposition [12]. Ding et al. and Marrouh et al. emphasize the prospect of integrating polygenic risk scores with exercise-sensitive microRNA expression (miR-206, miR-133a, miR-486) as a foundation for precision sports medicine [15, 21].

Analyzing myomiRs (miR-1, miR-133a/b, miR-206) in combination with the methylation patterns of metabolic genes is considered a promising panel of biomarkers for assessing fitness status [17, 76]. Combining these markers with circulating proteins (creatine kinase, cytokines) may increase the sensitivity for the early detection of maladaptation; however, clinically validated panels currently do not exist.

The concept of individual “epigenetic memory” and varying epigenetic sensitivity to exercise potentially enables the design of training programs tailored to the epigenetic profile. Practical implementation requires the standardization of epigenetic analysis protocols and the development of a regulatory framework.

In the field of epigenetics and anti-doping control, the fight against doping increasingly relies on indirect detection methods based on long-term monitoring of

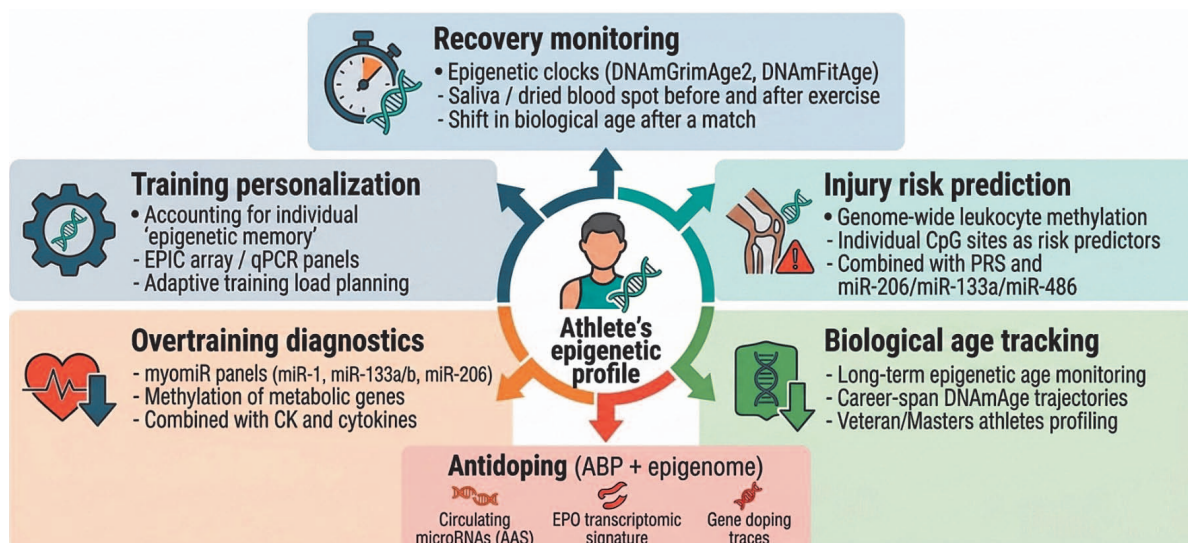


Figure prepared by the authors based on data from [14, 17, 64, 76]

Fig. 2. Application of epigenetic markers in sports medicine

biomarkers. This concept is currently implemented by the World Anti-Doping Agency (WADA) via the Athlete Biological Passport. The hematological and steroid modules of the passport were implemented in 2008 and 2014, respectively, both use a Bayesian adaptive model to assess individual deviation from the norm [77]. However, the narrow detection windows and the emergence of new pharmacological substances are making direct methods less and less effective — this creates prerequisites for expanding the Biological Passport with epigenetic and RNA markers.

Nicoli et al. proposed the using of circulating microRNAs as biomarkers of anabolic androgenic steroid (AAS) use [78]. AAS consumption causes organ damage (heart, liver, kidneys), and a concurrent elevation of tissue-specific microRNAs in the blood. For example, increased expression of miR-21 and miR-205 in the kidneys of AAS users, miR-146a after nandrolone administration in rats, as well as changes in miR-132 and miR-144 within the central nervous system [78]. An important advantage of microRNAs as biomarkers is their high stability at room temperature and during freeze/thaw cycles, which simplifies biobanking logistics.

Durussel et al. identified a transcriptomic signature in peripheral blood characteristic of recombinant human erythropoietin use. This signature persists even after drug discontinuation — including within those “detection windows” that are inaccessible to direct methods [79]. This fact is fundamentally important because epigenetic and expression changes can indicate banned substance use even when the substance itself is no longer detectable. The concept of the “epigenetic legacy” of doping — the long-term persistence of DNA methylation and microRNA changes after withdrawal — is being actively investigated. Given the existence of “epigenetic memory” in skeletal muscle [26], it is legitimate to ask: can methylation patterns acquired during AAS use persist for years and provide an athlete with a long-term advantage even after official drug discontinuation?

In 2021, WADA approved the first test for gene doping with methods currently being developed to detect exogenous DNA against the background of the athlete's genomic DNA [80]. Epigenetic markers serve as a complement here: the introduction of transgenes may leave characteristic epigenetic traces in the expression of target genes.

Limitations of data and the current review

When interpreting the data and presented conclusions, a number of significant limitations must be taken into account:

- small sample sizes: the vast majority of experimental studies have been conducted on groups of 6 to 30 people, which reduces statistical power and

increases the risk of false-positive results, especially during multi-testing (analysis of 850,000 CpG sites);

- sex bias: most studies exclusively enroll only men or feature highly gender-unbalanced cohorts, which seriously limits the extrapolation of findings to female athletes;
- a significant portion of data has been obtained from sedentary or moderately trained volunteers, rather than elite athletes — the population in which sports medicine is most interested. Extrapolation to professional athletes has limited justification;
- heterogeneity of protocols: exercise type, intensity, duration, modality, timing, analytical platforms, and normalization methods vary across studies, confounding direct comparison and meta-analysis. For EVs, adherence to MISEV2023 guidelines is particularly important, yet not all studies comply with them [43];
- correlation vs. causality: most data do not confirm causal relationships. Association of a specific epigenetic pattern with a phenotypic outcome (endurance, hypertrophy, injury) often remains presumptive. Functional validations (knockout, miRNA-mimic experiments) are largely limited to animal models;
- limited tissue availability: skeletal muscle biopsy is an invasive procedure, making it particularly challenging to perform in elite athletes during the competitive season; accessible “peripheral” tissues (blood, saliva) do not always adequately reflect the muscle epigenome.

CONCLUSION

Physical exercise is one of the most powerful environmental factors that modulating the epigenome. Unlike the genome, the epigenome possesses high plasticity and serves as a link between the training process, hereditary characteristics, and the developing athletic phenotype. Physical exercise consistently induces reversible changes in the three primary components of the epigenome: DNA methylation, histone modifications (acetylation, phosphorylation of H3.3-Ser-31, lactylation), and microRNA expression, as well as in lncRNA- and circRNA-mediated regulation. These mechanisms allow for the selective alteration of gene activity and signaling pathways — AMPK, PGC-1 α , MAPK, IGF-1/Akt, NF- κ B, NFE2L2. The epigenetic response is tissue-specific, depends on the type and nature of exercise, as well as on the sex, age, and ethnicity of the athlete.

The long-term stability of modifications, causal relationships between specific epigenetic changes and phenotypic outcomes, as well as epigenetic memory associated with pharmacological interventions, remain poorly understood. Overcoming these limitations requires prospective multicenter studies in large, ethnically diverse cohorts using multi-omics approaches.

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Additional information. A glossary of key genes and microRNAs is available on the website of the journal *Extreme Medicine*. <https://doi.org/10.47183/mes.2026-467-annex>

Authors' contributions. All authors confirm that their contributions meet the ICMJE criteria for authorship. The primary contributions are distributed as follows: Anastasia I. Kadykova — conceptualization, visualization; Evgeniy D. Kopylov — manuscript editing; Nikita S. Gladyshev — manuscript drafting; Roman V. Deev — supervision; Andrey V. Zholinsky — project administration.

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