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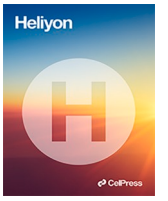

Review article

Global scientific trends in research of epigenetic response to exercise: A bibliometric analysis

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ABSTRACT

The purpose of this work is to comprehensively understand the adaptive response of multiple epigenetic modifications on gene expression changes driven by exercise. Here, we retrieved literatures from publications in the PubMed and Web of Science Core Collection databases up to and including October 15, 2023. After screening with the exclusion criteria, 1910 publications were selected in total, comprising 1399 articles and 511 reviews. Specifically, a total of 512, 224, and 772 publications is involved in DNA methylation, histone modification, and noncoding RNAs, respectively. The correlations between publication number, authors, institutions, countries, references, and the characteristics of hotspots were explored by CiteSpace. Here, the USA (621 publications) ranked the world's most-influential countries, the University of California System (68 publications) was the most productive, and Tiago Fernandes (14 publications) had the most-published publications. A comprehensive keyword analysis revealed that cardiovascular disease, cancer, skeletal muscle development, and metabolic syndrome, and are the research hotspots. The detailed impact of exercise was further discussed in different aspects of these three categories of epigenetic modifications. Detailed analysis of epigenetic modifications in response to exercise, including DNA methylation, histone modification, and changes in noncoding RNAs, will offer valuable information to help researchers understand hotspots and emerging trends.

1. Introduction

The health and fitness benefits conferred by physical exercise are widely appreciated to protect against an increasing variety of human diseases, such as cardiovascular conditions [1], metabolic syndrome [2], and cancer [3]. Although the cellular mechanism underlying the exercise-induced improvements has been generally explored, the molecular-level mechanism of epigenetic modifications is not completely understood.

Epigenetic events refer to almost all heritable and stable changes that affect gene expression and activity independently of genetic code alterations [4]. The epigenome consists of various covalent modifications on DNA and chromatin that exert conformational changes to regulate gene expression and function [5,6], and aberrant epigenetic patterns are closely related to numerous human

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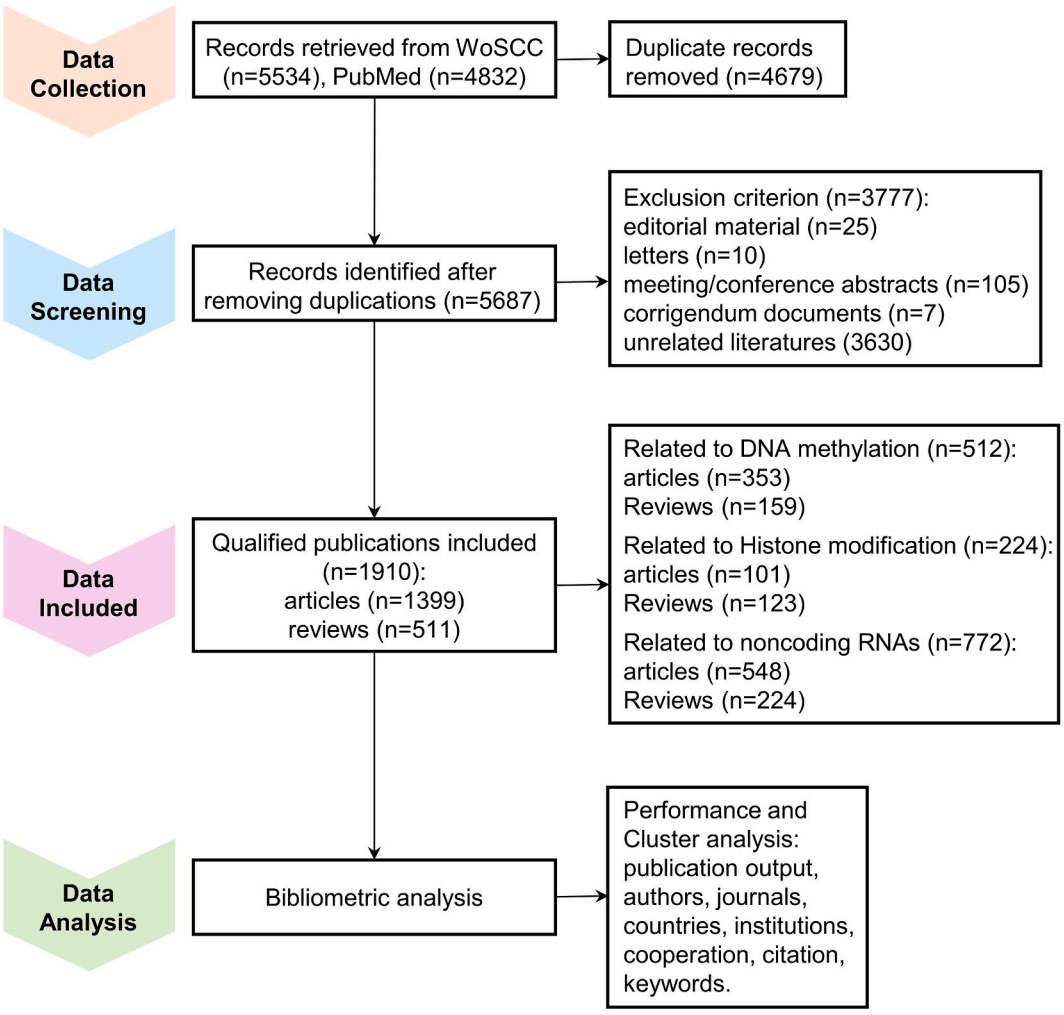


Fig. 1. Flow chart of the screened publications included in the study.

diseases [7,8]. Lifestyle and different environmental cues have been demonstrated to stimulate epigenetic gene regulation that, in turn, influences health via the modulation of gene expression, with exercise highlighted as a critical factor for health promotion and disease prevention.

Emerging evidence shows that a large proportion of the positive effects of exercise is controlled by epigenetic events, which further would influence gene expression and activity related to physiological and pathological conditions [9,10]. Epigenetics, as a mediator of the intergenerational transmission of exercise effects, has been demonstrated to be involved in various aspects of exercise [11,12]. The comprehensive study of the epigenetic modifications following exercise should provide an understanding of the effect of exercise on the epigenome. Bibliometrics is a popular and rigorous method for analyzing research on qualitative characteristics [13,14]. To date, there is no bibliometric analysis involving epigenetics and exercise. Therefore, this study aimed to summarize the status of previous research and to use scientific data to understand the emerging trends and lay a solid foundation for future study.

2. Materials & methods

2.1. Search strategy

We searched literature from the PubMed and Web of Science Core Collection (WoSCC) databases from library inception to the updates of October 15, 2023. A collection of documents was retrieved from the bibliographic databases using the following retrieval formula: (ALL=((epigenetic) or (dna methylation) or (histone modification) or (dna replication time) or (nuclear location) or (heterochromatinization) or (rna methylation) or (non-coding rna) or (noncoding rna) or (mirna) or (microrna) or (lncrna))) AND ALL=((exercise) or (exercise training) or (physical activity)). In total, 5534 and 4832 results were retrieved and downloaded on October 15, 2023, from the PubMed and WoSCC databases, respectively.

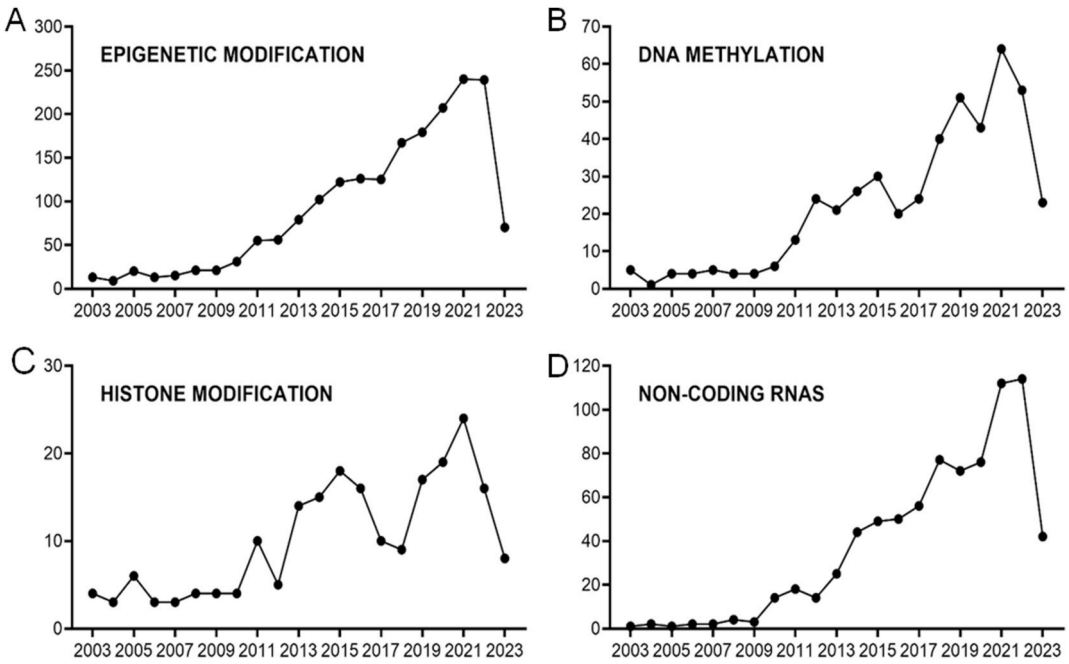


Fig. 2. Global number of related publications by year. (A) Annual numbers of papers on epigenetics and exercise; (B) Annual numbers of papers on DNA methylation and exercise; (C) Annual numbers of papers on histone modification and exercise; (D) Annual numbers of papers on noncoding RNAs and exercise.

2.2. Study selection

To merge the collections obtained from WoSCC and PubMed, we imported the 10366 literatures searched from WoSCC (n = 5534) and PubMed (n = 4832) into the EndNote program. Next, we used the duplicate search function in the EndNote software to remove 4679 duplicates via browsing the titles, authors, years, etc. We then excluded a total of 3777 literatures due to the exclusion criteria, including editorial material (n = 25), letters (n = 10), meeting/conference abstracts (n = 105), corrigendum documents (n = 7), and unrelated articles (n = 3630). Finally, a total of 1910 publications has been selected for further analysis, comprising 1399 articles and 511 reviews. Subsequently, we converted these selected publications into the refworks-citespace format on the Note-Express program and imported them into the CiteSpace software for further analysis. Specifically, a total of 512 publications is involved in DNA methylation and consist of 353 articles and 159 reviews, a total of 224 publications is related to histone modification and comprise 101 articles and 123 reviews, a total of 772 publications is belonged to noncoding RNAs (ncRNAs) and consist of 548 articles and 224 reviews (Fig. 1). In order to get more scientific and rigorous conclusions, all the retrieved literature have been filtered to remove duplicate publications. Data entries and collections have been verified by two authors (Huijuan Wu and Yue Hu).

2.3. Bibliometrics and visualization analysis

The selected publications were imported into CiteSpace for the subsequent analysis. We processed the publications strictly following the CiteSpace procedure [13]. The visualization network generated consisted mainly of burst detection, betweenness centrality, and heterogeneous network, to provide a visualization of research status, hotspots, and trends [14]. Nodes are shown as countries, institutions, authors, or keywords, and the connections indicate the cooperating relationships. The size and color of nodes represents the frequency and the occurrence, respectively. Moreover, the nodes with red rings represent those with high betweenness centrality, which can generally be considered as a focus of the research field.

3. Results

3.1. Annual publications output

Overall, 1910 publications were used and analyzed in the study. The number of publications generally followed a constant upward trend from 2003 and a sharp upward trend from 2010 (Fig. 2). These trends indicate that the study of the association between epigenetics and exercise has attracted growing interest from researchers. Further analysis revealed that the number of publications related to three types of epigenetic modifications has increased similarly, but with some fluctuations (Fig. 2B–D). There were fewer publications in 2023, consistent with the cut-off point. Overall, the number of studies on the epigenetic consequences of exercise are

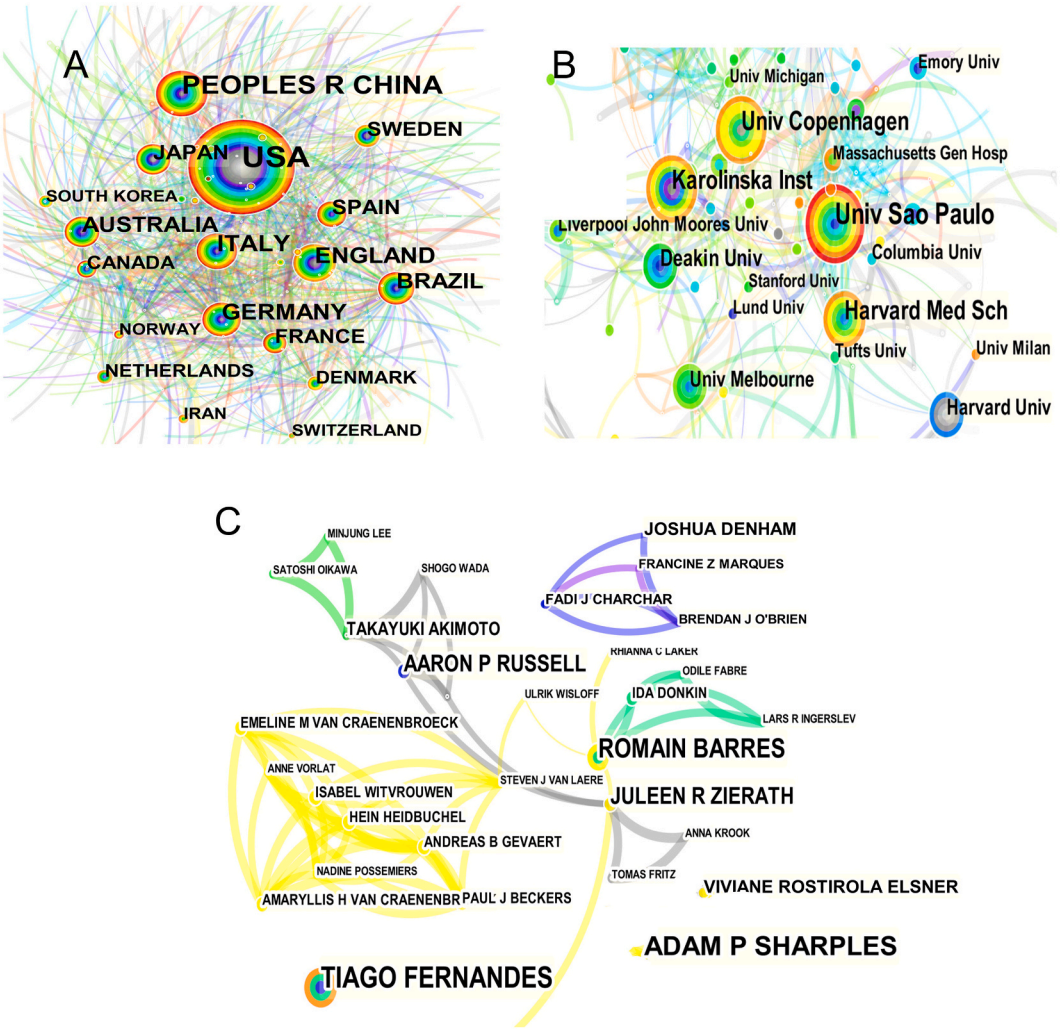


Fig. 3. A visualization graph of contributors. (A) Network visualization of countries; (B) Network visualization of institutions; (C) Network visualization of authors.

Table 1
Top five institutions in terms of frequency and centrality related to epigenetics and exercise research.

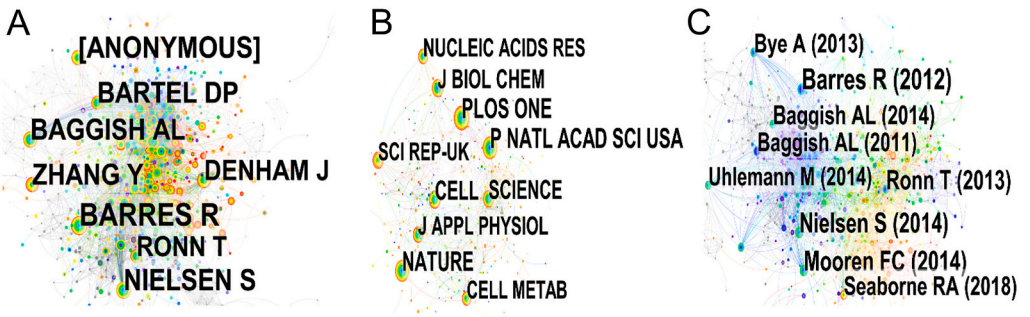
Rank	Frequency	Centrality	Institutions
1	68	0.14	University of California System
2	61	0.22	Harvard University
3	48	0.05	University of São Paulo
4	40	0.08	Karolinska Institute
5	37	0.17	Research Libraries UK

increasing, indicating that this is a focus of research.

3.2. Analysis of scientific collaboration network

The 1910 publications on PubMed and WoSCC originated from 79 countries, and the analysis of collaboration between countries revealed 79 nodes and 621 connections (Fig. 3A). The top five countries ranked by occurrence were the USA (621 publications, 32.5%), China (294 publications, 15.4%), England (158 publications, 8.3%), Italy (157 publications, 8.2%), and Germany (147 publications, 7.7%). The connections between nodes showed extensive cooperation between countries. The results suggest a strong interest in the effect of epigenetics on exercise in these countries.

The network of collaborative institutions, shown in Fig. 3B, consists of 516 nodes and 1787 connections. The publications in this



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Top 10 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2003-2023
Barres R, 2012, CELL METAB, V15, P405, DOI 10.1016/j.cmet.2012.01.001, DOI	2012	19.12	2013	2017	
Baggish AL, 2011, J PHYSIOL-LONDON, V589, P3983, DOI 10.1113/jphysiol.2011.213363, DOI	2011	15.32	2013	2016	
Nielsen S, 2010, J PHYSIOL-LONDON, V588, P4029, DOI 10.1113/ jphysiol.2010.189860, DOI	2010	11.94	2013	2015	
Davidsen PK, 2011, J APPL PHYSIOL, V110, P309, DOI 10.1152/ japplphysiol.00901.2010, DOI	2011	11.84	2013	2016	
Nitert MD, 2012, DIABETES, V61, P3322, DOI 10.2337/db11-1653, DOI	2012	11.31	2014	2017	
Nielsen S, 2014, PLOS ONE, V9, PO, DOI 10.1371/ journal.pone.0087308, DOI	2014	13.37	2015	2019	
Seaborne RA, 2018, SCI REP-UK, V8, PO, DOI 10.1038/s41598-018-20287-3, DOI	2018	13.64	2019	2023	
Whitham M, 2018, CELL METAB, V27, P237, DOI 10.1016/j.cmet.2017.12.001, DOI	2018	10.62	2019	2023	
Levine ME, 2018, AGING-US, V10, P573, DOI 10.18632/aging.101414, DOI	2018	11.15	2020	2023	
Lu AT, 2019, AGING-US, V11, P303, DOI 10.18632/aging.101684, DOI	2019	11.91	2021	2023	

Fig. 4. Network visualization of citations. (A) Network of author co-citations; (B) Network of journal co-citations; (C) Network of co-cited references; (D) Top 10 references with the strongest citation bursts.

Table 2
Top five cited-journals related to epigenetics and exercise research.

Rank	Frequency	Cited journal	IF[a](2022)
1	1178	PLOS ONE	3.7
2	1142	P NATL ACAD SCI USA	11.1
3	1087	NATURE	64.8
4	935	CELL	64.5
5	805	SCIENCE	56.9

[a] IF according to Journal Citation Reports (2022). IF, impact factor.

area were contributed by 516 institutions. Table 1 listed the top five institutions in terms of frequency and centrality. Among these institutions, the University of California System was the most productive with 68 publications, followed by Harvard University with 61 publications, the University of São Paulo with 48 publications, the Karolinska Institute with 40 publications, and Research Libraries UK with 37 publications. The betweenness centrality greater than 0.1, when arranged in order, was the Harvard University (0.22) first, followed by RLUK-Research Libraries UK (0.17), and University of California System (0.14), indicating an important role in the collaboration relationship.

The analysis of the merged co-authorship network of authors yielded 695 nodes and 821 connections, suggesting 695 authors contributed to the publications for the research field (Fig. 3C). The top five most productive authors were Tiago Fernandes (14 publications), Adam P Sharples (10 publications), Romain Barres (10 publications), Joshua Denham (8 publications), and Viviane Rostirola Elsner (8 publications). Even though many authors and groups have published articles, there is relatively less contact between them. In addition, the relatively low centrality of authors showed the demand for more large-scale and high-quality cooperation in future studies.

Overall, the network among countries, institutions and authors have showed that the collaborative institutions with high centrality were typically located in the countries with high frequency of publications. Among the top five institutions, three of them are belonged to the top five countries. For example, University of California System and Harvard University are in the USA, and the Research Libraries UK is in England. It has indicated that the USA and England were with higher levels of the field, in which not only published a large number of articles, but also had good quality and strong influence in the field. Importantly, other countries should cooperate with the USA and England to improve their scientific research. It is worth looking forward to strengthening the deep cooperation among

Table 3
Top five cited references related to epigenetics and exercise research.

Rank	First author	Frequency	Year	Cited references	References
1	Barrès R	63	2012	Acute Exercise Remodels Promoter Methylation in Human Skeletal	Cell Metab
2	Nielsen S	53	2014	The miRNA plasma signature in response to acute aerobic exercise and endurance training	PLos One
3	Mooren FC	52	2014	Circulating microRNAs as potential biomarkers of aerobic exercise capacity	Am J Physiol Heart Circ Physiol
4	Rönn T	45	2013	A Six Months Exercise Intervention Influences the Genome-wide DNA Methylation Pattern in Human Adipose Tissue	Plos Genet
5	Baggish AL	42	2014	Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise	J Appl Physiol (1985)

countries, affiliations, and authors in the future.

3.3. Analysis of citations from authors, journals, and references

The visual network of co-cited authors is presented in Fig. 4A. The authors with the highest number of citations are Barrès R with 191 citations, followed by Nielsen S, Baggish AL, Zhang Y, and Bartel DP with 138, 133, 132, and 131 citations, respectively Moreover, Table 2 showed cited-journals combined with frequency and impact factor (IF). According to the citation counts, PLOS One (1178 citations) was the top-ranked journal, followed by PNAS (1142 citations), Nature (1087 citations), Cell (935 citations), and Science (805 citations) (Fig. 4B).

In addition, 1035 references were collected from 1910 publications to analyze the co-cited references (Fig. 4C). Table 3 listed the top 5 cited references related to epigenetics and exercise research. Among them, the most-cited reference was published by Barrès R (63 citations); this publication demonstrated that acute exercise remodeled the promoter of DNA methylation in human skeletal muscle [15]. The second reference was published by Nielsen S and 53 cited times; this study reported the signature of plasma miRNA in response to acute aerobic exercise/chronic endurance [16]. The third reference was the study of Mooren FC, 52 cited times, which considers circulating miRNAs as possible targets for exercise capacity [17]. The fourth and fifth references were by Rönn T and Baggish AL, respectively. Rönn T described a pattern of genomic DNA methylation in human adipose tissue after exercise intervention [18]. Biggish AL reported a unique alteration of c-miRNAs after prolonged aerobic exercise [19]. In brief, the most co-cited references generally form part of the most vigorous citation bursts. Fig. 4D listed the top 10 references with the strongest citation bursts, which exhibiting the research frontiers related to the field.

3.4. Analysis of hotspots and frontiers for epigenetic modification in exercise

As keywords are the representatives of the core content of a publication, the cooperative analysis of keywords can reflect hotspots and research frontiers. Fig. 5A displays the network of keyword co-occurrence with 628 nodes and 2434 connections. The node size indicates the frequency of keyword occurrence that larger nodes represent higher frequency. As shown in Table 4, the most common keywords are DNA methylation (317 times), expression (301 times), gene-expression (282 times), skeletal muscle (173 times), exercise (147 times), physical activity (140 times), oxidative stress (123 times), cells (91 times), mechanisms (87 times), and endurance exercise (86). Among them, gene-expression exhibited as the highest centrality (0.13). The analysis of keyword clustering illustrated the main research topics. Based on the keyword co-occurrence network, the keyword clustering was analyzed using the log-likelihood ratio (LLR) algorithm in the CiteSpace and following automatically yields the corresponding clustered tag terms. The output clustering was further evaluated for its scientificity and usability of visual knowledge graphs by the Modularity Q (Q-value) and Silhouette value (S-value). The Q-value is more than 0.3 and S-value is greater than 0.7 indicated that the network clustering is significant and reliable. In this study, all the co-occurring keywords were clustered into eleven items (Q-value $>$0.8, S-value $>$0.8), and cancer and cardiovascular disease were revealed as two major topics related to epigenetic and exercise (Fig. 5B).

To further review and predict the phased hotspots and their evolutionary frontiers in the studies of epigenetics on exercise, the co-occurring keywords bursts were analyzed. In Fig. 5C, the blue line shows the time interval, and the red line indicates the time when the keyword appeared. The keyword “acetylation” was most common earlier, indicating it was the topic of early attention. The keyword “skeletal muscle” with the highest intensity indicated that it was a focus of epigenetic modification on exercise. The keywords “risk”, “insulin”, “mortality”, “long ncRNAs”, and “epigenetic clock” have appeared and persisted until now, suggesting they may be a research frontier in the field. The visualization of the timeline of keywords reveals the development of epigenetics and exercise research between 2003 and 2023 (Fig. 5D).

3.5. Analysis of research hotspots within in the field of epigenetics and exercise

Exercise is considered as a potential epigenetic modifier through various epigenetic events, including DNA methylation, histone modification, and ncRNAs, to mediate gene transcriptional inhibition or activation. An analysis of high-frequency keywords can help to identify the hotspots and research frontiers [20]. In the area of DNA methylation in exercise, all the co-occurring keywords were

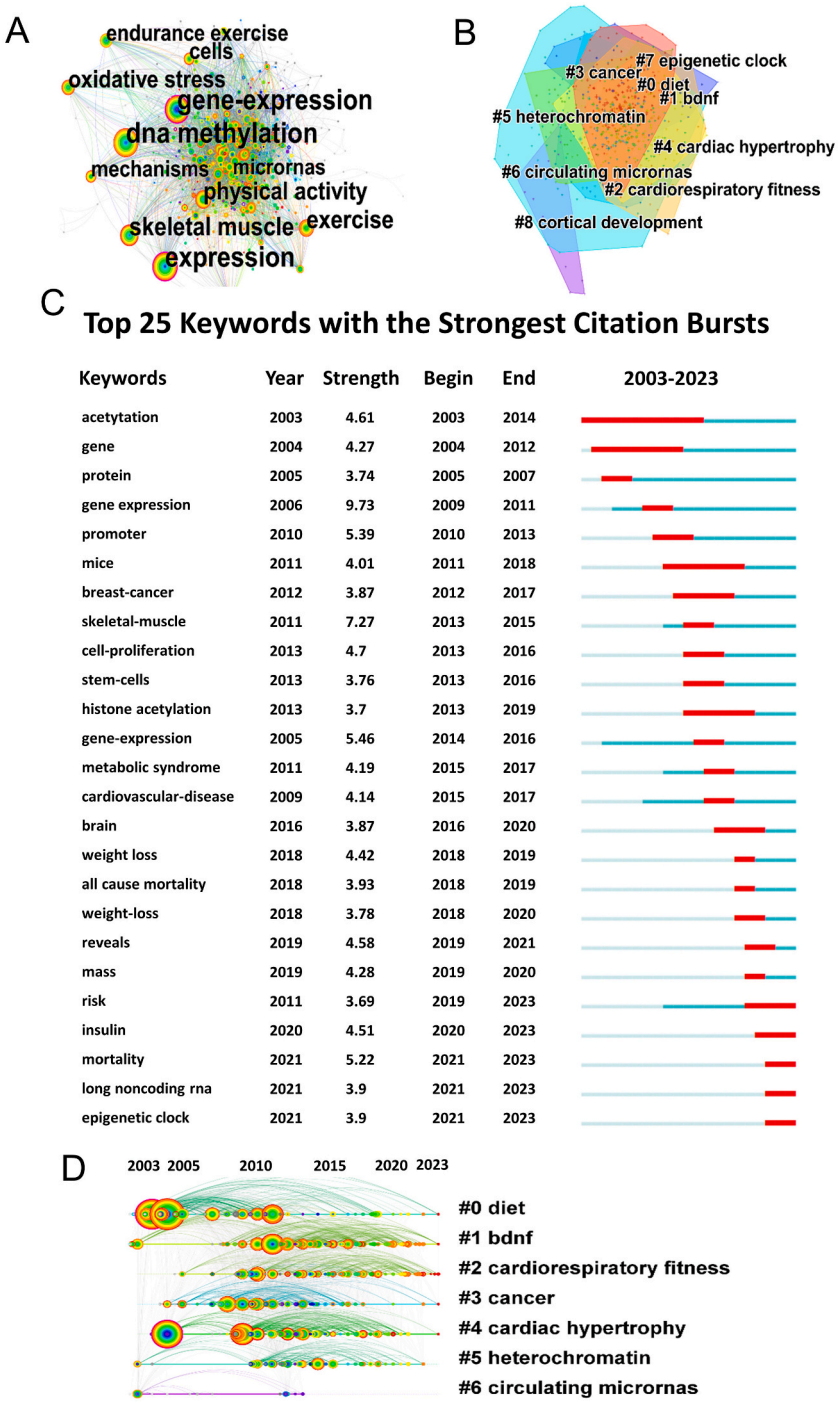

Fig. 5. Co-occurrence analysis of global research on epigenetics and exercise. (A) Mapping of keywords; (B) Cluster diagram of the co-occurring keywords; (C) Top 25 keywords with the strongest citation bursts; (D) Keyword timeline.

clustered into 11 items. Among these items, type 2 diabetes, inflammation, and biological age were identified as the three main topics (Fig. 6A). In the area of histone modification with exercise, the analysis of keyword clustering showed that the two most commonly used keywords were osteogenic differentiation and coronary artery disease (Fig. 6B). In the ncRNAs' mechanism research cluster, the main keywords were cardiac hypertrophy, breast cancer, and metabolic syndrome (Fig. 6C). The above results illustrate that exercise can extensively impact different aspects of these three categories of epigenetic modification, which may form the basis of its positive effects in human health and diseases.

Table 4
Top ten keywords related to epigenetics and exercise research.

Rank	Frequency	Centrality	Keyword
1	317	0.1	DNA methylation
2	301	0.11	expression
3	282	0.13	gene-expression
4	173	0.03	skeletal muscle
5	147	0.03	exercise
6	140	0.02	physical activity
7	123	0.04	oxidative stress
8	91	0.03	cells
9	87	0.04	mechanisms
10	86	0.03	endurance exercise

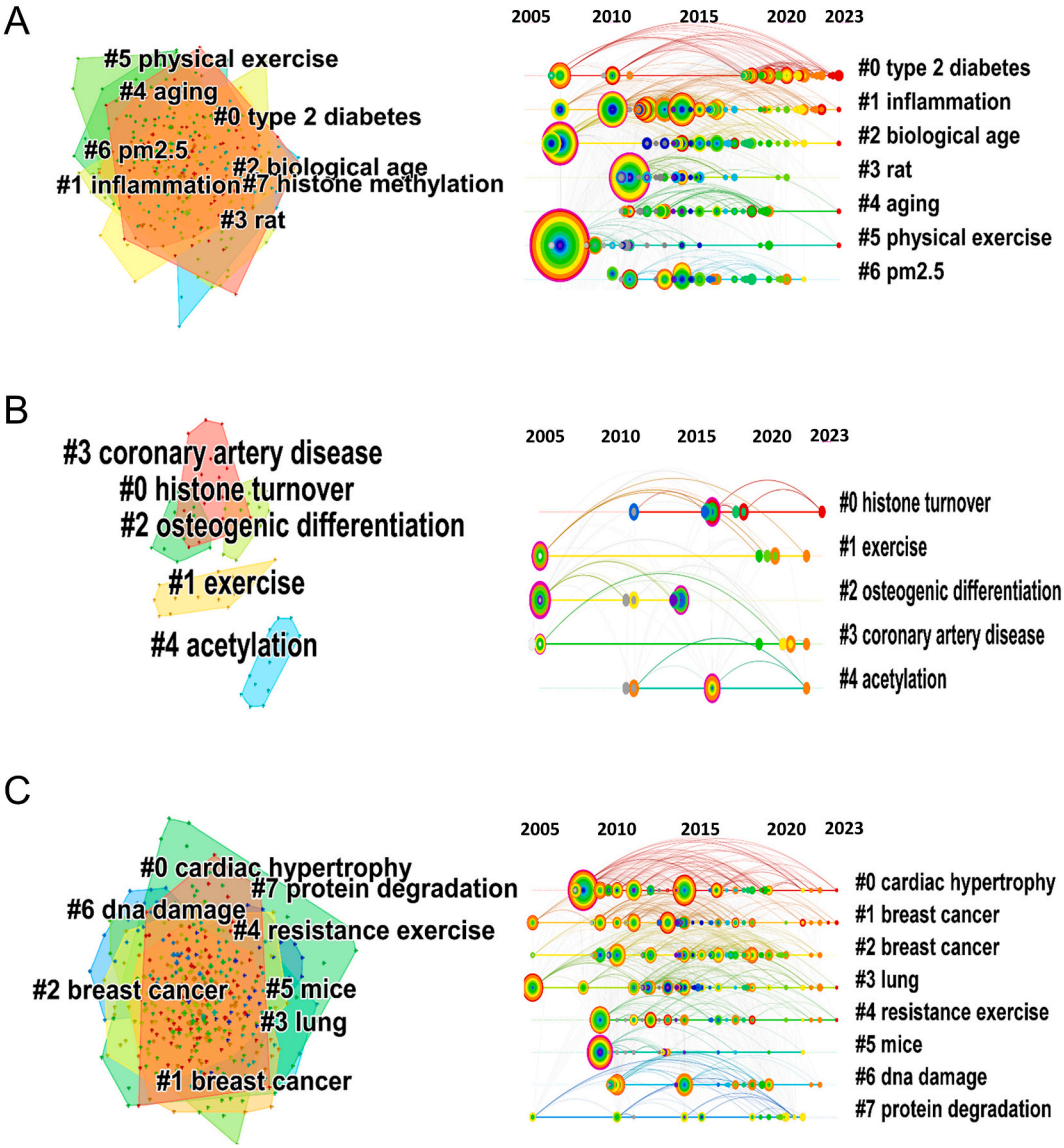

Fig. 6. Clustering analysis of keywords. (A) Network of co-occurring keywords clusters (*left*) and timeline view (*right*) for DNA methylation and exercise; (B) Network of co-occurring keyword clusters (*left*) and timeline view (*right*) for histone modification and exercise; (C) Network of co-occurring keyword clusters (*left*) and timeline view (*right*) for ncRNAs and exercise.

4. Discussion

Exercise has profound impacts on all physiological systems in humans by driving adaptive responses of molecules [21,22]. Mounting evidence indicates that the action of exercise can trigger the epigenetic modulation of gene activity through various epigenomic targets, resulting in an improved functional capacity within the body [23,24]. Over the past decades, the field of epigenetics and exercise has received tremendous attention. Notably, multiple epigenetic modifications have been strongly correlated with previously established disease-induced abnormal gene expression, and consequently emerged as promising candidates for clinical biomarkers [25–27]. In this study, through the analysis of publications in the PubMed and WoSCC databases, we provide a comprehensive overview of global hotspots and emerging frontiers in epigenetics and exercise research from database inception to 2023 (up to October 15, 2023). Our analysis showed a steady increase, from 13 article in 2003 to 239 articles in 2022, indicating the gradual expansion of this field. An increasing number of investigators has begun to study the epigenetic response to exercise, with a small group of the most prolific authors emerging, namely Tiago Fernandes, Adam P Sharples, and Romain Barres. The USA leads in terms of output (621 publications), indicating it is a world leader within the field. The top three institutions were the University of California System and Harvard University in the USA, and the University of São Paulo in Brazil. Unlike the collaboration between countries, communication and collaboration between academic institutions was not apparent. Indeed, scientific research cooperation is important for further research development and allows researchers to exchange thoughts, ideas, and resources. Therefore, stronger cooperation in research should be established between national, institutions, and global researchers. Furthermore, a comprehensive keyword analysis indicated that “acetylation” and “gene” reflected the earliest research regarding epigenetic studies in the field of exercise. Importantly, keyword with the strongest citation bursts has been considered as an indicator of frontier topic. Five emerging trends, including “risk”, “insulin”, “mortality”, “long ncRNAs” and “epigenetic clock”, have become the latest research hot spots and trends for epigenetic studies in the field of exercise since 2019, which would facilitate more in-depth studies regarding this field.

In the following sections, we summarized three main aspects of the epigenetic response to exercise: DNA methylation, histone modification, and ncRNAs. We also discussed the current research status and hotspots of exercise-induced three epigenetic mechanisms and their transcriptional adaptation. This study may provide possible implications for the development of exercise-based therapeutic epigenetic strategies.

4.1. DNA methylation

DNA methylation is one of the most well-studied epigenetic modifications and participates in a variety of regulatory process. It predominantly occurs on cytosine guanine (CpG) dinucleotides [28] and is critical for cell activity under both physiological and pathological conditions through the regulation of gene expression [29]. It has been reported that intensity-dependent exercise can trigger various degrees of adaptive change in DNA methylation profiles, which suggest a significant relationship between exercise and DNA methylation [15]. In this study, the network of co-occurring keywords revealed that the study of DNA methylation in response to exercise is mainly focused on three topics: type 2 diabetes (T2D), inflammation, and biological age.

4.1.1. Type 2 diabetes

Exercise is a key component in the management of T2D. Numerous evidence supports that DNA methylation can improve whole-body metabolic health by mediating the interaction between exercise and genetic variation [30,31]. For example, acute exercise induced a decrease DNA methylation and further resulted in a dose-dependent expression of critical metabolic genes in human skeletal muscle [15], which indicated DNA methylation as a necessary factor for exercise-associated adaptations. Further analysis indicated that multiple key metabolic and regulatory genes were closely related to exercise-stimulated DNA hypomethylation, including peroxisome proliferator-activated receptor δ (PPAR-δ) [15], myocyte enhancer factor 2 (MEF2) [32], and PPARG coactivator 1α (PGC-1α) [33]. A study reported that chronic exercise could result in hypomethylation at promoters for GLUT4 and fatty acid transporter (SLC27A4) in patients with T2D [34]. The research reported thus far provides sufficient evidence that exercise is closely related to the modulation of susceptible genes by DNA methylation for the improvement of T2D.

4.1.2. Inflammation

Data indicate that exercise may exert its anti-inflammatory effects via the epigenetic regulation of inflammatory gene expression in a manner dependent on exercise duration and intensity [35,36]. For example, interval walking enhanced the promoter methylation of the NFKB2 gene, which suggested that physical activity might be a epigenetic modulator for inflammatory susceptibility [37]. Additionally, acute eccentric resistance training changed the pattern of DNA methylation modifications on interleukin 6 (IL6) and tumor necrosis factor α (TNFα) [38]. Notably, an aberrant level of DNA methylation on the IL6 promoter is closely associated with the etiology and pathogenesis of obesity [39]. Furthermore, exercise intervention in patients with heart failure is related to DNA methylation changes on the key components of the inflammasome, ASC and IL-1β [40]. In the past decades, numerous studies on exercise and systemic inflammation have been performed and there is clear evidence that DNA methylation is involved in this process. However, more research is needed to further elucidate the potential mechanism of exercise-induced DNA methylation and inflammation.

4.1.3. Biological age

A telomere is a genetically conserved region with repeated DNA sequences at the ends of a chromosome [41]; telomeres are implicated as a critical factor in ageing and mortality risk [42,43]. Owing to the importance of sub-telomeric DNA methylation in

telomere maintenance and chromosomal stability, DNA methylation and telomere length could act as useful biomarkers for predicting human chronological age [44,45]. A variety of physical activities, such as regular aerobic endurance exercise, has been shown to be associated with retarded telomere attrition and may therefore slow down biological aging and improve physical function via epigenetic reprogramming [46,47]. Tai chi training ameliorated the epigenetic patterns associated with age-related DNA methylation at six CpG sites, two of which were located at the sub-telomeric region [48]. Moreover, resistance exercise significantly diminished the level of mitochondrial methylation in aged human skeletal muscle and partially alleviated aging-related body deterioration in the muscle gene methylome [49]. There is evidence that the vast majority of CpG sites in the human genome are highly methylated [50,51] and that DNA methylation loss in leukocytes usually occurs across cell types and tissues with advancing age [52,53]. However, a 6-month period of moderate-intensity aerobic exercise alleviated the age-associated degeneration of DNA methylation at CpG sites for the ASC gene in circulating leukocytes of older adults [54]. Although DNA methylation changes appear to be correlated with biological ageing, further investigation is needed to confirm whether these changes are prevented or modulated by exercise.

Collectively, the current research hotspots related to DNA methylation in the epigenetic response to exercise are mainly focused on T2D, inflammation, and biological age; however, the potential molecular mechanisms underlying exercise-induced DNA methylation changes have yet to be fully elucidated. The dynamic changes in DNA methylation are a critical and valuable factor in exercise intervention, especially in ameliorating the symptoms of T2D, alleviating body inflammation, and slowing biological aging of the body.

4.2. Histone modification

Histone modification affects DNA accessibility by regulating histone binding to DNA and, consequently, gene expression [5,55,56]. Modification methods mainly comprise acetylation, methylation, phosphorylation, and ubiquitination [57,58]. Numerous studies have sought to uncover the effects of exercise on histone modification, with exploration either across the genome or at the level of specific genes. Here, two emerging hotspots in histone modification relating to exercise were identified by the comprehensive analysis of keywords: osteogenic differentiation and coronary artery disease. Osteogenic differentiation is involved in skeletal muscle development, and coronary artery disease is a cardiovascular disease. Therefore, we have reviewed existing publications on the effect of exercise-induced histone modification on skeletal muscle development and cardiovascular disease.

4.2.1. Skeletal muscle development

Exercise can alter some sites of histone methylation, thereby affecting diseases by altering the epigenetic response, especially in controlling skeletal muscle transcriptional patterns [59,60]. Owing to its direct responses and adaptation to different exercise stimuli, the adaptations of skeletal muscle contribute importantly to improve athletic performance and health. Evidence accumulated over the past decades highlights a relationship between changes in histone modification and exercise intervention in human skeletal muscle. For example, exercise can stimulate skeletal muscle histone 3 (H3) serine phosphorylation in both untrained and trained subjects [61]. A 60-min cycling training promoted the acetylation of histone protein 3 lysine 36 (H3K36), which is related to exercised-induced gene transcription [59]. Moreover, chronic exercise activated histone H3 trimethylation at lysine 27 (H3K27me3) at transcriptionally upregulated loci in skeletal muscle and enhanced the gene response to exercise [62,63]. This evidence, together with animal data, indicate that histone modifications exert a critical function in the adaptive response to exercise [64]. To date, the involvement of a complex array of molecular mechanisms in histone modification, such as contracting skeletal muscle to release numerous biologically active proteins, nucleic acids, and metabolites, has been identified in skeletal muscle [65–67]. Given the mechanical sensitivity of bone tissue, exercise also may regulate its expression by altering the epigenetic state of bone formation and bone resorption genes, thereby affecting bone mass and microstructure, and ultimately improving bone metabolism imbalance. Indeed, numerous studies have connected these key genes with specific histone modifications after exercise. Myocyte enhancer factor 2 (MEF2), a critical transcriptional factor during skeletal muscle development, is a typical example of the regulation of histone post-translational modification exerted by exercise [68]. The nuclear abundance of MEF2-related HDACs in skeletal muscle directly influenced the activity of MEF2 DNA binding [59,69,70]. Moreover, numerous genes have also been found to be regulated by histone modification, including Pgc-1α [24703492], carnitine palmitoyltransferase 1 (CPT-1) [71], sirtuin 1 (Sirt1) [72,73], and protein kinase B (Akt) [74].

In addition, the signaling pathway with specific histone modifications in response to exercise in skeletal muscle has been well elucidated. These pathways, including the calcium/calmodulin protein kinase II (CaMKII), mitogen activated protein kinases (MAPK), protein kinase A (PKA), and the AMP-activated protein kinase (AMPK), are critical for the regulation of exercised-induced histone modification driving the phosphorylation-dependent signaling in skeletal muscle [59,75–77]. These studies revealed that exercise-mediated histone modification modulate transcriptional control and signaling pathways, highlighting the importance of multiple epigenetic mechanisms in response to exercise.

4.2.2. Cardiovascular disease

Although the cardiovascular transcriptional response to various exercise modalities has been better clarified in the past years, our understanding of the involvement of histone modification in exercise-mediated cardioprotection is still in a rudimentary stage. There is some evidence that histone modifications that occur following exercise can alleviate cardiac disease risk. Exercise increased HDAC4 N-terminal fragment, which regulated downstream of the hexosamine biosynthetic pathway, and further promoted cardiac function to protect against heart failure [78]. It has been reported that HDAC1 and HDAC2 exert beneficial cardiac effects on cardiovascular health when modulated by exercise. Emerging evidence shows that exercise enhanced the binding between the switch-independent 3A (mSin3A)/HDAC1/HDAC2 complex and O-linked β-*N*-acetylglucosamine transferase (OGT) to reverse the progression of diabetic heart

disease [79].

Specifically, several studies have also indicated that exercise-stimulated histone modification in other multiple tissues led indirectly to cardiac improvement. Swimming activated H3K9/14 acetylation in muscle and regulated the transcriptional level of Glut4 and Mef2a [80], which mediated indirect cardiac reprogramming [81,82]. The SIRT-dependent pathway is induced by exercise and modulates chromatin structure and gene expression, exhibiting a vital role in the various pathologic processes [72,83–85]. The above results revealed that exercise-activated histone modifications in various tissues might contribute to cardioprotection directly or indirectly; however, the specific role of other histone modifications in the cardiac response requires further evaluation.

4.3. Noncoding RNAs

ncRNAs have been identified as key modulators governing the gene regulatory network in several biological processes and human diseases, as well as being involved in epigenetic, transcriptional, and post-transcriptional levels [86–88]. Among ncRNAs, microRNAs (miRNAs) and long ncRNAs (lncRNAs) are the most widely investigated. It is well-established that miRNAs are post-transcriptional regulators of genes by interacting with the 3'-UTR or 5'-UTR regions [89]. The modulation of gene expression and genome structure by mediating lncRNAs is a much more complex process, involving transcription machinery recruitment, chromatin structure remodeling, and mRNA processing transportation [90]. There is accumulating evidence that exercise-induced ncRNAs also participate in the modulation of gene expression during physiological and disease processes. In this study, our analysis of keywords and their co-occurrence clusters indicated that cardiac disease and breast cancer are two critical topics associated with exercise-induced regulation of ncRNAs.

4.3.1. Cardiac disease

4.3.1.1. miRNAs. Within the past decade, a dramatic increase in the number of miRNA genes has been identified in exercise-induced adaptations related to cardiac disease. There is ample evidence that miRNAs in the heart are particularly important for many processes, including cardiomyocyte survival, angiogenesis, and cardiac physiological hypertrophy. Some researchers have analyzed the expression profile of cardiac miRNAs after exercise training, and consequently identified a variety of miRNAs as key regulators of cardiac physiological and pathological processes [91,92]. However, depending on the exercise modality and duration, extensive differences are found in the number and species of exercise-induced miRNAs. For example, swimming mediated miR-29 expression to suppress collagen genes and mitigate cardiac fibrosis, thus enhancing left ventricular compliance [93]. And it could also revert the unusual expression of miR-1, miR-2142, and miR-9a in myocardial infarction hearts [94,95]. Moreover, swimming could increase miR-126 expression to modulate Sprouty-related protein 1 (SPRED1) and phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2), which further promotes cardiac angiogenesis [96]. As compared with aerobic exercise, resistance training could inhibit cardiac-derived miR-124 to regulate sarcoplasmic reticulum Ca^{+}-ATPase, which enhances cardiomyocyte contractility [97]. Exercise-induced cardiac miRNAs are clearly implicated in various cardioprotective processes, such as the suppression of cardiac fibrosis, enhanced contractility, and the promotion of angiogenesis. Different exercise modalities can also cause significant stimulation of various expression profiles of miRNAs in other tissues that may influence cardiac function. These exercise-modulated circulating miRNAs are derived from various tissues, such as blood vessels, skeletal muscle, adipose, and liver tissue, and act as messengers to modulate gene expression and cardiac activity [98].

4.3.1.2. lncRNAs. Several lncRNAs have been identified in the cardioprotective effect of exercise [99]. There is evidence that swimming alleviates the vascular injury arising from insulin resistance through FR030200-Col3A1 and FR402720-Rnd1 in contrast to the consumption of a high-fat diet [100]. Another important lncRNA in this context might be lncRNA CPhar, which has been shown to be required for exercise-stimulated physiological cardiac hypertrophy in mice based on a forced swim training model [101]. Collectively, the vast majority of study of the complex functions and mechanisms of lncRNAs has focused on uncovering their roles in pathological and physiological processes [102–104]; however, research into the link association between lncRNAs, exercise, and cardioprotection is still in its infancy.

4.3.2. Breast cancer

4.3.2.1. miRNAs. In the different types of cancer research, our analysis revealed that the most common cancer studied relating to exercise-induced ncRNAs is breast cancer (BC). Numerous studies show that miRNAs in body fluids (e.g., saliva, blood, urine) are used as an indicator of the response to exercise in both healthy subjects and cancer patients. Intriguingly, there is mounting evidence that exercise-induced miRNAs are related to a low risk of BC through the control of key cellular processes [105]. For example, miR-21 expression is promoted in various cancers, and its clinical importance as a valuable non-invasive biomarker and a therapeutic target has been proposed in the past few years [106,107]. Indeed, miR-21 overexpression has been closely associated with several hallmarks of BC, including the epithelial to mesenchymal transition, motility, and proliferation [106]. It was reported that a high-intensity training caused a decrease in the serum level of miR-21 in 52 patients with breast cancer [108]. Similar data in mice also show that interval exercise training induced a decrease in the levels of miR-21 and let-7a, which was accompanied by reductions in tumor size and angiogenesis [109]. As a relevant tumor suppressor miRNA, downregulation of the miR-133 is reported in patients with breast cancer [110], whereas several forms of exercise (treadmill walking and resistance training) promoted its expression [111,112].

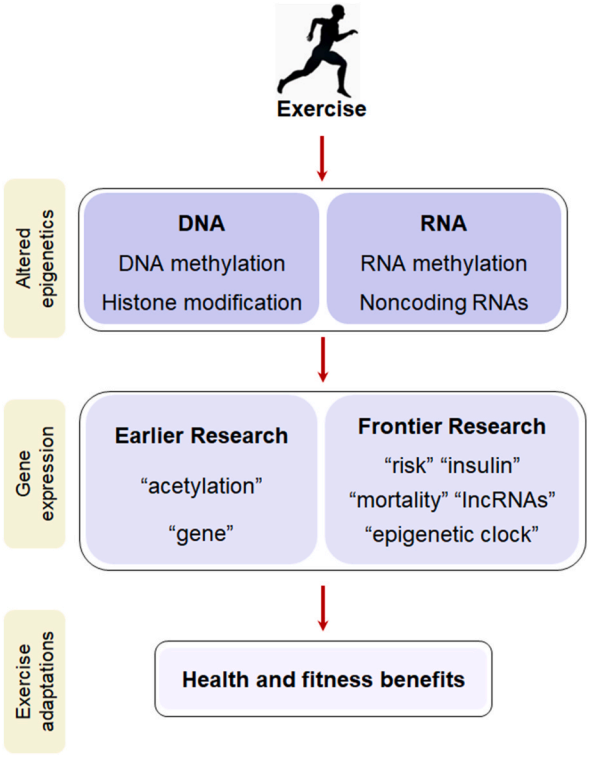

Fig. 7. A diagram showing the research in epigenetics response to exercise.

miRNAs in the let-7 family are also important; these are highly conserved in a variety of species and participate in biological processes. Recent evidence indicated that some exercise modalities, such as aerobic exercise, endurance, and high-intensity training, promote the expression of let-7 family members in the serum [105,108] and in breast cancer tissue in mice [113,114]. Overall, we believe that targeting exercise-induced miRNAs could represent a significant strategy for the development of potential therapies for breast cancer prevention and treatment.

4.3.2.2. lncRNAs. Recent studies have gradually revealed the important role of lncRNAs in the BC progression, including DNA damage repair, cell metabolism, immune regulation, and cell signal transduction [115,116]. However, lncRNAs are still being investigated and have not, as yet, been annotated during exercise training in BC. Therefore, in-depth exploration of exercise-induced lncRNAs would facilitating better understanding on the pathogenesis and progress of BC, and even might bring a new revolution in the clinical approaches.

5. Conclusion

In summary, the rapid growth in studies across the field of epigenetics in exercise demonstrates the important research prospects. The bibliometric data were used to explore the research hotspots and frontiers on three interconnected categories in the field of epigenetics in exercise, namely DNA methylation, histone modification, and ncRNAs (Fig. 7). An in-depth study of this field will help researchers to develop a more comprehensive understanding of exercise-induced epigenetic adaptations. It may allow the identification of additional biomarkers to prevent susceptibility to human illness. Future research should include further investigation of the roles of different epigenetic mechanisms that may aid in preventing health-related disorders mediated by regulating epigenetic reprogramming with exercise.

Data availability statement

The datasets in the study are available from corresponding author on reasonable request.

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CRediT authorship contribution statement

Huijuan Wu: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yue Hu:** Writing – original draft, Formal analysis, Data curation. **Cai Jiang:** Formal analysis, Data curation. **Cong Chen:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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