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A bibliometric analysis of DNA methylation in cardiovascular diseases from 2001 to 2021

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Abstract

Background: DNA methylation is a dynamically reversible form of epigenetics. Dynamic regulation plays an important role in cardiovascular diseases (CVDs). However, there have been few bibliometric studies in this field. We aimed to visualize the research results and hotspots of DNA methylation in CVDs using a bibliometric analysis to provide a scientific direction for future research.

Methods: Publications related to DNA methylation in CVDs from January 1, 2001, to September 15, 2021, were searched and confirmed from the Web of Science Core Collection. CiteSpace 5.7 and VOSviewer 1.6.15 were used for bibliometric and knowledge-map analyses.

Results: A total of 2617 publications were included in 912 academic journals by 15,584 authors from 963 institutions from 85 countries/regions. Among them, the United States of America, China, and England were the top 3 countries contributing to the field of DNA methylation. Harvard University, Columbia University, and University of Cambridge were the top 3 contributing institutions in terms of publications and were closely linked. *PLoS One* was the most published and co-cited journal. Baccarelli Andrea A published the most content, while Barker DJP had the highest frequency of co-citations. The keyword cluster focused on the mechanism, methyl-containing substance, exposure/risk factor, and biomarker. In terms of research hotspots, references with strong bursts, which are still ongoing, recently included "epigenetic clock" (2017–2021), "obesity, smoking, aging, and DNA methylation" (2017–2021), and "biomarker and epigenome-wide association study" (2019–2021).

Conclusions: We used bibliometric and visual methods to identify research hotspots and trends in DNA methylation in CVDs. Epigenetic clocks, biomarkers, environmental exposure, and lifestyle may become the focus and frontier of future research.

Abbreviations: CVDs = cardiovascular diseases, EAA = epigenetic age acceleration, ESC = European Society of Cardiology, IF = impact factors, JCR = Journal Citation Reports, USA = United States of America, WoSCC = Web of Science Core Collection.

Keywords: bibliometrics analysis, cardiovascular diseases, CiteSpace, DNA methylation, VOSviewer

1. Introduction

DNA methylation induces changes in gene expression without changing the DNA sequence by adding methyl groups to cytosine in a CpG-containing nucleotide to form 5-methylcytosine.[1,2] DNA methylation is a dynamically reversible process regulated by methyltransferases and demethyltransferases.[3] Currently, DNA methyltransferase inhibitors are recommended for clinical use in various cancers such as myelodysplastic syndromes and chronic myelomonocytic leukemia.[4] DNA methyltransferase inhibitors, including decitabine, azacytidine, and RG108, can reverse atherosclerosis, diabetes, and cardiac hypertrophy[5–7]; however, they have not been used clinically against cardiovascular diseases (CVDs). Therefore, DNA methylation has a long way to go in terms of cardiovascular research.

Recent studies have shown that DNA methylation has made great progress in basic and clinical research.[8–10] A lot of basic studies have shown that DNA methylation was involved in inflammation,[11] oxidative stress,[12] and apoptosis[13] in CVDs. For example, Hu et al showed that immunoprecipitation in ApoE$^{-/-}$ mice showed hypermethylation in the STAT6 promoter region, accompanied by downregulation of STAT6/VCAM-1 gene expression, inflammation level, and

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors declare that the research was conducted in the absence of any commercial or financial relationships.

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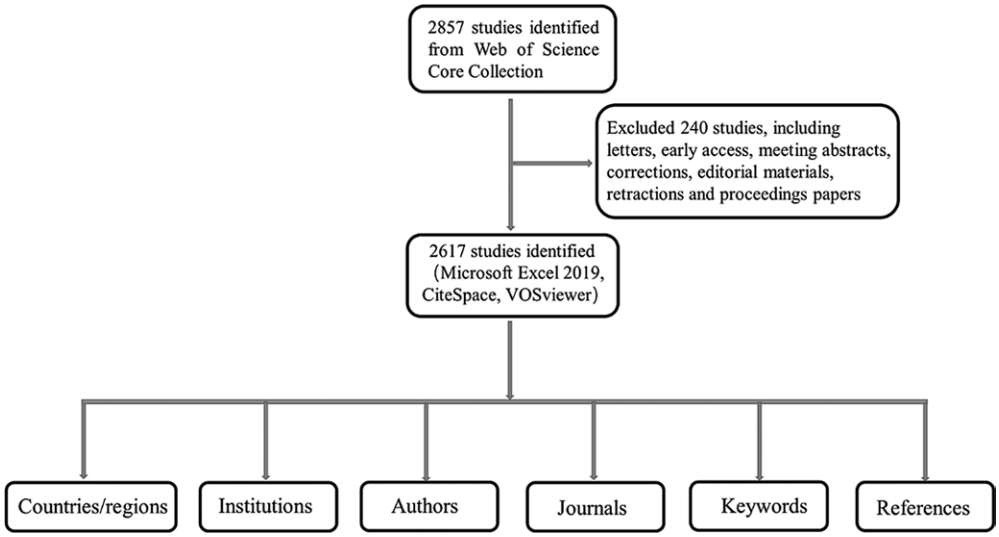

Figure 1. Flowchart of literature selection.

the degree of atherosclerosis in ApoE$^{-/-}$ mice decreased.[11] In the clinical stage, DNA methylation is mainly used for biomarker recognition.[14,15] Diet, obesity, aging, and the environment are not only risk factors for CVDs, but also the medium for DNA methylation to promote the development of CVDs.[16–19] Studies have shown that lifestyle changes can regulate DNA methylation.[20,21] As DNA methylation between individuals is determined by the interaction of genotype and environmental influences,[22] it may be more accurate than either genotypic or lifestyle factors alone in predicting disease. For example, Hedman et al[23] found that high-density lipoprotein cholesterol and triglyceride were related to the differential methylation and expression of ABCG1, and the methylation levels of the ABCG1 promoter could be used to predict the risk of cardiovascular heart disease in cohort studies.

Bibliometrics analysis summarizes the characteristics of literature and highlights the development status and research trends of a specific field by qualitative and quantitative means.[24–26] This type of analysis technology plays an increasingly important role in developing guidelines and evaluating research trends.[27,28] At present, bibliometric studies have been conducted on diseases of acupuncture,[29,30] mechanism,[31–33] cancer,[34] and nervous system disease.[35,36]

In this study, CiteSpace and VOSviewer were used to analyze the DNA methylation studies in CVDs over the past 20 years, mainly in the following 2 aspects: identifying the overall landscape of DNA methylation in the CVDs field by analyzing authors, countries, institutions, and journals; carrying out burst analysis of keywords and references and identifying research priorities and future research hotspots. Through the above analysis, the research status and hotspots of DNA methylation in CVD fields can be determined.

2. Methods

2.1. Source database

Literature was extracted from the Citation Index and Chemistry Citation Index of Web of Science Core Collection database (WoSCC) (http://apps.webofknowledge.com) and was downloaded within 1 day on September 15, 2021. The WoSCC database is considered one of the most authoritative and systematic indexing tools for scientific literature and is widely used for scientometric analysis and visualization in a large amount of studies.[31,32]

2.2. Retrieval strategies

Data were extracted from the WoSCC database. The search formula was set to TS = ("cardiovascular" OR "heart" OR "circulation") AND TS = (DNA methylation). The date of the search was from January 1, 2001, to September 15, 2021. A total of 2617 articles and reviews were retrieved, and all other document types were excluded (Fig. 1).

2.3. Data analysis and visualization

All data were collected in the WoSCC database, downloaded as "Plain Text," saved as "download_.txt" and imported into Microsoft Excel 2019, CiteSpace, and VOSviewer for visual analysis. CiteSpace (http://cluster.ischool.drexel.edu), developed by Dr Chen, is a scientific literature visualization analysis software based on Java, which focuses on the analysis of scientific literature containing potential knowledge. Visualization refers to the organization rule of scientific knowledge and distribution.[37,38] The CiteSpace settings were as follows: time slicing (2001.1–2021.10), years per slice (N = 1), selection criteria (Top N = 50), and other parameters followed the default. CiteSpace is used to analyze countries, institutions, keyword bursts, reference bursts, and double graph superposition. VOSviewer (https://www.vosviewer.com) is software for constructing and visualizing scientometric networks developed by the Center for Science and Technology Studies at Leiden University in the Netherlands. The functionality of VOSviewer is to display large bibliometric maps in a clearly visible manner, including the label, density, cluster density, and scatter views.[39] The VOSviewer parameters were set as follows: method (linlog/modularity). VOSviewer was used to analyze the authors, co-cited authors, and clusters of keywords.

2.4. Research ethics

The data used in this study were downloaded from a public database and did not involve patient clinical information, so ethical approval was not required.

3. Results

3.1. Annual publication trends

The annual number of publications represents the development of a research area (Fig. 2). From 2001 to 2020, the number of

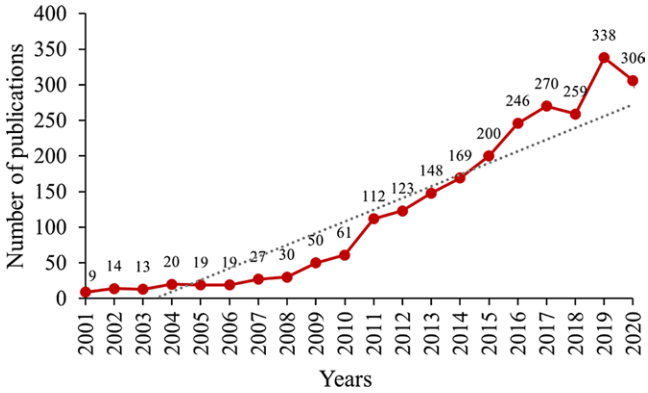

Figure 2. Annual trends in DNA methylation in CVDs over the last 20 years. CVD = cardiovascular disease.

DNA methylation studies in the field of CVDs showed an overall upward trend. The number of articles published between 2001 and 2010 was small, and the research and development of DNA methylation in cardiovascular science was in its infancy. In 2011, the number of papers published doubled, DNA methylation gained increasing attention in the cardiovascular field, and the research trend was observed to be steadily increasing.

3.2. Countries/regions and institutions

A total of 2617 publications were published by 963 institutions from 85 countries/regions. The top 3 producing countries were the United States of America (USA) with the most publications (1044, 39.89%), China (487, 18.61%), and England (263, 10.05%), accounting for 68.55% of the total number of publications. The country visualization map included 116 nodes and 781 links with a density of 0.1171, indicating that different countries were closely connected. The USA, England, Germany, and Italy centrality (>0.10), which is often seen as an important turning point that may lead to transformative discoveries, acted as a bridge.[38,40] In addition, according to the color of the links, the USA (2001), China (2004), and Germany (2007) were the first countries to conduct DNA methylation studies (Table 1, Fig. 3A). The institution visualization diagram contained 963 nodes and 3376 links with a density of 0.0073. Harvard University institution centrality (>0.10), Boston University, Harvard Medical School, Harvard University, Columbia University, and other institutions had close cooperation (Table 1, Fig. 3B).

3.3. Authors and co-cited authors

A total of 15,584 authors participated in the study of DNA methylation in the field of CVD, and 71 authors published >10 articles. The top 10 most productive authors contributed 392 articles (14.98%) to DNA methylation in CVDs. Baccarelli Andrea A, from the Columbia Mailman School of Public Health, published the most papers (n = 63; 2.41%), followed by Levy Daniel (n = 38; 1.45%) and Lifang Hou (n = 35; 1.34%; Table 2, Fig. 4A). Co-cited authors are those cited in a large number of publications. The authors (n = 198) with co-citations of at least 50 publications were used to create a network visualization map (Table 2, Fig. 4B). Four clusters were formed in the network visualization map, among which Barker DJP, Baccarelli Andrea A, Jones Peter A, Yan Zhang, and Horvath Steve occupied the core position of the co-cited author network, Baccarelli Andrea A ranked not only first in the number of articles published but also second among co-cited authors, indicating that these authors have more outputs in this field.

3.4. Journals and co-cited journals

We found that 2617 articles related to DNA methylation were published in 912 academic journals. *PLoS One* published the most papers (n = 110; 4.20%), followed by *Clinical Epigenetics* (n = 79; 3.02%), and the *International Journal of Molecular Sciences* (n = 67; 2.56%). According to the 2021 Journal Citation Reports, among the top 10 journals, 4 have been in the Q1 Journal Citation Reports department, and 5 journals' impact factor (IF) have exceeded 5 (Table 3). Among the top 10 co-cited academic journals, 8 have been cited > 1000 times. As shown in Table 3, journals with the highest number of citations were *PLoS One* (n = 1684), followed by the *Proceedings of the National Academy of Sciences of the United States of America* (n = 1607) and *Nature* (n = 1501). In addition, it can be seen from Table 3 that 70% of journals belonged to Q1. Highly co-cited journals were concentrated in England and the USA.

Dual-map overlay is the embodiment of academic relationships in journals.[41] The citing journals are located on the left, the cited journals are located on the right, and the color path represents the citation relationship. The main citation paths are marked in green and orange. Studies published in Health, Nursing, Medicine (No. 5), Dermatology, Dentistry, Surgery (No. 14), and Sports, Rehabilitation, Sport (No. 9) journals were mainly cited by the studies published in Medicine, Medical, Clinical (No. 2), Neurology, Sports, Ophthalmology (No. 8), and Dentistry, Dermatology and Surgery (No. 9) journals, which are shown in the green paths. Articles published in Molecular, Biological, and Genetic studies (No. 8) are mainly cited by Molecular, Biological, and Immunology (No. 4), as shown in the orange path (Fig. 5).

3.5. Keyword co-occurrence, clusters, and bursts

Keywords highly condense the content of the article and are often used to reflect hotspots in the field. Analysis of

Table 1

The top 10 countries and institutions involved in DNA methylation research.

No.	Country	Count (%)	Centrality	Institution	Count (%)	Centrality
1	USA	1044 (39.89%)	0.63	Harvard University	78 (2.98%)	0.11
2	China	487 (18.61%)	0.01	Columbia University	71 (2.71%)	0.08
3	England	263 (10.05%)	0.15	University of Cambridge	65 (2.48%)	0.08
4	Germany	231 (8.83%)	0.11	Tufts University	57 (2.18%)	0.08
5	Italy	231 (8.83%)	0.12	Boston University	55 (2.10%)	0.07
6	Spain	144 (5.50%)	0.1	University of Michigan	49 (1.87%)	0.07
7	Canada	143 (5.46%)	0.03	Northwestern University	47 (1.80%)	0.06
8	Netherlands	140 (5.35%)	0.08	University of California, Los Angeles	46 (1.76%)	0.05
9	Australia	117 (4.47%)	0.05	University of Washington	44 (1.68%)	0.05
10	Sweden	97 (3.71%)	0.02	Duke University	41 (1.57%)	0.05

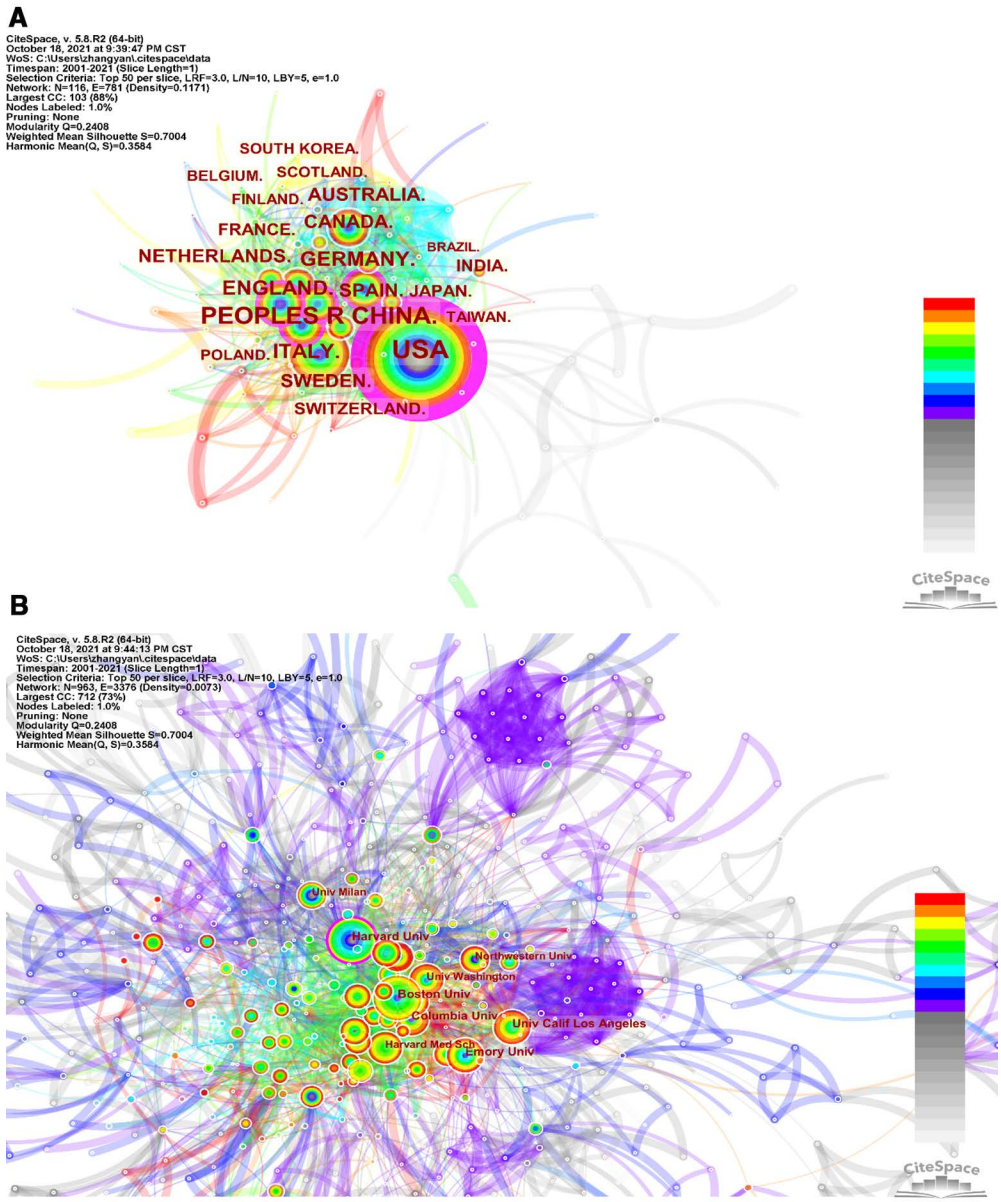

Figure 3. The visual map of (A) countries/regions and (B) institutions in DNA methylation in CVDs. Node size represents co-occurrence frequency, and the links represent co-occurrence relationship. CVD = cardiovascular disease.

Table 2

The top 10 authors and co-cited authors associated with DNA methylation in CVDs.

No.	Author	Count (%)	Co-cited author	Citation
1	Baccarelli Andrea A	63 (2.41%)	Barker DJP	493
2	Levy Daniel	38 (1.45%)	Baccarelli Andrea A	373
3	Lifang Hou	35 (1.34%)	Horvath Steve	350
4	Peters Annette	28 (1.07%)	Jones Peter A	336
4	Schwartz Joel	28 (1.07%)	Gluckman Peter David	268
4	Lubo Zhang	28 (1.07%)	Waterland Robert A	262
5	Chunyu Liu	25 (0.96%)	Yan Zhang	252
5	Waldenberger Melanie	25 (0.96%)	Feinberg Andrew Paul	209
6	Horvath Steve	24 (0.92%)	Bird A	202
7	Joehanes Roby	22 (0.84%)	Lillycrop Karen A	189
8	Fornage Myriam	20 (0.76%)		
9	Arnett Donna K	19 (0.73%)		
9	Napoli Claudio	19 (0.73%)		
10	Deary Ian J	18 (0.69%)		

CVD = cardiovascular disease.

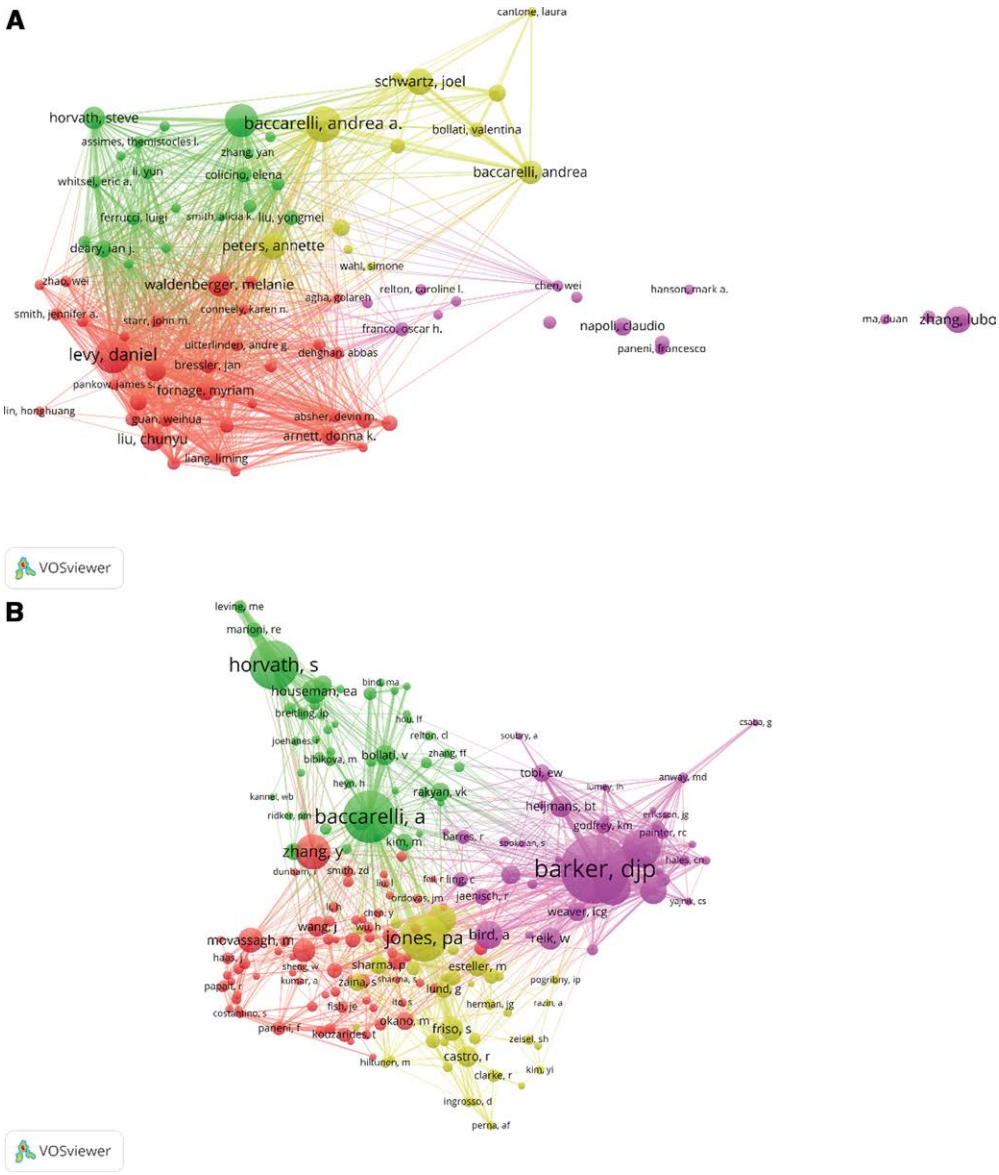

Figure 4. The authors' collaboration (A) and cocitation (B) network visualization map. Node size represents the author's co-occurrence frequencies, the links represent the co-occurrence relationship between the authors. The different clusters are shown in varying colors.

the first 20 keywords showed that DNA methylation was mainly related to gene expression; CVDs mainly involved coronary heart disease, blood pressure, insulin resistance, and heart failure, while other major concerns included the risk factors, oxidative stress, inflammation, exposure, cell, and cancer. Gene expression centrality (>0.10) acted as a bridge (Table 4).

VOSviewer was used for clustering analysis of 1000 keywords. The frames and labels form an element, and the colors distinguish different clusters. Figure 6 shows that the keywords form 8 clusters, indicating 8 research directions. The red cluster is the largest cluster, which is classified as a regulatory mechanism. The keywords are DNA methylation, hypermethylation, gene expression, hypoxia, microRNA, and mechanisms, among others; the purple cluster is classified as an environmental factor, and keywords are risk, air pollution, smoking, prevalence, and inflammation; yellow clusters are classified as methyl-containing substances, and keywords are homocysteine, folate, and B vitamins; the green clusters are lifestyle, and keywords are obesity, insulin resistance, body mass index, and prenatal exposure; epigenetics, heart failure, fibrosis, and histone deacetylases are the keywords in the blue cluster; the keywords of the cyan cluster are hypomethylation and atherosclerosis; the keywords of the orange cluster are biomarkers, cancer, plaques, and apoptosis; and the keywords of the brown cluster are Alzheimer disease and children.

Keywords with strong explosive power are another important index reflecting research frontiers and hotspots (Fig. 7). The citation burst time of keywords including "epigenome wide association" (2016–2021),[42] "long non-coding RNA" (2017–2021), "population" (2017–2021), "metabolism" (2017–2021),[43] "biomarker" (2019–2021),[44] "protein" (2019–2021), "age" (2019–2021),[3] and "cardiovascular risk" (2019–2021)[45] have continued to 2021, and the burst is still ongoing, indicating that these research contents have received great attention in recent years and may become new research frontiers in the future.

3.6. References burst

"References with citation bursts" refer to references frequently cited over a period of time.[40] The burst interval was

Table 3

The top 10 journals and co-cited journals associated with DNA methylation in CVDs.

No.	Journal	Count (%)	IF (2021)	JCR division	Country	Co-cited journal	Count	Centrality	IF (2021)	JCR division	Country
1	*PLoS One*	110 (4.20%)	3.240	Q2	USA	*PLoS One*	1684	0.04	3.240	Q2	USA
2	*Clinical Epigenetics*	79 (3.02%)	6.551	Q1	England	*Proceedings f the National Academy of Sciences of the United States of America*	1607	0.04	11.205	Q1	USA
3	*International Journal of Molecular Sciences*	67 (2.56%)	5.923	Q2	USA	*Nature*	1501	0.09	49.962	Q1	England
4	*Epigenetics*	44 (1.68%)	4.528	Q2	USA	*Circulation*	1206	0.06	29.690	Q1	USA
5	*Scientific Reports*	41 (1.57%)	4.379	Q1	England	*Journal of Biological Chemistry*	1191	0.03	5.157	Q2	USA
6	*Circulation research*	28 (1.07%)	17.367	Q1	USA	*Science*	1179	0.06	47.728	Q1	USA
7	*Frontiers in Genetics*	24 (0.92%)	4.599	Q2	Switzerland	*Cell*	1125	0.07	41.582	Q1	USA
8	*Nutrients*	23 (0.88%)	5.717	Q1	Switzerland	*Nature Genetics*	1069	0.03	38.330	Q1	USA
9	*Epigenomics*	22 (0.84%)	4.778	Q3	England	*Nucleic Acids Research*	932	0.02	16.971	Q1	England

CVD = cardiovascular disease, IF = impact factor, JCR = Journal Citation Reports.

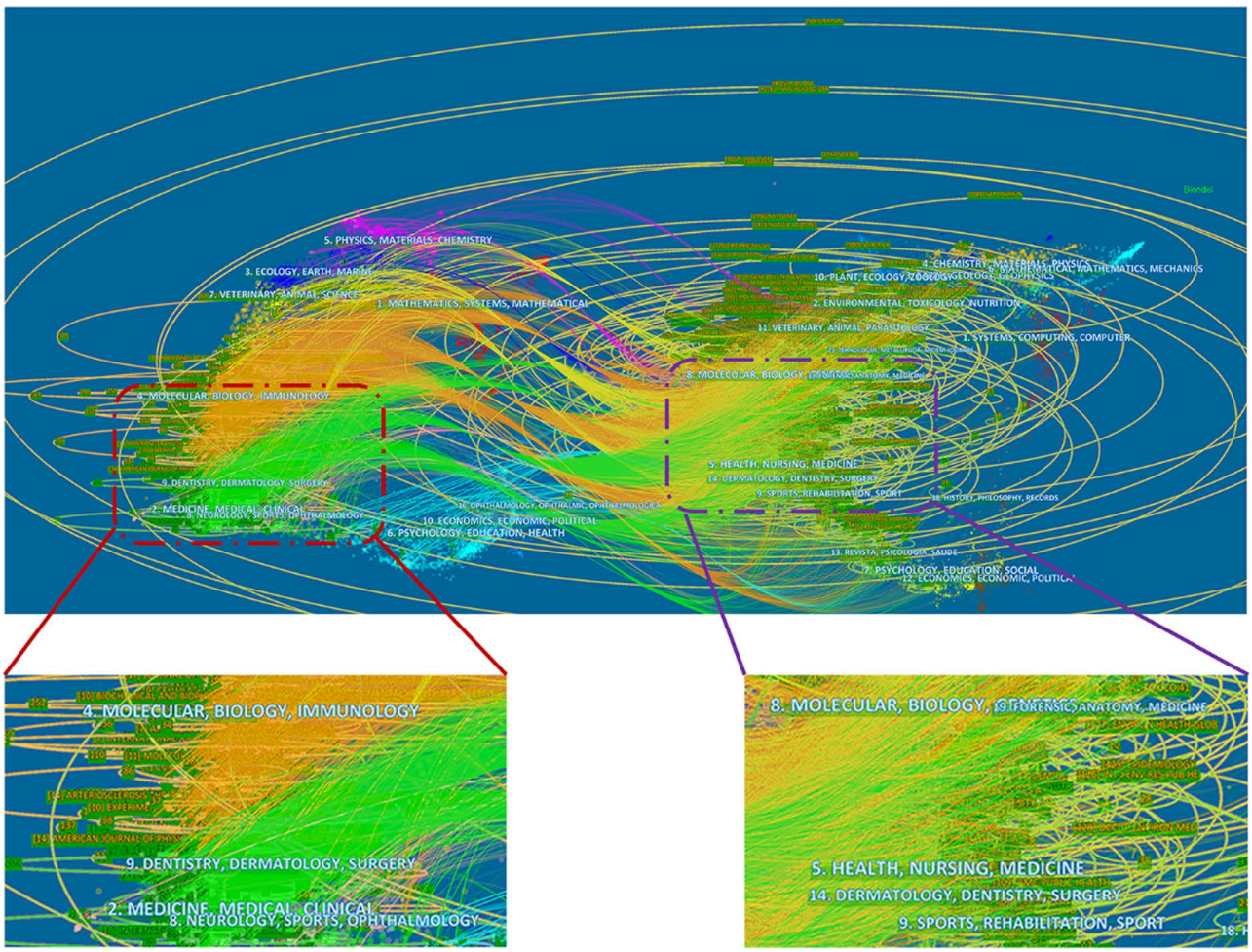

Figure 5. The dual-map overlay of journals in DNA methylation in CVDs. CVD = cardiovascular disease.

set to 2 years, and 35 burst studies were screened (Fig. 8). The earliest outbreak occurred in 2008. The most recent citation burst reference was observed in 2019, and the burst is still ongoing. These bursts of literature involve the role of DNA methylation in CVD and risk (2017–2021),[46] the relationship between obesity, smoking, aging, and DNA methylation (2017–2021),[47–51] inflammation and DNA methylation (2018–2021),[52] biomarkers, and epigenome-wide association study (2019–2021).[53] Epigenetic clocks are both the research breakout point and the longest-lasting research content (2019–2021).[48,54]

4. Discussion

4.1. General information

According to the WoSCC database, 2617 studies on DNA methylation in CVDs were published in 912 journals by 15,584 authors from 963 institutions in 85 countries. The small number of articles published before 2010 indicates that the field was in a nascent stage. In 2011, the number of articles exploded, indicating that researchers recognized the importance of DNA methylation and began studying it extensively. Subsequently, the number of articles published in this research direction has been

Table 4

The top 20 keywords of DNA methylation in CVDs.

No.	Keyword	Count	Centrality	No.	Keyword	Count	Centrality
1	DNA methylation	1126	0.07	11	Coronary heart disease	131	0.1
2	Gene expression	809	0.19	12	Insulin resistance	108	0.02
3	Cardiovascular disease	352	0.16	13	Blood pressure	106	0.02
4	Risk	232	0.02	14	Cell	104	0.04
5	Gene	223	0.02	15	Mechanism	101	0.03
6	Disease	206	0.04	16	Risk factor	98	0.04
7	Association	181	0.08	17	Atherosclerosis	93	0.04
8	Oxidative stress	163	0.04	18	Exposure	92	0.02
9	Methylation	160	0.06	19	Heart disease	88	0.02
10	Cancer	134	0.09	20	Inflammation	83	0.01

CVD = cardiovascular disease.

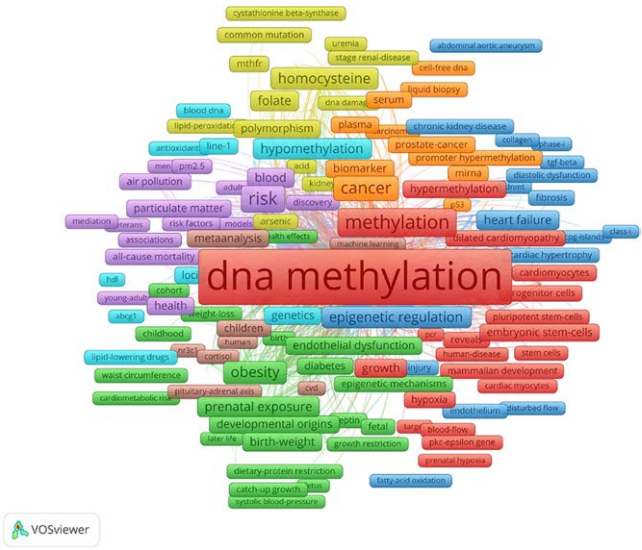

Figure 6. Keywords clustering in DNA methylation in CVDs. CVD = cardiovascular disease.

steadily increasing, and DNA methylation has become a hotspot in the cardiovascular field.

Through the analysis of countries, it was found that the USA, China, and England published the most documents. Australia and Italy have made rapid progress in recent years. Of the top 10 contributing institutions, 90% were from the USA. The close collaboration between institutions such as Boston University, Harvard University, and Columbia University, and their concentration in the USA, indicate that these institutions significantly contribute to the field of methylation; on the other hand, links between institutions are limited to internal countries. In the future, transnational institutions should be encouraged to remove academic barriers, strengthen cooperation, and promote the progress of DNA methylation research.

The journals and co-cited journals are listed in Table 3. DNA methylation articles were mainly published in bioinformatics journals, and the top 3 publishing journals were *PLoS One* (n = 110, IF = 3.240, Q2), *Clinical Epigenetics* (n = 79, IF = 6.551, Q1), and *International Journal of Molecular Science*s (n = 67, IF = 5.923, Q2), which can provide reference for the selection of contributing journals. Among the top 10 co-cited journals, 7 belonged to Q1. It can be seen that the cited literature is all from high-impact journals, indicating that research on DNA methylation is highly influenced in the global academic field.

Professor Baccarelli Andrea A of Columbia University and Horvath Steve of the University of California, Los Angeles, are not only among the top 10 authors but also among the top 3 co-cited authors. Prof Baccarelli's research interest is the association between environmental exposure and the epigenome, and Prof Horvath is a leader in the field of epigenetic clocks. Because academics from top institutions receive more research funding, they are perfect candidates for collaboration.

4.2. The hotspots and frontiers

In econometric analysis, high-frequency keywords can show the changing trends and topics, which is crucial to understanding the development of this research field. Keywords in the early stages of development (2001–2010) included homocysteine, folic acid, and breast cancer, among others, and new terms in the fast-developing phase (2011–2021) include biomarkers, aging, epigenetic clock, epigenome-wide association study, long noncoding RNA, environment, and lifestyle.

"References with citation bursts" means that the documents have been frequently cited over a period of time.[40] This also indicates that the papers have attracted the attention of the scientific research circle and reflect the hotspots and development trend of DNA methylation research. According to the burst of keywords and references, the research hotspots of DNA methylation in CVDs are summarized as biomarkers, epigenetic clocks, environmental exposure, and lifestyle.

4.3. Application of DNA methylation as a CVD biomarker

In recent years, it has been found that epigenomes are more likely to serve as biomarkers than transcriptomes because of their stability.[55] DNA methylation is dynamic throughout the life course and is potentially modifiable by interventions; therefore, disease status can be tracked using real-time markers.[56]

Symptoms and physical signs are important means for the diagnosis of heart failure; however, there is a significant difference between individuals,[57] which are often not specific, affecting the timeliness and accuracy of diagnosis. The 2021 European Society of Cardiology (ESC) guideline reduced the recommendation for invasive coronary angiography in heart failure with reduced ejection fraction caused by coronary artery disease from category IIa to IIb.[58] Given the further development of precision medicine, noninvasive biomarkers have attracted extensive attention in clinical practice. Genetic biomarkers have the characteristic of moment-to-moment capture. A number of studies have identified DNA methylation biomarkers of heart failure through peripheral blood[53,59,60] and heart tissue data.[53,61] Meder et al compared methylation patterns in the myocardial and peripheral blood. The B9 protein domain 1 (hypomethylation), bicortical protein-like kinase 2 (hypomethylation), and neurotrimin (hypermethylation) were found to overlap significantly between tissue and blood (odds ratio: 28, $P < .001$). Among them, B9D1 in the peripheral blood training cohort and peripheral blood validation cohort, the area under the curve > 87%, as a biomarker, is more likely.[53]

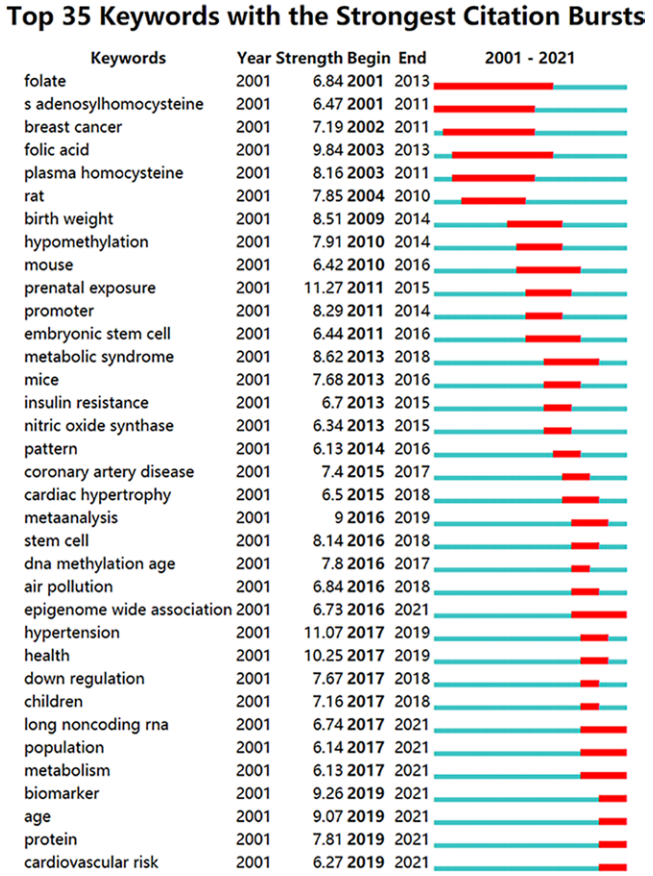

Figure 7. The top 35 references with the strongest keywords had burst during the time period 2001 to 2021. The red stripe indicates the time period when the research content emerged.

The epitransgenerational network modeling for stratification of heart morbidity platform combines liquid biopsy with artificial intelligence analysis to identify noninvasive biomarkers produced by cardiomyocytes or other circulating cells at different points in time.[62] The epitransgenerational network modeling for stratification of heart morbidity platform provides a new perspective for the treatment of patients with early asymptomatic subjects and end-stage heart failure by continuously observing changes from the fetal-perinatal stage until childhood and older age.[63] However, there are no mature clinical therapies for heart failure.

4.4. Application of epigenetic clocks in CVDs

Age is an unchangeable risk factor for CVD. The aging process is characterized by the presence of high interindividual variation between individuals of the same chronological age, prompting a search for biomarkers that capture this heterogeneity. Epigenetic age acceleration (EAA) is associated with reduced cardiovascular health factors, including diet, smoking, physical activity, body mass index, blood pressure, total cholesterol, and glucose.[64] DNA methylation-based GrimAge is new research and development of epigenetic age estimator, which is calculated based on the residual of age regression and used to estimate the deviation between biological age and actual age.[65,66] Specifically, the DNA methylation-based GrimAge was built as a linear combination of 7 DNAm-based surrogate markers of plasma proteins: tissue inhibitor metalloproteinases 1, plasminogen activator inhibitor-1, leptin, growth differentiation factor 15, cystatin C, beta-2-microglobulin, adrenomedullin, sex, age, and DNAm-based biomarkers for smoking pack year, using DNAm values of 1030 unique CpG sites.[66] Compared with other epigenetic clocks, GrimAge has a higher accuracy in predicting all-cause mortality and age-related clinical phenotypes, which facilitates the precise treatment of CVDs.[54,67] GrimAge acceleration also predicted a positive correlation between obese individuals and the occurrence of type-2 diabetes 10 years later (odds ratio: 2.57, 95% confidence interval: 1.61–4.11).[68] The epigenetic clock reflects age-independent exposure and disease risk and is reversible, allowing for early prevention and treatment of disease through lifestyle and environmental interventions.[21,66,69] Epigenetic age may be a useful biomarker for CVD risk and provide a biological perspective on the role of epigenetic mechanisms in age-related CVD loss and CVDs.[70–72] GrimAge can predict CVD risk not only for White people, but also for African Americans.[73] The DNA methylation aging clock is also currently used as a biomarker for other diseases, such as stroke, Alzheimer disease, and cancer.[74–76]

4.5. Environmental exposure, lifestyle, and DNA methylation in CVDs

The living environment and lifestyle can change the regulation of gene expression and play an important role in epigenetics.[77] Due to the reversibility of DNA methylation, lifestyle interventions can regulate its changes and influence the course of the disease. Currently, epigenetics is rapidly developing in this field.

Cigarette smoking is a major risk factor for CVDs. Tobacco use confers long-term risk of diseases, even decades after cessation, which is not well understood. Recently, epigenetic changes have been suggested to explain these phenomena. Cigarettes cause multiple genetic changes in DNA methylation. Methylation at these sites could also serve as sensitive and stable biomarkers of lifetime exposure to tobacco.[49] Joehanes et al conducted a meta-analysis of DNA methylation associated with cigarettes in 15,907 individuals from 16 cohorts and found that methylation changes persisted in past smokers. There were statistically significant differences between current smokers and nonsmokers with cardiovascular heart disease, stroke, and hypertension.[49] Blood levels of aryl hydrocarbon receptor repressor and F2R like thrombin or trypsin receptor 3 methylation tended to converge in those who quit smoking compared with those who never smoke.[78]

Overweight and obesity are major risk factors for type-2 diabetes, CVD, metabolic and inflammatory disturbances.[79] Longitudinal studies of obesity and related phenotypes suggest that body mass index/obesity is the cause of the evolution of DNA methylation over time and that DNA methylation levels may influence the association between obesity and its health outcomes. Blacks and whites also show significant racial differences.[80] In obese people, DNA methylation is moderately correlated in blood and other tissues. A total of 187 differential methylation sites were associated with lipid and lipoprotein metabolism, substrate transport, and inflammatory pathways.[51] Aryl hydrocarbon receptor repressor is 2.1% higher in offspring of obese mothers than in offspring of normal-weight mothers,[81] and aryl hydrocarbon receptor repressor methylation genes have also been shown to be downregulated in smoking cessation,[78] indicating the importance of regulating methylation levels of this gene. As obesity and methylation sites continue to be discovered, further experimental studies are needed to elucidate the specific mechanisms.

4.6. Strengths and limitations

In this study, CiteSpace and VOSviewer software were used for the first time to study DNA methylation in the field of CVDs.

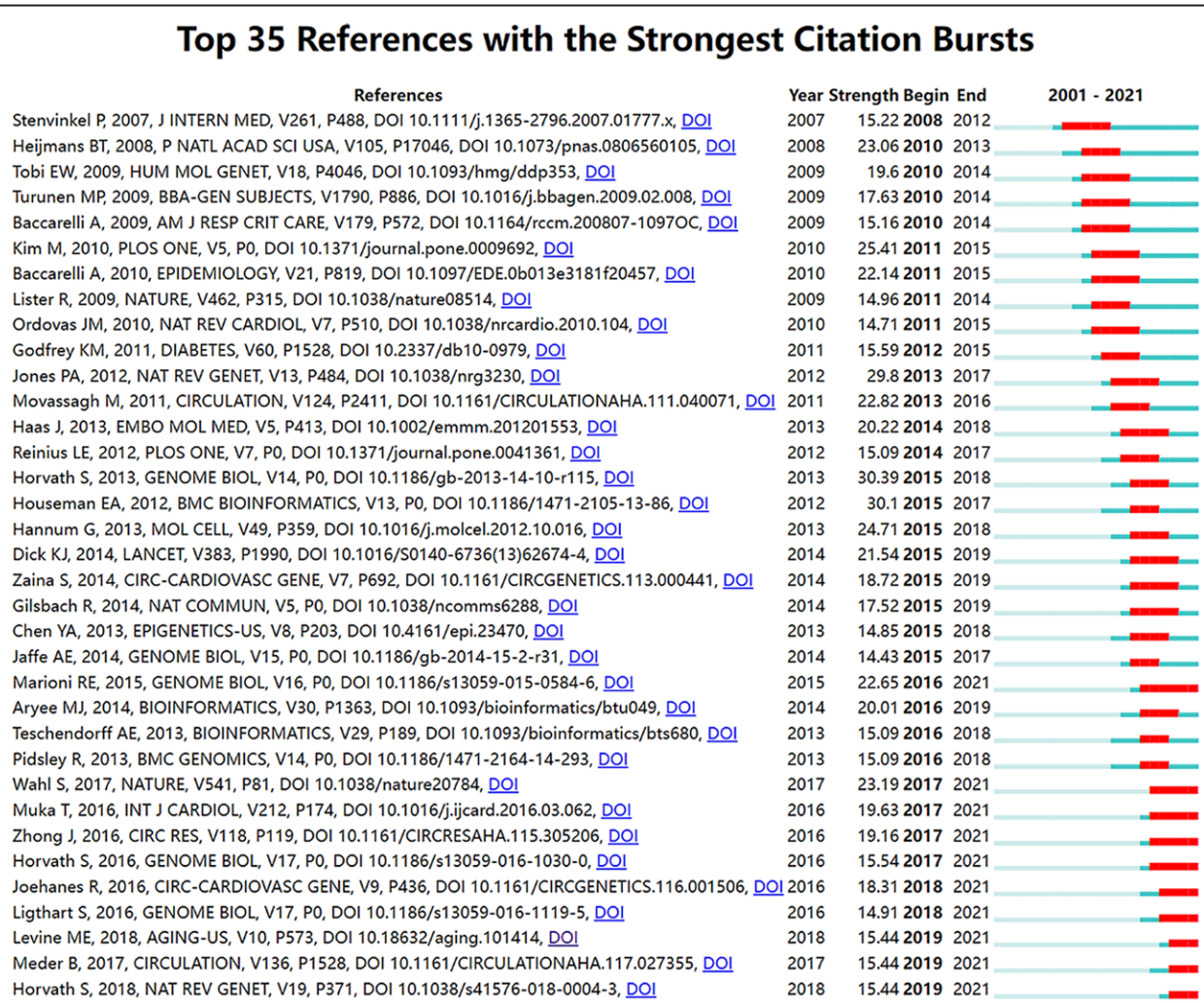

Figure 8. The top 35 references with the strongest citation bursts during 2001 to 2021.

Through the analysis of the authors, countries/regions, institutions, journals, references, and keywords, objective information can be provided to support interinstitutional cooperation. At the same time, it provides an overview for researchers to understand the prevailing trends in CVD-related epigenetic research. In addition to the advantages mentioned above, this study also has the following shortcomings: the literature only relied on the WoSCC database, while publications in other databases, such as PubMed and Cochrane, may not have been identified; only English publications were included in the study, which were language restricted; bibliometrics analysis only analyzed the authors, references, keywords, and other contents in the research field from the macro level, without discussing the specific mechanism, which lacks depth in the literature.

5. Conclusions

Based on the analysis of VOSviewer and CiteSpace software, DNA methylation publications published in international journals in the field of cardiovascular science are on the rise, which have important academic value and application prospects. DNA methylation studies in CVDs are mainly conducted in the USA and China, with the USA and all its institutions dominating the field. Although the number of publications continues to grow, there are academic barriers between national institutions, which require enhancing cooperation and exchange between countries/regions and institutions. In the future, the clinical transformation of DNA methylation in CVDs should be enhanced. At the moment, research on DNA methylation mainly focuses on its molecular mechanisms, environmental factors, methyl nutrition, and biomarkers. References Burst speculated that future hotspots will focus on biomarkers, epigenetic clocks, environmental exposure, and lifestyle.

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