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REVIEW
Cardiovascular disease

Epigenetics in the primary and secondary prevention of cardiovascular disease: influence of exercise and nutrition

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Increasing evidence links changes in epigenetic systems, such as DNA methylation, histone modification, and non-coding RNA expression, to the occurrence of cardiovascular disease (CVD). These epigenetic modifications can change genetic function under influence of exogenous stimuli and can be transferred to next generations, providing a potential mechanism for inheritance of behavioural intervention effects. The benefits of exercise and nutritional interventions in the primary and secondary prevention of CVD are well established, but the mechanisms are not completely understood. In this review, we describe the acute and chronic epigenetic effects of physical activity and dietary changes. We propose exercise and nutrition as potential triggers of epigenetic signals, promoting the reshaping of transcriptional programmes with effects on CVD phenotypes. Finally, we highlight recent developments in epigenetic therapeutics with implications for primary and secondary CVD prevention.

Keywords DNA methylation • Histone modification • Non-coding RNA • Epigenetic editing • RNA therapeutics • Heart failure • Coronary artery disease • Hypertension • Physical activity

Background

As cardiovascular disease (CVD) remains the most common cause of death worldwide, preventing CVD is a top public health priority.[1] Primary prevention consists of controlling CVD risk factors (such as smoking, hypertension, and diabetes) in people free of CVD; secondary prevention entails reducing the risk of a subsequent cardiovascular event in patients with existing CVD. Clinical outcomes are improved following implementation of primary or secondary CVD prevention strategies, but the biological mechanisms responsible for these improvements remain only partially resolved despite extensive research.[2] Heritability of CVD is insufficiently explained

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by DNA sequence changes alone.[3] Rather, increasing evidence shows that environmental and lifestyle factors influence epigenetic systems, which include DNA methylation, histone modification, and non-coding RNA expression. Epigenetic systems are flexible genomic parameters that can change genome function under exogenous influence, while also providing a mechanism for stable propagation of gene activity states from one generation of cells to the next.[4] Exercise and nutrition are powerful epigenetic modifiers that induce both transient and lasting epigenetic changes, thereby activating signalling cascades associated with cardiovascular benefits.[5,6]

The separate role of exercise or nutrition in CVD prevention has been reviewed previously, and excellent reviews exist on epigenetic treatments of established CVD.[3,4,7,8] In this review, we focus on how epigenetic systems could act as central regulators of clinical outcomes in CVD. By concentrating on the distinctive aspects of primary and secondary CVD prevention, we aim to: (i) summarize current evidence for modulation of epigenetic systems through exercise and nutrition; and (ii) evaluate emerging data on therapeutic epigenetic interventions. Wherever possible, we focus on human studies and highlight current gaps in knowledge to aid clinical translation. Overall, we propose the interaction between key environmental stimuli of exercise and nutrition influences CVD via direct epigenetic modifications, which in turn may be targeted and translated for direct therapeutic use.

Part 1: understanding basic epigenetics

Epigenetics is the study of heritable alterations in phenotypes and gene expression that occurs without changes in DNA sequence, i.e. when environmental changes induce different phenotypical traits in organisms with identical genotype.[9] Epigenetic mechanisms determine reversible changes to gene function under exogenous stimuli and may explain gene expression from one generation of cells to the next.[4] These modifications fall into three main categories: chemical modification of DNA (e.g. methylation), alteration of chromatin structure (e.g. histone modification), and post-transcriptional gene regulation by non-coding RNAs (e.g. microRNAs, miRNAs; *Figure 1*). A complex network of interactions results from these modifications, as methylation and histone modifications also affect non-coding RNA expression, and DNA methylation associates with certain histone modifications.[3]

DNA methylation

DNA methylation is a covalent modification that forms 5-methylcytosines (5mCs). DNA methylation is performed by DNA methyltransferases (DNMTs) in the presence of the methyl donor adenosyl-methionine (*Figure 1*). Methylation of cytosine is known as 5mC, occurring predominantly at cytosine followed by guanine (CpG) sites. CpG-dense regions at 5′ transcriptional start sites are called CpG islands, and methylation within gene promoters and CpG islands seems to have the highest functional relevance for gene expression.[3] In humans, 60–80% of CpG sites are typically methylated. Genes may be methylated differently in response to exogenous stimuli such as exercise or nutrition, either becoming hypermethylated or hypomethylated. Hypermethylation of gene promotors in general decreases accessibility of chromatin and functionally inhibits binding to DNA to effectively reduce gene expression, hypomethylation acts in a reverse manner increasing gene expression. Of note, different DNMTs have subtle differences in function, e.g. DNMT1 mostly maintains existing methylation patterns, while DNMT3a and 3b are more involved in *de novo* methylation.[10] In addition to 5mC, adenosine methylation and intermediate forms of cytosine methylation have been discovered, but their functional role in humans remains to be determined. For technical reasons, DNA methylation of circulating cells is the most studied epigenetic modification.

Histone modifications

In the nucleosome, around which DNA is wound, histones are the key structural proteins. Nucleosomes occur in repeating units to form chromatin and chromosomes, thus organizing the genetic

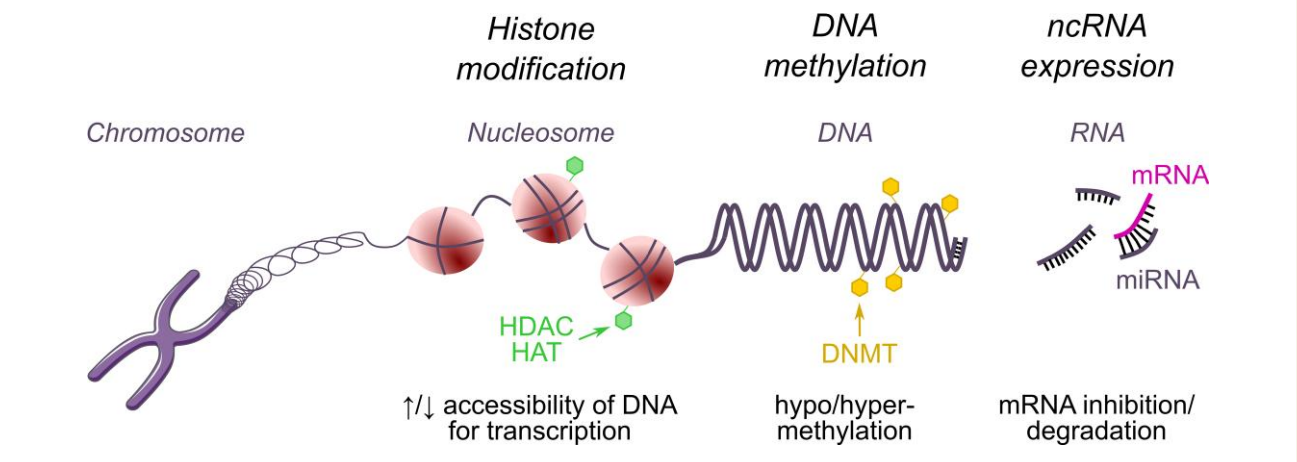

Figure 1 Epigenetic modifications. Major epigenetic mechanisms include histone modification, DNA methylation, and ncRNA expression, occurring at different levels of DNA expression. See text for explanation. DNMT, DNA methyl transferase; HAT, histone acetyltransferase; HDAC, histone deacetylase; mRNA, messenger RNA; miRNA, microRNA; ncRNA, non-coding RNA.

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material in the cell nucleus. The four histone proteins (H2A, H2B, H3, and H4) can be modified through post-translational modifications of specific amino acid residues, influencing the accessibility of DNA and thus gene expression (*Figure 1*). Histone modification results from different biochemical processes, such as acetylation, methylation, ADP ribosylation, and others.[3] These modifications alter the physical interaction between the histone and the DNA wound around it, influencing the accessibility of genes for transcription. Histone modification may induce either repression or activation of transcription, depending on the type of modification and the position of the amino acid residue. For instance, *methylation* of histone H3 lysine 9 (H3K9) is associated with chromatin *inactivation*, while *acetylation* of histone H3 *activates* transcription.[11] The combination of diverse modifications, large number of modifiable amino acid residues, and many enzymes capable of modifying histones results in a complex network of interactions. A single histone modification is thus unlikely to modify gene expression significantly. However, changes in histone modifying enzymes are likely to have important downstream consequences. For example, interference in histone acetyltransferase (HAT) or histone deacetylase (HDAC) function has been shown to influence cardiac hypertrophy.[12]

Non-coding RNA expression

Over 97% of the human genome does not encode protein sequences. About 80% of this non-coding DNA is highly transcriptionally active, transcribing into non-coding RNA with structural and cellular functions, including transfer RNA and ribosomal RNA.[7] Of more interest are non-coding RNA molecules with regulatory functions, including miRNAs, small interfering RNAs, piwi-interacting RNA, small nucleolar RNAs, and long non-coding RNAs. These non-coding transcripts participate in most biological processes and play a causative role in human pathologies such as CVD.[4] Of these, miRNAs have been most intensely studied. miRNAs are short (20–25 nucleotides) RNA molecules, transcribed by RNA Polymerase II into primary miRNAs and processed in the nucleus and cytoplasm by RNases into final mature miRNAs. These bind to their target mRNAs (*Figure 1*), influencing their translation in several ways, usually resulting in inhibition of protein synthesis.[7] While this review will focus predominantly on miRNAs given these have been the focal point in most studies related to CVD, exercise, and nutrition, it is important to recognize that other non-coding RNAs may also play a key role in this interaction which includes small non-coding (sncRNA), long non-coding (lncRNA), circular RNA (circRNA; as reviewed in detail elsewhere[13]).

Evidence for epigenetic regulation of cardiovascular disease

Inherited genetic variance can predispose individuals towards CVD.[14] Twin studies have demonstrated the importance of heritability in CVD: monozygotic twins have higher concordance in the risk of premature death due to CVD compared with dizygotic twins.[15] A genetic component is demonstrated for CVD risk factors such as dyslipidaemia, hypertension, diabetes, and obesity.[15] Subsequent genome-wide association studies identified hundreds of single-nucleotide polymorphisms (SNPs) related to coronary artery disease.[16] However, these combined SNPs can only explain a small fraction of CVD heritability, suggesting gene–gene interaction and/or epigenetic mechanisms could contribute more than genetic variation. Experimental evidence further supports a strong link between epigenetic modifications and risk of CVD.[3]

This link between epigenetics and CVD can potentially exist on various levels. In cardiomyocytes, prenatal development, postnatal maturation, and disease development are all characterized by a co-operation of active CpG methylation and histone marks shaping the cardiac myocyte transcriptome.[17] In biopsies of failing human hearts, profound DNA hypomethylation was found, and these were associated with differential expression of angiogenic factors.[18] In human atherosclerotic plaques, global DNA hypomethylation was demonstrated, clustering at locations known to interact with vascular function-related genes and miRNAs.[19] Histone modifications associate with foetal cardiac genes, which are known to be reactivated in human heart failure (HF).[20] The importance of individual non-coding RNAs in CVD is attested by several studies linking dysregulated circulating non-coding RNA levels to disease states such as CAD, HF, and myocardial infarction as reviewed elsewhere.[7,21]

Of note, these studies have all been conducted in the absence of a reference of a 'normal' epigenetic state. There are ongoing efforts to establish a reference for the human epigenome across different cellular states and methodologies.[3] Finally, exposure to CVD risk factors such as smoking, diabetes, air pollution, physical inactivity, and dietary behaviour can modify epigenetic mechanisms.[3] For example, air pollution rapidly decreased DNA methylation which associated with elevated CVD biomarkers.[22] Overall, evidence indicates the potential for a direct link between epigenetic modification and the onset of CVD, but the underlying mechanisms remain poorly understood. Here, we describe the emerging role of two environmental stimuli, physical exercise, and nutritional changes, as potential triggers of epigenetic signals promoting the reshaping of transcriptional programmes with effects on CVD phenotypes (*Figure 2*).

Part 2: epigenetics in the primary prevention of cardiovascular disease

Epigenetic modulation in primary cardiovascular disease prevention: exercise effects

Exercise has numerous health benefits, with protective effects against at least 35 chronic conditions including CVD.[8] Exercise is a physiological stressor that provokes widespread perturbations in all the body's physiological systems via increasing metabolic activity of contracting skeletal muscles (i.e. the largest organ by mass). Although the molecular mechanisms underlying the exercise response remain only partially resolved, the current paradigm highlights the importance of transient increases in mRNA levels of various metabolic, myogenic, and regulatory genes in skeletal muscles in response to each individual bout of exercise.[23] When exercise is repeated regularly over time (i.e. exercise training), transient increases in gene expression cumulatively induce adaptations which confer positive health benefits.[23] Muscle-specific changes in DNA methylation, histone modifications, and miRNAs are proposed to regulate skeletal muscle and myocardial interactions during and after exercise.[23,24] This adaptive response is

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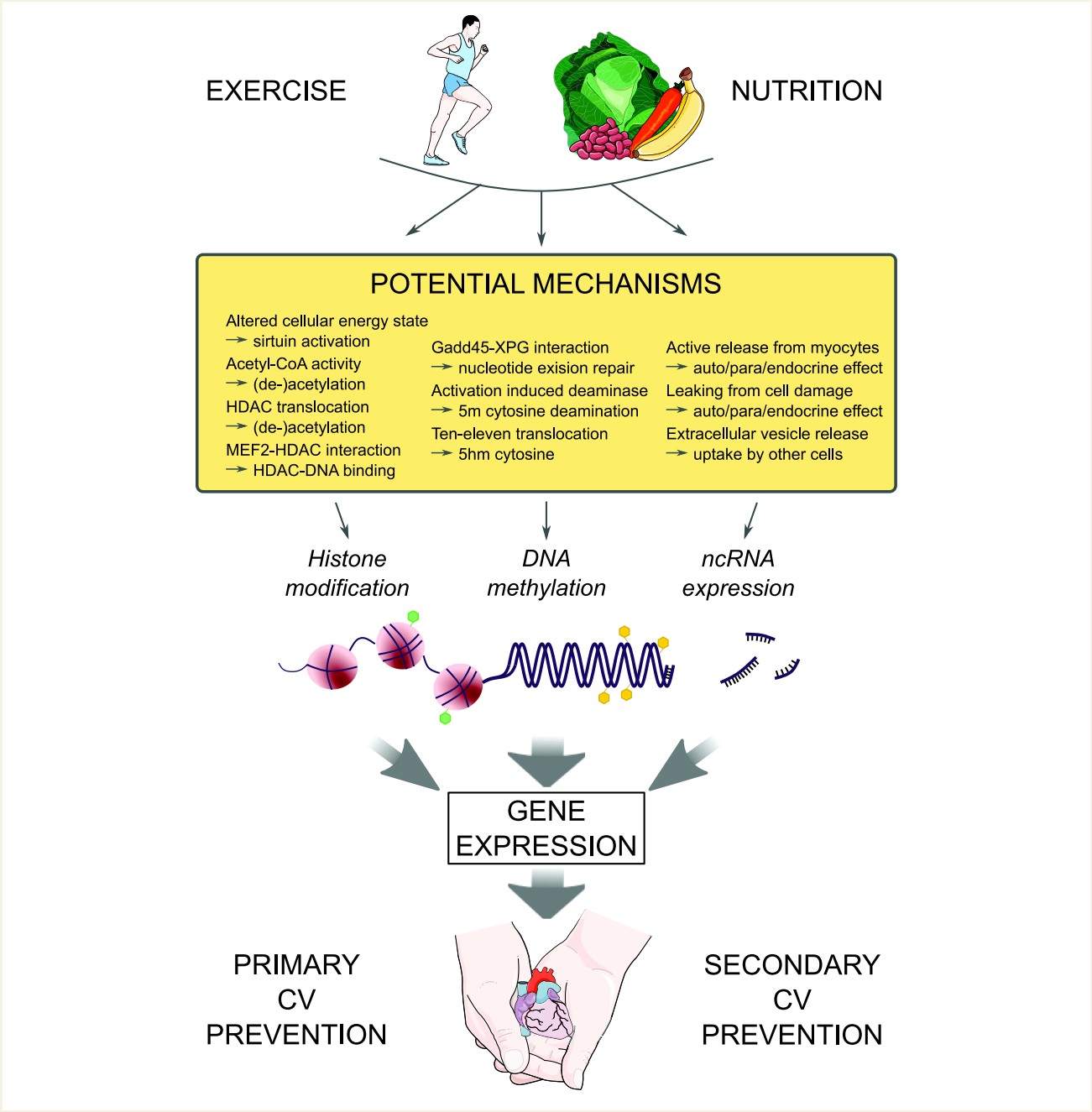

Figure 2 Epigenetic mechanisms underlying the effects of exercise and nutrition in cardiovascular disease. Exercise and nutrition influence gene expression through epigenetic mechanisms, thereby contributing to primary and secondary CV prevention. Potential mechanisms for regulation of epigenetic modifications through exercise and nutrition are outlined. 5m, 5-methyl; 5hm, 5-hydroxymethyl; CV, cardiovascular; Gadd45, growth arrest and DNA damage; HDAC, histone deacetylase; MEF2, myocyte enhancer factor 2; ncRNA, non-coding RNA; XPG, xeroderma pigmentosum Group G endonuclease.

heavily influenced by exercise type, duration, and intensity,[25] with both resistance and endurance training changing DNA methylation and miRNA expression in a time-dependent manner (i.e. acute vs. chronic).[26] A few animal studies have demonstrated links between exercise-induced epigenetic modulation and improvements in CV function.[27–29] In humans, epigenetic modifications associated to physical activity have been correlated to indirect markers of reduced CV risk, such as improved physical performance, endothelial function, or arterial compliance.[30–37] A direct influence of exercise-induced epigenetic modifications on primary CV prevention in human subjects remains to be established.

Acute epigenetic effects of exercise

(1) *DNA methylation*: Evidence indicates dynamic changes in DNA methylation in skeletal muscle as an early event in

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contraction-induced gene activation.[38,39] Global hypomethylation in skeletal muscle from healthy males occurs 20 min after the completion of a maximal exercise test (i.e. peak oxygen uptake; VO_{2peak}).[39] Hypomethylation was evident in promoters of metabolic genes resulting in increased gene expression, with exercise intensity dependent expression of *PGC-1α*, *PPAR-δ*, and *PDK4* accompanied by hypomethylation of each respective promoter either immediately or 3 h after an exercise bout.[39] Interindividual differences observed in the exercise response may partly be explained by epigenetic regulation, with evidence indicating DNA methylation status of the skeletal muscle *PGC-1α* promoter involved for endurance training.[38] Fewer studies exist on the acute effect of exercise on DNA methylation in circulating cells. No changes in global DNA methylation were detected in peripheral blood mononuclear cells (PBMCs) after a prolonged exercise bout in trained male runners.[40] In contrast, hypomethylation in leucocytes (both globally and in the *PGC-1α* promoter) was shown 60 min following cycling exercise, with a positive correlation between leucocyte *PPARGC1A* methylation and exercise performance.[41] Less is known about the acute epigenetic effects of resistance exercise, although four genes demonstrated hypomethylation after a single bout of acute exercise and these changes were maintained 22 weeks later, indicating a role for epigenetic regulation in the muscle hypertrophic response.[42]

(2) *Histone modification*: Although exercise-induced histone modifications are less studied, there is some evidence for histone modifications to occur following acute exercise in human skeletal muscle. For example, 60 min of cycling increased acetylation of histone protein 3 lysine 36 (H3K36) associated with enhanced transcription of exercise-associated genes.[43] In addition, some HDACs (HDAC4 and 5) were exported from the nucleus during exercise, thereby removing transcriptional suppression.[43] This evidence, together with evidence from rodent studies, indicates that histone modifications play a key role in the transcriptional response to exercise.[23]

(3) *Non-coding RNA*: Changes to miRNAs are the most studied exercise-induced epigenetic modification and are implicated as molecular markers of physiological adaptive responses to exercise.[24] Skeletal muscle-specific miRNAs (myomiRs) are proposed to regulate the exercise response, being released into the circulation by exercising muscles and remotely influencing cellular function in other tissues through exercise-associated signalling pathways. After acute exercise, miR-1 and -133a are the most consistently up-regulated miRNAs in skeletal muscle and blood (*Table 1*). Variability in sampling time, statistical power, exercise mode, and miRNA determination likely contribute to some of the discrepancies seen in *Table 1*.[50,75]

Epigenetic effects of sustained exercise training

(1) *DNA methylation*: While some studies in healthy populations have investigated genome-wide DNA methylation changes following exercise training using human skeletal muscle,[42,76–78] limitations include heterogeneity in age, sex, and exercise regimes. Following 6 months of endurance training, 18 genes decreased and 20 genes increased methylation status in individuals without vs. with a family history of diabetes.[76] Hypomethylation included genes for MAPK and calcium signalling pathways, which play an important role in the muscle metabolic response. After 7 weeks of resistance training in healthy young men, most CpG sites showed hypomethylation with subsequent enhanced gene expression.[42] In this study, partial maintenance of the hypomethylated state was observed after detraining, indicating some degree of 'muscle memory' for methylation signatures. In a one-legged knee-extension intervention for 3 months, methylation changes of >5% occurred at 839 sites across the genome towards a trained muscle phenotype in the exercised leg, with sex as a key determinant of DNA methylation variability.[77] Two studies have investigated the effects of exercise on methylation of the *ASC* gene, responsible for interleukin (IL)-1β and IL-18 secretion in the circulation.[79,80] In healthy individuals, *ASC* from whole blood was hypermethylated after 6 months of walking-based exercise, potentially counteracting the *ASC* hypomethylation with age.[80] Exercise-induced hypermethylation of $p66^{shc}$ gene promotor was accompanied by a reduced $p66^{shc}$ gene expression and lower systemic oxidative stress.[35] Overall, the magnitude of DNA methylation changes appear to be smaller for chronic compared with acute exercise, despite key DNA methylation changes being maintained and accumulating over multiple exercise sessions.[39,78]

(2) *Histone modification*: Histone acetylation is involved in the adaptations to resistance exercise training in healthy volunteers.[81,82] Responders (displaying myofibre hypertrophy) were found to have higher levels of acetylated histone H3 (K36) in the pre-training transcriptome, priming them to more efficient exercise-induced adaptations. Accordingly, a differential expression of characteristic genes for cell-cycle progression, such as α-tubulin, was observed after the first exercise stimulus. In contrast, metabolically demanding high-intensity resistance training decreased p38 MAPK phosphorylation and H3K4 trimethylation in human skeletal muscle.[83] Another study found an up-regulation of acetylated H3, H3 monomethylated at lysine 4, and trimethylated at lysine 27, as well as a down-regulation of the distribution of H3.3 variant after intense resistance training in healthy men.[84] We conclude that histone modifications are closely related to an up-regulation of gene expression stimulating muscle metabolism and training adaptations after resistance training; however, the clinical importance remains uncertain.

(3) *Non-coding RNA*: Some evidence, but less than for acute responses to exercise, are available on the chronic effects of exercise on miRNA expression in skeletal muscle (*Table 1*). The working skeletal muscle is a key organ and place of origin responsible for endogenous exercise-induced release of miRNAs into the circulation. Interestingly, miR-1 and -133a expression significantly increased after acute exercise, whereas these miRNAs decreased in most exercise training studies (*Table 1*). It can be concluded that, compared with acute exercise, chronic exercise induces moderate but more consistent changes in skeletal muscle miRNA expression. In mice as well as humans, it has been found that training increased circulating miR-133 while it decreased muscular levels.[50] This suggests that miRNA species may be secreted from muscle into the circulation upon exercise.

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Table 1 Important miRNAs implicated in the response to exercise and nutrition

MiRNA	Increase–decrease	Most important biological pathways[a]	Tissue, exercise/nutrition type [Reference][b]
Acute exercise			
hsa-let-7e-5p	↓	Apoptosis, adipogenesis, DNA damage response	Circulation, 30 min cycling[44,45]
hsa-let-7i-5p	↓	Oligodendrocyte specification and differentiation, cytokines and inflammatory response, extracellular vesicles in the crosstalk of cardiac cells	Circulation, 30–60 min cycling[46,47]
hsa-miR-1-5p	↑	PI3K-Akt signalling, Hippo signalling, TGF-β signalling	Skeletal muscle, 60 min cycling[48] Skeletal muscle, 60 min cycling[49] Circulation, 30–240 min running[50–55]
hsa-miR-15a-5p	↑	TGF-β signalling, cell-cycle control, PI3K-Akt signalling	Circulation, 30 min cycling[45,56]
hsa-miR-21-5p	↑	Spinal cord injury, viral acute myocarditis, DNA damage response	Circulation, 30–130 min cycling, or maximal test[45,57,58]
hsa-miR-23a-5p	↓	Platelet-mediated interactions with vascular and circulating cells, interleukin-1-induced activation of NF-kB, brain-derived neurotrophic factor signalling	Skeletal muscle, 60 min cycling[48] Skeletal muscle, 45 min resistance[59]
hsa-miR-23b-5p	↓	Extracellular vesicle mediated signalling, TGF-β signalling, NRF2 signalling	Skeletal muscle, 60 min cycling[48] Circulation, 30 min cycling[45,56]
hsa-miR-29b-5p	↑	Endoderm differentiation, TGF-β signalling, mesodermal commitment	Skeletal muscle, 60 min cycling[49] Circulation, 30 min cycling[44,56]
hsa-miR-29c-5p	↑	Methylene tetrahydrofolate deficiency, one carbon metabolism, haematopoietic stem-cell gene regulation	Circulation, 30 min cycling[44,56]
hsa-miR-30e-5p	↑	Rett syndrome, Oncostatin M signalling, endoderm differentiation	Circulation, 30 min cycling[44,56]
hsa-miR-31-5p	↓	Regulation of microtubule cytoskeleton, DNA damage response, trans-sulphuration, and one carbon metabolism	Skeletal muscle, 60 min cycling[48,49] Circulation, 30 min cycling[45]
hsa-miR-106a-5p	↓	DNA damage response, sudden infant death syndrome susceptibility, TGF-β signalling	Circulation, 30–60 min cycling[46,47]
hsa-miR-126-5p	↑	Endoderm differentiation, ErbB signalling, mesodermal commitment	Circulation, 10–240 min cycling or 240 min running[55,58,60]
	↓		Circulation, 30 min cycling[44,45,47]
hsa-miR-130a-5p	↓	Mesodermal commitment, Rett syndrome, oestrogen signalling	Circulation, 30 min cycling[44,45,47,56]
hsa-miR-133a-5p	↑	Spinal cord injury, advanced glycation end-product signalling, extracellular vesicles in the crosstalk of cardiac cells	Skeletal muscle, 60 min cycling[48] Skeletal muscle & plasma, 45 min resistance[59,60] Circulation, 30–240 min running or walking[50–55,60,61]
hsa-miR-133b-5p	↑	Advanced glycation end-product signalling, androgen receptor signalling, adipocyte regulation	Skeletal muscle, 60 min cycling[48] Circulation, 30–45 min running or walking[54,61,62]
hsa-miR-140-5p	↑	Endochondral ossification, cardiac progenitor differentiation, angiogenesis	Circulation, 30 min cycling[45,56]
hsa-miR-146a-5p	↑	Toll-like receptor signalling, NF-kB signalling, VEGF signalling	Skeletal muscle, 45 min resistance[59] Circulation, 30–240 min running or cycling[46,50,55,57]
hsa-miR-151-5p	↓	ErbB signalling, Notch signalling, p53 network	Circulation, 30–60 min cycling[44–47,56]
hsa-miR-181a-5p	↑	DNA damage response, aryl hydrocarbon receptor, hepatocyte growth factor receptor signalling	Circulation, 30 min cycling[45,62]
hsa-miR-181b-5p	↑	EGFR signalling, somatroph axis, regulation of microtubule cytoskeleton	Circulation, 30 min cycling or walking[45,47,61]
hsa-miR-199a-5p	↓	VEGF signalling, extracellular vesicle-mediated signalling, TGF-β signalling	Circulation, 30 min cycling[44,56]
hsa-miR-206-5p	↑	PI3K-Akt signalling, pentose phosphate metabolism, endochondral ossification	Skeletal muscle, 45 min resistance[59] Circulation, 45–240 min running[51,52,54]
hsa-miR-208b-5p	↑	ErbB signalling, phosphodiesterases in neuronal function, endoderm differentiation	Circulation, 30–240 min running or walking[52,61]
hsa-miR-214-5p	↑	Cell cycle, DNA damage response, Prader–Willi and Angelman syndrome	Circulation, 30 min walking[47,61]

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Table 1 *Continued*

MiRNA	Increase–decrease	Most important biological pathways[a]	Tissue, exercise/nutrition type [Reference][b]
hsa-miR-221-5p	↓	Endochondral ossification, cell cycle, oxidative damage	Circulation, maximal cycling test or 30–60 min cycling[44,46,56,57]
hsa-miR-222-5p	↑	Anti-angiogenesis	Circulation, maximal cycling test[57]
hsa-miR-338-5p	↑	ErbB signalling, leptin signalling, VEGF signalling	Circulation, 30 min cycling[44,45,56]
hsa-miR-363-5p	↑	Histone modifications, ErbB signalling, integrin-mediated cell adhesion	Circulation, 30 min cycling[44,45]
hsa-miR-486-5p	↓	Somatroph axis, insulin-like growth factor-Akt signalling, PI3K-Akt signalling	Circulation, 30–60 min cycling[45,63]
hsa-miR-499-5p	↑	Adipogenesis, apoptosis, Aryl hydrocarbon receptor	Circulation, 240 min running[52,55]
hsa-miR-652-5p	↓	ErbB signalling, leptin signalling, ATM signalling	Circulation, 30–60 min cycling[44,46]
hsa-miR-939-5p	↑	Integrin-mediated cell adhesion, sudden infant death syndrome susceptibility, Wnt signalling	Circulation, 30 min cycling[45,47]
hsa-miR-940-5p	↑	MAPK signalling, STAT3 signalling, NF-kB signalling	Circulation, 30 min cycling[45,47]
hsa-miR-1225-5p	↑	Interferon type 1 signalling, eptin signalling, prolactin signalling	Circulation, 30 min cycling[45,47]
hsa-miR-1238-5p	↑	Endochondral ossification, Histone modification, ErbB signalling	Circulation, 30 min cycling[45,47]
Exercise training			
hsa-miR-1-5p	↑	PI3K-Akt signalling, Hippo signalling, TGF-β signalling	Skeletal muscle, 10 days cycling[48]
	=		Circulation, 10 weeks running[53]
	↓		Skeletal muscle, 12 weeks cycling[49]
			Skeletal muscle, 12 weeks resistance[64]
hsa-miR-29b-5p	↑	Endoderm differentiation, TGF-β signalling, mesodermal commitment	Skeletal muscle, 10 days cycling[48]
	=		Circulation, 10 weeks running[53]
hsa-miR-92a-5p	↑	Cytoplasmic ribosomal proteins, cell cycle, Notch signalling	Circulation, 10 weeks endurance[65]
	↓		Circulation, 12 weeks cycling[46]
hsa-miR-133a-5p	↓	Spinal cord injury, advanced glycation end-product signalling, extracellular vesicles in the crosstalk of cardiac cells	Skeletal muscle, 12 weeks cycling[49]
			Circulation, 12 weeks cycling[46]
	=		Circulation, 10 weeks running[53]
hsa-miR-486-5p	↓	Somatroph axis, insulin-like growth factor-Akt signalling, PI3K-Akt signalling	Circulation, 4 weeks cycling[46,63]
Nutrition			
hsa-miR-15b-5p	↑	TGF-β signalling, cell cycle, nanoparticle effects	Circulation, diet rich in sodium[66]
	↓		Circulation, diet rich in vitamin E[66]
hsa-miR-17-5p	↑	Cell cycle, adipogenesis, DNA damage response	Rectal mucosa, diet high in red meat[67]
			Circulation, olive oil consumption[68]
hsa-miR-18a-5p	↑	Haematopoietic stem-cell gene regulation, pathogenesis of cardiovascular disease, TGF-β signalling	Rectal mucosa, diet high in red meat[67]
			Circulation, polyunsaturated fatty acid intake[69]
hsa-miR-19a-3p	↑	DNA damage response, insulin signalling, cardiac hypertrophic response	Circulation, selenium + Q10 supplement[70]
	↓		PBMC, olive oil intake[71]
hsa-miR-19b-5p	↑	Energy metabolism, insulin signalling, TGF-β signalling	Rectal mucosa, diet high in red meat[67]
			Circulation, polyunsaturated fatty acid intake[69]
hsa-miR-20a-5p	↑	TGF-β signalling, adipogenesis, TGF-β receptor signalling	Rectal mucosa, diet high in red meat[67]
			Circulation, olive oil consumption[68]
hsa-miR-23a-3p	↑	Copper homeostasis, interleukin-6 signalling, apoptosis	Circulation, diet rich in sodium[66]
	↓		Circulation, diet rich in fatty acids, or vitamin E[66]
hsa-miR-92a-5p	↑	DNA damage response, cell cycle, apoptosis	Circulation & stool, vegan diet[72]
			Rectal mucosa, diet high in red meat[67]
	↓		Circulation, zinc deficiency[73]
hsa-miR-125a-5p	↓	ErbB signalling, brain-derived neurotrophic factor signalling, leptin signalling	Circulation, selenium + Q10 supplement[70]
			Circulation, polyunsaturated fatty acid intake[69]

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Table 1 *Continued*

MiRNA	Increase–decrease	Most important biological pathways[a]	Tissue, exercise/nutrition type [Reference][b]
hsa-miR-155-5p	↑	PI3K-Akt signalling, prolactin signalling, ciliary landscape	Circulation, alcohol consumption[74]
	↓		Circulation, zinc deficiency[73]
hsa-miR-192-5p	↑	DNA damage response, oestrogen signalling, focal adhesion	Circulation, polyunsaturated fatty acid intake[69]
	↓		PBMC, olive oil intake[71]
hsa-miR-221-3p	↓	ErbB signalling, DNA damage response, apoptosis	Circulation, selenium + Q10 supplement[70]
			Circulation, polyunsaturated fatty acid intake[69]
hsa-miR-328-3p	↑	TGF-β signalling, EGFR signalling, DNA damage response	Circulation, alcohol consumption[74]
	↓		Circulation, polyunsaturated fatty acid intake[69]
hsa-miR-423-5p	↑	Angiopoeietin-like protein 8 regulation, ErbB signalling, neural crest differentiation	Circulation, diet rich in vitamin E[66]
	↓		Circulation, diet rich in sodium[66]
hsa-miR-769-5p	↑	Leptin signalling, STAT3 signalling, TGF-β signalling	Circulation, polyunsaturated fatty acid intake[69]
	↓		PBMC, olive oil intake[71]
hsa-miR-7977-3p	↑	Membrane trafficking, neuronal system, generic transcription	Circulation, diet rich in sodium[66]
	↓		Circulation, diet rich in vitamin E[66]

Only miRNAs mentioned in ≥2 papers are included in the table.
ATM, ataxia telangiectasia mutated; EGFR, epidermal growth factor receptor; ErbB, erythroblastic leukaemia viral oncogene; MAPK, mitogen-activated protein kinase; NF-kB, nuclear factor kappa B; NRF2, nuclear factor-erythroid factor 2-related factor 2; PBMC, peripheral blood mononuclear cells; PI3K-Akt, phosphoinositide 3 kinase—protein kinase B; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; Wnt, Wingless and Int-1.
[a]Three most significantly enriched non-cancer biological pathways from Wiki pathways in miRPathDB v2.0 (http://mpd.bioinf.uni-sb.de).
[b]For simplification, estimates of exercise time were made (e.g. marathon: 240 min running).

Summary and knowledge gaps

The acute and chronic effects of exercise on epigenetic systems are heterogeneous and affected by exercise type, mode, duration, and intensity as well as tissue type, age, sex, population, and disease state. Acute and chronic exercise predominantly induce DNA hypomethylation of key genes in skeletal muscle, leading to increased expression.[85] No global trend can be observed for histone modifications or miRNA expression, but individual changes usually lead to increased expression of exercise-related genes. The effects of chronic exercise on miRNA expression in circulating blood differ from those in skeletal muscle, although the interrelation remains to be investigated.

Most of the studies on epigenetic modulation through exercise have investigated effects of endurance exercise, with less evidence for resistance training. Furthermore, potential sex differences have largely been ignored[86] and most studies included males only. Overall, validating the causal relationship between exercise-induced epigenetic modifications and physiological adaptations (i.e. beneficial metabolic benefits) in health and disease represents a major future challenge. Noteworthy, however, recent data highlighted a functional link between epigenetic rewiring and risk of CVD following exercise training in humans[82] but more evidence is required. Epigenetic markers are indeed vulnerable to confounding and reverse causation. In this setting, Framework of Mendelian randomization—a process which interrogates the causal relationships between exposure, epigenetic marks, and outcome—could help to establish meaningful hierarchies, thus discriminate between epigenetic phenomena and epi-phenomena.[87] Large epigenomic studies over the next years will help decipher the complex link between epigenetics and CVD.[4] Molecular pathways explaining *how* exercise influence epigenetic mechanisms remain understudied, potential mechanisms are outlined in *Figure 2* and reviewed extensively elsewhere.[24,88,89]

Epigenetic modulation in primary cardiovascular disease prevention: nutritional effects

Beyond exercise, epigenetic mechanisms involved in CVD risk are likely modified by nutrition, occurring not only in adulthood but already start in infancy. Links between diet-induced epigenetic modulation and improvements in CV function have been mainly demonstrated in animal studies, similar to exercise.[90–92] In humans, indirect evidence of benefits on CV prevention of nutritional epigenetic changes includes lower lipid levels and improved vascular function.[30,93,94] A direct influence of diet-induced epigenetic modifications on primary CV prevention in human subjects remains to be established.

Interaction between epigenetics and nutrition during early life

Early evidence showed that nutrition during infancy and even *in utero* influence the occurrence of CVD in adulthood. The relationship between birth size and weight and long-term CVD was first established in the 1990s: male offspring with a small head circumference had an increased CVD risk until the age of 65 years.[95] CVD risk was also

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related to postnatal growth: in males, the highest risk was in babies who were below average weight at birth and still small at 1 year of age, whereas in women the highest risk was in babies born with below average body weight but above average weight at 1 year of age.[95] These findings are among the pillars of the 'Developmental Origins of Health and Disease' concept. Later studies since revealed that prenatal malnutrition (during famine) was associated with differential methylation of genes involved in growth, metabolic homeostasis, inflammation, and longevity, key processes underlying the pathogenesis of cardiometabolic disease.[96] Current research has shifted the attention to the link between maternal overnutrition during pregnancy and the increased risk of obesity in offspring, and has shown that maternal overnutrition changes global DNA methylation patterns.[97] Specific patterns of foetal DNA methylation, histone modification and non-coding RNA expression have been linked to maternal nutritional and physical activity behavior.[98] Epigenetic inheritance via the paternal line is also gaining increasing attention.[99] Others have reviewed animal studies on nutrition and the epigenome in extensive detail.[6,100]

Nutritional influence on cardiovascular disease–related epigenetic changes

Several genome-wide studies identified correlations between dietary patterns and the epigenetic signature,[101,102] whereas other studies found associations between epigenetic marks and CVD (reviewed in van der Harst *et al.*[3]). Few studies, however, have identified dietary patterns which lead to epigenetic changes with relevance for CVD.

(1) *DNA methylation*: In 9724 participants from five population-based study on leucocyte DNA methylation, nutritional quality scores (Mediterranean-style diet score and the Alternative Healthy Eating Index score) were associated with either hypo- or hypermethylation at 30 CpG positions, out of which 12 were associated with all-cause mortality.[103] Six CpG positions pointed to mechanistic links with CVD risk and metabolic health, which included functional measures of body weight, triglycerides, high-density lipoprotein cholesterol concentrations, and T2D. Overall, diet was associated with epigenetic modifications related to risk factors of CVD, but a direct link with CVD occurrence was not established.[103] Specific targets of nutrition-related DNA methylation affecting CVD risk factors include *CPT1A*, encoding carnitine palmitoyltransferase-1A, and *MTHFR* (encoding methylenetetrahydrofolate reductase). Methylation of *CPT1A* was strongly associated with fat and carbohydrate intake as well as metabolic phenotype (including weight, lipids, and glucose).[104] Regarding *MTHFR*, supplementation with its cofactor riboflavin led to specific changes in DNA methylation of *NOS3*, which is involved in blood pressure regulation.[105] Specific dietary fatty acids are known to influence epigenetic mechanisms, with DNA methylation the most widely studied.[106] However, no CVD-specific effects have been investigated.

(2) *Histone modification*: Similarly, several dietary components are able to inhibit HDACs, such as phytochemicals (e.g. flavonols, quinones) and stilbene, which inhibit specific HDAC classes to cause more acetylated histones.[107] Short-chain fatty acids, which are created in large amounts by gut bacteria, are also known to inhibit HDACs (see below). miRNAs are promising targets of dietary intervention as well.

(3) *Non-coding RNA expression*: Dietary interventions are hypothesized to influence plasma miRNA expression via the gut–liver axis[108] as well as the renin–angiotensin system (i.e. to modulate blood pressure[108]). Key changes in microRNA expression related to nutritional interventions and dietary habits are summarized in *Table 1*.

Role of the gut microbiome

The gut microbiome could play a role as a mediator between diet and host epigenome. Bacterial metabolites, such as short-chain fatty acids, influence the host epigenome in breast-fed and formula-fed infants.[109] This hypothesis has been transferred to adults: dietary patterns (such as fibre, protein, and fat content, and the source of the nutrient), modify the composition of the gut microbiota, which influences the metabolites available for the host. Bacterial metabolites can either work as co-factors for epigenetic reactions, among them methylation reactions of both DNA and histones, or inhibit enzymatic reactions, such as short-chain fatty acids inhibiting HDACs.[110] Dietary regulation of circulating miRNAs may also be controlled via gut–liver axis,[108] with multi-organ crosstalk linked via nutrient filtering, which influences synthesis of specific molecules such as miRNAs in hepatocytes, and liver–gut communication by bile salt and antibody secretion. However, evidence for specific targets is scarce.

Summary and knowledge gaps

Taken together, evidence indicates that dietary factors in combination with the gut microbiota influence epigenetic mechanisms. Some links to metabolic risk factors involved in CVD have been shown such as cholesterol, blood glucose, and body mass; however, a direct influence on CVD remains poorly established. There is also limited information on how these changes are linked to CVD at the molecular level, meaning specific dietary recommendations to influence epigenetic changes are not yet available. In addition, combining diet and exercise interventions induces superior reductions in CVD risk factors compared with diet or physical activity alone,[111–113] which could occur via complex interactions of epigenetic modifications.[114] Future research should determine the isolated and combined effect of dietary and exercise interventions on epigenetic modifications relevant for CVD risk.

Novel epigenetic therapies in primary cardiovascular disease prevention

Besides exercise and nutrition to enhance epigenetic modifications for primary CVD prevention, reversible epigenetic signals acquired during the life course are also amenable to nutraceutical and pharmacological intervention.[4] Nutraceutical polyphenols such as resveratrol, curcumin, or cocoa polyphenols may interfere with genome-wide epigenetic modifications in humans. As DNA hypomethylation in many cells (e.g. cardiac, endothelial, immune; although not always c.f. skeletal muscle) is generally associated with increased cardiovascular risk, DNMTs offer a potential therapeutic target. Nutraceutical DNMT inhibitors include resveratrol and cocoa polyphenols, which may offer primary prophylaxis against CVD (*Table 2*). The evidence remains largely indirect, i.e. cocoa polyphenols inhibit

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Table 2 Epigenetic therapies

Component	Mechanism of action	Physiological effect	Clinical effect—primary prevention	Clinical effect—secondary prevention
Nutraceuticals				
Cocoa polyphenols	DNMT inhibition	↑ endothelial function (rodents & humans)[115]	↓ blood pressure, modify lipid profile[115]	
Curcumin	Histone acetyltransferase inhibition	↓ inflammation, ↓ LV hypertrophy, ↓ atherosclerotic lesions, ↑ endothelial function, ↑ mitochondrial function (rodents)[116]	Modify lipid profile[116]	
Resveratrol	HDAC modulation, Sirtuin deacetylase activation, DNMT inhibition	↓ blood pressure, ↓ pulmonary hypertension, ↓ LV hypertrophy (rodents) ↑ LV function (rodents), ↑ endothelial function (rodents & humans),[117] ↓ mitochondrial oxidative stress[118]	↓ blood pressure,[117] modify lipid profile[117,119]	↑ LV diastolic function in patients with CAD[119]
Existing pharmaceuticals with epigenetic effects				
Statins	HDAC inhibition	Renoprotection (rodents)[120]	↓ all-cause death and CV events in primary prevention[1]	↓ all-cause death and CV events in secondary prevention[1]
Metformin	Sirtuin deacetylase activation	↓ LV hypertrophy (rodents), ↑ LV function (rodents)[121,122]	↓ all-cause death and CV events in diabetic patients[1]	↓ all-cause death and CV events in diabetic patients with CAD[1]
SGLT2 inhibitors	Sirtuin deacetylase activation, HDAC inhibition	Modified cardiac energy metabolism, ↑ autophagy, ↑ mitochondrial function (rodents)[123,124]	↓ all-cause death and CV events in patients with diabetes[125]	↓ all-cause death and CV events in patients with CAD or HF[126]
Pharmaceuticals designed for epigenetic modulation				
5-Azacytidine	DNMT inhibition	↑ endothelial function, ↓ atherosclerotic lesions, ↓ inflammation[19] (*in vitro*)		
Vorinostat	HDAC inhibition	↓ reperfusion injury, ↑ autophagy (rodents)[127]		
Sodium butyrate	HDAC inhibition	↑ lipolysis, ↑ mitochondrial function (rodents)[128]		
BET inhibitors	Modulate protein–histone interaction	↓ atherosclerosis, ↓ angiogenesis, ↓ intimal hyperplasia, ↓ LV hypertrophy[129]	No reduction of CV events in patients with diabetes[130]	↓ CV events in patients with CAD[131]

BET, bromodomain and extra-terminal motif; CAD, coronary artery disease; CV, cardiovascular; DNMT, DNA methyltransferase; HDAC, histone deacetylase; HF, heart failure; LV, left ventricular; SGLT2, sodium glucose transporter 2.

the expression of DNMTs in circulating inflammatory cells,[132] and intake of cocoa polyphenols is associated with a reduced cardiovascular risk.[115] Editing-specific chromatin marks by epigenetic drugs represent a promising approach to reset maladaptive epigenetic and transcriptional signatures (*Table 2*). These epigenetic drugs are either repurposed existing pharmaceuticals or newly developed to target a specific epigenetic modification.

Epigenetic drugs have shown potential to prevent vascular inflammation, endothelial dysfunction, and atherosclerosis through diverse molecular mechanisms such as reduced autophagy, modified cardiac energy metabolism, and improved mitochondrial function (*Table 2*). Various epigenetic drugs are approved by the United States Food and Drugs Administration and are currently being tested in clinical trials.[4,133] One of these, using the Bromodomain and Extra-Terminal motif (BET) inhibitor apabetalone in CV prevention, has been published.[130] BET inhibitors represent an emerging class of drugs that prevent protein–protein interaction between BET proteins, acetylated histones, and transcription factors. In rodents, BET inhibition attenuated atherosclerosis and intimal hyperplasia by suppressing vascular inflammation as well as by lipid-lowering effects.[129,134] Apabetalone was also shown to decrease systemic inflammation in humans.[135] However, the BETonMACE trial (Effect of RVX000222 on Time to Major Adverse CV Events in High-Risk Type 2 Diabetes Mellitus Subjects with CAD) did not demonstrate a reduction in CV events among diabetic patients taking apabetalone in primary prevention.[130] Interestingly, the drug was associated with a rather striking effect on HF hospitalizations (first hospitalization: 29 vs. 48, $P = 0.03$; first and recurrent hospitalizations: 35 vs. 70). A recent subanalysis of the BETonMACE trial suggests that apabetalone may be particularly effective in patients with diabetes and

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chronic kidney disease: patients randomized to apabetalone experienced fewer CV events and HF-related hospitalizations.[136] More studies are needed to establish the role of currently marketed, repurposed, or newly developed epigenetic drugs in the setting of primary prevention in CVD.

Part 3: epigenetics in secondary prevention of cardiovascular disease

Role of exercise after cardiovascular disease

Exercise-based multidisciplinary cardiac rehabilitation leads to significant reductions in cardiovascular mortality and hospitalizations in secondary prevention of CVD (i.e. in CAD or HF[137,138]). These effects are, at least in part, explained by improvements in CVD risk factors and physical fitness that likely involve epigenetic regulation (as discussed earlier). For example, in patients with established CVD different patterns of exercise-induced miRNA expression are noted, with miRNA expression patterns able to distinguish CAD patients from healthy counterparts.[139] As a result, it is relevant to address the impact of different exercise modalities on these epigenetic markers and their relation to current guidelines on exercise-based cardiac rehabilitation. Patients with CVD are recommended to engage in aerobic exercise at a frequency of at least three (but preferably more) days per week, at moderate or moderate-to-high intensity, with additional resistance exercises (twice per week).[140] Numerous studies have examined the impact of chronic exercise training on epigenetic mechanisms in patients with CVD within these recommended guidelines (*Table 1*).

The interindividual variability in response to exercise training response could be caused by differences in the epigenetic response to exercise. A failure to increase VO_{2peak} after exercise training is seen in up to 33% of patients with CVD, despite adequate compliance to the exercise protocol and the underlying mechanism(s) remains unclear.[2] However, several miRNAs have been identified as predictors of the training response in patients with HF,[141,142] which may be useful in identifying 'low responders' to training. Identifying 'low responders' would provide the possibility of early individualized management in high-risk patients with a poor exercise response. miRNAs have also been able to differentiate patient subpopulations, such as between individuals with HF and CAD, or between HF with preserved vs. reduced ejection fraction (HFpEF vs. HFrEF). For example, cardiac rehabilitation up-regulated the miR-92 family in CAD patients,[65] which can differentiate between stable and vulnerable CAD.[143] In patients with T2D, both moderate endurance and resistance training independently up-regulated circulating miR-451a,[144] while in HF patients, endurance exercise decreased miR-1 levels in skeletal muscle and miR-146 in blood.[145,146] Subsequent target analysis revealed a significant relation between changes in miR-1, follistatin expression, and VO_{2peak}.[145] Divergent findings in miRNA expression between circulating blood and skeletal muscle have been reported and may be explained by secretion of miRNAs from muscle into circulation: high-intensity treadmill running in mice increased circulating but decreased muscular levels of miR-133.[50] In patients with HF, *ASC* hypermethylation from PBMCs was associated with gene silencing, as confirmed by lower ASC mRNA and IL-1β plasma levels after walking-based exercise.[79] In another targeted approach, the effect of a 12-week high-intensity interval training on DNA methylation of $p66^{shc}$ gene, a key regulator of oxidative stress, was assessed in older patients with obesity and additional cardiovascular risk.[35] Exercise-induced hypermethylation of $p66^{shc}$ gene promotor was accompanied by a reduction in its gene expression parallel to decreased systemic oxidative stress but increased VO_{2peak} and muscle mass, as well improved metabolic health related to lower body mass and LDL concentrations.[35] Another group found >17 000 CpG sites altered in adipose tissue after 6 months of exercise training, mapped to gene regions involved in obesity and Type 2 diabetes.[147] Importantly, the acute response to exercise is modulated by chronic exercise training: the lower miR-191 levels observed after acute exercise in patients with HF was blunted following a training programme.[146] Overall, the impact of different exercise modalities (e.g. intensity, duration/volume, frequency, and type) on epigenetic modifications remain poorly studied in patients with established CVD, highlighting a future area with potential to optimize exercise prescription.

Role of nutrition after cardiovascular disease

Optimal nutrition is a key strategy to prevent secondary cardiovascular events, as detailed elsewhere,[148] although the mechanisms of action (including epigenetic modifications) remain poorly defined. Current dietary recommendations are mainly based on population-level primary prevention studies or surrogate outcomes such as lipid levels and blood pressure.[1] Few studies have robustly examined the effect of nutritional interventions on clinical outcomes in patients with established CVD.[149] The largest randomized trial to date demonstrated that a Mediterranean-style dietary pattern was associated with lower all-cause and cardiovascular mortality among individuals with CVD,[150] while more indirect evidence derived from diet scores reported a similar trend.[151,152] Furthermore, indices of cardiac diastolic function as well as carotid intima media thickness were improved with a Mediterranean diet.[153,154] Consistent with primary prevention, therefore, a causal role of a high-quality diet in secondary CVD prevention is likely, but firm evidence remains scarce.

In terms of epigenetic modifications following dietary interventions in established CVD, little data are available. The CORDIOPREV study assessed epigenetic modifications as a direct consequence of nutritional intervention (Mediterranean or low-fat diet) in patients with established CVD and endothelial dysfunction.[155] Patients classified as having severe endothelial dysfunction had altered miRNA expression levels, differing among Mediterranean or low-fat diet. Of interest, lower levels of miR181c, let-7e, and miR-939, and higher levels of miR-188 and miR-25 were observed in the Mediterranean diet group. These miRNAs were associated with reduced ROS production, reduced NF-κB activation, increased cell proliferation, reduced endothelial cell senescence, and inhibition of pro-inflammatory pathways, and linked to improved endothelial function in CHD patients. To our knowledge, there is no available evidence concerning DNA methylation or histone modification following dietary interventions in patients with established CVD. In individuals

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with obesity, energy-restricted diets induce altered DNA methylation in high responders (losing >3% body fat) compared with low responders.[156] In summary, dietary interventions are associated with improved secondary prevention of CVD and this has been linked to evidence of altered miRNA expression. Nevertheless, more randomized control studies implementing specific nutritional interventions and determining epigenetic modifications in patients with established CVD are required.

Novel epigenetic therapies in secondary cardiovascular disease prevention

Experimental evidence indicates the potential of epigenetic therapies in established CVD (*Table 2*). Several HDAC inhibitors prevented pathological cardiac remodelling in experimental models of myocardial infarction or pressure overload.[157] HDAC inhibitors consistently improved cardiac function in rodent HFrEF models.[157,158] Vorinostat blunts pro-inflammatory cytokines in hypertensive cardiomyopathy, thus preventing perivascular fibrosis, cardiac hypertrophy, and diastolic dysfunction.[159] Moreover, this compound was recently found to ameliorate ventricular passive stiffness in experimental models of HFpEF.[160] Most epigenetic drugs under investigation, however, act genome-wide and may not be fully selective leading to undesired side effects. With numerous gene-specific causal epigenetic modifications being discovered,[4] precision medicine by epigenetic editing (the targeted modification of a specific epigenetic mark), may pose new solutions in cardiovascular medicine.[157,161] Already, experimental data suggested that renal fibrosis can be treated by silencing *RASAL1* or *Klotho* through epigenetic editing.[162]

Translational studies in humans with CVD are emerging but have used surrogate outcomes. Treatment with resveratrol in patients with stable CAD improved LV diastolic function in a double-blind, placebo-controlled clinical trial.[119] In patients with ischaemic heart disease, treatment with resveratrol decreased B-type natriuretic peptide, suggesting a favourable impact on left ventricular remodelling and function.[163] The ongoing RES-HF randomized trial (NCT01914081) will provide information on the efficacy of resveratrol on quality of life in HF patients. The BET inhibitor apabetalone showed that improvements in cholesterol levels were associated with a reduction in the incidence of major adverse cardiac events in patients with CVD.[131] Future trials will help to define the potential clinical application of these epigenetic drugs among patients with established CVD. Besides chromatin modifying agents, a growing number of miRNA-based therapies are reaching clinical trials.[133] Phases I and II clinical trials are investigating the therapeutic modulation of several microRNAs (e.g. miR-29, miR-21, miR-155, and miR-33) for the treatment of extracellular matrix remodelling, cardiac fibrosis, inflammation, and cardiometabolic disorders.[164] A first-in-human Phase Ib randomized, double-blind, placebo-controlled study showed that miR-132 inhibition was safe and associated with a dose-dependent, sustained miR-132 reduction in plasma.[165] CDR132L treatment reduced natriuretic peptides, narrowed the QRS complex, and reduced biomarkers related to cardiac fibrosis. Although this study was limited by small numbers, its findings justify further clinical studies using miR-132 inhibition and are encouraging for other non-coding RNA therapies for secondary prevention of CVD.

Part 4: future directions and conclusions

We have summarized current knowledge on the role of epigenetics in the primary and secondary prevention of CVD, with a focus on the impact of exercise and nutrition. The following areas could be explored to improve translation towards clinical use:

(1) *Human randomized trials*: A greater number of clinical randomized trials with large sample sizes that directly address whether epigenetic modifications occur as a consequence of interventions for primary and secondary CVD prevention. Further evidence is required to link epigenetic changes directly to improved cardiometabolic health. This will identify what epigenetic modifications are most closely linked to CVD prevention.

(2) *Mechanisms of exercise and nutrition*: There is a lack of studies focusing on epigenetic mechanisms underlying exercise or nutritional interventions in patients with established CVD. This is particularly pertinent for secondary CVD prevention.

(3) *Optimal doses of exercise and/or nutrition*: Determining the optimal exercise regime or dietary recommendation for maximizing epigenetic modifications linked to CVD prevention are unclear. This information would help optimize rehabilitation prescription guidelines in CVD, where adherence is often challenging.

(4) *Precision epigenetic therapies*: More focus on developing precision epigenetic therapies that benefit CVD prevention. Tissue- or cell-specific therapies may overcome off-target toxic effects. Attention on developing the most effective epigenetic therapies (using currently marketed, repurposed, or newly developed drugs) will accelerate identification of those providing the greatest benefits to CVD prevention.

In conclusion, epigenetic modifications appear to play an important role in the pathophysiology of CVD. Evidence indicates exercise and nutrition are important stimuli that can be used to promote beneficial epigenetic modifications in health, but little evidence is currently available to strongly support a direct role in the primary, and especially secondary, prevention of CVD. However, recent developments of novel epigenetic therapeutics could hold great promise for CVD prevention in the future. As such, improved understanding of epigenetic modifications via exercise or nutrition could result in more targeted and novel epigenetic treatments for preventing CVD in both the primary and secondary setting.

Authors' contributions

A.B.G., C.H.D., D.H., R.F.E.P., M.S., and T.S.B. contributed to the conception and design of the study. All authors participated in writing of the study and substantively revised it. All authors approved the submitted version and have agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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