The "brain-heart-gut" axis and novel mechanisms of future cardiovascular disease

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Abstract

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in the globe. Both established cardiovascular disease (eCVD) and future CVD (fCVD) need to further explore the mechanisms. This article briefly introduces current major studies on axis and CVD, which were published in cardiovascular journals and non-cardiovascular journals (Table 1 & Table 2), and brings up and discusses the new origins of fCVD linking to major risk factors in early life due to unhealthy "environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi] lifestyle referred as to a "Golden Hoop Curse", and the "brain-heart-gut" axis—a fresh theory on novel mechanisms of fCVD (Figure 1 & Figure 2), which are mediated by E(e)SEEDi lifestyle and microbiome. As a new theory, the "brain-heart-gut" axis will help us to earlier and better prevent and control both eCVD and fCVD with healthy E(e)SEEDi lifestyle.

REVIEW

The "brain-heart-gut" axis and novel mechanisms of future cardiovascular disease

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Running Title: "Brain-Heart-Gut" Axis & Future CVD

ABSTRACT

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in the globe. Both established cardiovascular disease (eCVD) and future CVD (fCVD) need to further explore the mechanisms. This article briefly introduces current major studies on axis and CVD, which were published in cardiovascular

journals and non-cardiovascular journals (Table 1 & Table 2), and brings up and discusses the new origins of fCVD linking to major risk factors in early life due to unhealthy "environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi] lifestyle referred as to a "Golden Hoop Curse", and the "brain-heart-gut" axis—a fresh theory on novel mechanisms of fCVD (Figure 1 & Figure 2), which are mediated by E(e)SEEDi lifestyle and microbiome. As a new theory, the "brain-heart-gut" axis will help us to earlier and better prevent and control both eCVD and fCVD with healthy E(e)SEEDi lifestyle.

KEYWORDS:

"brain-heart-gut" axis, cardiovascular disease, COVID-19, E(e)SEEDi lifestyle, mechanism

INTRODUCTION

As we all known, cardiovascular disease (CVD) is still a leading cause of death in the globe. Currently, it is more and more common due to aging and unhealthy lifestyle. With the rapid development of biomedical technology, novel diagnostic and research tools, new insights into mechanisms and therapeutic agents, and fresh evaluation and preventive methods (e.g., a magic "polypills", that is, "environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi]) (1) make a big change in its mortality and outcomes.

As a front-line clinical doctor, the author has made giant efforts to trace the origin and mechanisms of future CVD (fCVD). Luckily, five core elements, "environment-sleep-emotion-exercise-diet" [E(e)SEED], have been discovered and highly contribute to human cardiovascular health. Based on this discovery, a novel classification of clinical risk factors based on unhealthy E(e)SEED intervention [E(e)SEEDi] lifestyle has been developed. In fact, many major risk factors related to unhealthy E(e)SEEDi lifestyle could result in fCVD.

For example, as one's internal environment, on the one hand, a genetic or family history is an important risk factor of fCVD; On the other hand, as major non-communicable diseases, both established CVD (eCVD) and fCVD highly link to acute or chronic infection, which leads to abnormal status in one's internal environment. So far, the COVID-19 pandemics are still continuing due to the Omicron variant of SARS-CoV-2. A recent study found that COVID-19 is a high risk factor of adverse cardiovascular outcomes (2). It can be said that SARS-CoV-2 and its variants are new origins of both eCVD and fCVD since there are more than 522.783 million confirmed cases and over 6.27 million deaths in the globe (May 23, 2022) according to the report of the World Health Organization.

CURRENT MAJOR STUDIES ON AXIS AND CVD

Since *Laragh JH* reviewed the renin-aldosterone axis in cardiovascular system in the *New England Journal of Medicine* in 1985 (3), Bayes-Genis A, et al. reviewed the insulin-like growth factor axis on atherosclerosis and restenosis in 2000 (4), and the cardiorenal axis (Bush EW and McKinsey TA, 2010) (5) and the RAGE axis (6) (Yan SF, et al. 2010) on cardiovascular mechanisms were also reviewed. So far, there were many studies and some reviews on axis and CVD. It's really a hot topic in life science and biomedicine. Here are summarized tables on major studies of axis and eCVD or fCVD in cardiovascular journals (7-24) and non-cardiovascular journals (25-42) (Table 1 & Table 2). However, exception of several reviews on "Brain-Gut-Bone Marrow Axis" (Santisteban MM, et al. 2016) (43) and "Heart-Brain Axis" (Tahsili-Fahadan P & Geocadin RG, 2017) (44), which involved in cardiovascular risk, the mechanisms and treatment, most of these studies, and reviews or comments just only involved in targeting these "branch axis" of eCVD (atherosclerosis, hypertension, and others), for example, the CCL2-CCR2 axis (Georgakis MK, et al. 2022; Crea F, 2022) (45, 46). Although there was a new theory on the artery-brain circuit (ABC) of atherosclerosis (Mohanta SK, et al. 202) (47), little is known about the novel "total axis" on the brain, heart, and the gut.

"BRAIN-HEART-GUT" AXIS AND FUTURE CVD

As we know, some risk factors associated with unhealthy E(e)SEEDi lifestyle play a vital role in the development of fCVD. Due to the role of parental genetic disposition, epigenetic modifications, inflammatory cytokines, DNA methylation or mutation, endothelial dysfunction, arteriosclerosis, chronic fetal hypoxia

(48), and gut microbiota (49), its mechanism may link to a novel theory of the "brain-heart-gut" axis (Figure 1). Since there is "prevention first, combination of prevention and treatment", tracing the origin and elaborating the mechanism of fCVD is very valuable and meaningful. And the control and prevention of fCVD highly links to less major adverse cardio-cerebrovascular events (MACCE), healthy aging, and longevity.

Major risk factors associated with early unhealthy E(e)SEEDi lifestyle play a pivotal role in the development of fCVD by disruption of the "brain-heart-gut" axis. And early unhealthy E(e)SEEDi lifestyle is like a "Golden Hoop Curse", it may restrict and control one's physical and mental health. Like the "Tang Monk", each of us should manage the "Golden Hoop Curse" with healthy E(e)SEEDi lifestyle by ourselves, make it relax and maintain the health of brain, heart, and gut, and control and prevent hypertension, ischemic heart disease or coronary artery disease (stable or unstable angina, acute myocardial infarction), arrhythmia (atrial fibrillation, premature beat or tachycardia), congenital heart disease, infectious disease due to reduction of human immunity, cardiac injury, cardiomyopathy, heart failure, type 2 diabetes, stroke, sudden cardiac death, mental disease (anxiety or depression, schizophrenia), neurodegenerative diseases (Parkinson's disease, cognitive aging or declines, dementia, and Alzheimer's disease), and cancer.

MECHANISMS MEDIATED BY E(e)SEEDi LIFESTYLE AND MICROBIOME

Mechanisms mediated by environment and microbiome

Currently, environment is still the No. 1 element of health. It highly associates with one's cardiovascular health and CVD, and other mNCDs, such as diabetes and cancer. First, socioeconomic environment or vulnerabilities (50, 51), which includes ethnic differences, educational attainment, employment, occupational class, income, and personal relationships may affect individual health. For example, as a proxy phenotype, there is an obvious link between educational attainment and cognitive function (52-54). Second, natural (neighborhoods or built) environment and air quality (55) are important factors of cardiocerebrovascular health. "Water-Air-Radiation-Sound (WARS)" pollutions (e.g., e-noise) (56-58) greatly increase the hazard of fCVD (acute myocardial infarction, stroke).

Third, internal environment with a genetic or family history, new or traditional modifiable risk factors (59), is a critical variable, such as maternal adverse pregnancy outcomes (preterm birth, low birth weight) (60, 61) as well as acute or chronic infection, e.g., COVID-19 (2), abnormal blood pressure, diabetes, dyslipidemia, hyperuricemia, and obesity. A recent study found that a genetic factor (ABO genotype) can alter the composition of the gut microbiota (62), and this is a strong evidence for internal environment associated with human health. Herein, the gut microbiota[4] may play a crucial role in the development and progression of eCVD and fCVD. Sometimes positive intracellular environmental stress in the cardiac cells can help the heart repair (63). However, changes in the concentrations of intracellular sodium, calcium, potassium, and ATP/ADP may link to arrhythmias (64, 65). In addition, in a murine inflammation resolution model of atherosclerotic plaque, reshaping of the gut microbiome has a therapeutic effect (66).

Several known risk factors such as age, genetic variants, Y chromosome (ChrY) structural aberrations and environmental stressors, link to mosaic loss of ChrY (LOY) in human somatic cells (67), and as the most commonly acquired mutation, it is associated with mNCDs including cancer, Alzheimer's disease, and fCVD. Maternal risk factors in pregnancy (68) such as advanced age and a suboptimal in utero environment (fetal growth restriction, preterm birth, and/or preeclampsia) link to an increased risk of fCVD in adulthood for both the mother and offspring. Sudden cardiac death in younger patients is associated with isolated congenital coronary artery anomalies (69). Acute coronary syndrome have distinct serum metabolome and gut microbial profiling, which link to an increased risk of coronary artery disease (CAD) (70).

Mechanisms mediated by sleep and microbiome

A clinical study found that night shift exposure may increase incident atrial fibrillation and the risk of CAD (71). Self-reported sleep quality (insufficient sleep or loss of sleep) is associated with cardiometabolic diseases, such as obesity and diabetes, CVD, and neurological and cognitive impairments, due to shifts in gut microbiome composition (72, 73). Disrupted sleep may lead to cardiovascular pathology since there are

associations between sleep fragmentation, mean arterial pressure, and the gut/fecal metabolome (74). And the acute circadian rhythm disturbance caused by sleep-wake shifts affect the human gut microbiota (75), especially the functional profiles of gut microbes and interactions among them. Thus, the gut microbiome is a potential target for reducing the impact of chronic insomnia on cardiometabolic health (76). Due to a causal relationship between the gut microbiome and hypertension (77), the former may be a target for treatment of OSA-related and other typical hypertension.

Mechanisms mediated by emotion and microbiome

Since psychological or emotional stress links to cardiovascular health (78), current available literatures have showed the health benefits of meditation (79-81), which is like "keeping the pubic region (Dantian)". In fact, mindfulness-based meditation may reduce not only cardiovascular risk factors but also both eCVD (atherosclerosis, hypertension, and hear failure) (82) and fCVD by lowering psychological stress, improvement of psychological health and human gut microbiota (83). More basic studies found that there are some associations (84-86) among animal behaviors and emotional phenotypes (e.g., anxiety-like behavior), the gut mycobiota, and host-protective immunity, since the gut microbiota can regulate central activity by different G proteins and changes in cellular calcium levels (87). In addition, a new study showed that high chronic social and psychosocial stressors link to immune aging and poor health (88) due to changes in naïve and terminally differentiated T cells and the ratio of $CD4^+$:$CD8^+$.

Mechanisms mediated by exercise and microbiome

At the same time, positive and effective physical activity or exercise in children and adolescents (89) can prevent fCVD in adult. Animal experiments showed that physical activity or exercise results in a persistent decrease in systolic blood pressure in the spontaneously hypertensive rats (SHRs) since it can reshape gut microbiota and improve impaired gut-brain axis (90). As a non-medical treatment, when combination of vitamin C intake, it can modify the composition of gut microflora and improve the inflammatory state, therefore, alleviate the blood pressure in the SHRs (91). The gut microbiome also mediates the protective effects of moderate-intensity exercise on cardiac function in myocardial infarction mice by its metabolites 3-Hydroxyphenylacetic acid (3-HPA) and 4-Hydroxybenzoic acid (4-HBA) (92, 93).

There are the associations between the gut microbiota and cardiometabolic phenotypes, however, short-term endurance exercise has little effect on gut microbiota in elderly individuals (94). Regular physical activity or endurance exercise can reduce a Western diet -induced atherosclerosis through the amelioration of obesity, inflammation, and chemotaxis signaling, which are modulated by the microbiota and its metabolites (95). Particularly, the molecular and cellular mechanisms on the metabolic benefits of physical activity has been accurately disclosed in a recent study since an exercise-inducible metabolite can control food intake and prevent cardiometabolic diseases (96), such as obesity, T2D and fCVD.

Mechanisms mediated by diet and microbiome

As we known, medicine and food are homology. The composition of the gut microbiota following early-life antibiotic exposure affects host health and longevity (97) due to an impaired immunity, increased insulin resistance and inflammaging in later life. But metformin increases lifespan by altering the gut microbiota and methionine metabolism (98). As a part of diet, a high-throughput screening platform found that host-microbe-drug-nutrient interactions improve health and longevity through targeted the gut microbiome therapies (99). For example, the interactions between the gut microbiome and vitamin D are associated with better human health (100). In fact, microbiome interactions can shape host fitness (such as development, fecundity, and lifespan) (101).

There are also interactions between the gut and the brain in inflammation-associated diseases and their molecular and cellular mechanisms link to sensing and communicating the levels of diet- and microbiome-derived essential amino acids (EAAs) (102, 103). High dietary fiber intake may improve maternal obesity-induced cognitive and social dysfunctions (104) since microbiome associations with some traits (105), such as age, dietary intake, and the specific gut microbiome can affect social behaviours through discrete neuronal

circuits that mediate stress responses in the brain (106). These studies further confirm the novel "brain-heart-gut" axis theory. Herein, healthy E(e)SEEDi lifestyle can be adopted for the secondary prevention of eCVD and the primary prevention of fCVD.

UNHEALTHY LIFESTYLE, GUT MICROBIOME, AND FCVD

Clinical studies showed that the gut microbiota play a pivotal role in human vascular physiology, and they may be potential therapeutic and preventive targets for CVD, such as atherosclerosis (107), heart failure with preserved ejection fraction (HFpEF) (108). Morevover, gut-related metabolites, L-carnitine, acetyl-L-carnitine, and Trimethylamine N-oxide (TMAO), show associations with adverse short-term and long-term outcomes in acute HF (109), respectively. And the gut microbiome is a vital mediator of age-related arterial endothelial dysfunction, arterial stiffening, vascular oxidative stress and inflammation (110), therefore may be a promising therapeutic target for preserving arterial function with ageing and reducing the risk of CVD.

As we known, the gut microbiome is associated with human diseases. A recent study found that lifestyle (socioeconomic factors, genetics, current exposome, diet and medication), particular early life shape the microbiome in health and disease due to significant association with microbiome function and composition (111). Risk factors related to unhealthy lifestyle may disrupt the "brain-heart-gut" axis by negative regulations of the gut microbiome and induce fCVD, but a healthy lifestyle intervention (brain and physical activities and diet) among older adults is effective in preventing MACCE (112). And current the microbiome-based "brain-heart-gut" axis explains the vital mechanisms of fCVD (Figure 2), since the microbiome contributes to many cardiometabolic traits by modulating human inflammation and metabolism (113). Herein, healthy E(e)SEEDi lifestyle plays a vital role in the "brain-heart-gut" axis and novel mechanisms of fCVD.

All in all, there is indeed a direct association between the gut microbiota and host aging, diseases, and health by changes in mitochondrial dynamics (114). And currently, fecal microbiota transplantation is a novel method and an effective strategy against age-related human diseases (115, 116). And there is also a definite association between major risk factors in early life (117) and fCVD. Developments in artificial intelligence and big data will help us to setup a population-based risk algorithm (118, 119) or a scoring algorithm linking to unhealthy E(e)SEEDi lifestyle for evaluation, prediction, and prevention of fCVD.

With the development of cellular and molecular biology in brain and cardiovascular system and new tools of biomedicine (120-122), the scientist will further disclose the mechanisms of eCVD and fCVD under the help of this novel theory of "brain-heart-gut axis". And it is believed that with the further understanding of new origins and novel mechanisms, there will be better prospects in healthy aging and longevity due to better protection of brain and cardiovascular system. Here, wish everyone health, peace and happiness when the World Heart Day in this September is coming.

CONCLUSIONS

Since unhealthy E(e)SEEDi lifestyle links to the new origins and novel mechanisms of fCVD, the author setup a fresh theory, that is, the "brain-heart-gut" axis. The novel mechanisms of fCVD are mediated by the role of "environment-sleep-emotion-exercise-diet" and the gut microbiota in early life, which is like a "Golden Hoop Curse". On the one hand, the "brain-heart-gut" axis provides a theoretical basis not only for the cardiovascular health benefits of "keeping the pubic region" advocated by traditional Chinese medicine, but also for the control and prevention of both eCVD and fCVD; On the other hand, "keeping the pubic region" is the best example on the fresh theory of "brain-heart-gut" axis. As a new theory, the "brain-heart-gut" axis will help us to earlier and better prevent and control both eCVD and fCVD with healthy E(e)SEEDi lifestyle.

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C.H. did conception and design, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article.

DECLARATION OF INTERESTS

The author declares no competing interests.

Figure 1.

The "brain-heart-gut" axis and novel mechanisms of future cardiovascular disease (fCVD).

The new origins and novel mechanisms of fCVD link to the "brain-heart-gut" axis disrupted by early unhealthy E(e)SEEDi lifestyle, which is like a "Golden Hoop Curse". In the "brain-heart-gut" axis, the brain is the decision system, the heart is the power system, the gut is the execution system. The three closely cooperate and interact with each other to form the new mechanisms of fCVD. Here, E: environment (external); e: environment (internal); S: sleep; Em: emotion; Ex: exercise; D: diet. E(e)SEEDi: "environment-sleep-emotion-exercise-diet" intervention. Green : positive biofeedback by healthy E(e)SEEDi lifestyle; Grey : negative disruption by unhealthy E(e)SEEDi lifestyle.

Figure 2

Unhealthy E(e)SEEDi Lifestyle, Gut Microbiome, and fCVD.

According to the novel theory of the "brain-heart-gut" axis, since the E(e)SEEDi highly links to the brain, heart, and cardiovascular system, unhealthy E(e)SEEDi lifestyle will result in fCVD and its major cerebrocardiovascular events (MCCVE) by playing a role in the gut microbiome and its metabolites. In contrast, healthy E(e)SEEDi lifestyle will prolong brain and cardiac aging and promote human longevity due to beneficial effects on the gut microbiome. Here, E: environment (external); e: environment (internal); S: sleep; E: emotion; E: exercise; D: diet; i: intervention. E(e)SEEDi: "environment-sleep-emotion-exercise-diet" intervention. fCVD: future cardiovascular disease. $/#/&: gut microbiota; o/*/¿: metabolites.

Table 1 Current major studies on axis and CVD in cardiovascular journals.

Axis	**Chemicals, Gene, or Molecule**	**Targets**	**CVD**
CaMKII/$Na_v1.5$ axis (7)	Ca^{2+}/calmodulin-dependent kinase II (CaMKII), PP2A-B56α	PP2A regulates $Na_v1.5$ activity in cardiomyocytes, B56α as a novel target	Congenital and acquired human arrhythmia
Cardiosplenic axis (8)	Proinflammatory leukocytes	Splenic activation after ACS, leukocyte proinflammatory remodeling	Acute coronary syndrome (ACS)
Cardiosplenic axis (9)	Mononuclear phagocytes, antigen processing in the spleen	Splenocytes immune-mediated injurious responses & the spleen to cardiac remodeling	chronic heart failure (CHF)
CXCL1-CXCR2 axis (10)	Angiotensin II-induced infiltration of monocytes CXCL1-CXCR2 signalling	Inhibition of CXCL1 and/or CXCR2 & cardiac remodeling	Hypertensive heart diseases (cardiac remodeling)
CXCL12/CXCR4 chemokine ligand/receptor axis (11)	Arterial CXCR4 (atheroprotective role)	Arterial integrity, endothelial barrier function, and a normal contractile SMC phenotype	Atherosclerosis
CXCR4/SDF-1 axis (12)	The thrombin inhibitor bivalirudin did not interfere with BMC homing or SDF-1/CXCR4 signaling	Bivalirudin but not heparin recommended as an anticoagulant for intracoronary infusion of BMCs for cell therapy	Acute or chronic myocardial ischemia
KLF10-IL-9 signaling axis (13)	Ang II (angiotensin II) promoting CD4+ T-cell activation via upregulation of interleukins (IL)-9	Kruppel like factor 10 (KLF10 or Klf10) or IL-9 in T cells (novel therapeutic targets)	Perivascular Fibrosis & vascular disease
Leucopoietic-arterial axis (14)	Higher air pollution exposure & socioeconomics, traffic noise, and risk factors	Higher leucopoietic tissue activity and arterial inflammation (ArtI)	CVD & major adverse cardiovascular events (MACE)
Lipoprotein(a)-lipoprotein-associated phospholipase A2-oxidized phospholipid axis (Lp-PLA2 axis) (15)	Ysophosphatidylcholine	Valve interstitial cells	Calcific aortic valve stenosis (CAVS), acquired valvular heart disease
miR-208-Mef2 axis (Mef2-microRNAs axis) (16)	Myocyte enhancer factor 2 (Mef2)	Mef2 regulates microRNAs for cardiac development and disease	Pulmonary hypertension & Right ventricular failure

miR-223/PDGFRβ VSMC Axis (17)	Platelet miR-223 or VSMC PDGFRβ	Lack of miR-223 & VSMC dedifferentiation and medial damage	Coronary artery pathology in Kawasaki Disease (acute vasculitis of early childhood)
NFATc3/miR-204 axis (18)	Macrophage NFATc3, a negative regulator of atherogenesis	Up-regulation of NFATc3 in macrophages, up-regulates miR-204 to reduce SR-A and CD36 levels	Atherosclerosis (preventing foam cell formation)
Nuclear Ca^{2+}-CaMKIIδC axis (19)	CaMKII (Ca^{2+}-Calmodulin dependent protein kinase) δC	Early transaortic constriction perinuclear CaMKIIδC activation, myocyte Ca^{2+} transients and nuclear transcriptional responses	Eccentric hypertrophy and heart failure (HF)
p38α-CREB-OGDH axis (20)	Plasma succinate concentrations	Macrophages	Aortic aneurysm and dissection (AAD)
p-Erk1/2-MMP axis (21)	Lower serum uric acid (SUA) levels	Smooth muscle cell (SMC)-elastin contractile units (degradation of elastin)	Recurrent intracerebral hemorrhage (R-ICH)
Sirt1/p53/p21 axis (22)	Metoprolol	Arginine vasopressin (AVP)-Induced Cellular Senescence in H9C2 Cardiomyocytes & the AVP-induced expression of acetylated p53 and p21	Ischemia injury in cardiovascular system
SR-A1-c-Myc axis (23)	Tissue-resident and monocyte-derived cardiac macrophage	Endothelial progenitor cells differentiation & neovascularization	Doxorubicin-Induced Cardiomyopathy (DiCM)
Vegfc-Emilin2a-Cxcl8a Signaling axis (24)	Vegfc, emilin2a and cxcl8a for coronary revascularization & Cardiac Regeneration	Coronary endothelial cells upregulate vegfc, vegfc signaling upregulates epicardial emilin2a and cxcl8a expression	Ischemic heart disease

Table 2 Current major studies on axis and CVD in non-cardiovascular journals.

Axis	**Chemicals, Gene, or Molecule**	**Targets**	**CVD**
Autophagy-apoptosis axis (25)	Melatonin	Vascular endothelial cell damage and apoptosis mediated by macrophages	Kawasaki disease (KD)-associated vasculitis

BCAA-BCKA axis Branched-chain amino acid (BCAA)-Branched-chain keto acid (BCKA) axis (26)	Telmisartan (anti-hypertension drug)	Significantly represses Bcat2 activity via direct binding & enhanced white adipose tissue (WAT) browning and reduced adiposity	Obesity & metabolic syndrome
Circ_ROBO2/miR-149 axis (27)	CircRNAs (circ_ROBO2 & miR-149)	Activating NF-κB Signaling, aortic smooth muscle cells	Atherosclerosis & coronary artery disease (CAD)
Microbiome-brain-β-cell axis (28)	Acetate	A nutrient-gut microbiota interaction & activation of the parasympathetic nervous system	Obesity, insulin resistance & metabolic syndrome
miR-1277-5p/KLF5 axis (29)	LINC01123	Vascular smooth muscle cells (VSMCs)	Carotid atherosclerosis (CAS)
miR-149-5p/MMP9 axis (30)	Circular RNAs (circRNAs): circDHCR24 & miR-149-5p & MMP9	Human aortic vascular smooth muscle cells (HA-VSMCs) proliferation, migration and phenotypic switching	Atherosclerosis and CAD
miR-185-5p/PAK2 axis (31)	Long noncoding RNA (lncRNA) FGF9-associated factor (FAF)	Hypoxia/ischaemia-induced pyroptosis in cardiomyocytes, a potential therapeutic target of AMI	Various CVDs & acute myocardial infarction (AMI)
miR-206/216b-Atg13 axis (32)	Serum histamine, Histidine decarboxylase (HDC)	Histamine regulating myocardial autophagy and apoptosis in cardiomyocytes	Hypoxia and AMI
miR-344b-5p/FAIM3 axis (33)	Long noncoding RNA (lncRNA) XR_596701	Proliferation and apoptosis of intermittent hypoxia (IH)-induced H9c2 cells	Obstructive sleep apnea (OSA), IH -induced myocardial injury
miR-577/COBLL1 axis (34)	Fibrosis and apoptosis	Long non-coding RNA (lncRNAs) NORAD	AMI
miR-6873-3p/MyD88/NF-κB axis (35)	Circular RNAs (circRNAs) & circ-RELL1	Endothelial cells, the expression of ICAM1 and VCAM1 in ox-LDL induced endothelium inflammation	Atherosclerotic CVD (ASCVD)
OTUD7B/KLF4/NMHC IIA axis (36)	Bioactive components of Salvia miltiorrhiza	Sal-miR-1 and 3 inhibition of VSMC migration and monocyte adhesion to VSMCs	Vascular remodeling
p62/Nrf2/ARE axis (37)	Autophagy	The pyroptosis of macrophages	Atherosclerosis

PTEN/AKT/mTOR axis (38)	A plant-derived flavone tangeretin	Myocardial autophagy, a novel cardioprotective therapeutic target	Sepsis-Induced Myocardial Dysfunction
RAC1-MEK-ERK-CHD4 axis (39)	Harmine (a natural compound)	Chromodomain helicase DNA binding protein 4 (CHD4), a negative modulator of Ucp1 & harmine-mediated ERK activation in adipocytes	Obesity
RORα-erythropoietin-AMPK axis (40)	Bavachalcone, a natural bioactive compound or a promising angiogenesis agent	Endothelial progenitor cells (EPCs) differentiation & neovascularization	Angiogenesis and tissue repair in CVD
T helper 17 (T_H17) axis (41)	High salt intake	The effects of salt on the gut microbiome (a potential therapeutic target) & autoimmunity related to T_H17 cells	Salt-sensitive hypertension & CVD
TNFα-NLRP3 signalling axis (42)	Aconitine, the natural product extracted from Aconitum species	A TNFα inhibitor and BNIP3-mediated mitophagy.	Aconitine-induced cardiotoxicity and neurotoxicity

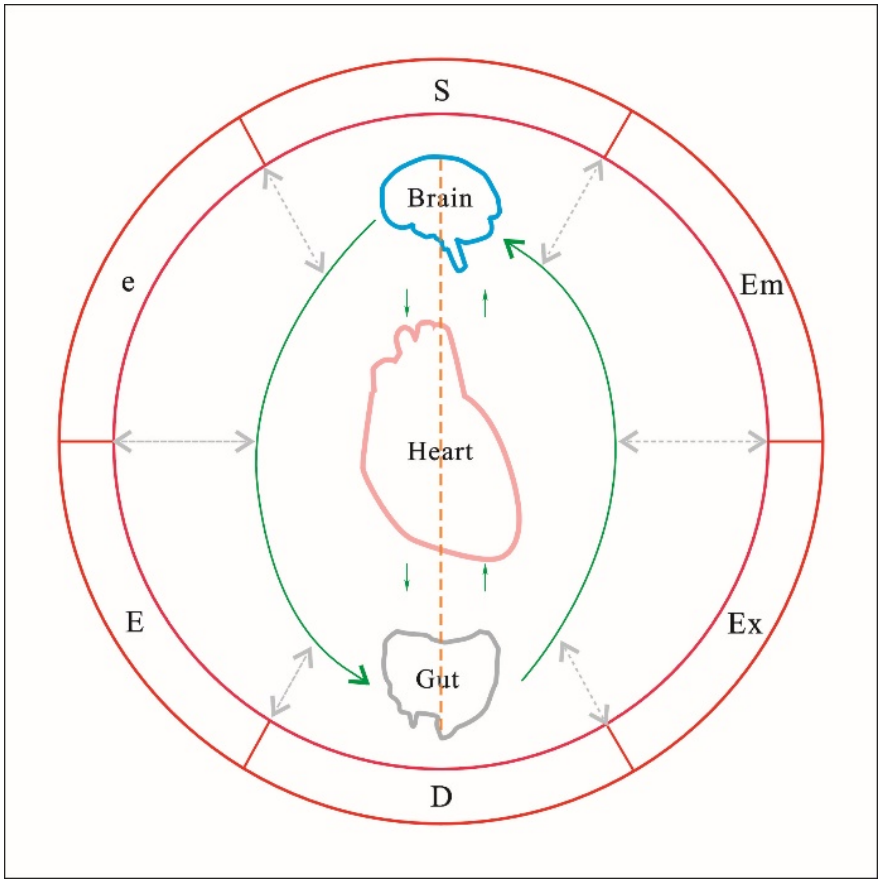

Figure 1.

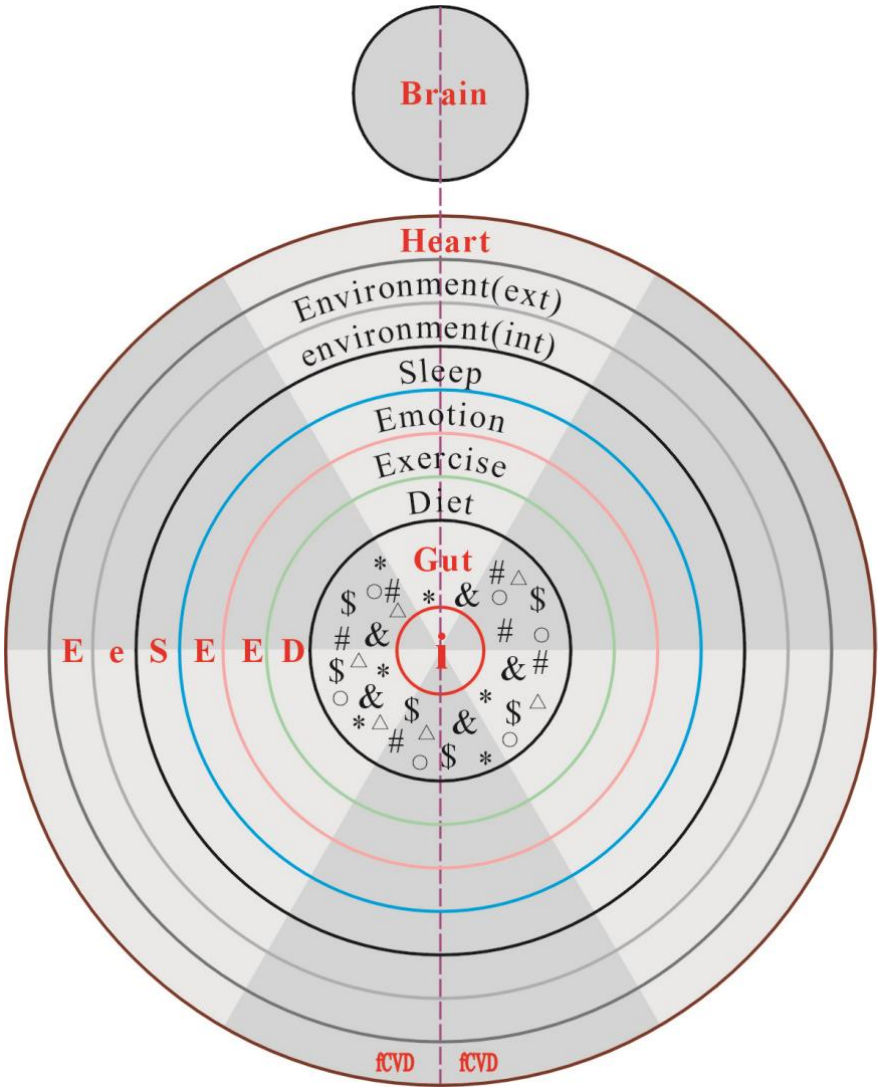

Figure 2.