Research Article

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Elevated Homocysteine a Key Risk Factor in Cardiovascular Disease

Abstract

Coronary heart disease (CHD) remains the leading cause of mortality in developed nations. With age, fatty deposits accumulate in the walls of the coronary arteries and other blood vessels supplying the heart. This buildup restricts blood flow, leading to angina, shortness of breath, and, in some cases, fatal myocardial infarction. While there are several modifiable risk factors for CHD, elevated levels of the amino acid homocysteine (HCY) have emerged as a significant contributor. Experimental and epidemiological studies consistently demonstrate a strong correlation between hyperhomocysteinemia and cardiovascular disease (CVD), and clinical data confirm that HCY functions as an independent risk factor. This article explores the molecular mechanisms underlying HCY's contribution to CVD risk, offering deeper insights into the pathophysiology of CHD and its associations with elevated homocysteine levels.

Keywords: homocysteine, cardiovascular disease, hyperhomocysteinemia, coronary heart disease, pathophysiology

1 Introduction

Cardiovascular disease (CVD) refers to a collection of conditions characterized by improper functioning of the heart and blood vessels, encompassing disorders such as stroke, congenital heart anomalies, hypertension, congestive heart failure, and atherosclerosis—the hardening or narrowing of arteries, including the coronary arteries [1, 2]. Over the course of the twentieth century, the world experienced an unprecedented shift in the leading causes of morbidity and mortality. This change, often described as the epidemiologic transition, has been significantly influenced by factors such as urbanization, industrialization, and associated lifestyle changes. As populations moved to more urban and industrial settings, the adoption of sedentary behaviors, diets rich in processed foods, and exposure to environmental stressors collectively contributed to a rise in cardiovascular conditions. Consequently, CVD now accounts for nearly 30% of deaths worldwide, a figure that is projected to increase in the coming years [3].

Among the various forms of CVD, coronary heart disease (CHD) is a dominant cause of mortality. In 2010, CHD alone was responsible for approximately 13% of all deaths globally and accounted for a large portion of disability-adjusted life years (DALYs) and years of life lost (YLLs) [3]. Stroke, another significant subset of CVD, ranked second, accounting for about 11.1% of all deaths worldwide. It also emerged as the third most common contributor to DALYs and YLLs, underscoring the extensive burden of cardiovascular disorders on healthcare systems and societies. These statistics highlight the urgency of understanding both the

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etiology and the prevention strategies associated with CVD.

CHD, in particular, is predominant in developed nations, where it is the primary cause of death among adults. The pathophysiological basis often involves the formation of atherosclerotic plaques—fat deposits that accumulate within the arterial walls. These plaques form progressively over years and are influenced by factors such as high cholesterol, hypertension, inflammation, and oxidative stress [4]. As atherosclerosis advances, the arteries supplying the heart become increasingly narrowed, restricting blood flow and oxygen delivery. When arterial occlusion reaches a critical level, individuals may experience angina—chest pain typically relieved by rest—or more severe outcomes, including myocardial infarction (heart attack) and sudden cardiac death.

The underlying process of atherosclerosis is complex and multifactorial. While genetic predisposition can play a role, lifestyle factors are notably modifiable and have a substantial impact on disease progression. Physical inactivity, a diet high in saturated fats and refined carbohydrates, obesity, and smoking have long been established as major contributors to the development of CHD [4]. These factors interact in a way that exacerbates endothelial dysfunction and promotes inflammation, creating a favorable environment for plaque formation. Effective public health strategies, therefore, often focus on encouraging regular exercise, balanced nutrition, smoking cessation, and weight management to mitigate these risks.

In addition to these well-known risk factors, emerging evidence has identified elevated levels of homocysteine (HCY) as a critical yet modifiable contributor to cardiovascular disease. Homocysteine is an amino acid derived from the metabolism of methionine. Under normal circumstances, homocysteine is metabolized efficiently, aided by vitamins such as folate (vitamin B9), vitamin B6, and vitamin B12. However, when these nutrients are deficient or when specific genetic variants affecting homocysteine metabolism are present, plasma homocysteine levels can rise, a condition referred to as hyperhomocysteinemia [4].

Several mechanisms have been proposed to explain how hyperhomocysteinemia may lead to vascular damage. First, elevated homocysteine levels can cause oxidative stress, which damages the endothelial lining of the arteries. Endothelial cells play a crucial role in maintaining vascular tone and preventing platelet aggregation. When the endothelium is compromised, it becomes more susceptible to inflammation and plaque formation. Second, homocysteine can promote smooth muscle cell proliferation and subsequent thickening of the arterial wall, exacerbating atherosclerosis. Additionally, hyperhomocysteinemia has been associated with an increased tendency for blood to clot, potentially leading to thrombosis and acute vascular events such as heart attack and stroke.

Numerous epidemiological studies have established a robust link between elevated homocysteine levels and a heightened risk of CHD. While it is important to note that homocysteine is not the only factor driving CVD, its status as a potentially modifiable element makes it an attractive target for intervention. Dietary modification, for instance, can help reduce homocysteine concentrations. Increasing the intake of folate-rich foods—such as green leafy vegetables, beans, and fortified cereals—along with adequate dietary sources of vitamins B6 and B12, can support healthy homocysteine metabolism. In some cases, supplementation with these vitamins may be recommended, particularly for individuals with known deficiencies or specific genetic polymorphisms in enzymes responsible for homocysteine clear-

ance.

Beyond dietary measures, broader lifestyle interventions remain critical in combating CVD. Engaging in regular physical activity can improve endothelial function, reduce inflammation, and aid in weight management—each of which indirectly influences homocysteine metabolism. Smoking cessation is equally vital, as the toxic components of cigarette smoke exacerbate oxidative stress and can further compromise endothelial integrity. Moreover, maintaining a healthy body mass index (BMI) through balanced nutrition and consistent exercise can lessen the overall burden on the cardiovascular system, reducing the risk of hypertension, dyslipidemia, and insulin resistance, all of which contribute to CHD progression.

Given the global burden of CVD, it is clear that multi-faceted strategies are required to address both traditional and emerging risk factors. Public health initiatives that promote healthier lifestyles, improve access to nutritional education, and encourage routine medical check-ups can significantly reduce the incidence and impact of CHD. Research suggests that interventions aimed at lowering homocysteine levels—either through dietary modifications or supplementation—may serve as a valuable component of an integrated approach to cardiovascular disease prevention. By recognizing the interplay between established risk factors (e.g., smoking, high-fat diets, physical inactivity) and modifiable biochemical markers such as homocysteine, healthcare providers and policymakers can more effectively tailor prevention and treatment programs. Ultimately, such efforts have the potential to alleviate the global burden of CVD and improve the quality of life for millions of individuals worldwide.

2 History of Homocysteine

Homocysteine was first identified in 1932 by the American biochemist Vincent DuVigneaud, who was investigating the chemical properties of methionine. By subjecting methionine to sulfuric acid, DuVigneaud isolated a novel amino acid that closely resembled cysteine but contained one additional carbon atom. This structural distinction led to the naming of the compound as "homocysteine," signifying its status as a homologue of cysteine. Subsequent research by DuVigneaud and others revealed that homocysteine serves as a critical intermediate in the metabolism of sulfur-containing amino acids, as well as in transmethylation reactions—a series of processes essential for numerous physiological functions.

Despite its early discovery, homocysteine did not attract significant attention for nearly three decades. Before 1962, its biological importance was not well understood. That began to change when a group of children exhibiting a distinctive collection of clinical features—developmental delays (historically termed "mental retardation"), accelerated growth, skeletal abnormalities such as osteoporosis, dislocated ocular lenses (ectopia lentis), and a notable propensity for both arterial and venous thrombosis—were found to excrete large amounts of homocysteine in their urine. This condition was subsequently named homocystinuria.

Investigations into homocystinuria revealed that the underlying defect in most affected infants was a deficiency in the enzyme cystathionine beta-synthase (CBS). This enzyme, which depends on the cofactor pyridoxal phosphate (the active form of vitamin B6), facilitates the conversion of homocysteine and serine into cystathionine. When CBS activity is compromised, homocysteine

is not efficiently transformed into cystathionine, resulting in a buildup of homocysteine and methionine in the bloodstream. Concurrently, homocystine—the disulfide dimer of homocysteine—is excreted at elevated levels in the urine [5].

The discovery of homocystinuria and its link to severe clinical manifestations offered the first clear indication of homocysteine's significance in human health. Not only did affected children experience developmental and skeletal problems, but they were also plagued by frequent thrombotic events, emphasizing how disrupted homocysteine metabolism could adversely affect the vascular system. These observations led scientists to investigate whether milder elevations in homocysteine, even outside the context of severe genetic disorders, could similarly pose a risk for vascular disease in the general population.

By the late 1960s, further research solidified the connection between homocysteine and vascular pathology. In particular, some investigators proposed that hyperhomocysteinemia—elevated homocysteine levels in the blood—could be an independent factor contributing to atherosclerosis. This hypothesis expanded the clinical relevance of homocysteine from a rare inborn error of metabolism to a broader public health concern, prompting researchers to explore nutritional, genetic, and lifestyle factors that influence homocysteine concentrations.

In the decades that followed, numerous studies explored how vitamins involved in homocysteine metabolism (notably folate, vitamin B6, and vitamin B12) could reduce plasma homocysteine levels. These vitamins act as cofactors or coenzymes in the remethylation and transsulfuration pathways of homocysteine metabolism. When these nutrients are deficient—or when genetic variants impact the enzymes in these pathways—homocysteine can accumulate and potentially damage the vascular endothelium, leading to an increased risk of blood clots and contributing to the pathogenesis of coronary artery disease, stroke, and other forms of cardiovascular disease.

From a historical perspective, homocysteine's journey from a laboratory curiosity to a recognized player in human pathology underscores the importance of basic biochemical research in shaping clinical understanding. Vincent DuVigneaud's initial identification of homocysteine laid the foundation for decades of scientific inquiry, revealing not only an inborn metabolic disease (homocystinuria) but also broader implications for cardiovascular health. What began as a sulfuric acid treatment of methionine in 1932 ultimately sparked a line of investigation that now spans genetics, nutrition, cardiovascular medicine, and beyond.

Today, homocysteine is acknowledged as more than just a byproduct of amino acid metabolism. Its levels in the blood are considered a biomarker for cardiovascular risk, offering insights into how diet, genetic predispositions, and lifestyle factors interact to influence disease outcomes. This shift in understanding—from an obscure biochemical entity to a recognized risk factor—has prompted clinicians to consider measuring and managing homocysteine in specific patient populations, particularly those with known genetic disorders, vitamin deficiencies, or a strong family history of early cardiovascular disease.

Thus, the historical narrative of homocysteine highlights a quintessential example of how scientific discoveries evolve over time. What seemed an esoteric biochemical finding in the 1930s paved the way for significant breakthroughs in our understanding of vascular biology, bridging the gap between basic research and clinical application. As research progresses, homocysteine continues to be a subject of interest not only for those studying

inborn errors of metabolism but also for scientists and clinicians investigating the multifactorial underpinnings of cardiovascular disease.

3 The Homocysteine Theory of Arteriosclerosis was Discovered

In 1969, clinicians revisited the case of an eight-year-old boy who had first been diagnosed with homocystinuria in 1933. Although homocystinuria is a rare inborn error of metabolism, the boy's clinical outcome highlighted a striking possibility: he had suffered a major stroke caused by thrombosis and carotid arteriosclerosis. Autopsy findings revealed that the large arteries supplying vital organs were studded with atherosclerotic plaques, suggesting that an elevated homocysteine level was intricately involved in the process of atherogenesis.

Another early case further strengthened this connection. A two-month-old infant with homocystinuria, linked to a deficiency in the enzyme methionine synthase, was found to have extensive and advanced arteriosclerotic plaques throughout the arterial system. In this infant, homocysteine levels were the only metabolic abnormality shared with the older child. This parallel underscored homocysteine's apparent capacity to damage arterial cells and tissues, fueling the development of atherosclerosis.

Shortly thereafter, researchers in Chicago documented a third major type of homocystinuria resulting from methylenetetrahydrofolate reductase (MTHFR) deficiency. Once again, they observed an unusual accumulation of atherosclerotic plaques. The common thread in all three forms of homocystinuria—elevated homocysteine—pointed to a broader pathophysiological mechanism. While the specific genetic defects differed (affecting cystathionine beta-synthase, methionine synthase, or MTHFR), each scenario resulted in hyperhomocysteinemia, providing clear evidence that high homocysteine levels were directly implicated in arterial damage and plaque formation [5].

When these cases first came to light, researchers proposed a bold hypothesis: that hyperhomocysteinemia could play a significant role in atherosclerosis even among individuals who do not have these rare genetic disorders. In other words, moderately elevated homocysteine in the general population—due to factors such as diet, lifestyle, hormonal influences, environmental exposures, or other metabolic irregularities—might provoke similar endothelial damage over time. The lining cells of arteries are uniquely vulnerable to biochemical stressors, and prolonged exposure to elevated homocysteine can exacerbate oxidative stress, inflammation, and smooth muscle cell proliferation, all of which are hallmarks of atherosclerotic plaque development.

This revelation revolutionized how scientists and clinicians viewed homocysteine. Rather than being a mere biochemical curiosity or a metabolite relevant only to rare hereditary conditions, homocysteine emerged as a potential independent risk factor for vascular disease. Further epidemiological and clinical studies supported this perspective, correlating even mild hyperhomocysteinemia with an increased incidence of coronary artery disease, stroke, and peripheral vascular disease in larger populations.

By drawing attention to the destructive impact of elevated homocysteine on arterial tissues, early homocystinuria case reports became pivotal in broadening the scientific community's understanding of atherosclerosis. Their legacy persists in modern cardiovascular research and clinical practice, where

there is ongoing interest in monitoring and managing homocysteine levels—particularly through nutritional interventions (e.g., B-complex vitamins such as folate, vitamin B6, and vitamin B12) or targeted genetic testing when warranted. The ultimate lesson from these foundational observations is that homocysteine, albeit one biochemical factor among many, can significantly alter vascular integrity and thus merits careful consideration in the quest to prevent and treat atherosclerotic disease [6].

4 Blood Homocysteine Levels and Hyperhomocysteinemia

Under normal physiological conditions, blood homocysteine concentrations range from 5 to 15 µmol/L. In pathological states, however, homocysteine can surge to levels that are 50–100 times higher than normal. Several factors contribute to moderate increases in plasma homocysteine, including advancing age, vitamin B_6 or B_{12} deficiency, tobacco use, excessive alcohol consumption, and hypothyroidism. By contrast, congenital enzyme deficiencies often lead to pronounced elevations in homocysteine. In all these scenarios, elevated homocysteine is collectively referred to as hyperhomocysteinemia (HHcy) [7].

4.1 Hyperhomocysteinemia Classification (as per Selhub, 1999)

Extremely High Homocysteinemia: This refers to consistently elevated total homocysteine (tHcy) levels (¿31–100 µmol/L). Such profound elevations may be caused by genetic or metabolic disruptions in vitamin B_{12} metabolism or by defects in key enzymes, including methylenetetrahydrofolate reductase (MTHFR) and cystathionine beta-synthase (CBS).

Mild (or Moderately Elevated) Homocysteinemia: Slightly increased tHcy levels (15–30 µmol/L) during fasting often indicate subtle enzyme deficiencies—such as the thermolabile variant of MTHFR—or diminished capacity for homocysteine remethylation.

Abnormal Post-Methionine Load: In this category, an individual receives a methionine load of 100 mg/kg, and tHcy levels rise abnormally above 15 µmol/L. Such a response is typically attributed to impaired homocysteine transsulfuration, which may be due to heterozygous CBS mutations or vitamin B_6 insufficiency [8].

When homocysteine accumulates in the blood, its disulfide form (homocystine) may appear in the urine. Under normal conditions, urine does not contain homocystine or homocysteine; thus, detecting these substances can be a clinical marker of abnormal homocysteine metabolism. Elevated homocysteine in plasma has been linked to an increased risk of coronary heart disease (CHD), and some studies suggest a correlation between mild hyperhomocysteinemia and myocardial infarction. In fact, a 5 µmol/L rise in plasma homocysteine is estimated to confer a level of CHD risk comparable to a 20 mg/dL increase in serum cholesterol [9].

4.2 Pathways of Homocysteine Metabolism

Homocysteine (Hcy) is formed by the demethylation of the essential amino acid methionine. Under normal circumstances, most homocysteine is either:

- Transsulfurated to cystathionine via cystathionine beta-synthase (CBS)—an enzyme that requires pyridoxal phosphate (active vitamin B_6).
- Remethylated to methionine via two

primary enzymes:

- Betaine-homocysteine methyltransferase, which uses betaine as a methyl donor.
- 5-methyltetrahydrofolate-homocysteine methyltransferase, which depends on vitamin B_{12} and folate to transfer a methyl group back to homocysteine.

Deficiencies in vitamin B_6, vitamin B_{12}, or folate—or genetic variations in MTHFR or CBS—can disrupt these pathways, leading to hyperhomocysteinemia. Elevated homocysteine is implicated in endothelial dysfunction through several mechanisms, including oxidative damage, stimulation of smooth muscle proliferation, enhanced platelet aggregation, increased low-density lipoprotein (LDL) oxidation, and prothrombotic changes in the coagulation cascade [10].

4.3 Clinical and Public Health Implications

Because hyperhomocysteinemia represents a potentially modifiable risk factor, efforts have been made to lower homocysteine levels in the general population. Fortification of grains with folate has proved effective in reducing plasma homocysteine. In addition, supplementation with B vitamins (particularly folate, vitamin B_6, and vitamin B_{12}) can help normalize elevated homocysteine in many individuals. A pooled analysis of prospective observational studies showed that modest reductions in homocysteine—achievable with folate supplementation—correlate with an 11% decrease in the risk of developing CHD [11].

4.4 Molecular Basis of Atherogenesis

Homocysteine promotes atherogenesis through multiple, interrelated pathways that can disrupt normal vascular integrity [12]:

- **Endothelial Injury and Cellular Degeneration:** High homocysteine levels induce oxidative stress, damaging the endothelial cells that line arteries.
- **Increased Collagen Production and Disruption of Elastic Fibers:** Homocysteine can interfere with collagen cross-linking by binding lysyl residues and activating elastase enzymes, leading to the fragmentation of the internal elastic membrane. At the same time, it stimulates smooth muscle cells to overproduce collagen, contributing to plaque fibrosis.
- **Smooth Muscle Cell Proliferation:** By activating cyclins and promoting insulin-like growth factor (IGF) activity, homocysteine encourages smooth muscle proliferation, a key event in plaque formation and vascular remodeling.
- **Enhanced LDL Aggregation and Uptake:** Homocysteine thiolactone, a reactive free radical derivative of homocysteine, thiolates LDL particles, making them more prone to aggregation and uptake by macrophages—a critical step in foam cell formation and atherosclerosis progression.
- **Prothrombotic Effects:** Elevated homocysteine can increase platelet aggregation and alter the coagulation cascade, heightening the risk of thrombosis.

5 Molecular Aspects of Homocysteine

Homocysteine metabolism is governed by several genes, most notably those encod-

ing the enzymes involved in folate utilization and remethylation pathways. Among these, two genes play particularly important roles in maintaining balanced homocysteine levels: the MTHFR gene (5,10-methylenetetrahydrofolate reductase) and the FTO (fat mass and obesity-associated) gene.

5.1 The MTHFR Gene

Located on chromosome 1 at 1p36.3, the MTHFR gene spans approximately 2.2 kilobases of complementary DNA (cDNA) and is composed of 11 exons. Two common allelic variants—A1298C and C677T—have been extensively studied for their effects on enzyme function and homocysteine levels.

5.1.1 Function of MTHFR

The MTHFR enzyme is crucial in folate metabolism. It converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is the primary circulating form of folate. This 5-methyl form transfers a single carbon group during the synthesis of S-adenosylmethionine (SAM), which is vital for methylation reactions involving proteins, DNA, neurotransmitters, and phospholipids. It also plays a key role in remethylating homocysteine to methionine. Sufficient MTHFR activity helps maintain steady levels of methionine, folate, and homocysteine in the bloodstream, preventing homocysteine accumulation [13].

5.2 MTHFR Gene Mutation

5.2.1 C677T Allele

The C677T allele arises from a point mutation in the MTHFR gene at position 677, where cytosine (C) is replaced by thymine (T). This substitution changes the encoded amino acid from alanine to valine, rendering the enzyme "thermolabile." At temperatures of 37°C or higher, the activity of this mutant enzyme decreases significantly. Homozygous carriers of the C677T variant can exhibit 50–60% lower MTHFR activity at 37°C and up to 65% lower activity at 46°C compared to controls. Heterozygotes typically have intermediate enzyme activity. Individuals who are homozygous for C677T often display mildly elevated homocysteine levels if their folate intake is inadequate, whereas adequate folate consumption can normalize their homocysteine concentrations [14, 15].

5.2.2 A1298C Allele

The A1298C variant (also referred to as C1289A in some literature) involves a point mutation in exon 7 of the MTHFR gene, resulting in a glutamate-for-alanine substitution [16]. Although this substitution also reduces MTHFR activity, the effect on enzyme thermolability and homocysteine levels is generally less pronounced than that of C677T. Homozygous carriers of A1298C do not typically exhibit significantly elevated homocysteine concentrations compared to the general population. However, compound heterozygotes carrying both the A1298C and C677T alleles often resemble C677T homozygotes, with higher plasma homocysteine and lower folate levels [17].

5.3 The FTO Gene

The FTO gene (alpha-ketoglutarate-dependent dioxygenase) is located on chromosome 16 (16q10) and is strongly associated with increased fat mass and a heightened risk for type 2 diabetes (T2D) [18]. The enzyme encoded by the FTO gene has been implicated in energy balance, appetite regulation, and other metabolic processes.

5.4 Genotype Effect on Homocysteine Levels

Recent studies have explored how variants in the FTO gene may impact homocysteine metabolism. In one investigation, individuals with the FTO rs9939609 AA genotype had significantly higher homocysteine levels than those without this variant [19]. Elevated homocysteine has been linked to increased neuroinflammation, hypomethylation, and alterations in immune cell function. Hypomethylation—caused, in part, by reduced S-adenosylmethionine (SAM)—can lead to dysregulation of adhesion molecules, lymphocyte activity, and overall vascular integrity. Moreover, the deposition of lipids in the aorta (a predictive marker for future atherosclerosis) has also been associated with hypomethylation, suggesting that the interplay between homocysteine, genetic factors, and methylation status may contribute substantially to early cardiovascular risk.

Together, these findings underscore the multifactorial nature of hyperhomocysteinemia, where both MTHFR and FTO gene variants, along with dietary and lifestyle factors, can significantly influence homocysteine levels. Understanding these genetic and metabolic interactions is crucial for designing targeted interventions—such as folate supplementation and dietary modifications—to mitigate the risk of homocysteine-associated vascular and metabolic diseases.

6 Homocysteine and Coronary Heart Disease

In four cross-sectional investigations examining the relationship between homocysteine and coronary heart disease (CHD), researchers diagnosed CHD using angiographic evidence of at least 50% blockage in one or more coronary arteries. Blood samples were collected at the time of CHD diagnosis, allowing for simultaneous measurement of plasma homocysteine. While the earliest of these studies reported no significant difference in mean homocysteine levels between participants with and without CHD, the second through fourth studies showed that those with CHD had mean homocysteine levels 30%–90% higher than those without CHD. Across all four cross-sectional investigations that defined elevated homocysteine levels, individuals in the high-homocysteine group had a significantly elevated risk of developing CHD.

Turning to the case-control studies on homocysteine and CHD, the majority also reported a positive association. Among the fifteen studies evaluating mean homocysteine levels, all but three [14, 15] found that participants with CHD had considerably higher homocysteine concentrations (often 10%–30% higher), measured either after fasting or following a methionine load. Furthermore, fifteen out of sixteen studies comparing the proportion of individuals with elevated homocysteine levels reported an increased risk of CHD in these high-homocysteine groups. In most of these investigations, the increase in risk was not only statistically significant (p ¡ 0.05) but also exhibited a confidence interval for the relative risk (RR) estimate that excluded the null value of 1.0 [18].

Abbreviations commonly used in these studies include RR for relative risk, HR for hazard ratio, OR for odds ratio, “Prosp” for prospective studies, “Rev-Meta” for review and meta-analysis, “cross-sect” for cross-sectional studies, and “RCT” for randomized controlled trials. Cardiac outcomes and conditions are likewise abbreviated: HF for heart failure, CHD for coronary heart disease, CVD for cardiovascular disease, CAD for coronary artery disease, and “Cerebrovasc” for cerebrovascular disease. Additionally, “NA” stands for not available, while

"W" and "M" refer to women and men, respectively.

In prospective case-control studies, reviews, meta-analyses, and randomized controlled trials, treatments that lower homocysteine—such as folic acid supplementation alone or in combination with B vitamins—have demonstrated reductions in cardiovascular and stroke complications. These findings further suggest an association between hyperhomocysteinemia and increased incidences of CVD and stroke.

7 Future Directions

Homocysteine has the potential to serve as a biomarker for the early detection of CVD risk in both individual patients and broader populations. Early identification could inform targeted interventions—such as dietary changes, vitamin supplementation, and lifestyle modifications—aimed at minimizing long-term cardiovascular complications.

Despite numerous studies pointing to a link between homocysteine and heightened CVD risk, some recent prospective research has questioned the overall prognostic value of plasma homocysteine levels. These conflicting observations underscore the need for a comprehensive and quantitative evaluation of the available evidence. Further investigations should emphasize:

- **Epigenetic Mechanisms:** Exploring how homocysteine-induced DNA methylation changes or other epigenetic modifications might contribute to the pathogenesis of CVD.
- **Independent Risk Factor Clarification:** Determining whether homocysteine itself is an independent risk factor for CVD or whether it operates synergistically with other metabolic and lifestyle factors.
- **Long-Term Clinical Outcomes:** Conducting larger-scale and longer-duration trials to assess whether interventions that reduce homocysteine levels translate into sustained reductions in morbidity and mortality.

In conclusion, while a substantial body of evidence supports a positive correlation between elevated homocysteine levels and heightened cardiovascular risk, further rigorous research will help clarify the epigenetic underpinnings of this relationship and refine our understanding of homocysteine's role as an independent or contributory factor in CVD.

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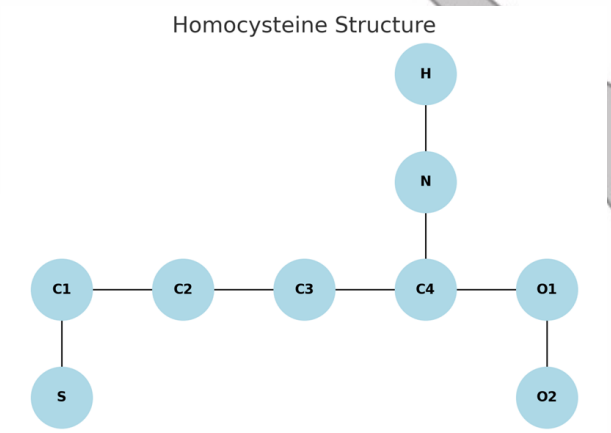

Figure 1: Structure of Homocysteine

Table 1: Properties of homocysteine

Chemical formula	C4H9NO2S
Molar mass	135.18 g/mol
Appearance	White crystalline powder
Melting point	238–240 ∘ C (460–464 ∘ F; 511–513 K) (decomposes)
Solubility in water	Highly Soluble
log P	-2.42
Acidity (pKa)	2.15

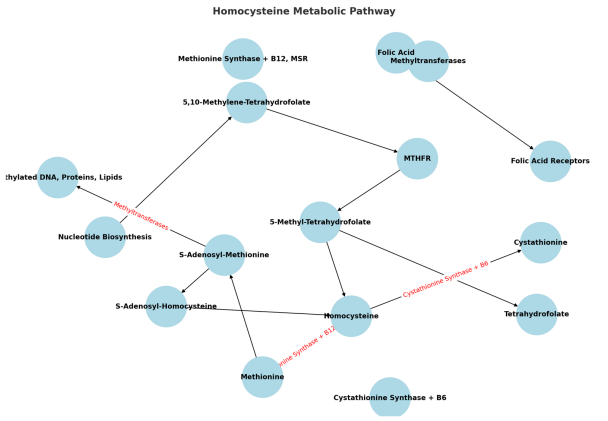

Figure 2: Homocysteine metabolic pathway

Table 2: Summary of studies on homocysteine levels across different populations and conditions

Age, y	Sample Size		Mean Homocysteine, mol/L		
	Cases	Controls	Cases	Controls	
30-70	120 Cases	50 Controls	0.05	0.08	NS
			0.8	0.7 (P)	NS
75	260 Cases	210 Controls	6	4.8	0.001
Mean, 65	105 Cases	270 Controls	14.2	11	0.001
20-85	90 Cases	30 Controls	0.85	0.45 (P)	0.001