Addiction & Health

https://ahj.kmu.ac.ir
10.34172/ahj.1722
AHJ. 2025;17:1722

Review Article

A Review of Cardiovascular Diseases in Substance Use Disorders: Current Knowledge and Future Perspectives

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Abstract

Background: Nowadays, the emergence of new types of substances and the growing prevalence of addiction have made substance use a global challenge for public health. At the same time, the complications of substance use are observed in various physical and psychological dimensions, including a range of acute and chronic cardiovascular diseases. This issue is significant, as many young people are affected by these complications. Therefore, understanding these complications is both important and practical.

Methods: Clinical articles related to the acute and chronic cardiovascular effects of the main groups of substances were searched in the PubMed, Web of Science, Scopus, and Google Scholar databases from 2015 to 2025.

Results: Evidence of cardiovascular complications related to the use of major substance groups, including opioids, stimulants, nicotine, caffeine, alcohol, cannabinoids, tranquilizers, and anabolic steroids, has been obtained. Some of this evidence only indicates an increase in risk factors for the disease, while some reports also point to acute and chronic cardiac complications and even cardiorespiratory arrest and death.

Conclusion: Given the cardiac complications of substance use, cessation and treatment should be personalized to each patient's circumstances.

Keywords: Cardiovascular diseases, Risk factors, Substance-related disorders

Citation: Zarei F, Simani M, Rajabi Moghaddam H, Ghaderi A. A review of cardiovascular diseases in substance use disorders: current knowledge and future perspectives. *Addict Health*. 2025;17:1722. doi:10.34172/ahj.1722

Received: July 28, 2025, **Revised:** September 24, 2025, **Accepted:** December 10, 2025, **ePublished:** December 20, 2025

Introduction

Due to its increasing prevalence, substance use has become a global public health issue. The World Health Organization (WHO) describes substance use as the persistent or sporadic consumption of substances that are medically and functionally unacceptable, incompatible, or irrelevant. Along with the rise in substance use, its serious consequences are also increasing, which are observed in various physical and psychological dimensions. Studies show that substance use is generally more common among young people than older individuals, with about 14% of the overall health burden in young men being attributable to alcohol and substance use. Young people are also more likely to die because of substance use disorders.[1]

Substance use produces numerous changes in the human body, affecting it on behavioral, biochemical, and toxic levels. Behaviorally, it can alter cognitive function, impair judgment, and change a person's mood and emotions. At the biochemical level, substance use affects the normal function of neurotransmitters (e.g., serotonin, dopamine, and gamma-aminobutyric acid (GABA)). These effects in turn impact mood regulation, the brain's reward system, and general brain function. Furthermore, chronic substance use may lead to toxic effects and organ damage.[2]

Cardiovascular diseases (CVDs) are the most important cause of death and disability worldwide, with approximately 18.6 million related deaths in 2019.[3] CVDs take a significant socioeconomic and public health burden on society and healthcare systems. The Global Burden of Disease (GBD) study has monitored the status of cardiovascular diseases, the burden of illness, injuries, and risk factors since 1990. The GBD study estimated the influence of several leading risk factors for cardiovascular diseases. These include environmental risks such as ambient particulate matter air pollution; metabolic risks such as hypertension, elevated LDL-C, and hyperglycemia; and behavioral risks including smoking, exposure to secondhand smoke, and heavy alcohol use.[4]

The relationship between substance use and an elevated

risk of cardiovascular diseases is extensively documented. The use of various substances is related to an elevated risk of cardiovascular disease, such as coronary artery disease (CAD), heart failure, and arrhythmias. For individuals who already have a cardiovascular condition, substance use further increases the risk of death and complications related to CVD. For example, stimulants trigger sympathomimetic effects, leading to an increase in heart rate (HR), contractility, vasoconstriction, and blood pressure (BP). This combination of consequences creates a critical imbalance where oxygen demand is increased while supply is simultaneously decreased, raising the risk of cardiomyopathy, myocardial infarction, arrhythmia, and other CVDs. In contrast to stimulants, opioids stimulate the vasomotor center to increase parasympathetic activity, leading to reduced heart rate (HR), blood pressure (BP), and various electrocardiogram (ECG) abnormalities. The literature also discusses about destructive cardiovascular effects of cannabis (e.g., vasospasm, decreased myocardial contractility, tachycardia, and increased systolic blood pressure). These consequences are recognized as factors that contribute to the progression of atherosclerotic cardiovascular disease (ASCVD). Furthermore, some studies have also noted evidence for the influence of cannabis on atrial fibrillation and ischemic stroke (IS).[5]

Substance use affects the cardiovascular system through a variety of complex mechanisms, including elevated oxidative stress, persistent systemic inflammation, impaired endothelial function, pathological remodeling of cardiac tissue (necrosis and fibrosis), thrombosis, and a heightened hyper-adrenergic state. Furthermore, substance use promotes the development of risk factors such as metabolic disorders and exerts direct toxic effects on cardiovascular tissues.[6] At the molecular level, substance-induced oxidative stress, inflammation, and direct toxic effects cause damage to cardiomyocytes, leading to necrosis and fibrosis. These processes also disrupt myocardial contractility and alter the heart's electrical activity. Chronic cardiac fibrosis is related to the development of heart failure. Furthermore, these substances damage the vascular endothelium, resulting in vasoconstriction and elevated blood pressure, while also promoting platelet adhesion and elevating the risk of thrombosis and cardiovascular diseases. Central nervous system stimulants, through the stimulation of the dopaminergic system, trigger a rapid rise in blood pressure and heart rate and increase the risk of acute CVDs. Additionally, the use of certain substances is linked to metabolic profile alterations that heighten the risk of CVDs.[7]

In parallel with efforts to combat drug addiction over recent decades, researchers have also focused on understanding the toxic mechanisms of substance use. Importantly, some of these effects are specifically observed on the cardiovascular system, affecting blood pressure and heart rate, and may even be fatal. Therefore, it is useful and practical for specialists to understand the cardiovascular effects of all types of substances, including opioids, stimulants, sedatives, and others. This knowledge can empower healthcare professionals to more effectively identify, diagnose, and treat, as well as prevent, cardiovascular events in individuals with substance use, especially those in high-risk groups. Ultimately, this leads to more effective treatment and a higher quality of life (QOL) among these cases. This knowledge also allows researchers to more efficiently understand the relationship between CVDs and substance use by elucidating its underlying mechanisms, thus suggesting more effective interventions and providing a foundation for future research. Given the value, importance, and applicability of this topic, the present review article investigated and analyzed studies on the cardiovascular effects of substance use.

Methods

Study Overview

This review study was conducted to explore the cardiovascular effects of substance use. A summary of the study design is presented in Figure 1.

Search Strategy

The search was performed using a combination of the words: (Opioids OR Cannabinoids OR Alcohol OR Nicotine OR Amphetamines OR Methamphetamine OR "Sedative Drugs") AND ("Cardiovascular disease"), and a keyword search method in the PubMed, Web of Science, Scopus, and Google Scholar databases from 2015 to 2025. In addition, the search was restricted to clinical (human) articles, free full text written in English language.

Inclusion and Exclusion Criteria

The main inclusion criteria for article selection were information on acute and chronic effects of substance use and the mechanisms of these effects. Additionally, articles related to increasing risk factors for cardiovascular disease due to substance use were included, e.g., hypertension, dyslipidemia, and atherosclerosis. Both original (clinical) and review articles were included; furthermore, observational studies, meta-analyses, systematic reviews, conference papers, and case reports were also included.

Topics unrelated to the cardiovascular effects of substance abuse and duplicate information were excluded.

Finally, the obtained information was categorized based on the type of substance, which is presented below. Table 1 refers to the inclusion and exclusion criteria.

Results

Cardiovascular Effects of Opioids

Opioid use is the most important public health issue, leading to widespread addiction. While global opioid

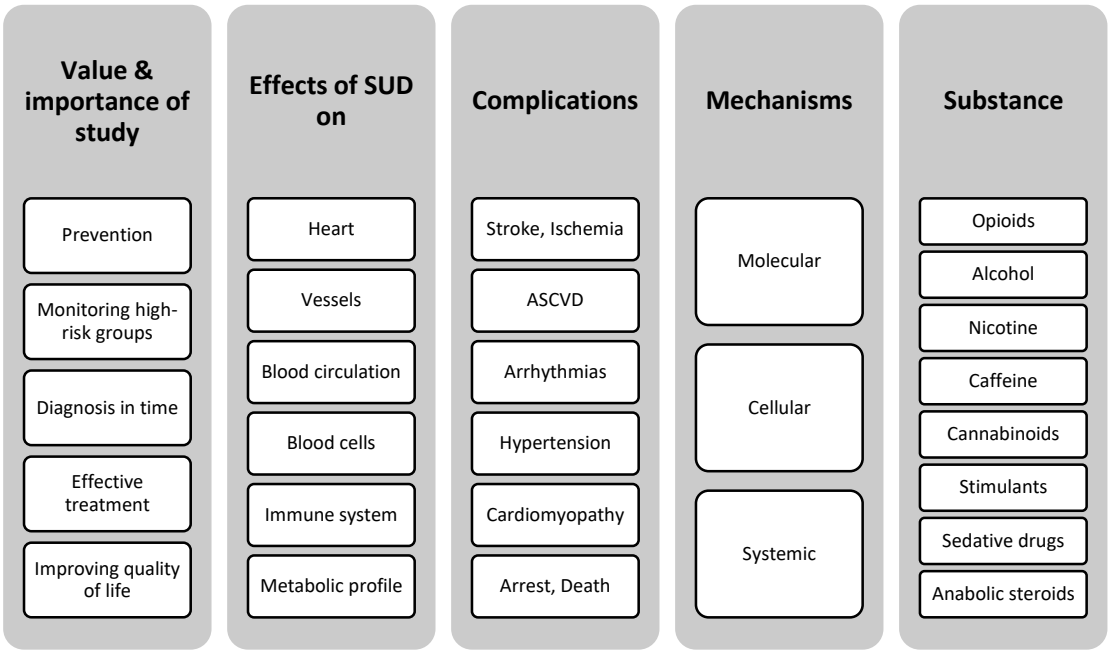

Figure 1. Study overview

Table 1. Study inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Acute or chronic effects of substance use • Effects of medication with substances (e.g., for pain management or anesthesia in a surgical procedure) • Mechanisms of cardiovascular effects of substances • Risk factors for cardiovascular disease related to substance use • Clinical trial studies • Observational studies • Meta-analyses articles • Case series and case reports • Review articles • Systematic review articles • Conference articles	• Articles unrelated to the cardiovascular effects of substance abuse • Articles with duplicate results • Non-human studies • Non-original articles (including editorials, letters, and protocols) • Non-English articles • Non-free full-text articles

dependence affects an estimated 1.2% of the adult population,[8] opium use is mainly common in developing countries such as Asia and the Middle East. For example, the overall prevalence of opium addiction in Iran is estimated at 2.3% of the adult population, and a rate that escalates to 22% in certain rural regions.[9] In some communities, opium is not only used recreationally but is also believed to offer protection against heart attacks and improve cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia. Contrary to this traditional belief, scientific evidence indicates an elevated risk of these conditions in opium consumers compared to non-users. Additionally, the adverse cardiovascular complications of opioid medications prescribed for pain management are important and notable.[10]

A review published in 2021 found strong evidence of a positive relationship between opiate injection and the occurrence of infective endocarditis. It also found a positive association between non-chronic use (mainly medically prescribed) and myocardial infarction. However, there was little evidence concerning the association between non-chronic use and other CVDs, such as stroke, congestive heart failure, and cardiac arrhythmias.[11]

There are still uncertainties about the mechanism of action of opioids on the cardiovascular system. While opioid receptors have been determined in the heart, the biological pathways through which they act are not yet completely understood. Research has revealed that the activation of these receptors through temporary administration of opioid medications already acute ischemic events has a protective effect on the heart. However, prolonged exposure to opioids is related to an increased incidence of acute myocardial infarction. Furthermore, some opioids (e.g., methadone, tramadol, and oxycodone) are linked to an elevated risk of long QT syndrome, which can lead to risky arrhythmias like torsade de pointes.[12]

Some studies have also indicated that chronic opioid use increases pro-inflammatory cytokines, such as interleukin-6, C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α), which leads to systemic

inflammation. This inflammation is associated with the pathophysiology of atherosclerosis, coronary artery disease, and myocarditis. Evidence also suggests that opioid consumption is linked to elevated oxidative stress levels and the development of reactive oxygen species, resulting in vascular damage and endothelial dysfunction.[13]

Cardiovascular Effects of Alcohol

Based on the Global Status Report on Alcohol and Health, alcohol use disorders affect a significant population, with an estimated 237,000,000 men and 46,000,000 women suffering from these conditions.[14] According to global data, countries with a Muslim-majority population, such as Iran, show the lowest per capita rates of alcohol consumption. This trend is largely attributed to religious and social norms that prohibit or discourage the use of alcohol. Although extreme alcohol use is a major cause of death and disability, the relationship between moderate alcohol use and CVDs is multifaceted. Observational studies commonly indicate that alcohol use is positively associated with an increased risk of heart failure, atrial fibrillation, and hemorrhagic stroke, while moderate alcohol consumption is linked to a lesser risk of ischemic stroke and coronary artery disease.[15]

Long-term excessive alcohol consumption (200 grams/day) may lead to several cardiovascular diseases, including alcoholic cardiomyopathy, systemic hypertension, atrial arrhythmia, and stroke. High doses of alcohol initiate oxidative stress and toxic mechanisms within heart cells, leading to the progression of arrhythmias, heart failure, and cardiomyopathy. Additionally, studies show that alcohol consumption causes several pathological changes in the gut, such as the reorganization of the microbial community, a leaky intestinal barrier, and altered immune function. This can lead to the release of metabolites that directly increase the risk of CVDs.[16] However, lower doses of alcohol (around 30 grams/day for men and 20 grams/day for women) do not pose a significant risk of increased blood pressure and may even have protective effects against cardiovascular complications. Some studies have also shown increased life expectancy and reduced blood pressure following alcohol reduction or abstinence, especially among individuals who maintain this lifestyle over the long term.[17] Additionally, genetic variations, gender, metabolism, and lifestyle factors may contribute to differences in the alcohol threshold required to induce cardiovascular complications in individuals. Studies show that both the acute and long-term cardiovascular consequences of alcohol consumption are caused by alcohol molecules and their active metabolites.

Cardiovascular Effects of Nicotine

Smoking is a leading cause of early heart problems worldwide. All over the world, more than 80% of 1.3 billion tobacco users live in poor communities and middle-income countries and bear the disproportionate burden of tobacco-related morbidity and mortality.[18] Based on the World Health Organization (WHO) report, 20% of men and 0.8% of women in Iran, aged 15 and over, use tobacco daily.[19] This report is further supported by the National Surveys of Risk Factors of Non-Communicable Diseases (STEPS), which estimated the prevalence of cigarette and hookah consumption to be 23.7% among men and 3.0% among women.[20] Smoking significantly increases the risk of cerebrovascular complications and acute coronary events, including stroke, myocardial infarction, and unexpected death. However, its harmful consequences are considerable and relatively rapidly reversible after quitting.

Based on this evidence, the American Heart Association outlines 10 guidelines for preventing cardiovascular diseases. These include strict recommendations to avoid tobacco use, encourage quitting, and minimize exposure to secondhand smoke.[21] However, the role of other issues, such as vitamin D, metabolic profile, inflammation, and oxidative stress, is also significant in cardiovascular complications among smokers.[22]

Here's a summary of the primary mechanisms by which smoking contributes to cardiovascular diseases:[23]

- *Endothelial Dysfunction:* Nicotine and other toxins in cigarette smoke harm the inner lining of blood vessels, known as the endothelium. This damage impairs the endothelium's ability to regulate blood vessel tone and blood clotting, promoting inflammation and the buildup of plaque.
- *Increased Oxidative Stress:* The chemicals in cigarette smoke generate a high level of free radicals in the body, leading to oxidative stress. This process damages cells and tissues, remodeling cardiomyocytes, accelerating the progression of fibrosis and atherosclerosis, and arrhythmias.
- *Atherosclerosis:* Smoking promotes the formation of fatty plaques inside arteries. This buildup, known as atherosclerosis, narrows the blood vessels and hardens the arterial walls, which can limit blood flow and lead to stroke and heart attack.
- *Increased Platelet Aggregation:* The toxic compounds in smoke make blood platelets stickier. This increases the risk of blood clots forming in arteries, which can stop blood flow to the heart or brain, leading to a heart attack or stroke.
- *Increased Blood Pressure and Heart Rate:* Nicotine stimulates the sympathetic nervous system and causes an immediate increase in blood pressure and heart rate. Over time, these chronic consequences damage the heart muscle and blood vessels.
- *Dyslipidemia:* Smoking lowers levels of "good" High-density lipoprotein (HDL) cholesterol while increasing "bad" low-density lipoprotein (LDL)

cholesterol and triglycerides, which promotes plaque buildup.

- *Insulin Resistance:* Smoking can also cause insulin resistance, raising the risk of developing type 2 diabetes, the most important independent risk factor for CVD.
- *Diminished Oxygen Transport:* Carbon monoxide in cigarette smoke binds to hemoglobin in erythrocytes, reducing the volume of oxygen delivered to the heart and other tissues.

These mechanisms collectively increase the risk of serious CVDs, making smoking a cause of preventable death worldwide.

Regarding the adverse effects of nicotine-containing electronic cigarettes, there is still no evidence confirming whether they increase the risk of CVDs such as stroke, myocardial infarction, and heart disease-related mortality. However, precise evidence suggests that nicotine-containing e-cigarettes significantly increase systolic blood pressure, heart rate, diastolic blood pressure, and arterial fibrillation. Additionally, studies on whether quitting e-cigarettes after long-term use reduces blood pressure remain limited.[24]

Cardiovascular Effects of Caffeine

Coffee is one of the most common drinks in the world, with an estimated 3 billion cups used every day.[25] Based on a cross-sectional study, in Iran, the prevalence of Caffeine Use Disorder (CUD) was estimated to be 19.5%, while the prevalence of caffeine withdrawal (C.W.) was found to be 46.62%.[26] Caffeine consumption has been related to various reversible and short-lived physiological changes, specifically cardiovascular effects. However, some evidence suggests that moderate caffeine intake (levels up to 600 mg per day) is not related to higher risks of CVDs or blood pressure changes in coffee drinkers, and the documentation of cardiovascular effects from daily intakes exceeding 600 mg is not adequate.[27]

However, based on research, the cardiovascular effects of caffeine consumption in patients are slightly different from those in healthy individuals. For example, in some vulnerable individuals, including patients with CVDs, sleep disorders and substance use issues may be unsafe and risky.[28]

In general, caffeine consumption increases blood pressure, which is related to its impact on endothelial and vascular function. In addition, it may increase cardiac workload and reduce cerebral blood flow velocity. However, more research using standard methods is required for more accurate results.

Cardiovascular Effects of Cannabinoids

Cannabinoid compounds have gained significant popularity, especially among young people, and are commonly between illegal substances. Cannabis use disorder (CUD) is an important and often overlooked risk related to cannabis use, affecting about 10% of the world's 193 million cannabis users.[29] Based on a systematic review, written by Nazarzadeh et al., the prevalence of cannabis abuse was found to be 4% among high school and college students in Iran.[30] While there is extensive information on the psychological effects of cannabinoids, less attention has been given to the cardiovascular effects associated with their use. Cannabis consumption can lead to increased blood pressure, heart rate, and the development of arrhythmia and myocardial infarction, likely due to enhanced cardiac function resulting from the stimulation of CB1 receptors in the heart.[31] These effects are dose-dependent, and continued use leads to a decline in cardiac function and blood pressure. Generally, cardiovascular symptoms caused by cannabis are well tolerated by most healthy young individuals, but for patients with heart disease, these consequences are unpredictable, and sudden death after use is a possibility. Some studies suggest that CB1 receptor antagonists (restricted to peripheral action) may be a hopeful strategy for reducing cardiac dysfunction and myocardial apoptosis caused by cannabinoid use.[32]

Cardiovascular Effects of Stimulants

Globally, people use stimulants for their effects, which include producing euphoria, boosting confidence and energy, and reducing hunger. While this group includes many natural and synthetic compounds, cocaine and amphetamines, particularly methamphetamine, have drawn significant attention due to their widespread non-medical use and the serious complications they can cause. An estimated 0.4% of the worldwide population used cocaine, and 0.7% used amphetamines. Among these users, dependence affected 16% of those who used cocaine and 11% of those who used amphetamines.[33] The lifetime prevalence of stimulants use in Iran is at an intermediate level. Based on a meta-analysis published in 2021, the pooled lifetime prevalence of non-prescription use of amphetamine-type stimulants, methamphetamine, ecstasy, and methylphenidate (Ritalin) in Iran was 5.4%, 6.7%, 5.9%, and 16.4%, respectively.[34] Methamphetamine use is on the rise globally, leading to significant complications and mortality, partly due to methamphetamine-related cardiovascular diseases. Human studies have shown that methamphetamine consumption results in a rapid and acute increase in blood pressure and heart rate. Chronic methamphetamine use can cause a considerable rise in systemic and pulmonary blood pressure. Additionally, chronic exposure to methamphetamine leads to vascular constriction and persistent reduction in cerebral blood flow, caused by vascular damage and an imbalance in compounds that regulate vessel diameter.[35]

Due to methamphetamine-induced vasoconstriction,

its consumption is often associated with acute angina, linked to vascular spasms in coronary arteries or small coronary vessels, leading to severe reductions in blood flow to heart tissue. This condition may not even respond to vasodilator treatments, as methamphetamine affects both vascular function and myocardial performance, reducing sensitivity to nitroglycerin.[36] Furthermore, methamphetamine use leads to fibrosis and structural changes in the heart's electrical conduction, increasing QT interval and susceptibility to arrhythmias. Some chronic toxic effects of methamphetamine are also linked to increased inflammation, activation of T cells and macrophages, and enhanced formation of atherosclerotic plaques.[36]

Cocaine use leads to permanent structural and functional abnormalities in the heart, resulting in chronic reductions in left ventricular contraction ability and an increased incidence of certain arrhythmias. Additionally, coronary artery constriction and atherosclerosis develop, making cocaine users more susceptible to myocardial infarction.[37]

The primary side effect of cocaine on the heart is excessive stimulation of the adrenergic system. Many toxic effects of cocaine at the molecular level are derived from increased oxidative stress and mitochondrial dysfunction due to the metabolism of additional catechol amines, leading to myocyte cell death via both apoptosis and necrosis pathways.[32]

Furthermore, cocaine increases the production of endothelin-1 (a vasoconstrictor) while also causing a chronic decrease in nitric oxide production and endothelial nitric oxide synthase expression, which contributes to chronic hypertension.[38]

Cardiovascular Effects of Sedative Drugs

Sedative drugs, which include benzodiazepines, z-drugs (including Zolpidem, zopiclone, and zaleplon), and barbiturates, are widely prescribed for the treatment of anxiety and insomnia. However, they have a potential risk of misuse and abuse, and they are all classified as controlled substances. In 2018, approximately 6.5 million residents in the United States misused prescription tranquilizers or sedatives, including benzodiazepines and Z-drugs.[39] According to a cross-sectional study, the prevalence of non-prescription use of sedative-hypnotic drugs among university students was reported to be 10.3% in Iran.[40] While there is restricted and conflicting evidence regarding the cardiovascular effects of sedative drugs, including benzodiazepines alone,[41] it is still essential to consider these effects for several reasons:

1. The concurrent use of sedatives with certain addictive substances, such as opioids and alcohol, is associated with severe cardiac and respiratory complications, ultimately leading to cardiac arrest.
2. Anxiety disorders are significant risk factors for cardiovascular diseases. Treating anxiety is crucial due to its high prevalence in individuals with heart disease, but the potential side effects of sedative medications in these patients must be considered.
3. Some studies highlight the cardiovascular risks associated with medical treatments using sedatives. For example, in surgical settings, patients who receive additional sedatives have double the risk of cardiopulmonary arrest compared to those treated only with opioid analgesics.[42]

Cardiovascular Effects of Anabolic Steroids

Anabolic androgenic steroids (AAS) are synthetic androgens derived from testosterone, commonly used by athletes, particularly bodybuilders, to build lean muscle mass and enhance performance. A lifetime prevalence of anabolic-androgenic steroid use is expected to affect about 6% of men.[43] Reports indicate that 3,000,000 people in the United States have used non-therapeutic AASs.[44] Based on a systematic review and meta-analysis, the overall prevalence of AAS use was reported to be 36.2% among the Iranian athletic population.[45] The use of anabolic steroids may be related to an increased risk of atherosclerosis, thrombosis, vascular spasms, and myocardial infarction due to harmful effects on blood lipids, platelets, and the hematopoietic system.[46, 47]

Although it is worth noting that anabolic steroids are also used as testosterone replacement therapy in conditions such as organic hypogonadism. This treatment is FDA-approved and carries a relatively low risk of cardiovascular disease.[48]

Table 2 shows an overview of the acute and chronic impacts of substance consumption on the cardiovascular system, along with the associated mechanisms. In addition, Table 3 provides a list of selected clinical studies conducted on the cardiovascular effects of various substances.

Discussion

In the results section, this study presented a comprehensive review of existing literature, with a particular focus on the cardiovascular effects of substance use. Accordingly, the discussion offers an overview of the underlying mechanisms contributing to these effects, highlighting their potential overlaps. At the end of the discussion, a forward-looking perspective on this topic and outlining directions for future research are presented.

Cardiotoxic Mechanisms of Substance Use

Severe Sympathetic Nervous System Stimulation

This is the most important mechanism of cardiac damage from stimulants. Substances including cocaine and methamphetamine (crystal meth) severely activate the sympathetic nervous system. This system controls the "fight-or-flight" response:

Table 2. Summary of acute and chronic cardiovascular complications induced by substance use and their mechanisms

Substance	Acute effects	Chronic effects	Mechanisms
Opioids	• Myocardial infarction • Long QT syndrome • Cardiac arrhythmias	• Infective endocarditis • Coronary artery disease • Atherosclerosis • Cardiomyopathy • Exacerbation of hyperlipidemia, hypertension, and diabetes	• Inflammation • Oxidative stress
Alcohol	• Atrial tachyarrhythmia • Reduced myocardial contractility • Myocardial inflammation • High blood pressure • Hemorrhagic stroke	• Atrial fibrillation • CAD • Alcoholic cardiomyopathy	
Nicotine	• Myocardial infarction	• High blood pressure • Coronary artery disease • Cardiomyopathy • Insulin resistance and diabetes • Increase in undesirable blood fats	• Oxidative stress • Activation of platelets and thrombosis • Induces chronic inflammation • Reduced oxygen-carrying capacity of red blood cells
Cannabinoids	• Tachycardia • High blood pressure • Myocardial infarction • Stress cardiomyopathy • Cardiac arrhythmias • Persistent hypotension	• Coronary artery disease • High blood pressure	• Cardiac CB1 receptor stimulation
Stimulants	• Sudden increase in blood pressure • Myocardial infarction • Stroke • Cardiac arrhythmias • Infective endocarditis • Stress cardiomyopathy	• Cardiomyopathy • Accelerated atherosclerosis • Pulmonary hypertension	• Overactivation of the adrenergic system • Production of endothelin and other vaso-constrictors • Oxidative stress • Blockage of cardiac sodium/potassium channels • Infection following intravenous injection
Sedative drugs	• Cardiorespiratory arrest • (in case of overdose or combination with other substances)	• Chronic hypotension	• Interactions with other substances and medications, especially opioids
Anabolic steroids	• Cardiac arrhythmias • Myocardial infarction	• Accelerated atherosclerosis • Cardiomyopathy Vascular spasms • Metabolic syndrome • Hypertension • Hyperlipidemia	• Adverse effects on the coagulation system and thrombosis
Caffeine	• Hypertension • Tachycardia • Increased blood circulation velocity	• Increased risk of cardiovascular disease and stroke in vulnerable individuals	• Stimulation of the sympathetic system • Dopamine release stimulation • Induction of vasoconstrictor factors

- *Increased Blood Pressure and Heart Rate:* These substances cause a rapid increase in heart rate and blood pressure, forcing the heart to work much harder.
- *Coronary Artery Spasm:* They can cause a sudden and severe constriction of the coronary arteries and vessels. This spasm severely reduces blood flow to the heart, which can lead to acute cardiovascular events, especially in high-risk groups.
- *Increased Oxygen Demand:* The increased heart rate and blood pressure raise the heart muscle's demand for oxygen, while the artery spasm limits the oxygen supply. This imbalance can lead to acute damage or even cell death (myocardial infarction).

Direct Damage to Cardiac Cells

Some addictive substances directly damage the heart cells (cardiomyocytes). This mechanism involves the destruction and death of heart muscle cells:

- *Oxidative Stress:* Substances such as methamphetamine can cause an overproduction of reactive oxygen species (ROS). ROS molecules damage cellular components such as DNA, proteins, mitochondria, and cell membranes, leading to the death of heart cells. This process is similar to the mechanism of some chemotherapy drugs.
- *Fibrosis and Remodeling:* Chronic damage to the cells activates inflammatory processes and leads to the production of fibrotic (scar) tissue in the heart. This scar tissue makes the heart inflexible and impairs heart function, eventually leading to arrhythmias and heart failure. This process is particularly common with long-term stimulant use.

Conduction System Dysfunction

Some substances, particularly stimulants and even alcohol, can affect the cardiac channel function (channels for potassium, sodium, and calcium ions) in heart cells. This mechanism leads to irregular heart rhythms (arrhythmias):

Table 3. Examples of human studies conducted on the cardiovascular effects of addictive substances

Substance	Reference	Study characteristics	Target groups	Variables	Study outcome
Methadone	Vallecillo et al [49]	• Observational Study • 94 users and 495 from the general population • Men over 50 years old	Elderly individuals undergoing methadone treatment	• Obesity • High blood pressure • Dyslipidemia • Smoking	Higher prevalence of cardiovascular risk factors in methadone users
Opioids	Ozen et al[50]	• Cohort (23 years) • 6866 opioid users and 13689 NSAID users • Patients with rheumatoid arthritis (RA)	Groups: • Opioids • Non-steroidal anti-inflammatory drugs (NSAIDs)	• Main adverse cardiovascular event (MACE) risk: (myocardial infarction, heart failure, stroke, venous thromboembolism, and mortality)	• The risk of MACE in the opioids group was similar to that in the NSAIDs group. • Mortality in opioid users was 33% higher than in NSAID users. • Heavy opioids have a higher risk of mortality and VTE than weak opioids and NSAIDs. There is a dose-dependent relationship between the risk of MACE and opioid use.
Caffeine	Agudelo-Ochoa et al [51]	• Randomized Control Trial • 38 men and 37 women, healthy • Healthy men and women • The mean age of them was 38.5 years	Groups: • Control group • High-dose coffee group with CGA (chlorogenic acids) (780 mg) • Low-dose coffee group with CGA (420 mg) • Daily coffee consumption of 400 ml (193 mg/day) • Duration: 8 weeks	• Plasma levels of caffeic and ferulic acid • Blood lipid profile • Blood nitric oxide (NO) and vascular endothelial function • Blood pressure	• Significant elevations in concentrations of caffeic acid and ferulic acid were observed in the coffee-consuming groups ($P<0.001$). • After eight weeks, no significant alterations were observed in lipid levels, vascular function, blood pressure, or plasma NO between the groups. • Plasma antioxidant capacity acutely increased in both caffeine groups (one hour after coffee consumption)
Caffeine (Coffee, caffeine, tea)	Zheng et al [52]	• Cohort • 626 participants • Patients with cardiovascular disease • Aged≥18 years old	Groups: • Survival group (304) • Non-CVD death (223) • CVD death group (99)	• CVD death: (Death due to congestive heart failure (CHF), disease (CHD), angina pectoris, coronary heart disease, heart attack, or stroke) • Coffee, caffeine tea use • Decaffeinated coffee/tea use	• Association between coffee, caffeine, iced tea, and hot tea consumption (≥4 cups per day) and an increased risk of death in CVD patients. • Consumption of hot tea (1-3 cups per day) or decaffeinated coffee/tea reduced the risk of death. • Relationship between extreme consumption of coffee, tea, and caffeine and an increased risk of CVD death for CVD patients.
Caffeine	Zhou and Hyppönen [25]	• A prospective cohort analysis based on the UK Biobank data • 347,077 participants including 8368 incident CVD cases	Groups: • Very high coffee or tea intakes (≥16 cups/day, N=1437) • Other groups: based on daily coffee intake were grouped: (<1, 1–2, 3–4, 5–6, and>6 cups)	• CVDs (coronary artery disease, stroke, and peripheral artery disease), blood pressure • Genetic factor of caffeine metabolism: The CYP1A2 (rs762551) genotype	• Heavy coffee consumption was associated with a modest increase in CVDs risk. • CYP1A2 genotype was not related to CVDs (P≥0.22). • There was no evidence for a connection between the CYP1A2 genotype and coffee intake with CVDs (P≥0.53).
Alcohol	Biddinger et al[53]	• 10-year cohort • 371,463 participants • Men with an average age of 57 years	Non-European men who consume alcohol in different dosages	• Alcohol consumption dosage • Types of cardiovascular diseases	• The link between alcohol use at all levels and increased cardiovascular risk • The exponential rise in cardiovascular disease risk following heavy alcohol consumption

Table 3. Continued.

Substance	Reference	Study characteristics	Target groups	Variables	Study outcome
Alcohol	Shao et al [54]	• Prospective cohort • 502,490 participants • Men and women aged 40 to 69 years	Alcohol consumers participating in the large-scale UK Biobank study	• Alcohol consumption dosage • Mortality caused by cardiovascular disease, kidney disease, cancer, and other chronic diseases	• The safe alcohol consumption dose was: lower than 11 grams/day for men and lower than 10 grams/day for women • A safe dose is related to a lower risk of heart and kidney diseases, whereas higher doses are directly linked to mortality from cardiovascular and chronic kidney diseases • The protective effect of a safe alcohol dose against depression, diabetes, dementia, epilepsy, and liver cirrhosis is noted. • Alcohol does not increase the risk of cancer
Nicotine	Allagbé et al [55]	• Observational study (16 years) • 36,864 people, 42% women, 58% men • Men and women over 18 years old • Having more than one cardiovascular risk factor	Groups • Men • Women	• Risk factors and burden of cardiovascular problems	• Female smokers had an elevated burden of risk factors, particularly lung disease, obesity, anxiety-depression symptoms, and lower cessation rates. • The prevalence of hypercholesterolemia, hypertension, diabetes, CVDs, nicotine dependency, and addiction was higher in men. • There is a necessity to plan comprehensive smoking cessation interventions tailored to gender.
Nicotine (Electronic cigarettes)	George et al [56]	• Prospective, randomized controlled trial study • Men and women over 18 years old • Smokers who had used more than 15 cigarettes/day for over 2 years and did not have heart disease	Groups: • Nicotine-containing electronic cigarettes (37) • Nicotine-free electronic cigarettes (37) • Parallel smoking group (40)	• Arterial blood flow • Resting heart rate • Blood pressure • Coagulation and inflammation factor	• Significant improvement in arterial blood flow in the e-cigarette groups compared to traditional smoking ($P<0.0001$). • This improvement in vascular function was more pronounced in women. • There was no significant dissimilarity in arterial blood flow among the nicotine-containing and nicotine-free e-cigarette groups ($P=0.78$). • No notable dissimilarities were observed in heart rate, inflammatory biomarkers, and platelet response among the three groups. • However, a reduction in heart rate was observed in heavy smokers (over 20 packs per year) who switched to e-cigarettes
Nicotine (electronic nicotine delivery systems: ENDS)	Tattersall et al [57]	• Observational challenge study (before and after) • Participants were ≥18 years old and without cardiovascular or pulmonary diseases or COVID-19 infection	• EDNS participants • Participants who smoke cigarettes exclusively • The control group did not use tobacco or vape Groups: • 164 who used ENDS • 114 as Control participants • 117 Cigarette Users	• Acute cardiovascular and pulmonary responses to 15-min ENDS use • Exhaled carbon monoxide level • Urine Nicotine Check results	• Acute vasoconstriction, exercise tolerance, impaired blood pressure, heart rate, and increased airflow obstruction after vaping were seen in the ENDS group, compared to the control group.
Cigarette	Duncan et al [58]	• Observational cohort study • 8770 participants	Groups: • Former heavy smokers (≥20 pack-years) • Current smokers • Non-smokers	• Risk of CVDs: stroke, myocardial infarction, heart failure, or cardiovascular death	• Among heavy smokers, smoking cessation was related to significantly lower risk of CVDs within 5 years compared to current smokers (hazard ratio, 0.61) • Risk of cardiovascular disease remained elevated for at least 5 to 10 years and possibly for 25 years after cessation relative to never smokers.

Table 3. Continued.

Substance	Reference	Study characteristics	Target groups	Variables	Study outcome
Cannabinoids (marijuana)	Khan et al[59]	Case report • A 25-year-old African-American man • No history of disease • No family history of cardiovascular disease	• History of past cigarette smoking • Current marijuana use	• Acute confusion, right-sided weakness • Reduced left ventricular ejection fraction (EF) • Deep vein thrombosis of the left brachiocephalic vein • Brain edema and ischemia of the cerebral artery	• Diagnosis of acute ischemic stroke with ischemic cardiomyopathy induced by cannabinoids.
Cannabis	Jeffers et al[60]	• Population-based, cross-sectional study • 434104 respondents • Adults aged 18 to 74 years old	-	• Cannabis use • Cardiovascular outcomes as Self-reporting (stroke, coronary heart disease, myocardial infarction) • Tobacco use	• The prevalence of daily cannabis consumption was 4%, while non-daily use was 7.1%. • Cannabis consumption was related to cardiovascular outcomes. • With heavier use (more days of the month), higher odds of outcomes appeared. • In the never-tobacco-smoker group, and among younger participants, daily cannabis consumption was also related to cardiovascular outcomes.
Amphetamine	Alzeer et al[61]	Case report • A 28-year-old man • No history of heart disease • History of asthma	• Recreational amphetamine use • Smoking two packs per day for 14 years	• Chest pain • Shortness of breath during exercise • Cardiac arrest 7 minutes after arriving at the emergency department	• Myocardial infarction, ventricular fibrillation, and cardiac arrest • Three rounds of CPR were performed • Coronary angiography, stent placement, and resolution of coronary artery stenosis
Methamphetamine	Dalal et al[62]	Case report • A 29-year-old man • No history of heart disease	• History of past heroin use • Urine test positive for fentanyl and benzodiazepines • Development of cardiac symptoms after two intravenous methamphetamine doses	• Shortness of breath • Progressive respiratory failure	• Cardiomyopathy with delayed onset and severe cardiogenic shock • Support for Cardiovascular and respiratory functions • Recovery after three weeks
Cocaine	Almalouf et al[63]	Case report • A 54-year-old man • History of obesity, bipolar disorder, and diabetes	• Cocaine and alcohol use	• Cardiac arrest before hospital arrival	• Diagnosis of Takotsubo cardiomyopathy (TCM) • Two rounds of CPR performed • Cardiopulmonary arrest and death due to cocaine use
Cannabis, amphetamine & Lisdexamfetamin	Saeed et al[64]	Case report • A 39-year-old man	• History of amphetamine and cannabis use (14 years) • Lisdexamfetamin for ADHD (2 years)	• Severe chest pain for 6 hours • ST-segment elevation	• Chronic fibrotic lesions • Decreased left ventricular ejection fraction (48%) • Acute coronary vasospasm • Stress-cardiomyopathy (Takotsubo syndrome)
Methylphenidate & other Norepinephrine–dopamine reuptake inhibitors (NDRIs)	Kandukuru et al[65]	• Pharmacovigilance study: • A retrospective analysis of the adverse effects of drugs • From 2004 to 2021	Drugs included: • Bupropion • Methylphenidate • Atomoxetine • Reboxetine	• 5086 events for Methylphenidate were reported.	The most diverse cardiovascular events associated with Methylphenidate: • Arrhythmias • Palpitations • Hypertension • The risk of stroke and coronary heart disease increased about 25% and 66%, respectively.

Table 3. Continued.

Substance	Reference	Study characteristics	Target groups	Variables	Study outcome
Sedative drugs	Xie et al [66]	Cohort • 124445 patients • General individuals with insomnia	• Z-meds (Zolpidem, …) • Benzodiazepines	• Dependable use of hypnotic agents • Cardiovascular outcomes: stroke, coronary heart diseases (CHD), heart failure (HF), cardiovascular death	• The association between benzodiazepine use and the increasing risk of CHD, HF, and cardiovascular mortality. • Lack of relationship between Z-meds and stroke, CHD, and cardiovascular mortality. • Cardiovascular events in patients with insomnia were heterogeneous due to different categories of hypnotics. • The cardiovascular effects of benzodiazepines are a matter of concern.
Anabolic Androgenic Steroid (AAS)	Neupane and Kalra [67]	Case Report • A 46-year-old healthy man	• Recent history of anabolic steroid use	• Complaint of swelling and pain in the left lower limb, • Spontaneous bruising of the lower leg, • and Shortness of breath	• Uncontrolled hypertension • Congestive heart failure with reduced ejection fraction (30%)
Anabolic Androgenic Steroid	Thiblin et al [68]	Cohort study • Between 2002 and 2009	2013 men with Non-medical use of AASs, Groups: • 409 men (20%) with positive test for AAS. • Others have a negative test.	Mortality and morbidity	• The positive test group had twice the cardiovascular morbidity and mortality ratio as the negative test group (adjusted hazard ratio (aHR) 2.0; 95% confidence interval (CI) 1.2–3.3). • All men had an elevated risk of early death.
Anabolic Androgenic Steroid (AAS)	Windfeld-Mathiasen et al [46]	Cohort study: • Study between 2006 and 2018, • Follow up until 2023	Groups: • AAS users (n = 1189) • Controls (n = 59 450)	The occurrence of: • Coronary artery bypass graft • Ischemic stroke • Arrhythmia • Cardiomyopathy • Heart failure • Cardiac arrest • Acute myocardial infarction, • Percutaneous coronary intervention	AASs were related to an increased risk of: • Acute myocardial infarction (aHR 3.00 [95% CI, 1.67–5.39]) • Venous thromboembolism (aHR 2.42 [95% CI, 1.54–3.80]) • Arrhythmias (aHR 2.26 [95% CI, 1.53–3.32]), • Cardiomyopathy (aHR 8.90 [95% CI, 4.99–15.88]) • Heart failure (aHR 3.63 [95% CI, 2.01–6.55])

- *Increased Risk of Arrhythmias:* These ionic disturbances can cause irregularities in the heart's rhythm. In severe cases, these arrhythmias can be fatal. For example, cocaine can cause lethal arrhythmias, including ventricular tachycardia or ventricular fibrillation.

Overlap Zones Between Different Substances

Cardiotoxicity from addictive substances is often a result of overlapping damage mechanisms.

Overlapping Mechanisms in Stimulants (Cocaine, Methamphetamine)

These two substances are very similar in their mechanisms. They both cause stimulation of the sympathetic nervous system, increased heart rate and blood pressure, and vascular spasm. They can also both lead to direct cellular damage and fibrosis. Therefore, complications such as heart attacks, cardiomyopathy, and arrhythmias are common to both of them.

Overlapping Mechanisms in Opioids (Opium, Methadone, Heroin, and Fentanyl)

These substances are better known for their effects on the respiratory and central nervous systems. Although opioids can indirectly damage the heart.

- *Reduced Heart Rate:* High doses of opioids can cause severe bradycardia and hypotension, which can be dangerous.
- *Increased Risk of Infection:* The injection use of substances can lead to an infection of the heart valves (endocarditis), which is a serious and potentially fatal complication.
- *Hypoxemia and Apneas:* Opioids disturb the control of breathing and weaken upper airway function. This leads to upper airway obstruction, central apneas, and low blood oxygen levels (hypoxemia) during sleep. These sleep-disordered breathing problems are linked to various CVDs, including stroke, heart failure, atrial fibrillation, and coronary artery disease,

as well as a greater risk of death from CVDs.

Overlapping Mechanisms in Alcohol

Long-term and heavy alcohol drinking may lead to alcoholic cardiomyopathy, a type of heart failure. The mechanism involves direct damage to heart cells. Factors affecting the pathogenesis of alcohol in heart disease include:

- *Direct Toxic Effect of Ethanol:* Ethanol stimulates oxidative stress reactions in the myocardium and activates the renin-angiotensin system.[69]
- *Acetaldehyde (the Metabolite of Alcohol):* Acetaldehyde contributes to myocardial damage, actin-myosin malfunction, and mitochondrial dysfunction [69].
- *Neuro-Hormonal Changes:* Alcohol affects the nervous and endocrine systems, leading to an increase in stress hormones, e.g., cortisol, and changes in other hormones that regulate blood pressure and heart rate.
- *Genetic Factors:* Genetic variations in enzymes that metabolize alcohol, e.g., aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH), may affect a person's vulnerability to heart damage. Genetic mutations in specific cardiac proteins, such as titin, can also make some individuals more vulnerable to developing alcoholic cardiomyopathy.[70]
- *The Synergistic Conditions:* People with pre-existing conditions such as obesity, diabetes, hypertension, or liver disease are at an even greater risk of developing alcohol-related heart problems.
- *Gender:* Women may be more vulnerable to the cardio-toxic consequences of alcohol, even at lower consumption levels, possibly due to differences in metabolism and body structure.
- *Nutrient Deficiencies:* Heavy alcohol drinking may lead to insufficiencies in essential nutrients, for example, thiamine (vitamin B1), which is crucial for heart function.

Therefore, many of these substances, either alone or in combination, can cause a spectrum of heart complications, e.g., arrhythmias, heart failure, and sudden cardiac death. Understanding these mechanisms is essential to prevent and treat them. Figure 2 provides an overview of the cardiovascular effects of substance use.

Figures 3 and 4 show the cardiovascular effects of substance use on the various components of the circulatory system and the cardiovascular system, respectively.

Future Perspectives on the Association Between Substance Use and CVDs

While current research has established a clear relationship between substance use and cardiovascular disease, significant gaps in our knowledge remain. Future research is vital for developing our understanding of these complex relationships and for developing more efficient strategies for prevention, diagnosis, and treatment. Several key areas warrant further investigation:

Molecular and Cellular Mechanisms

We need more detailed studies to fully understand the specific molecular and cellular pathways through which different substances cause cardiovascular damage. This includes clarifying how factors like oxidative stress,

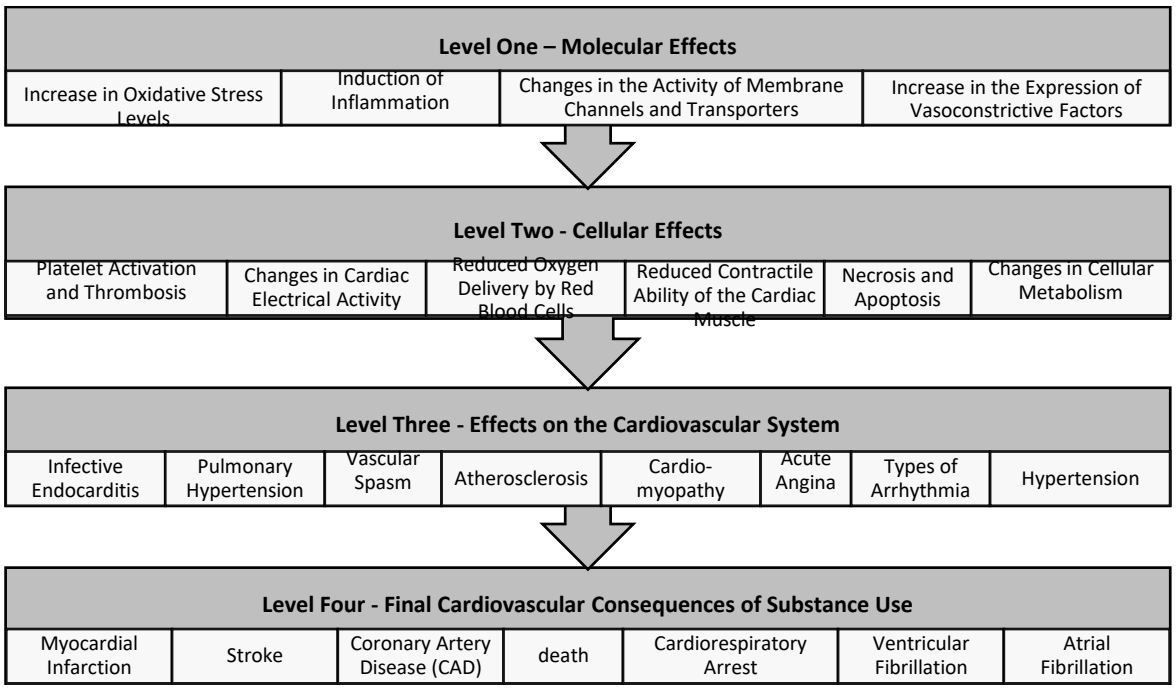

Figure 2. An overview of the effects of substance use on the human cardiovascular system at different levels, including biological molecules, heart and blood vessel tissue, blood circulation, the entire cardiovascular system, and the final cardiovascular outcomes of substance use

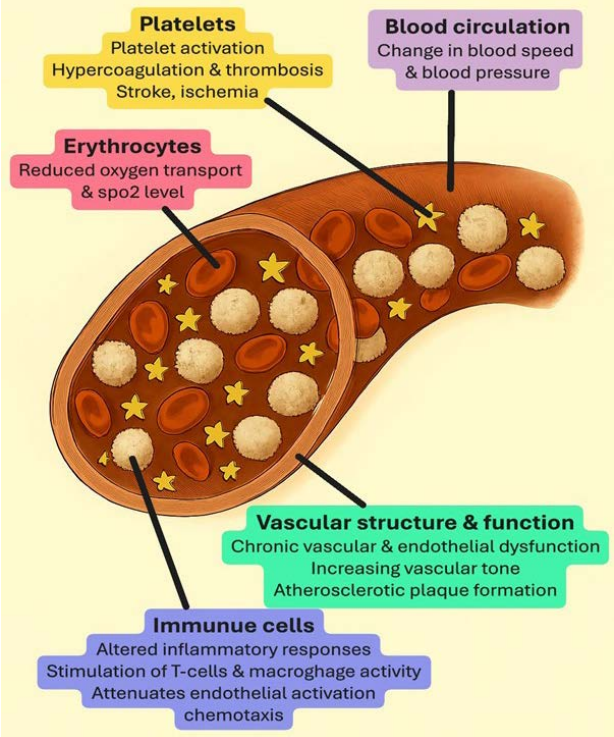

Figure 3. The effect of substances on general blood circulation and blood cells

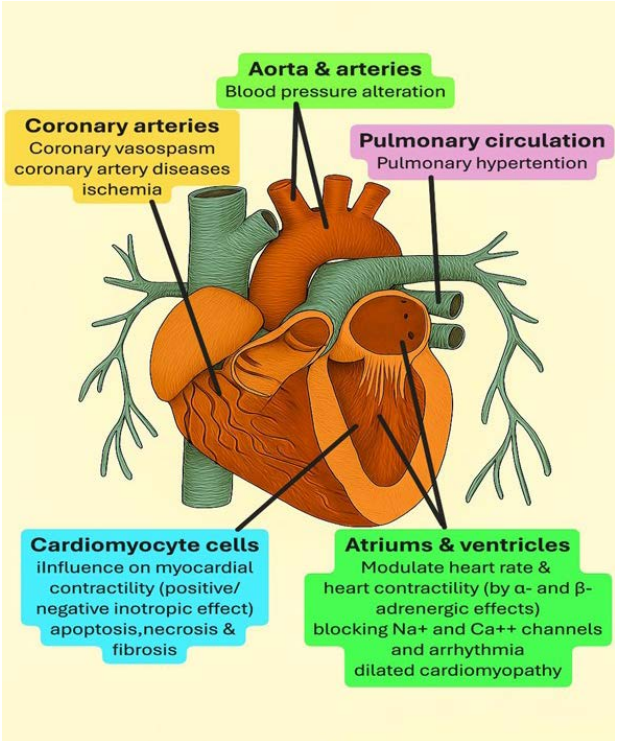

Figure 4. The effect of substance use on the heart, veins, and arteries

inflammation, and cellular toxicity differ across various substances and how they interact with pre-existing genetic predispositions.

Emerging and Synthetic Substances

The cardiovascular effects of new psychoactive substances (NPS), synthetic cannabinoids, and potent synthetic opioids like fentanyl are largely unknown. Research is urgently needed to identify the unique cardio-toxic profiles of these substances and to understand their acute and long-term effects on the heart and vasculature.

Long-Term and Poly-Substance Use

Most studies focus on single substances, but in reality, many individuals use multiple substances (poly-substance use). Future research should use large, longitudinal cohorts to investigate the cumulative and synergistic effects of multiple substances on cardiovascular health over an individual's lifetime.

Genetic and Epigenetic Factors

The role of genetics in an individual's susceptibility to substance-induced cardiotoxicity is still poorly understood. Future studies should focus on pharmacogenomics and epigenetics to identify genetic markers that predict a higher risk of cardiovascular events in substance users.

Clinical Management and Therapeutic Strategies

This knowledge must be translated into clinical practice. Future research should aim to develop specific clinical guidelines for screening and managing cardiovascular risk in substance-using populations, as well as exploring novel therapeutic interventions that can counteract the cardiotoxic effects of these substances.

Limitations

Since determining risk factors and the incidence of heart disease following substance abuse requires long-term follow-up of samples, the number of retrospective or prospective studies with large sample populations in this field is limited. A significant portion of the existing studies consists of case reports or research conducted with small sample sizes. Additionally, the high likelihood of sample dropout in such studies presents further challenges to research in this area.

Moreover, due to the necessity of multiple examinations and laboratory tests, these studies incur relatively high costs. Nonetheless, the importance and practical aspects of the subject justify further research, and the findings of such studies hold substantial value.

Conclusion

The acute and chronic cardiovascular effects of substance use are extensive and clinically important. Therefore, the individualized diagnosis and management of substance use disorders are essential, tailored to each patient's unique characteristics. Based on this, the outcome of this study can offer an initial perspective for specialists to implement cardiovascular interventions. Additionally,

it may offer evidence for future study about the consequences and mechanisms of substance use on the cardiovascular system.

Acknowledgments
The authors would like to thank the Clinical Research Development Unit of Kashan Shahid Beheshti Hospital.

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Competing Interests
The authors declare no conflict of interest.

Ethical Approval
This article is a review with no human or animal sample.

Funding
This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

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