**ABSTRACT**

Background: Smoking increases the risk of cardiovascular disease (CVD) and significantly affects the severity and pattern of coronary artery disease (CAD). Moreover, tobacco smoking increases the risk of CVD and finally will cause morbidity and mortality. It has been proved that the increment of habitual consumption of cigarettes per day up to 20 increases the risk of myocardial infarction by about three times greater than in nonsmokers. **Objective:** In this study, we are trying to review the effect of cigarettes and their nicotine content on heart health and the heart disease which are induced by smoking. **Method:** A comprehensive literature search was performed in PubMed, EMBASE, Cochrane Library, PubMed Central (PMC), UpToDate databases, and Google Scholar databases from 2012 till Feb 2020. In this regard, pre-decided keywords were used and specific inclusion/exclusion criteria were considered to achieve more accurate and related papers. Data were extracted from all the included studies through a precise review of the articles. **Conclusion:** In this study, the evidence regarding the effect of smoking on coronary heart disease (CHD) and the severity and pattern of CVD are reviewed. Based on our study, smoking increases the risk of nearly all CVD subtypes such as acute myocardial infarction (AMI), cerebrovascular disease, and heart failure. Smoking has some relative risks that their fatal and non-fatal outcomes are similar. The risk of heart diseases related to smoking will decrease significantly after quitting smoking.

**Keywords:** Smoking, Nicotine, Heart, Coronary Heart Disease, Cardiovascular Disease
Introduction

Cardiovascular disease (CVD) is known to be one of the main leading factors which increase mortality globally. CVD includes heart failure, peripheral arterial disease (PAD), cerebrovascular disease, cardiac dysrhythmias, and coronary heart disease (CHD) [1]. Recent studies have shown that tobacco smoke from cigarettes is one of the main leading causes of deadly diseases such as cardiovascular disease (CVD) which increased the rate of morbidity and premature death and is considered an urgent public health target [2, 3].

However, despite the fact that this deadly factor could be prevented, smoking has remained a major public health problem worldwide. The rate of people who die because of lung cancer, heart diseases, chronic obstructive pulmonary disease (COPD), and other diseases is higher among smokers compared to those who do not smoke [4, 5]. This risk increases with the increment of the duration of smoking or its intensity [6].

One of the methods for decrement of the health risk for individuals who do not decide to quit smoking is tobacco harm reduction (THR). In this regard, less harmful tobacco and/or nicotine products (TNP), or modified risk tobacco products (MRTP) should be produced [7].

Although the health problem of the prevalence of cardiovascular risk factors has been studied by numerous researchers worldwide, contradictory results have been achieved because CHD is a multifactorial disorder with a majority of risk factors including demographic factors, age, family history, gender, genetic factors, diabetes mellitus, high cholesterol, smoking, and hypertension [8-10].

Smoking is considered to be a primary risk factor that has a significant role in premature CAD and accelerates atherosclerosis as a result of damaging coronary endothelial vasodilation and increment of oxidation of low-density lipoprotein (LDL) [11]. The severity and extent of vascular occlusion could be determined by premature and accelerated coronary atherosclerosis [12]. An appropriate option to achieve a successful treatment is having knowledge about the patient’s pattern and severity of vascular occlusion [13]. The effect of different risk factors such as demographic factors, gender, age, smoking, diabetes, hypertension, and hyperlipidemia on the pattern and severity of CHD have been studied by a lot of researchers [14, 15]. Among them, smoking is the most crucial risk factor, while related studies have reported conflicting results.
Generally, the studies related to the smoking side effects, have concentrated on fatal CVD outcomes, while the evidence on non-fatal outcomes is limited. The same as CVD risk factors, the excess relative risks that are related to smoking decrease with age while excess absolute risks (EAR) will increase [16]. Despite the limitations of the data about the risk factors associated with smoking, adequate evidence is available about the greater effect of smoking on CHD in women compared to men [17].

Since progress has been achieved in the medical treatment of diseases and the global burden of disease has shifted from etiologies to chronic disease, the most logical population health intervention is to decrease the administration of manufactured remedial products which may worsen the chronic disease. One of the most effective approaches which help in smoking cessation and decrement of smoking harm is to promote the administration of non-combustible products that deliver nicotine to the body [18]. Up to now, it has been proved that the most effective way to eliminate the health risks of smoking, is to never smoke for normal people and to quit smoking for those who smoke regularly [19]. Anyway, the present study is aimed to assess the effect of cigarette and its nicotine content on heart health.

**Material and Method**

The present study was aimed to investigate the effect of cigarettes and their nicotine content on heart health. In this regard, a comprehensive set of papers were searched from the most well-known databases of PubMed, EMBASE, Cochrane Library, PubMed Central (PMC), UpToDate. In this regard, the Systematic Reviews and Meta-Analyses (PRISMA) protocol was used to restrict searched articles, select the ones that are more related, and delete the ones which are less related. To perform the present research a comprehensive search was carried out using international databases from 2012 up to Feb 2022. At first, 407 articles were searched using keywords of cardiovascular disease (CVD), risk factors, smoking, nicotine, tobacco, heart disease, and coronary artery. Figure (1) shows the schematic diagram of the PRISMA method performed in this study.

**Inclusion Criteria**

One of the main criteria for evaluating the results of published reports is their quality which could be specified through the qualitative screening process. Similar review studies and observational studies were included in this study which includes all cohort studies, and descriptive or analytical
studies. In this regard, some clinical trials were also included in which the studies that reported the rate of coronary occlusion, and the severity of CHD in smoker patients. After selecting the most appropriate articles, eligible studies and those with powerful content were selected to be reviewed more carefully. The abstract also the text of the selected articles was screened carefully by the research team authors. In the end, the article which met the inclusion criteria were screened carefully and the required data were taken out from them. All the processes of finding, screening, elimination, and selection of the articles were carried out based on the PRISMA method.

**Association of cigarette smoking and heart disease**

To know the possible side effects of nicotine on heart health, we should have adequate knowledge about cigarette smoking and CHD. Smoking and nicotine consumption are both the main causes of premature CHD in the world [20]. Premature CHD is a situation in which coronary arteries get narrower because of cholesterol plaques. Premature CHD in men and women happens before the age of 55 and 65 years respectively. In the early course, premature CHD is often asymptomatic which then may lead to a heart attack with the progressive development of pyloric stenosis [21]. Smoking and nicotine consumption noticeably increase the risk of acute coronary syndrome and also cerebrovascular events such as sudden death, stroke, and heart attack [22]. The process of producing premature atherosclerosis in carotid arteries, cerebral arteries, epicardial coronary arteries, and aorta is accelerated by smoking [23]. Smoking also has some extra cardiovascular effects such as vasospastic angina (VSA), vascular claudication, aggravate angina pectoris, and peripheral arterial disease. Moreover, smoking increases the risk of heart failure, chronic kidney disease (CKD), cardiovascular morbidity, and increase the risk of atrial fibrillation (A-fib) [24]. All possible side effects of smoking are summarized in table (1). Acute myocardial infarction is experienced by smokers commonly at a younger age compared to those who do not smoke. It should be noted that heart attack is associated with less severe underlying atherosclerosis and more thrombus. On the other hand, patients who quit smoking after a heart attack have a higher prognostic ability compared to non-smokers since smokers had experienced more reversible pathophysiological side effects and less severe underlying atherosclerosis [25].
Figure 1. Schematic diagram of PRISMA method based on which the present study was performed.

Table 1. Possible Cardiovascular Disorders Induced from Smoking

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Inducing Cardiac Risk Factors</th>
<th>- Diabetes, type 2</th>
</tr>
</thead>
</table>
Vascular Disease
- Dyslipidemia
- Hypertension, including malignant hypertension
- Hypertensive renal disease
- Accelerated atherosclerosis
- Acute myocardial infarction
- Shorter exercise time to angina
- Coronary spasm
- Stroke
- Aortic Aneurysm
- Peripheral obstructive arterial disease
- Stent thrombosis after PCI
- Graft occlusion after coronary bypass surgery

Arrhythmias
- Sudden cardiac death
- Atrial fibrillation
- Implantable debrillator shocks

Myocardial Disease
- Increases risk and aggravation of heart failure
- Hypertensive heart disease

Other diseases
- Impaired wound healing
- Reproductive disorders
- Erectile dysfunction
- Macular degeneration

How does nicotine cause CVD
The mechanisms of action by which smoking and the consumption of nicotine causes CVD have been examined by several recent studies [26]. Concisely, the main mechanisms of which smoking causes CVD are oxidative stress, decrement of oxygen delivery by red blood cells, arrhythmogenesis, adverse effects on lipids in the blood, increment of thrombosis risk, causes diabetes, and insulin resistance, chronic inflammation, hemodynamic stresses, and endothelial dysfunction. Another concern that is health-threatening is enhanced angiogenesis, while its association with cardiovascular disease has not yet been established [27]. In this regard, table (2) shows the mechanism of actions that contribute to cardiovascular diseases.
### Table 2. The mechanism of actions through which smoking causes cardiovascular diseases

<table>
<thead>
<tr>
<th>Smoking Products and compounds</th>
<th>Cardiovascular event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First stage side effects</strong></td>
<td><strong>Second stage side effects</strong></td>
</tr>
<tr>
<td><strong>Oxidant chemicals and Particulates</strong></td>
<td>- Inflammation</td>
</tr>
<tr>
<td></td>
<td>- Endothelial dysfunction</td>
</tr>
<tr>
<td><strong>Carbon monoxide</strong></td>
<td>- Reduced oxygen availability</td>
</tr>
<tr>
<td><strong>Nicotine</strong></td>
<td>- Sympathetic nervous system activation</td>
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</table>

**Association of tobacco use with CHD**
People who expose to nicotine, both smokers, and second-hand smoke (SHS) are prone to heart disease through several mechanisms, including Hypoxia, blood clot formation, vasoconstriction,
and inflammation [28]. Other damages of smoking to the body include direct damages to coronary arteries, decrement useful levels of harmful oxidized low-density lipoprotein (HDL), and increment of levels of harmful oxidized low-density lipoprotein (LDL), which leads to increased risk of plaques at the site of the injury which is known as atherosclerosis [29]. The content of extracellular lipid is higher among smokers compared to other people. The increment of the level of extracellular lipid causes plaque vulnerable to rupture [30]. Endothelial dysfunction increases the adhesion of platelets and causes blood clotting which is known as the thrombosis process. Hypercoagulable states and the increment of the risk of acute thrombosis will happen due to tobacco smoking. Coronary thrombosis which happens due to smoking is one of the main factors in the pathogenesis of acute cardiovascular events [31]. Moreover, coronary thrombosis causes a reduction in vital nutrients and oxygen to the heart muscle leads to catastrophic heart damage ad even sudden death. Consumption of nicotine stimulates the sympathetic nervous system and heart increases myocardial oxygen demand which causes angina [32]. Being exposed to smoke as SHS has adverse effects on the heart as great as the side effects of smoking itself. It should be noted that in both groups of SHS and smokers the smoke operates exactly in the same biological mechanisms [33]. Exposure to SHS even for less than one hour increases the possibility of the inner layer of the coronary arteries damage which leads to a heart attack [34]. Tobacco products which are smokeless are also damaging because they contain more than 2000 chemical compounds such as nicotine [35,36]. Nickel and cadmium are amongst toxic metals which are added to smokeless tobacco to make them palatable are detected to have adverse effects on the cardiovascular system. Some studies also have shown that smokeless tobacco cause hypertension both of which are major risk factors for CHD [37-39].

Association between tobacco smoking and CHD

Studies have shown a powerful causal relationship between tobacco smoking and morbidity and mortality related to CHD. Coronary heart disease induced by smoking leads to about 17% of global annual deaths [40]. The duration of smoking and the type of smoked tobacco products is directly related to the risk of damage to the cardiovascular system. The risk of this disease significantly increases even at low exposure levels to those who smoke only one cigarette per day [41]. Smoking tobacco not only is one of the main independent risk factors for CHD but it has a synergistic effect
on other major risk factors for CHD. These effects include diabetes mellitus, high blood cholesterol, and uncontrolled high blood pressure [42].

**Association of SHS and CHD**

A systematic analysis for the Global Burden of Disease in 2017 revealed that nearly 380,000 people died of CHD because of being exposed to secondhand smoke. In their review analysis study, it was reported that nearly 30% of all deaths are due to being exposed to SHS and about 5% of them are due to CHD. Based on their study, every year more than 8 million people die due to CHD as being exposed to SHS [43]. Based on different studies in various countries, it has been proved that being exposed to SHS is associated with the development of CHD based on income levels ranging from high to low [44, 45]. Childhood exposure to SHS has a lot of side effects that lead to coronary heart disease. However, accurate assessment of lifetime exposure to SHS is not such an easy job. Since lifetime cumulative exposure to SHS is significantly higher in comparison with the one that has been measured in previous studies, estimation of the exact risk and impact of SHS exposure on CHD is not possible [46, 47].

**Association of cigarette smoking and severity of CAD**

Coronary heart diseases are resulting from coronary artery diseases. Based on the studies carried out by Salehi et al [48], the number of damaged coronary arteries in patients with CAD is not notably associated with smoking, which is not represented by many studies. One of the main reasons for achieving such results is that the period of studies was not sufficient [49]. Cigarette smoking dose, duration of smoking, and illness duration could increase the rate of coronary occlusion. Nearly, all recent studies have revealed that smoking is significantly associated with the severity of CAD. Moreover, smoking could notably increase the risk of occlusion of the left anterior descending coronary artery (LAD).

Garshick et al [50] showed that the association of smoking with occlusion of the LAD artery may be due to the destructive effect of nicotine on the vascular epithelium layers. Coronary vascular epithelium can be spoiled because of smoking and nicotine. Vasospasm and sympathetic tone are among the most destructive disorders which are induced from smoking [51]. Nicotine consumption could also cause myocardial injury. Smoking and nicotine consumption could cause two types of necrosis which are toxic necrosis and ischemic necrosis, through which
the chemicals in cigarettes affect the cardiac muscle [52]. In addition, nicotine could cause calcium precipitate as atheromatous plaque. Another mechanism of nicotine is its destructive effect on the increment of serum LDL and triglycerides in the blood and also the decrement of high-density lipoprotein. Moreover, nicotine consumption causes vascular inflammation as well as the production of C-reactive protein (CRP) [53]. Mohammadi et al [54] revealed that increasing the consumption of nicotine could cause inflammation, atherosclerosis through inhibiting vasodilation, increment of abnormal narrowing of intracranial arteries, and also stabilizing thrombosis. Smoking cessation has explicit effects of improving patients’ cardiovascular condition. A study by de Hoog et al [55] reported that stopping smoking in patients with CAD decreases the risk of heart attack by about 20% in the coming years. It could be said that smoking is one of the main risk factors significantly is associated with CAD, occluded coronary arteries, and the location of CAD.

**Association of Nicotine with CVD**

Nicotine is a naturally occurring organic compound of alkaloids that could be found fundamentally in tobacco. Nicotine generally is absorbed from various cigarette smoke which is also is available in smokeless tobacco, hookah tobacco, heated tobacco products, and even E-cigarettes. Some insecticides also have nicotine which could cause accidental or intentional poisoning [56].

**Systemic Hemodynamic Effects of Nicotine**

Nicotine has systemic hemodynamic effects which are mediated commonly through activating the sympathetic nervous system. Norepinephrine is released from adrenergic neurons after the consumption of nicotine, after which adrenal release of epinephrine will be increased [57]. After activation of Nicotinic acetylcholine receptors (nAChRs) as a result of nicotine consumption, sympathetic nervous system will be stimulated in the peripheral nervous system (PNS). Plasma epinephrine and cardiac work are both increased after cigarette smoking as it stimulates heart rate, blood pressure, and myocardial contractility [58]. Moreover, after the consumption of nicotine or smoking both blood pressure and heart rate will increase. The increment of cardiac contractility, cardiac filling, and heart rate will result in increase of cardiac output all of which are because of systemic vasoconstriction [59].
Blood vessels will be constricted due to the consumption of nicotine such as the skin's blood vessel system while opening blood vessels in skeletal muscle. The skin blood flow and the fingertip skin temperature will be decreased as a result of vasoconstriction of the skin. Nicotine decreases blood flow in microvascular beds which may impair the process of wound healing, lead to progressive renal disease, macular degeneration, and also placental insufficiency [60].

**Association of nicotine with inflammation**

Being exposed to the smoke of tobacco leads to a chronic systemic inflammatory response through multiple pathways which are interrelated [61]. Atherogenesis and acute ischemic events will result from inflammation. After the adherence of activated monocytes to the site of damaged endothelium atherosclerotic plaque will be formed, after that they migrate into the sub-endothelium and then will be differentiated into macrophages and eventually foam cells. Macrophages secreting inflammatory mediators will result in chronic inflammatory states which leads to spread, destabilization, and finally plaque rupture that ultimately causes thrombosis and local vasoconstriction [62]. The increment of the number of white blood cells, the level of C-reactive protein (CRP), and Fibrinogen (factor I) are amongst the main markers of inflammation in smokers known to be obvious predictors of future cardiovascular diseases [63].

The effect of nicotine is directly on the immune system by activating the sympathetic nervous system, on the neuronal nicotinic acetylcholine receptors (nAChRs) which has a significant role in modulating the immune function. Homomeric α7 type of nAChRs as a non-neuronal cell of nAChRs mediates cholinergic nervous system. Generally, when this system is stimulated anti-inflammatory effect will happen [64]. However, in animal studies, it has been proved that systemic administration of nicotine could suppress inflammation and decrease the mortality rate in diseases such as sepsis, acute lung injury and viral myocarditis [65].

In a study by Dutta et al [66] it was reported that nicotine may has pro-inflammatory effects and make inflammation worse. Nicotine is a chemotactic factor that attracts and extravasates neutrophils into the subendothelium. In an animal study by Golforoush et al [67] it was reported that in mice with atherosclerosis, the sympathetic nervous system will be activated after acute myocardial infarction. Consequently, an inflammatory state will appear after which hematopoietic stem and progenitor cells are released from bone marrow, accelerating atherosclerosis and boosting monocyte production. Therefore, nicotine has strong sympathetic activating effects due to its role
in creating chronic inflammation which leads to ischemic vascular disease. The studies on smoking cessation by administration of nicotine medications have revealed that a notable improvement in inflammatory markers would be seen over time. However, it has appeared that nicotine could not be assumed as one of the main contributors to the chronic inflammatory state caused by smoking [68, 69].

**Smokeless tobacco and heart diseases**

Based on the data reported by WHO more than 350 million people use smokeless tobacco products worldwide [70]. The majority of people who use smokeless tobacco are in South-East Asia. However, its usage is being increased in other regions of the world. Unlike smoked tobacco, the data on the health effects of smokeless tobacco is limited and nearly all are recent. Studies related to smokeless tobacco have reported that it could cause fatal and non-fatal heart disease worldwide [71].

A study by Gupta et al [72] revealed that the risk of fatal heart disease has increased due to the increment of smokeless tobacco in Asia. A similar meta-analysis study by Vidyasagaran et al [73] revealed the same data about Asia. Another study by Gupta et al [74] proved the previous data on the side effects of consumption of smokeless tobacco and stated that there is a significant association between smokeless tobacco use and non-fatal cardiac disease in south-east Asian countries.

Please do not misunderstand that smoke-less tobaccos are safe. A study by Siddiqi et al [75] reported that more than 200000 deaths are reported every year which may be due to smokeless tobacco use. Moreover, using smokeless tobacco causes nearly five million DALYs lost because of CHD in 2015. Although smokeless tobacco has been known to have destructive effects on health such as oral cavity cancer, addiction, pancreas, esophagus (gullet), and poor reproductive outcomes, its association with CVD has not been known broadly in the world [76]. Recent studies have shown that the consumption of smokeless tobacco increases the risk of CHD, myocardial infarction (MI)/heart failure, and stroke [77,78].

The most common studied issue about heart disease is investigating the cardiovascular consequences of smokeless tobacco consumption. In this regard, regional variation should be considered in the results on the association of smokeless tobacco use with heart disease. The majority of studies from the South-East Asia Region have reported a notable association between
the increased risk of CHD and smokeless tobacco consumption, while this association among studies from European Region was not significant [79,80]. Based on the studies carried out by Elemam et al and a review article by Khosravaniardakani [81,82], this regional difference may be due to the variation in the chemical mixture of the products used in these Regions. However, no adequate evidence has been reported on the association of smokeless tobacco with the risk of hypertension.

**Conclusion**

Smoking is related to the number of occluded coronary arteries, the severity of CAD, and also occlusion of the LAD artery. The decrement in the number of cigarettes per day has a significant effect on the reduction of cancer risk and notable benefits to cardiovascular disease. Smoking will be associated with the increment of coronary heart disease and stroke whether it is a cigarette or 5 cigarettes per day. It can be said with confidence, the is no level of safety for smoking at which even light smoking could be assumed safe.

To understand the association of smoking with the number of occluded coronary arteries, the location of occlusion in coronary arteries among patients with CAD, and the location of occluded coronary arteries in the heart extra high-quality studies should be done. Moreover, all possible risk factors of CAD should be investigated similarly. One of the most notable options for improving the health of patients with CAD is smoking cessation. It is proved that, for the elimination of the risk associated with heart disease and stroke, smokers should quit smoking completely. In this regard, advanced programs prepared based on the community should be prepared to help in the prevention of smoking and the reduction of the risk of CAD development in the population. According to recent studies, in people who don't suffer from CVD nicotine’s-related cardiovascular risks from e-cigarettes are not high. However, researchers are concerned about the risks that nicotine from e-cigarettes has to people with CVD. Despite the concerns that researchers have about some increased risk from e-cigarette use, this risk is surely much less compared to that of smoking. Despite the ambiguity about the health problems of e-cigarettes, some studies have reported that CVD patients do quit successfully using e-cigarettes. However, in patients with CVD, it is recommended to discontinue both smoking and e-cigarette as they are.
References


How to Cite This Article