Opium and cardiovascular health: A devil or an angel?

Pegah Roayaeia, Arya Aminorroayab, Ali Vasheghani-Farahani, Alireza Oraic, Saeed Sadeghid, Hamidreza Poorhosseinid, Farzad Masoudkabira, d, *  

Article history:  
Received 21 April 2020  
Accepted 14 October 2020  
Available online 20 October 2020  

Keywords:  
Opium  
Papaver  
Coronary artery disease  
Acute coronary syndrome  
Stroke

A R T I C L E I N F O  
Opioids have the highest rate of illicit drug consumption after cannabis worldwide. Opium, after tobacco, is still the most commonly abused substance in the Middle East. In addition to the ease of availability, one reason for the high consumption of opium in Asian countries might be a traditional belief among Eastern people and even medical staff that opium may have ameliorating effects on cardiovascular diseases (CVDs) as well as diabetes mellitus, hypertension, and dyslipidemia. Over the last decade, many studies have been performed on humans and animals to evaluate the interplay between opium consumption and stable coronary artery disease, acute coronary syndromes, and atherosclerosis. In this review, we conclude that opium consumption should be considered a risk factor for CVDs. Healthy individuals, as well as cardiac and diabetic patients, should be informed and educated about the hazardous effects of opium consumption on cardiovascular and other chronic diseases.

© 2020 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Papaversomniferum L. is amongst the oldest medicinal plants, and the dried latex of its poppy, opium, has been used for medicinal or recreational purposes conventionally. Opioids have the highest rate of illicit drug consumption after cannabis worldwide. In 2017, the United Nations Office on Drugs and Crime reported that 29 million persons, 50% higher than estimates, had used opiates in the preceding year globally. Notably, opium, after tobacco, is still the most commonly abused substance in the Middle East. One of the reasons for the high use of opium in this region might be the ease of access and also the location in the main pathway of the opium transit as the main opium-producing countries such as Afghanistan, and to a lesser extent, Myanmar, and Laos are located in this region. In addition to the ease of availability, another reason might be a traditional belief among Eastern people and even medical staff that opium may have ameliorating effects on cardiovascular diseases (CVDs) as well as diabetes mellitus, hypertension, and dyslipidemia.4-9

Over the last decade, many studies have been performed on humans and animals to evaluate the effect of opium consumption on blood lipid and glucose profiles, and also on CVDs. In 2013, we published the first review article on the cardio-metabolic effects of opium consumption.1 In this review, we aimed to collect and integrate the newest evidence with our previous knowledge to clarify the effects of opium on CVDs and its underlying mechanisms.

2. Pharmacotoxicology

The word opium (lachrymopapaveris, Teriak) is derived from the Greek name for juice; a milky juice extracted by incising the unripe capsules (poppy) of Papaversomniferum L.10 After being exposed to air, it becomes a brown, sticky, or crumbly substance. It is a complex...
cocktail of substances that, in addition to water, contains more than 40 alkaloids\textsuperscript{11} and over 70 components.\textsuperscript{12} Only five of these alkaloids account for virtually all of the quantitative alkaloid content of opium (Fig. 1), including morphine (8–17% by weight), noscapine (1–10%), papaverine (0.5–1.5%), codeine (0.7–5%), and thebaine (about 0.2%).\textsuperscript{11} Morphine and codeine are effective pain relievers through the activation of the $\mu$ (mu) opioid receptor. However, they are also abused for recreational purposes because the activation of the $\mu$ receptor causes euphoria and drowsiness.\textsuperscript{12} Noscapine (formerly known as narcotine) is an antitussive agent.\textsuperscript{14} Papaverine has no morphine-like actions, but as it relaxes smooth muscles, it is commonly used for the prevention and treatment of vasospastic diseases such as the spasm of coronary artery bypass grafts.\textsuperscript{11,14}

Opium is used through different routes. It can be ingested orally or smoked after direct heating with burning charcoal in specialized devices such as an opium pipe (Vafour). In another route (Sikh-Sang), a stick is heated and the opium is put on the heated stick with a hairpin, and then the smoke is inhaled.\textsuperscript{15} When opium is ingested, the onset of action is delayed.\textsuperscript{1} This is while, in the case of opium smoking, morphine reaches the brain within seconds due to the rapid absorption of its vapor across the pulmonary capillaries into the bloodstream. Therefore, the onset of action is much more rapid and intense after smoking, but the duration of action is longer after oral intake because the absorption from the intestine, although slower, continues over a prolonged period.\textsuperscript{14}

### 3. Stable coronary artery disease

#### 3.1. Clinical studies

In the very first study on the association between opiates and coronary artery disease (CAD), investigators compared 98 deceased with methadone or opiate (M/O) in their blood at the time of autopsy and 97 deceased without M/O, and found a decreased severity of CAD among the former.\textsuperscript{16} Although they concluded that long-term opiate exposure might mitigate CAD severity and its fatal consequences, they called for caution while interpreting their results based on several limitations, including a lack of data on the deceaseds’ smoking histories, lipid profiles, and lifestyles.\textsuperscript{16} Subsequently, majority of studies except few found that opium consumption is associated with more severe and extensive involvements of coronary arteries, even after adjustments for...
possible confounders (Table 1). A cross-sectional study found no association between opium consumption by any route and ischemic heart diseases. However, the authors called for caution while interpreting their results as the opium dosage, the mean duration of opium consumption, and the purity of opium were not assessed in their study (Table 1). A recent meta-analysis showed that opium consumption was associated with a significantly greater risk of CAD (odds ratio [OR]: 2.77, 95% confidence interval [CI]: 2.04 to 3.75).

Besides studies evaluating the association between opium consumption and the presence, severity, and extension of stable CAD, opium abuse has been demonstrated to be related to coronary microvascular dysfunction. Opium abuse was an independent predictor of coronary microvascular dysfunction (OR: 3.575, 95% CI: 1.418 to 9.016; \( p = 0.0069 \)) in a cross-sectional study on patients with documented microvascular dysfunction. Further, another recent study revealed that opium consumption was an independent risk factor for CAD and coronary artery ectasia.

3.2. Animal studies

It has been demonstrated that opium addiction has aggravating effects on the progression of atherosclerosis in the aorta of hypercholesterolemic rabbits. However, this atherogenic effect was limited to hypercholesterolemic rather than normocholesterolemic conditions. Concordantly, four weeks of opium smoking increased the atherogenic index in hypercholesterolemic rabbits and not in normocholesterolemic ones. Another study showed that despite the attenuation of myocardial necrosis in rabbits with myocardial ischemia, opium exposure aggravated ischemia susceptibility, myocardial congestion, and hemorrhage.

In summary, there is consistent evidence supporting the association between opium consumption and stable CAD.

4. Acute coronary syndromes

Although there is an agreement among current studies that opium consumption is positively associated with the presence and severity of CAD, there is controversy about the association between opium consumption and acute myocardial infarction (MI). Some investigations have reported detrimental effects, while others have shown neutral effects (Table 2).

Despite the controversy regarding the association between opium consumption and the incidence of acute MI, there is an agreement regarding the impact of opium consumption on the inhospital and mid-term outcomes of acute MI. Research has demonstrated that opium use is not correlated with increased rates of post–MI mortality, morbidity, and readmission. Nevertheless, a few investigators have reported remarkably longer hospital lengths of stay, higher readmission rates, and borderline significantly higher in-hospital mortality rates (11.3% vs.

### Table 1
Summary of studies evaluating the association of opium consumption with stable coronary artery disease and its outcomes.

| Study            | Methodology     | Consumption pattern | Population                                                                 | Results                                                                 |
|------------------|-----------------|---------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Sadeghian et al. | Cross-sectional | Use of opium ≥1 time in life | n = 2405 (322 opium user and 2083 non-opium users) | A higher prevalence of CAD in opium users than non-users (OR = 1.8, \( p = 0.01 \)) even after the exclusion of cigarette smokers (OR = 2.06) |
| Safaei, 2008     | Cohort          | Opium user          | n = 200 post-CABG patients (14 current opium user, 9 past opium user, and 177 non-opium users) | A significant dose–response relationship between the dose of opium consumption and severity of CAD by clinical vessel score (OR = 26.1% versus 4% in opium users than non-opium users) |
| Masoomi et al., | Cross-sectional | Addicted            | n = 299 (118 opium-addicted and 181 non-opium users) | Similar post-operation complications and hospital stay |
| 2010             |                 |                     |                                                                            | Higher readmission rates (26.1% versus 4%) in opium users than non-opium users during 6 months follow-up |
| Masoomi et al., | Nested case–control | Addicted          | n = 91 (58 CAD and 33 normal coronary) | After adjustment for potential confounders like age, sex, and smoking, patients who regularly consume the opium are more likely to have severe CAD borderline (OR = 1.82, \( p = 0.08 \)) |
| 2010             |                 |                     |                                                                            | Opium addiction was an independent risk factor for CAD in non-cigarette smoking cases (OR = 38.95, CI = 2.7–531.7), but in cigarette smokers, opium was not a significant risk factor (OR = 13.2, 95%CI: 0.85–206.5) |
| Sadeghian et al. | Cross-sectional | Opium user          | n = 940 (387 men aged<45 years) | Opium consumption was the most important risk factor for CAD in male patients under the age of 45 years in an Iranian sample (OR = 4.47, \( p < 0.001 \)) |
| Hosseini et al., | Cross-sectional | Use of opium for ≥3months | n = 456 (228 diabetic opium users and 228 age, sex, and smoking matched diabetic non-opium users) | Greater severity of CAD measured by Gensini's score among opium users than non-users (86.9 versus 59.6, respectively, \( p < 0.0001 \)) |
| 2011             |                 |                     |                                                                            | More extensive atherosclerotic plaques among opium users than non-users |
| Rezvani et al., | Cross-sectional | Addicted            | n = 558 (161 opium-addicted and 397 non-opium users) | A significant independent dose–response relationship between the dose of opium and the Gensini's score (\( \beta = 0.27, p = 0.038 \)) |
| 2011             |                 |                     |                                                                            | No association between opium consumption by any route and CAD |
| Hosseini, 2012   | Cross-sectional | Opium user          | n = 5442 (2874 opium users and 2568 non-opium users) | Opium was an independent risk factor for CAD (OR = 1.31, 95% CI: 1.01–1.69) |
| Khademni et al., | Cross-sectional | Use of opium at least once a week for ≥6 months | n = 50,045 (8487 opium users and 41,558 non-opium users) | Increased risk of all-cause mortality in opium users (adjusted HR = 1.16, 95% CI: 1.68–2.06) |
| 2012             |                 |                     |                                                                            | Increased risk of death from ischemic heart disease in opium users (adjusted HR = 1.9, 95% CI: 1.57–2.29) |
| Rahimi et al.,   | Cross-sectional | Addicted            | n = 1170 (121 opium-dependents and 1049 non-opium users) | A dose–response association between the duration of opium use and cardiovascular as well as all-cause mortality |
| 2014             |                 |                     |                                                                            | Opium dependence was independently associated with the presence of CAD (OR = 2.08) |

CABG, Coronary artery bypass grafting surgery; CAD, Coronary artery disease; CI, Confidence interval; HR, Hazard ratio; OR, Odds ratio.

\( \text{97.3\% of opium users (222 out of 228) were using opium for ≥12 months (unpublished data).} \)
5.9% (p = 0.072) in opium-dependent patients with acute MI rather than non-opium users (Table 2).

Altogether, not only is there no evidence for supporting a decreased risk of acute MI or a favorable post–MI outcome in opium-dependent patients but also it may be associated with more post–MI complications.

4.1. Clinical studies on patients undergoing revascularization

Some studies on coronary artery bypass grafting surgery (CABG) candidates have demonstrated that opium consumption is not correlated with increased in-hospital mortality rates, postoperative complication rates, or hospital lengths of stay.37–40 However, others have shown that opium use is directly correlated with intra- and post-operative bleeding,41 readmission,42 and longer hospital lengths of stay.43 Recently, we studied 28,691 patients who underwent CABG for a median of 56 months to evaluate the effects of opium consumption and cessation on the long-term outcomes of these patients.44 In this cohort, 3636 patients continued opium consumption after surgery, while 1436 patients stopped opium use. After adjustments for possible confounders, we found that in comparison with the never users of opium, persistent opium consumption after CABG was associated with increased 5-year all-cause mortality (hazard ratio [HR]: 1.28, 95% CI: 1.06 to 1.54; p = 0.009) and 5-year major adverse cardiac events (MACE) (HR: 1.25, 95% CI: 1.13 to 1.40; P = 0.0001). Still, those who quitted opium use after surgery were not at an increased risk of mortality (HR: 1.09, 95% CI: 0.83 to 1.43; p = 0.514) or MACE (HR: 1.03, 95% CI: 0.88 to 1.21; p = 0.645) at five years compared with the never users of opium.45

In a retrospective cohort study, opium consumption was not associated with 12-month MACE among male patients after elective percutaneous coronary interventions, and none of the components of MACE, consisting of target vessel revascularization, target lesion revascularization, CABG, and non-fatal MI, was different between opium users and non-users.46 Nonetheless, it should be noted that while age is an important predictor of MACE, especially mortality, the authors did not make adjustments for the confounding effect of age on MACE despite the significantly lower age of the opium users by comparison with the non-users (55.7 versus 58.4 years, respectively; p < 0.001). This bias might potentially underestimate MACE in the opium user group.47

Altogether, it appears that opium consumption not only has no ameliorating effect on patients undergoing coronary revascularization but also may have hazardous effects on mid-term and long-term outcomes.

5. Stroke

There are scarce reports about the correlation between opium and stroke (Table 3). In a case–control study, opium abuse was independently associated with ischemic stroke.48 Other studies have demonstrated that opium addiction is associated with increased carotid intima-media thickness, more atherosclerotic plaques, and a greater pulsatility index and mean flow velocity of the middle cerebral artery, which are the markers of cerebral atherosclerosis.49,50 In a study on male CABG candidates, there was no difference in the prevalence of significant carotid artery stenosis between opium-addicted and non-addicted patients.51 Nevertheless, there is a significant bias in this study as the authors reported a higher prevalence of diabetes (17% versus 11.4%) and hypertension (88.6% versus 11.4%) as well as a lower prevalence of smoking (27.1% versus 65.5%) in the non-addicted patients than in the opium-addicted ones, respectively. Indeed, no conclusion can be drawn about the association between opium consumption and carotid stenosis without adjusting for such important confounding factors (Table 3).48

In summary, the currently limited evidence suggests the detrimental effects of opium on cerebral atherosclerosis and hemodynamic abnormalities, and its association with ischemic stroke.
Nonetheless, further studies are needed to elucidate the association between opium consumption and stroke.

6. Peripheral arterial disease

Despite several studies assessing the relationship between opium consumption and CAD, there is limited data regarding the association between opium consumption and peripheral arterial disease. In a study on patients with peripheral arterial disease who underwent lower extremity vascular reconstruction surgery, investigators observed that the patency rate was significantly lower in opium users than non-users (32% versus 67%, respectively). However, the authors failed to adjust this finding for potential confounders. Future well-designed studies should elucidate the exact role of opium consumption in peripheral arterial disease.

7. Heart failure

The association between opium consumption and left ventricular systolic dysfunction has been evaluated in many recent studies. The current evidence implies that opium consumption is not associated with a decreased functional class. Nevertheless, there are conflicting results regarding the association between opium consumption and the left ventricular ejection fraction (LVEF). Some studies have shown that opium users, with or without CAD, are more likely to have reduced LVEF than non-users, while others have found a neutral effect in this regard. A recent meta-analysis showed that opium use was associated with significantly lower LVEF in opium users who were candidates for CABG (mean differences = −2.15, 95% CI: −3.31 to −1). However, this statistically significant difference of 2%, may be of no or minimal clinical significance. Moreover, this correlation did not reach statistical significance in other subgroups of patients with CAD (mean differences = 0.29, CI: −0.57 to 1.14). Taken all these lines of evidence together, we may conclude that opium consumption has neutral effects on the LVEF and functional class of individuals with heart failure.

8. Cardiac arrhythmias

Studies have demonstrated that opium use is associated with a higher incidence of ventricular arrhythmias in the post-MI course, even after adjustments for confounders, while another study showed a neutral effect in this regard. Whereas a study showed that opium addiction was linked with higher post-CABG arrhythmias, another study found protective effects for opium use in terms of post-CABG atrial fibrillation. Despite these controversies in clinical studies, animal studies have consistently indicated a proarrhythmic effect for opium. Future well-designed prospective clinical studies should elucidate the exact role of opium consumption in inducing or preventing cardiac arrhythmias.

9. Interactions with cardiovascular drugs

The current evidence shows that opiates can interfere with cardiovascular medications through alterations in their pharmacokinetics or pharmacodynamics. In a large study, an analysis of prescriptions for patients with non-valvular atrial fibrillation who were under treatment with warfarin and had a stable international normalized ratio (INR) indicated that the consumption of opiates, including natural opium, buprenorphine, and tramadol, was associated with an increased INR in these patients, which might suggest a clinically important interaction. Furthermore, it has been shown that the concomitant use of opium and digoxin may increase the risk of digoxin toxicity. Another clinically relevant interaction of opium is with antiplatelets. Research has shown that the administration of opioids such as opium, methadone, and morphine attenuates the antiplatelet actions of aspirin, ticagrelor, prasugrel, and clopidogrel. This list of potentially lethal interactions between opium and cardiovascular drugs suggests that cardiologists and cardiac surgeons act cautiously when prescribing antiplatelets, digoxin, and warfarin for an opium-abusing patient.

10. Temporal relationship between opium consumption and cardiovascular diseases

Although the clinical studies on the association between opium consumption, and CAD and stroke have established a scientific base in the evidence pyramid, there are two common limitations in their methodologies that call for caution in interpreting their results. First, all of these studies have case-control or cross-sectional designs. Some patients with CAD or stroke likely start using opium because of their symptoms or their beliefs about the beneficial effects of opium use on CVDs following the development of their diseases. Hence, while we observe a higher prevalence of opium consumption among patients with CVDs than healthy individuals, we cannot make a causal interpretation because the temporal
relationship between opium consumption and CVDs cannot be determined in these studies. Another limitation is the possible prevalence-incidence bias, which should be considered in cross-sectional and case-control studies. If opium consumption affects the survival of patients with ischemic heart diseases, then the results of cross-sectional studies with prevalent rather than incident cases could be biased. Community-based cohort studies can overcome these two limitations and help us to make causal interpretations of the relationship between opium and CVDs. With the increasing use of opioids for chronic non-cancer pain, a large nested case-control study demonstrated that the use of opioids was associated with an increased risk of MI (OR: 1.28, 95% CI: 1.19 to 1.37).69

In our opinion, the most supportive evidence for a possible hazardous role of opium consumption in CVDs came from the Golestan Cohort Study.70 The Golestan Cohort Study recruited 50,045 people aged 40–75 years from January 2004 to June 2008 from Golestan Province, located in North Iran. As detailed exposure data, a systematic follow-up approach, and the ascertainment of the cause of death were available, the investigators evaluated the association between opium consumption and all-cause mortality and major categories, including circulatory causes for mortality after a median follow-up of 4.7 years. The adjusted HR for all-cause mortality associated with ever use of opium was 1.86 (95% CI: 1.68 to 2.06). They also observed that opium users were at an increased risk of death from ischemic heart diseases (adjusted HR: 1.90; 95% CI: 1.57 to 2.29). Moreover, after excluding the persons who started opium use after receiving a diagnosis of major illnesses, namely ischemic heart diseases, cerebrovascular events, diabetes mellitus, and hypertension, they found a dose-response association between the duration of opium use and cardiovascular as well as all-cause mortality. Unlike previous cross-sectional and case-control studies, the Golestan Cohort Study was not subject to the aforementioned major limitations and, therefore, it is reasonable to conclude causality based on its findings.

11. Association between opium consumption and cardiovascular diseases: independent or confounded by smoking?

Cigarette smoking is one of the major risk factors for CVDs. It has been shown in all previous studies that opium abusers smoke cigarettes more frequently.10,36,48 Thus, it is not clear whether the association between opium consumption and CVDs is a dependent association confounded by smoking or opium consumption is an independent risk factor for CVDs. Numerous studies have tried to answer this question. In a propensity score matched analysis, the study revealed that diabetic opium users had more severe CAD than matched diabetic non-users.10 A large cross-sectional study indicated a higher prevalence of CAD in opium users than non-users, even after the exclusion of cigarette smokers (Table 1).17 In a nested case-control study, opium addiction was an independent risk factor for CAD among non-smokers, while this association was not significant in cigarette smokers.20 Hence, we can conclude that the relationship between opium consumption and CVDs is independent.

12. Why should opium consumption be associated with cardiovascular diseases?

Current knowledge is scarce about the effects of opium on blood glucose, dyslipidemia, and hypertension.71 Although animal studies demonstrate the hazardous effects of opium on the aforementioned risk factors, there are some discrepancies in clinical studies.71 Thus, it calls for future well-designed clinical studies to address this gap of knowledge. Here, we will focus on other risk factors and novel mechanisms of opium effects on CVD.

Studies have demonstrated that opium exerts its harmful effects on CVDs through increased inflammation and oxidative stress, increased thrombosis, and vascular smooth cell hyperplasia (Fig. 1). Although there is a complex relationship, we briefly discuss these interwoven factors here.

Recent studies have increasingly reported that opium addicts have elevated levels of pro-inflammatory mediators75,72–76 and lower levels of anti-inflammatory cytokines.74,75 On the other hand, it has been shown in several studies that morphine and heroin induce systemic oxidative stress and reduce the total antioxidant capacity independent of cigarette smoking.7

Hypotestosteronemia and hypogestrogenemia in opium addicts may result in CVDs through all of the aforementioned mechanisms. These hormonal imbalances are associated with increased levels of procoagulant factors and insulin resistance.76 Studies have also demonstrated that opium-addicted individuals have remarkably higher levels of procoagulant factors than non-addicted individuals.79–84 Additionally, research has proven a state of insulin resistance, similar to patients with type 2 diabetes mellitus,85 which causes CVDs.79–86,89,92,93 Opium abusers have hyperprolactinemia,84,94 which results in the proliferation of vascular smooth muscle cells and CVDs.85 Another mechanism is the reduction of physical activity due to the depressive effects of opium on the central nervous system,96 which is associated with an increased risk of CVDs.97–100

Last but not least, is the resistance to aspirin and P2Y12 inhibitors in opium users. We previously discussed that opium consumption blunts the pharmacological effects of aspirin,16,52 ticagrelor,63–65 prasugrel,64,66 and clopidogrel.67,68 These findings may render opium users with previous CVDs more vulnerable to acute thrombotic events and might be a novel justification for higher risks of MI and stroke in these patients.

13. Strategies for the treatment of opioid dependence

For the successful treatment of opioid dependence, we should employ pharmacological interventions besides psychosocial supportive measures. There are two approaches toward pharmacological treatment: 1) opioid agonist maintenance treatment with long-acting opioids such as methadone or buprenorphine, which is the most effective and the preferred method, and 2) detoxification, followed by treatment with long-acting opioid antagonists such as naltrexone, to prevent relapses. Other than these medications, alpha-2 adrenergic agonists such as clonidine for the treatment of opioid withdrawal and naloxone for the treatment of opioid overdose should be available.101

14. Conclusion

People have used opium for many years not only as a habit, but based on their traditional beliefs about its beneficial effects on diabetes mellitus, dyslipidemia, hypertension, and CVDs. Considering the current evidence, opium not only has no ameliorating effect on CVDs, but the clinical, animal, and prospective cohort studies consistently indicate that opium consumption is associated with CVDs and cardiovascular mortality. Moreover, the rapidly growing biological explanations for a causal relationship between opium consumption and CVDs underscore the warning that opium consumption should be considered a risk factor for CVDs. Unfortunately, false beliefs regarding the beneficial effects of opium are common, and it is the responsibility of health professionals and
health authorities to battle these false beliefs. Healthy people, as well as cardiac and diabetic patients, should be informed and educated about the hazardous effects of opium consumption on cardiovascular and other chronic diseases (Box 1).

Funding
This work was supported by the Research Council of Tehran University of Medical Sciences. The funding source had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Declaration of competing interest
All authors have none to declare.

Acknowledgments
None.

References
1. Masoudbakht F, Sarrafzadeh N, Eisenberg MJ. Effects of opium consumption on cardiometabolic diseases. Nat Rev Cardiol. 2013;10:733–740.
2. UNDCP. World Drug Report. 2019.
3. Amin-Esmaeili M, Rahimi-Movaghar A, Sharifi V, et al. Epidemiology of illicit drug use disorders in Iran: prevalence, correlates, comorbidity and service utilization results from the Iranian Mental Health Survey. Addiction. 2016;111:1836–1847.
4. Mohammadi A, Darabi M, Nasry M, Saabte-Jahromi MJ, Malek-Pour-Afshar R, Sheibani H. Effect of opium addiction on lipid profile and atherosclerosis formation in hypercholesterolemia rabbits. Exp Toxicol Pathol. 2009;61:145–149.
5. Karam GA, Reisi M, Kaseb AA, Khalsari M, Mohammadi A, Mahmoodi M. Effects of opium addiction on some serum factors in addicts with non-insulin-dependent diabetes mellitus. Addiction. 2004;9:53–58.
6. Sadr Bahghi SM, Rafiei M, Bahadorzadeh L, et al. Is opium addiction a risk factor for acute myocardial infarction? Acta Med Iran. 2005;43:218–222.
7. Farahani MA, Mohammadi E, Ahmadi F, Maleki M, Hajizadeh E. Cultural barriers in the education of cardiovascular disease patients in Iran. Int Nurs Rev. 2008;55:360–366.
8. Richards JF. Opium and the British Indian Empire: The Royal Commission of 1895. Opium and the British Indian Empire: The Royal Commission of 1895. Cambridge University Press; 2001.
9. Chopra RN, Chopra KC. Quasi-Medical Use of Opium in India and Its Effects. UNODC; 1955.
10. Hosseini SK, Masoudkabir F, Vasheghani-Farahani A, et al. Opium consumption and coronary atherosclerosis in diabetic patients: a propensity score-matched study. Planta Med. 2011;77:1870–1875.
11. Schiff JR, Pl. Opium and its alkaloids. Am J Pharmacist Educ. 2002;66:186–194.
12. Buchbauer G, Nikiforov A, Remberg B. Headspace constituents of opium. Planta Med. 1994;60:181–183.
13. Tournier J. mu-Opioid receptors and regulators of G protein signaling (RGS) proteins: from a symposium on new concepts in mu-opioid pharmacology. Drug Alcohol Depend. 2012;121:173–180.
14. Kalant H. Opium revisited: a brief review of its nature, composition, non-medical use and relative risks. Addiction. 1997;92:267–277.
15. Asgary S, Sarrafzadeh N, Naderi GA, Rezabehi R. Effect of opium addiction on new and traditional cardiovascular risk factors: do duration of addiction and route of administration matter? Ljudps Health Dis. 2008;7:42.
16. Marmor M, Penn A, Widner K, Levin RJ, Malansky L. Coronary artery disease and opiod use. Am J Cardiol. 2004;93:1295–1297.
17. Sadeghian S, Darvish S, Davoodi G, et al. The association of opium with coronary artery disease. Eur J Cardiovasc Prev Rehabil. 2007;14:715–717.
18. Sadeghian S, Grailli P, Safarshar M, Karimi AA, Darvish S, Abassi SH. Opium consumption in men and diabetes mellitus in women are the most important risk factors of premature coronary artery disease in Iran. Int J Cardiol. 2010;141:116–118.
19. Masoumi M, Shahsenaali M, Mirzaaadeh Z, Tavakoli M, Ali AZ. Opium addiction and severity of coronary artery disease: a case-control study. J Res Med Sci. 2010;15:27–32.
20. Masoumi M, Arash Ramezani M, Karimzadeh H. The relationship of opium addiction with coronary artery disease. Int J Prev Med. 2010;1:182–186.
21. Hosseini SA, Abdollahi AA, Behnampour N, Salehi A. The relationship between coronary risk factors and coronary artery involvement based on angiography findings. Koomesh. 2012;14:7–12.
22. Rahimi Darab B, Vatandust J, Pourousavi Khoshkhab MM, Hajihamidi Poororfasanjani M. Survey of the effect of opioid abuse on the extent of coronary artery diseases. Global J Health Sci. 2014;6:83–91.
23. Rezvani MR, Ghandehari K. Is opium addiction a risk factor for ischemic heart disease and ischemic stroke? J Res Med Sci. 2012;17:958–961.
24. Nakhhae S, Amrabiadazesh A, Qorbani M, Lamarine RJ, Mehrpour O. Opium use and cardiovascular diseases: a systematic review and meta-analysis. Crit Rev Toxicol. 2020;50:201–212.
25. Esmaeili Nadimi A, Pour Amiri F, Sheikh Fathollahi M, Hassanshahi G, Ahmadi Z, Sayadi AR. Opium addiction as an independent risk factor for coronary microvascular dysfunction: a case-control study of 250 consecutive patients with slow-flow angiography. Int J Cardiol. 2016;219:301–307.
26. Masoumi M. Opium Is An Important Risk Factor For Coronal Artery Ectasia; A Cross-Sectional Study, PREPRINT (Version 1) available at: Research Square; 04 November 2019. https://doi.org/10.21203/rs.2.16809/v1.
27. Najafipour H, Joukar S. Combination of opium smoking and hypercholesterolemia augments susceptibility for lethal cardiac arrhythmia and atherogenesis in rabbit. Environ Toxicol Pharmacol. 2012;34:154–159.
28. Joukar S, Najafipour H, Malekpour-Afshar R, Mirzaeinpour F, Nasri HR. The effect of passive opium smoking on cardiovascular indices of rabbits with normal and ischemic hearts. Open Cardiovasc Med J. 2010;4:1–6.
29. Nakhhae S, Ghasemi S, Karimzadeh K, Zarnani A, Alinejad-Mofrad S, Mehrpour O. The effects of opium on the cardiovascular system: a review of side effects, uses, and potential mechanisms. Subst Abuse Treat Prev Pol. 2020;15:30.
30. Niazi MK, Mahdizadeh H, Farshidi F, Mohammadpour M, Omran MTS. Evaluation of the role of opium addiction in acute myocardial infarction as a risk factor. Cepapin J Int Med. 2012;4:585–589.
31. Roohafza H, Talaei M, Sadeghi M, Haghani P, Shokouh P, Sarrafzadeh N. Opium decreases the age at myocardial infarction and sudden cardiac death: a long- and short-term outcome evaluation. Arch Iran Med. 2013;16:154–160.
32. Azizmazde-Sarwar B, Yousefzade G, Narooey S. A case-control study of effect of opium addiction on myocardial infarction. Am J Appl Sci. 2005;2:1134–1135.
33. Dehghani F, Masoomi M, Haghdoost A. Relation of opium addiction with the severity and extension of myocardial infarction and its related mortality. Addict Health. 2013;5:1–7.
34. Javadi HR, Allami A, Mohammadi N, Alauddin R. Opium dependency and in-hospital outcome of acute myocardial infarction. Med J Islam Repub Iran. 2014;28:122.
35. Davoodi G, Sadeghian S, Akhondzadeh S, Darvish S, Alidosti M, Amirzadegan A. Comparison of specifiers, short-term outcome and prognosis of acute myocardial infarction in opium dependent patients and non-dependents. Ger J Psychol. 2005;8:33–37.
36. Harati H, Shamsi A, Moghadam MF, Zadeh FSS, Ghazi A. The mortality rate of opioid addiction and relative risks. J Addict. 2014;9:277.
37. Safaei N. Outcomes of coronary artery bypass grafting in patients with a history of opiate use. Pak J Biol Sci. 2008;11:2594–2598.
38. Safaei N, Kazemi B. Effect of opium use on short-term outcome in patients undergoing coronary artery bypass surgery. Gener Thorac Cardiovascu Surgery. 2010;58:62–67.
39. Azarasa M, Azarfarin R, Changizi A, Alizadehahai A. Substance use among Iranian cardiac surgery patients and its effects on short-term outcome. Aesth Alg. 2009;10:1533–1559.
98. Held C, Iqbal R, Lear SA, et al. Physical activity levels, ownership of goods promoting sedentary behaviour and risk of myocardial infarction: results of the INTERHEART study. *Eur Heart J*. 2012;33:e452–e466.

99. Sallam N, Laher I. Exercise modulates oxidative stress and inflammation in aging and cardiovascular diseases. *Oxid Med Cell Longev*. 2016;2016, 7239639–7239639.

100. Laufs U, Wassmann S, Czech T, et al. Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2005;25:809–814.

101. Alcohol DaABWT. *International Standards for the Treatment of Drug Use Disorders*. 2020.

102. Farahani MA, Ghaffari F, Seyed Fatemi N. Opium addiction in patients with coronary artery disease: a grounded theory study. *Med J Islam Repub Iran*. 2015;29, 267-267.