IJMS
Vol 47, No 4, July 2022

Original Article

Trends in the Prevalence and Incidence of Opium Abuse and its Association with Coronary Artery Risk Factors in Adult Population in Iran: Findings from Kerman Coronary Artery Disease Risk Factors Study

Hamid Najafipour[1], PhD; Mohammad Masoumi[2], MD; Rahele Amirzadeh[3], MSc; Farzaneh Rostamzadeh[4], PhD; Rahim Foad[1], MD; Mitra Shadkam Farrokhi[5], MSc

[1]Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran;
[2]Cardiovascular Research Center, Department of Cardiology, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran;
[3]Social Determinants of Health Research Center, Institute of Future Studies in Health, Kerman University of Medical Sciences, Kerman, Iran;
[4]Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran;
[5]Gastroenterology and Hepathology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran

Correspondence:
Mohammad Masoumi, MD;
Department of Cardiology and Cardiovascular Research Center, Shafa Hospital, Shafa St., Kerman, Iran
Tel: +98 34 32264071
Fax: +98 34 32264097
Email: masoomidnr@yahoo.com
kerman.physiology@gmail.com
Received: 30 January 2021
Revised: 02 May 2021
Accepted: 07 June 2021

What's Known

- Opioids addiction is one of the major public concerns in all societies, including Iran, due to its adverse side effects on health.
- The prevalence of opium use is high probably due to the belief that opium has preventive effects against cardiovascular diseases

What's New

- Opium consumption was closely associated with coronary artery disease risk factors (CADRFs), higher gingival inflammation, and periodontal disease.
- Opium showed no protective or ameliorative effects on CADRFs. Its incidence use was higher in diabetic, hypertensive, obese, and anxious patients; meanwhile, the prevalence of opium use decreased in the last five years.

Abstract

Background: The prevalence of opium addiction in Iran is high probably due to the belief that opium has preventive effects against cardiovascular diseases. In the second phase of Kerman coronary artery disease risk factors study, the prevalence, incidence rate, and the association between opium use and other coronary artery disease risk factors (CADRFs) were assessed.

Methods: In a cross-sectional study (2014-2018), 9996 inhabitants of Kerman, southeastern Iran, aged 15-80 years were recruited to the study. After taking fasting blood samples, the participants were examined or interviewed for demographic data and CADRFs, including opium use. The participants were categorized into "never", "occasional", and "dependent" users. The association between opium use and CADRFs was assessed with adjusted regression analysis (Stata v.11 software).

Results: The overall prevalence of opium consumption was lower than that of five years earlier ($P<0.01$). The prevalence was currently higher in men than women and decreased in men between the two phases ($P<0.001$). There was a positive correlation between opium use and depression ($P<0.001$), anxiety ($P<0.05$), and a negative association with the level of physical activity ($P<0.001$). The five-year incident rate of dependent and occasional opium use was 4.2 and 3.9 persons/100 person-years, respectively. The incidence of opium use was higher in diabetic, hypertensive, depressed, anxious, and obese subjects.

Conclusion: The study did not demonstrate any protective effects of opium on CADRFs. Considering the higher rate of opium use in subjects with hypertension, diabetes, obesity, and psychological disorders, the health authorities should implement educational programs to warn and correct the unsafe belief.

Please cite this article as: Najafipour H, Masoumi M, Amirzadeh R, Rostamzadeh F, Foad R, Shadkam Farrokhi M. Trends in the Prevalence and Incidence of Opium Abuse and its Association with Coronary Artery Risk Factors in Adult Population in Iran: Findings from Kerman Coronary Artery Disease Risk Factors Study. Iran J Med Sci. 2022;47(4):328-337. doi: 10.30476/IJMS.2021.89898.2065.

Keywords ● Opium dependence ● Prevalence ● Incidence ● Coronary artery disease ● Risk factors

Introduction

Opioid addiction is one of the major public concerns in all societies, including Iran, due to its adverse side effects on health.[1] Almost 66% of deaths related to drug abuse are attributed to opioid

consumption.[1, 2] The use of opioids is 2.6% in the Middle East and southwestern Asia, which is higher than that of the affected countries in the world. The history of opioid addiction in Iran backs to five centuries ago.[3] It is estimated that an overall 2.3% of the Iranian adult population are addicted to opium.[4] The prevalence is even higher (22%) in some rural areas.[5]

Despite a large body of evidence stating that opioid addiction causes many diseases, such as cancer, in some societies, particularly in Asia and the Middle East, there is a belief that opium has a preventive effect against coronary artery diseases (CAD) risk factors (dyslipidemia, hypertension, and diabetes). Thus, the high rate of addiction in these societies is most probably due to this belief.[6, 7]

The beneficial effects of opioids in the acute phase of cardio-vascular events are well-known.[7] However, the chronic effects of cardiovascular diseases are not truly understood. Several studies have assessed the relationship between opium abuse and some CAD risk factors.[8] The recent investigations suggested that opium addiction increases the risk of cardiovascular diseases.[8, 9] It has been revealed that opium addiction increases coronary atherosclerosis and deaths related to coronary artery diseases.[8] The mechanisms proposed are an increase in insulin resistance, oxidative stress, Apolipoprotein B/Apo lipoprotein A ratio, serum fibrinogen, coagulation factor VII, and inflammatory responses.[9] In addition to the direct effects of opium on cardiovascular disease, it may contradict cardiovascular medicines.[9] Nevertheless, there are some controversies in this regard. The Pars Cohort Study reported an increase in the probability of cardiovascular events and stroke in opium-addicted individuals.[10] Several other experiments demonstrated no effect;[11-14] on the other hand, some other studies found an ameliorative effect on some of these risk factors.[15]

The first phase of Kerman Coronary Artery Diseases Risk Factors study (KERCADRS), population-based research, conducted on 5900 adults aged 15-75 years in Kerman, Iran in 2009-2011, showed that 11.6% of the adult population consumed opium,[16] which was higher than the average use of the country, Middle East, and southwestern Asia.[2] The current work did not reveal any protective effects of opium on CAD risk factors.[16] The present study is the second phase of KERCADRS, which was performed on a larger sample size of close to 10,000 people aged 15-80 years to determine the trend of changes in the predominance of occasional and dependent opium use during the past five years and its association with other CAD risk factors in subpopulation groups with hypertension, diabetes, dyslipidemia, obesity, psychological disorders, oral health problems, and low physical activity.

The study also assessed the five-year incidence rate of occasional and dependent opium use, overall and in subpopulation groups regarding other CAD risk factors. This will also provide a better insight into the efficiency of local health programs in the prevention of unhealthy behaviors in the population of the study.

Materials and Methods

Study Population and Sampling Method

The study was performed in conformity with the international guidelines for conducting human studies and approved by the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran (Permission no IR.KMU.REC.1392/405).[17]

In the second phase of KERCADRS (2014 to 2018), in a cross-sectional study, 9996 subjects aged 15-80 years in Kerman, Iran, were recruited. The sampling method was one-stage cluster sampling in which 420 postal codes (called seeds) were selected randomly among the city's postcodes. The data collection team attended the seeds addresses and asked all the eligible people (Iranians aged 15-80, with at least one-year residency in Kerman, who signed a written informed consent) to participate in the study. The recruitment was continued on the right side of the alley to reach 24 subjects in each cluster (to reach the target sample size of 10,000). The participants were given an appointment card to attend a collaborating clinic while fasting for 12 hours for blood sampling, medical examination, and face-to-face interview and were told to bring their medicines. More details of sampling and sample size calculation and related risk factors questionnaires are accessible in the previous publication about the first phase of KERCADRS.[18] Concisely, measurements were based on: Hypertension (BP≥140/90 mmHg or taking anti-hypertensive drugs), Diabetes (Fasting Blood Sugar (FBS) ≥126 mg/dL or taking anti-diabetic pills or using insulin), hypercholesterolemia (Chol>200 mg/dL), hypertriglyceridemia (TG>200 mg/dL), anxiety (Beck anxiety questionnaire), and depression (Beck depression questionnaire).[19, 20] Demographic measurements (weight, height, age, sex, education, and familial history were assessed via interviewing or measurement by trained nurses. Global Physical Activity Questionnaire (GPAQ) and Metabolic Equivalent

of Task (MET) were employed to evaluate the level of physical activity.[21, 22] MET is defined as the rate of energy use by a person while sitting (equivalent to 3.5 ml oxygen consumption/kg body weight in a minute). The subjects with less than four METs in a minute were regarded as low, between four to eight METs as moderate, and more than eight METs as intense physical activity. All the medical examinations and laboratory blood tests were free of charge for the participants.

Oral examination was performed by a dentist under light by the use of a dental mirror and a dental CPI-probe. The presence of microbial plaque or any sign of infected teeth was recorded. World Health Organization (WHO) criteria and codes were utilized for assessing dentition status.[23] Gingival health status was assessed through standard Gingival Inflammation Index (GI) and scored from mild to severe inflammation. Periodontal health status was assessed with community periodontal index (CPI). GI and CPI scores were calculated according to reference instruction.[24]

Opium Addiction Definition

Opium addiction was defined according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria.[25] A physician, after taking blood pressure, medical history, and clinical examination, asked the participants to disclose, whether they have ever used any type of drugs, assuring them that the information will be analyzed anonymously and used only for research purposes. Almost all the people in Iran rely on medical doctors to disclose their confidential health-related information. The subjects were categorized into three groups: “never users”, who had never consumed opium, “occasional users”, who were not dependent but irregularly used opium (mostly for entertainment), and “dependent users”, who regularly consumed opium.

Incidence Rate of Addiction

Out of 9996 participants, 2820 individuals were present in both phases of the study. To calculate the incidence rate of opium use, we employed the data from those people, who participated in both phases, did not use opium either occasional or dependent in phase one and therefore were at the risk of becoming opium users during the follow-up (figure 1). Thus, 10.6% of 5895 participants (625 cases) in phase one, who had already used opium were excluded from the incidence rate calculation. Out of the remaining participants (5270 cases), 2450 persons (41.5% of the participants) were lost to follow-up or died during these five years. The new opium-user cases (among 5270 cases) were considered as the numerator. For those, who were non-users in the phase one visit, the time difference (in a year) between the visit in phase one and phase two was calculated as person-years at risk. Hence, the denominator is the sum of the time each person was followed (person-year), totaled for all the 5270 persons, who were at risk of becoming opium-user. For those, who were lost to follow-up, we assumed they had been followed on an average of 2.5 years (half of overall follow time between phase one1 and two) and were then lost to follow-up. Then, the incidence rate (expressed as a person per 100 person-years) was calculated with this formula.[26]

$$\text{Incidence rate of opium use} = \frac{\text{Number of new cases of opium user during 5 years}}{\text{Total person-years for all persons at risk of opium use}} \times 100$$

Statistical Analysis

All data were analyzed under survey data analysis via Stata software (v.11, Stata Corp LLC, Texas 77845-4512, USA). Households were considered as the primary sampling unit (cluster). The prevalence of opium dependency and occasional use in both phases were standardized based on the same reference (Kerman population in 2016) to facilitate the comparison of the predominance between the two phases. The Chi square test was utilized to compare the prevalence between sex groups, age groups, and regions of residency. The standardized mean and 95% confidence interval (CI) for opium consumption was calculated and compared between men and women through the Post-Survey Estimation Student *t* test. The association between opium consumption and CAD risk factors was studied by the use of the Poisson regression model and adjusted

Figure 1: The flow chart indicates people, who participated in both phases of the study.

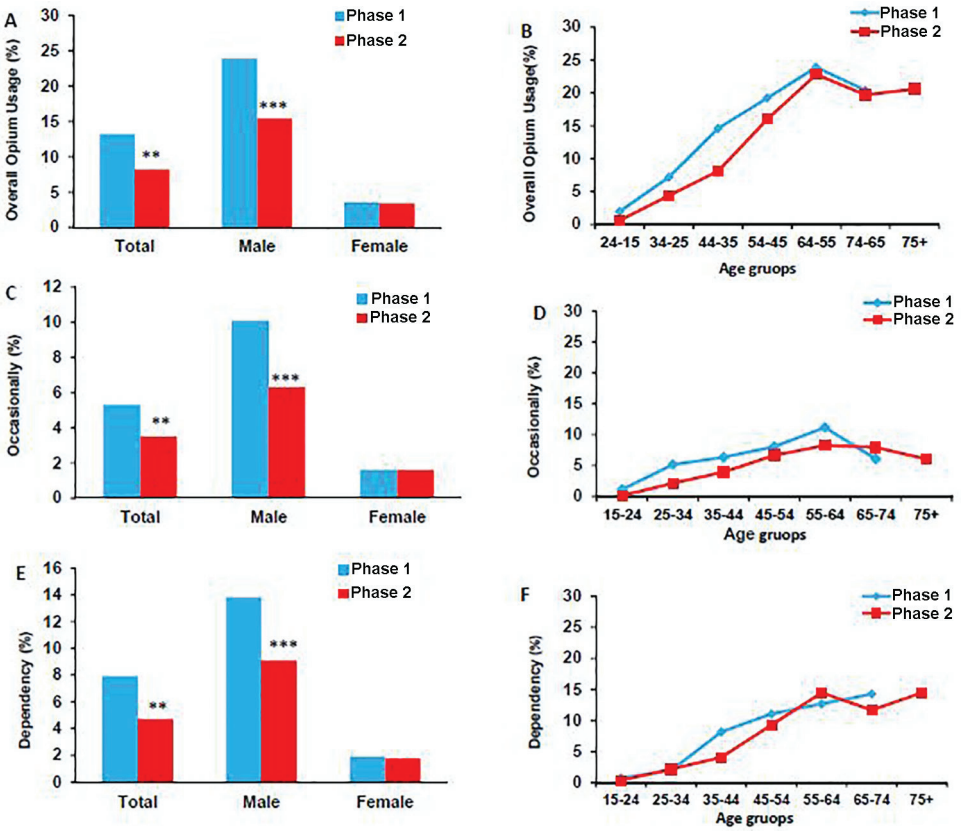

Figure 2: Comparison of the prevalence (%) of overall, occasional, and dependent opium use between the two phases of the study (KERCADRS) via sex and age groups is illustrated. Total participants equal 9996 in the second phase and 5895 in the first phase one. **P<0.01, ***P<0.001 versus first phase after standardization based on Kerman census 2016.

odds ratios (AOR) were calculated, according to potential confounders, such as age, sex, and other CAD risk factors, including serum lipids, level of physical activity, and level of psychological disorders. P values of less than 0.05 were considered as the significant level.

Results

The data from 9996 subjects in this survey revealed that the standardized prevalence of overall opium use was 8.1%, which was significantly lower than the phase one (13.2%) (P<0.01). The prevalence of opium dependency in follow-up in the last five years decreased from 7.9% to 4.7% (P<0.01) (figure 2). The predominance of occasional opium use also decreased in the second phase (3.5% versus 5.3%) (P<0.01) (figure 2 and table 1). The prevalence of opium use decreased significantly in men during five years (15.3% versus 23.9%) (P<0.001). The prevalence was significantly higher in men than women in both phases (P<0.001). The highest prevalence of opium consumption was in the 55-64 age group in both phases (22.8 % and 23.9%). The age-dependent reduction of overall and dependent opium use was heterogenic and mostly in middle-aged participants (figure 2 B, F). The data of phase one were extracted from the paper published previously for comparison following standardization based on Kerman census 2016.[16]

Chi square test was used to compare the prevalence rates between sex groups, age groups, and the regions of residency. The standardized mean and 95% confidence interval (CI) for opium consumption was calculated and compared between men and women using the Post-Survey Estimation Student *t* test.

The relationship between the status of opium consumption and cardiovascular disease risk factors is presented in table 2. The risk of depression in opium-dependent and occasional users was significantly higher than that of non-users (AOR=1.9) (P=0.001) and (AOR=1.4) (P=0.017,) respectively. The risk of anxiety in addicted people was 30% more than the non-addicted people (AOR=1.3) (P=0.009). Regarding the oral health status, the high gingival inflammation index (GI) (AOR=1.6) and CPI score (AOR=1.4) were observed with opium addiction. The risk of overweight/obesity in opium-dependent users was lower than non-users (AOR=0.6, CI 95% 0.4-0.8). Low physical activity was significantly higher in opium-dependent users (AOR=1.4 CI 95% 1.0-1.7). There were no

Table 1: The age-sex standardized prevalence of opium abuse (occasional and dependent use), community-based study (KERCARD-2nd Phase N=9996), Kerman, Iran, 2014-2018

Variables	Subgroups	Standardized prevalence* (95% CI) of opium abuse			
		Occasional	Dependent	Total	P
Overall	-	3.4 (3.1-3.8)	4.7 (4.3-5.0)	8.1 (7.6-8.6)	-
Sex	Male	6.3 (5.6-7.0)	9.0 (8.2-9.8)	15.3 (14.3-16.4)	<0.0001
	Female	1.6 (0.0-0.04)	1.8 (1.5-2.1)	3.4 (3.0-3.9)	
Age groups	15-24	0.2 (0.0-0.04)	0.3 (0.0-0.6)	0.6 (0.2-0.9)	<0.0001
	25-34	2.2 (1.7-2.7)	2.1 (1.6-2.6)	4.3 (3.6-5.1)	
	35-44	4.0 (3.3-4.6)	4.1 (3.4-4.8)	8.1 (7.2-9.0)	
	45-54	6.7 (5.9-7.5)	9.2 (8.3-10.2)	16.0 (14.8-17.1)	
	55-64	8.3 (7.4-9.2)	14.4 (13.3-15.5)	22.8 (21.5-24.1)	
	65-74	7.9 (6.7-9.1)	11.7 (10.2-13.1)	19.6 (17.9-21.4)	
	≥75	6.1 (4.3-7.8)	14.4 (11.8-17.1)	20.6 (17.6-23.5)	

Table 2: Prevalence and adjusted odds ratio (AOR) for the association between the status of opium consumption and coronary artery disease risk factors (KERCARD-Second Phase- 2014-2018, N=9996), Kerman, Iran

Risk factor	Addiction status	Risk factor prevalence		Adjusted analysis		
		N (%)	95% CI	AOR	P	95% CI
Diabetes (normal versus diabetic)	Nonuser	1384 (15.9)	(15.1-16.7)	1		
	Occasional user	107 (21.8)	(18.2-25.7)	1.1	0.2	(0.8-1.6)
	Dependent user	146 (20.5)	(17.5-23.6)	1.0	0.9	(0.7-1.4)
Depression (BDI<15 versus BDI>15)	Non-user	1359 (15.6)	(14.8-16.3)	1		
	Occasional user	74 (15.1)	(12.0-18.5)	1.4	0.02	(1.0-2.0)
	Dependent user	156 (21.9)	(21.5-28.0)	1.9	0.001	(1.3-2.6)
Anxiety (BAI<7 versus BAI>7)	Non-user	3600 (41.3)	(40.2-42.3)	1		
	Occasional user	183 (37.3)	(32.9-41.7)	1.0	0.5	(0.8-1.4)
	Dependent user	287 (40.3)	(36.6-43.9)	1.3	0.05	(0.9-1.7)
Hyper TG (TG<200 versus TG>200)	Non-user	3314 (38.0)	(36.9-39.0)	1		
	Occasional user	233 (47.5)	(42.9-51.9)	1.1	0.3	(0.8-1.4)
	Dependent user	311 (43.6)	(39.8-47.2)	1.0	0.5	(0.8-1.3)
Poor HDL/LDL ratio (under 0.3 versus above 0.3)	Non-user	7523 (87.1)	(86.4-87.8)	1		
	Occasional user	413 (84.3)	(80.7-87.3)	1.1	0.5	(0.8-1.5)
	Dependent user	594 (83.9)	(80.9-86.5)	0.9	0.8	(0.6-1.3)
Hypertension (BP<140/90 versus BP>140/90)	Non-user	2514 (28.8)	(27.8-29.7)	1		
	Occasional user	187 (37.5)	(33.1-41.9)	0.9	0.4	(0.7-1.1)
	Dependent user	291 (40.8)	(37.1-44.4)	1.1	0.3	(0.8-1.5)
Poor GI (GI<1 versus GI>1)	Non-user	2095 (29.4)	(28.3-30.4)	1		
	Occasional user	144 (41.0)	(35.8-46.3)	1.1	0.1	(0.9-1.5)
	Dependent user	159 (51.0)	(45.2-56.6)	1.6	0.001	(1.2-2.1)
High CPI (CPI<2 versus CPI>3)	Non-user	468 (6.6)	(5.9-7.1)	1		
	Occasional user	51 (14.4)	(10.9-18.5)	1.1	0.6	(0.7-1.5)
	Dependent user	68 (21.4)	(17.0-26.3)	1.4	0.03	(1.0-2.0)
Overweight/obesity (BMI<25 versus BMI>25)	Non-user	5755 (66.1)	(65.1-67.1)	1		
	Occasional user	322 (65.8)	(61.4-70.0)	0.9	0.8	(0.7-1.2)
	Dependent user	378 (53.3)	(49.5-57.0)	0.6	0.0	(0.4-0.8)
Low physical activity (Weekly min<150 versus>150)	Non-user	4125 (47.3)	(46.2-48.3)	1		
	Occasional user	233 (47.5)	(42.9-51.9)	1.1	0.3	(0.9-1.4)
	Dependent user	387 (54.2)	(50.4-59.9)	1.4	0.001	(1.0-1.7)

The association between opium consumption and CAD risk factors was assessed using the Poisson regression model and adjusted odds ratios (according to potential confounders, such as age, sex, and other CAD risk factors, including serum lipids, level of physical activity, and level of psychological disorders). GI: Gingival inflammation index; CPI: Community periodontal index.

significant relationships between opium use and the risk of diabetes (P=0.9), hypertension (P=0.3), high TG (P=0.5), and HDL/LDL ratio (P=0.8).

As the prevalence of cigarette smoking is high in opium-addicted people, and their combination may intensify the risks, the odds of having a CAD risk factor considering the interactions between opium use and cigarette smoking was studied and was added to table 3. The risk of depression was higher in persons, who only consumed opium, either occasional (AOR=1.7, CI 95% 1.2-2.3) or dependent (AOR=2.3, CI 95% 1.6-3.3).

Table 3: Adjusted odds ratio (AOR) for the statues of opium consumption and coronary artery disease risk factors considering the interactions between addiction and cigarette smoking (KERCARD second phase- N=9996), Kerman, Iran, 2014-2018

Risk factor	Addiction status	No Cigarette smoking		Yes Cigarette smoking	
		AOR	P	AOR	P
Depression (BDI<15 versus BDI>15)	Nonuser	1		1	
	Occasional user	1.7 (1.2-2.3)	0.001	0.7(0.3-1.7)	0.5
	Dependent user	2.3 (1.6-3.3)	0.001	1.3 (0.7-2.3)	0.3
Poor GI (GI<1 versus GI>1)	Nonuser	1		1	
	Occasional user	1.3 (1.0-1.7)	0.02	0.5 (0.3-1.0)	0.09
	Dependent user	1.4 (1.0-1.9)	0.04	1.7 (1.0-2.8)	0.02
High CPI (CPI<2 versus CPI>3)	Non-user	1		1	
	Occasional user	0.9 (0.5-1.3)	0.5	2.3 (1.0-5.1)	0.03
	Dependent user	1.6 (1.0-2.4)	0.02	1.1 (0.6-2.2)	0.16
Overweight/obesity (BMI<25 versus BMI>25)	Non-user	1		1	
	Occasional user	1.0 (0.8-1.3)	0.7	0.7 (0.4-1.3)	0.3
	Dependent user	7.3 (0.5-.9)	0.04	0.6 (0.4-0.9)	0.04
Low physical activity (weekly min<150 versus >150)	Non-user	1		1	
	Occasional user	1.0 (0.7-1.2)	0.9	1.6 (0.9-2.8)	0.06
	Dependent user	1.3 (1.0-1.8)	0.02	1.3 (0.8-2.0)	0.21

The association between opium consumption and CAD risk factors was assessed with the Poisson regression model and adjusted odds ratios (according to potential confounders such as age, sex, and other CAD risk factors, including serum lipids, level of physical activity, and level of psychological, disorders). GI: Gingival inflammation index; CPI: Community periodontal index.

Table 4: Incidence rate (persons/100 person-years) of opium consumption related to coronary artery disease risk factors in the community-based cohort study (KERCADRS, phases 1, 2009-2011 and 2, 2014-2018 (n=2820 match cases) Kerman, Iran

Subgroups		Occasional user		Dependent user	
Overall		Incidence (95% CI), (person/100 person-years)	P	Incidence (95% CI), (person/100 person-years)	P
Sex	Male	3.9 (3.2-4.8)	0.001	4.2 (3.5-5.1)	0.001
	Female	6.7 (5.2-8.5)		4.9 (3.7-6.3)	
Diabetes	No (normal)	2.1 (1.4-3.0)	0.003	1.3 (0.8-2.0)	0.005
	Yes (diabetic)	3.8 (3.0-4.7)		2.4 (1.8-3.3)	
Hypertension	No (BP<140/90)	4.6 (3.2-6.3)	0.001	3.8 (2.6-5.3)	0.001
	Yes (BP>140/90)	3.6 (2.8-4.7)		2.4 (1.8-3.3)	
Depression	No	4.6 (3.2-6.3)	0.001	3.8 (2.6-5.3)	0.001
	Yes	4.8 (3.8-5.9)		2.2 (1.6-3.1)	
Anxiety	No	2.3 (1.4-3.6)	0.001	3.6 (2.5-5.0)	0.160
	Yes	6.2 (4.4-8.5)		1.5 (0.7-2.8)	

High GI was observed in opium-dependent users either without (AOR=1.4, CI 95% 1.0-1.9) or with smoking cigarettes (AOR=1.7, CI 95% 1.0-2.8). There was a higher GI in the occasional opium users (AOR=1.3, CI 95% 1.0-1.7). CPI score was higher in occasional users, who were also smokers (AOR=2.3, CI 95% 1.0-5.1).

The risk of overweight/obesity was significantly lower in opium-dependent users (AOR=0.73, CI 95% 0.5-0.9) that did not change with cigarette smoking (AOR=0.6, CI 95% 0.4-0.9). The chances of being low physically active were significantly higher in dependent opium users (AOR=1.3, CI 95% 1.0-1.8). Cigarette smoking did not change AOR (AOR=1.3, CI 95% 0.8-2.0).

Incidence Rate of Opium Use

Overall, the incidence rate of dependent and occasional opium use was 4.2 and 3.9 persons/100-person-years. Both incidence rates were higher in men than in women (4.9 versus 1.3 and 6.7 versus 2.1, respectively). The lowest age-related incidence rate of dependent opium use belonged to young participants (aged 15-24 years with 0.7 persons/100 person-years), while the highest one was related to those aged 55-64 years (4.1 persons/100 person-years). Both anxiety and depression are with a lower incidence rate of occasional opium use and a higher incidence rate of dependent opium use. In addition, diabetes, hypertension, obesity, depression, and anxiety were all associated with an increase in the incidence rate of dependent opium use. There was a reverse relationship between the level of physical activity and the incidence rate of dependent opium use (table 4).

Discussion

Overall, the main findings of this study were that the overall prevalence of total, occasional, and dependent opium use was reduced in the span of five years between the two phases of the study. The prevalence was higher in men than women in both phases and decreased in men in this period. There was a positive association between opium use, depression, and anxiety and a negative association with the level of physical activity. We also found an increased risk of poor GI and high CPI in opium users. The five-year incidence rate of opium use was higher in people with diabetes, hypertension, depression, anxiety, and in obese subjects.

Although the prevalence of opium consumption decreased in the last five years, specifically in age groups of less than 54 years, the prevalence is still higher than average levels in the Middle East and southwestern Asia (2.6%) and the overall prevalence in Iran (2.3%).[2, 3] In addition, men are at greater risk than women. The lower rate in women is due to cultural barriers, since opium use in women is much less acceptable in Iran.

We found a 90% increase in the risk of depression in dependent and a 40% increase in occasional users. A significant relationship between opium consumption and anxiety was also observed. Depression is an important and independent risk factor for developing coronary heart disease.[27] It has been demonstrated that *Mu-opioid receptors* (MORs), located in emotional-related regions of the brain, mediate the depressive and anxious effects of opioids. Destruction of amygdala circuits in addicted subjects makes them prone to depression and anxiety.[28] There could also be a reverse causation, as the rate of opioid use increased in depressed and anxious subjects (table 4). Furthermore, it has been shown that 9-12% of addicted persons experienced depression after addiction.[27] Psychological disorders may be one of the main reasons for having tendency towards opioid abuse. The prevalence of cigarette smoking is also higher in opium-addicted people.[16] Moreover, it has been revealed that depression and anxiety are also more prevalent in cigarette smokers.[28] The finding that the odds of becoming depressed was significant in opium users without cigarette smoking compared to those smoking cigarettes (table 3), suggesting that opioids may induce depression independently from cigarette smoking.

The results implied that in diabetic and hypertensive patients the incidence rate of opium consumption significantly increased. This may confirm that these patients believe that opium ameliorates their diseases. There are some controversies on the association between opium use and blood pressure.[9, 29] We did not see a reduced risk of diabetes and hypertension in occasional and dependent opium users. The experimental studies have also indicated that exposure to opium in long times increases blood pressure probably due to the harmful changes in the cardiovascular system, such as induction of atherosclerosis and increasing oxidative stress.[9, 29] Our previous study has also revealed that opium addiction does not have any ameliorative effects on lipids profiles, the preliminary stage of atherosclerosis.[16] It has been shown that opiates can induce insulin resistance, metabolic syndrome, increase plasma glucose and worsen diabetes, increase the chance of coronary heart disease in diabetic patients,[30] or increase the prevalence of diabetes.[31, 32] Meanwhile, several studies did not find a relationship between opium consumption and blood glucose or diabetes;[11-13] on the other hand, a few ones detected a decreased level of blood glucose in opium-addicted subjects.[15] The differences may be due to sample size, study methodology (case-control versus cohort or experimental), or duration of opium use.[29]

Poor oral health status has been introduced as a cardiovascular disease risk factor.[33] The findings demonstrated that oral health indices were significantly lower in addicted individuals. Since smoking is common in opium-addicted people, poor oral health status was likely mediated by smoking. However, our results suggest that opium independent from smoking causes poor GI, and smoking increases the risk of poor GI in opium-addicted individuals (AOR increased from 1.4 in addicted non-smokers to 1.7 in addicted smokers, a 30% increase in the risk). Poor oral health might be indirectly the result of the effects of opium on health behaviors. Addicted people have lower hygienic performance due to the expenses for opium provision and are ordinarily more from lower socioeconomic classes.

The prevalence of obesity decreased through opium use, and this effect did not differ with or without smoking cigarettes. We have revealed that smoking cigarette also reduces body weight, implying that this effect of opium is independent of cigarette smoking, and the two CAD risk factors induce their weight reducing the effects through a common pathway. The influence of opium on weight may be also attributed to poorer nutrition in addicted people.

Overall, the higher rate of addiction in

individuals with hypertension, diabetes, low physical activity, depression, and anxiety augments the odds of incidence of CAD in these individuals. It has been confirmed that the effects of multiple risk factors can be multiplicatively increased.[34]

We acknowledge the limitation of our study as a cross-sectional survey in exploring causality between opium use and CAD risk factors. Additionally, this paper has advantages, such as random selection community-based sampling, a large sample size covering a wide range of age (15-80 years), and both sexes. Although due to the large sample size (high expenses) and ethical considerations we were not able to confirm the addiction status via laboratory tests on urine or blood, we are sure that the participants who disclose their addiction were addicts. However, some addicts may introduce themselves as occasional users, and some users may hide their opium use. These may have caused an underestimation of opium addiction prevalence in our research. To minimize the information bias, we arranged the interviews with the participants to be performed in a medical clinic and that the questions about opium use be asked by the medical physician after assuring them that the data will be anonymous and used only for research purposes.

Conclusion

The current work indicated that opium addiction as a CAD risk factor is closely associated with several other CAD risk factors, such as depression, anxiety, low physical activity, and poor oral health conditions. The study also shed light on the tendency to use opium in persons, who have other CAD risk factors, such as hypertension, diabetes, obesity, and psychological disorders. These may be the results of a common fallacy that opioid use may alleviate and/or cure these diseases. Hence, informing people with appropriate educational programs on the ineffectiveness of opium could be a good way towards preventing opium use.

Acknowledgment

The KERCADR study phase two was funded by the Deputy of Research and Technology at Kerman University of Medical Sciences (Grant No: IR.KMU.REC.1393.310). The authors would like to profoundly thank the participants of the study and special thanks to the colleagues in the Physiology Research Center, who helped us recruit, interview, and examine the study participants.

Authors' Contribution

H.N, M.M contributed to study concept and design, and critical revision of the manuscript. F.R, R.A, R.F and M.S participated in data acquisition, analysis, and drafting the manuscript. H.N, M.M, F.R, R.A, R.F and M.S contributed to interpretation of the data. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

References

1 Network GBoDC. Global burden of disease study 2017 (GBD 2017) results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME). 2018.
2 UNODC. World Drug Report (United Nations Office on Drugs and Crime). Vienna: United Nations Office on Drugs and Crime; 2020.
3 Mohebbi E, Haghdoost AA, Noroozi A, Molavi Vardanjani H, Hajebi A, Nikbakht R, et al. Awareness and Attitude Towards Opioid and Stimulant Use and Lifetime Prevalence of the Drugs: A Study in 5 Large Cities of Iran. Int J Health Policy Manag. 2019;8:222-32. doi: 10.15171/ijhpm.2018.128. PubMed PMID: 31050967; PubMed Central PMCID: PMCPMC6499902.
4 Amin-Esmaeili M, Rahimi-Movaghar A, Sharifi V, Hajebi A, Radgoodarzi R, Mojtabai R, 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;111:1836-47. doi: 10.1111/add.13453. PubMed PMID: 27177849.
5 Bashardoost N, Tirani M. Prevalence of addiction in males: Isfahan 2003. ARYA Atherosclerosis. 2010;1.
6 Menati W, Valizadeh R, Menati R, Niazi M, Nazarzadeh M, Bidel Z. Determination of opium abuse prevalence in Iranian young people: a systematic review and meta-analysis. Journal of Substance Use. 2017;22:3-10. doi: 10.3109/14659891.2015.1130181.
7 Masoomi M, Ramezani MA, Karimzadeh H. The relationship of opium addiction with coronary artery disease. Int J Prev Med. 2010;1:182-6. PubMed PMID: 21566789; PubMed Central PMCID: PMCPMC3075529.
8 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 angina. Int J Cardiol. 2016;219:301-7. doi: 10.1016/j.ijcard.2016.06.034. PubMed PMID: 27343424.

9 Ziaee M, Hajizadeh R, Khorrami A, Sepehrvand N, Momtaz S, Ghaffari S. Cardiovascular Complications of Chronic Opium Consumption: A Narrative Review Article. Iran J Public Health. 2019;48:2154-64. PubMed PMID: 31993383; PubMed Central PMCID: PMCPMC6974854.

10 Fallahzadeh MA, Salehi A, Naghshvarian M, Fallahzadeh MH, Poustchi H, Sepanlou SG, et al. Epidemiologic Study of Opium Use in Pars Cohort Study: A Study of 9000 Adults in a Rural Southern Area of Iran. Arch Iran Med. 2017;20:205-10. PubMed PMID: 28412823.

11 Sadeghian S, Boroumand MA, Sotoudeh-Anvari M, Rabbani S, Sheikhfathollahi M, Abbasi A. Effect of opium on glucose metabolism and lipid profiles in rats with streptozotocin-induced diabetes. Endokrynol Pol. 2009;60:258-62. PubMed PMID: 19753539.

12 Rezvanfar MR, Farahany H, Rafiee M, Kaboli S. Opium consumption challenge and diabetes mellitus control. Iranian Journal of Diabetes and Obesity. 2011;3:72-6.

13 Mahmoodi M, Hosseini-Zijoud S-M, Hosseini J, Sayyadi A, Hajizadeh M, Hassanshahi G, et al. Opium withdrawal and some blood biochemical factors in addicts' individuals. Advances in biological chemistry. 2012;2:167-70. doi: 10.4236/abc.2012.22020.

14 Asgary S, Naderi G, Soghraty M, Ahmady P, Shahrezaee J. A study of plasma lipid peroxidation, lipids and blood sugar level in opium addicts compared with control group. ARYA Atherosclerosis. 2010;1.

15 Kouros D, Tahereh H, Mohammadreza A, Minoo MZ. Opium and heroin alter biochemical parameters of human's serum. Am J Drug Alcohol Abuse. 2010;36:135-9. doi: 10.3109/00952991003734277. PubMed PMID: 20465370.

16 Najafipour H, Masoomi M, Shahesmaeili A, Haghdoost AA, Afshari M, Nasri HR, et al. Effects of opium consumption on coronary artery disease risk factors and oral health: Results of Kerman Coronary Artery Disease Risk factors Study a population-based survey on 5900 subjects aged 15-75 years. Int J Prev Med. 2015;6:42. doi: 10.4103/2008-7802.157470. PubMed PMID: 26097671; PubMed Central PMCID: PMCPMC4455126.

17 World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310:2191-4. doi: 10.1001/jama.2013.281053. PubMed PMID: 24141714.

18 Najafipour H, Mirzazadeh A, Haghdoost A, Shadkam M, Afshari M, Moazenzadeh M, et al. Coronary Artery Disease Risk Factors in an Urban and Peri-urban Setting, Kerman, Southeastern Iran (KERCADR Study): Methodology and Preliminary Report. Iran J Public Health. 2012;41:86-92. PubMed PMID: 23193513; PubMed Central PMCID: PMCPMC3494222.

19 Osman A, Kopper BA, Barrios FX, Osman JR, Wade T. The Beck Anxiety Inventory: reexamination of factor structure and psychometric properties. J Clin Psychol. 1997;53:7-14. doi: 10.1002/(sici)1097-4679(199701)53:1<7::aid-jclp2>3.0.co;2-s. PubMed PMID: 9120035.

20 Jackson-Koku G. Beck Depression Inventory. Occup Med (Lond). 2016;66:174-5. doi: 10.1093/occmed/kqv087. PubMed PMID: 26892598.

21 Herrmann SD, Heumann KJ, Der Ananian CA, Ainsworth BE. Validity and reliability of the global physical activity questionnaire (GPAQ). Measurement in Physical Education and Exercise Science. 2013;17:221-35. doi: 10.1080/1091367X.2013.805139.

22 Morris CK, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. J Am Coll Cardiol. 1993;22:175-82. doi: 10.1016/0735-1097(93)90832-l. PubMed PMID: 8509539.

23 Organization WH. Dentition status and criteria for diagnosis and coding (Caries). Geneva: WHO Oral Health Surveys: Basic methods. 1997:39-44.

24 Greene JC, Vermillion JR. The Simplified Oral Hygiene Index. J Am Dent Assoc. 1964;68:7-13. doi: 10.14219/jada.archive.1964.0034. PubMed PMID: 14076341.

25 Hasin D, Hatzenbuehler ML, Keyes K, Ogburn E. Substance use disorders: Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and International Classification of Diseases, tenth edition (ICD-10). Addiction. 2006;101:59-75. doi: 10.1111/j.1360-0443.2006.01584.x. PubMed PMID: 16930162.

26 Dicker RC, Coronado F, Koo D, Parrish RG. Principles of epidemiology in public health practice; an introduction to applied epidemiology and biostatistics. Atlanta: CDC Stacks; 2006.

27 Dhar AK, Barton DA. Depression and the Link with Cardiovascular Disease. Front Psychiatry. 2016;7:33. doi: 10.3389/fpsyt.2016.00033. PubMed PMID: 27047396; PubMed Central PMCID: PMCPMC4800172.
28 Fluharty M, Taylor AE, Grabski M, Munafo MR. The Association of Cigarette Smoking With Depression and Anxiety: A Systematic Review. Nicotine Tob Res. 2017;19:3-13. doi: 10.1093/ntr/ntw140. PubMed PMID: 27199385; PubMed Central PMCID: PMCPMC5157710.
29 Najafipour H, Beik A. The Impact of Opium Consumption on Blood Glucose, Serum Lipids and Blood Pressure, and Related Mechanisms. Front Physiol. 2016;7:436. doi: 10.3389/fphys.2016.00436. PubMed PMID: 27790151; PubMed Central PMCID: PMCPMC5061814.
30 Moezi Bady SA, Soltani M, Kazemi T, Khosravi Bizhaem S, Hanafi Bojd N, Partovi N, et al. Surveying the Effect of Opioid Abuse on the Extent of Coronary Artery Diseases in Diabetic Patients. J Addict. 2020;2020:8619805. doi: 10.1155/2020/8619805. PubMed PMID: 32765923; PubMed Central PMCID: PMCPMC7387960.
31 Golozar A, Khademi H, Kamangar F, Poutschi H, Islami F, Abnet CC, et al. Diabetes mellitus and its correlates in an Iranian adult population. PLoS One. 2011;6:e26725. doi: 10.1371/journal.pone.0026725. PubMed PMID: 22053206; PubMed Central PMCID: PMCPMC3203882.
32 Mami S, Eghbali M, Cheraghi J, Mami F, Borujeni MP, Salati AP. Effect of opium addiction on some serum parameters in rabbit. Glob Vet. 2011;7:310-4.
33 Holmlund A, Lampa E, Lind L. Oral health and cardiovascular disease risk in a cohort of periodontitis patients. Atherosclerosis. 2017;262:101-6. doi: 10.1016/j.atherosclerosis.2017.05.009. PubMed PMID: 28531825.
34 Najafipour H, Afshari M, Rostamzadeh F. Prevalence of Multiple Coronary Artery Disease Risk Factors in Kerman: A Population-Based Study in Southeast Iran. Iran J Med Sci. 2018;43:140-9. PubMed PMID: 29749982; PubMed Central PMCID: PMCPMC5936845.