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FULL RESEARCH PAPER

Long-term opiate use and risk of cardiovascular mortality: results from the Golestan Cohort Study

Mahdi Nalini[1,2], Ramin Shakeri[1], Hossein Poustchi[3,4], Akram Pourshams[1,4], Arash Etemadi [1,5], Farhad Islami [1,6], Masoud Khoshnia[1,7], Abdolsamad Gharavi[1,7], Gholamreza Roshandel [7,1], Hooman Khademi[1], Mahdi Zahedi[8], Behnoush Abedi-Ardekani[9], Rajesh Vedanthan [10], Paolo Boffetta[11], Sanford M. Dawsey[5], Paul D. Pharaoh [12], Masoud Sotoudeh [1], Christian C. Abnet[5], Nicholas E. Day[12], Paul Brennan[9], Farin Kamangar [13]*, and Reza Malekzadeh[1,3,4]*

[1]Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Shariati Hospital, North Kargar Avenue, Tehran 14117-13135, Iran; [2]Cardiovascular Research Center, Kermanshah University of Medical Sciences, Imam Ali Hospital, Shahid Beheshti Boulevard, Kermanshah, Iran; [3]Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Shariati Hospital, North Kargar Avenue, Tehran 14117-13135, Iran; [4]Digestive Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Shariati Hospital, North Kargar Avenue, Tehran 14117-13135, Iran; [5]Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; [6]Surveillance and Health Services Research, American Cancer Society, Atlanta, GA, USA; [7]Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran; [8]Ischemic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran; [9]Section of Genetics, International Agency for Research on Cancer, World Health Organization, Lyon, France; [10]Department of Population Health, NYU Grossman School of Medicine, New York, NY, USA; [11]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [12]Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; and [13]Department of Biology, School of Computer, Mathematical, and Natural Sciences, Morgan State University Portage Avenue Campus, Room 103, Baltimore, MD 21251, USA

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Aims Tens of millions of people worldwide use opiates but little is known about their potential role in causing cardiovascular diseases. We aimed to study the association of long-term opiate use with cardiovascular mortality and whether this association is independent of the known risk factors.

Methods and results In the population-based Golestan Cohort Study—50 045 Iranian participants, 40–75 years, 58% women—we used Cox regression to estimate hazard ratios and 95% confidence intervals (HRs, 95% CIs) for the association of opiate use (at least once a week for a period of 6 months) with cardiovascular mortality, adjusting for potential confounders—i.e. age, sex, education, wealth, residential place, marital status, ethnicity, and tobacco and alcohol use. To show independent association, the models were further adjusted for hypertension, diabetes, waist and hip circumferences, physical activity, fruit/vegetable intake, aspirin and statin use, and history of cardiovascular diseases and cancers. In total, 8487 participants (72.2% men) were opiate users for a median (IQR) of 10 (4–20) years. During 548 940 person-years—median of 11.3 years, >99% success follow-up—3079 cardiovascular deaths occurred, with substantially higher rates in opiate users than non-users (1005 vs. 478 deaths/100 000 person-years). Opiate use was associated with increased cardiovascular mortality, with adjusted HR (95% CI) of 1.63 (1.49–1.79). Overall 10.9% of cardiovascular deaths were attributable to opiate use. The association was independent of the traditional cardiovascular risk factors.

Conclusion Long-term opiate use was associated with an increased cardiovascular mortality independent of the traditional risk factors. Further research, particularly on mechanisms of action, is recommended.

Keywords Adverse effects • Cardiovascular diseases • Death • Opioid • Opium

* Corresponding authors. Tel: 001-301-655-9280, Email: farin.kamangar@morgan.edu (F.K.); Tel: 0098-21-82415000, Fax: 0098-21-82415400, Email: malek@tums.ac.ir (R.M.)

Introduction

Cardiovascular diseases (CVDs) are the most common causes of premature mortality worldwide,[1] necessitating identification and control of their risk factors. In addition to known risk factors—i.e. hypertension, dyslipidaemia, diabetes mellitus, tobacco use, obesity, low fruit and vegetable intake, harmful alcohol use, and physical inactivity[2]—the research for identification of novel risk factors, such as use of opiates and other opioids, continues.[3,4]

Opiates, such as opium, morphine, and codeine, are natural alkaloid compounds comprising the various products derived from the opium poppy plant. They are a subclass of opioids, which include natural opiates and their synthetic analogues.[5]

While prescription opioids are essential to alleviate pain in many patients, overmedication and illicit use of these substances are major health and societal problems. Worldwide, 29.2 million people use opiates and another 24.2 million use other opioids, primarily as illicit drugs.[5] In the USA, the years of life lost related to opioid mortality now exceeds those attributed to high blood pressure.[6]

Despite wide use, relatively little is known about the effects of long-term opioid use in causing CVDs.[7] Current estimates of opioid-related mortality are mainly focused on acute overdose[6] and blood-borne infectious diseases.[5] However, opioids may cause death due to other reasons too. For example, in a study of long-acting prescription opioids, a third of the excess deaths were attributed to CVDs.[8]

Randomized controlled trials to assess long-term opioid use are challenging and unlikely to be ever conducted,[7] therefore much of our information in this field comes from observational human studies. Some,[8–15] but not all,[4,16] observational studies have suggested that opioid use is associated with increased risk of CVDs. These findings, however, come mainly from retrospective studies that used prescription data or administrative claims databases, and thus had substantial methodological limitations such as challenges with obtaining valid data and confounding by indication.

To our knowledge, the Golestan Cohort Study (GCS) is the only long-term population-based prospective study in the world that has detailed and validated information on prolonged opiate use from a large number of users. In the study area (Golestan Province), recreational use of opium and its related natural products is widespread and largely without stigma, making it possible to obtain validated data from the general population. Initial results of this study, published in 2012, indicated increased risk of all-cause and cause-specific mortality in opiate users.[9] The aim of this article is to use updated data from the GCS to evaluate the association of long-term opiate use with risk of CVD mortality and to assess whether this association is independent of the known CVD risk factors.

Methods

Design and study population

The design of the GCS has been described previously.[17] The primary purpose was to study risk factors of oesophageal cancer in the northeastern Iran. This population-based cohort enrolled 50 045 men and women aged 40–75 years, without history of upper gastrointestinal cancers, from Gonbad City ($n = 10\ 032$) and 326 villages ($n = 40\ 013$) in Golestan Province, between 2004 and 2008. A subset of cohort members ($n = 11\ 418$) was invited to participate in a repeated measurement study in 2011–12. All participants gave written informed consent for taking part in the study. The study protocol was approved by the ethical review committees of the Digestive Disease Research Institute of Tehran University of Medical Sciences, the US National Cancer Institute, and the International Agency for Research on Cancer.

Baseline assessment of the main exposure

Opiate use was considered one of the potential risk factors for oesophageal cancer.[18] Therefore, the GCS questionnaire included detailed queries about opiate use, i.e. age of starting and ending use, types of opiates, and routes of administration. In the area, opiates are typically either smoked or eaten in two forms: teriak (crude opium) or shireh (an opium product mainly obtained from dross opium remaining after opium smoking with or without adding teriak, boiled in water and filtered).[9] Using other opiates such as sukhteh (opium dross) and heroin is rare. The questionnaire was administrated to all study participants by trained physicians. Individuals were considered opiate users if they had ever used opiates at least once a week for a period of 6 months. A validation study found that questionnaire responses were highly correlated with the levels of urinary opiate metabolites, with a sensitivity of 93% and specificity of 89%.[19]

Baseline assessment of potential confounders and effect modifiers

Detailed data were collected about age, sex, ethnicity, education, history of chronic diseases, drug history, cigarette smoking, the use of other types of tobacco such as hookah and nass (a local chewing tobacco product), alcohol consumption, and elements of wealth. A wealth score was created as previously described.[20]Self-reported data on intensity, frequency, and duration of physical activities were recorded. Fruits and vegetable consumption were recorded based on self-report. Blood pressure and waist and hip circumferences were measured. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, based on the European Society of Cardiology definition of the grade 1 hypertension.[21] Also, physician-confirmed diagnosis of hypertension or use of anti-hypertensive drugs were considered as hypertension. Diabetes was defined as self-report based on a physician diagnosis or use of anti-diabetes drugs. Sensitivity and specificity of the self-reported diabetes in these participants were 61.5% and 97.6%, respectively, using fasting plasma glucose and medical records.[22]

Repeated measurement

In the repeated measurement phase, a random sample of the participants ($n = 11\ 418$; 80% rural) were assessed again. Opiate, tobacco, nass, and alcohol use, blood pressure, waist and hip circumferences, and history of chronic diseases were re-evaluated. In addition, fasting blood glucose and lipids were measured.

Follow-up and ascertainment of cause of death

Follow-up methods and ascertainment of causes of death have been described previously.[17] In brief, during annual phone calls, the vital status of study participants was checked and information about any admission to hospitals or outpatient clinics was collected. When there was a report of a death, the follow-up team collected all medical documents including physician notes, findings on electrocardiography and radiology, pathology reports, laboratory test results, hospital discharge documents, etc., from all medical centres, either within the province or neighbouring provinces. In addition, if needed, the team physicians used a validated verbal autopsy questionnaire to interview the closest relative of the deceased. Two

separate internists independently reviewed all collected medical documents to make a diagnosis based on the ICD-10 codes (International Classification of Diseases, 10th revision). If the two diagnoses were not concordant, a third more experienced internist reviewed all documents and the two initial diagnoses to make the final diagnosis. We previously showed both high reliability, including between-reviewer reliability (kappa statistics > 0.75) and validity (sensitivity, specificity, positive predictive value, and negative predicting values > 0.81) in determining causes of death.[23] We categorized all CVD deaths (ICD-10 codes: I00-I99) into six groups: ischaemic heart disease (IHD: I20-I25), pulmonary embolism (I26), cardiac arrest (I46), heart failure (I50), cerebrovascular events (intracranial haemorrhage, I60-I62; cerebral infarction, I63; and not specified strokes, I64), and other CVDs.

Statistical analysis

Statistical analyses were conducted using Stata statistical software (version 12, StataCorp, College Station, TX). We used Cox proportional hazard regression models, with age as the timescale, to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for CVD mortality, comparing opiate users with non-users. The proportionality of hazards was verified using log–log plots. Follow-up continued until CVD death, loss to follow-up, death due to other reasons, or 1 February 2019, whichever came first. In the main model, HRs were adjusted for variables which could potentially confound the association between opiate use and CVD mortality, including age at enrolment (continuous), sex, education level (none, ≤5, and >5 years of formal education), residential place (urban, rural), marital status (married, unmarried), ethnicity (Turkmen, non-Turkmen), tobacco smoking (current, former, or never use of cigarette, pipe, or hookah), nass chewing (current, former, never), alcohol drinking, (ever, never), and wealth score (quintiles). We used logistic regression and Cox regression models to show the associations of these potential confounders with opiate use and CVD mortality, respectively (Supplementary material online, *Table S1*). Population attributable fractions were calculated based on the main model, using the following equation[24]:

$$\mathrm{PAF} = \mathrm{pd} \times \left(1 - \frac{1}{\mathrm{HR}_{\mathrm{adjusted}}}\right),$$

where pd is the proportion of cases (i.e. deceased participants) exposed to the risk factor (i.e. opiate use). To minimize the effects of reverse causality, two sensitivity analyses were conducted: (i) after excluding death in the first 2 years of follow-up; and (ii) after further excluding participants with history of IHD, heart failure, stroke, diabetes, or cancers. Subgroup analyses were conducted and multiplicative interactions were assessed for several potential effect modifiers. To eliminate the residual confounding of tobacco smoking, a subgroup analysis was in those who never smoked tobacco. The associations were also evaluated in subgroups by opiate types and routes of consumption. To eliminate the potential risks related to burning organic materials, we assessed the association in opiate users who reported only oral teriak in their life.

In order to investigate the independence of the association of opiate use with CVD mortality from other CVD risk factors, we further adjusted the main model for the potential intermediate variables including hypertension (yes/no), diabetes (yes/no), waist and hip circumferences (continuous), physical activity (tertiles), fruit/vegetable consumption (tertiles), and history of IHD (yes/no), stroke (yes/no), and cancers (yes/no). Adjustment for aspirin use and statin use —known protective drugs in CVDs—was also performed. Furthermore, using repeated measurement data, we adjusted the models for fasting blood glucose, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, in addition to the above-mentioned variables.

There were no missing values for the variables in the main model. In further analysis to show the independent effect of opiate use, the number of missing values was <0.01% for waist and hip circumferences, 0.06% for hypertension, 1.8% for fruit and vegetable intake, and 4.2% for physical activity data. In these cases, we used separate missing indicators to keep participants with missing data in the models. All *P*-values are two-sided. *P*-values <0.05 and 95% CIs not including one were considered as statistically significant.

Results

Table 1 shows baseline characteristics of the 50 045 cohort participants. The mean (SD) age was 52.1 (8.9) years and 58% were women. Among all participants, 8487 (17.0%) had a history of long-term opiate use, of whom 7422 (87.5%) were current users. Opiate users reported using teriak only ($n = 7308$, 86.1%), shireh only ($n = 781$, 9.2%), both teriak and shireh (288, 3.4%), or mixed/other opiates ($n = 110$, 1.3%). Routes of opiate consumption were smoking ($n = 5805$, 68.4%), eating ($n = 2153$, 25.4%), smoking and eating (506, 6.0%), or mixed/others ($n = 23$, 0.3%). Among opiate users, 1880 participants (22.2%) reported only oral teriak use. The medians (25th–75th percentiles) were 40 (30–48) years for age of opiate initiation, 10 (4–20) years for duration of use, and 0.6 (0.2–1.2) grams for daily amount of use. Long-term opiate users were more likely to have used tobacco and alcohol, be men, reside in rural areas, and have lower wealth score (*Table 1* and Supplementary material online, *Table S1*).

During 548 940 person-years of follow-up (median 11.3; 25th–75th percentile: 10.6–12.3 years), 7354 deaths occurred, and only 469 (<1%) participants were lost to follow-up. Among 6866 deaths with confirmed ICD codes, 3079 were due to CVDs. The CVD mortality rates per 10^5 person-years follow-up were 1005 in opiate users compared with 478 in non-users. Only 14 deaths were reported due to underlying causes related to poisoning and opioids (Supplementary material online, *Table S2*). *Table 1* shows numbers and rates of CVD deaths.

Table 2 and Supplementary material online, *Table S3* show the association of opiate use and CVD mortality, with crude and adjusted HRs (95% CIs) of 1.95 (1.81–2.11) and 1.63 (1.49–1.79), respectively. The fraction (95% CI) of CVD death attributable to opiate use was 10.9% (9.31–12.5%) for the entire cohort. Associations with specific causes of CVD death are also shown in *Table 2*. Strong associations were seen with death due to heart failure, pulmonary embolism, and IHD. Associations were less strong, yet statistically significant, for all cerebrovascular events combined.

In sensitivity analyses, the associations changed little after exclusion of participants with history of chronic diseases at baseline and the first 2 years of follow-up (*Table 3*).

Figure 1 shows the results across subgroups of several potential effect modifiers. The significant association between long-term opiate use and CVD mortality persisted and were even stronger (*P* for interaction <0.001) among those who never smoked tobacco and those who never ingested nass, with adjusted HRs (95% CIs) of 1.82 (1.63–2.05) and 1.73 (1.56–1.91), respectively. *Figure 2* shows the cardiovascular survival of the participants based on sex and history of tobacco use. Subgroup analyses also showed that the associations

Table 1 Baseline characteristics and cardiovascular death in the Golestan Cohort Study by opiate use

	No. of participants (%)		No. (rates[a]) of cardiovascular deaths	
	Opiate users 8487 (17.0)	Non-users 41 558 (83.0)	Opiate users 871 (1005)	Non-users 2208 (478)
Sex				
Female	2354 (8.2)	26 457 (91.8)	261 (1083)	1163 (391)
Male	6133 (28.9)	15 101 (71.1)	610 (975)	1045 (633)
Age at enrolment				
<55 years	5258 (15.7)	28 167 (84.3)	297 (521)	680 (211)
≥55 years	3229 (19.4)	13 391 (80.6)	574 (1932)	1528 (1094)
Residence				
Rural	7485 (18.7)	32 526 (81.3)	739 (965)	1681 (469)
Urban	1002 (10.0)	9032 (90.0)	132 (1312)	527 (506)
Ethnicity				
Turkmen	6552 (17.6)	30 701 (82.4)	665 (980)	1607 (464)
Non-Turkmen	1935 (15.1)	10 857 (84.9)	206 (1093)	601 (518)
Formal education				
No education	5628 (16.0)	29 490 (84.0)	694 (1231)	1803 (554)
≤5 years	1700 (20.1)	6763 (79.9)	113 (635)	224 (295)
>5 years	1159 (17.9)	5305 (82.1)	64 (512)	181 (297)
Marital status				
Married	7552 (17.2)	36 403 (82.8)	725 (931)	1754 (431)
Unmarried[b]	935 (15.4)	5155 (84.6)	146 (1664)	454 (820)
Tobacco smoking				
Current	2599 (50.2)	2578 (49.8)	224 (833)	166 (586)
Former	1980 (50.3)	1956 (49.7)	208 (1054)	193 (927)
Never	3908 (9.5)	37 024 (90.5)	439 (1096)	1849 (448)
Nass				
Current	2111 (66.5)	1063 (33.5)	248 (1181)	122 (1109)
Former	422 (59.9)	282 (40.1)	46 (1117)	30 (1022)
Never	5954 (12.9)	40 213 (87.1)	577 (937)	2056 (459)
Alcohol				
Ever	925 (53.5)	804 (46.5)	82 (854)	64 (702)
Never	7562 (15.7)	40 754 (84.3)	789 (1024)	2144 (473)
Wealth Score (quintiles)				
First	2639 (24.6)	8107 (75.4)	321 (1210)	564 (626)
Second	1747 (18.8)	7541 (81.2)	185 (1038)	478 (574)
Third	1763 (16.2)	9111 (83.8)	161 (887)	427 (424)
Fourth	1334 (14.1)	8148 (85.9)	103 (752)	400 (443)
Fifth	1004 (10.4)	8651 (89.6)	101 (963)	339 (346)

[a]Crude rates calculated in 10^5 person-years.
[b]Single, divorced, or widowed.

were seen for all types and routes of opiate use (Supplementary material online, *Table S4*). In those who only ingested teriak, crude and adjusted HRs (95% CIs) were 2.15 (1.89–2.44) and 1.71 (1.49–1.97), respectively.

After further adjusting the models for potential intermediate variables and aspirin and statin use, the associations did not change materially with HRs (95% CIs) of 1.54 (1.41–1.70) and 1.54 (1.40–1.69), respectively (*Table 2* and Supplementary material online, *Table S3*).

Results using data from the repeated measurement phase were similar to those from baseline (Supplementary material online, *Table S5*). After further adjustment for fasting blood glucose and lipids, HR (95% CI) was 1.68 (1.28–2.19). Adjustment for statin and aspirin use did not change the results.

Discussion

Our results show that long-term opiate use is associated with higher risk of CVD mortality and this association is independent of the traditional CVD risk factors, including hypertension, dyslipidaemia, diabetes, tobacco use, obesity, low fruit and vegetable intake, alcohol use, and physical inactivity. Cardiovascular disease mortality among

Table 2 Association of long-term opiate use and cardiovascular mortality[a] in the Golestan Cohort Study

	ICD-10 Codes	No. (Rates[b] of death in opiate users/non-users)	Crude model	Main model[c]	Fully adjusted model[d]
All cardiovascular deaths	I00-I99	3079 (1005/478)	1.95 (1.81–2.11)	1.63 (1.49–1.79)	1.54 (1.40–1.69)
Ischaemic heart disease	I20-I25	1483 (496/228)	2.04 (1.82–2.28)	1.68 (1.47–1.91)	1.55 (1.35–1.77)
Pulmonary embolism	I26	76 (30/11)	2.55 (1.58–4.09)	2.27 (1.29–3.97)	1.98 (1.12–3.48)
Cardiac arrest	I46	304 (108/45)	2.21 (1.74–2.82)	1.56 (1.16–2.10)	1.51 (1.12–2.03)
Heart failure	I50	201 (85/27)	2.86 (2.15–3.81)	2.97 (2.10–4.19)	2.79 (1.97–3.96)
Cerebrovascular events	I60–I64	913 (250/151)	1.53 (1.31–1.78)	1.28 (1.07–1.54)	1.26 (1.05–1.51)
Intracranial haemorrhage	I60–I62	215 (52/37)	1.33 (0.95–1.84)	1.13 (0.76–1.67)	1.11 (0.75–1.65)
Cerebral infarction	I63	346 (90/58)	1.42 (1.11–1.83)	1.09 (0.81–1.47)	1.09 (0.81–1.46)
Stroke, not specified	I64	352 (108/56)	1.77 (1.40–2.25)	1.61 (1.22–2.12)	1.56 (1.18–2.07)
Others	—	102 (35/16)	2.04 (1.33–3.12)	2.09 (1.27–3.46)	1.90 (1.15–3.13)

[a]Hazard ratios and 95% confidence intervals were estimated using Cox regression models with age as the time scale.
[b]Crude rates calculated in 10^5 person-years.
[c]Adjusted for potential confounders, including age at enrolment, sex, education, residential place, ethnicity, marital status, tobacco smoking, nass chewing, alcohol drinking, and wealth score.
[d]Further adjustment for intermediate or risk/protective factors, including hypertension, diabetes, waist and hip circumferences, physical activity, fruit/vegetable consumption, history of ischaemic heart disease, stroke, and cancers, aspirin use, and statin use.

Table 3 Sensitivity analyses for the association of long-term opiate use with cardiovascular deaths

	Sensitivity analysis 1[a] (*n* = 49 207)	Sensitivity analysis 2[b] (*n* = 43 068)
	HRs (95%CI)	HRs (95%CI)
All cardiovascular deaths	1.61 (1.45–1.78)	1.66 (1.47–1.87)
Ischaemic heart disease	1.55 (1.34–1.80)	1.45 (1.21–1.74)
Pulmonary embolism	2.17 (1.21–3.89)	2.11 (1.08–4.12)
Cardiac arrest	1.62 (1.19–2.19)	2.11 (1.49–3.00)
Heart failure	3.35 (2.36–4.77)	4.01 (2.61–6.16)
Cerebrovascular events	1.30 (1.07–1.58)	1.37 (1.09–1.72)
Intracranial haemorrhage	1.22 (0.79–1.89)	1.24 (0.76–2.03)
Cerebral infarction	1.01 (0.74–1.39)	1.01 (0.69–1.48)
Stroke, not specified	1.71 (1.27–2.29)	1.91 (1.36–2.70)
Others	2.11 (1.21–3.67)	2.67 (1.40–5.12)

Data are adjusted hazard ratios (95% confidence intervals), using Cox regression models with age as the time scale; adjusted for age at enrolment, sex, education, residential place, ethnicity, marital status, tobacco smoking, nass chewing, alcohol drinking, and wealth score.
[a]After exclusion of deaths in the first 2 years of the follow-up.
[b]After exclusion of those with history of ischaemic heart disease, heart failure, stroke, diabetes and cancers at enrolment and death <2 years of the follow-up.

opiate users was ~60% higher than non-users. Assuming causality, nearly 11% of all CVD deaths in this population were attributable to opiate use. The higher risk of CVD mortality was seen in nearly all subgroups of study participants, including those defined by sex, age, ethnicity, place of residence, marital status, tobacco smoking, and education and wealth levels. Both eating and smoking of opiates and either teriak or shireh use were associated with increased risk of CVD death.

To our knowledge, the GCS is the only long-term prospective study with a large number of opiate users in the world that has evaluated the association of opiate use and CVD mortality using detailed and validated opiate use information and data on a variety of potential confounding and intermediate variables. The cohort had an over 99% follow-up success rate and data came from nearly 550 000 person-years of follow-up with accurate causes of death ascertainment. The population-based design of the study minimized concerns about confounding by indication. Assessment of the repeated measurement phase data further confirmed our results.

The findings of this study are compatible with a causal relationship. Large sample size, narrow confidence intervals, and the robustness of significant association in sensitivity and subgroup analyses make it unlikely that the findings were due to chance. Indeed, in our study, long-term opiate use was a stronger predictor of CVD mortality than tobacco use (Supplementary material online, *Table S3*). After adjusting for many potential confounders, the associations persisted. In the adjusted models, the associations of the traditional risk factors with

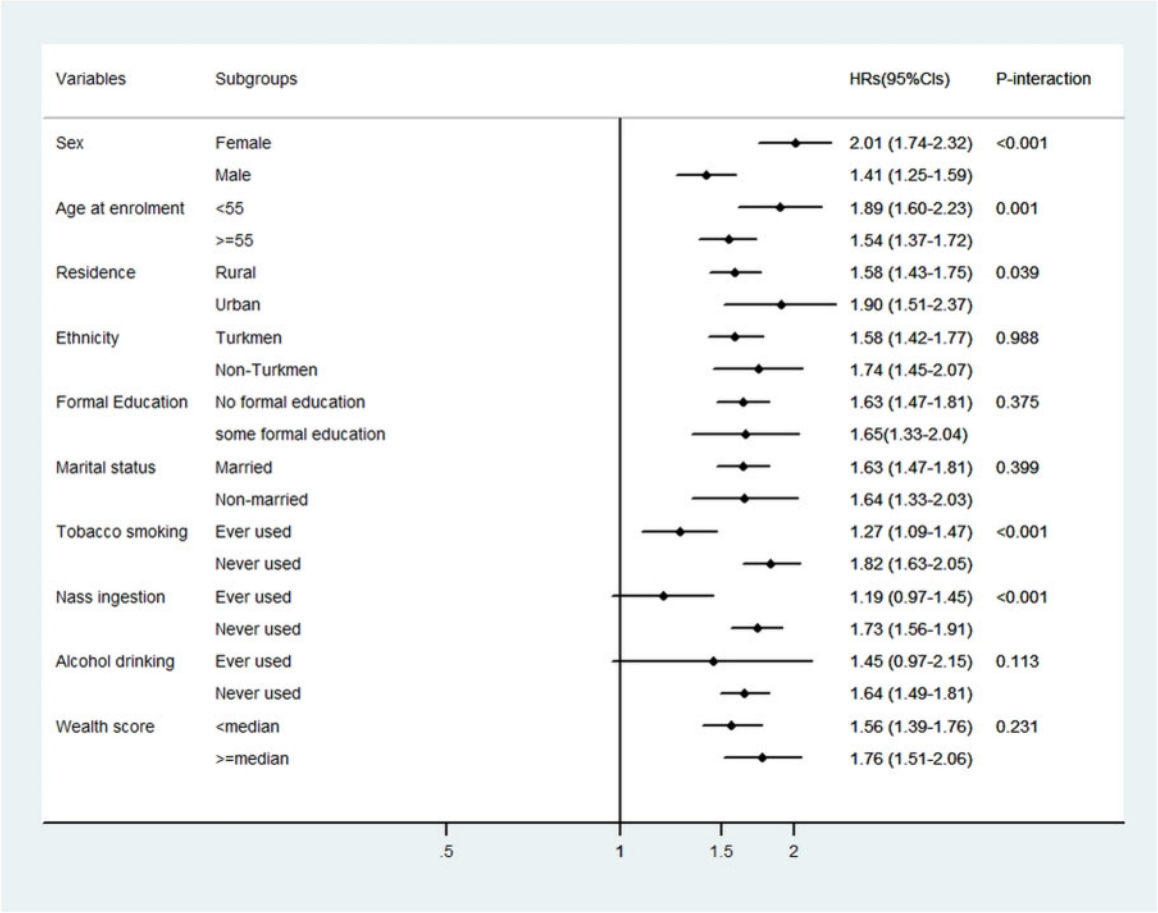

Figure 1 Subgroup analysis of the association between long-term opiate use and cardiovascular mortality. Data are adjusted hazard ratios (95% confidence intervals), using Cox regression models with age as the time scale; adjusted for age at enrolment, sex, education, residential place, ethnicity, marital status, tobacco smoking, nass chewing, alcohol drinking, and wealth score.

CVD mortality were consistent with the literature (Supplementary material online, *Table S3*), which may further support the validity of the association between opiate use and CVD death found in our study. When the analyses were limited to never smokers, the associations became even stronger, effectively eliminating the possibility of confounding by smoking. The prospective nature of the study, the long follow-up, and sensitivity analyses ruled out, to a large extent, the possibility of reverse causality.

Unlike the pure prescription opioids,[5] opiates in this study (mainly teriak and shireh) are mixtures of various chemical compounds, including alkaloids (e.g. morphine and codeine) and non-alkaloid constituents (e.g. water, sugar, and several simple organic acids),[25] however, alkaloid substances, particularly morphine, are responsible for almost all the beneficial and non-beneficial effects of opiates.[25,26] Eating and smoking opiates and using only teriak orally had significant associations with CVD mortality, so it is unlikely that these associations were related to burning organic material.

There are no previous studies that are very similar in design to our study. However, previous studies have examined the association of prescription opioids, and some have found increased risk in users.[8,10–14] For example, using large administrative claims databases, Solomon *et al.*[14] and Carman *et al.*[11] found that opioid prescriptions were associated with increased risk of CVDs. Generalizability and confounding by indication were major limitations in these studies. Indication (i.e. chronic non-cancer pain) can be a confounder as it correlates with both opioid use and risk of CVD death.[10,27] Furthermore, using retrospective claims databases may suffer from other limitations, such as confounding bias related to unmeasured variables and incomplete information on exposure and outcomes. For example, lack of data about tobacco and alcohol use and missing data on over-the-counter or illegal opioids were of limitations of the Solomon study.[14]

In contrast, some other studies have found no major association between opioids and CVD risk, either as whole or in certain subgroups. A Danish national cohort of people seeking treatment for drug use disorders ($n = 17\ 642$) found that it was only prescribed methadone, but not other opioids or illicit use of methadone, that was associated with an increased risk of CVD.[15] Lack of data about CVD risk factors, including smoking, and using record linkage data of different registries without adequate quality control were important

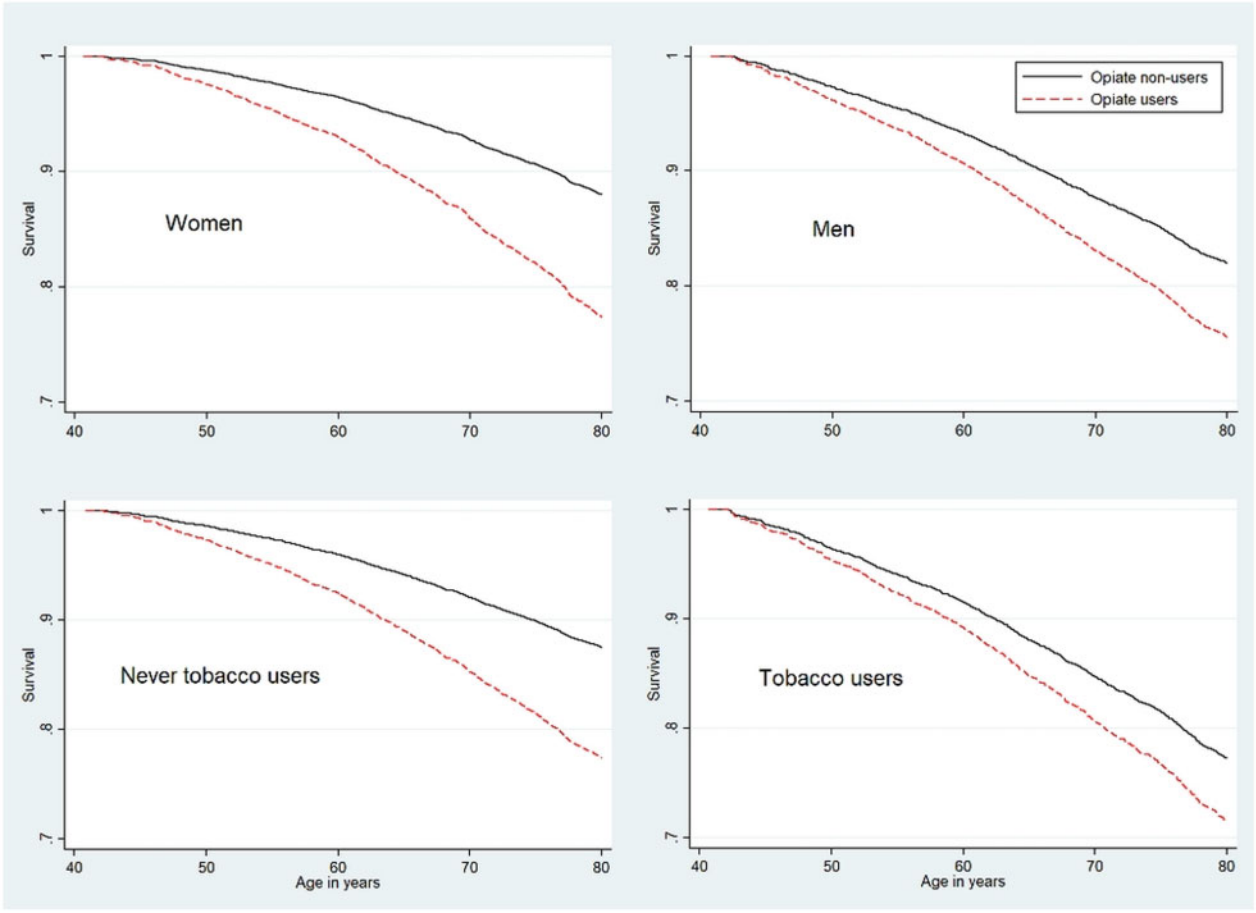

Figure 2 Cardiovascular survival of the participants in the Golestan Cohort Study. The curves are based on Cox regression models adjusted for age at enrolment, sex, ethnicity, marital status, education, residential place, tobacco smoking, nass chewing, alcohol drinking, and wealth score, if applicable.

limitations of that study. A cross-sectional study using the National Hospital Ambulatory Medical Care Survey reported no significant association between prescription opioids and coronary disease.[4] In cross-sectional studies, the temporal order of the exposure and the outcome is not considered; also a gap in time between exposure and selection of outcome positive participants may underestimate the association, because fatal events might be missed before selection of patients.[3]

Our findings suggest that potential effects of opiate use in increasing risk of CVD mortality are mainly independent of traditional risk factors. An independent risk factor is 'a risk factor that retains its statistical association with the outcome when other established risk factors for the outcome are included in a statistical model'.[28] Using both baseline and repeated measurements, the association of long-term opiate use with CVD mortality persisted after adjusting for traditional risk factors. These findings are consistent with reviews of literature, which have shown no consistent evidence of the effect of opiates and other opioids on blood lipids, diabetes, or hypertension.[3,29]

Potential pathways or mechanisms that link opioids to CVD mortality may include arrhythmia,[30] adverse respiratory effects,[8] inflammation,[3] oxidative stress,[3] microvascular coronary dysfunction,[31] hypogonadism,[25] and insulin resistance.[3] In a previous study using urinary biomarkers, opiate users were exposed to high levels of toxicant compounds such as metabolites of volatile organic compounds (e.g. acrolein, benzene, and acrylamide) and polycyclic aromatic hydrocarbons (e.g. phenanthrene).[32] Some of these compounds are known for their cardiovascular toxicity by the US Food and Drug Administration.[33]

In a report from the UN Office on Drugs and Crime,[34] 42% of all opium that is not converted into heroin, is consumed in Iran. Therefore, assuming causality, interventions associated with opiate use prevention/cessation can be crucial in primary and secondary prevention of CVDs, which are responsible for 46% of total mortality in Iran.[35]

Our study has some potential limitations and methodological challenges. First, recreational opiate use in the area is relatively common, typically in low doses, and many may not consider it taboo. However, because opiate use has some legal issues and is not entirely perceived as a positive behaviour, there were some concerns about the accuracy of reporting. To minimize reporting issues, only trained physicians

asked participants about opiate use, in a private setting and in a confidential way. At the end of the study, a large proportion (17%) of the study participants reported opiate use, and a pilot study[19] showed a high sensitivity and specificity for reporting compared with urine biomarkers of opiate use, alleviating concerns about reporting. Second, we had blood lipid data for only a subset of study participants, which slightly limited our ability to study if the opiates' effects were independent of traditional risk factors. However, we still had lipid data from over 11 000 participants. Furthermore, we had data on waist and hip circumferences from all study participants. We previously showed that using waist and hip circumferences simultaneously in the models strongly correlated with CVD deaths and its metabolic risk factors.[36] Third, opiates used by our study participants were opium extracts with mixtures of various types and amounts of alkaloid and non-alkaloid compounds,[25] and one must be cautious about generalizing these findings to pure prescription opioids. Fourth, we did not have data for possible chemicals added to opiates. To increase profit, drug traffickers may adulterate opium with substances such as lead,[37] with potential cardiovascular toxic effects.[33] Fifth, as an observational study, we acknowledge limitations about misclassification and participation bias. Finally, lower access to care for financial reasons is unlikely to explain higher CVD mortality among opiate users in our study, as we adjusted our results for important indicators of socioeconomic status in this population, including education level, wealth, and urban/rural residence.

Conclusion

Long-term opiate use was associated with a substantially increased risk of CVD mortality, independent of the traditional risk factors. Further research, particularly on associations with specific CVD subtypes and mechanisms of action, is recommended.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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