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RESEARCH

Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50 000 adults in Iran


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Abstract

Objectives To investigate the association between opium use and subsequent risk of death.

Design Prospective cohort study.

Setting The Golestan Cohort Study in north-eastern Iran collected detailed validated data on opium use and other exposures at baseline. Participants were enrolled between January 2004 and June 2008 and were followed to May 2011, with a follow-up success rate of over 99%.

Participants 50 045 participants aged 40-75 at baseline.

Main outcomes Mortality, all cause and major subcategories.

Results 17% (n=8487) of the participants reported opium use, with a mean duration of 12.7 years. During the follow-up period 2145 deaths were reported. The adjusted hazard ratio for all cause mortality associated with ever use of opium was 1.86 (95% confidence interval 1.68 to 2.06). Opium consumption was significantly associated with increased risks of deaths from several causes including circulatory diseases (hazard ratio 1.81) and cancer (1.61). The strongest associations were seen with deaths from asthma, tuberculosis, and chronic obstructive pulmonary disease (11.0, 6.22, and 5.44, respectively). After exclusion of people who self prescribed opium after the onset of major chronic illnesses, the associations remained strong with a dose-response relation.

Conclusion Opium users have an increased risk of death from multiple causes compared with non-users. Increased risks were also seen in people who used low amounts of opium for a long period and those who had no major illness before use.

Introduction

Use of opium (lachryma papaveris) for medicinal or recreational purposes has a long history in many parts of the world[1] and continues to be common. In 2008 an estimated 13-22 million people worldwide used opium or its derivatives as illicit drugs: 6.5-12.5 million in Asia; 3.3-3.8 million in Europe; 2.3-2.4 million in the Americas; and the rest in Africa and Oceania.[2]

A small number of retrospective case-control studies or case series have described the possible role of opium in oesophageal cancer,[3 4] bladder cancer,[5-7] coronary heart disease,[8-11] and a few other select health conditions.[12-14] There is little information from well designed prospective epidemiological studies on the effect of the use of opium on overall or cause specific mortality, partly because of relatively low opium use in most established

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Appendix: Supplementary tables A-E

cohort studies and the difficulty of obtaining validated data. There is also scant information on the effect of different types of opium with respect to health outcomes.

The Golestan Cohort Study (GCS), a prospective study established in north eastern Iran,[15] where opium consumption is exceptionally common,[16] has collected detailed validated data on opium use from over 50 000 people.[17] This study has collected data on typical amounts used, duration of use, and the four major types of opiates used locally—that is, teriak, shireh, sukhteh, and heroin. The first two can be smoked or ingested. Sukhteh can only be ingested, and heroin can be injected, sniffed, or smoked.[4] Using data on over 2000 deaths identified in the initial four years of follow-up, we report the effects of opium use, including by subtypes,[4 18] on overall and cause specific mortality.

Methods

Study population

The Golestan Cohort Study was launched in January 2004 in north eastern Iran after completion of a pilot study in 2003.[16] In brief, a total of 50 045 people aged 40-75 were recruited from January 2004 to June 2008. The cohort study was designed to investigate the causes of oesophageal squamous cell carcinoma in Golestan province, where the risk of this cancer is extremely high. Study participants were enrolled from those who lived in Gonbad City and 326 villages in Golestan province, north eastern Iran. Further details have been discussed elsewhere.[15]

Assessment of exposure

Trained interviewers used a general questionnaire and a food frequency questionnaire to collect data. The general questionnaire included detailed queries on opium use (see below), tobacco use, and alcohol drinking and questions on demographic characteristics, residential history, occupation, education, and medical history. Height, weight, and waist and hip circumferences were also measured. Blood pressure for each participant was measured twice from both arms, with 10 minute intervals, while the person was seated and relaxed. Nutritional data were collected with a food frequency questionnaire that was specifically designed and validated for this area.[19] Biospecimens included 10 ml of blood, 4.5 ml of midstream urine, and hair and nail samples from each individual.

Detailed data on opium use were collected as opium use is common in Golestan and could be a risk factor for oesophageal cancer. Data were obtained on age of start and end of opium use, typical amount of use in nokhod (the local unit for opium use, equivalent to about 0.2 g), frequency of use (how many days a week if weekly or more), and routes of administration for the different types of opiates commonly used—namely, teriak, sukhteh, shireh, and heroin. If participants used multiple types of opium, or if they used opium intermittently, data were recorded separately for each type and period of use.

Teriak, or raw opium, is directly obtained from the seed capsule of the opium poppy, *Papaver somniferum*.[20] The ripening poppy capsules are incised to extract a milky juice, which turns into a dark sticky or crumbly mass, known locally as teriak. Teriak can be taken orally or smoked after direct heating with burning charcoal in specialised devices such as an opium pipe. Sukhteh is the opium dross remaining after the opium is smoked and is taken orally. This form of opium, which is generally cheaper than teriak, has been shown to have high mutagenic activity.[18] Shireh is a refined product of opium that is mainly obtained from sukhteh, with or without adding teriak, boiled in water and filtered several times to remove the insoluble materials.[18] Shireh can be ingested or smoked, by indirect heating, in a special type of opium pipe. As indirect heating is used, the vapour of opiate is inhaled, not its smoke. In this region users who smoke opium generally do not mix it with any other substances such as tobacco.

Ascertainment of cause of death

As nearly all study participants have telephones, they are actively followed by annual telephone calls. Detailed questions are asked regarding their health status and any admission to hospital or outpatient procedures. All data are recorded on hard copies as well as on a computerised database. If a study participant is inaccessible through telephone calls, after seven attempts during a two week period, researchers contacted friends or local health workers. Using this method, we successfully obtained follow-up information for over 99% of all participants.[15 21] On learning of a reported death through the phone calls or through the local health workers or monthly provincial reports of death registration, a general practitioner who is a member of the follow-up team visits the home of the dead person and completes a validated verbal autopsy questionnaire[21] by interviewing the closest relative of the dead person. At the same time other members of the team gather all available and relevant medical documents including medical charts, radiographs, pathology reports, hospital discharge documents, etc, from all hospitals or pathology centres, either within the province or neighbouring provinces.

For 65% of all deaths, in addition to the verbal autopsy, extensive medical documents—including physician notes, test results, findings on electrocardiography and radiology, endoscopy results, and pathology reports—were retrieved to determine cause of death.[21] For the remaining deaths, cause was determined only by verbal autopsy. Our previous studies show high accuracy (all measures of accuracy above 81%) and reliability ($\kappa > 0.75$), particularly for major groups of cause of death, for this verbal autopsy.[21] Two separate internists independently reviewed all collected documents, including the verbal autopsy information and medical charts, and the cause of death was documented with ICD-10 codes (international classification of diseases, 10th revision). If the results were concordant, a diagnosis was made. In case of discordance a third, more experienced internist reviewed all documents and the two initial diagnoses and made the final diagnosis. If a final diagnosis could not be made for any reason, the cause of death was coded as "unknown."

Though cause of death should ideally be assessed by someone blinded to the exposure data, the physician who completed the verbal autopsy by interviewing the next of kin of the dead person also collected some information on medical history and habits (such as smoking and alcohol and opium use). Nevertheless, total deaths, the main outcome of the study, could not be biased by knowledge of the exposure. Furthermore, as the internists who determined the cause of death had no prior belief regarding the association between opium use and any specific cause of death, except perhaps for oesophageal cancer, we believe such information should have minimal impact on classification of cause of death.

The major categories of death evaluated in this analysis were the most prevalent causes of death among the participants, including circulatory, cancer, respiratory, digestive, infectious, external (mainly from motor vehicle crashes or other unintentional injury and suicide), unknown, or other.

Statistical analysis

After examining the proportional hazard assumption using Schoenfeld residuals, we fitted a Cox proportional hazards model, with age as the timescale, to estimate unadjusted and adjusted hazard ratios and 95% confidence intervals for total and cause specific mortality in relation to the exposures of interest, including any opium use, type of opium used, duration of use, cumulative use, and the method of opium consumption. Follow-up continued until loss to follow-up, death, or 20 May 2011, whichever came first. While opium use is a potentially important factor in all cause mortality, age is still the most important risk factor for death and is biologically more important than the time of recruitment into the cohort. Hence we chose age as the Cox regression time variable, implying that all risk comparisons are made between individuals of the same age. As deaths before recruitment were not observed, participants were left censored at the age of enrolment. We also used accumulated exposure at the time of enrolment as a fixed variable, rather than allowing it to increment with time in the study as might seem more natural. This was done because we had no data on continued exposure after enrolment; we do not know how the risk from accumulated exposure changes after cessation of consumption; and the time within the study is typically short compared with the accumulated years of exposure. We adjusted for potential confounders—including sex, place of residence (urban or rural), marital status, highest educational level, ethnicity (Turkmen or others), and cigarette smoking—by including indicator variables in the Cox regression models. Further inclusion of alcohol consumption, body mass index (BMI, either categorical or continuous), height (as a measure of health during early adulthood), and consumption of fruit and vegetables did not materially change the hazard ratios. As adjustment for a composite wealth score (including information on ownership of car or motorbike, black and white TV, colour TV, refrigerator, freezer, vacuum cleaner, and washing machine, as well as having bath in the home) that has been previously used to estimate socioeconomic status in Golestan Province[22] did not change the results, we have presented the main results without adjustment for these variables. Interactions were examined by including appropriate interaction terms in the Cox regression models.

For the purpose of this analysis, we defined opium users as those who consumed opium at least once a week for at least six months. Opium users were further classified as former users and current users. Opium types analysed in this study were teriak, sukhteh, shireh, and heroin. Among current users, duration of use, which was calculated by summing the years using any type of opium, was categorised into fifths. We then calculated cumulative use by multiplying duration of use by amount used. If study participants used opium intermittently during several periods of their life, we obtained overall cumulative use by summing cumulative use during each period of use. The methods of opium consumption were classified into three categories: smoking, ingestion, or both. As the number of heroin users was small, we did not consider injection as one of the categories of use.

People of this area may use opium to alleviate pain from chronic illnesses, which could lead to associations from reverse causality. To assess this possibility, we used data collected at enrolment to exclude from analysis any participants who started opium use after experiencing ischaemic heart disease, cerebrovascular event, hypertension, or diabetes mellitus. To further study reverse causality, we also conducted a sensitivity analysis by excluding deaths that occurred in the first 6, 12, 18, and 24 months of follow-up.

We calculated both age and age-sex standardised mortality rates based on World Population 2000. We also calculated the fraction of deaths attributed to opium use in this population using the hazard ratios and prevalence of opium use. All statistical analyses were conducted with Stata statistical software, version 11 (StataCorp, College Station, TX).

Results

Data from all 50 045 cohort participants were used for this study, with a total of 234 928 person years of follow-up (median 4.7 years per participant). The mean age of participants at baseline was 52.1 (SD 8.9) years. Most participants were women (58%), 74% were Turkmen, 80% lived in rural areas, 88% were married, 83% were non-smokers, and 70% had no formal education.

Of the 17% (n=8487) of cohort members who reported ever using opium, the mean age at enrolment was 53.4 (SD 9.2), the mean age at which they started using opium was 39.7 (SD 9.2), and the mean reported duration of use was 12.7 (SD 11.1) years. The median daily amount of opium used was 0.6 g (25th-75th centile 0.2-1.2g). Opium users were more likely than the rest of the cohort to be men, rural dwellers, and cigarette smokers. The proportion of Turkmen people, married individuals, and those with no formal education was similar to the entire cohort.

During the follow-up period until 20 May 2011, 293 (0.6%) of the study participants, including 226 (0.5%) of those who had never used opium and 67 (0.8%) of the opium users, were lost to follow-up, and 2145 deaths were reported, resulting in a crude death rate of 913 per 100 000 person years. As shown in table 1⇓, an overall increased risk of death was observed for being male, being illiterate, not being married (single, widowed, divorced), and medical history of myocardial infarction, cerebrovascular events, hypertension, and diabetes, whereas ethnicity and place of residence were not associated with an increased risk.

In all, 8660 (17%) participants reported ever smoking cigarettes, with an adjusted hazard ratio of 1.53 (95% confidence interval of 1.37 to 1.70) for all causes of death. The hazard ratio for death associated with opium use was 1.98 (1.80 to 2.17), before adjustment for cigarette smoking and 1.86 (1.68 to 2.06) after adjustment for cigarette smoking.

Table 2⇓ compares hazard ratios for overall mortality among opium users stratified by sex, ethnicity, education, marital status, place of residence, history of chronic diseases, BMI, and categories of cigarette smoking, with tests for interaction across each group. With the exception of people with history of cerebrovascular events, a relatively small group, opium use was associated with an increased risk of mortality among all strata. Significantly higher increased risks of mortality were observed among women than men (P<0.001), urban than rural dwellers (P=0.008), obese than non-obese people (P=0.020), and those who had never smoked than those who did (P=0.001).

Table 3⇓ shows the hazard ratios (95% confidence intervals) for major causes of death in relation to opium use. Opium use was associated with an increased risk of death in all major categories, except the category classified as "external," which mainly included unintentional injuries and trauma. The strongest associations were found for infections (adjusted hazard ratio 5.47), respiratory diseases (3.78), and digestive diseases (3.12). Consistent with the overall association, the hazard ratios were higher in women than in men for most causes of deaths. Among deaths from circulatory causes, opium use was associated with an increased risk of ischaemic heart disease and cerebrovascular events (table 3⇓). Among deaths from cancer, opium use was associated with an increased risk of three common cancers that

have been shown to be related to tobacco smoking—that is, oesophageal, gastric, and lung cancers—though this was significant only for lung cancer. Additional examination of the association between opium use and deaths from respiratory conditions showed that the adjusted hazard ratios were 11.0 (95% confidence interval 3.97 to 30.6) for asthma, 6.22 (2.36 to 16.4) for tuberculosis, and 5.44 (2.03 to 14.5) for chronic obstructive pulmonary disease.

Amongst 8487 opium users, most used teriak only (7308), shireh only (721), or a combination of the two. Other forms of opium use were far less common. Increased mortality was seen for each subtype of opium (see table A in appendix), with the strongest risk with heroin, albeit with wide confidence intervals. Use of shireh (adjusted hazard ratio 2.19) was associated with a slightly higher hazard of death than teriak (1.83), but the difference was not significant.

To assess the dose-response relation, we classified opium users as former users and current users. Current opium users had a higher hazard of death than former users (table 4⇓). Among current users, longer duration of use was not associated with a higher mortality hazard (P=0.497 for trend). When we excluded 542 people who started opium use after receiving a diagnosis of a major illness (6.4% of all opium users), however, we found a dose-response association with duration of opium use (P=0.001 for trend). This pattern was also seen for several major causes of death. Assessment of the dose-response relation with cumulative use yielded similar results (see table B in appendix). Further sensitivity analysis with exclusion of deaths that occurred in the first 6, 12, 18, and 24 months of follow up did not have a material effect on the point estimates (see table C in appendix). Further adjustment did not change the results meaningfully (see table D in appendix), reducing the possibility of residual and unmeasured confounding. When we created a "healthy group" by excluding participants with any history of hypertension, ischemic heart disease, diabetes mellitus, or cerebrovascular events and underweight participants and those who had ever smoked cigarettes, the adjusted Cox hazard ratio for opium use in relation to overall mortality was 1.90 (95% confidence interval of 1.55 to 2.33).

Table E in the appendix shows the results by broad categories of opium use—that is, ingestion and smoking. After exclusion of rare methods of opium use—for instance, the four and six participants who exclusively used heroin and sukhteh, respectively—of the remaining individuals, 5804 only smoked opium, 2176 exclusively ingested opium, and 497 reported both smoking and ingestion. Both methods were associated with increased risk of mortality: adjusted hazard ratio 2.08 for ingestion; 1.68 for smoking; and 2.34 for both. There was a similar pattern for most major causes of death, both before and after adjustment for either duration of opium use or its cumulative consumption.

The figure⇓ presents Cox hazard ratios in former users by years after cessation of opium use until they were enrolled into the study. The longer duration of cessation was associated with a decreasing hazard ratio (P=0.003 for trend).

Based on the overall adjusted hazard ratio for opium use of 1.86 (1.68 to 2.06), and assuming this represents a causal association, we calculate the fraction of deaths attributable to opium in this population as 14.9% (12.3% to 17.5%).

Discussion

Major findings

Opium use is common in this population in Iran and is associated with an estimated 86% increased risk of death overall; in women the increase was 143%. This increased risk was present for several major causes of death, including death from circulatory disorders and cancer, for different subtypes of opium (teriak, shireh, heroin, or combinations), for various routes of use (smoking and ingestion), and in several study subgroups (sex, ethnicity, residence, and others).

Evidence for causality

This large prospective study looked at opium use in relation to overall mortality and cause specific mortality. Although causal inferences from this study could be premature, the findings are consistent with those from retrospective case-control studies that have shown increased risk of oesophageal cancer,[3 4] bladder cancer,[5-7] coronary heart disease,[8 10 11] and other diseases[12-14] in relation to opium use. Also, several of our findings point toward a causal role for opium in increasing mortality. A nearly twofold risk of mortality in opium users is substantial and is stronger than the estimated risk posed by tobacco use in this population. After adjustment for several factors, including tobacco use, the associations diminished only slightly but were still strong and significant.

People in this region might use opium to alleviate pain from chronic conditions, which could result in associations from reverse causality. To avoid misleading conclusions, we carried out a sensitivity analysis by excluding participants who started using self prescribed opium after the onset of four major chronic diseases. This resulted in some attenuation of risk that was restricted to recent users, as expected, but little change in risks for longer term users of eight years or more. Further sensitivity analysis excluding deaths occurring in the first 24 months of follow-up did not make a material difference either. Finally, longer opium cessation was associated with lower risk of death.

Opium alkaloid (such as morphine) and non-alkaloid (such as meconic acid) constituents, and other chemicals added during processing or generated during smoking, have a wide range of effects and can potentially explain the diverse increased risk of morbidity and mortality with opium use. Activation of μ-opioid receptors in pre-Bötzinger complex, located in the ventrolateral medulla, can reduce breathing frequency, tidal volume, chest wall compliance, and respiratory response to increased arterial carbon dioxide concentration.[23] Opium use can also cause upper airway constriction through inhibition of acetylcholine release[23] and increased bronchial tone through provocation of histamine release from mast cells.[11 24] Smoking opium can also cause histological damage to the bronchi and lungs.[20] Prolonged administration of exogenous opioids can have inhibitory effects on both humoral and cell mediated immune response.[25] All of these mechanisms could underlie the strong associations seen with deaths from asthma, tuberculosis, and chronic obstructive pulmonary disease. Smoking opium can expose the body to carcinogenic polycyclic aromatic hydrocarbons, heterocyclic aromatic hydrocarbons, and primary aromatic amines.[26] There is a growing body of evidence indicating that opiates could act as cancer promoters through impairing immune function, activating angiogenesis and tumour neovascularisation,[25] increasing the concentrations of N-nitrosamines through modifying their pharmacokinetics,[27] increasing the release of nitric oxide,[28] or inhibiting production and release of hydrogen peroxide.[29] Although opium use might have cardioprotective effects in short term use,[30] it can have deleterious effects in the

long term through causing hypotension, bradycardia, and respiratory depression that could decrease myocardial oxygenation and hence increase the infarct size and mortality.[31] Morphine, like other opiate alkaloids, is metabolised principally in the liver via conjugation with glucuronic acid.[32] Similar to other substances metabolised by the liver, morphine can result in hepatotoxicity.[33] Extensive animal research has shown that morphine and morphine-like agents can increase liver enzyme activity and lead to perivenular and focal hepatocellular necrosis.[34-37] Chronic administration of morphine in rats is thought to increase inflammatory infiltration and focal parenchymal necrosis in the liver, in addition to an increase in total lipid content of hepatocytes, all leading to lipid fibrosis and hepatic damage.[38]

Opium users in our cohort reported relatively low amounts of use (median 0.6 g/day), considerably lower than ranges of 1-24 g reported elsewhere.[20] Although study participants might under-report the amount used, average daily use is likely to be low in this group as these were people who were able and willing to participate in the study, had low rates of loss to follow-up (<1%), and whose education, ethnic background, and marital status was similar to non-users. Therefore, the opium users perhaps had a lifestyle that was not substantially different from others. These findings are in favour of a causal connection and suggest that even relatively small amounts of opium use over a long period can have a substantial effect on mortality.

Both opium ingestion and opium smoking were associated with an increased risk of death. Compared with ingestion, smoking exposes individuals to more polycyclic and heterocyclic aromatic hydrocarbons and primary aromatic amines[26] but also exposes users to nearly 10 times less morphine. Almost 50% of opium that is smoked adheres to the opium pipe and of the other half that is vaporised in the pipe, a large proportion is lost in the smoke that escapes into the surrounding air.[20]

We found that opium increased the risk of death in nearly all subgroups of the study participants, including men and women, Turkmen and non-Turkmen people, people who lived in urban and rural areas, people with and without major chronic diseases, and smokers and non-smokers. The strength of association, however, differed in some subgroup analyses. Most importantly, the hazards ratios were higher in women than in men and in non-smokers than tobacco smokers.

Opium use is probably accurately reported in this population. A previous pilot study nested in this population showed that there was a strong correspondence between self reported opium use and opium metabolites in urine, with a sensitivity and specificity of 93% and 89%, respectively.[17] Unlike alcohol, opium is not considered to be strictly religiously forbidden in this area, and recreational low dose consumption is culturally acceptable. Although there is evidence that the participants' report of any opium use was valid, we do not know whether their reported amount of use was also correct. In our analyses, cumulative use of opium, estimated by multiplying duration and amount of use, did not result in stronger associations than duration of use alone. Therefore, responses to amount of use could be subject to misclassification.

We used several methods to control for the effect of known and unknown confounders. Statistical adjustment for important potential confounders such as age, sex, place of residence, levels of education, marital status, BMI, height, intake of fruit and vegetables, a composite wealth score, alcohol consumption, and cigarette smoking status had little effect on the risk estimates. Compared with those who never used opium, stratified analyses showed a consistently significant increased risk of mortality among people who had ever used opium in almost all strata, including in those who had ever or never smoked cigarettes. Dose-response analyses showed a significant increasing trend of overall and cause specific risks of mortality for increasing doses of opium use. Finally, sensitivity analyses, through both classic and customised methods in our study, consistently showed the same results for the effect of opium use on risks of mortality. Although there could still be some unmeasured confounders or residual confounding from modelling or measurement errors, we believe their presence and effect would not be considerable because of extensive adjustment for several known confounders.[39 40] Confounding factors should be strongly associated with both the exposure and outcomes to have a material effect,[41] and we have adequately adjusted for age, smoking, and other confounders strongly related to both opium use and death; other unknown factors are unlikely to be significantly associated with both opium use and death. Whereas large scale randomised controlled clinical trials are the best design to eliminate or limit residual confounding, conducting randomised studies of opium and mortality is not ethically feasible; therefore prospective observational studies remain the design of choice in this setting.

Assuming a causal relation, the impact of opium use on mortality is substantial. About 20 million people in the world use opium or its derivatives, and these individuals are at a substantially increased risk of death.

Strengths and limitations of the study

The strengths of this study include its prospective design, large sample size, availability of data to adjust for confounders, prior validation of exposure and outcome measurement, and minimal loss to follow-up. This study also has limitations, which include its observational design and therefore the potential for residual confounding and reverse causality. There is also a possibility of outcome misclassification as the cause of death was determined solely based on verbal autopsy in 35% of the cases. However, we used several methods to increase the validity of our outcome determination and to reduce the possibility of confounding and reverse causality.

Conclusions and implications

In summary, in this large scale prospective study we found strong increased risks of death from multiple causes in opium users compared with non-users, even among those who used low doses of opium. These results are consistent with results of previous case-control studies in humans and animal studies suggesting deleterious health consequences of exogenous opioids such as morphine. Further epidemiological studies on opium use in relation to morality are needed. Also, follow-up studies of patients taking opioid analgesics long term for treatment of pain could shed further light on this issue.

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What is already known on this topic

A small number of retrospective case-control studies or case series have described the possible role of opium in causing oesophageal cancer, bladder cancer, coronary heart disease, and a few other select health conditions

There is little information from well designed prospective epidemiological studies on the effect of opium use, particularly low doses over a long period, on overall or cause specific mortality

What this study adds

Long term opium use, even in relatively low doses, is associated with an estimated 86% increased risk of death overall

Users have an increased risk for several major causes of death, including circulatory disorders and cancer

Contributors: HK, RM, AP, FK, EJ, BA, CCA, SMD, PDP, PBo and PBr designed and implemented the study. HK, RM, AP, EJ, RS, SS, BA, FI, and S-NM acquired the data. HK, FK, and GB planned and conducted data analysis. HK, PBr, FK, GB, AE, NED, PDP, FI, PBo, and RM interpreted the data. HK, FK, and PBren drafted the manuscript. All authors reviewed the manuscript and approved the final version to be published. PBr and RM are guarantors.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the ethical review boards of Digestive Disease Research Centre (DDRC), International Agency for Research on Cancer (IARC), and National Cancer Institute (NCI). All participants gave written informed consent.

Data sharing: No additional data available

1 Schiff PL. Opium and its alkaloids. *Am J Pharm Educ* 2002;66:186-94.
2 UNODC, World Drug Report 2010. United Nations Publication, 2010.
3 Ghadirian P, Stein GF, Gorodetzky C, Roberfroid MB, Mahon GA, Bartsch H, et al. Oesophageal cancer studies in the Caspian littoral of Iran: some residual results, including opium use as a risk factor. *Int J Cancer* 1985;35:593-7.
4 Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer* 2008;98:1857-63.
5 Aliasgari MA, Kaviani A, Gachkar L, Hosseini-Nassab SR. Is bladder cancer more common among opium addicts? *Urol J* 2004;1:253-5.
6 Shakhssalim N, Hosseini SY, Basiri A, Eshrati B, Mazaheri M, Soleimanirahbar A. Prominent bladder cancer risk factors in Iran. *Asian Pac J Cancer Prev* 2010;11:601-6.
7 Hosseini SY, Safarinejad MR, Amini E, Hooshyar H. Opium consumption and risk of bladder cancer: a case-control analysis. *Urol Oncol* 2010;28:610-6.
8 Masoumi MR, MA. Karimzadeh, H. The relationship of opium addiction with coronary artery disease. *Int J Prev Med* 2010;1:182-6.
9 Masoumi M, Shahesmaeili A, Mirzazadeh A, Tavakoli M, Ali AZ. Opium addiction and severity of coronary artery disease: a case-control study. *J Res Med Sci* 2010;15:27-32.
10 Sadeghian S, Graili P, Salarifar M, Karimi AA, Darvish S, Abbasi 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;141:116-8.
11 Safaii N, Kazemi B. Effect of opium use on short-term outcome in patients undergoing coronary artery bypass surgery. *Gen Thorac Cardiovasc Surg* 2010;58:62-7.
12 Da Costa JL, Tock EP, Boey HK. Lung disease with chronic obstruction in opium smokers in Singapore. Clinical, electrocardiographic, radiological, functional and pathological features. *Thorax* 1971;26:555-71.
13 Masoomi M, Ramezani MA, Shahriari S, Shahesmaeeli A, Mirzaeepour F. Is opium addiction a risk factor for deep vein thrombosis? A case-control study. *Blood Coagul Fibrinolysis* 2010;21:109-12.
14 Mousavi MR, Damghani MA, Haghdoust AA, Khamesipour A. Opium and risk of laryngeal cancer. *Laryngoscope* 2003;113:1939-43.
15 Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR, et al. Cohort profile: the Golestan Cohort Study—a prospective study of oesophageal cancer in northern Iran. *Int J Epidemiol* 2010;39:52-9.
16 Pourshams A, Saadatian-Elahi M, Nouraie M, Malekshah AF, Rakhshani N, Salahi R, et al. Golestan Cohort Study of oesophageal cancer: feasibility and first results. *Br J Cancer* 2005;92:176-81.
17 Abnet CC, Saadatian-Elahi M, Pourshams A, Boffetta P, Feizzadeh A, Brennan P, et al. Reliability and validity of opiate use self-report in a population at high risk for esophageal cancer in Golestan, Iran. *Cancer Epidemiol Biomarkers Prev* 2004;13:1068-70.
18 Hewer T, Rose E, Ghadirian P, Castegnaro M, Malaveille C, Bartsch H, et al. Ingested mutagens from opium and tobacco pyrolysis products and cancer of the oesophagus. *Lancet* 1978;ii:494-6.
19 Malekshah AF, Kimiagar M, Saadatian-Elahi M, Pourshams A, Nouraie M, Goglani G, et al. Validity and reliability of a new food frequency questionnaire compared to 24 h recalls and biochemical measurements: pilot phase of Golestan Cohort Study of esophageal cancer. *Eur J Clin Nutr* 2006;60:971-7.
20 Kalant H. Opium revisited: a brief review of its nature, composition, non-medical use and relative risks. *Addiction* 1997;92:267-77.
21 Khademi H, Etemadi A, Kamangar F, Nouraie M, Shakeri R, Abaie B, et al. Verbal autopsy: reliability and validity estimates for causes of death in the Golestan Cohort Study in Iran. *PLoS ONE* 2010;5:e11183.
22 Islami F, Kamangar F, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, Abedi-Ardekani B, et al. Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. *Int J Epidemiol* 2009;38:978-88.
23 McCrimmon DR, Alheid GF. On the opiate trail of respiratory depression. *Am J Physiol Regul Integr Comp Physiol* 2003;285:R1274-5.
24 Elia D, Marinou A, Chetta A. Life-threatening asthma after heroin inhalation. A case report and a review of the literature. *Acta Biomed* 2010;81:63-7.
25 Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. *Am J Ther* 2004;11:354-65.
26 Friesen M, O'Neill IK, Malaveille C, Garren L, Hautefeuille A, Cabral JR, et al. Characterization and identification of 6 mutagens in opium pyrolysates implicated in oesophageal cancer in Iran. *Mutat Res* 1985;150:177-91.
27 Ribeiro Pinto LF, Swann PF. Opium and oesophageal cancer: effect of morphine and opium on the metabolism of N-nitrosodimethylamine and N-nitrosodiethylamine in the rat. *Carcinogenesis* 1997;18:365-9.
28 Fimiani C, Arcuri E, Santoni A, Rialas CM, Bilfinger TV, Peter D, et al. Mu3 opiate receptor expression in lung and lung carcinoma: ligand binding and coupling to nitric oxide release. *Cancer Lett* 1999;146:45-51.
29 Bosshart H. Morphine and cancer progression: hydrogen peroxide points to need for more research. *J Opioid Manag* 2011;7:93-6.
30 Maslov LN, Lishmanov YB, Oeltgen PR, Barzakh EI, Krylatov AV, Govindaswami M, et al. Activation of peripheral delta2 opioid receptors increases cardiac tolerance to ischemia/reperfusion injury Involvement of protein kinase C, NO-synthase, KATP channels and the autonomic nervous system. *Life Sci* 2009;84:657-63.
31 Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J* 2005;149:1043-9.
32 Pacifici GM, Bencini C, Rane A. Presystemic glucuronidation of morphine in humans and rhesus monkeys: subcellular distribution of the UDP-glucuronyltransferase in the liver and intestine. *Xenobiotica* 1986;16:123-8.
33 Van der Laan JW, Krajnc EI, Krajnc-Franken MA, van Loveren H. Immunotoxicological screening of morphine and methadone in an extended 28 day study in rats. *Int J Immunopharmacol* 1995;17:535-43.
34 Sumathi T, Niranjali Devaraj S. Effect of Bacopa monniera on liver and kidney toxicity in chronic use of opioids. *Phytomedicine* 2009;16:897-903.
35 Borzelleca JF, Egle JL, Jr., Harris LS, Johnson DN, Terrill JB, Belleville JA. Toxicological evaluation of mu-agonists. Part I: Assessment of toxicity following 30 days of repeated oral dosing of male and female rats with levo-alpha-acetylmethadol HCl (LAAM). *J Appl Toxicol* 1994;14:435-46.
36 Nagamatsu K, Ohno Y, Ikebuchi H, Takahashi A, Terao T, Takanaka A. Morphine metabolism in isolated rat hepatocytes and its implications for hepatotoxicity. *Biochem Pharmacol* 1986;35:3543-8.
37 Atici S, Cinel I, Cinel L, Doruk N, Eskandari G, Oral U. Liver and kidney toxicity in chronic use of opioids: an experimental long term treatment model. *J Biosci* 2005;30:245-52.
38 Bekheet SH. Morphine sulphate induced histopathological and histochemical changes in the rat liver. *Tissue Cell* 2010;42:266-72.
39 Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *Am J Epidemiol* 2007;166:646-55.
40 McCandless LC, Gustafson P, Levy AR. A sensitivity analysis using information about measured confounders yielded improved uncertainty assessments for unmeasured confounding. *J Clin Epidemiol* 2008;61:247-55.
41 Siemiatycki J, Wacholder S, Dewar R, Cardis E, Greenwood C, Richardson L. Degree of confounding bias related to smoking, ethnic group, and socioeconomic status in estimates of the associations between occupation and cancer. *J Occup Med* 1988;30:617-25.

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Tables

Table 1| Demographic and anthropometric characteristics, medical history, and habits in relation to death in participants of Golestan Cohort Study

Variables	No of participants (person years)	No of deaths (crude rate*)	SMR†	Relative rate
Sex:				
Female	28 811 (136 279)	893 (655)	727	Reference
Male	21 234 (98 649)	1252 (1269)	1207	1.66
Ethnicity:				
Non-Turkmen	12 792 (57 038)	520 (912)	972	Reference
Turkmen	37 253 (177 890)	1625 (914)	959	0.99
Education (highest level):				
No formal	35 118 (163 647)	1708 (1044)	1050	Reference
Up to eight years	10 708 (49 753)	316 (635)	704	0.67
High school	3155 (15 883)	89 (560)	460	0.44
University	1064 (5644)	32 (567)	505	0.48
Marital status:				
Married	43 890 (205 921)	1732 (841)	924	Reference
Single	302 (1449)	22 (1519)	1738	1.88
Widow/er	5603 (26 422)	376 (1423)	1703	1.84
Divorced/other	135 (635)	10 (1575)	1700	1.84
Place of residence:				
Rural	40 012 (179 745)	1625 (904)	979	Reference
Urban	10 033 (55 183)	520 (942)	942	0.96
History of ischaemic heart disease:				
No	46 994 (221 407)	1797 (812)	886	Reference
Yes	3051 (13 521)	348 (2574)	2032	2.29
History of cerebrovascular event:				
No	49 616 (233 040)	2078 (892)	948	Reference
Yes	429 (1,888)	67 (3548)	2646	2.79
Hypertension:				
No	40 170 (189 871)	1388 (731)	827	Reference
Yes	9875 (45 057)	757 (1680)	1627	1.97
History of diabetes mellitus:				
No	46 591 (219 541)	1836 (836)	897	Reference
Yes	3454 (15 387)	309 (2008)	1997	2.23
Cigarette smoking:				
Never smoker	41 385 (194 823)	1537 (789)	878	Reference
Ever smoker	8660 (40 105)	608 (1516)	1429	1.63
Opium use:				
Never user	41 558 (196 825)	1440 (732)	818	Reference
Ever user	8487 (38 103)	705 (1850)	1650	2.02

*Crude rates calculated in 10^5 person years.

†Age and sex standardised mortality rate based on 2000 world standard population.

Table 2| Hazard ratios for association between opium use and mortality by subgroups in participants in Golestan Cohort Study

Variable	No (%) who never used opium	No (%) who ever used opium	Cox hazard ratio* (95% CI)		P for interaction
			Unadjusted	Adjusted†	
All cohort	41 558	8487	2.26 (2.06 to 2.47)	1.86 (1.68 to 2.06)	—
Sex:					
Women	26 456 (63.7)	2355 (27.7)	2.54 (2.16 to 2.98)	2.43 (2.05 to 2.88)	<0.001
Men	15 102 (36.3)	6132 (72.3)	1.82 (1.62 to 2.03)	1.63 (1.44 to 1.84)	
Ethnicity:					
Turkmen	30 701 (73.9)	6552 (77.2)	2.24 (2.02 to 2.48)	1.82 (1.62 to 2.05)	0.578
Non-Turkmen	10 857 (26.1)	1935 (22.8)	2.28 (1.89 to 2.76)	1.99 (1.62 to 2.45)	
Education:					
Illiterate	29 490 (71.0)	5628 (66.3)	2.24 (2.02 to 2.48)	1.89 (1.68 to 2.11)	0.558
Up to 8 years	8480 (20.4)	2228 (26.3)	2.23 (1.77 to 2.82)	1.76 (1.35 to 2.29)	
High school	2601 (6.30)	554 (6.50)	2.68 (1.71 to 4.18)	1.61 (0.98 to 2.67)	
University	987 (2.30)	77 (0.90)	3.90 (1.55 to 9.81)	3.65 (1.28 to 10.4)	
Marital status:					
Married	36 345 (87.7)	7545 (89.0)	2.22 (2.00 to 2.45)	1.80 (1.61 to 2.02)	0.629
Single	240 (0.60)	62 (0.70)	3.22 (1.32 to 7.81)	2.36 (0.81 to 6.90)	
Widow/er	4760 (11.5)	843 (9.90)	2.40 (1.92 to 2.99)	2.16 (1.69 to 2.75)	
Divorced/other	108 (0.20)	27 (0.40)	2.22 (0.60 to 8.26)	2.10 (0.41 to 10.9)	
Place of residence:					
Rural	32 527 (78.3)	7485 (88.2)	2.12 (1.91 to 2.35)	1.77 (1.58 to 1.99)	0.008
Urban	9031 (21.7)	1002 (11.8)	2.97 (2.43 to 3.61)	2.32 (1.85 to 2.92)	
History of ischaemic heart disease:					
No	39 210 (94.3)	7784 (91.7)	2.30 (2.09 to 2.54)	1.87 (1.67 to 2.09)	0.053
Yes	2348 (5.70)	703 (8.30)	1.82 (1.46 to 2.28)	1.58 (1.23 to 2.04)	
History of cerebrovascular event:					
No	41 237 (99.2)	8379 (98.7)	2.28 (2.08 to 2.50)	1.88 (1.69 to 2.08)	0.164
Yes	321 (0.80)	108 (1.30)	1.34 (0.78 to 2.33)	1.12 (0.59 to 2.13)	
Hypertension:					
No	33 148 (79.8)	7022 (82.7)	2.30 (2.06 to 2.57)	1.81 (1.59 to 2.05)	0.685
Yes	8410 (20.2)	1465 (17.3)	2.39 (2.04 to 2.79)	1.94 (1.63 to 2.32)	
History of diabetes mellitus:					
No	38 647 (93.0)	7944 (93.6)	2.33 (2.12 to 2.57)	1.87 (1.67 to 2.08)	0.320
Yes	2911 (7.00)	543 (6.40)	2.00 (1.55 to 2.57)	1.67 (1.26 to 2.22)	
Body mass index (BMI):					
Underweight	1328 (3.20)	1080 (12.7)	1.76 (1.32 to 2.35)	1.54 (1.12 to 2.10)	0.020
Normal weight	13 585 (32.7)	4344 (51.2)	1.99 (1.74 to 2.28)	1.77 (1.53 to 2.06)	
Overweight	14 884 (35.8)	2088 (24.6)	2.30 (1.92 to 2.75)	1.83 (1.50 to 2.23)	
Obese	11 753 (28.3)	971 (11.5)	2.93 (2.30 to 3.72)	2.25 (1.72 to 2.93)	
Cigarette smoking:					
Never smoked	37 373 (89.9)	4012 (47.3)	2.25 (1.99 to 2.53)	2.07 (1.83 to 2.35)	0.001
Ever smoked	4185 (10.1)	4475 (52.7)	1.53 (1.30 to 1.81)	1.50 (1.27 to 1.77)	

*Hazard ratio of dying in opium users in each stratum.

‡Adjusted for variables including sex, ethnicity, education level, marital status, residential place, and cigarette smoking, except if each of them is considered as stratifying variable.

Table 3| Hazard ratios for major causes of death in relation to opium use in Golestan Cohort Study

Cause of death	Total (n=50 045)	No (%) of opium users (n=8487, 17%)	Cox hazard ratio* (95% CI)		
			Total	Men	Women
Any	2145	705 (33)	1.86 (1.68 to 2.06)	1.63 (1.44 to 1.84)	2.43 (2.05 to 2.88)
Circulatory:					
All	1073	335 (31)	1.81 (1.56 to 2.09)	1.53 (1.28 to 1.82)	2.52 (1.98 to 3.20)
Ischaemic heart disease	624	208 (33)	1.90 (1.57 to 2.29)	1.58 (1.26 to 1.98)	2.90 (2.10 to 3.99)
Cerebrovascular event	352	98 (28)	1.68 (1.29 to 2.18)	1.49 (1.07 to 2.08)	1.97 (1.30 to 2.97)
Other circulatory	97	29 (30)	1.73 (1.06 to 2.82)	1.30 (0.71 to 2.36)	2.98 (1.35 to 6.58)
Cancer:					
All	449	137 (31)	1.61 (1.28 to 2.03)	1.70 (1.30 to 2.24)	1.42 (0.92 to 2.20)
Oesophagus	100	30 (30)	1.51 (0.93 to 2.43)	1.12 (0.62 to 2.04)	2.40 (1.13 to 5.10)
Stomach	75	25 (33)	1.32 (0.77 to 2.26)	1.33 (0.74 to 2.40)	1.23 (0.33 to 4.65)
Lung	37	18 (49)	2.27 (1.07 to 4.80)	2.65 (1.13 to 6.21)	1.19 (0.15 to 9.72)
Other cancer	237	64 (27)	1.67 (1.21 to 2.31)	2.09 (1.40 to 3.13)	1.10 (0.59 to 2.07)
Respiratory:					
All	95	52 (55)	3.78 (2.36 to 6.04)	2.64 (1.50 to 4.73)	6.64 (3.30 to 13.3)
Asthma	23	17 (74)	11.0 (3.97 to 30.6)	21.5 (2.60 to 177)	8.04 (2.26 to 28.6)
COPD	24	17 (71)	5.44 (2.03 to 14.5)	3.18 (1.11 to 9.14)	34.1 (3.29 to 353)
Other respiratory	48	18 (38)	1.87 (0.94 to 3.71)	1.15 (0.49 to 2.70)	4.08 (1.51 to 11.0)
Digestive:					
All	69	32 (46)	3.12 (1.82 to 5.37)	3.05 (1.60 to 5.79)	3.32 (1.24 to 8.84)
Liver cirrhosis	36	14 (39)	2.28 (1.05 to 4.97)	2.90 (1.14 to 7.34)	1.17 (0.21 to 6.40)
Other digestive	33	18 (55)	4.35 (2.01 to 9.39)	3.25 (1.34 to 7.90)	8.89 (2.20 to 35.9)
Infectious:					
All	51	30 (59)	5.47 (2.87 to 10.4)	3.44 (1.54 to 7.69)	8.85 (3.51 to 22.3)
Tuberculosis	24	16 (67)	6.22 (2.36 to 16.4)	4.12 (1.33 to 12.7)	10.6 (2.33 to 48.7)
Other infectious	27	14 (52)	5.07 (2.11 to 12.2)	2.90 (0.91 to 9.23)	8.11 (2.48 to 26.5)
External	135	30 (22)	0.86 (0.54 to 1.35)	0.73 (0.44 to 1.21)	1.45 (0.58 to 3.64)
Other	150	43 (29)	1.66 (1.11 to 2.48)	1.21 (0.73 to 2.02)	2.78 (1.52 to 5.06)
Unknown	123	46 (37)	2.42 (1.59 to 3.67)	2.66 (1.55 to 4.55)	2.03 (1.02 to 4.03)

COPD=chronic obstructive pulmonary disease.

*Cox hazard ratios for opium use, adjusted for sex (except when stratified by sex), ethnicity, education level, marital status, residential place, and cigarette smoking

Table 4| **Cox hazard ratios* (95% confidence intervals) by duration of opium use in relation to all mortality and cause specific mortality overall and after exclusion of participants who started using opium after diagnosis of serious disease (ischaemic heart disease, cerebrovascular event, hypertension, or diabetes mellitus) in Golestan Cohort Study**

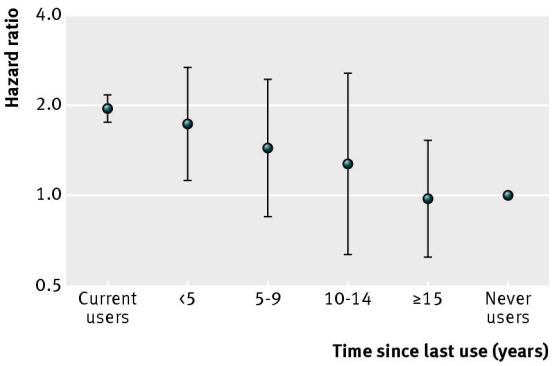
	Never users	Former users	Current users	Fifth of duration (years) of opium use in current opium users					P for trend†
				1 (≤3 years)	2 (4-7 years)	3 (8-12 years)	4 (13-20 years)	5 (≥21 years)	
All causes									
No of deaths	1440	63	642	131	107	99	122	183	—
Overall	Reference	1.29 (1.00 to 1.67)	1.94 (1.75 to 2.16)	2.14 (1.79 to 2.57)	1.85 (1.51 to 2.26)	1.97 (1.59 to 2.42)	1.81 (1.49 to 2.19)	1.94 (1.64 to 2.29)	0.497
Before diagnosis‡	Reference	1.27 (0.98 to 1.65)	1.70 (1.52 to 1.90)	1.62 (1.31 to 1.99)	1.39 (1.09 to 1.78)	2.00 (1.62 to 2.48)	1.79 (1.46 to 2.18)	1.90 (1.60 to 2.25)	0.001
Circulatory causes									
No of deaths	738	38	297	63	53	50	59	72	—
Overall	Reference	1.57 (1.12 to 2.20)	1.84 (1.58 to 2.14)	2.09 (1.61 to 2.72)	1.87 (1.41 to 2.49)	2.05 (1.52 to 2.75)	1.79 (1.36 to 2.35)	1.55 (1.20 to 2.01)	0.490
Before diagnosis‡	Reference	1.40 (0.98 to 1.99)	1.53 (1.30 to 1.80)	1.21 (0.86 to 1.69)	1.36 (0.95 to 1.94)	1.99 (1.47 to 2.70)	1.76 (1.32 to 2.34)	1.48 (1.13 to 1.93)	0.039
Cancer causes									
No of deaths	312	8	129	13	22	17	30	47	—
Overall	Reference	0.77 (0.38 to 1.57)	1.73 (1.37 to 2.18)	0.96 (0.55 to 1.68)	1.71 (1.10 to 2.66)	1.52 (0.92 to 2.51)	2.01 (1.36 to 2.98)	2.26 (1.61 to 3.17)	0.003
Before diagnosis‡	Reference	0.81 (0.39 to 1.64)	1.79 (1.41 to 2.26)	1.57 (1.00 to 2.47)	1.19 (0.68 to 2.10)	1.70 (1.05 to 2.78)	1.87 (1.23 to 2.86)	2.32 (1.65 to 3.26)	0.016
Respiratory causes									
No of deaths	43	4	48	9	5	6	8	20	—
Overall	Reference	2.02 (0.70 to 5.84)	4.05 (2.52 to 6.52)	4.25 (2.02 to 8.93)	2.64 (1.02 to 6.83)	3.52 (1.45 to 8.56)	3.36 (1.52 to 7.46)	5.75 (3.11 to 10.6)	0.117
Before diagnosis‡	Reference	2.01 (0.69 to 5.82)	3.85 (2.36 to 6.29)	3.75 (1.71 to 8.23)	2.42 (0.84 to 6.92)	2.98 (1.14 to 7.77)	3.56 (1.60 to 7.92)	5.51 (2.94 to 10.3)	0.078
Digestive causes									
No of deaths	37	4	28	5	6	8	5	4	—
All	Reference	3.01 (1.02 to 8.85)	3.14 (1.80 to 5.47)	2.98 (1.14 to 7.75)	3.93 (1.61 to 9.60)	5.60 (2.49 to 12.6)	2.60 (0.98 to 6.88)	1.58 (0.53 to 4.67)	0.168
Before diagnosis‡	Reference	3.06 (1.04 to 9.02)	3.16 (1.78 to 5.60)	3.01 (1.15 to 7.88)	3.15 (1.09 to 9.12)	6.22 (2.76 to 14.0)	2.87 (1.08 to 7.63)	1.66 (0.56 to 4.93)	0.219
Infectious causes									
No of deaths	21	1	29	11	2	4	5	7	—
Overall	Reference	1.37 (0.18 to 10.5)	6.05 (3.17 to 11.6)	12.3 (5.69 to 26.7)	2.23 (0.50 to 9.80)	5.54 (1.81 to 16.9)	5.07 (1.81 to 14.2)	4.70 (1.80 to 12.3)	0.270
Before diagnosis‡	Reference	1.25 (0.16 to 9.70)	5.23 (2.66 to 10.3)	8.62 (3.63 to 20.5)	2.54 (0.57 to 11.2)	7.06 (2.52 to 19.8)	4.22 (1.37 to 13.0)	3.80 (1.38 to 10.5)	0.424

*Adjusted for sex, ethnicity, education level, marital status, residential place, and cigarette smoking.

†P for trend calculated by assigning consecutive integers to fifths of duration of opium use in current opium users.

‡Excludes those who started opium use after diagnosis with serious disease.

Figure



Hazard ratios on logarithmic scale for all cause mortality in current and former users of opium according to time since last use, with never users as reference group (P=0.003 for trend)