Hazards of cigarettes, smokeless tobacco and waterpipe in a Middle Eastern Population: a Cohort Study of 50 000 individuals from Iran

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ABSTRACT

Background There is limited information about the hazards of cigarettes, smokeless tobacco and waterpipe in the Middle East. The aim of this study was to determine the association between different types of tobacco use and earlier death in the Golestan Cohort Study.

Methods The Study includes 50 045 adults (aged 40–75 years) from north eastern Iran. The baseline questionnaire (2004–2008) assessed information about use of cigarettes, chewing tobacco (nass) and waterpipe. To assess the use of each type of tobacco compared with never tobacco users, we used Cox regression models adjusted for age, socioeconomic status, area of residence, education and other tobacco used, and stratified by sex, ethnicity and opium use.

Results 17% of participants reported a history of cigarette smoking, 7.5% chewing tobacco (nass) and 1.1% smoking waterpipe, and these figures declined in the later birth cohorts. During a median follow-up of 8 years, 4524 deaths occurred (mean age 64.8 +9.9 years). Current (HR=1.44; 95% CI 1.28 to 1.61) and former (HR=1.35; 95% CI 1.16 to 1.56) cigarette smokers had higher overall mortality relative to never tobacco users. The highest cigarette-associated risk was for cancer death among current heavy smokers (HR=2.32; 95% CI 1.66 to 3.24). Current nass chewing was associated with overall mortality (HR=1.16; 95% CI 1.01 to 1.34), and there was a 61% higher risk of cancer death in people chewing nass more than five times a day. We observed an association between the cumulative lifetime waterpipe use (waterpipe-years≥28) and both overall (HR=1.66; 95% CI 1.11 to 2.47), and cancer mortality (HR=2.82; 95% CI 1.30 to 6.11).

Conclusions Regular use of cigarettes, smokeless tobacco and waterpipe were associated with the risk of earlier death (particularly from cancer) in our cohort.

INTRODUCTION

Most high-income countries have experienced an epidemic of smoking-related diseases during the 20th century, first in men and then in women.[1] While this epidemic seems to have plateaued in many of these countries,[2] tobacco use, including cigarette smoking and alternative tobacco products, are gradually reaching similar epidemic proportions in many low and middle-income countries, where 85% of the world's 1.3 billion smokers live.[3] Many of these countries do not have effective tobacco control policies and strategies in place.[4] A pooled analysis of cohort studies in Asia showed that in adults above the age of 45 years, smoking accounted for 15.8% of deaths among men and 3.3% of deaths in women in 2004.[5] This study also showed diversity in smoking habits and its health effects across different countries in Asia, but there were no countries from the Middle East in this analysis.

Alternative tobacco products, such as smokeless tobacco and the waterpipe are gaining popularity in many parts of the world, particularly among the youth.[3 6] Promotional materials targeted at smokers often suggest that smokeless tobacco (chewed or snuff) may be a safer alternative to smoking.[7] Waterpipe use has also regained popularity since 1990 in many parts of the world, particularly the Middle East and Africa and this trend is extending to the US and other Western countries.[8] This is thought to be mainly driven by its renewed popularity among women and the youth, caused by the introduction of flavoured tobacco, the café culture associated with waterpipe smoking, easier cultural exchange[8] and the lack of specific regulatory policies.[9] The WHO has identified an urgent need to study the health effects of waterpipe smoking.[10] Against claims regarding the 'relative safety' of such alternative products compared to cigarettes, studies have shown many potential hazards,[11–13] but their long-term impact on earlier death is largely unknown.[14] Regular use of many such products in the Middle East provides a good opportunity to study this aspect of tobacco toxicity.

We conducted this study to compare the overall and cause-specific mortality rates among users of cigarettes, chewing tobacco and waterpipe, with never tobacco users in the Golestan Cohort Study, a prospective cohort of 50 045 adults in Iran, during which detailed and validated information have been collected on the lifetime exposure to all of these risk factors.[15]

METHODS

Study population

After a feasibility pilot study in 2003,[16] a total of 50 045 adult participants, aged 40–75 years, were enrolled prospectively in the Golestan Cohort Study (GCS) from January 2004 through June 2008.[15] The cohort participants were enrolled from those who lived in Gonbad City (20%) and 326 villages (80%) in Golestan Province, north eastern Iran.

Measurements

The GCS general questionnaire included detailed information on the participants' lifestyle including

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the use of different types of tobacco products, opium use and alcohol drinking, as well as demographic characteristics, residential history, occupation, socioeconomic status and medical history of chronic diseases. Data were obtained on the types of tobacco used including cigarettes, chewed tobacco (nass), waterpipe and pipe, and the ages of starting and stopping, daily consumption amount and frequency of use. Nass, also known as Naswar, a chewable smokeless tobacco, is a mixture of tobacco, ash and lime that is widely used in the Central Asian Republics, Afghanistan, Iran, Pakistan and in South Africa.[12 17] Waterpipe, also known as hookah, shisha, hubbly bubbly, narghile or qualyan, is a device used to smoke tobacco which passes the smoke through water before it is inhaled and it is estimated to be used by 100 million people around the world.[18]

Definition of exposures

Tobacco users were defined as those who consumed any type of tobacco product at least once a week for 6 months. Cigarette and nass users were further classified as former (those who quit more than 1 year before enrolment) or current users at baseline, and categorised by starting age and average lifetime intensity of use. Waterpipe use could not be classified in a similar way both because of the small number of users and the intermittent nature of its use.[19] Cumulative waterpipe use (waterpipe-years) was calculated by multiplying duration of use by average number of times per day during each period of use, and was summed over the periods. Waterpipe-years were then categorised into tertiles (<5, 5–28 and more than 28). If the participant used multiple types of tobacco, or used them intermittently, data were recorded separately for each type and period of use. Pipe use was very uncommon, and very few used it exclusively, so it was not assigned a separate category for analysis. To assess the accuracy of the baseline tobacco questionnaire, we compared the answers with a second reassessment after an average of 5 years among 11 418 randomly selected individuals and only 3.6% of smoking reports were inconsistent with the baseline.

Cause of death ascertainment

All of the GCS participants were annually followed up through active telephone surveys and home visits. The follow-up success rate through March 2015 was over 99% (402 lost to follow-up). In addition to annual active follow-up, the GCS uses other sources, such as local health workers' reports and monthly provincial death registration reports, to reduce the time interval between death and ascertainment of the cause. The details of the GCS methods to evaluate the cause of death are discussed elsewhere.[20] We used the 10th revision of International Classification of Diseases (ICD-10) codes to classify the cause of death; the most prevalent causes of death in this population were ischaemic heart disease (IHD) (ICD-10 codes I20-I25), cerebrovascular accidents (CVAs) (I60-I69), cancer (C00-C97), respiratory disease (J00-J99) and external causes (S00-T88).

Statistical analysis

Follow-up continued until loss to follow-up, death or 31 March 2015, whichever came first. We fitted Cox proportional hazards models to estimate unadjusted and adjusted total and cause-specific mortality HRs and 95% CIs in relation to the exposures of interest, including type of tobacco used, age at start and per day average consumption. The potential confounders in the models were sex, age at baseline, residential place (urban vs rural), ethnicity (Turkmen vs others), highest attained educational level (none/less than high school/high school/college or higher), opium use (yes vs no), quartiles of a composite wealth score[21] and the use of other tobacco types (never, former and current). Further inclusion of alcohol consumption and body mass index (BMI) did not materially change the HRs (data not shown), so they were not included in the final models. In all the models, 'never tobacco users' (people who reported they had never used any tobacco product) were the universal reference category and we used age as the time-scale variable.

All survival analyses were stratified by sex. Two variables did not meet the proportionality assumption using Schoenfeld residuals (ethnicity and opium use), so all multivariable Cox models were also stratified on these variables.[22] Individuals with a prior diagnosis of IHD, CVA, chronic obstructive pulmonary disease and cancer at baseline were excluded from survival analyses. Three types of sensitivity analysis were also performed: (1) excluding the first 24 months of follow-up, (2) restricting all analyses to men as about 95% of cigarette smokers were men and (3) classifying the individuals who quit smoking within 5 years of enrolment as current smokers.

In a random subgroup of the original cohort (n=11 418), a second round of risk factor assessment was carried out about 5 years after the initial enrolment. These results were used to compare smoking trends over time. Standardised mortality rates per 100 000 person-years of follow-up were calculated using the WHO 2000 standard world population.

All statistical analyses were conducted using STATA statistical software, version13 (StataCorp , College Station, Texas, USA).

RESULTS

A history of cigarette smoking was reported by 8662 participants (17%), 94.9% of whom were men (table 1). They smoked, on average, 14.6 (SD:10.7) cigarettes per day and began smoking at an average age of 25.9 (SD:10.5). Table 1 shows other characteristics of the cohort participants by their smoking status. Cigarette smokers were more likely to be Turkmen, rural and have BMI below 25. There were significantly more opium users among both former and current smokers (50.6% and 52.6%, respectively) than among never smokers (9.7%). Also, on average, former smokers smoked more cigarettes per day and had started smoking at an earlier age than current smokers. Nass and waterpipe use was significantly more common among former cigarette smokers compared with both current smokers and never smokers (table 1). Figure 1 shows the trends of tobacco use at baseline and the reassessment after an average of 5 years, by the birth year of the participants. As the figure shows, except for an increase among individuals born during 1955-1965, there are fewer cigarette smokers among younger cohorts and about 32% of current smokers quit as they grew older, while only 1% of non-smokers picked up smoking. Nass use shows a constant drop by age and birth cohort.

During 391 208 person-years of follow-up (median duration of 8 years), until 31 March 2015, 4524 deaths occurred among 50 045 cohort participants. The underlying cause of death was confirmed in 3796 individuals. Among these, the major causes of death were IHD (1294 deaths: 34%), cancer (897 deaths: 24%), CVAs (624 deaths: 16%), external causes (217 deaths: 6%) and respiratory diseases (187: 5%). The most common causes of cancer death were cancers of the oesophagus (20.0%), stomach (19.7%) and lung (6.2%). Individuals who had reported a history of any of these diseases at baseline were excluded from survival analyses (IHD (n=3051), CVA (n=429), chronic respiratory disease (n=3035) and cancer (n=159), since the diagnosis may have altered their smoking habits.

Table 1 Baseline characteristics of Golestan Cohort Study participants according to cigarette smoking status

	Men			Women		
	Never smoker (n=13 016)	Former smoker (n=3087)	Current smoker (n=5131)	Never smoker (n=28 367)	Former smoker (n=126)	Current smoker (n=318)
SMR per 10^5 person-years (95% CI)	1106 (1043 to 1169)	1560 (1412 to 1708)	1682 (1521 to 1844)	1028 (726 to 1331)	1474 (870 to 2079)	2234 (1428 to 3041)
Age*	53.5 (9.6)	55.5 (9.5)	51.2 (8.5)	51.3 (8.6)	57.5 (9.1)	53.1 (8.4)
Ethnicity						
Turkmen	9698 (74.5)	2257 (73.1)	4097 (79.8)	20 983 (74.0)	39 (31.0)	179 (56.3)
Non-Turkmen	3318 (25.5)	830 (26.9)	1034 (20.2)	7384 (26.0)	87 (69.0)	139 (43.7)
Residence						
Urban	2176 (16.7)	661 (21.4)	1095 (21.3)	5988 (21.1)	34 (27.0)	78 (24.5)
Rural	10 840 (83.3)	2426 (78.6)	4036 (78.7)	22 379 (78.9)	92 (73.0)	240 (75.5)
Education						
None	6583 (50.6)	1624 (52.6)	2210 (43.1)	24 308 (85.7)	109 (86.5)	284 (89.3)
Up to 8 years	4321 (33.2)	1057 (34.2)	1960 (38.2)	3328 (11.7)	12 (9.5)	30 (9.4)
High school	1490 (11.4)	292 (9.5)	764 (14.9)	604 (2.1)	2 (1.6)	3 (0.9)
University	622 (4.8)	114 (3.7)	197 (3.8)	127 (0.4)	3 (2.4)	1 (0.3)
BMI						
<25	5892 (45.2)	1688 (54.7)	3289 (64.1)	9205 (32.5)	66 (52.4)	199 (62.6)
25–29	4970 (38.2)	960 (31.1)	1341 (26.1)	9600 (33.8)	34 (27.0)	67 (21.1)
≥30	2154 (16.5)	439 (14.2)	501 (9.8)	9562 (33.7)	26 (20.6)	52 (16.4)
Opium ever use	1942 (14.9)	1546 (50.1)	2658 (51.8)	2072 (7.3)	72 (57.1)	210 (66.0)
Alcohol ever use	396 (3.0)	439 (14.2)	873 (17)	17 (0.1)	1 (0.8)	3 (0.9)
Nass use						
Never	11 516 (88.5)	1648 (53.4)	4502 (87.7)	28 092 (99.0)	101 (80.2)	308 (96.9)
Former	153 (1.2)	147 (4.8)	37 (0.7)	23 (0.1)	4 (3.2)	2 (0.6)
Current	1347 (10.3)	1292 (41.9)	592 (11.5)	252 (0.9)	21 (16.7)	8 (2.5)
Waterpipe use						
Never	12 913 (99.2)	3013 (97.6)	5105 (99.5)	28 024 (98.8)	112 (88.9)	306 (96.2)
Former	50 (0.4)	47 (1.5)	7 (0.1)	106 (0.4)	10 (7.9)	3 (0.9)
Current	53 (0.4)	27 (0.9)	19 (0.4)	237 (0.8)	4 (3.2)	9 (2.8)
Age when smoking started						
<20		1081 (35.0)	1150 (22.4)		9 (7.1)	19 (6.0)
20–24		956 (31.0)	1391 (27.1)		25 (19.8)	18 (5.7)
25–29		425 (13.8)	705 (13.7)		18 (14.3)	20 (6.3)
≥30		625 (20.2)	1885 (36.7)		74 (58.7)	261 (82.1)
Years of cigarette smoking						
<10		1299 (42.1)	921 (17.9)		83 (65.9)	178 (56.0)
10–19		789 (25.6)	1063 (20.7)		22 (17.5)	68 (21.4)
20–29		510 (16.5)	1528 (29.8)		11 (8.7)	30 (9.4)
≥30		489 (15.8)	1619 (31.6)		10 (7.9)	42 (13.2)
Average lifetime cigarettes per day†						
<10		889 (28.8)	1744 (34.0)		72 (57.1)	200 (62.9)
10–19		518 (16.8)	1385 (27.0)		8 (6.3)	53 (16.7)
≥20		1662 (53.8)	1957 (38.1)		45 (35.7)	55 (17.3)

*Numbers show frequencies (percentage) except for age which is mean (SD), and SMR which is rate per 100 000 (95% CI).
†Mean number of cigarettes smoked per day during the time the person smoked. The numbers do not add up since in 71 men and 11 women, average cigarettes per day could not be calculated.
BMI, body mass index; SMR, standardised mortality rate.

Both current (HR=1.44; 95% CI 1.28 to 1.61) and former (HR=1.35; 95% CI 1.16 to 1.516) cigarette smokers had higher mortality compared with never tobacco users (table 2).

Current cigarette smoking had a stronger association with mortality due to IHD (HR=1.34; 95% CI 1.07 to 1.68), cancer (HR=1.69; 95% CI 1.33 to 2.16) and respiratory diseases (HR=1.76; 95% CI 1.00 to 3.19). Earlier age of smoking initiation was also associated with higher overall and cause-specific mortality (table 2). We also observed a dose-dependent increase in the risk of all-cause mortality among current smokers with the average number of cigarettes smoked per day (table 2). Among cause-specific deaths, in particular, cancer mortality more than doubled in the current heavy smokers (>20 cigarettes per day) compared to never tobacco users.

In order to evaluate the effects of cessation on earlier death in former cigarette smokers, we analysed the duration of smoking before they quit (figure 2). Former smokers who quit after 15 years of cigarette smoking had identical survival curves to current smokers, and had worse survival than former smokers with a shorter smoking history or never tobacco users. Those who smoked for <5 years had similar survival curves as never tobacco users.

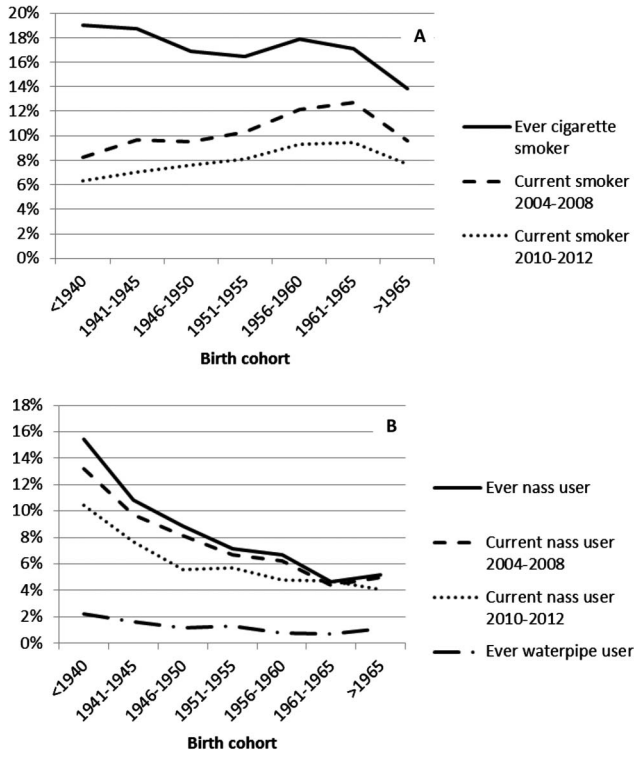

Figure 1 Proportion of (A) cigarette smoking, and (B) alternative tobacco use, by birth cohorts in the Golestan Cohort Study.

Current nass chewing was associated with overall mortality (HR=1.16; 95% CI 1.01 to 1.34). The highest mortality risk associated with nass chewing was a 61% higher risk of cancer death in people chewing nass, on average, more than five times a day (table 3). The association between nass initiation age and mortality was more complex, and seemed to peak among people starting around the ages of 25–30 years. However, it is important to consider nass use in the context of cigarette smoking, as about 41% of former cigarette smokers currently used nass (table 1) and out of 1464 former smokers who used nass, 1211 (82.7%) started nass after quitting cigarettes. Therefore, we also analysed mortality in association with different combinations of cigarette and nass use (table 4). Chewing nass had a particularly strong association with cancer mortality: while being a former cigarette smoker alone was not associated with a higher risk, nass use substantially increased the risk of death from cancer among former smokers.

As table 3 shows, any waterpipe use showed a borderline association with higher overall and cancer mortality and there was a significant association between the highest level of cumulative lifetime waterpipe use (waterpipe-years≥28) and both overall (HR=1.66; 95% CI 1.11 to 2.47), and cancer mortality (HR=2.82; 95% CI 1.30 to 6.11). The number of regular waterpipe smokers was relatively small, and the models for death from respiratory disease did not converge.

Since opium use affected the risk estimates in our models more than other confounders, we stratified our main results by opium use in online supplementary tables S1 and S2. In general, the associations with cigarette smoking were stronger among opium users, while waterpipe use was only associated with overall and cancer mortality among never opium users.

We conducted three types of sensitivity analysis. First, we dropped the first 2 years of the follow-up (861 of the deaths occurred in this period). The results were essentially the same as those including all of the follow-up period, and thus they are not shown. Since cigarette smokers and nass users were mainly men, we conducted a men-only analysis as well, which did not show any changes in the results (data not shown). Finally, we grouped individuals who quit smoking within 5 years from enrolment (n=647) with current smokers. This resulted in some attenuation of the association between both current smoking and overall mortality from 1.44 to 1.36 (95% CI 1.23 to 1.51) and former cigarette smoking and overall mortality from 1.35 to 1.23 (95% CI 1.07 to 1.41).

DISCUSSION

In this population, current and former cigarette smokers and current nass users were at increased risk of earlier mortality, particularly from cancer. Former cigarette smokers who smoked for <5 years had similar survival curves to never tobacco users, but using smokeless tobacco after quitting increased the chance of dying from cancer compared to those who did not use it. Waterpipe use had similar but weaker effects on mortality, which were most pronounced with high lifetime cumulative use.

Current cigarette smokers in our study had a 44% increased risk of earlier death compared to never tobacco users. The magnitudes of the associations between cigarette smoking and earlier death in our study were smaller than those seen in most high-income countries,[23 24] but similar to those from East Asia[14 25] and other low-income and middle-income countries still in the early stages of the tobacco epidemic.[5 26] The risk ratios in these populations are also very similar to those seen in the USA at the beginning of the tobacco epidemic: current smokers in the CPS-I cohort (1959–1965) had relative risks of 1.76 (men) and 1.35 (women) for mortality from all causes, which increased in CPS-II (1982–1988) and reached 2.8 (both sexes) in five contemporary US cohorts (2000–2010).[1] As one possible explanation, standardised mortality rates among non-smokers in the USA have dropped from 4142 per 10^5 in men above 55 and 2884 per 10^5 in women above 55 in CPS-I cohort, to 1918 and 1248, respectively, in the contemporary cohorts. In our population, never smoking men and women above 55 had standardised mortality rates of 2435 and 2351, respectively (data not shown), which are also higher than contemporary rates in the USA.

Another possible reason for the differences in risk may be due to smoking patterns: smokers in our population generally smoked fewer cigarettes, and started smoking later compared to many Western countries. Many previous studies,[27] as well as our findings, have shown a strong association between early age at smoking initiation and earlier death. Although the type of cigarettes used may be considered as another potential source of differences, cigarettes used in Iran are almost exclusively manufactured and more than 60% are foreign cigarettes.[28] These cigarettes are imported, or smuggled mainly from other Middle East countries.[29] Many of the domestically-produced cigarettes are also under international brands, and a large volume of the tobacco used in them is imported. A study comparing the nicotine levels of foreign and domestic brands showed no difference between the two.[30]

The prevalence of smoking in Golestan province is lower than the national average in Iran; the prevalence of current smoking among above the age of 45 years in the 2007 national survey of adults (the same time our cohort study started) was 29.5% in men and 3.3% in women.[31] Countries in the Middle East share many features of this smoking pattern; in most of them male smoking prevalence is 19.7–34.7%, and women smoke up to 10 times less than men.[32] These rates, which are

Table 2 Overall and cause-specific mortality by cigarette use in the Golestan Cohort Study

	Number†	Deaths†	Overall mortality Crude HR (95% CI)	IHD mortality Adjusted HR‡ (95% CI)	CVA mortality Adjusted HR (95% CI)	Cancer mortality Adjusted HR (95% CI)	Respiratory disease mortality Adjusted HR (95% CI)	Adjusted HR (95% CI)
Never tobacco users	34 544	2141	1	1	1	1	1	1
Former smokers§	2551	353	1.55 (1.37 to 1.75)**	1.35 (1.16 to 1.56)**	1.17 (0.87 to 1.58)	1.10 (0.72 to 1.69)	1.36 (0.97 to 1.88)	1.58 (0.74 to 3.37)
Current smokers	4889	566	1.79 (1.61 to 1.99)**	1.44 (1.28 to 1.61)**	1.34 (1.07 to 1.68)**	1.06 (0.75 to 1.50)	1.69 (1.33 to 2.16)**	1.76 (1.00 to 3.19)*
Smoking start age§								
Former								
<20	887	109	1.62 (1.33 to 1.98)**	1.37 (1.09 to 1.73)**	1.46 (0.93 to 2.30)	1.44 (0.76 to 2.72)	1.31 (0.79 to 2.19)	2.00 (0.63 to 6.42)
20–24	773	107	1.59 (1.30 to 1.94)**	1.38 (1.09 to 1.75)**	0.86 (0.50 to 1.50)	1.36 (0.71 to 2.60)	1.33 (0.79 to 2.23)	1.32 (0.37 to 4.70)
25–29	345	45	1.40 (1.04 to 1.89)**	1.20 (0.87 to 1.66)	1.35 (0.73 to 2.51)	0.79 (0.27 to 2.27)	1.13 (0.56 to 2.28)	1.25 (0.25 to 6.28)
≥30	546	92	1.41 (1.14 to 1.75)**	1.17 (0.92 to 1.49)	1.26 (0.79 to 1.99)	0.77 (0.37 to 1.62)	0.90 (0.50 to 1.63)	0.69 (0.17 to 2.84)
Current								
<20	1031	123	2.03 (1.68 to 2.46)**	1.71 (1.40 to 2.09)**	1.21 (0.79 to 1.86)	1.19 (0.63 to 2.27)	2.30 (1.54 to 3.44)**	3.25 (1.28 to 8.23)**
20–24	1271	132	1.78 (1.48 to 2.14)**	1.50 (1.23 to 1.82)**	1.78 (1.27 to 2.50)**	0.86 (0.43 to 1.70)	1.54 (1.00 to 2.38)*	1.83 (0.65 to 5.19)
25–29	646	70	1.92 (1.51 to 2.46)**	1.61 (1.25 to 2.07)**	0.92 (0.51 to 1.68)	0.89 (0.35 to 2.23)	2.06 (1.24 to 3.40)**	2.86 (0.93 to 8.83)
≥30	1941	241	1.69 (1.47 to 1.95)**	1.36 (1.17 to 1.58)**	1.18 (0.88 to 1.60)	1.16 (0.75 to 1.78)	1.63 (1.19 to 2.24)*	1.46 (0.68 to 3.14)
Cigarettes per day§,¶								
Former								
<10	784	113	1.43 (1.17 to 1.74)**	1.32 (1.06 to 1.64)**	1.51 (1.01 to 2.28)*	0.73 (0.35 to 1.53)	1.09 (0.65 to 1.83)	1.46 (0.46 to 4.60)
10–19	424	49	1.34 (1.00 to 1.79)**	1.20 (0.89 to 1.64)	0.72 (0.33 to 1.56)	0.72 (0.25 to 2.02)	1.49 (0.82 to 2.70)	1.12 (0.22 to 5.74)
≥20	1328	188	1.64 (1.40 to 1.92)**	1.31 (1.06 to 1.62)**	1.26 (0.82 to 1.93)	1.47 (0.84 to 2.55)	1.03 (0.63 to 1.69)	1.09 (0.35 to 3.42)
Current								
<10	1783	187	1.68 (1.43 to 1.96)**	1.40 (1.19 to 1.66)**	1.28 (0.92 to 1.78)	1.16 (0.71 to 1.89)	1.45 (1.01 to 2.10)*	1.34 (0.55 to 3.29)
10–19	1283	135	1.58 (1.31 to 1.89)**	1.34 (1.10 to 1.63)**	1.14 (0.77 to 1.69)	0.59 (0.28 to 1.24)	1.75 (1.18 to 2.59)**	2.10 (0.87 to 5.09)
≥20	1772	240	2.20 (1.90 to 2.54)**	1.76 (1.50 to 2.07)**	1.63 (1.19 to 2.24)**	1.28 (0.78 to 2.09)	2.32 (1.66 to 3.24)**	2.01 (0.87 to 4.62)

*p<0.05, **p<0.001.
†Excluding individuals with a baseline disease.
‡Cox regression models stratified by sex, ethnicity and opium, and adjusted for age, socioeconomic status, residence, education, nass and waterpipe use.
§The reference category for all models is the same 'never tobacco users'.
¶In 59 smokers (7 dead), average cigarettes per day could not be calculated.
CVA, cerebrovascular accident; IHD, ischaemic heart disease.

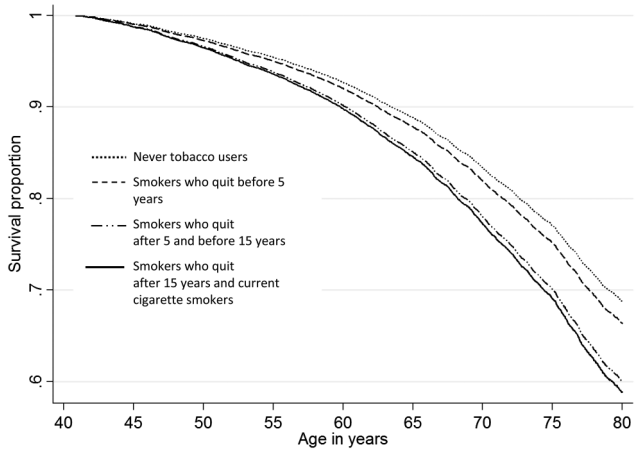

Figure 2 Survival among never tobacco users and cigarette smokers, by the duration of smoking, in the Golestan Cohort Study. The curves are based on Cox regression models adjusted for age, socioeconomic status, residence, education, nass and waterpipe use, sex, ethnicity and opium.

higher than those in sub-Saharan Africa but lower than the rates in Southeast Asia and Eastern Europe, are also lower than the smoking prevalence in the USA at the beginning of the tobacco epidemic (54.1% in men and 38.1% in women).[33] However, a meta-regression of the WHO global smoking data showed that in the past decade, the Eastern Mediterranean region has experienced the fastest growth in smoking rates in the world among both among men and women, and about 73% of its population live in areas experiencing such a rapid rise.[34] Given our findings of higher mortality risk, particularly from cancer, this rapid growth heralds a rapid rise in tobacco-related mortality in this region. Moreover, the use of opium and alternative tobacco products may affect the health risks associated with smoking. For example, opium use increases the overall and cause-specific mortality rates,[35] and modifies the association between tobacco use and mortality (see online supplementary table S1).

We observed an association between chewing tobacco and earlier mortality, particularly from cancer. Association between chewing tobacco and cancers, especially those of the oesophagus, lung, pancreas and oral cavity have been previously reported.[11] Many people who use smokeless tobacco want to avoid the restriction of smoking in public places, many have had multiple quitting efforts in the past, and many become dual users.[36] Our results also showed that dual users, especially former smokers who chew tobacco and those who pick up the habit in early adulthood are particularly at risk of dying from cancer. Studies from India, where chewing tobacco is a common form of smokeless tobacco particularly among women, have shown higher mortality compared with non-users, from a number of specific causes, including respiratory diseases and cancer.[37 38] For example, the Bombay Cohort Study showed a relative risk of 2.60 (95% CI 1.78 to 3.80) for deaths due to neoplasms among smokeless tobacco users. We did not find a significant association between using nass and cardiovascular death. The cardiovascular health risks of chewing smokeless tobacco have also been studied in several previous studies, and the results have been inconsistent.[11–13 39–41] In the INTERHEART study, which was a case–control study including 27 089 myocardial infarction (MI) cases and controls from 52 countries, an OR of 2.23 was observed for non-fatal MI among tobacco chewers, which rose to 4.09 in people who also smoked cigarettes.[42] One difficulty in comparing the results of different studies is that the smokeless tobacco is used in many different forms and preparations.[43]

Previous epidemiological studies have suggested increased risk of several health conditions associated with waterpipe use, but most of these studies have been cross sectional or retrospective.[44] We have also previously reported a correlation between cumulative waterpipe smoking and self-reported heart disease in a separate cross-sectional analysis in this population.[41] In 2010, Akl *et al*,[45] systematically reviewed all previous evidence and reported that among 24 eligible studies, the quality of evidence for the different outcomes varied from very low to low, according to the GRADE approach for rating the quality of evidence. The updated review in 2016, showed a promising number of 19 new studies added in the 6 years between the two studies, but still most of these were cross-sectional studies.[46] To the best of our knowledge, only one previous prospective cohort study has reported the association of waterpipe use and mortality.[47] In this study of 20 033 individuals in the Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh, although waterpipe use was associated with earlier mortality, it was difficult to distinguish the effects from cigarette smoking, as more than 99% of waterpipe users also smoked cigarettes.

One problem that complicates studying waterpipe is the fact that its use is most often intermittent, and many measures of intensity and dependence devised for cigarettes (past month smoking, former vs current use, etc) cannot capture its variation.[19 48] On the other hand, lifetime cumulative exposure to waterpipe has been collected in a few studies, including a report by Sibai *et al*[49] showing a threefold increased risk of severe coronary stenosis associated with 40 waterpipe-years or more use. We did not observe any association between waterpipe use and cardiovascular mortality, but showed higher risks of total and cancer mortality in waterpipe users compared to never tobacco users among people with more than 28 waterpipe-years of cumulative exposure.

Our study had several limitations: within a subset of the cohort with a second data collection 5 years after enrolment, about 25% of current cigarette smokers quit smoking during the follow-up; this might have resulted in some bias towards null, as these people are still classified as current smokers in our analyses. We did not have any assessment of exposure to secondhand tobacco smoke, so some of our never tobacco users may have actually been exposed to tobacco products to some extent. As another limitation, waterpipe use in Golestan is lower than the national average, and our waterpipe analyses were underpowered, particularly when compared to those of cigarettes and nass. Our study has several strengths, including its prospective design, large sample size, minimal loss to follow-up, prior validation of self-reported opium use and outcome measures, and the availability of data on important potential confounders. We also collected detailed data on lifetime tobacco and opium use, allowing us to investigate the mortality hazards of all of the main types of tobacco use and their combinations in a single population.

Although former smokers in our study started smoking at an earlier age and smoked more cigarettes, they had lower risks of overall and cause-specific mortality compared with current smokers. The magnitude of this decrease in risk depended on how long they smoked before quitting; among former smokers, people who smoked <5 years before they quit had the most favourable outcome and had mortality risks very similar to never tobacco users. Among all risk factors of non-communicable diseases, tobacco is the one that can be best reduced by appropriate policies.[50] The measures by the WHO Framework Convention

Table 3 Overall and cause-specific mortality by use of alternative tobacco products (smokeless tobacco (nass) and waterpipe) in the Golestan Cohort Study

			Overall mortality		IHD mortality	CVA mortality	Cancer mortality	Respiratory disease mortality
	Number†	Deaths†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Never tobacco users	34 544	2141	1	1	1		1	1
Former nass users§	275	45	1.26 (0.93 to 1.70)	0.98 (0.73 to 1.30)	1.04 (0.55 to 1.96)	0.53 (0.19 to 1.51)	1.31 (0.70 to 2.45)	1.14 (0.31 to 4.16)
Current nass users	2999	480	1.73 (1.56 to 1.93)**	1.16 (1.01 to 1.34)*	1.16 (0.87 to 1.55)	0.98 (0.65 to 1.47)	1.42 (1.04 to 1.94)**	0.7 (0.29 to 1.70)
Nass chewing start age§								
<20	200	40	1.57 (1.15 to 2.16)**	1.11 (0.79 to 1.54)	1.20 (0.63 to 2.30)	0.55 (0.17 to 1.76)	1.67 (0.89 to 3.15)	ND
20–24	256	36	1.34 (0.96 to 1.87)	1.13 (0.83 to 1.54)	1.05 (0.53 to 2.11)	0.54 (0.16 to 1.75)	1.28 (0.63 to 2.58)	1.38 (0.35 to 5.46)
25–29	203	40	2.36 (1.72 to 3.24)**	1.61 (1.17 to 2.21)**	0.83 (0.34 to 2.06)	0.84 (0.26 to 2.72)	2.04 (1.04 to 3.97)*	0.69 (0.08 to 5.60)
30–34	419	76	2.06 (1.63 to 2.61)**	1.26 (0.98 to 1.63)	1.40 (0.83 to 2.36)	1.43 (0.73 to 2.80)	1.54 (0.89 to 2.67)	1.25 (0.37 to 4.27)
≥35	2196	333	1.61 (1.43 to 1.82)**	1.08 (0.93 to 1.26)	1.13 (0.82 to 1.56)	0.96 (0.62 to 1.50)	1.30 (0.92 to 1.83)	0.7 (0.27 to 1.80)
Nass chewing times per day§,¶								
≤3	798	117	1.48 (1.22 to 1.79)**	1.07 (0.87 to 1.32)	1.45 (1.00 to 2.11)	0.78 (0.42 to 1.44)	1.01 (0.62 to 1.66)	0.16 (0.02 to 1.32)
3–5	872	147	1.95 (1.64 to 2.32)**	1.34 (1.09 to 1.63)*	1.42 (0.96 to 2.11)	0.87 (0.47 to 1.61)	1.55 (1.02 to 2.38)*	0.89 (0.30 to 2.66)
>5	1496	249	1.65 (1.44 to 1.90)**	1.13 (0.95 to 1.35)	0.81 (0.55 to 1.20)	1.06 (0.66 to 1.70)	1.61 (1.12 to 2.30)**	0.99 (0.37 to 2.60)
Ever Waterpipe users[3]	411	54	1.41 (1.08 to 1.85)*	1.30 (0.98 to 1.73)	0.85 (0.46 to 1.63)	1.10 (0.50 to 2.42)	1.75 (0.95 to 3.21)	0.40 (0.05 to 3.15)
Cumulative waterpipe-years (Tertiles)§								
<4.5	156	10	0.98 (0.53 to 1.82)	0.87 (0.46 to 1.64)	0.59 (0.15 to 2.42)	0.58 (0.08 to 4.26)	2.08 (0.76 to 5.70)	ND
4.5–28	156	17	1.39 (0.86 to 2.24)	1.30 (0.80 to 2.12)	0.88 (0.28 to 2.76)	2.00 (0.72 to 5.57)	0.45 (0.06 to 3.21)	ND
>28	140	26	1.77 (1.20 to 2.60)**	1.66 (1.11 to 2.47)*	1.08 (0.44 to 2.67)	0.82 (0.20 to 3.36)	2.82 (1.30 to 6.11)**	ND

*p<0.05, **p<0.001.
†Excluding individuals with a baseline disease.
‡Cox regression models stratified by sex, ethnicity and opium, and adjusted for age, socioeconomic status, residence, education, and cigarette smoking.
§The reference category for all models is the same 'never tobacco users'.
¶In 96 nass users (12 dead), average nass use per day could not be calculated.
CVA: cerebrovascular accident; IHD: ischaemic heart disease; ND, not determined.

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Table 4 Overall and cause-specific mortality by combinations of cigarette and smokeless tobacco (nass) in the Golestan Cohort Study

	Number†	Deaths†	Overall mortality		IHD mortality	CVA mortality	Cancer mortality	Respiratory disease mortality
			Crude HR (95% CI)	Adjusted HR‡ (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Never tobacco users§	34 544	2141	1	1	1	1	1	1
Former cigarette only	1320	162	1.37 (1.16 to 1.62)**	1.30 (1.10 to 1.54)**	1.23 (0.89 to 1.70)	1.06 (0.65 to 1.73)	1.15 (0.77 to 1.73)	1.17 (0.44 to 3.09)
Current cigarette only	4299	482	1.79 (1.60 to 1.99)**	1.45 (1.29 to 1.64)**	1.32 (1.05 to 1.67)*	1.06 (0.74 to 1.53)	1.75 (1.37 to 2.25)**	1.73 (0.94 to 3.19)
Current nass only¶	1393	236	1.60 (1.39 to 1.85)**	1.17 (1.00 to 1.36)*	1.15 (0.85 to 1.55)*	0.64 (0.16 to 2.61)	1.40 (1.01 to 1.95)*	0.56 (0.20 to 1.52)
Former cigarette +current Nass¶	1056	163	1.87 (1.58 to 2.21)**	1.33 (1.11 to 1.59)**	0.92 (0.62 to 1.37)	1.15 (0.69 to 1.91)	1.65 (1.13 to 2.39)**	1.80 (0.80 to 4.04)
Current cigarette +current Nass¶	523	75	1.94 (1.53 to 2.46)**	1.28 (1.00 to 1.64)*	1.17 (0.71 to 1.92)	1.07 (0.53 to 2.18)	1.67 (1.02 to 2.75)*	1.09 (0.31 to 3.82)

*p<0.05, **p<0.001.
†Excluding individuals with a baseline disease.
‡Cox regression models stratified by sex, ethnicity and opium, and adjusted for age, socioeconomic status, residence, education, and waterpipe use.
§The reference category for all models is the same 'never tobacco users'.
¶There were only 97 exclusive former nass users, so the models for this category and its combinations could not be constructed.
CVA, cerebrovascular accident; IHD, ischaemic heart disease.

on Tobacco Control (WHO MPOWER measures) target a 30% reduction in tobacco use in adults by 2025. This is while 70% of the population in the Eastern Mediterranean region live in countries where this goal seems unachievable.[34] To avert an already increasing tide of mortality due to non-communicable diseases, especially cancer, reinforcement of local policies to implement MPOWER mandates, focusing on all types of tobacco use and local tobacco culture, is essential.

What this paper adds

- All types of tobacco increased the risk of earlier death (particularly from cancer) in our study. We also showed increased risk of earlier death, compared to never tobacco users, among people who switched to smokeless tobacco after quitting cigarettes and those who have regularly smoked the waterpipe for a long time.
- These results emphasise the need for global tobacco control and show that the focus of antitobacco efforts must not be confined to cigarette smoking.

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Competing interests None declared.

Patient consent Obtained.

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