# BMJ Open

# Causes of premature death and their associated risk factors in the Golestan Cohort Study, Iran

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## ABSTRACT

**Objectives** To examine the causes of premature mortality (<70 years) and associated risk factors in the Golestan Cohort Study.

**Design** Prospective.

**Setting** The Golestan Cohort Study in northeastern Iran.

**Participants** 50 045 people aged 40 or more participated in this population-based study from baseline (2004–2008) to August 2017, with over 99% success follow-up rate.

**Main outcome measures** The top causes of premature death, HR and their 95% CI and population attributable fraction (PAF) for risk factors.

**Results** After 444 168 person-years of follow-up (median of 10 years), 6347 deaths were reported, of which 4018 (63.3%) occurred prematurely. Ischaemic heart disease (IHD) accounted for 33.9% of premature death, followed by stroke (14.0%), road injuries (4.7%), stomach cancer (4.6%) and oesophageal cancer (4.6%). Significant risk/protective factors were: wealth score (HR for highest vs lowest quintile: 0.57, PAF for lowest four quintiles vs top quintile: 28%), physical activity (highest vs lowest tertile: 0.67, lowest two tertiles vs top tertile: 22%), hypertension (1.50, 19%), opium use (1.69, 14%), education (middle school or higher vs illiterate: 0.84, illiterate or primary vs middle school or higher: 13%), tobacco use (1.38, 11%), diabetes (2.39, 8%) and vegetable/fruit consumption (highest vs lowest tertile: 0.87, lowest two tertiles vs top tertile: 8%). Collectively, these factors accounted for 76% of PAF in men and 69% in women.

**Conclusion** IHD and stroke are the leading causes of premature mortality in the Golestan Cohort Study. Enhancing socioeconomic status and physical activity, reducing opium and tobacco use, increasing vegetable/fruit consumption and controlling hypertension and diabetes are recommended to reduce premature deaths.

## Strengths and limitations of this study

► The Golestan Cohort Study is one of the largest and oldest population-based cohort studies in the Middle East, with over 50 000 participants, and less than 1% loss to follow-up after 10 years.

► The accuracy of the follow-up and cause of death ascertainment, as well as availability of detailed and validated data on risk factors, are important strengths of this study.

► The cohort has no data on people younger than 40 years old, and the participants are mainly representative of the rural population.

with decreased income, poor mental health, loss of education and childhood and increased mortality in the affected families.[2–4]

The burden of premature mortality is particularly high in the low/middle-income countries (LMICs); over 80% of these premature deaths—defined as death before 70 years of age—occur in the LMICs.[5] The WHO estimates that economic losses associated with premature deaths in LMICs is expected to increase to about US$7 trillion by 2030.[6]

While death is inevitable, extending life expectancy and avoiding premature death are quite feasible.[7] For example, the life expectancy at birth in the USA in the short span between 1990 and 2015 increased from 75.4 to 78.8.[8] Reduction of premature deaths, a major public health focus, is one of the United Nation's sustainable development goals for 2030.[9]

The causes of premature death vary widely between regions.[10] Identification of the major causes of premature death and their associated risk factors in each population is crucial to health planning, policy development and budget prioritising.[10]

## INTRODUCTION

The loss of middle-aged family members is often devastating to the household, as families often rely on them as the primary breadwinners and caregivers.[1] Premature death of a middle-aged person is thus often associated

Iran is a middle-income country, with a relatively high burden of premature deaths. The average life expectancy for Iranian women and men were 73.2 and 70.5 years in 2004 and 76.6 and 74.5 years in 2015, respectively.[11] We have used data from the Golestan Cohort Study (GCS), a very large prospective study in northeastern Iran, to examine the main causes of premature mortality and its associated risk factors. We have also determined and reported the burden of the major causes of premature death in terms of standard expected years of life lost (SEYLL) and the population attributable fraction (PAF) of significant modifiable risk factors.

## METHODS
### GCS design
The design and methods of the population-based GCS have been described previously.[12] From 2004 to 2008, 50 045 people aged 40–75 from Golestan Province were recruited in the study. Trained interviewers used structured questionnaires to collect data on demographics, medical history, lifestyle and physical examination.[12] Data on the intensity, duration and frequency of physical activity were collected. Wealth score was calculated for each participant based on the ownership of household appliances and other variables such as house ownership, structure and size.[13] Height, weight and blood pressure were measured. Nutritional data were collected with a valid and reliable food frequency questionnaire (FFQ) that was designed for the GCS.[14] Validity was assessed by comparing FFQ results with 24-hour diet recalls and biochemical markers in serum and urine. Reliability was tested using intraclass correlation coefficients between four FFQ results administrated to the same persons.[14]

### Follow-up and death cause ascertainment
All study participants were followed annually. The GCS team completed a case review questionnaire during each phone call or home visit and recorded the vital status of the participants. If a death was reported, all clinical reports and hospital records were collected within the entire province and the neighbouring provinces and a verbal autopsy (estimation of death cause using signs and symptoms during the period leading up to death, in the absence of reliable medical records)[15] was completed if needed. Using the collected documents, two independent internists determined the cause of death based on the International Classification of Diseases 10th version (ICD-10) codes. The two codes were compared, and if they were different, a third more senior internist reviewed the data and made the final code.

### Statistical methods
Continuous variables were expressed as mean (SD) and categorical variables as percentages. History of ischaemic heart disease (IHD), stroke and diabetes mellitus was considered positive if the study participant reported diagnosis by a physician. High blood pressure was defined as any of these conditions: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or being known case of hypertension (diagnosed by a physician). Individuals were considered tobacco users if they had smoked or had chewed nass (a kind of smokeless tobacco[12]) at least once a week for a period of 6 months or more. Likewise, opium users or alcohol drinkers were defined as those who consumed these substances at least once a week or once a month, respectively, for a minimum of 6 months. Physical activity was categorised based on the metabolic equivalent of task per minute per week into tertiles. Wealth score was categorised into quintiles, and consumption of vegetables and fruits (grams/day) was categorised into tertiles.

The analysis of deaths by cause was carried out based on the WHO methods and data sources for country-level causes of death in 2000–2015.[16] Accordingly, the top 10 causes of death were determined after redistribution of garbage codes, for example, ill-defined cardiovascular diseases (I10, I26.9, I46, I47.2, I49.0, I50, I51.4, I51.5, I51.6, I51.9 and I70.9), injuries undetermined whether intentional or unintentional (Y10–Y34, Y87.2), and ill-defined cancers (C76, C80, and C97), and symptoms, signs and ill-defined conditions (ICD10 codes R00–R94, R96–R99).

For the purpose of our analysis, death among people aged <70 years was considered premature. Follow-up time extended from the date of cohort enrolment to the date of premature death, age 70 years, loss to follow-up or 13 August 2017, whichever came first. We used the life table method to calculate the probability of reaching the age of 70 years for those who had reached age 40. To do this, we calculated and multiplied the probabilities of survival for each year between ages 40 and 70 (ie, 40 to 41, 41 to 42, …, 69 to 70). To determine the association between premature death with independent covariates, Cox proportional hazard regression models were used to estimate HRs and 95% CIs. For this analysis, we excluded participants with age 70 years or older, and those with a history of chronic diseases (ie, IHD, stroke or cancer) at baseline. In the Cox models, unadjusted, age-adjusted and sex-adjusted and fully adjusted HRs were calculated for each covariate. In the mutual model, the HRs were adjusted for potential confounders including age at baseline, sex, ethnicity, marital status, place of residence, education, wealth score, history of alcohol, tobacco/nass and opium consumption, physical activity, body mass index, vegetables and fruit consumption, hypertension and diabetes.

We also calculated the PAF for significant modifiable covariates based on mutual regression models, using 'punaf' command in Stata. The reference distribution was set so that each participant was unexposed to the risk factor, or in the category of the risk factor associated with the lowest risk of premature death (eg, the highest quintile of wealth score, the highest tertile of physical activity, etc).

We report SEYLL as measure of burden disease due to premature mortality. To obtain SEYLL, we first calculated

the difference between life expectancy and age of death for each deceased person, and then summed up all these differences; SEYLL=$\sum(y_i - x_i)$, where $y_i$ is the life expectancy and $x_i$ is age of death for deceased person i. Life expectancy at each age was obtained from the Global Burden of Diseases (GBD) Study.[10] All statistical analyses were done with Stata statistical software, V.12 (StataCorp, College Station, Texas, USA).

## Patient and public involvement

Prior to developing the study, the research group informed the local authorities and university officials, local physicians, elders and religious leaders about the aims of the GCS to gain their support. Local people and physicians were consulted about various exposures, as well as the appropriate ways of asking questions. For example, local people provided information about commonly consumed foods, types of housing used over decades and common jobs. All interviews, data and sample collection were done by interviewers trained from among the local population. Results of blood analyses (eg, cholesterol) were reported to cohort participants. All participants received cohort membership cards, which allowed them to use certain medical services for free in Atrak Clinic, a gastroenterology clinic established by the research team. Salient results of the GCS are routinely shared with the Ministry of Health, university officials, local physicians and the public.

## RESULTS

The mean age (SD) of participants at baseline was 52.1 (8.9) years. Fifty-eight per cent were women, 74.4% were Turkmen, 79.9% lived in rural areas, 87.8% were married and 70.2% had no formal education (online supplementary appendix table S1). Of the 50 045 cohort participants, 47 547 (95.0%) were younger than 70 years old, potentially at risk of premature death.

The follow-up duration up to age 70 years was 444 168 person-years (median 10, IQR: 8.9–11.1, and maximum 14.2 years). During the follow-up, 6347 of the cohort members died and 439 were lost to follow-up. Of the reported deaths, 445 (7.0%) occurred before age 50, 1937 (30.5%) before 60 and 4018 (63.3%) before the of age 70. The probability of reaching the age of 70, conditional on surviving to age 40 years, was 79.2%.

The ICD-10 codes were determined for 5550 (87.4%) of all cohort deaths. A final cause of death determination has not yet been completed for the remaining, more recent, deaths (n=797). Table 1 shows the top 10 causes of death based on age categories. IHD was the leading cause of death in all age categories. Stroke was the second cause of death except for deaths that occurred younger than 50, for which road injury was the second cause of death. With rising age, the proportion of deaths due to stroke increased while deaths due to road injury decreased. Of 169 premature deaths of road injury, 119 deaths occurred

in men and 50 in women. The general classification of death causes is shown in online supplementary table S2.

Overall, communicable, maternal, prenatal and nutritional (CMPN) group of diseases accounted for 168 (4.7%), non-communicable diseases (NCDs) for 3174 (88.8%) and injuries for 234 (6.5%) of premature deaths. In these three groups of disease, 50.0%, 64.4% and 81.8% of deaths occurred before age 70, respectively.

Table 2 shows the HRs for the association between demographic and lifestyle risk factors and premature mortality. The risk of premature death was higher in men and unmarried participants, and in those with history of hypertension, diabetes, tobacco/nass use and opium consumption. The strongest associations were found for diabetes, opium consumption and hypertension, respectively. Risk of death increased 139% in diabetic participants (HR: 2.39, 95% CI 2.15 to 2.65). Higher wealth, physical activity, education and consumption of vegetables and fruits were protective factors. Our results did not change materially after exclusion of deaths occurred in the first year of follow-up (online supplementary tables S3, S4), and after stratification by sex and age (online supplementary tables S5, S6)

The PAF for eight significant modifiable risk factors is shown in table 3. Wealth score had the highest PAF. The role of tobacco/nass use and opium consumption was more important among men, while the role of diabetes and hypertension was more pronounced in women. Collectively, these eight risk factors accounted for 76% of the PAF in men and 69% in women.

The total burden of premature mortality in the GCS was 107 417 (SE=393) SEYLL. Among the 5550 deaths for which ICD-codes were determined, over 60% of the burden was due to only five causes: IHD, stroke, road injury, oesophageal cancer and stomach cancer (table 4).

## DISCUSSION

In our study, among 50 045 participants over 40 years old at the baseline, 63% of all deaths were premature, including 50% of CMPN, 64% of NCD and 82% of injury deaths. IHD and stroke were the leading causes of premature mortality and accounted for almost 50% of all causes of premature deaths and their burden based on SEYLL. Other significant causes of premature mortality in this study were road injuries, stomach cancer and oesophageal cancer. Higher wealth, physical activity, education and consumption of fruits and vegetables were protective factors. Conversely, hypertension, diabetes, opium and tobacco use increased risk. These factors are potentially modifiable, and together accounted for 69% and 76% of PAF in women and men, respectively.

The premature death rate in our study participants was very similar to the average premature death rate in all of Iran. Forty-year-old people in this cohort had a 79% probability of reaching the age of 70 years. The survival probabilities of the entire Iranian population of comparable age were 75% and 80% in 2005 and 2015, respectively.[17]

**Table 1** The top 10 causes of death (Global Health Estimation, WHO Methods) in the Golestan Cohort Study*

| | 40–49years n=432 | 50–59years n=1322 | 60–69years n=1822 | All premature deaths (<70) n=3576 | ≥70years n=1974 | All ages n=5550 |
|---|---|---|---|---|---|---|
| 1 | IHD 151 (34.95) | IHD 423 (32.00) | IHD 638 (35.02) | IHD 1212 (33.89) | IHD 571 (28.93) | IHD 1783 (32.13) |
| 2 | Road injury 53 (12.27) | Stroke 170 (12.86) | Stroke 289 (15.86) | Stroke 502 (14.04) | Stroke 384 (19.45) | Stroke 886 (15.96) |
| 3 | Stroke 43 (9.95) | Road injury 65 (4.92) | Stomach cancer 96 (5.27) | Road injury 169 (4.73) | Alzheimer† 94 (4.76) | Stomach cancer 255 (4.59) |
| 4 | Oesophagus cancer 19 (4.40) | Stomach cancer 63 (4.77) | Oesophagus cancer 92 (5.05) | Stomach cancer 165 (4.61) | COPD 93 (4.71) | Oesophagus cancer 253 (4.56) |
| 5 | Cirrhosis 12 (2.78) | Oesophagus cancer 52 (3.93) | COPD 73 (4.01) | Oesophagus cancer 163 (4.56) | Oesophagus cancer 90 (4.56); Stomach cancer 90 (4.56) | COPD 211 (3.80) |
| 6 | Breast cancer 10 (2.31) | COPD 40 (3.03) | Road injury 51 (2.80) | COPD 118 (3.30) | LRT infection 60 (3.04) | Road injury 203 (3.66) |
| 7 | Kidney diseases 9 (2.08) | Kidney diseases 34 (2.57) | Kidney diseases 42 (2.31) | Kidney diseases 85 (2.38) | Kidney diseases 56 (2.84) | Kidney diseases 141 (2.54) |
| 8 | Liver cancer 8 (1.85) | Colorectal cancers‡ 27 (2.04) | Lung cancers§ 38 (2.09) | Lung cancers§ 67 (1.87); Cirrhosis 67 (1.87) | Road injury 34 (1.72) | Alzheimer† 134 (2.41) |
| 9 | Brain cancers¶ 7 (1.62) | Pancreas cancer 26 (1.97) | Pancreas cancer 33 (1.81) | Pancreas cancer 55 (1.53) | Pancreas cancer 29 (1.47) | LRT infections 106 (1.91) |
| 10 | Diabetes mellitus 6 (1.39); Stomach cancer 6 (1.39); Ovary cancer 6 (1.39) | Cirrhosis 25 (1.89); Lung cancers§ 25 (1.89) | Colorectal cancers‡ 30 (1.65) | Colorectal cancers‡ 49 (1.37) | Lung cancers§ 24 (1.22) | Lung cancers§ 91 (1.64) |

*After redistribution of the garbage codes (489 cardiovascular disease cases: I10, I26.9, I46, I47.2, I49.0 and I50; 6 cancer cases: C76, C80 and C97; and 9 external cause cases: Y10–Y34 and Y87.2); and 335 cases of symptoms, signs and ill-defined conditions (R00–R94, R96–R99). Excluded: 797 undetermined mortality causes.
COPD, chronic obstructive respiratory diseases; IHD, ischaemic heart disease; LRT, lower respiratory tract.
†Alzheimer and other dementias.
‡Colon and rectum cancers.
§Trachea, bronchus, lung cancers.
¶Brain and nervous system cancers.

**Table 2** HR for associations between demographic and lifestyle risk factors and premature mortality in the Golestan Cohort Study*

| Variable | Prevalence (w/o premature death) n=40 972 | Prevalence (premature death) n=3390 | HR (95% CI) Crude | HR (95% CI) Adjusted 1** | HR (95% CI) Adjusted 2** |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| Women (reference) | 24 307 (59.33) | 1544 (45.55) | 1 | | 1 |
| Men | 16 665 (40.67) | 1846 (54.45) | 1.74 (1.63–1.87) | – | 1.37 (1.24–1.51) |
| **Ethnicity** | | | | | |
| Turkmen (reference) | 30 823 (75.23) | 2614 (77.11) | 1 | 1 | 1 |
| Non-Turkmen | 10 149 (24.77) | 776 (22.89) | 0.97 (0.90–1.06) | 0.96 (0.89–1.04) | 1.00 (0.92–1.09) |
| **Marital status** | | | | | |
| Married (reference) | 36 616 (89.37) | 2928 (86.37) | 1 | 1 | 1 |
| Other | 4356 (10.63) | 462 (13.63) | 1.50 (1.36–1.65) | 1.37 (1.23–1.52) | 1.17 (1.05–1.31) |
| **Residence** | | | | | |
| Urban (reference) | 8058 (19.67) | 597 (17.61) | 1 | 1 | 1 |
| Rural | 32 914 (80.33) | 2793 (82.39) | 1.24 (1.14–1.36) | 1.27 (1.16–1.38) | 0.91 (0.82–1.01) |
| **Education** | | | | | |
| No formal schooling (reference) | 28 009 (68.36) | 2523 (74.42) | 1 | 1 | 1 |
| Primary education | 7328 (17.89) | 505 (14.90) | 0.74 (0.67–0.81) | 0.73 (0.66–0.81) | 0.85 (0.77–0.95) |
| Middle school or higher | 5635 (13.75) | 362 (10.68) | 0.65 (0.58–0.73) | 0.65 (0.58–0.73) | 0.84 (0.73–0.97) |
| **Wealth score** | | | | | |
| First quintile (reference) | 8391 (20.48) | 986 (29.09) | 1 | 1 | 1 |
| Second quintile | 7508 (18.32) | 741 (21.86) | 0.84 (0.77–0.93) | 0.86 (0.78–0.94) | 0.91 (0.82–1.00) |
| Third quintile | 9007 (21.98) | 651 (19.20) | 0.63 (0.57–0.70) | 0.64 (0.58–0.71) | 0.70 (0.63–0.77) |
| Fourth quintile | 7858 (19.18) | 560 (16.52) | 0.62 (0.56–0.69) | 0.63 (0.57–0.70) | 0.72 (0.64–0.80) |
| Fifth quintile | 8208 (20.03) | 452 (13.33) | 0.46 (0.41–0.52) | 0.48 (0.43–0.54) | 0.57 (0.50–0.65) |
| **Alcohol use** | | | | | |
| Never (reference) | 39 685 (96.86) | 3206 (94.57) | 1 | 1 | 1 |
| Ever used | 1287 (3.14) | 184 (5.43) | 1.65 (1.42–1.91) | 1.20 (1.03–1.40) | 1.04 (0.89–1.22) |
| **Tobacco smoking/nass chewing** | | | | | |
| Never (reference) | 32 887 (80.28) | 2182 (64.37) | 1 | 1 | 1 |
| Ever used | 8078 (19.72) | 1208 (35.63) | 2.25 (2.09–2.41) | 1.84 (1.69–2.00) | 1.38 (1.26–1.53) |
| **Opium consumption** | | | | | |
| Never (reference) | 34 840 (85.03) | 2320 (68.44) | 1 | 1 | 1 |
| Ever used | 6132 (14.97) | 1070 (31.56) | 2.60 (2.42–2.79) | 2.18 (2.02–2.35) | 1.69 (1.55–1.85) |
| **Physical activity (MET min/week)** | | | | | |
| First tertile (Reference) | 12 797 (31.31) | 1567 (46.32) | 1 | 1 | 1 |
| Second tertile | 13 158 (32.19) | 1039 (30.71) | 0.62 (0.58–0.67) | 0.79 (0.72–0.86) | 0.81 (0.75–0.89) |
| Third tertile | 14 918 (36.50) | 777 (22.97) | 0.40 (0.37–0.43) | 0.63 (0.57–0.69) | 0.67 (0.61–0.74) |
| **Body mass index (kg/m$^2$)** | | | | | |
| <18.5 | 1792 (4.37) | 285 (8.41) | 1.76 (1.55–2.01) | 1.67 (1.47–1.89) | 1.40 (1.22–1.59) |
| 18.5–24.9 (Reference) | 14 506 (35.41) | 1315 (38.80) | 1 | 1 | 1 |
| 25–29.9 | 14 010 (34.20) | 1064 (31.40) | 0.82 (0.76–0.89) | 0.90 (0.83–0.98) | 0.96 (0.88–1.04) |
| ≥30 | 10 660 (26.02) | 725 (21.39) | 0.72 (0.66–0.79) | 0.90 (0.82–0.99) | 0.92 (0.83–1.01) |

Continued

**Table 2** Continued

| Variable | Prevalence (w/o premature death) n=40 972 | Prevalence (premature death) n=3390 | HR (95% CI) Crude | HR (95% CI) Adjusted 1** | HR (95% CI) Adjusted 2** |
|---|---|---|---|---|---|
| Vegetable/Fruit consumption (g/day) | | | | | |
| First tertile (reference) | 13 099 (32.53) | 1206 (36.42) | 1 | 1 | 1 |
| Second tertile | 13 546 (33.64) | 1092 (32.98) | 0.86 (0.79–0.93) | 0.87 (0.80–0.95) | 0.95 (0.88–1.04) |
| Third tertile | 13 627 (33.84) | 1013 (30.59) | 0.75 (0.69–0.82) | 0.74 (0.68–0.80) | 0.87 (0.80–0.95) |
| High blood pressure | | | | | |
| No (reference) | 25 177 (61.45) | 1648 (48.61) | 1 | 1 | 1 |
| Yes | 15 795 (38.55) | 1742 (51.39) | 1.78 (1.66–1.90) | 1.47 (1.37–1.58) | 1.50 (1.39–1.61) |
| Diabetes mellitus | | | | | |
| No (reference) | 38 746 (94.57) | 2956 (87.20) | 1 | 1 | 1 |
| Yes | 2226 (5.43) | 434 (12.80) | 2.55 (2.31–2.82) | 2.34 (2.11–2.59) | 2.39 (2.15–2.65) |

*Exclude: age ≥70 years at baseline and history of ischaemic heart disease, stroke or cancer.
**Adjusted 1: Adjusted for sex and age at enrolment; Adjusted 2: Adjusted for age at enrolment and all variables listed.
MET, metabolic equivalent of task.

Globally, in 2015, 54% of all deaths were premature, including 79% of CMPN, 43% of NCD and 82% of injury deaths. These estimates for high/low-income countries are substantially different: 27.5% and 80% for all deaths, 22% and 91% for CMPN, 26% and 62% for NCD and 58% and 91% for injury, respectively.[18] In 2015, the premature NCD death rate for Iran was estimated to be 35%. For comparison, the percentage of all NCD deaths occurring under the age of 70 ranged from 17% to 18% in Italy, Japan, Sweden and Greece to more than 75% in Angola, Sierra Leone and the United Arab Emirates.[19]

Our findings are consistent with those of the GBD study, which showed IHD, stroke and road injuries are the three leading causes of premature deaths in Iran,[20] as well as upper-middle-income countries.[10] The GBD study, using years of life lost (YLLs) as a measure of premature mortality, showed the causes that contributed the most YLLs varied worldwide. For example, IHD and stroke were the leading causes for both sexes for 123 countries, including in China (stroke) and India (IHD); but the leading causes were interpersonal violence or lower respiratory infection in some locations in Latin America and the Caribbean; HIV/AIDS, malaria, diarrhoeal diseases, or lower respiratory infections across much of sub-Saharan Africa; road injury in Ecuador, Qatar, Oman and United Arab Emirates; diabetes in Jamaica, Mauritius and Fiji; neonatal preterm birth complications in Palestine; conflict in Syria, Yemen and Afghanistan; and self-harm in Greenland and South Korea.[10]

**Table 3** Population attributable fraction (PAF) of significant modifiable risk factors (mutually adjusted) for premature mortality in the Golestan Cohort Study

| Variable* | PAF (all) | PAF (women) | PAF (men) |
|---|---|---|---|
| Education | 0.13 (0.01–0.23) | 0.15 (0.03–0.26) | 0.11 (0.00–0.20) |
| Wealth score | 0.28 (0.20–0.35) | 0.28 (0.21–0.35) | 0.28 (0.20–0.34) |
| Tobacco/nass use | 0.11 (0.08–0.14) | 0.02 (0.02–0.03) | 0.17 (0.12–0.22) |
| Opium consumption | 0.14 (0.12–0.17) | 0.07 (0.06–0.09) | 0.19 (0.16–0.22) |
| Physical activity | 0.22 (0.17–0.28) | 0.18 (0.12–0.23) | 0.26 (0.20–0.31) |
| Vegetable and fruit consumption (g/day) | 0.08 (0.02–0.13) | 0.08 (0.03–0.14) | 0.07 (0.02–0.12) |
| High blood pressure | 0.19 (0.15–0.22) | 0.21 (0.17–0.24) | 0.17 (0.14–0.20) |
| Diabetes mellitus | 0.08 (0.07–0.10) | 0.11 (0.09–0.12) | 0.06 (0.05–0.07) |
| All socioeconomic status† | 0.37 (0.28–0.45) | 0.39 (0.29–0.47) | 0.35 (0.26–0.43) |
| All individual risk factors‡ | 0.58 (0.53–0.62) | 0.51 (0.45–0.55) | 0.64 (0.59–0.68) |
| All | 0.73 (0.68–0.77) | 0.69 (0.64–0.74) | 0.76 (0.72–0.80) |

*Variable (reference category): education (middle school or higher), wealth score (fifth quintile), tobacco/nass use (never), opium consumption (never), physical activity (third tertile), vegetable and fruit consumption (third tertile), high blood pressure (no), diabetes mellitus (no).
†Education and wealth score.
‡Tobacco/nass use, opium consumption, physical activity, vegetable/fruit consumption, high blood pressure and diabetes mellitus.

**Table 4** Standard expected years of life lost (SEYLL) due to premature death in the Golestan Cohort Study

| Causes of premature death | SEYLL (SE) | % |
|---|---|---|
| Ischaemic heart diseases | 32 466 (218) | 33.74 |
| Stroke | 13 004 (135) | 13.52 |
| Road injury | 5160 (89) | 5.36 |
| Oesophageal cancer | 4301 (78) | 4.47 |
| Stomach cancer | 4220 (71) | 4.39 |
| Chronic obstructive pulmonary diseases | 2972 (59) | 3.09 |
| Kidney diseases | 2295 (58) | 2.39 |
| Cirrhosis of the liver | 1866 (55) | 1.94 |
| Trachea, bronchus, lung cancers | 1711 (47) | 1.78 |
| Pancreas cancer | 1483 (42) | 1.54 |
| All* | 96 219 (376) | 100 |

*Exclude 797 non-determined ICD-codes.

Out of the 17 million premature deaths due to NCDs, 82% are in LMICs, of which 37% are caused by cardiovascular diseases.[21] IHD and stroke have remained the leading causes of death globally in the last 15 years.[22] In our study, about 90% of deaths were due to NCDs; of this, IHD and stroke accounted for 38% and 16% of deaths, respectively. According to WHO reports, between 2005 and 2015, at these ages, NCDs cause almost 80%–82% of all deaths globally; of this, 21.5% were IHD and 16% were stroke.[18] In our study, death due to IHD played the most important role in premature NCD death. Also, we found that stomach cancer accounted for 5.2% and oesophageal cancer for 5.1% of NCD deaths, whereas these figures globally were 2.5%–3% and 1.6%–2%, respectively.[18] Our results are in line with other studies that have shown a high prevalence of oesophageal cancer[23] and gastric cancer[24] in the northeast of Iran.

In 2013, Iran was the eighth highest country, among 186 countries, for road traffic mortality rate (32.1 per 100 000 population).[25] Around 1.25 million people died from road traffic injuries, and up to 50 million people sustained non-fatal injuries as a result of road traffic accidents.[25] In our study, 72.2% of all injuries were due to road injuries, compared with a global average of 30%.[18] This result is consistent with a report by WHO, which showed that 58% of all injuries in Iran were due to road traffic injuries.[26] Similar to our results, other studies in Iran showed deaths due to road accident were higher in men versus women, also death rates due to accidents in adults decreased with age.[27 28]

Our results showed the strong effects of socioeconomic factors on premature mortality. Lack of wealth and education accounted for 37% of all premature deaths, stronger than any other individual risk factor. A study of over 1.7 million participants from seven countries found that the independent association between socioeconomic status and premature mortality is comparable

in strength and consistency to known risk factors such as hypertension, diabetes and smoking.[29] The participants of our cohort were mostly from villages in a remote area of Iran, and 70% were entirely illiterate. This may be an important reason for observing high premature rates in this population.

We found a significant HR for premature mortality associated with the use of opium. Our findings are consistent with previous findings from some studies that have shown the association of long-term opium use with IHD[30–32] and several cancers.[31 32] In fact, the very common consumption of opium by nearly 17% of the cohort members may be another reason for high rates of premature mortality in this population.

Overall, our results showed that the eight potentially modifiable risk factors are collectively associated with about 70% of the PAF of premature deaths. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study[33] showed that the PAF for premature mortality for smoking, diet, overweight or obesity, hypertension, physical inactivity and alcohol intake was 57%. There is evidence of regional variation in the importance of risk factors, which are related to variations in the magnitude of association and differences in the prevalence of risk factors among regions.[34 35] For example, the magnitude of smoking in Golestan Province, one of the most prevalent areas for oesophagus cancer worldwide, is almost half of that reported from western countries.[36] On the other hand, whereas in the EPIC cohort study in Western Europe, high alcohol intake (>2 drink/day) was reported in 23% of participants and was a significant risk factor for premature death,[33] in our study, reported alcohol consumption was not associated with premature death. This may be because a small proportion of the participants (only 3.45%) used alcohol, and they used alcohol in amounts that are quite low compared with consumption averages in Western countries.

In recent decades, the Iranian policymakers have started to pay attention to the burden of different diseases. Yet more needs to be done. In Golestan Province, socioeconomic factors—such as education, safe drinking water, roads, access to electricity and natural gas for heating and cooking—have improved dramatically.[37 38] Although there has been some decline in road traffic mortality rates because of police enforcement activities and promotion of the prehospital emergency system, Iran still has one of the highest rates in the world.[20] Despite several interventions to reduce harm from opium use, the burden is still rising in the country.[20] Evidence is mounting that opium is a carcinogen[39] and increases mortality.[31] If an international body, such as the International Agency for Research on Cancer/WHO recognises opium as a carcinogen, public awareness of opium's harmful effects will increase. Salt intake in the Iranian population is about two times the recommended level in Iran and it most likely plays an important role in the high prevalence of hypertension and cardiovascular premature mortality.[40 41] A very

important intervention that has been recently started is decreasing intake of salt, especially in bread which is the main food item in Iran. Also, taxation of cigarette and other tobacco products has recently been established by the Iranian Parliament.

To effectively prevent premature mortality, ongoing national efforts need to be strengthened and supplemented with effective innovative actions. Some of these actions include: using premature death as a performance measure at the national and provincial levels and setting appropriate targets, which offers policymakers a major opportunity for securing health system improvement and accountability[42]; use of fixed-dose combination (poly-pill) therapy for primary and secondary prevention of cardiovascular diseases,[43 44] based on simple and practical guidelines that involve non-physician health workers; infusing the culture with taking care of chronic diseases in the primary healthcare system; comprehensive research programmes about the health effects of opium use and opium control policies; and focusing on improving socio-economic status as a national health strategy, alongside reduction of established risk factors.

This study has several strengths including its prospective design, the availability of data to adjust for confounders and the extremely low loss to follow-up rate. One of the most important strengths of our study is the accuracy of the follow-up and cause of death ascertainment. Our principal limitation is that the participants in the GCS are mainly representative of the rural Iranian population, and not the urban dwellers who presently make up 70% of the total Iranian population and who may have a different distribution of demographic and risk factors. Also, we had no data on people younger than 40 years old. And finally, we did not have data on some known risk factors such as dyslipidaemia and psychological factors.

## Conclusion
The premature mortality rate of the GCS population is comparable with the average rate of Iran. IHD, stroke, road injury and stomach and oesophagus cancers are the leading causes of premature mortality. Substantial improvements in premature mortality rates should be possible by reducing the consumption of opium and tobacco, increasing physical activity, increasing consumption of fruits and vegetables and controlling high blood pressure and diabetes. Also, the growing wealth and education in this area will likely lower premature mortality. Further research, wide dissemination of gained knowledge and supplementing the activities of the health infrastructure will all be important to increasing life expectancy.

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