Determinants of Gastroesophageal Reflux Disease, Including Hookah Smoking and Opium Use– A Cross-Sectional Analysis of 50,000 Individuals

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a common cause of discomfort and morbidity worldwide. However, information on determinants of GERD from large-scale studies in low- to medium-income countries is limited. We investigated the factors associated with different measures of GERD symptoms, including frequency, patient-perceived severity, and onset time.

Methods: We performed a cross-sectional analysis of the baseline data from a population-based cohort study of ~50,000 individuals in in Golestan Province, Iran. GERD symptoms in this study included regurgitation and/or heartburn.

Results: Approximately 20% of participants reported at least weekly symptoms. Daily symptoms were less commonly reported by men, those of Turkmen ethnicity, and nass chewers. On the other hand, age, body mass index, alcohol drinking, cigarette smoking, opium use, lower socioeconomic status, and lower physical activity were associated with daily symptoms. Most of these factors showed similar associations with severe symptoms. Women with higher BMI and waist to hip ratio were more likely to report frequent and severe GERD symptoms. Hookah smoking (OR 1.34, 95% CI 1.02–1.75) and opium use (OR 1.70, 95% CI 1.55–1.87) were associated with severe symptoms, whereas nass chewing had an inverse association (OR 0.87, 95% CI 0.76–0.99). After exclusion of cigarette smokers, hookah smoking was still positively associated and nass chewing was inversely associated with GERD symptoms (all frequencies combined).

Conclusion: GERD is common in this population. The associations of hookah and opium use and inverse association of nass use with GERD symptoms are reported for the first time. Further studies are required to investigate the nature of these associations. Other determinants of GERD were mostly comparable to those reported elsewhere.

Introduction

Gastroesophageal reflux disease (GERD) has increased in Europe and the United States over the past decades [1–3]. GERD symptoms are among the most common gastrointestinal symptoms in those regions [4], with prevalence rates of 10–25% reported from population-based studies [2,5–8]. Several population-based studies from Iran, in West Asia, have reported prevalence rates similar to those in Western countries [9–11]. The incidence of GERD is increasing in Iran [12], and currently it is the most common outpatient gastrointestinal disease encountered there [13].

Determinants of GERD in the general population have been examined in a number of studies [14–24], but some potential determinants have shown conflicting results and are yet to be established. Also, data from low- to medium income countries are limited, as only a few of the population-based studies on determinants of GERD have been conducted in those countries.
Exposure Measurements

Study Population

The Golestan Cohort Study was primarily designed to investigate risk factors for upper gastrointestinal cancers. The design of this cohort has been described elsewhere [31]. Briefly, the Golestan Cohort Study is a prospective population-based cohort of 40–75 years old individuals in eastern parts of Golestan Province, Iran. Urban inhabitants in the specified age range were selected randomly from Gonbad City, the main urban area in eastern Golestan, by systematic clustering based on the household number. In rural areas, all residents of 326 villages in the study catchment area in the specified age range were invited to participate. A total of 50,045 adults without history of upper gastrointestinal cancers were enrolled in the study between January 2004 and June 2008.

Ethics Statement

Written consent was obtained from all participants. The conduct of the Golestan Cohort Study, including the consent procedure, was approved by the Institutional Review Boards of the Digestive Disease Research Center of Tehran University of Medical Sciences, the US National Cancer Institute, and the International Agency for Research on Cancer.

Methods

Outcome Measurements

As baseline, trained nurses and physicians conducted face-to-face interviews using structured questionnaires to collect data on GERD, potential determinants of GERD, and confounding factors. Weight, height, and waist and hip circumferences were measured by trained research staff. Body mass index (BMI) was calculated by dividing weight (kg) by the squared value of height (m).

Individuals who had ever used alcohol, cigarettes, hookah (also known as water-pipe, shisha, nargileh, and qalyan), nass (a mixture of tobacco, lime, and ash), or opium at least once a week for a period of 6 months or more were considered as users of the respective substance. In hookah smoking, tobacco is placed at the top of the hookah inside a bowl, which is separated with a perforated metal foil from burning coal placed on top [32]. Hookah smoke passes through a water basin and cools down, and then it is inhaled using a hose attached to the upper part of the water basin (Figure 1). Some people may believe that hookah smoking is harmless, assuming that its harmful compounds are filtered in the water [32]. However, there are several biomarker studies in humans that have shown appreciable amounts of tobacco related-compounds following hookah smoking [33–35], refuting the harmlessness of hookah. Although cigarette and hookah are both tobacco smoking products, we considered them as separate entities because patterns of use of these products might be different, and there have been few published studies on the association between hookah smoking and GERD. We calculated cumulative amount of cigarette use (as pack-years) using data on duration and quantity of use. In accord with our earlier publications [36], we calculated a composite score for wealth by applying multiple correspondence analysis to appliance ownership data (including personal car, motorbike, black and white TV, color TV, refrigerator, freezer, vacuum cleaner, and washing machine). We only considered occupational physical activity because recreational physical activity is uncommon in the study population.

Figure 1. Diagram of a hookah. Source: Wikipedia (http://en.wikipedia.org/wiki/File:Hookah-lookthrough.svg), after modification. doi:10.1371/journal.pone.0089256.g001

The number of individuals with missing values in all GERD variables (<0.1% of the cohort participants) and in individual

Statistical Analysis

The number of individuals with missing values in all GERD variables (<0.1% of the cohort participants) and in individual
GERD variables (<0.7% for each of the variables) was small, so the first group was excluded from the current analyses, and the second group was excluded from the analyses of the respective variable. Numbers and percentages were calculated and presented for categorical variables, as well as means and standard deviations for continuous variables. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association of sociodemographic and lifestyle factors and anthropometric indices with frequency and severity of GERD symptoms were calculated using multinomial logistic regression models. In the analyses of frequency, <weekly, weekly, and daily symptoms, and in the analyses of severity, mild, moderate, and severe symptoms, as separate categories were compared with never having GERD symptoms. P values for trend were obtained from the same multinomial logistic regression models by assigning consecutive numbers to categories within each categorical variable.

Multivariate models were adjusted for several potential confounding factors as indicated in the table footnotes. As participants in our study could have shifted from using cigarettes to hookah or nass following the development of GERD, we also investigated the associations between hookah and nass use and GERD among never-cigarette smokers. All statistical analyses were performed using Stata statistical software version 11 (Stata Corporation, College Station, Texas, USA). All reported P values are two-sided, and P<0.05 was considered to be statistically significant.

Results

Data on reflux were available for 50,001 individuals. Approximately 12% of participants reported daily and 11% reported severe GERD symptoms; 16% of participants reported GERD symptoms with the first episode happening >10 years before the interview (Table 1).

| Table 1. GERD symptoms in 50,001 individuals with data on GERD in the Golestan Cohort Study. |
|-----------------------------------------------|
| **GERD symptoms** | **Number (%)** |
| Symptom frequency | |
| Never | 19,560 (39.12) |
| <Weekly | 20,471 (40.94) |
| Weekly | 4029 (8.06) |
| Daily | 5915 (11.83) |
| Missing | 26 (0.05) |
| Symptom severity | |
| Mild | 4449 (8.90) |
| Moderate | 20,315 (40.63) |
| Severe | 5663 (11.33) |
| Missing | 16 (0.03) |
| Symptom start | |
| <1 year ago | 5326 (10.65) |
| 1–5 years ago | 12,534 (25.07) |
| 6–10 years ago | 4444 (8.89) |
| >10 years ago | 7895 (15.79) |
| Missing | 304 (0.61) |

GERD, gastroesophageal reflux disease. doi:10.1371/journal.pone.0089256.t001

Daily GERD symptoms had inverse associations with being a male (OR 0.36, 95% CI 0.33–0.39) or of Turkmen ethnicity (OR 0.66, 95% CI 0.61–0.70), formal education (P<0.01), wealth score (P<0.001), regular non-intensive physical activity (OR 0.90, 95% CI 0.83–0.98), and nass chewing (OR 0.86, 95% CI 0.75–0.90) (Table 2). On the other hand, daily symptoms were positively associated with older age (7% increase in risk per 10-year increase in age), higher BMI (P<0.001), alcohol drinking (OR 1.36, 95% CI 1.13–1.64), cigarette smoking (OR 1.43, 95% CI 1.23–1.67 for smoking ≥20 pack-years), and opium use (OR 1.82, 95% CI 1.67–1.99). The association between age and daily symptoms was linear (data not shown).

Being a male, having formal education or higher wealth scores, and chewing nass were inversely associated with reporting severe symptoms (Table 2). On the other hand, severe symptoms were positively associated with BMI, alcohol drinking, or cigarette, hookah, or opium use. In never cigarette smokers (Table 3), hookah smoking was positively associated (OR 1.26, 95% CI 1.01–1.56) and nass chewing was inversely associated (OR 0.85, 95% CI 0.76–0.94) with GERD symptoms (any frequency or severity combined).

The associations with <weekly and weekly symptoms (Table S2) or mild to moderate symptoms (Table S3) in most cases were similar to those of daily or severe symptoms, respectively. However, those with education levels of above high school were more likely to report <weekly or mild to moderate symptoms than those with no formal education.

The associations of cigarette smoking and opium use and inverse association of nass use were stronger with longer duration of the time period between the onset of GERD symptoms and baseline interview (Table S4). As expected, age was also associated with this duration.

In women, both higher BMI and higher waist to hip ratio were associated with daily and severe symptoms (Table 4). The association between waist to hip ratio and reflux symptoms persisted after adjustments for BMI, suggesting an independent role of central obesity in GERD in women. Waist to hip ratio showed a trend of association with daily GERD symptoms in men (P for trend 0.04), but this association attenuated after adjustment for BMI. None of the categories of BMI or waist to hip ratio had statistically significant associations with GERD symptoms in men. The patterns of association between waist circumference and GERD symptoms in men and women were comparable with those of waist to hip ratio and GERD (data not shown).

Discussion

In this study, approximately 20% of participants had weekly or more frequent GERD symptoms. Several sociodemographic and lifestyle factors were associated with GERD symptoms. Many of these associations have been reported in other populations. We found an association between hookah or opium use and GERD symptoms and an inverse association between nass use and the symptoms for the first time. To the best of our knowledge, this is one of the largest studies on determinants of GERD symptoms worldwide and by far the largest study in low- and medium-income countries [37].

Alcohol, Tobacco, and Opium Use

Associations of alcohol drinking and cigarette smoking with GERD symptoms and esophagitis have previously been reported (generally with OR <2), although these associations have not been shown in all studies [28,38,39]. We found modest but statistically significant associations between alcohol or cigarette use and
Table 2. Association of several demographic and lifestyle factors with daily and severe GERD symptoms.

| Variables | All (N=50,001) | No symptoms (N=19,560) | Daily symptoms (N=5915) | Severe symptoms (N=5663) |
|-----------|----------------|------------------------|------------------------|------------------------|
|           | N (%) | (%) | N (%) | (%) | OR (95% CI) | N (%) | (%) | OR (95% CI) |
| Total     | 50,001 (100) | 19,560 (100) | 5915 (100) | – | – |
| Age *     | 52.1 (9.0) | 52.1 (9.0) | 52.7 (9.2) | 1.07 (1.04–1.11) | 52.2 (8.9) | 1.01 (0.98–1.05) |
| Sex       |          |          |          |          |          |          |          |
| Women     | 28,785 (57.57) | 9947 (50.85) | 4241 (71.70) | Referent |
| Men       | 21,216 (42.43) | 9613 (49.15) | 1674 (28.30) | 0.36 (0.33–0.39) | 1682 (29.70) | 0.36 (0.33–0.39) |
| Ethnicity |          |          |          |          |          |          |          |
| Non-Turkmen | 12,786 (25.57) | 4913 (25.12) | 2001 (33.83) | Referent |
| Turkmen   | 37,215 (74.43) | 14,647 (74.88) | 3914 (66.17) | 0.66 (0.61–0.70) | 4186 (73.92) | 0.98 (0.91–1.06) |
| Residence |          |          |          |          |          |          |          |
| Rural     | 39,366 (78.73) | 15,962 (81.61) | 4802 (81.18) | Referent |
| Urban     | 10,634 (21.27) | 3598 (18.39) | 1113 (18.82) | 1.01 (0.93–1.11) | 1145 (20.22) | 1.13 (1.04–1.23) |
| Education |          |          |          |          |          |          |          |
| No school | 35,089 (70.18) | 13,319 (68.09) | 4672 (78.99) | Referent |
| 1–8th grade | 10,698 (21.40) | 4479 (22.90) | 985 (16.65) | 0.92 (0.84–1.00) | 919 (16.23) | 0.84 (0.77–0.93) |
| High School | 3150 (6.30) | 1342 (6.86) | 197 (3.33) | 0.78 (0.66–0.93) | 220 (3.88) | 0.73 (0.62–0.87) |
| Higher    | 1064 (2.13) | 420 (2.15) | 61 (1.03) | 0.92 (0.69–1.23) | 80 (1.41) | 0.99 (0.76–1.29) |
| Wealth score |          |          |          |          |          |          |          |
| Quintile 1-lowest | 13,455 (26.91) | 5089 (26.02) | 1948 (32.93) | Referent |
| Quintile 2 | 8469 (16.94) | 3394 (17.35) | 976 (16.50) | 0.86 (0.79–0.94) | 936 (16.23) | 0.84 (0.77–0.93) |
| Quintile 3 | 9790 (19.58) | 3845 (19.66) | 1180 (19.95) | 0.90 (0.83–0.98) | 1111 (19.62) | 0.80 (0.73–0.87) |
| Quintile 4 | 8345 (16.69) | 3344 (17.10) | 933 (15.77) | 0.82 (0.75–0.90) | 801 (14.14) | 0.66 (0.60–0.73) |
| Quintile 5 | 9942 (19.88) | 3888 (19.88) | 878 (14.84) | 0.68 (0.61–0.75) | 927 (16.37) | 0.65 (0.59–0.72) |
| Body mass index |          |          |          |          |          |          |          |
| <18.5 kg/m² | 2410 (4.82) | 989 (5.06) | 324 (5.48) | 0.94 (0.81–1.07) | 298 (5.26) | 0.96 (0.83–1.11) |
| 18.5–24.9 | 17,914 (35.83) | 7452 (38.11) | 2083 (35.23) | Referent |
| 25–29.9 | 16,958 (33.92) | 6576 (33.63) | 1945 (32.89) | 1.11 (1.04–1.20) | 1840 (32.50) | 1.10 (1.02–1.18) |
| ≥30 | 12,710 (25.42) | 4539 (23.21) | 1561 (26.40) | 1.15 (1.06–1.25) | 1570 (27.33) | 1.21 (1.11–1.31) |
| Physical activity |          |          |          |          |          |          |          |
| Irregular non-intense | 30,619 (61.44) | 11,579 (59.36) | 4235 (71.85) | Referent |
| Regular non-intense | 13,524 (27.14) | 5411 (27.74) | 1294 (21.89) | 1.11 (1.04–1.20) | 1840 (32.50) | 1.10 (1.02–1.18) |
| Regular or irregular intense | 5691 (11.42) | 2518 (12.91) | 572 (9.71) | 0.94 (0.84–1.05) | 484 (8.57) | 0.97 (0.87–1.09) |
| Alcohol drinking |          |          |          |          |          |          |          |
| Never | 48,274 (96.55) | 18917 (96.71) | 5740 (97.04) | Referent |
| Ever | 1727 (3.45) | 643 (3.29) | 175 (2.96) | 1.36 (1.13–1.64) | 203 (3.58) | 1.53 (1.28–1.83) |
| Cigarette smoking |          |          |          |          |          |          |          |
| Never | 41,409 (82.84) | 16,186 (82.77) | 5066 (85.65) | Referent |
| 0.1–5 pack-years | 2764 (5.53) | 1118 (5.72) | 268 (4.53) | 1.20 (1.04–1.40) | 266 (4.70) | 1.24 (1.07–1.45) |
| 5.1–10 | 1261 (2.52) | 490 (2.51) | 122 (2.06) | 1.37 (1.10–1.70) | 126 (2.22) | 1.42 (1.15–1.76) |
| 10.1–20 | 1799 (3.60) | 692 (3.54) | 154 (2.60) | 1.21 (1.00–1.46) | 177 (3.13) | 1.40 (1.16–1.68) |
| ≥20 | 2753 (5.51) | 1069 (5.47) | 305 (5.16) | 1.43 (1.23–1.67) | 290 (5.12) | 1.42 (1.22–1.66) |
| Hookah smoking |          |          |          |          |          |          |          |
| Never | 49,445 (98.93) | 19,379 (99.12) | 5812 (98.31) | Referent |
| Ever | 533 (1.07) | 173 (0.88) | 100 (1.69) | 1.19 (0.92–1.54) | 82 (1.45) | 1.34 (1.02–1.75) |
GERD symptoms, with a significant exposure-response trend for the latter. Cigarette smoking usually starts in young adulthood, so temporal relationship between this habit and GERD is likely. Ever hookah smoking was also associated with GERD. The association between hookah smoking and GERD (any symptoms) persisted even after exclusion of cigarette smokers. Among never cigarette smokers, hookah smoking had statistically significant or borderline significant associations with mild and moderate GERD symptoms, but the association with severe symptoms was non-significant. The number of hookah smokers with severe symptoms was modest, which may be a reason for the above pattern. The magnitude of association was slightly stronger with mild to moderate symptoms. This may be because many hookah smokers in our study smoked hookah recreationally and with relatively low frequencies, so the symptoms associated with hookah smoking might be more likely to be mild to moderate. In fact, approximately half of the hookah smokers in this study had smoked less than 11 unit-years, which was equivalent to smoking hookah only once a day for 11 years (data not shown). Due to the modest number of hookah smokers in our study, we were not able to investigate the association by categories of use. The association between hookah use and GERD symptoms may be explainable by the comparability of the exposures in cigarette and hookah smoking [40]. Cigarette smoking increases frequency of gastro-esophageal reflux episodes by reducing the lower esophageal sphincter pressure [41] and reduces salivary secretion of bicarbonates [42]. However, some other mechanisms might also be involved in the association between hookah smoking and GERD symptoms. For example, mean puff volume in hookah smoking is generally over 500 mL [33,43,44], which is several times bigger than usual puff volumes in cigarette smoking (40–70 mL) [43]. Therefore, hookah smoking can induce strong negative intrathoracic pressure and increase thoraco-abdominal pressure gradient, which may increase gastroesophageal reflux [45].

The reasons for the inverse association of use and positive association of opium use with GERD symptoms in our study are unclear. Nass contains tobacco specific N-nitroso compounds and volatile N-nitrosamines, but the levels of these compounds in nass seem to be lower than in chewing tobacco products in Western countries [46,47]. Besides tobacco-related compounds, nass contains other compounds that are added during processing and have unknown effects on GERD symptoms. These ingredients increase the pH of nass to above 11 [46], whereas the pH of many other chewing tobacco products is between five to seven [46,48]. The alkaline pH of nass may outweigh the potential harmful effects of tobacco with regard to GERD symptoms and may play a role in the inverse association between nass and the symptoms. Furthermore, using nass may be associated with increased saliva secretion and frequent swallowing, and similar to chewing gum [49,50], it may reduce esophageal acid exposure. Morphine may reduce acid reflux in GERD patients [51], but the effects of opium on GERD symptoms are unclear. Opium also contains several compounds other than morphine, including other opiate alkaloids (such as papaverine), non-alkaloid compounds from opium poppy (such as meconic acid), and other compounds added or generated during processing or smoking, including heterocyclic and polycyclic aromatic hydrocarbons and primary aromatic amines [52–55], which may have various, but yet unknown, effects on GERD symptoms. Opium is usually ingested or smoked [56].

The associations of hookah, nass, and opium use with GERD may all be true, but all of them were modest and may in part be related to the effects of unknown confounding factors or residual confounding. Furthermore, opium use might be secondary to the development of GERD symptoms, as some patients in this population may use opium for alleviation of their symptoms [56]. On the other hand, as hookah and cigarette smoke have several common compounds, a casual association between hookah smoking and GERD symptoms is plausible, assuming that cigarette smoking is causally associated with GERD. To the best of our knowledge, this is the first report on the association of hookah, nass, and opium use with GERD symptoms, and these associations merit further scrutiny. The investigations on hookah smoking may be of particular interest, as the prevalence of hookah smoking has been increasing among young adults in many populations, including in some European and North American countries [32].

Sociodemographic Factors

Several, but not all [28,38,37], studies have reported a positive association between age and GERD, either as a linear association [26,58] or with a peak and a slight decrease afterwards [59–61]. The histological damage in the esophageal epithelium, including esophagitis, may be more common in the elderly than in younger individuals [62–64], but older people may report severe symptoms...
Table 3. Association of hookah and nass use with GERD symptoms in never cigarette smokers.

| Variables | Frequency | Severity | Mild | Moderate | Severe |
|-----------|-----------|----------|------|----------|--------|
| Hookah smoking | Never | 40,973 | Referent | 16,625 (99.11) | Referent | 3300 (98.42) | Referent | 4980 | Referent | 3562 (98.73) | Referent | 59 (1.23) | 1.19 (0.87–1.64) |
| | Ever | 150 | 0.89 | 1.22 (1.01–1.56) | 53 (1.58) | 1.32 (0.95–1.83) | 84 (1.66) | 1.22 (0.92–1.63) | 131 (0.81) | 1.41 (0.99–1.57) | 182 (1.08) | 1.25 (0.99–1.57) | 59 (1.23) | 1.19 (0.87–1.64) |
| Nass chewing | Never | 39,965 | Referent | 16,198 (96.52) | Referent | 3202 (95.77) | Referent | 4873 | Referent | 3468 (95.12) | Referent | 3468 (95.12) | Referent | 4626 | Referent |
| | Ever | 1751 | 0.85 | 1.01 (0.73–1.39) | 584 (3.48) | 0.84 (0.74–0.94) | 153 (4.56) | 1.01 (0.83–1.25) | 193 (3.81) | 0.79 (0.66–0.95) | 140 (3.81) | 0.79 (0.66–0.95) | 179 (3.71) | 0.85 (0.71–1.03) |

Controls are those with no heartburn or regurgitation. Numbers may not add up to the total numbers due to missing data. The odds ratios (95% confidence intervals) were adjusted for age, sex, ethnicity, place of residence, socioeconomic status which may influence GERD symptoms need not be a biologic factor, the factors that are associated with daily and severe GERD symptoms. As socioeconomic status and high school were the most commonly attained levels among anthropometric indices, education, weight, height, body mass index, physical activity, and consumption of alcohol and opium, and the other tobacco products shown in this table hookah or nass.

Determinants of GERD in Golestan, Iran

Anthropometric Indices

The majority of previous studies have shown an association between higher BMI and GERD symptoms [72,73]. Central adiposity seems to be a more important factor in this association than overall obesity [74]. The association between obesity and GERD seems to be causal, as exposure–response associations have been reported in multiple studies [72,73], obesity has been associated with histological indicators of esophageal epithelium damage [72,74], and weight loss has been associated with decreased GERD symptoms [15,17].

Increased intra-abdominal pressure or thoraco-abdominal pressure gradients may be among the main possible explanations for the association of GERD with BMI and, in particular, central obesity [45,75]. However, there seems to be other mechanisms contributing to this association, including reduced lower esophageal sphincter pressure in obese individuals [75,76]. In any case, esophageal acid exposure has been positively associated with BMI [75] and waist circumference [76,77]. The association between esophageal acid exposure and waist circumference has been reported in both groups of people with [76] or without [77] GERD symptoms.

In our study, high BMI and central obesity were associated with GERD symptoms in women. In men, central obesity showed trends for association with daily symptoms, but categories of neither BMI nor waist to hip ratio had significant associations with GERD symptoms. A stronger association between obesity and GERD symptoms or esophagitis in women [15,70,78], and an
association between estrogen hormone therapy and GERD [15,79] have previously been reported. However, several other studies have not shown a difference in the association between obesity and GERD by gender [68,80]. The reasons for this variation in results are unclear. Some speculative explanations include: other risk factors for GERD may be so common in a population (or a subpopulation, such as men) that they may reduce the apparent effect of obesity. Also, we cannot exclude presence of unknown confounding factors or residual confounding. Furthermore, anthropometric indices may change after development of GERD. In this case, losing or gaining weight can reduce or increase, respectively, the association between obesity and GERD in cross-sectional studies.

Table 4. Association between anthropometric indices and daily and severe GERD symptoms by sex.

| Variables | All participants | No symptoms | Daily symptoms | Severe symptoms |
|-----------|-----------------|-------------|---------------|----------------|
|           | N (%)           | N (%)       | N (%)         | OR 1 (95% CI)  | OR 2 (95% CI)  |
| Women     | 28,785 (100)    | 9947 (100)  | 4241 (100)    | 3981 (100)     |

### Body mass index

| Level       | N (%)       | N (%)       | OR 1 (95% CI)  | OR 2 (95% CI)  |
|-------------|-------------|-------------|----------------|----------------|
| <18.5 kg/m² | 1153 (4.01) | 411 (4.13)  | 0.87 (0.72–1.05) | -              |
| 18.5–24.9   | 8311 (28.88)| 3049 (30.66)| Referent        | 1953 (34.50)   |
| 25.0–29.9   | 9691 (33.67)| 3348 (33.66)| 1.12 (1.02–1.22) | 1840 (32.50)   |
| ≥30         | 9627 (33.45)| 3138 (31.55)| 1.21 (1.10–1.33) | 1570 (27.73)   |

**P for trend**

- <0.001
- <0.001

### Waist to hip ratio

#### WHO Criteria

| Level       | N (%)       | N (%)       | OR 1 (95% CI)  | OR 2 (95% CI)  |
|-------------|-------------|-------------|----------------|----------------|
| Normal      | 3091 (10.74)| 1249 (12.56)| Referent       | Referent       |
| At risk     | 25,680 (89.26)| 8692 (87.44)| 1.34 (1.19–1.51) | 1.25 (1.09–1.43) |
| Quintiles   |             |             |                |                |
| <0.88       | 5551 (19.29)| 2186 (21.99)| Referent       | Referent       |
| 0.88–0.934  | 5772 (20.06)| 1981 (19.93)| 1.21 (1.07–1.36) | Referent       |
| 0.93–0.978  | 5595 (19.45)| 1919 (19.30)| 1.13 (1.18–1.49) | Referent       |
| 0.979–1.027 | 5850 (20.33)| 1909 (19.20)| 1.43 (1.27–1.61) | Referent       |
| ≥1.028      | 6003 (20.86)| 1946 (19.58)| 1.52 (1.35–1.71) | Referent       |

**P for trend**

- 0.17
- 0.42

#### Men

| Level       | N (%)       | N (%)       | OR 1 (95% CI)  | OR 2 (95% CI)  |
|-------------|-------------|-------------|----------------|----------------|
| Normal      | 5457 (25.74)| 2550 (26.55)| Referent       | Referent       |
| At risk     | 15741 (74.26)| 7054 (73.45)| 1.10 (0.97–1.24) | 1.08 (0.93–1.24) |
| Quintiles   |             |             |                |                |
| <0.88       | 4204 (19.83)| 1980 (20.62)| Referent       | Referent       |
| 0.88–0.929  | 4048 (19.10)| 1789 (18.63)| 1.04 (0.88–1.23) | Referent       |
| 0.93–0.971  | 4351 (20.53)| 1954 (20.35)| 1.05 (0.89–1.24) | Referent       |
| 0.972–1.018 | 4217 (19.89)| 1868 (19.45)| 1.14 (0.96–1.34) | Referent       |
| ≥1.019      | 4378 (20.65)| 2013 (20.96)| 1.15 (0.97–1.36) | Referent       |

**P for trend**

- 0.04
- 0.09
- 0.37
- 0.58

CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio; WHO, World Health Organization.

Numbers may not add up to the total numbers due to missing data. The ORs (95% CIs) were calculated using multinomial logistic regression models. In the analyses of frequency, weekly, and daily symptoms, and in the analyses of severity, mild, moderate, and severe symptoms, as separate categories were compared with never having GERD symptoms. Results for weekly, weekly, and daily symptoms, and in the analyses of severity, mild, moderate, and severe symptoms, as separate categories were compared with never having GERD symptoms. Results for severe symptoms are not shown. OR 1s (95% CIs) were adjusted for age, sex, ethnicity, place of residence, education, wealth score, physical activity, consumption of alcohol, cigarette, hookah, nass, and opium (variables as shown in Table 2). OR 2s (95% CIs) were additionally adjusted for body mass index.

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Physical Activity
Although vigorous exercise has been associated with GERD [81], moderate physical activity may have an inverse association with GERD symptoms in the general population [30,82] or in obese patients only [83]. A study has also suggested a positive association between physical activity at work and GERD symptoms but an inverse association with recreational physical activity [84]. In our study, the associations between occupational physical activity and frequency or severity of GERD symptoms were mixed. These conflicting results may partly be related to variation in the definition and assessment of physical activity across studies. Also, a clinical trial has shown that actively training the diaphragm by breathing exercise may relieve GERD symptoms [85]. Therefore, different types of exercise and physical activity may have various effects on GERD depending on their impact on different parts of the body. Further longitudinal studies in this regard using standard measurement methods are required.

Strengths and Limitations of the Study
A relatively large sample size, collection of detailed information on GERD symptoms and other factors, and adjustments for multiple potential confounding factors are among the strengths of this study. One limitation was the lack of data on endoscopic and histological damage associated with GERD. However, as GERD is a clinical diagnosis in most instances, especially in the primary care setting, and its symptoms are a common source of discomfort regardless of the presence or absence of endoscopic and histologic findings, investigation of determinants of GERD per se may have clinical implications. Another limitation was that we collected data only on regurgitation and heartburn and not on less common symptoms of GERD. However, the common definition of GERD is based on regurgitation and heartburn, and most studies have used this definition. Furthermore, using other less specific symptoms might have introduced substantial measurement error. For example, GERD can cause cough [38], but cough can also be related to many other disorders [86].

Cross-sectional studies may not be able to ascertain the temporal relationship between exposures and outcomes. However, this may not be a major drawback for some socio-demographic factors, including age, sex, ethnicity, and education. On the other hand, we did not analyze the collected dietary data (which covered dietary intakes over the one year before the interview) because of the probability of a modification in diet following GERD symptoms. However, we adjusted the results for several factors that may be important indicators of original dietary patterns, including age, ethnicity, place of residence (rural/urban), education, and wealth, in order to reduce the potential confounding effect of diet on the observed associations.

Conclusions
GERD is common in Golestan Province. Several factors associated with GERD in other populations were associated with GERD in our study as well. We also observed associations of hookah and opium use and an inverse association of nass use with GERD. These associations, like many other currently known ones, may not be causal and merit further investigation. Several modifiable lifestyle factors have consistently been associated with GERD. The possibility that modifying these factors may alleviate or prevent GERD symptoms needs to be clarified in controlled studies.

Supporting Information
Table S1 Frequency and severity of gastroesophageal reflux disease (GERD) symptoms in two time periods (the last year before interview and earlier).
(DOCX)
Table S2 Association of sociodemographic and lifestyle factors with weekly and weekly GERD symptoms.
(DOCX)
Table S3 Association of sociodemographic and lifestyle factors with mild and moderate GERD symptoms.
(DOCX)
Table S4 Association between several demographic and lifestyle factors and first start of gastroesophageal reflux symptoms (≥weekly).
(DOCX)

Author Contributions
Conceived and designed the experiments: FI S-NM AP FK SMD PDP P. Brennan CCA P. Boffetta RM. Performed the experiments: FI HP SS AE SM MK. Analyzed the data: FI. Wrote the paper: FI S-NM SMD. Critical revision of the manuscript for important intellectual content: FI S-NM AP FK SMD PDP P. Brennan CCA P. Boffetta RM. Approval of the final manuscript: FI S-NM AP FK SMD PDP P. Brennan CCA P. Boffetta RM HP SS AE SM MK.

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