

## Gastroesophageal reflux disease and body mass index among adults in PERSIAN Guilan cohort study

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### Abstract

**Background and objective:** Gastroesophageal reflux disease (GERD) is a digestive complication that is common in adults and defined by heartburn and regurgitation. Due to the increasing frequency and problems of the disease, epidemiological features of GERD have been considered in recent years. Therefore, we examined the factors related to GERD in different body mass index (BMI) categories.

**Materials and methods:** We did a cross-sectional analysis of the primary information from a population-based cohort study of 10520 people in Guilan Province, Iran. Demographic characteristics such as age, gender, smoking history, and alcohol consumption were collected using a self-administered questionnaire; also, anthropometric and clinical information were surveyed. Data analyzed with SPSS version 21.0.

**Results and conclusion:** A total of 10520 participants were aged 35 to 70 years and included 5633 (53.55%) females and 4887 (46.45%) males. The frequency of GERD was 13.2% in the present study and was more prevalent in people with high BMI levels. According to analysis, GERD was significantly associated with female gender and low physical activity. Alcohol and smoke use was inversely associated with GERD. This large population-based study indicated risk factors in people with high BMI increased occurrence of GERD that altering these variables may reduce or prevent GERD indications must be elucidated in controlled trials.

**Keywords:** Body mass index, gastroesophageal reflux disease, lifestyle, risk factors

### 1. Introduction

Gastroesophageal reflux disease (GERD) is described in typical indications of heartburn and acid regurgitation that are related to damage to the esophageal mucosal [1,2]. GERD is a common complication, influencing up to 60% of people at some point in the year and 20%–30% of people at least weekly [3,4]. The prevalence of GERD varies worldwide and is reported as 23%

in South America, 18% to 28% in North America, 12% in Australia, 2% to 7% in East Asia, 9% to 26% in Europe, and 9% to 33% in the Middle East [1,2,5].

Inflammatory cytokines such as interleukin 1 $\beta$  (IL- $\beta$ ) and tumor necrosing factor (TNF- $\alpha$ ) are helpful for the differential diagnosis of different types of GERD [6]. An upper level of TNF- $\alpha$  and IL-6 was reported in obese diabetic patients

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compared to non-obese diabetic ones that highlighted the impact of exceeded adipose tissue on the inflammatory process [7]. Not only in GERD but in immunopathology status of laryngopharyngeal reflux, the role of the immune system's response such as colocalization of CD1d- with natural killer T (NKT) cell axis is seen [8]. Numerous risk factors have been related to GERD, containing dietary factors, family history, physical activity, salt intake, alcohol, and smoking history, which is related to the patient's lifestyle [9-11]. Age, sex, pregnancy, and geographic differences have also been revealed to be correlated to GERD [11].

Several investigations have shown a relationship between increased body mass index (BMI) and GERD symptoms [12-14]. Though, in previous investigations, analyses were limited to overweight and obese subjects, using those with a BMI > 25 kg/m<sup>2</sup>. In this regard, we attempted to fully examine the association between BMI and GERD by determining the relative risks among a broader range of BMI categories and people with and without GERD.

## 2. Materials and methods

### 2.1. Patients and study design

This cross-sectional study was derived from the Prospective Epidemiological Research Studies of the Iranian Adults (PERSIAN) cohort study [15], began in 2014 in Sowmeh' E Sara (GPS coordinator Latitude: 37.308003 & Longitude: 49.315022), Guilan, Northern of Iran and employed with both genders aged 35-70 years. A total population of 10520 people were participated, of which 4613 were from urban areas and 5907 people were from rural areas. Guilan cohort profile was previously published in detail [16]. Demographic characteristics including age, gender, smoking history, and alcohol consumption were surveyed. The Metabolic Equivalent of Task (MET) was divided into three tertiles according to low (<36.1), moderate (36.1-42.8), and high (>42.8) activity levels in a day by the number of hours of walking, working, exer-

cise, etc. Anthropometric indices containing weight (kg) and height (cm) were measured. The people were divided into groups based on BMI: underweight (BMI <18.5 kg/m<sup>2</sup>), normal weight (BMI = 18.5–24.99 kg/m<sup>2</sup>), overweight (BMI = 25–29.9 kg/m<sup>2</sup>), and obese (BMI ≥30 kg/m<sup>2</sup>). In the medical field, face-to-face interviews and established questionnaires were carried out to record data.

Written consent was taken after informing the purpose and importance of the study to each participant. To ensure the confidentiality of participants' information, codes were used whereby name and any identifier of the participant was not written on the questionnaire. This study was approved by ethics committees at Ministry of Health and Medical Education, Digestive Diseases Research Institute (Tehran University of Medical Sciences), and also Guilan University of Medical Sciences (P/3/132/215).

### 2.2. Statistical analysis

In this study, categorical variables were reported as numbers and percentages. Statistical analysis was performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA) and the significance level was set at 0.05.

## 3. Results and discussion

The features of participants with GERD and those without GERD are presented in Table 1. A total of 10520 participants were between 35 to 70 years old and contained 5633 (53.55%) women and 4887 (46.45%) men. Most of the participants 3513 (33.39%) had high physical activity. The frequency of current daily smoking was dramatically higher in men than in women (32.9% vs. 0.4%). The prevalence of smoking and alcohol consumption among people with GERD were 1395 (12.0%) and 2584 (12.3%), respectively. A total number of 1385 (13.2%) patients have GERD. Among people with GERD, the majority (553; 39.92%) had BMI between 25-30. About 520 (37.54%) of people with GERD were in the age group of 45-55 years old; in which 39.42%

were in the 25-30 category of BMI. No statistical relationship ( $P < 0.784$ ) was seen between age and GERD. Women had a higher rate of GERD (834; 60.21%) and the majority of them (48.2%) were seen in BMI  $> 30$  categories ( $P < 0.001$ ). A high proportion of participants with GERD (501; 36.17%) had low physical activity and 40.5% of them had higher BMI  $> 30$  ( $P < 0.001$ ). Alcohol consumption and cigarette smoking have an inverse association with GERD among people ( $P < 0.001$ ).

This descriptive and analytical cross-sectional study evaluated the prevalence and risk factors for GERD in different BMI categories. GERD is accepted worldwide as a main health problem in adults, with an important effect on the health, economic, and health-related quality-of-life implications for patients. In our study, the prevalence of GERD in PGCS was 13.2%, which is considered relatively high. Numerous epidemiological investigations have been performed in Iran and other nations to define the frequency of GERD, but the reports show interesting variety. This diversity is the result of different definitions, genetic diversity, as well as various environmental factors such as diet and nutrition. The frequency of GERD in the Iranian population is stated from a least of 2.8% [17] to a greatest of 58.5% in the Pars cohort study [18]. Based on the better methodology, a representative prevalence rate of 20% was estimated in a big cohort study with 50,000 participants in the North of Iran [19] and in Fasa cohort studies, the prevalence of GERD was respectively 58.50% and 16.9% [20]. Regarding unmodifiable risk factors, we found a higher incidence of GERD in the 45-55-year-old group, but this association was not statistically significant. Likewise, this was investigated by Murray et al., among Southwest England people in a wide range of age groups (20-59 years) which revealed the same association [21]. In contrast to these results, numerous investigations have revealed a relationship between age and GERD, either as a linear relationship [22,23], or it is a

peak followed by a modest decline [24-26]. Moreover, the female gender with high BMI represented a remarkably higher prevalence of GERD. This same trend was reported in a large cohort of women. This association extended across all BMI categories, suggesting that GERD risk increases with BMI in both normal and obese individuals [14]. As reported in some studies GERD is more common in females, but most studies have not shown an association [27].

This present study found that a low prevalence of physical activity was related to a higher incidence of GERD in obese people, and such a relationship was consistent with normal-weight or overweight individuals in the moderate and high physical activity categories. While dynamic exercise has been related to GERD [28], intermediate physical activity may be inversely associated with GERD indications in people [29,30], or only in obese individuals [13]. In our study, the association between physical activity and the incidence of GERD was varied. These contradictory consequences may be associated with differences in how physical activity was defined and assessed between studies. In addition, clinical studies have shown that active diaphragmatic exercise through respiratory exercise reduces symptoms of GERD [31]. So, various kinds of exercise and physical activity may have various influences on GERD, dependent on how they affect various parts of the body. This requires more longitudinal investigations using standard measurement techniques. Other studies showed that the consumption of alcohol and smoking aggravates GERD [32,33], while in study of Murray et al. smoking was associated with incidence and severity of heartburn and acid reflux. Light and moderate alcohol consumption (less than 20 units per week) seemed to be controversially associated with incidence and severity of these symptoms, whereas coffee consumption was only controversially associated with worsen symptoms [21].

Table 1- Characteristics of the participants with and without GERD

Variables	Total (n)	GERD n (%)				P-value	Total (n)	No-GERD n (%)				P-value
		BMI (kg/m <sup>2</sup> )						BMI (kg/m <sup>2</sup> )				
		< 18.5	Normal	25-30	> 30			< 18.5	Normal	25-30	> 30	
Age (year)	35-45	394	5 (1.3%)	88 (22.3%)	168 (42.6%)	133 (33.8%)	2745	40 (1.5%)	682 (24.8%)	1097 (40.0%)	926 (33.7%)	< 0.001
	45-55	520	4 (0.8%)	125 (24.0%)	205 (39.4%)	186 (35.8%)	3334	38 (1.1%)	838 (25.1%)	1340 (40.2%)	1118 (33.5%)	
	55<	471	3 (0.6%)	117 (24.8%)	180 (38.2%)	171 (36.3%)	3056	51 (1.7%)	896 (29.3%)	1207 (39.5%)	902 (29.5%)	
Gender	Male	551	12 (2.2%)	206 (37.4%)	245 (44.5%)	88 (16.0%)	4336	98 (2.3%)	1688 (38.9%)	1850 (42.7%)	700 (16.1%)	< 0.001
	Female	834	0 (0.0%)	124 (14.9%)	308 (36.9%)	402 (48.2%)	4799	31 (0.6%)	728 (15.2%)	1794 (37.4%)	2246 (46.8%)	
Physical activity	Low	501	3 (0.6%)	97 (19.4%)	198 (39.5%)	203 (40.5%)	3001	35 (1.2%)	636 (21.2%)	1188 (39.6%)	1142 (38.1%)	< 0.001
	Moderate	467	2 (0.4%)	98 (21.0%)	194 (41.5%)	173 (37.0%)	3038	33 (1.1%)	719 (23.7%)	1225 (40.3%)	1061 (34.9%)	
	High	417	7 (1.7%)	135 (32.4%)	161 (38.6%)	114 (27.3%)	3096	61 (2.0%)	1061 (34.3%)	1231 (39.8%)	743 (24.0%)	
Alcohol consumption	Yes	172	6 (3.5%)	59 (34.3%)	68 (39.5%)	39 (22.7%)	1223	62 (5.1%)	517 (42.3%)	405 (33.1%)	239 (19.5%)	< 0.001
	No	1213	6 (0.5%)	271 (22.3%)	485 (40.0%)	451 (37.2%)	7910	67 (0.8%)	1899 (24.0%)	3239 (40.9%)	2705 (34.2%)	
Cigarette smoking	Yes	309	7 (2.3%)	108 (35.0%)	140 (45.3%)	54 (17.5%)	2275	76 (3.3%)	982 (43.2%)	877 (38.5%)	340 (14.9%)	< 0.001
	No	1076	5 (0.5%)	222 (20.6%)	413 (38.4%)	436 (40.5%)	6860	53 (0.8%)	1434 (20.9%)	2767 (40.3%)	2606 (38.0%)	

PCS results also showed a reverse relationship between tobacco products and GERD symptoms, possibly associated with increased salivation and recurrent swallowing, similar to chewing gum [19,34,35], it could alleviate esophageal acid exposure. In our study, GERD was lower in those consuming alcohol and smoking, these people were among the overweight and obese groups. The prior studies have led to the claim that being overweight and obese are risk factors for GERD symptoms [12,36].

Our study extends these findings; in particular, the risk of GERD seems to be directly related to BMI unrelatedly to whether or not to smoke or drink alcohol. This suggests that weight gain, even in people who do not consume alcohol or smoke, can lead to the development or worsening of GERD. This study has some powerful advantages including sample size and stratified analysis for BMI categories. We had some limitations in the present study. The cross-sectional nature of this study could not exclude the possibility of reverse causality to explain the results. Another limitation was the use of questionnaires to define GERD. Additionally, underprivileged people may have a lower rate of physician referral, which may result in lower rates of GERD diagnosis. This problem may lead to increased information distortion.

#### 4. Conclusion

Our findings suggest that patients with GERD had higher levels of BMI. Alcohol consumption and smoking had an inverse association with GERD, which requires further investigation.

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#### 6. Conflict of interests

The authors declare no competing interest.

#### References

1. Alsuwat OB, Alzahrani AA, Alzhrani MA, Alkhathami AM, Mahfouz MEM. Prevalence of gastroesophageal reflux disease in Saudi Arabia. *Journal of Clinical Medicine Research*. 2018;10(3): 221-225.  
<https://doi.org/10.14740%2Fjocmr3292w>
2. Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. *Journal of Gastroenterology*. 2009;44(6): 518-534.  
<https://doi.org/10.1007/s00535-009-0047-5>
3. Locke GR, 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ, 3rd. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*. 1997;112(5):1448-1456.  
[https://doi.org/10.1016/s0016-5085\(97\)70025-8](https://doi.org/10.1016/s0016-5085(97)70025-8)
4. El-Serag HB, Petersen NJ, Carter J, Graham DY, Richardson P, Genta RM, et al. Gastroesophageal reflux among different racial groups in the United States. *Gastroenterology*. 2004;126(7):1692-1699.  
<https://doi.org/10.1053/j.gastro.2004.03.077>
5. Revicki DA, Wood M, Maton PN, Sorensen S. The impact of gastroesophageal reflux disease on health-related quality of life. *American Journal of Medicine*. 1998;104(3):252-258.  
[https://doi.org/10.1016/s0002-9343\(97\)00354-9](https://doi.org/10.1016/s0002-9343(97)00354-9)
6. Zavala-Solares MR, Fonseca-Camarillo G, Valdovinos M, Granados J, Grajales-Figueroa G, Zamora-Nava L, et al. Gene expression profiling of inflammatory cytokines in esophageal biopsies of different phenotypes of gastroesophageal reflux disease: a cross-sectional study. *BMC Gastroenterology*. 2021;21(1):201.  
<https://doi.org/10.1186/s12876-021-01707-7>
7. Goyal R, Faizy AF, Siddiqui SS, Singhai M. Evaluation of TNF- $\alpha$  and IL-6 levels in obese and non-obese diabetics: pre- and postinsulin effects. *North American Journal of Medical Sciences*. 2012;4(4): 180-184.  
<https://doi.org/10.4103%2F1947-2714.94944>
8. Rees LE, Pazmany L, Gutowska-Owsiak D, Inman CF, Phillips A, Stokes CR, et al. The mucosal immune response to laryngopharyngeal reflux. *American Journal of Respiratory and Critical Care Medicine*. 2008;177(11):1187-1193.  
<https://doi.org/10.1164%2Frcm.200706-895OC>
9. Buckles DC, Sarosiek I, McMillin C, McCallum RW. Delayed gastric emptying in gastroesophageal reflux disease: reassessment with new methods and

symptomatic correlations. *American Journal of Medical Sciences*. 2004;327(1):1-4.

<https://doi.org/10.1097/00000441-200401000-00001>

10. Wong WM, Lam KF, Lai KC, Hui WM, Hu WH, Lam CL, et al. A validated symptoms questionnaire (Chinese GERDQ) for the diagnosis of gastro-oesophageal reflux disease in the Chinese population. *Alimentary Pharmacology and Therapeutics*. 2003;17(11):1407-1413.

<https://doi.org/10.1046/j.1365-2036.2003.01576.x>

11. Kim O, Jang HJ, Kim S, Lee HY, Cho E, Lee JE, et al. Gastroesophageal reflux disease and its related factors among women of reproductive age: Korea Nurses' Health Study. *BMC Public Health*. 2018;18(1):1133.

<https://doi.org/10.1186/s12889-018-6031-3>

12. El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. *American Journal of Gastroenterology*. 2005;100(6):1243-1250.

<https://doi.org/10.1111/j.1572-0241.2005.41703.x>

13. Djarv T, Wikman A, Nordenstedt H, Johar A, Lagergren J, Lagergren P. Physical activity, obesity and gastroesophageal reflux disease in the general population. *World Journal of Gastroenterology*. 2012;18(28):3710-3714.

<https://doi.org/10.3748%2Fwjg.v18.i28.3710>

14. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo Jr CA. Body-mass index and symptoms of gastroesophageal reflux in women. *New England Journal of Medicine*. 2006;354(22):2340-2348.

<https://doi.org/10.1056/nejmoa054391>

15. Poustchi H, Egtesad S, Kamangar F, Etemadi A, Keshtkar AA, Hekmatdoost A, et al. Prospective epidemiological research studies in Iran (the PERSIAN cohort study): rationale, objectives, and design. *American Journal of Epidemiology*. 2018;187(4):647-655.

<https://doi.org/10.1093/aje/kwx314>

16. Mansour-Ghanaei F, Joukar F, Naghipour MR, Sepanlou SG, Poustchi H, Mojtahedi K, et al. The PERSIAN Guilan Cohort Study (PGCS). *Archives of Iranian Medicine*. 2019;22(1):39-45.

17. Moghimi-Dehkordi B, Vahedi M, Khoshkrood Mansoori B, Kasaeian A, Safaei A, Habibi M, et al. Economic burden of gastro-oesophageal reflux disease and dyspepsia: A community-based study. *Arab Journal of Gastroenterology : the official publication of the Pan-Arab Association of Gastroenterology*. 2011;12(2):86-89.

<https://doi.org/10.1016/j.ajg.2011.03.005>

18. Khodamoradi Z, Gandomkar A, Poustchi H, Salehi A, Imanieh MH, Etemadi A, et al. Prevalence and correlates of gastroesophageal reflux disease in southern Iran: Pars cohort study. *Middle East Journal of Digestive Diseases*. 2017;9(3):129-138.

19. Islami F, Nasseri-Moghaddam S, Pourshams A, Poustchi H, Semnani S, Kamangar F, et al. Determinants of gastroesophageal reflux disease, including hookah smoking and opium use- a cross-sectional analysis of 50,000 individuals. *PloS One*. 2014;9(2):e89256.

<https://doi.org/10.1371/journal.pone.0089256>

20. Farjam M, Sharafi M, Bahramali E, Rezaei S, Hassanzadeh J, Rezaeian S. Socioeconomic inequalities in gastroesophageal reflux disorder: results from an Iranian cohort study. *Middle East Journal of Digestive Diseases*. 2018;10(3):180-187.

<https://doi.org/10.15171/mejdd.2018.108>

21. Murray L, Johnston B, Lane A, Harvey I, Donovan J, Nair P, et al. Relationship between body mass and gastro-oesophageal reflux symptoms: The Bristol Helicobacter Project. *International Journal of Epidemiology*. 2003;32(4):645-650.

<https://doi.org/10.1093/ije/dyg108>

22. Cho YS, Choi MG, Jeong JJ, Chung WC, Lee IS, Kim SW, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Asan-si, Korea. *American Journal of Gastroenterology*. 2005;100(4):747-753.

<https://doi.org/10.1111/j.1572-0241.2005.41245.x>

23. Li YM, Du J, Zhang H, Yu CH. Epidemiological investigation in outpatients with symptomatic gastroesophageal reflux from the Department of Medicine in Zhejiang Province, east China. *Journal of Gastroenterology and Hepatology*. 2008;23(2):283-289.

<https://doi.org/10.1111/j.1440-1746.2007.05045.x>

24. Kotzan J, Wade W, Yu HH. Assessing NSAID prescription use as a predisposing factor for gastroesophageal reflux disease in a Medicaid population. *Pharmaceutical Research*. 2001;18(9):1367-1372.

<https://doi.org/10.1023/a:1013010616496>

25. Nocon M, Keil T, Willich SN. Prevalence and sociodemographics of reflux symptoms in Germany--results from a national survey. *Alimentary Pharmacology and Therapeutics*. 2006;23(11):1601-1605.

<https://doi.org/10.1111/j.1365-2036.2006.02924.x>

26. El-Serag H, Hill C, Jones R. Systematic review: the epidemiology of gastro-oesophageal reflux disease

in primary care, using the UK General Practice Research Database. *Alimentary Pharmacology and Therapeutics*. 2009;29(5):470-480.

<https://doi.org/10.1111/j.1365-2036.2008.03901.x>

27. Nusrat S, Nusrat S, Bielefeldt K. Reflux and sex: what drives testing, what drives treatment? *European Journal of Gastroenterology and Hepatology*. 2012;24(3):233-247.

<https://doi.org/10.1097/meg.0b013e32834f6baa>

28. Collings KL, Pierce Pratt F, Rodriguez-Stanley S, Bembem M, Miner PB. Esophageal reflux in conditioned runners, cyclists, and weightlifters. *Medicine and Science in Sports and Exercise*. 2003;35(5):730-735.

<https://doi.org/10.1249/01.mss.0000064937.99001.56>

29. Murao T, Sakurai K, Mihara S, Marubayashi T, Murakami Y, Sasaki Y. Lifestyle change influences on GERD in Japan: a study of participants in a health examination program. *Digestive Diseases and Sciences*. 2011;56(10):2857-2864.

<https://doi.org/10.1007/s10620-011-1679-x>

30. Kumar S, Sharma S, Norboo T, Dolma D, Norboo A, Stobdan T, et al. Population based study to assess prevalence and risk factors of gastroesophageal reflux disease in a high altitude area. *Indian Journal of Gastroenterology: Official Journal of the Indian Society of Gastroenterology*. 2011;30(3):135-143.

<https://doi.org/10.1007/s12664-010-0066-4>

31. Eherer AJ, Netolitzky F, Hogenauer C, Puschnig G, Hinterleitner TA, Scheidl S, et al. Positive effect of abdominal breathing exercise on gastroesophageal reflux disease: a randomized, controlled study. *American Journal of Gastroenterology*. 2012;107(3):372-378.

<https://doi.org/10.1038/ajg.2011.420>

32. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. *Gut*. 2004;53(12):1730-1735.

<https://doi.org/10.1136%2Fgut.2004.043265>

33. Pan J, Cen L, Chen W, Yu C, Li Y, Shen Z. Alcohol consumption and the risk of gastroesophageal reflux disease: a systematic review and meta-analysis. *Alcohol and Alcoholism (Oxford, Oxfordshire)*. 2019;54(1):62-69.

<https://doi.org/10.1093/alcalc/agy063>

34. Smoak BR, Koufman JA. Effects of gum chewing on pharyngeal and esophageal pH. *Annals of Otology, Rhinology, and Laryngology*. 2001;110(12):1117-1119.

<https://doi.org/10.1177/000348940111001206>

35. Moazzez R, Bartlett D, Anggiansah A. The effect of chewing sugar-free gum on gastro-esophageal reflux. *Journal of Dental Research*. 2005;84(11):1062-1065.

<https://doi.org/10.1177/154405910508401118>

36. Yuan S, Larsson SC. Adiposity, diabetes, lifestyle factors and risk of gastroesophageal reflux disease: a Mendelian randomization study. *European Journal of Epidemiology*. 2022;37(7):747-754.

<http://dx.doi.org/10.1007/s10654-022-00842-z>