Published in final edited form as:
Gastroenterology. 2007 January ; 132(1): 87–95.

Lifestyle Factors and Risk for Symptomatic Gastroesophageal Reflux in Monozygotic Twins

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Abstract

Background & Aims—Lifestyle and genetic factors dominate the etiology of gastroesophageal reflux disease. We investigated associations between lifestyle factors and gastroesophageal reflux (GER) symptoms, with and without controlling for genetic predisposition.

Methods—In the Swedish Twin Registry, lifestyle exposures were collected by questionnaires in 1967 and 1973, and GER symptoms were interviewed by telephone during 1998-2002. Two analytic methods were used, external control analysis (4,083 twins with GER symptoms and 21,383 controls) using Generalized Estimating Equations model and monozygotic co-twin control analysis (869 monozygotic twin pairs discordant for GER symptoms) using conditional logistic regression model.

Results—In the external control analysis, leanness (body-mass index [BMI] <20), upper normal weight (BMI 22.5-24.9), overweightness (BMI 25-29.9) and obese (BMI ≥30) conferred -19%, 25%, 46% and 59% increased risk of frequent GER symptoms compared with normal weight (BMI 20-22.4), respectively, among women, while no such associations were evident among men. When adjusted for genetic and non-genetic familial factors, these estimates were -28%, 44%, 187% and 277% among men. Frequent smoking rendered a 37% increased risk of frequent GER symptoms among women and 53% among men compared with nonsmokers. Physical activity at work was dose-dependently associated with increased risk of frequent GER symptoms, while recreational physical activity decreased this risk.

Conclusions—BMI, tobacco smoking and physical activity at work appear to be risk factors for frequent GER symptoms, whereas recreational physical activity appears to be beneficial. Association between BMI and frequent GER symptoms among men seems to be attenuated by genetic factors.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common health problem in industrialized countries.[1-4] GERD strongly affects the quality of patients' life and increases the risk for esophageal adenocarcinoma,[5, 6] of which the incidence has increased greatly in recent years.[7] Over $10 billion is spent annually for the care of GERD in the United States, of which $6 billion is spent for anti-reflux medication.[8] Identification of any lifestyle habits that could serve as the basis for alternative or complementary treatment of GERD or preferably prevent this

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disorder is therefore highly warranted. Recommended changing of certain lifestyle habits that might contribute to the treatment or prevention of GERD include controlling weight, giving up tobacco smoking, alcohol drinking, reducing or avoiding coffee, tea or peppermint.[9, 10] These maneuvers, however, often lack convincing efficacy.[9] Whether these factors are also etiologic, i.e. involved in the development of GERD, is uncertain.

Obesity is an established risk factor for GERD, but with a significant degree of heterogeneity in magnitude and previous studies often lack of sex-specific analyses.[11, 12] Tobacco smoking can reduce the pressure of the lower esophageal sphincter (LES),[13] and decrease salivary bicarbonate secretion, thus reducing the physiological neutralizing effect of the saliva on intraesophageal acid.[14] Thus, smoking may be a risk factor for GERD as indicated by some,[15-18] but not all,[19, 20] epidemiological studies. Alcohol and coffee may have a direct toxic effect on the esophageal mucosa and, lower the LES pressure or prolong gastric emptying time.[21, 22] However, epidemiological studies on alcohol and coffee consumption and GERD have revealed conflicting results.[15-19, 23-25] Physical exercise may provoke gastroesophageal reflux (GER) symptoms via a mechanism of increased esophageal acid exposure during exercise,[26] and GER symptoms are common among athletes.[27] In previous epidemiological studies of relatively small sample sizes, physical exercise was[28] or was not[29] associated with an increased frequency of GER. However, in one large population-based study from our group, we found that physical exercise renders a protective effect against GERD.[15] In that study, we suggested a mechanism of an exercise-strengthened anti-reflux barrier, possibly constituted by striated muscle. The effect and underlying mechanism of physical exercise on GER symptoms are still unclear. Physicians often advise GERD patients to avoid certain foods that might provoke reflux. Nonetheless, previous studies on dietary intake of fat, high caloric items, fiber, bread, fruits and vegetables, yielded conflicting results.[18, 25, 28, 29]

Twin studies indicate that the heritability of GERD is about 31 – 43%,[16, 30] i.e. genetic factors should account for a considerable part of the variation in liability to GERD. In addition, genetic factors account for 40 – 80% for obesity[31] and to some extent for various health behaviors.[32] Thus, to better understand GERD etiology, investigations should ideally adjust the results for potential effects by genetic predisposition and non-genetic familial effects. The monozygotic (MZ) co-twin control method, which compares MZ twins who are discordant for a disease, provides a valid tool to achieve this aim. To our knowledge, no epidemiological study to date has examined the role of lifestyle factors in GERD taking genetic factors into consideration. The Swedish Twin Registry, the largest population-based twin registry in the world, offers a particularly strong basis for exploring the importance of potential lifestyle risk factors with controlling for genetic background.[33] We therefore used this register for studying the associations between selected lifestyle factors and GER symptoms, including evaluation of the potential influence of genetic factors.

MATERIALS AND METHODS

Subjects

In 1967 and 1973, questionnaires including lifestyle exposures were mailed to same-sex twins in the Swedish Twin Registry who were born in 1958 or earlier.[33] During the period 1998 to 2002, the Screening Across the Lifespan of Twins (SALT) study collected data on GER symptoms through telephone interviews with all twins born in 1958 or earlier. A total of 28,486 twin individuals responded both to the questionnaires about lifestyle in the 1960-70s and to the questions regarding GER symptoms in 1998-2002. Those who at the telephone interview reported onset of GER before the assessment of lifestyle exposures were excluded (n=769), resulting in 27,717 individuals remaining for analysis. Among these persons, 869 were members of MZ twin pairs discordant for GER symptoms.

This study was approved by the Regional Ethics Committee of the Karolinska Institutet, and by the Mayo Institutional Review Board.

Determination of exposures

In the questionnaires sent out in 1967 and 1973, information was collected about age, sex, education, height, weight, tobacco smoking, consumption of alcohol and coffee, and physical exercise.[33] Body-mass index (BMI), the weight in kilograms divided by the square of height in meters (kg/m^2), was categorized into <20 (lean), 20-22.4 (referred as normal and severed as reference), 22.5-24.9 (upper normal weight), 25-29.9 (overweight) and ≥30 (obese). Smoking status was categorized into ever smokers (including past and current smokers at the time of filling in the questionnaires) and never smokers. Tobacco smoking was assessed by consumption of cigarettes, cigars or pipe tobacco. A cigarette equivalent index was created to assess the amount of smoking on the basis of nicotine content (1 cigarette = 1 cigarette if inhaled in lungs or 0.25 if not, 1 cigar = 4 cigarettes if inhaled in lungs or 1 if not, 1 gram of pipe tobacco = 1.43 cigarettes if inhaled in lungs or 0.36 if not). Total alcohol consumption was evaluated by summing total amount of ethanol (beer, wine and spirits) consumed per month in grams. Physical exercise was assessed separately at work (level 1 to level 4: primarily sedentary / standing and walking / standing, lifting and carrying / physically strenuous) and at leisure time (level 1 to level 4: almost no / little / medium / much). Specific dietary items, including vegetables, fruits, fish, meat, rice, flour-based foods, milk, sandwiches, grilled or fried food, were all rated on a scale from 1 to 5 (<1 time/month, occasionally/month, several times/month or once/week, several times/week, and daily).

Determination of GER

Occurrence of lifetime GER symptoms was assessed during the period March 1998 through December 2002, i.e. about 30 years after the collection of exposure data. Details of the ascertainment of GERD using validated questions of GER symptoms have been described previously.[5] In brief, computer-assisted telephone interviews were conducted by trained professional interviewers with each study participant.[33] The questionnaire covered a large number of disorders. Occurrence of GER was assessed using a structured reflux symptom questionnaire.[30] If a positive response was given to any of these three key symptoms, i.e. regurgitation of bitter or sour fluid into the mouth, heartburn or pain behind the breastbone (This was modified after the start of study with the intent to distinguish cardiac from reflux symptoms. Because the modification had little effect, data from earlier and modified questions were pooled), seven further questions were asked. Frequent GER was defined a priori as the occurrence, at least once a week, of either retrosternal pain with antacid relief or retrosternal burning with antacid relief or radiation toward the neck; or regurgitation of bitter fluid. Those with an onset of frequent GER symptoms after the assessment of the exposure data comprised our study GER patients. Onset of GER was defined as the start (in calendar year) of recurrent GER symptoms. Twins without reflux symptoms, or symptoms less than once a week, were defined as non-GER group. The agreement between two occasions for frequent GER symptoms, questioned two weeks apart, was 84.3% (κ value 0.44).

Determination of zygosity

Each twin was independently asked "During childhood, were you and your twin partner as alike as 'two peas in a pod' or not more alike than siblings in general?". If both individuals of a pair responded "alike as two peas in a pod", they were classified as MZ, and if both responded "not alike", they were classified as dizygotic (DZ). If the twins did not agree, at a later time, they were further asked "How often did strangers have difficulty in distinguishing between you and your twin partner when you were children?" If both individuals of a pair responded "almost always or always" or "often", they were classified as MZ, if they responded "seldom" or “almost never or never”, they were classified as DZ. This method of determination has been validated and shown to be 99% accurate compared with analysis of DNA polymorphisms.[33]

Statistical analysis

We used two methods of comparison of controls in the analyses. In the external control analysis, we compared twins with frequent GER symptoms (n=4,083) with unrelated non-GER twins (n=21,383, not related to the index probands). In the MZ co-twin control analysis, GER twins were compared with their non-GER MZ co-twins (n=869 pairs).

In the external control analysis, in view of the correlation within twin pairs, odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were obtained by Generalized Estimating Equations model,[34] by applying the GENMOD procedure of SAS software (SAS Institute, Cary, NC). In the MZ co-twin control analysis, ORs and 95% CIs were obtained by conditional logistic regression using PHREG procedure. Since previous studies have indicated gender differences in the studied associations,[35] all analyses were stratified by sex. In univariate analyses, year of birth was included in each model. In multivariate analyses, BMI (5 categories), smoking (ever or never), coffee (4 categories), physical activity at work (4 categories) and at leisure time (4 categories) and education (2 categories) were further included in the models. Evidence of a dose-response association between the tested factor and frequent GER symptoms was examined using a test for trend in the logistic regression, based on ordinal categories of that factor. To test the difference between the ORs derived from the external control and MZ co-twin control analyses, we compared the regression coefficients derived from these two models by the Wald statistic.[36] The degree of freedom equals to n-1 when comparing an n-level factor and 1 when comparing trend test. Similarly, the differences between the ORs derived from women and men were tested both in the external control and MZ control analyses.

RESULTS

In total, 15014 women and 12703 men were included in this study, with 523 and 346 MZ twin pairs discordant for frequent GER symptoms in women and men, respectively. The prevalence of frequent GER symptoms was 15.5% in women and 13.8% in men. The study subjects suffered from GER symptoms at a median start age of 45.

BMI

A dose-response association between increasing BMI and frequent GER symptoms was observed in women. Compared with normal weight women, underweight women had 19% decreased risk, while upper normal weight, overweight and obese women had about 25%, 46% and 59% increased risk for frequent GER symptoms, respectively (Table 2). These estimates in the MZ co-twin control analysis were of similar magnitudes. In external control comparison, no association between BMI and frequent GER symptoms was observed for men. However, in the MZ co-twin control analysis, there was a clear trend with 28% decrease, 44%, 187% and 277% increase in the risk for lean, upper normal weight, overweight and obese men compared with normal weight men (Table 3). The difference between the estimates derived from the external-control and MZ-control analyses was statistically significant ($P=0.0203$). In the external-control analysis, the estimates for women were significantly different from those for men ($P<0.0001$).

Tobacco

There was a dose-response pattern in the association between tobacco smoking and frequent GER symptoms. In external control analysis, ever tobacco smoking and smoking more than 20 cigarettes per day was associated with 18% and 37% increased risk among women when compared with never smoking (Table 2). These estimates tend to be attenuated in the MZ co-twin control analysis, but the attenuation did not reach a significant level. In men, the corresponding estimates were about 36% and 53% in the external control analysis, and were of similar strength in the MZ co-twin control analysis (Table 3).

Alcohol

In women, alcohol consumption was not associated with risk of frequent GER symptoms in the external control analysis, while an inverse dose-response association was observed in the MZ control analysis (Table 2). When consumption of beer, wine and spirits were analyzed separately by dichotomous (yes/no) categories or by amount (quartiles), none of them was associated with frequent GER symptoms in the MZ control analysis (data not shown). In men, alcohol consumption was associated with a modestly decreased risk of frequent GER symptoms but was of borderline statistical significance and without dose-response pattern in the external control analysis. Similar estimates were observed in the MZ co-twin analysis (Table 3).

Coffee

In the external analysis, coffee use was dose-dependently associated with risk of frequent GER symptoms in women, with about 45% increased risk among heavy users (≥7 cups per day) compared with non-users in the univariate analysis, but no such association was observed when controlled for BMI, smoking, physical activity at work and at leisure time in the multivariate analysis (Table 2). In men, an inversely dose-dependent association, with 25% decreased risk was observed for heavy users in the multivariate analysis (Tables 3). The gender difference in the associations were statistically significant (*P* for trend = 0.0127). The MZ co-twin analysis did not reveal significantly different results (Tables 2 and 3).

Physical activity

In both sexes, physical activity at work was associated with an occurrence of frequent GER symptoms, while physical activity at leisure time in contrast decreased the risk in the external control analyses (Tables 2 and 3). A 40% increased risk for frequent GER symptoms was observed in women with physically strenuous work compared with primarily sedentary work, but the excess risk was attenuated to 16% in the multivariate analysis. This change, occurring specifically when introducing the variables education and BMI into the model, indicated these two factors as confounders (Table 2). In men, the corresponding figures were 27% and 23% in the univariate and multivariate analyses, respectively. In contrast, those who exercised much (the highest of 4 categories) at leisure time had about 40% decreased risk of frequent GER symptoms compared with those who almost did not exercise, in both sexes. The MZ co-twin control analyses showed no significantly different results for both sexes.

Education

Lower education rendered a 21% increase risk for the development of frequent GER symptoms in women, but not in men, with a statistically significant gender difference (*P* = 0.0057), in the external control analysis. The association did not significantly change in the MZ co-twin analyses.

Dietary variables

None of the studied dietary items, i.e. vegetables, fruits, fish, meat, rice, flour-based foods, milk, sandwiches, potatoes, and grilled and fried food, was associated with risk of frequent GER symptoms in either the external control or the co-twin analysis (data not shown).

DISCUSSION

This monozygotic co-twin study, based on twins in the nationwide Swedish Twin Registry, provides compelling evidence that BMI, tobacco smoking and physical activity at work increase the risks for occurrence of frequent GER symptoms, whereas physical activity at leisure time decreases the risk. Heavy coffee intake may decrease the risk for frequent GER symptoms in men and lower education may increase the risk in women. Moreover, the study revealed no evidence of an association between intake of alcohol, vegetables, fruit, fish, meat, rice, flour-based food, milk, sandwiches, potatoes, or grilled and fried foods and risk of GER development.

Previous studies, epidemiological or clinical, population-based or case series, have shown heterogeneous associations between BMI and GERD and conflicting results regarding the use of tobacco, alcohol, coffee and tea in the etiology of GERD.[15-20, 23-25] These inconsistencies might be due to differences in methodology and study design. Effects of genetic factors may be additionally a problem in the previous literature, since genetic effects have been established as a main risk factor both for the development of GER symptoms[16, 30] and health-related behaviors such as obesity, smoking, alcohol habits and physical exercise.[32] Nonetheless, no previous study has adjusted the results for such potential effects. Therefore, our ability to adjust for genetic factors is among the main advantages of the present study. The accuracy of the zygosity determination was high, and the twin study design allowed comparisons of the results from co-twin control design with those from the ordinary case-control design. Another asset of our study is the prospective exposure data collection and the ability to assess the time of onset of GER symptoms. Analyses using exposures collected before onset of the disease enabled us to evaluate the role of lifestyles in the initiation of GER symptoms and reduce possible reversed causality that often appear in cross-sectional studies. Moreover, the large sample size enabled us to perform stratified analyses by sex. Other strengths include the population-based design, the use of a validated tool for the assessment of GER symptoms, and the large amount of factors available for adjustment.

Lifetime GER symptoms were assessed about three decades after the exposures were collected and could only be assessed in persons still alive at the time of GER symptoms ascertainment. Therefore, the risk of selection (survival) bias cannot be ruled out and thus belongs to the limitations of our study. However, the median age of our study participants at the time of GER symptoms ascertainment was 57 years, which was much younger than the life expectancy of 69 for the birth cohort from 1942 (median birth year of our participants) in Sweden.[37] This fact should allay concerns about survival bias. A major limitation of our study lies in the possibility of change of the exposure information collected possibly decades before the development of GER symptoms. This misclassification was likely to happen and, if happened, was very likely to be non-differential between GER group and non-GERD controls, which would bias the associations toward null. Thus, our results could have been underestimated. An additional possible limitation of our study is the incomplete report of GER symptoms that occurred long time ago. This might lead to an under-ascertainment of young-onset GERD patients. However, the median age of reported onset of frequent GER symptoms in the whole SALT study participants was 40 (mean age 39.2) (Data not shown. Part of the SALT participants, i.e. those developed GER symptoms before the exposures assessment in 1967 and 1973, were excluded from our study), which is consistent with the natural history of GER symptoms that typically begins in middle age,[38] indicating that the likelihood of this source of under-ascertainment is small. The association observed in the comparison within monozygotic twins could suffer from overmatching to non-genetic familial factors. Overmatching bias may exist in our study, but the extent is subjected to the effects of non-genetic familial factors on the exposure and on the outcome. However, our previous study showed no evidence that non-genetic familial effects contributed to the increased concordance for reflux twins.[30] Thus, this overmatching must have had little influence on the effect estimates. Finally, the GERD diagnosis, based on symptoms only, might have been misclassified. However, several studies have indicated that the assessment of GERD through structured questionnaires might be the best tool available for defining true GERD.[39-42] Our GERD definition was based on weekly symptoms, and the prevalence, about 15%, coincided with that from other studies, 10-20%.[11] Admittedly, our results were somewhat underestimated due to mixture of those heterogeneous GER patients, i.e. less frequent than once a week, in the control group. We did not follow the procedure employed in previous studies[12, 15, 43] to exclude patients with less frequent GER symptoms, as this would greatly decrease the statistical power in our MZ co-twin control analysis.

Our results emphasize the importance of body mass in the development of GER symptoms. We found that leanness conferred beneficial effect and increasing BMI increased risk of GER symptoms across the whole BMI range, even among conventional normal weight (BMI 22.5-24.9). This was consistent with a recent study from the Nurse Health Study.[12] More importantly, we found that the association between BMI and frequent GER symptoms seemed to be negatively influenced by genetic factors among men. The underlying mechanism is unknown although it is tempting to speculate that certain gene (or genes in linkage disequilibrium) is positively (or inversely) associated with obesity and inversely (or positively) associated with GERD. The higher heritability of obesity observed in men than in women[44] seems to support this sex-differential confounding.

The finding of a dose-dependent association between smoking and frequent GER symptoms, regardless of sex, provides evidence that smoking is a true risk factor for GERD. Alcohol consumption was not associated with occurrence of frequent GER symptoms in the present study. The observed inverse association between alcohol consumption and GER symptoms in the MZ co-twin control analysis in women might be due to chance. Moreover, none of the any specific types of alcoholic beverages, i.e., beer, wine or spirits, was associated with GER symptoms, indicating no true risk. This is consistent with previous population-based epidemiological studies.[15, 18] We found that coffee intake might be a protective factor for frequent GER symptoms in men, but not in women. The previous large scale study on Norwegians from our group also showed a beneficial effect. Our prospective information should act against reversed causality, i.e. patients with frequent GER symptoms avoided coffee use due to their disease, which was of particular concern in previous studies.[15, 18] The protective effect may be a result of reduction of long-term weight gain among coffee consumers.[45] The sex discrepancy observed in our results might be due to their difference in caffeine metabolism. The conversion of caffeine to paraxanthine, which in humans accounts for about 84% of primary degradation of caffeine,[46] is markedly inhibited by exogenous estrogen in oral contraceptives[47] or HRT among postmenopausal women.[48]

We found a hazardous effect of exercise at work and a protective effect of exercise at leisure time, regardless of sex. These opposite effects are not necessarily contradictory. Physical activity at work might be linked with postprandial exercise, which has been found to be a risk factor for development of GER symptoms.[49, 50] Unlike physical activity at work, it is likely that leisure physical exercise is predominantly performed at time without a feeling of stomach fullness, and therefore most unlikely to be reflux-provoking postprandial exercise.[49, 50] Moreover, strenuous physical activity at work is generally associated with lower education level, as supported by our result that the association between physical activity at work and GER symptoms was confounded mainly by education level and secondary by BMI. One reason for the conflicting results in previous studies regarding effects of physical activity might be due to unable to separate these two kinds of physical activites.[28, 29] The present result is consistent, in terms of both direction and strength of association, with our previous large population-based study, where physical exercise was defined as leisure time exercise, such as jogging, cross country skiing and exercise swimming.[15]

Previous studies on the association between education and GERD yield inconsistent results.[28, 29] We observed an increased risk of frequent GER symptoms in women with lower education, but no association in men. The mechanism for this sex discrepancy is still unclear. We found no associations between any of the studied dietary factors and the development of GER symptoms. These results are consistent with another population-based study in Sweden.[25] BMI may be an intermediate step in the associations between dietary foods and GER symptoms, since both are closely related with obesity.[11] Therefore, we examined the associations between dietary foods and frequent GER symptoms with and without adjusting for BMI, but no clear differences were found. One study using the same analytic method showed results consistent with our findings that the lack of association between studied dietary factors and GER symptoms was not influenced by BMI.[28]

In conclusion, this large monozygotic co-twin study provides evidence that BMI, tobacco smoking and physical activity at work facilitate the development of GER, while physical activity at leisure time appears to be a protective factor. The association between BMI and frequent GER symptoms among men may be attenuated by genetic factors. In addition, heavy coffee intake may be a protective factor of GER in men and lower education may be a potential risk factor in women.

Acknowledgements

Thanks to Dr. Olof Nyrén from Dept. of Medical Epidemiology and Biostatistics, Karolinska Institutet, and Dr. Alan J. Cameron and G. Richard Locke III from Mayo Clinic, Minnesota in the study design phase and their contributions that made this study possible.

Grant support: The Swedish Twin Registry is supported by grants from the Swedish Department of Higher Education, the Swedish Scientific Council, and Astra Zeneca. Data collection in SALT was supported in part by funds from NIH (AG 08724). The analyses were supported financially by the Swedish Research Council and the Swedish Medical Society.

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Table 1

Characteristics of study subjects

	Women	Men
No. of non-GERD subjects	12684	10950
No. of GERD (%) subjects	2330 (15.5)	1753 (13.8)
No. of monozygotic twin pairs discordant for GER	523	346
Age at assessment of GER, median (range)	58 (42-104)	57 (42-99)
Age at onset of GER, median (range)	46 (17-83)	45 (18-83)

Table 2

Associations between lifestyle factors and frequent gastroesophageal reflux symptoms among women

	External control comparison				Monozygotic co-twin control comparison		
	Control (n)	**Case (n)**	**Univariate [a] OR (95%CI) [c]**	**Adjusted [b] OR (95%CI) [c]**	**Univariate [d] OR (95%CI) [c]**	**Adjusted [b] OR (95%CI) [c]**	**P^e Value**
BMI [f]							
<20	3432	638	0.78 (0.69-0.88)	0.81 (0.71-0.92)	0.77 (0.51-1.17)	0.76 (0.46-1.26)	
20-22.4	3644	754	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
22.5-24.9	1939	412	1.16 (1.02-1.33)	1.25 (1.06-1.46)	1.19 (0.73-1.92)	1.38 (0.75-2.54)	
25-29.9	1058	249	1.38 (1.17-1.62)	1.46 (1.19-1.80)	1.42 (0.67-2.97)	1.89 (0.72-5.01)	
≥30	154	33	1.27 (0.86-1.87)	1.59 (1.00-2.54)	0.91 (0.14-6.11)	1.71 (0.20-14.6)	0.9863
P value for trend			<0.0001	<0.0001	0.1303	0.0825	0.5718
Ever smoking							
no	5671	1014	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
Yes	4578	1063	1.23 (1.11-1.35)	1.18 (1.05-1.32)	0.92 (0.61-1.38)	1.08 (0.66-1.74)	0.7166
cigarettes equivalent /day							
1-9	1900	386	1.09 (0.96-1.24)	1.12 (0.97-1.30)	0.75 (0.47-1.22)	0.82 (0.45-1.48)	
10-19	1968	478	1.27 (1.13-1.44)	1.16 (1.01-1.34)	1.04 (0.61-1.74)	1.32 (0.71-2.44)	
≥20	621	178	1.51 (1.26-1.81)	1.37 (1.12-1.68)	1.03 (0.54-1.97)	1.10 (0.49-2.45)	0.5234
P value for trend			<0.0001	0.0027	0.9590	0.6390	0.7896
Alcohol							
No	4714	1000	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
Yes	6567	1324	0.97 (0.89-1.07)	1.01 (0.89-1.13)	0.77 (0.55-1.09)	0.73 (0.45-1.19)	0.2120
absolute alcohol (grams /month)							
1-150	2127	409	1.05 (0.92-1.20)	1.03 (0.86-1.23)	1.03 (0.65-1.66)	1.13 (0.58-2.17)	
151-1200	1792	413	1.09 (0.95-1.23)	1.21 (1.04-1.42)	0.80 (0.51-1.27)	0.84 (0.45-1.59)	
1201 -2400	963	166	0.76 (0.64-0.91)	0.80 (0.65-0.98)	0.46 (0.25-0.83)	0.48 (0.22-1.04)	
>2400	760	171	1.00 (0.83-1.19)	0.96 (0.78-1.19)	0.56 (0.28-1.11)	0.31 (0.11-0.84)	0.1498
P value for trend			0.3554	0.5331	0.0127	0.0093	0.0161
Coffee (cups /day) [g]							
0	886	191	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
1-3	3449	694	1.02 (0.84-1.23)	0.92 (0.76-1.12)	1.27 (0.65-2.50)	1.11 (0.51-2.41)	
4-6	3187	718	1.19 (0.98-1.45)	1.01 (0.82-1.25)	1.62 (0.77-3.40)	1.40 (0.60-3.23)	
≥7	696	190	1.45 (1.14-1.84)	1.10 (0.85-1.43)	1.58 (0.63-3.93)	1.04 (0.35-3.08)	0.7062
P value for trend			0.0002	0.2042	0.1866	0.5614	0.8126
Physical activity at work							
primarily sedentary	2879	574	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
standing and walking	1948	383	1.06 (0.91-1.23)	1.03 (0.89-1.20)	1.15 (0.71-1.87)	1.27 (0.72-2.23)	
standing, lifting and carrying	3055	761	1.34 (1.18-1.52)	1.24 (1.09-1.42)	1.22 (0.78-1.92)	1.32 (0.79-2.19)	
physically strenuous	148	38	1.40 (0.97-2.03)	1.16 (0.78-1.72)	0.88 (0.19-4.13)	1.43 (0.18-11.2)	0.9138
P value for trend			<0.0001	0.0023	0.4409	0.3033	0.8453
Physical activity at leisure time							
almost no	898	262	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
light	2462	573	0.80 (0.68-0.94)	0.83 (0.70-0.99)	0.67 (0.37-1.20)	0.57 (0.29-1.10)	
medium	4433	902	0.70 (0.59-0.81)	0.76 (0.65-0.89)	0.63 (0.33-1.18)	0.61 (0.30-1.23)	
much	473	72	0.50 (0.37-0.67)	0.56 (0.41-0.75)	0.65 (0.24-1.79)	0.63 (0.20-1.93)	0.5670
P value for trend			<0.0001	0.0001	0.2744	0.4688	0.7869
Education [h]							
above elementary	5187	992	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
elementary	4962	1072	1.17 (1.07-1.29)	1.21 (1.08-1.35)	1.67 (1.06-2.62)	1.87 (1.07-3.28)	0.1347

[a] Year of birth was included in each univariate analysis.

[b]Adjusted for year of birth, BMI (5 categories), smoking (ever or never), coffee (4 categories), physical activity at work (4 categories) and at leisure time (4 categories) and education (2 categories), wherever appropriate.

[c]OR Odds ratio, CI confident interval.

[d]The number of twin pairs included in analysis for each factor ranged from 416 (physical activity at work) to 522 (alcohol) due to missing data.

[e]*P* value of the Wald test of comparing ORs derived from the external and MZ control multivariate analyses.

[f]*P* value of the Wald test of comparing ORs derived from women and men in the external control analysis is <0.0001, and the corresponding *P* value for trend is <0.0001

[g]*P* value of the Wald test of comparing ORs derived from women and men in the external control analysis is 0.0682, and the corresponding *P* value for trend is 0.0127.

[h]*P* value of the Wald test of comparing ORs derived from women and men in the external control analysis is 0.0057.

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Table 3

Associations between lifestyle factors and frequent gastroesophageal reflux symptoms among men

	External control comparison				Monozygotic co-twin control comparison		
	control (n)	**case (n)**	**Univariate [a] OR (95%CI) [c]**	**Adjusted [b] OR (95%CI) [c]**	**Univariate [d] OR (95%CI) [c]**	**Adjusted [b] OR (95%CI) [c]**	***P*[e] value**
BMI [f]							
<20	1278	240	0.92 (0.77-1.09)	1.00 (0.83-1.20)	0.69 (0.36-1.34)	0.72 (0.35-1.49)	
20-22.4	2884	548	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
22.5-24.9	2858	430	0.84 (0.73-0.97)	0.85 (0.73-1.00)	1.45 (0.84-2.51)	1.44 (0.77-2.68)	
25-29.9	1585	295	1.08 (0.91-1.26)	1.03 (0.85-1.24)	2.47 (1.15-5.31)	2.87 (1.08-7.59)	
≥30	100	20	1.15 (0.70-1.88)	1.01 (0.56-1.83)	2.99 (0.42-21.0)	3.77 (0.40-35.9)	0.2230
P value for trend			0.8843	0.6533	0.0088	0.0232	0.0203
Ever smoking							
No	3383	495	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
Yes	5138	989	1.36 (1.20-1.53)	1.36 (1.18-1.55)	1.18 (0.67-2.08)	1.37 (0.70-2.66)	0.9801
cigarettes equivalent /day							
1-9	1196	178	1.13 (0.93-1.36)	1.22 (0.98-1.52)	1.05 (0.46-2.40)	1.21 (0.44-3.27)	
10-19	1735	327	1.32 (1.13-1.54)	1.30 (1.09-1.54)	1.01 (0.51-1.99)	1.05 (0.47-2.37)	
≥20	2003	460	1.57 (1.36-1.81)	1.53 (1.30-1.79)	1.52 (0.80-2.89)	1.82 (0.86-3.83)	0.7324
P value for trend			<0.0001	<0.0001	0.1677	0.1034	0.6413
Alcohol							
No	2897	512	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
Yes	7059	1235	1.02 (0.91-1.15)	0.85 (0.72-1.01)	0.76 (0.46-1.27)	0.65 (0.32-1.33)	0.4722
absolute alcohol (grams /month)							
1-150	1492	253	1.10 (0.93-1.32)	0.88 (0.70-1.11)	0.88 (0.47-1.66)	0.75 (0.31-1.79)	
151-1200	1587	242	0.96 (0.81-1.14)	0.86 (0.69-1.07)	0.70 (0.37-1.33)	0.79 (0.34-1.83)	
1201 -2400	1109	180	0.89 (0.74-1.08)	0.76 (0.60-0.95)	0.77 (0.39-1.52)	0.66 (0.26-1.64)	
>2400	2483	493	1.09 (0.94-1.25)	0.85 (0.70-1.03)	0.76 (0.41-1.41)	0.57 (0.24-1.32)	0.8658
P value for trend			0.6367	0.1618	0.4385	0.1845	0.3422
Coffee (cups /day) [g]							
0	906	176	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
1-3	2738	500	0.94 (0.77-1.14)	0.91 (0.73-1.12)	0.60 (0.27-1.31)	0.81 (0.31-2.11)	
4-6	2759	514	0.96 (0.79-1.18)	0.86 (0.69-1.08)	1.20 (0.50-2.85)	1.31 (0.47-3.67)	
≥7	964	167	0.90 (0.70-1.15)	0.75 (0.57-0.98)	0.73 (0.26-2.06)	0.78 (0.23-2.63)	0.3235
P value for trend			0.6253	0.0424	0.4438	0.6880	0.3831
Physical activity at work							
primarily sedentary	2690	471	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
standing and walking	1282	214	0.97 (0.81-1.15)	0.97 (0.81-1.17)	0.78 (0.46-1.32)	0.85 (0.48-1.50)	
standing, lifting and carrying	2640	518	1.12 (0.98-1.29)	1.09 (0.94-1.27)	0.67 (0.38-1.16)	0.68 (0.36-1.31)	
physically strenuous	728	161	1.27 (1.04-1.55)	1.23 (0.99-1.53)	0.79 (0.35-1.78)	0.74 (0.28-1.96)	0.5570
p value for trend			0.0168	0.0549	0.2385	0.3113	0.1511
Physical activity at leisure time							
almost no	717	177	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
light	1702	340	0.82 (0.67-1.00)	0.86 (0.69-1.06)	0.57 (0.30-1.11)	0.64 (0.29-1.42)	
medium	3677	679	0.75 (0.63-0.91)	0.83 (0.68-1.01)	0.82 (0.42-1.60)	0.88 (0.40-1.96)	
much	1370	185	0.54 (0.43-0.68)	0.60 (0.47-0.77)	0.78 (0.32-1.90)	0.90 (0.30-2.69)	0.4572
p value for trend			<0.0001	0.0002	1.0000	0.7621	0.2584
Education [h]							
above elementary	4719	845	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	
elementary	3992	692	0.97 (0.87-1.08)	0.95 (0.84-1.08)	1.00 (0.57-1.76)	0.86 (0.44-1.71)	0.7806

[a]Year of birth was included in each univariate analysis.

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[b] Adjusted for year of birth, BMI (5 categories), smoking (ever or never), coffee (4 categories), physical activity at work (4 categories) and at leisure time (4 categories) and education (2 categories), wherever appropriate.

[c] OR Odds ratio, CI confident interval.

[d] The number of twin pairs included in analysis for each factor ranged from 297 (cigarettes equivalent per day) to 346 (alcohol) due to missing data.

[e] *P* value of the Wald test of comparing ORs derived from the external and MZ control multivariate analyses.

[f] *P* value of the Wald test of comparing ORs derived from women and men in the external control analysis is <0.0001, and the corresponding *P* value for trend is <0.0001

[g] *P* value of the Wald test of comparing ORs derived from women and men in the external control analysis is 0.0682, and the corresponding *P* value for trend is 0.0127.

[h] *P* value of the Wald test of comparing ORs derived from women and men in the external control analysis is 0.0057.