Atrophic gastritis is inversely associated with gastroesophageal reflux disease in a twin register based study

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Abstract
Background: The association between atrophic gastritis (AG) and symptomatic gastroesophageal reflux disease (GERD) needs to be better assessed.
Objective: We aimed to study this association in a twin setting, controlling for genetic and familial factors, in addition to a range of known covariates.
Methods: We performed a co-twin control study based on the Swedish Twin Register, including confirmed monozygotic (MZ) and dizygotic (DZ) twins. AG was determined by the measurement of serum pepsinogen I (PGI) and pepsinogen II (PGII), with different cut-off values. GERD was defined using a structured questionnaire, by questions on symptoms of heartburn, acid regurgitation, pain behind the breastbone, and drug history. Patients were grouped into total GERD, less frequent (<1/week), and frequent GERD (≥1/week).
Results: A total of 12,533 twins were included in the study, among whom 37.7% showed less frequent GERD, and 18.7% had frequent GERD. There was an inverse association between AG and GERD, especially for frequent GERD. When PGI < 30 was used as cut-off value for AG, the odds ratio (OR) and corresponding 95% confidence interval (CI) was 0.52 (0.44, 0.62). When PGI < 70 and PGI/PGII < 3 was used as cut-off value for AG, the OR (95% CI) was 0.53 (0.46, 0.63). A risk reduction for GERD was also observed in AG patients when the analysis was restricted in MZ or DZ twins.
Conclusion: In this co-twin control study from the Swedish Twin Register, AG is persistently associated with a reduced risk for GERD, after controlling for genetic and shared familial factors.

Keywords
atrophic gastritis, familial factors, gastroesophageal reflux disease, pepsinogen, twin register
INTRODUCTION

Gastroesophageal reflux disease (GERD), one of the most common complications in the western countries with diverse troublesome symptoms, is associated with the reflux of stomach contents into the esophagus. Typical criteria for the diagnosis of GERD include at least weekly heartburn, regurgitation, and response to empirical treatment. The prevalence of GERD shows considerable variation in different regions, ranging between 18.1% and 27.8% in North America and 8.8%–25.9% in Europe from meta-analysis. Moreover, the prevalence trends in the North America, Europe and East Asia were reported to be increasing since 1995, but heterogeneity in the definitions for GERD in different studies exists. GERD is one of the confirmed major risk factors for the malignant esophageal adenocarcinoma (EAC) and its precursor disease, Barrett’s Esophagus, and the risk increases dramatically with the duration of the GERD symptoms, which makes GERD a global problem for public health, and effective strategy for the prevention of GERD is therefore warranted.

Atrophic gastritis (AG) is a chronic, complex disorder mostly caused by H. pylori infection, and is an early precancerous lesion of distal stomach cancer. Clinical diagnosis for AG is usually made by endoscopic and histopathology examination, whereas serological biomarkers, like pepsinogen I (PGI) and pepsinogen II (PGII) are often used in large-scale, screening studies. Presence of AG is suggested to be inversely associated with GERD. But this relationship is yet to be confirmed as conflicting results have been reported in previous studies which often suffered from insufficient controlling for covariates, small sample size, lack of checkup for complex interaction with bacteria and medicines. Besides, previous twin studies have shown that genetic factors accounted for 31%–43% of the liability to GERD. Thus it is worthwhile to take into consideration the genetic variations in the etiological studies for GERD, which can be achieved using the co-twin control study design.

The aim of this study is to examine the association between atrophic gastritis and GERD, adjusting for heritable genetics and shared familiar factors using a co-twin control study design.

MATERIAL AND METHODS

Study participants

This co-twin control study is based on the Swedish Twin Registry, which was initiated in the 1950s and is the largest twin register worldwide. Details of the data compilation is described elsewhere. Specifically, this study is stemmed from the Screening Across the Lifespan Twin Study (SALT), which interviewed all available twins born before 1958 in the year 1998–2002. Later from 2004 to 2008, 12,614 participants in SALT further responded to a questionnaire regarding a group of common diseases including GERD, provided their blood samples, and information of height and weight was collected in the TwinGene study. Participants who attended both studies with GERD information and blood sample available comprised the participants of this study (n = 12,533). This study was approved by the Regional Ethical Review Board in Stockholm (Dnr: 2007/644-31, 2018/984-32).

Identification of exposure

Atrophic gastritis (AG) was determined by the test of PGI and PGII using serum samples. The collection, transportation, and storage of blood specimen has been described elsewhere. The serum was stored at −70°C until being tested. PGI and PGII concentrations were measured using enzyme immunoassay kits (Biohit ELISA kit, Helsinki, Finland) according to the manufacturer’s instructions. To monitor the quality of the tests, a duplication of kit standard sample and externally prepared control samples were added to each plate and tested at the same time with the samples of the study. In summary, based on 150 plates for PGI and 150 plates for PGII, the within-plate coefficient of variation (CV) was 2% for kit standard samples and 1% for external batch samples in PGI test; the within-plate CV was 5% for kit standard samples and 5% for external batch samples in PGII test. The between-plate CV was 6% for kit standard samples and 9% for external batch samples in PGI test; the between-plate CV was 5% for kit standard samples and 13% for external batch samples in PGII test. Since there is no agreement for the cut-off values for the identification of AG, we used different cut-off values from the literature to assure the robustness of the results: PGI<30; PGII<70 and PGII<3; PGII<3; and PGII<25 or PGII<3.
Identification of outcome

Symptoms of GERD were measured by 10 questions in a structured questionnaire which has been described previously. Briefly, the participants were asked about the experiences of recurrent heartburn, regurgitation of bitter liquid in the mouth, and pain behind the breastbone, and each positive response was followed by several questions with more details. Frequent GERD was defined by at least weekly symptoms, or the combination of pain behind the breastbone 1–3 times per month with either waking up during night for the pain, use of medicines to prevent the pain, pain radiating towards the throat or neck. This definition is in line with the globally agreed Montreal definition (Table S1). Notably, GERD symptoms with a frequency less than once per week was analyzed as less frequent GERD in this study.

Covariates

Body mass index (BMI, kg/m²) was calculated by dividing weight (kilograms) by the square of height (meters). It was then grouped into underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), and obesity (≥30). Smoking status was categorized into non-smoker, party-smoker, and is or has been a smoker. Total alcohol consumption was defined using the National Institute on Alcohol Abuse and Alcoholism (NIAAA) units per week by summing up the total beer, wine and spirit consumption per week. It was further categorized as non-drinker (0 drink unit per day), light (1–3 drink unit per day), moderate (1 to <4 drink unit per day), or heavy (≥4 drink unit per day). Coffee drinking was categorized as 0, 1–3, 4–5 and ≥6 cups per day. Physical exercise was assessed using activity type and frequency, which was then grouped into almost no exercise, light exercise, medium exercise, and hard exercise. Education level was obtained by different kinds of school, and was further categorized into years of education 0–9 years (elementary and primary school), 10–12 years (secondary school, vocational school, military school, high school and adult high school), and ≥13 years (college and above).

Statistical methods

The patients with GERD symptoms were compared with all controls without symptoms, MZ co-twin controls and DZ co-twin controls. The twin pair zygosity was determined by genotype, intra-pair similarity algorithm, or opposite sex for DZ. Odds ratios (ORs) with the corresponding confidence intervals (CIs) were used to measure the association between AG and GERD, after controlling for potential covariates mentioned above.

Firstly, GERD patients were compared with all the symptom-free controls. Generalized estimation equation (GEE) models with the robust option were fitted to estimate the ORs. Secondly, in the comparison with MZ co-twin controls and DZ co-twin controls, only complete twin pairs with discordant GERD experiences (one person reported GERD whereas the co-twin did not) were included in the study. Specifically, conditional logistic regression models were used to control for the matching within co-twin pairs when GERD was studied as a binary variable (no GERD, GERD). A multinomial fixed-effect model was instead used when GERD was studied as a three-level variable (no GERD, less frequent GERD, frequent GERD).

The crude model only included birth year and sex as covariates, and the fully adjusted model further adjusted for all the covariates mentioned above. The missing values in smoking and alcohol consumption were initially treated as a separate category in the statistical analysis to ensure statistical power.

As a sensitivity analysis, all the models were repeated after excluding the individuals who reported a medication history of histamine-receptor antagonists, proton pump inhibitors, or other anti-acid medicines by questions from the interview (Table S1).

All analyses were performed using Stata 17.0 (Stata Corporation, College Station, TX). Stata procedures based on mlogit and xtgee were used to fit the GEE model, clogit was used to run conditional logistic regression model, and femlogit was used to run multinomial fixed effect model.

RESULTS

In total, 12,599 people were tested for PGI and PGII concentrations, and 66 people were excluded due to missing information on GERD. There were 7067 GERD patients, with a prevalence of 37.7% (4729/12,533) for less frequent GERD, and 18.7% (2338/12,533) for frequent GERD. The distribution of the risk factors by AG defined according to different cut-off values are summarized in Table 1, stratified by GERD (without, or with (total, less frequent, and frequent)). Compared with patients with GERD, people without GERD tended to have lower BMI, drink more coffee, less likely to be a smoker, drink less alcohol, and exercise more. The concordance of GERD within MZ and DZ twin pairs, age at interview, and age at the onset of GERD are summarized in Table 2. In summary, there were 4190 (1002 MZ and 3188 DZ) twins discordant with GERD symptoms (yes, no). Concordant GERD was more likely to happen in MZ twins than in DZ twins, and the age at interview was a bit younger in MZ twins than in DZ twins.

Association between AG and GERD in the comparison with all controls without GERD symptoms

Around 40%–50% reduced risk for GERD was estimated for individuals with a positive AG test, using either cut-off values, in the
| Table 1 Characteristics of 12,533 twin study participants with and without symptomatic gastroesophageal reflux disease (GERD) |
|---|
| **Education (Years)** | Without GERD | With GERD | Less frequent GERD | Frequent GERD |
| 0–9 | 1632 (29.9) | 2077 (29.4) | 1322 (28.0) | 755 (32.3) |
| 10–12 | 2354 (43.1) | 3080 (43.6) | 2076 (43.9) | 1004 (42.9) |
| ≥13 | 1478 (27.0) | 1902 (26.9) | 1326 (28.0) | 576 (24.6) |
| Missing | 2 (0.0) | 8 (0.1) | 5 (0.1) | 3 (0.1) |
| **Body mass index (BMI)** | Without GERD | With GERD | Less frequent GERD | Frequent GERD |
| Underweight (<18.5) | 65 (1.2) | 45 (0.6) | 25 (0.5) | 20 (0.9) |
| Normal (18.5–24.9) | 3160 (57.8) | 3480 (49.2) | 2427 (51.3) | 1053 (45.0) |
| Overweight (25–29.9) | 1872 (34.2) | 2856 (40.4) | 1860 (39.3) | 996 (42.6) |
| Obesity (≥30) | 313 (5.7) | 624 (8.8) | 373 (7.9) | 251 (10.7) |
| Missing | 56 (1.0) | 62 (0.9) | 44 (0.9) | 18 (0.8) |
| **Coffee (cups/day)** | Without GERD | With GERD | Less frequent GERD | Frequent GERD |
| 0 | 267 (4.9) | 452 (6.4) | 253 (5.3) | 199 (8.5) |
| 1–3 | 2557 (46.8) | 3243 (45.9) | 2178 (46.1) | 1065 (45.6) |
| 4–5 | 1660 (30.4) | 2104 (29.8) | 1435 (30.3) | 669 (28.6) |
| ≥6 | 978 (17.9) | 1261 (17.8) | 860 (18.2) | 401 (17.2) |
| Missing | 4 (0.1) | 7 (0.1) | 3 (0.1) | 4 (0.2) |
| **Smoking** | Without GERD | With GERD | Less frequent GERD | Frequent GERD |
| Non-smoker | 1439 (26.3) | 1419 (20.1) | 946 (20.0) | 473 (20.2) |
| Party-smoker | 1626 (29.7) | 2064 (29.2) | 1435 (30.3) | 629 (26.9) |
| Is or has been a smoker | 2261 (41.4) | 3426 (48.5) | 2230 (47.2) | 1196 (51.2) |
| Missing | 140 (2.6) | 158 (2.2) | 118 (2.5) | 40 (1.7) |
| **Alcohol consumption**a | Without GERD | With GERD | Less frequent GERD | Frequent GERD |
| Non-drinker | 806 (14.7) | 1074 (15.2) | 711 (15.0) | 363 (15.5) |
| Light | 3969 (72.6) | 5079 (71.9) | 3387 (71.6) | 1692 (72.4) |
| Moderate | 335 (6.1) | 493 (7.0) | 335 (7.1) | 158 (6.8) |
| Heavy | 4 (0.1) | 20 (0.3) | 15 (0.3) | 5 (0.2) |
| Missing | 352 (6.4) | 401 (5.7) | 281 (5.9) | 120 (5.1) |
| **Physical activity** | Without GERD | With GERD | Less frequent GERD | Frequent GERD |
| Almost no | 209 (3.8) | 315 (4.5) | 193 (4.1) | 122 (5.2) |
| Light | 960 (17.6) | 1461 (20.7) | 945 (20.0) | 516 (22.1) |
| Medium | 3635 (66.5) | 4616 (65.3) | 3109 (65.7) | 1507 (64.5) |
| Hard | 641 (11.7) | 645 (9.1) | 463 (9.8) | 182 (7.8) |
| Missing | 21 (0.4) | 30 (0.4) | 19 (0.4) | 11 (0.5) |
| **Atrophic gastritis** | Without GERD | With GERD | Less frequent GERD | Frequent GERD |
| PGI <30 | 5132 (93.9) | 6838 (96.8) | 4566 (96.6) | 2272 (97.2) |
| Yes | 334 (6.1) | 229 (3.2) | 163 (3.4) | 66 (2.8) |
| PGI< 70 and PGI/PGII<3 | Without GERD | With GERD | Less frequent GERD | Frequent GERD |
| No | 5050 (92.4) | 6775 (95.9) | 4527 (95.7) | 2248 (96.2) |
| Yes | 416 (7.6) | 292 (4.1) | 202 (4.3) | 90 (3.8) |
analysis with all controls without GERD symptoms (Table 3). The ORs were 0.52 (95% CI 0.44–0.62) for AG defined by PGI < 30 and 0.53 (95% CI 0.46–0.63) for AG defined by PGI < 70 and PGI/PGII < 3. When the GERD symptoms were further stratified by frequency as < 1/week and ≥ 1/week, ORs for frequent GERD tended to be lower than those for less frequent GERD. Results for AG using other definitions are shown in the Supplementary Table S2.

### Table 2: The distribution of symptomatic gastroesophageal reflux disease (GERD) in dizygotic (DZ) and monozygotic (MZ) twins

|                        | MZ pairs, n (%) | DZ pairs, n (%) | P       |
|------------------------|-----------------|-----------------|---------|
| Concordant, both twins have GERD | 1104 (39)       | 2382 (34)       | <0.01   |
| Concordant, neither twin has GERD | 728 (26)        | 1506 (21)       |         |
| Discordant for GERD*    | 1002 (35)       | 3188 (45)       |         |
| Age at interview for GERD (median; interquartile range) | 56; 9 | 57; 10 | <0.01 |
| Age at onset of GERD (median; interquartile range) | 40; 20 | 40; 25 | 0.78  |

Abbreviations: DZ, dizygotic; GERD, gastroesophageal reflux disease; MZ, monozygotic.

*Chi-squared test comparing the distribution of GERD in MZ and DZ twin pairs.

### Table 3: Association between atrophic gastritis and the occurrence of gastroesophageal reflux disease (GERD) among 12,533 twins

| Atrophic gastritis (PGI<30) | Crude model,a OR (95% CI) | Full model,b OR (95% CI) | Atrophic gastritis (PGI<70 and PGI/PGII<3) | Crude model,a OR (95% CI) | Full model,b OR (95% CI) |
|----------------------------|---------------------------|--------------------------|---------------------------------------------|---------------------------|--------------------------|
| No GERD                    | 1.0 (reference)           | 1.0 (reference)          | 1.0 (reference)                             | 1.0 (reference)           | 1.0 (reference)          |
| GERD                       | 0.53 (0.45–0.64)          | 0.52 (0.44–0.63)         | 0.54 (0.46–0.63)                            | 0.53 (0.46–0.63)          | 0.54 (0.46–0.63)         |
| Less frequent GERD         | 0.55 (0.45–0.67)          | 0.54 (0.45–0.66)         | 0.55 (0.46–0.65)                            | 0.54 (0.46–0.65)          | 0.49 (0.39–0.63)         |
| Frequent GERD              | 0.46 (0.35–0.61)          | 0.45 (0.34–0.59)         | 0.50 (0.39–0.63)                            | 0.49 (0.39–0.63)          | 0.49 (0.39–0.63)         |

Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio; PGI, pepsinogen I; PGII, pepsinogen II. Models were fitted using generalized estimation equation (GEE) model.

*aCrude model adjusted for year of birth and sex.

*bFull model adjusted for year of birth, sex, BMI, education level, coffee intake, physical activity, smoking, and alcohol consumption.

### Association between AG and symptomatic GERD in DZ twins

When the comparison was restricted within DZ twins, similar magnitude of risk reduction for symptomatic GERD was reported in individuals with a positive AG test (Table 4). The ORs were 0.58 (95% CI 0.40–0.83) for AG defined by PGI < 30, and 0.58 (95% CI 0.42–0.81) for AG defined by PGI < 70 and PGI/PGII < 3. The inverse association...
between AG and frequent GERD was more prominent than that for the association between AG and less frequent GERD. Results using other definitions of AG are shown in the Supplementary Table S3.

TABLE 4 Association between atrophic gastritis and the occurrence of symptomatic gastroesophageal reflux disease (GERD), among 1594 dizygotic (DZ) twin pairs discordant for GERD

| Atrophic gastritis (PGI<30) | Crude model, OR (95% CI) | Full model, OR (95% CI) | Atrophic gastritis (PGI<70 and PGI/PGII<3) | Crude model, OR (95% CI) | Full model, OR (95% CI) |
|---------------------------|--------------------------|-------------------------|------------------------------------------|--------------------------|-------------------------|
| No GERD                   | 1.0 (reference)          | 1.0 (reference)         | 1.0 (reference)                          | 1.0 (reference)          | 1.0 (reference)         |
| GERD†                     | 0.64 (0.45–0.90)         | 0.58 (0.40–0.83)        | 0.59 (0.43–0.82)                        | 0.58 (0.42–0.81)        |
| Less frequent GERD        | 0.80 (0.53–1.19)         | 0.69 (0.45–1.05)        | 0.66 (0.46–0.94)                        | 0.64 (0.44–0.92)        |
| Frequent GERD             | 0.43 (0.26–0.73)         | 0.41 (0.24–0.71)        | 0.49 (0.31–0.76)                        | 0.48 (0.33–0.77)        |

Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio; PGI, pepsinogen I; PGII, pepsinogen II.

aCrude model adjusted for sex; year of birth was not adjusted since there was no variance within DZ twins.

bFull model adjusted for sex, BMI, education level, coffee intake, physical activity, smoking, and alcohol consumption; year of birth was not adjusted since there was no variance within DZ twins.

cConditional logistic regression model was used when symptomatic GERD was treated as binary variable (without or with GERD); multinomial fixed effect model was used when symptomatic GERD was treated as a 3-level variable (without GERD, with GERD (less frequent, frequent)).

TABLE 5 Association between atrophic gastritis and the occurrence of gastroesophageal reflux disease (GERD) among 501 monozygotic (MZ) twin pairs discordant for GERD

| Atrophic gastritis (PGI<30) | Crude model, OR (95% CI) | Full model, OR (95% CI) | Atrophic gastritis (PGI<70 and PGI/PGII<3) | Crude model, OR (95% CI) | Full model, OR (95% CI) |
|---------------------------|--------------------------|-------------------------|------------------------------------------|--------------------------|-------------------------|
| No GERD                   | 1.0 (reference)          | 1.0 (reference)         | 1.0 (reference)                          | 1.0 (reference)          | 1.0 (reference)         |
| GERD†                     | 0.60 (0.26–1.37)         | 0.75 (0.31–1.80)        | 0.39 (0.18–0.85)                        | 0.34 (0.14–0.81)        |
| Less frequent GERD        | 0.61 (0.26–1.46)         | 0.71 (0.29–1.78)        | 0.43 (0.19–0.97)                        | 0.42 (0.18–0.99)        |
| Frequent GERD             | 0.56 (0.17–1.84)         | 0.61 (0.18–2.05)        | 0.32 (0.12–0.85)                        | 0.34 (0.13–0.92)        |

Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio; PGI, pepsinogen I; PGII, pepsinogen II.

aCrude model did not adjust for year of birth and sex, since there was no variance within MZ twins.

bFull model adjusted for BMI, education level, coffee intake, physical activity, smoking, and alcohol consumption; year of birth and sex were not adjusted since there was no variance within MZ twins.

cConditional logistic regression model was used when GERD was studied as binary variable (no GERD, GERD); multinomial fixed effect model was used when GERD was treated as a 3-level variable (without GERD, with GERD (less frequent, frequent)).

Association between AG and symptomatic GERD in MZ twins

Risk reductions were also observed within MZ twins (Table 5). The ORs were 0.75 (95% CI 0.31–1.80) for AG defined by PGI<30 and 0.34 (95% CI 0.14–0.81) for AG defined by PGI<70 and PGI/PGII<3. Similarly, the inverse association was less prominent for the association between AG and less frequent GERD, than that for the association between AG and frequent GERD in the MZ twins. Results using other definitions of AG are shown in the Supplementary Table S4.

Sensitivity analysis

Sensitivity analyses after excluding the individuals who reported a medication history of histamine-receptor antagonists, proton pump inhibitors, or other anti-acid medicines did not show major differences compared to the main results (Supplementary Tables S5–S8); also no interaction was found between AG and sex (data not shown).

DISCUSSION

This co-twin control study performed in the Swedish Twin Registry adds up to the evidence that AG is associated with a reduced risk for symptomatic GERD, and this relationship persisted after adjusting for known confounders, family-wise factors and genes shared by the twin pairs. Moreover, this inverse association tended to be stronger for frequent GERD (≥1/week) compared to less frequent GERD (<1/week).

Possible mechanism for this association is still unclear. One possible explanation is that chronic AG of the corpus and fundus could cause failure in secretion of the hydrochloric acid, due to the loss of the oxyntic glands and the destruction of parietal cells. On the other hand, the occurrence of GERD is often the outcome of acid injury and a series of inflammation response at esophageal epithelial cells when the acidic secretions in the stomach reflux into the...
Nevertheless, in this study, results did not substantially change with esophagus. Therefore, achlorhydria caused by corpus AG might prevent GERD by reducing the interaction between gastric acid and esophageal mucosa. In addition, corpus AG is shown to be common among adults in Sweden. However, a prospective study showed that GERD still occurred among a quarter of body AG patients, suggesting hypochlorhydria caused by AG could not fully prevent the occurrence of GERD, and further studies for the underlying mechanisms are warranted.

The inverse association between AG and GERD has been reported in previous studies. However, all studies were performed using either a retrospective or cross-sectional study design, without taking into account for the genetic or familial factors. The definition for GERD and the ascertainment for AG were different in the studies, thus introducing remarkable heterogeneity for the estimation. Studies using endoscopic examination as the method for the identification of AG are often affected by small sample size. The reverse causation between AG and GERD might be a concern since long term continuous treatment of PPI medications for the treatment of GERD symptoms could induce AG in the H. pylori infected patients. But in the sensitivity study, when people with a history of PPI or other anti-acid medications were excluded from the analysis, results were not remarkably different from the main results, suggesting this reverse association could not be fully explained by medication history.

The biomarkers used in this study for AG are PGI and PGII, which are precursors of pepsin. PGI is mainly secreted by the gastric glands at fundus whereas PGII is secreted by pyloric and Brunner’s glands without specific site. The concentration of PGI and PGII in the peripheral blood have been shown to be associated with the inflammation level of gastric mucosa, H. pylori infection, and therefore the severity of AG. Disruption of fundic mucosa in severe corpus gastritis is related with a decreased level of synthesis and output of PGI in the blood, and PGII remains unchanged at early stage. PGII constantly elevates with the abnormal mucosa progression of AG, regardless of the site. Besides, H. pylori infection could also affect the serum PGI and PGII level by its interaction with gastrin. However, we were unable to assess this interaction due to missing information on H. pylori. The optimal cut-off values of PGI, PGII, and PGI/PGII for the differentiation of AG patients have been studied in different populations with various sensitivities and specificities. Nevertheless, in this study, results did not substantially change with different cut-off values, suggesting a robust protective role of AG for GERD.

Strengths of this study include the large scale co-twin study design, which enables the adjustment for familial and genetic factors, in addition to a group of well-known risk factors in the analysis. The association remained largely consistent within twin pairs, suggesting a causal association between AG and GERD, and this association was not confounded by genetics or shared family environment. Multiple cut-off values were used to ensure the robustness of the results. There are also several limitations for this study. The accurate diagnosis of GERD is a problem in population-based studies, but by using the structuralized questionnaire validated in several studies, the identification of symptomatic GERD cases in this study should have reliable accuracy. Of note, it is estimated there are around 28% of people with GERD symptoms are caused by non-acid reflux, which can only be confirmed by impedance-pH monitoring. Although we cannot determine the type of reflux in this study, it is known that individuals with non-acid reflux associated GERD are less likely to respond to PPI treatment, thus they are more likely to be in the group of people without PPI treatment. Since in our sensitivity analysis restricted in people without PPI or other anti-acid medication treatment history, the results were similar to those of the main results, we don’t concern non-acid reflux would invalidate our conclusion. In addition, individuals in this study were those who participated in all 3 different waves of studies across decades of years. It might be a concern that people who participated in the study had different characteristics compared to those who did not participate. But the prevalence of frequent GERD in this study is 18.7%, which is at a similar range comparing to the prevalence in the whole twin dataset. Thus people in this study should not be substantially different from those of the whole population. Besides, because of the cross-sectional design in the collection of blood sample and telephone interview, it is hard to conclude a causal direction for this association between AG and GERD. Recall bias also could not be avoided during telephone interview.

In conclusion, this twin-based co-twin control study showed a persistent inverse association between AG and symptomatic GERD after adjusting for potential covariates and familial and genetic factors shared within co-twin pairs.

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CONFLICT OF INTEREST
All authors declare that they have no known competing financial, professional, or personal conflicts that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT
Data used in the current study are sensitive personal data and thus not publicly available due to legal and ethical reasons. However, data can be requested from the Swedish Twin Registry (STR) by an
application to the Steering Group. Conditions for access can be found on the STR homepage (http://ki.se/en/research/the-swedish-twin-registry).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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