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Association between gastroesophageal reflux disease and atrial fibrillation: a systematic review and meta-analysis

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ABSTRACT

Background and objective: associations between gastroesophageal reflux disease (GERD) and atrial fibrillation (AF) are inconclusive. Some studies found that AF was a risk factor for GERD whereas other studies showed opposite results. The primary objective of this study was to systematically evaluate whether GERD and AF have a bidirectional association using a meta-analysis.

Methods: a systematic review was conducted of studies on the association between GERD and AF, written in the English language and included in Cochrane CENTRAL, PubMed and EMBASE until February 2017. The search was limited to longitudinal, case-control, and cross-sectional studies.

Results: among 548 studies found in the above-mentioned databases, seven fulfilled the inclusion criteria. Among these seven studies, two were longitudinal studies, two were case-control studies, and three were cross-sectional studies. The summary adjusted relative risks (RRs) for AF-induced GERD and GERD-induced AF were 1.54 (95% CI, 1.08-2.17) and 1.06 (95% CI, 0.86-1.31), respectively. The subgroup analysis showed that the associations were not significantly modified by sample size, study design, age, or geographic area.

Conclusions: this meta-analysis supported the association of AF with increased risk of GERD.

Key words: Gastroesophageal reflux disease. Esophagitis. Atrial fibrillation.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common diseases in gastroenterology. It is described as the existence of esophageal mucosal injury secondary to gastric reflux. In recent epidemiological studies, GERD has been reported to have a prevalence of up to 11.6%-27.8% in developed countries and nearly 2.5%-7.8% in Asia (1). Furthermore, a number of severe complications including hemorrhage, stricture and Barrett's esophagus would arise following GERD (2).

Atrial fibrillation (AF) is a common chronic cardiac dysrhythmia in clinical practice, which has been increasingly associated with morbidity in recent years. Approximately 25% of subjects older than 40 years will suffer from AF during their lifetime (3). AF is associated with a five-fold risk of stroke, a three-fold incidence of heart failure, and higher mortality (4). It seriously impairs the quality of life of patients, and is a heavy burden for public health. In previous studies, factors such as age, male gender, hypertension, diabetes mellitus, obesity, and heart failure were shown to be related to AF (5,6).

Several researchers have studied the relationship between AF and GERD (7-14). Ludwig Roemheld et al. were the first investigators to analyze the link between gastrointestinal symptoms and arrhythmias, giving it the name "Roemheld gastrocardiac syndrome", and defining it as arrhythmia symptoms secondary to esophageal or gastrointestinal tract stimulation (7). However, the relationship of these two entities remains controversial. Several studies have supported the association between AF and GERD (9,11-13,15), while other studies did not find a significant association or confounding factors in the study design (8,14). Furthermore, previous reviews have only vaguely referred to the association between GERD and AF (16-20).

So far, no meta-analysis has been conducted to explore the associations between GERD and AF. The present study is the first attempt to address this issue since the work by Carina Roman et al. (19), and to conduct a meta-analysis to systematically evaluate whether there is a bidirectional association between GERD and AF.

METHODS

Search strategies

A systematic literature search was conducted in Cochrane CENTRAL, PubMed, and EMBASE up to February 2017. The following relevant keywords and combinations were used: "gastroesophageal reflux", "gastroesophageal reflux disease", "GERD", "esophageal reflux", AND "atrial fibrillation", "auricular fibrillation", and "AF". The meta-analysis of observational studies in epidemiology (MOOSE) guidelines were applied (21).

Inclusion and exclusion criteria

Inclusion criteria: a) original research articles; b) observational studies or randomized controlled trials; and c) studies that explicitly expressed the association of GERD and AF. Exclusion criteria: a) uncontrolled studies; b) review articles, case reports, and studies published in languages other than the English language; c) non-human studies; and d) multiple studies that provided results from the same survey.

Study selection

Two independent investigators screened the titles or abstracts of the studies obtained from these electronic databases to classify all potential qualifying studies. Potentially relevant studies were subsequently acquired, and the full manuscripts were assessed for conformity with the inclusion criteria. Any ambiguity or disparity between the two investigators was solved by consensus after re-evaluating the source data and deliberating with a third reviewer.

Data extraction and quality assessment

Two investigators reviewed and extracted the relevant information from each study obtained from these databases. Relevant key data from these correlative studies included: first author and year of publication, country of origin, sample size, study design, mean age in years, diagnostic criteria of GERD and AF, RR (or HR) and its 95% confidence interval (CI), and study conclusion. Two authors completed the quality assessment using the Newcastle-Ottawa Scale (NOS) (22).

Statistical analysis

We examined the relationships between GERD (or AF) and risk of AF (or GERD) based on the relative risk (RR), odds ratio (OR), and 95% confidence intervals (CI) published in each of the cohort studies and case-control studies. Odds ratios and incidence rate ratios were considered as equivalent to RRs. For the two cross-sectional studies the primary outcome we analyzed was the rate ratio between a positive rate of AF in patients with GERD and without GERD. Accordingly, the 95% CIs were calculated by the p-value in the corresponding studies, and the normal inverse cumulative distribution function (NICF) (23). Heterogeneity across studies was examined using Cochrane's Q and I^2 statistics (24). Regarding the Q statistic, a *p*-value < 0.1 was considered as statistically significant for heterogeneity; for the I^2 statistic the following cutoff points were used: < 30% (little or no heterogeneity), 30-75% (moderate heterogeneity), and > 75% (high heterogeneity) (25). The combined RRs were computed using either fixed-effects models or, in the presence of heterogeneity, random-effects models (26). Forest plots were produced to visually assess RRs and their corresponding 95% CIs across studies, both for individual studies and all studies combined.

To explore potential sources of heterogeneity, subgroup analyses based on the adjusted RRs were conducted considering primary results, sample size, study design, age, and geographic area. Any potential publication bias was evaluated by visual inspection of funnel plots, Egger's test, and Begg's test (27,28). All reported *p*-values were 2-sided, and a $p < 0.05$ was considered as statistically significant. Statistical analyses were performed using the Stata, version 12.0 tool (STATA Corporation, College Station, TX, USA).

RESULTS

Studies and patient characteristics

A total of 548 studies were identified as potentially relevant to the review in this study. Among them, 73 studies were included from PubMed, 458 from EMBASE, and 17 from Cochrane CENTRAL. Simultaneously, 52 duplicate studies were excluded by using the Endnote software. Furthermore, the titles and abstracts of the remaining 496 studies were screened. Among these, 305 studies were irrelevant or had no abstract; 110 studies were case reports; three studies had non-human subjects; 57 studies were reviews, and one study

was a meta-analysis. The remaining 20 studies were evaluated, and seven of them were found to be original works on the association between GERD and AF. Thus, these studies were finally included in the current meta-analysis (the details of the search strategy are presented in figure 1).

The characteristics of the studies included are listed in table 1 and table 2. In general, all these studies were observational studies. Furthermore, two of the seven studies were cohort studies, while three were cross-sectional studies, and two were case-control studies. Moreover, two studies were conducted in the US, two were conducted in Japan, one was conducted in Taiwan, one was conducted in South Korea, and one was conducted in Romania. All these studies were published between 2008 and 2017. The NOS scores were used to assess research quality (21) (21). Overall, one study had a score of 8, three studies had a score of 7, one study had a score of 5, and the remaining two studies were not scored since the articles lacked a relevant evaluation index (Tables 1 and 2).

GERD and risk of AF

A total of four studies, including one cohort study, two case-control studies and one cross-sectional study for a total of 29,671 healthy participants and 82,882 GERD cases showed no statistically significant association between GERD and risk of AF. The summary RR was 1.06 (95% CI, 0.86-1.31) and heterogeneity was high (p = 0.004; I^2 = 77.6%) (Fig. 2).

AF and risk of GERD

One cohort study and two cross-sectional studies with a total of 2,168 normal participants and 1,723 AF cases indicated that AF was a risk factor for GERD. The summary RR was 1.54 (95% CI, 1.08-2.17), and heterogeneity was moderate among studies (p = 0.154, I^2 = 46.6%) (Fig. 2).

Subgroup and sensitivity analyses

According to the RR in each study, we performed subgroup and sensitivity analyses to assess the potential sources of heterogeneity and the robustness of the pooled estimation (Table 3). The results showed that the summary adjusted RR of AF or GERD did not significantly change when restricting the assessment by sample size, study design, age, or geographic

area.

Publication bias

A review of funnel plots could not eliminate the potential for publication bias for GERD and AF (Figs. 3 and 4). Therefore, we carried out Begg and Egger tests to evaluate publication bias, which showed no evidence of publication bias for GERD and AF (Begg's: p = 0.12 for AF can increase the incidence of GERD, p = 0.96 for GERD can increase the incidence of AF; Egger's: p = 0.37 for AF can increase the incidence of GERD, p = 0.78 for GERD can increase the incidence of AF).

DISCUSSION

The current meta-analysis of seven observational studies provides evidence that the summary adjusted relative risks (RRs) for AF-induced GERD were 1.54 (95% CI, 1.08-2.17) and those for GERD-induced AF were 1.06 (95% CI, 0.86-1.31). These associations were not significantly modified by sample size, study design, age, or geographic area.

During the past decades conflicting findings on the association between AF and GERD were reported. In 2012, Chin-Chou Huang et al. (11) performed a nationwide population-based study of the Taiwanese population and showed that GERD was an independent risk factor for AF (HR: 1.31; 95% CI, 1.06-1.61). A recent case-control study in the Korean population (13) showed that the AF group's adjusted hazard ratio (HR) of GERD identification was 1.37 (95% CI, 1.16-1.57) according to a Cox's proportional hazard model. These studies had some obvious weak points, especially poor study design and small sample size, which may induce some bias and limit statistical power for the detection of important associations. This meta-analysis allowed the pooling and quantification of results from different studies to enhance statistical power, and provided more precise and reliable risk estimates. The results of the reported meta-analysis of seven observational studies suggested that AF was a risk factor for GERD. However, a potential publication bias could not be discarded because statistical tests were not significant, which could result from the limited number of studies included in the analysis, which in turn may lead to lack of statistical power.

Although the pathophysiological mechanism of AF-induced GERD remains unclear, two potential mechanisms have been presumed since the adjacent anatomical relationship

between the left atrium and lower esophagus may result in vagal nerve overstimulation and local inflammation. First, an enlarged, fibrotic left atrium may stimulate the adjoining esophagus (10,12,13). Furthermore, Kubota et al. (12) pointed out that prandial AF paroxysms resulted from amplified efferent vagal nerve activity, which activates the secretion of gastric acid and relaxes the esophageal sphincter, thus inducing acid reflux. Second, local inflammation has been shown to be involved in the pathophysiology of both AF and GERD (10,12,13). Inflammatory factors such as oxidative stress, interleukin 6 (IL-6) and IL-8 might play a significant role in the occurrence of GERD and AF initiation (12,13). Heterogeneity across AF-induced GERD studies was found to be moderate. We attempted to explore any potential sources of heterogeneity by subgroup analyses, but moderate heterogeneity remained unsatisfactorily explained.

Study limitations

First, only seven studies met the inclusion criteria and were included, and the search for studies was restricted to the English language and observational studies. Second, the direction of the associations between GERD and AF could not be established due to lack of temporality in the two cross-sectional studies. Third, these studies had relevant discrepancies concerning factors such as selection criteria, type of study, choice of statistical analysis method, and significant trial results. Fourth, a potential publication bias may have influenced the findings. Although there was no evidence of small study effects with the statistical tests in our analysis, it is still possible that a number of studies with null results remained unpublished, and this may have led to exaggerated risk estimates.

CONCLUSIONS

This meta-analysis found that there is no bidirectional association between AF and GERD, as well as further evidence supporting that AF is associated with increased risk for GERD. Further large-scale, prospective cohort studies among the general population, and randomized controlled trials are required to explore the correlation between GERD and AF.

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Table 1. Atrial fibrillation (AF) associated with the risk of gastroesophageal reflux disease (GERD)

Author, year	*Study design*	*Country*	*Sample size*	*Mean age (years)*	*GE dia*
Hwang, 2015	Case-control study	South Korea	AF (n = 1,612), non-AF (n = 1,612)	AF: 68.34 ± 10.60; Non-AF: 68.42 ± 11.55	Typ syr
Shimazu, 2011	Cross sectional study	Japan	n = 188	60.4 ± 0.9	F-s
Kubota, 2013	Cross sectional study	Japan	Outpatients (n = 201), non-outpatients (n = 278)	60.4 ± 12.8	Qu F-s

AF: atrial fibrillation; GERD: gastroesophageal reflux disease; ECG: electrocardiogram; ICD-9: International Classification of Diseases, Ninth Revision; F-scale: the frequency scale for symptoms of GERD; RAF: radiofrequency catheter ablation; OR: odds ratio; IR: incidence ratio; N/A: not available.

Table 2. Gastroesophageal reflux disease (GERD) associated with the risk of atrial fibrillation (AF)

Author, year	*Study design*	*Country*	*Sample size*	*Mean age (years)*	*GERD diagnosis*	*AF diagnosis*	*Estimated effects (95% CI)*	*NOS*	*Conclusion*
Bunch, 2008	Cohort study	USA	n = 5,288	53 ± 17	A self-report instrument	ECG	RR, 0.81 (0.68-0.96)	7	There was no relationship between AF and GERD. Patients with esophagitis were more likely to develop AF
Huang, 2012	Cohort study	Taiwan	GERD (n = 29,688), comparison cohort (n = 29,597)	50.99 ± 16.61, 50.85 ± 16.8	Endoscopy or 24-hour pH-metry inspection	Electrocardiography and Holter monitors	RR, 1.31 (1.06-1.61)	8	GERD was independently associated with an increased risk of future AF in a nationwide population-based cohort
Kunz, 2009	Cohort study	USA	n = 163,627	51.8	ICD-9	ICD-9	RR, 1.08 (1.02-1.33)	7	GERD is associated with increased risk of diagnosis of atrial fibrillation
Floria, 2017	Case-control study	Romania	GERD (n = 64),	GERD: 61.5 ± 9 Non-GERD: 58 ± 9	According to the Montreal Consensus	ECG	OR, 1.17 (0.78-1.75)	5	Sympathovagal balance seems to be disrupted in patients with GERD, with dominance of the parasympathetic system and increased risk for arrhythmias

AF: atrial fibrillation; GERD: gastroesophageal reflux disease; ECG: electrocardiogram; ICD-9: International Classification of Diseases, Ninth Revision; F-scale: the frequency scale for symptoms of GERD; RAF: radiofrequency catheter ablation; RR: risk ratio; OR: odds ratio; N/A: not available.

Table 3. Subgroup analyses of the association between GERD and AF

Subgroup	*RR*	*95% CI*	$p_{heterogeneity}$	I^2 *(%)*
GERD increased AF				
Sample size, N				
< 5,000	1.17	0.78-1.75	0	0
≥ 5,000	1.04	0.81-1.34	0.001	84.7
Study design				
Cohort	1.04	0.81-1.34	0.001	84.7
Case-control	1.17	0.78-1.75	0	0
Age, years				
< 60	1.04	0.81-1.34	0.001	84.7

≥ 60	1.17	0.78-1.75	0	0
Geographic area				
Asia	1.31	1.06-1.61	0	0
Europe	1.17	0.78-1.75	0	0
North America	0.94	0.71-1.25	0.01	85.1
AF increased GERD				
Study design				
Cross-sectional	1.73	0.82-3.64	0	0
Case-control	1.37	1.18-1.59	0.23	29.3

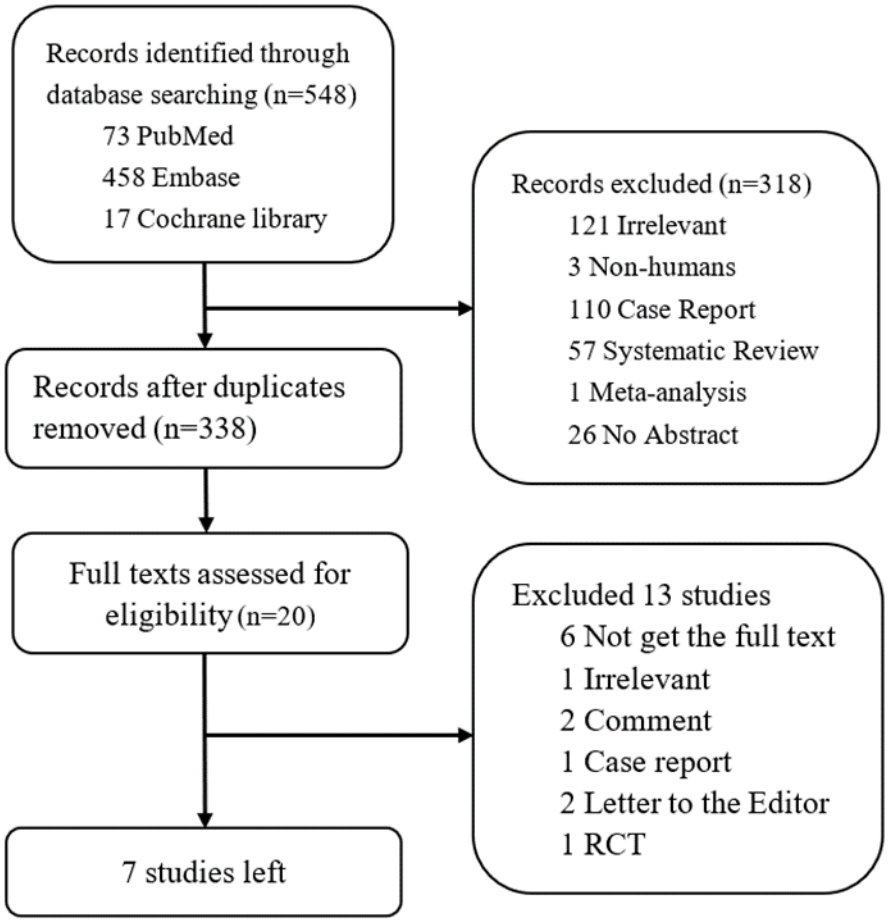

Fig. 1. Flow diagram for the inclusion of studies in the systematic review.

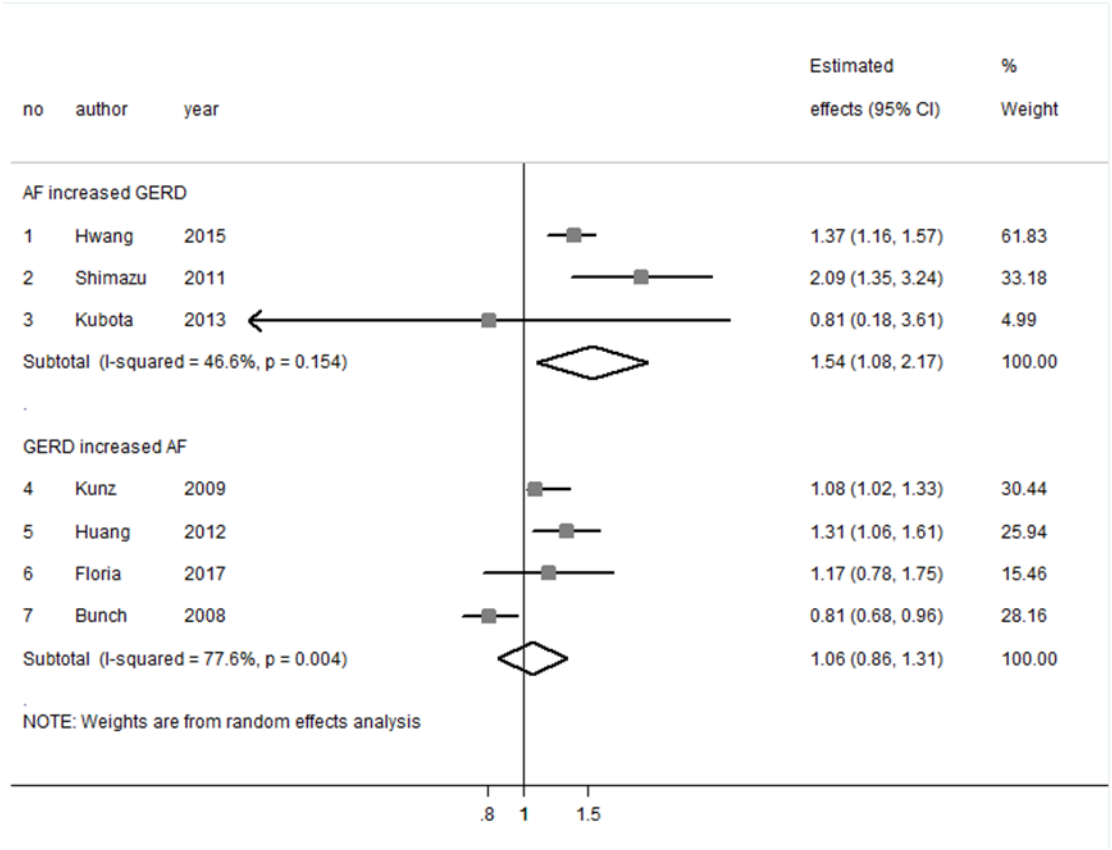

Fig. 2. Forest plot of the included studies examining the associations between GERD and AF.

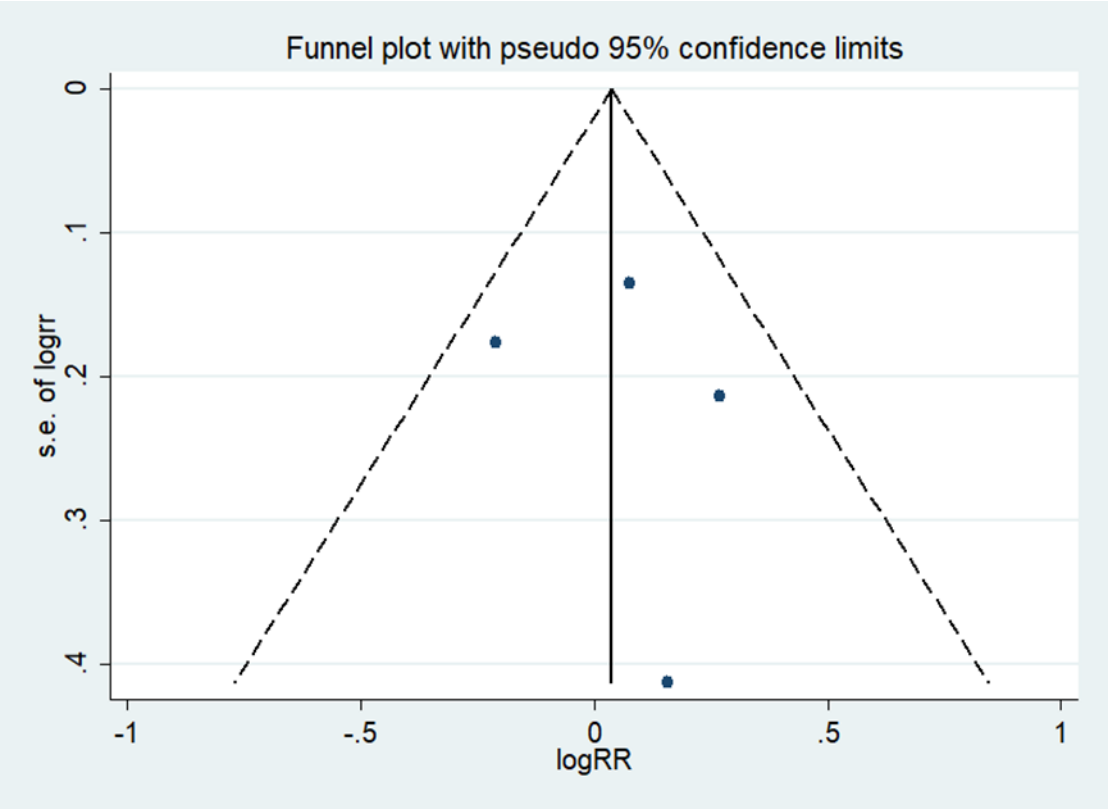

Fig. 3. Funnel plots of GERD and risk of AF.

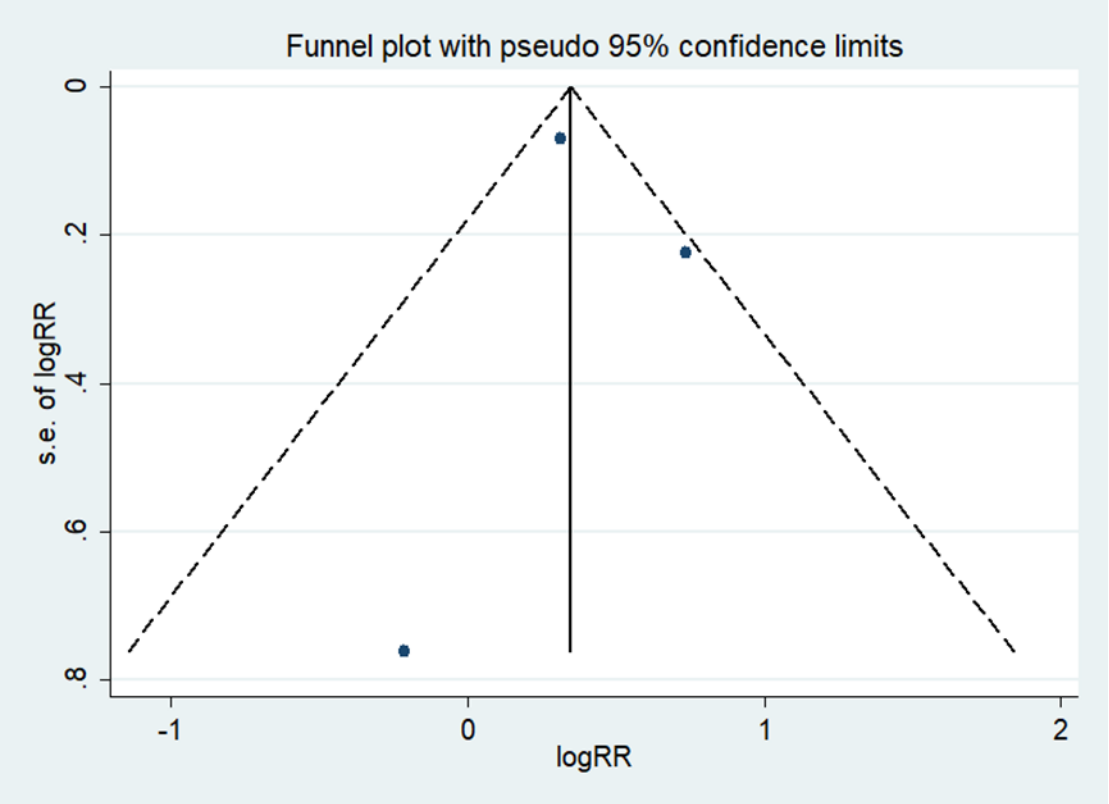

Fig. 4. Funnel plots of AF and risk of GERD.