The relationship between metabolic syndrome and increased risk of Barrett's esophagus: An Updated systematic review and meta-analysis

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Abstract

Background: The relationship between metabolic syndrome (MetS) and Barrett's esophagus (BE) is still a challenging issue, and inconsistent results have been reported in different studies. Therefore, this study was conducted to determine the relationship between MetS and BE.

Methods : In this study, we followed the MOOSE protocol and the PRISMA guidelines for reporting the results. All study steps were performed independently by two authors. If necessary, the dispute was resolved by consultation with a third author. The search strategy is designed to find published studies. Comprehensive search was done in the following biomedical databases until July 2019: Cochrane Library, PubMed/Medline, Web of Science, Science Direct, EMBASE, Scopus, CINAHL, EBSCO, and Google Scholar search engine. All analyses were performed using Comprehensive Meta-Analysis Software Ver.2, while p-value lower than 0.05 was considered significant.

Results : In 14 studies with a sample size of 108416, MetS significantly increased the risk of BE (OR=1.315; 95% CI: 1.110-1.558; P<0.001; Heterogeneity: I 2 = 81.55; P<0.001). Sensitivity analysis by omitting one study showed that overall estimates are still robust. Subgroup analysis was significant for continent (P<0.001) and MetS diagnostic criteria (P=0.043), but was not significant for variables of study type (P=0.899), study setting (P=0.115), control groups (P=0.671) and quality of studies (P=0.603). The Begg (P=0.912) and Egger's (P=0.094) tests were not significant; therefore, the publication bias did not play a role in the results.

Conclusion: MetS increases the risk of BE compared to control groups. Future studies should examine whether treatment for metabolic syndrome reduces the risk of BE.

1. Introduction

Barrett's esophagus (BE) is often defined as a change in any length of the epithelium of the esophagus that can be diagnosed as columnar-type mucosa in endoscopy and is confirmed as intestinal metaplasia through esophageal biopsy (1). BE is considered a precancerous condition that is closely related to esophageal cancer, especially esophageal adenocarcinoma (EAC) (2). The prevalence of BE and the incidence of EAC has increased in Western countries (3). The most important risk factor for BE is gastroesophageal reflux disease (GERD), while other risk factors include male gender, hiatus hernia, and smoking (4-5).

Metabolic syndrome (MetS) is a complex disorder that includes central obesity, hypertension (HTN), hyperglycemia, hypertriglyceridemia and high-density lipoprotein cholesterol (HDL-C). In addition to being related to cardiovascular disease, diabetes, and polycystic ovary syndrome, MetS and its elements are also linked with various gastrointestinal diseases and abnormal liver function (6-7). This disease affects one-fifth of the population in developed countries and its incidence increases with age. The prevalence of MetS is approximately 24% in the United States, 12% in Europe and 10-40% in most Asian countries (8-9).

Based on recent evidence, the prevalence of both diseases is increasing rapidly. Hence, the relationship between MetS and BE has been hypothesized (8-9). Most studies investigating the relationship between obesity and BE have shown that obesity can lead to a significant increase in the risk of BE (4-5).

Although numerous studies have shown that any of the MetS criteria (i.e., abdominal obesity, hyperglycemia, and hypertension) can be a risk factor for BE, the relationship between MetS and BE is still a challenging issue, and inconsistent results have been reported in different studies (10-20). Therefore, this study was conducted to determine the relationship between MetS and BE.

2. Method

- **2.1 Study Protocol**

In this study, we followed the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) (21-23) protocol and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (S1 file) (24) guidelines for reporting the results. All study steps were performed independently by two authors. If necessary, the dispute was resolved by consultation with a third author.

- **2.2 Search strategy**

The search strategy is designed to find published studies. Comprehensive search was done in the following biomedical databases until July 2019:

Cochrane Library (Cochrane Database of Systematic Reviews - CDSR), PubMed/Medline, Web of Science (ISI), Science Direct, EMBASE, Scopus, CINAHL, EBSCO, and Google Scholar search engine.

There were no restrictions based on language or release date. The search was done using the following MeSH keywords: "Metabolic Syndrome"[Mesh], "Gastroesophageal Reflux"[Mesh], "Esophagitis"[Mesh], "Barrett Esophagus"[Mesh], and "Esophagus"[Mesh].

Combined search in PubMed was done as follows: ((("Metabolic Syndrome"[Mesh]) AND "Gastroesophageal Reflux"[Mesh]) OR (“Esophagus"[Mesh] OR "Barrett Esophagus"[Mesh])) OR "Esophagitis"[Mesh]. Reference lists were screened from all relevant studies to find potential articles.

- **2.3 Study selection**

Two authors (M.A, M.K, or M.S) screened the titles and abstracts independently and then reviewed the full text of the retrieved studies for eligibility based on the defined criteria. If necessary, the dispute was resolved by consultation with a third reviewer.

- **2.4 Inclusion and exclusion criteria**

This study included prospective and retrospective studies (e.g. cohort, case-control and cross-sectional studies). The language of the published articles was considered in all languages and no historical restrictions were placed on the search. Google Translate and a relevant language teacher were referred to for the translation of non-English texts if necessary. The exclusion criteria were: duplicate studies, studies that did not differentiate BE from GERD, being irrelevant; low quality in qualitative assessment; case studies, review articles, letters to the editor without quantitative data and theses.

- **2.5 Data Extraction**

If available, the following data were extracted according to the aim of the study: first author's name, year of publication, year of review, country/continent, in formation about the study population (specific groups, population size for the entire sample, case, control, male and female in each case and control groups), number of BE positive patients in each case and control, study design, setting, adjusted or unadjusted odds ratio (OR_s) or relative risk (RR_s), diagnostic criteria for MetS, and quality assessment score.

- **2.6 Quality Assessment**

Methodological quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (25) for both cohort or case-control studies based on study design and its adapted type for cross-sectional studies. The scale is based on three categories: 1. sample selection (4 points), 2. Comparability of groups (2 points), and 3. Level of exposure/outcome (3 points). Therefore, a maximum of 9 points can be attained. The different levels of methodological quality were defined as follows: 0-4 points: low quality, 5-7 points: average quality, and 8-9 points: high quality.

- **2.7 Statistical analysis**

We combined the studies with the odds ratio (OR_s) index and 95% confidence interval. In studies that did not report OR_s and 95% confidence intervals, we calculated them based on the total sample size of each group as well as the number of MetS positive cases in each of the case (BE) and control (Non-BE) groups. A P value below 0.10 in the Q test for heterogeneity is considered as significant. I^2 index and Q test were used to evaluate the heterogeneity of studies. Cut-off points for I^2 were defined as 0-24%, 25-49%, 50-74%, and 75-100% for low, medium, high and very high, respectively (26, 27). According to significant heterogeneity, we used random effects model in meta-analysis. We performed sensitivity analysis for the stability of pooled estimation through omission of only one study. To find out the cause of the heterogeneity, we performed subgroup analysis based on study type, setting, control groups, MetS diagnostic criteria, and continent. Meta-regression analysis was also performed based on the year of publication. Funnel plot and Begg and Egger's tests were used to assess publication bias (28, 29). All analyses were performed using Comprehensive Meta-Analysis Software Ver.2, while p-value lower than 0.05 was considered statistically significant.

3. Results

- **3.1 Search results and study characteristics**

The electronic search has identified 2510 studies. A total of 2492 studies were excluded based on the review of title and abstract. Another 7 articles were excluded because they did not meet our inclusion criteria. Eleven articles met our inclusion criteria and were included in the meta-analysis (the studies of Drahos J, 2015 [13], Leggett CL, 2013 [14], and Thrift AP, 2015 [15] each were considered as two studies, since they reported the data in two different populations) (Figure 1). The characteristics of the studies are shown in Table 1.

- **3.2 Meta-analysis of MetS and increased risk BE and sensitivity analysis**

In 14 studies with a sample size of 108416, MetS significantly increased the risk of BE (OR=1.315; 95% CI: 1.110-1.558; P< 0.001; Heterogeneity: I^2= 81.55; P< 0.001) (Figure 2-A). Sensitivity analysis by omitting one study showed that overall estimates are still robust (Figure B-2).

- **3.3 MetS subgroup analysis and increased risk of BE**

Subgroup analysis was significant for continent (P < 0.001) and MetS diagnostic criteria (P = 0.043), but was not significant for variables of study type (P = 0.899), study setting (P = 0.115), control groups (P = 0.671) and quality of studies (P = 0.603) (Figure 3).

- **3.4 Meta-regression and publication bias**

The meta-regression model based on year of publication of articles was not significant for the relationship between MetS and BE (meta-regression coefficient: 0.041; 95% CI -0.017 to 0.101; P = 0.167) (Figure 4-A).

The publication bias is shown as a funnel plot, and the Begg (P = 0.912) and Egger's (P = 0.094) tests were not significant; therefore, the publication bias did not play a role in the results (Figure B-4).

4. Discussion

The present study is an update to the previous meta-analysis in 2016 (30), which found a significant relationship between MetS and BE (OR = 1.23; 95% CI: 1.03–1.47; P = 0.024) by combining eight studies. In the present study, a combination of 14 studies showed that MetS significantly increases the risk of BE (OR = 1.315; 95% CI: 1.110-1.558; P < 0.001). The strengths of the present study were the increase in the number of studies involved in meta-analysis and finding a more accurate relationship and a stronger level of significance for the relationship between MetS and BE. The causes of heterogeneity between the studies include the continent (P < 0.001) and MetS diagnostic criteria (P = 0.043).

In a systematic review and meta-analysis, age, male gender, smoking, longer BE segment, and low-grade dysplasia were risk factors for BE progression (31). However, other studies continue to suggest that GERD is the strongest risk factor for BE. Moreover, the use of statin alone or in combination with aspirin as well as proton pump inhibitors (PPI) significantly reduced the risk of BE (31, 32). In another meta-analysis, infection with Helicobacter pylori (H. pylori) also reduced the risk of BE (33).

BE is a precancerous condition for the EAC (2). EAC is the most common type of esophageal cancer in the United States. Although GERD, smoking, and obesity have been suggested as associated risk factors, the major predictor of progression from non-dysplastic BE to esophageal adenocarcinoma is the presence of dysplastic changes in esophageal histology (34). Clinical guidelines recommend that periodic endoscopy be used to diagnose dysplasia and primary cancer in patients with BE, and this monitoring for BE patients may improve the prognosis of EAC (35).

A meta-analysis confirmed the conclusion that central adiposity can be strongly associated with esophageal inflammation and reflux (36). Studies have shown that visceral obesity, as the main criterion for MetS, can increase the transient lower esophageal sphincter relaxation, the incidence of hiatal hernia, or even intra-abdominal pressure and acid reflux (37, 38).

In studies about hypertriglyceridemia, even after adjusting for obesity and other metabolic factors, it is associated with increased risk of BE (8). Impairment of lipid metabolism is common in MetS. Abdominal obesity is a known risk factor associated with MetS. MetS is the result of obesity-related hormonal and systemic inflammatory changes and is associated with multi-system cancers in humans. There are several possible explanations for this relationship. First, insulin resistance and fatty liver may be responsible for elevated serum triglyceride (TG) levels, since fatty liver is significantly associated with fasting glucose and TG levels (39). Hypertriglyceridemia is also associated with increased insulin resistance (40). Second, since H. pylori infection is known to be a protective factor for EE (41, 42) and chronic H. pylori infections can alter serum lipid profile, such as increasing total cholesterol and TG (43, 44), the increased serum TG levels can only be a side effect associated with H. pylori infection.

In other studies, the association between HTN and hypercholesterolemia (as MetS components) has also been demonstrated (45). Atherosclerosis is recognized as an important factor for the development of HTN. In previous studies, atherosclerosis was associated with a high incidence of hiatal hernia. Loss of flexibility in the phrenoesophageal ligament in patients with arthrosclerosis and HTN is one of the causes of increased incidence of hiatal hernia (46).

In the present study, the meta-regression model based on year of publication of articles was not significant for the relationship between MetS and BE, which means that year of publication could not be a influencing factor on heterogeneity of studies.

This study has several strengths, including the fact that we used a comprehensive, concurrent search strategy to maximize the ability to identify all relevant literature. All stages of the research were conducted by two researchers independently, and the differences were resolved by discussion. We contacted the authors of the studies to obtain additional data. Based on the available data, we were able to identify some of the causes of heterogeneity between the studies.

One of the limitations of the present study is the high heterogeneity between the studies, though we attempted to discover the causes of heterogeneity through subgroup analysis. In addition, most studies were conducted in the United States, which may influence the results, according to continental analysis subgroup.

5. Conclusion

MetS increases the risk of BE compared to control groups. The results of this study can help health practitioners by identifying a treatable risk factor for the most important risk factor for esophageal carcinoma (ie, BE). Future studies should examine whether treatment for metabolic syndrome reduces the risk of BE and EA.

Abbreviations

BE Barrett's esophagus

EAC Esophageal adenocarcinoma

GERD Gastroesophageal reflux disease

MetS Metabolic syndrome

HTN Hypertension

HDL-C High-density lipoprotein cholesterol

MOOSE Meta-analyses Of Observational Studies in Epidemiology

PRISMA Systematic Reviews and Meta-analysis

OR Odds ratio

CI Confidence interval

Declarations

Authors' contributions

MA, MS, and MK acquired the data. MA and MK analyzed and interpreted the data. MA drafted the manuscript; MA, MS, and MK critically revised the manuscript for important intellectual content. MK supervised the study.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

We declare no competing interests.

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Tables

Table 1: Summary of characteristics in studies into a meta-analysis

Ref.	First author, Published Year	Design	Year of study	Place	Study setting	Special groups	Controls groups	criteria for MetS	Sample size				
									All	Case		Control	
										All	M,F	All	M,F
10	Lee SW, 2017	Cross-sectional	2006-9	Taiwan	Population_based		Endoscopy control	IDF	6594	95	61:34	6499	3447:30
11	Healy L.A, 2010	Case-control	2003	Ireland	Hospital_based	-	Control with reflux symptoms	IDF	231	118	79 : 39	113	67 : 46
12	Wani SB, 2008	Case-control	NR	USA	Hospital_based	93.2% Caucasians	Control with reflux symptoms	Not mentioned	309	103		206	
13	Duggan C, 2013	Cohort	1995-2009	USA	Hospital_based	96.4% White	BE baseline	IDF	388				
14	Drahos J, 2015	Cross-sectional	2009	USA	Population_based	87.4% White	Endoscopy control	NCEP-ATP III	8792	2198	1150:1048	6594	3450:31
14	Drahos J, 2015	Cross-sectional	2009	USA	Population_based	85.3% White	Endoscopy control	NCEP-ATP III	8170	2198	1150:1048	5972	3036:29
15	Leggett CL, 2013	Case-control	1999-2006	USA	Population_based	96.4% Caucasians	Control without reflux symptoms	IDF and WHO	206	103	70:33	103	70:33
15	Leggett CL, 2013	Case-control	1999-2006	USA	Population_based	96.4% Caucasians	Control with reflux symptoms	IDF and WHO	206	103	70:33	103	70:33
16	Thrift AP, 2015	Case-control	2008-2011	USA	Hospital_based	100% White man	Colonoscopy control	NCEP-ATP III	453	244		209	
16	Thrift AP, 2015	Case-control	2008-2011	USA	Hospital_based	100% White man	Endoscopy control	NCEP-ATP III	859	244		615	
17	Drahos J, 2016	Cross-sectional	1992-2012	United Kingdom	Population_based		Endoscopy control	NCEP-ATP III	60382	10215	6399:3816	50167	31375:1
18	Wu P-C, 2019	Cross-sectional	2016-2018	South Korea	Population_based		Endoscopy control	IDF	4943	88	66:22	4855	2475:23
19	Drahos J, 2017	Cross-sectional	2003-2009	USA	Population_based		Endoscopy control	NCEP-ATP III	16410	575		15835	
20	Kendall B, 2010	Case-control	2003-6	Australia	Population_based		Endoscopy control	Not mentioned	473	236		237	

MetS: Metabolic Syndrome; M,F: Male, female; QS: Quality Score; OR: Odds Ratio; CI: Confidence Interval; IDF: International Diabetes Federation; WHO: world Health Organization; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III: LA: Los Angeles classification; NR: Not Reported. * was calculated.

Figures

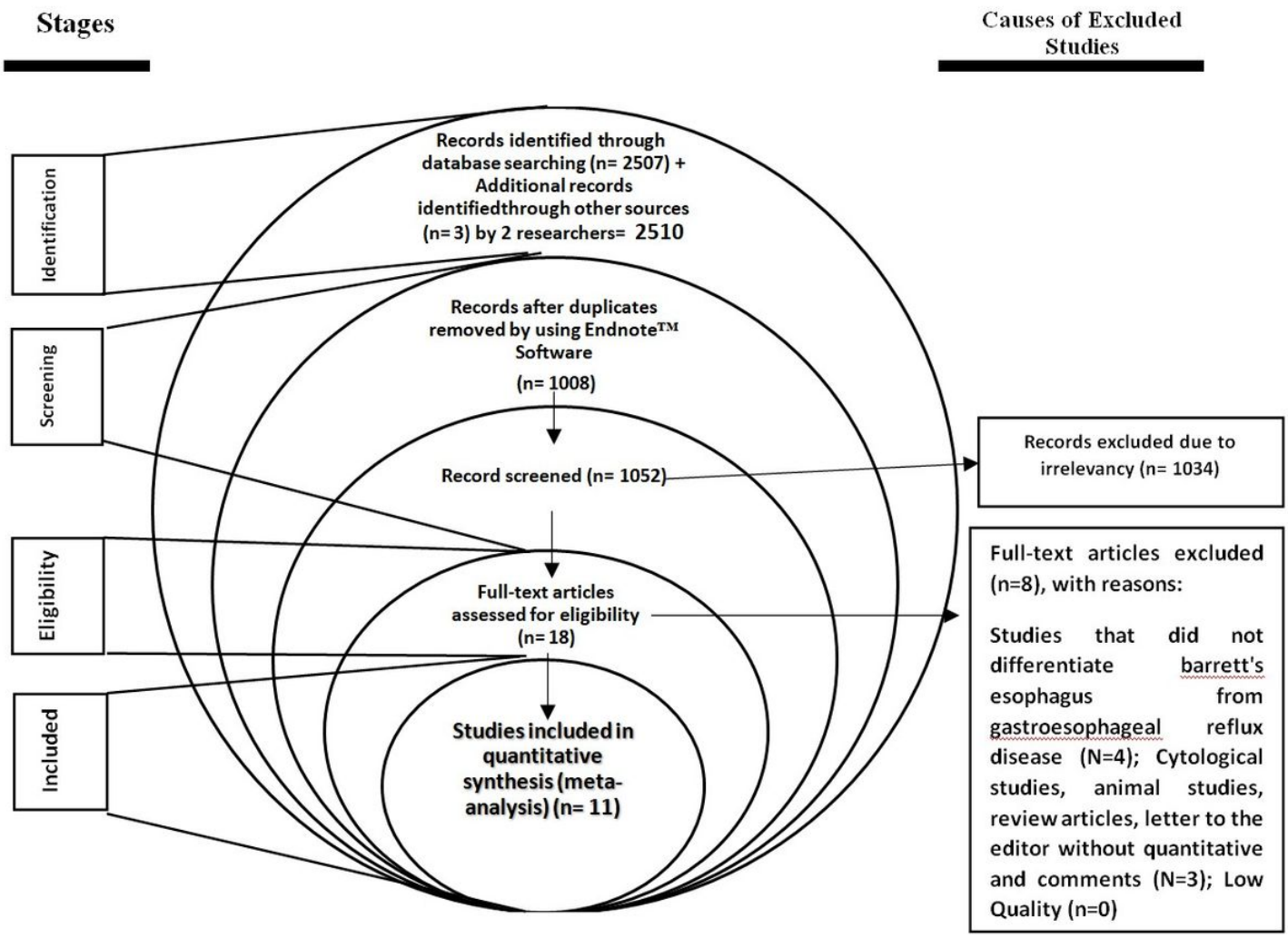

Figure 1

The studies selection process for meta-analysis.

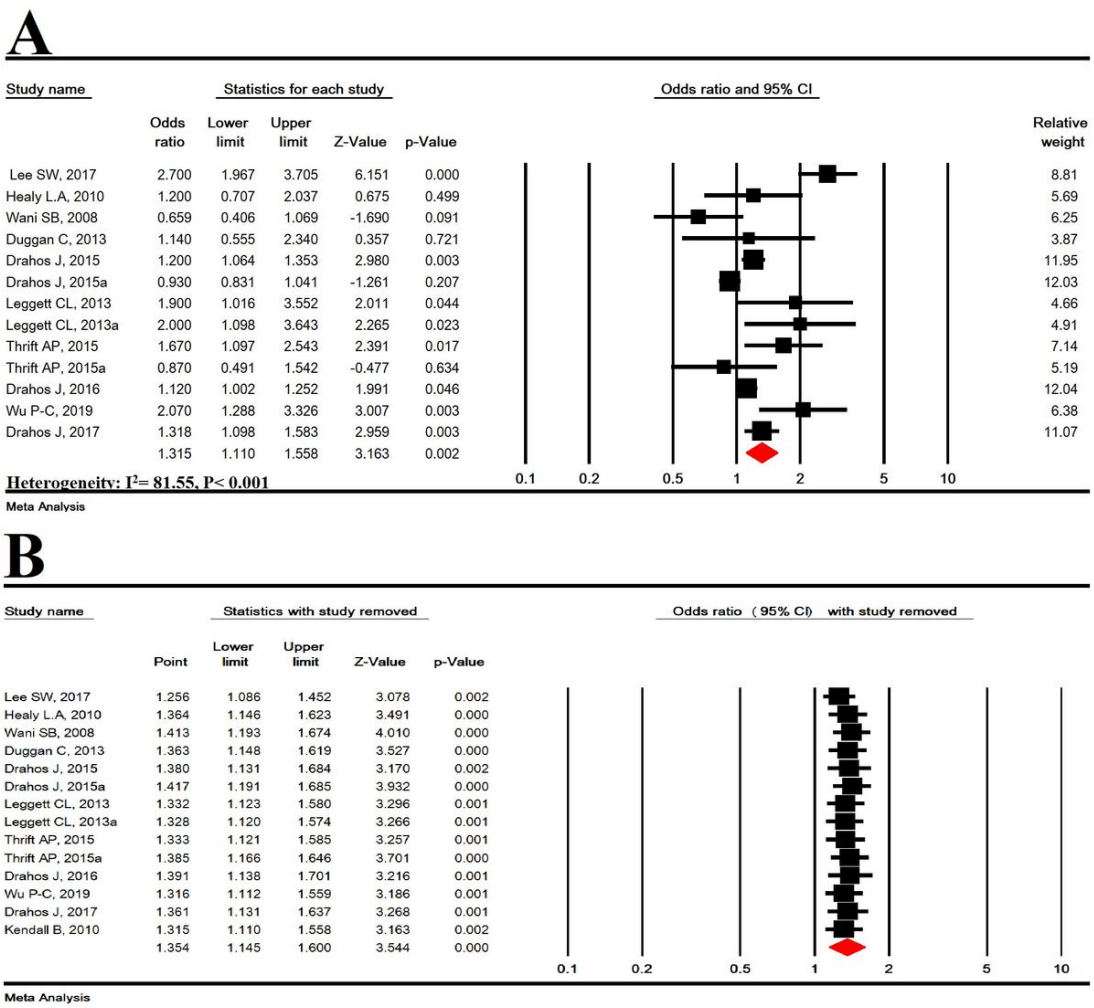

Figure 2

Meta-analysis (A) and sensitivity analysis (B) for the association between metabolic syndrome and increased risk of barrett's esophagus.

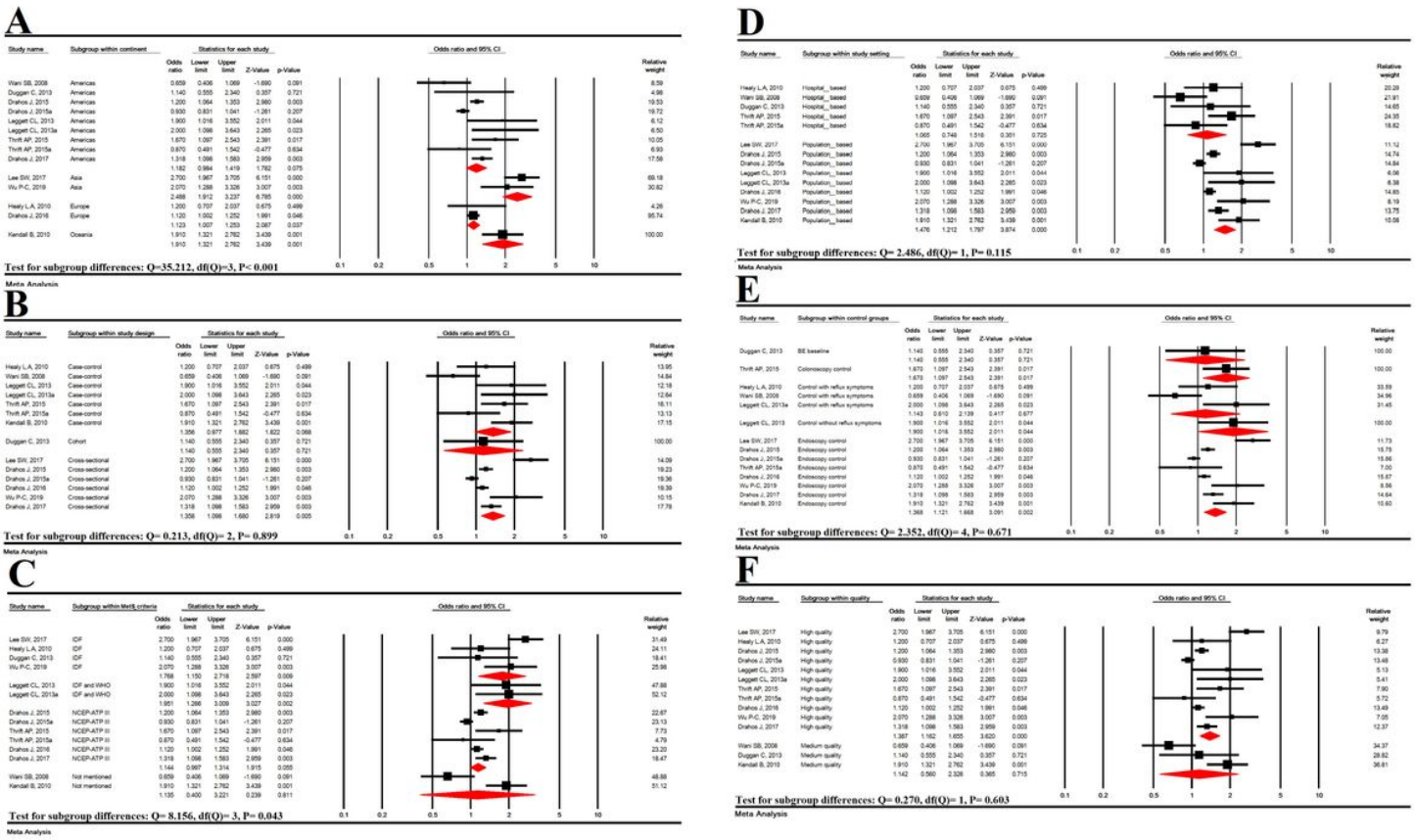

Figure 3

Subgroup analysis based on continents (A), study design (B), MetS diagnostic criteria (C), study setting (D) and control groups (E), study quality (F)

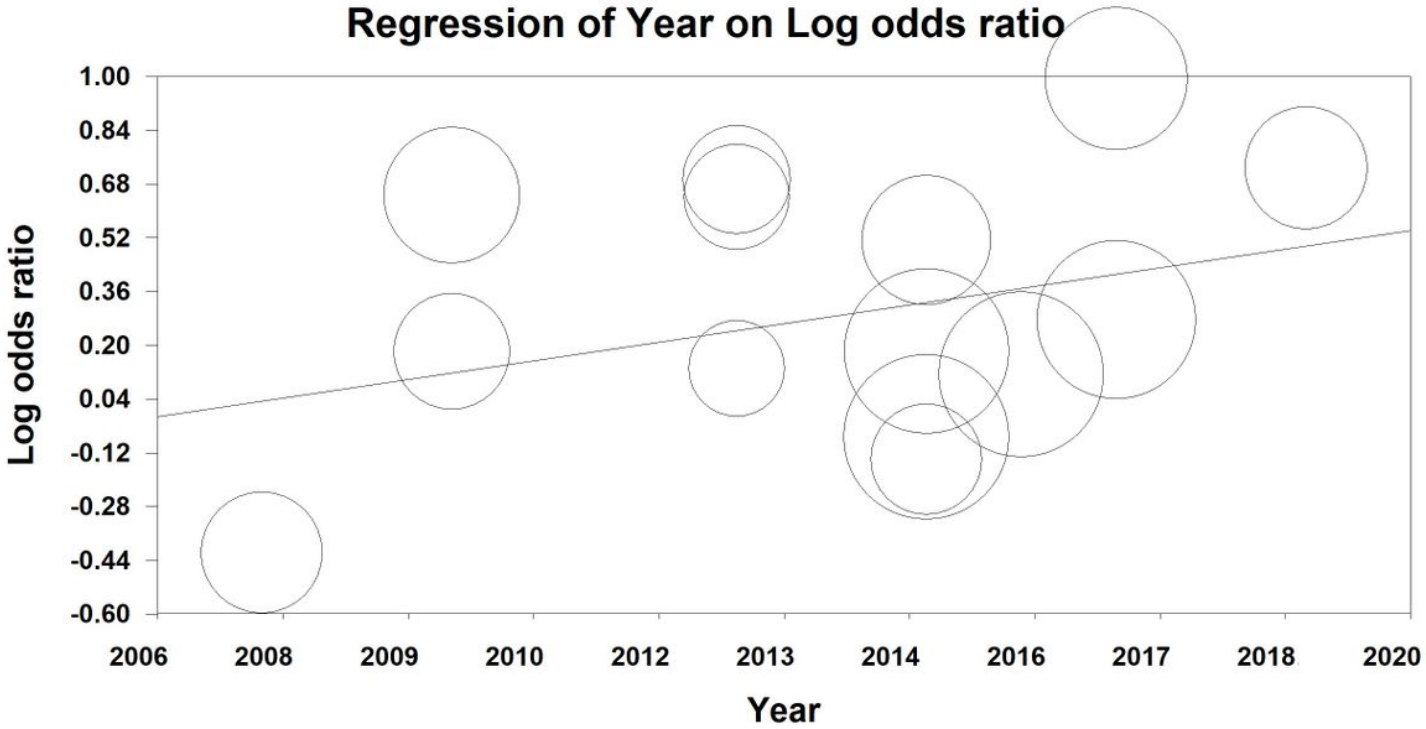

Figure 4

Meta-regression based on published year

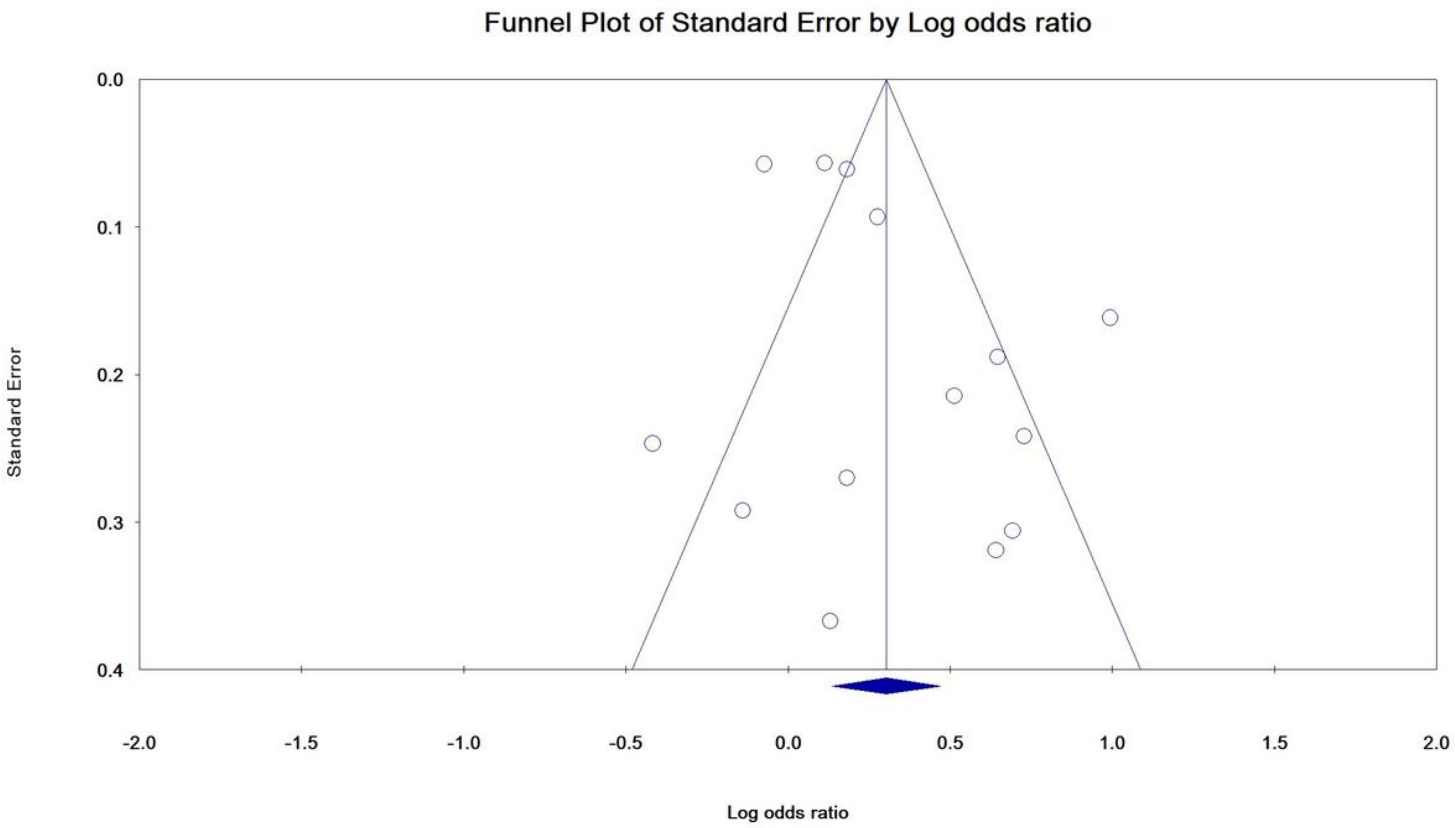

Figure 5

Publication bias

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