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Metabolic syndrome is associated with increased risk of Barrett esophagus

A meta-analysis

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Abstract

Background: Barrett esophagus (BE) is considered precursor condition of esophageal adenocarcinoma. Its incidence and prevalence are increasing in general population. Studies reported that metabolic syndrome (MS) or diabetes mellitus (DM) is related to increased risk of BE. Current study was to assess and better understand the relationship between MS /DM and BE.

Methods: Electronic search was conducted in the database Pubmed/Medline (-December, 2015), Embase (-December, 2015), Cochrane Library (-December, 2015), and Web of Knowledge (-December, 2015). Studies included were assessed with summary odds ratios (ORs) with 95% confidence intervals (CIs) and compared exposure group with control group. The heterogeneity was examined by the funnel plot and the Egger's test. Subgroup analyses and sensitive analyses were performed for the detection of possible heterogeneity and impact on stability of analysis results.

Results: Twelve publications met the criteria and included 355,311 subjects were analyzed. The pooled results showed MS was closely associated with increased risk of BE (OR = 1.23; 95%CI 1.03–1.47; $P = 0.024$), and yet DM did not significantly increase the risk of BE (OR = 1.07; 95%CI 0.82–1.38; $P = 0.627$). Substantial heterogeneities were detected. No significant publication bias was detected by Egger's test ($P = 0.23$).

Conclusions: Based on the results of current meta-analysis, MS is associated with increased risk of BE. Further long-term follow-up prospective study needs to verify the current results, and definite pathophysiological mechanism needs to be further investigated and clearly elucidated.

Abbreviations: BE = Barrett esophagus, DM = diabetes mellitus, EAC = esophageal adenocarcinoma, EGC = esophageal cancer, MS = metabolic syndrome.

Keywords: Barrett esophagus, diabetes mellitus, esophageal cancer, metabolic syndrome, risk factor

1. Introduction

The incidence and prevalence of esophageal cancer (EGC) are increasing in the worldwide,[1] especially among patients with Barrett esophagus (BE).[2] BE is considered as a kind of premalignant conditions and closely associated with EGC, especially esophageal adenocarcinoma (EAC).[3] Several factors previously reported could have impact on long-term outcomes of BE in high-risk general population. It is generally known that gastroesophageal reflux disease is the primary risk factor for BE.[1] In addition, central adiposity also significantly increases the risk of erosive esophagitis, esophageal metaplasia, BE, and EAC.[4,5] Its effects may be mediated by reflux-dependent/independent mechanisms.[6] However, the exact mechanism now is unclear and needs to be deeply investigated. Furthermore, several studies published in recent years showed that statins use may be associated with lower risk of EGC, particularly in patients with BE.[7]

Lipid metabolism disorder is an established factor and closely related with increased risk of cardiovascular events and endocrine diseases such as metabolic syndrome (MS) or type 2 diabetes mellitus (DM). A recent epidemiologic survey found that MS is diagnosed in 46% patients with BE; moreover, central obesity is found in 78.4% of those patients.[8] Some studies also revealed that the proportion of MS in BE patients far exceeds that of normal population.[9,10] And yet it is unclear that the

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QH and J-dL contributed equally to this study.

Authorship: QH conceived and designed the study; QH and J-dL collected original raw data and analyzed the data analysis; WH and W-cZ contributed to final statistical analysis; and J-QY and WH arbitrated in the event of any lack of consensus during screening original publications.

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relationship between MS or DM and BE. Several observational studies also revealed that MS[8,9] or DM[11,12] was detected in BE patients and accounted for a quite large proportion of those patients. Furthermore, in those patients with established DM, BE is more commonly detected in DM patients compared with those without this disease.[13] However, a few studies drew the opposite conclusion.[14] In order to better understand the correlation of MS or DM and BE, we undertook a systematic review and meta-analysis based on observational studies that investigated the relationship between MS/DM and the risk of BE. Furthermore, subgroup analysis was conducted in consideration of other impact factors so as to understand whether MS or DM is independent effect on BE.

2. Materials and methods

2.1. Search strategy

We followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement during performing this meta-analysis. Ethics committee and/or institutional board approval was not necessary because this is a meta-analysis. Computer-aided search strategy was conducted by using the databases Pubmed/Medline (-December, 2015), Embase (-December, 2015), Cochrane Library (-December, 2015), and Web of Knowledge (-December, 2015). The starting year at initial retrieval was not restricted for searching potential studies. We used the following key terms: metabolic syndrome, diabetes mellitus, Barrett's oesophagus, Barrett's esophagus. Manual searches were performed for abstracts published in major international conferences, and additional trials were identified through cited bibliographies of original articles or relevant reviews. Language was not restricted in the initial search. Both English and non-English language publications were searched and retrieved.

2.2. Study selection

Studies considered in this meta-analysis were either RCTs or observational studies that met the following inclusion criteria: clear diagnosis of MS and DM were reported; correlations between MS or DM and BE were described; relative risk (RR) (for cohort studies), odds ratio (OR) (for case–control studies), or data for their calculation were provided; repeated publications were deleted using the reference management software EndNote; and overlapping contents published in different versions were identified, then the most recent record was eligible for inclusion. Inclusion criteria were not otherwise restricted by study sample size, language, or publication type. Retrieved publications were excluded from the final analysis if there were incomplete or insufficient data to determine an estimate of RR/OR and a 95% confidence interval (CI), although these studies were included the this review and reported qualitatively.

2.3. Data extraction and quality assessment

The retrieved citations were reviewed independently by 2 investigators (QH, JDL), discrepancies were resolved by consensus plus views of another investigators (WH, JQY). The data from each study were extracted as follows: the first author of each study, publication year, publication region, number of participants, study period, study setting, study design, the proportion of males/females, and the rate/number of MS or DM cases. The data extraction was completed independently by the 2 investigators.

The methodologic quality assessment was performed independently by 2 reviewers (QH and JDL) using the Newcastle–Ottawa scale (NOS) for evaluating the quality of nonrandomized studies.[15] In this scale, assessment for case–control studies included 3 categories (selection, comparability, and exposure), incorporating 4 items, 1 item, 2 items, respectively. Likewise, evaluation for cohort studies had 3 categories (selection, comparability, and outcome), including 4 items, 1 item, 3 items, respectively. Each item had a score of 1 except for comparability (2 of scores). The maximum score was 9. Re-evaluation for included original studies was conducted and resolved once any discrepancy or conflict occurred.

2.4. Statistical analysis

The software STATA/SE version 11.2 (Stata, College Station, TX) was used to perform statistical analysis. Effect size for pooled discontinuous variables was expressed as odds risks (ORs) and mean difference with 95% confidence interval (95%CI). The OR and 95%CI of each outcome was calculated with random effect model (DerSimonian–Laird) and pooled for summary estimation if significant heterogeneity was detected. Since outcomes were relatively rare, ORs were considered approximations of RR. The heterogeneity cross-included studies were evaluated by calculating the I^2 statistic and P value. The smaller I^2 value shows insignificant heterogeneity, otherwise, the larger value indicates increasing heterogeneity. Where no statistically significant heterogeneity was found, we planned to use a fixed-effect model. A P value < 0.10 was considered statistically significant. If considerable heterogeneity was detected, sources of heterogeneity between studies were further investigated using subgroup analysis by stratification estimate of characteristics of each study, with P value < 0.10 for differences between subgroups being considered statistically significant. Furthermore, a sensitivity analysis was also conducted, whereby each study was omitted in turn. Publication bias was evaluated by visual inspection of funnel plot and examined by the Egger's test. A P value < 0.10 on Egger's test was considered to indicate risk of publication bias.

3. Results

3.1. Characteristics of included studies

A total of 160 potential publications were obtained based on the initial search strategy. Ninety five complete duplications were excluded on the basis of the titles and abstracts. Sixty five citations were further screened by 2 investigators. Twenty four relevant pits were fully reviewed after excluding 41 completely irrelevant publications. Twenty one citations were further identified after excluding 1 case report,[16] 2 reviews.[17,18] Twelve publications including 13 studies[6,10,14,19–27] met the inclusion criteria, and were finally included the data quantitative synthesis analysis after excluding 3 noncontrol citations,[8,9,28] 4 overlapped citations,[11,12,29,30] and 2 other study contents of citations.[13,31]Figure 1 indicated a flow diagram of search strategy.

In the included studies, the vast majority of them were performed in the US population (9 studies), and the remainders were in the Ireland (1 publication) population and Australia population (2 publications). All of the studies incorporated 4 abstracts and 8 full-texts. Most majority of included studies were

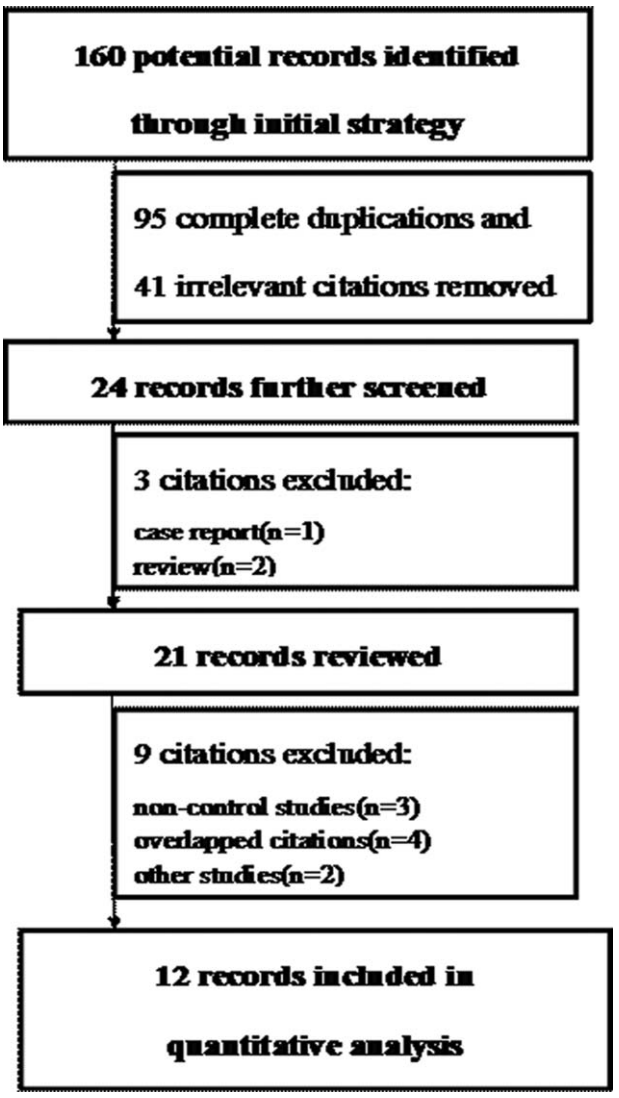

Figure 1. Search strategy for identifying studies to be included in the meta-analysis.

case–control design except one.[22] Identified studies included more than 300 thousand individuals for the final analysis. Four publications studied the association DM and BE;[6,20,23,25] 1 publication investigated the influence of DM, MS on BE;[24] the remainders focused on impact of MS on BE.[10,14,19,21,22,26,27] In addition, a large proportion of population (more than a half) incorporated in the included studies were male individuals.[6,10,22–27] Furthermore, White people was the chief study race identified in the these included studies.[14,22,24–27] The characteristics of the included studies were listed in Table 1.

3.2. Outcomes of meta-analysis

Because of substantial heterogeneity detected by fix-effects model ($I^2=62.8\%$, $P=0.001$), random-effect model was used in the meta-analysis. The overall effect revealed that MS and DM significantly increased the risk of BE (OR=1.16; 95%CI 1.03–1.31; $P=0.018$) ($\chi^2=32.26$; $I^2=62.8\%$, $P=0.018$). Based on the diagnosis of MS and DM, the results revealed that DM was not associated with the risk of BE (OR=1.07; 95%CI 0.82–1.38; $P=0.627$); however, MS considerably increased the risk of BE (OR=1.23; 95%CI 1.03–1.47; $P=0.024$) (Fig. 2, Table 2).

3.3. Subgroup analysis and publication bias

Subgroup analyses were further conducted by stratifying publication type, study design, and study setting (Table 2). As far as 2 publication types were concerned, no significant statistical differences were detected (abstracts: OR 1.26, 95% CI 0.86–1.85, $P=0.232$ vs full text: OR 1.11, 95%CI 0.98–1.25, $P=0.113$). Considering inclusion of overwhelming majority case–control studies (12 studies) and only 1 cohort study, subgroup analyses revealed markedly significance was observed in case–control group (OR=1.16, 95%CI 1.03–1.32, $P=0.019$ vs OR=1.16, 95%CI 1.03–1.31, $P=0.871$). In addition, based on different study settings, analysis result including population-based studies showed statistically significant difference (OR=1.21, 95%CI 1.07–1.36, $P=0.003$). Significant heterogeneity was observed in the overall effect analysis ($\chi^2=32.26$; $P=0.001$, $I^2=62.8\%$). The results were stable according to subgroup interaction heterogeneity analysis (Table 2). Sensitive analysis by omitting 1 study in each turn indicated the results were unaffected. No single study notably affected the overall summary estimate or P value for heterogeneity. Publication bias was evaluated by a funnel plot and Egger's test. Asymmetry was observed by inspection of the funnel plot. Trim and fill method was subsequently analyzed, and the results had no obvious changes (data no shown). No significant publication bias was detected by Egger's test in the meta-analysis ($P=0.23$) (Fig. 3).

Table 1

Characteristics of studies included in the meta-analysis.

Study	Diagnosis	Type	Regions	Study setting	Study design	Study period	Total subjects (n)	MS/DM cases (n)	Special population	M, %	Total quality score (maximum, 9)
Wani (2008)	MS	Abstract	USA	Hospital_based	Case–control	–	309	138	93.2% Caucasians	–	7
Healy (2010)	MS	Full text	Ireland	Hospital_based	Case–control	–	231	91	–	63.2	8
Kendall (2010)	MS	Abstract	Australia	Population_based	Case–control	06/2003	473	260	–	–	5
Kendall (2011)	DM	Abstract	Australia	Population_based	Case–control	06/2003	483	43	–	–	6
Drahos (2013)	MS	Abstract	USA	Population_based	Case–control	–	251,196	30,575	–	–	9
Duggan (2013)	MS	Full text	USA	Hospital_based	Prospective cohort	2/1995–9/2009	388	43	96.4% White	81.9	7
Iyer (2013)	DM	Full text	USA	Population_based	Case–control	5/1991–4/2010	84,606	4582	–	63.6	9
Leggett (2013)	MS and DM	Full text	USA	Population_based	Case–control	1999–2006	309	215	96.4% Caucasians	68	8
Rubenstein (2013)	DM	Full text	USA	Population_based	Case–control	–	901	165	–	100	6
Agrawal (2014)	DM	Full text	USA	Hospital_based	Case–control	1992–2012	583	158	95.7% White	97.4	6
Drahos (2015)	MS	Full text	USA	Population_based	Case–control	–	14,764	4227	85.6% White	51.7	8
Thrift (2015)	MS	Full text	USA	Hospital_based	Case–control	–	1068	689	100% White man	100	8

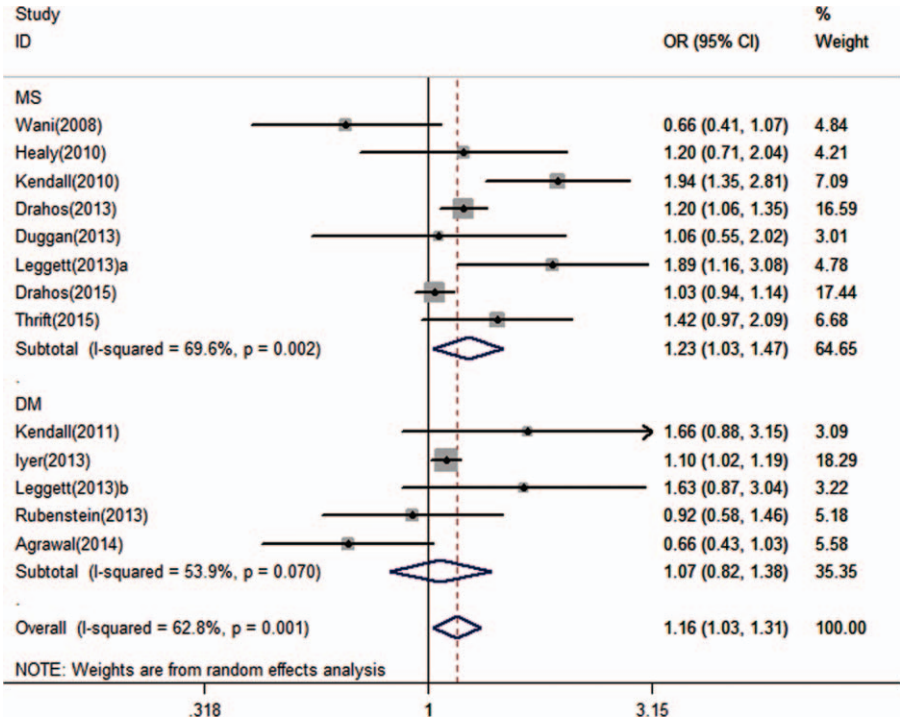

Figure 2. Forest plot based on diagnosis of MS and DM for the risk of BE. BE = Barrett esophagus, DM = diabetes mellitus, MS = metabolic syndrome

Table 2

Subgroups analysis for metabolic syndrome and diabetes mellitus and risk of Barrett esophagus.

Subgroups	Categories	N	OR	95%CI	Heterogeneity between groups (I^2)	Heterogeneity between groups (*P* value)
Publication type	Abstracts	4	1.26	0.86–1.85	61.23%	0.62
	Full-text	9	1.11	0.98–1.25		
Study design	Case–control	12	1.16	1.03–1.32	65.28%	0.702
	Cohort	1	1.06	0.55–2.02		
Study setting	Population_based	9	1.21	1.07–1.36	63.85%	0.145
	Hospital_based	4	0.94	0.62–1.41		
Disease type	Metabolic syndrome	8	1.23	1.03–1.47	65.28%	0.479
	Diabetes mellitus	5	1.07	0.82–1.38		

CI = confidence interval, OR = odds ratio.

4. Discussion

Current study conducted comprehensive review and meta-analysis to provide available information of MS and DM in connection with BE. Our study included over 300 thousand individuals for quantitative assessment. Finally, the pooled results revealed MS is positively correlated with risk of BE while DM did not increase the risk of BE. The confirmation of these results is from data analysis of including large sample population, the reliability of the outcomes have been primarily proved to certain extent. Second, the data calculated from each study almost based on independent of other confound factors, therefore, the facticity of the data is guaranteed.

Multiple previous observational studies as well as meta-analysis have noted a strong positive association between central obesity and BE.[32,33,5,34] Furthermore, recent studies demonstrated that statin use may be associated with lower risk of EAC, particularly risk of EAC in patients with BE.[7,35–38] Lipid

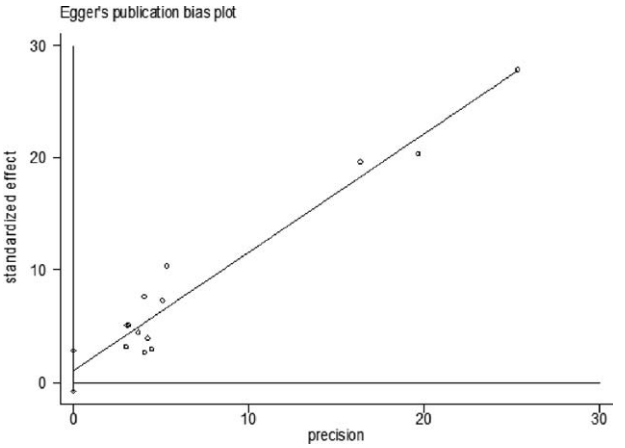

Figure 3. Publication bias detected by Egger test.

metabolism dysfunction is common in MS and DM. Abdominal fat is metabolically active, abdominal obesity is an established risk factor associated with MS. MS results from obesity related hormonal and systemic inflammatory changes and is associated with cancers of multiple systems in human. There are published observational studies suggest that the combined use of a statin and aspirin or another cyclooxygenase inhibitor is associated with a significantly reduced cancer incidence in patients with BE.[39] DM is also correlated with obesity-related hormonal changes and is a recognized risk for numerous epithelium-originating cancers. Considering these factors above and different disease type, we assessed and analyzed outcomes, respectively. In current meta-analysis, we found that MS is associated with an increased risk of BE, and yet DM is not. A recent study concluded that metformin use in DM patients had no influence on risk of BE and EGC, neither an increased risk nor an decreased risk.[25] Therefore, metformin use may not have any statistically significant protective effect for BE. Thus, the concrete mechanism of this association between MS and BE remains unknown and is warranting further study and explored.

In addition, we did not further assess the association of BMI status between MS/DM individuals and BE because several previous published observation and review studies all revealed BMI has no predictive value with respect to gastroesophageal reflux disease patients and their risk of progression to BE.[5,40,41] So, this association is not explained simply by higher BMI among subjects.

There were substantial heterogeneities (I^2 with 50%–70%) detected in quantitative synthesis analysis. Subgroup analyses via investigating publication type, study design, and study setting provided no evidence to support this as a source of heterogeneity.

Year of patient recruitment, human race, human age, diagnosis criteria, and methods of data analysis variables could not be further investigated due to the lack of data and unavailable/insufficient information.

As any meta-analysis previously reported, there were several limitations in our study. First, almost all of including studies were case–control design, information bias, selection bias, and confounding bias are possible. Second, majority of studies are from USA and most of White people are selected for analysis, selection bias is inevitable. Third, significant heterogeneity was observed in the overall analysis. The heterogeneity could be explained by differences in region, ethnicity, the proportion of male subjects, and confound factors such as smoking of exposure ascertainment. Moreover, due to unavailable or insufficient data, these factors were not used for pooled analysis. Such significant heterogeneity has also been observed in previous meta-analyses assessing the risk of obesity/statins and BE, EGC.[5,7] Fourth, there are a few long/short BE described in included studies, the interaction between them and MS/DM is not sure through the studies.

In summary, current study indicates that MS is associated with increased risk of development of BE. DM poses no additional risk for BE according to our results. Future prospective long-term observational study should be investigated, and physiopathological mechanism needs to be further elucidated so as to take protective measures.

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