Metabolic syndrome and the incidence of lung cancer: a meta-analysis of cohort studies

Dong Li[1] **and Heinv Yang**[1]

[1]Department of Cardiac and Thoracic Surgery, Weihai Central Hospital, Weihai 264400, China

Correspondence to: Heinv Yang, **email:** statin2016@163.com

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ABSTRACT

Background: Metabolic syndrome (MetS) has been related to the pathogenesis of variety categories of cancers. This meta-analysis aimed to determine the association between MetS and the incidence of lung cancer.

Materials and Methods: Relevant cohort studies were identified by searching of PubMed and Embase databases. Cochrane's *Q* test and I^2 statistic were used to analyze the heterogeneity. Random effect model was used for the meta-analysis.

Results: Five cohort studies with 188,970 participants and 1,295 lung cancer cases during follow-up were included. No significant association between MetS and lung cancer incidence was found in studies that MetS was defined by the revised NCEP-ATP III criteria (hazard ratio [HR]: 0.94, 95% confidence interval [CI]: 0.84 to 1.05, $p = 0.25$; $I^2 = 0$), or IDF criteria (HR: 0.82, 95% CI: 0.61 to 1.11, $p = 0.20$; $I^2 = 0$). Results were consistent in male and female participants, or in those smoking status was adjusted (HR: 0.91, 95% CI: 0.80 to 1.05, $p = 0.21$; $I^2 = 0$). Sensitivity analyses omitting one study at a time did not significantly change the results. No publication bias was detected based on the Egger regression test ($p = 0.32$).

Conclusions: Presence of MetS does not significantly influence the subsequent incidence of lung cancer.

INTRODUCTION

Metabolic syndrome (MetS) is a cluster of metabolic disorders characterized by the pathophysiological presence of central obesity, insulin resistance, high blood pressure, and dyslipidemia [1–3]. With the aging of the global population, MetS has become a common health problem in both the developed and the developing countries, with the reported prevalence of 10–30% of the adult populations [4–6]. Accumulating evidence confirmed that patients with MetS are at higher risk for the development of many other diseases, such as cardiovascular diseases [7], venous thromboembolism [8] and osteoporosis [9]. Pathophysiologically, MetS is considered as a status of low-grade chronic inflammation [10], which may also be involved in the pathogenesis of tumor development [11]. Consistently, results of epidemiology studies suggested that presence of MetS may confer higher risks for the development of variety categories of cancers, such the colorectal cancer [12], pancreatic cancer [13], breast cancer [14], endometrial cancer [15], hepatocellular carcinoma [16], and prostate cancer [17]. However, the association between MetS and the incidence of lung cancer, the most common malignant tumor of the world [18], has not been fully determined. In a previous meta-analysis [19], by including four cohort studies [20–23], the authors concluded that presence MetS did not affect the risk of lung cancer. However, besides studies reporting the incidence of lung cancer, they also included a study which reported the lung cancer mortality [20]. Since the outcome of cancer mortality could be affected by many clinical factors besides the anticancer treatments, including studies with mortality data may confound the overall result. Moreover, MetS has been defined by a few recently proposed sets of criteria, and these diagnostic criteria vary on whether

abdominal circumference or obesity was included as an essential criteria, whether different cut-off value of the MetS components was used, and whether patients with medications targeting each components of Mets were included [24]. Accordingly, whether MetS defined by two of the most commonly used diagnostic criteria of MetS, the International Diabetes Federation (IDF) criteria [2], and the revised National Cholesterol Education Program's Adults Treatment Panel III (NCEP-ATP III) [3], are associated differently with lung cancer risk remain to be determined. More importantly, some recently published cohort studies were not included in the previous meta-analysis [25–27]. Therefore, we performed an updated meta-analysis to evaluate the association between MetS and subsequent incidence of lung cancer.

RESULTS

Literature searching

The processes of database searching were presented in Figure 1. Briefly, 791 articles were found via initial literature searching of the PubMed and Embase databases, and 770 were excluded through screening of the titles and abstracts mainly because they were not relevant to the purpose of the meta-analysis. Subsequently, 21 potential relevant records underwent full-text review. Of these, 16 were further excluded because two of them were case-control studies, 11 did not report the incidence of lung cancer, two reported the outcome of lung cancer mortality, and the other one included lung cancer patients at baseline. Finally, five cohort studies were included [21–23, 25, 26].

Study characteristics and quality evaluation

The characteristics of the included cohort studies were presented in Table 1. Briefly, our meta-analysis included 188,970 participants from five cohorts. Two studies were from Europe [21, 25], and the other three were from Asia [22, 23, 26]. Regard the design, two studies were retrospective [23, 26], whereas the other three were prospective [21, 22, 25]. Four of the studies included general populations [21–23, 26], whereas the other one included patients with vascular disease [25]. All of the included cohorts defined MetS according to the criteria of revised NCEP-ATP III [3], and two of them also included data regarding MetS as diagnosed with the IDF criteria [2]. The incidence of lung cancer cases were mainly confirmed by the local cancer registries and 1,295 lung cancer cases occurred during follow-up. Age and gender were adjusted in all of the included studies when presenting the results, whereas smoking and alcohol intake were adjusted in four cohorts [22, 23, 25, 26] except for one study [21]. The Newcastle-Ottawa scale varied from 7 to 9 in the included cohort studies (Table 1).

Association between the revised NCEP-ATP III defined MetS and lung cancer risk

Five cohort studies [21–23, 25, 26] with 188,970 participants reported the association between MetS diagnosed by revised NCEP-ATP III at baseline and the subsequent risk of lung cancer incidence. Result of the meta-analysis did not support a significant association between MetS at baseline and the risk of lung cancer incidence in the future (adjusted HR: 0.94, 95% CI: 0.84 to 1.05, $p = 0.25$; Figure 2A) with no significant heterogeneity (p for Cochrane's Q test = 0.72, $I^2 = 0$). Results of sensitivity analyses by excluding one study at a time did not significantly affect the result (adjusted HR: 0.91~0.96, $p = 0.21$~0.44), suggesting the stability of the main result. Moreover, excluding the study [21] in which smoking status was not adjusted showed similar result (adjusted HR: 0.91, 95% CI: 0.80 to 1.05, $p = 0.21$) with no significant heterogeneity (p for Cochrane's Q test = 0.65, $I^2 = 0$). Results of subgroup analyses according to the gender of the participants were also similar (for male: adjusted HR: 0.95, 95% CI: 0.80 to 1.12, $p = 0.55$, $I^2 = 27\%$; for female: adjusted HR: 0.84, 95% CI: 0.66 to 1.07, $p = 0.15$, $I^2 = 0$; Figure 2B). The difference between the results in male and female participants was not statistically significant ($p = 0.40$; Figure 2B).

Association between IDF defined MetS and lung cancer risk

Two cohorts [22, 23] with 66,556 participants reported the association between IDF defined MetS and the subsequent risk of lung cancer. Results of the meta-analysis did not show a significant association (adjusted HR: 0.82, 95% CI: 0.61 to 1.11, $p = 0.20$; I $I^2 = 0$; Figure 3). Results of subgroup analyses according to the gender of the participants were also similar (for male: adjusted HR: 0.78, 95% CI: 0.44 to 1.39, $p = 0.40$, $I^2 = 50\%$; for female: adjusted HR: 0.81, 95% CI: 0.50 to 1.31, $p = 0.39$, $I^2 = 0$; Figure 3). The difference between subgroups was not statistically significant ($p = 0.93$).

Publication bias

The funnel plot regarding MetS diagnosed by revised NCEP-ATP III at baseline and risk of cognitive decline was shown in Figure 4. The funnel plot was symmetry on visual inspection. Results of Egger regression test suggested that no significant publication bias was detected ($p = 0.32$). The publication bias for the meta-analysis of association between IDF defined MetS and the subsequent risk of lung cancer was difficult to estimate since limited cohorts were included.

DISCUSSION

In this meta-analysis, by pooling the results of five cohort studies of 188,970 participants, the result showed

Table 1: Characteristics of the included cohort studies

Study	Country	Design	Characteristics of the participants	Number of participants	Diagnostic criteria of MetS	Follow-up period	Diagnosis of lung cancer	Number of lung cancer cases	Outcome reported	Variables adjusted	NOS
						years					
Russo 2008	Italy	PC	Community based population	16677	NCEP-ATP III	1999~2005	Local Cancer Registry	118	M, F, T	Age, gender	7
Inoue 2009	Japan	PC	Community based population	27724	NCEP-ATP III and IDF	1990~2014	National cancer registries	224	M, F	Age, study area, smoking status, alcohol intake, daily total physical activity level, and TC	9
Osaki 2012	Japan	RC	General health examinees	38832	NCEP-ATP III and IDF	1992~2007	Tottori prefectural cancer registry	211	M, F	Age, smoking status, alcohol intake	9
Kruijsdijk 2013	the Netherlands	PC	Patients with vascular diseases	6172	NCEP-ATP III	1996~2011	Netherlands Cancer Registry	118	T	Age, gender, smoking status, alcohol intake	8
Ko 2016	Korea	RC	National sample cohort for health check-up	99565	NCEP-ATP III	2002~2013	Local Cancer Registry	624	M, F	Age, gender, smoking status, alcohol intake, and exercise	9

Abbreviations: NOS, the Newcastle-Ottawa Scale; PC, prospective cohort; RC, retrospective cohort; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program's Adults Treatment Panel III; IDF: International Diabetes Federation; M, male; F, female; T, total; TC, total cholesterol.

that presence of MetS does not significantly influence the subsequent incidence of lung cancer. The results were consistent in male and female participants, and in studies in which the smoking habit was adjusted when presenting the result. Moreover, the association between MetS and lung cancer incidence was not affected by the definitions of MetS (based on the revised NCEP-ATP III or IDF criteria). These results suggested that based on current evidence, MetS may not be a risk factor for the development of lung cancer.

Results of our study may have important clinical implications because these findings are contrast to the conventional viewpoint that patients with Mets are at higher risk for developing lung cancer because the

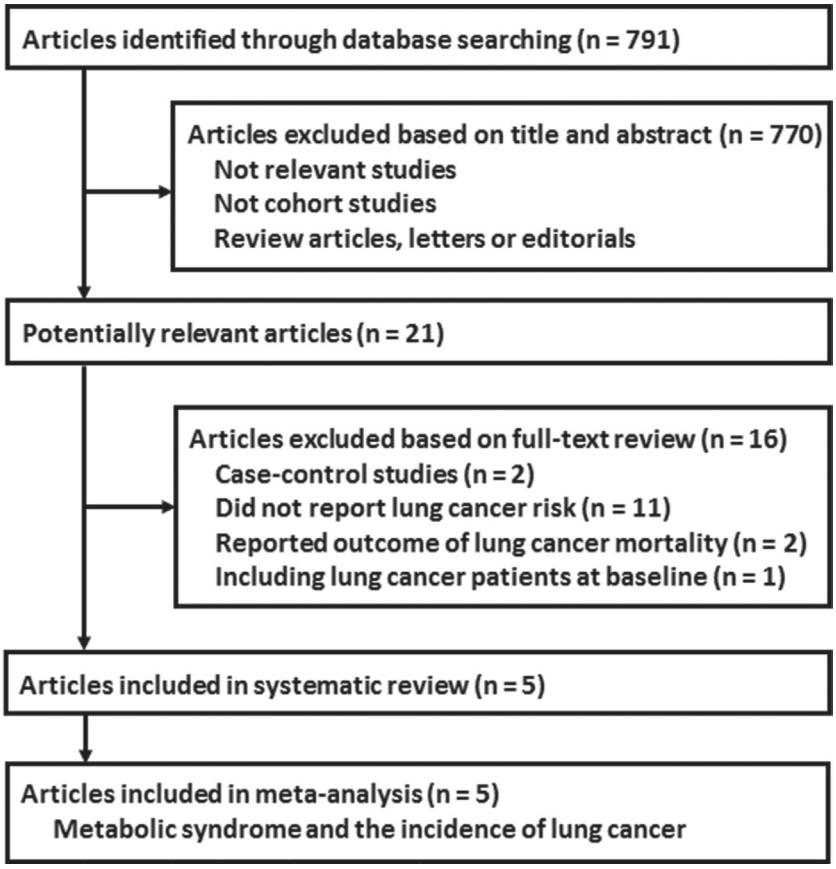

Figure 1: Flowchart for database searching and literature screening.

components of MetS are potential risk factors for lung cancer, and these patients are with poor living habits, such as smoking, unhealthy diet, and alcohol drinking. Accordingly, results of our meta-analysis may reflect the fact that the components of MetS may have different influence on the risk of lung cancer. For the association between obesity and lung cancer risk, current evidence is not consistent. A previous meta-analysis 31 studies showed that obesity is protective factor against lung cancer [28], whereas another study in Chinese patients suggested that the protective effect of obesity against lung cancer may be confounded by the smoking status [29]. Subsequent meta-analysis of six prospective cohort studies indicated that abdominal obesity may be a risk factor for the incidence of lung cancer [30]. Moreover, as for the lipids profiles, recent evidence indicated that higher high-density lipoprotein cholesterol level is protective against the lung cancer, whereas higher triglyceride is associated with higher lung cancer incidence [31]. In addition, results regarding the association between hypertension and lung cancer risk are inconsistent. The result Metabolic Syndrome and Cancer Project indicated a small increased lung cancer risk in men with elevated blood pressure level, but not in women [32]. However, an early study in Korean men showed that hypertension was not an independent risk factor in lung cancer mortality [33]. Similarly, result of a meta-analysis of 14 cohort studies also indicated that no association between diabetes and lung cancer risk exists [34]. Taken together, only higher triglyceride of MetS components may relate to the higher risk of lung cancer, and the association between MetS and subsequent risk of lung cancer may depend on the predominance of the distribution of the components. Also, since patients with MetS often have unhealthy life styles, such as smoking, alcohol drinking and less exercise, these factors may confound the association between MetS and lung cancer.

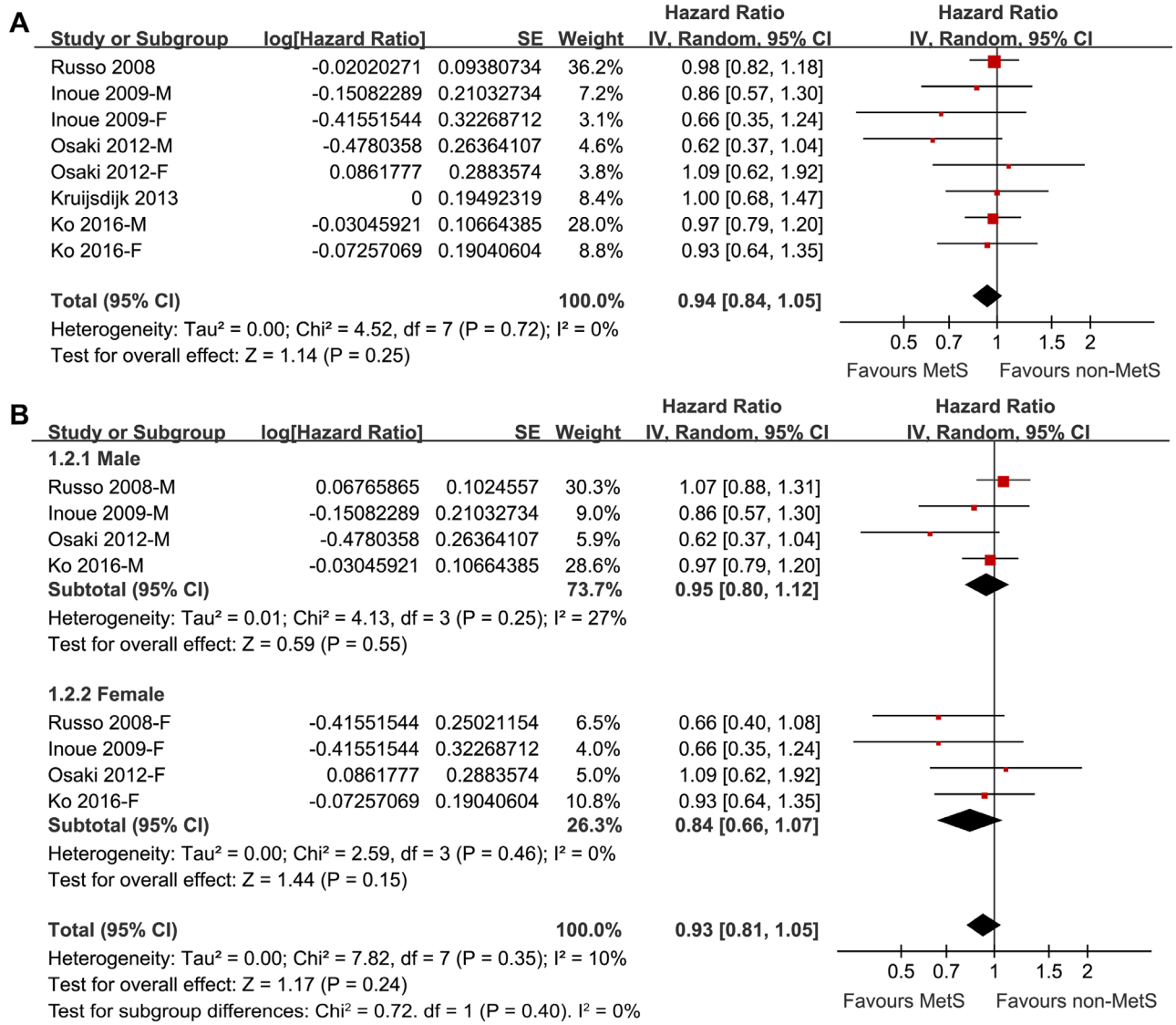

Figure 2: Forest plot for the meta-analysis of the association between the revised NCEP-ATP III defined MetS and lung cancer risk. (**A**) forest plot for the overall participants; (**B**) forest plot for the subgroup analysis by gender.

Most of our included studies adjusted these factors, which may therefore weaken the association between MetS and Lung cancer incidence. Moreover, accumulating evidence showed that treatments against the components of Mets, such as metformin [35], may lead to a reduced risk of lung cancer incidence. Whether these factors may confound the association between MetS and Lung cancer risk also deserves further investigation.

Our study has limitations which should be considered when interpreting the results. Firstly, as a meta-analysis of observational studies, results of our study did not support a sequential association between MetS and lung cancer incidence. Whether Mets plays a causative role in the pathogenesis of lung cancer remains to be determined. Clinical trials evaluating the influence of the treatments against the components of MetS on the incidence lung cancer may be optimal. Secondly, although MetS defined by revised NCEP-ATP III or IDF criteria was not associated with lung cancer incidence, association between MetS defined by other criteria and

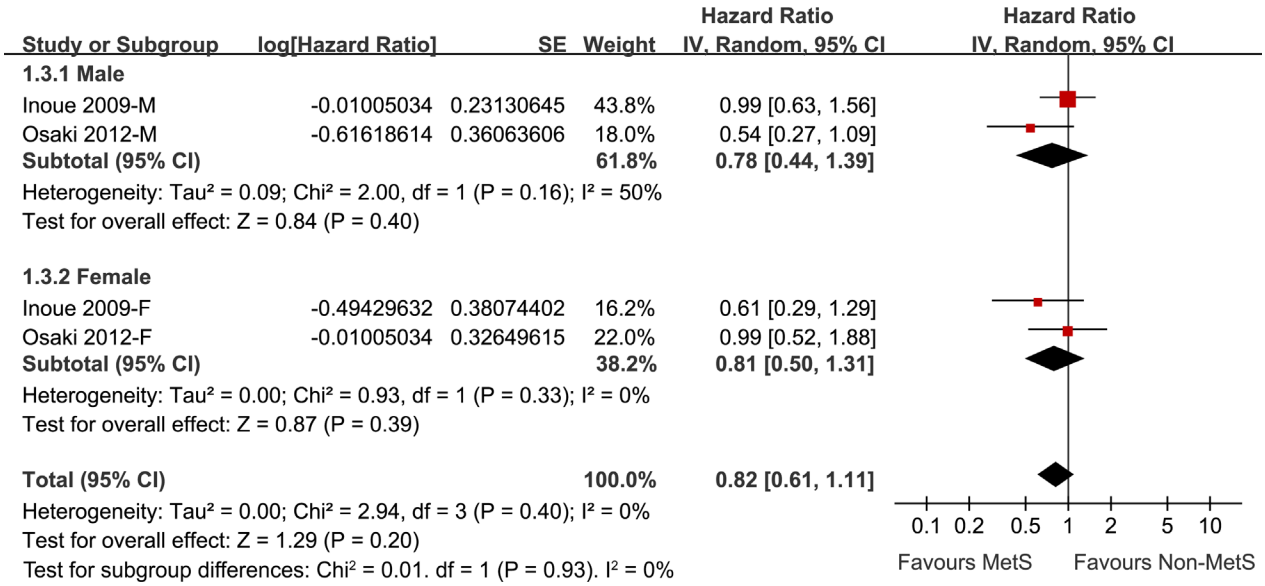

Figure 3: Forest plot for the meta-analysis of the association between IDF defined MetS and lung cancer risk stratified by gender.

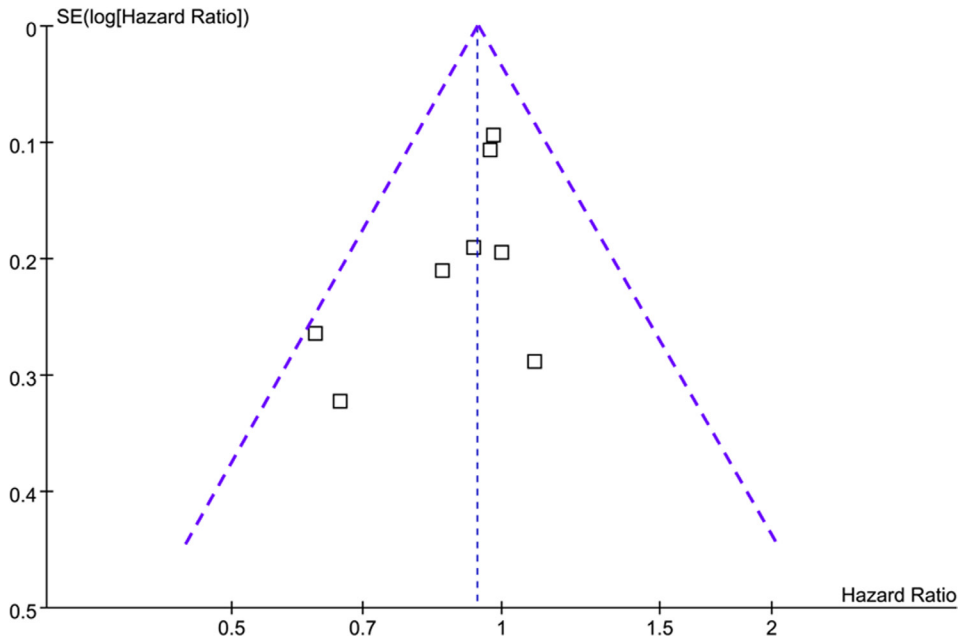

Figure 4: Funnel plot for the meta-analysis of the association between the revised NCEP-ATP III defined MetS and lung cancer risk.

subsequent lung cancer incidence remains undetermined. Thirdly, although our study combined the data of 188,970 participants and 1,295 cases of lung cancer, we could not fully exclude the possibility that the scale of the study is not adequate to be statistically powered for the detection of the association between MetS and lung cancer incidence. Finally, since no pathological data were available, we were unable to determine whether no association between MetS and lung cancer exist regardless of the pathologic categories of the cancer.

In conclusion, results of our meta-analysis showed that presence of MetS does not significantly influence the subsequent incidence of lung cancer. The previous supposition that MetS patients may have higher risk of lung cancer may be confounded by the factors of poor lifestyle, including smoking.

MATERIALS AND METHODS

We performed the meta-analysis in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) [36] and Cochrane's Handbook [37] guidelines.

Literature searching

Databases of PubMed and Embase were searched for relevant records, using the terms "metabolic syndrome", "insulin resistance syndrome", or "syndrome X", combined with "cancer", "neoplasm", "carcinoma", and "prospective", "prospectively", "retrospective", "retrospectively", "followed", "follow-up", "cohort", or "cohorts". The searching was limited to studies in humans and published in English language. The reference lists of original and review articles were also analyzed using a manual approach. The final literature search was performed on June 20, 2017.

Study selection

Articles were included in the meta-analysis if they met all the following criteria: (1) published as full-length article in English; (2) reported as cohort studies (prospective or retrospective, regardless of sample size) with the follow-up duration of at least one year; (3) included adult population (≥ 18 years of age) without lung cancer at baseline; (4) MetS defined according to the criteria of the original articles was identified as exposure of interest at baseline; (5) participants without MetS at baseline was used as controls; (6) documented the incidences of lung cancer during follow-up; and (7) reported the adjusted hazard ratios (HRs, at least adjusted for age) and their corresponding 95% confidence intervals (CIs) for the incidence of lung cancer comparing individuals with MetS at baseline to those without MetS. Reviews, letters, editorials, and studies with designs other than cohort study were excluded.

Data extracting and quality evaluation

Two authors independently performed literature searching, data extraction, and quality assessment according to the predefined inclusion criteria. Discrepancies were resolved by consensus. Data that were extracted include: (1) name of first author, year of publication and country where the study was performed; (2) design characteristics (prospective or retrospective); (3) characteristics and numbers of the participants; (4) criteria for the diagnosis of MetS; (5) follow-up period; (6) Number of lung cancer case in each study; and (7) variables adjusted when presenting the results. The quality of each study was evaluated using the Newcastle-Ottawa Scale [38] which ranges from 1 to 9 stars and judges each study regarding three aspects: selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.

Statistical analyses

We used HRs as the general measure for the association between MetS at baseline and the incidence of lung cancer. Data of HRs and their corresponding stand errors (SEs) were calculated from 95% CIs or p values, and were logarithmically transformed to stabilize variance and normalized the distribution [37]. The Cochrane's Q test and I^2 test were used to evaluate the heterogeneity among the include cohort studies [39]. A significant heterogeneity was considered if $I^2 > 50\%$. We used a random effect model to synthesize the HR data because this model is considered as a more generalized method which incorporates of the potential heterogeneity [37]. Sensitivity analyses, by removing individual study one at a time, were performed to test the robustness of the results [40]. Predefined subgroup analyses were performed to evaluate whether the association between MetS and lung cancer incidence was affected by gender of the participants, or adjustment of the smoking habit, in view of the fact that smoking has been proved to be a major risk factor of lung cancer [41]. Moreover, potential publication bias was assessed by funnel plots with the Egger regression asymmetry test [42]. We used the RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and STATA software for the meta-analysis and statistics.

Author contributions

Dong Li and Heinv Yang designed the study, performed the literature retrieval and information extraction, statistical analysis, drafted the manuscript, and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

None.

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