

Association Between Metabolic Syndrome and the Risk of Lung Cancer: A Meta-Analysis

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ABSTRACT

Previous studies showed conflicting results regarding the association between metabolic syndrome (MetS) and risk of lung cancer. We performed a systemic review and meta-analysis to determine the relationship between MetS and lung cancer incidence and mortality in adults. Longitudinal follow-up studies were identified by search of Medline, Embase, Cochrane Library, and Web of Science. By incorporating potential heterogeneity into the model, a randomized-effects model was selected to pool the results. Fourteen observational studies were included. Pooled results showed that MetS was associated with a higher risk of lung cancer incidence [risk ratio (RR): 1.15, 95% confidence interval (CI): 1.05 to 1.26, $p = 0.002$; $I^2 = 89\%$]. Subgroup analysis suggested that the association was not significantly affected by study country, design, sex of the participants, adjustment of smoking, or different study quality scores (p for subgroup difference all > 0.05). The association was predominantly contributed by studies with MetS defined by the National Cholesterol Education Program Adult Treatment Panel-III rather than those with MetS defined by the International Diabetes Foundation criteria, and the association seemed to be stronger in studies with follow-up within 6 years than those over 6 years (p for subgroup difference = 0.03 and 0.04, respectively). In addition, pooled results also showed that MetS was associated with a higher risk of lung cancer mortality (RR: 1.46, 95% CI: 1.19 to 1.79, $p < 0.001$; $I^2 = 0\%$). In conclusion, in adult population, MetS may be a risk factor of lung cancer incidence and mortality.

Introduction

Lung cancer is a widely prevalent malignancy that has a significant impact on the global population [1, 2]. Global cancer statistics from 2020 reveal that lung cancer comprised 11.4% of all cancer cases

and contributed to 18.0% of cancer-related deaths worldwide [3]. Histologically, lung cancer can be classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with treatment options primarily consisting of surgery, radiation therapy, chemotherapy, and targeted drug therapy [4, 5]. However, despite of the above comprehensive treatment strategies, the prognosis of patients with lung cancer remains poor, highlighting the importance

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of primary prevention. Traditional risk factors for lung cancer, such as male gender, advancing age, and smoking, have been widely acknowledged [6]. However, investigating additional factors associated with an elevated risk of lung cancer in the general populace is imperative for enhancing screening and prevention measures [7]. Furthermore, there is evidence suggesting that metabolic disorders may have a detrimental impact on the occurrence and prognosis of lung cancer, such as obesity [8], hyperglycemia [9], and dyslipidemia [10].

Collectively, metabolic syndrome (MetS) is a conglomeration of metabolic disorders distinguished by the pathophysiological manifestation of central obesity, insulin resistance, hypertension, and dyslipidemia [11, 12]. As the global population ages, MetS has emerged as a prevalent health concern in both developed and developing nations, affecting approximately 10–30% of adult populations [13]. Given that both MetS and cancer share a common underlying mechanism of low-grade chronic inflammation [14, 15], it is plausible to hypothesize that MetS may be associated with an increased risk of cancer. An initial meta-analysis revealed a potential association between MetS and an elevated risk of developing cancer overall, although the findings varied depending on the specific site of the cancer [16]. A subsequent meta-analysis indicated that MetS may not be a contributing factor to the development of lung cancer [17]. However, it is important to note that this latter analysis only included five cohort studies, and a few relevant studies have been published subsequently [18–24]. Given the conflicting results from previous researches, we conducted a comprehensive meta-analysis to ascertain the connection between MetS and the incidence and mortality rates of lung cancer in the adult population.

Materials and Methods

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline [25] and Cochrane Handbook [26] were followed in this systematic review and meta-analysis.

Database search

In order to identify studies that met the meta-analysis' objectives, the following terms were combined: (1) “metabolic syndrome” OR “insulin resistance syndrome” OR “syndrome X”; (2) “lung” OR “pulmonary”; and (3) “carcinoma” OR “cancer” OR “tumor” OR “malignancy” OR “malignant” OR “neoplasm”. Electronic databases including PubMed, Embase, Cochrane Library, and Web of Science were searched with the combined terms from inception of the databases to June 5, 2023. Our selection criteria were limited to studies conducted on humans and published in English as full-length papers. Additionally, we manually checked the references of the related original and review articles to identify the original studies that were not included.

Study identification

The PICOS criteria were followed in determining study selection criteria:

- (1). P (Participants): Adult population without a known diagnosis of cancer at baseline.

- (2). I (Intervention): People with MetS at baseline. The diagnosis of MetS was in accordance with the criteria used in the original studies.
- (3). C (Control): People without MetS at baseline.
- (4). (Outcome): At least one of the following outcomes was reported: the incidence of lung cancer and/or the incidence of lung-cancer specific mortality during follow-up durations.
- (5). S (Study design): Observational studies with longitudinal follow-up, including cohort studies, post-hoc analyses of clinical trials, and nested case-control studies (NCC).

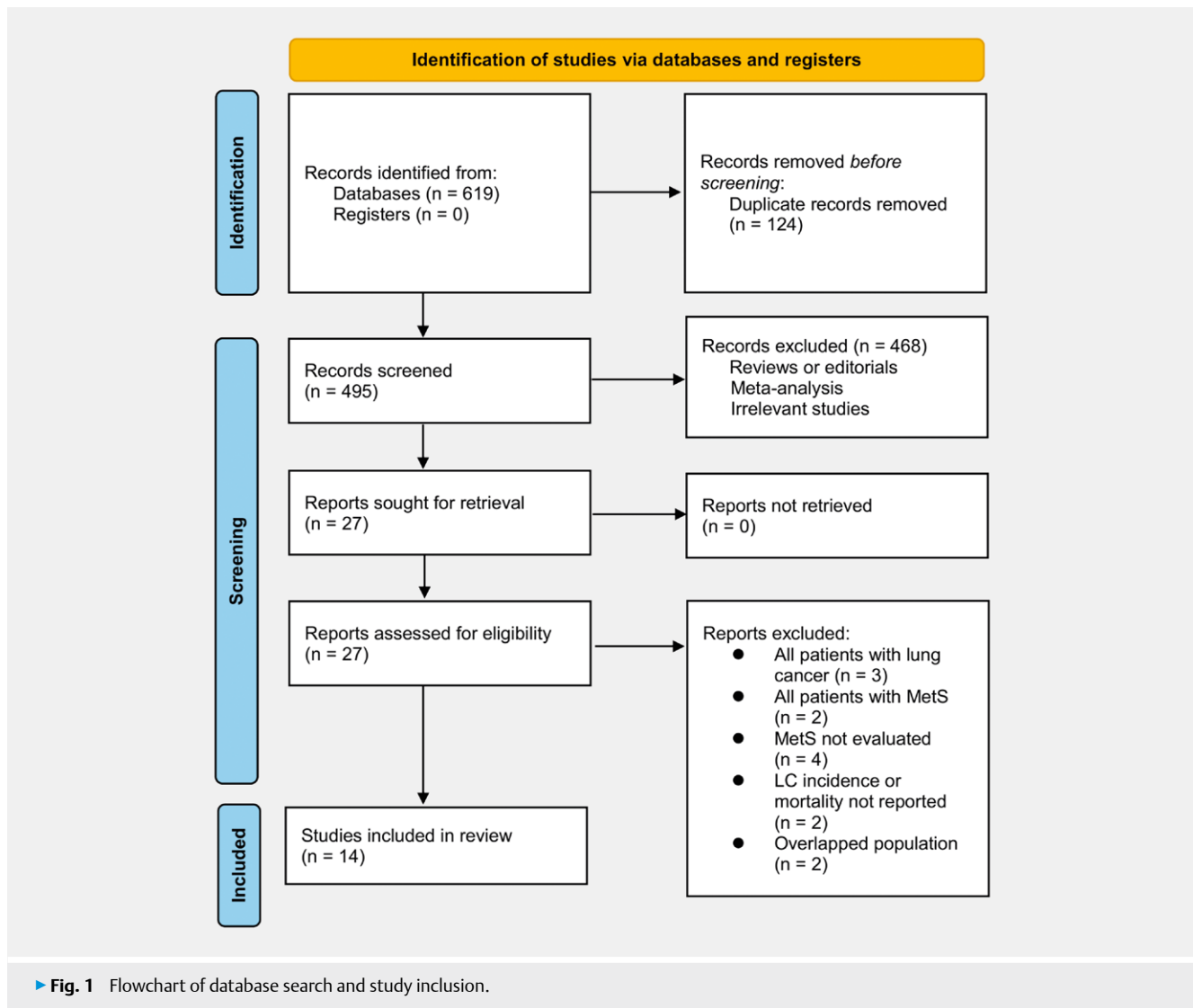
Reviews, meta-analyses, editorials, studies enrolling patients with known cancer at baseline, studies without longitudinal follow-up, studies did not investigate MetS as exposure, or studies with no relevant outcomes were excluded.

Study quality assessment and data extraction

For the purpose of assessing the study quality, the Newcastle-Ottawa Scale (NOS) [27] was used, which was composite of three domains involving defining groups of the study, comparing groups between them, and validating outcomes. The NOS incorporates nine criteria, and each study receives one point if it meets a specific criterion. As detailed above, two authors conducted electronic database searches, extracted study data independently, and assessed study quality independently. Disagreements between the two authors should be discussed in order to resolve them. The data collected were: (1) study information (authors, countries, publication year, and study design); (2) sources and sample sizes of the included population and number of adults included in each study; (3) diagnostic criteria for MetS; (4) mean follow-up durations, outcomes reported, and methods for validating the outcomes; and (5) variables included in the multivariate regression analysis for the association between MetS and risks of lung cancer incidence and mortality.

Statistical methods

Risk ratios (RRs) and 95% confidence intervals (CIs) were used to assess the association between MetS and lung cancer related outcomes. For variance stabilization and normalization, we performed a logarithmical transformation followed by a calculation of the RRs and standard errors (SE) [26]. An evaluation of heterogeneity was conducted using the Cochrane Q test and an I^2 statistic [28]. If $I^2 > 50\%$, heterogeneity was considered significant. In order to synthesize data, we used a randomized-effects model, which incorporates between-study heterogeneity and provides a more generalized result [26]. Subgroup analysis was carried out to evaluate whether the association between MetS and lung cancer related outcomes were significantly affected by study characteristics such as design, country, sex of the participants, definition of MetS, follow-up duration, adjustment of smoking, and different quality scores. In order to reflect publication bias, funnel plots were constructed, and symmetry was examined visually. In addition, publication bias was simultaneously evaluated using Egger's regression asymmetry test [29]. The RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata (version 12.0; Stata Corporation, College Station, TX) software were employed for the statistical analyses.



Results

Database search results

An overview of the database search process is shown in ► **Fig. 1**. As a result of the initial literature search, 619 articles were found; after excluding duplications, 495 articles remained. As a result of screening the titles and abstracts, an additional 468 studies were excluded from the meta-analysis. A full-text review was conducted on the remaining 27 studies, of which 13 were further excluded for the reasons listed in ► **Fig. 1**. As a final step, fourteen observational studies [18–24, 30–36] were eligible for this meta-analysis.

Characteristics of the included studies

Characteristics of the included studies are displayed in ► **Table 1**. Overall, nine prospective cohorts [18, 19, 23, 24, 30–32, 34, 36], three retrospective cohort studies [20, 33, 35], and two NCC [21, 22] were included in the meta-analysis. These studies were published between 2008 and 2023, and performed in Italy, the United States, Japan, the Netherlands, Korea, China, the United

Kingdom, and Spain. Most of the included studies enrolled community-derived adult population, while two of them included patients with vascular diseases [34] and hepatitis B virus infection [20]. In total, 12 562 361 adults who were not with a known diagnosis of cancer at baseline were included in this meta-analysis. By definition, MetS was diagnosed via the National Cholesterol Education Program Adult Treatment Panel-III (NCEP-ATP III) criteria in 11 studies [19–24, 30, 32, 34–36], via the International Diabetes Foundation (IDF) criteria in one study [18], and via the both above criteria in two studies [31, 33]. The mean follow-up duration was 2.7 to 18.5 years. The outcome of lung cancer incidence was reported in 11 studies [19–24, 30, 31, 33–35], and the outcome of lung cancer mortality was also reported in four studies [18, 24, 32, 36]. The outcomes were validated with databases such as national cancer registries, national death index, medical records, or death certificates, etc. Multivariate analyses were used to estimate the association between MetS and lung cancer related outcomes in all of the included studies. Variables such as age and sex were adjusted in all the studies, while other variables such as smoking etc. were adjusted in some of the studies [18–24, 31–33, 35, 36].

▶ Table 1 Characteristics of the included studies.									
Author year [Ref]	Location	Design	General status of the population	Number of participants	Definition of MetS	Follow-up duration	LC outcome reported	Validation of LC outcome	Variables adjusted
Russo 2008 [30]	Italy	P	Community-derived population	16677	NCEP-ATP III	2.7	LC incidence	Local cancer registry	Age and sex
Jagers 2009 [32]	USA	P	Community-derived men	33230	NCEP-ATP III	14	LC mortality	National death index	Age, examination year, height, smoking, alcohol intake, physically inactive, hypercholesterolemia, cardiovascular disease, family history of cancer and cardiorespiratory fitness
Inoue 2009 [31]	Japan	P	Community-derived population aged 40 years or older	27724	NCEP-ATP III and IDF	10.2	LC incidence	National cancer registry	Age, sex, study area, smoking, weekly alcohol intake, and TC
Osaki 2012 [33]	Japan	R	Community-derived population	23625	NCEP-ATP III and IDF	9.1	LC incidence	Local cancer registry	Age, sex, smoking, and heavy drinking
van Kruijsdijk 2013 [34]	the Netherlands	P	Patients with vascular diseases	6172	NCEP-ATP III	5.5	LC incidence	National cancer registry	Age, sex, and calendar year
Ko 2016 [35]	Korea	R	Community-derived population	61758	NCEP-ATP III	10.4	LC incidence	National cancer registry	Age, smoking status, alcohol intake, and exercise
Gathirua 2017 [36]	USA	P	Community-derived population	19106	NCEP-ATP III	13.1	LC mortality	National death index	Age, sex, race, education, smoking, alcohol intake, and concurrent medications
Watanabe 2019 [18]	Japan	P	Community-derived population	10379	IDF	18.5	LC mortality	Death certificates	Age, sex, smoking, alcohol drinking, education, physical activity, and occupation category
Sin 2020 [19]	Korea	P	Community-derived population	9586753	NCEP-ATP III	6.3	LC incidence	National cancer registry	Age, sex, physical activity, and smoking status
Choe 2021 [20]	Korea	R	HBV-infected people over 40 years	1504880	NCEP-ATP III	4.9	LC incidence	National cancer registry	Age, sex, BMI, smoking, alcohol consumption, physical activity
Li 2022 [21]	China	NCC	Community-derived population aged 45 years or older	17708	NCEP-ATP III	4.5	LC incidence	Medical chart	Age, sex, education, smoking status, drinking status, and depression score
Shao 2022 [23]	UK	P	Community-derived population	450482	NCEP-ATP III	6.3	LC incidence	National cancer registry	Age, sex, physical activity, and smoking status
Lopez 2022 [22]	Spain	NCC	Community based population over 40 years	732992	NCEP-ATP III	5.5	LC incidence	National cancer registry	Age, sex socioeconomic status, smoking status, and nationality
Van Hoang 2023 [24]	Japan	P	Community-derived population	70875	NCEP-ATP III	6.1	LC incidence and mortality	National cancer registry and death certificates	Age, sex, smoking, and worksite

LC: Lung cancer; MetS: Metabolic syndrome; P: Prospective; R: Retrospective; NCC: Nested case-control; NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel-III; IDF: International Diabetes Foundation; HBV: Hepatitis B virus; TC: Total cholesterol; BMI: Body mass index.

► **Table 2** Study quality evaluation via the Newcastle-Ottawa Scale.

Cohort Study [Ref]	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Russo 2008 [30]	1	1	1	1	1	0	1	0	1	7
Jaggers 2009 [32]	1	1	1	1	1	1	1	1	1	9
Inoue 2009 [31]	1	1	1	1	1	1	1	1	1	9
Osaki 2012 [33]	0	1	1	1	1	1	1	1	1	8
van Kruijsdijk 2013 [34]	1	1	1	1	1	0	1	1	1	8
Ko 2016 [35]	0	1	1	1	1	1	1	1	1	8
Gathirua 2017 [36]	1	1	1	1	1	1	1	1	1	9
Watanabe 2019 [18]	1	1	1	1	1	1	1	1	1	9
Sin 2020 [19]	1	1	1	1	1	1	1	1	1	9
Choe 2021 [20]	0	1	1	1	1	1	1	0	1	7
Li 2022 [21]	0	1	1	1	1	1	1	0	1	7
Shao 2022 [23]	1	1	1	1	1	1	1	1	1	9
Lopez 2022 [22]	0	1	1	1	1	1	1	1	1	8
Van Hoang 2023 [24]	1	1	1	1	1	1	0	1	1	8

A good quality study was indicated by a NOS range of seven to nine stars (► **Table 2**).

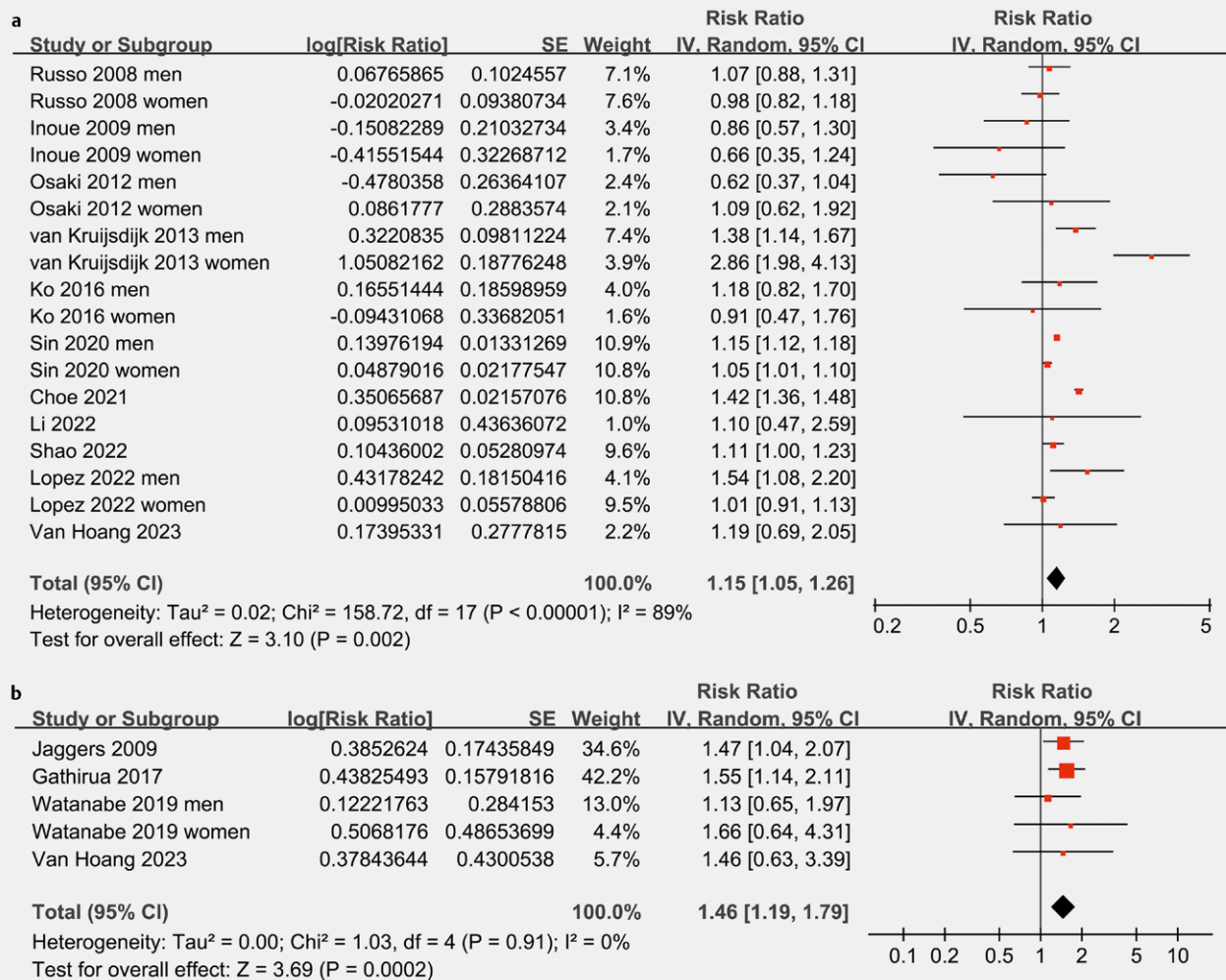
Association between Mets and lung cancer risk

Eight of the included studies [18, 19, 22, 30, 31, 33–35] reported the results according to the sex of the participants. Accordingly, these datasets were included independently into the meta-analysis. Overall, 18 datasets from 11 studies [19–24, 30, 31, 33–35] reported the association between MetS and lung cancer incidence. Pooled results showed that MetS was associated with a higher risk of lung cancer incidence (RR: 1.15, 95% CI: 1.05 to 1.26, $p=0.002$; $I^2=89\%$; ► **Fig. 2a**). Subgroup analysis suggested that the association was not significantly affected by study country, design, sex of the participants, adjustment of smoking, or different study quality scores (p for subgroup difference all >0.05 ; ► **Table 3**). The association was predominantly contributed by studies with MetS defined by the NCEP-ATP III criteria rather than those with MetS defined by

the IDF criteria, and the association seemed to be stronger in studies with follow-up within 6 years than those over 6 years (p for subgroup difference = 0.03 and 0.04, respectively; ► **Table 3**). In addition, pooled results of five datasets from four studies [18, 24, 32, 36] showed that MetS was associated with a higher risk of lung cancer mortality (RR: 1.46, 95% CI: 1.19 to 1.79, $p<0.001$; $I^2=0\%$; ► **Fig. 2b**).

Publication bias

► **Fig. 3** shows the funnel plots regarding the association between MetS the risk of lung cancer incidence in adult populations. According to visual inspection, the plots are symmetrical, which suggested risk of publication bias is low. Additionally, Egger's regression test also indicated a low risk of publication bias ($p=0.49$). The publication bias for the meta-analysis of MetS and lung cancer mortality was unable to be determined because only five datasets were available.



► **Fig. 2** Forest plots for the meta-analysis of the association between MetS and lung cancer risk. **a:** Forest plots for the meta-analysis of the association between MetS and lung cancer incidence; and **b:** Forest plots for the subgroup analysis of the association between MetS and lung cancer mortality.

Discussion

According to the findings of this meta-analysis, there is evidence to suggest that the adult population diagnosed with MetS may have a 15% higher likelihood of developing lung cancer compared to adults without MetS. Further analysis revealed that this association was primarily observed in studies that utilized the NCEP-ATP III criteria for diagnosing MetS. Additionally, it was observed that the strength of the association between MetS and increased lung cancer risk appeared to be more pronounced in studies with a mean follow-up duration of less than 6 years, as opposed to those with a follow-up duration exceeding 6 years. Furthermore, the aforementioned correlation appeared to exhibit consistency among both males and females and was not significantly influenced by factors such as the country of study, research design, adjustment for smoking, and variations in study quality scores. Additionally, our findings indicate that MetS is associated with a 46% elevated likelihood of mortality due to lung cancer in the adult population. Taken

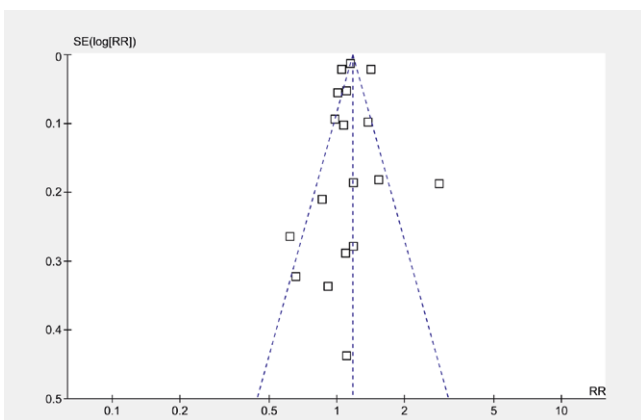
together, these outcomes imply that MetS could potentially serve as a risk factor for the occurrence of lung cancer events in adults.

As far as we know, few meta-analyses have evaluated the association between MetS and lung cancer risk. In an early meta-analysis evaluating the risk of overall cancer in people with MetS, a subgroup analysis including four studies suggested that MetS was not associated with an increased risk of lung cancer [16]. However, limited data were included and studies reporting lung cancer incidence and lung cancer mortality were combined in the meta-analysis, which may confound the results [16]. Although both the lung cancer incidence and lung cancer mortality indicate lung cancer related events, these two outcomes are not always consistent because lung cancer mortality outcome is also affected by therapeutic factors. A subsequent meta-analysis in 2020 included five cohort studies and showed that MetS was not related to a higher risk of lung cancer incidence [17]. However, the number of available data remained limited, and the results need to be updated in view of the fact that a few relevant studies were published after the meta-analysis. In the present systematic review and meta-analysis,

► **Table 3** Subgroup analyses for the association between MetS and the incidence of lung cancer.

Study characteristics	Datasets number	RR (95% CI)	I ²	p for subgroup effect	p for subgroup difference
Country					
Asian	11	1.10 [0.97, 1.24]	92%	0.14	
Western	7	1.25 [1.06, 1.48]	84%	0.01	0.22
Design					
PC	10	1.14 [1.04, 1.24]	82%	<0.001	
RC or NCC	8	1.13 [0.91, 1.39]	84%	<0.001	0.93
Sex					
Men	7	1.15 [1.01, 1.31]	57%	0.04	
Women	7	1.12 [0.94, 1.33]	81%	0.20	0.84
Definition of MetS					
NCEP-ATP III	18	1.15 [1.05, 1.26]	89%	0.002	
IDF	4	0.82 [0.61, 1.11]	0%	0.20	0.03
Follow-up duration					
Within 6 years	8	1.31 [1.09, 1.57]	89%	0.004	
Over 6 years	10	1.08 [1.01, 1.16]	60%	0.03	0.04
Adjustment of smoking status					
Yes	14	1.11 [1.00, 1.23]	90%	0.04	
No	4	1.38 [0.98, 1.95]	90%	0.07	0.23
Quality score					
NOS = 7	4	1.15 [0.90, 1.48]	86%	0.27	
NOS = 8	9	1.24 [0.97, 1.58]	81%	0.08	
NOS = 9	5	1.09 [1.01, 1.17]	76%	0.03	0.56

PC: Prospective cohort; RC: Retrospective cohort; NCC: Nested case-control; RR: Risk ratio; CI: Confidence interval; NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel-III; IDF: International Diabetes Foundation.



► **Fig. 3** Funnel plots for the publication bias underlying the meta-analysis of the association between MetS and lung cancer incidence.

sis, we conducted separate analyses to examine the correlation between MetS and the incidence and mortality of lung cancer. A thorough search of four commonly utilized electronic databases yielded 14 observational studies that fulfilled the objective of the meta-analysis. The quantity of included studies and the overall sample size of the participants were considerably greater than those of previous meta-analyses. Furthermore, it is noteworthy that all the studies incorporated in this analysis employed a longitudinal follow-up design, suggesting a potential longitudinal correlation between MetS and the incidence and mortality of lung cancer. Moreover, it is pertinent to mention that all the included studies utilized multivariate analysis to ascertain the risk of lung cancer events associated with MetS. Consequently, these findings lend support to the notion that the relationship between MetS and the risk of developing lung cancer may be independent of confounding variables, such as age, gender, and smoking status. In aggregate, the results of this meta-analysis underscore the significance of lung cancer screening and prophylaxis in people with MetS.

The subgroup analysis conducted in our study revealed that the relationship between MetS and the risk of developing lung cancer was not significantly influenced by the country in which the study

was conducted or the sex of the participants. This suggests that the aforementioned association may not be susceptible to variations in ethnicity and sex within the population. Furthermore, our findings indicated that the association between MetS and lung cancer risk appeared to be more pronounced in studies that utilized the NCEP-ATP III criteria for diagnosing MetS, compared to those employing the IDF criteria. However, it is important to exercise caution when interpreting these results due to the limited availability of only four datasets for the subgroup of IDF studies, as well as the presence of significant heterogeneity within the subgroup of NCEP-ATP III studies. In addition, it was suggested that the association between MetS and lung cancer risk may be stronger in studies with follow-up duration within 6 years (RR: 1.31) compared to those over 6 years (RR: 1.08). Since MetS has become more prevalent in middle-aged population [37], these findings may suggest the importance of lung cancer screening in middle-aged people with MetS.

The association between Metabolic Syndrome (MetS) and lung cancer is likely influenced by a multifactorial process. Pathophysiologically, the presence of low-grade systemic inflammation may serve as an intermediate mechanism in the development of MetS and the pathogenesis of lung cancer [38]. Furthermore, emerging evidence suggests that insulin resistance, a fundamental mechanism in MetS [39], is also implicated in the pathogenesis of lung cancer [40]. Moreover, several components of MetS, including central obesity [41], hyperglycemia [9], and dyslipidemia [42], have been increasingly linked to an elevated risk of developing lung cancer. These findings may also be the mechanisms underlying the association between MetS and lung cancer risk.

This study possesses certain limitations. The meta-analysis conducted on lung cancer mortality is constrained by the inclusion of a limited number of studies, necessitating the need for additional prospective cohort studies to authenticate the findings. Furthermore, caution must be exercised when interpreting the outcomes of certain subgroup analyses due to the scarcity of available datasets pertaining to these subgroups, such as those involving studies utilizing the IDF diagnostic criteria for MetS. Additionally, since lung cancers of different histopathological type may have different biological features, the association between MetS and different histopathological type of lung cancer should be analyzed. However, since data according to the histopathological type of lung cancer were not reported in either of the included cohort studies, we were unable to evaluate the outcomes according to the histopathological type of lung cancer. Future studies are warranted in this regard. Furthermore, it should be noted that although all the studies chosen for analysis employed multivariate regression analysis, the presence of residual confounding factors, including the potential impact of dietary [43] and other lifestyle factors [44] associated with lung cancer risk, could not be entirely eliminated. Moreover, the confounding factors adjusted in the original studies were different among the included studies, which may also affect the results of the meta-analysis. Lastly, due to the inclusion of observational studies in this meta-analysis, it is not feasible to establish a causal relationship between MetS and lung cancer solely based on these findings.

Conclusion

According to the results of the meta-analysis, there appears to be a potential correlation between the presence of MetS in adults and an elevated incidence and mortality rate of lung cancer. These findings indicate that MetS could potentially serve as a risk factor for the occurrence of lung cancer in the adult population, thereby emphasizing the significance of implementing lung cancer screening and prevention measures among individuals with MetS.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Notice

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Erratum

In the above-mentioned article, the authors Zhao Zhang and Qinxiang Liu contributed equally. The affiliations of the co-authors were corrected in the online version