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Reviewer A

This is a meta-analysis that aimed to study pulmonary nodule epidemiology, risk factors and management. The idea is not particularly novel and despite the authors' best efforts, due to the heterogeneity of studies pertaining to lung nodules, drawing uniform conclusions was difficult. The main findings of the analysis, namely age and smoking history were the main risk factors for nodule development, are well-known so there is minimal gain in terms of contribution to our understanding of pulmonary nodules. However, I'm glad that the authors attempted this analysis so that we have a more recent "baseline" for pulmonary nodule epidemiology, risk factors and management.

One major confusion I hope the authors can clarify is that I thought the authors said they included screening studies only, but they kept mentioning the Fleischner Society guidelines when it comes to management. LungRADS is the management system for screening exams, while Fleischner guideline is for incidentally detected nodules, hence the confusion.
Reply: Thank you for pointing out the confusion regarding the use of management guidelines. I have adjusted the article to talk less about the Fleischner Society guidelines and clarified that these guidelines are specifically for incidentally detected nodules. (see page 11, line 347-351)
Changes in the text: Fleischner Society Guidelines, which are designed for incidentally detected nodules, not only consider nodule size and morphology but also the patient's individual risk factors. This approach is paralleled in the British Thoracic Society (BTS) guidelines, which is for the screening detected pulmonary nodules(48).

Under "Prevalence of screen detected pulmonary nodules", the authors reported the prevalence of pulmonary nodules varied distinctly across the studies ranging from 1% (CI 0.01-0.01) to 80%. Is the CI for the 1% a typographical error?
Reply: Thank you for pointing out the mistake of the confidence interval for the 1% (CI 0.01-0.01). After rechecking our data sources, we found that this indeed was a problem with the rounding. (see page 9, line 250)
Changes in the text: The reported prevalence of pulmonary nodules varied distinctly across the 32 studies ranging from 1% (95% confidence interval (CI): 0.011–0.013)

Reviewer B

General Comments:

While this study addresses a significant topic in pulmonary medicine, there are several critical issues regarding the methodology, data interpretation, and overall presentation that undermine the credibility and impact of the findings. Below are the detailed comments highlighting the major concerns.

1. Methodological Flaws:

Selection Bias: The study's inclusion criteria for selecting studies from PubMed and CNKI databases lack clarity. It is unclear how the selection was balanced to prevent an overrepresentation of specific population groups or study types. This potentially introduces selection bias, affecting the generalizability of the findings.

Reply: Thank you for your insightful comment regarding the selection criteria for studies in our systematic review. In our methodology, we tried to minimize selection bias through using a comprehensive and systematic search strategy. We have detailed the specific inclusion and exclusion criteria inclusion criteria based on study type, population, and outcomes of interest, which were rigorously followed during the selection process used in our study selection process in the Methods section of our manuscript. (see page 6 line 155-156)

Changes in the text: The inclusion criteria were as follows: (I) the study evaluated data on the prevalence of pulmonary nodules; (II) CT imaging was employed for the detection of pulmonary nodules; (III) publication in peer-reviewed journals. Exclusion criteria included studies with non-original studies such as meta-analysis and reviews.

Heterogeneity: The high level of heterogeneity (I2 = 100%) among the included studies indicates significant variability that was not adequately addressed. The attempt to reduce heterogeneity by removing outliers did not succeed, suggesting fundamental methodological issues in how the meta-analysis was conducted.

Reply: Thank you for your comment regarding the heterogeneity problem. This heterogeneity is a critical aspect of our analysis, and we attempted to addressed it through different approaches. Initially, we attempted to reduce heterogeneity by excluding outliers. However, this approach did not substantially decrease the I^2 value. Then, we conducted subgroup analyses based on geographic location. However, the persistent high heterogeneity suggests unmeasured confounding factors across the studies that we did not capture. Now we are going to report the both the results before and after the removal of outliers. We also acknowledge in our discussion that this level of heterogeneity might limit the interpretability of the pooled effect estimates(see page 9 line263-276).

Change in the text: However, this estimated prevalence was highly unreliable due to considerable statistical heterogeneity with an I2 value of 100%. We then utilized the outliner

removal function provided by the R package 'dmetar' to minimize the heterogeneity. After the exclusion of 14 outlier studies, the heterogeneity was slightly reduced (I2=95%), accounting for 19,259 cases of pulmonary nodules among a total of 67,296 participants. The pooled estimated prevalence of pulmonary nodules for the remain 10 studies was 0.27 (95% CI: 0.25–0.29).

The studies included both Chinese and non-Chinese populations, with nearly half focusing on the Chinese population. To account for potential heterogeneity caused by the ethnic differences, we then conducted a subgroup analysis for Chinese and non-Chinese populations separately (Figure 2). Among 31270 non-Chinese participants, the overall prevalence of pulmonary nodules was 0.26 (95% CI: 0.23–0.29). In contrast, among 36026 Chinese participants, the prevalence was slightly higher at 0.29 (95% CI: 0.26–0.31), though this difference was not statistically significant (P=0.11). Heterogeneity was slightly higher among Chinese populations compared to non-Chinese populations.

Risk of Bias Assessment: The use of a modified Newcastle-Ottawa Scale for risk of bias assessment is not sufficiently justified or detailed. The criteria for categorizing studies into different risk levels are vague, leading to potential inconsistencies in the evaluation process.

Reply: We chose the Newcastle-Ottawa Scale (NOS) to align better with the specific characteristics of the studies included in our review, which primarily involve non-randomized studies focusing on epidemiological data on pulmonary nodules. We modified the NOS to omit sections not applicable to our analysis, such as exposure. We acknowledge that the criteria for categorizing studies into different risk were not sufficiently detailed in our initial report. We have now provided a more comprehensive description of these criteria in the methods section(see page 6 line 168-179).

Change in the text: Based on a previous study (14), we utilized a modified version of the Newcastle–Ottawa Scale (NOS) to assess the risk of bias in each included study to align better with the characteristics of the studies included in our review. We also modified the NOS to omit components not applicable to our analysis. The scoring methods are shown in Appendix 1. Each study was evaluated by 2 reviewers independently (L.Y. and W.Z.), focusing on domains such as representativeness of the sample, sample size, ascertainment methods, and completeness of the descriptive statistics provided. The overall risk of bias for each study was categorized as 'low', 'moderate', 'high', or 'no information'. Specifically, a study was classified as having a high risk of bias if one or more of the assessed domains were deemed high risk. Additionally, any study classified as having a risk of bias other than low in one or more of the assessed domains was counted as 'some concern'.

2. Data Interpretation Issues:

Prevalence Rates: The reported prevalence rates of pulmonary nodules range widely (1% to 80%), which is an alarmingly broad range. The pooled prevalence rate of 30% is difficult to trust given the significant heterogeneity. Additionally, the exclusion of certain studies to address outliers appears arbitrary and inadequately justified.

Reply: The wide range in pulmonary nodule prevalence rates reflects the diversity in study designs and populations, which is a common challenge in epidemiological research. Due to this diversity, we included a variety of studies and employed an outlier removal method to provide a more reliable pooled prevalence estimate. This method was rigorously applied to minimize the impact of extreme data points. Now we are going to report the both the results before and after the removal of outliers (see page 9 line 263-267).

Change in the text: However, this estimated prevalence was highly unreliable due to considerable statistical heterogeneity with an I2 value of 100%. We then utilized the outliner removal function provided by the R package 'dmetar' to minimize the heterogeneity. After the exclusion of 14 outlier studies, the heterogeneity was slightly reduced (I2=95%), accounting for 19,259 cases of pulmonary nodules among a total of 67,296 participants. The pooled estimated prevalence of pulmonary nodules for the remain 10 studies was 0.27 (95% CI: 0.25–0.29).

Subgroup Analysis: The subgroup analysis comparing Chinese and non-Chinese populations shows no significant difference. However, the high heterogeneity persists, raising questions about the validity of these subgroup findings. The authors fail to explore other potential sources of heterogeneity adequately.

Reply: We acknowledge the persistent high heterogeneity observed in our findings and understand the concerns it raises regarding the validity of these subgroup results. Due to limitations in the available data which did not provide detailed population demographic information, we were not able to explore other potential sources of heterogeneity. Now we are going to report the both the results before and after the removal of outliers (see page 9 line 271-276).

Change in the text:

The studies included both Chinese and non-Chinese populations, with nearly half focusing on the Chinese population. To account for potential heterogeneity caused by the ethnic differences, we then conducted a subgroup analysis for Chinese and non-Chinese populations separately (Figure 2). Among 31270 non-Chinese participants, the overall prevalence of pulmonary nodules was 0.26 (95% CI: 0.23–0.29). In contrast, among 36026 Chinese participants, the prevalence was slightly higher at 0.29 (95% CI: 0.26–0.31), though this difference was not statistically significant (P=0.11). Heterogeneity was slightly higher among Chinese populations compared to non-Chinese populations.

3. Lack of Comprehensive Data:

Age and Gender Stratification: The analysis of age and gender as risk factors for pulmonary nodules is incomplete and lacks depth. The description of age-associated risk is not quantitatively synthesized, leaving gaps in understanding how age specifically impacts nodule prevalence.

Reply: We acknowledge the lack of quantitatively synthesized of age-associated risk. However, the variability in how age-related data were reported across the studies included in our analysis significantly restricted our ability to conduct a quantitative synthesis of age-associated risks. Many studies reported age data in different categories, used odd ratio or only description, making it challenging to compare these findings directly and we were unable to obtain age-stratified data that could be quantitatively analyzed.

Definition of Pulmonary Nodules: There is inconsistency in how pulmonary nodules are defined across the included studies. Some studies have very stringent criteria, while others are broad, leading to discrepancies in reported prevalence. This variability undermines the study's conclusions.

Reply: We acknowledge that there is inconsistency in how pulmonary nodules are defined across the included studies. To solve this issue, we excluded studies that applied exceptionally stringent criteria for defining pulmonary nodules in the quantitative analysis.

4. Presentation and Clarity:

Abstract and Introduction: The abstract is poorly structured, lacking coherence and focus. It does not adequately summarize the study's objectives, methods, key findings, and implications. The introduction fails to provide a clear rationale for the study, with insufficient background information on the significance of investigating pulmonary nodule prevalence and management.

Figures and Tables: The figures and tables included in the manuscript are not sufficiently explained or integrated into the text. The flow diagram for the study selection process is particularly unclear and lacks necessary details.

Reply: We acknowledge that the abstract and introduction of our manuscript did not meet the expected standards of clarity and coherence. We revised part of the abstract and introduction. We also revisited each figure and table, especially the flow diagram of the study selection process, to ensure that they are clearly described (see page 3 line 50-55).

Change in text: Results: We identified 32 studies and included 10 of them in our meta-analysis. Pooled analysis showed that the overall prevalence of pulmonary nodules was 0.28 (95% confidence interval: 0.25–0.32). Subgroup analysis showed that there was no significant difference for prevalence between Chinese and non-Chinese populations. Males (0.38) were

shown to have slightly higher prevalence compared to females (0.36), but not significant (P=0.88). Age and smoking are the most frequently reported risk factors by studies.
Conclusions: Overall, 28% of participants were positive for pulmonary nodules.
Advancing age and smoking were consistently identified as a key risk factor for the incidence of pulmonary nodules. Although the management strategies are different across studies, recent guidelines recommend personalized management strategies, prioritizing nodule size, characteristics, and individual risk factors to optimize outcomes.

5. Ethical Considerations:

Conflict of Interest: The manuscript lacks a comprehensive statement on conflicts of interest. Given the potential implications of this research for public health policies and clinical practices, transparency in funding sources and potential conflicts is crucial.

Reply: We have a conflicts of interest statement in the Acknowledgments section (see page 16 line 503-507).

Conclusion:
In its current form, the manuscript has significant flaws that limit its contribution to the field of pulmonary medicine. The methodological issues, high heterogeneity, lack of comprehensive data synthesis, and presentation problems are substantial. A thorough revision addressing these critical issues is necessary before reconsideration for publication.

Reviewer C

Congratulations on a large study. There're a few comments I would like to make.
1. The study was not clear on the definition of nodules and inclusion criteria. Were Ground glass nodules or opacities included in this study or did a solid component need to be present for inclusion criteria?
Reply: Thank you for your question regarding the inclusion criteria for nodules in our study. In our systematic review, most of the studies included did not specify stringent criteria regarding the characteristics of the nodules. The inclusion criteria generally encompassed any type of pulmonary nodules, including both ground glass opacities and solid nodules.

2. Inflammatory lesions such as those due to tuberculosis are more frequently seen in Asian countries, this may affect differences in cancer incidences among nodules.
Could this be a factor in your country?

Reply: Yes, we agree with that tuberculosis could be a potential factor that caused the higher prevalence of PNs in China. We add it in our discussion section (see page 12 line 386-389).

Change in text: When comparing prevalence between Chinese and non-Chinese populations, our results indicated a slightly higher prevalence among Chinese participants compared to non-Chinese participants. This may potentially cause by the higher burden of tuberculosis cases in China which is a risk factor for pulmonary nodules (52, 53). However, this difference was not statistically significant (P=0.09), suggesting that ethnicity alone may not be a major contributor to the prevalence of pulmonary nodules.

3. The Fleischner Societu Guidelines recommend histologic confirmation or PET CT studies in nodules over 8mm. A trial of antibiotics sometimes may differentiate between cancer and inflammatory nodules, but I must agree, any nodule over 10mm should be considered for histologic confirmation.

The article was well written. However, there are areas of redundancy, such as in the discussion lines 360 to 367.

Stating that life styles are a risk for lung cancer would have multiple confounding variables.

Reply: We have cleared the areas of redundancy in the discussion section (see page 12 line 378).

Change in the text: The various requirements for nodule size and morphology such as calcification and solidity added complexity to the meta-analysis. These 32 studies were carried out in populations with diverse demographics, including age, ethnicity, gender, and smoking status.