Original Article

Prevalence and management of pulmonary nodules: a systematic review and meta-analysis

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Background: Pulmonary nodules are small, focal lesions often identified via computed tomography (CT) scans. Although the majority are benign, a small percentage of them may be malignant or potentially become malignant, underscoring the importance of early detection and effective management. This study systematically reviews the epidemiology, risk factors, and management strategies for pulmonary nodules, comparing findings across Chinese and non-Chinese populations to better inform the actuarial calculations for predicting the demand of medical services for patients with pulmonary nodules.

Methods: We performed a systematic analysis of the PubMed and China Knowledge Infrastructure (CNKI) databases for studies reporting the detection rate of pulmonary nodules through CT scans. Both cross-sectional studies and the baseline data from longitudinal studies were included. A modified version of the Newcastle-Ottawa Scale was used to assess the risk of bias and random effect models were used to estimate the overall prevalence.

Results: We identified 32 studies and included 24 of them in our meta-analysis. Pooled analysis showed that the overall prevalence of pulmonary nodules was 0.27 (95% confidence interval: 0.25–0.29) after outliers removal. 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, 27% 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.

Keywords: Pulmonary nodules; epidemiology; public health; meta-analysis

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Introduction

Pulmonary nodules, are small focal lesions in the lungs, typically round or oval, ≤30 mm, and have increased density compared to the surrounding lung tissue (1,2). They are commonly identified through computed tomography (CT) scans as localized, rounded areas of opacity. These nodules can be classified as solid or subsolid, based on appearance on CT scans (2,3). A systematic review encompassing 8 randomized controlled trials and 13 cohort studies revealed that the average rate of nodule detection per screening round stands at 20% (1). A large-scale study conducted in the United States between 2006 and 2012 estimated that approximately 1.57 million nodules were identified in 2010, with a notable increase in the rate of nodule identification, rising from 3.9 to 6.6 per 1,000 person-years during that period (4). Similarly, a screening study in China comprising 22,351 participants between 2015 and 2018 reported a detection rate of 31% for pulmonary nodules (5).

Highlight box

Key findings

- Overall prevalence of pulmonary nodules detected via computed tomography (CT) scans is 30% with no significant difference between Chinese and non-Chinese populations.
- Age and smoking are the primary risk factors for pulmonary nodules, and recent studies advocate for personalized management strategies based on individual risk factors and nodule characteristics.

What is known and what is new?

- Although most pulmonary nodules are benign, a small percentage can develop into lung cancer, making their detection and management crucial. The detection rate of pulmonary nodules varies widely; previous studies have reported detection rates of 10–60%.
- This study provides a comprehensive analysis of the prevalence of pulmonary nodules, showing an overall prevalence rate of 30% among participants. This study underscores the significance of age and smoking as the primary risk factors for pulmonary nodules, reinforcing the need for targeted screening and personalized management strategies.

What is the implication, and what should change now?

- Given the high prevalence of pulmonary nodules and the significant risk factors of age and smoking, public health policies should focus more on targeted screening programs among the high-risk population.
- That personalized management strategies have been shown to be more effective underscores the need for clinicians to adopt a more individualized approach in the management of pulmonary nodules.

Although pulmonary nodules are predominantly benign and pose minimal health risk, they can occasionally serve as early indicators of lung cancer, even considering the clinical possibility of slow-growth of pulmonary tumor (4,6). In a 2023 study of 4,181 patients with pulmonary nodules, 6% of cases developed into lung cancer during the 3-year follow-up period (7). Another study conducted in Shanghai observed that among 6,925 participants with pulmonary nodules during baseline screening, 0.7% developed lung cancer during a 35-month follow-up period (5). Furthermore, this study indicated that the incidence of lung cancers can vary based on factors such as age, sex, and nodule classification. The malignancy rate was notably high at 4.5% for participants with solid nodules larger than 5 mm (5).

Lung cancer is the second and third most commonly diagnosed cancer in China and globally, respectively (8). Unfortunately, it remains the leading cause of cancer-related mortality both on a global scale and in China, accounting for a significant proportion of deaths each year (8). Despite advancements in therapies, the prognosis of lung cancer is largely dependent on the stage at which the disease is detected. Many large-scale lung cancer and pulmonary nodule screening programs and trials have been initiated globally in many countries including China. Multiple studies such as National Lung Screening Trial (NLST), International Association for the Study of Lung Cancer (IASLC) and Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) have shown that lung cancer screening improves survival due to detection of early-stage disease (9-12). Early and accurate diagnosis, coupled with high quality follow-up management, is essential for the effective care of these nodules, particularly in the high-risk population.

Few studies have comprehensively reviewed the overall prevalence of pulmonary nodules in Chinese and non-Chinese populations. In this study, we aimed to review and compare the results of previous studies conducted in these populations to evaluate differences and similarities in prevalence of pulmonary nodules, and lung cancer detection rates. Through a comprehensive analysis, we also aimed to provide a clearer understanding of the epidemiology, risk factors, and management strategies pertaining to pulmonary nodules. The overarching goal of our project was to establish a foundational risk assessment for the actuarial calculations to support medical insurance coverage for lung cancer screening and pulmonary nodule management in China. We present this article in accordance with the

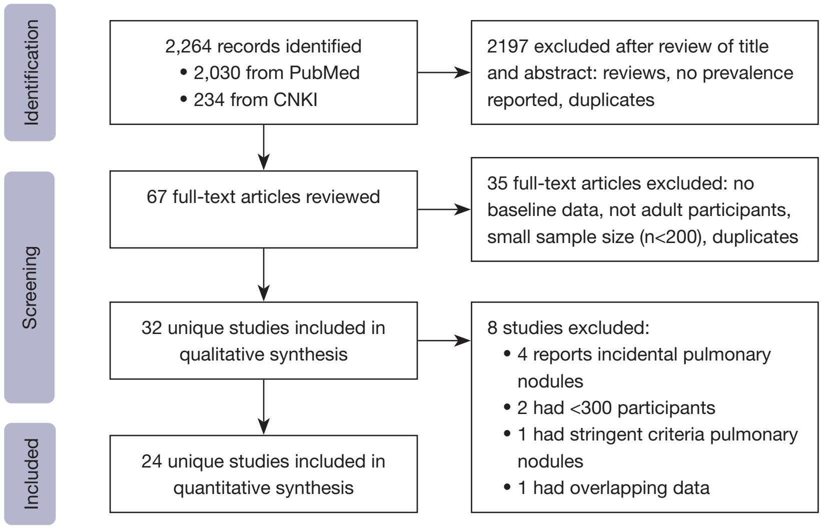

Figure 1 Flow diagram for study selection process. CNKI, China National Knowledge Infrastructure.

MOOSE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-874/rc) (13).

Methods

This is a systematic review encompassing both cross-sectional and longitudinal studies from 1990 to 2023 that investigated lung cancer screening and pulmonary nodule risk assessment and management. In conducting our meta-analysis, the protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 7 December 2023 (registration number: CRD42023485546).

Search strategy

We conducted the search on 2 platforms: PubMed for publications in English language and China National Knowledge Infrastructure (CNKI) for Chinese language publications. For PubMed, we employed the search terms "pulmonary nodules" AND ("incidence" OR "prevalence") to identify relevant studies. For the CNKI database, we used the Chinese-translated term "pulmonary nodules" AND ("Detection rate" OR "Incidence") with the period from 1990 to November 2023. Detailed searching strategies are reported in Table S1.

Study selection process

In the initial phase of our study selection, 2 reviewers independently examined the title and abstract of each identified article. This step ensured an unbiased and thorough screening process. Following the first round of assessment, articles that met our inclusion criteria were then subjected to a detailed full-text review by the same reviewers focusing on the study population and study designs. The flow diagram for study selection process is shown in *Figure 1*.

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.

Data collection process

We collected the following data from each of the included studies: geographic locations, study design, screening time frames, sample size, data collection institutions, average or median age of participants, percentage of male participants, the definition of pulmonary nodules, detection rate of pulmonary nodules, and the smoking status of the sample. A pre-designed table was used by 2 reviewers (J.S. and L.Y.) to extract data from all selected articles.

Risk of bias assessment

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'.

Statistical analysis

We employed a quantitative data synthesis approach to consolidate the detection data from the included studies. For longitudinal studies, only the detection data from the baseline would be used since we intended to analyze the prevalence of pulmonary nodules.

Based on the suggestions of a previous article (15), we utilized the random effect model to estimate the overall prevalence, employing the 'meta' package in R for data synthesis. To evaluate the heterogeneity among the included studies, we calculated the I^2 statistic.

A previous study suggest that incidental pulmonary nodules (IPNs) are often detected in populations that are different than the population that undergo lung cancer screening (16). To minimize the heterogeneity of the meta-analysis, we only included pulmonary nodules that were detected through screening programs in meta-analysis. A 'screen-detected' nodule is defined as one identified during a routine LDCT scan, conducted as part of an annual health examination or specific lung cancer screening program. We also excluded the study with overly rigorous criteria for pulmonary nodules that have requirements other than size and characteristics. For two studies used the same data source, the smaller study was excluded.

We used subgroup analysis to compare the difference of detection rate between male and female patients, and Chinese and non-Chinese populations. However, due to disparities and complexities in reporting age-associated detection rates across the studies, a quantitative synthesis of age-associated observations was not feasible. Consequently, we provided a descriptive summary of the age-associated risk of pulmonary nodules. Additionally, we descriptively synthesized other reported risk factors and the recommendations for the future management of pulmonary nodules based on included studies.

Results

Study characteristics and patient population

A total of 32 studies, including 21 cross-sectional (5,6,17-35) and 11 longitudinal studies (4,36-45) reporting on the prevalence and characteristics of pulmonary nodules, were identified and included in the analysis. These studies were performed in the years between 1993 and 2020, involving a total of 699,944 individuals (*Table 1*). The sample size for each study ranged from 243 to 415,581 with diverse age ranges and gender distributions. The data collection institutions were varied across the globe. The characteristics of the included studies are presented in detail in *Table 1*.

Risk of bias assessment

The summarized findings of our bias assessment are presented in Table S2. Notably, most studies exhibited low concerns across most categories. However, areas such as representation and descriptive statistics frequently demonstrated higher levels of concern. The main concern in the representation domain was the selective inclusion of participants at high risk for lung cancer, predominantly those with a significant history of smoking in some studies (44,46), while others allowed for individuals with perceived lower risk (19-22,27,32). Several studies also showed a lack of comprehensive descriptive data, particularly regarding the percentage of male participants and combustible tobacco users which brings concerns in descriptive statistics domain (4,6,42). These concerns suggest that although our results provide valuable insights, they may not be fully generalizable to all populations at risk for lung cancer.

Definition

The pulmonary nodule definitions varied significantly in nodule size and property (4-6,17,19-23,26,27,30-33, 35-43,45). Nodule size ranged from 4 to 30 mm (4,23,31,37). A total of 6 studies specifically mentioned non-calcified nodules in their definition (20,23,36,37,39,45). Nodule solidity is another property addressed in several studies; 1 study necessitated nodules to be either solid or partially solid (36), whereas another, conversely, excluded

Table 1 Characteristics of the included studies

Authors	Country/region	Screening years	Sample size	Age, years (mean)	Male, n (%)	Definition of pulmonary nodules	Current smokers, n (%)
Gould *et al.* (4)*	United States	2006–2012	415,581	45.6	NR	Any nodules 4–30 mm	NR
Zhao *et al.* (5)	China	2015–2018	22,351	50 (median)	9,149 (40.93)	Any nodules	NR
Hammerschlag *et al.* (6)*	Australia	2021	248	41 (median)	NR	Any nodules	NR
Ouyang *et al.* (17)	China	2018	1,372	58.97	503 (36.67)	Any nodules	NR
Xu *et al.* (18)	China	2018–2019	920	20–69 (range)	588 (63.91)	NR	NR
Pan *et al.* (19)	China	2016–2018	63,521	21–61 (range)	36,842 (57.99)	(I) A single round or oval dense shadow is found within the parenchyma of both lungs; (II) not accompanied by enlargement of the hilar or mediastinal lymph nodes, nor signs of lung atelectasis or pneumonia; (III) the longest diameter does not exceed 3 cm; (IV) the lesion has sufficiently measurable diameter and defined, sharp edges; (V) calcification or cavitation may be present within the lesion (excluding those where the cavity nearly occupies the entire lesion)	20,767 (32.69)
Wei *et al.* (20)	China	2020	2,311	35.76	537 (23.24)	5–14 mm solid/partially solid nodules and 8–14 mm non-solid nodules; ≥15 mm nodules (including solid nodules, partially solid nodules, and non-solid nodules)	176 (7.62)
Ji *et al.* (21)	China	2018–2020	3,068	50.29	1,484 (48.37)	Any nodules	679 (22.13)
Wu *et al.* (22)	China	2019	9,776	47	6,061 (62.00)	Any non-calcified nodule ≤30 mm	3,117 (31.88)
Wu *et al.* (23)	China	2021–2022	5,597	55.19	3,162 (58.88)	NR/any nodules	2,148 (38.38)
Zhang *et al.* (24)	China	2022	3,631	NR	1,379 (37.98)	NR	1,364 (37.57)
Tapio Vehmas (25)	Finland	2008	526	63	517 (98.29)	NR	144 (27.37)
Hall *et al.* (26)*	United States	2002–2005	589	53	218 (37.00)	Any new nodules	NR
Sigel *et al.* (27)*	United States	2003–2012	1,617	49.74	260 (16.08)	NR	317 (19.60)
Rinaldi *et al.* (28)*	Italy	2007	243	62.6	113 (46.50)	Any nodules	NR
Lin *et al.* (29)	China	2016–2019	2,082	56.35 (median)	1,556 (74.74)	NR	NR
Xu *et al.* (30)	China	2018–2019	23,695	50.52	16,142 (68.12)	Any non-calcified nodule ≤30 mm	15,281 (64.49)
Li *et al.* (31)	China	2020–2021	10,277	51.15	5,267 (51.25)	Any nodule ≤30 mm	NR
Zhang *et al.* (32)	China	2021	19,923	NR	15,696 (78.78)	Any nodules	NR
He *et al.* (33)	China	2014–2016	7,752	40–75 (range)	4,025 (51.92)	Any nodules	NR
Yorgun *et al.* (34)*	Turkey	2007–2008	1,206	58.75	701 (58.1)	NR	NR
Infante *et al.* (35)	Italy	2001–2006	1,276	60–74 (range)	1,276 (100.0)	Any dubious nodules	NR
The International Early Lung Cancer Action Program (36)	Worldwide	1993–2005	31,567	61	NR	Any solid or partly solid non-calcified pulmonary nodules ≥5 mm	23,052 (73.03)
The National Lung Screening Trial (37)	United States	2002–2004	26,715	55–74 (range)	15,765 (59.01)	Any noncalcified nodules ≥4 mm	12,643 (47.33)
Wilson *et al.* (38)	United States	2002–2005	3,642	59	1,872 (51.40)	Any suspicious nodules	2,192 (60.2)
Henschke *et al.* (39)	United States	1993	1,000	67 (median)	540 (54.0)	Any non-calcified nodules	NR

Table 1 *(continued)*

Table 1 *(continued)*

Authors	Country/region	Screening years	Sample size	Age, years (mean)	Male, n (%)	Definition of pulmonary nodules	Current smokers, n (%)
Pedersen *et al.* (40)	Denmark	2004–2006	2,052	49–74 (range)	1,120 (54.58)	Any suspicious nodules	1,052 (76.9)
Field *et al.* (41)	United Kingdom	2010–2014	2,028	67.1	1,529 (75.39)	Nodules greater than 15 mm^3 or 3 mm in maximum diameter	777 (38.3)
Hendrix *et al.* (42)	United States	2018–2019	13,286	58.1	NR	Any suspicious nodules	NR
Becker *et al.* (43)	German	2007–2011	2,029	50–69 (range)	1,315 (64.81)	Any nodules ≥5 mm	NR
Klaveren *et al.* (44)	Netherland	2006–2009	7,557	58	6,303 (83.41)	NR	7,557 (100.0)
Pegna *et al.* (45)	Italy	2004–2013	1,406	60.92	1,035 (64.17)	Any non-calcified nodule ≥5 mm or a non-solid nodule ≥10 mm or the presence of a part-solid nodule	1,060 (65.7)

*, studies reported incidental pulmonary nodules. NR, not reported by the study.

solid nodules in their definition (45). One study imposed stringent criteria for pulmonary nodules, including overall shape, absence of associated lymph node enlargement, distinctness of boundary, size, and calcification status (19), which may result in a lower positive rate when reporting the prevalence of pulmonary nodules. Meanwhile, 12 studies had broader definitions of pulmonary nodules, merely mentioning "any nodules", "any suspicious nodules", or "any new nodules" without specific size or property requirements (5,6,17,21,24-26,28,35,38,40,42).

Prevalence of screen detected pulmonary nodules

The reported prevalence of pulmonary nodules varied distinctly across the 32 studies ranging from 1% [95% confidence interval (CI): 0.011–0.013] (19) to 80% (95% CI: 0.79–0.81) (22). The notably low prevalence in the study by Pan *et al.* may be attributed to their stringent criteria for defining pulmonary nodules (19). We carried out a pooled meta-analysis of the prevalence data to reduce heterogeneity and excluded 1 study with overly rigorous criteria for pulmonary nodules (19), 4 studies that reported IPNs (26-28,34), 1 study with an overlapped dataset (22), and 2 studies with sample size lower than 300 (6,28). Consequently, only data from 24 studies were included for the quantitative analysis (*Figure 2*). The pooled estimated prevalence of pulmonary nodules for all 24 studies was 0.30 (95% CI: 0.24–0.38). However, this estimated prevalence was highly unreliable due to considerable statistical heterogeneity with an I^2 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 (I^2=95%). The remain 10 studies accounted for 19,259 cases of pulmonary nodules among a total of 67,296 participants (5,17,18,24,25,33,37,39,43,45). The pooled estimated prevalence of pulmonary nodules for the remain 10 studies was 0.27 (95% CI: 0.25–0.29) (*Figure 3*).

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 3*). Among 31,270 non-Chinese participants, the overall prevalence of pulmonary nodules was 0.26 (95% CI: 0.23–0.29). In contrast, among 36,026 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 higher among Chinese populations (I^2=95%) compared to non-Chinese populations (I^2=85%).

Age

A total of 19 of 32 included studies analyzed the relationship between age and the prevalence of pulmonary nodules (4,5,17-25,27,29-32,37,41,42). These studies either stratified participants by age or included age as a covariate in regression analyses to predict pulmonary nodule detection risks. In general, there was a noticeable correlation between advancing age and the incidence of pulmonary nodules. A total of 11 of the 20 studies reported an overall positive association between advanced age and the risk of pulmonary nodules (4,5,19,20,22,25,27,29-31,37). In contrast, only 3 studies reported an inverse association that advanced age is associated with lower risk of pulmonary

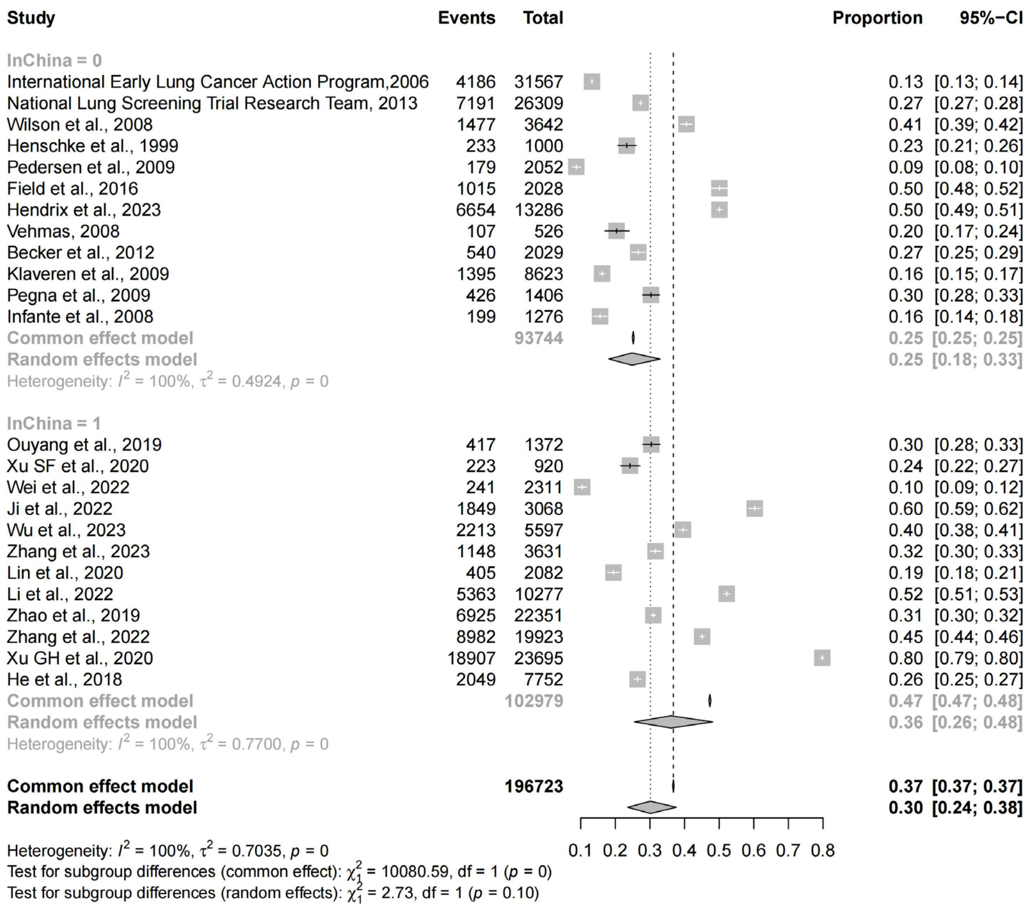

Figure 2 Forest plot of pulmonary nodules prevalence by Chinese and non-Chinese Studies. CI, confidence interval; df, degrees of freedom.

nodules (17,18,21). Interestingly, several studies identified a U-shaped relationship between age and prevalence (5,41,42). For instance, Hendrix *et al.* identified a peak prevalence of 47% in the 65–69-year age group, which subsequently decreased in older cohorts (42). Likewise, Field *et al.* noted a similar trend with a peak in the 74-year age group (41). These observed declines in the older age groups might be attributed to smaller sample sizes which caused unreliable results.

Gender

Of the 32 included studies, 12 reported on the prevalence difference of pulmonary nodules between males and females (5,17,18,20,21,24,29-33,37). Notable variations were observed in these data. For instance, several studies, observed significantly higher prevalence rates in males (5,21,30,42). Conversely, three studies documented slightly higher prevalence rates in females (32,33,37). Meanwhile, three studies revealed nearly identical rates between the genders (20,24,31). To synthesize these findings, we conducted a pooled meta-analysis of these studies. Adopting consistent criteria, 1 study with stringent pulmonary nodule criteria was excluded to minimize heterogeneity. As depicted in *Figure 4*, the overall prevalence of pulmonary nodules in males (0.38, 95% CI: 0.27–0.50) was slightly higher than in females (0.36, 95% CI: 0.25–0.49), but not statistically significant (P=0.88). This discrepancy might be attributable to the higher smoking rates and alcohol consumption observed in the male population, potentially increasing their risk for pulmonary nodules.

Other risk factors

Among the 32 included studies, 11 reported the risk factor of pulmonary nodules they identified (20-24,27,28,30,31,33,37). Smoking was shown as the predominant risk factor mentioned in 8 studies

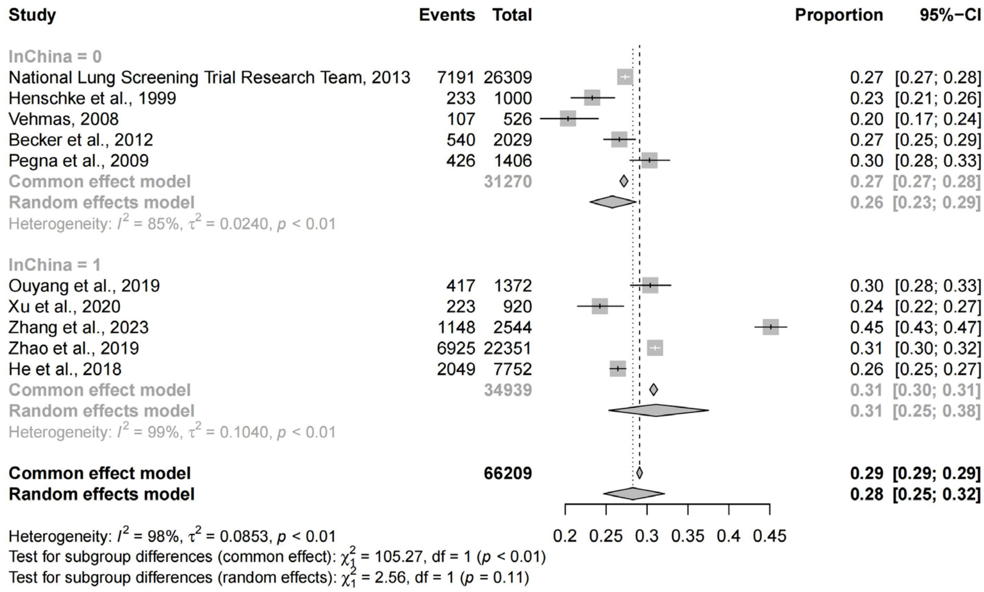

Figure 3 Forest plot of pulmonary nodules prevalence by Chinese and non-Chinese studies after removing outliners. CI, confidence interval; df, degrees of freedom.

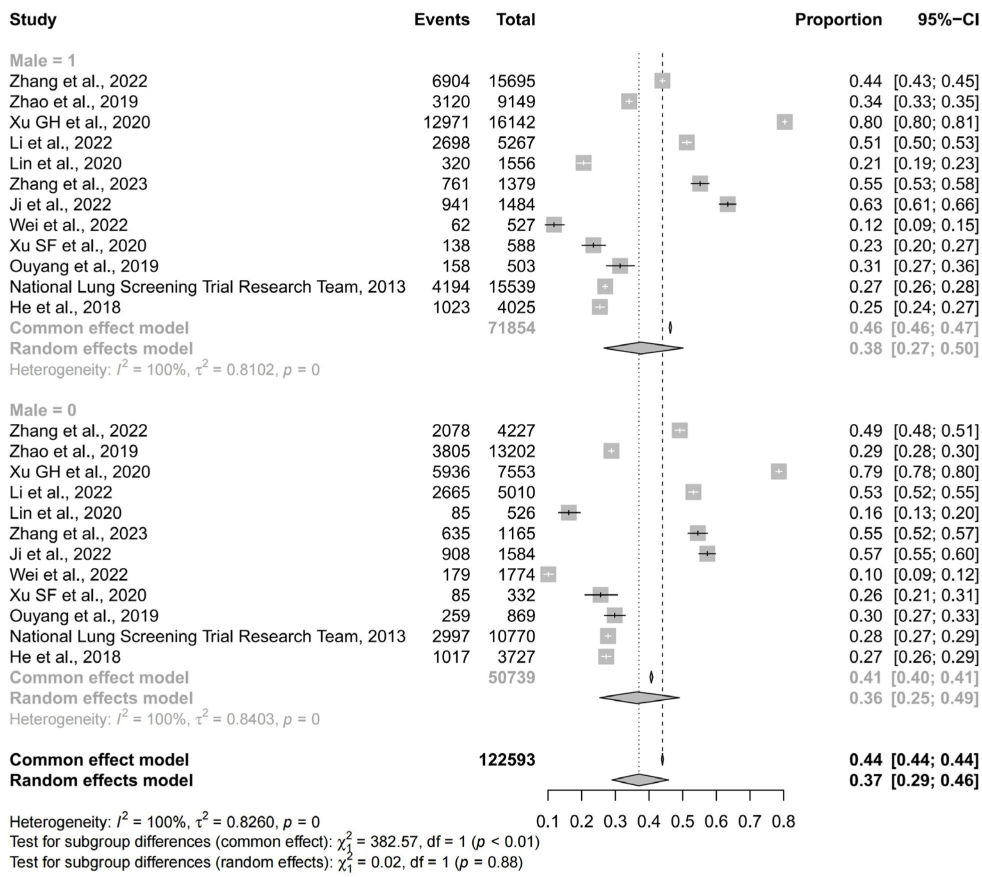

Figure 4 Forest plot of pulmonary nodules prevalence by gender. CI, confidence interval; df, degrees of freedom.

(21-24,27,28,30,37). For instance, both Sigel *et al.* and the NLST Research Team emphasized the significant influence of current smoking habits and the cumulative effect of pack-years (27,37).

The history of chronic diseases is commonly mentioned as risk factors. A total of 6 studies identified hypertension as the risk factor, 2 reported hyperlipidemias, and 3 pointed out diabetes. Zhang *et al.* revealed a prevalence of 52.7% for pulmonary nodules in participants with hypertension history, which was significantly higher than the 46.3% in those without (24).

Several studies highlighted unique risk factors. Xu *et al.* emphasized alcohol consumption, less physical activity, and a history of infectious diseases as contributory factors (30). Wu *et al.* pointed out environmental exposures, lung disease history, and lung cancer family history as risk factors (23). Wei *et al.* introduced dietary patterns into the analysis, identifying a high intake of vegetables, limited meat consumption, and regular meal times as protective against the development of pulmonary nodules (20). He *et al.* reported that dust and pesticide exposure, history of lung disease, family history of lung cancer, infrequent vegetable and fruit consumption, and a high intake of pickled foods all elevated the risk (33). Surprisingly, they also observed that single individuals were at a heightened risk for pulmonary nodules, suggesting potential risk induced by lack of social support.

Management of pulmonary nodules

A total of 11 of 32 studies give suggestions for future management of the detected pulmonary nodules cases (5,6,30,32,35,36,38,39,41,42,45). The recommendations varied from broad follow-up intervals of 3–6 months to detailed recommendations based on nodule size, including options for annual scans for nodules smaller than 5 mm or more frequent monitoring for larger nodules.

For studies outside China, the management recommendations were relatively consistent. Typically, these studies divided patients into several categories based on nodule size and morphology and offered specific suggestions for each. For example, Henschke *et al.* advised that patients with nodules ≤5 mm undergo follow-up CT scans at intervals of 3, 6, 12, and 24 months (39). For nodules between 6 to 10 mm, an optional biopsy and further monitoring scans were recommended, whereas for nodules >11 mm, a biopsy was strongly advised. Notably, Hammerschlag *et al.* referenced the 2017 Fleischner Society Guidelines (6). 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 (47). This approach is paralleled in the British Thoracic Society (BTS) guidelines, which is for the screening detected pulmonary nodules (48). The application of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is critical in further diagnosis and management of high-risk nodules (47,48). PET/CT can further investigate the nodules by identifying nodules that are metabolically active and helps in identification and characterization of potentially malignant nodules with high accuracy, particularly in nodules that are inappropriate for biopsy (49,50). Although there is variation in the criteria for pulmonary nodules categorization and the corresponding management recommendation, most were based on the size and morphology associated with the patient and recommend routine CT scans. The integration of individual risk factors into the decision-making process, highlighting the evolving nature of clinical guidance, emphasizes the need for continual research and importance of personalized plan in pulmonary nodule management.

Discussion

In this study, we reveal a significant variability in the prevalence of pulmonary nodules across different studies, with a pooled estimated prevalence of 27%. The reported prevalence of pulmonary nodules varied from 9% to 80% after the removal of 1 study with stringent criteria for pulmonary nodules. This is still much wider compared to a previous study which only included 8 large trials of lung cancer screening which were all in English language literature (51). The high differences reflected the variability in the inclusion criteria of pulmonary nodules across the included studies and the heterogeneity of the study population which cause challenges for comparison across studies and generate a reliable estimate through meta-analysis. 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. Additionally, differences in sample size and the time in which these studies were performed can introduce variations in the prevalence rates. Studies conducted over longer durations or with larger sample sizes may provide a more accurate estimation of pulmonary nodule prevalence.

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.

In this study, we saw an overall consistent trend of the relationship between advancing age and the increased prevalence of pulmonary nodules. In most studies, the detection rate of pulmonary nodules increased as age advanced (4,5,19,20,22,25,27,29-31,37). However, there were also several different observations. For instance, the U-shaped relationship in studies by Field *et al.* and Hendrix *et al.* emphasize the nonlinear relationship between age and pulmonary nodules prevalence (41,42). However, the decline in older age groups could also indeed be due to smaller sample sizes in those cohorts and lower life expectancy for population with worse lifestyle, leading to less reliable results, but further research is needed to explore if biological or other underlying factors might be responsible.

The overall higher prevalence of pulmonary nodules in male participants was also observed. Although there were several studies showing slightly higher rates in females, the overall trend from the meta-analysis supports the higher prevalence in males. The reasons behind the difference may be multi-factorial. Lifestyle factors such as smoking and alcohol consumption, which are statistically higher in males, are potential contributors (54,55).

Smoking is the predominant risk factor for pulmonary nodules. The association between smoking and pulmonary nodules was shown in 8 out of 11 studies (21-24,27,28,30,37). The effect of smoking could even be cumulative in that a higher smoking pack-year can also cause higher risk of pulmonary nodules. These results emphasize the importance of smoking cessation as a key prevention method in pulmonary nodules. Interestingly, a previous study showed that individuals with abnormal results in lung cancer screening are more likely to quit smoking (56). This highlights the potential positive impact of such screenings not only in detecting cancer at an early stage but also in motivating individuals to adopt healthier lifestyles.

Additionally, other risk factors such as chronic diseases, environmental exposures, dietary habits, and psychological stress, were also identified in various studies (20,23,24,30,33). It remains ambiguous whether the observed associations between the chronic diseases and pulmonary nodules is attributable. These chronic diseases, such as hypertension, are highly correlated with detrimental lifestyle factors such as smoking and alcohol consumption (57), which are recognized risk factors for pulmonary nodules (27,30). These results highlight the complexity of assessing the individual risk of developing pulmonary nodules. Combining smoking cessation with regular lung cancer screenings and lifestyle modifications can collectively contribute to reducing the incidence of pulmonary nodules.

The management strategies for the pulmonary nodules patients across different studies all focused on stratifying recommendations based on nodule size and morphology. However, the standards for stratifying and the follow-up protocols were slightly different across the studies. The BTS guidelines and Fleischner Society Guideline are both widely accepted guideline for the management of pulmonary nodules which provides an integrated approach that accounts not only for the nodule characteristics but also individual patient risk factors (47,48). Fleischner Society Guideline is applied to IPNs and BTS guidelines can be applied to broader range of pulmonary nodules (47,48). For high-risk individuals, especially those with a history of smoking, more progressive monitoring might be necessary. Guidelines recommend the use of PET/CT to assess the characteristics and potential malignancy of large pulmonary nodules which is essential in identifying nodules that are metabolically active (50). These guidelines underscores the need for personalized treatment plans, adapting the monitoring frequency and methods to each patient's personal risk. Incorporating advanced imaging data analysis into the management of pulmonary nodules provides a significant opportunity to enhance personalized management plans. With further advancement of imaging analysis techniques and machine learning algorithms, it becomes possible to characterize the morphology and potential malignancy risk of pulmonary nodules more accurately (58,59).

Although our review included a diverse range of studies, few studies have reported the patient's adherence to the follow-up management. Due to many barriers such as inadequate health care resources and financial problems, many nodules do not receive proper management based on well-established guidelines (60). Patient adherence is a critical issue in the management of pulmonary nodules. Previous studies have reported that only half of pulmonary nodule patients received guideline-concordant follow-up management (47,61) and patients with small size of nodules are less likely to adhere to the follow-up management (61). Patients may not fully understand the importance of regular follow-ups, particularly if they are asymptomatic and have nodules with low malignancy risk. Establishing support programs such as patient groups or commercial management programs may enhance the follow-up adherence and, consequently, the overall effectiveness of pulmonary nodule management.

Future direction

The large variation in the prevalence across varying studies underscores the necessity for a more standardized and harmonized approach in the future pulmonary nodules research. Future studies could consider the following directions. Firstly, the establishment of a more generalized definition for pulmonary nodules could reduce the variation observed across the studies. Adhering to widely accept guidelines such as the BTS guidelines may provide a more consistent understanding of pulmonary nodules. Secondly, utilizing a prospective longitudinal study design across multiple regions with diverse populations may provide a better understanding of the pulmonary nodules in diverse communities. A longitudinal design could also allow for a better assessment of the long-term impact of lifestyle factors on the risk of pulmonary nodules. Thirdly, few studies discuss the long-term effect of the proper follow-up management for pulmonary nodules patients. A future research direction would be to compare the malignant risk of the pulmonary nodules between patients with management and those with no proper management.

Limitation

This study has several limitations. Firstly, the significant heterogeneity of definition, population characteristics, and methodologies makes it challenging to provide a reliable conclusion for the results. Secondly, several included studies have relatively small sample sizes which could cause less accurate estimates for the results. Thirdly, most included studies are cross-section, the lack of long-term follow-up in some studies limits the understanding of the progression pulmonary nodules over time.

Conclusions

In this study, we systematically reviewed 32 studies across 11 regions. Overall, about 27% of the participants were positive for pulmonary nodules with significant heterogeneity across studies. These findings underscore the challenge in generating a unified conclusion for pulmonary nodules. Although several studies reported different results, advancing age was shown to be highly correlated with pulmonary nodules incidence in most of studies. Meanwhile, gender differences had more varied results across studies, although the overall pooled analysis shows a slightly higher risk in males. Smoking plays a significant role in the risk of pulmonary nodules which emphasize the importance of smoking cessation. Management strategies are different across studies, but recent guidance emphasized personalized approaches based on nodule size, characteristics, and individual risk factors.

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Footnote

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Supplementary

Table S1 Search strategy

Database	Searches	Results	Type
PubMed	("multiple pulmonary nodules"[MeSH Terms] OR ("multiple"[All Fields] AND "pulmonary"[All Fields] AND "nodules"[All Fields]) OR "multiple pulmonary nodules"[All Fields] OR ("pulmonary"[All Fields] AND "nodules"[All Fields]) OR "pulmonary nodules"[All Fields]) AND ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms] OR "incidences"[All Fields] OR "incident"[All Fields] OR "incidents"[All Fields] OR ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms] OR "prevalance"[All Fields] OR "prevalences"[All Fields] OR "prevalence s"[All Fields] OR "prevalent"[All Fields] OR "prevalently"[All Fields] OR "prevalents"[All Fields]))	2,030	Advanced
CNKI	"pulmonary nodules" AND ("detection rate" OR "incidence") in Chinese	234	Advanced

CNKI, China National Knowledge Infrastructure.

Appendix 1 Modified Newcastle-Ottawa risk-of-bias scoring system

Representativeness of the sample

- Low: samples are randomly selected and represent the general population.
- Some concerns: samples are selected with some criteria such as smoking history.
- High: samples contain only male or only participants with high risk of lung cancer.

Sample size

- Low: sample size was ≥1,000 participants.
- Some concerns: sample size was between 300 and 1,000 participants.
- High: sample size was <300 participants.

Ascertainment

- Low: studies with no criteria for pulmonary nodule.
- Some concerns: studies with some reasonable criteria for pulmonary nodule definitions.
- High: studies with stringent criteria for pulmonary nodules.

Quality of descriptive statistics reporting

- Low: studies reported descriptive statistics to describe the population (e.g., age, sex, and smoking history).
- Some concerns: studies missed one descriptive statistic.
- High: studies missed more than one descriptive statistic.

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Table S2 Risk of bias across studies

Study	Representativeness	Sample size	Ascertainment	Descriptive statistics	Overall
The International Early Lung Cancer Action Program, 2006	Low	Low	Some concerns	Some concerns	Some concerns
The National Lung Screening Trial, 2013	Some concerns	Low	Low	Low	Low
Wilson *et al.*, 2008	Some concerns	Low	Low	Low	Low
Henschke *et al.*, 1999	Some concerns	Low	Low	Low	Low
Pedersen *et al.*, 2009	Some concerns	Low	Low	Low	Low
Field *et al.*, 2016	Some concerns	Low	Some concerns	Low	Low
Hendrix *et al.*, 2023	Low	Low	Low	Some concerns	Low
Ouyang *et al.*, 2019	Low	Low	Low	Some concerns	Low
Xu *et al.*, 2020	Low	Some concerns	No information	Some concerns	Some concerns
Pan *et al.*, 2020	Low	Low	High	Low	High
Wei *et al.*, 2022	Low	Low	Some concerns	Low	Low
Ji *et al.*, 2022	Low	Low	Low	Low	Low
Wu *et al.*, 2022	Low	Low	Low	Low	Low
Wu *et al.*, 2023	Low	Low	No information	Low	Low
Zhang *et al.*, 2023	Low	Low	No information	High	High
Tapio Vehmas, 2008	Low	Some concerns	No information	Low	Some concerns
Hall *et al.*, 2009	Some concerns	Some concerns	Low	Some concerns	Some concerns
Sigel *et al.*, 2020	Low	Low	No information	Some concerns	Some concerns
Rinaldi *et al.*, 2010	Low	High	No information	Some concerns	High
Gould *et al.*, 2015	Low	Low	Low	High	High
Lin *et al.*, 2020	Low	Low	No information	Some concerns	Some concerns
Xu *et al.*, 2020	Low	Low	Low	Low	Low
Li *et al.*, 2022	Low	Low	Low	Some concerns	Low
Zhao *et al.*, 2019	Low	Low	Low	Some concerns	Low
Zhang *et al.*, 2022	Low	Low	Low	Some concerns	Low
He *et al.*, 2018	Low	Low	Low	Some concerns	Low
Hammerschlag *et al.*, 2015	Low	High	Low	High	High
Yorgun *et al.*, 2010	Low	Low	No information	Some concerns	Some concerns
Becker *et al.*, 2012	Some concerns	Low	Some concerns	Some concerns	Some concerns
Klaveren *et al.*, 2009	Some concerns	Low	No information	Low	Some concerns
Pegna *et al.*, 2009	High	Low	Some concerns	Low	High
Infante *et al.*, 2008	High	Low	Low	Some concerns	High

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