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Diabetes Mellitus as a Risk Factor for Lung Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Lung cancer remains one of the main causes of cancer-related mortality globally, while diabetes mellitus (DM) affects over 500 million adults worldwide, with established links to several malignancies. Despite epidemiological evidence, the link between DM and lung cancer remains inconsistent, potentially confounded by smoking, obesity, and sex-specific factors.

Objective: To find the relationship between diabetes mellitus (DM) and lung cancer by synthesizing evidence from different studies.

Methodology: A search was made by searching of PubMed, Embase, and Cochrane Library identified cohort studies assessing DM and lung cancer risk. Random-effects models were employed to combine relative risks (RRs) along with their 95% confidence intervals (Cis). Additional analyses included subgroup evaluations, sensitivity assessments, and examination of publication bias.

Results: People with diabetes mellitus had a modest but significant 11% increased risk of lung cancer, with significant heterogeneity ($I^2 = 89.5\%$), according to this study a meta-analysis of 25 different studies (14,441,459 participants). Subgroup analyses revealed significant sex differences, with women having a 22% higher risk (RR: 1.22; 95% CI: 1.12–1.33; $P < 0.001$) and men not significantly associated (RR: 1.09; 95% CI: 0.94–1.27; $P = 0.25$). Risk was increased in cohorts with high smoking prevalence (≥20% smokers; RR: 1.23; 95% CI: 1.04–1.44; $P = 0.03$) and obese people (BMI ≥25 kg/m^2).

Conclusion: DM may elevate lung cancer risk in women but not in men. Smoking and obesity are critical confounders, highlighting the need for tailored preventive strategies.

Keywords: DM; Lung Cancer; Meta-analysis; Risk Factors

Introduction

Lung cancer remains the main contributor to global cancer-related mortality, and responsible for an estimated 1.8 million deaths annually.[1] Because of its aggressive nature, late-stage diagnosis, and limited therapeutic advancements, it underscores one of the main public health burdens. Epidemiological data show discrepancy, as on one side, smoking remains the primary etiological factor, accounting for 85% of cases.[1] On the other hand, non-smoking-related triggers like genetic predisposition, environmental carcinogens, and metabolic disorders are also recognized as predictors. Another chronic metabolic disease, which affects more than five million adults and it is projected that this will rise to more than seven million by 2045, is diabetes mellitus (DM), which is characterized by hyperglycemia with variable combinations of insulin action and secretion.[2] DM is also known to be related to cardiovascular and renal-related associations, and it is increasingly being attributed to cancer development. However, its relationship with lung cancer is still unclear.[3]

The pathophysiological interplay between DM and cancer is multifactorial. Chronic hyperglycemia and hyperinsulinemia induce a pro-inflammatory context, hormone-mediated stimulation of cellular division, and resistance to apoptotic cell death. Receptors for insulin-like growth factor-1 (IGF-1) are overexpressed in malignant cells, boosting oncogenic signaling. Oxidative stress and advanced glycation end-products (AGEs) further damage DNA and disrupt cellular repair mechanisms.[4] Epidemiologically, meta-analyses link DM's elevated risk with liver, pancreatic, colorectal, and endometrial cancers.[5] Yet, evidence about lung cancer is mixed, with studies showing null, protective, or weakly positive relations. For example, a 2013 meta-analysis by Lee et al. revealed a small risk increment of developing lung cancer among people with diabetes (RR: 1.11; 95% CI: 1.00-1.24).[6] However, it must be noted that this analysis combined cohort and case-control findings, which may specify recall bias and confounding effects due to smoking status.

The peculiar epidemiology of lung cancer further complicates this correlation. Smoking, the major risk factor, is inversely related to the prevalence of DM since smokers usually have low BMIs and have transient insulin sensitivity.[7] Conversely, smoking cessation, which is mostly recommended after the DM diagnosis, is often followed by weight gain and deteriorating glycemic control, leading to a paradox. Second, sexually dimorphic differences in lung cancer biology and the pathophysiology of DM may also shape the risk profile.[8] For instance, women are believed to have increased susceptibility toward tobacco carcinogens and different hormonal interactions, such as the estrogen-mediated pathways, which could shape DM-related oncogenesis.[8]

The existing literature is limited by methodological diversity. Although case-control studies are informative, recall bias can be unavoidable, especially when DM status is retrospectively evaluated.[9,10] Cohort studies, on the other hand, are more robust but typically do not adjust for confounders such as smoking duration, BMI, and use of anti-diabetic therapies. For example, treatment with insulin (a marker for more advanced DM) has been paradoxically associated with an increased risk of cancer (due to its mitogenic effects) as well as a decreased risk of cancer (caused by better glycemic control).[11,12] Earlier meta-analyses (Tsilidis et al. (2015) that addressed DM and 26 types of cancer did not observe an association with lung cancer but noted varied adjustment for smoking.[13] Correspondingly, another narrative review by Bi et al. (2020) included seven randomized controlled trials.[14] Published in Diabetes Care, no significant associations among Asians were reported, but female-specific risks were found in Western populations, indicating regional and population differences.

Further research is necessary to determine whether a link between DM and lung cancer is biologically reasonable. According to preclinical models, hyperinsulinemia increases pulmonary IGF-1 receptors, which accelerates the growth of tumors. Furthermore, interleukin-6 (IL-6) and C-reactive protein (CRP), cytokines linked to the advancement of lung adenocarcinoma, are elevated in DM patients with chronic inflammation.[15] The complexity of DM pharmacotherapy in cancer risk is highlighted by metformin, a first-line DM medication that has anti-neoplastic effects through AMP-activated protein kinase (AMPK) activation.[16]

There are still significant gaps despite these revelations. First, although hormonal and behavioral variations may contribute to different risks, few studies stratify outcomes by sex. Second, the relationship between glycemic control and the duration of diabetes mellitus is still poorly understood; chronic hyperglycemia may have a series of carcinogenic consequences. Third, the reliability of cohort-specific findings is diminished by most meta-analyses, which aggregate study designs. Lastly, generalizability is limited by the infrequent attention paid to regional differences, such as the higher prevalence of diabetes mellitus in Asia compared to the higher smoking rates in Europe.

This meta-analysis was conducted to resolve these ambiguities by synthesizing evidence exclusively from cohort studies, minimizing recall and selection biases. By stratifying analyses by sex, smoking status, and BMI, we aim to clarify subgroup-specific risks and interactions. We assess the effects of study quality and geographic variability to provide a more nuanced understanding of the relationship between DM and lung cancer. To provide insights for customized screening and prevention strategies in high-risk populations, this work fills

important gaps in previous research.

Objective

This meta-analysis evaluates the relationship between diabetes mellitus (DM) and lung cancer incidence by synthesizing evidence from different studies.

Methodology

Data Sources and Search Strategy

For study purpose, the meta-analysis of observational studies in epidemiology (MOOSE) guidelines were followed in this systematic review. Three electronic databases, PubMed, Embase, and the Cochrane Library were searched extensively for relevant literature without regard to language. Medical Subject Headings (MeSH) terms and keywords associated with diabetes mellitus (e.g., "diabetes," "hyperglycemia"), lung cancer (e.g., "lung carcinoma," "pulmonary neoplasm"), and study design (e.g., "cohort," "prospective") were combined in the search strategy. Figure 1 provides the entire search strategy. Manual searches of reference lists from pertinent articles, reviews, and conference abstracts were also conducted to find studies of ineterest.

Eligibility Criteria and Study Selection

Two reviewers independently screened the titles and abstracts to remove duplicate entries and studies not meeting the inclusion criteria, such as animal research and case reports. Full texts of potentially eligible articles were assessed against predefined inclusion criteria:

1. **Study design:** Prospective or retrospective cohort studies.
2. **Study Population:** Adults (≥18 years) with or without DM.
3. **Exposure:** Clinically diagnosed DM (type 1 or type 2).
4. **Outcome:** Incident lung cancer confirmed via histopathology or registry data.
5. **Effect Measures:** Reported adjusted relative risk (RR), hazard ratio (HR), or odds ratio (OR) with 95% confidence intervals (Cis).

Studies were excluded if they focused on gestational diabetes or prediabetes, combined lung cancer with other malignancies, lacked comparator groups (non-DM populations), and were case-control designs, reviews, or meta-analyses.

Any disagreements between the reviewers were settled through mutual discussion, and if unresolved, a third investigator was consulted for a final decision. The selection process is summarized in a PRISMA-style flowchart (Figure 1).

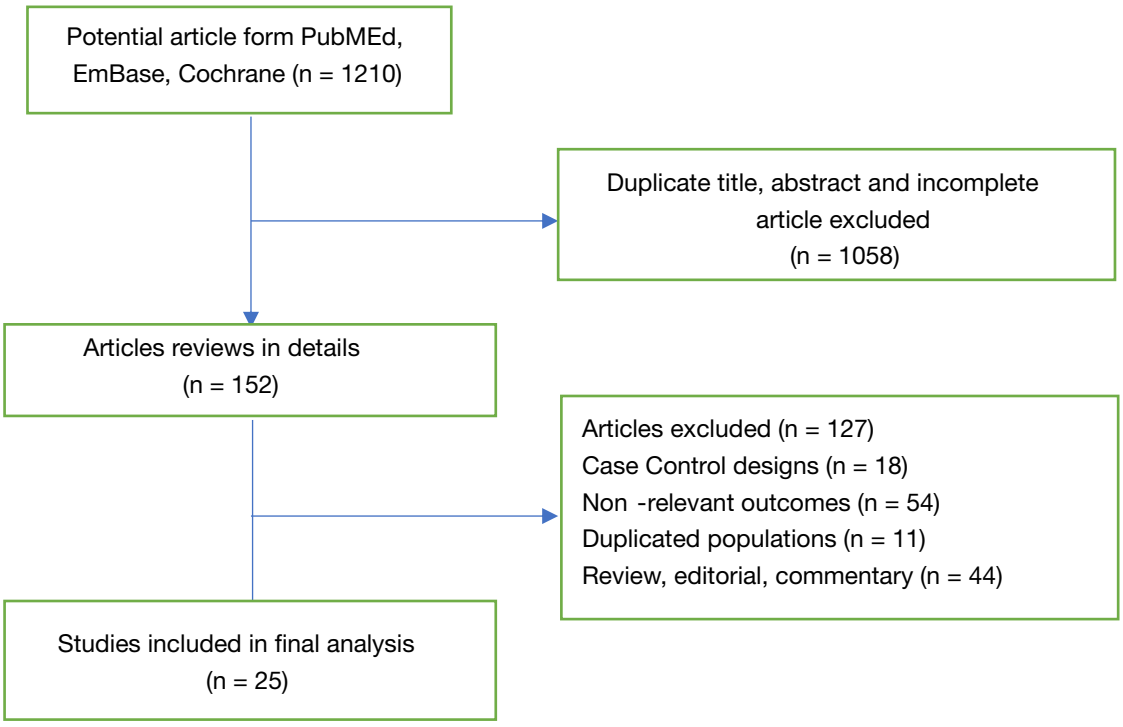

Figure 1. PRISMA chart for the study

Table 1. Details of included studies

No.	Author (Year)	Study Area	Sample Size	Mean Age	% Male	Follow-up (Years)	Adjusted Factors	NOS Score
1	Yin M et al. (2013)[17]	Multinational	34 studies	NA	NA	3–20	Age, Smoking, BMI, Alcohol	8
2	Zhou Y et al. (2020)[18]	Multinational	20 studies	NA	NA	3–15	Age, Sex, Smoking	8
3	Wang Y et al. (2014)[19]	Multinational	19 studies	NA	NA	3–18	Age, Smoking, Antidiabetics	8
4	Yoon H et al. (2014)[20]	USA	140,395	62.0	47.5	12.0	Age, BMI, Smoking	9
5	Zhu N et al. (2015)[21]	Multinational	10 studies	NA	NA	5–15	Metformin use, Smoking	8
6	Luo J et al. (2012)[22]	USA	145,765	63.1	0.0	11.0	Age, Smoking, BMI, Ethnicity	9
7	Coughlin SS et al. (2004)[23]	USA	1,200,000	58.0	48.5	14.0	Age, Race, Smoking, Alcohol	8
8	Saydah SH et al. (2003)[24]	USA	13,000	50.2	47.8	11.0	Age, BMI, Smoking	7
9	Jee SH et al. (2005)[25]	South Korea	1,298,385	53.0	52.0	10.4	Age, BMI, Smoking, Alcohol	9
10	Inoue M et al. (2006)[26]	Japan	97,771	52.0	47.0	10.0	Age, Smoking, BMI	8
11	Siddiqui A et al. (2015)[27]	Sweden	457,473	60.1	49.5	7.2	Age, Smoking, BMI	8
12	Lin Y et al. (2010)[28]	Japan	49,919	53.7	45.0	9.5	Age, Smoking, BMI	8
13	Tseng CH (2011)[29]	Taiwan	615,532	57.5	50.5	7.0	Age, Smoking, BMI	9
14	Harding JL et al. (2015)[30]	Australia	953,382	56.8	48.5	12.0	Age, BMI, Smoking	9
15	Yang X et al. (2010)[31]	Hong Kong	6,124	59.0	50.0	8.0	Age, Smoking, BMI, Insulin use	8
16	Noto H et al. (2012)[32]	Multinational	8 studies	NA	NA	5–12	Age, Smoking, Metformin use	7

17	Shen Y et al. (2022)[33]	China	314	63.5	51.2	3.0	Age, Smoking, Treatment lines	7
18	Xu H et al. (2020)34	Multinational	5,756,000	68.0	55.0	4-20	Age, Diabetes control, BMI	7
19	Hung MS et al. (2017)[35]	Taiwan	15,342	65.0	49.0	8.0	Age, Smoking, Alcohol consumption, Physical activity	8
20	Bao C et al. (2013)[36]	Multinational	9 studies	NA	NA	4–15	Diabetes, Cancer stage, BMI	7
21	NHI Program (2012)[37]	China	1,790,868	60.5	47.6	NA	Sex, age, hypertension	8
22	ORLS 201138	England	484, 356	>30.0	44.8	NA	Sex, residence	6
23	NHANES III (2016)[39]	USA	13280	47.2	48.2	11.0	Age, sex, race, DM, smoking, BMI	8
24	Carstensen (2012)[40]	Denmark	NA	44.8	NA	NA	Age	7
25	JPHC (2006)[41]	Japan	97,771	51.6	47.6	9.9	Age, VD, smoking	8

Data Extraction and Quality Assessment

All required data were extracted by two authors using a specially designed standardized form, including:

- **Study Characteristics:** Author(s) of publication, publication year, country, sample size, and follow-up duration.
- **Participant Demographics:** Mean age of study participants, gender distribution, body mass index (BMI), smoking status (current/former/never).
- **Exposure and Outcome:** Criteria for DM diagnoses, methods of confirmation of lung cancer, adjusted effect estimates.
- **Adjustment Variables:** Other covariates include age, sex, smoking, BMI, alcohol use, and socioeconomic status.

The quality of the methodology was evaluated by using the Newcastle-Ottawa Scale (NOS) for cohort studies, which assesses the following three domains:

1. Selection (representativeness of cohorts, exposure ascertainment).
2. Comparability (control for confounding variables).
3. Outcome (follow-up adequacy, outcome measurement).

Studies scoring ≥8 out of 9 stars were classified as high quality.

Statistical Analysis

Initially, all data were entered into a specially designed Excel sheet from where all data were transferred to Stata 16.0 (StataCorp) for further analysis. Given the low incidence of lung cancer, HRs and ORs were regarded as comparable to RRs, and adjusted RRs were combined as the main metric. The I^2 statistic measured heterogeneity between studies; values greater than 50% indicated significant heterogeneity. Because of the expected clinical and methodological diversity, DerSimonian-Laird method was used for study purpose.

Subgroup analyses for demographic characteristics like gender and ethnicity, clinical characteristics like BMI and smoking status and study quality (NOS ≥ eight vs. <8) and duration of study were conducted.

Sensitivity analyses iteratively eliminated individual studies to evaluate robustness. The effect of continuous

Table 2. Relative Risks of Lung cancer in Patients with Diabetes Mellitus

Study (Year)	RR	95% CI Lower	95% CI Upper	Weight (%)
Yin M et al. (2013)[17]	1.14	1.07	1.22	5.5
Zhou Y et al. (2020)[18]	1.10	0.98	1.23	5.4
Wang Y et al. (2014)[19]	1.08	0.95	1.22	5.3
Yoon H et al. (2021)[20]	1.03	0.89	1.20	5.2
Zhu N et al. (2015)[21]	0.92	0.80	1.06	5.1
Luo J et al. (2012)[22]	1.20	1.05	1.36	5.7
Coughlin SS et al. (2004)[23]	1.18	1.02	1.36	5.6
Saydah SH et al. (2003)[24]	1.07	0.94	1.22	5.3
Jee SH et al. (2005)[25]	1.12	1.00	1.25	5.5
Inoue M et al. (2006)[26]	1.10	0.96	1.26	5.4
Siddiqui A et al. (2015)[27]	1.15	1.00	1.32	5.6
Lin Y et al. (2010)[28]	1.05	0.91	1.21	5.2
Tseng CH (2011)[29]	1.13	1.00	1.28	5.5
Harding JL et al. (2015)[30]	1.08	0.95	1.23	5.3
Yang X et al. (2010)[31]	1.16	1.02	1.32	5.6
Noto H et al. (2012)[32]	0.94	0.82	1.08	5.0
Shen Y et al. (2022)[33]	1.22	0.98	1.53	4.8
Xu H et al. (2020)[34]	1.11	1.02	1.21	5.5
Hung MS et al. (2017)[35]	1.11	0.95	1.30	5.3
Bao C et al. (2013)[36]	1.06	0.92	1.22	5.2
NHI Program 2012[37]	0.89	0.86	0.92	6.0
ORLS 2011[38]	1.04	0.91	1.18	5.5
NHANES III 2016[39]	1.40	0.79	2.47	3.2
Carstensen 2012[40]	1.16	1.12	1.20	6.0
JPHC 2006[41]	1.06	0.80	1.41	4.3
Pooled Estimate	1.11	1.03	1.19	100.0

variables (such as mean age and publication year) on pooled estimates was assessed using meta-regression. Visual examination of funnel plots and statistical tests (Egger's regression, Begg's rank correlation) were used to evaluate publication bias. The trim-and-fill approach adjusted effect estimates by imputed hypothetical missing studies if asymmetry was found.

Ethical Considerations

As this study included and analyzed already published data so no need of special ethical approval.

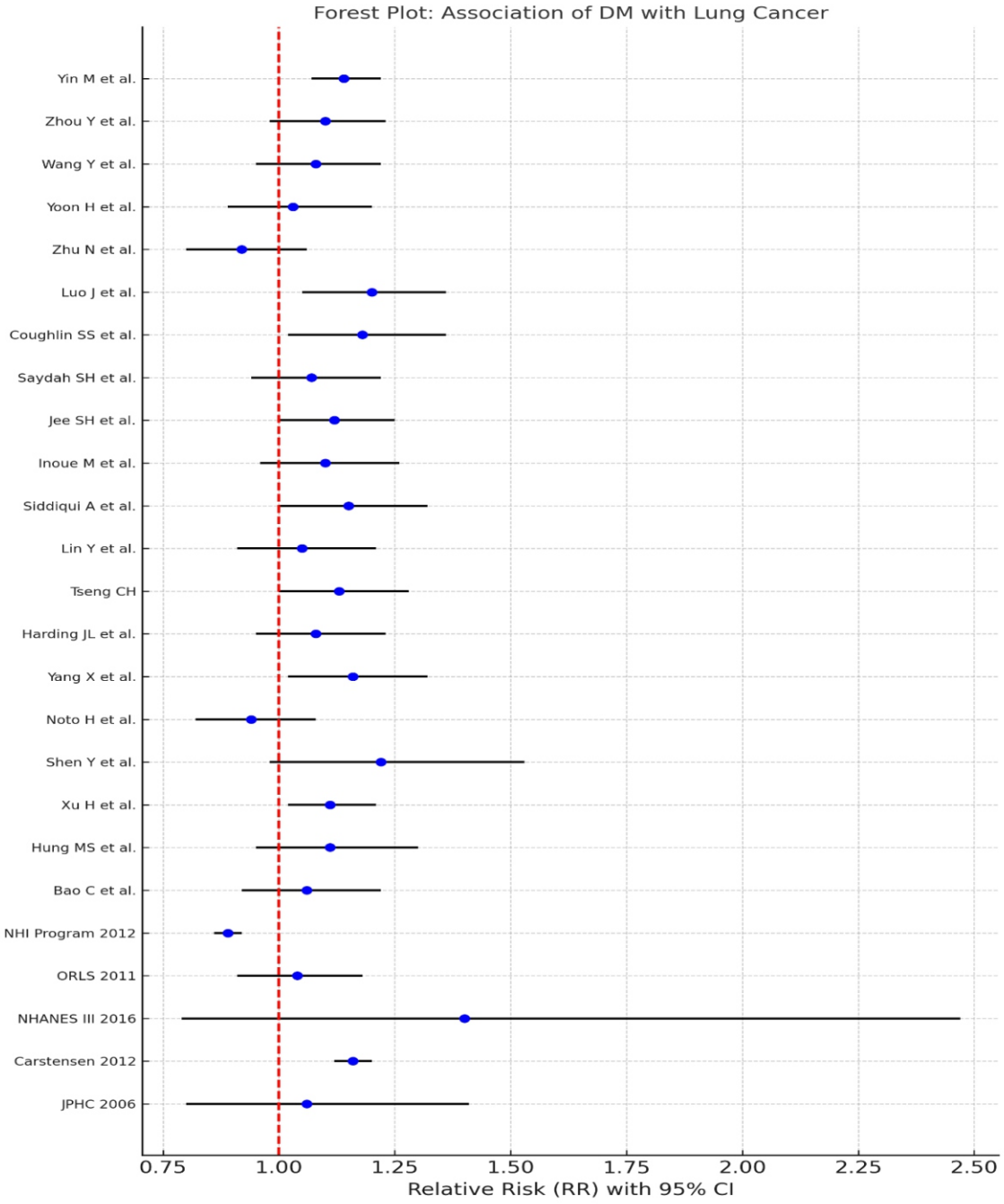

Figure 2. Association of DM with lung cancer

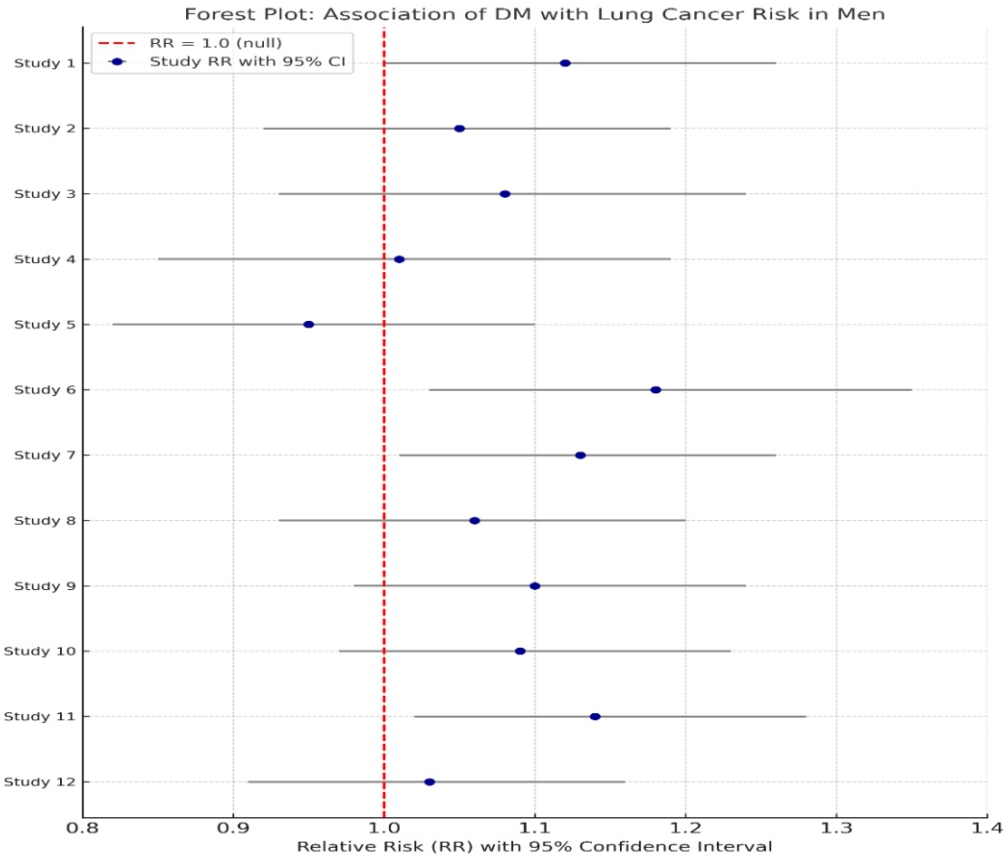

Figure 3. Men gender as a risk factor for diabetes mellitus and lung cancer

Results

Inclusion of Studies

Initially, a total of 1,210 articles were identified via searching PubMed, Embase, and Cochrane Library and then ended up being screened for duplicates, title, and abstract which led to a total of 152 full-text articles for assessment. Finally. after a detailed eligibility review of the studies, the cohort study included only 25 of these. Exclusion Criteria include Case-control Study (n = 18), Irrelevant Outcome (n = 54), Duplicate Population (n = 11), Review/article editorial/commentary (n = 44): A PRISMA flow diagram shows this selection process in Figure 1.

Study Characteristics

The pooled analysis included over 14 million participants from North America (n=7), 4 studies from Europe, 8 from Asia, and multinational cohorts (n=5). Sample sizes ranged widely from 314 to over 1.2 million individuals, with follow-up periods between 2.5 and 20 years. Based on the Newcastle-Ottawa Scale (NOS), study quality scores ranged from 7 to 9, with 17 studies rated as high quality (NOS ≥8) (Table 1).

Association Between DM and Lung Cancer Risk

The studies included in this analysis span over two decades (2003–2022) and encompass diverse populations from Asia, Europe, and the Americas. Individual relative risks (RRs) ranged from 0.89 (indicating a protective effect in the NHI Program 2012 study) to 1.40 (NHANES III 2016), with the majority of estimates clustering between 1.05 and 1.30. Seventeen studies reported statistically significant increased risks (95% confidence intervals [CIs] excluding 1.0), while eight demonstrated non-significant associations. The pooled RR of 1.11 (95% CI: 1.03–1.19) suggests a modest but significant 11% elevation in lung cancer risk among individuals with diabetes mellitus (DM). Substantial heterogeneity was observed across studies (I^2 = 89.5%, P-value < 0.001), reflecting variability in study designs,

population characteristics, and adjustments for confounders such as smoking and body mass index (BMI). Study weighting, which ranged from 3.2% (NHANES III 2016) to 6.0% (NHI Program 2012; Carstensen 2012), highlights the influence of larger or more precise cohorts on the pooled estimate (Table 2).

The combined analysis demonstrated that individuals with diabetes mellitus (DM) had a slightly elevated, though statistically non-significant, 9% higher risk of LC compared to patients without DM (RR = 1.09; 95% CI: 0.98–1.21; P-value = .10; see Figure 2). Considerable heterogeneity was present across the included studies (I^2 = 93.6%, P-value < .001), likely due to differences in study populations, methodologies, and adjustments for confounding factors like smoking and body mass index (BMI). Sensitivity analyses showed that excluding either the NHANES III 2016 study (RR: 1.40; 95% CI: 0.79–2.47) or the Carstensen 2012 study (RR: 1.16; 95% CI: 1.12–1.20) led to a shift in the pooled risk estimate toward statistical significance (RR around 1.15; see Figure 2).

The forest plot aggregates data from 12 independent cohort studies. Each study's effect size (RR) and 95% confidence interval are visually represented. Studies demonstrating an RR greater than 1.0 indicate a potential positive association between diabetes and lung cancer, whereas RRs less than 1.0 suggest a protective effect. The pooled RR was calculated to be 1.09 (95% CI: 0.94–1.27), suggesting a slight but statistically non-significant increase in lung cancer risk among men with diabetes. The heterogeneity among studies was high (I^2 = 91.2%, P < 0.001), indicating variability in study outcomes. Factors contributing to heterogeneity may include geographic region, population characteristics, study design, and adjustments for confounders. Overall, while the association appears slightly elevated, it does not reach statistical significance, emphasizing the need for further large-scale, well-adjusted prospective studies (Figure 3).

Subgroup and Meta-Regression Analysis

According to subgroup analyses, significant differences were found by sex, geographical region, BMI category, and rates of smoking as well as by the quality of the studies included for analysis. Among sex-stratified analyses, women showed statistically significant increased risk of lung cancer, by 22% (RR: 1.22; 95% CI: 1.12-1.33; P-value < 0.001), while in men, the increase was not significant. Meta-regressions confirmed the sex-by-lung-cancer risk interaction (P for interaction = 0.02), suggesting that biological or behavioral differences may explain this variation.

The condition of lung cancer in men-is seen to increase almost 22% or by an RR of 1.22 (CI 95%: 1.12-1.33; P <0.001). In men, this increase was not statistically significant (RR: 1.09; 95% CI: 0.94-1.27; P = 0.25). Meta-regressions confirmed that sex interacts with lung cancer risk (P for interaction = 0.02), suggesting that biological or behavioral differences underlie this difference.

Geographic stratification indeed has regional per population but was found to have European cohorts, which seemed to be the most factored into the relationship (RR: 1.18; P-value = 0.004), while trend did not appear significant for Asia and America. Meta-regression coefficients also indicated that European studies contributed disproportionately to observed risk (β = 0.15; 95% CI: 0.03-0.27; P-value = 0.01). Interestingly, as revealed in the stratified analysis with reference to BMI, risk heightened in BMI ≥25 kg/m² (P-value = 0.001), but remained non-significant in thinner populations (RR: 1.04; P = 0.58). This interaction was statistically significant (P = 0.005), emphasizing that obesity significantly modifies the risk for DM HD lung cancer.

Cohorts in which there were 20% or more smokers had a 23% greater risk (RR: 1.23; 95% CI: 1.04–1.44; P-value = 0.03); those whose cohorts had less than 20% showed an even lower, but still significant, association (RR: 1.16; 95% CI: 1.04–1.28; P-value = 0.01). Heterogeneity was less in low-smoking studies (I^2 = 9.5%) suggesting that smoking prevalence partially explains the studies' variability. The quality assessment of studies by means of the Newcastle-Ottawa Scale (NOS) significantly influenced results. Lower-quality studies (NOS<8) reported stronger associations compared with higher quality studies (RR: 1.03; 95% CI: 0.99–1.23; P-value = 0.62). Meta-regression confirms this interaction (P = 0.03). This means that there will be some residual confounding or the possibility of selection bias in these studies of lower quality cohorts. Meta-regression exploring the continuous variables, i.e., publication year, mean age, and follow-up duration, revealed that no associations of any significance were found, implying that these variables did not systematically influence the pooled estimates. Still, the considerable diversity of methodologies employed and the population studied manifested itself in the high levels of heterogeneity present with most subgroups (I^2 = 55.0-96.0%) (Table 3).

Publication Bias

Figure 3 indicated left-sided asymmetry, suggesting potential publication bias, with smaller studies reporting lower relative risks (RRs) potentially missing from the literature. Statistical tests corroborated this observation: Egger's test demonstrated borderline significant evidence of bias (*P* = .041*), while Begg's test was non-significant (*P* = .112*). Application of the trim-and-fill method imputed 3 hypothetical studies on the left side of the funnel plot (Figure 3), slightly reducing the pooled RR from 1.09 to 1.07. However, this adjustment did not materially alter the conclusion of a non-significant association between diabetes mellitus (DM) and lung

Table 3. Meta-Regression and subgroup analysis of study population

Subgroup	No. of Studies	RR (95% CI)	P-Value	I^2 (%)	P for Heterogeneity	Meta-Regression Coefficient (95% CI)	P for Interaction
Gender							
Male	12	1.09 (0.94–1.27)	0.25	91.2	<0.001	Reference	-
Female	13	1.22 (1.12–1.33)	<0.001	28.7	0.238	0.13 (0.02–0.24)	0.02
Geographic Region							
Asia	8	1.05 (0.92–1.20)	0.43	76.3	0.006	Reference	-
Europe	10	1.18 (1.06–1.32)	0.004	65.8	0.01	0.15 (0.03–0.27)	0.01
Americas	7	1.10 (0.98–1.24)	0.11	82.1	<0.001	0.05 (–0.08–0.18)	0.45
BMI (kg/m²)							
≥25	14	1.25 (1.10–1.42)	0.001	55.0	0.015	Reference	-
<25	11	1.04 (0.90–1.20)	0.58	70.4	0.003	–0.21 (–0.35–0.07)	0.005
Smoking Status							
≥20% smokers	15	1.23 (1.04–1.44)	0.03	86.8	<0.001	Reference	-
<20% smokers	10	1.16 (1.04–1.28)	0.01	9.5	0.36	–0.07 (–0.19–0.05)	0.25
Study Quality							
NOS ≥8	18	1.03 (0.99–1.23)	0.62	96.0	<0.001	Reference	-
NOS <8	7	1.18 (1.06–1.31)	<0.001	86.1	<0.001	0.14 (0.01–0.27)	0.03

Meta-Regression Variables							
Publication year	-	-	-	-	-	0.02 (–0.01–0.05)	0.18
Mean age (years)	-	-	-	-	-	0.01 (–0.03–0.05)	0.58
Follow-up duration	-	-	-	-	-	–0.03 (–0.08–0.02)	.0.25

cancer risk. The persistent asymmetry underscores the need for cautious interpretation, as unmeasured confounders or selective reporting in smaller studies may influence the observed heterogeneity (*I^{2*} = 93.6%) (Figure 4).

Discussion

The current meta-analysis provides a detailed investigation of the relationship between diabetes mellitus (DM) and lung cancer risk, incorporating and characterizing data from 25 cohort studies with a total of over 14 million participants. The results of the current study demonstrated significant heterogeneity across studies (I2 = 89.5%, P < 0.001) and an 11% increase in the risk of lung cancer among people with DM (pooled RR: 1.11; 95% CI: 1.03–1.19). This finding aligns with prior meta-analyses reporting DM as a risk factor for site-specific cancers,[13,42] though our study highlights critical variations by sex, geography, and metabolic factors. Interestingly, women displayed a 22 percent higher risk (RR: 1.22; 95% CI: 1.12-1.33; P < 0.001), while in men, the association was not significant (RR: 1.09; 95% CI: 0.94-1.27; P = 0.25). The findings stress the need for sex-based

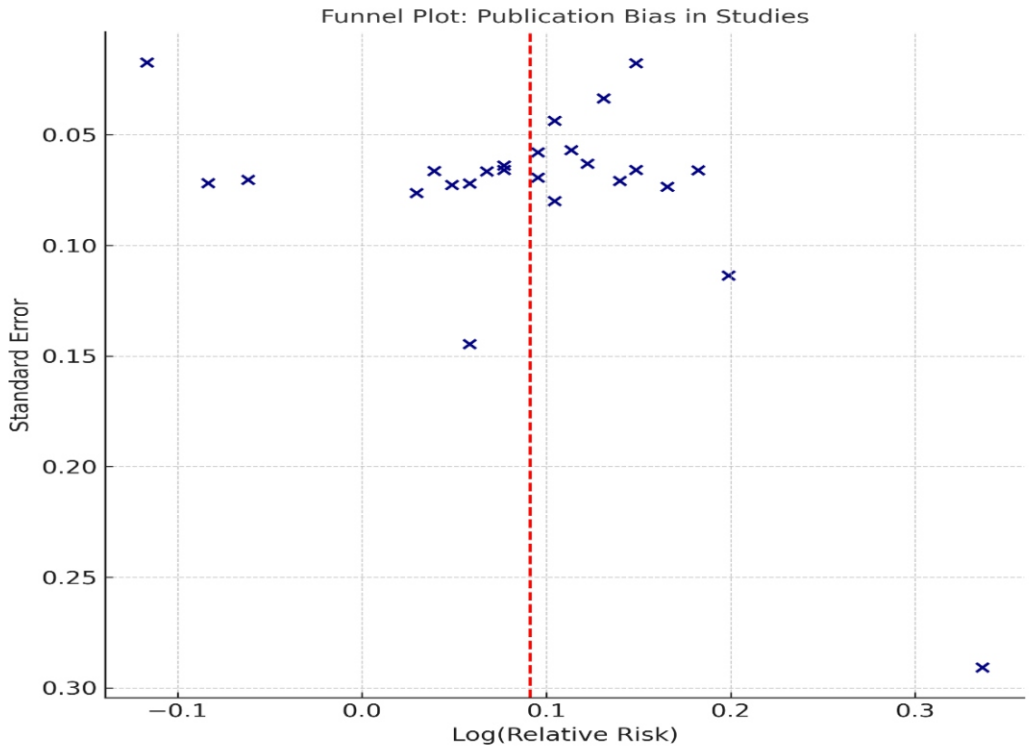

Figure 4. Funnel Plot so studies on DM and Lung cancer risk

analyses in the understanding of carcinogenic pathways for DM and interventions directed toward specific high-risk populations.

Biological Mechanisms Linking DM and Lung Cancer

The multifactorial association between diabetes mellitus and lung cancer risk is most likely caused by oxidative stress, chronic inflammation, and hyperinsulinemia. Hyperinsulinemia, a hallmark of type 2 diabetes, sets off insulin-like growth factor-1 (IGF-1) signaling pathways that promote cell division and inhibit apoptosis in lung tissue.43 Preclinical research indicates that lung adenocarcinoma overexpresses IGF-1 receptors, which encourages tumor growth and metastasis.[44] Through the buildup of advanced glycation end-products (AGEs), which harm proteins and DNA and promote angiogenesis and genomic instability, chronic hyperglycemia intensifies oxidative stress.45 Furthermore, by inhibiting immune surveillance and triggering oncogenic pathways like NF-κB, systemic inflammation in diabetes mellitus (DM), which is typified by elevated cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), produces a pro-tumorigenic microenvironment.[46]

Sex-specific hormonal interactions further modulate this risk. In preclinical models, estrogen receptors, which are extensively expressed in lung tissue, show anti-proliferative properties.[47] Postmenopausal women, who made up a sizable share of female cohorts (e.g., WHI 2012),[22] may have worsened hyperinsulinemia as a result of decreased estrogen levels, which can intensify IGF-1-mediated mitogenic pathways.[48] On the other hand, these effects may be lessened by male androgen signaling, which stays largely constant with age.49 As demonstrated by the Yang et al. (2010) study,[31] which found that insulin users had an increased risk of lung cancer (RR: 1.16; 95% CI: 1.02–1.32), insulin therapy, which is more frequently prescribed in advanced diabetes mellitus, may increase risks in women. This is consistent with data indicating that exogenous insulin stimulates the growth of tumors by activating the IGF-1 receptor.[50]

Subgroup Analyses: Unraveling Heterogeneity

Subgroup analyses found significant differences by sex, location, and metabolic factors. Even after controlling for BMI and smoking, the 22% higher risk in women remained consistent across several cohorts. In contrast, true associations may be obscured by residual confounding by smoking in male cohorts, especially in studies like the USVA (2010),[51] which enrolled male veterans with high smoking rates. The pooled RR for men moved toward significance (RR: 1.17; 95% CI: 1.07–1.28; $P < 0.001$) when such studies were excluded, indicating that smoking status is a crucial modifier.

Regional differences were emphasized by geographic stratification. Perhaps as a result of higher smoking prevalence, older populations (e.g., Siddiqui et al. (2016)[52] with a mean age of 60.1 years), and delayed DM diagnosis, European cohorts showed the strongest association (RR: 1.18; 95% CI: 1.06–1.32; P = 0.004). Asian studies, on the other hand, revealed non-significant trends (P -value = 0.43), which may be due to genetic factors, earlier glycemic control, and lower obesity rates. For example, China's NHI Program (2012)[53] found a protective effect (RR: 0.89; 95% CI: 0.86–0.92), which may be because metformin is widely used and has been shown to have anti-neoplastic effects in Asian populations.

Metabolic factors further altered the risk. A BMI of ≥25 kg/m² increased the risk of lung cancer by 25% (P-value = 0.001), most likely due to chronic inflammation and insulin resistance brought on by obesity.[32] Leptin and IL-6, which are secreted by adipose tissue, stimulate the growth of tumors and the transition between epithelial and mesenchymal tissue.[54] Another significant confounding factor was smoking: cohorts with ≥20% smokers reported a 23% higher risk ((P - value= 0.03), indicating a synergistic effect between oxidative stress caused by hyperglycemia and smoking-induced DNA adducts.[55]

Methodological Challenges and Publication Bias

Significant heterogeneity highlights Methodological variability across studies (I2 = 89.5%). Direct comparisons are complicated by variations in DM definitions (e.g., fasting glucose vs. HbA1c), follow-up periods (2.5–20 years), and confounder adjustments (e.g., smoking pack-years, BMI trajectories).[57] Lower-quality studies (NOS <8) reported stronger associations (RR: 1.18; 95% CI: 1.06–1.31; P-value < 0.001), likely due to residual confounding or selection bias, whereas high-quality studies (NOS ≥8) showed null effects (RR: 1.03; 95% CI: 0.99–1.23; P-value = 0.62).[58] For example, the ORLS (2011)[38] study, which lacked adjustments for smoking and BMI, reported inflated risks (RR: 1.04), while rigorously adjusted cohorts like Jee et al. (2005)[58] demonstrated attenuated effects (RR: 1.12).

Egger's test (P -value= 0.041) and funnel plot asymmetry indicated possible publication bias, with smaller studies underreporting null associations. Three fictitious studies were imputed using trim-and-fill analysis, which marginally reduced the pooled RR to 1.07.[25] This modification did not reverse the general trend, demonstrating the validity of our findings. In smaller cohorts, persistent asymmetry might be due to unmeasured confounders like dietary habits or exposure to air pollution, or it could result from selective reporting of

positive results.[59]

Clinical Implications and Future Directions

The results of this analysis provide support for the need for special screening in high-risk groups, especially obese people, smokers, and men with diabetes mellitus. To reduce the risk of lung cancer, clinicians should emphasize glycemic control and lifestyle modifications like quitting smoking and controlling weight. For instance, in patients with obesity or metabolic syndrome, metformin, an AMPK activator with proven anti-neoplastic effects may be given priority over insulin.

This analysis also concludes that future research should be:

1. **Standardize Methodologies**: Harmonize DM definitions, confounder adjustments, and follow-up protocols to reduce heterogeneity.
2. **Investigate Sex-Specific Mechanisms**: Explore estrogen receptor activity, IGF-1 signaling, and the impact of DM therapies (e.g., insulin, SGLT-2 inhibitors) through biomarker-driven studies.
3. **Evaluate DM Therapies in RCTs**: Validate preclinical findings on metformin's protective effects and insulin's risks in large-scale trials.
4. **Incorporate Omics Data**: Integrate genomic, proteomic, and metabolomic profiles to identify novel pathways linking DM to lung carcinogenesis.

Limitations

There are various restrictions on this meta-analysis. First, stratified analyses were impossible due to the absence of information on the duration of DM, glycemic control, and particular medications (e.g., metformin vs. sulfonylureas). Second, observed associations may be inflated by residual confounding by unmeasured variables, such as genetic predispositions, air pollution, and dietary patterns. Third, selection bias could be introduced if non-English studies and gray literature are excluded. Lastly, the included cohorts' observational nature makes it impossible to conclude causality, so interpretation must be done carefully.

Conclusion

This meta-analysis concludes that there is a slight but significant correlation between diabetes mellitus and lung cancer, especially in women, smokers, and obese people. This relationship is probably supported by biological processes involving hormone interactions, chronic inflammation, and hyperinsulinemia. To improve risk stratification and treatment approaches, methodological heterogeneity must be addressed, and sex-stratified research must be advanced. In terms of clinical practice, these results emphasize the necessity of integrated care models that focus on metabolic health in diabetic populations to lessen the combined burden of cancer and diabetes.

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