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Association between gamma-glutamyl transpeptidase and risk of lung neoplasms: a systematic review and meta-analysis

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Abstract

Introduction: Serum gamma-glutamyl transferase (GGT) elevation is a reliable marker for various chronic diseases, including cancer. Therefore, in this study, we investigated the association between increased serum GGT levels and the risk of lung cancer, employing a systematic review and meta-analysis approach.

Materials and Methods: To identify relevant articles up to 28 February 2026, the databases Web of Science, Cochrane, Scopus, PubMed, and Embase were searched, along with the Google Scholar search engine. The search strategy was applied without any restrictions on language or publication date. All statistical analyses were ultimately conducted using STATA software, version 14.

Results: In this meta-analysis, six observational studies were included, and the pooled findings indicated that elevated serum GGT levels were directly associated with an increased risk of lung cancer (HR: 1.11; 95% CI: 1.06–1.16). Furthermore, subgroup analyses showed that higher serum GGT levels were linked to a greater risk of lung cancer in studies conducted in Korea (HR: 1.10; 95% CI: 1.05–1.16), the United Kingdom (HR: 1.19; 95% CI: 1.03–1.37), cohort studies (HR: 1.12; 95% CI: 1.07–1.17), and among men (HR: 1.20; 95% CI: 1.13–1.27).

Conclusion: Elevated serum GGT levels increased the overall risk of lung cancer by 11% and, specifically, by 20% in men, whereas this association was not statistically significant in women.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD420261376343) and Research Registry (UIN: reviewregistry2103) websites.

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Introduction

Gamma-glutamyl transferase (GGT) is a liver enzyme that is also present in several extrahepatic tissues (1). Elevated serum GGT is considered a reliable marker for a range of chronic conditions, including hypertension, diabetes, cardiovascular disease, renal failure, and metabolic syndrome (2-4). Moreover, this enzyme plays an important role in carcinogenesis, tumour progression, metastasis, and the development of drug resistance (5,6).

An increase in serum GGT concentration may reflect the presence of oxidative stress in the body (7). In addition, both inflammation and oxidative stress are recognized risk factors for the occurrence of cancer (8-10). Among the various malignancies, lung cancer is one of the most frequently diagnosed cancers worldwide and remains the leading cause of cancer-related mortality (11). With an estimated 2.5 million new cases and 1.8 million deaths attributed to lung cancer in 2022 globally, this disease has emerged as a major public health challenge (12).

At the same time, the studies published on the association between elevated serum GGT levels and lung cancer risk have reported inconsistent findings. In a study conducted in 2025 (13), the authors concluded that higher GGT levels, compared with lower levels, were associated with an increased risk

Key point

This meta-analysis combined six observational studies and showed that individuals with higher serum gamma-glutamyl transferase (GGT) levels had an increased likelihood of developing lung cancer compared with those with lower levels, with this positive association consistently observed in studies from different regions, confirmed in analyses restricted to cohort designs, and particularly evident among men, whereas the corresponding relationship in women did not reach statistical significance.

of lung cancer. In contrast, a 2024 study (14) did not find a statistically significant relationship between elevated GGT and lung cancer risk. Therefore, in the present work, a systematic review and meta-analysis were undertaken to clarify the association between higher GGT levels and the risk of developing lung cancer and to derive a more definitive overall estimate.

Materials and Methods

Study design

The protocol for this investigation was formulated in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (15). In order to enhance methodological transparency and minimize the risk of selective reporting, the protocol was registered in international registries (PROSPERO [International Prospective Register of Systematic Reviews] and Research Registry) before the initiation of the review process.

Search strategy

To identify all relevant evidence, a comprehensive search was conducted up to 28 February 2026 in the Cochrane, Scopus, Web of Science, Embase, and PubMed databases, as well as through the Google Scholar search engine. The search process was performed without any restrictions on publication date or language. Standardized keywords, together with their corresponding Medical Subject Headings (MeSH) terms, were employed. In the advanced search stage, Boolean operators (AND, OR) were used to combine search terms appropriately. In addition, the reference lists of all eligible articles were manually screened to identify any further pertinent studies.

PECO component

- Population (P): Studies that evaluated the association between serum GGT levels and the risk of developing lung cancer.
- Exposure (E): Elevated serum GGT concentrations.
- Comparison (C): Lower serum GGT concentrations.
- Outcome (O): Risk of incidence lung cancer.

Eligibly criteria

Inclusion criterion: Studies that specifically examined the association between serum GGT levels and the risk of developing lung cancer.

Exclusion criteria: Studies that did not report the essential data required for quantitative synthesis; investigations that assessed the relationship between GGT and the risk of overall or composite cancer outcomes without providing separate data for lung cancer; studies for which the full text could not be obtained despite contacting the authors; reports that evaluated the association between GGT and cancers of the respiratory tract as a group without isolating lung cancer; duplicate publications indexed in more than one database; studies that failed to meet the predefined quality thresholds at the stage of methodological appraisal; and review articles.

Quality assessment

The quality of the included studies was independently assessed by two authors using the Newcastle–Ottawa Scale (NOS), which consists of nine items rated on a star-based system (16). Studies that received a score of at least six stars were classified as high quality and were eligible for inclusion in the present meta-analysis.

Data extraction

Data extraction was performed independently by two authors using SPSS software, version 19. The extracted variables included the first author's name, year of publication, country, serum GGT levels, patient sex, study design, mean age of participants, and the hazard ratio (HR) with its corresponding upper and lower limits for the association between elevated serum GGT and lung cancer risk.

Statistical synthesis

For the quantitative synthesis, the natural logarithm of the hazard ratio (HR) was calculated for each study, and these values were used as the summary measure in the meta-analysis. Between-study heterogeneity was assessed using the I^2 statistic. A fixed-effect model was applied when heterogeneity was low, whereas a random-effects model was used in the presence of moderate to substantial heterogeneity. All statistical analyses were conducted using STATA software, version 14, and a two-sided *P* value of less than 0.05 was considered indicative of statistical significance.

Results

A total of 321 records were initially identified through database searching. After removal of 179 duplicate records, 142 unique records remained for title and abstract screening, of which 34 were excluded as not relevant to the study objective. Full texts were sought for 108 records, but 39 reports could not be retrieved. The remaining 69 reports were assessed in detail for eligibility, and 63 were excluded based on the predefined inclusion and exclusion criteria. Ultimately, 6 studies met the eligibility criteria

and were included in the final qualitative and quantitative syntheses (Figure 1).

In this meta-analysis, six cohort and case–control studies comprising a total of 8,411,630 participants were included. Three of the eligible studies were conducted in Korea, two were carried out in the United Kingdom, and one was performed in Germany (Table 1).

The results presented in Figure 2 showed that higher serum levels of GGT were directly associated with an increased risk of lung cancer. In other words, as the concentration of this enzyme in serum increased, the probability of developing lung cancer rose significantly. Accordingly, elevated serum GGT can be regarded as an independent risk factor for lung cancer (HR: 1.11; 95% CI: 1.06–1.16).

Figure 3 showed that elevated serum GGT levels were directly associated with an increased risk of lung cancer among patients in Korea (HR: 1.10; 95% CI: 1.05–1.16) and the United Kingdom (HR: 1.19; 95% CI: 1.03–1.37). In contrast, among German patients, no statistically significant association was observed between higher serum GGT levels and lung cancer risk (HR: 0.75; 95% CI: 0.56–1.02).

Elevated serum GGT levels in cohort studies were associated with a higher risk of developing lung cancer (HR: 1.12; 95% CI: 1.07–1.17). In contrast, in the single case–control study (HR: 0.75; 95% CI: 0.56–1.02), no statistically significant relationship was observed between increased serum GGT and lung cancer risk. It should be noted that, of the six included investigations, five were cohort studies and only one employed a case–control design (Figure 4).

In men, elevated serum GGT levels were associated with a significantly increased risk of lung cancer (HR: 1.20; 95% CI: 1.13–1.27), whereas in women (HR: 1.01; 95% CI: 0.96–1.06) no statistically significant relationship was observed between higher GGT concentrations and lung cancer risk. This pattern suggests that the predictive value of serum GGT for lung cancer risk is likely to be sex dependent (Figure 5).

The meta-regression analysis demonstrated that the association between elevated serum GGT levels and the risk of lung cancer was not statistically influenced by the sample size of the included studies ($P = 0.539$; Figure 6).

Discussion

The findings of this meta-analysis demonstrated that higher serum GGT levels were associated with an increased risk of lung cancer, and that this relationship appeared to be modified by sex. Consistent with these results, a previous

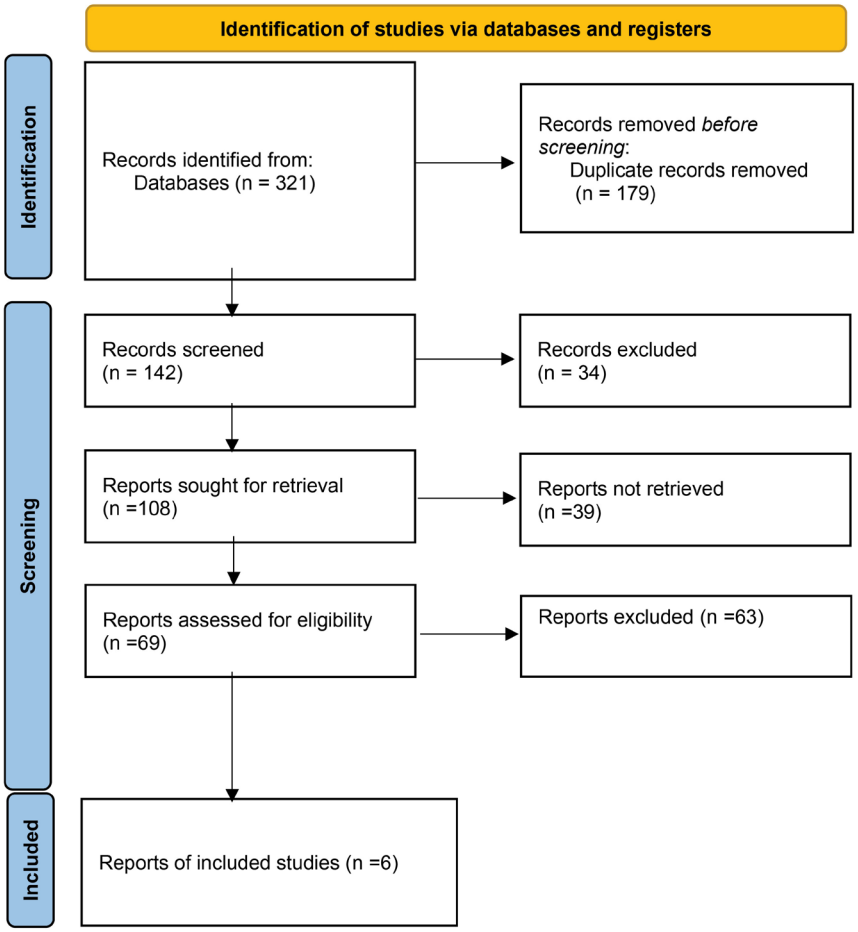

Figure 1. The PRISMA flowchart of study selection.

Table 1. The important data from the studies under review

Author, year	Country	Type of study	Duration of study	Sample size	Mean age (year)	Gender	Level of GGT	Serum of GGT	HR	Low	Up
Chung C, 2025 (17)	Korea	Cohort	2012-2022	2414755	46.7	Male	Quartile2	22–31 IU/L	1.13	1.09	1.17
							Quartile3	32–53 IU/L	1.21	1.17	1.25
							Quartile4	≥ 54 IU/L	1.37	1.32	1.42
						Female	Quartile2	13–16 IU/L	1	0.95	1.06
							Quartile3	17–23 IU/L	1.06	1	1.12
							Quartile4	≥ 24 IU/L	1.13	1.06	1.19
Chen T, 2025 (13)	UK	Cohort	2006-2010	412634	56.3	NR	Total	NR	1.01	1.01	1.02
							Quartile2	NR	1.22	1.09	1.36
							Quartile3	NR	1.30	1.16	1.45
							Quartile4	NR	1.45	1.29	1.62
Sun X, 2024 (14)	UK	Cohort	2006-2010	337499	37-73	NR	Level 1	30-38 U/L	0.97	0.86	1.09
							Level 2	>38 U/L	1.05	0.94	1.16
Lee YJ, 2021 (18)	Korea	Cohort	2009–2012	3559109	≥20	Male	Quintile1	NR	1.14	1.06	1.22
							Quintile2	NR	1.24	1.14	1.34
							Quintile3	NR	1.28	1.18	1.38
							Quintile4	NR	1.36	1.27	1.45
						Female	Quintile1	NR	0.99	0.86	1.16
							Quintile2	NR	0.88	0.73	1.06
							Quintile3	NR	1.10	0.92	1.32
							Quintile4	NR	0.95	0.81	1.11
Katzke V, 2020 (19)	Germany	Case-Cohort	1992-2000	25546	35-70	NR	Total	NR	0.96	0.80	1.15
							Quartile2	NR	0.77	0.45	1.31
							Quartile3	NR	0.67	0.4	1.11
							Quartile4	NR	0.83	0.5	1.37
Mok Y, 2016 (20)	Korea	Cohort	1995-1998	1662087	41.1	Male	Total	NR	1.05	1.04	1.06
							Quintile1	12–16 IU/L	1.01	0.92	1.11
							Quintile2	17-23 IU/L	1.09	1	1.19
							Quintile3	24-39 IU/L	1.10	1.01	1.2
							Quintile4	≥40	1.25	1.14	1.36
						Female	Total	NR	0.92	0.81	1.03
							Quintile1	12–16 IU/L	0.97	0.87	1.09
							Quintile2	17-23 IU/L	1.02	0.91	1.15
							Quintile3	24-39 IU/L	1.02	0.89	1.16
							Quintile4	≥40	0.77	0.63	0.95

NR: Not reported; HR: Hazard ratio; GGT: Gamma Glutamyl Transferase.

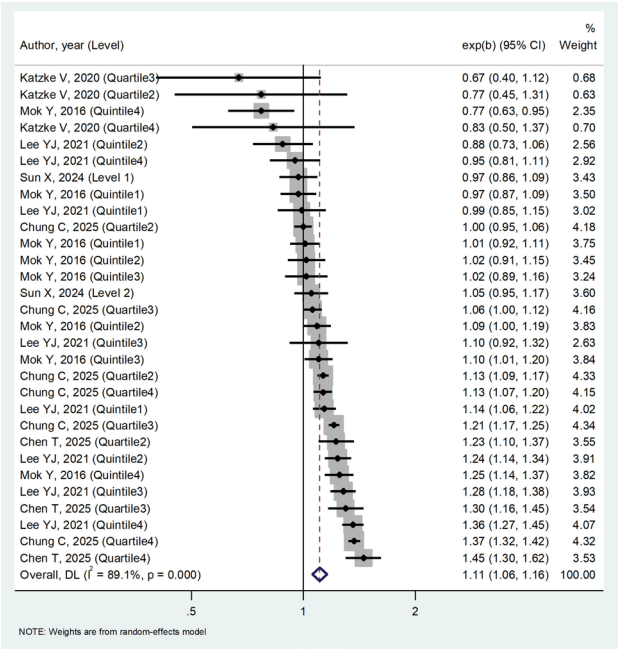

Figure 2. Forest plot related to the association between GGT and risk of lung cancer.

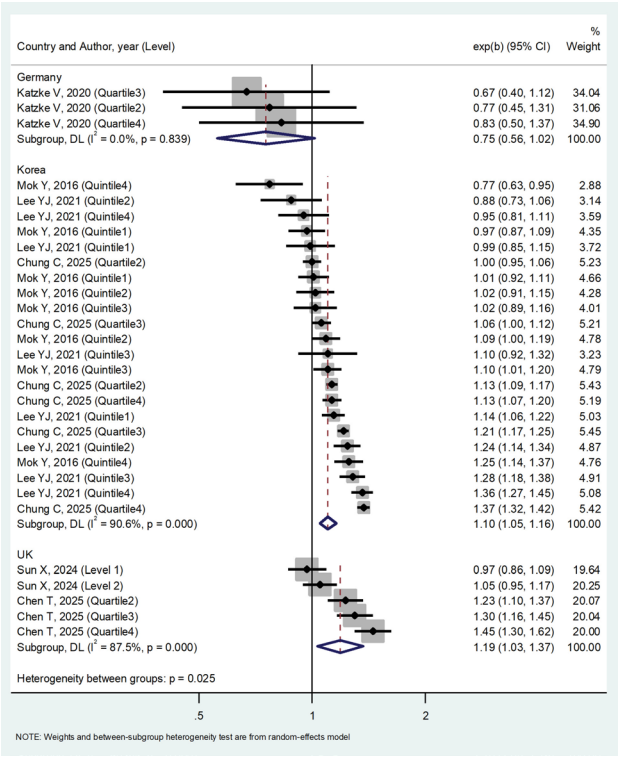

Figure 3. Forest plot related to the association between GGT and risk of lung cancer by place.

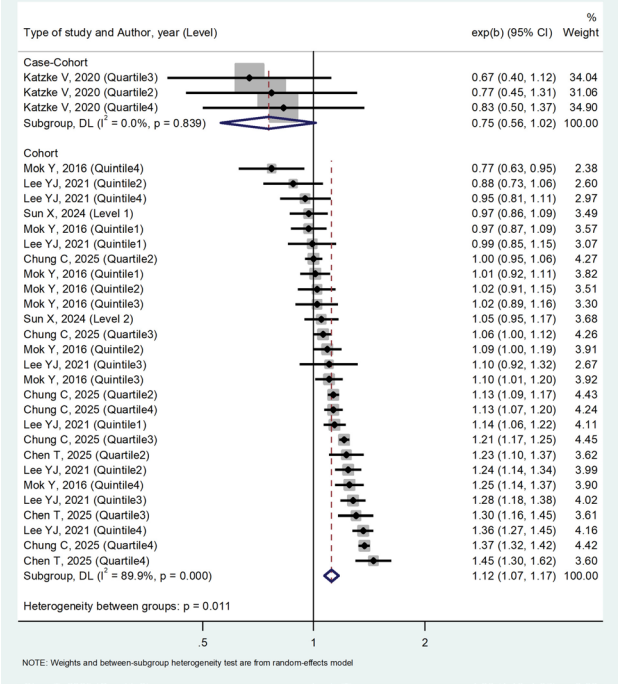

Figure 4. Forest plot related to the association between GGT and risk of lung cancer by type of study.

meta-analysis by Kunutsor et al reported that individuals in the highest category of baseline GGT had a significantly greater overall risk of cancer compared with those in the lowest category, supporting the concept of GGT as a biomarker linked to carcinogenesis more broadly (21). Thus, both the present work and the study by Kunutsor and colleagues suggest that elevated GGT may act as a risk factor for the development of several malignancies, including lung cancer.

In the cohort study conducted by Van Hemelrijck et al, which examined the association between GGT and overall cancer risk, higher GGT levels were found to be positively related to the incidence of several cancers, with the strongest associations reported for malignancies of the gastrointestinal tract and the respiratory system (HR: 1.31; 95% CI: 1.27–1.35 and HR: 1.30; 95% CI: 1.24–1.37, respectively) (22). In another cohort study by Chen et al, designed to investigate the relationship between GGT and lung cancer while accounting for inflammatory biomarkers, participants in the highest quartile of serum GGT had a markedly increased risk of lung cancer compared with those in the lowest quartile (HR: 1.45; 95% CI: 1.29–1.62) (13). Similarly, in a large population-based cohort from South Korea, Chung and colleagues observed that individuals in the fourth quartile of GGT had the greatest incidence of lung cancer, with this pattern evident in both men (HR: 1.37; 95% CI: 1.32–1.42) and women (HR: 1.13; 95% CI: 1.06–1.19) (17). Katzke et al also reported, in a cohort evaluating liver enzymes in relation to cardiovascular disease and four common cancers (breast, prostate, colorectal, and lung), that higher GGT concentrations were associated with an elevated risk of lung cancer (HR: 1.18; 95% CI: 1.01–1.38) (19). Collectively, these findings are concordant with the present meta-analysis, in which elevated serum GGT in cohort studies was likewise associated with a significantly increased risk of lung cancer, supporting the interpretation that higher GGT levels represent a reliable and independent marker

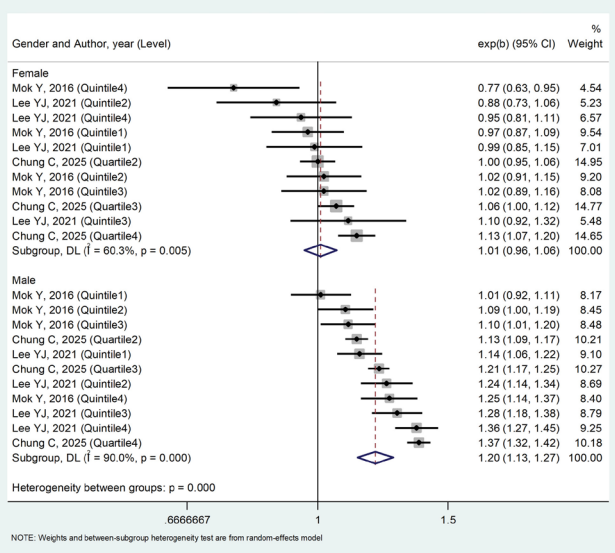

Figure 5. Forest plot related to the association between GGT and risk of lung cancer by gender.

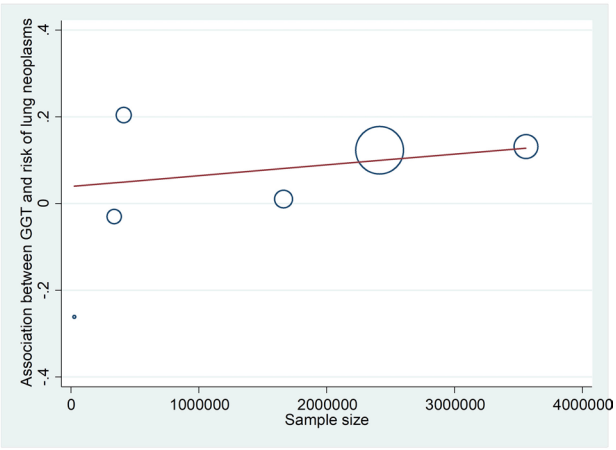

Figure 6. Meta-regression plot of the relationship between "association between GGT and risk of lung cancer" and sample size.

for lung cancer susceptibility.

In a cohort study by Lee et al, men with the highest GGT levels had a markedly increased risk of respiratory tract cancer and, more specifically, lung cancer, whereas no significant association was observed between GGT and lung cancer incidence in women (18). This pattern is concordant with the sex-stratified findings of the present meta-analysis, which likewise indicated that elevated GGT functions as a risk factor for lung cancer in men but not in women. In another large cohort study, Strasak et al reported that, among men, higher serum GGT was significantly associated with increased overall cancer risk, with particularly strong associations for cancers of the respiratory system (10). These results are in line with the current analysis and further support the notion that, in male populations, elevated GGT may act as an independent risk indicator for cancers of the respiratory tract, including lung cancer.

In another cohort investigation, Strasak and colleagues reported that, among women, higher GGT levels were significantly associated with an increased overall risk of cancer, and that elevated serum GGT was also strongly related to incident respiratory or intrathoracic cancers (9). These findings are not fully aligned with the present meta-analysis, in which no statistically significant association was observed between elevated GGT and lung cancer risk in women. A plausible explanation for this discrepancy is that the current study focused specifically on lung cancer, whereas the analysis by Strasak et al combined several types of malignancies, including but not limited to lung cancer, into broader cancer outcomes.

Conclusion

Elevated serum GGT levels were associated with an approximately 11% increase in the risk of developing lung cancer. Moreover, the prognostic value of GGT for lung cancer risk appeared to be sex dependent, as higher GGT concentrations were linked to a 20% increase in lung cancer risk among men, whereas no statistically significant association was observed in women. One plausible explanation for this discrepancy may relate to sex-related hormonal differences. From a clinical perspective, serum GGT may therefore serve as a useful indicator of lung cancer risk in men, while in women, this biomarker alone is unlikely to provide sufficient predictive power for lung cancer occurrence.

Limitations of the study

The classification of serum GGT levels differed across the included studies, which precluded an analysis of the association between elevated GGT and lung cancer risk according to specific GGT categories. Consequently, it was not possible to determine whether progressively higher GGT concentrations were associated with a correspondingly stronger relationship with lung cancer risk. In addition, the distribution of studies across subgroups such as sex, study design, and country was unbalanced, which may have limited the robustness of the subgroup analyses.

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Authors' contribution

Conceptualization: Leila Ashrafi, Seyed Amir Banikarim, and Naeem Nikpour.
Data curation: Afrooz Kargaran Dehkordi, Ahmadreza Maghsoudi, and Fatemeh Rostami
Formal analysis: Sajad Ataei Azimi and Afrooz Kargaran Dehkordi
Investigation: Shirin Shamsghahfarokhi, Seyed Amir Banikarim, and Zahed Karimi
Methodology: Leila Ashrafi, Sajad Ataei Azimi, and Zahed Karimi.
Project Management: Naeem Nikpour.
Supervision: All Authors.
Visualization: Ahmadreza Maghsoudi and Fatemeh Rostami.

Writing–original draft: All authors.
Writing–review and editing: All authors.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD420261376343) and the Research Registry website with (Unique Identifying Number [UIN]: reviewregistry2103). Besides, ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the author.

Conflicts of interest

The authors declare that they have no competing interests.

Funding/Support

None.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized AI (Perplexity) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the accuracy and content of the publication.

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