



Faculty of Resource Science and Technology

**Evaluation of Lung Cancer Risk from Incense Burning and Nitrogen
Dioxide Exposure through Meta-analyses and Molecular Docking**

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Evaluation of Lung Cancer Risk from Incense Burning and Nitrogen Dioxide
Exposure through Meta-analyses and Molecular Docking

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DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Malaysia Sarawak. Except where due acknowledgements have been made, the work is that of the author alone. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.

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ABSTRACT

Lung cancer (LC) remains a leading cause of cancer mortality worldwide, with environmental exposures playing a pivotal role in its aetiology. Nitrogen dioxide (NO₂), a primary toxicant released both from incense combustion and outdoor air pollution (AP), has been increasingly implicated in LC risk. To address this, three interlinked approaches were undertaken. First, a meta-analysis of case-control studies in Asian populations demonstrated that incense burning, a significant indoor source of NO₂ and other carcinogens, is associated with increased LC risk (pooled odds ratio [OR] = 1.33, 95% confidence interval [CI]: 1.20-1.48). Second, a meta-analysis of cohort studies beyond European countries suggested that NO₂ exposure is associated with elevated LC incidence and mortality (pooled hazard ratio [HR] per 10 parts per billion (ppb) increase in NO₂ = 1.08, 95% CI: 1.03-1.13). Third, molecular docking analyses were conducted to elucidate the mechanistic basis of these associations, revealing that NO₂ and its reactive surrogates, including peroxynitrite (ONOO⁻), 2-nitrophenol (2-NT), 3-nitrotyrosine (3-NT), and nitrobenzene, exhibit binding affinities with proteins central to oxidative stress, inflammation, and oncogenic signalling pathways implicated in LC pathogenesis. In conclusion, these findings provide converging evidence that NO₂, whether derived from indoor sources such as incense burning or from outdoor AP, contributes to lung carcinogenesis through both epidemiological associations and molecular interactions.

Keywords: lung cancer, nitrogen dioxide, incense burning, meta-analysis, molecular docking

Penilaian Risiko Kanker Paru-paru Akibat Pembakaran Dupa dan Pendedahan Nitrogen Dioksida melalui Meta-analisis dan Docking Molekul

ABSTRAK

Kanker paru-paru (LC) kekal sebagai punca utama kematian akibat kanser di seluruh dunia, dengan pendedahan persekitaran memainkan peranan penting dalam etiologinya. Nitrogen dioksida (NO₂), iaitu toksikan utama yang dilepaskan daripada pembakaran dupa serta pencemaran udara (AP) luaran, semakin banyak dikaitkan dengan risiko LC. Bagi menangani isu ini, tiga pendekatan saling berkait telah dijalankan. Pertama, meta-analisis kajian kawalan-kes dalam populasi Asia menunjukkan bahawa pembakaran dupa, sebagai sumber dalaman utama NO₂ dan karsinogen lain, dikaitkan dengan peningkatan risiko LC (nisbah ganjil [OR] keseluruhan = 1.33, selang keyakinan [CI] 95%: 1.20-1.48). Kedua, meta-analisis kajian kohort di luar negara Eropah mencadangkan bahawa pendedahan NO₂ berkait dengan peningkatan insiden dan mortaliti LC (nisbah bahaya [HR] keseluruhan bagi setiap peningkatan 10 bahagian per bilion [ppb] NO₂ = 1.08, 95% CI: 1.03-1.13). Ketiga, analisis dok molekul dijalankan bagi menjelaskan asas mekanistik hubungan ini, dan hasilnya menunjukkan bahawa NO₂ serta surrogat reaktifnya, termasuk peroksinitrit (ONOO⁻), 2-nitrofenol (2-NT), 3-nitrotirosin (3-NT), dan nitrobenzena, mempunyai pertalian pengikatan dengan protein yang berperanan penting dalam stres oksidatif, keradangan, dan laluan pensinyalan onkogenik yang terlibat dalam patogenesis LC. Kesimpulannya, dapatan ini memberikan bukti yang selaras bahawa NO₂, sama ada berpunca daripada sumber dalaman seperti pembakaran dupa atau daripada AP luaran, menyumbang kepada karsinogenesis paru-paru melalui hubungan epidemiologi dan interaksi molekul.

Kata kunci: *Kanser paru-paru, nitrogen dioksida, pembakaran dupa, meta-analisis, dok
docking molekul*

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LIST OF ABBREVIATIONS

2-NP	2-nitrophenol
3-NT	3-nitrotyrosine
Å	Angstrom
ALDH1A1	Aldehyde dehydrogenase family 1 member A1
ALK	Anaplastic lymphoma kinase
AP	Air pollution
AR	Androgen receptor
AREG	Amphiregulin
AuO	Auramine O
BH	Benjamini-Hochberg
BP	Biological process
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CanCHEC	Canadian Census Health and Environment Cohort
CC	Cellular component
CI	Confidence interval
CK	Cytokeratin
CKD6	Cyclin-dependent kinase 6
CNS	Central nervous system
CO	Carbon monoxide
CO ₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CTD	Comparative Toxicogenomics Database
ctDNA	Circulating tumour DNA

CXCL-8	C-X-C motif chemokine ligand 8
CYP1A1	Cytochrome P450 family 1 subfamily A member 1
CYP1B1	Cytochrome P450 family 1 subfamily B member 1
DALY	Disability-adjusted life year
DB[a,h]A	Dibenzo[a,h]anthracene
DBD	DNA-binding domain
DHT	Dihydrotestosterone
DNA	Deoxyribonucleic acid
EBRT	External beam radiotherapy
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
EPA	Environmental Protection Agency
FDR	False discovery rate
FOXM1	Forkhead box protein M1
GBD	Global Burden of Disease
GO	Gene Ontology
GPX1	Glutathione peroxidase 1
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GSTM1	Glutathione S-transferase mu 1
GSTT1	Glutathione S-transferase theta 1
GWAS	Genome-wide association studies
HMOX1	Heme oxygenase 1
HR	Hazard ratio
HSP	Heat-shock protein

IARC	International Agency for Research on Cancer
ICAM1	Intercellular adhesion molecule 1
ICI	Immune checkpoint inhibitors
IGRT	Image-guided radiotherapy
IL-1 β	Interleukin-1 β
IL-6	Interleukin-6
IL-6R α	Interleukin-6 receptor alpha subunit
IMRT	Intensity-modulated radiotherapy
kcal/mol	Kilocalories per mole
KEAP1	Kelch-like ECH-associated protein 1
KEGG	Kyoto Encyclopedia of Genes and Genomes
KRAS	KRAS proto-oncogene, GTPase
LBD	Ligand-binding domain
LC	Lung cancer
LDCT	Low-dose computed tomography
MAPK	Mitogen-activated protein kinase
MeSH	Medical Subject Headings
MET	MET proto-oncogene, receptor tyrosine kinase
MF	Molecular function
mg/g	Milligrams per gram
MH	Mantel-Haenszel
MMA	Multivariate meta-analysis
MPO	Myeloperoxidase
MRD	Minimal residual disease
MYC	MYC proto-oncogene, bHLH transcription factor

NCAM	Neural cell adhesion molecule
NF- κ B	Nuclear factor-kappa B
NMA	Network meta-analysis
NO ₂	Nitrogen dioxide
NOS	Newcastle-Ottawa Scale
NO _x	Nitrogen oxides
NSCLC	Non-small cell lung cancer
NTD	N-terminal transactivation domain
NTP	National Toxicology Program
O ₃	Ozone
OMIM	Online Mendelian Inheritance in Man
ONOO ⁻	Peroxynitrite
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbon
PCI	Prophylactic cranial irradiation
PD-1	Programmed death-1
PDB	Protein Data Bank
PD-L1	Programmed death-ligand 1
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PKB	Protein kinase B
PM	Particulate matter
ppb	Parts per billion

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRRT	Peptide receptor radionuclide therapy
RB1	RB transcriptional corepressor 1
RNA	Ribonucleic acid
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
ROS1	ROS proto-oncogene 1
RR	Relative ratio
RTK	Receptor tyrosine kinase
SBRT	Stereotactic body radiotherapy
SCLC	Small-cell lung cancer
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SO ₂	Sulfur dioxide
SOD1	Superoxide dismutase 1
SOD2	Superoxide dismutase 2
SOX2	SRY-box transcription factor 2
STITCH	Search Tool for Interacting Chemicals
STK11	Serine/threonine kinase 11
TIL	Tumour-infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
TMB	Tumour mutational burden
TNFRSF1B	tumour necrosis factor receptor superfamily member 1B
TNF- α	Tumour necrosis factor-alpha
TNM	Tumour, node, metastasis

TP53	Tumour protein p53
TTF-1	Thyroid transcription factor-1
UK	United Kingdom
US	United States
USPSTF	U.S. Preventive Services Task Force
VATS	Video-assisted thoracoscopic surgery
VOC	Volatile organic compound
WHO	World Health Organisation
$\mu\text{g}/\text{m}^3$	Micrograms per cubic meter
τ^2	Between-study variance

CHAPTER 1

INTRODUCTION

1.1 Study Background

Lung cancer (LC) remains a leading cause of cancer-related mortality globally, responsible for an estimated 1.8 million deaths in 2020 (Li et al., 2023). While tobacco smoking is the primary risk factor, an increasing number of LC cases, particularly in never-smokers, suggest that other environmental exposures play a substantial role, especially in Asia. In these regions, the rising burden of LC coincides with high levels of both indoor and ambient air pollution (AP) (Cheng et al., 2021; Myers et al., 2021; Zhou & Zhou, 2018).

One notable indoor exposure is incense burning, a widespread cultural and religious practice in many Asian households. Despite its traditional and spiritual significance, incense combustion releases a complex mix of potentially harmful pollutants, including fine particulate matter (PM_{2.5}), polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), and nitrogen dioxide (NO₂) (Lin et al., 2008; Yadav et al., 2022). Among these, NO₂ stands out as a reactive oxidant gas known to cause respiratory inflammation and has been increasingly implicated in carcinogenic processes. While NO₂ is commonly associated with traffic emissions, its presence in indoor environments, especially those with frequent incense burning, is often underestimated (Kovacic & Somanathan, 2014; Taha et al., 2025; Xia et al., 2024). Incense burning, therefore, represents an important indoor exposure, while NO₂ spans both indoor and outdoor environments. Examining them together enables a more comprehensive assessment of environmental risks for LC.

Although several studies have examined the respiratory effects of incense smoke, the epidemiological evidence linking incense burning and NO₂ exposure to LC risk remains fragmented, limited in geographic scope, and inconsistent in methodology (Cai & Wong, 2021; Lee et al., 2021; Mertha Adnyana et al., 2023). Many existing studies suffer from small sample sizes, insufficient control for confounders, or outdated exposure assessments, making it difficult to draw robust conclusions about the carcinogenic potential of these exposures. Moreover, the molecular mechanisms by which components like NO₂ contribute to lung carcinogenesis are still poorly defined.

To complement epidemiological evidence on incense and NO₂, recent advances in bioinformatics and molecular docking offer new avenues to investigate their biological plausibility (Yu et al., 2025; Zeng & Guo, 2025). Computational modelling allows researchers to simulate interactions between pollutant molecules, such as NO₂ and its reactive derivatives and proteins involved in cancer-related pathways, shedding light on potential mechanisms of action at the molecular level.

This study integrates systematic epidemiological synthesis and bioinformatics modelling to evaluate the role of non-tobacco environmental exposures in LC. Specifically, a meta-analysis examines incense burning in Asian populations, a second meta-analysis evaluates NO₂ exposure in non-European cohorts, and molecular docking analyses investigate how NO₂ and its reactive derivatives interact with LC-related proteins. The study quantifies population-level risks by linking these complementary approaches and provides mechanistic insight into how these exposures may contribute to lung carcinogenesis. Emphasising data from Asian and other underrepresented populations, including America, Oceania, and low- and middle-income countries, this study aims to clarify the risk and

underlying mechanisms of these exposures, thereby contributing to a more complete understanding of LC aetiology beyond smoking.

1.2 Problem Statement

LC remains one of the most common causes of cancer-related death worldwide. While smoking is the leading risk factor, exposure to environmental and indoor air pollutants is also linked to increased LC risk (Cheng et al., 2021; Myers et al., 2021; Zhou & Zhou, 2018). For example, specific exposures such as incense burning and NO₂ are poorly understood, especially in Asian and non-European settings.

Although incense burning is a widespread tradition in many Asian countries, the evidence on its association with LC is limited (Lee et al., 2021; Tran et al., 2021). Existing studies often involve small sample sizes and show inconsistent findings (Chen et al., 2022; Friberg et al., 2008; Koo & Ho, 1996; MacLennan et al., 1977). Most are case-control studies with varying methods and adjustments for confounding factors. A focused meta-analysis on the Asian population has not yet been conducted to provide a more reliable risk estimate.

In the case of NO₂, many studies have been carried out in Europe, leading to a lack of representation from other regions (Bauwelinck et al., 2022; Huang et al., 2021; Stafoggia et al., 2022). Differences in air quality, population exposure levels, and health systems may influence the results, making it difficult to apply findings from European-based studies to non-European populations.

In addition to limited epidemiological evidence, the biological mechanism linking NO₂ exposure to LC is not fully explained. Reactive nitrogen species (RNS), including NO₂

and its byproducts, may interact with key proteins in LC development. However, there is a lack of studies that used bioinformatics tools to model these interactions and explore possible pathways involved.

These gaps highlight the need for further research that includes population-specific analysis, updated exposure data, and mechanistic support through molecular-level studies. Accordingly, this study employs a unified framework that combines meta-analysis of incense burning in Asian populations, meta-analysis of NO₂ exposure in non-European cohorts, and molecular docking analyses to connect pollutant exposure with LC-related pathways mechanistically. Understanding these associations is essential for developing effective prevention strategies and informing public health guidelines.

The scope of the study is further defined to highlight its translational relevance to public health interventions in Asia, particularly Malaysia. Existing LC prevention efforts in the region, such as Malaysia's National Strategic Plan for Cancer Control Programme 2021-2025, predominantly focus on tobacco control and early detection, while environmental and household AP remain under emphasised (Ministry of Health Malaysia, 2021). In parallel, ambient air quality management under the Environmental Quality Act 1974 primarily targets industrial and traffic-related emissions, with limited consideration of long-term health risks from NO₂ exposure and indoor sources such as incense burning (*Environmental Quality Act 1974*, 1974). The current study, by offering region-specific epidemiological evidence and mechanistic insights, may enhance existing interventions, such as refinement of air quality standards, development of indoor air quality guidelines, and culturally tailored public health risk communication. Where such measures are currently lacking, the findings may support

the development of new preventive strategies aimed at reducing non-smoking-related LC risk in Asian populations.

1.3 Objectives

The objectives of this study were:

- i. To systematically review and meta-analyse case-control studies assessing the association between incense burning and LC risk in Asian populations.
- ii. To systematically review and meta-analyse epidemiological evidence on the association between NO₂ exposure and LC incidence and mortality in non-European countries.
- iii. To investigate the potential molecular interactions between NO₂ and its reactive surrogates and key LC-related proteins using bioinformatics and molecular docking approaches to elucidate possible mechanistic pathways linking environmental exposure to carcinogenesis.

Based on these objectives, it was hypothesised that:

- i. Incense burning is associated with an increased risk of LC in Asian populations.
- ii. NO₂ exposure is positively associated with LC incidence and mortality in non-European countries.

- iii. NO₂ and its reactive surrogates exhibit significant binding affinities with LC-related proteins involved in oxidative stress, inflammation, and oncogenic signalling, suggesting plausible molecular pathways for pollutant-induced carcinogenesis.

The organisation of the thesis is as follows:

The thesis is structured to address the three research objectives sequentially. Chapter 1 introduces the research background, problem statement, and study objectives. Chapter 2 presents the literature review, covering LC, AP, and molecular docking methodologies. Chapter 3 addresses Objective 1 through a meta-analysis of incense burning and lung cancer risk. Chapter 4 addresses Objective 2 through a meta-analysis examining NO₂ exposure and LC incidence and mortality. Chapter 5 addresses Objective 3 by detailing molecular docking analyses exploring potential mechanistic interactions between NO₂-related species and LC-associated proteins. Chapter 6 integrates the major findings and discusses their implications. Chapter 7 concludes the thesis and outlines recommendations for future research.

CHAPTER 2

LITERATURE REVIEW

2.1 Lung Cancer (LC)

2.1.1 Epidemiology of LC

LC continues to be a leading global health concern, being the most common cancer and the primary cause of cancer-related mortality. GLOBOCAN 2022 reported approximately 2.5 million new cases and 1.8 million deaths, which corresponds to 12.4% of total cancer incidence and 18.7% of cancer-related deaths worldwide (Bray et al., 2024; Li et al., 2023; Sung et al., 2021). The disease's aggressive nature and prevalent late-stage diagnoses contribute significantly to its high case-fatality ratio, which is compounded by systemic healthcare deficiencies and access issues, particularly in low- and middle-income countries (Deo et al., 2022).

Geographical variations play a crucial role in LC incidence, with higher rates predominantly observed in Eastern Asia, Northern and Eastern Europe, and North America (Ayubi et al., 2024). Conversely, lower incidence and mortality rates are found in sub-Saharan Africa and certain South Asian regions, although these areas are now experiencing upward trends in LC cases (Ayubi et al., 2024). The disparities in LC rates across regions can be attributed to multiple factors, including demographic characteristics, socioeconomic status, and variations in healthcare systems (Deo et al., 2022; Li et al., 2023).

LC incidence is notably higher among older adults, especially those over the age of 60 (Li et al., 2024). There is a significant historical gender disparity, with men traditionally

being more affected than women. Recent trends indicate a concerning rise in LC cases among females globally, likely due to changing patterns of smoking and exposure to carcinogenic factors, reflecting shifts in societal norms and public health challenges (Chen et al., 2025; Fu et al., 2023; Mederos et al., 2020; Siegel et al., 2022).

Temporal trends show that while several high-income countries have witnessed a decline in LC incidence due to improved public health interventions and increased awareness, many low- and middle-income nations are experiencing an increase in both incidence and mortality, signalling a potential public health crisis if not adequately addressed (Deo et al., 2022; Li et al., 2023). The rising burden of LC also translates into substantial economic consequences, with escalating direct medical costs related to diagnostics, long-term treatment, and advanced therapies, as well as significant indirect costs due to productivity loss and premature mortality. The financial strain disproportionately affects patients and healthcare systems in low- and middle-income countries, where limited resources further exacerbate inequities in access to timely and effective care (Nieto & Saucedo-Delgado, 2025; Ünal et al., 2025; Yang et al., 2022; Yousefi et al., 2022). Reflection on these trends highlights the critical need for bolstered healthcare infrastructure and enhanced early detection initiatives to mitigate the rising burden associated with LC (Li et al., 2022).

To further understand the current epidemiological landscape of LC, data from population-based cancer registries and global modelling initiatives are paramount. Such surveillance efforts are essential to track evolving trends, identify at-risk populations, and formulate effective policies that can respond to regional cancer burdens and improve healthcare accessibility (Li et al., 2022).

2.1.2 Signs and Symptoms of LC

The clinical presentation of LC is notably complex and often identified only at advanced stages. The symptoms are influenced by various factors, including the tumour's location, size, histological type, and potential metastasis (Carter & Erasmus, 2019; Hu et al., 2018; Milovanovic et al., 2017). Early-stage LC is frequently asymptomatic or manifests through seemingly innocuous complaints, which can be easily overlooked, leading to late diagnosis and poor prognosis (Polanco et al., 2021).

Respiratory symptoms are the most noteworthy indicators of LC, comprising chronic cough, dyspnea, chest pain, and haemoptysis. Chronic cough is one of the most frequently reported early symptoms, usually associated with endobronchial lesions or airway irritation (Feng et al., 2021; Hu et al., 2018). Dyspnea may arise from multiple pathophysiological mechanisms, including significant airway obstruction, pleural effusion, lymphangitic carcinomatosis, or reduced pulmonary compliance due to tumour burden (Keramida & Kostoulas, 2023). Chest pain is a notable symptom of LC, particularly when it exhibits pleuritic characteristics or results from the invasion of tumours into the chest wall, mediastinum, or pleura (Kennedy et al., 2019). Advanced LC patients often report such symptoms, indicating significant progression of the disease. Research also indicates that tissue invasion by the tumour can lead to the development of painful sensations, subsequently impacting the quality of life of affected individuals (Dimunová et al., 2018). Although haemoptysis is reported less frequently than other respiratory symptoms, it remains a clinically significant finding. It may occur due to tumour erosion into

pulmonary vasculature or endobronchial lesions, and is particularly alarming in high-risk individuals, such as chronic smokers (Gershman et al., 2019; Singer et al., 2023). Even when minimal, haemoptysis warrants prompt clinical investigation due to its potential association with malignancy.

Advanced stages of LC often present with systemic manifestations, including weight loss, anorexia, and fatigue, reflecting the tumour's local and systemic effects on the body (AlRabeeh et al., 2024; Saab et al., 2022). Additionally, paraneoplastic syndromes, especially prominent in small cell lung cancer (SCLC), can complicate the clinical picture by overshadowing the direct respiratory symptoms. These syndromes can involve complex metabolic disturbances such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cushing's syndrome, or Lambert-Eaton myasthenic syndrome, further complicating the patient's presentation (Rajan & Sahoo, 2023; Soomro et al., 2020).

Histological subtype significantly influences symptomatology. Adenocarcinoma, typically developing in peripheral lung regions, often remains asymptomatic until it extends or metastasises, sometimes presenting with vague chest discomfort or incidental radiographic findings (Myers & Wallen, 2023). In contrast, squamous cell carcinoma, typically central in location, is more likely to cause early symptoms such as cough or haemoptysis due to bronchial involvement (Sabbula et al., 2024). SCLC, characterised by aggressive growth and early metastasis, often presents with extensive systemic symptoms at the time of diagnosis, including neurological and endocrine signs, highlighting the aggressive nature of the disease (Bebb et al., 2023; Byers & Rudin, 2015).

Despite the recognition of these symptoms, delayed identification remains a significant barrier to effective treatment, particularly in low- and middle-income countries where diagnostic facilities are scarce and healthcare-seeking behaviour is often conditioned by societal factors (Nwagbara et al., 2020). The multicentre United Kingdom (UK)-based study found that more than 60% of patients presented with stage III or IV LC, evidencing a pattern of delayed healthcare access and symptom misattribution to benign conditions such as chronic obstructive pulmonary disease (COPD) or asthma (Mitchell et al., 2013; Rogers et al., 2024). This trend is further exacerbated in low- and middle-income countries with limited access to diagnostic imaging and specialist care.

Timely recognition of early signs is critical for improving prognosis. Several initiatives have been launched to raise public and healthcare provider awareness regarding LC warning signs. For example, the “Be Clear on Cancer” campaign in the UK has demonstrated effective strategies for raising awareness of chronic cough as a red flag, which could potentially mitigate the incidence of late-stage diagnoses (Ironmonger et al., 2015; Lai et al., 2021). However, similar population-based initiatives remain limited in many high-incidence regions, including parts of Asia and Africa.

2.1.3 Aetiology and Risk Factors of LC

LC is primarily driven by a multifactorial interplay between environmental exposures and intrinsic biological processes, resulting in the progressive accumulation of

genetic and epigenetic alterations that transform normal bronchial epithelial cells into malignant ones. These alterations disrupt cellular growth regulation by inducing deoxyribonucleic acid (DNA) damage, impairing tumour suppressor gene function, and activating oncogenic signalling pathways (Smolarz et al., 2025). Tobacco smoking remains the leading cause of LC worldwide, accounting for approximately 80% of cases in populations with high smoking prevalence. However, a growing body of evidence highlights the substantial roles of air pollution (AP), occupational exposures, and inherited genetic susceptibility, particularly in LC cases among non-smokers (Barta et al., 2019; Gupta et al., 2021; Mederos et al., 2020). The relationship between AP and LC will be elaborated in Section 2.2. In some instances, LC may also develop secondary metastasis from extrapulmonary malignancies, further complicating diagnosis and therapeutic decision-making (Hofmann et al., 2007; Jogondra et al., 2024). A comprehensive understanding of these aetiological mechanisms is essential for informing effective prevention strategies and guiding the development of targeted therapies.

2.1.3.1 Tobacco Smoking

Tobacco smoke remains the most well-established and dominant risk factor for LC globally (Gupta et al., 2021; Islami et al., 2015). Cigarette smoke contains numerous carcinogenic substances, including nitrosamines, benzene, formaldehyde, volatile organic compound (VOCs) and polycyclic aromatic hydrocarbon (PAHs), which contribute to genomic instability through DNA adduct formation and oxidative stress (Li & Hecht, 2022; Tang et al., 2022; U.S. Department of Health and Human Services et al., 2010). A substantial body of evidence demonstrates that between 80% to 90% of LC cases in males and 60% to 80% in females can be attributed to active smoking. A systematic review and meta-analysis

by O’Keeffe and colleagues found that smoking significantly increases LC risk, with relative risks associated with smoking being markedly elevated across various populations (O’Keeffe et al., 2018).

The relationship between smoking and LC is dose-dependent, with the risk increasing with the number of cigarettes consumed and the duration of exposure (Ai et al., 2023; Fry, 2013). Studies have shown that smokers are approximately 30 times more likely to develop LC compared to non-smokers (Walser et al., 2008). Even among former smokers, the risk remains elevated for several years after cessation, although it gradually declines over time (U.S. Department of Health and Human Services, 2020).

Geographical variations in smoking habits significantly influence the incidence of LC. Countries such as Malaysia and Indonesia continue to report high prevalence rates of smoking among males, contributing to a substantial LC burden (Dai et al., 2025). However, increasing rates among women in certain regions have raised concerns, particularly given the rising incidence of adenocarcinoma in non-smoking females, a phenomenon often linked to environmental factors rather than direct tobacco exposure (Islami et al., 2015; Kligerman & White, 2011; McAllister et al., 2025). Moreover, passive exposure to tobacco smoke, including second-hand and third-hand smoke, has also been associated with increased LC risk, especially within household environments (Elkefi et al., 2025; Kligerman & White, 2011; Qasim et al., 2024).

2.1.3.2 Genetic Factors

While environmental exposures remain central to LC pathogenesis, genetic susceptibility significantly modifies individual risk profiles. Variations in genes involved in carcinogen metabolism, DNA repair, and inflammatory pathways influence LC risk, even among those exposed to similar environmental conditions.

Genome-wide association studies (GWAS) have identified several susceptibility loci, including chromosomes 5p15 (*TERT/CLPTMIL*), 6p21 (*BAT3/MSH5*), and 15q25 (*CHRNA5/CHRNA3/CHRNA4*), which show significant association with LC across diverse populations (Broderick et al., 2009; Timofeeva et al., 2012; Wang et al., 2017). The 15q25 region regulates nicotine receptor behaviour, associating genetic predisposition with smoking habits and LC risk (Zanetti et al., 2016).

In lung tumourigenesis, somatic mutations in oncogenes and tumour suppressor genes are also crucial. Activating mutations in epidermal growth factor receptor (EGFR) and alterations in anaplastic lymphoma kinase (ALK) are frequently observed in non-smoking lung adenocarcinoma cases, especially among East Asian populations (Barta et al., 2019; Chapman et al., 2016; Ha et al., 2015; Midha et al., 2015). These mutations enhance the understanding of LC pathogenesis and significantly inform targeted therapeutic strategies.

In addition, polymorphisms in detoxification enzymes such as glutathione S-transferase mu 1 (GSTM1), glutathione S-transferase theta 1 (GSTT1), and cytochrome P450 family 1 subfamily A member 1 (CYP1A1) have been studied extensively. Deletions or mutations in these genes may hinder the ability to neutralise carcinogens, increasing susceptibility even at low exposure levels (Atinkaya et al., 2012; Chan-Yeung et al., 2004; Kiyohara et al., 2012; Peddireddy et al., 2016; Sreeja et al., 2005; Wenzlaff, 2004). Studies

have also reported interactions between genetic polymorphisms and AP, suggesting that some individuals may have heightened vulnerability to environmental carcinogens due to inherited traits (Santibáñez-Andrade et al., 2017).

2.1.4 Histopathology of LC

Histopathological classification plays a fundamental role in LC diagnosis, prognosis, and therapeutic decision-making. As shown in Figure 2.1, LC is broadly categorised into two major groups: non-small cell lung cancer (NSCLC), which accounts for approximately 85% of cases, and SCLC, comprising the remaining 15%. Each type demonstrates distinct histological features, molecular profiles, clinical behaviour, and treatment responses (Zappa & Mousa, 2016). Accurate histopathological identification is therefore critical for stratifying patients and guiding targeted interventions.

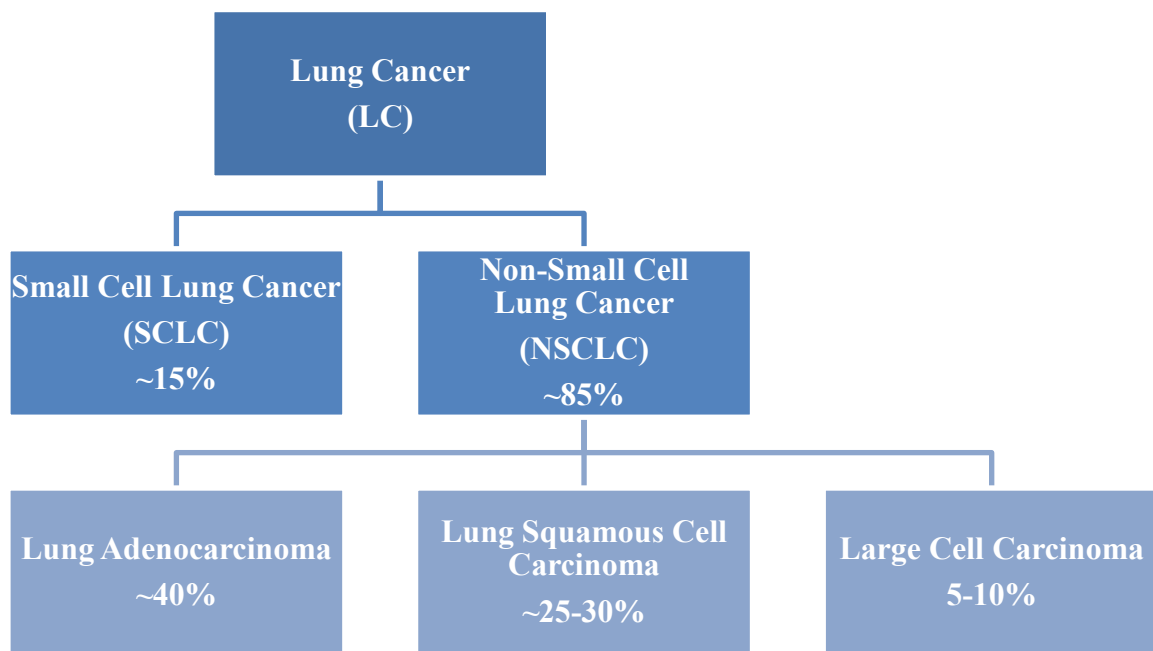


Figure 2.1: Major categories of LC. The chart illustrates the primary classification of LC into SCLC and NSCLC, with NSCLC further divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Zappa & Mousa, 2016).

NSCLC is the predominant subtype and includes three main histological categories: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Among these, adenocarcinoma has become the most frequently diagnosed subtype globally, representing around 40% of LCs, particularly in non-smokers and younger patients (Duma et al., 2019). It typically arises in the peripheral lung fields and is characterised histologically by glandular differentiation and mucin production (Zappa & Mousa, 2016). The presence of driver mutations such as *EGFR*, *ALK*, and ROS proto-oncogene 1 (*ROS1*) is commonly observed, especially in East Asian populations and among never-smokers and women (Pesch et al., 2012; Wistuba et al., 2018; Zhou & Zhou, 2018). Squamous cell carcinoma accounts for 25% to 30%, originates from the bronchial epithelium and is often centrally located (Zappa & Mousa, 2016). Histologically, it displays keratinisation and intercellular bridges (Wistuba

et al., 2018). This subtype is strongly associated with tobacco exposure and is more prevalent among male patients with a history of smoking (Pesch et al., 2012). Unlike adenocarcinoma, squamous cell carcinoma is less likely to harbour actionable mutations. However, it may show alterations in genes such as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), Kelch-like ECH-associated protein 1 (*KEAP1*) and SRY-box transcription factor 2 (*SOX2*) (Heist et al., 2012; The Cancer Genome Atlas Research Network, 2012). Large cell carcinoma accounts for approximately 5% to 10% of all LCs. It is a poorly differentiated subtype that lacks the glandular or squamous features required for classification as adenocarcinoma or squamous cell carcinoma (Zappa & Mousa, 2016). It is typically aggressive and diagnosed at advanced stages (Zander & Farver, 2018). Due to its rarity and diagnostic ambiguity, large cell carcinoma is often a diagnosis of exclusion based on immunohistochemical analysis (Wistuba et al., 2018).

SCLC is a highly aggressive neuroendocrine tumour with rapid growth, early metastasis, and high mitotic activity (Yin et al., 2022). Histologically, it consists of small, round-to-oval cells with scant cytoplasm, finely granular chromatin, and extensive necrosis (Basumallik & Agarwal, 2023). SCLC frequently expresses neuroendocrine markers such as synaptophysin, chromogranin A, and neural cell adhesion molecule (NCAM) (Pandjarova et al., 2024). This subtype is strongly linked to heavy tobacco use, and nearly all diagnosed cases occur in current or former smokers (Basumallik & Agarwal, 2023; Pesch et al., 2012). Although SCLC is initially highly responsive to chemotherapy and radiotherapy, recurrence is common, and long-term survival remains poor. Recent molecular profiling has revealed recurrent alterations in tumour protein p53 (*TP53*), RB transcriptional corepressor 1 (*RBI*), and MYC proto-oncogene, bHLH transcription factor (*MYC*), providing insight into its pathogenesis and opening avenues for novel therapeutic strategies (Yin et al., 2022).

In addition to the major categories, several rare histological variants have been documented, including adenosquamous carcinoma, sarcomatoid carcinoma, and carcinoid tumours (Harada et al., 2023; ‘Rare Lung Cancers’, 2015). Adenosquamous carcinoma was more frequently diagnosed at an earlier stage, showed higher rates of poor differentiation, and demonstrated better unadjusted survival outcomes than adenocarcinoma and squamous cell carcinoma (Benesch et al., 2024). However, due to its aggressive nature and elevated risk of recurrence and brain metastasis, adjuvant chemotherapy and prophylactic cranial irradiation are often recommended even following complete resection at Stage I (Siddiqui et al., 2025). Most individuals diagnosed with sarcomatoid carcinoma are current or former heavy smokers, with some also reporting prior asbestos exposure, suggesting a possible association. While the disease typically arises in the pleura and follows a slow-developing clinical course, similar to mesothelioma (‘Rare Lung Cancers’, 2015). Lung carcinoids are neuroendocrine tumours classified into typical and atypical types, with atypical carcinoids showing higher malignant potential. These tumours often grow slowly and are frequently discovered incidentally during imaging for unrelated reasons. While some patients present with symptoms such as cough, dyspnea, or recurrent pneumonia, endocrine syndromes like carcinoid syndrome or ectopic Cushing’s are rare. In most cases, surgical resection offers a potential cure, though metastatic disease may require treatments such as chemotherapy, targeted therapy, or peptide receptor radionuclide therapy (PRRT) (Granberg et al., 2023). These rare LC subtypes present diagnostic challenges and often require specialised histopathological and immunohistochemical evaluation.

The World Health Organisation (WHO) provides standardised criteria for the classification of lung tumours, with the 2021 WHO classification incorporating molecular alterations alongside histopathology to reflect advancements in the field (WHO

Classification of Tumours Editorial Board, 2021). Immunohistochemistry is frequently employed in routine diagnostic settings to differentiate subtypes, especially when morphology alone is insufficient. Markers such as thyroid transcription factor-1 (TTF-1), Napsin A (for adenocarcinoma), and p40, cytokeratin (CK) 5, CK6 (for squamous cell carcinoma) are routinely used (Yatabe et al., 2019).

2.1.5 Treatments and Prognosis of LC

LC treatment requires a multidisciplinary approach tailored to histology, molecular profile, stage, and patient performance status. LC treatments containing surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy, and adjunct modalities such as cryoablation and hyperthermia, are often used in combination to enhance outcomes (PDQ Adult Treatment Editorial Board, 2025).

2.1.5.1 Radiotherapy

Radiotherapy is widely used as a curative or palliative treatment in LC and remains a key component across multiple stages of disease. External beam radiotherapy (EBRT) delivers high-energy ionising radiation to tumour sites, damaging DNA and impairing cancer cell replication. In early-stage NSCLC, stereotactic body radiotherapy (SBRT) provides excellent local control rates and is the standard of care in patients unfit for surgery (PDQ Adult Treatment Editorial Board, 2025; Zappa & Mousa, 2016). In locally advanced NSCLC, concurrent chemoradiotherapy followed by immunotherapy has demonstrated marked improvements in survival outcomes (Lan et al., 2025).

For SCLC, radiotherapy plays a central role, particularly in limited-stage disease. Prophylactic cranial irradiation (PCI) reduces the risk of brain metastases, though its use in extensive-stage disease remains debated (Vojtišek, 2023). Advancements in treatment technologies, such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), have enabled oncologists to optimise treatment precision while minimising harm to healthy tissues (Cheung, 2006). Research illustrates that these technologies significantly enhance treatment efficacy and reduce side effects associated with radiotherapy (Arabloo et al., 2016; You & Hou, 2022). Indeed, the utilisation of high-quality radiotherapy can lead to lower rates of severe adverse events, thus highlighting the importance of ongoing methodological improvements.

2.1.5.2 Chemotherapy

Chemotherapy remains central for advanced-stage disease, especially in tumours lacking actionable mutations. Platinum-based compounds (cisplatin or carboplatin with pemetrexed, gemcitabine, or etoposide) remain standard, tailored to histology (PDQ Adult Treatment Editorial Board, 2025; Zappa & Mousa, 2016). While effective in prolonging survival, toxicities remain substantial, prompting ongoing research into combinations with immunotherapy and nanoparticle-based delivery (Amjad et al., 2025; Ghazal et al., 2024; PDQ Adult Treatment Editorial Board, 2025).

2.1.5.3 Targeted Therapy

Targeted therapies have transformed NSCLC management, offering precision treatment with fewer side effects (Liu et al., 2024). Agents target mutations in *EGFR*, *ALK*, *ROS1*, B-Raf proto-oncogene, serine/threonine kinase (*BRAF*), KRAS proto-oncogene, GTPase (*KRAS*) *G12C*, and MET proto-oncogene, receptor tyrosine kinase (*MET*) (Siddiqui et al., 2025; Xu et al., 2024). Third-generation tyrosine kinase inhibitors (TKIs) such as Osimertinib and next-generation *ALK* inhibitors, including alectinib, brigatinib, and lorlatinib, overcome resistance and achieve superior central nervous system (CNS) penetration (PDQ Adult Treatment Editorial Board, 2025; Xu et al., 2024). However, acquired resistance remains a challenge, driving research into combination strategies.

2.1.5.4 Immunotherapy

Immunotherapy with immune checkpoint inhibitors (ICIs) has reshaped advanced NSCLC treatment. Programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors such as pembrolizumab, nivolumab, and atezolizumab are used as monotherapy or with chemotherapy, depending on PD-L1 expression (PDQ Adult Treatment Editorial Board, 2025; Shields et al., 2021). In SCLC, combining ICIs with platinum-etoposide has improved outcomes, with atezolizumab and durvalumab now approved as first-line options (Rossi et al., 2023). Novel strategies, including vaccines and adoptive T-cell transfer, remain under investigation (Fan et al., 2023; Naffaa et al., 2025; Xie et al., 2023).

2.1.5.5 Surgery

Surgical resection is the treatment for early-stage NSCLC and remains the only potentially curative modality. Standard procedures include lobectomy, segmentectomy, or pneumonectomy, with the choice depending on tumour size, location, and lymph node involvement (PDQ Adult Treatment Editorial Board, 2025). Video-assisted thoracoscopic surgery (VATS) and robotic-assisted surgery have gained popularity due to lower morbidity and shorter recovery times (Rivero-Moreno et al., 2023; Zappa & Mousa, 2016).

Surgery is usually not used to treat SCLC because the disease spreads quickly and is often already widespread by the time it is diagnosed. However, in rare cases of very early-stage SCLC, surgical resection followed by adjuvant chemotherapy may be considered (Valli res, 2017). In NSCLC, resection is often complemented by neoadjuvant or adjuvant therapies to address micrometastatic disease and reduce recurrence risk (Lim & Yeo, 2022; Ravasin et al., 2025).

2.1.5.6 Cryoablation and Hyperthermia

Cryoablation is a minimally invasive technique that uses cryoprobes containing liquid nitrogen or compressed argon gas to destroy abnormal tissue under extremely low temperatures. This method induces cellular apoptosis and vascular disruption through repeated freeze-thaw cycles. It has shown clinical benefit in small peripheral lung tumours, particularly in patients unfit for surgery (Inoue et al., 2014).

In contrast, hyperthermia therapy uses elevated temperatures (typically 40-45°C) to damage cancer cells or enhance sensitivity to other treatments such as chemotherapy or radiotherapy (Zhou et al., 2022). Hyperthermia can be applied locally, regionally, or systemically and acts as a radiosensitizer or chemosensitizer (Bleehen, 1989; Kim et al., 2024; Logghe et al., 2024; Van Dieren et al., 2024). Although not yet part of standard LC treatment protocols, both techniques promise adjunct therapies, particularly in personalised or palliative contexts.

2.1.6 Prognosis and Predictive Biomarkers

LC remains a leading cause of cancer mortality, with global five-year survival rates estimated at approximately 19.4% (Sung et al., 2021). NSCLC generally offers a more favourable prognosis than SCLC, which is characterised by rapid disease progression and early systemic dissemination (Pandjarova et al., 2024). The tumour, node, metastasis (TNM) classification system of malignant tumours remains the primary prognostic tool, with stage I NSCLC achieving 60% to 80% five-year survival after surgery (Palma & Senan, 2013), whereas stage IV carries a median survival of less than one year without effective therapy (Guo et al., 2021). For SCLC, limited-stage patients may live 15 to 20 months with chemoradiotherapy, compared to 8 to 13 months for extensive-stage disease (Blackhall et al., 2023).

Prognosis is also influenced by patient-related characteristics such as age, sex, ethnicity, and performance status (Bachet et al., 2025; Simms et al., 2013). Women generally show superior survival, potentially due to biological and genetic factors (Fuentes et al., 2021;

Yu et al., 2022). Survival disparities persist across regions and socioeconomic groups, reflecting inequities in access to detection and treatment (Brouwer et al., 2022; Elkbuli et al., 2020; Harrison et al., 2022; Huang, Zhai, et al., 2023; Zhou et al., 2021).

Molecular diagnostics now refine both prognosis and therapy selection. PD-L1 expression predicts response to ICIs (Fumet et al., 2018; Schoenfeld et al., 2020), while high tumour mutational burden (TMB) correlates with enhanced immunotherapy benefit (Jardim et al., 2021; Wang et al., 2021). Driver mutations such as *EGFR* and *ALK* are predictive markers, with targeted therapy improving outcomes (Bai et al., 2024; Patel et al., 2015; Rubio-Perez et al., 2025). Conversely, serine/threonine kinase 11 (*STK11*) and *KEAP1* mutations predict poor response to immunotherapy and worse prognosis (Di Federico et al., 2021; Papillon-Cavanagh et al., 2020).

Liquid biopsy, particularly circulating tumour DNA (ctDNA), offers a non-invasive prognostic assessment. Persistent ctDNA after curative treatment indicates higher relapse risk and reduced survival, highlighting its value in monitoring minimal residual disease (MRD) and treatment response (Kurtz et al., 2021; Ma et al., 2024). Other emerging biomarkers include tumour-infiltrating lymphocytes (TILs), linked with favourable early-stage NSCLC outcomes (Horne et al., 2011), and exosomal ribonucleic acids (RNAs), though these remain investigational (Ratti et al., 2020).

Despite advances, widespread adoption of novel biomarkers is limited by the need for large-scale validation and persistent disparities in testing access. Prognosis in LC, therefore, reflects a multifactorial interplay of stage, tumour biology, molecular alterations, and healthcare availability, with precision oncology tools offering promise for improved outcomes.

2.1.7 Prevention of LC

2.1.7.1 Primary prevention

Primary prevention aims to eliminate or reduce exposure to genetic, environmental, biological, and physical factors that cause LC (Kloecker et al., 2021). Comprehensive tobacco control remains the central measure, implemented in many high-income countries through full enforcement of the WHO Framework Convention on Tobacco Control and the MPOWER technical package, which includes smoke-free legislation, tobacco taxation, pictorial health warnings, and advertising bans (World Health Organisation, 2025). These countries also apply stringent ambient air quality standards aligned with the 2021 WHO Air Quality Guidelines, regulate occupational carcinogen exposure, and promote radon testing and mitigation in high-exposure areas (Esan et al., 2020; Hashim & Boffetta, 2014; World Health Organisation, 2021). In contrast, low- and middle-income countries show uneven adoption and enforcement of tobacco control policies, limited radon control, and slower progress in air quality regulation, while reliance on solid fuels and kerosene for cooking and heating remains common, leading to high indoor pollution exposure (Lai et al., 2024; Tauras, 2024).

2.1.7.2 Secondary prevention

Secondary prevention focuses on detecting cancers in high-risk asymptomatic individuals to allow earlier treatment (Kloecker et al., 2021). Annual low-dose computed tomography (LDCT) screening has demonstrated reductions in LC mortality in high-risk populations, leading to its inclusion in national recommendations in the United States (US),

Canada, and several European countries, as well as targeted programs in China, South Korea, and Taiwan (Krist et al., 2021; Lam et al., 2023; Pinsky, 2018; Poon et al., 2022; Ward et al., 2023; Yang et al., 2024; Zhao & Wu, 2015). High-income countries have advanced implementation with quality assurance protocols and integrated cessation support, but participation rates remain suboptimal. Many low- and middle-income countries lack national screening guidelines or infrastructure, and uptake is limited by imaging capacity, workforce shortages, and costs (Lam et al., 2023; Lancaster et al., 2022; Pinsky, 2018; Poon et al., 2022; Triphuridet & Henschke, 2019).

2.1.7.3 Tertiary prevention

Tertiary prevention targets the reduction of recurrence, progression, and complications among LC survivors (Kloecker et al., 2021). Smoking cessation after diagnosis improves survival and reduces the risk of secondary malignancies, and it is recommended as a standard component of oncology care by the National Comprehensive Cancer Network and other agencies. Evidence-based cessation includes pharmacotherapy and behavioural counselling, delivered through routine oncology visits (National Comprehensive Cancer Network, 2024; Shields et al., 2023). Additional measures include vaccination against respiratory infections, pulmonary rehabilitation, and coordinated survivorship care, with more consistent integration in high-income settings than in resource-limited health systems (Association of Community Cancer Centers, 2016; dos Anjos et al., 2025; Wiwanitkit, 2010).

2.2 Air Pollution (AP)

2.2.1 Types of Air Pollutants

AP comprises a complex and heterogeneous mixture of atmospheric substances in solid, liquid, and gaseous phases (El Morabet, 2018; Leni et al., 2020). These pollutants can be broadly categorised into four major types: (i) particulate matter (PM), (ii) gaseous pollutants, (iii) VOCs, and (iv) semi-VOCs, including PAHs. Among these, fine PM (PM_{2.5}) and nitrogen dioxide (NO₂) are critical due to their capacity to penetrate deep into the pulmonary system, instigating molecular and cellular alterations that elevate the risk of lung carcinogenesis (Xing et al., 2016).

PM_{2.5}, defined as PM with an aerodynamic diameter of 2.5 micrometres or less, is a primary concern due to its potential for deep alveolar penetration, large surface area, and potential to carry adsorbed carcinogens (Thangavel et al., 2022; Xing et al., 2016). It serves as a vector for mutagenic compounds such as PAHs and transition metals, which can generate reactive oxygen species (ROS) and induce genotoxicity (Xing et al., 2016). In contrast, PM₁₀ ($\leq 10 \mu\text{m}$) is primarily trapped in the upper respiratory tract, but it still contributes to chronic inflammation and respiratory complications (Joshi et al., 2025).

Gaseous pollutants, including NO₂, sulfur dioxide (SO₂), carbon monoxide (CO), and ozone (O₃), primarily originate from combustion processes. NO₂, a reactive nitrogen oxide, has been identified not only as a marker of traffic-related AP but also as an active agent in oxidative and inflammatory pathways relevant to cancer initiation (Chen et al., 2015). O₃, although a secondary pollutant formed via photochemical reactions, has been shown to exacerbate respiratory pathology and impair DNA repair mechanisms (Berg et al., 2023; Russo et al., 2025).

VOCs, such as benzene, toluene, and formaldehyde, contribute to carcinogenic risk through both direct DNA-damaging effects and the formation of secondary organic aerosols (Srivastava et al., 2022). Among these, benzene is classified by International Agency for Research on Cancer (IARC) as a Group 1 carcinogen, and its chronic exposure has been linked to hematologic and pulmonary malignancies (Hussain et al., 2024; Zhang et al., 2020). Additionally, PAHs such as benzo[α]pyrene, present both in ambient air and indoor combustion emissions, are known to form DNA adducts and are metabolically activated by cytochrome P450 enzymes into genotoxic intermediates (Oh et al., 2006; Shiizaki et al., 2017).

Incense smoke is a significant source of indoor AP, particularly in regions where religious or cultural practices involve prolonged combustion. Incense burning releases a mixture of fine particles, carbonyls, and high-molecular-weight PAHs (Yadav et al., 2022). A study done by Lin and colleagues has shown that burning incense can release significantly higher levels of PM than tobacco smoke, with emissions averaging over 45 milligrams per gram (mg/g) burned, more than four times the amount produced by cigarettes, which emit approximately 10 mg/g burned (Lin et al., 2008). The chemical composition of different types of incense has shown variability, with materials such as sandalwood identified as particularly rich in PAH output and carbonyl compounds, marking them as pertinent contributors to indoor air quality concerns and associated health risks (Lui et al., 2016).

2.2.2 Sources of Air Pollutants

The origin of air pollutants is generally classified into natural and anthropogenic sources. While natural emissions such as volcanic activity, forest fires, and desert dust storms contribute episodically to AP, the overwhelming burden arises from human activities. Anthropogenic sources include industrial manufacturing, power generation from fossil fuels, vehicular emissions, agricultural practices, and domestic combustion. Each of these processes introduces a distinct chemical profile of pollutants, contributing cumulatively to ambient and localised exposures (National Academies of Sciences, Engineering, and Medicine, 2017; Smil, 2001).

Traffic-related AP remains a predominant source of PM_{2.5} and NO₂, especially in urban centres (Khreis et al., 2020; Sundvor et al., 2012). Diesel and gasoline-powered vehicles emit a complex mixture of primary particles, unburned hydrocarbons, nitrogen oxides, and transition metals, which have been repeatedly associated with increased LC risk in epidemiological cohorts across North America, Europe, and Asia (Benbrahim-Tallaa et al., 2012; Chen et al., 2015; Garshick et al., 2008; Olsson et al., 2011). Few studies demonstrated a significant association between residential proximity to major roadways and elevated LC incidence, independent of smoking and occupational exposures (Raaschou-Nielsen et al., 2011; Shao et al., 2019).

Industrial emissions, including those from petrochemical refineries, coal-fired power plants, and metallurgical facilities, are major contributors to ambient AP. These sources discharge high concentrations of SO₂, nitrogen oxides (NO_x), heavy metals such as lead, cadmium, and VOCs, many of which have established carcinogenic properties (Asif et al., 2022; Habashi, 2011; Izydorczyk et al., 2021; Tavella et al., 2025). In rapidly industrialising

countries, inadequate regulation of emission controls has led to severe episodes of atmospheric pollution, resulting in elevated morbidity and mortality from respiratory cancers.

Indoor sources of AP are increasingly recognised as critical exposure pathways, particularly in developing regions where biomass fuels and incense are routinely burned in poorly ventilated spaces (Fullerton et al., 2008; Neumann et al., 2024). Incense use is particularly interesting in the context of LC due to its widespread use and chemical complexity (Lee et al., 2021). Studies have reported that indoor PM_{2.5} levels during incense burning can far exceed WHO air quality guidelines, particularly in enclosed settings such as temples or homes (Hien et al., 2022; Shahi et al., 2024; Tran et al., 2021; World Health Organisation, 2021). Furthermore, frequent incense exposure has been linked with biomarker changes indicative of oxidative DNA damage, lipid peroxidation, and immune activation, reinforcing its relevance as a domestic carcinogen (Akingbade et al., 2021; Lee et al., 2021).

2.2.3 AP and LC

Ambient AP has emerged as a major non-tobacco contributor to LC. In 2013, the IARC classified outdoor AP and PM as Group 1 carcinogens. Among pollutants, PM_{2.5}, the fine PM with a diameter $\leq 2.5 \mu\text{m}$ and NO₂ are linked with elevated LC incidence, particularly adenocarcinoma (International Agency for Research on Cancer, 2025; Loomis et al., 2014; Straif et al., 2013).

Chronic exposure to PM_{2.5} promotes inflammation, oxidative damage, and genotoxic effects in lung tissue (Sangkham et al., 2024). A growing body of evidence highlights the detrimental impact of PM_{2.5} on LC development. One large-scale epidemiological study reported that every 5 micrograms per cubic meter ($\mu\text{g}/\text{m}^3$) increase in PM_{2.5} exposure was linked to a 13% higher risk of LC risk (Hvidtfeldt et al., 2021). Similarly, a meta-analysis by Huang and the team indicated that exposure to PM_{2.5} was associated with an 11% increase in LC mortality and an 8% increase in incidence, emphasising the consistency of this association across various populations (Huang et al., 2017).

NO₂, a marker of traffic-related pollution, has also been implicated in LC development. Long-term exposure may lead to nitrosative stress, impaired DNA repair, and epigenetic dysregulation (Pérez-Torres et al., 2020). Studies from Japan have demonstrated a positive association between NO₂ concentrations and LC mortality, even after adjusting for smoking and other confounders (Yorifuji et al., 2013). Besides, a meta-analysis revealed that a 10 $\mu\text{g}/\text{m}^3$ increase in NO₂ exposure is associated with a 4% increased risk of LC (Hamra et al., 2015). Importantly, these associations are particularly evident among non-smokers, highlighting the potential role of AP as a primary carcinogen independent of tobacco exposure.

Indoor AP, especially in low- and middle-income countries, contributes further to the LC burden. Exposure to biomass smoke from cooking, incense burning, and coal use in poorly ventilated homes has been strongly associated with increased risk, especially among women (Bhurosy et al., 2023; Hosgood et al., 2011; Kodgule & Salvi, 2012; McAllister et al., 2025; Tang et al., 2024). These findings are particularly relevant in Asian populations, where cultural practices and energy sources frequently involve biomass combustion.

2.2.4 Global Statistics of AP

AP is a leading global environmental determinant of disease burden, with wide-ranging health, economic, and ecological consequences. According to the Global Burden of Disease (GBD) 2019 study, ambient PM_{2.5} was responsible for approximately 4.14 million premature deaths worldwide and 118.2 million disability-adjusted life years (DALYs) worldwide. Notably, the global burden has increased by over 100% in deaths and nearly 68% in DALYs since 1990, primarily driven by population growth and ageing (Sang et al., 2022). These figures have continued to rise, particularly in low- and middle-income countries experiencing rapid urbanisation and industrial growth. In China, long-term exposure to PM_{2.5} has become a significant public health concern, accounting for over 1 million premature deaths annually. The associated mortality rate exceeds 90 deaths per 100,000 population, nearly 50% higher than the global average of 61 deaths per 100,000 in 2019 (Xue et al., 2025). This highlights the growing role of AP as a critical health risk factor, contributing substantially to diseases such as LC, beyond traditional causes like tobacco smoking.

According to the WHO, over 99% of the world's population breathes air with PM_{2.5} concentrations above the recommended annual mean limit of 5 µg/m³. South and East Asia bear a disproportionate burden, with urban PM_{2.5} concentrations frequently surpassing 100 µg/m³ during peak pollution episodes (World Health Organisation, 2024). Furthermore, NO₂, primarily a marker of traffic-related pollution, has been associated with increasing rates of LC, particularly among non-smokers in high-exposure regions (Hamra et al., 2015). Large-scale cohort analyses, such as the Canadian Census Health and Environment Cohort (CanCHEC), have demonstrated a 3.8% increase in LC mortality per 5 µg/m³ increase in PM_{2.5} exposure and a 6.7% increase per 8.1 parts per billion (ppb) increase in NO₂ exposure.

These associations were independent of each other and co-pollutants such as O₃, as well as other confounding factors, including smoking and occupational exposure (Crouse et al., 2015).

In Southeast Asia, indoor pollution remains a critical concern. In settings where incense burning is culturally embedded, studies have shown that incense burning could increase indoor PM_{2.5} concentrations by up to 120%, particularly in poorly ventilated homes and temples, thereby far exceeding the WHO air quality guidelines (Hien et al., 2022; Tran et al., 2021; World Health Organisation, 2021). Despite a relative paucity of systematic national surveillance data for indoor exposures, regional studies confirm elevated pollutant levels and LC biomarkers among habitual incense users, indicating a significant yet underappreciated exposure pathway.

2.2.5 Biological and Metabolic Pathways of AP Toxicity

The carcinogenicity of AP arises from a convergence of oxidative, inflammatory, genotoxic, and epigenetic mechanisms. Fine and ultrafine particles penetrate the alveolar region and activate resident macrophages, leading to the release of proinflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF- α), and interleukin-1 β (IL-1 β). These cytokines promote chronic inflammation, angiogenesis, and epithelial-mesenchymal transition (EMT), processes critical for tumour development and metastasis (Gavito-Covarrubias et al., 2024; Lu et al., 2018; Niu et al., 2020).

Simultaneously, PAHs and VOCs undergo metabolic activation by cytochrome P450 enzymes such as CYP1A1 and cytochrome P450 family 1 subfamily B member 1 (CYP1B1),

generating electrophilic intermediates that form covalent DNA adducts (Ewa & Danuta, 2017). These adducts can cause miscoding during DNA replication, particularly affecting tumour suppressor genes such as *TP53* and *KRAS* (Stratton et al., 2009; Yun et al., 2018). Incomplete repair of such damage may result in chromosomal instability, microsatellite alterations, and ultimately malignant transformation (Hakim et al., 2012; Saint-Georges et al., 2009).

AP also affects cellular redox homeostasis. Exposure to NO₂ and PM_{2.5} depletes intracellular glutathione, impairs antioxidant enzyme activity such as superoxide dismutase 1 (SOD1) and glutathione peroxidase 1 (GPX1), and promotes lipid peroxidation. These oxidative changes are further exacerbated by mitochondrial dysfunction and altered apoptotic signalling. Epigenetic modifications, including hypermethylation of *TP53* and cyclin-dependent kinase 6 (*CDK6*) promoter regions, histone deacetylation, and deregulated miRNA expression such as *miR-29*, *miR-34a* and *let-7a-3*, further contribute to dysregulated cell proliferation and apoptosis (Brueckner et al., 2007; Esfahani et al., 2025; Fabbri et al., 2007; Kondratyeva & Vitkina, 2023; Marengo et al., 2016; Saito et al., 2014; Sidebang et al., 2023; Wispriyono et al., 2021).

2.3 Meta-analysis in LC and AP research

2.3.1 Background and rationale for meta-analysis

Meta-analysis has become essential in epidemiological research, particularly in studying complex diseases such as LC. Individual observational studies frequently yield heterogeneous or inconclusive findings, often due to small sample sizes, variations in

exposure assessment, and population-specific confounders. By statistically synthesising evidence across multiple independent studies, meta-analysis enhances statistical power, provides more precise risk estimates, and enables the evaluation of subgroup effects that might otherwise remain obscured. (Colditz & Dart, 2023; Fagard et al., 1996; Haidich, 2010). In the context of environmental exposures and LC, meta-analysis clarifies the strength and consistency of associations. It helps prioritise exposures of high public health significance for mechanistic and preventive research.

2.3.2 Meta-analysis of LC and AP

Meta-analysis has been extensively applied to evaluate the relationship between AP and LC, providing more evidence than individual observational studies. A comprehensive meta-analysis of 17 cohort studies across nine European countries found that each 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} and each 5 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ were associated with higher LC risk, with these associations remaining robust across age, gender, and smoking status (Raaschou-Nielsen et al., 2013). An updated meta-analysis pooling data from studies in Denmark, England, Norway, and Rome similarly confirmed an elevated risk of LC incidence and mortality associated with long-term exposure to ambient $\text{PM}_{2.5}$, NO_2 and black carbon (Chen et al., 2024).

Indoor environmental pollution has also been the subject of recent meta-analysis, especially among never-smokers, where cumulative exposure to cooking fumes, radon, environmental tobacco smoke, and solid fuel combustion significantly increased LC risk. A recent meta-analysis found significant associations between several indoor environmental

pollutants and LC risk in non-smokers, with odds ratio (OR) often exceeding 1.5 (Hong et al., 2025). Similarly, meta-analyses of household AP in non-smoking populations demonstrated that use of solid fuels is strongly associated with elevated LC risk (Guercio et al., 2022; Kurmi et al., 2012). Another meta-analysis found that exposure to traffic-related AP, including pollutants like NO₂, NO_x, SO₂, and fine PM, was associated with an increased risk of LC, with meta-ORs ranging from 1.03 to 1.27, depending on the pollutant (Chen et al., 2015).

Overall, meta-analysis serves as a crucial approach for synthesising diverse evidence on environmental determinants of LC, particularly in relation to AP. By combining data from multiple studies, meta-analyses provide more precise effect estimates and enhance statistical power, thereby offering a clearer understanding of the complex relationship between long-term exposure to air pollutants and LC risk.

2.3.3 Integrating bioinformatics evidence

Meta-analysis findings on the association between AP and LC provide compelling epidemiological evidence, but often lack the mechanistic depth required to establish causality. Bioinformatics approaches have emerged as powerful tools in complementing population-level observations, offering more profound insights into underlying patterns and mechanisms. Molecular docking enables the prediction of interactions between pollutants or their reactive metabolites and LC-related proteins, offering insights into the molecular pathways that may underlie observed associations (Agu et al., 2023).

In silico studies have increasingly been applied to model the interactions between environmental toxicants and cancer-related proteins. These approaches suggest that

pollutants and their reactive metabolites may interfere with cellular pathways controlling oxidative stress, inflammatory signalling, and DNA repair, thereby creating conditions favourable for carcinogenesis (Abu-Bakar et al., 2024). Although still developing, such computational approaches complement meta-analytical findings by offering mechanistic insight that bridges population-level associations with molecular processes.

Overall, synthesising epidemiological meta-analyses with emerging bioinformatics approaches highlights the value of integrating multiple lines of evidence. While population-based studies establish robust associations between AP and LC, *in silico* analyses provide mechanistic plausibility that strengthens causal inference. This dual perspective advances understanding of how environmental exposures contribute to carcinogenesis and emphasises the importance of multidisciplinary methodologies in future research.

2.4 Bioinformatic Approach

Bioinformatics has become an indispensable component of contemporary biomedical research, offering computational and statistical tools to elucidate complex biological systems. In cancer research, bioinformatic techniques have enabled the identification of differentially expressed genes, mapping of signalling networks, functional annotation, and prediction of protein-ligand interactions. These methodologies provide mechanistic insight into disease development, progression, and therapeutic targets (Clark & Lillard, 2024). Bioinformatics offers a systems-level perspective that links molecular alterations to phenotypic consequences in the study of LC, particularly regarding environmental exposures such as air pollutants.

2.4.1 Pathway Analysis

Pathway analysis is a pivotal bioinformatic strategy to contextualise high-throughput genomic or transcriptomic data within biological systems. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) are two widely utilised frameworks for functional enrichment analysis (Silberstein et al., 2021).

GO enrichment analysis provides a structured vocabulary to describe gene function across three main categories: biological process (BP), molecular function (MF), and cellular component (CC) (Silberstein et al., 2021). GO enrichment analysis facilitates the identification of overrepresented functional terms among sets of differentially expressed or co-expressed genes, allowing interpretation of cellular mechanisms that may be disrupted under pathological conditions (Babichev et al., 2025). In the context of lung carcinogenesis, GO enrichment analysis has been applied to characterise processes such as xenobiotic metabolism, inflammatory response, and oxidative stress, which are known to be influenced by environmental carcinogens (Boei et al., 2017; Cao et al., 2025).

KEGG pathway enrichment analysis provides manually curated pathway maps representing molecular interaction and reaction networks, including metabolic pathways, regulatory pathways, and signalling cascades. KEGG pathway enrichment analysis enables the identification of signalling networks significantly associated with gene sets of interest (Kanehisa et al., 2025). Studies examining air pollutant-induced carcinogenesis have reported the enrichment of pathways such as mitogen-activated protein kinase (MAPK) signalling, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB, also known as AKT) signalling, nuclear factor-kappa B (NF- κ B) activation, and EGFR signalling pathways that are critically involved in cell proliferation, apoptosis inhibition, and tumour progression

(Cao et al., 2025; Tsay et al., 2018). KEGG pathway enrichment analysis has thus played a significant role in uncovering the molecular mechanisms underlying pollutant-induced oncogenic transformation in lung tissue.

Integrating GO and KEGG enrichment analyses enables a more comprehensive understanding of how environmental exposures perturb gene networks, thereby contributing to cancer initiation and progression. These analyses are often incorporated in transcriptomic or proteomic workflows to derive functional hypotheses for experimental validation.

2.4.2 Molecular Docking

Molecular docking is a structure-based computational method used to predict the binding orientation and affinity of small molecules, such as environmental toxicants or therapeutic compounds, to their biological targets, typically proteins. This approach plays a crucial role in drug discovery and toxicology by modelling the molecular interactions at an atomic level (Abdolmaleki et al., 2021; Agu et al., 2023).

In the context of environmental health and cancer, molecular docking has been employed to investigate how air pollutants, such as PAHs, interact with proteins implicated in LC pathogenesis (Montero-Pérez et al., 2024; Sheikh et al., 2025; Wang et al., 2024). In support of this, Cabral and the team (2022) employed AutoDock Vina to dock a panel of PAHs and VOCs against immune-related proteins, generating quantitative binding affinities and pose analyses that illustrate how these pollutants may interact with targets involved in inflammation and oxidative stress (Cabral et al., 2022). Furthermore, a study applied molecular docking to demonstrate that PAHs can interact with key inflammatory mediators

such as TNF- α and IL-6, supporting the role of these pathways in pollutant-induced immune and inflammatory responses (Liu et al., 2025).

Docking simulations provide insights into the binding conformation and interaction energy between ligands and receptors. These predictions, in turn, help to hypothesise potential molecular initiating events that may lead to cellular dysregulation and malignancy. For example, computational docking has been widely used to assess how environmental pollutants might interact with critical biomolecules, potentially disrupting normal cellular signalling or regulatory pathways (Lin et al., 2024). Recent studies utilising AutoDock, PyMOL, and LigPlot have visually and quantitatively demonstrated such interactions, emphasising the utility of docking approaches in environmental carcinogenesis research (Banu et al., 2025; Khan et al., 2021).

Moreover, docking studies are often complemented with additional computational analyses such as molecular dynamics simulations and binding free energy calculations, providing further validation of predicted interactions (Fu et al., 2018). These tools collectively contribute to understanding the structural basis of pollutant-protein interactions and offer preliminary evidence to guide *in vitro* or *in vivo* toxicological assessments.

CHAPTER 3

LUNG CANCER RISK LINKED TO INCENSE BURNING IN ASIAN POPULATIONS: EVIDENCE FROM NINE CASE-CONTROL STUDIES¹

3.1 Introduction

As discussed in Chapter 2, lung cancer (LC) represents a significant health burden in Asia, where incidence and mortality rates remain among the highest globally (International Agency for Research on Cancer, 2020). Beyond established causes such as tobacco use, attention has increasingly turned to environmental and cultural exposures that may contribute to lung carcinogenesis in Asian populations (Lim et al., 2014; Schuller, 2019; Tang et al., 2010; Thandra et al., 2021; Tse et al., 2011). One such factor is incense burning, a long-standing cultural and religious practice in many Asian countries (Cheng et al., 1995; Friberg et al., 2008; Seow & Lan, 2016). According to a Pew Research Centre survey, incense use remains widespread, with reported usage among 96% of Cambodians, 92% of Sri Lankans, 84% of Thais, and more than half of the populations in China, India, Hong Kong, Singapore, the United Arab Emirates and 40% of Japan (Evans et al., 2023; Geng et al., 2019; Moeran, 2009; Pan et al., 2014; Tse et al., 2011; Yeatts et al., 2012).

Burning incense involves slow and incomplete combustion, releasing complex mixtures of toxicants such as aerosols (Lin et al., 2008; Tran & Marriott, 2007), formaldehyde (Lin et al., 2008), benzene (Jetter et al., 2002; Navasumrit et al., 2008), NO₂

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(Guo et al., 2023; Koo et al., 1990), PAHs, significant levels of PM, and various VOCs (Guo et al., 2023; Lin et al., 2008; Tran & Marriott, 2007). Most listed compounds are known or suspected to promote LC among humans (International Agency for Research on Cancer, 2022; National Toxicology Program, 2021). Importantly, exposure occurs indoors and often in poorly ventilated environments, leading to high concentrations of inhaled pollutants.

Epidemiological investigations into the relationship between incense burning and LC have yielded inconsistent findings. While some studies observed a significant association between frequent incense use and elevated LC risk, particularly in Chinese populations and among those with indoor exposure (Chen et al., 2022; MacLennan et al., 1977), other research found no evidence of increased risk, even among smokers (Koo et al., 1995; Koo & Ho, 1996). Prospective cohort evidence similarly reported null associations (Friborg et al., 2008). These discrepancies emphasise the need for a systematic approach to synthesise available evidence.

Therefore, this chapter presents a meta-analysis assessing the association between incense burning and LC risk in Asian populations. By integrating findings from multiple case-control studies, this analysis aims to clarify whether incense exposure constitutes a significant carcinogenic risk in this high-incidence region.

3.2 Methodology

3.2.1 Search strategy

This meta-analysis was conducted under the guidelines (Page et al., 2021b). Three electronic databases (Google Scholar, PubMed, and Science Direct) were accessed until 7th

January 2024 for systematic literature searches. Appropriate keywords (“incense”, “agarbatti”, “bakhloor”, “lung”, “pulmonary”, “cancer”, “carcinoma”, “neoplasm”, and “tumour”) with the combination of Boolean operators (“AND” and “OR”) were applied during the literature search. All full texts of the papers were collected, and the lists of references for the papers of interest were reviewed to avoid missing potential articles.

3.2.2 Study Selection

Studies that fulfilled all the following inclusion criteria were included in this meta-analysis: (i) reported in English; (ii) containing LC patients; (iii) case-control studies; (iv) investigations conducted on humans; and (v) conducted in Asia. The articles were excluded if they contained any of the following exclusion criteria: (i) review articles or letters to the editor; (ii) publication in languages other than English; (iii) containing insufficient information to conduct meta-analysis; and (iv) meta-analysis.

Study selection was conducted independently by two reviewers. The first reviewer has formal training in systematic review methodology and meta-analytic techniques, while the second reviewer has expertise in epidemiology, public health research, and evidence synthesis. Any disagreements were resolved through discussion until consensus was achieved.

3.2.3 Quality assessment

A quality assessment was carried out for every selected study. Case-control study quality was evaluated using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2021). Studies

are categorised as high-quality, moderate-quality, and low-quality, with scores of ≥ 7 , 4-6, and ≤ 3 , respectively (Dietrich et al., 2019; Dong et al., 2022). Studies with low quality will be excluded from the meta-analysis.

3.2.4 Data extraction

The details listed below were taken from each of the chosen studies: the surname of the first author, year of publication, study population, study design, study period, case-control matching criteria, exposure to incense smoke, as well as the number of participants, and the outcome in each group.

3.2.5 Statistical analysis

The Mantel-Haenszel (MH) and inverse variance methods were implemented to evaluate the dichotomous data (ever exposed versus never exposed). Individuals ever exposed to incense burning refer to those who have been exposed or have ever been exposed to incense burning. In contrast, those never exposed are individuals who have never been exposed to incense burning. The results generated an odds ratio (OR) with corresponding 95% confidence intervals (CIs) and weights for each estimate, which were then visualised in a forest plot. A solid diamond indicated the pooled OR at the bottom of every forest plot. Heterogeneity between the selected studies was measured with Cochran's Q test and the Higgins I^2 test, together with visual inspection of forest plots (Cochran, 1950; Higgins et al., 2003). It reflects significant heterogeneity when $p < 0.05$ or $I^2 > 50\%$. Depending on the heterogeneities, either fixed- or random-effects models will be used in calculating the pooled

OR. Since there is no evidence of heterogeneity across the studies selected, fixed-effect models have been applied in all the analyses included in this meta-analysis (Greenland & Robins, 1985; Mantel & Haenszel, 1959). With Egger's test, the degree of publication bias was assessed and illustrated using funnel plots (Egger et al., 1997). R Studio with the meta package (version 2023.12.0, Build 369) was used for all statistical analyses (Balduzzi et al., 2019; R Core Team, 2023).

3.3 Results

3.3.1 Study selection

Figure 3.1 shows the flow chart illustrating the process of selecting articles for the study. In summary, 1,726 publications were identified through the electronic databases Google Scholar, PubMed, and Science Direct. Specifically, 1,500 articles were retrieved from Google Scholar, 189 from Science Direct, and 37 from PubMed. To conduct a comprehensive review, the remaining 1,637 articles were downloaded in full-text format after removing 89 articles that were found to be duplicated across the three databases. Three publications were excluded from the meta-analysis due to insufficient data: two were retrieved from Google Scholar (Li et al., 2016; Lo et al., 2013), and one was found through Google Scholar and PubMed (Friborg et al., 2008). Additionally, one paper (Tang et al., 2010) that examined the combined use of incense and mosquito coils was identified through both Google Scholar and PubMed. Three studies involving animal subjects were obtained from the PubMed database (Hussain et al., 2014, 2016; National Toxicology Program, 1996) and three from the Google Scholar database (Kim et al., 2016; Lin et al., 2018; Zierenberg-Ripoll et al., 2018). Additionally, 92 review articles did not meet the inclusion criteria, and

nine papers were published in languages other than English. Two studies (Tse et al., 2008, 2022) were excluded from the meta-analysis due to duplicate populations; both were retrieved from the Google Scholar database, while another 37 were not available in full text. Lastly, 1,478 studies that were irrelevant or lacked information on exposure to incense burning and LC risk were excluded. The remaining nine studies eligible for the meta-analysis were sourced as follows: one study from PubMed (Chen et al., 2022), four from Google Scholar (Koo et al., 1995; MacLennan et al., 1977; Maurya et al., 2023; Phukan et al., 2014), three from both Google Scholar and PubMed (Chen et al., 2007; Chen et al., 2008; Tse et al., 2011), and one study from all three databases: Google Scholar, PubMed, and another database (Chan-Yeung, 2003).

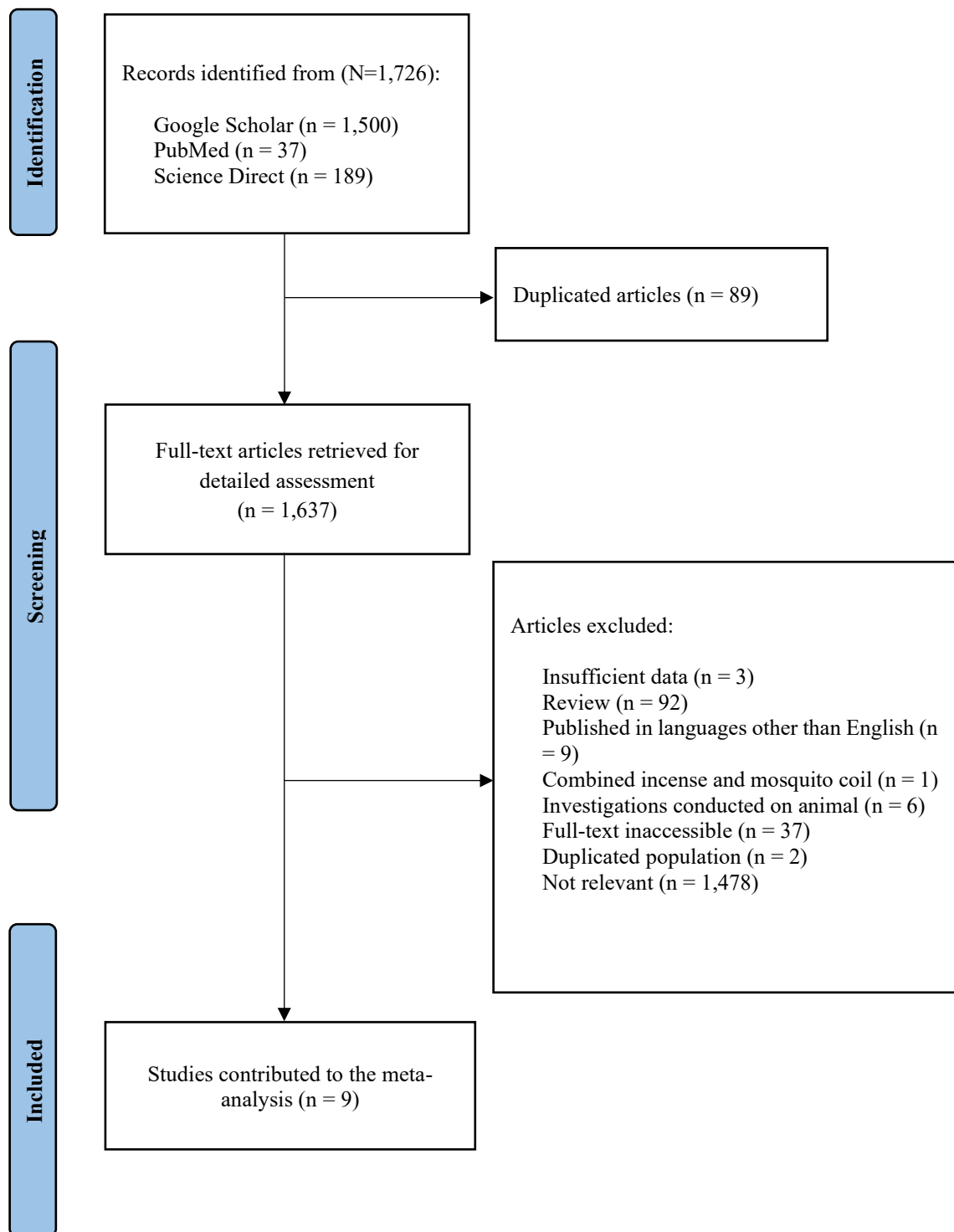


Figure 3.1: A flow diagram illustrating the process of the studies was chosen to be incorporated into the current meta-analysis.

3.3.2 Quality assessment

The quality of the nine case-control studies was evaluated using the NOS, which covered three main areas: selection, comparability, and exposure. In the selection domain, the evaluation examined whether cases were well-defined and if controls were chosen from the same population, thereby ensuring comparability between the groups at baseline. The comparability domain investigated how well the studies controlled for confounding variables and whether cases and controls were matched on relevant factors. Finally, the exposure domain assessed the precision and reliability of the methods used to measure exposure. This comprehensive assessment aimed to ensure that the included studies had reliable procedures and that the findings were supported by high-quality evidence. Studies are categorised as high-quality, moderate-quality, and low-quality, with scores of ≥ 7 , 4-6, and ≤ 3 , respectively. The scores are shown in Table 3.1, which indicates that all the selected studies fell into the moderate or high-quality category.

Table 3.1: Characteristics of studies derived for the meta-analysis

Author, year	Study population	Study design	Study period	Gender	Data Collection	Incense burning exposure	Case-control matching criteria	Smoking status	Cases		Controls		Quality assessment
									Total	Female	Total	Female	
Maurya et al., 2023	India	HCC	2015-2017	M, F	Interview and questionnaire	Yes [†] No [‡]	Age, gender	N/A	68	N/A	68	N/A	7/9
Chen et al., 2022	Taiwan	HCC	2018-2019	M, F	Face-to-face interview	Habitual indoor incense burning (More than three days a week for more than six months)	Age	N/A	39	N/A	40	N/A	7/9
Phukan et al., 2014	India	PCC	2009-2012	F	Interview	Yes [†] No [‡]	Age, ethnic tribe, gender, geographic	N/A	230	230	460	460	7/9
Tse et al., 2011	Hong Kong	PCC	2004-2006	M	Interview	Never [‡] < 2 times/day ≥ 2 times/day	Age, ethnicity, gender, residential district	Never [§] Ever [¶]	1,208	N/A	1,069	N/A	8/9

Table 3.1 continued

Chen et al., 2008	Taiwan	HCC	2002-2004	M, F	Face-to-face interview	Yes [†] No [‡]	Geographic area	N/A	147	N/A	400	N/A	7/9
Chen et al., 2007	Taiwan	HCC	2002-2006	F	Personal interviews based on a structured questionnaire	Ever [†] Never [‡]	Ethnic, gender	N/A	826	826	531	531	7/9
Chan-Yeung et al., 2003	Hong Kong	HCC	1999-2001	M, F	Interviewed using a questionnaire by one trained interviewer	No or < 2 years Festival only Daily	Age, ethnicity, gender	N/A	331	119	312	113	7/9
Koo et al., 1995	Hong Kong	PCC	1981-1983	F	Personally interview	0 exposure to incense, years 1-39 exposure to incense, years 40-70 exposure to incense, years	Age, gender, housing type, residential district	Never [§] Ever [¶]	189	N/A	197	N/A	6/9
MacLennan et al., 1977	Singapore	HCC	1972-1973	M, F	Interview	Incense burned	Age, dialect, gender	N/A	233	86	300	166	7/9

F, Female; HCC, Hospital-based case-control; M, Male; N/A, not applicable; PCC, Population-based case-control

[†] Individuals who have been exposed or have ever been exposed to incense burning; [‡] Individuals who have never been exposed to incense burning;

[§] Individuals who never smoked; [¶] Individuals who have smoked or have ever smoked

Among these, seven studies (Chan-Yeung, 2003; Chen et al., 2007; Chen et al., 2022; Chen et al., 2008; MacLennan et al., 1977; Maurya et al., 2023; Phukan et al., 2014) , each scoring 7 out of 9, and one study (Tse et al., 2011) scored 8, classified as high quality, indicating robust methodological rigour and reliable findings. These high-quality studies demonstrated clear case definitions, appropriate control selection from the same population, and accurate exposure measurement. The remaining study (Koo et al., 1995) was classified as moderate quality, reflecting generally sound methodology but with some limitations in areas such as selection assessment. All studies underwent a thorough evaluation to ensure they met the necessary standards for inclusion. Since all selected studies fell into the moderate or high-quality category, the integrity of the meta-analysis was maintained, ensuring that the results are based on strong, reliable evidence. This comprehensive selection process aimed to provide a reliable synthesis of the available data, enhancing the validity of the meta-analytic findings.

3.3.3 Study characteristics

Table 3.1 summarises the key characteristics of the nine case-control studies included in this meta-analysis. It summarised the various aspects of each study, such as the author and year of publication, the study population, and the study design. The information on the study period, gender distribution of participants, and data collection methods is also shown in Table 3.1. Specifics on incense burning exposure and case-control matching criteria were provided, along with smoking status information. Additionally, the table lists the number of cases and controls, including their gender distribution. All nine case-control studies were conducted in Asia and involved two distinct study designs: hospital-based case-control and population-based case-control. Data was primarily collected through interviews, with three

studies (Chan-Yeung, 2003; Chen et al., 2007; Maurya et al., 2023) also employing questionnaires. Only two studies (Koo et al., 1995; Tse et al., 2011) provided detailed information on smoking status, which was included in the current meta-analysis. This comprehensive overview highlighted the diversity in study populations, designs, and methodologies, offering essential context for interpreting the meta-analysis results.

3.3.4 Incense burning and LC risk

Depending on the heterogeneities, either fixed- or random-effects models were employed to compute the pooled OR for the association between incense burning and the risk of LC. A meta-analysis was conducted to identify the risk of LC associated with exposure to incense burning, treating it as a dichotomous variable (ever exposed versus never exposed). The findings were illustrated in Figure 3.2, which revealed that the pooled OR was 1.33 (95% CI: 1.20-1.48) for individuals exposed to incense burning compared to the control group, which was not exposed to incense burning, based on data extracted from the derived nine studies. This pooled OR of 1.33 suggests that individuals exposed to incense burning have a significantly higher chance (33% higher) of developing LC. The Cochran's Q test and the Higgins I^2 test did not reveal significant heterogeneities among the studies [$Q = 7.60$, $p = 0.47$, $I^2 = 0.00\%$ (95% CI: 0.00%-64.80%), $\tau^2 = 0.00$ (95% CI: 0.00-0.10)]. Both Egger's test ($p = 0.47$) and the funnel plot visualisation (Figure 3.3) did not provide evidence of publication bias.

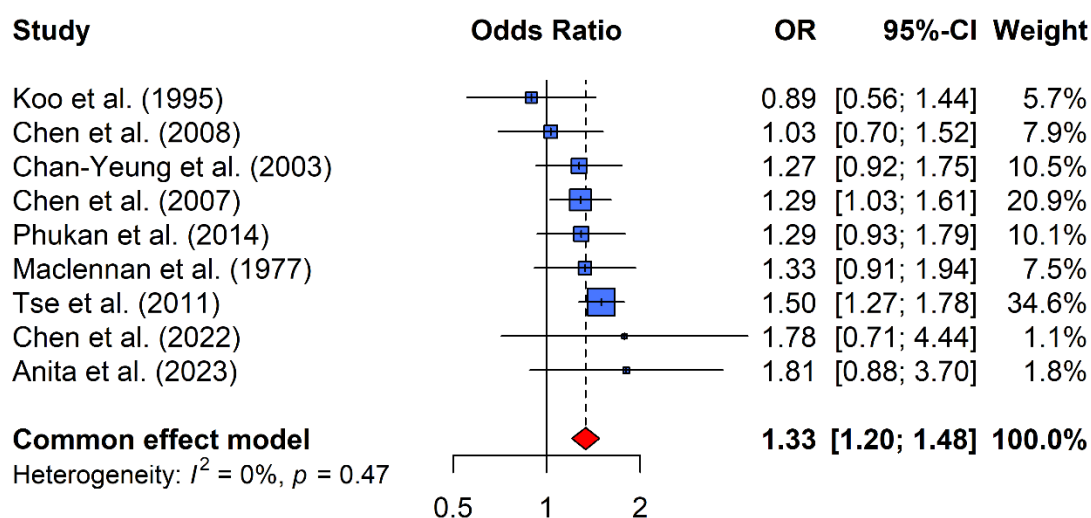


Figure 3.2: Forest plots were investigated to identify the association between exposure to incense burning (never versus ever) and LC risk. The squares represent the risk estimates specific to each study, with the size of the square reflecting the study's statistical weight, that is, the inverse of the variance. The horizontal lines indicate the 95% CI, and the diamond represents the pooled OR and its corresponding 95% CI. OR represents the risk of developing LC. (a) Exposed to incense burning versus unexposed.

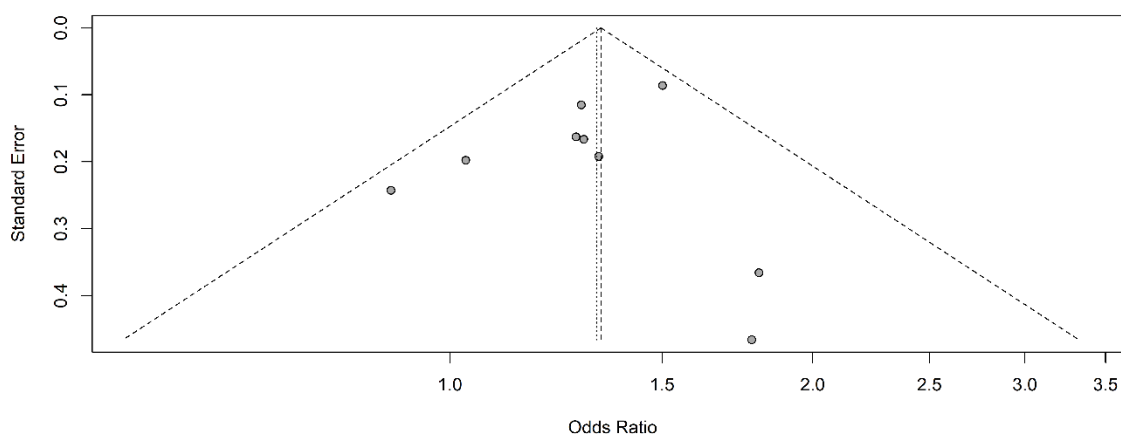


Figure 3.3: Funnel plot illustrating the publication bias in the studies analysed in this meta-analysis. The X-axis represents the OR, and the Y-axis shows the standard error. No indication of publication bias was noted from both the visualisation of the funnel plot and Egger's test ($p = 0.47$).

3.3.5 Subgroup analysis

The subgroup analysis by gender was depicted in Figures 3.4(a) and 3.4(b). Males had a statistically significant 40% greater risk of developing LC (OR = 1.40, 95% CI: 1.21-1.63), whereas females showed no significant association (OR = 1.76, 95% CI: 0.88-3.52). The investigation also explored the association between incense burning and the risk of LC in both ever-smokers and never-smokers. The results revealed a significant positive association among ever-smokers, with a pooled OR of 1.34 (95% CI: 1.09-1.65). However, no significant association was found with never-smokers, with a pooled OR of 1.04 (95% CI: 0.75-1.44). Moreover, a subgroup analysis was executed based on the sources of subjects' recruitment (hospital-based and population-based case-control). The pooled ORs for the hospital-based and population-based case-control studies were 1.28 (95% CI: 1.10-1.48) and 1.39 (95% CI: 1.21-1.60), respectively, as shown in Figures 3.4(c) and 3.4(d). These findings revealed a positive association between incense burning exposure and the risk of developing LC, and there was no noticeable heterogeneity among the studies.

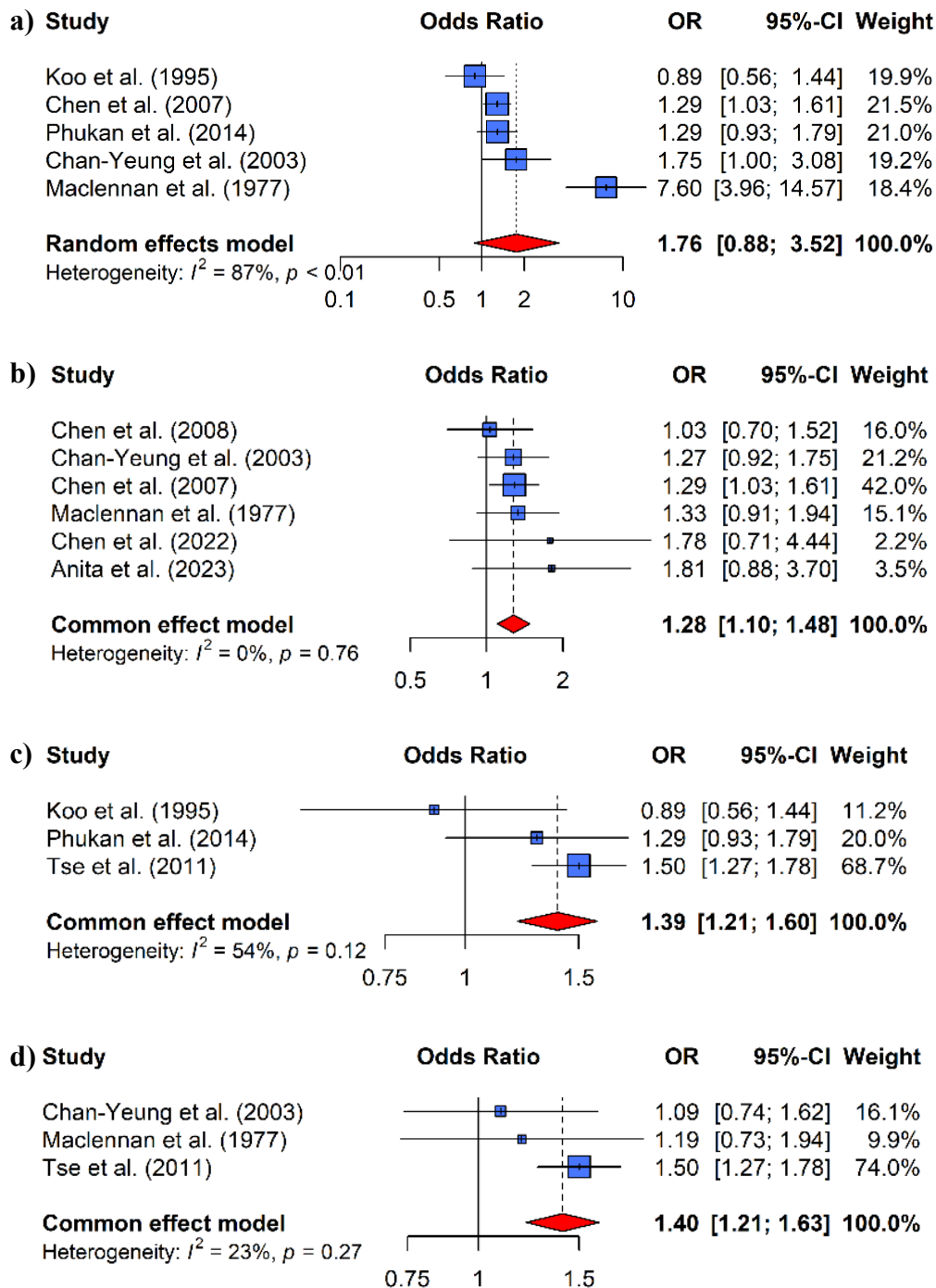


Figure 3.4: Forest plots were investigated to identify the association between exposure to incense burning (never versus ever) and LC risk. Subgroup analysis is based on (a) males. (b) females. (c) hospital-based case-control study. (d) population-based case-control study.

3.4 Discussion

The present study highlights a significant association between incense smoke exposure and increased LC risk. This finding aligns with broader research on air pollution (AP) and its effects on LC, including studies investigating the underlying mechanisms of these associations. Tung and colleagues (Tung et al., 2017) revealed that while auramine O (AuO), an incense ingredient, did not directly induce malignant transformation, it significantly exacerbated LC malignancy by promoting metastatic abilities and stemness in lung tumour cells. AuO accumulated in the nucleus, induced autophagy and enhanced the expression of aldehyde dehydrogenase family 1 member A1 (ALDH1A1). Knockdown of *ALDH1A1* attenuated AuO-induced autophagy and blocked its promotion of lung tumour malignancy. Besides, Tu and the team (Tu et al., 2018) demonstrated that incense smoke can sensitise LC cells to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) by inducing Amphiregulin (AREG) expression. AREG, a ligand of the EGFR pathway, plays a critical role in modulating EGFR signalling, which is crucial for cell proliferation and survival. While this study focused on the correlation between incense smoke and LC incidence, Tu and the team suggested that incense smoke influenced LC progression through mechanisms involving EGFR signalling pathways.

Yang and the team (Yang et al., 2019) reported that China, India, and Indonesia are the three Asian nations accounting for around half of the world's male smokers. More than 40% of men in Eastern Asia (South Korea), Southern Asia (Bangladesh and Maldives), and South-Eastern Asia (Malaysia and Timor-Leste) reported consuming tobacco products (Lee et al., 2021; Shariful Islam et al., 2022; Sreeramareddy et al., 2014). Thus, it is essential to note that the smoking factor confounds the possibility of an association between incense smoke and LC despite the biologically plausible effects of incense smoke on LC. Cigarette

smoking is a well-known risk factor for LC, and it has been reported that incense burning emits four times as much PM as smoking cigarettes. A meta-analysis by Kim and co-authors (Kim et al., 2018) found that exposure to second-hand smoke could elevate the risk of LC among individuals who have never smoked. Pollutants released from burning incense are reported to have health effects similar to second-hand smoke (Shrestha, 2020). Furthermore, the toxicity of incense smoke is further increased by several hazardous gases, such as carbon monoxide (CO), carbon dioxide (CO₂), nitrogen dioxide (NO₂), and sulfur dioxide (SO₂), as well as the unforeseen difficulties of getting rid of the burned incense ash (Yadav et al., 2022).

The stratified analysis based on smoking status in this study revealed a non-significant association between incense burning and LC in never-smokers but a significant positive relationship in ever-smokers. However, precautions should be taken when interpreting the results, given that only two studies (Koo et al., 1995; Tse et al., 2011) provided the relevant data on their smoking status. Gender-specific subgroup analysis showed that only a statistically significant positive association was noted among males and not among females. The observed difference may be attributed to biological variations between males and females, which could lead to varying susceptibility to the carcinogenic effects of incense burning (Dorak & Karpuzoglu, 2012; Fuentes et al., 2021). According to a study by May and colleagues (May et al., 2023), significant differences exist between the immune systems of males and females. For instance, females have been found to exhibit enriched immune gene sets compared to males, especially in the context of LC, as reported by Araujo and the team (Araujo et al., 2016). Females tend to have stronger innate and adaptive immune responses than males. Furthermore, the androgen receptor (AR), which is

primarily expressed in pneumocytes and lung epithelium in male patients (Fuentes et al., 2021), plays an essential role in the aetiology of LC (Mikkonen et al., 2010).

Figure 3.5 shows that androgens, including testosterone (Durovski et al., 2023; Michmerhuizen et al., 2020; Semenas et al., 2012), are converted to dihydrotestosterone (DHT) by the enzyme 5α -reductase. Once formed, DHT binds to the ligand-binding pocket of the AR, triggering the dissociation of heat-shock proteins (HSPs) from the AR, which in turn leads to AR activation. The AR protein consists of three major domains: the N-terminal transactivation domain (NTD), the DNA-binding domain (DBD), and the ligand-binding domain (LBD) (Durovski et al., 2023; Tan et al., 2015). A study by Vinggaard and Larsen (Vinggaard et al., 2000) demonstrated that the polycyclic aromatic hydrocarbons (PAHs) released upon incense combustion, particularly dibenzo[a,h]anthracene (DB[a,h]A) (Guo et al., 2004), possessed the additive effect in enhancing the activation of AR in the presence of androgen. Mechanistically, DB[a,h]A can associate with DHT and strengthen its binding to the LBD of AR, thereby amplifying AR activation (Vinggaard et al., 2000). The activation of AR increases the expression of downstream targets like cyclin D1 (Chang et al., 2014; Fuentes et al., 2021), which drives cell cycle progression and tumour growth (Becerra-Diaz et al., 2020; Fuentes et al., 2021). Moreover, pollutants can induce oxidative stress and inflammatory responses (Barbier et al., 2023; Hisamuddin et al., 2022; Hu et al., 2020; Mudway et al., 2020), further contributing to AR gene mutations and enhancing AR signalling. This process also promotes the polarisation of macrophages toward the M2 phenotype (Becerra-Díaz et al., 2018; Becerra-Diaz et al., 2020; Fuentes et al., 2021), which is associated with tumour progression and immune evasion. The differential expression and activation of AR in response to environmental pollutants, the inflammatory

microenvironment, and AR gene mutations could contribute to the observed gender disparities in LC incidence and progression.

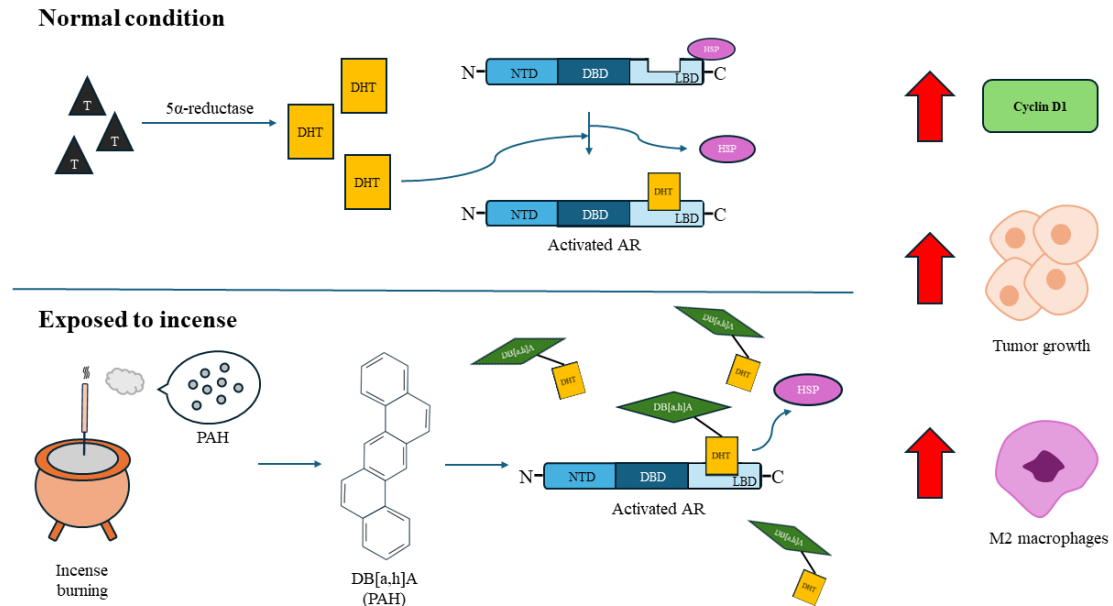


Figure 3.5: Schematic representation of AR activation and dysregulation by androgens and incense-derived pollutants. Testosterone (T) is converted to DHT, which binds to AR and induces activation. PAHs, such as DB[a,h]A, further enhance AR signalling and its tumour-promoting effects.

When sources of subjects' recruitment conducted subgroup analysis, it was found that hospital-based and population-based case-control studies showed statistically significant positive associations. This indicates that regardless of whether the subjects were recruited from hospitals, communities, or any other setting, there was a significant association between incense burning and the risk of LC. Furthermore, the consistency of these associations across multiple recruitment sources suggests that the relationship is not confined to a specific population or setting. This strengthens the generalizability of the findings. Therefore, the subgroup analysis based on the sources of subject recruitment enhances the

overall meta-analysis by providing an additional perspective on the association between incense burning and LC risk in various communities.

Despite understanding the exposure to incense burning and its associations with LC through this meta-analysis, the histology of LC remains inadequately addressed. Although a subgroup analysis focusing on LC histology was initially planned to explore associations with incense burning, data limitations precluded this analysis. However, the literature suggests that non-small cell lung cancer (NSCLC), particularly adenocarcinoma, might be more closely associated with incense smoke and other environmental exposures. This hypothesis aligns with previous studies linking adenocarcinoma to AP (Hill et al., 2023; Lee et al., 2022; Raaschou-Nielsen et al., 2013). Adenocarcinoma, the most common subtype of NSCLC, originates in the glandular cells of the lung and is often found in peripheral regions (Wistuba et al., 2018; Zappa & Mousa, 2016), making it particularly vulnerable to inhaled toxins. The current literature indicates that environmental factors like incense smoke may differentially impact various LC subtypes, underscoring the need for targeted research. As a result, the finding summarises the general associations between LC and incense burning without a specific focus on histologic subtypes. Future research should address this gap by incorporating detailed histological data and exploring the differential effects of environmental exposures on various LC subtypes to enhance understanding and risk assessment of these associations.

3.5 Limitations

It is crucial to acknowledge several limitations of this meta-analysis. Firstly, it is worth noting that this meta-analysis solely included observational studies. Even with strict controls, observational studies are susceptible to various biases, such as recall or information

bias. Second, the “ever or never” categorisation of incense burning exposure in the nine case-control studies disregards the frequency or quantity of incense burned daily, weekly, or monthly. This limited the analysis of the association between exposure to incense burning and the risk of LC. Thirdly, the relevant data extracted from the included studies spanned 46 years, from 1977 to 2023, due to the limited availability of recent data. Consequently, the accuracy of the results with current incense products may be questionable. Fourthly, it is crucial to note that this meta-analysis relied on data extracted from only nine studies. Therefore, the possibility of publication bias cannot be ruled out despite the absence of any indication of publication bias according to Egger’s test and the funnel plot visualisation. Furthermore, incorporating diverse hospital and population-based case-control studies increased the variability among study populations. While this broadens the generalizability of the findings, it also introduces variability that may reduce the precision of the meta-analysis results. Besides, with only two out of nine studies providing relevant data on smoking status, the meta-analysis may have reduced statistical power to detect genuine associations or differences between incense burning and the risk of LC based on smoking status.

3.6 Conclusion

This meta-analysis demonstrated a significant association between incense burning and increased LC risk in Asian populations, highlighting the importance of exploring how such environmental exposures may influence LC more broadly. However, the absence of cohort studies and limited reporting on histological subtypes restricts more detailed interpretation. Future research should prioritise longitudinal designs and histology-specific

analyses to clarify how incense smoke may differentially influence LC subtypes, particularly NSCLC.

CHAPTER 4

LUNG CANCER RISK FROM NITROGEN DIOXIDE EXPOSURE IN NON-EUROPEAN REGIONS: SYSTEMATIC REVIEW AND META-ANALYSIS, 2014-2024

4.1 Introduction

As outlined in Chapter 2, air pollution (AP) is recognised as a critical environmental determinant of lung cancer (LC), with growing attention directed toward nitrogen dioxide (NO₂) as a marker of traffic-related and industrial emissions (Brims et al., 2022; Turner, 2022). NO₂ is a reactive and corrosive gas produced predominantly by motor vehicles, fossil fuel combustion, and industrial activities, where it also contributes to the formation of secondary pollutants such as particulate matter (PM) and ozone (O₃) (American Lung Association, 2023; California Air Resources Board, n.d.; Fino, 2019; Gharibvand et al., 2023; *Nitrogen Dioxide*, 2021; Zhu & Yang, 2023). Despite evidence of its respiratory and cardiovascular toxicity (de Vries, 2021; Huang et al., 2012; Manisalidis et al., 2020), the carcinogenic classification of NO₂ remains inconclusive, with International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP) 15th Report on Carcinogens, and the US Environmental Protection Agency (EPA) not having classified NO₂ for potential carcinogenicity (Hamra et al., 2015; National Research Council, 2007; National Toxicology Program, 2021). Therefore, its role in the aetiology of LC remains a subject of ongoing investigation.

Epidemiological studies conducted mainly in Europe have demonstrated a positive association between long-term exposure to ambient NO₂ and increased incidence and mortality of LC (Bauwelinck et al., 2022; Hart et al., 2015; Huang et al., 2021; So et al., 2022; Stafoggia et al., 2022). However, evidence from regions outside Europe remains

limited and inconsistent, with studies in America and Asia reporting variable associations (Bai et al., 2020; Chen et al., 2016; Eum et al., 2019; Gowda et al., 2019; Hystad et al., 2013; Katanoda et al., 2011; Moon et al., 2020; Yorifuji & Kashima, 2020). These variances may reflect differences in population characteristics, healthcare infrastructure, pollution sources, and methodological approaches, including reliance on indirect exposure indicators such as proximity to roadways or ambient monitoring data (Beelen et al., 2008; Brunekreef et al., 2009; Cesaroni et al., 2013; Chen et al., 2015; Hamra et al., 2015; Heinrich et al., 2012; Hystad et al., 2013; Puett et al., 2014; Raaschou-Nielsen et al., 2011, 2013). Such heterogeneity highlights the challenge of drawing definitive conclusions about the global relevance of NO₂ exposure to LC risk.

This chapter presents meta-analysis synthesising available evidence on NO₂ exposure and LC risk beyond European populations to address these gaps. By integrating findings across diverse environmental and demographic contexts, the analysis seeks to provide a more comprehensive understanding of the potential carcinogenicity of NO₂ and to evaluate its global significance as an environmental health risk factor.

4.2 Methodology

4.2.1 Search strategy

Until June 6, 2024, systematic literature searches were conducted across three electronic databases (Google Scholar, PubMed, and Science Direct). The searches utilised relevant keywords (“nitrogen dioxide”, “lung”, “pulmonary”, “cancer”, “carcinoma”, “neoplasm”, and “tumour”) combined with Boolean operators (“AND” and “OR”) and

included a restriction on publication years from 2014 to 2024. Additionally, there were no restrictions on NO₂ of either indoor or outdoor origin during the literature search process. All the potential articles were gathered in full text to prevent any possible articles from being neglected. The reference lists of relevant papers, earlier systematic reviews, and meta-analyses were examined manually to identify additional studies.

4.2.2 Inclusion and exclusion criteria

If the study matches the following inclusion criteria, it will be included in this meta-analysis: (i) reported in English; (ii) containing LC patients; (iii) observational studies; (iv) investigations conducted on humans; and (v) publication years ranging from 2014 to 2024.

Articles meeting any of the following exclusion criteria were excluded: (i) were non-research articles such as review articles, editorials, short communications, etc.; (ii) were published in languages other than English; (iii) contained insufficient information to conduct meta-analyses; and (iv) were conducted in European countries.

4.2.3 Study selection

Two independent reviewers conducted the title and abstract screening, full-text review, and data extraction simultaneously. Each reviewer worked independently to assess the relevance of titles and abstracts, followed by a thorough review of full-text articles to confirm that they met the inclusion criteria. The first reviewer has formal training in systematic review methodology, environmental health research, and meta-analytic techniques, while the second reviewer has expertise in epidemiology, public health research,

and evidence synthesis. Any disagreements were resolved through discussion until consensus was achieved.

4.2.4 Data extraction

For each study, the following information was extracted: study characteristics (surname of the first author, year of publication, study population, study design, study period, number of cases and participants), exposure to NO₂ (increment for analysis), outcome of LC (incidence or mortality), hazard ratios (HRs) and 95% confidence interval (CIs), and adjustment.

4.2.5 Quality assessment

A quality assessment was carried out for every selected study. Cohort study quality was evaluated via the Newcastle-Ottawa Scale (NOS) (Wells et al., 2021). Studies are categorised as high-quality, moderate-quality, or low-quality, with scores of ≥ 7 , 4-6, and ≤ 3 , respectively (Peceliunaite et al., 2023). Studies of low quality were excluded from the meta-analysis. Two reviewers conducted the quality assessment.

4.2.6 Statistical analysis

The primary analysis investigated the association between exposure to NO₂ and LC risk. Within this meta-analysis, HRs were the risk estimates for evaluating the association between NO₂ exposure and LC risk. Considering that many exposure-response meta-

analyses assume a linear relationship between AP and outcomes (Kim et al., 2018; Yang et al., 2016), most selected studies use parts per billion (ppb) as their standard increment unit; therefore, all HRs and their corresponding 95% CIs in this study were adjusted to increments of 10 ppb for NO₂. For studies reporting measurements in micrograms per cubic meter (µg/m³), a conversion factor of 1.88 µg/m³ per 1 ppb was applied based on an ambient pressure of 1 atmosphere and a temperature of 25°C (Atkinson et al., 2018; Hamra et al., 2015). The outcomes produced an HR for each estimate and their corresponding 95% CIs and weights, which were then visualised in a forest plot. In each forest plot, the pooled HR is represented by a solid diamond at the base. In addition to visual inspection of forest plots, Cochran's Q test and Higgins *I*² test were used to evaluate the heterogeneity among the retrieved studies (Cochran, 1950; Higgins et al., 2003). When $p < 0.05$ or $I^2 > 50\%$ indicates significant heterogeneity, the pooled HR will be calculated with either fixed- or random-effects models, depending on the degree of heterogeneity (Greenland & Robins, 1985; Higgins & Thompson, 2002; Mantel & Haenszel, 1959; Spinelì & Pandis, 2020). The level of publication bias was evaluated via Egger's test, and funnel plots were generated to visualise the results (Egger et al., 1997). To explore potential sources of heterogeneity, subgroup analyses were conducted based on various factors, such as the outcome of LC, sex, histology, smoking status, and geographical region. All the statistical analyses were performed via R Studio (version 2024.04.2, Build 764) with the meta package (Balduzzi et al., 2019; R Core Team, 2023).

4.2.7 Assessment of Certainty

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to assess the certainty of the body of evidence for each outcome. This method assesses confidence in evidence based on study design, risk of bias, inconsistency, imprecision, and directness. Certainty in the body of evidence for each outcome was initially rated according to study design, with randomised controlled trials starting as high and observational studies starting as low. Adjustments were made based on the risk of bias (assessed via the NOS for cohort studies), statistical heterogeneity (evaluated via Higgins I^2 and Cochran's Q test), imprecision (examined via CIs), and the directness of the evidence. Publication bias was assessed via funnel plots and Egger's test. The final certainty rating for each outcome was categorised as high, moderate, low, or very low, reflecting the overall confidence in the effect estimates and guiding the interpretation of the findings.

4.3 Result

4.3.1 Literature search

The literature search process is depicted in Figure 4.1. A total of 1,237 articles published between 2014 and 2024 were found across electronic databases (Google Scholar, PubMed, and Science Direct), supplemented by manual searches of reference lists from relevant papers or review articles. The remaining 1,155 articles were retrieved in full-text format for a comprehensive review, excluding 82 duplicates identified across the three databases and additional sources. Insufficient data for a meta-analysis were found in two

publications. At the same time, three papers examined the exposure of NO₂ and LC alongside other diseases, and the other 20 studies reported risk estimates other than HRs. Furthermore, 187 articles were identified as review articles that failed to meet the inclusion criteria, and seven papers were excluded because they were published in languages other than English. Two studies were excluded because of population duplication, and 162 studies were animal model studies. A total of 13 studies conducted within European nations and 17 papers published beyond the years 2014 and 2024 were considered ineligible for inclusion in the meta-analysis. Additionally, a substantial exclusion of 731 studies occurred, justified by their irrelevance or insufficient information concerning exposure to NO₂ and the risk of LC. Following these exclusions, 11 studies remained and were retrieved for inclusion in the meta-analysis (Bai et al., 2020; Cheng et al., 2022; Eckel et al., 2016; Eum et al., 2022; Gowda et al., 2019; Lim et al., 2019; Lim et al., 2023; Liu et al., 2023; Yang et al., 2021; Yorifuji & Kashima, 2020; Zhou, et al., 2023).

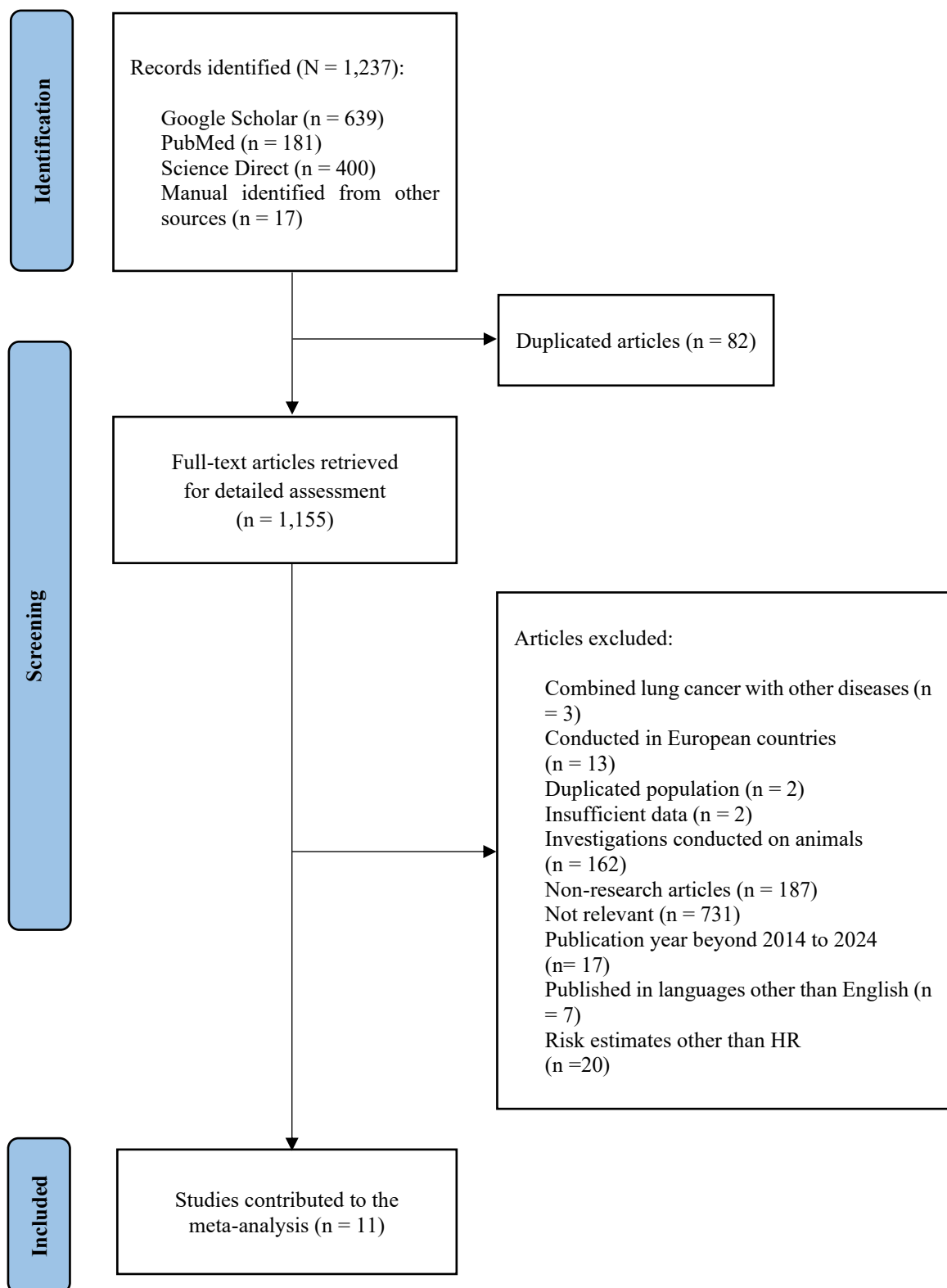


Figure 4.1: Flow chart illustrating the PRISMA literature search process.

4.3.2 Study characteristics

The overall characteristics of the 11 cohort studies included in this meta-analysis are summarised in Table 4.1. A total of 68,269,865 individuals participated in all the studies, which were published between 2014 and 2024. Among the 11 selected studies, 6 specifically focused on LC incidence as the outcome, and the remaining 5 investigated LC mortality. Among the 11 selected studies, 6 were conducted in the United States (US), while the remaining 5 were distributed across Australia, Canada, China, Japan, and South Korea, with one study from each. Appendix B shows the adjustments of each study.

4.3.3 Quality assessment

The NOS was used to assess the quality of the 11 cohort studies, and the overall quality of the methodology was high. Seven of the studies received a score of 8 out of 9, whereas four scored 7 out of 9, demonstrating a high degree of compliance with quality standards and little risk for bias. These studies stand out for their strong design and comprehensive reporting. The consistency of these high ratings across the majority of the studies enhances the reliability of the evidence base for the meta-analysis. The evaluations of quality are summarised in Table 4.1.

Table 4.1: General characteristics of cohort studies included in the meta-analysis.

Selected study (Publication year)	Population	Study design	Study period	Total participants	Lung cancer cases	Exposure to NO ₂ (increment for analysis)	Outcome of lung cancer	HR (95% CI)	Study	Quality assessment
Bai <i>et al.</i> (2019)	Canada	Population-based cohort study	2001-2015	4,952,022	100,146	13.9 ppb	Incidence	1.05 (1.03-1.07)	Ontario Population Health and Environment Cohort (ONPHEC)	8/9
Cheng <i>et al.</i> (2022)	US	Population-based prospective cohort study	1993-2013	97,288	2,775	20.0 ppb	Incidence	1.12 (0.95-1.32)	Multiethnic Cohort Study (MEC)	8/9
Eckel <i>et al.</i> (2016)	US	Population-based cohort study	1988-2011	352,053	305,721	10.2 ppb	Mortality	1.12 (1.11-1.12)	California Cancer Registry (CCR)	7/9
Eum <i>et al.</i> (2022)	US	Cohort study	2001-2008	49,712,702	824,558	10.0 ppb	Mortality	1.04 (1.02-1.07)	Medicare cohort	7/9
Gowda <i>et al.</i> (2019)	US	Prospective study	1993-2012	65,154	265	10.0 ppb	Incidence	0.92 (0.74-1.15)	Women's Health Initiative (WHI)	8/9
Huang <i>et al.</i> (2023)	China	Population-based cohort study	1998-2019	37,442	552	10.0 µg/m ³	Mortality	1.16 (1.08-1.26)	N/A	7/9
Lim <i>et al.</i> (2019)	US	Prospective cohort study	1995-2011	548,780	13,529	10.0 ppb	Mortality	1.00 (0.97-1.04)	NIH-AARP Diet and Health Study	8/9

Table 4.1 continued

Lim <i>et al.</i> (2023)	Australia	Cohort study	1996-2018	11,617	692	10.0 µg/m ³	Incidence	1.08 (0.88-1.33)	Health In Men Study (HIMS)	8/9
Liu <i>et al.</i> (2023)	US	Cohort study	2004-2016	12,429,951	166,860	1.0 ppb	Incidence	1.012 (1.011- 1.012)	Medicare cohort	8/9
Yang <i>et al.</i> (2021)	South Korea	Population- based cohort study	2007-2015	83,478	489	10.0 ppb	Incidence	0.98 (0.83-1.16)	National Health Insurance Service- National Sample Cohort (NHIS-NSC) 2.0	8/9
Yorifuji & Kashima (2020)	Japan	Cohort study	2006-2016	76,569	876	10.0 µg/m ³	Mortality	1.24 (1.04-1.48)	N/A	7/9

CI, confidence interval; HR, hazard ratio; µg/m³, micrograms per cubic meter; NO₂, nitrogen dioxide; N/A, not available; ppb, parts per billion; US, United States

4.3.4 Associations between NO₂ and the risk of LC

A meta-analysis was conducted to evaluate the risk of LC associated with exposure to NO₂. The pooled HR for LC in response to NO₂ exposure is presented in Figure 4.2. The pooled HR for the risk of LC was 1.08 (95% CI: 1.03-1.13) per 10 ppb increase in NO₂. The Cochran's Q test and Higgins I^2 test reveal significant heterogeneities among the studies [$Q = 208.00$, $p < 0.0001$, $I^2 = 95.20\%$ (95% CI: 93.00%-96.70%), $\tau^2 = 0.0037$ (95% CI: 0.0014-0.0442)]. Egger's tests and Begg's funnel plots were employed to analyse the degree of publication bias. Neither Egger's test ($p = 0.17$) nor funnel plot visualisation (Figure 4.3) provided evidence of publication bias. The certainty of the evidence for the association between exposure to NO₂ and LC risk was rated as moderate. The rating was based on an overall HR of 1.08 (95% CI: 1.03-1.13) from 11 cohort studies. The I^2 statistic was 95% ($p < 0.01$), indicating high statistical heterogeneity, although the NOS score was consistent with high ratings, suggesting a low risk of bias. The evidence was direct, and funnel plots and Egger's test did not reveal significant publication bias.

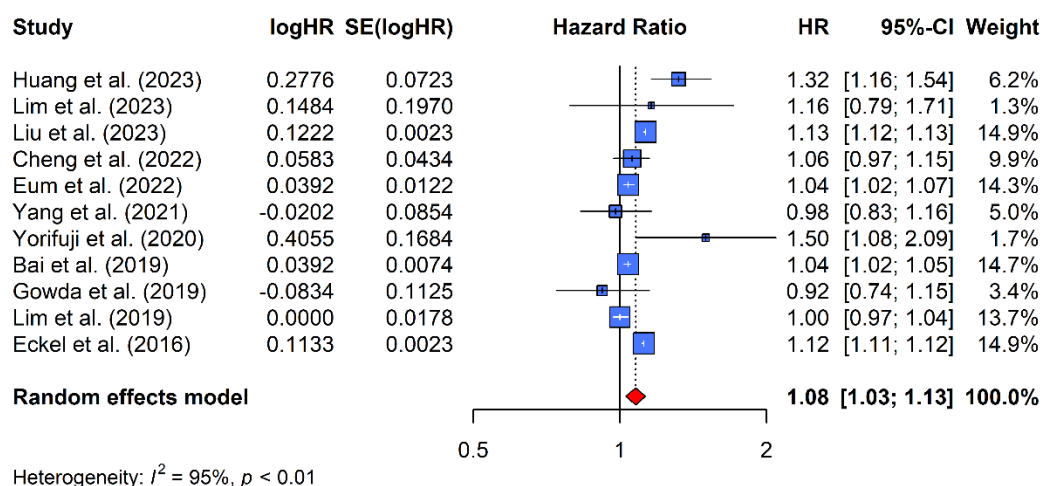


Figure 4.2: Forest plot demonstrates the association between NO₂ exposure and LC risk. Each square denotes risk estimates from individual studies, sized according to their statistical weight and inverse of variance. The horizontal lines indicate 95% CIs, with the diamonds representing the pooled HR and its corresponding 95% CI. HR represents the risk of LC.

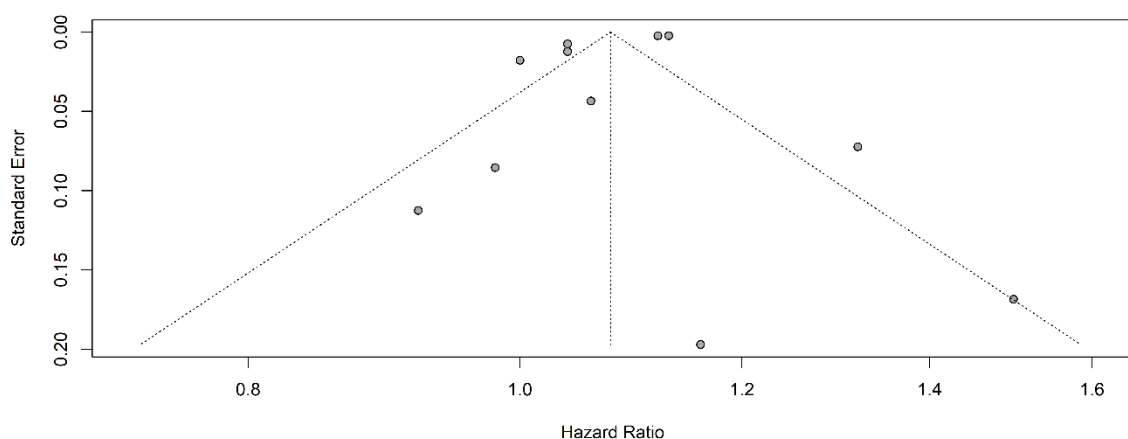


Figure 4.3: The funnel plot depicts publication bias among the studies included in the meta-analysis. Funnel plot visualisation and Egger's test ($p = 0.17$) revealed no indication of publication bias.

4.3.5 Subgroup analyses

The relationships between NO₂ and LC risk were further analysed in subgroups stratified by the outcome of LC, sex, histology, smoking status, and geographical region. A summary of the subgroup analysis is presented in Table 4.2. A pooled HR of 1.06 (95% CI: 1.01-1.12) and a pooled HR of 1.13 (1.01-1.26) indicated a significant association between NO₂ and LC outcomes (incidence and mortality), as illustrated in Figures 4.4(a) and 4.4(b). The significant positive associations between NO₂ exposure and LC risk in both males and females are presented in Appendices C and D, with HRs of 1.12 (95% CI: 1.10-1.14) and 1.14 (95% CI: 1.12-1.15), respectively. Appendices E and F demonstrate that both adenocarcinoma and squamous cell carcinoma histology were negatively associated with LC risk with NO₂ exposure, with adenocarcinoma having an HR of 0.98 (95% CI: 0.87-1.11) and squamous cell carcinoma having an HR of 0.96 (95% CI: 0.80-1.15). The HR for the association between NO₂ exposure and LC risk was 1.06 (95% CI: 0.98-1.15) among smokers (Appendix G). However, a null association was observed among nonsmokers (Appendix H). Across different geographical regions, America displayed a significant HR of 1.06 (95% CI: 1.02-1.1) for the association between NO₂ exposure and LC risk, whereas Asia demonstrated a nonsignificant association, as shown in Figures 4.4(c) and 4.4(d).

Table 4.2: Summary HRs, publication bias assessment and heterogeneity of subgroup analysis.

Population	Number of studies	Statistical model	Pooled HR (95% CI)	<i>p</i> -value [†]	<i>p</i> -value [‡] (Publication bias)	<i>p</i> -value [§] (Heterogeneity)	<i>I</i> ² (%)
Outcome of lung cancer							
Incidence	6	Random effects model	1.06 (1.01-1.12)*	0.027	0.307	< 0.001	95.9
Mortality	5	Random effects model	1.13 (1.01-1.26)*	0.037	0.541	< 0.001	95.1
Gender							
Male	4	Fixed effects model	1.12 (1.10-1.14)*	<0.001	0.272	0.226	31.0
Female	4	Fixed effects model	1.14 (1.12-1.15)*	<0.001	0.055	0.060	59.5
Histology							
Adenocarcinoma	3	Fixed effects model	0.98 (0.87-1.11)	0.800	0.486	0.891	0.0
Squamous Cell Carcinoma	2	Fixed effects model	0.96 (0.80-1.15)	0.652	N/A	1.000	0.0
Smoking status							
Smoker	6	Fixed effects model	1.06 (0.98-1.15)	0.157	0.609	0.615	0.0
Nonsmoker	4	Fixed effects model	0.96 (0.86-1.08)	0.544	0.762	0.517	0.0
Geographic region							
America	7	Random effects model	1.06 (1.02-1.11)*	0.004	0.052	< 0.001	97.0
Asia	3	Random effects model	1.22 (0.96-1.55)	0.107	0.831	0.011	78.0

CI, confidence interval; HR, hazard ratio; N/A, not available

[†] Random effects model was used when the *p*-value for heterogeneity test was <0.05 or *I*² > 50%, otherwise the fixed effect model was used

[‡] Egger's test was used to evaluate publication bias, and a *p*-value of <0.05 indicated statistical significance.

[§] *p*-value of <0.05 is considered statistically significant for Q statistics

*Significant *p*-value (< 0.05) for pooled HR

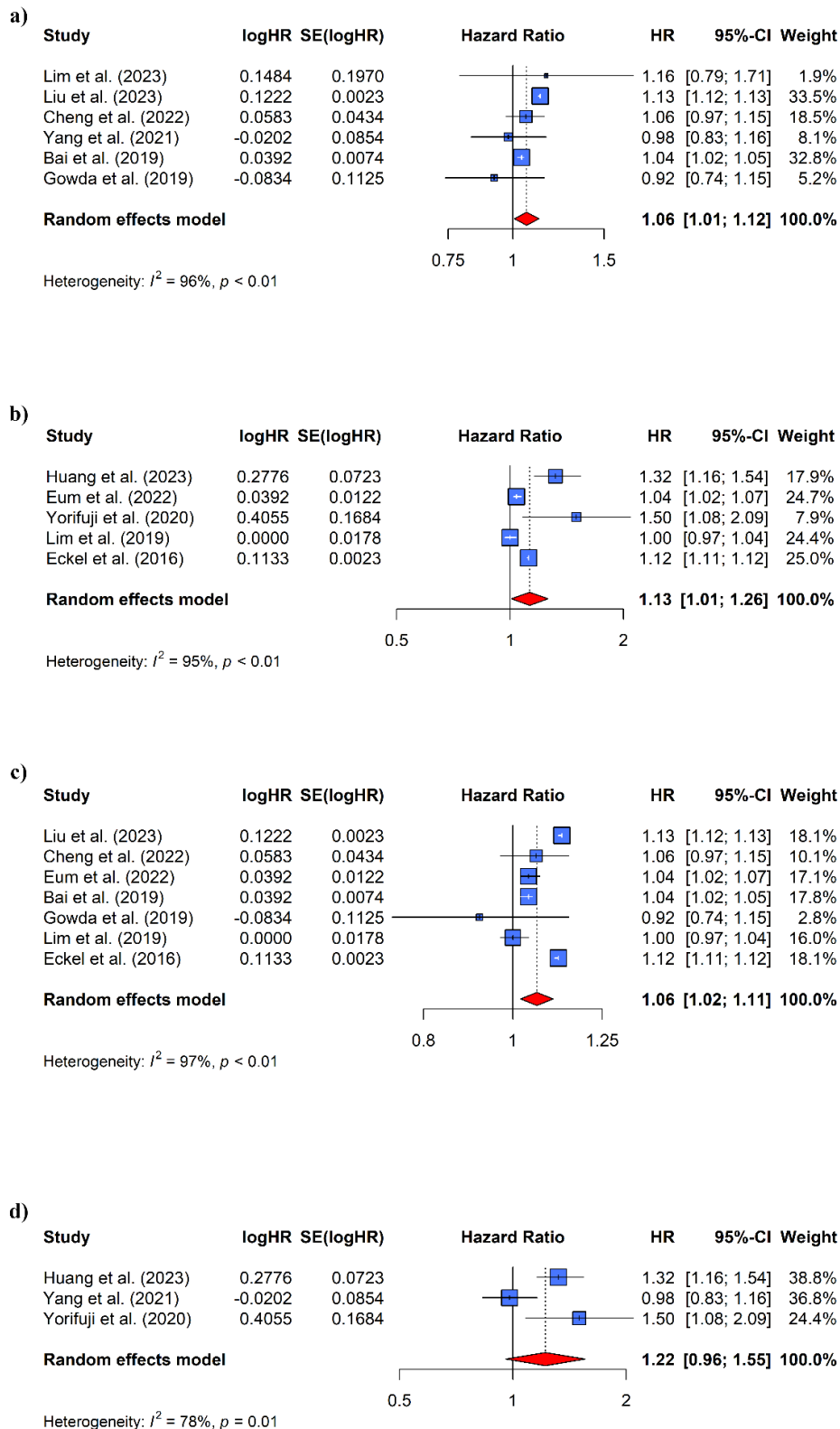


Figure 4.4: Forest plot of subgroup analysis of HRs for NO₂ exposure and LC risk based on (a) Incidence. (b) Mortality. (c) America. (d) Asia.

4.4 Discussion

This meta-analysis investigated the association between exposure to NO₂ and LC risk beyond European countries based on the findings of 11 selected studies. The pooled HR revealed a significantly increased risk of LC per 10 ppb increase in NO₂. This finding is consistent with those of previous meta-analyses (Chen et al., 2015; Chen et al., 2022; Hamra et al., 2015; Yang et al., 2016) and studies conducted in Europe (Bauwelinck et al., 2022; Hart et al., 2015; Huang et al., 2021; So et al., 2022; Stafoggia et al., 2022), which demonstrated that the generalisability of the relationship between NO₂ exposure and LC risk across diverse regions is supported by the consistency of the findings despite geographic differences among study populations, environmental regulations, and socioeconomic factors. This suggests that the association observed in European research is also evident in non-European settings, strengthening the findings' worldwide significance and robustness. Furthermore, many studies rely on proxy measures of NO₂ exposure, such as residential proximity to major roadways or single-source exposure (Boogaard et al., 2022; Chen et al., 2015; Gowda et al., 2019; Hamra et al., 2015; Stieb et al., 2021), which may introduce exposure misclassification and bias. The findings of the current meta-analysis also demonstrated a consistently significant association between exposure to NO₂ and LC risk, which is in line with the results of two previous meta-analyses (Chen et al., 2022; Hamra et al., 2015) and distinguishes the current focus from two other relevant meta-analyses. Chen and the team investigated NO₂ exposure within indoor environments, including homes and workplaces (Chen et al., 2022). These findings demonstrated the importance of indoor air quality management and the health burden attributable to NO₂. In contrast, Hamra and colleagues focused on NO₂ exposure from traffic sources, such as vehicle emissions and urban transportation networks (Hamra et al., 2015). This specific focus allows for a detailed exploration of how proximity to roadways and traffic intensity may influence LC risk.

Compared with the most recent meta-analysis by Ramamoorthy and the team, this meta-analysis evaluated the risk of LC by combining both incidence and mortality data in a single meta-analysis to provide a more comprehensive overview of the overall impact of NO₂ exposure on the risk of LC (Ramamoorthy et al., 2024). This methodology enables a more comprehensive evaluation of the association between various phases of the disease spectrum, from the initial diagnosis (incidence) to the disease's fatal effects (mortality). Current subgroup analysis reveals intriguing parallels and discrepancies with existing studies.

Current subgroup analysis revealed a significant association between NO₂ exposure and both outcomes of LC (incidence and mortality). This dual association illustrates how ubiquitous NO₂ is as a carcinogenic factor. The consistency of current findings across both incidence and mortality metrics aligns well with the findings reported in previous studies and strengthens the argument for the role of NO₂ in LC pathogenesis (Atkinson et al., 2018; Boogaard et al., 2022; Chen et al., 2022; Hamra et al., 2015; Ramamoorthy et al., 2024; Stafoggia et al., 2022; Stieb et al., 2021). These findings also highlight the potential for NO₂ not only to initiate but also exacerbate the progression of LC, leading to increased mortality. These results are consistent with previous research linking AP to adverse health outcomes, emphasising the need to improve air quality regulations worldwide (Chen et al., 2024; Faustini et al., 2014; Huangfu & Atkinson, 2020; Kim et al., 2018). However, the significant associations observed in this study may also reflect the broader environmental and genetic heterogeneity of the populations studied. Further research is essential to understand these complex interactions further, as differences in genetic susceptibilities, occupational exposures, and baseline health status could influence the observed outcomes.

The subgroup analysis of the current meta-analysis provides valuable insights into the association between NO₂ exposure and LC risk across different sexes, histological types, smoking statuses, and geographical regions. These findings indicate a significant association

between NO₂ exposure and LC risk for both the male subgroup and the female subgroup, which corroborates the findings of Yang and colleagues (Yang et al., 2016). This consistent association across genders emphasises the pervasive impact of NO₂ on lung carcinogenesis, regardless of sex-specific biological or behavioural differences.

The subgroup analysis based on histology observed in the present study aligns well with previous findings, which also reported a null association between NO₂ exposure and the risk of developing adenocarcinoma and squamous cell carcinoma (Lamichhane et al., 2017; Moon et al., 2020). However, Lee and colleagues demonstrated that the adenocarcinoma ratio increases when the concentration of NO₂ increases (Lee et al., 2022). This lack of association could be interpreted in several ways. The absence of a significant association in adenocarcinoma and squamous cell carcinoma might be due to differences in study methodologies and the limited number of available studies. Another possible explanation is the differential pathogenesis of these histological subtypes. Adenocarcinoma and squamous cell carcinoma may have distinct molecular and environmental aetiologies, whereas other histologies that were not included in the present study may be more sensitive to NO₂ exposure (Anusewicz et al., 2020; Chen & Dhahbi, 2021; Sy et al., 2004).

Despite the established prevalence of smoking as a risk factor for LC, the potential influence of other risk factors on outcomes remains intriguing. The lack of an association between NO₂ exposure and LC risk among nonsmokers and smokers observed in this study aligns well with the findings reported in a study conducted in Korea (Moon et al., 2020). Among nonsmokers, there was no significant association between NO₂ exposure and LC risk. This finding could indicate that nonsmokers are less susceptible to the carcinogenic effects of NO₂, potentially because of healthier baseline lung function or lower cumulative exposure levels. In contrast to current findings, Yang and coauthors reported a significant association between NO₂ exposure and LC risk among nonsmokers, although their subgroup analysis

included only two studies (Yang et al., 2016). However, this result might also reflect the influence of unmeasured confounding factors, such as exposure to secondhand smoke or occupational hazards, which were not adequately controlled for in the included studies. For smokers, the HR of 1.08 (95% CI: 0.98-1.17) suggested a borderline association between NO₂ exposure and LC risk. Although not statistically significant, this borderline result may suggest a potential synergistic effect between smoking and NO₂ exposure, where the combined impact of these risk factors exceeds their individual effects. The lack of significance may be attributed to the small sample size or variations in the design and quality of the studies, suggesting the need for further extensive research to validate these conclusions and examine the relationships between smoking status and NO₂ exposure.

Geographic analysis revealed a significant association between NO₂ exposure and LC risk in the American subgroup, contrasting with the nonsignificant association in the Asian subgroup. The consistency of American subgroup findings with Hamra and coauthors strengthens the current conclusions, although the discrepancy in Asian subgroup results highlights the need for further investigation (Hamra et al., 2015). The conclusions identified by Hamra and coauthors were based on a limited analysis involving only two studies conducted in Japan (Hamra et al., 2015). The geographic disparity may reflect differences in NO₂ levels, population susceptibility, or other region-specific environmental and lifestyle factors. In America, higher industrial activity and urbanisation levels might contribute to greater NO₂ exposure, thereby increasing the risk of LC (United Nations Department of Economic and Social Affairs, 2019). Conversely, lower NO₂ exposure levels, genetic differences, or varying baseline risk factors in Asian populations might explain the lack of a significant association. The divergent findings between regions highlight the importance of considering regional environmental factors and their potential impact on health outcomes. These findings indicate that the effects of NO₂ on the development of LC vary among populations and emphasise the

necessity of conducting research tailored to specific regions to identify regional risk factors and confounders.

4.5 Limitations

Several limitations of this meta-analysis must be acknowledged. First, the selected studies originated from diverse geographical regions with varying NO₂ exposure levels due to differences in industrialisation, traffic emissions, and environmental regulations. This heterogeneity can introduce significant variability in exposure levels, complicating the comparison and synthesis of results. Additionally, populations across countries present distinct baseline LC risk factors, such as smoking prevalence and occupational exposure, confounding the NO₂-LC relationship. In addition, the lack of comprehensive data from low- and middle-income countries potentially skews overall findings toward more studied regions. Furthermore, temporal changes in NO₂ levels and LC risk factors further complicate the interpretation of the results. Finally, studies published in non-English languages or those not indexed in major databases were excluded from the current meta-analysis, which may lead to selection bias. Future research should explore the molecular and genetic mechanisms underlying the differential impact of NO₂ on various histological subtypes of LC and focus on smoking status to explore the impact of NO₂ exposure, minimise the confounding effects of smoking and provide clearer insights into the environmental determinants of LC.

4.6 Conclusion

In summary, this meta-analysis provides evidence of a positive association between NO₂ exposure and LC risk in regions beyond Europe, extending the scope of existing epidemiological findings. The heterogeneity observed across sex, smoking status, histological

subtypes, and geographic regions highlights the multifactorial nature of LC and the variable impact of environmental pollutants. Future research should aim to disentangle these intricate interactions and provide a more comprehensive understanding of LC aetiology. Research on the molecular and genetic mechanisms underlying the differential impact of NO₂ on histological subtypes of LC could help identify susceptible populations. Additionally, studies based on smoking status could minimise smoking-related confounding factors, offering clearer insights into the environmental determinants of LC.

CHAPTER 5

BIOINFORMATICS-BASED ANALYSIS OF THE POTENTIAL LINK BETWEEN NITROGEN DIOXIDE EXPOSURE AND LUNG CANCER

5.1 Introduction

As reviewed in Chapter 2, air pollution (AP) is a major contributor to lung cancer (LC) burden, with epidemiological evidence implicating nitrogen dioxide (NO₂) as a key exposure of concern. The previous chapters examined this issue from a population perspective, with Chapter 3 evaluating the role of incense burning as an indoor source of NO₂ and Chapter 4 synthesising epidemiological evidence linking ambient NO₂ exposure to LC risk beyond European settings. These findings highlight a consistent association between NO₂ exposure and increased LC risk, yet the molecular mechanisms underlying this relationship remain poorly understood.

NO₂ is highly reactive and chemically unstable, making direct interactions with cellular macromolecules unlikely. Instead, it acts as a precursor to reactive nitrogen species (RNS), such as peroxynitrite (ONOO⁻), nitrated aromatic compounds, and post-translationally modified amino acids, such as 3-nitrotyrosine (3-NT) (Upadhyay et al., 2022; van der Vliet et al., 1999). These stable derivatives can persist in tissues and exert biological effects through protein nitration, deoxyribonucleic acid (DNA) modification, and redox imbalance (Kikugawa et al., 1994; Ozcan & Ogun, 2015).

In the context of LC, these interactions are particularly concerning due to the central role of oxidative and nitrosative stress in promoting genomic instability, inflammation, and aberrant signalling. For example, tyrosine nitration, a hallmark of nitrosative stress, can disrupt signalling cascades governed by receptor tyrosine kinases (RTKs) such as epidermal growth factor receptor (*EGFR*), which are frequently dysregulated in LC (Dev et al., 2023; Zhan et al.,

2018). Moreover, environmental phenols like nitrobenzene and 2-nitrophenol (2-NP), which can arise from NO₂ chemistry, have been shown to modulate redox-sensitive pathways relevant to carcinogenesis (Khan et al., 2022) .

The present study applies pathway analysis and molecular docking simulations to address this mechanistic gap and evaluate the potential interactions between NO₂ and LC-associated proteins. In addition, four relevant surrogates, ONOO⁻, 3-NT, nitrobenzene, and 2-NP, are assessed to model the downstream species likely responsible for the biological consequences of NO₂ exposure (Bauzá et al., 2019; Chen & Chen, 2001; Ng et al., 2013; Ozcan & Ogun, 2015; Piacenza et al., 2022; Zuercher et al., 2025). By integrating these computational approaches, this chapter aims to provide molecular-level insights that complement the epidemiological evidence from the preceding chapters, thereby advancing understanding of how NO₂ and its derivatives may contribute to LC pathogenesis.

5.2 Methodology

5.2.1 NO₂ Target Identification

The molecular structure of NO₂ was retrieved from the PubChem database (CID: 3032552). The corresponding canonical SMILES notation is N(=O)[O]. Potential NO₂ targets were identified using multiple databases, including PubChem (<https://pubchem.ncbi.nlm.nih.gov/>), Search Tool for Interacting Chemicals (STITCH) (<http://stitch.embl.de/>), and the Comparative Toxicogenomics Database (CTD) (<https://ctdbase.org/>). The search was restricted to *Homo sapiens* and conducted using the keyword “nitrogen dioxide”. All duplicate entries were carefully identified and removed before

further analysis to ensure data integrity and eliminate redundancy. Data collection was completed by December 5, 2024.

5.2.2 LC Target Identification

LC-associated targets were obtained from GeneCards (<https://www.genecards.org/>), Online Mendelian Inheritance in Man (OMIM) (<https://www.omim.org/>), and CTD using “lung cancer”. A Venn diagram analysis was performed to identify common targets between NO₂ and LC. Overlapping targets were considered as potential candidates for further study. Database searches were completed by December 5, 2024.

5.2.3 Functional and Pathway Enrichment Analysis

To investigate the biological roles of NO₂-associated LC targets, Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were conducted using the *clusterProfiler* package in R (version 4.4.2) (R Core Team, 2024), with gene annotations retrieved from *org.Hs.eg.db*. GO terms were categorised into three domains: biological process (BP), cellular component (CC) and molecular function (MF). Statistical significance was assessed using the Benjamini-Hochberg (BH) procedure to adjust for multiple comparisons and control the false discovery rate (FDR). KEGG pathway enrichment analysis identified key pathways related to NO₂-induced LC. An adjusted *p*-value of less than 0.05 was considered statistically significant. The results were interpreted and illustrated using appropriate graphical visualisation tools.

5.2.4 Selection of NO₂-Related Surrogates

While NO₂ was selected as the primary ligand for molecular docking analysis, additional small molecules structurally or functionally related to NO₂ were chosen to expand the investigation. Four surrogates (ONOO⁻, 3-NT, nitrobenzene, and 2-NP) were selected based on four key criteria: chemical similarity to NO₂, biological relevance as downstream products or intermediates of NO₂ activity, comparable electronic and steric properties, and practical feasibility for molecular docking simulations (Bauzá et al., 2019; Chen & Chen, 2001; Ng et al., 2013; Ozcan & Ogun, 2015; Piacenza et al., 2022; Zuercher et al., 2025). This approach enables a more realistic and mechanistic investigation into how NO₂ and NO₂-related species may influence protein function, particularly through oxidative and nitrosative pathways implicated in carcinogenesis.

Among these four surrogates, 2-NP and nitrobenzene offer structural analogues with nitro functional groups and planar aromatic systems conducive to molecular interactions (Bauzá et al., 2019; Chen & Chen, 2001), while 3-NT serves as a biologically relevant marker of protein nitration, reflecting post-translational modifications mediated by RNS (Ng et al., 2013). Additionally, ONOO⁻ is a potent oxidant formed *in vivo* from nitric oxide and superoxide, which can indirectly model the reactive potential of NO₂ and extend the scope of the study to include its oxidative stress-mediated mechanisms (Piacenza et al., 2022; Zuercher et al., 2025). Together, these surrogates provide a rational and multidimensional representation of NO₂-associated molecular effects suitable for computational docking analysis.

The chemical structures of the surrogate ligands were retrieved from the PubChem database and used alongside NO₂ in molecular docking studies targeting LC-associated proteins.

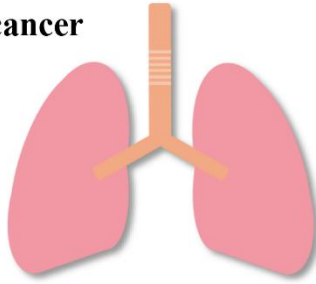
5.2.5 Molecular docking analysis

Molecular docking was conducted to evaluate the binding affinity and interaction patterns between NO₂ and its selected surrogates (3-NT, ONOO⁻, nitrobenzene, and 2-NP) with LC targets. Binding energies were reported in kilocalories per mole (kcal/mol). The target proteins, namely Interleukin-6 (IL-6), interleukin-6 receptor alpha subunit (IL-6R α), tumour necrosis factor-alpha (TNF- α), tumour necrosis factor receptor superfamily member 1B (TNFRSF1B), C-X-C motif chemokine ligand 8 (CXCL-8), superoxide dismutase 1 (SOD1), superoxide dismutase 2 (SOD2), heme oxygenase 1 (HMOX1), forkhead box protein M1 (FOXO1), intercellular adhesion molecule 1 (ICAM1), and myeloperoxidase (MPO) were selected based on the GO and KEGG pathway enrichment analyses. IL-6, IL-6R α , TNF- α , TNFRSF1B, CXCL-8, and ICAM1 were key inflammatory cytokines involved in inflammation and immune responses (Eulenfeld et al., 2012; Isacke & Horton, 2000; Kany et al., 2019; Pan et al., 2021; Silva et al., 2019), while FOXO1 and MPO are often involved in cancer-related signalling (Jannesar & Soraya, 2025; Kalathil et al., 2021; Liao et al., 2018; Valadez-Cosmes et al., 2022), and HMOX1 plays a key role in oxidative stress response (Pronk et al., 2014; Wu & Hsieh, 2022). These proteins were retrieved from the Protein Data Bank (PDB). Protein and ligand structures were prepared by converting them into PDBQT format, removing water molecules, and adding polar hydrogen atoms.

Molecular docking simulations were then carried out using AutoDock Vina (version 1.1.2) (Sanner, 1999). Blind docking was employed to allow an unbiased exploration of all potential binding sites on each target protein. Accordingly, the docking grid was defined to fully encompass the entire protein structure, ensuring that no specific binding pocket was predefined. This strategy enabled the ligands to sample all accessible regions on the protein surface and identify energetically favourable interaction sites (Hetényi & van der Spoel, 2006;

Roomi et al., 2025). Interaction analysis and visualisation were performed using BIOVIA Discovery Studio Visualiser (version 24.1.0.23298) (BIOVIA, 2024). Hydrogen bonds, hydrophobic contacts, electrostatic interactions, and π -related interactions were identified based on the software's default geometric criteria. Hydrogen bonds were defined using a donor-acceptor distance threshold of approximately 3.5 (angstrom) Å, while hydrophobic interactions were interpreted within a distance of up to 5.0 Å. No additional manual distance cut-offs were applied. The study workflow is summarised in Figure 5.1.

Lung cancer



Nitrogen dioxide

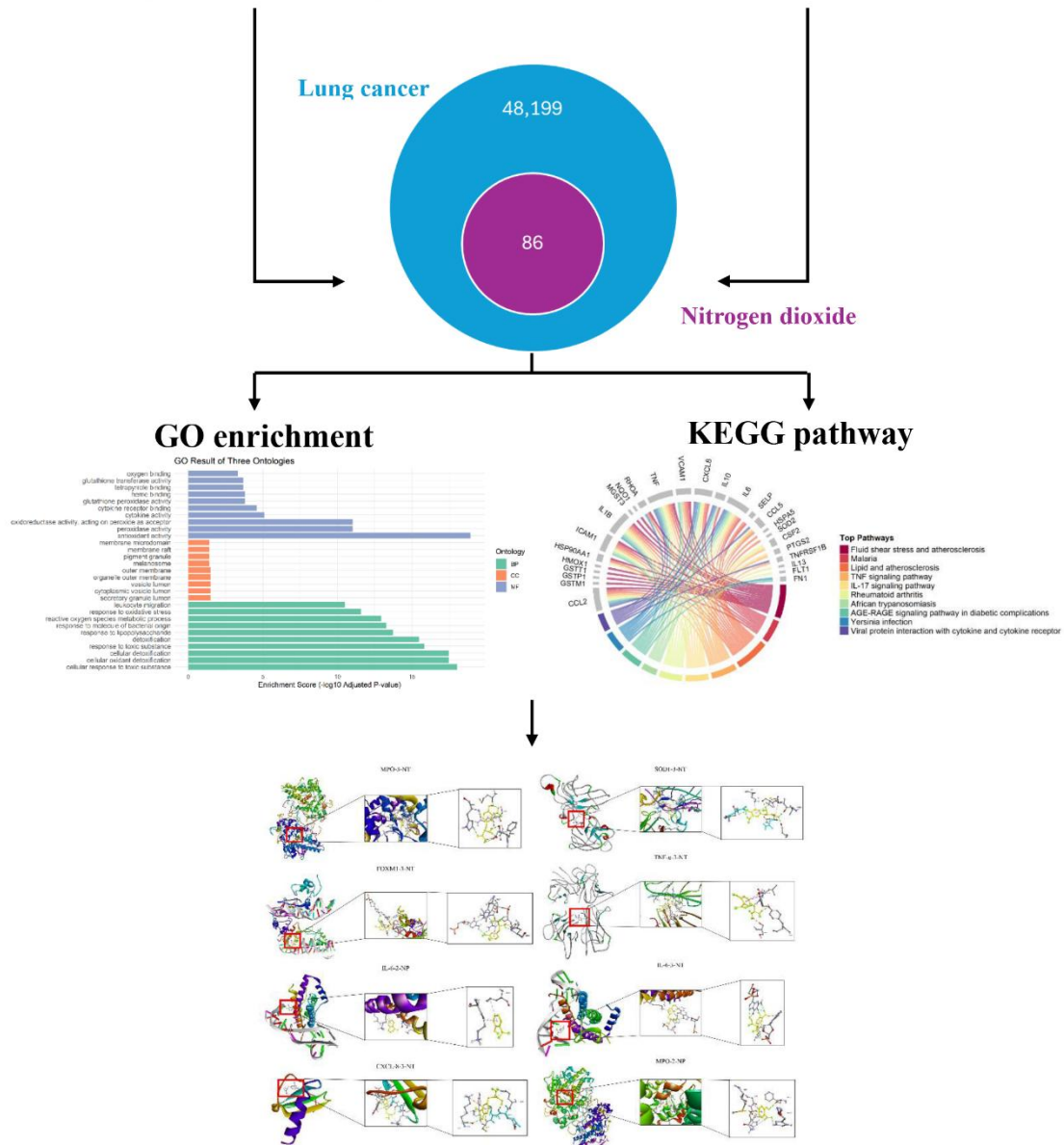
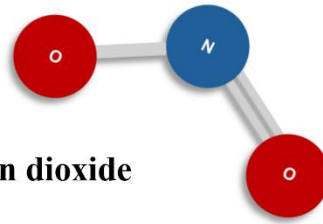


Figure 5.1: Overview of the study workflow.

5.3 Results

5.3.1 Identification of potential targets related to NO₂ and LC

An initial set of 314 NO₂-acting targets was collected from the PubChem, STITCH, and CTD databases, while 188,571 LC-associated targets were retrieved from GeneCards, OMIM, and CTD. After integrating these datasets and eliminating duplicates, 86 overlapping targets were identified. These shared targets are considered potential mediators of NO₂-induced carcinogenic effects in LC, as shown in Figure 5.2.

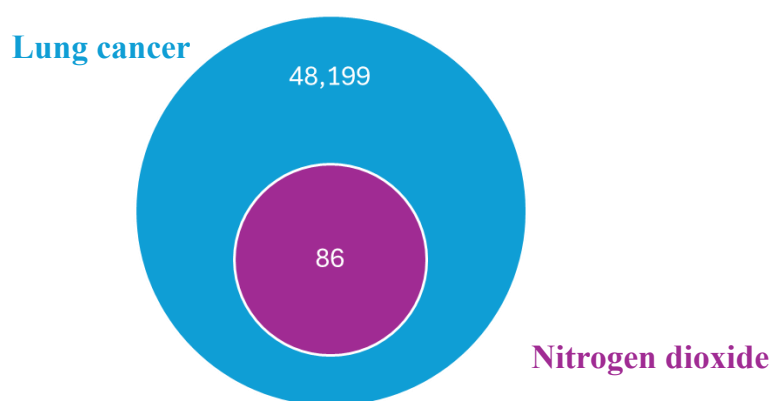


Figure 5.2: Venn diagram illustrating the intersection between targets associated with LC (blue circle, 48,199 genes) and those linked to NO₂ exposure (purple circle). A total of 86 shared targets were identified, highlighting potential molecular connections between NO₂ and the development of LC.

5.3.2 Target functional analysis and pathway enrichment analysis

GO and KEGG pathway enrichment analyses were performed on the 86 identified potential targets, explicitly focusing on *Homo sapiens*. The study revealed 823 statistically significant GO terms (Appendix I), including 793 BP, 9 CC, and 21 MF terms. Significance

was assessed using BH-adjusted p -values to control the FDR. GO terms were ranked by their score values, and the top 10 terms from each category were selected for visualisation, as presented in Figure 5.3(a). A total of 203 KEGG pathway enrichment analyses (Appendix J) were significantly enriched among the potential targets. The top 10 pathways, ranked by BH-adjusted p -values, are presented in Figure 5.3(b). Figures 5.4 to 5.8 illustrate KEGG pathway enrichment analysis maps of core targets involved in the development and progression of LC, generated using the Pathview package in R (Luo & Brouwer, 2013). In these visualisations, genes shown in red are those provided in the input gene list.

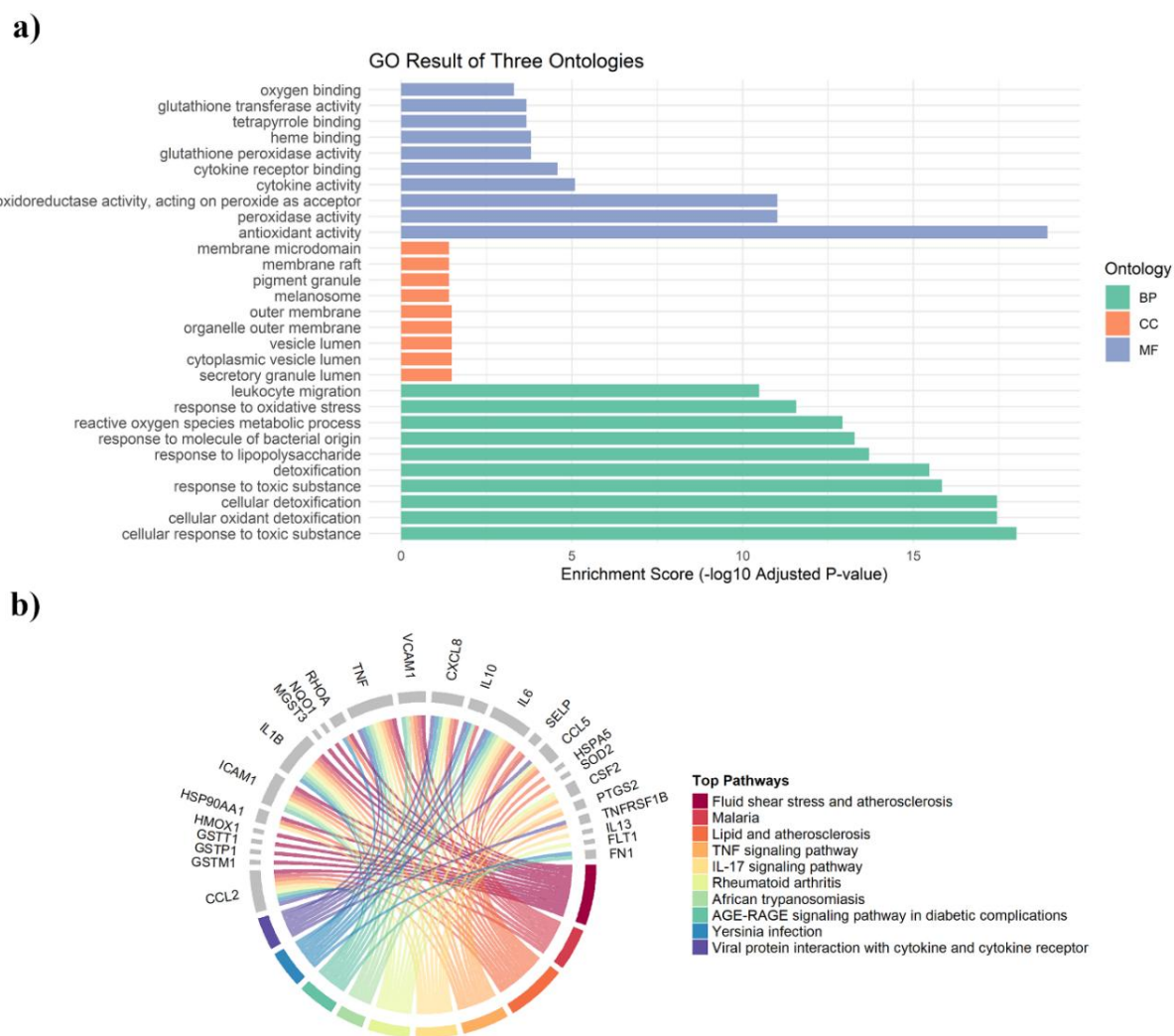


Figure 5.3: Enrichment analysis of the identified targets. (a) Top 10 enriched GO terms. (b) Top 10 enriched KEGG pathways.

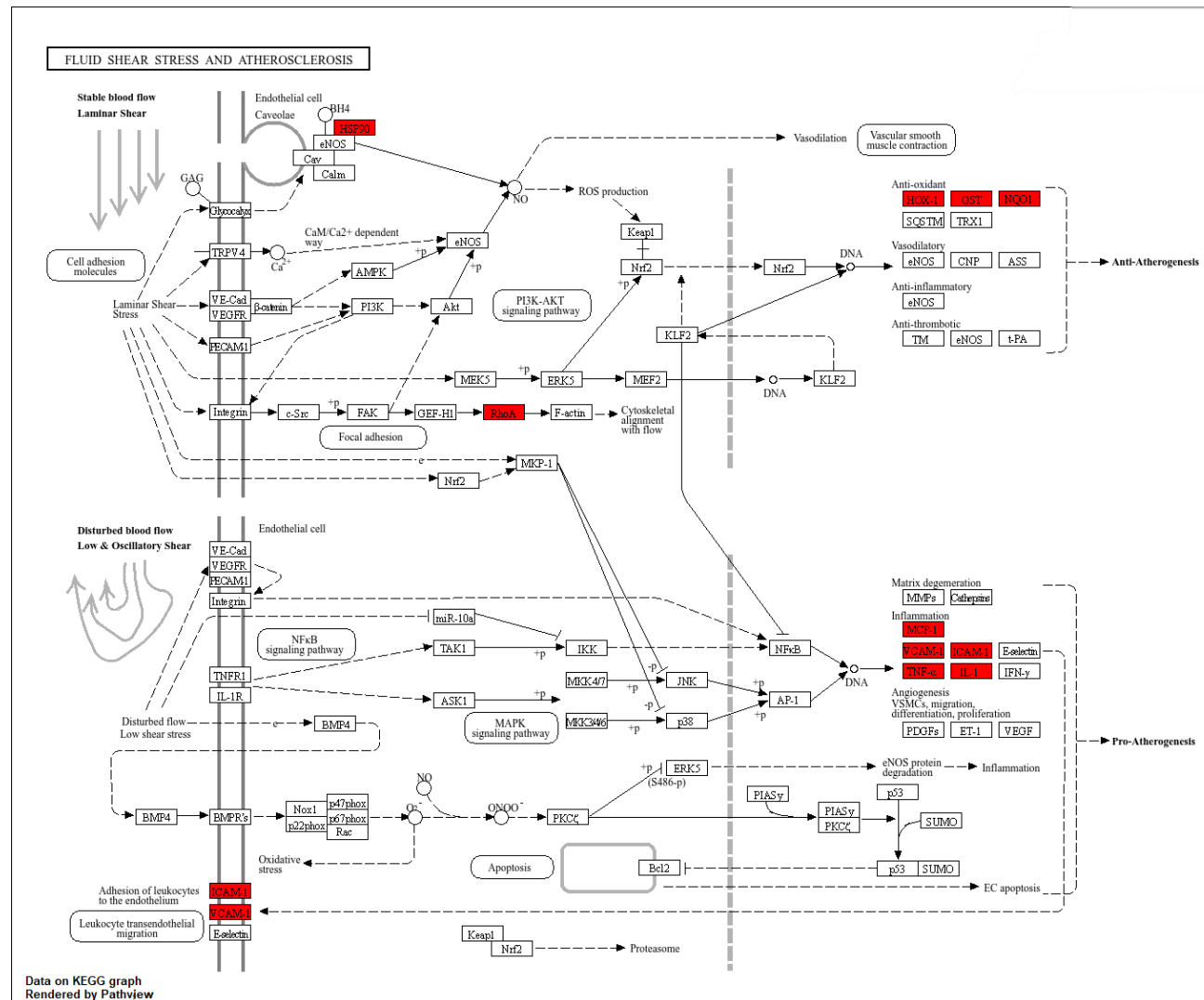


Figure 5.4: The KEGG pathway for fluid shear stress and atherosclerosis highlights molecular changes associated with LC progression. Red-highlighted genes correspond to those from the input list.

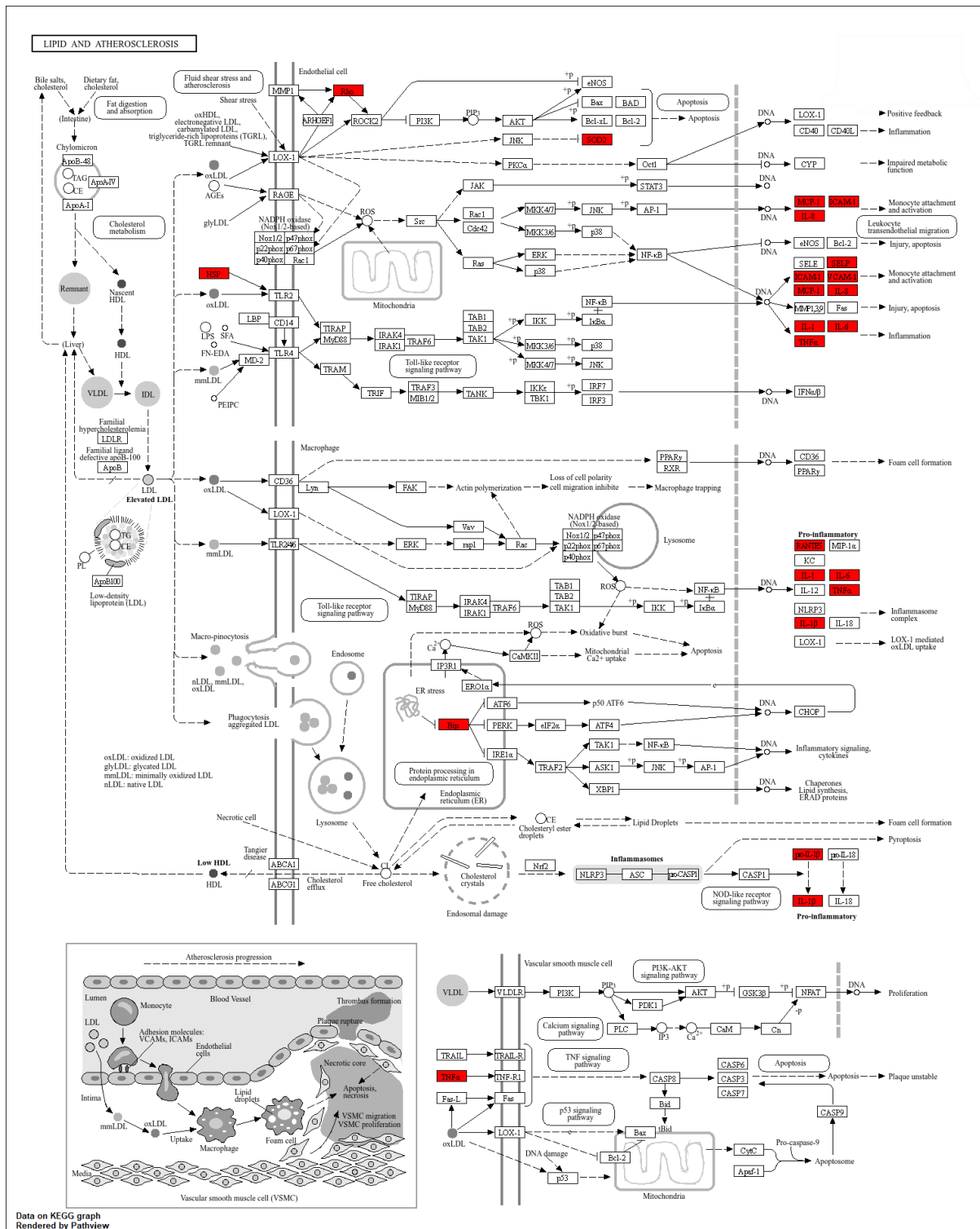


Figure 5.5: Pathview visualisation of the lipid and atherosclerosis pathway displays gene alterations linked to LC. Genes highlighted in red were identified from the input gene set.

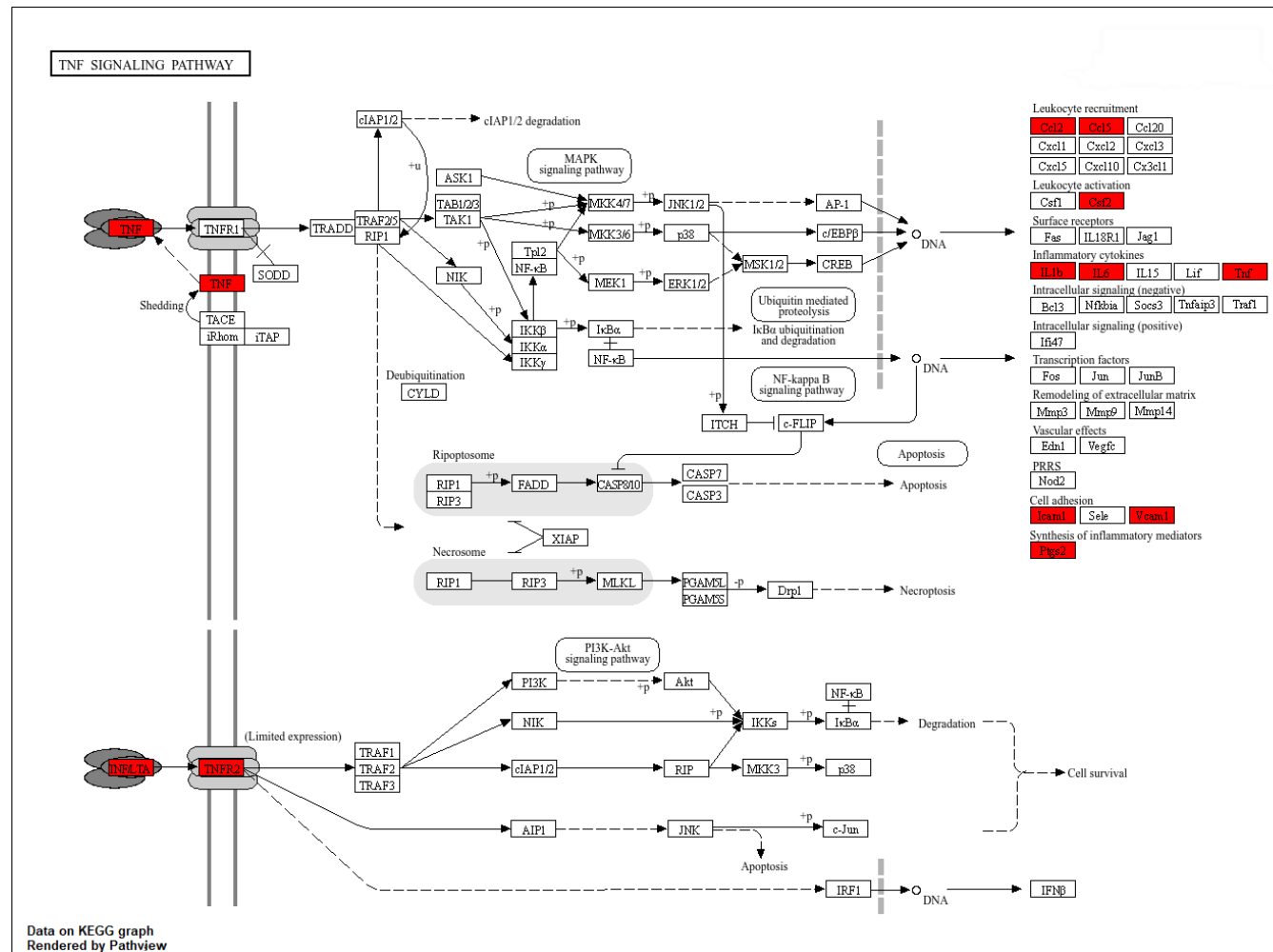
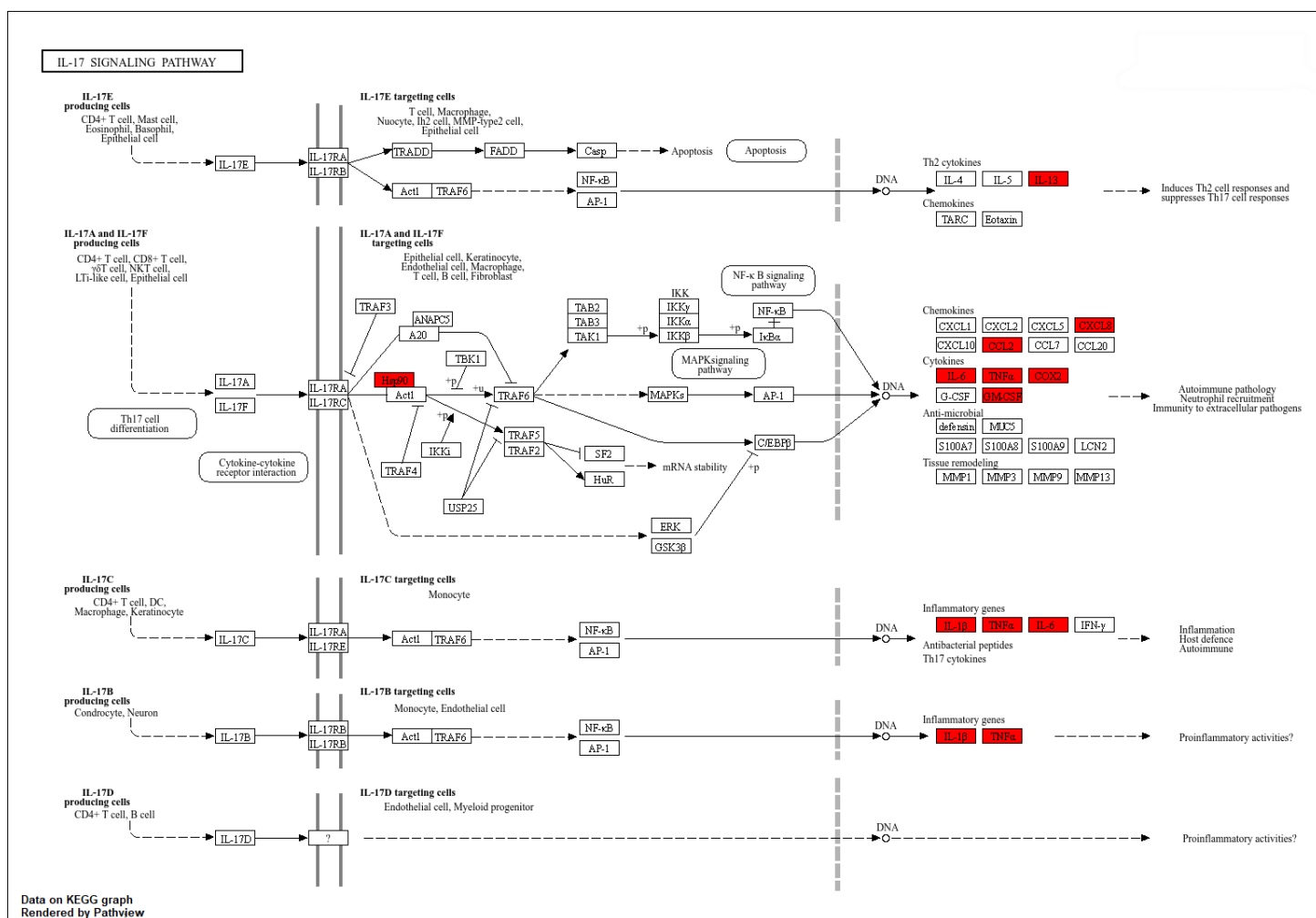


Figure 5.6: In the TNF signalling pathway map, dysregulated targets involved in LC development are marked. Genes marked in red originate from the input list.



5.3.3 Molecular docking analysis

Molecular docking analysis was performed to evaluate the binding affinities of NO₂, 3-NT, ONOO⁻, nitrobenzene, and 2-NP with 11 protein targets (IL-6, IL-6R α , TNF- α , TNFRSF1B, CXCL-8, SOD1, SOD2, HMOX1, FOXM1, ICAM1 and MPO) using AutoDock Vina version 1.1.2. The binding energies for each interaction were obtained and are visualised in the heatmap shown in Figure 5.9. The top eight complexes with the most negative binding energies were identified among the protein-ligand interactions analysed, as shown in Figure 5.10.

Among the compounds evaluated, 3-NT and ONOO⁻ consistently demonstrated the strongest binding affinities across multiple targets. Notably, 3-NT exhibited the lowest binding energies with MPO (-7.4 kcal/mol), SOD1 (-6.9 kcal/mol), and FOXM1 (-6.3 kcal/mol), suggesting a high binding stability with these proteins. Conversely, NO₂ showed comparatively weaker interactions with all targets, with binding energies ranging from -2.6 to -3.8 kcal/mol.

To further validate docking predictions beyond binding affinity values, the top eight protein-ligand complexes were analysed for intermolecular interactions using Discovery Studio Visualiser. Table 5.1 summarises the interacting amino acid residues, bond distances, interaction categories, and bond types. Interaction distances ranged from 1.8 Å to 6.0 Å, consistent with hydrogen bonding (shorter distances) and weaker hydrophobic or π interactions (longer distances). Notably, multiple hydrogen bonds were observed predominantly in the MPO-3-NT and SOD1-3-NT complexes, suggesting strong polar stabilisation, whereas IL-6-2-NP and CXCL-8-3-NT complexes demonstrated mainly hydrophobic and π -cation interactions, indicating non-polar contributions to binding stability. The corresponding three-dimensional representations are shown in Figure 5.11, which highlight ligand positioning within the binding pockets and visualise the key intermolecular contacts described in Table 5.1.

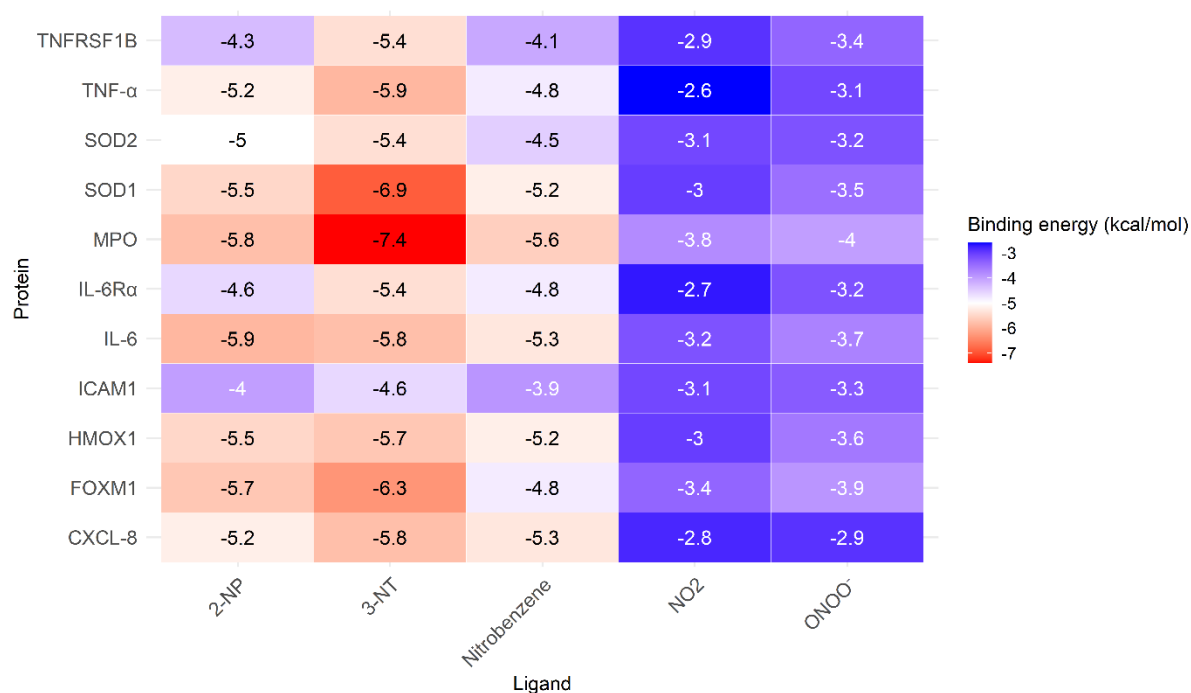


Figure 5.9: Heatmap of binding energies (kcal/mol) of NO₂, 3-NT, ONOO⁻, nitrobenzene, and 2-NP with 11 protein targets (IL-6, IL-6R α , TNF- α , TNFRSF1B, CXCL-8, SOD1, SOD2, HMOX1, FOXO1, ICAM1 and MPO). The colour gradient represents binding affinity, where red indicates the strongest binding (most negative binding energy) and blue means the weakest binding (least negative binding energy).

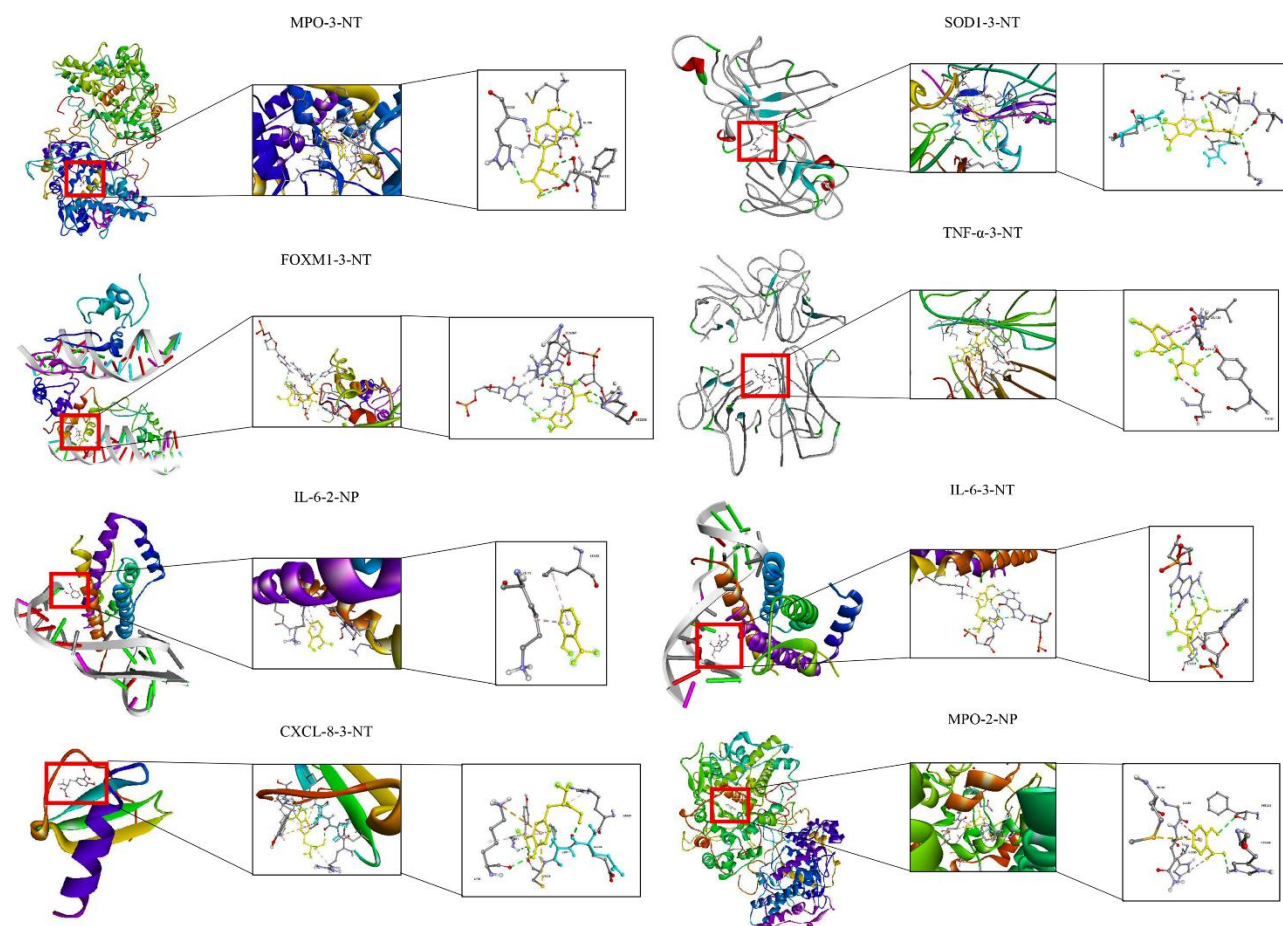


Figure 5.10: Molecular docking results showing the top eight protein-ligand interactions with the most negative binding energies. These interactions represent the strongest predicted binding affinities between NO₂-related surrogates and selected LC-associated proteins. Binding energies were calculated using AutoDock Vina and visualised in Discovery Studio.

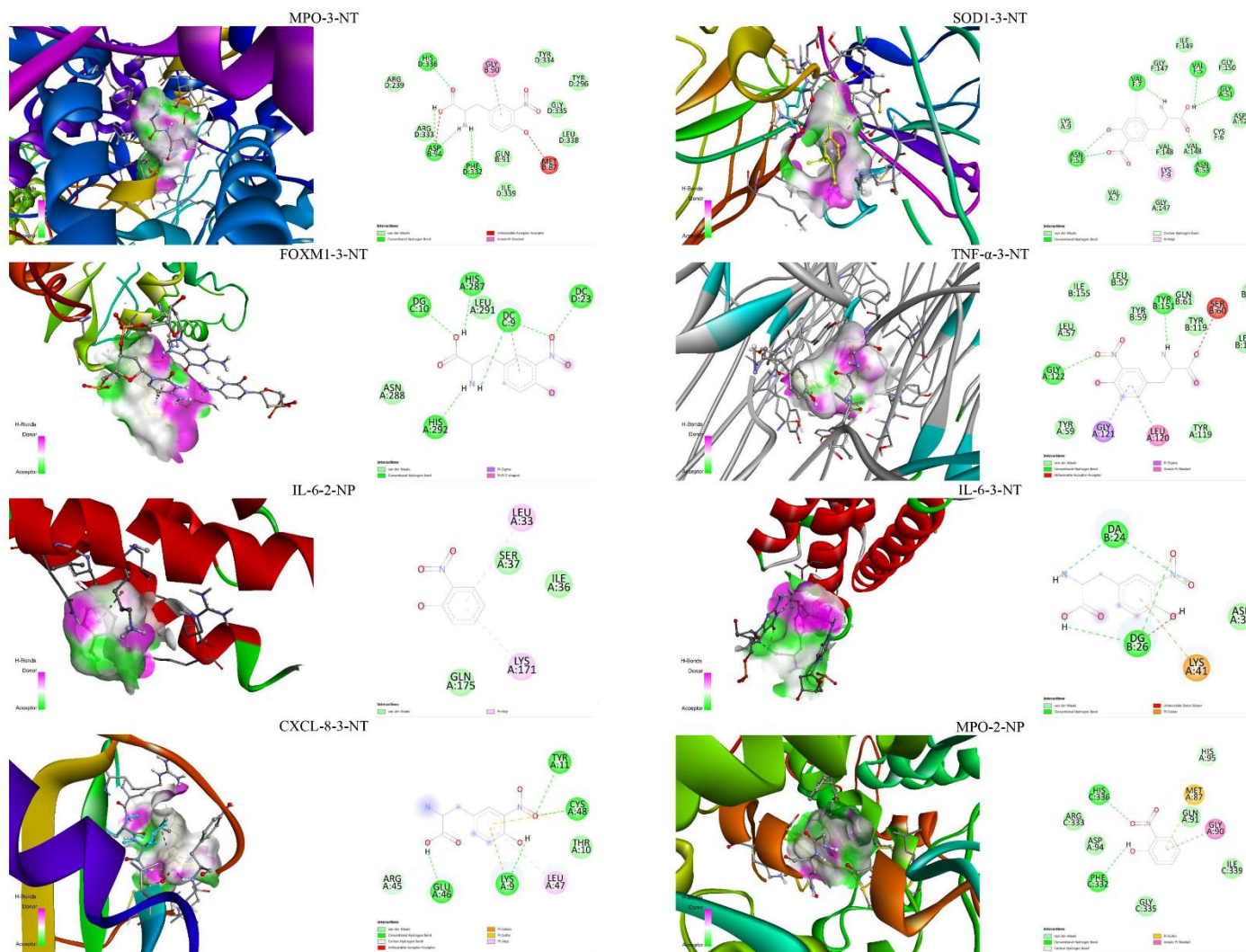


Figure 5.11: Structural visualisation of the top eight protein-ligand docking interactions between NO₂-related surrogates and selected LC-associated proteins.

Table 5.1: Docking interactions of the top eight protein-ligand interactions, showing key residues, interaction distances, categories, and bond types.

Protein	Ligand	Amino acid residues	Distance (Å)	Category	Types
MPO	3-NT	HIS336	2.437	Hydrogen Bond	Conventional Hydrogen Bond
		PHE332	2.427	Hydrogen Bond	Conventional Hydrogen Bond
		ASP94	1.805	Hydrogen Bond	Conventional Hydrogen Bond
		ASP94	3.040	Hydrogen Bond	Conventional Hydrogen Bond
SOD1	3-NT	GLY90	4.038	Hydrophobic	Amide-Pi Stacked
		ASN53	2.979	Hydrogen Bond	Conventional Hydrogen Bond
		ASN53	2.682	Hydrogen Bond	Conventional Hydrogen Bond
		ASN53	2.447	Hydrogen Bond	Conventional Hydrogen Bond
		VAL7	2.284	Hydrogen Bond	Conventional Hydrogen Bond
		GLY51	2.170	Hydrogen Bond	Conventional Hydrogen Bond
		VAL5	2.593	Hydrogen Bond	Conventional Hydrogen Bond
		CYS6	3.536	Hydrogen Bond	Carbon Hydrogen Bond
		VAL7	5.217	Hydrophobic	Pi-Alkyl
		LYS9	5.423	Hydrophobic	Pi-Alkyl
FOXMI	3-NT	DC9	2.198	Hydrogen Bond	Conventional Hydrogen Bond
		DG10	2.082	Hydrogen Bond	Conventional Hydrogen Bond
		DC23	2.412	Hydrogen Bond	Conventional Hydrogen Bond
		DC9	2.432	Hydrogen Bond	Conventional Hydrogen Bond
		HIS292	2.163	Hydrogen Bond	Conventional Hydrogen Bond
		HIS287	2.104	Hydrogen Bond	Conventional Hydrogen Bond
		DC9	3.877	Hydrophobic	Pi-Sigma
		DC9	5.230	Hydrophobic	Pi-Pi T-shaped
TNF- α	3-NT	GLY122	2.437	Hydrogen Bond	Conventional Hydrogen Bond
		TYR151	2.210	Hydrogen Bond	Conventional Hydrogen Bond
		GLY121	3.583	Hydrophobic	Pi-Sigma
IL-6	2-NP	LEU120	4.216	Hydrophobic	Amide-Pi Stacked
		LEU33	5.117	Hydrophobic	Pi-Alkyl
		LYS171	4.148	Hydrophobic	Pi-Alkyl
IL-6	3-NT	DA24	2.499	Hydrogen Bond	Conventional Hydrogen Bond
		DG26	2.404	Hydrogen Bond	Conventional Hydrogen Bond

Table 5.1 continued

CXCL-8	3-NT	DG26	2.539	Hydrogen Bond	Conventional Hydrogen Bond
		DA24	2.070	Hydrogen Bond	Conventional Hydrogen Bond
		DG26	2.429	Hydrogen Bond	Conventional Hydrogen Bond
		DG26	2.460	Hydrogen Bond	Conventional Hydrogen Bond
		LYS41	4.441	Electrostatic	Pi-Cation
		TYR11	2.817	Hydrogen Bond	Conventional Hydrogen Bond
		CYS48	2.226	Hydrogen Bond	Conventional Hydrogen Bond
		LYS9	2.435	Hydrogen Bond	Conventional Hydrogen Bond
		GLU46	1.980	Hydrogen Bond	Conventional Hydrogen Bond
		GLU46	1.960	Hydrogen Bond	Conventional Hydrogen Bond
		ARG45	3.566	Hydrogen Bond	Carbon Hydrogen Bond
		LYS9	4.856	Electrostatic	Pi-Cation
		CYS48	5.977	Other	Pi-Sulfur
		LYS9	5.083	Hydrophobic	Pi-Alkyl
MPO	2-NP	LEU47	5.169	Hydrophobic	Pi-Alkyl
		HIS336	2.543	Hydrogen Bond	Conventional Hydrogen Bond
		PHE332	2.896	Hydrogen Bond	Conventional Hydrogen Bond
		HIS95	3.749	Hydrogen Bond	Carbon Hydrogen Bond
		MET87	5.169	Other	Pi-Sulfur
		GLY90	4.266	Hydrophobic	Amide-Pi Stacked

5.4 Discussion

The recent meta-analysis suggests that incense burning is associated with an increased risk of LC among Asian populations (Tang et al., 2024). Furthermore, findings from an unpublished meta-analysis conducted by the present laboratory showed a significant global correlation between exposure to NO₂, a byproduct of incense combustion, and elevated LC risk. These findings prompted the present computational study investigating the interactions between LC-related proteins and NO₂, along with relevant NO₂ surrogates.

GO enrichment analysis performed on genes identified as being associated with both LC and NO₂ exposure revealed significant overrepresentation of biological processes related to detoxification and oxidative stress response, including cellular response to toxic substance (GO:0097237), cellular oxidant detoxification (GO:0098869), cellular detoxification (GO:1990748), response to poisonous substance (GO:0009636) and detoxification (GO:0098754). These enriched terms highlight the functional involvement of identified proteins in maintaining redox homeostasis under nitrosative stress conditions, a well-established factor in pulmonary oncogenesis.

Enriching detoxification-related pathways is consistent with previous findings linking environmental NO₂ exposure to redox imbalance and chronic inflammation in the lung microenvironment (Peng et al., 2025). The implicated proteins include key phase I and II detoxifying enzymes, suggesting that NO₂-related species may directly impair cellular defence mechanisms against reactive electrophiles and oxidative intermediates. Such disruption may contribute to genomic instability and increased mutation rates characteristic of lung tumourigenesis (Ngo & Duennwald, 2022).

Pathway-level analysis via KEGG and Pathview revealed consistent enrichment in TNF signalling (hsa04668), IL-17 signalling (hsa04657), cytokine-cytokine receptor interaction

(hsa04060), fluid shear stress and atherosclerosis (hsa05418), and lipid and atherosclerosis pathways (hsa05417). These findings reflect activation of inflammatory, oxidative, and vascular remodelling processes commonly associated with LC progression. Integration with gene-level data showed that pro-inflammatory mediators such as IL-6, TNF- α , TNFRSF1B, CXCL-8, and ICAM1 were strongly represented across these pathways, consistent with known mechanisms of immune cell recruitment, endothelial activation, and nuclear factor-kappa B (NF- κ B)/mitogen-activated protein kinase (MAPK)-driven signalling. Additionally, oxidative stress-related genes *SOD2*, *HMOX1*, and *MPO* were enriched in redox-responsive networks, indicating disruption of antioxidant defence and endothelial function (Chang & Dong, 2011; Chu, 2013; Gaffen et al., 2006; Hopkins, 2013; Jomova et al., 2024; Kattoor et al., 2019; Lee et al., 2022; Newton & Dixit, 2012; Raghunandan et al., 2021; Shing et al., 2023; Song & Qian, 2013; Tabas et al., 2015; Wu et al., 2025).

These molecular signatures align with exposure to NO₂ and its reactive surrogates, including ONOO⁻, 3-NT, 2-NP, and nitrobenzene, which are known to induce nitrative and oxidative stress. These species can trigger post-translational modifications and redox imbalance, thereby modulating the expression and activity of key inflammatory and oxidative genes (Li et al., 2024; Nascimento et al., 2019). The concurrent upregulation of *FOXMI* further supports the activation of stress-responsive proliferative programs that may contribute to tumour development (Khan et al., 2023). Together, these findings support a model in which NO₂ and its nitrative byproducts disrupt immunometabolic and vascular homeostasis, promoting conditions favourable for lung carcinogenesis.

NO₂ is a major environmental pollutant that has long been associated with increased risk of health issues through epidemiological studies. However, its precise molecular role in carcinogenesis remains insufficiently characterised. Given its small size, low polarity, and radical nature, NO₂ is chemically constrained in its ability to form stable, high-affinity

complexes with proteins, thereby limiting its role as a direct-acting ligand in classical biochemical pathways (Pandey & Singh, 2021; Wang, 2024). Molecular docking simulations support this, demonstrating weak binding affinities (-2.6 to -3.8 kcal/mol) of NO₂ to several LC-related protein targets. This aligns with the understanding that NO₂ acts more as a reactive intermediate, inducing oxidative and nitrosative stress, rather than functioning as a direct-acting ligand in molecular signalling.

All four surrogates displayed significantly stronger binding affinities (-5.6 to -6.5 kcal/mol) with LC-associated proteins than NO₂. Among them, 3-NT exhibited the strongest interactions, particularly with MPO and SOD1. ONOO⁻ and 3-NT reflect endogenous nitrosative stress pathways that modify proteins and nucleic acids, contributing to mutagenesis, inflammation, and signal transduction dysregulation (Butterfield et al., 2007; Mikhed et al., 2016; Ngo & Duennwald, 2022). The interaction between 3-NT and MPO may reflect a positive feedback mechanism wherein nitrated species stabilise or modulate MPO activity, perpetuating nitrosative stress and inflammatory signalling in the tumour microenvironment. MPO-driven generation of 3-NT has been associated with mutagenesis, DNA damage, and immune evasion in LC (Mohiuddin et al., 2006; Murata & Kawanishi, 2004; Quevedo-Abeledo et al., 2025; Syslová et al., 2014; Wu et al., 2007). Meanwhile, 3-NT binding to SOD1 may impair its antioxidant function through tyrosine nitration, leading to elevated superoxide levels and oxidative DNA damage, both hallmarks of cancer progression (Chidambaram et al., 2024; Khan et al., 2010). Analysis of intermolecular contacts further demonstrated these observations. For instance, 3-NT formed multiple hydrogen bonds with MPO and SOD1 within 2.0-3.0 Å, indicating strong polar stabilisation, whereas CXCL-8-3-NT and IL-6-2-NP complexes were primarily stabilised by hydrophobic and π -cation interactions at longer distances (~ 4.0-6.0 Å). These contrasting binding modes suggest that nitrated species may differentially perturb antioxidant and pro-inflammatory proteins through polar disruption of redox enzymes or non-

polar stabilisation of cytokine signalling mediators. Visualisation of these complexes in Figure 5.11 corroborates these findings, illustrating ligand orientation and the spatial context of hydrogen bonds and hydrophobic contacts that underlie the stabilisation patterns described. These results support the hypothesis that 3-NT may contribute to lung carcinogenesis by destabilising key redox enzymes while enhancing inflammatory signalling, thereby disrupting cellular homeostasis.

Nitrobenzene and 2-NP, while originating from environmental reactions, exhibit biological activities that mirror endogenous oxidative insults. These compounds are known to generate reactive oxygen species (ROS), impair antioxidant defences, and cause DNA damage, thereby contributing to redox imbalance and genomic instability (Khan et al., 2018; Liu et al., 2015). Their toxicological profiles include hematotoxicity, methemoglobinemia, and hepatic injury, with recognised risk upon inhalation exposure (Agency for Toxic Substances and Disease Registry, 2024; Davies, 2003). The predominance of hydrophobic contacts in nitrobenzene- and 2-NP-protein complexes further reflects their non-polar aromatic structures, favouring van der Waals and π -stacking interactions rather than hydrogen bonding. This may explain their capacity to insert into hydrophobic protein pockets and perturb structural integrity.

Together, these findings suggest that NO_2 contributes to lung carcinogenesis not through direct protein targeting but by forming RNS and nitrated organics that alter signalling, damage biomolecules, and dysregulate redox and inflammatory pathways. Surrogates such as 3-NT and ONOO^- exemplify endogenous nitrosative stress mechanisms, while nitrobenzene and 2-NP serve as environmental amplifiers of oxidative injury. These compounds offer valuable mechanistic insights and may serve as exposure biomarkers for ecological risk assessment.

These findings are consistent with existing literature that implicates NO₂ in indirect mechanisms of carcinogenesis, particularly through the generation of secondary reactive species. Previous studies have shown that ONOO⁻ can induce DNA strand breaks and protein nitration, contributing to mutagenesis and altered cellular signalling (Islam et al., 2015). Similarly, nitrated proteins such as 3-NT have been detected in smokers and individuals exposed to AP, highlighting their relevance as nitrosative stress biomarkers (Jin et al., 2011; Szumska et al., 2012). The docking-based identification of 3-NT as a potential modulator of EGFR activity expands on this by suggesting a functional consequence of such modifications in oncogenic signalling. Additionally, the current observation that nitrophenolic compounds bind to redox-related proteins aligns with studies linking environmental phenols to oxidative stress and inflammation (Kruk et al., 2022; Watkins et al., 2015). These comparisons validate our surrogate-based approach and emphasise the importance of considering downstream NO₂ products in understanding its carcinogenic potential.

5.5 Limitation

It is crucial to acknowledge several limitations of the current study. Molecular docking provides a simplified, static view of protein-ligand interactions and cannot fully reflect proteins' dynamic, ever-changing nature within living systems. This is especially important when dealing with highly reactive or short-lived species like NO₂ and ONOO⁻, which may not be well-represented by standard docking tools mainly designed for stable, non-covalent interactions. The protein structures we used were based on crystallographic data, which might not capture the shapes or modifications these proteins undergo in the LC microenvironment. Standard docking workflows cannot adequately represent post-translational modifications such as tyrosine nitration, central to 3-NT biology. While the selected surrogates are chemically and biologically relevant, they only represent a fraction of the possible NO₂-derived compounds

that could be involved. Finally, the biological relevance of the predicted interactions remains uncertain and requires experimental validation in cellular or animal models. Moreover, focusing on a limited set of proteins may have excluded other critical redox-regulating or signalling molecules relevant to lung carcinogenesis, potentially underestimating the broader impact of NO₂-derived species. These limitations highlight the need for future studies that combine computational work with experimental validation.

To strengthen the translational relevance of this study, experimental validation through enzymatic activity assays, cell-based functional studies, and proteomic analyses will be crucial to confirm the biological significance of these docking interactions. Moreover, exploring a broader range of NO₂-derived species, including adducts formed with lipids, nucleic acids, or proteins, could offer a more complete picture of its carcinogenic potential. Understanding these mechanisms is essential for elucidating how environmental exposures contribute to LC progression and identifying potential intervention points in environmentally linked oncogenesis.

5.6 Conclusions

This molecular docking analysis suggests that NO₂ and its reactive surrogates can interact with key proteins involved in oxidative stress and inflammatory pathways relevant to LC. These predicted interactions provide mechanistic hypotheses linking environmental pollutants to tumour-promoting biological processes. Future studies integrating *in vitro* or *in vivo* validation and dynamic modelling approaches are essential to confirm these interactions and explore their downstream biological effects in a more physiologically relevant context.

CHAPTER 6

GENERAL DISCUSSION

This study advances understanding of how environmental exposures contribute to lung cancer (LC) through three interrelated studies: (i) a meta-analysis examining the association between incense burning and LC risk in Asian populations, (ii) a meta-analysis assessing the effects of nitrogen dioxide (NO₂) exposure outside of Europe, and (iii) a molecular docking study investigating the interaction between NO₂ and related compounds with proteins involved in LC. Together, these investigations reflect the complex nature of LC causation and offer new perspectives on population-level associations and potential biological mechanisms.

The central observation is that air pollutants from domestic incense combustion or outdoor traffic-related emissions converge on shared biological mechanisms, including oxidative stress, inflammation, and deoxyribonucleic acid (DNA) damage. Notably, NO₂ serves as a unifying pollutant across both contexts, where it is released during incense combustion (Guo et al., 2023; Koo et al., 1990) and is also a significant marker of traffic-related pollution (Brims et al., 2022; Turner, 2022). This dual presence highlights NO₂ as a critical exposure pathway that links indoor and outdoor environments to LC risk. Molecular docking analyses strengthen this interpretation by suggesting biologically plausible interactions between NO₂, its reactive surrogates, and key proteins implicated in lung carcinogenesis.

The incense burning meta-analysis demonstrated that cultural practices represent a substantial but often unacknowledged source of carcinogenic exposure. Incense smoke contains particulate matter (PM)_{2.5}, polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), and NO₂, where these compounds are known to be carcinogenic (Bootdee

et al., 2016; Goel et al., 2017; International Agency for Research on Cancer, 2022; Lin et al., 2008; National Toxicology Program, 2021). Recent toxicological investigations have further demonstrated that chronic exposure to incense smoke induces oxidative stress, DNA adduct formation, and inflammatory responses, all of which are hallmarks of lung carcinogenesis (Lee et al., 2021; Yadav et al., 2022). These findings align with epidemiological studies linking indoor air pollution (AP) from combustion sources to LC, particularly among nonsmokers and women in Asian populations (Chen et al., 2022b; Fang et al., 2025; Mu et al., 2013).

The NO₂ meta-analysis extended these findings to outdoor and urban environments, showing that chronic NO₂ exposure is significantly associated with LC incidence and mortality beyond European populations. Beyond being a direct respiratory irritant, NO₂ is also a proxy for traffic-related mixtures that include PAHs, ultrafine particles, and secondary oxidants (World Health Organization & Regional Office for Europe, 2021). Long-term exposure has been shown to promote airway inflammation, oxidative DNA damage, and dysregulated signalling pathways conducive to tumour development (Chen et al., 2024; Wang et al., 2025). Mendelian randomisation analysis further supports a casual association between NO₂ and LC risk, validating epidemiological associations (Wang et al., 2025). Together with incense findings, this highlights how NO₂ bridges indoor cultural exposures and outdoor urban pollution in contributing to lung carcinogenesis.

These two meta-analyses highlight the multifaceted nature of AP exposure: incense burning represents a localised, indoor risk factor, while NO₂ reflects broader, urban-scale exposures linked to industrialisation and traffic emissions. Despite these differences in origin, both exposures converge on common mechanistic pathways, including oxidative stress, inflammation, and DNA damage, that are central to LC pathogenesis.

To further investigate these mechanisms, the molecular docking study simulated the interactions of NO₂ and its reactive surrogates, including 3-nitrotyrosine (3-NT), peroxynitrite (ONOO⁻), and 2-nitrophenol (2-NP), and nitrobenzene with a panel of LC-related proteins. These analyses revealed that surrogates exhibited stronger binding affinities than NO₂, suggesting that secondary reactive nitrogen species (RNS) may play a more significant role in protein modification and signalling disruption. Key protein targets included Interleukin-6 (IL-6), interleukin-6 receptor alpha subunit (IL-6R α), tumour necrosis factor-alpha (TNF- α), tumour necrosis factor receptor superfamily member 1B (TNFRSF1B), C-X-C motif chemokine ligand 8 (CXCL-8), superoxide dismutase 1 (SOD1), superoxide dismutase 2 (SOD2), heme oxygenase 1 (HMOX1), forkhead box protein M1 (FOXO1), intercellular adhesion molecule 1 (ICAM1), and myeloperoxidase (MPO), which are integral to oxidative stress response, inflammatory signalling, and immune regulation.

Proteins involved in antioxidant defence, including SOD1, SOD2, and HMOX1, inflammatory mediators such as TNF- α and IL-6R, and enzymes of xenobiotic metabolism, including MPO, were identified as potential binding targets (Hofstra & Uetrecht, 1993; Ighodaro & Akinloye, 2018; Lv et al., 2015; Poss & Tonegawa, 1997; Unver & McAllister, 2018). The interaction of RNS with these proteins may impair their enzymatic activity, leading to disruption of redox balance, accumulation of reactive oxygen species (ROS), and sustained oxidative stress (Bellanti et al., 2025; Di Meo et al., 2016; Liu et al., 2025). In parallel, modification of inflammatory mediators may amplify cytokine signalling and perpetuate chronic inflammation within the lung microenvironment (Gong et al., 2021; Yao & Rahman, 2009). Such combined effects create conditions that favour DNA damage, genomic instability, and uncontrolled cellular proliferation, hallmarks of lung carcinogenesis. These results therefore provide mechanistic plausibility to the associations demonstrated in both meta-

analyses, establishing a cause-and-effect association between environmental exposure to air pollutants and LC pathogenesis.

A concept map (Figure 6.1) was developed to integrate the findings from all three studies. It illustrates how incense burning and NO₂ exposure converge on shared biological mechanisms, including oxidative stress, inflammation, and DNA damage, despite arising from different sources. The molecular docking results provide mechanistic support by identifying specific protein targets involved in these pathways. Ultimately, these processes contribute to the initiation and progression of LC.

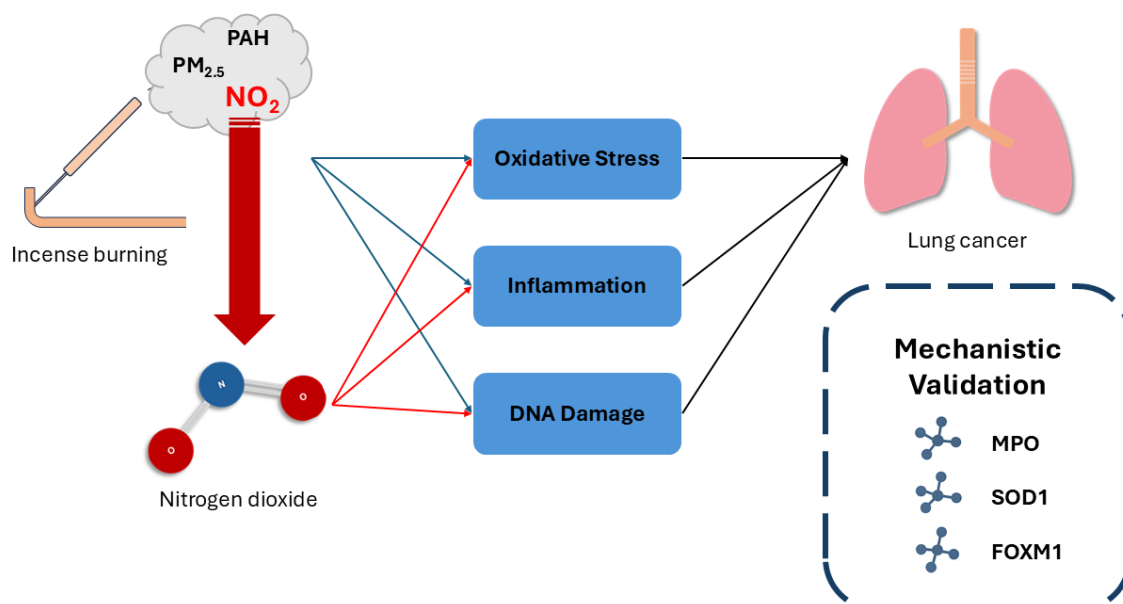


Figure 6.1: Integrated concept map linking environmental exposures, molecular mechanisms, and LC risk.

It is crucial to acknowledge several limitations of the study. The meta-analyses relied exclusively on observational studies subject to confounding, recall or information bias, and exposure misclassification. Differences in exposure categorisation, measurement methods,

population characteristics, and diagnostic criteria may have introduced heterogeneity. Limited geographic coverage, particularly from low- and middle-income countries, and excluding non-English publications, may have resulted in selection bias. Variations in study periods, pollutant levels, and baseline LC risk factors, such as smoking and occupational exposures, further complicate causal interpretation. In the molecular docking analysis, the method provides a simplified, static view of protein-ligand interactions, limiting its ability to capture protein dynamics, especially for highly reactive species such as NO_2 and ONOO^- . Using crystallographic protein structures may not reflect conformations in the LC microenvironment, and the selected surrogates represent only a subset of possible NO_2 -derived compounds. The biological relevance of the predicted interactions remains uncertain and requires experimental validation.

CHAPTER 7

CONCLUSION AND RECOMMENDATIONS

7.1 Conclusion

The collective findings from the study provide consistent evidence that environmental exposures, specifically incense burning and nitrogen dioxide (NO₂), are associated with an increased risk of lung cancer (LC). The meta-analysis on incense burning indicated a higher risk among males compared with females, and among ever-smokers compared with never-smokers, suggesting an interaction between lifestyle factors and environmental exposure. The meta-analysis on NO₂ exposure demonstrated a significant association with LC across various regions, consistent with previous findings from European countries. It revealed subgroup-specific differences based on sex, histological subtype, smoking status, and geographic location. These epidemiological observations emphasise the multifactorial nature of LC and the influence of both environmental and personal risk factors. The molecular docking analysis further supported these associations by revealing plausible interactions between NO₂-derived reactive species and proteins relevant to LC biology, suggesting mechanistic pathways involving oxidative stress and inflammation. Together, the study emphasises the value of integrating epidemiological evidence with molecular-level analyses to strengthen the understanding of environmental determinants in lung carcinogenesis.

7.2 Recommendations

Further research should prioritise updated and high-quality epidemiological studies that address current patterns of incense burning and NO₂ exposure, with improved exposure

assessment methods capturing frequency, intensity, and duration. Studies should aim to minimise confounding by incorporating detailed smoking history, occupational exposure data, and other relevant risk factors. Greater inclusion of data from underrepresented low- and middle-income countries such as Asia and Oceania is needed to enhance the global applicability of findings. Subgroup analyses stratified by sex, histological subtype, and genetic susceptibility are recommended to identify particularly vulnerable populations. From a mechanistic perspective, molecular investigations should extend beyond static docking models by employing molecular dynamics simulations to account for protein flexibility and solvent interactions. Experimental validation using *in vitro* and *in vivo* models and clinical cohort studies is essential to confirm computational predictions and clarify pollutant-specific pathways in LC development, providing strong evidence to establish causal relationships. Integrating epidemiological, molecular, and experimental approaches will provide a more comprehensive understanding of environmental contributions to LC and guide effective preventive strategies.

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APPENDICES

Appendix A: Journal Publications

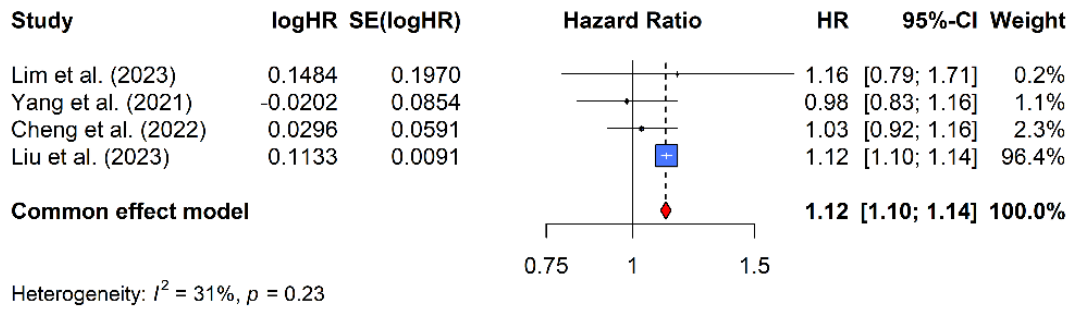
1. **Tang, H. W.,** Voon, F. L., & Sim, E. U. H. (2024). Association between incense burning and the risk of lung cancer in Asian population: Meta-Analysis of nine Case-Control studies. *Cancer Reports*, 7(12). <https://doi.org/10.1002/cnr2.70095>

Appendix B: Adjustments of the 11 cohort studies selected in the meta-analysis.

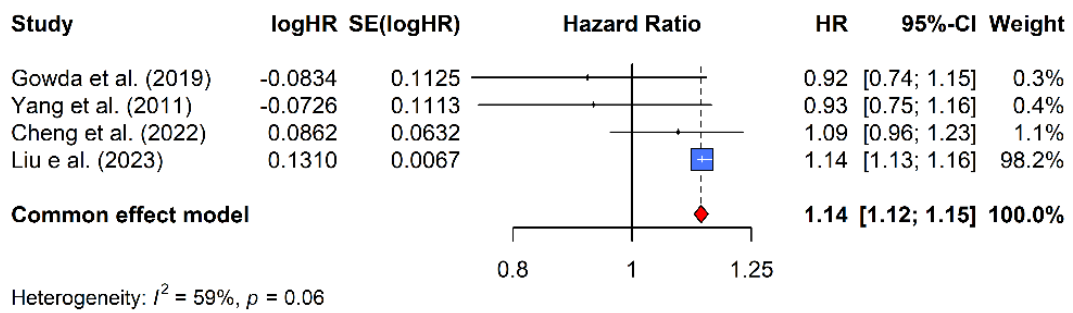
Selected study (Publication year)	Adjustment
Bai et al. (2019)	Age, sex, region (whether living in Toronto), census tract-level recent immigrants (arrived in the 5 years prior to census), unemployment rate, education and annual household income, urban residency and a north/south indicator
Cheng et al. (2022)	Sex, race/ethnicity, education, marital status, smoking intensity and duration, family history of lung cancer, occupation, neighbourhood socioeconomic status, nonsteroidal anti-inflammatory drug use, body mass index, drinking, physical activity, energy intake, red meat intake, and processed meat intake with age at cohort entry as the stratum variable
Eckel et al. (2016)	Age, sex, race/ethnicity, marital status, education index, SES, RUCA, distance to primary interstate highway, distance to primary US and State highways, histology at diagnosis, month of diagnosis, year of diagnosis, and initial treatment
Eum et al. (2022)	Age (1 year age categories with 90+ years old as one category), sex (male, female), race (White, non-White), ZIP code and adjusted for ZIP code- and state-level socio-economic status (SES) by including the two SES variables as covariates
Gowda et al. (2019)	Age at baseline, race, BMI, US region, history of emphysema, history of asthma and neighbourhood socioeconomic status
Huang et al. (2023)	Age, sex, BMI, level of education, income, occupational exposure, physical exercise and status of marital, smoking and drinking
Lim et al. (2019)	Age, sex, and location, as strata; for race, body mass index, education, smoking, diet, and marital status, at individual level; and for median income and percentage with high school education at census-tract level
Lim et al. (2023)	Smoking status and socioeconomic status

Liu et al. (2023)	Sex, race (Black/White/Other), Medicaid eligibility (yes/no), temperature, population density, % Black population, % American Indian and Alaska Native population, % Asian population, % Two or More Races population, % Native Hawaiian and Other Pacific Islander population, % Hispanic population, % population using automobile to transport, % population receiving less than high school education, % population above 65 years of age living below the poverty line, median household income, % population living in rented houses or apartments, distance to the nearest hospital, % of Medicare enrollees having at least one ambulatory visit to a primary care clinician in a year, % of diabetic Medicare enrollees aged 65–75 having haemoglobin A1c test in a year, number of hospitals, number of medical doctors, number of hospital beds, NDVI, BMI, and smoking rate
Yang et al. (2021)	Age, sex, health insurance premium, employment, smoking status, alcohol consumption, physical activity, diet, BMI, obesity, disease history (hypertension, diabetes mellitus, and hyperlipidaemia), family history of disease (cancer, hypertension, and diabetes), medical use, district-level proportion of the elderly and completeness of high school education, gross regional domestic production, population size, and area type
Yorifuji & Kashima (2020)	Age, sex, examination year, hypertension, diabetes, effort to reduce salt intake, effort to consume more vegetable, alcohol consumption, current smoking status, regular exercise, height, body mass index, and total cholesterol

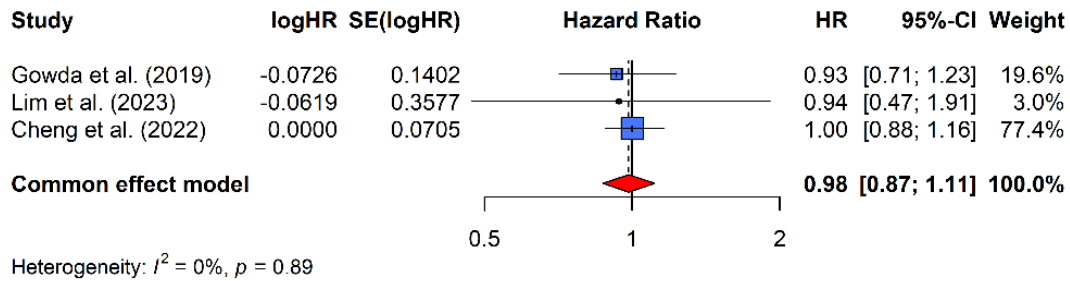
Appendix C: Association between NO₂ exposure and LC risk in males.



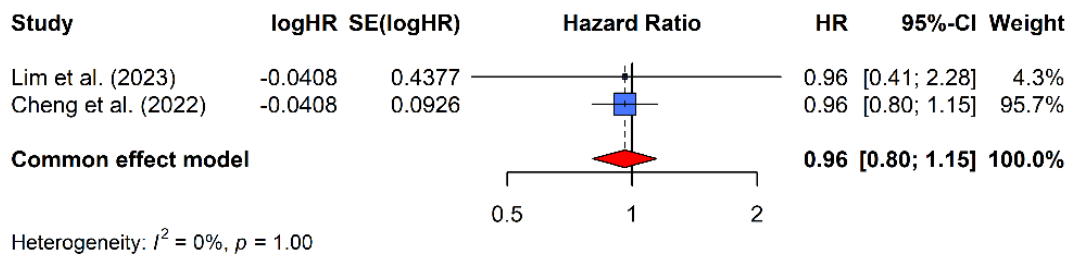
Appendix D: Association between NO₂ exposure and LC risk in females.



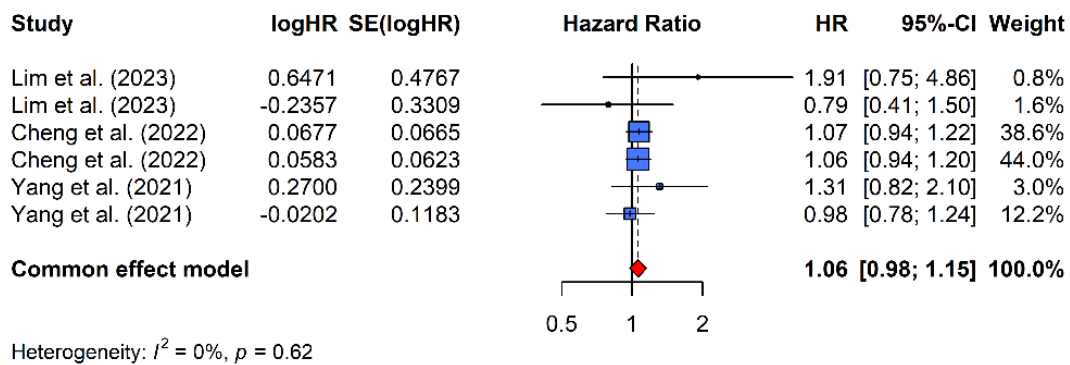
Appendix E: Subgroup analysis of HR for NO₂ exposure and LC risk by histology type of adenocarcinoma.



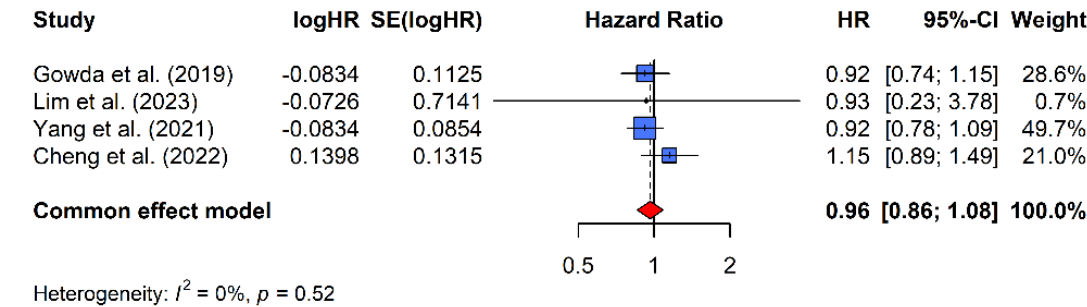
Appendix F: Subgroup analysis of HR for NO₂ exposure and lung cancer risk by histology type of squamous cell carcinoma.



Appendix G: Effect of NO₂ exposure on the risk of LC among smokers.



Appendix H: Effect of NO₂ exposure on the risk of LC among non-smokers.



Appendix I: Top GO terms identified in the enrichment analysis.

ID	Description	GeneRatio	BgRatio	RichFactor	FoldEnrichment	zScore	pvalue	p.adjust	qvalue	geneID	Count	Ontology
GO:0097237	cellular response to toxic substance	18/63	135/18886	0.13333333	30.49959839	22.70564734	3.39E-22	9.57E-19	6.02E-19	213/847/2880/2944/2950/2952/2603/44259/4353/4504/1728/5743/6647/6648/7124/7173/84203/7296	18	BP
GO:0096899	cellular oxidant detoxification	19/63	98/18886	0.16161632	36.98021017	23.77638298	3.27E-21	3.55E-18	2.23E-18	213/847/2880/2950/2952/2603/44259/4353/4504/1728/5743/6647/6648/7173/84203/7296	16	BP
GO:1990740	cellular detoxification	17/63	125/18886	0.130	31.10969236	22.77861415	3.77E-21	3.55E-18	2.23E-18	213/847/2880/2944/2950/2952/2603/44259/4353/4504/1728/5743/6647/6648/7173/84203/7296	17	BP
GO:0006706	response to toxic substance	20/63	270/18886	0.074074074	16.94422133	17.48467878	2.07E-19	1.46E-16	9.20E-17	213/847/2880/2944/2950/2952/2603/44259/4353/4504/1728/5743/6647/6648/7173/84203/7296	20	BP
GO:0098754	detoxification	17/63	167/18886	0.101796407	23.28562153	19.16742157	6.08E-19	3.43E-16	2.16E-16	213/847/2880/2944/2950/2952/2603/44259/4353/4504/1728/5743/6647/6648/7173/84203/7296	17	BP
GO:0032496	response to lipopolysaccharide	20/63	354/18886	0.056407175	12.92350864	15.05717746	4.25E-17	2.08E-14	1.26E-14	6347/1437/3576/2048/50843/2950/3586/3596/3553/3569/4353/1728/5743/3878/6403/6648/7054/7124/7173/133/7412	20	BP
GO:0002237	response to molecule of bacterial origin	20/63	375/18886	0.05333333	12.19983906	14.51551081	1.30E-16	5.23E-14	3.29E-14	6347/1437/3576/2048/50843/2950/3586/3596/3553/3569/4353/1728/5743/3878/6403/6648/7054/7124/7173/133/7412	20	BP
GO:0072593	reactive oxygen species metabolic process	17/63	242/18886	0.070247934	16.09900329	15.6329181	3.40E-16	1.20E-13	7.53E-14	664/847/875/1401/2305/2950/4353/4504/79400/1728/5743/3878/6403/6648/7124/7173	17	BP
GO:0006979	response to oxidative stress	19/63	405/18886	0.04891358	10.73124018	13.11734602	8.59E-15	2.69E-12	1.69E-12	388/664/847/139/189/2880/2950/140/3569/2603/44259/4353/4504/1728/4521/1089/15743/6647/6648/7173	19	BP
GO:0050900	leukocyte migration	18/63	404/18886	0.04454455	10.19189748	12.37425772	1.16E-13	3.27E-11	2.05E-11	6347/6352/3576/2321/3162/3383/3586/3553/3569/5025/5228/7943/5780/3878/6403/6647/7124/7412	18	BP
GO:0034774	secretory granule lumen	07/64	324/19960	0.021804938	5.133744856	4.876791619	0.000432715	0.032960979	0.027218231	213/302/847/2335/2950/3320/4353	7	CC
GO:0060205	cytoplasmic vesicle lumen	07/64	329/19960	0.021769996	5.055724427	4.822338987	0.000474117	0.032960979	0.027218231	213/302/847/2335/2950/3320/4353	7	CC
GO:0031583	vesicle lumen	07/64	330/19960	0.021212121	5.040484044	4.811341185	0.00046795	0.032960979	0.027218231	213/302/847/2335/2950/3320/4353	7	CC
GO:0031586	organelle outer membrane	06/64	252/19960	0.023899524	5.65796372	4.837103515	0.000616959	0.032960979	0.027218231	27113/664/3162/4259/4504/5743	6	CC
GO:0013867	outer membrane	06/64	254/19960	0.023622647	5.613048369	4.810056364	0.000710366	0.032960979	0.027218231	27113/664/3162/4259/4504/5743	6	CC
GO:0042470	melanosome	04/64	112/19960	0.035714286	8.468284508	5.164670982	0.01283337	0.03954215	0.02682774	302/3320/3309/7054	4	CC
GO:0048770	pigment granule	04/64	112/19960	0.035714286	8.468384508	5.164670982	0.01283337	0.03954215	0.02682774	302/3320/3309/7054	4	CC
GO:0045121	membrane raft	06/64	253/19960	0.020477816	4.865916054	4.33373196	0.01481909	0.03954215	0.02682774	302/7430/3383/5743/7124/7133	6	CC
GO:0086857	membrane microdomain	06/64	253/19960	0.020238983	4.832829782	4.321688036	0.01513963	0.03954215	0.02682774	302/7430/3383/5743/7124/7133	6	CC
GO:0016209	antioxidant activity	16/63	86/18737	0.186046512	41.99943962	25.1993398	3.60E-22	1.19E-19	9.55E-20	213/847/2880/2950/2952/2603/44259/4353/4504/1728/5743/6647/6648/7173/84203/7296	16	MF
GO:0004601	peroxidase activity	10/63	57/18737	0.175438596	39.60473473	19.47067749	6.06E-14	9.63E-12	7.74E-12	847/2880/2950/2952/2603/44259/4353/5743/7173/7296	10	MF
GO:0016994	peroxidase activity, acting on peroxide as acceptor	10/63	58/18737	0.169491235	38.26220135	19.12244023	8.76E-14	9.63E-12	7.74E-12	847/2880/2950/2952/2603/44259/4353/5743/7173/7296	10	MF
GO:0005125	cytokine activity	10/63	238/18737	0.042016807	9.48517961	6.787518941	9.78E-08	8.07E-06	6.49E-06	6347/6352/1437/3576/3586/3596/3553/3569/7124	10	MF
GO:0005126	cytokine receptor binding	10/63	277/18737	0.036101083	8.149710766	7.996574868	3.99E-07	2.63E-05	2.12E-05	6347/6352/1437/3576/3586/3596/3553/3569/5228/7124	10	MF
GO:0004602	glutathione peroxidase activity	04/63	23/18737	0.17951843	39.26034573	12.246754	2.97E-06	0.000157007	0.000126095	2880/2950/2952/4259	4	MF
GO:0020077	home binding	07/63	143/18737	0.048951049	11.00051186	8.847357972	3.33E-06	0.000157007	0.000126095	847/875/3162/4353/79400/5743/7173	7	MF
GO:0046006	tetrapyrrole binding	07/63	153/18737	0.045751634	10.32829557	7.728048179	5.21E-06	0.000211225	0.00011316	847/875/3162/4353/79400/5743/7173	7	MF
GO:0043964	glutathione transferase activity	04/63	27/18737	0.148148148	33.44399622	11.23306574	5.81E-06	0.000211225	0.00011316	2944/2950/2952/4259	4	MF
GO:0019525	oxygen binding	04/63	34/18737	0.137647059	26.58649517	9.940703948	1.59E-05	0.000495046	0.00003762	213/875/6648/7054	4	MF

Appendix J: Top 10 enriched KEGG pathways identified in the analysis.

category	subcategory	ID	Description	GeneRatio	BgRatio	RichFactor	FoldEnrichment	zScore	pvalue	p.adjust	qvalue	geneID	Count
Human Diseases	Cardiovascular disease	hsa05418	Fluid shear stress and atherosclerosis	13/62	142/9397	0.091549296	13.47502472	12.59865307	5.43E-12	1.11E-09	7.14E-10	6347/2944/2950/2952/3162/3320/3383/3553/4259/1728/3877/124/7412	13
Human Diseases	Infectious disease: parasitic	hsa04144	Malaria	5/62	50/9397	0.18	27.2818129	15.18487016	2.63E-11	1.68E-09	1.75E-09	6347/3576/3383/3553/3569/6403/7124/7412	9
Human Diseases	Cardiovascular disease	hsa05417	Lipid and atherosclerosis	13/62	216/9397	0.060181585	9.84128399	1.07E-09	7.29E-08	4.71E-08	6347/6352/3576/3320/3309/3383/3553/3569/3878/6403/6648/7124/7412	13	
Environmental Information Processing	Signal transduction	hsa04668	TNF signaling pathway	10/62	119/9397	0.084030613	12.73651396	10.50015244	4.47E-09	2.28E-07	1.47E-07	6347/6352/1437/3583/3553/3569/5743/7124/7133/7412	10
Organismal Systems	Immune system	hsa04667	IL-12 signaling pathway	5/62	59/9397	0.094738642	14.35871363	10.66471952	9.80E-09	3.23E-07	2.15E-07	6347/1437/3576/3320/3309/3553/3569/5743/7124	9
Human Diseases	Immune disease	hsa05323	Rheumatoid arthritis	5/62	59/9397	0.094738642	14.35871363	10.66471952	9.80E-09	3.23E-07	2.15E-07	6347/6352/1437/3576/3321/3383/3553/3569/7124	10
Human Diseases	Infectious disease: parasitic	hsa05143	African trypanosomiasis	6/62	27/9397	0.162182162	24.57802964	11.71064012	1.28E-07	3.72E-06	2.40E-06	3383/3586/3553/3569/7124/7412	6
Human Diseases	Endocrine and metabolic disease	hsa04933	ACE-RAGE signaling pathway in diabetic complications	5/62	101/9397	0.076079521	12.05511019	9.66185782	2.82E-07	7.19E-06	4.84E-06	6347/3576/2335/3383/3553/3569/7124/7412	8
Human Diseases	Infectious disease: bacterial	hsa05135	Yersinia infection	6/62	138/9397	0.05797014	8.78634876	7.50933807	3.06E-06	6.65E-05	4.29E-05	6347/875/2335/3586/3553/3569/3877/7124	8
Environmental Information Processing	Signaling molecules and interaction	hsa04060	Cytokine-cytokine receptor interaction	11/62	288/9397	0.036912752	5.58466334	6.56885380	3.20E-06	6.65E-05	4.29E-05	6347/6352/1437/3576/3586/3596/3553/3569/7124/7412	11