UNIVERSITY OF EAST ANGLIA

Treatment Selection in Pulmonary-Critical Care Medicine

A Dissertation Submitted in Satisfaction of the Requirements
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in

Medicine

by

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The critical analysis of this thesis, including footnotes, endnotes, abstract, and bibliography, comprises 19842 words.

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The Dissertation of Tyler Pitre is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of East Anglia

October 1, 2025

DEDICATION

I would like to first dedicate this to Dr Dena Zeraatkar. I have no doubt in my mind that nothing could have been accomplished without you. From my very first research endeavour, you were the most essential ingredient. I would also like to dedicate this to my late grandfather, Amos Carrier, who taught me about the value of hard work and dedication, for which I will be eternally grateful. Lastly, I would be nowhere without my mother Tammy Carrier and father, Arthur Lapointe, thank you for always making me feel I could do anything.

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LIST OF ABBREVIATIONS

AHRF: Acute Hypoxemic Respiratory Failure

ARDS: Acute Respiratory Distress Syndrome

ATS: American Thoracic Society

CAP: Community-Acquired Pneumonia

COPD: Chronic Obstructive Pulmonary Disease

CPAP: Continuous Positive Airway Pressure

CRP: C-reactive Protein

CURB-65: Confusion, Urea, Respiratory Rate, Blood Pressure, Age ≥65 – A scoring system to assess pneumonia severity.

ECMO: Extracorporeal Membrane Oxygenation

ED: Emergency Department

FEV1: Forced Expiratory Volume in 1 Second

fHP: Fibrotic Hypersensitivity Pneumonitis

fILD: Fibrotic Interstitial Lung Disease

FVC: Forced Vital Capacity

GOLD: Global Initiative for Chronic Obstructive Lung Disease

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HAT: Hydrocortisone-Ascorbic Acid-Thiamine

HFNC: High-Flow Nasal Cannula

I^2: I-squared

ICEMAN: Instrument to assess the Credibility of Effect Modification Analyses

ICS: Inhaled Corticosteroids

ICU: Intensive Care Unit

ILD: Interstitial Lung Disease

IMV: Invasive Mechanical Ventilation

IPD: Individual Patient Data

IPF: Idiopathic Pulmonary Fibrosis

LTOT: Long-Term Oxygen Therapy

MD: Mean Difference

NIPPV: Non-Invasive Positive Pressure Ventilation

NMA: Network Meta-Analysis

NSIP: Non-Specific Interstitial Pneumonia

OR: Odds Ratio

PaCO2: Partial Pressure of Carbon Dioxide in Arterial Blood

PaO2/FiO2: Partial Pressure of Oxygen to Fraction of Inspired Oxygen Ratio

PICO: Patient, Intervention, Comparator, Outcome

PSI: Pneumonia Severity Index

RCT: Randomised Controlled Trial

REMAP-CAP: Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia

REML: Restricted Maximum Likelihood

RoB: Risk of Bias

RoB 2.0: Risk of Bias 2.0

ROBINS-I: Risk Of Bias In Non-randomised Studies of Interventions

RR: Relative Risk

SCCM: Society of Critical Care Medicine

SGRQ: St. George's Respiratory Questionnaire

SOT: Standard Oxygen Therapy

SSc-ILD: Systemic Sclerosis-Associated Interstitial Lung Disease

Tau^2: Tau-squared

TSA: Trial Sequential Analysis

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SUBMITTED PUBLICATIONS

1. **Pitre T**, Abbasi S, Su J, Mah J, Zeraatkar D. Home high flow nasal cannula for chronic hypercapnic respiratory failure in COPD: A systematic review and meta-analysis. Respir Med. 2023 Nov-Dec;219:107420. doi: 10.1016/j.rmed.2023.107420. Epub 2023 Oct 5. PMID: 37804997.[1]
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8. **Pitre T**, Drover K, Chaudhuri D, Zeraaktkar D, Menon K, Gershengorn HB, Jayaprakash N, Spencer-Segal JL, Pastores SM, Nei AM, Annane D, Rochwerg B. Corticosteroids in Sepsis and Septic Shock: A Systematic Review, Pairwise, and Dose-Response Meta-Analysis. Crit Care Explor. 2024 Jan 19;6(1):e1000. doi: 10.1097/CCE.0000000000001000. PMID: 38250247; PMCID: PMC10798738.[8]
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STATEMENT ON PRIOR SUBMISSION AND JOINT WORK

For all ten publications submitted as part of this PhD thesis by publication, I, Dr Tyler Pitre, served as the lead author. I led the design of each study, including the formulation of research questions and the development of PICO frameworks. I was responsible for the conduct of the research, overseeing literature searches, data extraction, and risk of bias assessments. I performed the statistical analyses, including pairwise, network, dose-response, and Bayesian meta-analyses, and synthesized the findings to derive clinical and methodological insights. Additionally, I drafted the manuscripts, managed the peer-review process, and prepared each paper for publication. Co-authors provided valuable input, including protocol review, data interpretation, and manuscript editing, but my contributions were central to each study's conceptualization, execution, analysis, and dissemination.

No part of this thesis has been previously submitted for a degree at this or any other university.

ABSTRACT

This PhD by publication applies advanced evidence synthesis to address clinical uncertainty in pulmonary and critical care medicine, focusing on heterogeneity in chronic obstructive pulmonary disease, interstitial lung disease, acute hypoxemic respiratory failure and sepsis. It investigates non-invasive oxygenation strategies (high-flow nasal cannula, non-invasive ventilation, conventional oxygen) and corticosteroids (inhaled, systemic) across diverse respiratory contexts to enhance clinical evidence precision.

Through systematic reviews and meta-analyses published in journals like *Annals of ATS, CHEST, Intensive Care Medicine* and *The Lancet Respiratory Medicine,* the research employs pairwise, network and dose-response meta-analytic techniques. Key findings include high-flow nasal cannula reducing COPD exacerbations, helmet continuous positive airway pressure lowering mortality in acute settings and corticosteroids showing limited efficacy in fibrotic interstitial lung disease but dose-dependent benefits in severe COVID-19, sepsis and community-acquired pneumonia. Moderate-certainty evidence supports non-invasive ventilation for preventing hypoxemia during intubation and corticosteroids for reducing mortality in severe pneumonia and sepsis.

Informing the Society of Critical Care Medicine's 2024 guidelines, the thesis highlights practical impacts despite challenges like conflicting trial results (e.g., REMAP-CAP). It demonstrates advanced meta-analytic methods' utility in synthesizing heterogeneous evidence, laying a foundation for future biomarker-driven and protocol-standardised research to advance evidence-based, patient-centred care.

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Word count: 195

Introduction

Heterogeneity in Pulmonary and Critical Care Medicine

Pulmonary and critical care medicine encompasses a wide range of acute and chronic diseases marked by substantial variability in presentation, progression and treatment response. This heterogeneity is both a defining feature of the field and a persistent source of uncertainty in clinical practice and evidence generation.[11,12] Across conditions such as chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), community-acquired pneumonia (CAP) and acute hypoxemic respiratory failure (AHRF), patient-level, disease-level and treatment-related variability complicate the evaluation and implementation of therapeutic strategies.[12]

At the disease level, diagnostic categories often mask considerable biological and clinical diversity. For example, COPD encompasses multiple phenotypes with differing patterns of inflammation, exacerbation frequency and lung function decline.[13] Similarly, acute respiratory failure may result from a variety of underlying aetiologies—including viral and bacterial pneumonia, sepsis, or aspiration—each with distinct implications for treatment.[9] At the patient level, comorbid conditions, baseline respiratory function and prior treatments contribute to variability in both prognosis and therapeutic response. These factors create a heterogeneous treatment landscape in which interventions rarely have uniform effects across all patient subgroups.

This complexity is particularly evident in the use of non-invasive oxygenation and ventilatory strategies, which are now widely employed across outpatient, ward and intensive care settings.[14] Modalities such as high-flow nasal cannula (HFNC), non-invasive positive pressure ventilation (NIPPV) and conventional oxygen therapy are applied to patients with a range of clinical conditions and levels of acuity. However, evidence regarding their relative effectiveness is often conflicting or context-dependent.[14] Trials comparing these modalities frequently differ in terms of patient selection criteria, disease severity, interfaces used and timing of intervention. Moreover, clinical outcomes are influenced by a range of contextual factors—

including staffing ratios, sedation protocols and provider expertise—which further limit the generalisability of trial findings.[15]

In acute settings, such as the management of hypoxemic respiratory failure or preoxygenation before intubation, these issues are particularly pronounced. Trials in these areas often enrol heterogeneous populations and report composite outcomes that are variably defined.[16] As a result, meta-analyses attempting to synthesise these data frequently encounter problems of inconsistency, intransitivity and imprecision.[17,18] These limitations are not simply statistical artefacts but reflect real clinical variation that is difficult to reconcile using standard evidence synthesis approaches.

Pharmacologic interventions in respiratory and critical care face similar challenges. Corticosteroids are widely used across a spectrum of indications—including COPD, ILD, pneumonia, COVID-19 and sepsis—despite ongoing uncertainty regarding optimal dosing, timing and patient selection. Although corticosteroids are biologically plausible as immunomodulatory agents, their pleiotropic effects and the diversity of underlying disease processes have led to divergent findings in the literature.[19] Trials in community-acquired pneumonia, for instance, have reported variable effects on mortality, length of stay and mechanical ventilation requirements. These discrepancies are often attributed to differences in baseline disease severity, co-interventions and definitions of clinical endpoints.[20,21]

In the context of emerging diseases such as COVID-19, the heterogeneity of patient populations and rapid evolution of care standards have further complicated efforts to determine the most effective corticosteroid regimens. While some trials have shown the benefits of low-dose dexamethasone in critically ill patients, others have questioned whether higher doses confer additional advantages or pose increased risks.[22-24] Similar uncertainties exist in the management of sepsis and non-COVID pneumonia, where corticosteroid trials have produced inconsistent findings, and concerns about adverse events remain prominent.[25]

Despite these complexities, corticosteroids remain embedded in clinical guidelines across multiple conditions, often without a clear understanding of which patients benefit most. This

reflects a broader tension in the field: the need to make therapeutic decisions in the face of incomplete or heterogeneous evidence.

These examples illustrate a central methodological problem in respiratory and critical care research: the traditional tools of evidence appraisal—randomised controlled trials and pairwise meta-analyses—often fail to adequately account for the diversity of clinical presentations and treatment contexts. The result is a body of literature that is large but often inconclusive, with limited applicability to complex, real-world patient populations.

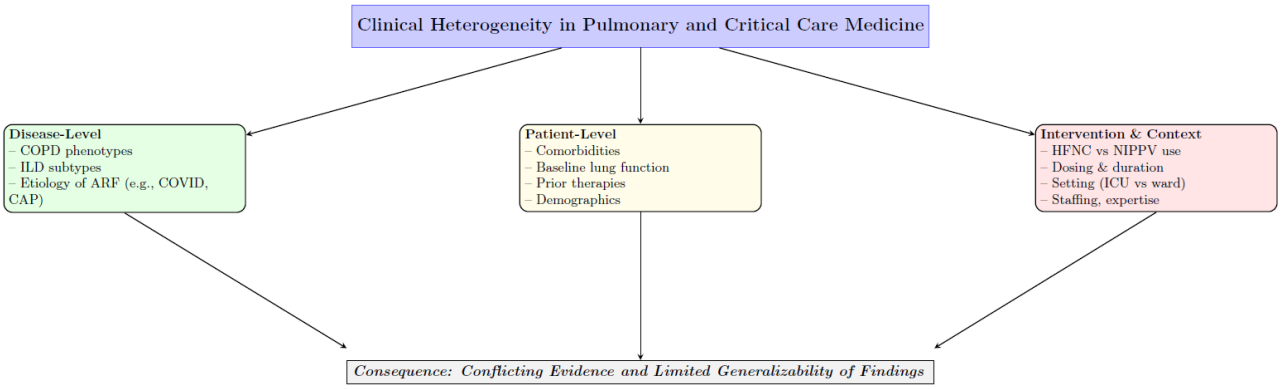

Figure 1. Sources of heterogeneity in pulmonary critical care

Methodological Innovation in Evidence Synthesis

High-quality clinical practice guidelines are built on rigorous evidence synthesis, typically structured around the Patient, Intervention, Comparator and Outcome (PICO) framework.[26,27] This structure ensures that the research question is clinically relevant and that outcomes reflect patient-important priorities. Systematic reviews use this framework to identify, appraise and synthesise evidence from relevant studies, integrating both narrative and quantitative approaches depending on the complexity of the data and the heterogeneity across trials.[28]

While randomised controlled trials remain the gold standard for determining efficacy, their external validity can be limited. Meta-analysis thus plays a crucial role in pooling data across trials to enhance precision and generalisability. However, traditional approaches to meta-

analysis are increasingly challenged by the presence of multiple interventions, variation in treatment doses and significant heterogeneity across patient populations. These limitations have motivated the development and refinement of more advanced methods for evidence synthesis.

Table 1. Methods and strengths of strategies for meta-analysis

Challenge	Method	Strength
Binary comparison (A vs B)	Pairwise meta-analysis	Straightforward, intuitive
No head-to-head trials	Network meta-analysis	Enables indirect comparisons
Unclear dose effects	Dose-response meta-analysis	Models gradient of effect by dose
Variability across subgroups	Meta-regression	Identifies effect modifiers
Conflicting estimates	Sensitivity/subgroup analysis	Tests robustness, identifies sources of inconsistency

Pairwise meta-analysis remains the most used form of synthesis, particularly when direct comparisons between two interventions are available. However, its utility is limited when multiple treatments exist or when variability in dose and population characteristics precludes meaningful aggregation. In such cases, pairwise analysis may obscure important differences or produce misleading summary estimates.[29,30]

Dose-response meta-analysis offers an approach to address variability in treatment intensity by modelling the relationship between different levels of exposure (e.g., drug dose or duration) and clinical outcomes. This method is particularly useful in assessing pharmacologic interventions such as corticosteroids, where the magnitude of treatment effect may vary by dose. By accounting for this variation, dose-response meta-analysis can refine treatment recommendations and reduce unexplained heterogeneity.[31]

Network meta-analysis (NMA) provides a more comprehensive solution when multiple interventions are of interest, allowing for both direct and indirect comparisons within a single analytical framework. NMA can estimate the relative effectiveness of treatments that have not been compared directly in head-to-head trials, enabling more complete assessments of the evidence base. However, NMA relies on key assumptions of transitivity (i.e., comparability of populations across trials) and coherence (i.e., consistency between direct and indirect estimates). Violations of these assumptions can undermine the validity of the analysis and must be rigorously assessed.[30,32-34] Lastly, NMA can be done using either a frequentist or a Bayesian approach. Although studies have generally indicated the results are comparable, there are advantages and disadvantages of each approach.[35]

Table 2. Comparing and contrasting benefits and disadvantages of Bayesian and Frequentist NMA

Feature	**Bayesian NMA**	**Frequentist NMA**
Core Approach	Uses prior distributions and probability for inference	Relies on long-run frequency properties of estimators
Meta-regression	Fully supported	Not available with current standard methods
Interpretation	Probabilistic (e.g., "Treatment A has 70% chance of being best")	Based on confidence intervals and p-values
Model Flexibility	Easily handles complex models (multi-arm, missing data)	Limited to simpler model structures
Computation	Slower, requires MCMC	Faster, based on closed-form or iterative methods

Assessment of heterogeneity remains critical across all synthesis methods. Quantitative measures such as the I^2 and Tau^2 statistics are useful but limited.[36] These metrics do not capture clinical heterogeneity related to patient populations, intervention protocols, or outcome definitions. As such, a combined approach using both quantitative assessment and

qualitative appraisal of study characteristics is necessary. Techniques such as subgroup analysis, meta-regression and sensitivity analyses further support the identification of effect modifiers and help tailor conclusions to specific clinical contexts.

Evidence Synthesis as Clinical Translation

The purpose of evidence synthesis extends beyond statistical aggregation to the generation of insights that apply to patient care. In complex fields such as respiratory and critical care, advanced synthesis methods provide a means of navigating uncertainty and supporting the development of practice guidelines that are both evidence-based and contextually appropriate.[37]

In the absence of comprehensive head-to-head trials, network meta-analysis fills a critical gap by enabling indirect comparisons and supporting treatment rankings. This is particularly relevant in areas where multiple oxygenation or pharmacologic strategies are available but rarely compared directly. Similarly, dose-response analysis informs dosing decisions by modelling the relationship between treatment intensity and clinical outcomes, helping to avoid both under-treatment and excessive exposure.

More broadly, these tools contribute to resolving ambiguity in the existing literature, particularly where previous studies have yielded conflicting results. By structuring heterogeneity and facilitating the exploration of subgroups and treatment interactions, advanced meta-analytic approaches enhance the clarity and applicability of evidence. They also support health systems and guideline panels in prioritizing interventions and resource allocation.

Aims and Objectives of the Thesis

This thesis aims to demonstrate how advanced methods of evidence synthesis can be used to improve the precision, interpretability and clinical utility of research findings in pulmonary and critical care medicine. Specifically, the thesis focuses on two commonly used but variably applied interventions:

1. **Non-invasive oxygenation strategies**, including HFNC, NIPPV and conventional oxygen, across both outpatient and acute care settings.
2. **Corticosteroids**, including inhaled and systemic formulations, across a range of conditions including COPD, ILD, CAP, COVID-19 and sepsis.

The objectives of the thesis are:

- To apply pairwise, network and dose-response meta-analytic methods to synthesise evidence on the effectiveness and safety of non-invasive oxygenation modalities and corticosteroids in heterogeneous respiratory populations.
- To evaluate the capacity of these methods to manage clinical and methodological heterogeneity, including the identification of subgroups, exploration of dose-response relationships and resolution of inconsistent findings across trials.
- To illustrate how these methods inform clinical practice guidelines, particularly in contexts where head-to-head evidence is lacking and multiple therapeutic options are available.
- To critically assess the limitations and assumptions of each methodological approach, with attention to their implications for validity, certainty of evidence and applicability to real-world clinical scenarios.

By pursuing these objectives, this thesis contributes to the evolving methodology of evidence synthesis and its role in supporting high-quality, patient-centred care in pulmonary and critical care medicine.

Section 1: Non-Invasive Oxygenation Modalities

Chapter 1: Home High-Flow Nasal Cannula for Chronic Hypercapnic Respiratory Failure in COPD: A Systematic Review and Meta-Analysis

Scientific question. In adults with stable chronic obstructive pulmonary disease (COPD) and chronic hypercapnic respiratory failure managed at home, does home high-flow nasal cannula (HFNC)—compared with standard care (usually long-term oxygen therapy [LTOT] ± usual pharmacotherapy)—reduce acute exacerbations and improve other patient-important outcomes?

PICO. P: Adults with stable hypercapnic COPD at home. I: Home HFNC. C: Standard care (usually LTOT ± usual care; trials did not use long-term non-invasive positive-pressure ventilation, NIPPV, as the comparator). O (primary): Fewer COPD exacerbations. O (secondary): Hospitalisations, all-cause mortality, health-related quality of life (St George's Respiratory Questionnaire, SGRQ).

Links. Appendix 1A (protocol), 1B (published paper in *Respiratory Medicine*), 1C (supplementary tables/figures).

1.1 Introduction

The management of COPD with chronic hypercapnia remains a critical challenge in respiratory care.[38] While long-term NIPPV is an established therapy that improves outcomes in select patients, it is often limited by tolerability, resource requirements and variable implementation across health systems.[39,40] An alternative strategy—HFNC—has emerged as a potentially scalable and better-tolerated intervention, offering physiologic benefits such as improved oxygenation, reduced dead space and low levels of positive end-expiratory pressure.[41] However, the clinical effectiveness of home HFNC for stable hypercapnic COPD had not been systematically examined in terms of patient-centred outcomes.

This chapter addresses that gap by synthesizing the available evidence using pairwise meta-analysis—a foundational method in comparative effectiveness research. At the time of this analysis, all eligible trials had directly compared HFNC to standard care, making pairwise meta-analysis the appropriate method to estimate pooled treatment effects. Unlike network meta-analysis (explored in Chapter 2), the pairwise approach is grounded entirely in direct

comparisons, allowing for cleaner inference and avoiding the assumptions of transitivity and consistency that NMAs require.[30,34]

More broadly, this chapter represents an early step in my academic development: learning to apply core meta-analytic techniques with rigour, transparency and attention to clinical applicability. It also served as my introduction to key methodological tools that would become central to the rest of this thesis, including Grading of Recommendations Assessment, Development, and Evaluation" methodology (GRADE), risk of bias appraisal and modelling heterogeneity.

1.2 Meta-Analysis and Heterogeneity: A Reflection

This study also serves as a stepping stone in understanding heterogeneity. Heterogeneity in meta-analysis is often seen as a problem to overcome, but it is an inevitable consequence of including studies that differ in design, population, geography and care context. The very strength of meta-analysis lies in its ability to accommodate this heterogeneity and—when done well—to translate it into nuanced, generalisable insight.

By contrast, heterogeneity in single trials is more difficult to quantify and often underappreciated. Even 'homogeneous' trials may mask considerable variability in patient characteristics and contextual factors. Throughout this thesis, I have learned that meta-analysis serves not as a tool that simply averages effects but as a method for understanding variation. In this chapter, pairwise methods with only four trials provide scaffolding for the much more challenging cases later in this thesis. The analysis, published in *Respiratory Medicine*, evaluates outcomes including mortality, exacerbation, hospitalisations and quality of life.[1]

1.3 Summary of Results

This systematic review included four randomised controlled trials (RCTs) totalling 440 participants. All studies compared home HFNC with standard care (usually LTOT) over at least one month of follow-up. The patients were predominantly male, aged 67–75, with moderate-to-severe airflow limitation (FEV_1 26–45%) and mild-to-moderate hypercapnia.

Main Findings:

- **Acute Exacerbations**: HFNC probably reduces acute exacerbations compared to standard care (RR 0.77, 95% CI 0.66–0.89; moderate certainty), suggesting 69 fewer events per 1,000 patients.
- **Hospital Admissions**: HFNC may reduce hospitalisations (RR 0.87, 95% CI 0.69–1.09; low certainty), equivalent to 20 fewer admissions per 1,000.
- **All-Cause Mortality**: HFNC may not affect mortality (RR 1.22, 95% CI 0.64–2.35; low certainty); though, power was limited due to small sample sizes.
- **Health-Related Quality of Life (SGRQ)**: HFNC may improve quality of life (mean difference –8.1 units; 95% CI –13.3 to –2.95); although, heterogeneity was substantial (I^2 = 70.8%).

No credible subgroup effects were detected based on PaCO2, FEV1, or risk of bias. The risk of bias was moderate across most outcomes due to a lack of blinding and attrition.

1.3 Discussion

1.3.1 Methodological Insights and Academic Development

This study helped me internalise two critical lessons in evidence synthesis:

First, pairwise meta-analysis, when applied rigorously, can yield clinically meaningful insights even from a small evidence base. It avoids the complexity of indirect comparisons and focuses squarely on what is known. The use of restricted maximum likelihood (REML) random-effects modelling, GRADE assessments and absolute effect estimates per 1,000 patients sharpened my ability to translate statistical findings into clinical implications—skills I carry forward into more advanced methods in later chapters.

Second, this analysis deepened my appreciation of heterogeneity as a feature, not a flaw. Even in this small sample, we saw variations in HFNC settings, follow-up duration and patient profiles. Yet, instead of discarding these differences, pairwise synthesis allowed me to quantify

and contextualise them. Of course, the benefit of having fewer studies helped me learn this lesson.

1.3.2 Clinical Implications

The findings suggest that HFNC may be a viable outpatient strategy for select patients with stable hypercapnic COPD. The reduction in exacerbations, an outcome closely tied to future decline, hospitalisation and mortality, is both statistically significant and clinically important. Improvements in SGRQ further suggest potential quality-of-life benefits. That said, uncertainty around mortality effects and hospitalisation risk, along with variability in HFNC implementation, warrant cautious interpretation.

Clinicians may consider HFNC as an option for patients who are intolerant of NIPPV or at high risk of exacerbation, but guidelines should await more robust evidence.

1.3.3 Research implications and Future Directions

The study highlights several priorities for future research:

- **Larger RCTs:** Larger RCTs with standardised HFNC protocols and longer follow-ups are needed to assess the durability of benefit and mortality impact.
- **Head-to-head:** Comparative trials of HFNC versus NIPPV could help determine relative effectiveness and guide therapy selection.
- **Subgroups**: Additional work is needed to explore which subgroups benefit most—an effort that may require IPD meta-analysis or adaptive trial designs.[42]

This chapter presents the first part of my section on non-invasive oxygenation strategies. The methodological simplicity of pairwise meta-analysis serves as a baseline for the more complex questions that follow—questions that require network meta-analysis (Chapters 2, 3, 4) and ultimately cross-domain synthesis (in the corticosteroid chapters).

Chapter 2: Home Respiratory Strategies in Patients With COPD With Chronic Hypercapnic Respiratory Failure

Scientific question. In adults with stable chronic obstructive pulmonary disease (COPD) and chronic hypercapnic respiratory failure managed at home, which strategy—non-invasive positive-pressure ventilation (NIPPV), high-flow nasal cannula (HFNC), or standard care—best reduces exacerbations and improves other patient-important outcomes?

PICO. P**:** Adults with stable hypercapnic COPD at home. I/C: NIPPV, HFNC, standard care. O (primary): Fewer COPD exacerbations. O (secondary): All-cause mortality, hospitalisations, health-related quality of life (St George's Respiratory Questionnaire, SGRQ).

Links. *Appendix 2A* (protocol), *2B* (published paper in *Respiratory Care*), *2C* (supplementary tables/figures),

2.1 Introduction

Building on the findings of Chapter 1, which established the potential of HFNC as an outpatient therapy for stable hypercapnic COPD, this chapter expands the scope of inquiry to compare HFNC with NIPPV and standard care in the same population. While Chapter 1 utilised pairwise meta-analysis to assess HFNC against standard care, the presence of multiple therapeutic options such as NIPPV, HFNC and standard care, necessitates a more advanced methodological approach: network meta-analysis. This method allows for both direct and indirect comparisons, providing a comprehensive framework to evaluate the relative effectiveness of these interventions across patient-important outcomes.[30]

Chronic hypercapnic respiratory failure in COPD is a debilitating condition associated with frequent exacerbations, hospitalisations and reduced quality of life.[38] NIPPV has long been the cornerstone of home-based respiratory support, with evidence supporting its role in reducing exacerbations and possibly mortality.[40] However, its practical challenges, including poor tolerability and complex implementation, have spurred interest in HFNC as a potentially more comfortable and scalable alternative. [41] Despite this, direct comparisons between NIPPV and HFNC are sparse, and prior systematic reviews have not fully addressed their comparative efficacy in a unified analytical framework.

This chapter presents a network meta-analysis that synthesises evidence from 24 randomised controlled trials to compare NIPPV, HFNC and standard care in adults with COPD and chronic hypercapnic respiratory failure. The analysis, published in *Respiratory Care*, evaluates outcomes including mortality, exacerbations, hospitalisations and quality of life.[2] By employing NMA, this study addresses the limitations of pairwise comparisons and provides a more nuanced understanding of treatment effects in a heterogeneous clinical context.

This work marks an important step in my academic development, transitioning from the foundational pairwise meta-analysis of Chapter 1 to the more complex NMA framework. It required mastering additional methodological considerations, such as assessing transitivity, coherence and network heterogeneity, while maintaining a focus on clinical applicability.[30,34,43] The study also underscores the thesis's broader aim: to leverage advanced evidence synthesis to navigate clinical uncertainty and inform patient-centred care in pulmonary and critical care medicine.

2.2 Network Meta-Analysis and Methodological Evolution

Network meta-analysis represents a significant evolution from the pairwise approach used in Chapter 1. While pairwise meta-analysis is well-suited for direct comparisons, it is limited when multiple interventions are available, and head-to-head trials are scarce. NMA overcomes this by integrating direct and indirect evidence within a single model, enabling the estimation of relative treatment effects even for interventions not compared directly in trials. This is particularly relevant in COPD, where NIPPV and HFNC have rarely been evaluated head-to-head, yet both are viable therapeutic options.[30]

The application of NMA in this study introduced new methodological challenges. Ensuring transitivity—i.e., that the populations, interventions and outcomes across trials are sufficiently comparable—required careful assessment of trial characteristics and baseline patient profiles.[43] Similarly, evaluating coherence—i.e., consistency between direct and indirect effect estimates—was critical to validate the model's findings. These considerations deepened my

understanding of evidence synthesis as a balance between statistical rigour and clinical judgment.

Heterogeneity, a central theme in this thesis, remained a key focus. While Chapter 1 explored heterogeneity through pairwise comparisons and subgroup analyses, NMA allowed for a more systematic exploration of variability across multiple interventions. By incorporating network geometry, P-score rankings and GRADE, this study provided a robust framework to quantify and contextualise heterogeneity, aligning with the thesis's objective to enhance the interpretability of evidence in complex clinical settings.

2.3 Summary of Results

The network meta-analysis included 24 RCTs with 1,850 participants, comparing NIPPV, HFNC and standard care in adults with COPD and chronic hypercapnic respiratory failure. The trials predominantly enrolled male patients (61.3%), aged 61.8–75.1 years, with moderate-to-severe airflow limitation (FEV_1 23.4–35.2% predicted) and baseline PaCO2 ranging from 42.17 to 59 mm Hg. The median follow-up was 12 months. Most trials compared NIPPV to standard care (19 trials), with four trials comparing HFNC to standard care, one trial directly comparing NIPPV to HFNC and two trials comparing NIPPV to sham NIPPV.

Main Findings:

- **Mortality**: NIPPV may reduce the risk of death compared to standard care (relative risk [RR] 0.82, 95% CI 0.66–1.00; low certainty), suggesting 37 fewer deaths per 1,000 patients. HFNC had an uncertain effect on mortality (RR 1.20, 95% CI 0.63–2.28; very low certainty). Head-to-head comparisons between NIPPV and HFNC were inconclusive due to imprecision.
- **Exacerbations**: NIPPV probably reduces exacerbations compared to standard care (RR 0.71, 95% CI 0.58–0.87; moderate certainty), equivalent to 101 fewer events per 1,000. HFNC also probably reduces exacerbations (RR 0.77, 95% CI 0.68–0.88; moderate

certainty), corresponding to 80 fewer events per 1,000. No significant difference was observed between NIPPV and HFNC.

- **Hospitalisations**: HFNC may reduce hospitalisations compared to standard care (RR 0.87, 95% CI 0.69–1.09; low certainty), suggesting 20 fewer admissions per 1,000. NIPPV's effect on hospitalisations was less certain (RR 0.87, 95% CI 0.64–1.18; low certainty). Direct comparisons between NIPPV and HFNC were limited by sparse data.
- **Quality of Life (SGRQ)**: HFNC probably improves SGRQ scores compared to standard care (mean difference [MD] –7.01, 95% CI –12.27 to –1.77; moderate certainty), indicating a clinically meaningful improvement. NIPPV's effect on SGRQ was uncertain and not clinically significant (MD –3.81, 95% CI –10.00 to 3.23; low certainty). The comparison between NIPPV and HFNC was inconclusive (MD 3.22, 95% CI –4.18 to 10.61; very low certainty).

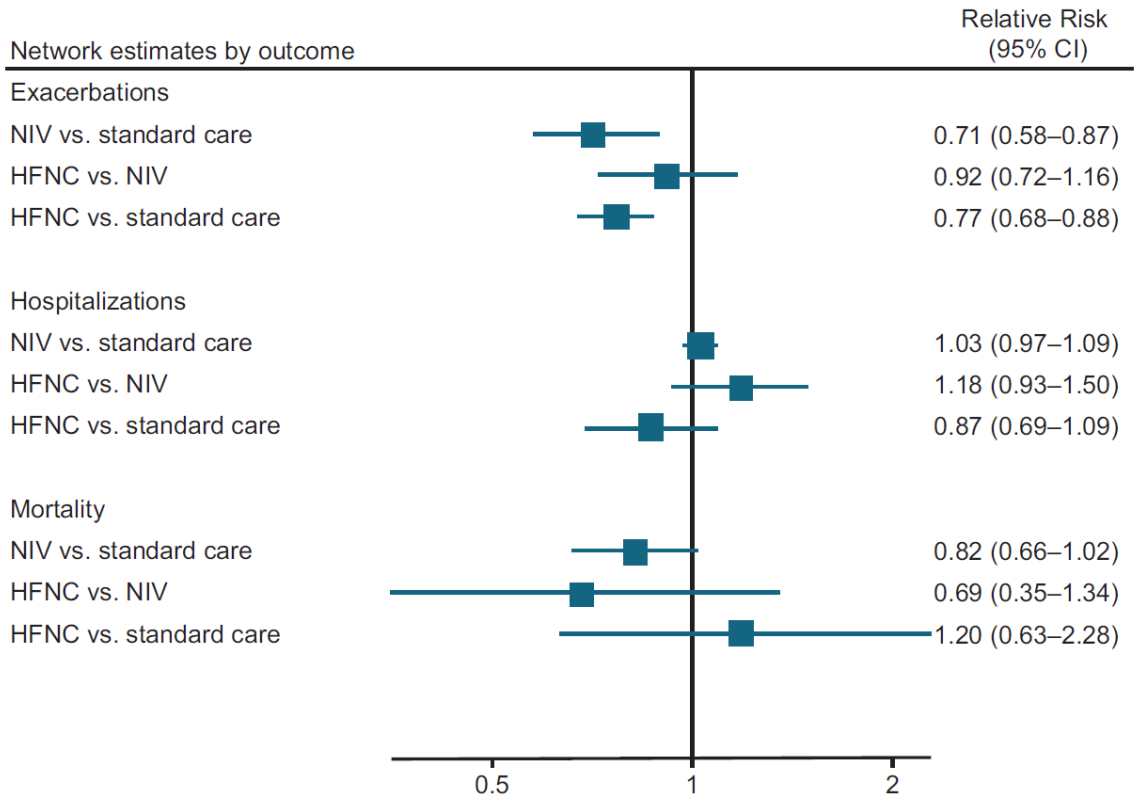

Figure 2. Network estimates for all comparisons across dichotomous outcomes

Risk of Bias and Heterogeneity: Most trials had a moderate to high risk of bias due to a lack of blinding and missing outcome data. Network heterogeneity was low for most outcomes, and no evidence of incoherence was detected in node-split models. Subgroup analyses found a low-credibility effect for NIPPV on mortality in low-risk-of-bias trials (RR 0.35, 95% CI 0.19–0.64) compared to high-risk-of-bias trials (RR 0.90, 95% CI 0.74–1.09).

2.4 Discussion

2.4.1 Methodological Insights and Academic Development

This study marked a significant milestone in my methodological journey, transitioning from the straightforward pairwise meta-analysis of Chapter 1 to the more sophisticated NMA framework. Mastering NMA required grappling with new concepts, such as network geometry, transitivity and coherence, which challenged me to think beyond direct comparisons and consider the interconnectedness of evidence. The use of tools like the *netmeta* package in R and GRADE for NMA enhanced my technical proficiency and underscored the importance of rigorous assumption-checking in complex analyses.[44]

The study also reinforced the value of heterogeneity as a lens for understanding clinical variation. While Chapter 2 highlighted heterogeneity in HFNC trials, this analysis extended that perspective to a broader network of interventions. By quantifying heterogeneity (e.g., via I^2 and Tau^2) and exploring it through subgroup analyses, I learned to balance statistical precision with clinical nuance—a skill that informs the subsequent chapters of this thesis. Furthermore, it opened new problems—namely how to interpret network-wide subgroup analyses. I did not attempt this interpretation in this particular analysis but highlighted it in the final chapter of this section.

2.4.2 Clinical Implications

The findings suggest that both NIPPV and HFNC are effective in reducing exacerbations in patients with COPD and chronic hypercapnic respiratory failure, with HFNC offering potential advantages in improving quality of life. NIPPV may confer a mortality benefit, particularly in studies with low risk of bias, but the evidence for HFNC's effect on mortality remains uncertain.

These results support the use of either modality as an outpatient strategy, with HFNC potentially serving as a more tolerable alternative for patients who struggle with NIPPV adherence.

Clinicians should consider patient preferences, tolerability and resource availability when selecting between NIPPV and HFNC. The lack of significant differences in exacerbation reduction between the two modalities suggests that HFNC could be a viable option in settings where NIPPV is impractical. However, the uncertainty around mortality and hospitalisation outcomes highlights the need for cautious interpretation and individualised decision-making.

2.4.3 Implications for Research

This study identifies several priorities for future research:

- **Head-to-Head Trials**: Larger RCTs directly comparing NIPPV and HFNC are needed to clarify their relative effects on mortality and hospitalisations, addressing the current reliance on indirect comparisons.
- **Subgroup Analyses**: Further exploration of patient subgroups (e.g., based on PaCO2, disease stability or comorbidities) could identify those most likely to benefit from each modality.
- **Standardised Protocols**: Variability in NIPPV and HFNC settings across trials underscores the need for standardised protocols to enhance comparability and generalisability.
- **Cost-Effectiveness**: Studies evaluating the cost-effectiveness of HFNC versus NIPPV could inform resource allocation and guideline development.

2.4.4 Next Steps in the Thesis Narrative

This chapter builds on the methodological foundation of Chapter 1 by introducing NMA as a tool to address complex treatment comparisons. It sets the stage for subsequent chapters, which will explore NMA in acute care settings (e.g., hypoxemic respiratory failure) and extend the synthesis framework to pharmacologic interventions (e.g., corticosteroids). By demonstrating the utility of NMA in navigating clinical heterogeneity, this study advances the

thesis's overarching aim: to enhance the precision and applicability of evidence synthesis in pulmonary and critical care medicine.

Chapter 3: Oxygenation Strategies in Acute Hypoxemic Respiratory Failure: A Network Meta-Analysis

Scientific question. In adults with acute hypoxemic respiratory failure (AHRF) managed without invasive ventilation, which strategy—helmet continuous positive airway pressure (CPAP), helmet bilevel ventilation, face-mask CPAP, face-mask non-invasive positive-pressure ventilation (NIPPV), high-flow nasal cannula (HFNC), or standard oxygen—best reduces mortality and the need for invasive mechanical ventilation (IMV) and improves other patient-important outcomes?

PICO. P: Adults with AHRF (ICU/ED; COVID-19 and non-COVID-19), not intubated. I/C: Helmet CPAP, helmet bilevel (NIPPV), face-mask CPAP, face-mask bilevel (NIPPV), HFNC, standard oxygen. O (primary): All-cause mortality; need for IMV. O (secondary): Hospital and ICU length of stay, ventilator-free days, patient comfort/intolerance.

Links. Appendix 3A (protocol), 3B (published paper in CHEST), 3C (supplementary tables/figures)

3.1 Introduction

Following the exploration of HFNC in stable chronic obstructive pulmonary disease (COPD) in Chapter 1 and the comparison of NIPPV and HFNC in chronic hypercapnic respiratory failure in Chapter 2, this chapter shifts focus to AHRF. AHRF, characterised by severe hypoxemia often due to pneumonia, acute respiratory distress syndrome (ARDS), or COVID-19, represents a critical challenge in intensive care settings.[45,46] Non-invasive oxygenation strategies, including HFNC, continuous positive airway pressure (CPAP) and bilevel ventilation, delivered via face mask or helmet interfaces, have emerged as alternatives to invasive mechanical ventilation (IMV). However, their comparative effectiveness remains uncertain, particularly regarding patient-important outcomes like mortality and the need for intubation.

This chapter presents a network meta-analysis published in *CHEST*, which synthesises evidence from 36 randomised controlled trials (RCTs) involving 7,046 patients to compare six non-invasive oxygenation strategies—standard oxygen therapy (SOT), HFNC, face mask CPAP, face mask bilevel ventilation, helmet CPAP and helmet bilevel ventilation—in adults with AHRF.[3] The analysis evaluates outcomes including mortality, IMV, duration of hospitalisation and ICU stay, ventilator-free days and patient comfort.

The transition to AHRF required adapting the NMA framework from the chronic settings of Chapters 1 and 2 to an acute, heterogeneous context. This involved addressing new clinical and methodological complexities, such as varying aetiologies of AHRF (e.g., COVID-19 vs. non-COVID-19 causes) and the influence of interfaces (helmet vs. face mask) on outcomes. This chapter marks a significant step in my academic journey, demonstrating the versatility of NMA in addressing diverse clinical questions and reinforcing the thesis's aim: to advance evidence synthesis methods to guide patient-centred care in pulmonary and critical care medicine.

3.2 Methodological Advancements and Contextual Adaptation

The application of NMA in AHRF builds on the methodological foundation established in Chapter 2, where I transitioned from pairwise meta-analysis to NMA to compare multiple interventions in chronic hypercapnic respiratory failure. In this study, NMA was critical to synthesizing a complex evidence base, as direct comparisons between all non-invasive strategies (e.g., helmet CPAP vs. HFNC) were limited. The six-node network structure—differentiating interventions by both modality (CPAP, bilevel, HFNC) and interface (helmet, face mask)—allowed for granular analysis of treatment effects, capturing nuances that pairwise comparisons could not address. It addressed a key question at the time: does interface matter?

Adapting NMA to AHRF introduced unique challenges. The heterogeneity of AHRF aetiologies, ranging from viral pneumonia to ARDS, required rigorous assessment of transitivity to ensure that trials were comparable across interventions.[47] Subgroup analyses (e.g., COVID-19 vs. non-COVID-19) and sensitivity analyses (e.g., by risk of bias) were employed to explore potential effect modifiers, building on the heterogeneity focus of prior chapters. Additionally, the inclusion of comfort as an outcome necessitated a separate four-node network focused on interfaces, reflecting the hypothesis that patient experience varies more by interface than by ventilatory mode in acute settings. Lastly, the introduction of the interface was of keen interest. During COVID-19, many trials assessing the effectiveness of NIPPV in AHRF used different interfaces, with no evidence of choosing between one or the other (i.e., helmet vs facemask).[48]

This study deepened my expertise in NMA, particularly in handling sparse networks and assessing incoherence. Tools like the *netmeta* package in R and node-splitting models became integral to ensuring model validity, while the GRADE framework for NMA enhanced my ability to communicate evidence certainty to clinicians and guideline developers.[44,49] These advancements align with the thesis's objective to refine evidence synthesis for complex clinical scenarios.

3.3 Summary of Results

The NMA included 36 RCTs with 7,046 patients (median age 59.4 years, 61.4% male, median PaO_2/FiO_2 ratio 148). Trials primarily enrolled ICU patients (83.3%), with 22.2% studying COVID-19-related AHRF and 30.5% focusing on pneumonia. Interventions included SOT, HFNC (19 trials), face mask CPAP (5 trials), face mask bilevel ventilation (20 trials), helmet CPAP (2 trials) and helmet bilevel ventilation (4 trials). Most trials had a high risk of bias due to a lack of blinding, with additional concerns related to randomisation and selective reporting in some studies.

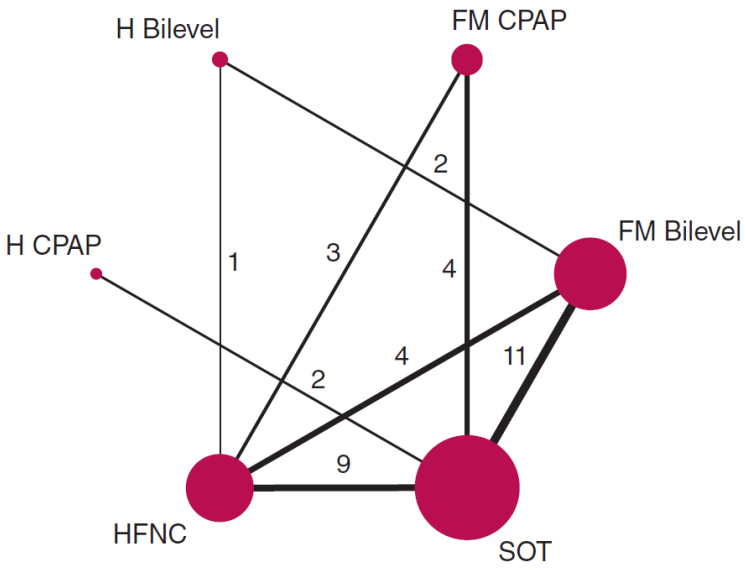

Figure 3. Network diagram for mortality. The size of the circles represents the number of patients for each intervention, and the thickness of the lines indicates the number of trials for

each comparison, which is indicated by the number next to the line.
H=helmet, FM=facemask, HFNC=High flow nasal canula, CPAP=continuous positive airway pressure.

Main Findings:

- **Mortality**: Helmet CPAP probably reduces mortality compared to SOT (231 fewer deaths per 1,000; 95% CI, 126–273 fewer; moderate certainty). HFNC may reduce mortality (63 fewer deaths per 1,000; 95% CI, 15–102 fewer; low certainty). Helmet bilevel ventilation (129 fewer deaths per 1,000; 95% CI, 24–195 fewer) and face mask bilevel ventilation (36 fewer deaths per 1,000; 95% CI, 84 fewer to 24 more) may reduce mortality (both low certainty). Face mask CPAP's effect was uncertain (9 fewer deaths per 1,000; 95% CI, 81 fewer to 84 more; very low certainty). Helmet CPAP probably outperforms HFNC in head-to-head comparisons (198 fewer deaths per 1,000; 95% CI, 70–248 fewer; moderate certainty).
- **Invasive Mechanical Ventilation (IMV)**: HFNC (103.5 fewer events per 1,000; 95% CI, 40.5–157.5 fewer) and face mask bilevel ventilation (99 fewer events per 1,000; 95% CI, 2–157.5 fewer) probably reduce IMV risk compared to SOT (both moderate certainty). Helmet bilevel ventilation (351 fewer events per 1,000; 95% CI, 256.5–400.5 fewer) and helmet CPAP (306 fewer events per 1,000; 95% CI, 189–373.5 fewer) may reduce IMV (both low certainty). Face mask CPAP's effect was uncertain (76.5 fewer events per 1,000; 95% CI, 166.5 fewer to 36 more; very low certainty). Helmet bilevel ventilation probably outperforms face mask bilevel ventilation (249.5 fewer events per 1,000; 95% CI, 83.2–572.7 fewer; moderate certainty).
- **Duration of Hospitalisation**: All non-invasive strategies may reduce hospital stay compared to SOT (low certainty): helmet bilevel ventilation (6.2 days fewer; 95% CI, 1.63–10.72 fewer), helmet CPAP (1.42 days fewer; 95% CI, 3.77 fewer to 0.93 more), HFNC (1.35 days fewer; 95% CI, 0.28–2.42 fewer) and face mask CPAP (1.0 day fewer; 95% CI, 2.62 fewer to 0.66 more). Helmet bilevel ventilation probably outperforms face mask bilevel ventilation (low certainty).

- **Duration of ICU Stay**: Helmet bilevel ventilation (4.84 days fewer; 95% CI, 2.33–7.36 fewer) and helmet CPAP (1.74 days fewer; 95% CI, 4.49 fewer to 1.01 more) may reduce ICU stay compared to SOT (both low certainty). Other modalities showed uncertain effects.
- **Comfort**: SOT may be more comfortable than face mask NIPPV (low certainty) and is probably as comfortable as HFNC (low certainty). Data on helmet interfaces were sparse, limiting conclusions.

Heterogeneity and Risk of Bias: Heterogeneity was low to moderate across outcomes (I^2 0%–60%). No significant incoherence was detected via node-splitting. Subgroup analyses showed no credible effect modification by COVID-19 status, disease severity or level of care. Publication bias was not evident.

3.4 Discussion

3.4.1 Methodological Insights and Academic Growth

This study represents a culmination of my methodological progression across the dissertation. While Chapter 1 introduced meta-analytic principles and Chapter 2 advanced to NMA in a chronic setting, this chapter applied NMA to a dynamic, acute context, requiring nuanced handling of clinical heterogeneity and sparse data. The six-node network structure demanded careful consideration of transitivity, particularly given the diversity of AHRF aetiologies. My experience with GRADE for NMA, refined in Chapter 2, was critical here in translating complex findings into actionable certainty ratings for guideline developers.

The inclusion of comfort as an outcome challenged me to adapt the NMA framework to patient-centred metrics, reinforcing the thesis's emphasis on balancing statistical rigour with clinical relevance. This study also honed my ability to communicate uncertainty, a skill essential for informing guidelines like the forthcoming ATS document. These experiences have solidified my expertise in evidence synthesis, preparing me for the pharmacologic focus of subsequent chapters.

3.4.2 Clinical Implications and Guideline Relevance

The findings highlight helmet CPAP as a promising strategy for reducing mortality and IMV in AHRF, with moderate-certainty evidence supporting its superiority over SOT and HFNC. HFNC and face mask bilevel ventilation also reduces IMV risk, with HFNC offering comparable comfort to SOT, making it a practical option in resource-limited settings. Helmet interfaces appear superior to face mask interfaces, likely due to better tolerability and seal, particularly in prolonged use.

For upcoming guidelines, these results suggest prioritizing helmet NIPPV strategies, particularly CPAP for patients with AHRF, while endorsing HFNC as an effective alternative to reduce IMV. Clinicians should weigh interface availability, patient comfort and local expertise when selecting therapies. The low-certainty evidence for hospital and ICU stay reductions underscores the need for cautious interpretation, but the trends favour non-invasive strategies over standard oxygen therapies.

This was the first study where I attempted to perform complex subgroup analysis using network meta-analysis. Currently, there is no method for conducting network meta-regression within the existing frequentist framework. There I attempted to perform overlapping networks for sensitivity analyses and eventually defaulted to doing pairwise subgroups. This led me to rethink how to perform subgroups using frequentist network meta-analyses and the need to shift to Bayesian methods—which allow for network-wide meta-regression—or to at least use a mixed approach.

3.4.3 Implications for Research

The study identifies key research priorities:

- **Helmet Interface Trials**: Larger RCTs evaluating helmet CPAP and bilevel ventilation are needed to increase evidence certainty, particularly for mortality and ICU stay.
- **Comfort Metrics**: Standardised measures of patient comfort could clarify the role of interfaces in treatment adherence and outcomes.

- **Aetiology-Specific Analyses**: Trials focusing on specific AHRF causes (e.g., COVID-19, ARDS) could reduce heterogeneity and refine treatment recommendations.
- **Cost-Effectiveness**: Studies comparing the cost-effectiveness of helmet NIPPV and HFNC could guide resource allocation, especially in low-resource settings.

3.4.4 ATS Guideline Contribution

This NMA will directly inform the upcoming ATS guidelines by providing a comprehensive synthesis of non-invasive oxygenation strategies, addressing gaps noted in prior guidelines (e.g., lack of evidence on mortality and comfort for HFNC). The moderate-certainty findings for helmet CPAP and HFNC offer a robust foundation for recommendations, while the granular node structure (by modality and interface) allows guideline panels to tailor advice to specific clinical contexts. My involvement in this study has prepared me to contribute to guideline development, bridging evidence synthesis with policy impact.

3.4.5 Next Steps in the Thesis Narrative

This chapter extends the thesis's methodological arc by applying NMA to acute care, setting the stage for Chapter 4, which will explore a similar topic on pre-oxygenation of patients prior to rapid sequence intubation.

Chapter 4: Preoxygenation Strategies for Intubation in Critically Ill Patients: A Network Meta-Analysis

Scientific question. In adults undergoing tracheal intubation in the intensive care unit (ICU) or emergency department (ED), which preoxygenation strategy—non-invasive positive-pressure ventilation (NIPPV), high-flow nasal cannula (HFNC), NIPPV + HFNC, or facemask oxygen—best reduces hypoxemia and improves other patient-important outcomes?

PICO. P: Adults requiring intubation (ICU/ED). I/C: NIPPV, HFNC, NIPPV + HFNC, facemask oxygen. O (primary): Hypoxemia during intubation. O (secondary): First-attempt success, serious adverse events (e.g., aspiration, cardiac arrest), all-cause mortality.

Links. Appendix 4A (protocol), 4B (published paper in *The Lancet Respiratory Medicine*), 4C (supplementary tables/figures).

4.1 Introduction

Building on the exploration of non-invasive oxygenation strategies in AHRF in Chapter 3, this chapter examines preoxygenation strategies for tracheal intubation in critically ill patients. Intubation in the intensive care unit (ICU) or emergency department (ED) carries significant risks, particularly hypoxemia, due to patients' limited oxygen reserves and physiological vulnerabilities.[17,50] Preoxygenation, a critical preparatory step, aims to maximise oxygen stores to extend the safe apnoeic time and minimise complications like hypoxemia, which occurs in approximately 9.3% of cases.[17,51,52] Strategies such as HFNC, NIPPV and facemask oxygen (including bag-valve mask, non-rebreather mask or simple mask) are commonly used, yet their comparative efficacy remains uncertain.

This chapter presents a network meta-analysis published in *The Lancet Respiratory Medicine*, synthesizing evidence from 15 randomised controlled trials (RCTs) involving 3,420 patients.[4] The analysis compares HFNC, NIPPV, NIPPV plus HFNC and facemask oxygen for preoxygenation in adults requiring intubation in ICU or ED settings. Outcomes include hypoxemia during intubation, successful first-attempt intubation, serious adverse events (e.g., aspiration, cardiac arrest) and all-cause mortality. Conducted in collaboration with PREOXI study investigators,[52] this NMA is going to inform the same ATS guideline as Chapter 3, ensuring cohesive evidence synthesis for acute care.

This study marks a methodological evolution in my thesis, applying NMA to a procedure-specific context (preoxygenation) rather than a disease state (AHRF). It required integrating sparse data from a smaller trial set and addressing clinical nuances, such as NIPPV interface variations (e.g., helmet vs. mask). My collaboration with PREOXI investigators enriched the analysis, reflecting my growing role in bridging primary research with evidence synthesis. This chapter advances the thesis's aim: to refine evidence synthesis methods for patient-centred critical care. It also forced me to learn new methods of performing subgroup analysis in this more complex statistical framework.

4.2 Methodological Advancements and Contextual Adaptation

The NMA in this chapter extends the six-node framework of Chapter 3 to a four-node network (HFNC, NIPPV, NIPPV plus HFNC, facemask oxygen), tailored to preoxygenation's procedural focus. Unlike the chronic-to-acute progression of prior chapters, this study required synthesizing evidence across heterogeneous critical care settings (ICU and ED) and patient conditions (e.g., AHRF, neurological emergencies). The inclusion of PREOXI data—the largest trial to date—enhanced precision, addressing limitations of earlier reviews like Fong et al. (2019).[16,17]

Methodological challenges included managing sparse networks, particularly for NIPPV plus HFNC (one trial), and ensuring transitivity across trials with varying hypoxemia definitions. I employed frequentist random-effects NMA using the *netmeta* package in R, with node-splitting to assess incoherence. I performed Bayesian meta-regression for subgroups. Subgroup analyses (e.g., by BMI, PaO_2/FiO_2 ratio) and sensitivity analyses (e.g., including surgical patients) explored heterogeneity, building on Chapter 3's approach. The GRADE framework for NMA was critical in assigning certainty ratings and refining my ability to translate statistical findings into clinical recommendations.

This study deepened my expertise in handling small trial sets and integrating high-impact trials like PREOXI. My collaboration with PREOXI investigators required aligning data extraction with NMA assumptions, a skill that will inform future chapters on pharmacologic interventions. This

work underscores the thesis's methodological arc: progressing from broad disease-based NMAs to focused, procedure-specific syntheses.

4.3 Summary of Results

The NMA included 15 RCTs with 3,420 patients (specific demographics not detailed in the provided text, but trials focused on adults ≥18 years in ICU/ED). Interventions were HFNC, NIPPV (via various interfaces), NIPPV plus HFNC, and facemask oxygen (bag-valve mask, non-rebreather or simple mask). Most trials had moderate-to-high risk of bias (RoB 2.0), primarily due to blinding challenges.

Main Findings:

- **Hypoxemia During Intubation**:
    - NIPPV probably reduces hypoxemia vs. HFNC (RR 0.73, 95% CI 0.55–0.98; moderate certainty) and facemask oxygen (RR 0.51, 95% CI 0.39–0.65; high certainty).
    - HFNC reduces hypoxemia vs. facemask oxygen (RR 0.69, 95% CI 0.54–0.88; high certainty).
    - NIPPV plus HFNC may reduce hypoxemia vs. facemask oxygen (RR 0.10, 95% CI 0.01–0.78; very low certainty, based on one trial).
- **Successful First-Attempt Intubation**:
    - No strategy significantly improved first-attempt success (e.g., NIPPV vs. HFNC: RR 1.02, 95% CI 0.92–1.14; low certainty; HFNC vs. facemask: RR 0.99, 95% CI 0.90–1.09; low certainty).
- **Serious Adverse Events**:
    - NIPPV probably reduces serious adverse events vs. facemask oxygen (RR 0.30, 95% CI 0.12–0.77; moderate certainty) and may reduce them vs. HFNC (RR 0.32, 95% CI 0.11–0.91; low certainty).
    - HFNC shows no clear reduction vs. facemask oxygen (RR 0.95, 95% CI 0.60–1.51; low certainty).

    - NIPPV plus HFNC data were inconclusive (RR 0.52 vs. NIPPV, 95% CI 0.09–2.94; very low certainty).
- **All-Cause Mortality**:
    - No strategy significantly reduced mortality (e.g., NIPPV vs. HFNC: RR 1.09, 95% CI 0.91–1.31; moderate certainty; HFNC vs. facemask: RR 0.86, 95% CI 0.73–1.01; low certainty).

Heterogeneity and Bias: Heterogeneity was low. No incoherence was detected. Subgroup analyses (e.g., BMI, setting) showed no effect modification. Sensitivity analyses including surgical patients aligned with the main findings. Publication bias was not assessed due to limited trials.

4.4 Discussion

4.4.1 Methodological Insights and Academic Growth

This NMA reflects my methodological maturation, transitioning from disease-focused analyses (Chapters 1–3) to a procedure-specific context. The four-node network, though simpler than Chapter 3's in terms of number of studies and number of intervention, required careful handling of sparse data, particularly for NIPPV plus HFNC. My collaboration with PREOXI investigators enhanced data integration, a novel challenge that strengthened my synthesis skills. Applying GRADE to a smaller trial set refined my ability to communicate uncertainty, a critical skill for guideline development.

The study also highlighted NMA's flexibility in procedural settings, where direct comparisons (e.g., NIPPV vs. HFNC) are scarce. It also forced me to learn how to apply subgroup analyses in this complex statistical framework, something that I struggled with in Chapter 3's analysis. In this study, I learned new methods to use a mixed-method Bayesian meta-regression. Interpretation remained difficult and applying subgroups on sparse data itself is its own problem, but it provided a scaffolding for future studies.

4.4.2 Clinical Implications and Guideline Relevance

The findings endorse NIPPV as the preferred preoxygenation strategy, reducing hypoxemia (high certainty vs. facemask, moderate vs. HFNC) and serious adverse events (moderate certainty vs. facemask). HFNC is a viable alternative, reducing hypoxemia vs. facemask (high certainty) with simpler implementation, ideal for resource-limited settings. NIPPV plus HFNC shows promise but requires further study due to limited data. No strategy impacts first-attempt success or mortality, suggesting other factors (e.g., operator skill) drive these outcomes.

These results complement Chapter 3's findings, suggesting NIPPV for high-risk intubations (e.g., severe hypoxemia) and HFNC for broader applicability. Clinicians should consider patient risk (e.g., obesity, low PaO2/FiO2) and resource availability.[53] The absence of increased aspiration risk with NIPPV alleviates a common concern, supporting its use.

4.4.3 Implications for Research

Key research gaps include:

- **Helmet NIPPV**: No trials evaluated helmet interfaces, despite their promise in AHRF (Chapter 3). RCTs are needed to assess efficacy and tolerability.
- **NIPPV plus HFNC**: Additional trials could confirm its potential hypoxemia reduction and clarify adverse event risks.
- **Subgroup Effects**: Individual patient data meta-analyses could identify benefits in specific groups (e.g., obese patients).
- **Long-Term Outcomes**: Studies should explore post-intubation outcomes like ventilator-free days.

One of the key lessons from this chapter was the difficulty of assessing important subgroups within a network meta-analysis framework. First, methodologically it became complicated, as I had to switch to the Bayesian framework to perform the statistical analysis. This first required me to ensure there were no significant differences between the frequentist and Bayesian

results. Then, I had to try to understand and interpret the results of a Bayesian regression, which there are currently no guidelines for, especially for a network metanalysis.

4.4.4 ATS Guideline Contribution

This NMA, alongside Chapter 3, forms a comprehensive evidence base for the ATS guideline. It provides high-to-moderate certainty that NIPPV and HFNC outperform facemask oxygen for hypoxemia prevention, guiding recommendations for intubation protocols. My collaboration with PREOXI investigators ensured robust data, enhancing the guideline's credibility. The findings support tailored preoxygenation based on patient and setting, aligning with Chapter 3's emphasis on individualised care.

4.4.5 Next Steps in the Thesis Narrative

This chapter transitions the thesis toward pharmacologic interventions in Chapter 5 (e.g., corticosteroids in respiratory failure), leveraging NMA to synthesise sparse evidence. The focus on guideline development here and in Chapter 3 foreshadows later exploration of implementation science, fulfilling the thesis's goal to advance evidence-based critical care.

Section 2: Corticosteroids in Pulmonary Critical Care Medicine

Chapter 5: Systemic Corticosteroids in Fibrotic Lung Disease: A Systematic Review and Meta-Analysis

Scientific question. In adults with stable fibrotic interstitial lung disease (fILD)—including idiopathic pulmonary fibrosis (IPF) and non-IPF subtypes—does systemic corticosteroid therapy, compared with no corticosteroids/standard care, improve lung function and other patient-important outcomes?

PICO. P: Adults with stable fILD (IPF and non-IPF). I/C: Systemic corticosteroids (e.g., prednisone/prednisolone) vs no corticosteroids/standard care. O (primary): Change in forced vital capacity (FVC, % predicted). O (secondary): All-cause mortality.

Links. Appendix 5A (protocol), 5B (published paper in BMJ Open Respiratory Research), 5C (supplementary tables/figures), 5D (contributions)

5.1 Introduction

Building on the foundational evidence synthesis approaches established in earlier chapters, which explored non-invasive ventilation and high-flow nasal cannula in COPD, this chapter shifts focus to the role of systemic corticosteroids in fibrotic interstitial lung disease (fILD). fILD, encompassing idiopathic pulmonary fibrosis (IPF) and non-IPF subtypes like fibrotic hypersensitivity pneumonitis (fHP) and systemic sclerosis-associated interstitial lung disease (SSc-ILD), is a group of progressive lung disorders with limited treatment options.[54,55] Systemic corticosteroids have been used since the 1950s, yet their efficacy and safety in stable fILD remain uncertain, with conflicting evidence from observational studies and trials like PANTHER, which showed harm in IPF.[56]

This chapter begins with a systematic review and meta-analysis published in *BMJ Open Respiratory Research*, conducted in collaboration with the REMAP-ILD consortium.[5,57] As one of the first reviews since the early 2000s Cochrane review to evaluate corticosteroids in stable fILD, it employs a pairwise meta-analysis to assess outcomes like forced vital capacity (FVC) and mortality.[58] This study marks a methodological bridge in the thesis, transitioning from the NMA of Chapter 2 to simpler pairwise comparisons, which lay the groundwork for subsequent dose-

response analyses in COPD, COVID-19, sepsis and pneumonia. By demonstrating clinical equipoise and highlighting evidence gaps, this study advances the thesis's aim: to leverage evidence synthesis to navigate clinical uncertainty in pulmonary and critical care medicine.

5.2 Pairwise Meta-Analysis and Methodological Evolution

Pairwise meta-analysis, the methodological cornerstone of Chapter 1, represents a step back from the complexity of NMA used in Chapter 2 but is well-suited for evaluating corticosteroids in fILD, where direct comparisons are limited, and no RCTs were available. Unlike NMA, which integrates direct and indirect evidence, pairwise meta-analysis focuses on head-to-head comparisons, offering simplicity and interpretability when evidence is sparse. This approach aligns with the thesis's progression, providing a methodological contrast to NMA while maintaining rigour through tools like random-effects modelling, GRADE assessments and subgroup analyses.[59]

Applying pairwise meta-analysis in this study introduced distinct challenges. The absence of RCTs necessitated reliance on cohort studies, raising concerns about confounding and selection bias.[59] Ensuring comparability across studies required careful assessment of patient characteristics, fILD subtypes and corticosteroid regimens. Heterogeneity, a recurring theme in this thesis, was addressed through random-effects models and subgroup analyses (e.g., IPF vs. non-IPF fILD), deepening my understanding of evidence synthesis as a balance between statistical precision and clinical context. This study also marked my first collaboration with the REMAP-ILD consortium, exposing me to adaptive platform trial designs and reinforcing the importance of evidence synthesis in informing innovative research frameworks.[57]

5.3 Summary of Results

We screened 13,229 unique citations but identified no RCTs meeting the inclusion criteria. Ten cohort studies (1,639 patients) were included, spanning the USA, Japan, Belgium, China, the UK and South Korea. Participants were predominantly male (61%), aged 56.2–71.7 years, with six studies on IPF and five on non-IPF fILD (nfHP, nSSc-ILD, nNSIP). Corticosteroid regimens

involved prednisolone or prednisone (22.5–53.25 mg/day prednisolone equivalent), with varying tapering schedules.

Main Findings:

- **Mortality**: Corticosteroids had an uncertain effect on mortality compared to no treatment (relative risk [RR] 1.03, 95% CI 0.85 to 1.25; very low certainty), equivalent to 30 more deaths per 1,000 (95% CI 107 fewer to 209 more). No subgroup differences were found between IPF and non-IPF fILD (p=0.36), and meta-regression showed no dose-mortality association (p=0.66).
- **Change in FVC**: Corticosteroids had an uncertain overall effect on FVC decline (% predicted) (mean difference [MD] 4.29%, 95% CI -8.26% to 16.83%; very low certainty). Subgroup analysis suggested a benefit in non-IPF fILD (MD 10.89%, 95% CI 5.25% to 16.53%; low certainty), but not in IPF (MD -3.80%, 95% CI -8.94% to 1.34%; very low certainty), with a significant subgroup difference (p<0.001).

Risk of Bias and Heterogeneity: All studies were at high risk of bias due to confounding and selective reporting. Heterogeneity was substantial for FVC (I^2=84.56%) but low for mortality. No publication bias was detected (Egger's test, p=0.26). Subgroup credibility was assessed using ICEMAN, supporting the IPF vs. non-IPF difference.

5.4 Discussion

5.4.1 Methodological Insights and Academic Development

This study marked a pivotal moment in my methodological journey, transitioning from the complex NMA of Chapter 2 to the simpler, yet equally rigorous, pairwise meta-analysis. Utilizing pairwise meta-analysis in this context required navigating challenges like cohort study bias and heterogeneity, which I addressed using random-effects models and GRADE assessments..

The study also deepened my appreciation for heterogeneity as a lens for clinical variation. While Chapter 2 explored heterogeneity across NMA networks, this analysis focused on pairwise comparisons, highlighting the limitations of low-quality data ("garbage in, garbage

out"). Learning to balance statistical rigour with clinical interpretability has been a cornerstone of my academic development, shaping the analytical approaches in later chapters.

5.4.2 Clinical Implications

The findings suggest that corticosteroids may slow FVC decline in non-IPF fILD but have no benefit in IPF, consistent with PANTHER trial evidence of harm in IPF.[56] Clinicians should avoid routine corticosteroid use in IPF and approach their use in non-IPF fILD cautiously, monitoring for adverse effects given low-certainty evidence. Shared decision-making and considering patient preferences and disease characteristics are critical until higher-quality evidence emerges.

5.4.3 Implications for Research

This study identifies key research priorities:

- **Randomised Controlled Trials**: RCTs comparing corticosteroid monotherapy to placebo or standard care are urgently needed, particularly for non-IPF fILD.
- **Endotype Exploration**: Studies should investigate fILD endotypes to identify corticosteroid-responsive patients, supporting precision medicine.
- **Dose Optimisation**: Research on optimal corticosteroid dosing and types is warranted, given data limitations in this review.
- **Adaptive Trials**: The REMAP-ILD platform trial offers a framework to address these gaps, testing corticosteroids alongside other interventions.

5.4.4 Next Steps in the Thesis Narrative

This chapter builds on the methodological foundation of earlier chapters by demonstrating the utility of pairwise meta-analysis in addressing evidence gaps. It sets the stage for subsequent sections, which introduce dose-response analyses in COPD and explore corticosteroid efficacy in acute settings (COVID-19, sepsis, pneumonia). By highlighting clinical equipoise and the need for innovative trial designs, this study advances the thesis's overarching aim: to enhance the precision and applicability of evidence synthesis in pulmonary and critical care medicine. Most

importantly, this study is the first of the REMAP-ILD consortium that will inform treatment selection choices for the upcoming clinical trial.

Chapter 6: Inhaled Corticosteroids, COPD and the Incidence of Lung Cancer: A Systematic Review and Dose-Response Meta-Analysis

Scientific question. In adults with chronic obstructive pulmonary disease (COPD), do inhaled corticosteroids (ICS) reduce the incidence of lung cancer compared with no ICS (or lower exposure), and how does any effect vary by dose?

PICO. P (Population): Adults with COPD (including COPD-only and mixed asthma/COPD cohorts). I/C (Intervention/Comparator): ICS at varying daily doses (converted to fluticasone-equivalents) vs non-use or lower exposure. O (Outcomes): Primary: Incident lung cancer. (Dose-response modeled per unit fluticasone-equivalent exposure.)

Links. Appendix 6A (protocol), 6B (published paper: *BMC Pulmonary Medicine*, 2022), 6C (supplementary tables/figures).

6.1 Introduction

Building on Chapter 5's exploration of systemic corticosteroids in fILD, which employed pairwise meta-analysis to highlight clinical equipoise and evidence gaps, this chapter shifts focus to inhaled corticosteroids (ICS) in COPD and their potential role in reducing lung cancer incidence. Lung cancer, a leading cause of mortality in COPD patients due to shared risk factors like smoking, has sparked interest in ICS as a chemopreventive agent. However, prior meta-analyses, relying on cohort data of dubious quality and lacking rigorous bias assessment, have overstated ICS's protective effects, prompting a need for more robust evidence synthesis.[60-63]

This section presents a systematic review and dose-response meta-analysis, published in *BMC Pulmonary Medicine*, which critically evaluates ICS's effect on lung cancer incidence in COPD patients.[6] By applying the ROBINS-I tool for risk of bias and the GRADE framework for evidence certainty, the study aimed to temper overly enthusiastic claims from earlier reviews, demonstrating a potential dose-dependent reduction in lung cancer incidence but with low to very low certainty evidence.[60-63] This work marks a methodological progression in the thesis, transitioning from pairwise meta-analysis in fILD to dose-response analysis, aligning with the broader aim of leveraging advanced evidence synthesis to navigate clinical uncertainty in pulmonary and critical care medicine. It sets the stage for subsequent sections in Chapter 6, which will explore corticosteroid applications in other contexts, further advancing the thesis's narrative.

6.2 Dose-Response Meta-Analysis and Methodological Evolution

Dose-response meta-analysis extends beyond the pairwise meta-analysis of Chapter 5 by quantifying the relationship between ICS dose and lung cancer incidence across a continuum. This approach, employing methods by Greenland, Longnecker, Crippa and Orsini, provides a nuanced perspective on treatment effects, offering greater clinical relevance than high-versus-low comparisons.[31] Within the thesis, dose-response analysis represents a methodological evolution, building on the network meta-analysis (NMA) of Chapters 2-4 and the pairwise approach in fILD and enabling exploration of dose-dependent effects in a field marked by inconsistent observational data.

Implementing dose-response meta-analysis posed significant challenges. The absence of randomised controlled trials necessitated reliance on cohort studies, introducing serious risks of bias, particularly confounding from unadjusted factors like smoking history, COPD duration and prior cancer. Converting diverse ICS types to fluticasone equivalents required assumptions, and incomplete dose data limited some studies' inclusion. Heterogeneity, a recurring theme in this thesis, was addressed through random-effects models and subgroup analyses (COPD-only vs. mixed asthma/COPD cohorts). This study enhanced my methodological expertise, particularly in applying ROBINS-I for rigorous bias assessment and GRADE for evidence appraisal, skills that strengthen the thesis's analytical rigour and prepare for subsequent analyses.[59]

6.3 Summary of Results

The systematic review screened 3,964 citations, including 13 cohort studies with 268,363 patients from Europe, Asia and North America (data collected from 1966–2014). Participants were predominantly male (median age 66.4 years), with 10 studies on COPD-only cohorts and three on mixed asthma/COPD cohorts. Two studies included only female patients. ICS doses were converted to fluticasone equivalents (e.g., 500 μg/day for one prescription, 1,000 μg/day for two), with assumptions for ranges and adherence.

Main Findings:

- **Dose-Response Meta-Analysis (7 studies)**:
    - For every 500 µg/day of fluticasone equivalent ICS, lung cancer incidence may be reduced (relative risk [RR] 0.82, 95% CI 0.68–0.95; very low certainty), equivalent to 14 fewer cases per 1,000 (95% CI 24.7–3.8 fewer) at a baseline risk of 7.2%.
    - For every 1,000 µg/day, a larger reduction was suggested (RR 0.68, 95% CI 0.44–0.93; very low certainty), equivalent to 24.7 fewer cases per 1,000 (95% CI 43.2–5.4 fewer).
- **High vs. Low ICS Meta-Analysis (11 studies)**:
    - Higher ICS doses suggested a reduced risk (RR 0.70, 95% CI 0.52–0.96; very low certainty), equivalent to 19.8 fewer cases per 1,000 (95% CI 35–2.9 fewer).
- **Subgroup Analysis**:
    - No significant difference between COPD-only and mixed asthma/COPD cohorts (p=0.36). Sex was not a significant moderator (p=0.5).

Risk of Bias and Heterogeneity: All studies were at serious risk of bias, primarily due to confounding (e.g., lack of adjustment for smoking, prior cancer) and selection bias. Heterogeneity was considerable (I^2=87.33–88.69%) for both analyses. No evidence of non-linearity (p=0.16) or publication bias (Egger's test, p=0.07) was detected.

6.4 Discussion

6.4.1 Methodological Insights and Academic Development

This study marked a significant milestone in my methodological journey, advancing from the pairwise meta-analysis of Chapter 5 to the more sophisticated dose-response meta-analysis. Mastering dose-response methods required navigating complex data transformations (e.g., fluticasone equivalents) and addressing serious biases inherent in cohort studies. The use of ROBINS-I and GRADE frameworks deepened my understanding of evidence appraisal, emphasizing the importance of rigorous bias assessment to counter overstated claims, as seen in prior meta-analyses. This experience, coupled with the application of R packages like *dosresmeta,*[31,64] enhanced my technical proficiency and underscored the balance between statistical rigour and clinical interpretability, a skill that informs subsequent chapters.

The study also reinforced the thesis's focus on heterogeneity as a lens for understanding clinical variation. While Chapter 5 highlighted heterogeneity in fILD cohorts, this analysis extended that perspective to dose-response modelling, revealing inconsistencies (e.g., two studies showing harm with higher ICS doses) that tempered conclusions. Learning to communicate low-certainty evidence cautiously, has been a cornerstone of my academic development, shaping the narrative of this thesis.

6.4.2 Clinical Implications

The findings suggest that ICS may reduce lung cancer incidence in COPD patients in a dose-dependent manner, but the very low certainty evidence precludes strong clinical recommendations. Clinicians should approach ICS for chemoprevention cautiously, weighing potential benefits against risks (e.g., pneumonia, oral candidiasis) and considering patient-specific factors like smoking history and COPD severity. Unlike systemic corticosteroids in fILD, where no benefit was observed in IPF, ICS in COPD shows a potential effect, but the lack of RCTs limits actionable guidance. Shared decision-making, informed by current evidence limitations, is essential.

6.4.3 Implications for Research

This study identifies critical research priorities:

- **Randomised Controlled Trials**: Adequately powered RCTs are needed to confirm ICS's chemopreventive effects, addressing the reliance on biased cohort data.
- **Subgroup Analyses**: Exploration of COPD phenotypes (e.g., emphysema vs. chronic bronchitis) and severity (GOLD stages) could identify patients most likely to benefit.
- **Dose Optimisation**: Studies should clarify optimal ICS doses and adherence patterns to refine chemoprevention strategies.
- **Improved Cohort Studies**: Future observational studies must adjust for key confounders (e.g., smoking intensity, prior cancer) and report detailed dose data.

6.4.4 Next Steps in the Thesis Narrative

This chapter builds on Chapter 5's methodological foundation by introducing dose-response meta-analysis as a tool to explore treatment effects in COPD. It sets the stage for subsequent sections in Chapter 6, which will examine corticosteroid efficacy in other contexts, potentially including acute conditions like COVID-19, sepsis and pneumonia. By demonstrating the challenges of low-certainty evidence and the need for rigorous evidence synthesis, this study advances the thesis's overarching aim: to enhance the precision and applicability of evidence synthesis in pulmonary and critical care medicine.

Chapter 7: Higher- versus Lower-Dose Corticosteroids for Severe to Critical COVID-19: A Systematic Review and Dose-Response Meta-Analysis

Scientific question. In adults hospitalized with severe to critical COVID-19, do higher-dose systemic corticosteroids—compared with lower-dose regimens—reduce mortality and improve other patient-important outcomes?

PICO. P: Adults with severe to critical COVID-19 on oxygen or ventilatory support. I/C: Higher-dose vs lower-dose systemic corticosteroids (dexamethasone-equivalent). O (primary): All-cause mortality. O (secondary): Need for invasive mechanical ventilation (IMV), ventilator-free days, nosocomial infections, hospital/ICU length of stay.

Links. Appendix 7A (protocol), 7B (published paper in *Annals of the American Thoracic Society*), 7C (supplementary tables/figures)

7.1 Introduction

Building on Chapter 6's exploration of ICS in COPD for lung cancer prevention and Chapter 5's analysis of systemic corticosteroids in fILD, this chapter shifts focus to systemic corticosteroids in the acute setting of severe-to-critical coronavirus disease (COVID-19). The COVID-19 pandemic, with over 640 million cases and 6.6 million deaths by November 2022, highlighted the critical need to optimise treatments for severe cases.[7] Following the RECOVERY trial's establishment of corticosteroids as standard care with 6 mg dexamethasone daily,[65] the COVID-STEROID-2 trial sparked debate about whether higher doses (e.g., 12 mg) could further improve outcomes.

This section presents a systematic review and dose-response meta-analysis, published in *Annals of the American Thoracic Society*, which evaluates higher- versus lower-dose corticosteroids in severe-to-critical COVID-19.[7] Marking my first application of dose-response meta-analysis to randomised controlled trials (RCTs)—a method typically reserved for observational studies—this study modelled optimal dosing regimens, suggesting a probable mortality benefit with higher doses. However, the subsequent updated RECOVERY trial's findings, influenced by evolving patient characteristics like vaccination status and less severe cases, underscored the limitations of these conclusions.[23] This work advances the thesis's methodological progression, transitioning from pairwise meta-analysis in fILD (Chapter 5) and observational dose-response

analysis in COPD (Chapter 6) to RCT-based dose-response analysis, aligning with the goal to leverage evidence synthesis to navigate clinical uncertainty in pulmonary and critical care medicine.

7.2 Dose-Response Meta-Analysis and Methodological Evolution

Dose-response meta-analysis, as discussed in Chapter 6, extends beyond the pairwise meta-analysis of Chapter 5 and the observational dose-response analysis of Chapter 6 by modelling the relationship between corticosteroid dose and clinical outcomes in RCTs. Using methods by Orsini, Greenland and Longnecker, this approach quantifies treatment effects across a dose continuum, offering clinicians insights into optimal dosing regimens.[31,64] In the thesis, this represents a methodological leap, applying a technique typically used to bolster causality in observational studies to RCTs, a rare and innovative application in evidence synthesis.

Implementing dose-response meta-analysis in RCTs posed unique challenges. Converting diverse corticosteroids (dexamethasone, methylprednisolone, hydrocortisone) to dexamethasone equivalents required precise assumptions, and varying trial durations necessitated calculating cumulative intended doses. Heterogeneity, a recurring theme in this thesis, was addressed through random-effects models and sensitivity analyses, including meta-regression for treatment duration. This study deepened my expertise in advanced meta-analytic techniques and highlighted the challenges of evidence synthesis in a rapidly evolving pandemic, skills that inform subsequent analyses in Chapter 7.

7.3 Summary of Results

The systematic review screened 4,929 unique records, including 20 RCTs with 10,155 patients (64% male, median age 61 years) from peer-reviewed and preprint sources. All patients had severe-to-critical COVID-19, with all on oxygen therapy and approximately 20% mechanically ventilated at baseline. Trials used dexamethasone (10 trials), methylprednisolone (8), or hydrocortisone (3), with doses converted to dexamethasone equivalents (e.g., 6 mg/day for 10 days = 60 mg cumulative).

Main Findings:

- **Mortality (18 trials, 8,438 patients)**: Higher-dose corticosteroids probably reduce mortality compared to lower doses (relative risk [RR] 0.92, 95% CI 0.85–0.98; moderate certainty), equivalent to 14 fewer deaths per 1,000 (95% CI 26 fewer to 2 fewer) at a baseline risk of 20%. Sensitivity analysis showed a larger effect in non-mechanically ventilated patients.
- **Mechanical Ventilation (12 trials, 5,173 patients)**: Higher doses may reduce the need for invasive mechanical ventilation (RR 0.91, 95% CI 0.87–1.03; low certainty), equivalent to 11.6 fewer cases per 1,000 (95% CI 23.2 fewer to 6.9 more).
- **Nosocomial Infections (9 trials, 2,311 patients)**: The effect on infections is uncertain (RR 0.90, 95% CI 0.83–0.97; very low certainty), equivalent to 16.7 fewer infections per 1,000 (95% CI 25.0 fewer to 5.4 fewer).
- **Other Outcomes**: Higher doses may reduce mechanical ventilation duration (mean difference 2.6 fewer days, 95% CI 6.1 fewer to 0.8 more; low certainty) but have no clear effect on hospitalisation duration (mean difference 0.34 more days, 95% CI 0.74 fewer to 1.46 more; low certainty).

Risk of Bias and Heterogeneity: Four trials were at high/probably high risk of bias, primarily due to randomisation issues. Heterogeneity was notable for secondary outcomes (e.g., mechanical ventilation duration and hospitalisation). No evidence of non-linearity or publication bias was detected.

7.4 Discussion

7.4.1 Methodological Insights and Academic Development

This study marked a pivotal moment in my methodological journey, as my first application of dose-response meta-analysis to RCTs. Unlike Chapter 6's observational dose-response analysis, modelling RCT data required navigating trial-specific challenges, such as dose conversions and varying follow-up periods. This experience taught me humility, as the RECOVERY trial's later findings—showing no benefit with higher doses—revealed the limitations of early pandemic

data, driven by evolving patient profiles (e.g., vaccinated, less severe cases).[23,24] The challenge of synthesizing evidence in a rapidly changing environment, has shaped my approach to subsequent analyses, emphasizing adaptability and caution in interpretation.

7.4.2 Clinical Implications

The findings suggest that higher-dose corticosteroids probably reduce mortality in severe-to-critical COVID-19, particularly in non-mechanically ventilated patients, with potential benefits in reducing mechanical ventilation. However, the very low certainty for nosocomial infections and the RECOVERY trial's contradictory results urge caution. This study was done in the earlier stages of the COVID-19 pandemic, where most patients included in the study were not vaccinated. It highlights the challenges of evidence synthesis efforts in rapidly changing disease states in a pandemic.

7.4.3 Implications for Research

This study highlights key research priorities:

- **Updated Trials**: RCTs reflecting current patient populations (e.g., vaccinated, post-Omicron) are needed to clarify higher-dose benefits.
- **Subgroup Analyses**: Studies should explore oxygen modalities (e.g., high-flow nasal cannula vs. non-invasive ventilation) and disease severity to refine dosing strategies.
- **Infection Risks**: Higher-quality data on nosocomial infections are required to assess immunosuppressive risks.
- **Dynamic Evidence Synthesis**: Methods to adapt meta-analyses to rapidly changing clinical contexts should be developed.

7.4.4 Next Steps in the Thesis Narrative

This chapter advances the thesis's methodological progression by applying dose-response meta-analysis to RCTs, building on Chapter 5's pairwise meta-analysis and Chapter 6's observational dose-response analysis. It sets the stage for subsequent chapters, which explore corticosteroids in other acute conditions (e.g., sepsis, pneumonia), further examining optimal

dosing in critical care. By highlighting the challenges of evidence synthesis in a dynamic pandemic, this study reinforces the thesis's aim: to enhance the precision and applicability of evidence synthesis in pulmonary and critical care medicine.

Chapter 8: Corticosteroids in Sepsis and Septic Shock: A Systematic Review, Pairwise and Dose-Response Meta-Analysis

Scientific question. In adults with sepsis or septic shock, do systemic corticosteroids—compared with placebo/standard care—reduce short-term mortality and improve other patient-important outcomes?

PICO. P: Adults with sepsis or septic shock (ICU/ED). I/C: Systemic corticosteroids (e.g., hydrocortisone-equivalent regimens) vs placebo/standard care. O (primary): Short-term all-cause mortality. O (secondary): Shock reversal by 7 days, ICU/hospital length of stay, adverse events (hyperglycaemia, hypernatremia, neuromuscular weakness).

Links. Appendix 8A (protocol), 8B (published paper in *Critical Care Explorations*), 8C (supplementary tables/figures)

8.1 Introduction

Following Chapter 7's exploration of higher- versus lower-dose corticosteroids in severe-to-critical COVID-19 and Chapter 6's analysis of ICS in COPD, this chapter shifts to systemic corticosteroids in sepsis and septic shock, a highly controversial topic in critical care medicine.[66] Decades of debate, fuelled by conflicting trial results and variable dosing regimens, have left uncertainty about corticosteroids' efficacy and safety in sepsis. This section presents a systematic review and meta-analysis published in *Critical Care Explorations,*[8] which informed the Society of Critical Care Medicine (SCCM) 2024 guideline and was highlighted as a breaking article at the SCCM 2024 conference in Phoenix.[8,67]

Employing pairwise, subgroup and dose-response meta-analyses, this study provided robust evidence of a probable mortality benefit and increased shock reversal, while identifying an optimal dosing regimen of approximately 260 mg/day of hydrocortisone equivalent. As part of the SCCM guideline development, this work resolved longstanding uncertainties, offering precise guidance for clinicians. Within the thesis, this study represents a methodological culmination, integrating pairwise meta-analysis (Chapter 5), observational dose-response analysis (Chapter 6) and RCT-based dose-response analysis (Chapter 7) to address a critical care controversy, aligning with the aim of enhancing evidence synthesis in pulmonary and critical care medicine.

8.2 Dose-Response Meta-Analysis and Methodological Evolution

This study combined pairwise, subgroup and dose-response meta-analyses, building on the methodological progression of prior chapters. Pairwise meta-analysis, used in Chapter 5 for fILD, provided pooled effect estimates, while subgroup analyses explored heterogeneity across sepsis severity, corticosteroid type and patient populations. Dose-response meta-analysis, advanced from Chapter 6's observational approach and Chapter 7's RCT application, modelled the relationship between corticosteroid dose and outcomes using methods by Greenland, Longnecker and Orsini.[31,64] This comprehensive approach, novel in sepsis research, enabled precise identification of an optimal dose, a critical advancement for guideline development.

Challenges included managing clinical heterogeneity across trials spanning six decades, converting diverse corticosteroids to hydrocortisone equivalents and addressing the high risk of bias in nearly half of the studies. The use of the Cochrane RoB 2.0 tool and GRADE framework ensured rigorous appraisal, while meta-regression and sensitivity analyses (e.g., excluding hydrocortisone-ascorbic acid-thiamine [HAT] therapy) mitigated heterogeneity. This study refined my expertise in integrating multiple meta-analytic techniques, a skill honed through the thesis, and underscored the importance of balancing statistical precision with clinical relevance in controversial topics like sepsis.

8.3 Summary of Results

The systematic review screened 1,702 unique citations, including 45 RCTs with 9,563 patients (adults and children) diagnosed with sepsis or septic shock (Sepsis 1 or 2 criteria). Most trials (27) focused on septic shock, with 26 using hydrocortisone, 7 methylprednisolone, 5 dexamethasone and 3 prednisolone. Doses were typically low (<400 mg/day hydrocortisone equivalent).

Main Findings:

- **Short-Term Mortality (39 RCTs, 9,711 patients)**: Corticosteroids probably reduce mortality (risk ratio [RR] 0.93, 95% CI 0.88–0.99; moderate certainty), equivalent to 21 fewer deaths per 1,000 (95% CI 36 fewer to 3 fewer).
- **Shock Reversal at 7 Days (13 RCTs, 2,922 patients)**: Corticosteroids increase shock reversal (RR 1.24, 95% CI 1.11–1.38; high certainty), equivalent to 150 more reversals per 1,000 (95% CI 69 to 238 more).
- **Adverse Events**: Corticosteroids probably increase hyperglycaemia (RR 1.13, 95% CI 1.08–1.18; moderate certainty; 38 more cases per 1,000) and hypernatremia (RR 1.64, 95% CI 1.32–2.03; moderate certainty; 26 more cases per 1,000). They may increase neuromuscular weakness (RR 1.21, 95% CI 1.01–1.45; low certainty; 12 more cases per 1,000).
- **Other Outcomes**: Corticosteroids may not affect ICU length of stay (mean difference [MD] 0.60 days fewer, 95% CI 1.48 fewer to 0.27 more; low certainty) or hospital length of stay (MD 0.74 days fewer, 95% CI 2.06 fewer to 0.57 more; low certainty).
- **Dose-Response Analysis**: Optimal dosing was approximately 260 mg/day hydrocortisone equivalent (RR 0.90, 95% CI 0.83–0.98), with no increased benefit at higher doses.

Risk of Bias and Heterogeneity: Twenty-two trials (48.8%) were at high/probably high risk of bias, primarily due to allocation concealment and blinding issues. Heterogeneity was low for mortality (I^2=0%) but notable for secondary outcomes. No significant subgroup effects were found (e.g., sepsis vs. septic shock, adults vs. children).

8.4 Discussion

8.4.1 Methodological Insights and Academic Development

This study was a methodological milestone, integrating pairwise, subgroup and dose-response meta-analyses to inform a major SCCM guideline. Building on Chapter 7's RCT-based dose-response analysis, the inclusion of pairwise and subgroup analyses allowed a comprehensive exploration of heterogeneity, a persistent challenge in sepsis research. Navigating trials spanning decades required careful handling of clinical and methodological variability,

reinforcing the importance of robust tools like RoB 2.0 and GRADE. The dose-response analysis, identifying 260 mg/day hydrocortisone as optimal, highlighted the power of advanced meta-analytic techniques to provide actionable clinical guidance. This experience, coupled with the study's high-profile presentation at SCCM 2024, deepened my ability to translate complex evidence into impactful recommendations, a cornerstone of this thesis.

8.4.2 Clinical Implications

The findings provide moderate-certainty evidence that corticosteroids reduce mortality and high-certainty evidence for shock reversal in sepsis, supporting their use in septic shock per SCCM 2024 guidelines. The optimal dose of 260 mg/day hydrocortisone equivalent offers clinicians a practical reference, balancing efficacy against risks like hyperglycaemia, hypernatremia and neuromuscular weakness. Unlike Chapter 7's COVID-19 findings, which were limited by pandemic dynamics, this study's broader evidence base strengthens its applicability. Clinicians should engage in shared decision-making, considering patient-specific factors and monitoring for adverse events.

8.4.3 Implications for Research

Key research priorities include:

- **Long-Term Outcomes**: Trials should assess long-term mortality and functional outcomes to better characterise corticosteroid benefits.
- **Paediatric Populations**: More RCTs, such as the ongoing Stress Hydrocortisone in Paediatric Septic Shock trial, are needed to clarify effects in children.
- **Adverse Events**: Systematic assessment of glycaemic, neuromuscular and neuropsychiatric outcomes is essential to quantify risks.
- **Sepsis-3 Criteria**: Studies using updated Sepsis-3 definitions could validate findings in modern contexts.

8.4.4 Next Steps in the Thesis Narrative

This chapter marks a methodological and clinical culmination, synthesizing techniques from prior chapters to address a controversial critical care topic. The problem with the COVID-19 pandemic was the rapidity of the data and the changing population. In some ways, this represents the opposite problem: decades with over 40 trials. By demonstrating the impact of evidence synthesis on guideline development, this study reinforces the thesis's aim: to advance precision and applicability in pulmonary and critical care medicine.

Chapter 9: Corticosteroids in Community-Acquired Bacterial Pneumonia: A Systematic Review, Pairwise and Dose-Response Meta-Analysis

Scientific question. In adults hospitalized with community-acquired bacterial pneumonia (CAP), do systemic corticosteroids—and at what dose/duration—reduce mortality and improve other patient-important outcomes compared with placebo/standard care?

PICO. P: Adults with CAP (severe and non-severe). I/C: Systemic corticosteroids (e.g., dexamethasone, hydrocortisone, methylprednisolone, prednisone; dexamethasone-equivalent dosing) vs placebo/standard care. O (primary): All-cause mortality. O (secondary): Need for invasive mechanical ventilation (IMV), ICU admission, hospital/ICU length of stay, adverse events (hyperglycaemia, secondary infections, gastrointestinal bleeding).

Links. Appendix 9A (protocol), 9B (published paper in *Journal of General Internal Medicine*), 9C (supplementary tables/figures), 9D (contributions).

9.1 Introduction

Building on Chapter 8's analysis of corticosteroids in sepsis and septic shock, this chapter examines their role in CAP, a condition marked by even greater controversy in critical care medicine. Since 1956, trials have investigated corticosteroids in CAP, with the pendulum of clinical opinion swinging due to conflicting results and the disease's inherent heterogeneity.[19,68] CAP's diverse aetiologies (bacterial, viral or mixed) and varying severities complicate evidence synthesis, contributing to inconsistent guideline recommendations. This section presents a systematic review and meta-analysis, published in the *Journal of General Internal Medicine,*[9] which informed a strong recommendation for corticosteroids in the SCCM 2024 guideline.[67]

Using pairwise, subgroup and dose-response meta-analyses, the study demonstrated a mortality benefit in severe CAP, identified an optimal dose of approximately 6 mg/day dexamethasone equivalent for 7 days and suggested a potential molecular subgroup effect (hydrocortisone vs. other corticosteroids), though with lower credibility. This work resolved longstanding debates by providing precise dosing guidance and robust evidence for severe CAP. Within the thesis, this study advances the narrative of integrating advanced meta-analytic techniques (from Chapters 5–8) to address controversial topics, culminating in guideline-informing recommendations for acute pulmonary and critical care conditions.

9.2 Dose-Response Meta-Analysis and Methodological Evolution

This study employed pairwise, subgroup and dose-response meta-analyses, extending the methodological framework of prior chapters. Pairwise meta-analysis, refined in Chapter 5 for fILD, provided pooled effect estimates, while subgroup analyses explored heterogeneity by disease severity, corticosteroid type and treatment duration. Dose-response meta-analysis, evolved from Chapter 6's observational approach, Chapter 7's RCT-based analysis and Chapter 8's sepsis application, used restricted cubic splines to model non-linear relationships between corticosteroid dose and outcomes, following Greenland et al.'s methods. This approach, identified an optimal dose, addressing a key gap in prior CAP research.

Challenges included heterogeneity in CAP definitions, severity scores (e.g., pneumonia severity index (PSI), Confusion, Urea, Respiratory rate, Blood pressure, and Age (CURB-65)) and trial designs spanning decades. The study converted corticosteroids to dexamethasone equivalents (1 mg dexamethasone = 26.7 mg hydrocortisone = 5.3 mg methylprednisolone = 6.7 mg prednisone) and used the Cochrane RoB 2.0 tool and GRADE framework to assess bias and evidence certainty. Meta-regression and sensitivity analyses mitigated heterogeneity, while the ICEMAN tool evaluated subgroup credibility. [69] This study enhanced my expertise in navigating complex, heterogeneous datasets, reinforcing the thesis's focus on methodological rigour in evidence synthesis.

9.3 Summary of Results

The systematic review screened 2,666 unique citations, including 18 RCTs with 4,661 adult patients hospitalised with suspected or probable bacterial CAP. Ten trials focused on severe CAP (≥50% patients with PSI IV/V, CURB-65 ≥3, or ICU admission) and eight on less severe CAP. Seven trials used hydrocortisone, four methylprednisolone, five prednisolone/prednisone and two dexamethasone, with a median treatment duration of 7 days.

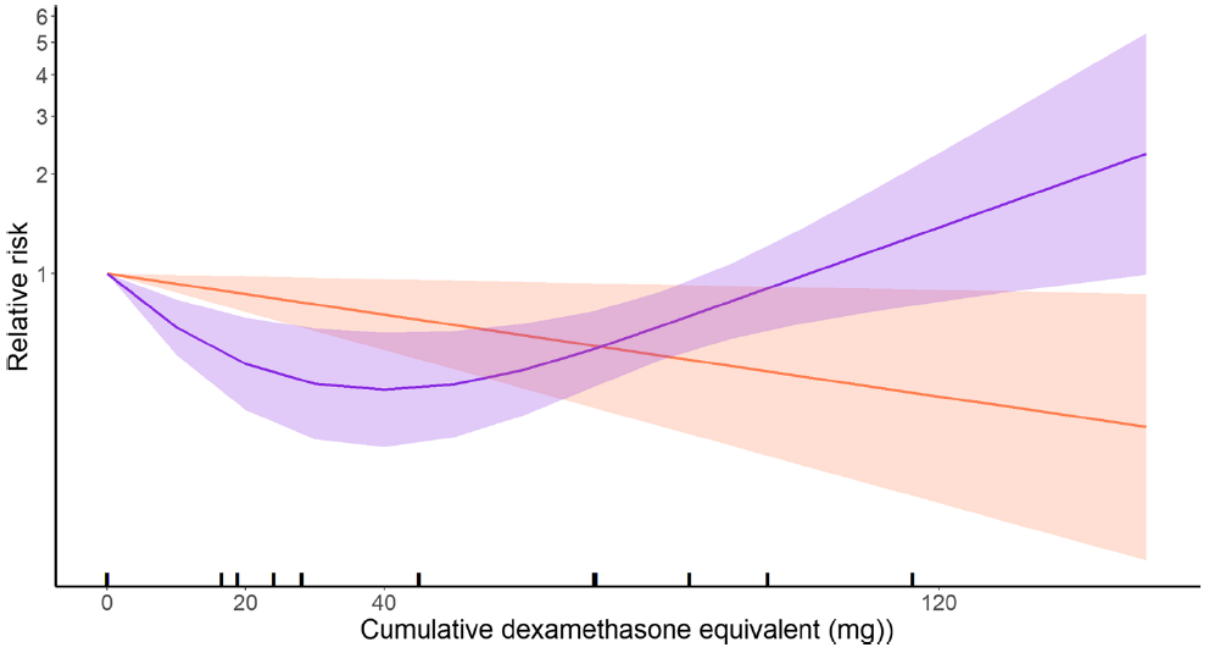

Figure 4. Dose-response curve. The curved purple line represents the non-linear dose-response relationship, and the purple ribbons represent 95% confidence intervals (95% CI). The yellow linear line represents the linear dose-response relationship, and the ribbons represent 95% CI.

Main Findings:

- **Mortality (17 RCTs, 4,567 patients)**: Corticosteroids likely reduce mortality in severe CAP (RR 0.62, 95% CI 0.45–0.85; moderate certainty; 56 fewer deaths per 1,000, 95% CI 81 to 22 fewer) but may have no effect in less severe CAP (RR 1.08, 95% CI 0.83–1.42; low certainty; 6 more deaths per 1,000, 95% CI 13 fewer to 32 more). A significant subgroup effect by severity (p=0.01) was moderately credible (ICEMAN).
- **Invasive Mechanical Ventilation (IMV, 9 RCTs, 2,895 patients)**: Corticosteroids likely reduce the need for IMV (RR 0.56, 95% CI 0.42–0.74; moderate certainty; 82 fewer events per 1,000, 95% CI 21 to 48 fewer).
- **ICU Admission (5 RCTs, 2,227 patients)**: Corticosteroids likely reduce ICU admission (RR 0.65, 95% CI 0.43–0.97; moderate certainty; 18 fewer cases per 1,000, 95% CI 2 to 29 fewer).

- **Duration of Hospitalisation (13 RCTs, 3,442 patients)**: Corticosteroids may reduce hospitalisation duration (MD 2.31 days fewer, 95% CI 0.76–3.85; low certainty).
- **Duration of ICU Stay (11 RCTs, 926 patients)**: Corticosteroids may reduce ICU stay (MD 2.1 days fewer, 95% CI 0.50–3.61; low certainty).
- **Adverse Events**: Corticosteroids may increase hyperglycaemia (RR 1.76, 95% CI 1.46–2.14; low certainty; 58 more cases per 1,000, 95% CI 35 to 32 more). No significant effect was found for secondary infections (RR 1.09, 95% CI 0.85–1.41; low certainty) or gastrointestinal bleeding (RR 0.95, 95% CI 0.56–1.60; low certainty).
- **Dose-Response Analysis**: An optimal dose of approximately 6 mg/day dexamethasone equivalent for 7 days reduced mortality (RR 0.45, 95% CI 0.32–0.68). Higher doses (>11.5 mg/day) showed no benefit or potential harm.
- **Subgroup Analysis**: A potential molecular subgroup effect favoured hydrocortisone (RR 0.45, 95% CI 0.31–0.65) over other corticosteroids (p=0.001), but credibility was moderate/low (ICEMAN). No subgroup effects were found for risk of bias or treatment duration.

Risk of Bias and Heterogeneity: Seven trials (43.7%) were at high/probably high risk of bias, primarily due to randomisation and intervention deviations. Heterogeneity was low for mortality (I^2=25.97%) but moderate for secondary outcomes. Trial sequential analysis indicated the required information size was not met.

9.4 Discussion

9.4.1 Methodological Insights and Academic Development

This study represents a methodological pinnacle, combining pairwise, subgroup and dose-response meta-analyses to inform a strong SCCM 2024 guideline recommendation.[67] Extending Chapter 8's sepsis analysis, the dose-response approach using restricted cubic splines provided precise dosing guidance, addressing a critical gap in CAP research. Navigating heterogeneity in CAP severity and trial designs required advanced techniques like meta-regression and ICEMAN, building on skills developed in Chapters 5–8. The study's high-profile role in the updated SCCM 2024 guideline and its resolution of decades-long debates underscored the power of evidence

synthesis to shape clinical practice, advancing my expertise in translating complex data into actionable recommendations.

9.4.2 Clinical Implications

The findings provide moderate-certainty evidence that corticosteroids reduce mortality, IMV and ICU admission in severe CAP, supporting their use per SCCM 2024 guidelines. The optimal dose of 6 mg/day dexamethasone equivalent for 7 days offers clinicians a practical regimen, balancing efficacy against hyperglycaemia risks. Unlike Chapter 8's sepsis findings, which applied broadly, the benefit here is confined to severe CAP, highlighting the need for severity-based decision-making. Clinicians should monitor for hyperglycaemia and engage in shared decision-making, particularly for patients with milder disease where benefits are uncertain.

9.4.3 Implications for Research

Key research priorities include:

- **Microbiologic Subgroups**: Trials should examine corticosteroid effects across bacterial aetiologies (e.g., Streptococcus pneumoniae vs. others).
- **Severity Standardisation**: Studies using consistent severity criteria (e.g., Sepsis-3, updated PSI) could reduce heterogeneity.
- **Adverse Events**: Systematic assessment of hyperglycaemia and long-term outcomes is needed to quantify risks.
- **Optimal Duration**: RCTs comparing 5 vs. 7 vs. longer durations could refine treatment protocols.

9.4.4 Next Steps in the Thesis Narrative

This chapter advances the thesis's aim of enhancing evidence synthesis in critical care by addressing a highly controversial topic with robust meta-analytic techniques. The strong SCCM 2024 recommendation for corticosteroids in severe CAP marks a resolution of historical debates.

However, as Dr Rochwerg wrote, this is a story without an ending.[19] Recent data from the REMAP-CAP trial, reported no benefit with the use of hydrocortisone.[70,71] Chapter 10 will incorporate REMAP-CAP data into a final meta-analysis, synthesizing findings from Chapters 5–9 to provide a comprehensive perspective on corticosteroids in acute pulmonary conditions, further refining guideline recommendations.

Chapter 10: Corticosteroids for Adult Patients Hospitalised with Non-Viral Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis

Scientific question. In adults hospitalized with community-acquired bacterial pneumonia (CAP) with or without ARDS, do systemic corticosteroids—and at what dose/duration—reduce mortality and improve other patient-important outcomes compared with placebo/standard care?

PICO. P: Adults with CAP with or without ARDS (severe and non-severe). I/C: Systemic corticosteroids (e.g., dexamethasone, hydrocortisone, methylprednisolone, prednisone; dexamethasone-equivalent dosing) vs placebo/standard care. O (primary): All-cause mortality. O (secondary): Need for invasive mechanical ventilation (IMV), ICU admission, hospital/ICU length of stay, adverse events (hyperglycaemia, secondary infections, gastrointestinal bleeding).

Links. Appendix 10A (protocol), 10B (published paper in *Journal of General Internal Medicine*), 10C (supplementary tables/figures)

10.1 Introduction

Building on Chapter 9's analysis of corticosteroids in CAP, this chapter culminates the thesis's exploration of evidence synthesis in critical care by presenting a comprehensive meta-analysis. It is both an update and an expansion of the paper presented in Chapter 9. First, after the publication of our analyses, several new studies were published including subgroup analyses of ARDS trials, with CAP-specific subgroups showing benefit.[72] This was again in line with our analysis. However, many readers had their concerns.

The most challenging issue was the upcoming REMAP-CAP trial results.[71] I worked with the authors of the REMAP-CAP group before the publication of their study to update our analysis. Both the REMAP-CAP study and our analysis were published in *Intensive Care Medicine.*[10,71] In an almost contradictory fashion, the REMAP-CAP trial results showed no effect and our meta-analysis, which included the new data from REMAP-CAP, extolled the benefit of corticosteroids in CAP. Collaborating with global investigators, this study aimed to build consensus on corticosteroid use despite persistent challenges. This section synthesises these findings, advancing the thesis's narrative of integrating advanced meta-analytic techniques to address controversial critical care topics and inform clinical practice.

We employed many of the older methods described in the thesis and employed a Bayesian analysis to further bolster the methodological rigour.

10.2 Dose-Response Meta-Analysis and Methodological Evolution

This study utilised pairwise, subgroup, dose-response and Bayesian meta-analyses, extending methodologies refined in Chapters 5–9. Pairwise meta-analysis, established in Chapters 1 and 5, provided pooled effect estimates, while subgroup analyses explored heterogeneity by CAP severity, corticosteroid type, age, sex and trial population (CAP, sepsis, ARDS). Dose-response meta-analysis—evolved from Chapter 6's observational approach, Chapter 7's RCT focus, Chapter 8's sepsis application and Chapter 9's CAP analysis—used restricted cubic splines to model non-linear dose-outcome relationships, per Greenland et al.'s methods.[31,64] Bayesian meta-analysis, newly introduced, provided posterior probabilities to assess effect robustness, enhancing precision over the previous study. The study identified an optimal dose of 60 mg/day prednisone equivalent, contrasting with the 6 mg/day dexamethasone equivalent (≈40 mg prednisone) in our previous study, reflecting a broader dose range.

Challenges included heterogeneity in CAP definitions, severity criteria (e.g., ATS/IDSA guidelines, ICU admission) and trial designs spanning 1956–2024. Corticosteroids were converted to prednisone equivalents (1 mg dexamethasone = 6.7 mg prednisone = 26.7 mg hydrocortisone = 5.3 mg methylprednisolone), and the Cochrane RoB 2.0 tool and GRADE framework assessed bias and evidence certainty. Meta-regression, sensitivity analyses and the ICEMAN tool mitigated heterogeneity and evaluated subgroup credibility. TSA-informed (trial sequential analysis-informed) precision and Bayesian methods addressed uncertainty in smaller subgroups. This study deepened my expertise in synthesizing diverse, heterogeneous datasets, reinforcing the thesis's focus on methodological rigour.

10.3 Summary of Results

This study included 30 RCTs (7,519 patients), expanding on the previous study's 18 RCTs (4,661 patients) by adding REMAP-CAP, 1 post-hoc RCT subgroup and CAP-specific data from 4 sepsis and 4 ARDS trials. Trials spanned 1956–2024, with 79% from 2014 onward. Twenty-two trials

(4,730 patients) focused on severe CAP (ATS/IDSA criteria or ICU admission) and eight (2,789 patients) on non-severe CAP. Corticosteroids included hydrocortisone (13 trials), methylprednisolone (8), prednisone/prednisolone (5), dexamethasone (3) and hydrocortisone with fludrocortisone (1), with daily prednisone-equivalent doses of 29–100 mg.

Main Findings:

- **Short-Term Mortality (29 RCTs, 7,494 patients)**: Corticosteroids probably reduce short-term (30–60 days) mortality (RR 0.82, 95% CI 0.74–0.91; moderate certainty; 31 fewer deaths per 1,000, 95% CI 45 to 16 fewer). Bayesian analysis showed an 86.8% posterior probability of OR < 0.9.
- **Long-Term Mortality (10 RCTs, 4,363 patients)**: Corticosteroids may reduce long-term (90–180 days) mortality (RR 0.89, 95% CI 0.76–1.03; low certainty; 31 fewer deaths per 1,000, 95% CI 67 fewer to 8 more), with a 78.7% posterior probability of OR < 0.9.
- **Invasive Mechanical Ventilation (IMV, 10 RCTs, 2,774 patients)**: Corticosteroids reduce IMV need (RR 0.63, 95% CI 0.48–0.82; high certainty; 37 fewer events per 1,000, 95% CI 52 to 18 fewer).
- **Duration of IMV (9 RCTs, 1,777 patients)**: Corticosteroids probably reduce IMV duration (MD 3.15 days fewer, 95% CI 1.61–4.16; moderate certainty).
- **ICU Stay (11 RCTs, 1,825 patients)**: Corticosteroids may reduce ICU stay (MD 1.53 days fewer, 95% CI 0.31–2.75; low certainty).
- **Hospital Stay (14 RCTs, 3,546 patients)**: Corticosteroids may reduce hospitalisation (MD 2.30 days fewer, 95% CI 0.81–3.81; low certainty).
- **Ventilator-Free Days (7 RCTs, 2,980 patients)**: Corticosteroids may increase ventilator-free days (MD 2.03 days more, 95% CI 0.05 fewer to 4.10 more; low certainty).
- **ECMO (2 RCTs, 602 patients)**: The effect on ECMO need is uncertain (RR 0.90, 95% CI 0.26–3.13; very low certainty).
- **Adverse Events**: Corticosteroids probably increase hyperglycaemia (RR 1.32, 95% CI 1.12–1.56; moderate certainty; 84 more cases per 1,000, 95% CI 31 to 146 more). Effects on secondary infections (RR 0.97, 95% CI 0.85–1.11; moderate certainty),

gastrointestinal bleeding (RR 0.84, 95% CI 0.54–1.30; low certainty) and neuropsychiatric effects (RR 1.25, 95% CI 0.78–2.00; low certainty) are uncertain. Serious adverse events may be reduced (RR 0.75, 95% CI 0.57–0.99; low certainty).

- **Dose-Response Analysis**: A non-linear relationship showed an optimal dose of 60 mg/day prednisone equivalent for short-term mortality (RR 0.78, 95% CI 0.68–0.89).
- **Subgroup Analysis**: No effect modification by corticosteroid type, age, sex or trial population (CAP, sepsis, ARDS). Severity subgroup analysis showed benefits in severe CAP (RR 0.85, 95% CI 0.73–1.00) but not non-severe CAP (RR 1.13, 95% CI 0.83–1.55), with low credibility (ICEMAN). Early vs. late administration showed no difference.

Risk of Bias and Heterogeneity: Eleven trials (36.7%) were at high risk of bias, primarily due to randomisation and intervention deviations. Heterogeneity was moderate for short-term mortality (I^2=47.52%) and higher for secondary outcomes. TSA indicated the required information size was not met for mortality outcomes.

10.4 Discussion

10.4.1 Methodological Insights and Academic Development

This study represents the thesis's methodological apex, synthesizing 30 RCTs with advanced techniques to address CAP's complexity. The integration of Bayesian meta-analysis, alongside pairwise, subgroup and dose-response methods, enhanced precision over the previous study, while collaboration with REMAP-CAP and global investigators broadened the evidence base. Navigating seven decades of trials required meta-regression, ICEMAN and GRADE, building on skills from Chapters 5–9.[73] The study's role in reinforcing the SCCM 2024 guideline underscores evidence synthesis' impact on clinical practice, advancing my expertise in translating heterogeneous data into actionable recommendations.[67]

10.4.2 Clinical Implications

The findings provide moderate-certainty evidence that corticosteroids reduce short-term mortality and IMV need in hospitalised CAP patients, particularly in severe cases, supporting the SCCM 2024 guideline's strong recommendation.[67] The optimal 60 mg/day prednisone-

equivalent dose offers practical guidance, though higher than the 2023 study's 6 mg/day dexamethasone equivalent, reflecting diverse trial regimens. Clinicians should prioritise severe CAP patients, monitor hyperglycaemia and engage in shared decision-making for non-severe cases, where benefits are uncertain. REMAP-CAP's null findings highlight the need for reflection, given its severe CAP focus and potential design differences.

10.4.3 Implications for Research

This update, incorporating REMAP-CAP and ARDS/sepsis subgroup data, reveals new research priorities distinct from prior analyses:

- **Understanding REMAP-CAP's Null Findings**: Investigate why REMAP-CAP showed no benefit, exploring trial design (e.g., adaptive platform vs. traditional RCTs), patient selection (e.g., severe CAP with high baseline mortality) or dosing regimens (e.g., hydrocortisone vs. other corticosteroids). Comparative analyses of REMAP-CAP's protocol against CAPE-COD's could clarify discrepancies.
- **Leveraging ARDS/Sepsis Subgroup Data**: Further analyse CAP-specific subgroups in ARDS and sepsis trials to assess corticosteroid effects in overlapping conditions (e.g., CAP with septic shock or ARDS). Trials targeting these intersections could refine patient stratification.
- **Consensus-Driven Protocol Standardisation**: Build on the 2025 study's global collaboration to develop standardised CAP severity criteria (e.g., updated PSI, Sepsis-3 integration) and outcome measures (e.g., ventilator-free days, 30-day mortality) for future RCTs, reducing heterogeneity.
- **Dose Optimisation Around 60 mg/day**: Conduct RCTs comparing doses near the identified 60 mg/day prednisone-equivalent optimum (e.g., 50 vs. 70 mg/day) to confirm the dose-response curve and assess safety trade-offs, particularly hyperglycaemia.
- **Biomarker-Driven Stratification**: Explore biomarkers (e.g., C-reactive protein, procalcitonin) to identify CAP patients likely to benefit from corticosteroids, leveraging the 2025 study's broader dataset to guide precision medicine approaches.

10.4.4 Next Steps in the Thesis Narrative

This chapter concludes the thesis's exploration of corticosteroids in critical care, synthesizing evidence from Chapters 5–9 to address CAP's controversy. The study's consensus-building effort, despite REMAP-CAP's null results, reinforces the SCCM 2024 guideline but underscores persistent heterogeneity challenges, echoing Dr Rochwerg's editorial on this never-ending story.[19] Future work should integrate biomarkers and precision medicine to tailor corticosteroid use, advancing critical care evidence synthesis beyond this thesis's scope.

Most importantly, this last chapter gives an important lesson: we need continued evidence synthesis to understand the complexity of pulmonary critical care medicine, especially in the face of complex heterogeneity.

Chapter 11: Conclusion and reflections

This PhD by publication has built a narrative of methodological evolution and clinical impact, navigating the landscape of pulmonary and critical care medicine through advanced evidence synthesis. As framed in the Introduction, heterogeneity—clinical (case-mix, severity, co-interventions), methodological (trial design, risk of bias), and statistical (between-study variance)—is the field's central obstacle and the animating problem of this thesis. Accordingly, I made transitivity assumptions explicit, quantified variability (e.g., τ^2 and prediction intervals), and sought to explain it via a priori effect-modifier analyses and model choice. By focusing on two pivotal interventions—non-invasive oxygenation strategies and corticosteroids—across diverse conditions such as COPD, AHRF, fILD, COVID-19, sepsis, and CAP, this thesis has demonstrated how rigorous meta-analytic techniques can transform heterogeneous evidence into actionable clinical guidance. The journey from foundational pairwise meta-analysis to sophisticated network and dose-response methods, culminating in Bayesian approaches, reflects a deliberate progression to address the field's inherent variability and inform patient-centred care.

The narrative begins with the simplicity of pairwise meta-analysis in Chapter 1, where HFNC for chronic hypercapnic COPD was established with moderate-certainty evidence of reduced exacerbations. Here, statistical heterogeneity (I^2, τ^2, and prediction intervals) was made transparent, but this approach, while effective for direct comparisons, proved insufficient for the multifaceted treatment landscapes encountered in subsequent chapters. Pairwise meta-analysis laid a critical foundation, teaching the value of rigorous statistical synthesis and clinical translation, but its limitations in handling multiple interventions underscored the need for more advanced tools. This is the first "loop": the initial heterogeneity problem demanded methods that can compare several active options while preserving assumptions about exchangeability (transitivity). This lesson—that pairwise methods are powerful yet often inadequate alone—set the stage for the thesis's methodological expansion.

NMA, introduced in Chapter 2 and refined in Chapters 3 and 4, emerged as an indispensable tool for clinicians facing complex treatment choices. By enabling both direct and indirect

comparisons, and by explicitly testing for inconsistency (design-by-treatment and comparison-wise checks) and scrutinising pre-specified effect modifiers, NMA allowed for comprehensive evaluations of non-invasive oxygenation strategies, such as HFNC, NIPPV, and helmet CPAP, across chronic and acute settings. In AHRF (Chapter 3), helmet CPAP's superiority in reducing mortality and IMV informed forthcoming ATS guidelines, while in preoxygenation (Chapter 4), NIPPV's benefit in preventing hypoxemia offered practical guidance for critical care. Treatment rankings were presented probabilistically with uncertainty to avoid over-interpreting heterogeneity. NMA's ability to rank treatments and synthesise sparse evidence proved essential, providing clinicians with a clearer path to select effective interventions where head-to-head trials are scarce.

The introduction of dose-response meta-analysis in Chapters 6 through 10 marked a pivotal advancement, directly targeting the most consequential driver of clinical heterogeneity: dose. In COPD (Chapter 6), dose-response analysis suggested a potential chemopreventive effect of ICS against lung cancer, though limited by low-certainty evidence. In acute settings—COVID-19 (Chapter 7), sepsis (Chapter 8) and CAP (Chapters 9 and 10)—this method identified optimal dosing regimens (e.g., 260 mg/day hydrocortisone for sepsis, 6 mg/day dexamethasone for severe CAP, 60 mg/day prednisone for CAP), converting unexplained between-study variability into interpretable exposure–response relationships that map to patient severity and trial design. By modelling treatment effects across dose continuums, dose-response meta-analysis unravelled heterogeneity driven by variable dosing, patient severity and trial designs, offering precise recommendations that informed the SCCM 2024 guidelines. This is the second "loop": what the Introduction flagged as heterogeneity in dose and severity is here decomposed and re-expressed as clinically usable dose–effect contours. This approach proved transformative, demonstrating that heterogeneity, when systematically explored, can yield clarity rather than confusion.

Yet, the thesis's most important lesson is that evidence synthesis is an unending endeavour. The field of pulmonary and critical care medicine, marked by rapidly evolving diseases and conflicting trial results, demands continuous re-evaluation. The contrasting findings of Chapter

9's strong endorsement of corticosteroids in severe CAP and Chapter 10's integration of the REMAP-CAP trial's null results exemplify this challenge. By collaborating with global investigators and publishing updated systematic reviews two years apart (2023 and 2025), this thesis illustrates the necessity of living evidence synthesis to build consensus amidst heterogeneity. In practical terms, this meant restating transitivity assumptions, re-checking inconsistency, and re-estimating effects as new randomised controlled trials (RCTs) arrived—operationalising the Introduction's claim that heterogeneity must be mapped, not averaged away. The REMAP-CAP discrepancy, potentially driven by trial design or patient selection, underscores the need for ongoing RCTs to validate findings, alongside adaptive meta-analyses that incorporate new data. This iterative process, exemplified by the incorporation of ARDS and sepsis subgroup data in Chapter 10, highlights the dynamic interplay between evidence generation and synthesis, ensuring that clinical guidance remains relevant.

11.1 Future directions and next steps:

The thesis's contributions extend beyond methodology to tangible clinical impact. By informing SCCM 2024 guidelines for sepsis and CAP and shaping forthcoming ATS recommendations for AHRF, the findings provide clinicians with evidence-based tools to navigate treatment decisions. However, the persistent challenges—conflicting trial results, the need for biomarker-driven stratification and the call for standardised protocols—point to future directions. Precision medicine, leveraging biomarkers like C-reactive protein or procalcitonin, offers a path to tailor interventions, while methodological innovations, such as Bayesian meta-regression, promise to further refine subgroup analyses. A compact forward framework follows naturally from the Introduction: declare effect-modifier sets a priori (the transitivity set), quantify τ^2 and report prediction intervals, check and explain inconsistency, model dose whenever a gradient is plausible, and maintain living updates as evidence accrues. As Dr Rochwerg aptly noted, the story of corticosteroids in CAP is "without an ending," a reminder that the pursuit of evidence-based care is a continuous journey [19].

Overall, this thesis has charted a course through the complexities of pulmonary and critical care medicine, from the foundational insights of pairwise meta-analysis to the transformative power

of NMA and dose-response methods. It returns to its opening premise: heterogeneity is not noise to be averaged away but structure to be modelled and, when possible, harnessed. It underscores that while heterogeneity poses challenges, it also fuels discovery when met with rigorous synthesis. The call for living evidence synthesis, demonstrated by iterative reviews and global collaboration, ensures that this work is not an endpoint but a foundation for future inquiry. By advancing methodological rigour and clinical applicability, this thesis contributes to the enduring goal of evidence-based, patient-centred care, closing the loop from initial problem statement to practical solutions and paving the way for a new era of precision and clarity in critical care medicine.

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