The epidemiology of hypercapnic respiratory failure

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

Yewon Chung MBBS FRACP

School of Clinical Medicine, UNSW Medicine & Health

South Western Sydney Clinical Campuses

Discipline of Medicine

November 2024

Declarations

ORIGINALITY STATEMENT

☑ I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at UNSW or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at UNSW or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

COPYRIGHT STATEMENT

☑ I hereby grant the University of New South Wales or its agents a non-exclusive licence to archive and to make available (including to members of the public) my thesis or dissertation in whole or part in the University libraries in all forms of media, now or here after known. I acknowledge that I retain all intellectual property rights which subsist in my thesis or dissertation, such as copyright and patent rights, subject to applicable law. I also retain the right to use all or part of my thesis or dissertation in future works (such as articles or books).

For any substantial portions of copyright material used in this thesis, written permission for use has been obtained, or the copyright material is removed from the final public version of the thesis.

AUTHENTICITY STATEMENT

☑ I certify that the Library deposit digital copy is a direct equivalent of the final officially approved version of my thesis.

Inclusion of publications statement

☑ The candidate has declared that **their thesis has publications - either published or submitted for publication - incorporated into it in lieu of a Chapter/s. Details of these publications are provided below.**.

Publication Details #1

Full Title:	Population prevalence of hypercapnic respiratory failure from any cause
Authors:	Yewon Chung, Frances L Garden, Guy B Marks, Hima Vedam
Journal or Book Name:	American Journal of Respiratory and Critical Care Medicine
Volume/Page Numbers:	205(8):968-970
Date Accepted/Published:	15 April 2022
Status:	published
The Candidate's Contribution to the Work:	Yewon Chung conceived and designed the study (equal), developed the study protocol (primary), collected and analysed data (primary), drafted the first manuscript (primary), reviewed the work critically for important intellectual content (equal), submitted the final version for publication and responded to reviewer comments (equal).
Location of the work in the thesis and/or how the work is incorporated in the thesis:	This work is located in Chapter 4. This chapter describes the population prevalence of hypercapnic respiratory failure due to any cause. An introductory section is followed by the work reproduced verbatim in Section 4.2.

Publication Details #2

Full Title:	Causes of hypercapnic respiratory failure and associated in-hospital mortality
Authors:	Yewon Chung, Frances L Garden, Guy B Marks, Hima Vedam
Journal or Book Name:	Respirology
Volume/Page Numbers:	28(2):176-182
Date Accepted/Published:	19 September 2022
Status:	published
The Candidate's Contribution to the Work:	Yewon Chung conceived and designed the study (equal), developed the study protocol (equal), collected and analysed data (equal), drafted the first manuscript (equal), reviewed the work critically for important intellectual content (equal), submitted the final version for publication and responded to reviewer comments (equal).
Location of the work in the thesis and/or how the work is incorporated in the thesis:	This work is located in Chapter 5. This chapter describes the range of potential causes among people with hypercapnic respiratory failure. An introductory section is followed by the work reproduced verbatim in Section 5.2.

Publication Details #3

Full Title:	Causes of hypercapnic respiratory failure: a population-based case-control study
Authors:	Yewon Chung, Frances L Garden, Guy B Marks, Hima Vedam
Journal or Book Name:	BMC Pulmonary Medicine
Volume/Page Numbers:	23:347
Date Accepted/Published:	7 September 2023
Status:	published
The Candidate's Contribution to the Work:	Yewon Chung conceived and designed the study (equal), developed the study protocol (primary), collected and analysed data (primary), drafted the first manuscript (primary), reviewed the work critically for important intellectual content (equal), submitted the final version for publication and responded to reviewer comments (equal).
Location of the work in the thesis and/or how the work is incorporated in the thesis:	This work is located in Chapter 6. This chapter describes the strength of association between potential causes and the outcome of hypercapnic respiratory failure. An introductory section is followed by the work reproduced verbatim in Section 6.2.

Publication Details #4

Full Title:	Long-term cohort study of patients presenting with hypercapnic respiratory failure
Authors:	Yewon Chung, Frances L Garden, Guy B Marks, Hima Vedam
Journal or Book Name:	BMJ Open Respiratory Research
Volume/Page Numbers:	11:e002266
Date Accepted/Published:	20 July 2024
Status:	published
The Candidate's Contribution to the Work:	Yewon Chung conceived and designed the study (equal), developed the study protocol (primary), collected and analysed data (primary), drafted the first manuscript (primary), reviewed the work critically for important intellectual content (equal), submitted the final version for publication and responded to reviewer comments (equal).
Location of the work in the thesis and/or how the work is incorporated in the thesis:	This work is located in Chapter 7. This chapter describes the clinical outcomes, including risk of death, associated with hypercapnic respiratory failure. An introductory section is followed by the work reproduced verbatim in Section 7.2.

Candidate's Declaration

I confirm that where I have used a publication in lieu of a chapter, the listed publication(s) above meet(s) the requirements to be included in the thesis. I also declare that I have complied with the Thesis Examination Procedure.

Abstract

Hypercapnic respiratory failure is a condition that is encountered commonly by many clinicians. It can occur in association with a range of respiratory, cardiovascular, metabolic and neurological disorders, either alone or in combination. Most of the current literature is limited to case series with specific underlying diagnoses or in receipt of a particular medical intervention. There have been no epidemiological studies on hypercapnic respiratory failure irrespective of the underlying cause.

This thesis includes four original research publications addressing the epidemiology of hypercapnic respiratory failure. These studies are based on the same population, residents of the metropolitan area of Liverpool in Sydney, Australia. The first is a cross-sectional study describing, for the first time, the prevalence of this condition within a given population. The second study uses medical record data to describe the frequency of potential causes. The third is a field study in which cases of hypercapnic respiratory failure are compared with control participants recruited from the same population. This case-control study is the first to describe causal associations with reference to a control group. The fourth is an historical cohort study using linked health data to describe clinical outcomes including rates of death and rehospitalisation.

There are several important findings arising from this work. Hypercapnic respiratory failure is shown to be a common condition, affecting 163 (95% confidence interval 154 to 172) cases per 100,000 population. The most important risk factor in a population is confirmed to be chronic obstructive pulmonary disease, with opioid use and congestive heart failure also demonstrated to be substantial contributors. The standardised mortality ratio of 9.2 (95% confidence interval 7.6 to 11.0) indicates a near ten-fold risk of death compared with unaffected persons of a similar age.

The body of work comprising this thesis represents a significant contribution to knowledge regarding the epidemiology of hypercapnic respiratory failure. This information is of fundamental importance in both clinical practice and health policy. The data provided in these studies allows for comparison across multiple populations and forms a foundation for future studies including evaluation of interventions directed at prevention and management.

Table of contents

Acknowledgements

This work could not have been completed without the support and contributions of many, to whom I wish to express my sincere thanks.

I am privileged to have been supervised by a trio of tremendously talented individuals. Dear Hima, thank you for your encouragement and support. Your enthusiasm for research and passion for patient care has been, and continues to be, an inspiration. To Guy, thank you for your generosity and guidance, particularly in fostering a spirit of systematic discovery. To Frances, thank you for your patience and understanding; your teaching and advice have been second to none. I have learned so much from you all, not only in how to conduct research, but how to conduct myself as a clinician, colleague, supervisor, and friend.

To everyone in the Department of Respiratory and Sleep Medicine at Liverpool Hospital, thank you for being so accommodating during this period. A special thanks to Zinta for her ceaseless enthusiasm and allowing me enough reprieve from clinical duties to complete this thesis. I would also like to extent my gratitude to the research staff at the Ingham Institute without whom study recruitment would not have been possible.

I would like to acknowledge Maridulu Budyari Gumal, the Sydney Partnership for Health, Education, Research and Enterprise, for providing much of the funding for this study.

Thank you to the Medical Records Department at Liverpool Hospital for responding to each and every request, to Sydney South West Pathology Service for providing the necessary data, and to the Centre for Health Record Linkage for their indispensable services. I would also like to thank Lauren Wang for her assistance with many of the illustrations.

To the people of south-western Sydney, especially those from the Liverpool Local Government Area who contributed by participating in the case-control study, you have my deepest appreciation and respect. Thank you.

Behind any successful researcher is a long-suffering family, for whom these expressions of gratitude seem woefully inadequate. To Amma and Appa, thank you for your warmth and love. To my amazing Amma especially, who has cared for my son during the many hours of my candidature. To my irreplaceable sister Lauren, whose perspective on life and love and work has been invaluable. To my precious Jay, for whom I wish the most amazing future.

And most of all, my heartfelt gratitude to the love of my life and best friend, Ahilan, who has borne the brunt of all that entails when one embarks on this journey. Thank you for being my rock, for allowing me to flourish, and for always knowing how to make me laugh. I could not have done this without you.

Abbreviations and symbols

ABG	Arterial blood gas
AHI	Apnoea-hypopnoea index
APDC	Admitted Patient Data Collection
AUC	Area under the receiver operator characteristic curve
BMI	Body mass index
CCF	Congestive cardiac failure
CCI	Charlson Comorbidity Index
CHeReL	Centre for Health Record Linkage
CI	Confidence intervals
COPD	Chronic obstructive pulmonary disease
DAG	Directed acyclic graph
EDDC	Emergency Department Data Collection
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
HR	Hazard ratio
HRF	Hypercapnic respiratory failure
ICD	International Classification of Diseases
IQR	Interquartile range
LGA	Local government area
LLN	Lower limit of normal
NIV	Non-invasive ventilation
NMD	Neuromuscular disease
NSW	New South Wales
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
OR	Odds ratio
OSA	Obstructive sleep apnoea
PAF	Population attributable fraction
PAP	Positive airway pressure
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
RBDM	Registry of Births, Deaths and Marriages
ROC	Receiver operator characteristic

SaO_2	Oxygen saturation of arterial blood
SpO_2	Oxygen saturation of arterial blood as detected by pulse oximetry
SD	Standard deviation
SDB	Sleep-disordered breathing
SMR	Standardised mortality ratio
SNIP	Sniff nasal inspiratory pressure
$SNIP_{max}$	Maximum sniff nasal inspiratory pressure
SRG	Service related group
$\dot{V}_A$	Alveolar ventilation
$\dot{V}_{CO2}$	Carbon dioxide production
$\dot{V}_D$	Dead space ventilation
$\dot{V}_E$	Minute ventilation

List of figures

List of tables

1. Introduction

1.1 Introduction

The primary function of the human respiratory system is facilitating the exchange of gases between the host and atmosphere by means of ventilation, the movement of air in and out of the lungs. Ventilation is required to support cellular respiration, the oxygen-dependent process by which the body extracts energy. Atmospheric oxygen (O_2) is taken up during inhalation, and waste carbon dioxide (CO_2) is excreted during exhalation. When the respiratory system fails to function adequately or appropriately, one of the potential consequences is the accumulation of excess carbon dioxide in the blood, otherwise known as hypercapnia or hypercarbia. The presence of hypercapnia is, *ipso facto*, the defining feature of hypercapnic respiratory failure. This is a serious condition associated with adverse clinical outcomes including increased risks of hospitalisation and death.

Hypercapnic respiratory failure can occur as a consequence of pathology affecting any component of the respiratory system involved in ventilation. As such, there are a multitude of potential causes for hypercapnic respiratory failure. Some people have a single disease, such as chronic obstructive pulmonary disease (COPD), of such severity that hypercapnia ensues. Others have more than one coexistent cause with the potential to contribute to hypercapnia. Even though hypercapnic respiratory failure is clearly a heterogenous entity, there are several arguments to support its consideration as a distinct clinical phenomenon.

For instance, in some people who attend hospital with hypercapnia, the underlying cause or causes may not be immediately apparent. Therefore, epidemiological data from studies limited to specific conditions have limited generalisability to clinical scenarios involving multi-morbid patients or patients with undifferentiated hypercapnic respiratory failure.

The body of work described in this thesis arose in response to the multitude of questions, arising from my clinical encounters involving patients with hypercapnic respiratory failure, that were unable to be answered from review of the available literature. *How common is this condition? Why does it occur? What are the most important causes? What is the prognosis?* It became clear that further information would be required in order to develop and implement evidence-based interventions to reduce associated morbidity and mortality.

1.2 Thesis goal and objectives

The overall goal of this thesis was to describe the epidemiology of hypercapnic respiratory failure at a population level. Much of the information generated from this work is the first of its type and provides a basis for future studies on screening and intervention for at-risk groups, and evaluation of management pathways for those with established disease.

My specific aims were:

1. To describe the population prevalence of hypercapnic respiratory failure;
2. To describe the contributing causes of hypercapnic respiratory failure and their relative importance in contributing to the overall disease burden; and
3. To describe the clinical outcomes associated with this condition.

1.3 Thesis structure and overview

This thesis is comprised of written chapters interspersed with four scientific publications arising from my work in the area of hypercapnic respiratory failure. These publications, included in lieu of some chapters, have already been peer reviewed and published in their respective journals. The text in these chapters are verbatim reports of the original publications, although page layouts, some headings, table and figure numbers and referencing styles have been edited to improve readability.

Following this introductory Chapter, a background literature review and the rationale to consider hypercapnic respiratory failure as a single entity is presented in Chapter 2. The overall study design is presented in Chapter 3, forming the basis for the research works presented in subsequent chapters.

Chapter 4 describes the population prevalence of hypercapnic respiratory failure. Included is a research letter published in the *American Journal of Respiratory and Critical Care Medicine*, a publication of the American Thoracic Society.

Chapter 5 describes the range of potential causes contributing to hypercapnic respiratory failure. Included is an original research article published in *Respirology*, the official journal of the Asian Pacific Society of Respirology. Chapter 6 further explores the causes of hypercapnic respiratory failure, including the relative importance of each cause at a population level. This is an original research article published in *BMC Pulmonary Medicine*.

Chapter 7 describes the long-term risk of death and rehospitalisation in a cohort of people who develop hypercapnic respiratory failure. Included is an original article that has been published in *BMJ Open Respiratory Research*.

A summary of key findings and discussion particularly with respect to implications for future research are presented in Chapter 8.

1.4 Chapter summary

The work described in this thesis represents the first epidemiological exploration of hypercapnic respiratory failure as a single entity, at the population level. It addresses a number of relevant clinical questions and a gap in knowledge unable to be answered from previous studies. The results from these studies provide baseline data to plan future studies on interventions to mitigate the impact of this condition.

2. Background

2.1 Definitions

The respiratory system in humans consists of the tracheobronchial tree, the lung parenchyma, and supporting vascular and musculoskeletal structures (Figure 2.1). For effective ventilation and gas exchange to occur, these components must work in coordination seamlessly. This system must also be able to respond to perturbations, mediated through a range of biochemical processes and neural inputs. When compensatory mechanisms are insufficient to overcome pathology affecting any component part or process in this system, respiratory failure occurs.

Conventional definitions of respiratory failure relate to the primary function of the respiratory system, to exchange atmospheric oxygen with the waste product of aerobic metabolism, carbon dioxide. That is, respiratory failure is typically based on the degree of hypoxia or hypercapnia, confirmed by measurement of these gases in arterial blood. Hypercapnic respiratory failure (HRF), or 'type 2' respiratory failure, refers to a subcategory of respiratory failure caused by insufficient or ineffective ventilation that leads to elevated levels of carbon dioxide. Alveolar hypoventilation ($\dot{V}_A$), either due to decreased minute ventilation ($\dot{V}_E$) or increased dead space ventilation ($\dot{V}_D$), with or without excess carbon dioxide production ($\dot{V}_{CO2}$), leads to excess carbon dioxide accumulation. These physiological mechanisms for hypercapnia are illustrated in the respiratory equation:

$$PaCO_2 = k \cdot \frac{\dot{V}_{CO_2}}{\dot{V}_A} = k \cdot \frac{\dot{V}_{CO_2}}{\dot{V}_E - \dot{V}_D}$$

where k is the constant of proportionality (0.863). The generally accepted upper limit of normal for arterial carbon dioxide tension ($PaCO_2$) is 45 mmHg (6.0 kPa), and values above this threshold allow for a laboratory diagnosis of hypercapnia (1).

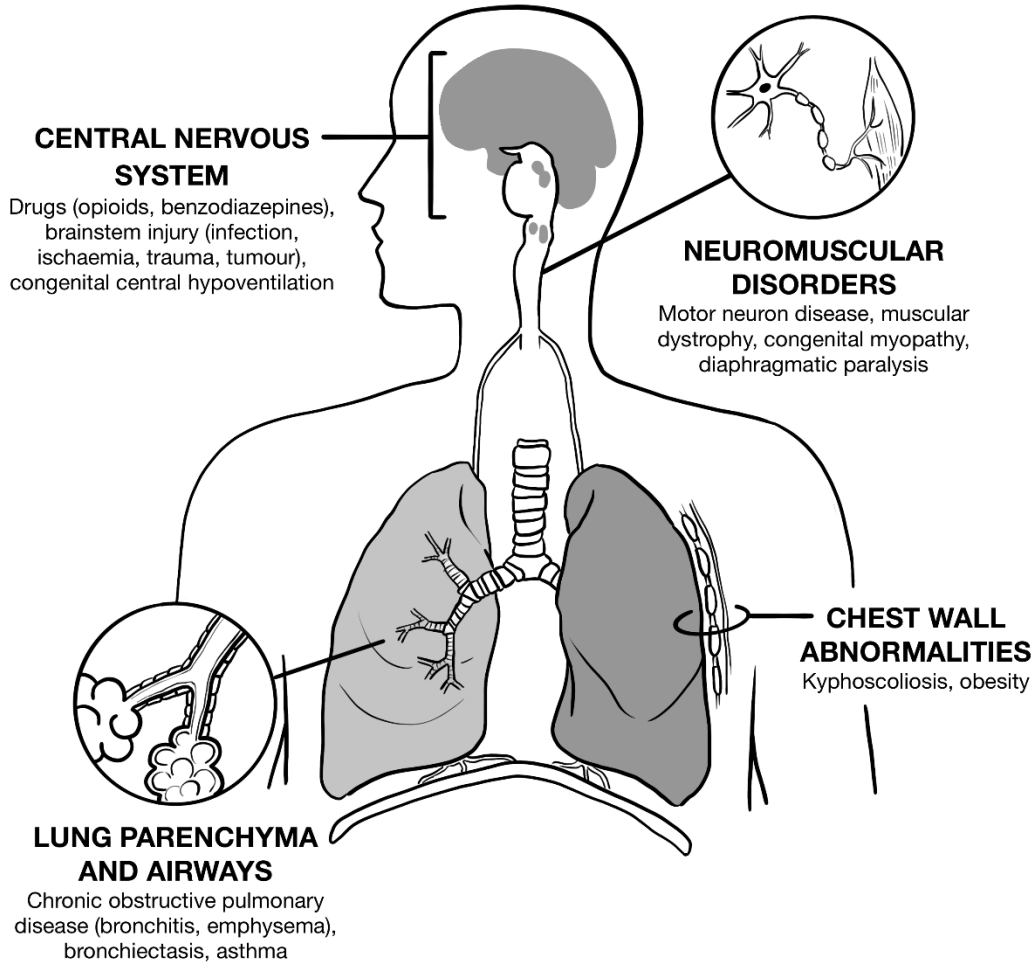

Figure 2.1. *Causes of hypercapnic respiratory failure. A diverse range of potential causes can affect various components of the respiratory system and contribute to the development of hypercapnia. This is a non-exhaustive list of causes. Illustration by L. Wang.*

In its simplest iteration, HRF can be defined, *ipso facto*, by a $PaCO_2$ greater than 45 mmHg (1). Whilst convenient, this threshold is not consistently employed in current literature. Different groups have used higher $PaCO_2$ cutoff values of 47 mmHg (6.3 kPa) (2), 50 mmHg (6.5 kPa) (3), and 60 mmHg (8.0 kPa) (4). The reasons for selection of these values are not explicitly stated, but a higher $PaCO_2$ threshold may identify people at greater risk of adverse outcomes (3), and hence an operational definition of HRF with greater clinical utility.

Another defining criterion used inconsistently throughout studies of persons with HRF is the arterial pH. Acute hypercapnia is accompanied by a respiratory acidosis as reflected by a pH less than 7.35, the lower limit of normal. However, when hypercapnia persists over days to weeks, renal compensatory (or homeostatic) mechanisms increase serum bicarbonate tending to increase pH towards normal (5). Thus, studies of HRF often distinguish between acute and chronic HRF based on the observed pH (3,6). However, the distinction between these two states can be challenging, as acute clinical deterioration and a fall in pH can be observed in patients with chronic HRF after a seemingly minor pathological insult (1). Conversely, repeated, transient episodes of acute CO_2 retention in obstructive sleep apnoea are postulated to stimulate renal bicarbonate retention and the diurnal hypercapnia that occurs in obesity hypoventilation syndrome (5). A pH above 7.45 indicates alkalosis, and an elevated $PaCO_2$ in this context is usually considered compensatory hypoventilation due to primary metabolic pathology.

A precise and unambiguous case definition is essential for describing the epidemiology of HRF (7). Quantitative thresholds for the presence and/or degree of hypercapnia, acidosis, hypoxia and respiratory symptoms, among other diagnostic criteria for HRF, have neither been explicitly nor consistently stated in previous studies. As such, a flexible and iterative process was implemented in order to identify a range of previous studies relating to the epidemiology of this condition.

2.2 Rationale to consider HRF for epidemiological study

HRF is a physiological derangement and can be observed in association with a range of different disease processes. However, there are several reasons to consider HRF as a single condition for the purposes of epidemiological study.

2.2.1. Multimorbidity

The first reason to consider HRF as a distinct phenomenon is that, in many individuals, multiple underlying causes with the potential to cause hypercapnia may coexist. As such, epidemiological studies relating to individual, specific causes have limited generalisability to clinical encounters with multimorbid patients. In 1976, Rothman conceptualised disease as the effect of *sufficient cause*, which can be decomposed into *necessary* and *component* causes (8). HRF is associated with a range of sufficient cause sets (Figure 2.2). Some patients with hypercapnia have one disease, such as COPD, that is severe enough to cause ventilatory insufficiency in the absence of other pathologies. Others with HRF have multiple diseases which may act together in parallel or even synergistically. For instance, systematic evaluation of survivors of an episode of acute hypercapnic respiratory failure revealed that more than half had at least three comorbidities that might have potentiated HRF (2). A focus on individual diagnoses fails to recognise the co-occurrence of multiple diseases, or multimorbidity, that is frequently encountered in clinical practice. Studies of HRF as a single, unified entity are required to understand the relative importance of these contributing diseases.

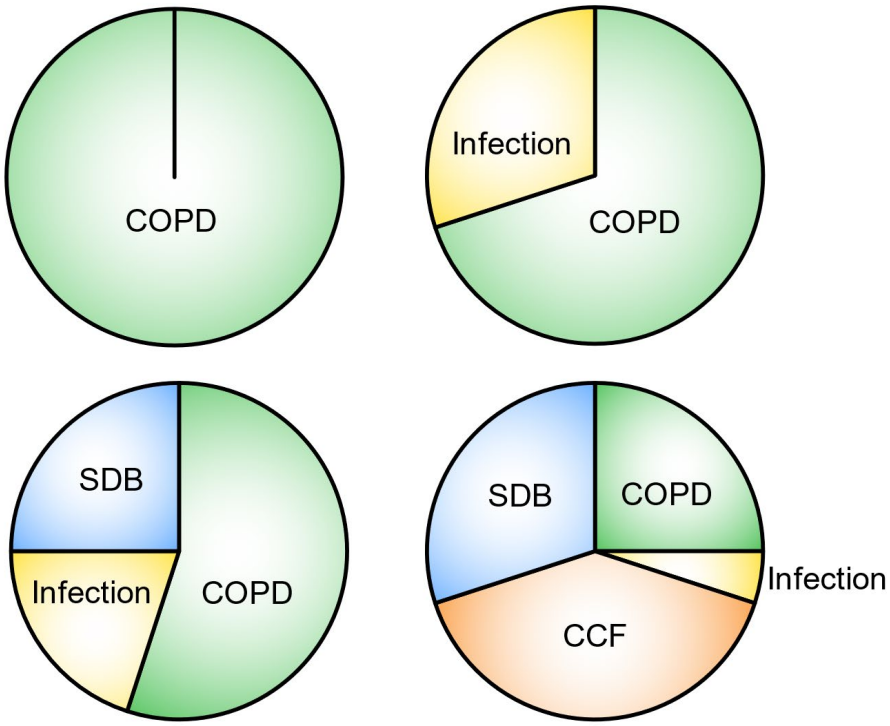

Figure 2.2. *Cause sets for hypercapnic respiratory failure. A single diagnosis of sufficient severity or multiple diagnoses working together may lead to hypercapnic respiratory failure. COPD Chronic obstructive pulmonary disease, SDB Sleep-disordered breathing, CCF Congestive cardiac failure.*

2.2.2. Prognostication

The second reason to focus on hypercapnia is that it represents a subset of patients at greater risk of adverse clinical outcomes. In many diseases, hypercapnia is a marker of severe disease and worse prognosis. For instance, $PaCO_2$ is proposed to be an independent risk factor for mortality among patients with COPD (9). Obese patients with hypercapnia have increased measures of healthcare utilisation compared with age- and BMI-matched controls (10). Ventilatory failure resulting from respiratory muscle weakness is a common cause of death among patients with neuromuscular disease (5). As such, people with hypercapnic respiratory failure represent a high-risk group and a potential target for interventions to reduce adverse health outcomes in a population.

2.2.3. Common treatments

Another reason to consider HRF as a single condition is that many people with hypercapnia receive similar treatments. Whilst most patients with hypercapnia require disease-specific therapies, many require non-specific interventions such as hospitalisation, often to a dedicated respiratory or intensive care unit, and mechanical ventilatory support. A robust body of evidence exists for the efficacy of non-invasive ventilation (NIV) therapy in acute HRF due to COPD (11). There is also increasing data regarding the efficacy of domiciliary NIV for COPD associated with chronic hypercapnia (12). However, these trials typically exclude patients with additional causes for HRF. It is worthwhile noting that many current clinical guidelines support the use of NIV for acute HRF due to multiple causes, despite a lack of trials in multimorbid patients. Shifting the paradigm to consider HRF as a unified entity will improve the generalisability of future studies to clinical practice.

2.2.4. Improved research focus

Finally, it is time to consider HRF as its own entity, analogous to other diseases that have received greater focus in clinical research. Many studies of interventions in acute respiratory failure have focused on the presence of hypoxia, irrespective of the underlying cause. For example, one study on the efficacy of high-flow oxygen delivered through nasal cannulae recruited patients with a range of causes for acute, non-hypercapnic, hypoxaemic respiratory failure (13). Outside the discipline of pulmonary medicine, a wealth of epidemiological data is available on chronic renal failure (14), congestive cardiac failure (15) and many other conditions associated with substantial heterogeneity in cause and clinical features. Overall, there is little to justify the current lack of evidence on the epidemiology of HRF, as described in the remainder of this Chapter.

2.3 Previous studies: Incidence and prevalence

The occurrence of disease in a given population can be quantified using the epidemiological measures prevalence and incidence. Prevalence, or point prevalence, measures the proportion of people with disease at a given point in time. In contrast, incidence measures the proportion who develops the disease for the first time over a pre-specified time period (7). Together, these measures form the basis for descriptive epidemiology and provide a template for answering the first question addressed in this thesis: *How common is this condition?*

Surprisingly, no studies exist on the prevalence or incidence of hypercapnic respiratory failure due to any cause. Traditional disease surveillance methods rely upon conducting epidemiological surveys, undertaking direct measurements in a carefully and systematically selected sample representative of the target population (7). Notwithstanding the variations in diagnostic $PaCO_2$ thresholds as already described above, a field study to determine the prevalence of hypercapnia is currently unfeasible due to the absence of a suitable method of measurement. The detection of hypercapnia requires arterial blood gas (ABG) sampling to directly measure $PaCO_2$. Obtaining an ABG is an invasive procedure that imposes some degree of discomfort, and must be performed by a skilled technician with timely access to a blood gas analyser machine. It is thus impracticable to perform ABG measurements across a large population sample to identify cases of hypercapnia.

Several alternative techniques are available to obtain indirect estimates of $PaCO_2$. These include arterialised capillary blood gas and venous blood gas analysis, measurement of carbon dioxide from exhaled air, via capnography, and from the skin, using a transcutaneous sensor. Many of these techniques have reasonable accuracy and are used variably in a range of clinical settings in conjunction with $PaCO_2$ measurements (16).

However, none are sufficiently accurate, accessible or affordable to replace ABG sampling for the purpose of screening an entire population.

Another approach to estimate disease frequency is to repurpose routinely collected clinical information. The repurposing of data for clinical research is particularly convenient when data have been digitised and/or structured into standardised disease codes (17). The most widely recognised of these codes is the International Classification of Diseases (ICD), a globally used system published and routinely updated by the World Health Organization (WHO) and co-opted for use, at times with modification, by health services around the world (18). However, specific codes for respiratory failure associated with hypercapnia were introduced only in 2009 as an update to the 10th revision of the ICD (19). There are no studies validating the use of these codes to confirm the presence of HRF, and studies of other conditions such as obstructive sleep apnoea have found that diagnostic codes can have extremely poor sensitivity due to incomplete recording of health information (20).

While there are no data on HRF as a single entity, limited prevalence data are available for specific subgroups according to the underlying diagnosis or treatment received. Some people with chronic HRF require domiciliary mechanical ventilation and are enrolled into treatment databases. These databases serve administrative and clinical needs but also provide some information on disease frequency as most patients enrolled in these databases have chronic HRF (21-28). Given that not all patients with HRF receive home ventilation treatment, the population prevalence derived in each of these studies can be considered a minimum value only.

There is only one published population-based study reporting the prevalence of HRF in patients with chronic obstructive pulmonary disease (COPD) (29). The prevalence of respiratory acidosis reflecting cases of acute and acute-on-chronic HRF, for a one year period (1997-1998), standardised for the population of England and Wales, was 75 per

100,000 per year (95% confidence interval 61 to 90) for men and 57 per 100,000 per year (46 to 69) for women. Of note, the purpose of conducting this study was to model the requirements for NIV services, a treatment that is applicable to other causes of HRF besides COPD, further justifying the need to measure the prevalence of HRF as a whole.

2.4 Previous studies: Causes

Understanding the cause or causes of a health problem is of fundamental importance in public health and one of the major aspirations in analytical epidemiology. To identify specific causes, comparisons of disease occurrence must be made between those with and without the cause, or exposure, of interest. It is only by making these comparisons that associations can be quantified in order to answer the question: *Why does this condition occur?*

Several studies have described the frequency of underlying diagnoses among selected groups of people with HRF. The majority of these studies have found COPD, particularly when associated with an acute exacerbation, is the most commonly reported cause for hypercapnia when encountered in the acute setting (2,6,30-35). For instance, in a study of 78 patients who survived an episode of acute HRF, 52 (67%) were subsequently confirmed to have COPD based on spirometric evaluation (2). In another study of 69 patients commenced on NIV therapy outside the intensive care unit, 41 (59%) had a recorded diagnosis of COPD in their hospital records. The relative importance of COPD in chronic HRF is also suggested by studies of home mechanical ventilation usage patterns, being recorded as the primary indication for therapy in 8 to 28% of the study sample (21,22).

Another frequently observed diagnosis in surveys of people with HRF is congestive cardiac failure (CCF), including episodes of acute pulmonary oedema (APO). In most studies, CCF

has been found to be the second most frequent potential cause, after COPD, to account for the episode of HRF (6,30-33). Furthermore, a study of 491 patients with compensated HRF without respiratory acidosis found CCF to be the most commonly recorded diagnosis, being present in 220 (44.8%) of the cohort (3). Previous studies have shown that hypercapnia is present in up to 33% of patients with acute heart failure (36,37), and HRF in association with CCF can occur even in the absence of COPD (38). A recent study found that the prevalence of respiratory failure in patients admitted to a cardiac intensive care unit had increased from 15% to 38% from 2007 to 2018, conceding that study measurements were based on ICD codes rather than specific arterial blood gas parameters (39).

Sleep-disordered breathing (SDB) is often implicated in patients with HRF. Previous studies of HRF survivors have demonstrated a high prevalence of obstructive sleep apnoea (OSA), up to 83%, based on objective testing with overnight polysomnography (2,40,41). A subset of these patients do not have other potential causes for hypercapnia, and meet the diagnostic criteria for obesity hypoventilation syndrome (OHS), a closely associated sleep-related breathing disorder (42). Although most (90%) patients with OHS have OSA, a minority do not (43,44). In these patients, it is postulated that the normal physiological changes that occur during sleep predispose vulnerable individuals to nocturnal hypoventilation, and subsequent daytime ventilatory failure. A similar process can occur in patients with other conditions such as obstructive or restrictive lung disease and neuromuscular disorders (5,45-47). As such, whilst the specific diagnosis of OSA may be considered a directly antecedent cause for HRF, the broader category of sleep-disordered breathing allows for inclusion of the intermediary diagnosis of sleep hypoventilation and other causes that contribute to the development of hypercapnia. These pathways are illustrated in Figure 2.3.

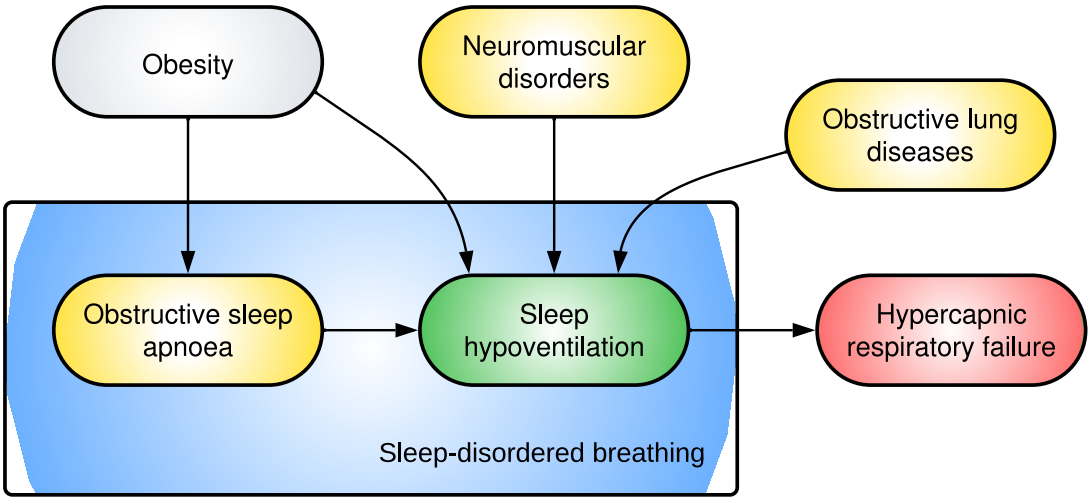

Figure 2.3. *Causal pathway between obstructive sleep apnoea and hypercapnic respiratory failure.*

Potential causes for HRF are diverse, and the detection of specific diagnoses appear limited only by the methodology in previous studies. Respiratory infections, including pneumonia, appear to be an important precipitant in the few studies in which it has been included as a potential cause (33,48,49). A range of drugs including benzodiazepines and opioids have sedative properties that may precipitate HRF; one study excluded four patients with drug overdose, yet found the prevalence of opioid use prior to baseline as 14.6% (6). In another study, opioids were determined to be the cause for HRF in 3.6% of presentations (33). A few studies have also described the relatively high prevalence of multiple potential causes occurring together within the same individual (2,6,32), giving credence to the assertion that HRF arises once the presence and severity of one or more of several conditions result in sufficient derangement of ventilation to trigger HRF.

The studies described so far vary substantially in design, particularly in their inclusion criteria and methods of measurement to ascertain contributing diagnoses. Of note, in many of these studies, screening for potential participants occurs upon admission to a critical

care unit or upon commencement of invasive or non-invasive ventilatory support therapy (2,30-32,48,49). Some people with HRF may not receive these interventions, and their exclusion can lead to under- or overrepresentation of certain diagnoses. The effect of selection bias is apparent when reviewing the range of causes among registry studies of patients receiving home non-invasive ventilation therapy, where conditions such as neuromuscular disease and kyphoscoliosis account for a much greater proportion of contributing causes (22,23). A number of studies of causes for HRF identified at hospital presentation have explicitly excluded patients with advanced cancer or limited life expectancy (2,34). However, these are not the only studies susceptible to survivorship bias because some investigations, such as sleep studies, can only be performed during a period of clinical stability and therefore only after survival of the initial HRF episode.

An important feature of all studies of HRF causes to date is that none have included a comparison group from the source population. That is, the likelihood of a specific cause being present in someone with HRF has never been compared with the likelihood of that same cause being present in someone without HRF from the same population. This is particularly important because some causes, such as COPD and OSA, are relatively common, particularly in older age groups (50,51). Hence, whilst previous studies provide some information on the range of diagnoses observed among people with HRF, further work is required to test the hypotheses that each of these diagnoses is actually causally related to the presence of HRF.

2.5 Previous studies: Outcomes

Accurate epidemiological data are fundamental to health planning and service provision. Social and health interventions may be directed towards prevention of a disease, thereby reducing the incidence rate. However, if the disease had previously been associated with an

increased risk of death, a treatment proven to reduce this risk may lead to an increased prevalence of people with the disease. Clearly, understanding the clinical trajectory or outcomes of a disease such as HRF are critical to interpreting associated measures of morbidity and mortality.

Many of the hospital-based studies described so far have documented the rates of in-hospital and subsequent death in respective cohorts. Again, the results of these studies are highly variable, likely due to the marked heterogeneity in study samples as well as the study settings. One study found that among 212 people who were discharged from hospital after an episode of undifferentiated, acute HRF, 19 (9%) had died after 1 year of follow-up (6). This is one of the more modest estimates, with other studies finding 36% and 44% of patients had died after a similar period (3,34). These studies did not differentiate between deaths that occurred at the time of index presentation, potentially accounting for some of the discrepancy.

A significant limitation of these studies is that they have, without exception, focused entirely on their respective case series, without reference to the population from which that case series was drawn. That is, no studies have described the crude mortality rate, nor determined the mortality rate relative to a standardised population. Although knowledge of survival rates can help counteract pessimism in clinical decision-making (35), understanding mortality rates can allow evaluation of health interventions on a broader scale. This is because survival time can be improved simply by early detection of disease without actually altering the natural history of the disease. However, mortality rate can only be improved by implementing measures that reduce the disease incidence or mortality, the incidence of death from that disease.

2.6 Summary

Few studies exist on the epidemiology of hypercapnic respiratory failure. A limited range of cross-sectional and cohort studies provide some information from which some inferences can be made regarding disease frequency, risk factors, and outcomes. These studies vary substantially in their methods, data sources, inclusion criteria and outcome measures. Whilst most are based on health record data, a few have also prospectively evaluated people with confirmed hypercapnia. However, no studies exist on the risks of HRF in association with hypothesised exposures. Overall, the frequency of HRF is inadequately documented and the relative importance of contributing causes in is poorly understood.

There are several reasons to account for the lack of literature: 1) there are no clearly defined criteria for what constitutes HRF; 2) HRF is a physiological state and not a specific disease; 3) the diagnosis of HRF requires a procedure that is not readily accessible for community-wide screening; 4) there are no disease-specific registries; and 5) routinely collected health information such as diagnosis codes have poor sensitivity for capturing this condition. Despite these impediments, understanding the population distribution and determinants of HRF is the first step, and a necessary one, to develop interventions to reduce the morbidity and mortality associated with this condition.

The purpose of this thesis is to address many of the deficiencies in the existing body of knowledge. Included as part of this thesis are several original research studies drawing on robust epidemiological methods to describe the frequency, cause and outcomes associated with hypercapnic respiratory failure. These studies are described further in the following chapter. The generalisability of findings from these studies will be limited to the sampled population. However, this research contributes valuable information specifically to the Australian context and provide a basis for comparing results from future studies locally and beyond.

2.7 Chapter references

1. Roussos C, Koutsoukou A. Respiratory failure. *Eur Respir J* 2003;22:3s–14s.
2. Adler D, Pépin JL, Dupuis-Lozeron E, Espa-Cervena K, Merlet-Violet R, Muller H, *et al*. Comorbidities and subgroups of patients surviving severe acute hypercapnic respiratory failure in the intensive care unit. *Am J Respir Crit Care Med* 2017;196:200–207.
3. Wilson MW, Labaki WW, Choi PJ. Mortality and healthcare use of patients with compensated hypercapnia. *Ann Am Thorac Soc* 2021;18:2027–2032.
4. Girault C, Briel A, Hellot MF, Tamion F, Woinet D, Leroy J, *et al*. Noninvasive mechanical ventilation in clinical practice: a 2-year experience in a medical intensive care unit. *Crit Care Med* 2003;31:552–559.
5. Piper AJ, Yee BJ. Hypoventilation Syndromes. *Compr Physiol* 2014;4:1639-76.
6. Cavalot G, Dounaevskaia V, Vieira F, Piraino T, Coudroy R, Smith O, *et al*. One-year readmission following undifferentiated acute hypercapnic respiratory failure. *COPD* 2021;18:602–611.
7. Coggon D, Barker D, Rose G. *Epidemiology for the Uninitiated*. John Wiley & Sons; 2009.
8. Rothman KJ. Causes. *Am J Epidemiol* 1976; 104: 587–592.
9. Yang H, Xiang P, Zhang E, Guo W, Shi Y, Zhang S, *et al*. Is hypercapnia associated with poor prognosis in chronic obstructive pulmonary disease? A long-term follow-up cohort study. *BMJ Open* 2015;5:e008909.
10. Berg G, Delaive K, Manfreda J, Walld R, Kryger MH. The use of health-care resources in obesity-hypoventilation syndrome. *Chest* 2001;120:377–383.
11. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017;7:CD004104.
12. Raveling T, Vonk J, Struik FM, Goldstein R, Kerstjens HA, Wijkstra PJ, *et al.* Chronic non-invasive ventilation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2021;8:CD002878.
13. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, *et al*. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185–2196.

14. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl* 2022;12:7–11.
15. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res* 2023;118:3272–3287.
16. Huttmann SE, Windisch W, Storre JH. Techniques for the measurement and monitoring of carbon dioxide in the blood. *Ann Am Thorac Soc* 2014;11:645–652.
17. Bagley SC, Altman RB. Computing disease incidence, prevalence and comorbidity from electronic medical records. *J Biomed Inform* 2016;63:108–111.
18. Alharbi MA, Isouard G, Tolchard B. Historical development of the statistical classification of causes of death and diseases. *Cogent Med* 2021;8:1893422.
19. World Health Organization. ICD-10 Updates 2009 [Internet]. 2009 [cited 2024 Jan 8]. Available from: https://www.who.int/standards/classifications/classification-of-diseases/list-of-official-icd-10-updates.
20. McIsaac DI, Gershon A, Wijeysundera D, Bryson GL, Badner N, van Walraven C. Identifying obstructive sleep apnea in administrative data: A study of diagnostic accuracy. *Anesthesiology* 2015;123:253–263.
21. Cantero C, Adler D, Pasquina P, Uldry C, Egger B, Prella M, *et al*. Long-term noninvasive ventilation in the Geneva Lake Area: Indications, prevalence, and modalities. *Chest* 2020;158:279–291.
22. Garner DJ, Berlowitz DJ, Douglas J, Harkness N, Howard M, McArdle N, *et al*. Home mechanical ventilation in Australia and New Zealand. *Eur Respir J* 2013;41:39–45.
23. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Fauroux B, *et al*. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J* 2005;25:1025–1031.
24. Chu CM, Yu WC, Tam CM, Lam CW, Hui DSC, Lai CKW. Home mechanical ventilation in Hong Kong. *Eur Respir J* 2004;23:136–141.
25. Kotanen P, Brander P, Kreivi H-R. The prevalence of non-invasive ventilation and long-term oxygen treatment in Helsinki University Hospital area, Finland. *BMC Pulm Med* 2022;22:248.
26. Rose L, McKim DA, Katz SL, Leasa D, Nonoyama M, Pedersen C, *et al*. Home mechanical ventilation in Canada: a national survey. *Respir Care* 2015;60:695–704.
27. Laub M, Berg S, Midgren B. Home mechanical ventilation in Sweden – inequalities within a homogenous health care system. *Respir Med* 2004;98:38–42.

28. Valko L, Baglyas S, Gal J, Lorx A. National survey: current prevalence and characteristics of home mechanical ventilation in Hungary. *BMC Pulm Med* 2018;18:190.
29. Plant PK, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of non-invasive ventilation and oxygen administration. *Thorax* 2000;55:550–554.
30. Çiftci F, Çiledağ A, Erol S, Kaya A. Non-invasive ventilation for acute hypercapnic respiratory failure in older patients. *Wien Klin Wochenschr* 2017;129:680–686.
31. Contou D, Fragnoli C, Córdoba-Izquierdo A, Boissier F, Brun-Buisson C, Thille AW. Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit. *Respir Care* 2013;58:2045–2052.
32. Smith DB, Tay GTP, Hay K, Antony J, Bell B, Kinnear FB, *et al*. Mortality in acute non-invasive ventilation. *Intern Med J* 2017;47:1437–1440.
33. Vonderbank S, Gibis N, Schulz A, Boyko M, Erbuth A, Gürleyen H, *et al*. Hypercapnia at hospital admission as a predictor of mortality. *Open Access Emerg Med* 2020;12:173–180.
34. Meservey AJ, Burton MC, Priest J, Teneback CC, Dixon AE. Risk of readmission and mortality Following hospitalization with hypercapnic respiratory failure. *Lung* 2020;198:121–134.
35. Scarpazza P, Incorvaia C, Amboni P, di Franco G, Raschi S, Usai P, *et al*. Long-term survival in elderly patients with a do-not-intubate order treated with noninvasive mechanical ventilation. *Int J Chron Obstruct Pulmon Dis* 2011;6:253–257.
36. Konishi M, Akiyama E, Suzuki H, Iwahashi N, Maejima N, Tsukahara K, *et al*. Hypercapnia in patients with acute heart failure. *ESC Heart Fail* 2015;2:12–19.
37. Aliberti S, Rosti VD, Travierso C, Brambilla AM, Piffer F, Petrelli G, *et al*. A real life evaluation of non invasive ventilation in acute cardiogenic pulmonary edema: a multicenter, perspective, observational study for the ACPE SIMEU study group. *BMC Emerg Med* 2018;18:61.
38. Valipour A, Cozzarini W, Burghuber OC. Non-invasive pressure support ventilation in patients with respiratory failure due to severe acute cardiogenic pulmonary edema. *Respiration* 2004;71:144–151.
39. Jentzer JC, Alviar CL, Miller PE, Metkus T, Bennett CE, Morrow DA, *et al*. Trends in therapy and outcomes associated with respiratory failure in patients admitted to the cardiac intensive care unit. *J Intensive Care Med* 2022;37:543–554.

40. Ouanes-Besbes L, Hammouda Z, Besbes S, Nouira W, Lahmar M, Ben Abdallah S, *et al*. Diagnosis of sleep apnea syndrome in the intensive care unit: A case series of survivors of hypercapnic respiratory failure. *Ann Am Thorac Soc* 2021;18:727–729.
41. Thille AW, Córdoba-Izquierdo A, Maitre B, Boyer L, Brochard L, Drouot X. High prevalence of sleep apnea syndrome in patients admitted to ICU for acute hypercapnic respiratory failure: a preliminary study. *Intensive Care Med* 2018;44:267–269.
42. Marik PE, Desai H. Characteristics of patients with the "malignant obesity hypoventilation syndrome" admitted to an ICU. *J Intensive Care Med* 2013;28:124–130.
43. Mokhlesi B, Kryger MH, Grunstein RR. Assessment and management of patients with obesity hypoventilation syndrome. *Proc Am Thorac Soc* 2008;5:218–225.
44. Kessler R, Chaouat A, Schinkewitch P, Faller M, Casel S, Krieger J, *et al*. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. *Chest* 2001;120:369–376.
45. Zewari S, van den Borst B, van den Heuvel M, van den Elshout F, Sastry M, Vos P. Sleep hypoventilation is common in diurnal normocapnic COPD patients with severe or very severe obstruction and is not associated with body mass index. *COPD* 2023;20:210–215.
46. Georges M, Nguyen-Baranoff D, Griffon L, Foignot C, Bonniaud P, Camus P, *et al*. Usefulness of transcutaneous PCO2 to assess nocturnal hypoventilation in restrictive lung disorders. *Respirology* 2016;21:1300–1306.
47. Bourke SC, Gibson GJ. Sleep and breathing in neuromuscular disease. *Eur Respir J* 2002;19:1194–1201.
48. Innocenti F, Giordano L, Gualtieri S, Gandini A, Taurino L, Nesa M, *et al*. Prediction of mortality with the use of noninvasive ventilation for acute respiratory failure. *Respir Care* 2020;65:1847–1856.
49. Phua J, Kong K, Lee KH, Shen L, Lim TK. Noninvasive ventilation in hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease vs. other conditions: effectiveness and predictors of failure. *Intensive Care Med* 2005;31:533–539.
50. Toelle BG, Xuan W, Bird TE, Abramson MJ, Atkinson DN, Burton DL, et al. Respiratory symptoms and illness in older Australians: the Burden of Obstructive Lung Disease (BOLD) study. *Med J Aust* 2013;198:144–148.
51. Cunningham J, Hunter M, Budgeon C, Murray K, Knuiman M, Hui J, *et al*. The prevalence and comorbidities of obstructive sleep apnea in middle-aged men and women: the Busselton Healthy Ageing Study. *J Clin Sleep Med* 2021;17:2029-2039.

3. Study design

3.1 Introduction

The goal of this thesis was to acquire robust, population-based epidemiological data on hypercapnic respiratory failure. Specific objectives were to describe its prevalence in the population, the range of contributing causes, and the clinical outcomes experienced by people with this condition. To achieve these objectives, I developed and implemented a cross-sectional study using health record data, a case-control study recruiting both cases and population-based controls, and a nested historical cohort study involving data linkage to state-held records. All cases of HRF were drawn from the same source population and selected based on arterial blood gas measurements. This chapter provides an overview of each of these studies, including some details unable to be included in the published manuscripts due to journal word count restrictions. The results of these studies are presented in subsequent chapters.

3.2 Study setting

The source population, defined as the population from which the study subjects were drawn, was residents of the Liverpool Local Government Area (LGA), New South Wales (NSW), Australia (Figure 3.1). This municipality encompasses a total land area of 305 square kilometres and is located in the south-western region of metropolitan Sydney. In 2016, the

year in which the studies described in this thesis were conceived, this region had an estimated population of 158,024 persons aged 15 years (1). Population characteristics of the Liverpool LGA are provided in Table 3.1. The results of the studies in this thesis are inferred to be generalisable to this source population and other similar populations.

Figure 3.1. *Study population. The Liverpool Local Government Area (LGA) is located in the south-western region of metropolitan Sydney, Australia. Illustration by L. Wang.*

Table 3.1. *Population characteristics of the Liverpool Local Government Area in 2016.*

Population characteristics	
Total persons (2016)	204,326
Age 15 years and over	158,024
Median age (years, median)	33
Average household size (persons)	3.2
Indigenous persons (Aboriginal and/or Torres Strait Islander)	3,012 (1.5%)
Country of birth (4 Most commonly listed)	
Australia	105,550 (51.7%)
Iraq	9,885 (4.8%)
Vietnam	6,651 (3.3%)
Fiji	6,541 (3.2%)
Labour force status	
Total labour force	90,672
Working full-time (35 hours or more)	55,767 (61.5%)
Working part-time	23,554 (26.0%)
Unemployed	6,766 (7.5%)
Highest year of school completed	
Year 12 or equivalent	81,128 (54.2%)
Year 10 or equivalent	34,436 (23.0%)
Below Year 10 or equivalent	20,715 (13.9%)

Liverpool Hospital is the major service provider for residents of the source population who require hospital care. Liverpool Hospital comprises approximately 900 beds (including dedicated intensive care beds) and provides a range of specialist respiratory and sleep services including provision of non-invasive ward-based ventilation for patients with acute respiratory failure, and outpatient services for patients requiring long-term non-invasive ventilatory support therapy. As part of Australia's public health care system, these and Emergency services are provided free of charge to Australian residents. As shown in Table 3.2, 86% of persons from the Liverpool LGA who were hospitalised within the state of New South Wales under the 'Service Related Group' (SRG) of *Respiratory Medicine* were

admitted to Liverpool Hospital (2). The SRG classification system categorises hospital admissions into groups according to the type of specialty care that is principally received, and is used by Australian health services to measure hospital activity and assist in planning services. Based on these data, it is reasonable to assume that most people with respiratory failure in the Liverpool LGA attended Liverpool Hospital. This assumption forms the basis for identification of cases of HRF in the studies described in this thesis.

Table 3.2. *Hospitalisations experienced by residents of the Liverpool Local Government Area in the three-year period from 2013/14 to 2015/16.*

Age Group (years)	**Average number of hospitalisations per year under the *Respiratory Medicine SRG***		**% Liverpool LGA residents admitted to Liverpool Hospital**
	Liverpool Hospital	**Other Hospitals**	
15–24	65	23	73%
25–34	74	25	74%
35–44	110	20	85%
45–54	162	28	85%
55–64	241	37	87%
65–74	353	52	87%
75–84	408	46	90%
85 and over	205	20	91%
Total	1,618	252	86%

LGA Local Government Area, SRG Service Related Group.

3.3 Case definition

There are no established criteria to confirm the diagnosis of hypercapnic respiratory failure. Based on the few previous studies, and consensus among expert clinicians, I developed a

working case definition for further epidemiological study. The minimum requirements to fulfil this case definition were:

1. An elevated partial pressure of carbon dioxide as measured in an arterial blood sample ($PaCO_2$ greater than 45 mmHg); and
2. Absence of a metabolic alkalosis that might be responsible for compensatory hypoventilation (pH 7.45 or less).

Arterial blood gas (ABG) results from Liverpool Hospital taken within 24 hours of first presentation were screened to identify potential cases meeting the above criteria. Following this initial screen, pathology results and medical records for all potential cases were reviewed manually. Persons who met the initial screen were excluded if:

1. A preceding arterial or venous blood gas sample demonstrated a low or normal $PaCO_2$, suggesting the absence of hypercapnia at the time of initial presentation;
2. There was a significant discrepancy (> 10%) between blood oxygen saturation on the ABG (SaO_2) and as measured by pulse oximetry (SpO_2), suggesting incorrect attribution of a mixed venous specimen as an ABG;
3. The person had received a sedative or anaesthetic medication immediately prior to the ABG measurement, suggesting a potentially iatrogenic cause of hypercapnia; and/or
4. If the person had presented with a traumatic injury or out-of-hospital cardiac arrest.

This case definition for HRF due to any cause was employed consistently for all of the studies described in this thesis.

3.4 Study design

3.4.1 Study 1: Prevalence of hypercapnic respiratory failure

The objective of the first study was to enumerate cases of HRF, and thereby determine the population prevalence of this condition. Cases were restricted to those aged at least 15 years and residing within the Liverpool LGA (Figure 3.2). The study period was limited to the 5-year calendar period from 2013 to 2017. By doing so, I was able to describe the average annual period prevalence of this condition; that is, the proportion of the population with HRF at any point during each 12-month period:

$$Period\ prevalence\ = \frac{Number\ of\ current\ cases\ (new\ and\ pre\text{-}existing)\ over\ a\ specified\ time\ period}{Average\ or\ mid\text{-}interval\ population}$$

The complete, published manuscript of this study is included in Chapter 4.

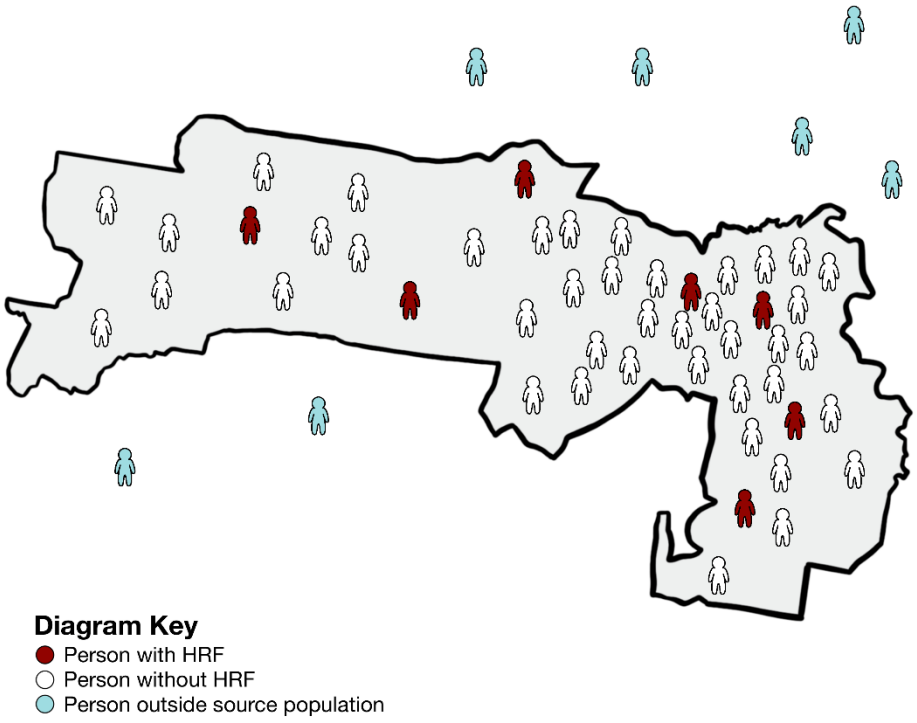

Figure 3.2. *Prevalence study design. Cases of hypercapnic respiratory failure (HRF) are enumerated within the source population to determine period prevalence. Illustration by L. Wang.*

3.4.2 Study 2: Causes of hypercapnic respiratory failure (Part 1)

The second objective of this thesis was to describe the relative frequency of underlying causes for hypercapnic respiratory failure. Following enumeration of persons with HRF in the first study, electronic health record data pertaining to the specific presentation or presentations with HRF were extracted for each case (Figure 3.3). The presence or absence of pre-specified causes was determined based on International Classification of Diseases codes (3). The causes of interest were selected based on previous studies of patients with HRF requiring hospitalisation, and consultation with expert clinicians. This cross-sectional study is the first to describe the prevalence of specific causes for HRF at a population level.

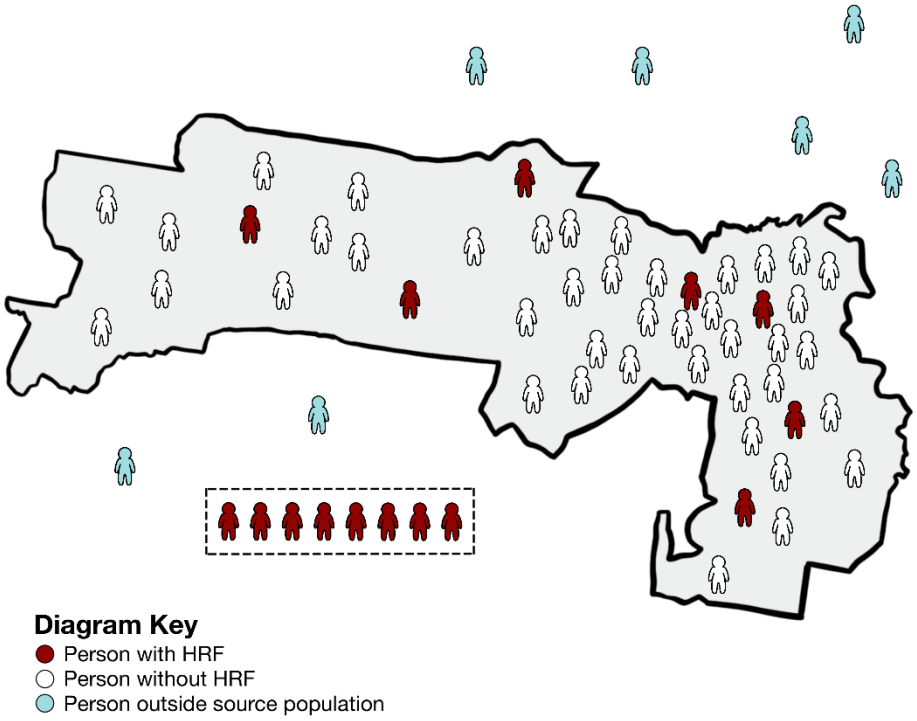

Figure 3.3. *Cross-sectional study design. A descriptive study is undertaken to identify the range of causes among cases of hypercapnic respiratory failure (HRF). Illustration by L. Wang.*

The full, published manuscript of this study is included in Chapter 5 and the supplementary data in Chapter 9.

3.4.3 Study 3: Causes of hypercapnic respiratory failure (Part 2)

In the second study, I had described the range of causes for HRF. However, a limitation of this study was the absence of a reference group; that is, although I had described the frequency of underlying causes in the study population, I was unable to comment whether this differed significantly from other people in the source population who did not have HRF. This limitation holds true for all previous studies on this topic; no previous studies have estimated the relative importance of underlying causes, or exposures. The optimal study design to answer this research question is a prospective cohort study. This would have involved recruitment of a representative cohort of sufficient size from a defined population, direct measurement for exposures, then, whilst withholding interventions for exposures that might not have been identified were it not for the study, observing participants over a period of time for the development of hypercapnia.

Because of the impracticalities and costs associated with such an approach, I designed a case-control study to investigate the population determinants of HRF (Figure 3.4). The case-control design overcomes many of the challenges associated with a cohort study, and allows simultaneous assessment of multiple exposures, or risk factors. Cases identified using the methods described previously were contacted and invited to participate in the study. Control participants were selected using a geography-based cluster sampling method in order to obtain a sample which closely represented the source population. This method was used in lieu of random sampling from a population list, as our proposed recruitment methods were considered excessively burdensome to potential participants by the custodians of the Australian Electoral Roll.

Direct measurements for a range of potential causes for HRF were undertaken in both cases and controls. By doing so, I was able to estimate both the odds ratio (OR) associated with

each risk factor, as well as the population attributable fraction (PAF). The PAF can be expressed as:

$$PAF = \frac{P_e(OR-1)}{P_e(OR-1)+1} \times 100$$

where P_e is the prevalence of the risk factor in the population, estimated by measuring the prevalence in the control group. This epidemiological measure reflects the proportion of disease occurring in a population that can be attributed to the exposure of interest.

The full, published manuscript relating to this study is included in Chapter 6.

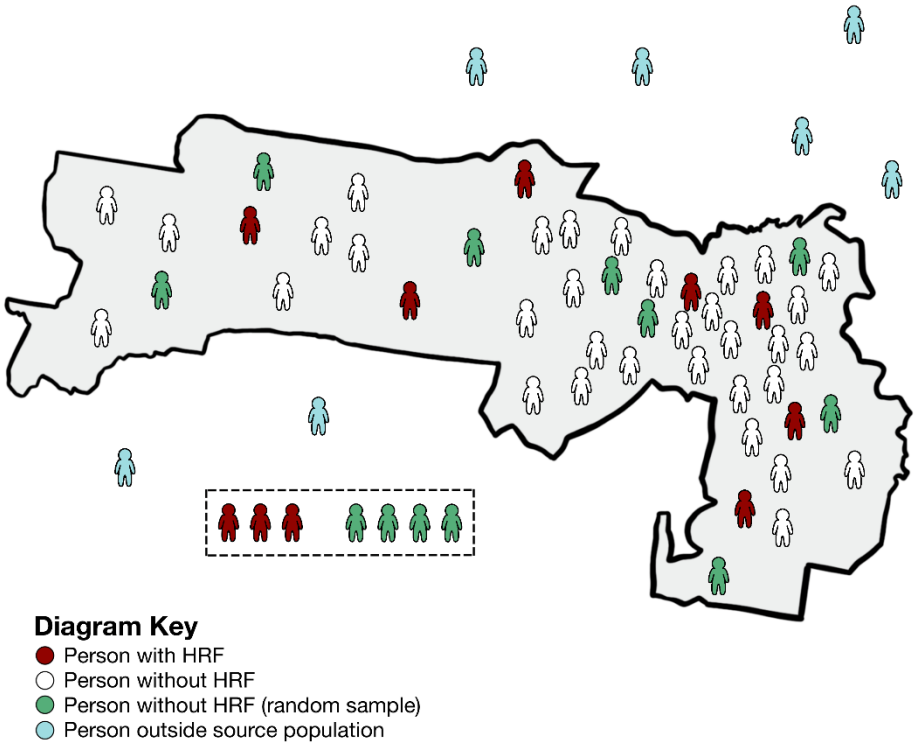

Figure 3.4. *Case-control study design. Measurements of potential causes for hypercapnic respiratory failure (HRF) are taken in both cases and in a randomly selected, representative sample drawn from the source population. Illustration by L. Wang.*

3.4.4 Study 4: Outcomes of hypercapnic respiratory failure

The final objective of this thesis was to describe clinical outcomes following the development of HRF. I undertook a nested historical cohort study, focusing on a subset of identified cases (Figure 3.5). This subset was based on year of presentation (2013 to 2015) to allow for a minimum follow-up period of 5 years; data collection were completed in 2022.

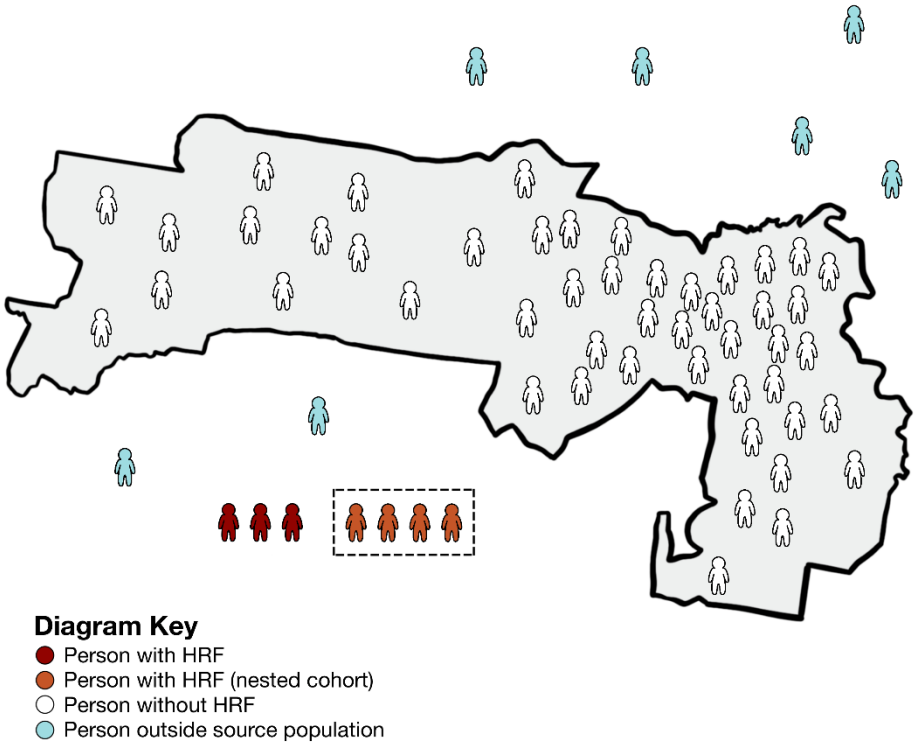

Figure 3.5. *Nested cohort study design. Clinical outcomes are measured longitudinally for a subset of people with hypercapnic respiratory failure (HRF). Illustration by L. Wang.*

A limitation of previous studies is that, similar to studies of the causes of HRF, there has been no comparison with a reference population. By drawing from a pre-specified source population, I was able to determine the standardised mortality ratio (SMR) associated with HRF. The SMR is the number of observed deaths in a study population over a specified time period compared with the number that would have been expected if the study population had the same mortality rate as the standard population:

$$SMR = \frac{Number\ of\ observed\ deaths}{Number\ of\ expected\ deaths} \times 100$$

An SMR of greater than one can be interpreted as excess mortality in the study population. The full manuscript of this study is included in Chapter 7.

3.5 Summary

A broad range of study methods and data sources were utilised to achieve the goals of this thesis. A prevalence survey of HRF was achieved using existing health data, and a cross-sectional observational study was conducted to describe the range of causes. A case-control study was implemented, recruiting cases of HRF and control participants from the source population, to quantify the associations with these causes and their respective population attributable fractions. An historical nested cohort study was completed using data linkage, allowing estimation of a standardised mortality ratio. By applying a variety of epidemiological concepts, I have been able to generate new data on hypercapnic respiratory failure as a single, albeit heterogeneous, entity, providing the basis for future studies on interventions on prevention and treatment for this condition.

3.6 Chapter references

1. Australian Bureau of Statistics. 1410.0 - Data by region, 2013-19. Australian Bureau of Statistics; 2020. Available from: https://www.abs.gov.au/AUSSTATS/ abs@.nsf/Details Page/1410.02013-18?OpenDocument.
2. NSW Ministry of Health. FlowInfo v15.1. Retrieved from the Clinical Services Planning Application Portal (CaSPA). 2017 [accessed 7 March 2018].
3. Independent Hospital Pricing Authority. *The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM)*. Darlinghurst, NSW (Australia): Independent Hospital Pricing Authority.

4. Prevalence of hypercapnic respiratory failure

4.1 Introduction

Estimating disease prevalence is a key objective in descriptive epidemiology and is essential to understanding the relevance and potential impact of a disease on populations. It is also a prerequisite to develop and evaluate strategies directed at prevention of disease within an at-risk population, and treatments for patients in whom disease has already occurred.

In my review of the existing literature on the prevalence of HRF, I found that no previous studies had addressed this fundamental question. The lack of a consistent case definition and the difficulties with obtaining reliable data are likely to account at least partly for this problem. I approached this challenge by developing an operational case definition for HRF irrespective of the underlying cause and applying it to a pre-defined population in whom sufficient data were available to confirm the diagnosis.

The objective of the study presented in this chapter was to determine the population prevalence of HRF. I found the annual period prevalence of HRF to be, on average, 163 cases per 100,000 population. This value was substantially higher than previously reported estimates for the prevalence of respiratory acidosis due to COPD, and likely reflects the importance of diseases other than COPD contributing to the frequency of this condition.

This work has been published in the *American Journal of Respiratory and Critical Care Medicine*, reproduced as follows.

4.2 Population prevalence of hypercapnic respiratory failure from any cause

Hypercapnic respiratory failure (HRF) is a severe sequela of many respiratory, cardiovascular, metabolic, and neurological diseases, yet there are no data on its prevalence at a population level. Previous studies are limited to reporting the prevalence of HRF as a complication of specific diseases, such as chronic obstructive pulmonary disease (COPD). However, this approach fails to recognize alternative diagnoses that contribute to the burden of disease associated with HRF. Furthermore, patients with COPD and HRF may have other conditions, such as sleep-disordered breathing, congestive cardiac failure, and obesity, which contribute to "multifactorial" HRF (1). In the setting of aging demography and multimorbidity, we believe better understanding of the population-level epidemiology of HRF is required to assist planning of health services and to provide context for future research on optimal management. Some of the following results have been previously reported in abstract form (2,3).

To estimate the 12-month period prevalence of HRF (including acute, chronic, and acute-on-chronic HRF) at a population level, we conducted a cross-sectional study of adults aged 15 or more years living in Liverpool, Australia, a large metropolitan area in southwestern Sydney. Cases were defined as members of the source population who attended Liverpool Hospital from January 1, 2013, to December 31, 2017, whose first arterial blood gas (ABG) sample taken within 24 hours of presentation revealed $PaCO_2 > 45$ mm Hg and $pH \leqslant 7.45$. We excluded blood gas results in which the SaO_2 was at least 10% lower than the pulse oximetry SpO_2, as these were assumed to be venous specimens. We also excluded

potentially nosocomial cases, defined as those in which the person had suffered an out-of-hospital cardiac arrest, traumatic injury, or if the specimen was collected during or shortly after a procedure requiring general anesthesia and/or sedation. We multiplied counts in each age stratum by the inverse of the proportion of persons in the source population who attended Liverpool Hospital for respiratory conditions, to account for underenumeration due to attendance at other hospitals. From Ministry of Health data, we ascertained that, on average, 86% of the source population who were hospitalized for respiratory conditions presented to Liverpool Hospital (4). This proportion ranged from 73% to 91% in the lowest and highest age strata, respectively. Age- and sex-specific mid-year population estimates were obtained from the Australian Bureau of Statistics (5). Average adjusted annual period prevalence rates and 95% confidence intervals (CI) were determined based on Poisson regression with the logarithm of 100,000 person-years as the offset term. Further regressions were performed to determine the associations between age group, sex, and their interaction on HRF prevalence. All analyses were performed in SAS (version 9.4; SAS Institute Inc.).

During the 5-year study period, we identified 2018 ABG records that met initial screening criteria. After excluding 144 probable venous specimens and 739 potential nosocomial cases, we found 1,135 episodes of HRF, attributable to 891 unique persons. Mean (SD) age was 69 (17) years, and 50.4% were males. Acidosis (pH < 7.35) was present in 488 (55%) cases. The average adjusted annual period prevalence of HRF during the study period was 163 (95% CI, 154–172) cases per 100,000 population.

HRF prevalence increased with age, from 14 (95% CI, 9–22) cases per 100,000 population for the age group 15–24 years, to 1,712 (95% CI, 1481–1,981) cases per 100,000 population for those aged 85 years or more (Table 4.1). Compared with those aged 45–54 years, each successive decade of life conferred increases in HRF prevalence by 2.1, 6.2, 15.7, and 26.2

times (P < 0.0001). There was no significant difference in HRF prevalence between males and females overall. However, among those less than 55 years of age, the prevalence rate of HRF among men was 4.4 (95% CI, 1.8–10.7) times that among women (P = 0.02).

Our study confirms that the population prevalence of HRF, estimated at 163 cases per 100,000 population, is substantially higher than previously estimated in studies limited to patients with COPD. A large study of COPD-related acidosis conducted in 1997 in the United Kingdom reported standardized yearly rates of 57 and 75 cases per 100,000 population for women and men aged 45–79 years, respectively (6). The comparatively high prevalence observed in this study may be attributable to an increase in COPD prevalence over time (7) but more likely reflects the importance of other conditions as contributors to the burden of HRF. This conclusion is supported by registry studies that show that obesity hypoventilation syndrome and neuromuscular disease together account for more patients receiving domiciliary noninvasive ventilation for HRF than does COPD (8,9). Our results highlight the need for further research to identify key drivers of HRF prevalence to guide clinically and cost-effective interventions at a population level.

The study has some limitations. Identifying HRF cases using hospital records and ABG results is novel and has not been validated. However, this method has strong face validity and has the advantage of being inclusive. Prior studies have relied on indirect measurements such as serum bicarbonate (10) or restricted inclusion criteria to specific diagnoses such as COPD. It is possible that we have underestimated true prevalence by excluding cases who did not attend hospital or have an ABG performed. Nevertheless, we suspect the number of cases missed in hospital to be low, as we typically obtain an ABG for all patients in whom there is a clinical suspicion of HRF and do not use venous blood gas or other measurements to confirm hypercapnia. In the absence of a readily accessible

screening tool in lieu of ABG sampling, our study provides valuable data on HRF prevalence estimates that should be considered minimum values in comparable populations.

This is the first report of HRF as a single entity assessed at a population level. Our prevalence estimates provide important context for future studies on the burden of respiratory disease. Further work is required to determine the relative prevalence of contributing causes to identify groups that might benefit from interventions such as home noninvasive ventilation therapy.

Table 4.1. *Average annual period prevalence of hypercapnic respiratory failure by age and sex*

	Number of Cases (95% CI) per 100,000 Population per Year		
Age Group (yr)	**Overall**	**Males**	**Females**
15–24	14 (9–22)	21 (13–34)	7 (3–17)
25–34	29 (22–39)	37 (26–53)	22 (14–35)
35–44	42 (33–54)	58 (43–78)	26 (17–41)
45–54	80 (66–96)	77 (59–100)	82 (63–107)
55–64	196 (71–25)	194 (160–237)	197 (162–239)
65–74	517 (463–577)	540 (464–629)	489 (417–574)
75–84	1,160 (1,046–1,286)	1,143 (979–1,333)	1,167 (1,017–1,341)
> 85	1,712 (1,481–1,980)	1,808 (1,430–2,284)	1,649 (1,370–1,985)

Definition of abbreviation: CI = confidence interval.

4.3 Chapter references

1. Adler D, Pépin JL, Dupuis-Lozeron E, Espa-Cervena K, Merlet-Violet R, Muller H, *et al*. Comorbidities and subgroups of patients surviving severe acute hypercapnic respiratory failure in the intensive care unit. *Am J Respir Crit Care Med* 2017;196:200-207.

2. Chung Y, Garden FL, Marks GB, Vedam H. Population prevalence of hypercapnic respiratory failure in south-western Sydney, Australia. Presented at the European Respiratory Society International Congress 2018, Paris, France. Abstract 4495.
3. Chung Y, Garden FL, Marks GB, Vedam H. Diagnoses among patients with hypercapnic respiratory failure and effect on in-hospital mortality. *J Sleep Res* 2018;27:21.
4. NSW Ministry of Health. FlowInfo v15.1. Retrieved from the Clinical Services Planning Application Portal (CaSPA). 2017 [accessed 7 March 2018].
5. Australian Bureau of Statistics. 1410.0 - Data by region, 2013-19. Australian Bureau of Statistics; 2020. Available from: https://www.abs.gov.au/AUSSTATS/ abs@.nsf/Details Page/1410.02013-18?OpenDocument.
6. Plant PK, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of non-invasive ventilation and oxygen administration. *Thorax* 2000;55:550–554.
7. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, *et al.*; GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017;5:691–706.
8. Cantero C, Adler D, Pasquina P, Uldry C, Egger B, Prella M, *et al*. Long-term noninvasive ventilation in the Geneva Lake area: indications, prevalence, and modalities. *Chest* 2020;158:279–291.
9. Garner DJ, Berlowitz DJ, Douglas J, Harkness N, Howard M, McArdle N, *et al*. Home mechanical ventilation in Australia and New Zealand. *Eur Respir J* 2013;41:39–45.
10. Borel JC, Guerber F, Jullian-Desayes I, Joyeux-Faure M, Arnol N, Taleux N, *et al*. Prevalence of obesity hypoventilation syndrome in ambulatory obese patients attending pathology laboratories. *Respirology* 2017;22:1190–1198.

Cite: Chung Y, Garden FL, Marks GB, Vedam H. Population prevalence of hypercapnic respiratory failure from any cause. *Am J Resp Crit Care Med* 2022;205:966-967.
The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

5. Causes of hypercapnic respiratory failure: Part 1

5.1 Introduction

When the prevalence of a disease is such that it imposes a substantial burden on the health of a population, that at-risk population must consider, where possible, adoption of preventative interventions. In order to implement effective prevention strategies, an understanding of modifiable risk factors or causes, of disease in that population is required. Cross-sectional, descriptive studies of a study population that has been appropriately sampled can provide clues to disease aetiology by determining the relative frequency of hypothesised causes, thus identifying high-risk or priority groups for further investigation.

A range of potential causes have been described among groups of patients with HRF. However, no previous studies have described these causes with reference to the population at risk. The samples from these previous studies represent incomplete and/or non-random selection of cases from the study or target population. As such, conclusions drawn from these studies may be susceptible to systematic error. I addressed this issue by defining a study population (residents of a local government area) where most (86%) at-risk individuals would be counted as cases if they had the disease being studied (HRF).

The primary objective of the study presented in this chapter was to describe the prevalence of potential causes among patients with HRF drawn from a specific population. I found that most (83%) had at least one of the following pre-specified conditions: obstructive lung

disease, lower respiratory tract infection, congestive cardiac failure, sleep-disordered breathing, neuromuscular disease, opioid or benzodiazepine use. A secondary objective was to describe the associations between these conditions and the outcome of in-hospital mortality.

This study is the first in this thesis to describe the use of directed acyclic graphs (DAGs) to inform regression models. DAGs are causal diagrams that show assumed relationships, and allow unbiased estimates of the relationship between a hypothesised cause and an outcome such as the development of a condition (such as HRF) or death.

This work has been published in *Respirology*, and awarded "Editor's Choice" for that issue. The publication is reproduced verbatim, with supplementary material ("Supporting Information") provided separately in Chapter 9.

5.2 Causes of hypercapnic respiratory failure and associated in-hospital mortality

5.2.1 Abstract

Background and objective: Hypercapnic respiratory failure (HRF) can occur due to severe respiratory disease but also because of multiple coexistent causes. There are few data on the prevalence of antecedent causes for HRF and the effect of these causes on prognosis, especially where study inclusion has not been biased with respect to primary diagnosis, interventions received or clinical outcome. We sought to determine the prevalence of pre-specified conditions among patients with HRF and to determine the effect of these causes on in-hospital mortality.

Methods: Cross-sectional study of patients with HRF from 2013 to 2017. Inclusion criteria were PaCO2 > 45 mm Hg and pH ≤7.45. Causes of interest were identified using diagnosis

codes from hospital records. We used directed acyclic graphs to inform logistic regression models for the outcome of in-hospital death.

Results: We identified 873 persons with HRF in the study period. Mean (SD) age was 69 years and 50.4% were males. Acidosis (pH < 7.35) was present in 488 (55%) cases. Most (83%) had one or more of the following: obstructive lung disease, lower respiratory tract infection, congestive cardiac failure, sleep disordered breathing, neuromuscular disease, opioid or benzodiazepine use. In-hospital mortality was 12.8%. Obstructive lung disease and cardiac failure were associated with a lower risk of death, whereas respiratory tract infection and neuromuscular disease were associated with increased risk of death.

Conclusion: HRF is associated with a range of potentially causative conditions, which significantly impact hospital survival. Systematic evaluation of patients with HRF may increase detection of treatable comorbidities.

5.2.2 Introduction

Hypercapnic respiratory failure (HRF) is a physiological endpoint with multiple potential causes. While individual causes of HRF warrant disease-specific treatments, most patients with HRF require hospitalization and many need ventilatory support in a dedicated critical care ward, invoking considerable healthcare costs. Hence, even though HRF can occur due to many diseases, it can also be viewed as a single, albeit heterogeneous, condition that constitutes a substantial problem for acute health facilities in many countries.

To date, there has been no systematic evaluation of contributing causes of HRF at a population level. Previous studies have been limited to patients with a specific, primary diagnosis such chronic obstructive pulmonary disease (COPD), or receiving a particular intervention such as non-invasive ventilation therapy (1–4). These studies are prone to selection bias and imprecise estimates for the prevalence of each cause due to exclusion of

potentially relevant participants, especially if participants have been selected based on survival of the acute episode. Few studies in recent years have reviewed causes of hypercapnia among hospitalized patients, without considering the source population (5, 6). Furthermore, there is increasing recognition that, in many instances, multiple causes can co-exist (1). We propose that valid assessment of the prevalence of causes of HRF in the general population requires systematic evaluation of an unselected cohort of patients with hypercapnia whose inclusion is not biased with respect to primary diagnosis, interventions received or clinical outcome.

We sought to determine the prevalence of specific causes among patients with hypercapnia in the general population. We hypothesized that we would observe a diverse range of causes and that many patients would have 'multifactorial' HRF, with obstructive lung disease, sleep disordered breathing (SDB) and congestive cardiac failure (CCF) all potentially contributing to ventilatory failure. Our second objective was to assess the associations between specific causes and in-hospital mortality. By providing these data, our goal was to provide context for clinicians involved in the care of such patients and to inform the development of appropriate management pathways focusing on key reversible causes for HRF in the community.

5.2.3 Methods

This cross-sectional study was conducted at Liverpool Hospital, an 850-bed, tertiary-referral hospital with over 80,000 presentations to the Emergency Department each year (7). Based in Sydney, Australia, it is the major service provider for adult residents of the City of Liverpool, which in 2016 had an estimated population of 158,036 persons aged 15 years and over (8). State-wide hospital admissions data show that 86% of residents from this region who are hospitalized for respiratory conditions attend Liverpool Hospital, the referral base for this study (9).

The cohort comprised people presenting to Liverpool Hospital from 1st January 2013 to 31st December 2017 whose first arterial blood gas (ABG) sample taken within 24 h of presentation revealed $PaCO_2$ > 45 mm Hg and pH ≤7.45. To exclude probable venous specimens we excluded results where the blood gas SaO_2 was at least 10% lower than pulse oximetry SpO_2, if the latter was recorded within 2 hours of the former. We excluded confirmed or suspected nosocomial cases where the person had suffered an out-of-hospital cardiac arrest or traumatic injury, or if the specimen was collected during or shortly after a procedure requiring any sedatives or general anaesthesia (e.g., after an emergency surgical procedure).

For each case, we extracted demographic and clinical details, including the outcome of in-hospital death, and data on potential contributing causes using electronically coded hospital records. Each cause was pre-specified using a directed acyclic graph (DAG) developed by the authors showing both direct and indirect pathways for the development of HRF and subsequent death (Figure 5.1).

We specified the following conditions as potentially directly antecedent to the development of HRF: obstructive lung disease (including COPD and asthma), SDB (obstructive sleep apnoea and obesity-related hypoventilation syndromes), CCF, lower respiratory tract infection, neuromuscular disease (including chest wall disorders) and complications from opioid and/or benzodiazepine use. We used corresponding diagnosis codes to identify the presence or absence of these causes among study participants, as well as the degree of comorbidity based on the Charlson Comorbidity Index (10, 11).

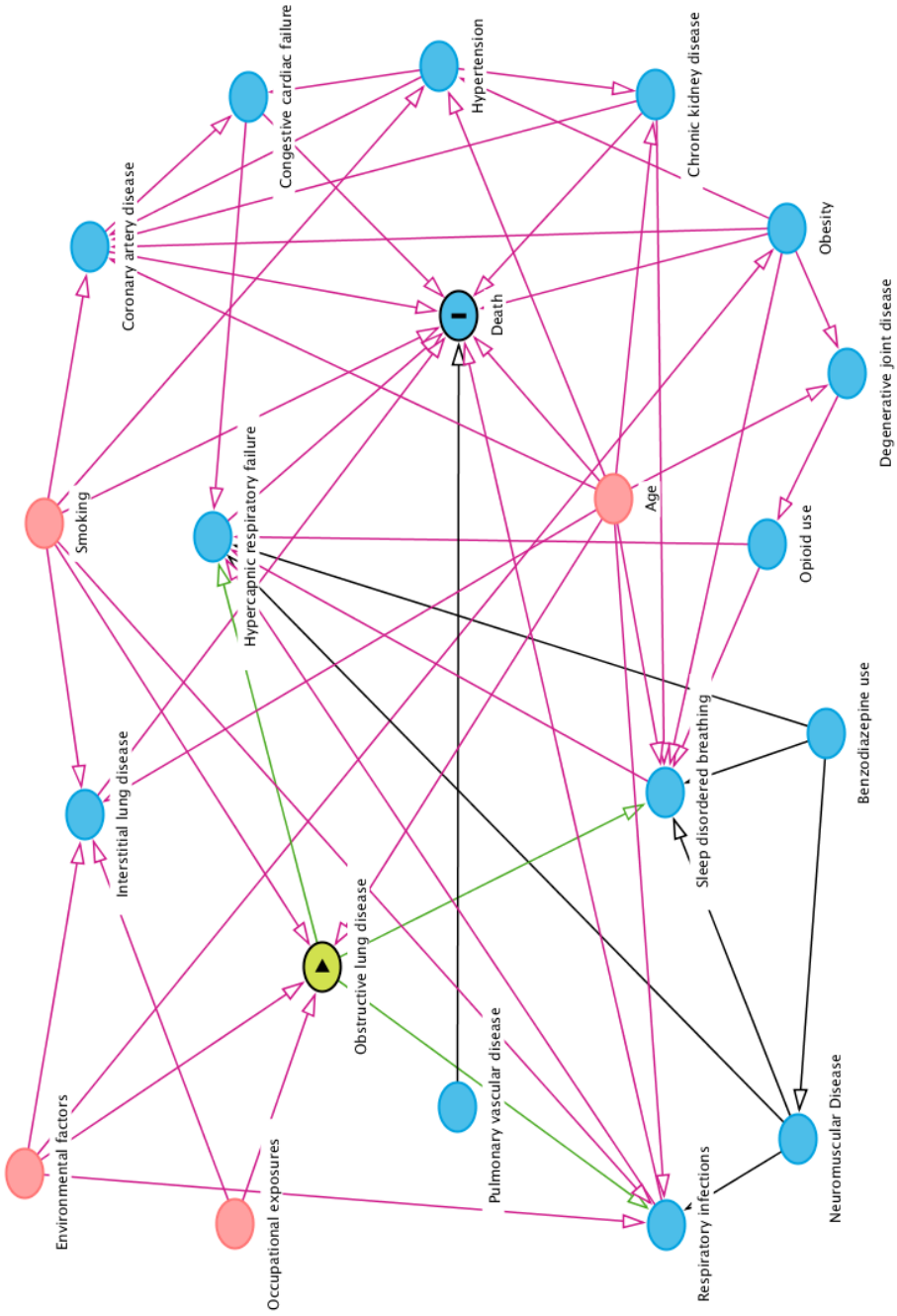

Figure 5.1. *Causal diagram for hypercapnic respiratory failure and death. This directed acyclic graph explicitly states assumed causal relationships and allows identification of minimally sufficient adjustment sets for use in multivariable analyses. In this case, the graph has been constructed to estimate the effect of obstructive lung disease on death. Green arrows represent causal paths. Red arrows represent biasing paths. Blue-shaded variables represent ancestors (causes) of the outcome (death). Red-shaded variables represent ancestors (causes) of both the exposure (obstructive lung disease) and outcome (death).*

Where possible, we used existing algorithms validated for use in identifying medical conditions from clinical records (Table 9.1 in the Supporting Information).

We described the prevalence of causative conditions using frequencies and percentages. To estimate the associations between specific causes and the risk of death, we fitted separate logistic regression models with each hypothesised cause as the main effect (independent variable). The dependent variable was the binary outcome of death, compared with survival at hospital discharge. Using our DAG, we identified minimally sufficient adjustment sets (covariates) for inclusion in each model. If multiple adjustment sets were available, we avoided sets with latent (unmeasured) variables, such as environmental factors, and sets containing variables we expected to be poorly recorded, such as SDB. Arterial pH was used as a marker of HRF severity. Covariates for each regression model are provided in the Supporting Information (Figures S1-S6). Further discussion on causal pathway analysis and the use of DAGs can be found elsewhere (12, 13). We used the web-based version of 'daggity' (14) to generate the DAG (Methods in the Supporting Information) and performed regression analyses in SAS (Version 9.4; SAS Institute Inc., Cary, NC).

5.2.4 Results

We identified 873 persons with HRF during the 5-year study period (Figure 5.2). Patient characteristics are shown in Table 5.1.

At least one directly antecedent cause for HRF based on our model was identified in 724 (83%) of study participants (Table 5.2). The most frequently recorded cause was obstructive lung disease, observed in 389 (44.6%) cases. CCF was the most prevalent non-respiratory diagnosis, potentially contributing to HRF in 278 (31.8%) cases. Adverse effects related to opioids and benzodiazepines were recorded in a minority of cases (6.5% and 3.0%, respectively), predominantly in younger age groups. SDB was recorded in 52 (6.0%) and

neuromuscular disease in 15 (1.7%) cases. With respect to indirect causes for HRF, we identified a history of tobacco exposure in 436 (49.9%) cases but documented obesity in 47 (5.4%) cases only.

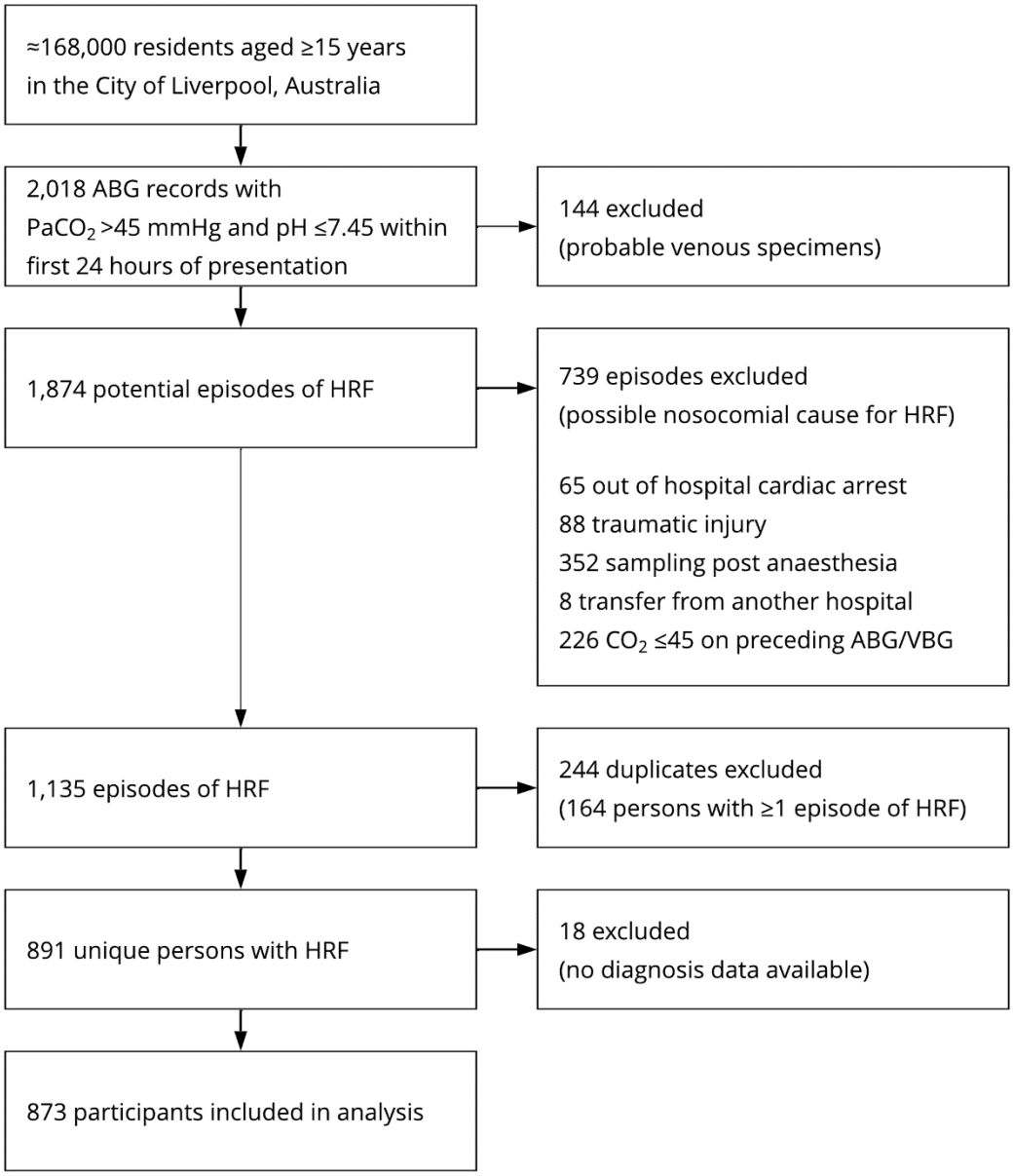

Figure 5.2. *Flow chart demonstrating identification of cases of hypercapnic respiratory failure from 2013 to 2017 inclusive. ABG, arterial blood gas; HRF, hypercapnic respiratory failure; VBG, venous blood gas.*

Table 5.1. *Characteristics of patients presenting with hypercapnic respiratory failure (N=873)*

Patient characteristic	***N* (%) unless otherwise specified**
Age, mean (SD)	69 (17)
Sex	
Male	440 (50.4%)
Female	433 (49.6%)
History of smoking (tobacco) exposure	436 (49.9%)
Residence in aged care (nursing home)	72 (8.3%)
Charlson comorbidity index (CCI) score	
0	59 (6.8%)
1–2	116 (13.3%)
3–4	240 (27.5%)
5 or more	458 (52.4%)
Arterial blood gas values, mean (SD)	
pH	7.31 (0.09)
pO_2	99 (65) mm Hg
pCO_2	58 (14) mm Hg
Bicarbonate	29 (5.3) mmol/L
Acidosis (pH < 7.35)	483 (55.3%)

Table 5.2. *Frequency and case fatality rate by antecedent cause among patients presenting with hypercapnic respiratory failure (N = 873)*

Cause	**Frequency *n* (%)**	**Death in hospital *n* (case fatality rate)**
Obstructive lung disease	389 (44.6%)	36 (9.3%)
Lower respiratory tract infection	291 (33.3%)	53 (18.2%)
Congestive cardiac failure	278 (31.8%)	36 (13.0%)
Opioid use	57 (6.5%)	2 (3.5%)
Sleep disordered breathing	52 (6.0%)	1 (1.9%)
Benzodiazepine use	26 (3.0%)	0 (0%)
Neuromuscular disease	15 (1.7%)	6 (40.0%)

Among patients with obstructive lung disease, 118 (30%) had concomitant CCF and 26 (6.7%) had concomitant SDB. Conversely, among those with CCF, 118 (42%) had concomitant obstructive lung disease and 26 (9.4%) had SDB recorded. Only 17 (2.0%) of the entire cohort had all three of these conditions recorded concurrently (Figure 5.3).

The in-hospital mortality rate was 12.8%. Most (94%) deaths occurred in patients aged 55 years and over. There was substantial variation in the case fatality rate among the various causes (Table 5.2).

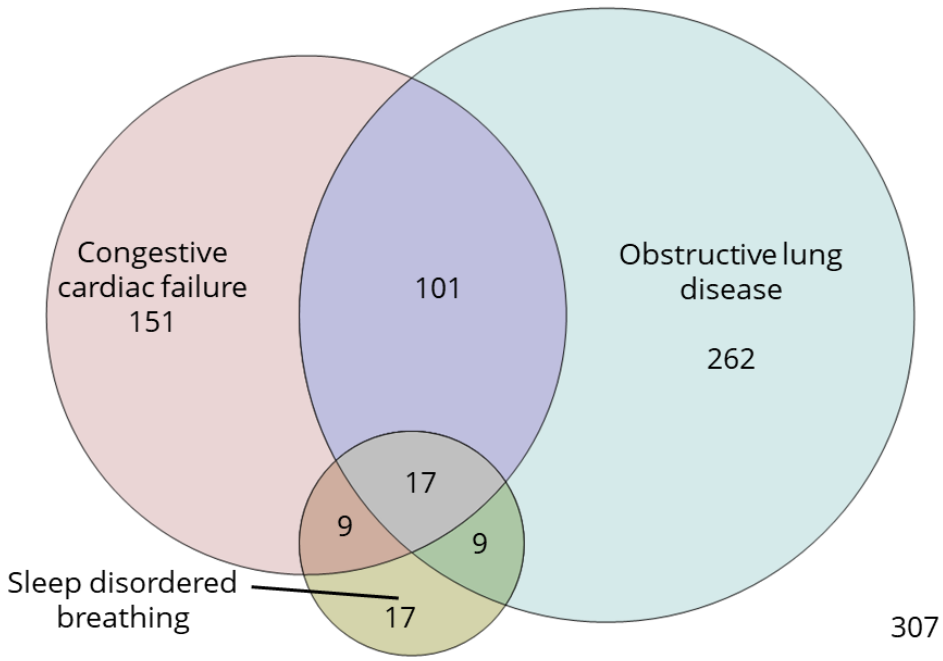

Figure 5.3. *Prevalence of obstructive lung disease, congestive cardiac failure and sleep disordered breathing, either alone or in combination, among patients with hypercapnic respiratory failure (N = 873).*

The risks of death according to antecedent cause are presented in Table 5.3. After adjustment, the presence of obstructive lung disease or CCF was associated with a reduced risk of death, compared to those without these diagnoses. SDB also appeared to be associated with lower odds of death, though there was imprecision in the estimate (p = 0.06). In contrast, the presence of lower respiratory tract infection increased the risk of death. Neuromuscular disease conferred the highest risk of death among the causes assessed in this study.

Table 5.3. *Associations between causes and in-hospital death among patients with hypercapnic respiratory failure*

Cause	**Risk of death if cause is present (95% CI)**			
	Unadjusted odds ratio	***p* value**	**Adjusted odds ratio**	***p* value**
Obstructive lung disease	0.55 (0.36–0.83)	<0.01	0.59 (0.36–0.98)	0.04
Lower respiratory tract infection	1.97 (1.32–2.95)	<0.01	1.68 (1.09–2.59)	0.02
Congestive cardiac failure	1.02 (0.66–1.55)	0.94	0.55 (0.34–0.90)	0.02
Opioid use	0.23 (0.06–0.97)	0.05	0.45 (0.10–1.94)	0.28
Sleep disordered breathing	0.13 (0.02–0.92)	0.04	0.14 (0.02–1.11)	0.06
Neuromuscular disease	4.73 (1.65–13.6)	<0.01	8.02 (2.56–25.2)	<0.01

Definition of abbreviation: CI = confidence interval.

5.2.5 Discussion

Our study demonstrates that HRF is frequently associated with obstructive lung disease and CCF, either alone or in combination, as well as a range of lesser common causes. In contrast to previous work, we found that few patients had 'multifactorial' HRF with at least three antecedent causes. Importantly, we found that the underlying aetiology for HRF had

a significant impact on in-hospital mortality. This is the first study to examine the causes of HRF at a population level, providing valuable information to assist clinicians caring for such patients and baseline data for future studies on HRF.

We found that obstructive lung disease was the most frequently recorded chronic condition antecedent to HRF. This finding is consistent with studies of patients with HRF referred for ventilatory support, which typically find COPD as the most common condition (1, 2, 3). In a recent study of 78 survivors of acute HRF, 52 (67%) had airflow limitation. However, only 19 (24%) had known COPD based on spirometry (1). The reliance on spirometry to confirm COPD may be overstated in the acute setting; in another series of patients with respiratory acidaemia, nearly 80% of patients with a clinical diagnosis of COPD were subsequently confirmed to have airflow obstruction (15). Our findings underscore the importance of obstructive lung disease as an aetiological factor for HRF and provide support for its assumed presence in most patients with ventilatory failure. Future research should focus on assessing the predictive value of clinical features, either alone or in combination as part of clinician gestalt, which may indicate responsiveness to treatments such as bronchodilators and corticosteroids among patients presenting with HRF.

A substantial proportion of our study population had non-respiratory causes, the most common being CCF. Although not typically associated with hypercapnia, systolic heart failure may lead to ventilatory failure by a number of mechanisms including dynamic airflow obstruction which resolves following the acute episode (16). Up to 44% of patients requiring ventilatory support for HRF have cardiac dysfunction and/or cardiogenic pulmonary oedema (1, 3, 17), and hypercapnia occurs in up to 58% of patients with acute heart failure (18, 19). Given that patients with COPD are at increased risk of heart failure, the presence of which is associated with worse prognosis (20), a bipartisan approach is

required to develop investigation pathways for patients with HRF that take into account both of these common conditions.

Unlike previous studies, we found that few patients had 'multifactorial' HRF. The discrepancy is probably attributable to the very low prevalence of SDB observed in our cohort. Prior studies have found that severe SDB is present in up to 83% of HRF survivors (1, 21). Our value of 6.0% is most likely an underestimate due to incomplete recording of the diagnosis, a well-recognized issue with detecting sleep disorders using medical records (22). Furthermore, SDB may be underrecognized in patients with HRF (23), at least in part due to the specialized nature of diagnostic testing which may not be equally accessible to all members of the community. Further work is required, ideally using long-term cohort data, to establish antecedent causes prior to the development of hypercapnia to confirm the true prevalence of multifactorial HRF. Multiple sufficient cause sets may exist, with some patients having one condition at an advanced stage (particularly COPD) and others having multiple co-existent diseases of lesser severity. Understanding the role that specific diagnoses play will allow clinicians to develop more effective treatment pathways for patients with undifferentiated HRF.

Our study found that the aetiology of HRF had a significant impact on in-hospital death. To our knowledge, this is the first study to demonstrate that the presence of COPD and heart failure are associated with a lower risk of death, whereas respiratory tract infections and neuromuscular disease are associated with increased risk of death. Although hypercapnia is associated with a worse prognosis among patients with a specific diagnosis such as COPD (24), there are scarce data on the impact of these diagnoses on those with undifferentiated HRF or HRF due to multiple causes. A study of 202 patients with HRF found that although the degree of comorbidity could predict survival after hospital discharge, there were no differences in comorbidities among survivors and those who died

during admission (25). A potential explanation for our results is the increased availability and use of non-invasive ventilation therapy for patients with HRF. Systematic reviews have confirmed the mortality benefit conferred by non-invasive ventilation therapy among patients with COPD and acute cardiogenic pulmonary oedema (26, 27). Another explanation is that the observed risk reduction is relative to the risk of death in all patients with HRF as a whole; COPD and heart failure are less lethal compared with neuromuscular disease. Appreciating the impact of comorbidities among patients with HRF may allow for a greater degree of informed decision making particularly with respect to goals of care and avoiding potentially futile medical interventions. Our results suggest that patients with HRF should not necessarily have treatment withheld for fear of worse outcomes based solely on the presence of COPD or heart failure. Future studies performed on patients who survive an episode of HRF should also consider the potential selection bias resulting from overrepresentation of patients with chronic cardiopulmonary disease and underrepresentation of neuromuscular conditions.

A key strength of our study is the focus on an unselected cohort identified based on ABG measurements. Case identification is an inherent difficulty for any study of patients with HRF, as there is no specific diagnosis code for this condition (28). We have chosen to consider both acute and chronic forms of HRF together as the duration of 'chronic' HRF can be variable, and there may be significant overlap in causes. Our method has good face validity, and by including patients with all causes we provide unique insights into contributing factors at a population level, appreciating that most people with respiratory illness requiring hospitalization in this population will be captured in this study. Furthermore, our study is unique in its use of theorized causal pathways to inform regression models for HRF and death. The model is necessarily complex and may require adjustment based on future research. However, it provides a foundation for studies to test

the relevance of hypothesised causal pathways (including multifactorial causal sets) and the effects of interventions to mitigate adverse outcomes associated with HRF.

Our study has some limitations. Being a retrospective study, we have relied on diagnosis codes for the detection of causes, and hence have no data on disease specifics, duration or severity. Under-diagnosis is likely to be present, especially for SDB as discussed above. However, in many instances, direct measurement of causes requires patients to survive the acute episode and/or achieve a degree of clinical stability whilst hospitalized. The mortality rate for our cohort is higher than that observed in previous smaller studies (25, 29) and highlights the potential for survivorship bias when causes are directly measured. Next, it is possible we may have missed HRF cases in whom an ABG was not performed. We suspect the number of cases missed in hospital to be low as we typically obtain an ABG for all patients in whom there is a clinical suspicion for HRF, and do not use venous blood gas or other measurements to confirm hypercapnia. The relative difficulty of obtaining arterial blood gases to confirm hypercapnia is one of the primary reasons for the paucity of data on this topic, and we acknowledge that our study will have missed community-dwelling patients with hypercapnia who do not attend hospital. Finally, our results may have limited generalizability, depending on the comparability of other contexts to our source population.

In summary, we found HRF to be associated with a range of causes which appeared to have independent, significant effects on hospital survival. Clinicians making management decisions for patients with HRF should incorporate information on underlying conditions when making management decisions. This is the first report of HRF as a single entity assessed at a population level, and provides context to previous work on HRF survivors which may be subject to selection bias. Further work is required particularly with respect to understanding sufficient cause sets for HRF to guide interventions directed at prevention and management.

5.3 Chapter references

1. Adler D, Pépin JL, Dupuis-Lozeron E, Espa-Cervena K, Merlet-Violet R, Muller H, *et al*. Comorbidities and subgroups of patients surviving severe acute hypercapnic respiratory failure in the intensive care unit. *Am J Respir Crit Care Med* 2017;196:200–207.
2. Cantero C, Adler D, Pasquina P, Uldry C, Egger B, Prella M, *et al*. Long-term noninvasive ventilation in the Geneva Lake Area: indications, prevalence, and modalities. *Chest* 2020;158:279–291.
3. Çiftci F, Çiledağ A, Erol S, Kaya A. Non-invasive ventilation for acute hypercapnic respiratory failure in older patients. *Wien Klin Wochenschr* 2017;129:680–686.
4. Borel JC, Burel B, Tamisier R, Dias-Domingos S, Baguet JP, Levy P, *et al*. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. *PLoS One* 2013;8:e52006.
5. Wilson MW, Labaki WW, Choi PJ. Mortality and healthcare use of patients with compensated hypercapnia. *Ann Am Thorac Soc* 2021;18:2027–2032.
6. Vonderbank S, Gibis N, Schulz A, Boyko M, Erbuth A, Gürleyen H, *et al*. Hypercapnia at hospital admission as a predictor of mortality. *Open Access Emerg Med* 2020;12:173–180.
7. Australian Institute of Health and Welfare. Liverpool Hospital. NSW, South Western Sydney (MyHospitals Data Download): AIHW 2021. [cited 2021 Mar 2]. Available from: https://www.aihw.gov.au/reports-data/myhospitals/content/data-downloads/hospital-downloads?page=1
8. Australian Bureau of Statistics. 1410.0 - Data by region, 2013–18. Australian Bureau of Statistics; 2020. Available from: https://www.abs.gov.au/AUSSTATS/ abs@.nsf/Details Page/1410.02013-18?OpenDocument.
9. NSW Ministry of Health Clinical Services Planning Application Portal (CaSPA). NSW Ministry of Health, Health System Planning and Investment Branch (HSPIB).
10. Independent Hospital Pricing Authority. *The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM)*. Darlinghurst, NSW (Australia): Independent Hospital Pricing Authority.
11. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, *et al*. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676–682.

12. Lederer DJ, Bell SC, Branson RD, Chalmers JD, Marshall R, Maslove DM, *et al*. Control of confounding and reporting of results in causal inference studies. Guidance for authors from editors of Respiratory, Sleep, and Critical Care Journals. *Ann Am Thorac Soc* 2019;16:22–28.
13. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008;8:70.
14. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty.' *Int J Epidemiol* 2016;45:1887–1894.
15. Lane N, Hartley T, Steer J, Elliott M, Sovani M, Curtis H, *et al*. Acute NIV in presumed ECOPD without previous spirometry. *Eur Respir J* 2019;54(Suppl 63):PA3694
16. Brenner S, Güder G, Berliner D, Deubner N, Fröhlich K, Ertl G, *et al*. Airway obstruction in systolic heart failure - COPD or congestion? *Int J Cardiol* 2013;168:1910–1916.
17. Contou D, Fragnoli C, Córdoba-Izquierdo A, Boissier F, Brun-Buisson C, Thille AW. Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit. *Respir Care* 2013;58:2045–2052.
18. Aliberti S, Rosti VD, Travierso C, Brambilla AM, Piffer F, Petrelli G, *et al*. A real life evaluation of non invasive ventilation in acute cardiogenic pulmonary edema: a multicenter, perspective, observational study for the ACPE SIMEU study group. *BMC Emerg Med* 2018;18:61
19. Konishi M, Akiyama E, Suzuki H, Iwahashi N, Maejima N, Tsukahara K, *et al*. Hypercapnia in patients with acute heart failure. *ESC Heart Fail* 2015;2:12–19.
20. Roversi S, Fabbri LM, Sin DD, Hawkins NM, Agustí A. Chronic obstructive pulmonary disease and cardiac diseases. An urgent need for integrated care. *Am J Respir Crit Care Med* 2016;194:1319–1336.
21. Ouanes-Besbes L, Hammouda Z, Besbes S, Nouira W, Lahmar M, Ben Abdallah S, *et al*. Diagnosis of sleep apnea syndrome in the intensive care unit: a case series of survivors of hypercapnic respiratory failure. Ann Am Thorac Soc. 2021. Apr 1;18(4):727–9.
22. McIsaac DI, Gershon A, Wijeysundera D, Bryson GL, Badner N, van Walraven C. Identifying obstructive sleep apnea in administrative data: a study of diagnostic accuracy. *Anesthesiology* 2015;123:253–263.
23. Marik PE, Desai H. Characteristics of patients with the "malignant obesity hypoventilation syndrome" admitted to an ICU. *J Intensive Care Med* 2013;28:124–30.

24. Yang H, Xiang P, Zhang E, Guo W, Shi Y, Zhang S, *et al*. Is hypercapnia associated with poor prognosis in chronic obstructive pulmonary disease? A long-term follow-up cohort study. *BMJ Open* 2015;5:e008909.
25. Meservey AJ, Burton MC, Priest J, Teneback CC, Dixon AE. Risk of readmission and mortality following hospitalization with hypercapnic respiratory failure. *Lung* 2020;198:121–134.
26. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017;7:CD004104.
27. Berbenetz N, Wang Y, Brown J, Godfrey C, Ahmad M, Vital FM, *et al*. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2019;4:CD005351.
28. Jones N, Schneider G, Kachroo S, Rotella P, Avetisyan R, Reynolds MW. A systematic review of validated methods for identifying acute respiratory failure using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;21(S1):261–264.
29. Cavalot G, Dounaevskaia V, Vieira F, Piraino T, Coudroy R, Smith O, *et al*. One-year readmission following undifferentiated acute hypercapnic respiratory failure. *COPD* 2021;18:602–611.

Cite: Chung Y, Garden FL, Marks GB, Vedam H. Causes of hypercapnic respiratory failure and associated in-hospital mortality. *Respirology* 2023;28(2):176-182.
Respirology is published by John Wiley & Sons Australia Ltd on behalf of the Asian Pacific Society of Respirology.

6. Causes of hypercapnic respiratory failure: Part 2

6.1 Introduction

Understanding the causes of disease in a population is of fundamental importance in public health. To assist in making a judgment as to whether a proposed risk factor is a cause of a specific disease, the strength of association between the two must be known. Analytical epidemiology involves testing hypotheses generated from previous descriptive studies to quantify associations between risk factors and the specific disease in question. When a strong association is observed consistently across observational studies, targeted action can be taken to implement prevention or treatment strategies.

There are several study types to determine the associations between exposures and a condition such as HRF. I considered undertaking a cohort study which would quantify these associations as well as providing evidence of temporality, a required criterion for determining causality. However, HRF is relatively uncommon with a potentially long induction period between exposure to hypothesised causes and the development of disease. As such, commencement and completion of a prospective cohort study is beyond the scope of a PhD project. Furthermore, there are no existing datasets of sufficient accuracy and completeness to allow undertaking of a retrospective cohort study. Therefore, I designed and implemented a case-control study, which allows comparisons of exposures between cases with and controls without the disease of interest.

The primary objective of the study described in this chapter is to describe the strength of association between HRF and a range of potential causes. By drawing on population-based controls, I was also able to estimate the population attributable fraction for each cause. I found that whilst there were strong associations between HRF and COPD, CCF, opioid use and respiratory muscle weakness, HRF appeared to have multiple potential causes with no single diagnosis responsible for the majority of cases in the population. This study is the first to describe causes for HRF with reference to a control group.

This work has been published in *BMC Pulmonary Medicine*, reproduced as follows. The supplementary material is provided separately in Chapter 9.

6.2 Causes of hypercapnic respiratory failure: a population-based case-control study

6.2.1 Abstract

Objective: There are no population-based data on the relative importance of specific causes of hypercapnic respiratory failure (HRF). We sought to quantify the associations between hospitalisation with HRF and potential antecedent causes including chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, and congestive cardiac failure. We used data on the prevalence of these conditions to estimate the population attributable fraction for each cause.

Methods: A case–control study was conducted among residents aged ≥ 40 years from the Liverpool local government area in Sydney, Australia. Cases were identified from hospital records based on $PaCO_2 > 45$ mmHg. Controls were randomly selected from the study population using a cluster sampling design. We collected self-reported data on medication use and performed spirometry, limited-channel sleep studies, venous sampling for N-

terminal pro-brain natriuretic peptide (NT-proBNP) levels, and sniff nasal inspiratory pressure (SNIP) measurements. Logistic regression analyses were performed using directed acyclic graphs to identify covariates.

Results: We recruited 42 cases and 105 controls. HRF was strongly associated with post-bronchodilator airflow obstruction, elevated NT-proBNP levels, reduced SNIP measurements and self-reported opioid medication use. There were no differences in the apnoea-hypopnea index or oxygen desaturation index between groups. COPD had the highest population attributable fraction (42%, 95% confidence interval 18% to 59%).

Conclusions: COPD, congestive cardiac failure, and self-reported use of opioid medications, but not obstructive sleep apnea, are important causes of HRF among adults over 40 years old. No single cause accounts for the majority of cases based on the population attributable fraction.

6.2.2 Background

Hypercapnic respiratory failure (HRF) is a commonly encountered clinical scenario for hospital clinicians in a wide range of disciplines. Many patients are known to have a predisposing condition such as severe chronic obstructive pulmonary disease (COPD). However, in some patients presenting with HRF, the underlying cause is not apparent at initial presentation, and there may be multiple underlying potential causes existing concurrently. Although each cause requires disease-specific therapies, most patients require hospitalisation and many benefit from ventilatory support in dedicated respiratory and critical care units. Hence, HRF can be considered a single, albeit heterogeneous entity, that constitutes a significant problem for health facilities worldwide.

Previous studies examining the underlying causative conditions among patients with HRF have typically included participants identified following admission to an intensive care or

respiratory admission and requiring ventilatory support therapy (1-5). Three studies selected cases based on arterial blood gas (ABG) values (6-8) and another relied on diagnosis codes suggestive for respiratory failure from hospital records (9). Although these studies illustrate the range of conditions contributing to hospitalisation with HRF, none describe the prevalence of these factors in the source population and, hence, are unable to estimate the relative importance of each cause. Previous population-based studies have been limited to studying persons receiving home mechanical ventilation (10-12), which exclude cases whose underlying disease, comorbidities or socioeconomic factors preclude this intervention. Understanding the relative importance of the causes of HRF at a population level, irrespective of the treatments received, is required to develop investigation and management strategies for patients with undifferentiated HRF, and interventions to reduce hospitalisations associated with this condition.

Using a community-based case control study design, we sought to determine the strength of association between hospitalisation with HRF and the following conditions: COPD, congestive cardiac failure (CCF), obstructive sleep apnea (OSA), respiratory muscle weakness, and the use of opioid and benzodiazepine medications. We selected these causes in consensus based on previous studies and our clinical experience. In addition to estimating the strength of association with HRF, we used data on the prevalence of these conditions in the general community to estimate, for each cause, the population attributable fraction (PAF), an epidemiologic measure to describe the relative importance and public health impact of a risk factor in a population.

6.2.3 Methods

Overview

This prospective study was based in the City of Liverpool, a metropolitan area within Sydney, Australia (13). The study population was restricted to persons aged 40 years and over. A case–control study design was implemented in which cases were people with HRF and controls were randomly selected members of the source population who did not have HRF. Non-English speaking persons were excluded if an interpreter was unavailable. We excluded nursing home residents due to difficulties in obtaining informed consent and accurate study measurements. Participants were reimbursed for their time with a gift card to the value of $40 AUD. Study procedures were approved by the South Western Sydney Local Health District Human Research Ethics Committee and all participants provided written, informed consent.

Cases and controls

Cases were patients who attended Liverpool Hospital between 2016 and 2018. Potential cases were identified based on an ABG, collected within 24 h of presentation, demonstrating $PaCO_2 > 45$ mmHg and $pH \leq 7.45$. We anticipated the number of cases of HRF missed by this screening method to be low due to the increased risk of hospitalisation associated with hypercapnia, the public healthcare scheme in Australia that provides free hospital services to all citizens and most permanent residents, and local data that indicate most people with respiratory conditions from this population who require hospitalisation attend Liverpool Hospital. Medical records were reviewed to exclude suspected nosocomial cases of HRF, or instances where the person had suffered an out-of-hospital cardiac arrest or traumatic injury. Cases were invited to participate first by mail and then by follow-up telephone calls.

Population-based controls were randomly selected using a two-stage geography-based cluster sampling design, implemented from 2018 to 2019. First, we randomly selected 40 census tracts from the 449 comprising this region, the City of Liverpool. The probability of tract selection was proportional to the number of eligible residents in each tract. Next, we undertook 'random walks' to select households units within each tract, from which control participants were recruited. Investigators starting from the geographical centre of each tract walked along streets in directions guided by a computer-based random number generator. This method of population-based sampling is a practical method for random selection of participants from a large population when a population list is incomplete or unavailable, and is modified from methods used by the World Health Organization (14). Letters of invitation were delivered to each household upon sampling, containing participant information sheets and multiple options for responding to the research team (telephone, e-mail, reply-paid envelope). All selected households received at least two letters of invitation and at least one home visit by study investigators in order to obtain a response, and record the number of eligible participants within each household.

Procedures

Standardised questionnaires were administered by members of the research team. Data were collected on sociodemographic factors, comorbidities, and medications, including the use of opioids and benzodiazepines, in the preceding two years.

Spirometry was performed using the EasyOne spirometer (NDD Medical Technologies), before and after administration of salbutamol 200 μg via metered dose inhaler and spacer. All spirograms were reviewed by the author (Y.C.) for acceptability and repeatability using published criteria (15). N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured from venous blood samples by electrochemiluminescent immunoassay (Roche Diagnostics). Sniff nasal inspiratory pressure (SNIP) measurements were taken using a

fitted nasal probe connected to a hand-held meter (MicroRPM, CareFusion). Up to 10 manoeuvres were performed per nostril (16). Overnight home-based sleep testing was performed using a portable device with airflow (pressure cannula), respiratory movement and oximetry channels (ApneaLink, ResMed). All recordings were reviewed by the author (Y.C.) and excluded if there were fewer than 3 h of adequate flow and oximetry data. Data were scored automatically using ApneaLink software (V10.2). Apneas were defined as at least 90% decrease in airflow for at least 10 s and hypopneas as a decrease by 30% for the same duration associated with desaturation of 3% or more. Investigators conducting measurements were unblinded as to whether participants were cases or controls.

Statistical analysis

Continuous variables are summarised as means with standard deviations (SD) and medians with interquartile ranges (IQR). Groups were compared using independent t-tests or Mann–Whitney U tests, as appropriate. Frequencies and percentages are used to describe categorical variables, and Fisher's chi-square test used to compare groups. Baseline logistic regression models were used to assess the relationship between the presence or absence of HRF and continuous variables: the post-bronchodilator forced expiratory volume (FEV_1)/forced vital capacity (FVC) ratio, NT-proBNP levels, maximum SNIP value ($SNIP_{max}$) and apnea-hypopnea index (AHI). Receiver operator characteristic (ROC) curves were generated from these models to determine the area under the ROC curve (AUC) in order to assess the predictive value of each of these variables for HRF. For subsequent analyses, participants were classified as having COPD if post-bronchodilator FEV_1/FVC was below the lower limit of normal, using Global Lung Initiative reference values (17). The diagnosis of CCF was based on NT-proBNP levels ≥ 100 pmol/L (846 pg/mL). Respiratory muscle weakness was recorded if $SNIP_{max}$ was less than 70 cmH_2O and 60 cmH_2O, among males

and females, respectively. A diagnosis of moderate-to-severe OSA was recorded if the AHI was ≥ 15 events per hour.

We determined the adjusted association with HRF for each potential cause, reported as odds ratios (OR) with 95% confidence intervals (CI). Covariates for each model were informed by a directed acyclic graph (DAG) developed by the authors using the web-based program 'daggity' (18) showing direct and indirect pathways for the development of HRF (Fig. 6.1). Regressions were performed in SAS (Version 9.4). PAF estimates were calculated in STATA (Version 17). Full details of our regression models are provided in the Supplementary Material.

Power calculation

We estimated 205 participants would be required in each group to detect an odds ratio of 2.8 and 2.0 for risk factors with prevalence values of 5% and 15%, respectively, with 80% power and two-sided alpha of 0.05. Study recruitment was stopped early due to low response rates and the COVID-19 pandemic.

6.2.4 Results

One hundred and forty-seven subjects (42 cases and 105 controls) completed the study, as shown in Fig. 6.2.

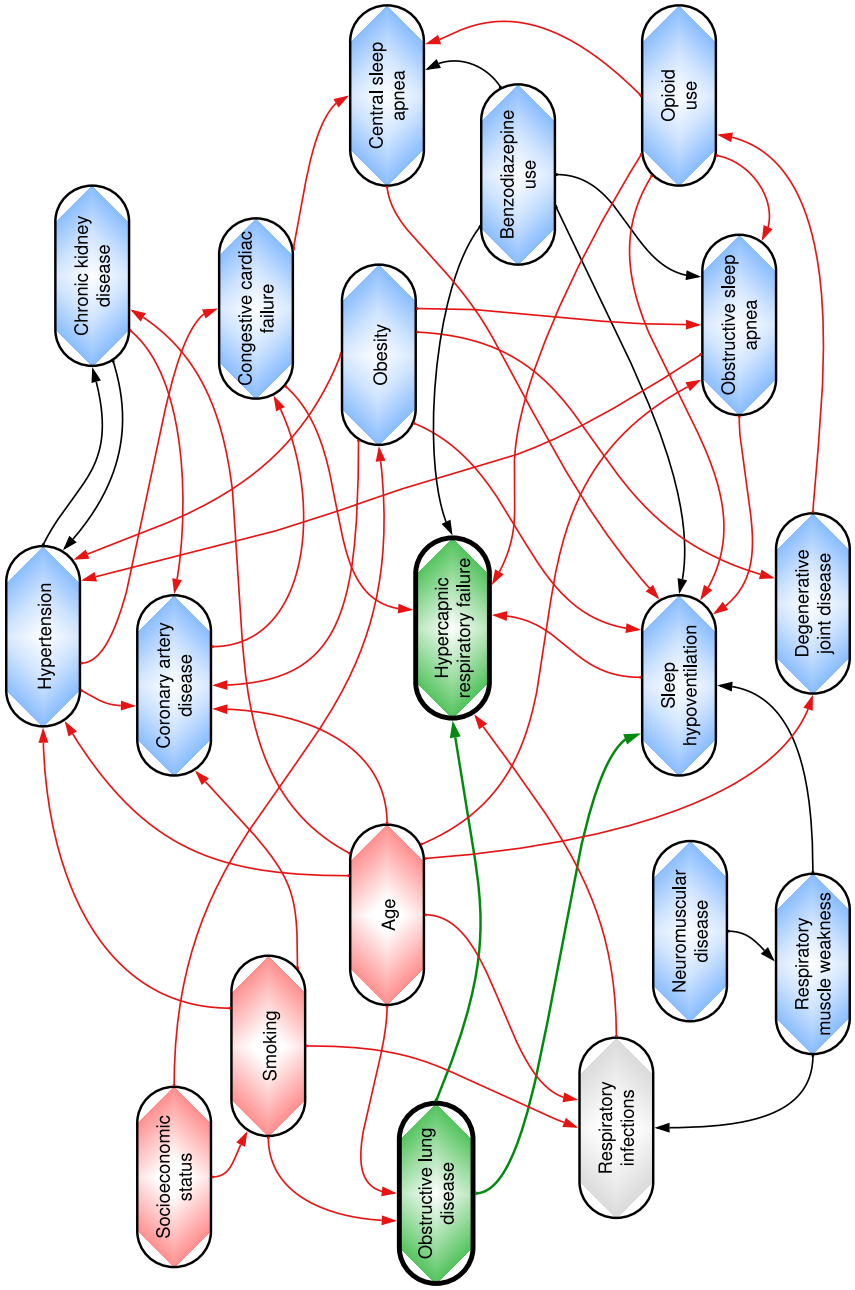

Figure 6.1. *Causal diagram for hypercapnic respiratory failure. Directed acyclic graph illustrating assumed causal relationships between pre-specified exposure variables and the outcome of hypercapnic respiratory failure. In this case, obstructive lung disease has been selected as the exposure (green-shaded variable). Green arrows represent causal paths. Blue-shaded variables represent ancestors of the outcome and red-shaded variables represent ancestors of both the exposure and outcome. Red arrows represent biasing paths. Based on this diagram, the minimum adjustment set of variables to estimate the total effect of obstructive lung disease on hypercapnic respiratory failure are: age, smoking*

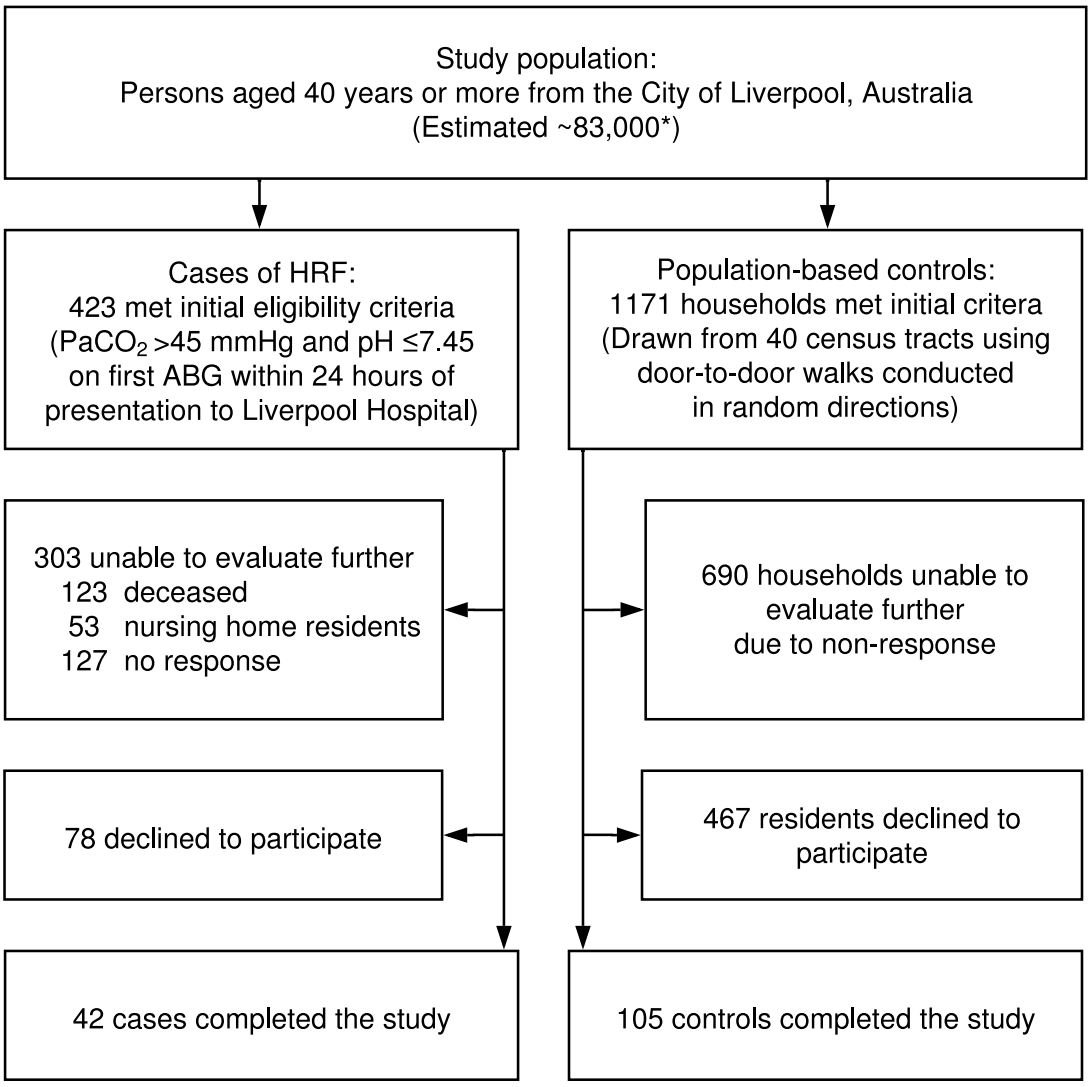

Figure 6.2. *Participant flowchart. * Estimated source population is based on 2016 Census data (13)*

Demographic and clinical characteristics are shown in Table 6.1. Compared with controls, cases were older, more likely to have been smokers, and had lower levels of educational attainment and household income. The most frequently reported respiratory conditions were asthma, COPD and OSA. Among cases, 34 (81%) reported at least one respiratory diagnosis, compared with 41 (39%) among controls ($p < 0.001$). The Charlson comorbidity index, a composite predictor of mortality (19), was significantly higher among cases ($p < 0.001$).

Table 6.1. *Participant characteristics*

	Cases	**Controls**	***P***
Subjects (n)	42	105	
Age (years, mean (SD))	66.8 (10.2)	59.4 (11.8)	<0.001
Sex, Male (n (%))	21 (50%)	50 (48%)	0.9
Body mass index (kg/m^2, mean (SD))	34.6 (11.0)	29.6 (6.1)	<0.001
Smoking exposure			
Ever smoked (n (%))	36 (86%)	54 (52%)	<0.001
Pack years (median (IQR))	45 (22.5, 67.5)	22.5 (2.5, 43.8)	0.04
Highest level of education (n **(%))**			0.02
Below upper secondary	23 (55%)	35 (33%)	
Upper secondary, post-secondary non-tertiary or tertiary	19 (45%)	70 (67%)	
Household income range[a] (n (%))			<0.001
Lowest quartile	1 (2%)	0 (0%)	
Medium lowest quartile	36 (86%)	54 (51%)	
Medium highest quartile	2 (5%)	23 (22%)	
Highest quartile	0 (0%)	22 (21%)	
No response	3 (7%)	6 (6%)	
Self-reported past medical history (n (%))			
Asthma	19 (45%)	26 (24%)	0.02
Chronic obstructive pulmonary disease	22 (52%)	16 (15%)	<0.001
Pulmonary fibrosis	3 (7%)	1 (1%)	0.07
Bronchiectasis	1 (2%)	2 (2%)	1
Obstructive sleep apnea	18 (43%)	13 (12%)	<0.001
Atrial fibrillation	11 (26%)	6 (6%)	0.001
Coronary artery disease	11 (26%)	8 (8%)	0.005
Congestive cardiac failure	14 (33%)	2 (2%)	<0.001
Cerebrovascular accident	8 (19%)	4 (4%)	0.005
Peripheral vascular disease	4 (10%)	1 (1%)	0.06
Chronic kidney disease	7 (17%)	9 (9%)	0.2
Chronic liver disease	4 (10%)	1 (1%)	0.02
Hypertension	27 (64%)	37 (35%)	0.002
Diabetes mellitus	17 (40%)	18 (17%)	0.005
Solid organ malignancy	5 (12%)	6 (6%)	0.3
Depression, anxiety or other chronic mental health disorder	18 (43%)	20 (19%)	0.006
Charlson Comorbidity Index (median (IQR))	2 (1 – 5)	1 (0 – 1)	<0.001

[a]*Household income comparisons are based on 2016 Census data (13).*

At least one pre-specified cause for HRF was identified in 42 (100%) cases, and 66 (63%) controls ($p < 0.001$) (Table 6.2). Among cases, 37 (88%) had two or more causes and 20 (48%) had three or more potential causes for HRF. The most common cause of HRF in cases was self-reported use of opioid medications (57%), followed by COPD (50%). Mean (SD) FEV_1 in cases was 51 (21) percent predicted. The most frequent potential cause for HRF among controls was moderate-to-severe OSA (34%). The median (IQR) AHI among all controls was 6.6 (3.1, 19.1) events per hour.

The risk of HRF associated with each cause is shown in Table 6.3. CCF, COPD, respiratory muscle weakness and opioid use were strongly associated with the presence of HRF. The AUC values for FEV_1/FVC, NT-proBNP, AHI and $SNIP_{max}$ as continuous variables were 0.81, 0.74, 0.50 and 0.67, respectively. At the pre-specified cutoff, CCF had the strongest association (OR 13.4, 95% CI 1.40 – 128). Post-hoc analysis showed that when a lower NT-proBNP cut-off value of 35 pmol/L (296 pg/mL) was used to determine the presence of CCF, the magnitude of association was attenuated but remained statistically significant with an OR of 4.25 (95% CI 1.16 – 15.6).

Moderate-to-severe OSA did not appear to be associated with increased risk of HRF, with more controls having this condition compared with cases. There was no difference between groups based on mean AHI, using a 4% desaturation threshold, or using the oxygen desaturation index. There were no significant differences in age, BMI, degree of comorbidity, reported sleepiness, and estimated risk of OSA based on the STOP-Bang score (20) between participants who did and did not complete the overnight sleep study.

Table 6.2. *Prevalence of potential causes for hypercapnic respiratory failure among cases and control participants*

Cause	**Cases** ***N*** **= 42**	**Controls** ***N*** **= 105**	***P***
Chronic obstructive pulmonary disease			
Frequency (FEV_1/FVC < LLN, n/N (%))	21/42 (50%)	11/105 (11%)	<0.001
Post-BD FEV_1 (L, mean (SD))	1.27 (0.52)	2.44 (0.71)	
Post-BD FEV_1 (% predicted, mean (SD))	51 (21)	90 (16)	
Post-BD FVC (L, mean (SD))	2.11 (0.59)	3.17 (0.88)	
Post-BD FVC (% predicted, mean (SD))	64 (15)	92 (13)	
FEV_1/FVC < 0.7 (n/N (%))	26/42 (62%)	24/105 (23%)	
Congestive cardiac failure			
Frequency (NT-proBNP ≥ 100 pmol/L, n/N (%))	9/35 (26%)	1/81 (1%)	<0.001
NT-pro-BNP (pmol/L, mean (SD))	101 (212)	14 (20)	0.003
Obstructive sleep apnea			
Frequency (AHI ≥ 15 events/hour, n/N (%))	7/25 (28%)	24/70 (34%)	0.6
AHI (mean (SD))	10.3 (8.6)	12.7 (13.2)	0.4
Oxygen desaturation index (mean (SD))	17.5 (11.2)	15.9 (14.2)	0.6
Respiratory muscle weakness			
Frequency ($SNIP_{max}$ < LLN, n/N (%))	16/42 (38%)	11/103 (11%)	<0.001
$SNIP_{max}$ (cmH2O, mean (SD))	78 (24)	93 (28)	0.002
Opioid use			
Frequency (n (%))	24 (57%)	27 (26%)	<0.001
Benzodiazepine use			
Frequency (n (%))	7 (17%)	14 (13%)	0.6

AHI Apnea-hypopnea index, BD bronchodilator, FEV_1 Forced expiratory volume in the first second, FVC Forced vital capacity, LLN Lower limit of normal, NT-proBNP N-terminal brain natriuretic peptide, $SNIP_{max}$ Maximum sniff nasal inspiratory pressure.

Table 6.3. *Risk of hypercapnic respiratory failure by potential underlying cause*

	Odds Ratio (95% CI)		PAF[a]
Cause	**Unadjusted**	**Adjusted**	**(95% CI)**
Chronic obstructive pulmonary disease	7.49 (3.16–17.8)	5.30 (1.95–14.4)	42% (18–59%)
Congestive cardiac failure	21.7 (2.80–166)	13.4 (1.40–128)	24% (7–38%)
Moderate-to-severe obstructive sleep apnea	1.14 (0.46–2.81)	0.38 (0.10–1.53)	NA
Respiratory muscle weakness	5.11 (2.11–12.3)	5.11 (2.11–12.3)	31% (11–46%)
Opioid use	3.85 (1.82–8.17)	3.64 (1.49–8.88)	41% (13–59%)
Benzodiazepine use	1.30 (0.48–3.49)	1.30 (0.48–3.49)	NA

[a]*The population attributable fraction (PAF) was determined separately for each cause, and thus adds to more than 100%. The PAF was not determined when there was no significant relationship between the specified cause and hypercapnic respiratory failure.*

No single cause was identified as being responsible for more than 50% of HRF cases, based on the PAF, as shown in Table 3. COPD had the highest adjusted PAF at 42% (95% CI 18% – 59%), followed by opioid use which had a PAF of 41% (13% – 59%). Despite its low prevalence in the general population (1%), CCF contributed substantially to the burden of HRF with a PAF of 24% (7% – 38%).

6.2.5 Discussion

In this population-based case–control study, we show that HRF is a multifactorial condition with no single disease responsible for the majority of cases. In addition to chronic health conditions such as COPD and CCF, opioid use and respiratory muscle weakness are significantly associated with HRF hospitalisations. Interventions to reduce the prevalence of these causes have the potential to substantially reduce HRF-associated hospitalisations in this and other comparable populations.

Of the hypothesised causes, COPD had the highest population attributable fraction. Most previous surveys have shown COPD to be the dominant cause of hospitalisation with HRF (1,2,3,7,8), and COPD is also an important indication for treatment with home non-invasive ventilation therapy (12). A prevalence study of hypercapnic COPD exacerbations has been used to approximate the requirements for hospital non-invasive ventilation services (21). However, a considerable proportion of our cases did not have objective evidence of airflow obstruction, nor a history of chronic airways disease. Furthermore, we suspect the proportion of cases with COPD to be overrepresented in our study, as we have previously demonstrated that among cases of HRF, the presence of chronic airways disease is associated with a lower risk of death (22). Hence, whilst COPD is an important contributor to HRF, it is not the only cause, and clinician judgment is required when assessing undifferentiated patients to identify alternative diagnoses.

In this population, CCF was an important contributor to hospitalisations with HRF. Patients with heart failure have reduced lung compliance and increased airways resistance, experiencing greater mechanical costs of breathing resulting in muscle fatigue and inability to maintain adequate ventilation (23). Hypercapnia is present in up to 33% of patients with acute heart failure (24), and this can occur even in the absence of COPD (25). One study of patients with compensated hypercapnia showed CCF to be more frequent than COPD (6). The methods used to detect heart failure in previous studies have varied widely, ranging from clinician-reported diagnoses to echocardiographic findings (1,3,6). We used the NT-pro-BNP to dichotomise patients, tolerating a degree of misclassification. NT-pro-BNP levels may be elevated with age, renal impairment and certain medications, but it has good negative predictive value when using low thresholds (26). We selected a higher cut-off point to achieve greater specificity, and found the prevalence of CCF in controls to be comparable to previously published data (27). Our study confirms the importance of CCF as a

contributor to ventilatory failure, and the need to consider this cause among people presenting with HRF.

Self-reported use of opioid medications contributed significantly, with a PAF comparable to that of COPD. In recent decades, Australia and other high-income countries have documented a marked increase in the use of prescription opioids (28). The clinical indication for most opioid prescriptions is acute pain (29), but chronic non-cancer pain is associated with continued opioid use (30). Opioids directly suppress respiration but can also contribute to ventilatory failure indirectly via the mediators of sleep-related hypoventilation, obstructive and central sleep apnea (31). Among adults with COPD, incident opioid prescriptions are associated with increased risk of adverse respiratory outcomes and death (32). However, safety data among patients with chronic respiratory disease are inconsistent, particularly when considering those who receive opioids for refractory breathlessness (33). Few previous studies have included drugs as a potential cause for HRF (3,8), generally excluding such patients (1,7). We found opioid use to be associated with at least a three-fold increase in the risk of HRF, and hence may be an important modifiable risk factor in similar populations. Our results emphasise the need to rationalise opioid use to clinical situations where potential harms are outweighed by the benefits of these medicines.

There was a relatively high prevalence of respiratory muscle weakness among cases, and there was a significant association between reduced muscle strength and HRF. Neuromuscular disease including motor neuron disease, polio and muscular dystrophy accounts for a substantial proportion of home mechanical ventilation users (10). We did not differentiate between such disorders and impaired respiratory muscle function due to other condition such as obesity and CCF, potentially leading to overestimates in PAF with respect to this risk factor.

Our study did not show a significant association between moderate-to-severe OSA and hospitalisation with HRF. Our analysis was based on the assumption that OSA could lead to HRF via sleep-related hypoventilation, or via an alternate pathway involving the development of CCF, with or without central sleep apnea and sleep hypoventilation (34) (Fig. 1). The apparent lack of association between OSA and HRF in our study might be explained by the very high prevalence of undiagnosed OSA among controls. A recent Australian study suggested the prevalence of moderate-to-severe OSA to be 20.2% in males and 10.0% of females (35). However, a Swiss study demonstrated higher prevalence figures of 49.7% and 23.4% in males and females, respectively (36). As such, whilst OSA is frequently diagnosed among patients with HRF, it might represent incorrect attribution as the cause of ventilatory failure. Alternatively, we may have missed a significant association due to the limitations of our testing methods. Previous studies have shown a high frequency of OSA among survivors of HRF, ranging from 51 to 83% when based on objective testing (1,37). The device we used in our study has 82% sensitivity for the diagnosis of moderate-to-severe OSA (38), but validation studies have typically excluded highly comorbid people and those with suspected hypoventilation. We also did not manually score data, relying on proprietary software for automatic detection of respiratory events. Hence, although we found a substantial prevalence of undiagnosed OSA which may be amenable to treatment, we did not find an association with HRF hospitalisations.

This study has some weaknesses. We were unable to achieve the recruitment target, but in our analysis we found that our sample size was sufficient to detect with statistical confidence the high magnitude of associations observed between HRF and the causes COPD, CCF and opioid use. Rather than the small groups per se, the primary limitation of this study is the potential selection bias induced by low response and non-participation rates. A relatively small proportion of potentially eligible people proceeded to study participation, despite attempts made by the investigators to minimise inconveniences and

provide financial reimbursement for the time provided. Controls may have been more likely to participate if they had symptoms of, or were concerned about, OSA. If this effect had occurred in controls but not cases, it would have led to an underestimation of the association with OSA. Potential cases may have been excluded due to frailty or death. The effect of this selection bias would have been under-estimation of the association with causes known to increase the risk of death, such as CCF. Due to the case–control design, risk factors for the outcome are measured after the occurrence of HRF, although we expect most to be chronic conditions that would have been present prior to hospitalisation. Finally, our results may not be generalisable to other populations depending on socioeconomic and other factors affecting the prevalence of each cause.

Nevertheless, our work has several strengths distinguishing it from previous studies. This is one of few studies that have selected cases based on ABG results. We have provided objective measurements of causes rather than self-reported diagnoses or medical records which may be incomplete. We employed causal diagrams to inform our statistical analysis in keeping with modern epidemiological theory. Importantly, this is the first study of HRF to provide data on a control group, allowing estimation of the association between specific causes and HRF at a population level as well as the relative importance of each cause as reflected in the population attributable fraction.

6.2.6 Conclusions

In summary, our study provides evidence for the multifactorial nature of HRF and the range of potential contributing factors. In addition to COPD, other causes including CCF, opioid use and respiratory muscle weaknesses are significantly associated with HRF hospitalisations. These findings have important implications for the assessment and management of patients with HRF and highlight the need for comprehensive evaluation to ensure that all treatable factors are addressed.

6.3 Chapter references

1. Adler D, Pépin JL, Dupuis-Lozeron E, Espa-Cervena K, Merlet-Violet R, Muller H, *et al*. Comorbidities and subgroups of patients surviving severe acute hypercapnic respiratory failure in the intensive care unit. *Am J Respir Crit Care Med* 2017;196:200–207.
2. Smith DB, Tay GTP, Hay K, Antony J, Bell B, Kinnear FB, et al. Mortality in acute non-invasive ventilation. *Intern Med J* 2017;47:1437–40.
3. Contou D, Fragnoli C, Córdoba-Izquierdo A, Boissier F, Brun-Buisson C, Thille AW. Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit. *Respir Care* 2013;58:2045–52.
4. Innocenti F, Giordano L, Gualtieri S, Gandini A, Taurino L, Nesa M, *et al*. Prediction of mortality with the use of noninvasive ventilation for acute respiratory failure. *Respir Care* 2020;65:1847–56.
5. Phua J, Kong K, Lee KH, Shen L, Lim TK. Noninvasive ventilation in hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease vs. other conditions: effectiveness and predictors of failure. *Intensive Care Med* 2005;31:533–9.
6. Wilson MW, Labaki WW, Choi PJ. Mortality and healthcare use of patients with compensated hypercapnia. *Ann Am Thorac Soc* 2021;18:2027–32.
7. Cavalot G, Dounaevskaia V, Vieira F, Piraino T, Coudroy R, Smith O, *et al*. One-year readmission following undifferentiated acute hypercapnic respiratory failure. *COPD* 2021;18:602–11.
8. Vonderbank S, Gibis N, Schulz A, Boyko M, Erbuth A, Gürleyen H, *et al*. Hypercapnia at hospital admission as a predictor of mortality. *Open Access Emerg Med* 2020;12:173–80.
9. Meservey AJ, Burton MC, Priest J, Teneback CC, Dixon AE. Risk of readmission and mortality following hospitalization with hypercapnic respiratory failure. *Lung* 2020;198:121–34.
10. Garner DJ, Berlowitz DJ, Douglas J, Harkness N, Howard M, McArdle N, *et al*. Home mechanical ventilation in Australia and New Zealand. *Eur Respir J* 2013;41:39–45.
11. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Fauroux B, *et al*. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J* 2005;25:1025–31.

12. Cantero C, Adler D, Pasquina P, Uldry C, Egger B, Prella M, *et al*. Long-term noninvasive ventilation in the Geneva lake area: indications, prevalence, and modalities. *Chest* 2020;158:279–91.
13. Australian Bureau of Statistics. 1410.0 - Data by Region, 2013–18. Australian Bureau of Statistics; 2019. Available from: https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1410.02013-18?OpenDocument.
14. Bennett S, Woods T, Liyanage WM, Smith DL. A simplified general method for cluster-sample surveys of health in developing countries. *World Health Stat Q* 1991;44:98–106.
15. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, *et al*. Standardization of spirometry 2019. Update an official American thoracic society and European respiratory society technical statement. *Am J Respir Crit Care Med* 2019;200:e70–88.
16. Lofaso F, Nicot F, Lejaille M, Falaize L, Louis A, Clement A, *et al*. Sniff nasal inspiratory pressure: what is the optimal number of sniffs? *Eur Respir J* 2006;27:980–2.
17. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, *et al*. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
18. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty.' *Int J Epidemiol* 2016;45:1887–94.
19. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, *et al*. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676–82.
20. Chung F, Abdullah HR, Liao P. STOP-Bang questionnaire: a practical approach to screen for obstructive sleep apnea. *Chest* 2016;149:631–8.
21. Plant PK, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of non-invasive ventilation and oxygen administration. *Thorax* 2000;55:550–4.
22. Chung Y, Garden FL, Marks GB, Vedam H. Causes of hypercapnic respiratory failure and associated in-hospital mortality. *Respirology* 2023;28:176–82.
23. Cross TJ, Kim C-H, Johnson BD, Lalande S. The interactions between respiratory and cardiovascular systems in systolic heart failure. *J Appl Physiol* 2020;128:214–24.
24. Konishi M, Akiyama E, Suzuki H, Iwahashi N, Maejima N, Tsukahara K, *et al*. Hypercapnia in patients with acute heart failure. *ESC Heart Fail* 2015;2:12–9.

25. Valipour A, Cozzarini W, Burghuber OC. Non-invasive pressure support ventilation in patients with respiratory failure due to severe acute cardiogenic pulmonary edema. *Respiration* 2004;71:144–51.
26. Castiglione V, Aimo A, Vergaro G, Saccaro L, Passino C, Emdin M. Biomarkers for the diagnosis and management of heart failure. *Heart Fail Rev* 2022;27:625–43.
27. Sahle BW, Owen AJ, Mutowo MP, Krum H, Reid CM. Prevalence of heart failure in Australia: a systematic review. *BMC Cardiovasc Disord* 2016;16:32.
28. Donovan PJ, Arroyo D, Pattullo C, Bell A. Trends in opioid prescribing in Australia: a systematic review. *Aust Health Rev* 2020;44:277–87.
29. Pasricha SV, Tadrous M, Khuu W, Juurlink DN, Mamdani MM, Paterson JM, *et al*. Clinical indications associated with opioid initiation for pain management in Ontario, Canada: a population-based cohort study. *Pain* 2018;159:1562–8.
30. Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use - United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:265–9.
31. Rosen IM, Aurora RN, Kirsch DB, Carden KA, Malhotra RK, Ramar K, *et al*. Chronic opioid therapy and sleep: an American academy of sleep medicine position statement. *J Clin Sleep Med* 2019;15:1671–3.
32. Vozoris NT, Wang X, Fischer HD, Bell CM, O'Donnell DE, Austin PC, *et al*. Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J* 2016;48:683–93.
33. Verberkt CA, van den Beuken-van MH, Schols JMGA, Datla S, Dirksen CD, Johnson MJ, *et al*. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. *Eur Respir J* 2017;50:1701153.
34. Naughton MT, Bradley TD. Sleep apnea in congestive heart failure. *Clin Chest Med* 1998;19:99–113.
35. Cunningham J, Hunter M, Budgeon C, Murray K, Knuiman M, Hui J, *et al*. The prevalence and comorbidities of obstructive sleep apnea in middle-aged men and women: the Busselton Healthy Ageing Study. *J Clin Sleep Med* 2021;17:2029–39.
36. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, *et al*. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015;3:310–8.
37. Ouanes-Besbes L, Hammouda Z, Besbes S, Nouira W, Lahmar M, Ben Abdallah S, *et al*. Diagnosis of sleep apnea syndrome in the intensive care unit: a case series of survivors of hypercapnic respiratory failure. *Ann Am Thorac Soc* 2021;18:727–9.

38. Smith D, Park J, Hay K, Hoey L, Leong G, Leong M, *et al*. Use of a limited-channel device for obstructive sleep apnea diagnosis in a tertiary sleep disorders centre. *Intern Med J* 2020;50:1109–14.

Cite: Chung Y, Garden FL, Marks GB, Vedam H. Causes of hypercapnic respiratory failure: a population-based case-control study. *BMC Pul Med* 2023;23:347.

7. Outcomes of hypercapnic respiratory failure

7.1 Introduction

Understanding the natural history of disease is critical to interpreting and evaluating the impact of population-based interventions. One of the most common measures of prognosis is survival time. Although many studies have reported survival following hospitalisation with hypercapnic respiratory failure, none have determined the mortality rate relative to a standard population. This standardised mortality ratio is crucial to understanding the impact of a particular condition, since populations with a higher proportion of elderly people are likely to have a higher death rate and therefore overall survival time.

The primary objective of this study was to describe the prognosis for people with HRF due to any cause, including deaths and time to rehospitalisation. I found that an episode of hypercapnic respiratory failure portends an abbreviated survival time with one-, three- and five-year survival probabilities of 81%, 59% and 45%, respectively. The standardised mortality ratio of 9.2 indicates a near-ten fold risk of death compared with an unaffected population of similar age. Among survivors, there was a high risk of rehospitalisation; 91% were readmitted at a median time of 3.9 months.

This work has been published in *BMJ Open Respiratory Research*, reproduced as follows. The supplementary material is provided separately in Chapter 9.

7.2 Long-term cohort study of patients presenting with hypercapnic respiratory failure

7.2.1 Abstract

Objective: We sought to describe the long-term prognosis for a population-based cohort of people with hypercapnic respiratory failure (HRF), and the associations between underlying diagnoses and the risks of death and rehospitalisation.

Methods: We performed a historical cohort study of all persons with HRF in the Liverpool local government area in New South Wales, Australia, in the 3-year period from 2013 to 2015. Cohort members were identified using arterial blood gas results from Liverpool Hospital demonstrating pH ≤7.45 and $PaCO_2$ >45 mmHg within 24 hours of presentation. Linked health data were obtained from statewide registries with a minimum follow-up period of 6 years. The primary outcomes were time to death from any cause and the standardised mortality ratio (SMR) which compares the observed to the expected number of deaths in the same population. Secondary outcomes were time to rehospitalisation, and the associations between death and/or hospitalisation and underlying diagnoses.

Results: The cohort comprised 590 adults aged between 15 and 101 years. Overall, 415 (70.3%) participants died in the follow-up period. Among those who survived the index admission, the probability of survival at 1, 3 and 5 years was 81%, 59% and 45%, respectively. The overall SMR was 9.2 (95% confidence interval 7.6 to 11.0), indicating a near 10-fold risk of death than otherwise expected for age. Most (91%) survivors experienced rehospitalisation, with median (IQR) time to readmission 3.9 (1.2-10.6) months. Congestive cardiac failure and neuromuscular disease were associated with an increased risk of death, whereas chronic obstructive pulmonary disease and sleep-disordered breathing increased the risk of rehospitalisation.

Conclusions: HRF is associated with poor survival and high risk of rehospitalisation in the 5 years following an index event. The underlying disease appears to have some influence on overall survival and subsequent hospitalisations.

7.2.2 Introduction

Most of the available epidemiological data on hypercapnic respiratory failure (HRF) relate to its association with specific underlying causes, such as chronic obstructive pulmonary disease (COPD) (1,2). However, there are few data on the prevalence and prognosis of HRF as a single entity. This is an important gap in knowledge because systematic evaluation of patients with HRF frequently demonstrates the co-occurrence of multiple diseases with the potential to cause ventilatory failure. For instance, Adler and colleagues found that over half of patients who survived a hospitalisation requiring ventilatory support had at least three major comorbidities known to precipitate acute HRF. Furthermore, in a substantial proportion of this cohort, many of these underlying causes had neither been diagnosed nor treated during the acute admission (3). Consequently, prognostic information based on prior research studies of persons with specific diagnoses may have limited generalizability to encounters with patients who have undifferentiated HRF and/or multimorbidity.

The few available studies on HRF due to any cause typically recruit participants based on arterial blood gas (ABG) measurements taken at time of admission to an intensive care unit, representing a highly selected cohort. Another limitation of the currently available literature is that most studies of prognosis are limited to a relatively short follow-up period. Despite the difficulties associated with defining and identifying a validly representative population-based cohort of patients with HRF, understanding the long-term outcomes of patients with this condition is needed to assist clinical decision-making for individual patients and to determine the effect of interventions directed at prevention and management.

In this study, we sought to determine the prognosis for survival and for rehospitalisation among adults presenting to hospital with HRF due to any cause. We also examined the associations between underlying diagnoses and the risks of death and rehospitalisation, hypothesising that the prognosis in patients with HRF is substantially related to the underlying cause of the condition.

7.2.3 Methods

We performed a population-based historical cohort study using linked health data. Patients and the public were not directly involved in the production of this study.

Study setting

The cohort comprised adult residents of the Liverpool local government area (LGA), a municipality in Sydney, New South Wales (NSW), Australia, who attended hospital with HRF in the 3-year period from 2013 to 2015. Potential cases were identified by screening ABG records collected at Liverpool Hospital, the major service provider for this region. Liverpool Hospital comprises approximately 900 beds (including dedicated intensive care beds) and provides a range of specialist respiratory and sleep services including provision of non-invasive ward-based ventilation for patients with acute respiratory failure and outpatient services for patients requiring long-term non-invasive ventilatory support therapy.

We considered the participants identified using the above methods a representative population cohort based on the following: most patients with HRF are likely to attend hospital in a country with universal (free) health care, local data from the Ministry of Health showed that 86% of people from the Liverpool LGA who attended a hospital for respiratory conditions presented to Liverpool Hospital (4), and patients presenting to our emergency

department with respiratory symptoms typically have a venous blood gas performed that prompts a confirmatory arterial sample if HRF is suspected.

Study participants

Inclusion criteria were pH ≤7.45 and $PaCO_2$ >45 mmHg on the first ABG collected within 24 hours of presentation. We excluded blood gas results in which the SaO_2 was at least 10% lower than the pulse oximetry SpO_2, as these were assumed to be venous specimens. We reviewed medical records to exclude patients who had suffered an out-of-hospital cardiac arrest or in whom the HRF may have been caused by in-hospital procedures requiring general anaesthesia and/or sedation. Further details on this method have been published elsewhere (5). In defining this cohort, we chose not to differentiate between acute, acute-on-chronic and chronic hypercapnic respiratory failure because the available data did not allow this distinction to be confidently identified and, furthermore, our objective was to assess prognosis of all patients with hypercapnic respiratory failure, regardless of time course.

Endpoints

The primary outcome was the time to death from any cause, measured from the date of initial presentation with HRF to the date of death, if this occurred during the follow-up period. In addition to crude death rate, we also estimated the standardised mortality ratio (SMR), defined as the ratio of the observed number of deaths to the expected number of deaths, for the observed age distribution. Secondary outcomes included time to rehospitalisation and the associations between these outcomes and underlying diagnoses.

Follow-up period

The minimum follow-up period for the primary outcome was 6 years. Participants were followed up from the date of initial presentation with HRF (between 1 Jan 2013 and 31 December 2015) and either the date of death or 31 December 2021, whichever occurred first. Hospital data were available to 30 June 2021, allowing a minimum follow-up period of 5.5 years for the secondary endpoint of rehospitalisation.

Data sources

Data on deaths and hospitalisation were obtained from the following datasets: the NSW Registry of Birth, Deaths and Marriages (RBDM), the NSW Admitted Patient Data Collection (APDC), the NSW Emergency Department Data Collection (EDDC). All deaths occurring in the state of NSW are recorded in the RBDM. The APDC and EDDC contain data on all attendances at NSW public and private hospitals. Members of the study cohort were linked to the deaths and hospitalisation data using probabilistic data linkage. This was performed securely by the Centre for Health Record Linkage (CHeReL) using the following identifiers: name, date of birth, sex, hospital record number, admission date and home address. CHeReL were not otherwise involved in this study and provided the investigators with an anonymised linked dataset.

Data collection

We obtained demographic and clinical information on members of the study cohort from the APDC. These data included the presence of specific diagnoses recorded at any admission and coded using the International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM) (6). Diagnoses were extracted from all available hospital admissions data, including those up to 5 years before the index admission, during the index admission, and during the period of follow-up after the initial presentation with

HRF. Specific diagnoses or potential causes of interest, because of their relation to HRF, were COPD, congestive cardiac failure (CCF), sleep disordered breathing (SDB), neuromuscular disease (NMD) and opioid use that were reliably recorded in the medical record. We identified a range of ICD-10-AM codes corresponding to each of these potential causes, then used these codes for data extraction. Some other factors of potential interest, such as smoking status, obesity status or body mass index (BMI) were not routinely recorded in the medical record and, hence, could not be used. Details of each of the ICD-10-AM codes used are provided in the Supplementary Material. The overall degree of comorbidity was quantified using the Charlson comorbidity index (CCI), which has been shown to be an independent predictor of mortality (7).

Data analysis

Data were summarised using frequencies with percentages for categorical variables, and either means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables depending on the distribution of values. Stratified Kaplan-Meier survival curves were generated for the primary outcome, death from any cause. Age-standardised death rates were calculated using person-years of follow-up. The SMR was calculated based on expected mortality in the NSW population stratified by age (8). We used Cox proportional hazards regression models to determine the associations between underlying causes and the risks of death and rehospitalisation. Covariates that were included in these models were selected to reflect explicit assumptions about causal pathways. These were encoded in a directed acyclic graph (DAG), shown in the online Supplement (9). The final multivariate model, based on these assumptions, included the following covariates: age, socioeconomic status (financial status on admission, marital status, country of birth), and the degree of hypercapnia ($PaCO_2$). DAGs were constructed

and minimum sets of adjustment covariates identified using the web-based program 'dagitty' (10). All analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC).

7.2.4 Results

The cohort comprised 590 adults aged between 15 and 101 years. Acidosis (pH <7.35) was present in 320 (54%) at initial presentation. All were admitted via the emergency department. Participant characteristics are shown in Table 7.1.

Table 7.1. *Cohort characteristics*

N	**590**
Age, mean (SD)	68.5 (16.3) years
Sex, male (%)	297 (50.3%)
Country of birth, n (%)	
Australia	265 (45%)
Other	324 (55%)
Not recorded	1 (<0.01%)
Arterial blood gas values, median (IQR)	
pH	7.34 (7.28-7.38)
pCO_2	53 (48-61)
pO_2	76 (60-113)
Bicarbonate	29 (26-32)
Potential underlying cause for hypercapnia, n (%)	
Chronic obstructive pulmonary disease	353 (60%)
Congestive cardiac failure	289 (49%)
Sleep-disordered breathing	121 (21%)
Opioid use	108 (18%)
Neuromuscular disease	15 (2.5%)
Charlson Comorbidity Index, median (IQR)	7 (4-9)

Mean follow-up time for the primary outcome was 7.5 years. At least one of the pre-specified causes of HRF was recorded in 84%, at least two causes in 47%, and at least three causes in

17% of study participants. The distribution and degree of overlap between various pre-specified causes is shown in Figure 7.1.

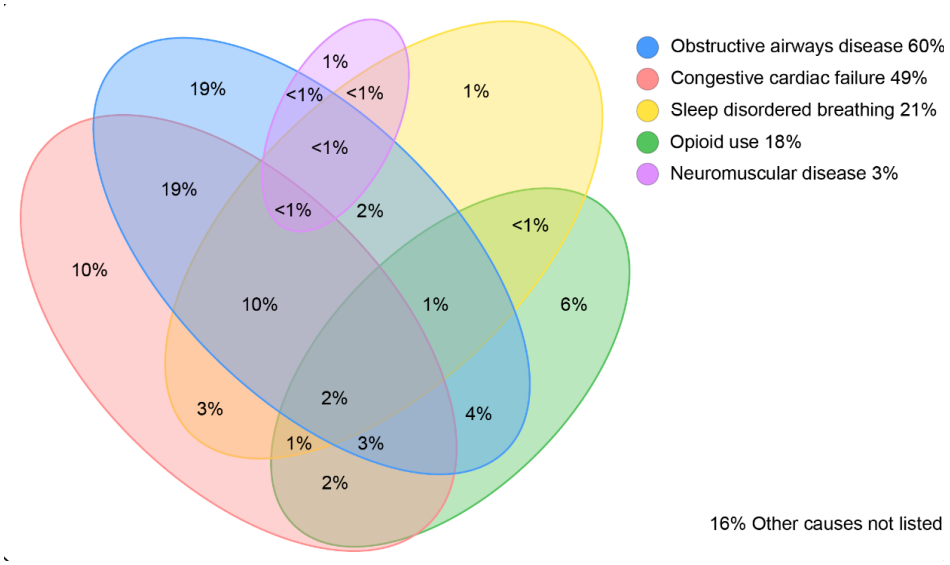

Figure 7.1. *Prevalence of potential causes for hypercapnic respiratory failure, alone and in combination, within study cohort. At least one pre-specified cause was recorded in 84%, at least two causes in 47%, and three causes in 17% of the cohort. This is a non-proportional (not-to-scale) Venn diagram.*

Deaths

Overall, 415 (70.3%) participants died during the follow-up period. Seventy-seven (13%) died during the index admission. Among those who survived the index admission, the probability of survival at 1, 3 and 5 years was 81%, 59% and 45%, respectively. There was significant variation across age groups, as shown in Figure 7.2. Median (IQR) survival was 5.2 (3.5, 7.4) years among those aged 60 to 69 years, 3.4 (2.6, 4.4) years among those aged 70 to 79 years, and 1.9 (1.4, 2.6) years among those aged 80 years or more. Both pH and severity of hypercapnia at presentation had a significant impact on subsequent survival (P<0.001); stratified survival curves are shown in Figure 7.3.

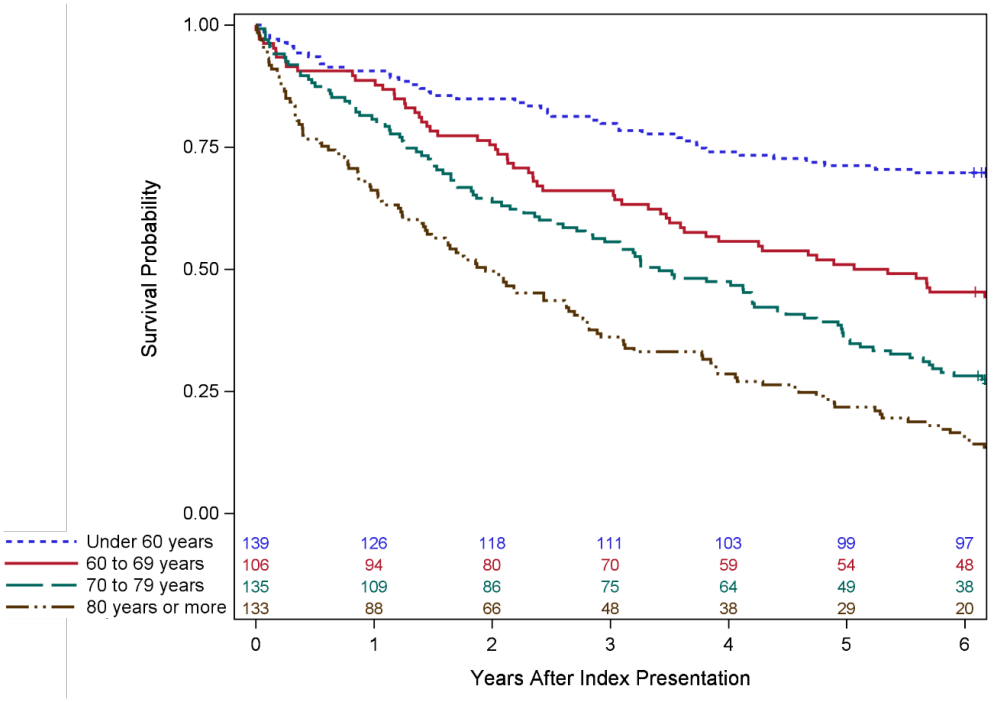

Figure 7.2. *Survival estimates by age strata following discharge from hospital with hypercapnic respiratory failure. Numbers in coloured font indicate number of subjects at risk at years after presentation.*

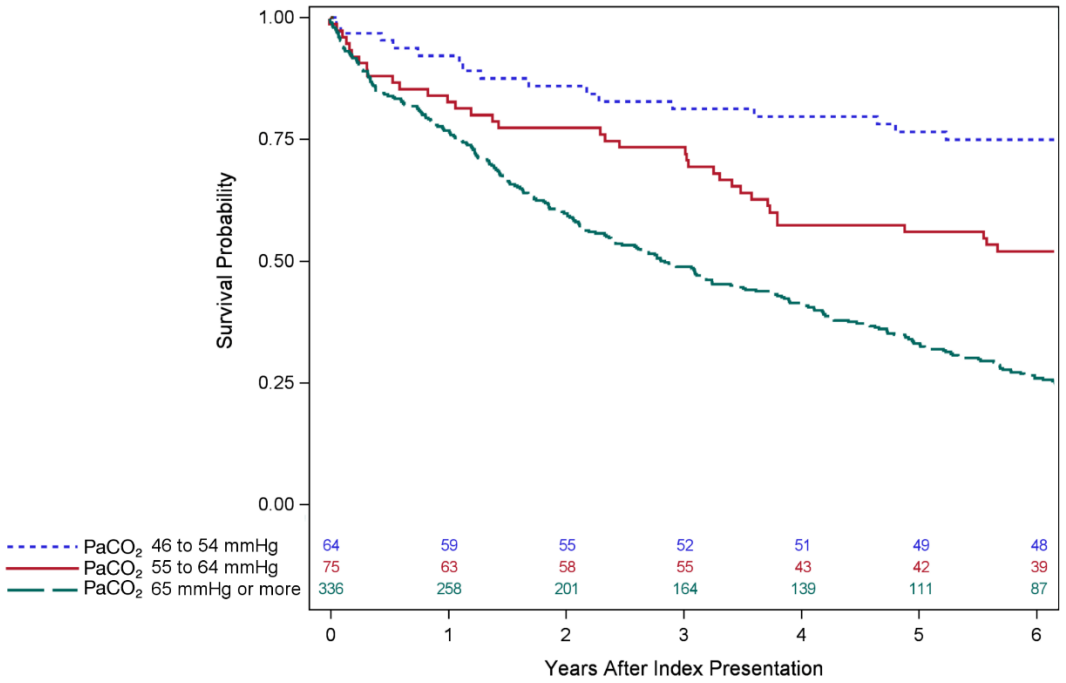

Figure 7.3. *Survival estimates stratified by admission $PaCO_2$ among survivors of the index presentation with hypercapnic respiratory failure. Numbers in coloured font indicate number of subjects at risk at years after presentation.*

The overall death rate was 144 (95% CI 117 to 171) deaths per 1,000 person-years at risk with SMR being 9.2 (95% CI 7.6 to 11.0), indicating that people admitted with HRF have substantially higher mortality than otherwise expected for their age. Age-stratified death rates are provided in the Supplementary material (Table 9.4).

Rehospitalisations

Of the 513 participants who survived the index presentation with HRF, 469 (91%) experienced rehospitalisation during the study period. Median (IQR) time to rehospitalisation was 3.9 (1.2-10.6) months. The HR for rehospitalisation was significantly associated with increasing age (P=0.003) but not the degree of hypercapnia (P=0.8) nor the presence of acidosis (P=0.2).

Effect of underlying cause

The frequency of underlying potential causes among survivors of the index admission and their associations with the risks of death and rehospitalisation are shown in Table 7.2. The presence of a diagnosis of CCF was associated with an adjusted hazard ratio of 1.62 (95% CI 1.30, 2.01) for death and 1.34 (1.10, 1.64) for rehospitalisation, compared with those without CCF. Recorded diagnoses of COPD and SDB were not associated with a significantly increased risk of death but were associated with increased of rehospitalisation. Patients in whom opioid use was recorded as a diagnosis had a lower risk of death compared to the rest of the cohort, with an adjusted HR of 0.74 (0.55, 0.99). Among the prespecified causes, NMD had the highest adjusted HR for death at 2.38 (1.16, 4.90).

Table 7.2. *Risk of death and rehospitalization among survivors of the initial HRF episode, by presence or absence of potential cause (N=513).*

		Risk of death		**Risk of rehospitalization**		**Risk of death or rehospitalization**	
		Hazard ratio (95% CI); *P-value*		**Hazard ratio (95% CI); P-value**		**Hazard ratio (95% CI); P-value**	
Cause	**n (%)**	**Unadjusted**	**Adjusted***	**Unadjusted**	**Adjusted***	**Unadjusted**	**Adjusted***
COPD	316 (62%)	1.24 (0.99, 1.56); *P=0.06*	1.11 (0.87, 1.40); *P=0.4*	1.60 (1.32, 1.94); *P<0.001*	1.58 (1.28, 1.95); *P<0.001*	1.55 (1.28, 1.88); *P<0.001*	1.42 (1.15, 1.76); *P=0.001*
CCF	253 (49%)	1.72 (1.38, 2.13); *P<0.001*	1.62 (1.30, 2.01); *P<0.001*	1.40 (1.17, 1.68); *P<0.001*	1.34 (1.10, 1.64); *P=0.003*	1.45 (1.21, 1.74); *P<0.001*	1.29 (1.05, 1.57); *P=0.01*
SDB	116 (23%)	0.91 (0.71, 1.18); *P=0.5*	0.83 (0.64, 1.09); *P=0.18*	1.37 (1.11, 1.70); *P=0.004*	1.48 (1.19, 1.85); *P<0.001*	1.36 (1.10, 1.69); *P=0.005*	1.44 (1.15, 1.80); *P=0.001*
Opioid use	101 (20%)	0.68 (0.51, 0.90); *P<0.001*	0.74 (0.55, 0.99); *P=0.04*	1.35 (1.08, 1.70); *P=0.008*	1.46 (1.16, 1.84); *P=0.001*	1.38 (1.10, 1.73); *P=0.005*	1.63 (1.29, 2.06); *P<0.001*
NMD	12 (2%)	2.48 (1.32, 4.66); *P<0.001*	2.38 (1.16, 4.90); *P=0.02*	0.65 (0.34, 1.27); *P=0.2*	0.62 (0.28, 1.36); *P=0.3*	1.18 (0.61, 2.29); *P=0.6*	1.47 (0.64, 3.33);

** Adjusted for age, financial status on admission, marital status, country of birth, and the degree of hypercapnia. Abbreviations: HRF: Hypercapnic respiratory failure. COPD: Chronic obstructive pulmonary disease. CCF: Congestive cardiac failure. SDB: Sleep disordered breathing. NMD: Neuromuscular disease.*

7.2.5 Discussion

This is the first population-based longitudinal study of people with hypercapnia, and the first cohort study to describe prognosis beyond five years. We found that hospitalisation with HRF heralds a high risk of rehospitalisation and death in subsequent years, particularly among older people. Most people had at least one identifiable underlying cause and many had two or more potential causes occurring concurrently. After adjustment for age and other potential confounders, people diagnosed with NMD and CCF had the worst prognosis for survival and people with opioid use as the potential cause for HRF had the best prognosis. Our findings underscore the importance of HRF and confirm the importance of addressing underlying diagnoses to improve clinical outcomes associated with this condition.

The overall 5-year survival probability of under 50% illustrates the substantial mortality imposed by HRF. There are limited data on the outcomes of patients with HRF, and there is considerable heterogeneity among existing studies. A recent study found that 44.2% of patients with hypercapnia but not acidosis died within a 2.5 year period (11). Compared with our study, these subjects were younger and had less comorbidity based on the CCI but had more severe HRF (based on higher $PaCO_2$ values). Another study found that 30% of patients with a documented history of HRF died over 19-31 months of follow up (12). However, potential participants with limited life expectancy were excluded from the analysis. Other studies have been limited to 1 year of follow-up (13,14), restricted to patients requiring non-invasive ventilation (NIV) (15), or based on groups with specific diagnoses such as COPD (2,16,17). Our study underscores the severe impact of a diagnosis of HRF on life expectancy, regardless of underlying cause, and provides prognostic evidence to inform clinical decision-making.

In addition to the high rate of death, we found HRF to be associated with a substantially high risk of rehospitalisation. The median readmission time of under 4 months shows the ongoing health impacts for those who survive the index admission. A previous study of patients with HRF found 30-day readmission rates of 23% (12), comparable to our dataset in which the 25th percentile for time to readmission was 1.2 months. This information is important to health service planners as better understanding of health care utilisation is critical to the development of evidence-based enhancements which have been proven to reduce readmission, including positive airway pressure therapy for COPD (18) and SDB (19).

A range of potential causes for HRF were identified among study participants, and we found that, within the limitations posed by the retrospective method of data collection and reliance on clinical diagnosis codes, these causes had effects on the risk of death and rehospitalisation. The increased risks of death observed with CCF and NMD, relative to other causes, likely reflect the severity of the underlying disease once hypercapnia becomes apparent. Although COPD and SDB did not affect mortality risk, these along with CCF and opioid use increased the risk of rehospitalisation in this cohort. There are inconsistent data on the role of underlying causes with respect to healthcare use; one study of patients with undifferentiated HRF found that hospitalisation in the preceding year was a significant predictor for readmission but the underlying cause was not (14). Another found peripheral vascular disease but not COPD or CCF increased the 30-day readmission rate (12). Our results emphasise the need to systematically evaluate and optimally manage conditions such as CCF and COPD, and rationalise opioid use to clinical situations where potential harms are outweighed by the benefits of these medicines.

Our study has several strengths. We have identified a population-based cohort of people with HRF using arterial blood gas measurements, thus providing an inclusive picture of this condition. There are several reasons to consider HRF as a single condition for the purpose

of epidemiological study. As already mentioned, in many individuals with HRF, multiple underlying causes with the potential to cause hypercapnia may coexist. In clinical practice, these causes may not be immediately apparent, and understanding the risk of death among people with HRF as a group allows for improved prognostication. Furthermore, many people with HRF receive similar treatments, such as domiciliary NIV, suggesting a potential target group for future intervention studies. Few studies have described clinical outcomes associated with a group of people with HRF irrespective of the underlying condition or selected by the type of treatments received (11,12,14), and none have a follow up period more than 3 years. As such, our study provides valuable and novel information regarding this group.

We have used the SMR to demonstrate the increased mortality associated with HRF, a key strength of our study in describing the epidemiological impact of this condition. Although we do not provide information on specific treatments such as ventilation support therapy, the observational nature of our study is such that any attempt to draw inferences based on the outcome of interventions are likely to be influenced by bias and hence obfuscate, rather than clarify, current knowledge based on randomized controlled trials. Rather, by using the SMR we are able to provide an indicator of the overall survival of this cohort compared with a control or reference population (those without HRF), an index that has never been reported previously in any population.

Our study has also a number of limitations. We did not differentiate between acute and chronic hypercapnia, unlike some previous studies that have done so based on the observed pH (11,14). As such, the data provided on prognosis and outcomes relate to people with HRF as a whole, with limited generalisability to acute or chronic cases. However, the distinction between acute and chronic states can be challenging, as acute deterioration and a fall in pH can be observed after a seemingly minor insult in patients with chronic HRF. Furthermore,

hypoventilation can occur episodically or acutely in patients without diurnal hypercapnia, for example in association with COPD (20). In the absence of a consensus case definition for HRF, we adopted an inclusive approach with the goal of estimating the overall prognosis for people with HRF even when the underlying cause or causes are not apparent at initial presentation.

We did not review ABG data prior to the index episode of HRF. Therefore, it is possible that our survival estimates are an underestimate of the true value following development of hypercapnia. Nevertheless, the SMR confirms that survival is abbreviated in this cohort. We also acknowledge that some patients with HRF may have been missed if an ABG was not performed within the first 24 hours of presentation. However, a key strength offered by data linkage is the accuracy in outcome measurements, with low likelihood of loss to follow-up, another strength of this study.

Some limitations are related to the historical cohort design of this study. Measurement of exposure variables was based on medical records, specifically whether these diagnoses were recorded in the form of ICD-10-AM codes. This method, while frequently employed in health services research, is a form of repurposing clinical data for research purposes and is a source of measurement error if these data were not recorded accurately. For instance, the diagnosis of SDB is likely to be underestimated based on administrative data (21). It is for this reason that we did not include chest wall disorders such as kyphoscoliosis or obesity in our analyses of contributing diagnoses, as we find that typically in clinical practice these conditions are often under-recognised (in case of the former) or poorly recorded (in case of the latter). We also did not differentiate between mild and severe forms of each of these potential causes. However, our approach provides an exploratory analysis of the potential impact of underlying causes on relevant clinical outcomes. Importantly, our results may also challenge perceptions of futility when COPD is found to be a cause of HRF, as this

condition was not found to be associated with an increased risk of death when compared with other causes such as CCF.

In conclusion, HRF is associated with poor survival in the 5 years following an index event. For those who survive the initial hospitalisation episode, most are readmitted within a year. The underlying disease appears to have some influence on overall survival and subsequent hospitalisations. Our findings highlight the need for better inventions for long-term management of people with HRF, provide guidance for health service planners in meeting needs for relevant health services and provide a basis for shared decision-making between patients with this condition and clinicians from a range of disciplines.

7.3 Chapter references

1. Yang H, Xiang P, Zhang E, Guo W, Shi Y, Zhang S, *et al*. Is hypercapnia associated with poor prognosis in chronic obstructive pulmonary disease? A long-term follow-up cohort study. *BMJ Open* 2015;5:e008909.
2. Fazekas AS, Aboulghaith M, Kriz RC, Urban M, Breyer M, Breyer-Kohansal R, *et al*. Long-term outcomes after acute hypercapnic COPD exacerbation: First-ever episode of non-invasive ventilation. *Wien Klin Wochenschr* 2018;130:561–568.
3. Adler D, Pépin JL, Dupuis-Lozeron E, Espa-Cervena K, Merlet-Violet R, Muller H, *et al*. Comorbidities and subgroups of patients surviving severe acute hypercapnic respiratory failure in the intensive care unit. *Am J Respir Crit Care Med* 2017;196:200–207.
4. NSW Ministry of Health. FlowInfo v15.1. Retrieved from the Clinical Services Planning Application Portal (CaSPA). 2017 [accessed 7 March 2018].
5. Chung Y, Garden FL, Marks GB, Vedam H. Population prevalence of hypercapnic respiratory failure from any cause. *Am J Respir Crit Care Med* 2022;205:966–967.
6. Independent Hospital Pricing Authority. *The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM).* Darlinghurst, NSW (Australia): Independent Hospital Pricing Authority.

7. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–1251.
8. Australian Bureau of Statistics. Deaths, Year of registration, Age at death, Age-specific death rates, Sex, States, Territories and Australia [Internet]. Data Explorer [cited 2023 May 30]. Available from: https://explore.data.abs.gov.au/.
9. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008;8:70.
10. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT et al. Robust causal inference using directed acyclic graphs: the R package 'dagitty.' *Int J Epidemiol* 2016;45:1887–1894.
11. Wilson MW, Labaki WW, Choi PJ. Mortality and healthcare use of patients with compensated hypercapnia. *Ann Am Thorac Soc* 2021;18:2027–2032.
12. Meservey AJ, Burton MC, Priest J, Teneback CC, Dixon AE. Risk of readmission and mortality following hospitalization with hypercapnic respiratory failure. *Lung* 2020;198:121–134.
13. Vonderbank S, Gibis N, Schulz A, Boyko M, Erbuth A, Gürleyen H, *et al*. Hypercapnia at hospital admission as a predictor of mortality. *Open Access Emerg Med* 2020;12:173–180.
14. Cavalot G, Dounaevskaia V, Vieira F, Piraino T, Coudroy R, Smith O, *et al*. One-year readmission following undifferentiated acute hypercapnic respiratory failure. *COPD* 2021;18:602–611.
15. Ahmad N, Taithongchai A, Sadiq R, Mustfa N. Acute hypercapnic respiratory failure (AHRF): looking at long-term mortality, prescription of long-term oxygen therapy and chronic non-invasive ventilation (NIV). *Clin Med (Lond)* 2012;12:188.
16. Chu CM, Chan VL, Lin AWN, Wong IWY, Leung WS, Lai CKW. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. *Thorax* 2004;59:1020–1025.
17. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 1995;274:1852–1857.
18. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, *et al*. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: A randomized clinical trial. *JAMA* 2017;317:2177–2186.

19. Povitz M, Tsai WH, Pendharkar SR, Hanly PJ, James MT. Healthcare use in individuals with obesity and chronic hypoxemia treated for sleep disordered breathing. *J Clin Sleep Med* 2016;12:543–548.
20. Holmedahl NH, Øverland B, Fondenes O, Ellingsen I, Hardie JA. Sleep hypoventilation and daytime hypercapnia in stable chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2014;9:265–275
21. McIsaac DI, Gershon A, Wijeysundera D, Bryson GL, Badner N, van Walraven C. Identifying obstructive sleep apnea in administrative data: A study of diagnostic accuracy. *Anesthesiology* 2015;123:253–263.

Cite: Chung Y, Garden FL, Marks GB, Vedam H. Long-term cohort study of patients presenting with hypercapnic respiratory failure. *BMJ Open Respir Res* 2024;11:e002266.

8. Summary and recommendations

8.1 Introduction

Understanding the epidemiology of a health problem is of fundamental importance in both health policy and clinical practice. Hypercapnic respiratory failure is a health problem that has been largely overlooked in previous epidemiological studies, despite evidence of associated increases in morbidity and mortality. The body of work comprising this thesis answers several of the unanswered questions with respect to the prevalence, determinants and outcomes of persons with hypercapnic respiratory failure at a population level. In this Chapter, the key findings and limitations of these studies are summarised, followed by recommendations for future research to be undertaken in this field.

8.2 Major findings arising from this thesis

1. *Hypercapnic respiratory failure is common, especially with increasing age.*

No prior studies have described the incidence or prevalence of hypercapnic respiratory failure. The work presented in Chapter 4 allows estimation, for the first time, of the prevalence of this condition within a specified population. In this descriptive study, I found the average annual period prevalence of HRF to be 163 (95% confidence interval 154 to 172) cases per 100,000 population. However, there was substantial variation in this estimate

across age strata; the period prevalence of HRF was 517 cases per 100,000 in those aged 65 to 74 years, 1,160 cases per 100,000 in those aged 75 to 84 years, and 1,172 cases per 100,000 in those aged 85 years or more (Table 4.1). Thus, hypercapnic respiratory failure is a common condition, especially in older persons. The findings from this study reaffirm the need for HRF to be recognised as a distinct entity, and to be the focus of future research in order to improve the health of populations.

2. *Chronic obstructive pulmonary disease is the most important risk factor for hypercapnic respiratory failure.*

Although a multitude of diagnoses have been described in association with hypercapnic respiratory failure, no previous studies have compared the rates of observed diagnoses in a study sample to those within the population from which that sample had been drawn. The work in Chapter 5 confirms the high frequency with which obstructive lung diseases are recorded among people with HRF, and the case-control study described in Chapter 6 provides a comparison against individuals without HRF from the same population. In the latter study, I found that objectively measured COPD was strongly associated with the presence of HRF with an adjusted odds ratio of 5.3 (95% confidence interval 1.95 to 14.4). Moreover, of the selected diagnoses, COPD had the highest population attributable fraction at 42% (95% confidence interval 18% to 59%). This work provides evidence to support interventions directed at reducing the burden of obstructive lung diseases to mitigate the effects of hypercapnic respiratory failure at a population level.

3. *Opioid use and congestive heart failure, among other causes, are frequently associated with hypercapnic respiratory failure.*

The work described in this thesis confirms that, in addition to COPD, a range of other diagnoses are significantly associated with hypercapnic respiratory failure. Even though COPD had the highest population attributable fraction, this value was less than 50%. Two

specific other diagnoses of importance are congestive cardiac failure and opioid use. With respect to the former, the work in Chapters 5 and 6 showed that CCF was present in a third of people attending hospital with HRF. When compared to individuals without HRF, CCF had the strongest association with HRF based on the odds ratio of 13.4 (95% CI 1.40 to 128). With respect to opioid use, this was also significantly associated with HRF, and had the second highest population attributable fraction after COPD at 41% (95% CI 13% to 59%). There was a considerable rate of multimorbidity observed among the cases described in Chapter 6; 37 (88%) had two or more and 20 (48%) had three or more diagnoses with the potential to cause HRF. Together, the findings from these studies support the concept of HRF as a multifactorial condition that arises once the presence and severity of one or more cause(s) reaches a certain threshold. From a clinical perspective, these results indicate systematic evaluation of all patients with HRF is required in order to diagnose and, where possible, treat all underlying causes.

4. *Hypercapnic respiratory failure is associated with increased mortality and, for survivors, a near-certain risk of rehospitalisation.*

The cohort study described in Chapter 7 is the first in published literature to describe the mortality associated with hypercapnic respiratory failure with reference to the source population. In this study, I found the standardised mortality ratio (SMR) associated with hypercapnic respiratory failure to be 9.2 (95% CI 7.6 to 11.0), indicating a near ten-fold risk of death compared with unaffected persons of a similar age. This study had the longest follow-up period compared with previous works, and confirmed an overall five-year survival probability of 45%. Among those who survived the index presentation, 91% were rehospitalised after a median (IQR) time of 3.9 (1.2 to 10.6) months. These findings indicate that hypercapnic respiratory failure is highly lethal, and when not immediately so, associated with increased use of healthcare services. Understanding the prognosis of this

condition has obvious value for discussing treatment options with individual patients. In addition, the data provided by the work in this thesis also has potential to inform the planning and evaluation of interventions on a broader scale, addressing potential contributing factors as described above.

8.3 Limitations

A central premise of this thesis is that HRF should be considered a single, composite entity, irrespective of underlying cause. This taxonomical approach may be useful for the reasons outlined in Chapter 2. However, the natural outcome of adopting an inclusive definition is the loss of specificity and a potential failure to appreciate patterns related to intrinsic variations. If HRF is to be treated as a single entity, then contributing causes such as COPD and opioid use are relegated to phenotypes or 'treatable traits'. The definition employed within the studies also combines both acute and chronic forms of hypercapnia, again for the reasons described in Chapter 2. The debate between 'lumpers' and 'splitters' is an ongoing one in many academic disciplines, and the conclusions arising from this work should be acknowledged as a reflection of the former rather than latter approach.

The methods used to identify potential cases in Chapter 3 are not validated, and are likely to impose a quantifiable degree of selection bias. Due to the screening process, the small (14%) proportion of the population who are admitted for a respiratory problem to a facility other than Liverpool Hospital will not have been identified. We have relied on ABG samples collected as part of routine clinical care, excluding people without suspected hypercapnia or a preceding venous blood gas prompting further evaluation. Furthermore, some patients with chronic hypercapnia, for instance those with slowly progressive neuromuscular disorders, may not require hospitalisation due to a lesser disease burden. Each of the

publications in Chapters 4 to 7 acknowledge this limitation explicitly whilst providing valuable data to inform future studies on this important topic.

Measurement biases, particularly regarding the detection of contributing causes, are likely to have influenced the results of the studies in Chapters 5 and 7. These studies relied on recorded diagnoses, potentially underestimating the impact of sleep-related breathing disorders. The case-control study in Chapter 6 employed objective testing to mitigate this limitation and determine the true relationship between OSA and HRF. Due to financial constraints, measurement was limited to limited-channel screening rather than full polysomnography and/or capnography. The surprising result of a non-significant relationship is discussed further in Chapter 6, and demonstrates the importance of testing causality assumptions from observational data.

The regression analyses performed in this thesis have been informed by causal diagrams, or directed acyclic graphs. Such graphs are used increasingly in clinical and epidemiological research to identify confounding variables that require conditioning, or adjustment for, when estimating causal effects. This is in contrast to traditional approaches where confounders are selected and included based on their strength of association as determined from univariate analyses and, typically, stepwise assessment. The advantage of using DAGs is that inherent biological or clinical relationships between exposures and outcomes are automatically taken into consideration. Whilst this is an inherent strength in our methods, it may also create some limitations if incorrect assumptions have been made. For instance, as demonstrated in Figure 5.1, we have assumed CCF can cause hypercapnic respiratory failure, but not included the assumption that HRF may cause CCF. However, by providing each model used, either in the main body of the publication or in a supplementary section

as detailed in Chapter 9, the process is made transparent and allows for iterative development of the ideal causal model in future work.

8.4 Recommendations for future research

1. *A consistent case definition for hypercapnic respiratory failure should be adopted to allow comparisons across different studies.*

A review of the previous literature on hypercapnic respiratory failure revealed substantial heterogeneity in the inclusion criteria for each study, as discussed in Chapter 2. In the absence of an established case definition, the studies described in this thesis were based on cases meeting the minimum criterion of the first arterial blood gas upon hospital presentation demonstrating a $PaCO_2$ greater than 45 mmHg (Chapter 3). This process relied on availability of blood gas data, and adjudication of potential cases based on manual review of medical records to exclude, among others, potentially nosocomial cases of hypercapnia. This method is impracticable to implement on a wider scale, although in future it may become a possibility with suitable computing algorithms and the increased availability of health data in electronic form. In the meantime, future studies of hypercapnic respiratory failure must demonstrate transparency in the case selection process, and consider adopting definitions available in current literature (such as the published work described in this thesis) in order to allow valid comparisons of confirmatory and/or novel findings.

2. *A prospective cohort study should be undertaken to confirm the role of underlying causes in relation to hypercapnic respiratory failure.*

The studies comprising this thesis provide important baseline data on the presence and magnitude of associations between potential causes and presentation to hospital with

hypercapnic respiratory failure. However, the inherent design of a case-control study such as the one described in Chapter 6 is such that it cannot provide evidence of temporality, a required criterion for determining causality. Many of the cases had died prior to study commencement, precluding inclusion and therefore measurement of underlying diagnoses in these individuals. Furthermore, despite considerable measures to minimise selection bias by systematically recruiting a random sample from the study population, the low response rate among control participants was one of the major challenges in conducting this study (Figure 6.2). Reproducing this study in a different study population will likely lead to investigators facing the same challenges and limitations. Therefore, to further investigate the role of underlying causes for hypercapnic respiratory failure, future observational studies should adopt a longitudinal, preferably prospective, cohort design.

3. *Future work must focus on the relationship between hypercapnic respiratory failure and obstructive sleep apnoea.*

In the first comparison of cases of hypercapnic respiratory failure against the source population, there was no evidence of a significant association with obstructive sleep apnoea (Chapter 6). This has been an otherwise assumed cause in all previous works. The disparity may relate to the study limitations described above. However, in view of the relatively high prevalence of previously undiagnosed obstructive sleep apnoea in the control population, ongoing work is required to determine whether there is a causal relationship associated with sleep apnoea, particularly in milder forms. A cohort study as described in the previous recommendation will be crucial in eliciting this information, acknowledging the potentially substantial resources required to undertake a longitudinal study.

4. *New models must be developed to integrate the role of multiple causes in precipitating hypercapnic respiratory failure within the same individual.*

The population attributable fractions reported in Chapter 6 (Table 3) were determined separately for each cause, and thus added to more than 100%. However, there was a high prevalence of multimorbidity, or the co-occurrence of multiple potential causes within the same individual, among studied cases. Additionally, whilst the presence or absence of underlying causes was determined based on pre-specified cutoff thresholds, for example based on the FEV1/FVC ratio for obstructive lung disease, this dichotomisation fails to accommodate the potential for varying degrees of severity based on the magnitude of the FEV1. Further work is required to incorporate models with multiple causes with the potential for interactions into existing statistical software programs. This work to understand population attributable fractions for non-communicable diseases where there may be multiple cause sets will have significant implications in other fields of health research also.

5. *Future studies should endeavour to describe the burden of disease associated with hypercapnic respiratory failure, particularly in its more chronic forms.*

Finally, the cohort study in Chapter 7 were limited to the discrete outcomes of death and rehospitalisation. The high incidence of the latter provides raises concerns regarding the potential for hypercapnic respiratory failure to impart a significant burden of disease on a population. Future studies should consider not only hospitalisations but other measures of disability and impairment to determine the costs imposed by hypercapnic respiratory failure upon both affected individuals and the wider society.

8.5 Conclusion

The original research comprising the body of this thesis reveals key insights into the epidemiology of hypercapnic respiratory failure. The studies adopt a range of established epidemiological approaches as well as using newer statistical techniques to adjust for potential confounders. Many of the findings are novel and of direct relevance to clinicians involved in the care of patients with hypercapnia. The study findings may also assist those involved in the planning of relevant health services. Importantly, these data form a robust foundation for further research into the *who*, *when* and *why*, and on interventions to alleviate the morbidity and mortality associated with this condition.

9. Appendix

9.1 Introduction

Due to journal word count restrictions, some methodological information and results could not be included in the original publications (Chapters 5 to 7). The main text in each publication makes references to the supporting information or supplementary material made available in each respective journal's online repository. This material is reproduced here in verbatim.

9.2 Supporting information for Chapter 5

Appendix S1 Methods. Proposed model for hypercapnic respiratory failure and death.

The following code may be entered into *Daggity*. We used the web-based version, accessed at http://www.daggity.net/dags/html

dag {bb="-4.292,-3.673,4.369,4.361"
"Benzodiazepine use" [pos="-0.441,3.364"]
"Chronic kidney disease" [pos="3.298,1.936"]
"Congestive cardiac failure" [pos="3.286,-1.486"]
"Coronary artery disease" [pos="2.405,-2.810"]
"Degenerative joint disease" [pos="1.668,3.543"]
"Environmental factors" [pos="-3.020,-3.361"]
"Hypercapnic respiratory failure" [pos="0.708,-1.784"]
"Interstitial lung disease" [pos="-0.921,-2.855"]

```
"Neuromuscular Disease" [pos="-2.819,3.126"]
"Obstructive lung disease" [exposure,pos="-1.814,-0.861"]
"Occupational exposures" [pos="-3.320,-1.590"]
"Opioid use" [pos="0.664,2.873"]
"Pulmonary vascular disease" [pos="-2.629,0.270"]
"Respiratory infections" [pos="-3.321,2.025"]
"Sleep disordered breathing" [pos="-0.787,2.010"]
Age [pos="0.931,1.579"]
Death [outcome,pos="2.003,0.284"]
Hypertension [pos="3.465,0.121"]
Obesity [pos="2.516,3.037"]
Smoking [pos="0.786,-3.197"]
"Benzodiazepine use" -> "Hypercapnic respiratory failure"
"Benzodiazepine use" -> "Neuromuscular Disease"
"Benzodiazepine use" -> "Sleep disordered breathing"
"Chronic kidney disease" -> "Coronary artery disease"
"Chronic kidney disease" -> "Sleep disordered breathing"
"Chronic kidney disease" -> Death
"Congestive cardiac failure" -> "Hypercapnic respiratory failure"
"Congestive cardiac failure" -> Death
"Coronary artery disease" -> "Congestive cardiac failure"
"Coronary artery disease" -> Death
"Degenerative joint disease" -> "Opioid use"
"Environmental factors" -> "Interstitial lung disease"
"Environmental factors" -> "Obstructive lung disease"
"Environmental factors" -> "Respiratory infections"
"Environmental factors" -> Obesity
"Hypercapnic respiratory failure" -> Death
"Interstitial lung disease" -> Death
"Neuromuscular Disease" -> "Hypercapnic respiratory failure"
"Neuromuscular Disease" -> "Respiratory infections"
"Neuromuscular Disease" -> "Sleep disordered breathing"
"Obstructive lung disease" -> "Hypercapnic respiratory failure"
"Obstructive lung disease" -> "Respiratory infections"
"Obstructive lung disease" -> "Sleep disordered breathing"
```

"Occupational exposures" -> "Interstitial lung disease"
"Occupational exposures" -> "Obstructive lung disease"
"Opioid use" -> "Hypercapnic respiratory failure"
"Opioid use" -> "Sleep disordered breathing"
"Pulmonary vascular disease" -> Death
"Respiratory infections" -> "Hypercapnic respiratory failure"
"Respiratory infections" -> Death
"Sleep disordered breathing" -> "Hypercapnic respiratory failure"
Age -> "Chronic kidney disease"
Age -> "Coronary artery disease"
Age -> "Degenerative joint disease"
Age -> "Interstitial lung disease"
Age -> "Obstructive lung disease"
Age -> "Respiratory infections"
Age -> "Sleep disordered breathing"
Age -> Death
Age -> Hypertension
Hypertension -> "Chronic kidney disease"
Hypertension -> "Congestive cardiac failure"
Hypertension -> "Coronary artery disease"
Obesity -> "Coronary artery disease"
Obesity -> "Degenerative joint disease"
Obesity -> "Sleep disordered breathing"
Obesity -> Death
Obesity -> Hypertension
Smoking -> "Coronary artery disease"
Smoking -> "Interstitial lung disease"
Smoking -> "Obstructive lung disease"
Smoking -> "Respiratory infections"
Smoking -> Death
Smoking -> Hypertension}

Table 9.1. *Diagnosis codes from the International Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) used for data abstraction.*

Condition associated with hypercapnic respiratory failure	**ICD Codes used for data extraction**
Benzodiazepine use	T42.4, Y47.1
Chronic kidney disease	I12.0, I12.9, I13.0, I13.1, I13.2, I13.9, N18.1, N18.2, N18.3, N18.4, N18.5, N18.9, Z99.2
Congestive cardiac failure	I09.0, I11.0, I13.0, I13.2, I25.5, I42.0, I42.1, I42.2, I42.3, I42.4, I42.5, I42.6, I42.7, I42.8, I42.9, I43.0, I43.1, I43.2, I43.8, I50.0, I50.1, I50.9
Coronary artery disease	I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I24.0, I24.8, I24.9, I25.0, I25.1, I25.10, I25.11, I25.12, I25.13, I25.2, I25.4, I25.5, I25.6, I25.8, I25.9
Hypertension	I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.1, I13.2, I13.9, I15.0, I15.1, I15.2, I15.8, I15.9
Interstitial lung disease	J60, J61, J62, J62.0, J62.8, J63, J63.0, J63.1, J63.2, J63.3, J63.4, J63.5, J63.8, J64, J65, J70.1, J70.3, J70.4, J84.1, J84.9, J92.0, J99.1, J99.8
Neuromuscular disease	G12.0, G12.1, G12.2, G12.8, G12.9, G61, G61.0, G61.8, G61.9, G70.0, G70.1, G70.2, G70.8, G70.9, G71.0, G71.1, G71.2, G71.3, G71.8, G71.9, G82.3, G82.30, G82.31, G82.32, G82.33, G82.34, G82.35, G82.36, G82.4, G82.40, G82.41, G82.42, G82.43, G82.44, G82.45, G82.46, G82.5, G82.51, G82.52, G82.53, G82.54, 82.55, G82.56, J98.6
Obesity	E66, E66.1, E66.10, E66.11, E66.12, E66.13, E66.2, E66.20, E66.21, E66.22, E66.23, E66.8, E66.9, E66.90, E66.91, E66.92, E66.93
Obstructive lung disease	J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.8, J44.9, J45.0, J45.1, J45.8, J45.9, J46, J47
Opioid use	F11.0, F11.1, F11.2, F11.3, F11.4, F11.5, F11.6, F11.7, F11.8, F11.9, T40.0, T40.1, T40.2, T40.3, T40.4, T40.6, Y45.0

(continued next page)

Table 9.1 (continued)

Condition associated with hypercapnic respiratory failure	ICD Codes used for data extraction
Respiratory tract infection	J09, J10, J10.0, J10.1, J10.8, J11.0, J11.1, J11.8, J12.0, J12.1, J12.2, J12.3, J12.8, J12.9, J13, J14, J15.0, J15.1, J15.2, J15.3, J15.4, J15.5, J15.6, J15.7, J15.8, J15.9, J16.0, J16.8, J17.0, J17.1, J17.2, J17.3, J17.8, J18.0, J18.1, J18.2, J18.8, J18.9, J20.0, J20.1, J20.2, J20.3, J20.4, J20.5, J20.6, J20.7, J20.8, J20.9, J21.0, J21.1, J21.8, J21.9, J22, J69.0, A15.0, A15.1, A15.2, A15.3, A15.5, A15.7, A15.8, A15.9, A16.0, A16.1, A16.2, A16.4, A16.7, A16.9, A16.9, A21.2, A22.1, A37.0, A37.1, A37.8, A37.9, A42.0, A43.0, A48.1, B25.0, B37.1, B38.0, B38.1, B38.2, B39.0, B39.1, B39.2, B40.0, B40.1, B40.2, B41.0, B42.0, B44.0, B44.1, B45.0, B46.0, B48.5
Sleep disordered breathing	G47.30, G47.33, E66.2, E66.20, E66.21, E66.22, E66.23
Smoking	F17.0, F17.1, F17.2, F17.3, F17.4, F17.5, F17.6, F17.7, F17.8, F17.9, T65.2, Z58.7, Z71.6, Z72.0, Z86.43

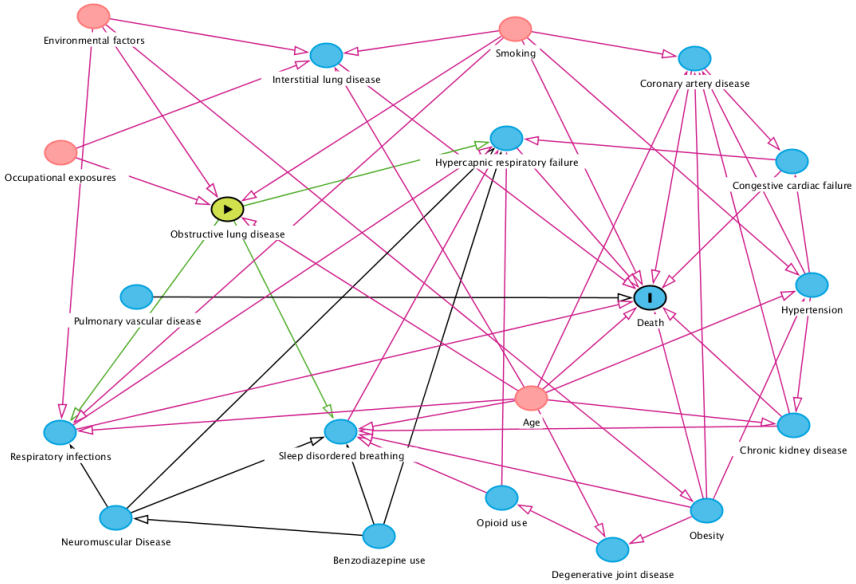

Figure 9.1. *Causal model for the effect of obstructive lung disease on death. Green arrows represent causal paths. Red arrows represent biasing paths. Blue-shaded variables represent ancestors (causes) of the outcome (death). Red-shaded variables represent ancestors (causes) of both the exposure (obstructive lung disease) and outcome (death). Based on this graph, the following covariates were included in the final regression model: Age, pH, chronic kidney disease, congestive cardiac failure, interstitial lung disease, obesity, respiratory infection and smoking.*

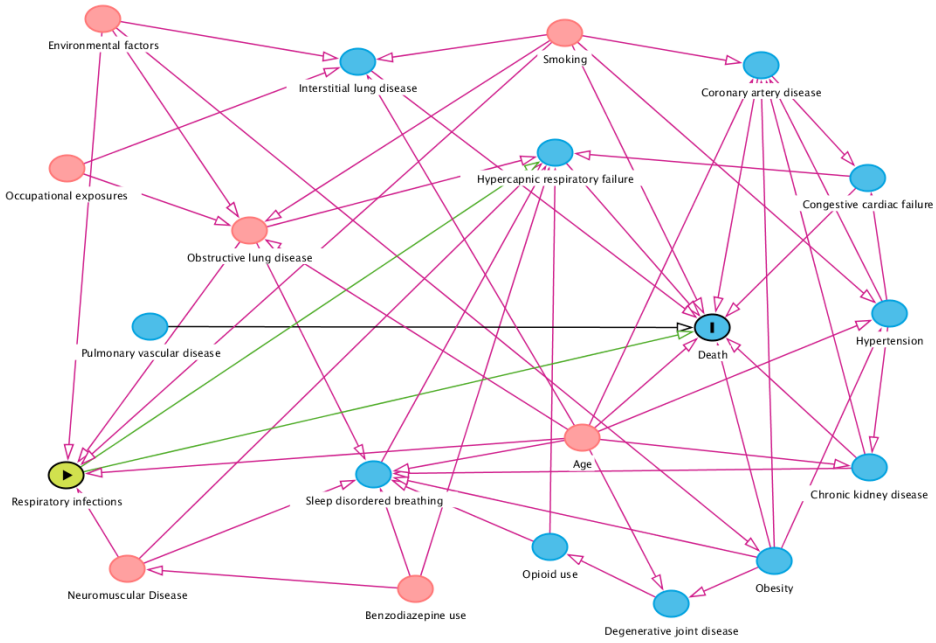

Figure 9.2. *Causal model for the effect of lower respiratory tract infection on death. Green arrows represent causal paths. Red arrows represent biasing paths. Blue-shaded variables represent ancestors (causes) of the outcome (death). Red-shaded variables represent ancestors (causes) of both the exposure (lower respiratory tract infection) and outcome (death). Based on this graph, the following covariates were included in the final regression model: Age, pH, benzodiazepine use, congestive cardiac failure, interstitial lung disease, neuromuscular disease, obesity, obstructive lung disease, opioid use, sleep disordered breathing, and smoking.*

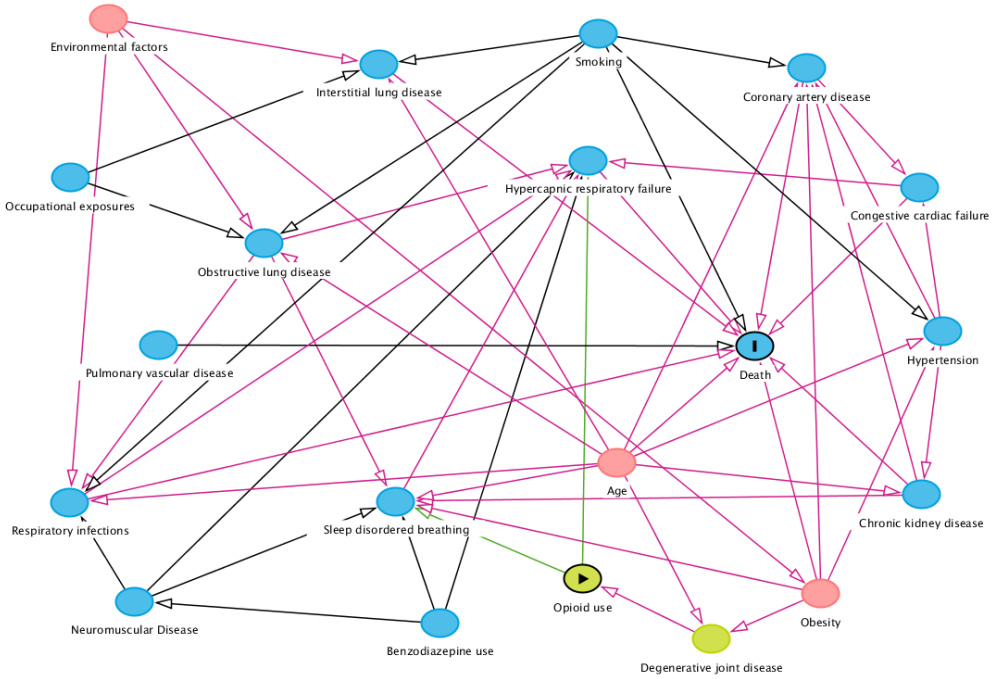

Figure 9.3. *Causal model for the effect of congestive cardiac failure on death. Green arrows represent causal paths. Red arrows represent biasing paths. Blue-shaded variables represent ancestors (causes) of the outcome (death). Red-shaded variables represent ancestors (causes) of both the exposure (congestive cardiac failure) and outcome (death). Based on this graph, the following covariates were included in the final regression model: Age, pH, chronic kidney disease, coronary artery disease, interstitial lung disease, obesity, respiratory infection, and smoking.*

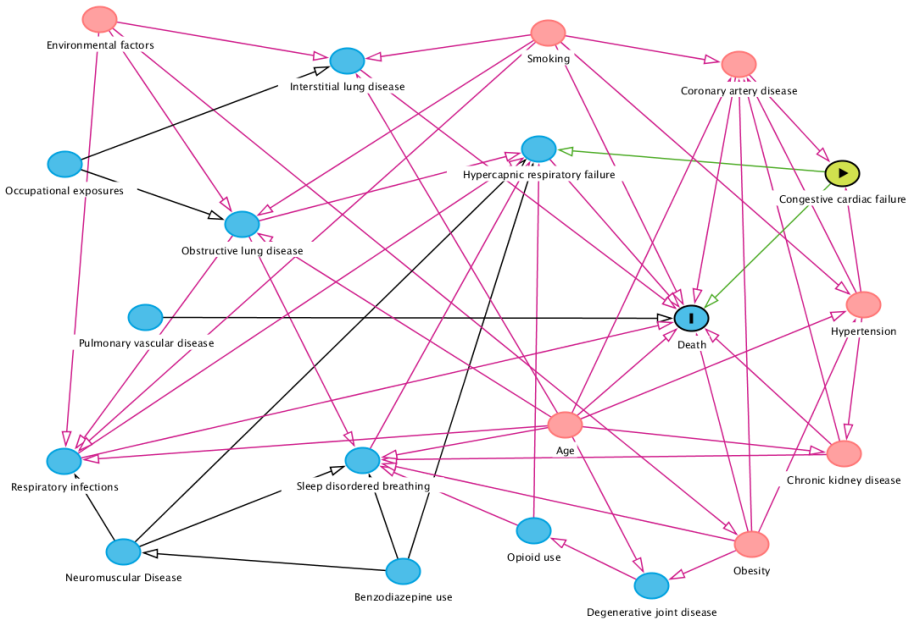

Figure 9.4. *Causal model for the effect of opioid use on death. Green arrows represent causal paths. Red arrows represent biasing paths. Blue-shaded variables represent ancestors (causes) of the outcome (death). Red-shaded variables represent ancestors (causes) of both the exposure (opioid use) and outcome (death). Based on this graph, the following covariates were included in the final regression model: Age, pH, chronic kidney disease, congestive cardiac failure, neuromuscular disease, obesity, obstructive airways disease, and respiratory infection.*

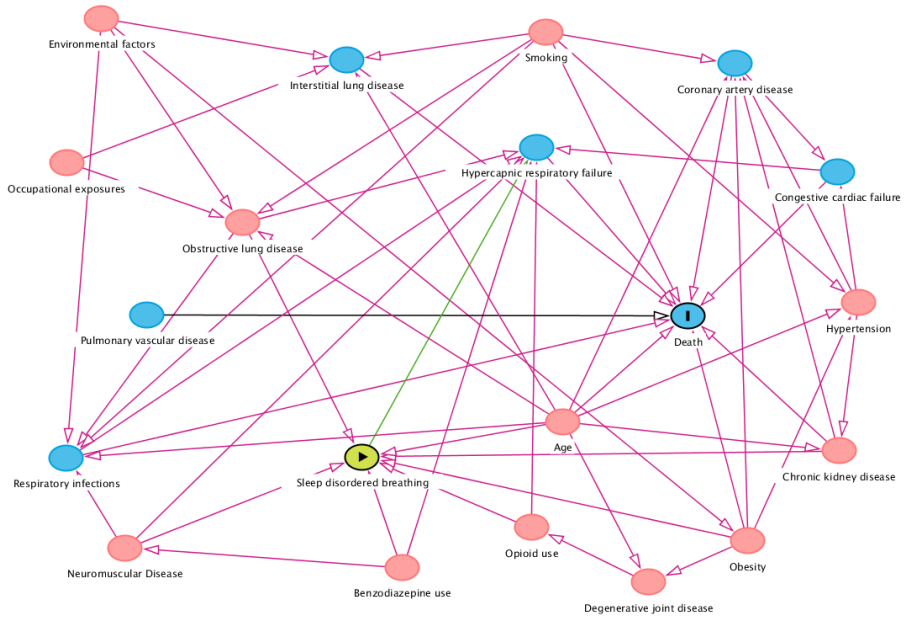

Figure 9.5. *Causal model for the effect of sleep disordered breathing on death. Green arrows represent causal paths. Red arrows represent biasing paths. Blue-shaded variables represent ancestors (causes) of the outcome (death). Red-shaded variables represent ancestors (causes) of both the exposure (sleep disordered breathing) and outcome (death). Based on this graph, the following covariates were included in the final regression model: Age, pH, chronic kidney disease, congestive cardiac failure, neuromuscular disease, obesity, obstructive airways disease, and respiratory infection.*

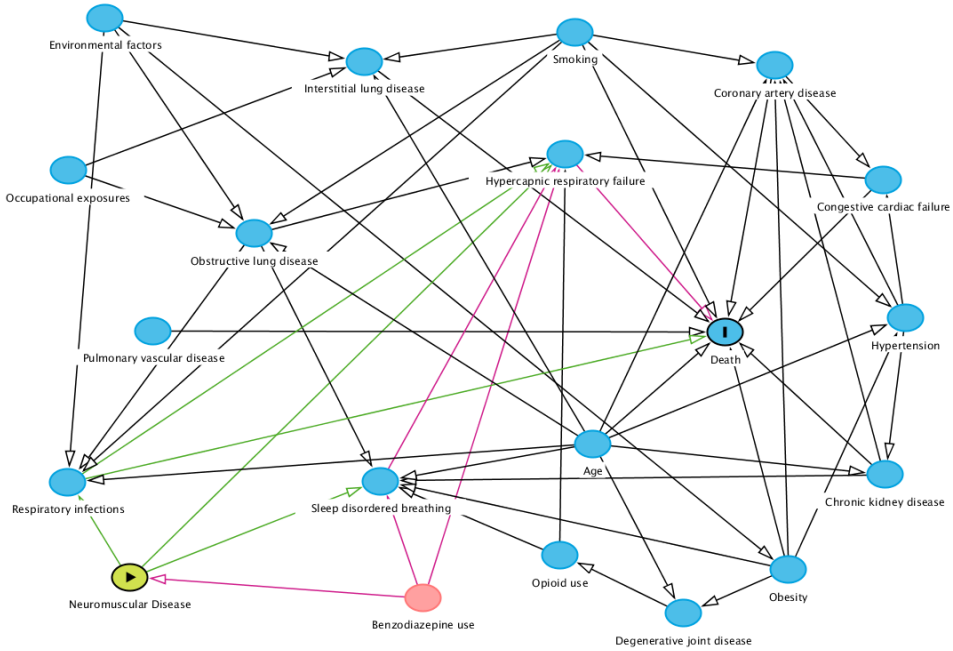

Figure 9.6. *Causal model for the effect of neuromuscular disease on death. Green arrows represent causal paths. Red arrows represent biasing paths. Blue-shaded variables represent ancestors (causes) of the outcome (death). Red-shaded variables represent ancestors (causes) of both the exposure (neuromuscular disease) and outcome (death). Based on this graph, the following covariates were included in the final regression model: Age, pH, chronic kidney disease, congestive cardiac failure, interstitial lung disease, obesity, respiratory infection, and sleep disordered breathing.*

9.3 Supporting information for Chapter 6

Table 9.2. *Details of regression models used to determine the associations between each cause and the outcome of hypercapnic respiratory failure.*

Cause	Covariates	Auxiliary variables
Obstructive lung disease	Age, Smoking	Self-reported chronic obstructive pulmonary disease, emphysema OR chronic bronchitis
Congestive cardiac failure	Coronary artery disease, Hypertension	Self-reported congestive cardiac failure, atrial fibrillation, myocardial infarction OR coronary artery disease
Obstructive sleep apnoea	Age, Obesity, Opioid use, Benzodiazepine use	STOP-BANG score total
Respiratory muscle weakness	No adjustment required	Age
Opioid use	Age, Obesity	No missing data
Benzodiazepine use	No adjustment required	No missing data

We estimated the crude and adjusted associations with hypercapnic respiratory failure (HRF) by fitting separate logistic regression models for each cause or exposure. The covariates used for each adjusted model were selected using a directed acyclic graph showing direct and indirect pathways for the development of HRF. If data were missing (e.g. if spirometry was unable to be performed to determine the presence or absence of obstructive lung disease), then auxiliary values were used to impute missing values using multivariate normal regression, using the PROC MI statement in SAS. Up to 40 imputed datasets were generated, depending on the fraction of missing information (FMI) for each model. Auxiliary values were identified by measuring their correlation (either alone or as a composite variable) with the exposure variable, and selecting those with Pearson correlation coefficient values of at least 0.4.

9.4 Supporting information for Chapter 7

Table 9.3. *Diagnosis codes from the International Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) used for data abstraction of potential cause for hypercapnic respiratory failure (HRF).*

Potential cause for HRF	ICD Code	Details
Congestive cardiac failure	I09.0	Rheumatic myocarditis
	I11.0	Rheumatic diseases of endocardium, valve unspecified
	I13.0	Hypertensive heart and kidney disease with (congestive) heart failure
	I13.2	Hypertensive heart and kidney disease with both (congestive) heart failure and kidney failure
	I25.5	Ischaemic cardiomyopathy
	I42	Cardiomyopathy
	I43	Cardiomyopathy in diseases classified elsewhere
	I50	Heart failure
Neuromuscular disease	G12	Spinal muscular atrophy and related syndromes (includes motor neuron disease)
	G61	Inflammatory polyneuropathy
	G70	Myasthenia gravis and other myoneural disorders
	G71	Primary disorders of muscles (includes muscular dystrophy, myotonic disorders, congenital myopathies, mitochondrial myopathy)
	G82.3	Flaccid tetraplegia
	G82.4	Spastic tetraplegia
	G82.5	Tetraplegia, unspecified
	J98.6	Disorders of diaphragm

(continued next page)

Table 9.3 (continued)

Potential cause for HRF	ICD Code	Details
Obstructive lung disease	J43	Emphysema
	J44	Other chronic obstructive pulmonary disease
	J45	Asthma
	J46	Status asthmaticus
	J47	Bronchiectasis
Opioid use	F11	Mental and behavioural disorders due to use of opioids
	T40.0	Poisoning by narcotics (opium)
	T40.1	Poisoning by narcotics (heroin)
	T40.2	Poisoning by narcotics (other opioids)
	T40.3	Poisoning by narcotics (methadone)
	T40.4	Poisoning by narcotics (other synthetic narcotics)
	T40.6	Poisoning by narcotics (other and unspecified)
	Y45.0	Analgesics, antipyretics and anti-inflammatory drugs causing adverse effects in therapeutic use (opioids and related analgesics)
Sleep-disordered breathing	G47.30	Sleep apnoea, unspecified
	G47.32	Obstructive sleep apnoea syndrome
	G47.33	Sleep hypoventilation syndrome
	E66.2	Obesity with alveolar hypoventilation
	E66.20	Obesity with alveolar hypoventilation, body mass index [BMI] not elsewhere classified
	E66.21	Obesity with alveolar hypoventilation, body mass index [BMI] ≥ 30 kg/m2 to ≤ 34.99 kg/m2
	E66.22	Obesity with alveolar hypoventilation, body mass index [BMI] ≥ 35 kg/m^2 to ≤ 39.99 kg/m^2
	E66.23	Obesity with alveolar hypoventilation, body mass index [BMI] ≥ 40 kg/m^2

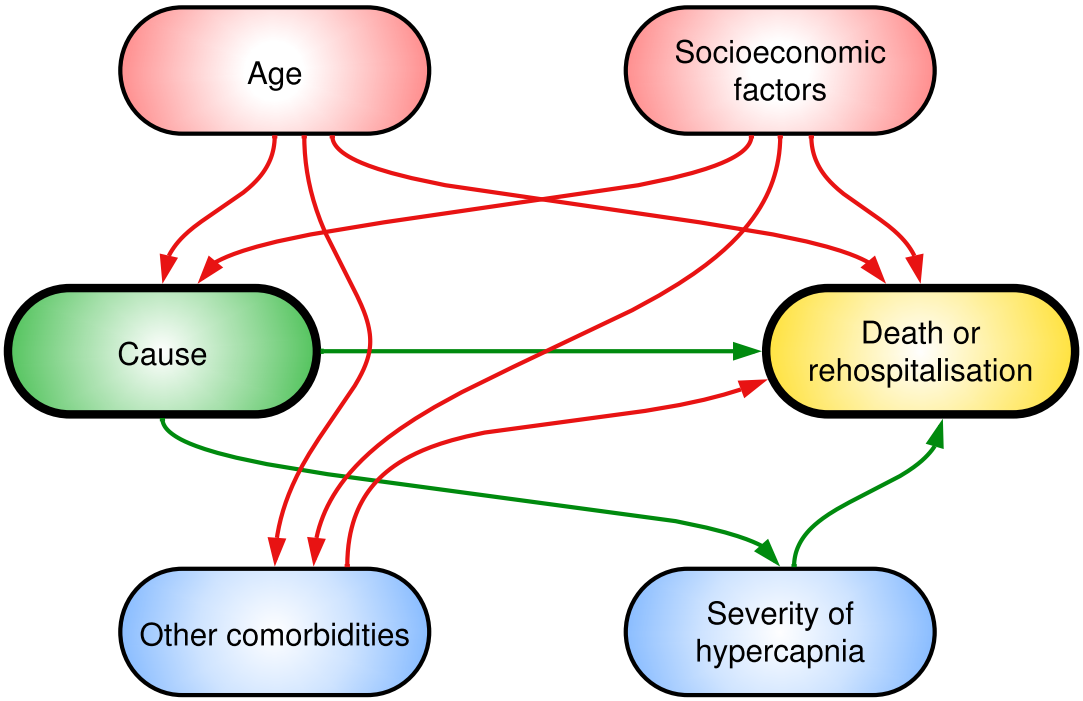

Figure 9.7. *Directed acyclic graph showing assumed relationships between the underlying cause, other covariates and the outcome of death or rehospitalization among adults with hypercapnic respiratory failure. Green arrows represent causal paths. Red arrows represent biasing paths. Blue variables are ancestors (causes) of the outcome. Red variables are ancestors (causes) of the exposure and outcome.*

Table 9.4. *Number of deaths per person-years at risk among adults surviving a hospital admission with hypercapnic respiratory failure for the period 2013 to 2021.*

Age at 2013 (years)	n (%)	Deaths (n)	Person-years of follow-up	Deaths/1,000 person-years
15-24	8 (1.6%)	2	50.8	39.4
25-34	20 (3.9%)	4	130.9	30.6
35-44	32 (6.2%)	6	211.5	28.4
45-54	42 (8.2%)	17	243.3	69.9
55-64	75 (14.6%)	40	374.0	107.0
65-74	140 (27.3%)	100	593.2	168.6
75-84	134 (26.1%)	114	454.0	251.1
85-94	60 (11.7%)	53	132.9	398.8
95+	2 (0.4%)	2	3.25	615.4