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Sex differences in the ICU patient population in Australia and New Zealand

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Preface

Abstract

Introduction

Around the world, more men than women are admitted to the Intensive Care Unit (ICU). Nonetheless, sex differences are not yet well described in critical care, with no previous studies of sex differences in the ICU patient population in Australia and New Zealand

Objectives

This PhD aimed to comprehensively describe sex differences – differences between the groups of women, men and patients classified as a third sex – admitted to intensive care units (ICUs) in Australia and New Zealand. Specifically, to describe sex differences in illness severity, mortality, vital organ support and representation in clinical research.

Methods

The existing literature on sex differences in the ICU patient population was synthesised using systematic review and meta-analysis. Sex differences in the local Australia and New Zealand ICU patient population were analysed in retrospective observational studies of ICU admissions recorded in the Australia and New Zealand Intensive Care Society's Adult Patient Database. These studies examined the broad ICU patient population, spanning all diagnostic groups and types of intensive care units in the two nations.

Results

Women composed between 42% and 43% of all ICU patients. Admissions following cardiovascular surgery accounted for over half of the overall sex imbalance in ICU admissions. In contrast to the findings of most previous studies from high-income countries, in Australia and New Zealand, women were admitted to ICU at lower average age and illness severity than men.

Sex balance varied substantially across diagnostic groups and was inversely associated with both the adjusted mortality and illness severity of women compared to men. In

diagnoses with relatively few women, women were more likely to die than men, and vice-versa.

Patients classified as third sex composed a small minority of ICU patients. This group had a different diagnostic casemix, but similar outcomes, to the groups classified as female or male.

Women were less likely to receive vital organ support than men in the ICU. However, they did not appear to be harmed by this conservative approach to treatment, with similar adjusted hospital mortality overall compared to men.

Critical care trials in Australia and New Zealand included a representative number of women overall when compared to matched target populations. However, these target populations had fewer women than the general ICU patient population, suggesting clinical trials focus on male-dominated clinical conditions.

Conclusion

This thesis confirmed a consistent sex imbalance in admissions to ICUs in high-income countries, driven largely by admissions for cardiovascular disease. Women received less treatment in ICU than men; despite this they were similarly likely to survive their critical illness. Further research is needed to understand the drivers of this differential approach to treatment.

Contemporary critical care trials examined relatively male-dominated critical illnesses, with even fewer women in their target populations than the overall ICU patient population. People with innate variations in sex differentiation and people with gender diverse experiences were not represented in contemporary critical care research.

Declaration

I hereby certify that:

The work contained in this thesis is my own original work, with supervision and advice from PhD supervisors Professor Bellomo, Professor Bailey and Dr Higgins. Contributions from other collaborators are acknowledged in the text.

I have appropriately acknowledged all other supporting materials used in the text.

This thesis is fewer than 100,000 words in length, exclusive of tables, bibliographies and appendices.

Dr Lucy Jane Modra
Melbourne, February 2025

Publication status and author contribution to thesis chapters

Thesis chapter	Authorship and manuscript title	Publication status	Percentage contribution by candidate
2	**Modra LJ**, Pilcher D, Bailey M, Bellomo R. Sex differences in Intensive Care Admissions in Australia and New Zealand.	*Critical Care and Resuscitation* 2021; 23(1): 86-93	**70%**
3	**Modra LJ**, Higgins A, Vithanage R, Abeygunawardana V, Bailey M, Bellomo R. Sex differences in illness severity and mortality among adult intensive care patients: A systematic review and meta-analysis.	*Journal of Critical Care* 2021; 65: 116-123	**60%**
4	**Modra LJ**, Higgins A, Pilcher D, Bailey M and Bellomo R. Sex differences in mortality of ICU patients according to diagnosis-related sex balance.	*American Journal of Respiratory and Critical Care Medicine* 2022; 206(11): 1353-1360	**70%**
5	**Modra LJ,** Higgins A, Abeygunawardana V, Vithanage R, Bailey M and Bellomo R. Sex differences in treatment of adult intensive care patients: a systematic review and meta-analysis	*Critical Care Medicine* 2022; 50(6): 913-923	**60%**
6	**Modra LJ**, Higgins AM, Pilcher DV, Bailey M, Bellomo R. Sex Differences in Vital Organ Support Provided to ICU Patients	*Critical Care Medicine* 2024; 52(1): 1-10	**70%**
7	**Modra LJ,** Higgins AM, Pilcher DV, Cheung AS, Carpenter MN, Bailey M, Zwickl S, Bellomo R. Epidemiology of Intensive Care Patients Classified as a Third Sex in Australia and New Zealand.	*Chest* 2024; 165(5): 1120-1128	**65%**
8, Appendix C	**Modra LJ,** Bone A, Pilcher DV, Woodward M, Thompson K. Sex representation within intensive care trials in Australia and New Zealand*	*Intensive Care Medicine* 2024; 50: 1529–1531	**65%**

Related manuscripts completed during candidature but not included in this thesis			
	Kotfis K, Olusanya S, **Modra LJ.** Equity in patient care in the intensive care unit.	*Intensive Care Medicine* 2024; 50(2): 291-293	**40%**
	Modra LJ, Casamento A. Why are men more restrained in the ICU?	*Annals of the American Thoracic Society* 2024; 1(12):1657-1658	**80%**
	Higgins AM, **Modra LJ.** Minority group representation in ECMO trials: where are they?	*Critical Care Medicine* 2025; in press	**30%**

***Chapter 8 presents a complete report of a study published in abridged form as a research letter. The published version is reproduced in Appendix C.*

Conference and Seminar presentations

2020 Research seminar: University of Melbourne Centre for Integrated Critical Care: Sex differences in ICU admissions.

2021 International Symposium on Intensive Care and Emergency Medicine
Poster presentation: Sex differences in treatment intensity of adult intensive care patients: a systematic review and meta-analysis.

2022 Invited Speaker, Mount Sinai Critical Care Grand Rounds, October 2022: Sex differences in outcomes and treatment of ICU patients.

University of Melbourne Faculty of Medicine, Dentistry and Health Sciences Graduate Research conference: research oral presentation. *Winner, Best presentation in Cardiovascular and Metabolic stream*

University of Melbourne Social Equity Institute's Gender Equity Symposium: research presentation.

University of Melbourne Department of Critical Care Women in Critical Care Seminar: invited panellist.

Invited speaker, Society of Critical Care Medicine (USA) Journal Club podcast: Sex differences in treatment of adult intensive care patients: a systematic review and meta-analysis.

ANZICS/ACCCN ASM Research Presentation: 'Sex differences in Illness severity and Mortality in Australia and New Zealand.' *Awarded Peter Hicks Fellowship for excellence in critical care data research.*

2023 College of Intensive Care Medicine of Australia and New Zealand Annual Scientific Meeting. Research Paper presentation: 'Sex differences in vital organ support provided to ICU patients.' *Awarded Best Free Medical Paper presentation.*

2024 Australia and New Zealand Intensive Care Society Clinical Trials Group Annual Meeting on Clinical Trials in Intensive Care ('Noosa meeting'): Sex representation in ICU trials in Australia and New Zealand.

Details of Professional Roles

During my enrolment in this degree, I have been employed as an Intensive Care Specialist at Austin Health, Heidelberg, and Clinical Tutor at the University of Melbourne. I sit on the Women in Intensive Care Medicine Network committee of the Australia and New Zealand Intensive Care Society. I serve as faculty on the College of Intensive Care Medicine's Communication Course.

Work submitted for other qualifications

None of the content of this thesis has been submitted to fulfil another qualification.

Work carried out prior to enrolment and third-party editorial assistance

None of the content of this thesis was carried out prior to enrolment in this degree.
I gratefully acknowledge the input of both peer reviewers and journal editors for each individual publication incorporated into this thesis.

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Australia and New Zealand Intensive Care Society Peter Hicks Fellowship Award 2022, *awarded for excellence in working with intensive care data.*

University of Melbourne Faculty of Medicine, Dentistry and Health Sciences Graduate Research conference 2022: *Winner, Best presentation in Cardiovascular and Metabolic stream.*

University of Melbourne Graeme Clark Institute Women in STEMM award 2022: *awarded second prize*.

A note on language

This thesis uses American English spelling of medical terms, as many chapters in this thesis were published in American medical journals.

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Many people supported me to complete this research, I gratefully acknowledge them here.

First and foremost, I would like to thank my world-class team of supervisors, Rinaldo Bellomo, Lisa Higgins and Michael Bailey, for their expert advice and support throughout my candidature. I was consistently buoyed by their wisdom and good humour. I have learnt an enormous amount from each of them – I simply could not have asked for a better team of supervisors.

Special thanks to David Pilcher for his generous mentoring and expert advice throughout my PhD. Many years ago, Dave very patiently introduced me to the idea of using the Adult Patient Database to answer questions about the intensive care patient population. His leadership of the Australia and New Zealand Intensive Care Society's Centre for Resource Excellence enabled my own research, and the work of many others.

I was lucky to work with a diverse array of researchers on the projects that make up this PhD. Thank you to each of my co-authors for their valuable contributions and insights.

Thank you to management committee and staff at ANZICS CORE, especially Shaila Chavan and Rocklyn Xavier. Thank you to all the data-collectors, clinicians and researchers at the ICUs contributing to the Adult Patient Database (Appendix A). Your contribution to this registry helps ensure that our ICUs are among the best in the world.

I have been lucky to complete this PhD while working in an ICU so committed to research. I would like to thank all my Austin ICU colleagues, especially Daryl Jones, Glenn Eastwood, Rahul Costa-Pinto, Caleb Fisher, Emily See, Ary Serpa Neto and Stephen Warrillow, for their support and very practical advice on 'getting it done'.

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Last but not least, thank you to my wonderful family – Jason, Nora and Etta – for their enthusiasm, support and patience as I completed this PhD. I've often mused that finishing this thesis felt much like getting small children ready to leave the house for the day. Hats went missing, bags were packed and unpacked again, the dog ran off with a shoe and I threatened to cancel the whole thing at least twice. On days like these I reassure the kids, 'We are sneaking up on Ready from behind. Ready is *not* going to expect us!' And so it is with this thesis. I snuck up on Finished from behind, and let me tell you, Finished got a real fright.

Acknowledgements: a sad addendum

In the liminal space between submitting this thesis and receiving the examiners' reports, my primary supervisor, mentor and friend, Professor Rinaldo Bellomo, suddenly died.

It was my privilege to work with Rinaldo over many years, both as a clinical colleague at the Austin ICU and, more recently, as his PhD student. To say that I have learnt a enormous amount from him comically understates the experience.

I would have loved the opportunity to thank him properly; to proudly hand him a copy of my completed thesis to sit on his shelf alongside the many other doctorates he supervised.

The world will remember Rinaldo's enormous contribution to critical care medicine, which has undoubtedly saved thousands of lives. I will sorely miss his infectious curiosity, joy, and love of the absurd.

'Stay with me…'

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List of acronyms

AAA	Abdominal aortic aneurysm
AMI	Acute myocardial infarction
ANZICS	Australia and New Zealand Intensive Care Society
ANZROD	Australia and New Zealand Risk of Death
APACHE	Acute Physiology and Chronic Health Evaluation
APD	Adult Patient Database, administered by ANZICS CORE
APS	Acute Physiology Score
CI	Confidence interval
CORE	Centre for Outcome and Resource Evaluation (ANZICS CORE)
CTG	Clinical Trials Group
ECMO	Extra-corporeal membrane oxygenation
GEMA	Gender Equity Model for liver Allocation
GRACE	Global Registry of Acute Coronary Events
ICU	Intensive care unit
LoMT	Limitation of medical treatment
LoS	Length of stay
MELD	Model for End-stage Liver Disease
MV	Mechanical ventilation
NIV	Non-invasive ventilation
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
RCTS	Randomised controlled trials
RRT	Renal replacement therapy
SAPS	Simplified Acute Physiology Score
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
USA	United States of America

Chapter 1. Introduction

1.1 BACKGROUND

Introductory remarks

In 1991, the New England Journal of Medicine (NEJM) published a pair of papers reporting that women with coronary artery disease were less likely to receive coronary angiography than men (1, 2). In her accompanying editorial, Dr Bernadine Healy coined the term 'Yentl syndrome' to describe a more conservative approach to treating women as compared to men with the same disease:

> *We must be challenged by the example of coronary artery disease to examine critically the extent to which the Yentl syndrome pervades medicine and medical research and to respond promptly whenever its influence is evident* (3).

Just two years earlier, *NEJM* published results from the Physicians' Health Study demonstrating the efficacy of prophylactic aspirin in preventing myocardial infarction (4). All 22,071 participants in the study were men. Similarly influential trials demonstrated the efficacy of coronary artery surgery and cardiovascular risk factor modification in entirely male study populations (5, 6). Against this backdrop, the idea of exploring systemic differences between women and men with heart disease was ground-breaking.

There have been dramatic advances in the understanding of sex differences in cardiovascular disease in the intervening decades, spanning differences in risk profile, clinical presentation and outcomes (7-12). Subsequent studies again demonstrated that women and men received different treatment when presenting with the same syndrome, including out of hospital cardiac arrest (8, 10, 13, 14). Women and men also respond differently to many treatments, including common medications, cardiac resynchronisation therapy and coronary artery bypass surgery (7, 12, 15, 16).

In contrast, research into sex differences in critical illness has lagged. This is notable given the sex imbalance in ICU admissions: women compose between 35% and 45% of the ICU patient population in high income countries around the world (17-22). This

imbalance points to potentially significant differences in the incidence, trajectory and/or management of critical illness in women and men.

At the time of commencing this program of research, there were few large studies examining sex differences in the ICU patient population, and none from Australia or New Zealand (19-21, 23-27). Only one study had examined a comprehensive nationwide cohort of ICU patient, in Sweden (24). Studies examining sex differences in illness severity and mortality of ICU patients had variable adjustment for important confounders and had reached conflicting results (19, 24). Several studies examined sex differences in specific critical illnesses like sepsis. However, there was limited description of how these illnesses may contribute to the sex differences observed in the overall ICU patient population (28, 29). No previous study had examined ICU patients who may be classified as belonging to a third or non-binary sex group.

Accordingly, this thesis aims to provide a comprehensive overview of sex differences in the ICU patient population of Australia and New Zealand, examining the domains of illness severity, mortality, vital organ support and representation in critical care research. Specifically, the objectives of this program of research are:

- to describe sex balance across diagnostic groups of ICU patients (chapter 2)
- to describe sex differences in illness severity and mortality of ICU patients (chapters 3-4)
- to describe sex differences in vital organ support provided to ICU patients (chapters 5-6)
- to describe the epidemiology of ICU patients classified as a third sex (chapter 7)
- to describe sex-based representation in critical care trials (chapter 8)

The Adult Patient Database

This thesis examines ICU admissions recorded in the Australia and New Zealand Intensive Care Society's Centre for Outcomes and Resource Evaluation's Adult Patient Database (APD). The APD is a clinical registry established in 1993 to monitor patient outcomes and facilitate benchmarking of ICUs in Australia and New Zealand (30). It is one of five ICU clinical registries administered by the Australia and New Zealand Intensive Care Society's Centre for Outcome and Resource Evaluation (ANZICS CORE).

The APD records admissions from 90% of ICUs in Australia and New Zealand, including all tertiary ICUs in the two nations (31). In financial year 2021-2022, the APD recorded 188,757 adult admissions to 196 ICUs (31). This includes medical and surgical admissions to ICUs in public and private hospitals, across major cities, regional and remote centres. The comprehensive nature of this clinical registry provides an important opportunity to systematically describe sex differences in a bi-national intensive care population.

Data recorded in the APD are defined in a standardised data dictionary, and include admission diagnosis, location prior to ICU admission, pre-defined limitations of treatment, co-morbidities, physiological variables in the first 24 hours, among other variables. ICU admission diagnoses, physiological variables and comorbidities are based on the Acute Physiology and Chronic Health Evaluation (APACHE) model, allowing calculation of the APACHE II and APACHE III scores (32). The APACHE II score is now the most widely used illness severity score in the world; major critical care trials use this score to report baseline illness severity among participants (33). This program of research uses the APACHE III score, which was derived more recently from a larger dataset, with improved discriminatory performance than the APACHE II score (34). The APACHE III score includes the patient's age, degree of physiological derangement in the first 24 hours of ICU admission, and chronic comorbidities (33). The related APACHE III risk of death model incorporates both the APACHE III score and the patient's ICU admission diagnosis.

The data dictionary is periodically revised by the CORE management committee, with new variables added if the data is anticipated to improve the quality of benchmarking information generated for participating ICUs. The study periods for individual studies in this thesis were informed by availability of relevant data in the APD. For example, vital organ support indicators were widely adopted from 2018, so the study examining the vital organ support examined admissions from 2018 onwards. Differences in study periods, and therefore study populations, contribute to minor variations in sex balance and outcomes between studies in this thesis.

Defining sex, gender and sex balance

Health differences between women and men may arise from biologically grounded sex differences, for example, differences in sex hormone levels; socially grounded gender differences, for example, differences in alcohol intake; or a complex interaction between the two. Therefore, it is helpful to consider the definitions of sex and gender, and the limitations of a binary distinction in each category.

Sex refers to a range of biological characteristics including sex-linked chromosomes, hormones, and reproductive organs, used to distinguish between male and female (35). In their 2022 book 'Measuring Sex, Gender Identity and Sexual Orientation', the US National Academies of Sciences, Engineering and Medicine adopted the following definition of sex:

> *Sex is a multidimensional construct based on a cluster of anatomical and physiological traits that include external genitalia, secondary sex characteristics, gonads, chromosomes, and hormones(36).*

Sex is often presented as a binary and mutually exclusive distinction between female and male. This is misleading. People with innate variations of sex characteristics, who have characteristics not entirely aligned with either category, compose up to 1.7% of the general population (36, 37). This group are sometimes classified as a third sex category, variously termed 'intersex', 'differences of sex differentiation' (DSD) or 'another term' (38).

However, many people with innate variations in sex differentiation prefer to maintain a binary sex distinction and note innate variations of sex characteristics as an additional descriptor. This reflects their lived experience: most people with innate variations of sex characteristics were assigned female or male at birth and discovered their innate variation in sex differentiation later in life. Therefore, the difference in sex differentiation is experienced as private medical information that exists alongside being female or male (38). Both the Australian Bureau of Statistics and the American National Academies of Sciences recommend that variation in sex differentiation be recorded as a separate descriptor, in addition to the primary sex descriptor of female or male (36, 38, 39). This practice is not yet widely adopted (40).

Gender is defined within a personal and social context, and relates to a person's identity as a man, a woman, a non-binary person, or another gender (35, 36). Cisgender describes people whose gender aligns with their sex assigned at birth, transgender refers to people whose gender does not concord with their sex (36). 'Sex and gender-based minorities' is an umbrella term describing diverse populations including people who identify as transgender, intersex or with a difference in sex development, queer, same-sex attracted and others (41).

In summary, sex and gender are distinct yet intertwined concepts; neither fits neatly into a binary categorisation. These points are not yet consistently reflected in medical practice and research. Hospital medical records, clinical registries and clinical trials usually record patient sex but not gender. The sex variable usually has binary options: female or male (40). These limitations have three important implications. First, sex and gender are commonly conflated into a sex/gender hybrid (42). Second, people with a difference in sex development and people who identify as transgender, or another gender are often excluded or obscured within binary sex categories. Finally, there is unquantifiable misclassification within the binary sex categories. For example, a transgender person may record their gender rather than their sex in the sole 'sex' category.

My own research is constrained by these limitations. The APD records patient sex, defined as 'the biological distinction between male and female', and does not record patient gender (43). Therefore, this research consistently refers to patient sex, acknowledging that this represents a 'sex/gender' hybrid. I refer to 'women' and 'men' throughout, rather than 'female patients' and 'male patients.' This is both a stylistic preference and an acknowledgement of the limitations of the sex-based groupings. In those chapters comparing women and men, 'sex balance' is arbitrarily defined as the percentage of ICU patients who are women.

In 2016, the APD added a third option to the sex variable, moving beyond a binary sex classification (43). This third sex category was labelled 'intersex/indeterminate', based on the Australian Government guidelines at the time (44). In this thesis I refer to 'patients classified as a third sex', to avoid the potentially pejorative 'indeterminate sex' and to foreground the limitations of the categorisation. In the absence of a well-established, acceptable process for recording sex, gender, and variations in sex differentiation in the medical record, this third sex group is likely to include some transgender people and some people with innate variations in sex differentiation. It is unlikely to include all people who self-identify as belonging to these categories.

Given these limitations, and the introduction of the third sex option midway through the study periods, patients classified as a third sex were not included in the initial studies examining sex differences in mortality and treatment (chapters 4 and 6). Instead, this group are comprehensively described in a dedicated paper, the first published epidemiology of ICU patients classified as a third sex (chapter 7).

1.2 MOTIVATION FOR AND SIGNIFICANCE OF SEX DIFFERENCES RESEARCH

Understanding sex differences can lead to improved clinical outcomes by two important mechanisms. First, identifying differences in the manifestations, trajectory and response to treatment between the sex groups is the first step to developing more personalised intervention for each group (12). Second, identifying any systemic differences in the treatment provided according to sex – where this is not a deliberate practice based on well-defined heterogeneity of treatment effect – can inform either more aggressive treatment of the previously under-served group or the avoidance of unnecessary interventions in the over-served group. Of note, even minor improvements in the treatment and outcomes of such large population groups can lead to significant gains for the population overall (45).

Three examples illustrate the ways in which understanding sex differences can lead to important improvements in treatment.

The first relates to the Model for End-Stage Liver Disease (MELD) score, a physiological scoring system used to prioritise patients with chronic liver disease awaiting liver transplantation (46, 47). The MELD score incorporates bilirubin, international normalised ratio and creatinine, with higher levels of each parameter indicating more severe disease. Creatinine is included as a biochemical marker of renal function, which is closely associated with prognosis in chronic liver disease. However, a patient's creatinine level reflects not only their renal function, but also their muscle mass. On average, women have less muscle mass than men, therefore they have poorer renal function for a given creatinine value than men (46). In this way, the MELD score relatively underestimates chronic liver disease severity in women compared to men by overestimating their true renal function (48). Since at least 2011, this was understood to contribute to the inequitable allocation of liver transplants among women and men (46). Women are less likely to receive a liver transplant than men and more likely to die whilst on the waiting list.

The Gender Equity Model for Liver Allocation (GEMA) was derived and validated in 2023, using a corrected estimate of renal function rather than creatinine alone (49). The GEMA model showed better discrimination compared to the MELD in predicting deterioration among those on the transplant waiting list. Crucially, the authors demonstrated that using this revised scoring system has the potential to decrease mortality overall for those on the waiting list – among both women and men – in addition to improving gender equity in transplant allocation (49).

A similar example relates to the Global Registry of Acute Coronary Events (GRACE) score, used to risk-stratify patients with acute coronary syndrome, guiding the level of monitoring and intervention provided. A recent study of patients with non-ST-elevation acute coronary syndrome found that the GRACE-2 score tended to under-estimate hospital mortality in women (50). The modified GRACE-3 score, developed using a sex-disaggregated approach, re-allocated more female patients to a higher risk category and more male patients to a lower risk category. Again, the newer model had improved predictive performance in both sex groups (50).

The final example relates to abdominal aortic aneurysms (AAA), a condition 4-6 times more prevalent in men than women (51, 52). Compared to men, women with AAAs have a greater rate of aneurysmal growth and are more likely to develop a rupture (51, 53). The mechanisms underlying these sex differences are complex and relate to aortic size, aortic tensile strength and blood pressure, in turn driven by sex differences in body size, sex hormone levels and the renin-angiotensin-aldosterone system (51).

Women are less likely to have AAAs that are morphologically suitable for endovascular repair, the lower risk intervention option compared to open surgical repair. Regardless of approach, women have higher mortality than men following elective AAA repair (52). This raises a challenging question: how to define an appropriate threshold for elective AAA repair in women without causing harm from unnecessary intervention? (53) The USA (United States of America) Society of Vascular surgery suggests intervening at a smaller aneurysm diameter in women; the UK (United Kingdom) guidelines do not suggest a sex-specific threshold (54, 55). Ideally, the efficacy of sex-

specific thresholds should be carefully examined in prospective studies that are adequately powered to understand the impact on female participants.

Given the relatively low prevalence of AAA in women, most clinical studies of this condition include very few women (52). This leads to a dearth of evidence on the clinical course and outcomes of women with AAA. A landmark study of AAA screening enrolled only male participants by design, concluding that AAA screening could save lives among men (56). Based on these findings, the UK adopted a nation-wide AAA screening program for men (55). Clinicians can consider screening older women with specific risk factors, however there is not robust evidence for the utility of such screening.

These examples illustrate the underlying motivations for this program of research. First, attending carefully to patient sex in all phases of research can help to identify systemic sex differences in clinical parameters – such as creatinine level or aortic size – in both health and disease. This informs more accurate estimates of prognosis for women and men. Second, recognising and addressing inequities in treatment – for example, in the allocation of liver transplant – can lead to the possibility of improving outcomes overall. Third, given that women and men may respond differently to treatment – for example, they have different risk of dying following elective AAA repairs – simply providing 'equal' or 'the same' treatment to each group will not necessarily improve outcomes. Instead, we must also attend to sex differences in outcomes. Finally, clinical trials need to include sex groups in adequate numbers to guide treatment of all people affected by the disease.

In each of these examples, the first step in improving treatment was recognising and defining systemic differences between women and men. Accordingly, this thesis highlights the areas of critical care with the most significant sex-based differences – for example, diagnostic groups and treatments – as potential loci for developing sex-sensitive prognostic and treatment models in future.

1.3 REVIEW OF THE LITERATURE: SEX DIFFERENCES IN OTHER FIELDS

Sex differences is a well-established field of research in cardiology, with substantial research into differences between women and men in coronary artery disease, cardiac arrest, cardiac failure, and arrhythmias (7, 8, 15, 57). These have highlighted significant differences in the presentation, biochemical and electrocardiographic changes, and response to treatment of women and men with heart disease.

This body of research demonstrates the contribution of both sex and gender factors to the observed differences between women and men. For example, differences in the prevalence of cardiovascular disease in women after menopause points to the impact of sex hormones on cardiovascular disease (7). However, there are also systemic differences in the way women and men present to healthcare if they experience chest pain, with women more likely to delay presentation to healthcare (7). These sex and gender-based factors interact with each other, making it difficult or even misleading to attempt to untangle them. In a recent *Lancet* review, Mauvais-Jarvis and colleagues explain, "Sex and gender are fundamentally and frequently reciprocally inter-related in biology and disease." (58)

A further complicating factor is that clinicians respond differently to women and men presenting with the same condition. Women receive less aggressive treatment than men when presenting with cardiac arrest, myocardial infarction and heart failure (8, 13, 15, 59). For example, an Australian study of 2989 patients (24.7% women) with ST-elevation myocardial infarctions found that women were less likely than men to receive coronary angiography and timely revascularization, be prescribed beta-blockers or statins on discharge, or be referred to cardiac rehabilitation (10). These findings echo those of the 1991 studies from which the term 'Yentl syndrome' originated.

Similar themes emerge in other fields of medicine: women and men with the same disease present differently, receive different treatment and respond differently to such treatment, and it is difficult to untangle the contributions of sex and gender factors to

these differences. In the field of nephrology, chronic kidney disease appears to progress more slowly in women than men. However, this may partly reflect the fact that women are less likely to be offered or accept dialysis, a defining feature of end stage kidney disease (60, 61). In the field of endocrinology, type 2 diabetes confers a higher risk of atherosclerotic disease in women compared to men; women with diabetes are less likely to receive aggressive management of their diabetes, and women and men respond differently to oral hypoglycaemic agents (58).

In the field of oncology, there are stark differences in the incidence of cancer in women and men. With few exceptions, non-reproductive cancers are at least twice as common in men than women (58). The male predominance in cancer begins in childhood, prior to the emergence of risk-taking behaviours like smoking or drinking alcohol (62). This clearly implicates sex chromosomes and hormones in the development of cancer. Nonetheless, gendered differences in behaviour remain relevant. For example, the higher incidence of colorectal cancer in men compared to women is attributed to gendered differences in smoking, diet and participation in screening programs in addition to biological factors such as visceral fat distribution patterns (63).

Overall, research into sex differences is somewhat uneven across different fields of medicine: sex differences are increasingly well-defined in some fields, less so in others. This makes it difficult to ascertain whether the relative abundance of reported sex differences in cardiovascular disease reflects particularly pronounced sex differences in this disease, or simply a better-established field of research. My program of research examines the broad population of ICU patients, comparing diagnostic groups of patients. This serves to illustrate the extent of sex differences across a broad range of diseases, identifying the critical illnesses with the most and least prominent sex differences.

There is very little research that directly compares the health of transgender and gender diverse people with cisgendered men and women. For example, in their extensive review of cardiovascular disease in women, Vogel and colleagues noted the paucity of data on cardiovascular disease in transgender women (7). This paucity of research is

largely due the limited recording of sex, gender and innate variations in sex differentiation in the medical record, clinical registries and clinical trials (40). In the absence of reliable representation of transgender people within large registries or trials, studies examining the health of transgender population often use non-probability sampling methods. For example, surveys with snowball sampling, or studying patients who self-present for gender-affirming treatment (64, 65). These research methods are extremely helpful in identifying the healthcare needs of a marginalised minority group, for example highlighting the high prevalence of anxiety and depression in the transgender population (64). However, it makes it difficult to reliably estimate the size of the transgender population, or to describe systemic differences in the health of trans and cisgendered people. Similar observations apply to research comparing people with and without differences in sex differentiation.

Gender bias in healthcare

One of the most consistent themes in sex differences research is a disparity in treatment provided to women and men presenting with the same condition. This disparity reflects not only sex and gender differences in the patient's clinical presentation, but also systemic differences in the way that clinicians respond to women and men. In other words, differences in treatment partly reflect the implicit bias of clinicians.

Implicit associations are defined as unconscious or automatic associations between concepts, for example gender or race, and attributes, for example, strong or weak (66). These implicit associations underpin implicit or unconscious biases and stereotypes. For example, gender bias can include unconscious associations between a patient's gender and their preferred intensity of treatment, or their presumed pain threshold. A systematic review of 42 studies examining the implicit biases of healthcare professionals concluded that they hold implicit associations and biases at similar rates to the general population (67). Therefore, unconscious biases are likely to affect healthcare interaction in the same way that they affect interpersonal interactions in other situations. This review also demonstrated the amplification of unconscious bias at the intersection of domains of privilege or disadvantage, for example ethnicity, socioeconomic status, age, and gender, a phenomenon referred to as 'intersectionality'(67).

It is notoriously difficult to quantify the impact of implicit biases in clinical practice. This is partly because they are grounded in unconscious processes, which can run counter to the clinicians' explicitly-held beliefs (67). Differences in the treatment provided to women and men usually have other plausible explanations, for example biological differences in disease presentation and trajectory, or gendered differences in a patient's healthcare-seeking behavior. Therefore, clinician gender bias tends to be treated as a 'diagnosis of exclusion,' perhaps because these biases contravene the ethical norm of impartiality in healthcare (67).

This thesis does not set out to directly examine or quantify gender bias in the provision of critical care. Nonetheless, the role of possible gender bias emerges as an important thread throughout the program of research, and therefore is an important focus for future research.

1.4 REVIEW OF THE LITERATURE: SEX DIFFERENCES IN INTENSIVE CARE MEDICINE

Sex balance in ICU admissions

There are two striking findings in the existing literature on sex balance in the ICU patient population.

First, more men than women are admitted to ICU. Women account for approximately 35 to 45% of ICU patients in high-income countries (19, 21, 23, 24, 26, 68). In our systematic review of studies explicitly examining sex differences in the ICU patient population, we identified only two small single-centre studies in which the majority of patients were women (69, 70).

Second, the reported sex balance in the ICU patient population varies substantially, from 31.3% women to 53.1 % women (69, 71). In contrast, the sex balance of the general population is reasonably consistent, with women composing approximately 49.7% of the world's total population, 50.3% of Australia's population and 50.4% of New Zealand's population (72). The variation in sex balance in ICU populations may be due to regional differences in admission practices, casemix or other factors. Therefore, one of the gaps in the literature that this PhD sought to address is describing how casemix – the balance of diagnostic groups within an ICU patient population – affects sex balance. This is addressed in chapter 2.

Sex-based equity of access to ICU

The sex imbalance in ICU admissions raises an important question. Is critical illness simply more common among men than women, or are men more likely to be admitted to the ICU than women? This question is important because equity of access, defined as equal use for equal need, is a key principle underpinning the healthcare systems of Australia and New Zealand (73, 74). Researchers have taken different approaches to investigating equity of access to ICU, with somewhat conflicting results.

One approach examines the sex-specific rate of ICU admission among critically ill hospitalized patients, who may be considered the denominator of 'potential ICU patients.' A series of studies from Canada adopted this approach, with somewhat conflicting results (22, 23, 75). In 2007, Fowler and colleagues reported on a cohort of nearly half a million hospitalised patients in Manitoba, finding that among patients over 50 years of age, women were less likely than men to be admitted to ICU, after adjustment for diagnosis and comorbidities (23). Two decades later, Garland and colleagues examined calculated sex-specific rates of critical illness in the general population in Manitoba, finding that the increased rate of ICU admission among men could be attributed to a higher incidence of critical illness in men compared to women (22). More recently, Todorov and colleagues examined a large cohort of hospitalized patients in Switzerland (n=450,948), finding that women were less likely to be admitted to ICU after adjusting for diagnosis and age (17).

Scandinavian researchers adopted a different approach, using surveys of critical care physicians to examine the sex-specific admission thresholds applied in ICU triage decisions. Larsson and colleagues surveyed critical care doctors in Sweden about their approach to ICU admission for a series of hypothetical cases, which were randomly allocated male or female names. They found no evidence of gender bias in the likelihood of ICU admission (76). Zettersten and colleagues repeated a similar study with over 1000 critical care doctors from 75 countries, again finding no evidence that the hypothetical patient's gender affected the likelihood they would be admitted to ICU (77).

A final approach, adopted in this program of research, is to compare the illness severity of sex-based groups at ICU admission and their mortality outcomes following ICU admission. These can be described as assessing 'horizontal' and 'vertical' equity (73). Horizontal equity exists when different groups of patients have similar illness severity at admission to ICU ('equal use for equal need'). Vertical equity occurs when groups of patients experience similar outcomes following ICU admission ('unequal use for unequal need'), acknowledging that one group may require a different admission

threshold to achieve the same outcome as another group. A key advantage of this approach is the simplicity of examining the easily identified cohort of ICU patients using familiar metrics such as ICU mortality. However, a limitation of this approach is that it overlooks the 'denominator' of all critically ill patients in hospital or the community.

In summary, it remains unclear whether there is equitable access to ICU between the sexes. Sex-based equity of access to the ICU is addressed obliquely in this thesis, by comparing sex differences in illness severity and mortality of ICU patients. Chapter 3 presents a meta-analysis of studies explicitly examining sex differences in illness severity and mortality in ICU patients. Chapter 4 examines sex differences in illness severity and mortality in the Australia and New Zealand ICU patient population using APD data.

Illness severity at ICU admission

Are women or men more unwell at the time of admission to ICU? Before this program of research commenced, the two largest studies to address this question reached diametrically opposing conclusions. Mahmood and colleagues (2012) examined 261,255 ICU patients in the USA, reporting that women had significantly higher APACHE IV scores at ICU admission (19). In contrast, Samuelsson and colleagues (2015), examined 127,254 patients admitted to Swedish ICUs, finding that women had significantly lower illness severity scores (Simplified Acute Physiology Score II) than men (24). In each study, the unadjusted ICU mortality of women compared to men concorded with their relative illness severity scores at admission, speaking against sex-based differences in the performance of the illness severity models. That is, in the American study, women had higher illness severity scores and higher unadjusted mortality at admission, and in the Swedish study women had lower illness severity scores and lower unadjusted or crude ICU mortality than men.

These conflicting observations may point to different sex-specific ICU admission thresholds in the USA and Sweden. In turn, this may reflect sociocultural differences in

the behaviour of patients and clinicians. The sex differences may also be due to differences in ICU casemix, for example, varying incidence of trauma or cardiac surgery between the two countries.

Given the heterogeneity of previous research findings, we undertook a systematic review and meta-analysis of sex differences in illness severity and mortality of ICU patients (chapter 3). In keeping with the overall approach in this thesis, our review examined studies of broad cohorts of ICU patients with multiple diagnostic groups, rather than studies of individual critical illnesses (e.g., sepsis). We identified 17 studies that explicitly examined sex differences in illness severity. All studies were from high income countries, mostly in North America and Europe. There were no studies from Australia or New Zealand. We found no statistically significant difference overall in the illness severity scores of women and men at ICU admission, though there was a tendency for women to be admitted at a higher illness severity score than men.

Since this meta-analysis, two important studies of sex differences in the illness severity of critically ill patients in Switzerland were published. These large studies both drew upon the Swiss Society of Intensive Care Medicine's Minimal Dataset for ICUs, a compulsory nation-wide clinical registry. Todorov and colleagues examined patients with neurovascular and cardiovascular conditions, finding that among the 77,803 patients (34.7% women) admitted to ICU, women had significantly higher SAPS II scores than men (17). In contrast, Zimmerman and colleagues examined 5078 patients (37% women) with sepsis or septic shock, finding that women had SAPS II scores compared to men at the time of ICU admission (78). In both studies, the opposing sex difference in illness severity was more significant in the younger cohort of patients. The starkly contrasting findings from these studies based on the same national clinical registry suggest that sex differences vary significantly between diagnostic groups of ICU patients.

In summary, previous studies of sex differences in illness severity in ICU patients report conflicting findings, variously attributed to differences in casemix, admission thresholds, differences in illness severity scores and sociocultural context. Prior to this

program of research, there were no published studies from Australia and New Zealand examining this issue. Taken together, these findings underscore the importance of describing sex differences in the illness severity of the local population of ICU patients in Australia and New Zealand.

Mortality following ICU admission

Are men or women more likely to survive their critical illness? Once again, it is difficult to offer a clear answer this deceptively simple question. The two largest studies prior to my research both reported no difference in the adjusted mortality of women compared to men. However, these studies reported outcomes at different time points: Mahmood and colleagues reported ICU mortality, whilst Samuelsson and colleagues reported mortality at 30 days. They also adjusted for different variables in their mortality models; the study by Mahmood and colleagues did not adjust for ICU admission diagnosis. Neither study adjusted for clinical orders to limit the intensity of medical treatment, otherwise known as limitation of medical treatment (LoMT) orders.

Our systematic review and meta-analysis identified 20 studies examining sex differences in mortality (chapter 3). Mortality was reported at a variety of different timepoints, from ICU discharge to 15 months after ICU admission, limiting comparison between studies. Among studies that adjusted mortality for two or more important confounders (including age, admission diagnosis, illness severity, and comorbidities), women had higher adjusted mortality than men at ICU discharge and at 12 months or more post discharge, and similar mortality at other time points. However, in a sensitivity analysis that excluded studies at high risk of bias, there was no sex difference in mortality at any timepoint.

Prior to this program of research there were no studies from Australia and New Zealand examining sex differences in mortality in diagnostically broad groups of ICU patients. Thompson and colleagues examined patients with sepsis admitted to Australia and New Zealand ICUs, finding that women had better survival than men for up to three years following the initial sepsis episode (79).

In 2023, Merdji and colleagues published a narrative review on the role of sex and gender in critical illness, again highlighting the inconsistencies in illness severity and mortality of women compared to men across different studies (80). They attribute these disparate findings to differences in casemix and sociocultural differences between study populations, identifying the sociocultural context as a dominant factor driving sex differences in the ICU patient population. This reinforces the importance of describing sex differences in the local Australia and New Zealand context, as our sociocultural context is different to that of the high-income countries in Europe and North America where most previous studies were performed.

In summary, the literature does not show a clear sex difference in mortality following critical illness in the ICU patient population. Sex differences in mortality varies across different critical illnesses; this observation informed our study of sex differences in mortality across diagnostic groups (chapter 4).

Limitation of medical treatment orders

In addition to illness severity and patient factors, the presence of a pre-existing limitation of medical treatment (LoMT) order is associated with mortality (81). Among ICU patients, women are more likely than men to have a limitation of medical treatment, also known as a limitation to life-sustaining treatment order (81-83). Women are also more likely to have LoMT orders established if hospitalised with a stroke or cardiac arrest (84-86). Therefore, any sex differences in ICU admission, treatment, or mortality may partly reflect sex differences in the incidence of LoMT orders.

Limitation of medical treatment orders may be based upon patient preferences, defined by the treating clinicians based on the perceived utility of medical therapy, or a combination of these factors. It is uncommon for a critically ill patient to be able to meaningfully participate in discussions regarding their treatment at the time of ICU admission. Therefore, clinicians most commonly ascertain the patient's values and treatment preferences through discussion with a surrogate decision-makers. Of note,

women admitted to the ICU are less likely than men to have a well-informed surrogate decision maker to act as their advocate, as they are more likely to be widowed or unmarried (75). Some patients have completed a formal advanced care directive outlining their preferences for treatment prior to their ICU admission, however this remains uncommon (87). Rubio and colleagues found that the vast majority of LoMT orders were established by clinicians based upon their assessment of the potential benefit (or lack thereof) associated with invasive treatment (87). Therefore, sex differences in LoMT orders may reflect sex differences in patient's preferred treatment intensity, their surrogate's perception of their preferences, the clinician's perception of their prognosis or some combination of these factors.

Few previous studies had considered LoMT orders as a potential confounder to sex differences in the ICU patient population. Therefore, we considered pre-defined LoMT as a potential confounder in our studies of sex differences in mortality and treatment.

Sex differences in vital organ support

There are quite consistent findings in the literature on sex differences in the treatment of ICU patients: women receive less vital organ support than men (20, 21, 23, 88, 89).

We considered three domains of treatment in our systematic review and meta-analysis: mechanical ventilation, renal replacement therapy and length of stay. As presented in chapter 5, we found that women received less treatment than men across each of these domains. Subsequent studies replicated these findings, and in addition reported women were also less likely to receive vasoactive medication than men (17, 90). In contrast, a US study published in 2023 observed that patient race but not sex was associated with intubation for the provision of mechanical ventilation (91).

Regarding other domains of treatment. Studies from both Germany and the USA found that women were less likely to receive ECMO than men (18, 92). Other researchers examined global treatment intensity scores (for example the therapeutic intervention

scoring system) to examine the treatment provided to ICU patients, again finding that women received less intensive treatment overall (21, 29).

Chapter 6 of this thesis provides the first description of sex differences in vital organ support for ICU patients in Australia and New Zealand, with an analysis that also considers limitations of life-sustaining therapy established prior to ICU admission. In addition, this study examines the association between sex differences in treatment and patient outcomes following critical illness.

Sex representation in research

Women were historically entirely excluded from clinical trials examining cardiovascular disease, even though cardiovascular disease is the leading cause of death for women worldwide (4-7). Therefore, key interventions such as the use of aspirin for the primary prevention of myocardial infarction were recommended in clinical practice prior to evidence of their efficacy in women. Sixteen years later, the Women's Health Study examined the effect of aspirin in the primary prevention of major cardiovascular events in nearly 40,000 women. Contrary to the findings of the landmark all-male Physician's Health Study, this trial found that aspirin was not effective in preventing myocardial infarction or cardiovascular death overall in women, but was helpful for the subgroup aged over 65 years (93). Other studies suggested that major drug classes used for cardiovascular disease including angiotensin-converting enzyme inhibitors and statins have different efficacy and/or side effect profiles in women (12).

The major national research bodies in the USA and Australia introduced policies to ensure adequate inclusion of women and other under-represented groups, in clinical trials (94, 95). Overall, sex-based representation in clinical trials has improved, with women now composing the majority of all participants in clinical trials conducted in the USA (96). However, women remain under-represented in some fields of clinical research including oncology and cardiology research and are also under-represented in trials of interventions as opposed to preventive strategies (97). The USA Veterans' Affairs Office of Research and Development oversees major clinical trials in which less than 5% of participants are women (98, 99). Women compose a minority of all USA

Veterans (11.3% in 2023), but the sex imbalance in these trials is noteworthy because their results influence the treatment of the general population in both the USA and other countries (100).

Prior to this PhD, representation of women in critical care trials was not well described. One study examined sex balance of in the study populations of critical care trials undertaken in 2011to 2012, finding that most trial participants were men (63.6% male participants) (101). However, this study did not examine the sex balance in the target populations of these clinical trials, and therefore could not assess sex-based representativeness. Other major studies that examined sex-based representation in clinical trials did not consider critical care as a specific discipline (97, 102, 103). Therefore, we undertook a study examining sex-based representation in critical care trials conducted in Australia and New Zealand (chapter 8), comparing the sex balance of study populations with their respective target populations.

1.5 THESIS OVERVIEW: OBJECTIVES, HYPOTHESES AND STRUCTURE

This thesis aims to comprehensively describe sex differences in the ICU patient population in Australia and New Zealand, across the domains of illness severity, treatment, outcomes, and representation in clinical research.

The key hypotheses underlying this research are the following:

- a sex imbalance exists across all major diagnostic categories of ICU admission
- among ICU patients, women have relatively better outcomes than men in diagnostic groups with a higher percentage of patients who are women, and vice-versa
- women are less likely to receive vital organ support than men
- ICU patients classified as third sex have significantly different admission characteristics, diagnoses, treatment, and outcomes compared to ICU patients classified as female or male.
- women are under-represented in critical care trials, relative to the sex balance of each trial's target population

Chapter 2 describes sex differences in ICU admissions in Australia and New Zealand across the domains of admission diagnosis, age and jurisdiction. This work highlights significant variation in sex balance within different diagnostic groups of ICU patients, which forms the conceptual basis for the subsequent study (chapter 4) examining sex differences in mortality according to ICU admission diagnosis.

The following chapters examine sex differences in illness severity and mortality of ICU patients, in the international research in a systematic review and meta-analysis, (chapter 3), and then examining local Australia and New Zealand data (chapter 4). Chapter 4 also closely examines sex differences in mortality within different diagnostic groups of ICU patients.

Chapters 5 and 6 comprehensively examine differences in treatment provided to critically ill women and men in the ICU. Chapter 5 comprehensively examines the

existing literature in a systematic review and meta-analysis, and then chapter 6 examines the local Australia and New Zealand data.

Chapter 7 describes the epidemiology of ICU patients classified as belonging to a third sex group within the APD. This provides the first published description of a non-male, non-female sex group of ICU patients. It also examines in more detail the limitations of the existing categorisation of sex in critical care registries, which has informed subsequent work to improve the recording of sex and gender in the APD.

Chapter 8 examines sex representation in critical care trials performed in Australia and New Zealand, comparing sex representation within clinical trials endorsed by the ANZICS Clinical Trials Group (CTG) over a 10-year period with sex balance in matched target populations drawn from the APD.

Chapter 9 of this thesis draws together my findings, identifying conclusions and key questions arising from the work.

Chapter 2. Sex differences in ICU admissions in Australia and New Zealand

2.1 ABSTRACT

Introduction: Fewer women than men are admitted to intensive care units (ICUs) worldwide.

Objectives: To quantify the relative contribution of each major diagnostic category to the overall sex balance in ICU admissions in Australia and New Zealand (ANZ). Additionally, to describe changes in the sex balance over time and with patient age.

Methods: Retrospective cross-sectional study of ANZ ICU admissions recorded in the ANZ Intensive Care Society Adult Patient Database between 2005 and 2018. Multivariable logistic regression for the likelihood of female admission considered key explanatory variables: diagnostic category, patient age, admission year, geographic region, hospital type and planned versus unplanned ICU admission.

Results: Overall, 42.3% of 1,616,856 ANZ ICU patients were women (99% CI 42.2 to 42.4%). 247,988 more men than women were admitted to ICU during the 14-year study period. There was a sex imbalance in most diagnostic categories: less than 48% women in 15 of 23 diagnostic categories and greater than 52% women in 4 diagnostic categories ($p<0.001$). Admissions following cardiovascular surgery accounted for over half of the total sex imbalance. The percentage of ICU patients who are women increased linearly from 40.8% in 2005 to 43.6% in 2018 ($R^2=93.1\%$, $p<0.001$). Compared to admission in 2005 the adjusted odds ratio for female admission in 2018 was 1.03 (99% CI 1.01 to 1.06).

Conclusion: There is a significant sex imbalance in ICU admissions in Australia and New Zealand, widespread across the diagnostic categories. Cardiovascular admissions contribute most to the observed preponderance of men. The proportion of female ICU patients is steadily increasing.

2.2 BACKGROUND

More men than women are admitted to intensive care units (ICUs) worldwide (19, 22, 25-27, 104). In studies of sex differences in ICU admissions from North America, the United Kingdom and Europe, the percentage of female patients ranges from 35% to 45% (19, 21-27, 105). This simple observation likely reflects complex sex differences in the incidence, presentation and management of critical illness.

Previous studies focused on quantifying sex differences in illness severity and outcomes from ICU admission, with conflicting results (19, 21, 23-27). These studies highlight two important features of the sex imbalance in ICU admissions that warrant further investigation.

First, the sex imbalance is not evenly distributed across diagnostic categories (21, 23, 27). Some critical illnesses have a marked male predominance – for example, trauma, cardiac surgery and aortic dissection (105-108). Other critical illnesses, such as SAH (subarachnoid haemorrhage) and asthma, are more common in women (109, 110). This raises the question: what is the relative contribution of different disease categories to the overall sex balance in ICU admissions?

Second, there is a wide variation in the reported percentage of female ICU patients in studies performed at different times in different regions of the world. Therefore, it is unclear if this variation is due to differences in casemix, differences in socio-cultural context or changes over time.

This study addressed these issues by systematically describing the sex balance in ICU admissions in Australia and New Zealand. We used the Australia and New Zealand Intensive Care Society Centre for Resource and Outcome Evaluation Adult Patient Data registry (ANZICS CORE APD). Our primary objective was to quantify the relative contribution of each major diagnostic category to the overall preponderance of men admitted to ICU in Australia and New Zealand. Previous researchers have identified a sex imbalance across multiple diagnostic groups of critical illness (26, 27, 105),

therefore we hypothesised that a sex imbalance (<48% or >52% women) existed across all major diagnostic categories of ICU admission. Secondary objectives were to identify the individual diagnoses with the most marked sex imbalance and to describe how the observed sex imbalance varied over time and with patient age.

2.3 METHODS

Population

We undertook a retrospective cross-sectional study of ICU admissions in the ANZICS CORE APD between 1 January 2005 and 31 December 2018. The Adult Patient Database (APD) lists more than 2.4 million ICU episodes since 1993. Presently over 180,000 ICU admissions are submitted every year, estimated to account for 90% of ICU admissions in Australia and 70% of admissions in New Zealand (111). Sex is recorded as part of basic demographic data in this registry, taken from the patient's hospital record.

We excluded patients aged under 17 years; patients with missing diagnoses, sex classification or outcome; and repeat ICU admissions during the same hospital visit. Patients classified as 'intersex or indeterminant sex' were excluded from analysis because this sex classification was only introduced to the registry in 2017.

Diagnostic categories

We considered 23 diagnostic categories based on the Acute Physiology And Chronic Illness Evaluation III-J (APACHE III-J) categories used in the APD [16]. Ten diagnostic groups had both post-operative and non-operative categories: cardiovascular, respiratory, gastrointestinal, neurologic, trauma, metabolic, hematologic, renal and genitourinary, female-specific, and musculoskeletal. The 'sepsis' and 'other' diagnoses had only non-operative categories and 'male-specific' diagnoses had a post-operative category only.

The female-specific diagnostic category included obstetric and gynaecological conditions and the male-specific category included disorders of male urogenital tract. Post-operative admission was defined as admission to ICU directly from the operating theatre or recovery after surgery.

Statistical analysis

Categorical variables are reported as counts with percentages to one decimal place. Given the size of the dataset, to increase robustness we set significance level at 0.01 (p<0.01 indicates statistical significance) and reported 99% confidence intervals. The exact binomial test was used for comparisons of binary data and chi-square tests for other categorical variables. We defined a significant sex imbalance within diagnostic categories as less than 48% or greater than 52% women. The relative contribution of each diagnostic category to the overall sex imbalance was calculated as the absolute difference between male and female admissions in the diagnostic category divided by the absolute difference between total male and total female admissions in the entire dataset.

Simple linear regression was used to assess the association between the percentage of female patients and year of admission. Multivariable logistic regression calculated the odds of an ICU admission being a female patient. Therefore, odds ratios greater than one are associated with female ICU admission and odds ratios less than one associated with male ICU admission. The multivariable model included the following categorical variables identified *a priori* as potentially associated with sex balance: APACHE III-J diagnostic category (post-operative and non-operative subcategories considered separately), patient age (ten-year cohorts), admission year, hospital type (tertiary, metropolitan, rural/regional or private), geographic region (New Zealand or individual states/territories of Australia) and planned versus unplanned ICU admission.

Sex-specific diagnostic categories were excluded from the multivariable logistic regression. Year of admission was firstly modelled as a categorical variable and secondly modelled as a continuous variable to enable assessment of annual change over

time. Results are reported as odds ratios (99% CI) with a Wald chi-square statistic enabling a comparison of the relative significance of variables in the model.

Statistical analyses were performed with STATA 16.1 (Statacorp, College Station, TX, USA) and SAS 9.4 (SAS Institute).

Ethics

Ethics approval for this study was granted by the Alfred Hospital Human Research Ethics Committee (HREC 712/18).

2.4 RESULTS

In the 14 years from 2005 to 2018, there were 1,800,523 ICU admissions in the ANZICS APD. After exclusions, 1,616,856 patients were examined in this study (see Figure 2.1). In total, 326 patients were excluded due to missing sex classification and 111 patients were classified as intersex. Intersex patients composed less than 0.1% of admissions in 2017 (24/158,786) and 2018 (87/151,368).

Overall, women accounted for 42.3% (99% CI 42.2 to 42.4%) of the 1,616,856 patients. There were 247,988 more men than women in the dataset. This absolute difference in the number of men and women represents the total sex imbalance.

Figure 2.1: STROBE diagram of progress through stages of analysis

Sex imbalance within diagnostic categories

A sex imbalance was observed in most diagnostic categories (Table 2.1). Less than 48% of patients were women in 15 of 23 categories ($p<0.001$ for all, Table 2.1). More than 52% of patients were women in the two metabolic categories (post-operative and non-operative) and the two female-specific categories (post-operative and non-operative, $p<0.001$ for all). Four categories had similar numbers of men and women: the post-operative musculoskeletal, neurological and hematological categories and the non-operative 'other' diagnostic category.

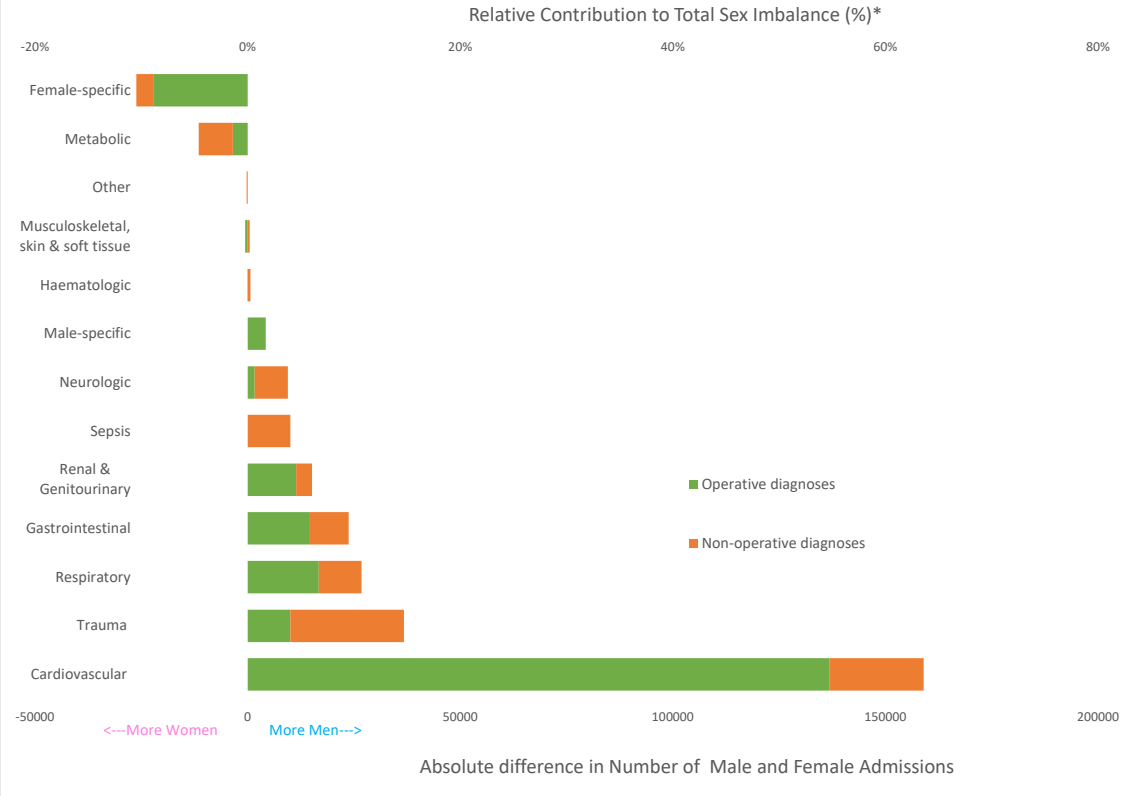
The sex imbalance was not evenly distributed across diagnostic categories, as illustrated in Figure 2.2.

Cardiovascular diagnoses contributed the most to the overall sex imbalance in ICU admissions. Post-operative cardiovascular surgery admissions account for over half (52%) of the total sex imbalance in the dataset; there were 136,868 more men than women in this diagnostic category. After removing cardiovascular surgery admissions from the dataset, 45.8% of remaining ICU admissions were women (99% CI: 45.7 to 45.9%).

Trauma, respiratory and gastrointestinal diagnoses all contributed substantially to the total sex imbalance, accounting for 14.8%, 10.8% and 9.6% of the total imbalance respectively (Figure 2.2). Sepsis diagnoses accounted for only 4.1% of the total sex imbalance: 10,082 more men than women were admitted with sepsis.

The female-specific diagnostic category (n= 26,425) had substantially more admissions than the corresponding male-specific diagnostic category (n= 4355). Aside from female-specific diagnoses, the metabolic categories – including endocrine and thermal emergencies and electrolyte disturbances - had the highest percentage female patients (55.1% overall).

Figure 2.2: Contribution to overall sex imbalance by diagnostic category



*Relative contribution to total sex imbalance = (male admissions– female admissions within diagnostic category)/(total male admissions – total female admissions).

Individual diagnoses with the largest sex imbalance

Aside from sex-specific diagnoses, the diagnoses with highest percentage of female patients were asthma (69.7% women), endocrine surgery (63.6% women) and subarachnoid haemorrhage (63.2% women; Table 2.2). The male-dominated diagnoses were all from the cardiovascular surgery and trauma categories, including endoluminal aortic repair (18.2% women), cervical spine injury (18.3% women) and ruptured aortic aneurysm (18.7% women).

Table 2.1: Female ICU admissions by diagnostic category

Diagnostic category	*Total Admissions n=1,616,856*	*Female Admissions n= 684,434*	*% Female Admissions*
Trauma			
Non-operative	53,224	13,249	24.9
Operative	25,916	7929	30.6
Cardiovascular			
Non-operative	120,883	49,404	40.9
Operative	301,806	82,469	27.3
Renal & genitourinary			
Non-operative	20,710	8505	41.1
Operative	32,330	10,443	32.3
Respiratory			
Non-operative	171,155	80,545	47.1
Operative	72,705	27,995	38.5
Gastrointestinal			
Non-operative	54,498	22,576	41.4
Operative	215,902	100,739	46.7
Sepsis			
Non-operative	103,390	46,654	45.1
Musculoskeletal, skin & soft tissue			
Non-operative	3935	1712	43.5
Operative	87,327	43,951	50.3
Neurologic			
Non-operative	81,241	36,724	45.2
Operative	112,271	55,292	49.2
Male-specific			
Operative	4355	32	0.7
Hematologic			
Non-operative	7182	3258	45.4
Operative	578	292	50.5
Other			
Non-operative	9070	4651	51.3
Metabolic			
Non-operative	99,302	53,681	54.1
Operative	12,651	8050	63.6
Female-specific			
Non-operative	4000	3975	99.4
Operative	22,425	22,308	99.5
TOTAL	**1,616,856**	**684,434**	**42.3**

*Odds ratios adjusted for patient age, admission year, hospital type (tertiary, metropolitan, rural/regional or private), geographic region and planned vs unplanned ICU admission. Sex-specific diagnoses were not modelled.

Table 2.2: Individual diagnoses with the highest and lowest percentage of female admissions

HIGHEST % FEMALE PATIENTS*

Diagnosis	*Diagnostic category*	*Total patients*	*N women*	*% women*
Asthma	Respiratory non-operative	12,990	9050	69.7
Endocrine surgery	Metabolic operative	12,649	8050	63.6
Subarachnoid haemorrhage	Neurological operative	7792	4925	63.2
Subarachnoid haemorrhage	Neurological non-operative	8833	5294	59.9
Metabolic & endocrine disorders†	Metabolic non-operative	18,117	10,472	57.8
Hypertension	Cardiovascular non-operative	2437	1395	57.2
Gastrointestinal obstruction	Gastrointestinal operative	24,190	13,115	54.2
Skin surgery	Musculoskeletal operative	9307	5033	54.1
Drug overdose	Metabolic non-operative	59,084	31,762	53.8
Gastrointestinal Ischemia	Gastrointestinal Operative	5129	2718	53.0

LOWEST % FEMALE PATIENTS*

Diagnosis	*Diagnostic category*	*Total patients*	*n women*	*% women*
Endoluminal aortic repair	Cardiovascular operative	7178	1307	18.2
Cervical spine injury	Trauma non-operative	1428	261	18.3
Ruptured aortic aneurysm	Cardiovascular operative	3101	581	18.7
CAGS	Cardiovascular operative	126,146	24,333	19.3
Burns	Trauma non-operative	3452	711	20.6
Elective AAA repair	Cardiovascular operative	12,617	2669	21.2
Head +/- multi-trauma	Trauma non-operative	21,957	4933	22.5
CAGS + valve	Cardiovascular operative	25,657	6404	25.0
Head +/- multi-trauma	Trauma operative	8290	2086	25.2
Multi-trauma with spinal injury	Trauma Operative	3710	1027	27.7

*excludes sex-specific diagnoses and diagnoses with fewer than 1000 admissions (<0.1% of study population)
†includes electrolyte abnormalities, thermal and endocrine emergencies

Change over time

Over 14 years, the proportion of all ICU patients who were women increased linearly from 40.8% in 2005 to 43.6% in 2018 (Figure 2.3.1). Simple linear regression of the proportion of female ICU patients based on admission year revealed a strong linear association ($p<0.001$, $R^2=93.1\%$). There was a significant increase over time in the relative odds of an ICU admission being a female patient after adjustment in the multivariable model with an annual change in the odds ratio for female admission of 1.004 (99% CI 1.003 to 1.005. $p<0.0001$) (Figure 2.3.2).

Change with patient age

There was a curvilinear relationship between the percentage of female admissions and patient age, with the highest percentage of female patients observed in the cohort aged 30-39 (51.2% women, 99% CI 50.8 to 51.6%) and in the oldest cohort aged 80 and over (46.9% women, 99% CI 46.6 to 47.1%, Figure 2.4.1). The cohort aged 60-69 had the lowest percentage of female patients (37.6% women, 99% CI 37.4 to 37.8%). This curvilinear association between age and sex balance persisted after adjusting for casemix variables including diagnostic category in the multivariable logistic regression (Figure 2.4.2). Compared to those aged less than thirty, the odds ratio for female admission in the cohort aged 60-69 was 0.77 (99% CI 0.76 to 0.78).

Multivariable logistic regression

The variable with the greatest impact on sex balance in our model was diagnostic category (Wald chi-square 41,522, $p<0.001$, Table 2.3), followed by patient age, hospital type, geographic region and year of admission (Wald chi-square 5097, 1294, 189 and 109 respectively, p value <0.001 for all). Planned versus unplanned ICU admission status was not statistically significant (Wald chi-squared 3, $p=0.08$). Compared to metropolitan hospitals, there was a decreased relative odds of female ICU admission at tertiary centres (OR 0.89, 99% CI 0.88 to 0.90), and increased relative odds of female ICU admission at private hospitals (OR 1.03, 99% CI 1.02 to 1.05). Several Australian regions had a significantly lower likelihood of female ICU admission compared to the reference region New Zealand, most notably WA (OR 0.88, 99% CI 0.86 to 0.91) and NT (0.91 99% CI 0.87 to 0.94).

Figure 2.3: Female ICU admissions over time

Figure 2.3.1: Female ICU patients as percentage of all ICU admissions

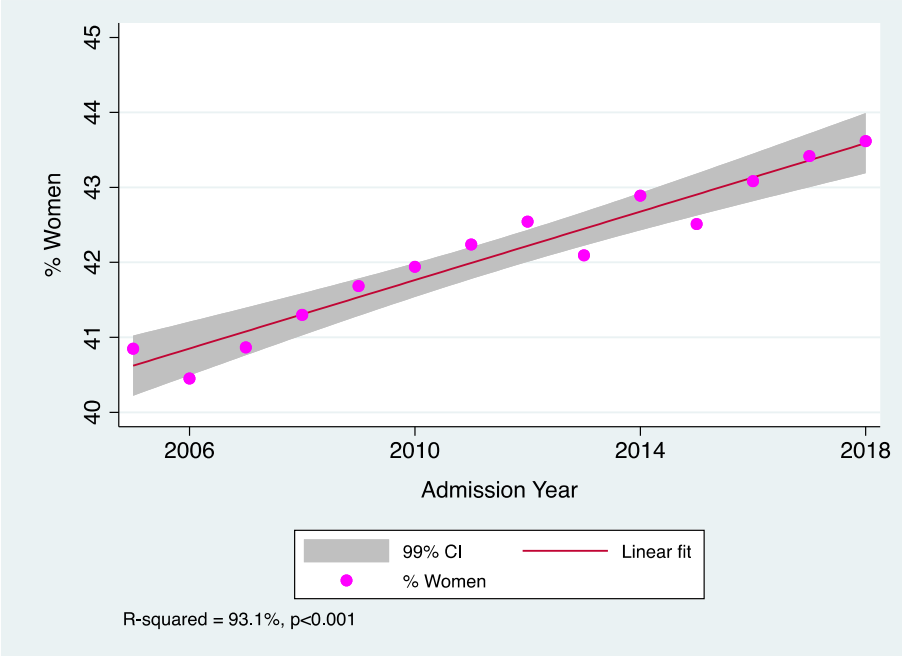
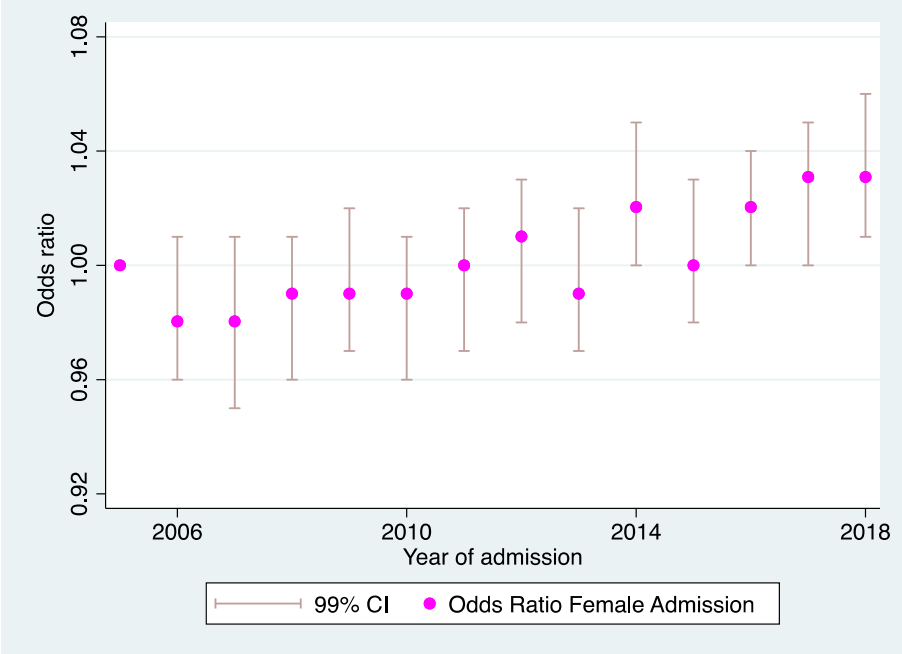


*Figure 2.3.2: Adjusted odds ratio for female ICU admission**



*adjusted for APACHE III-J diagnostic category, patient age, hospital type (tertiary, metropolitan, rural/regional or private), geographic region (state of Australia, or New Zealand) and planned vs unplanned ICU admissions. The year 2005 was used as the reference year.

Figure 2.4: Female ICU admissions by age group

Figure 2.4.1: Female ICU patients as percentage of all admissions by age group

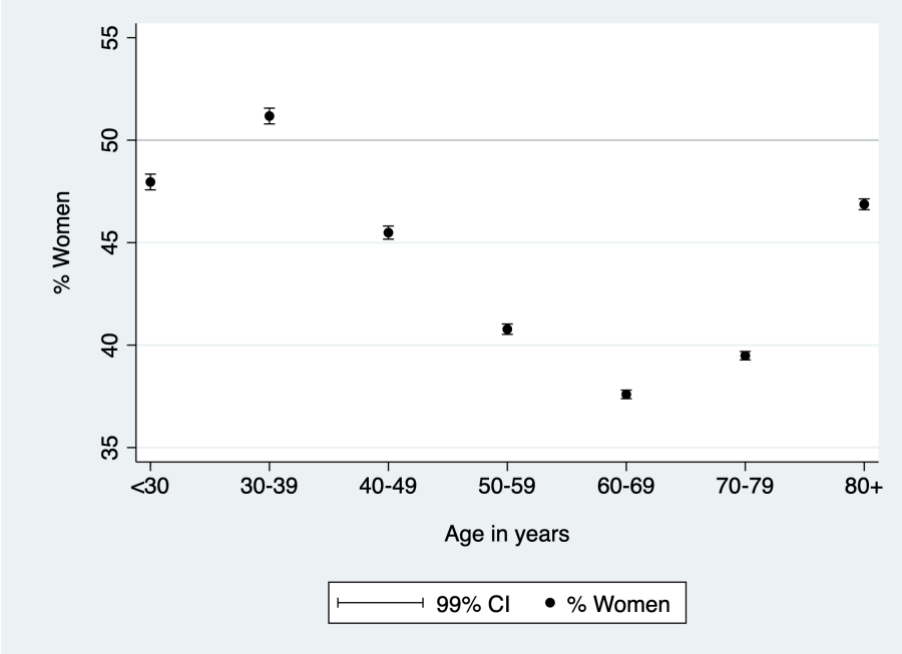
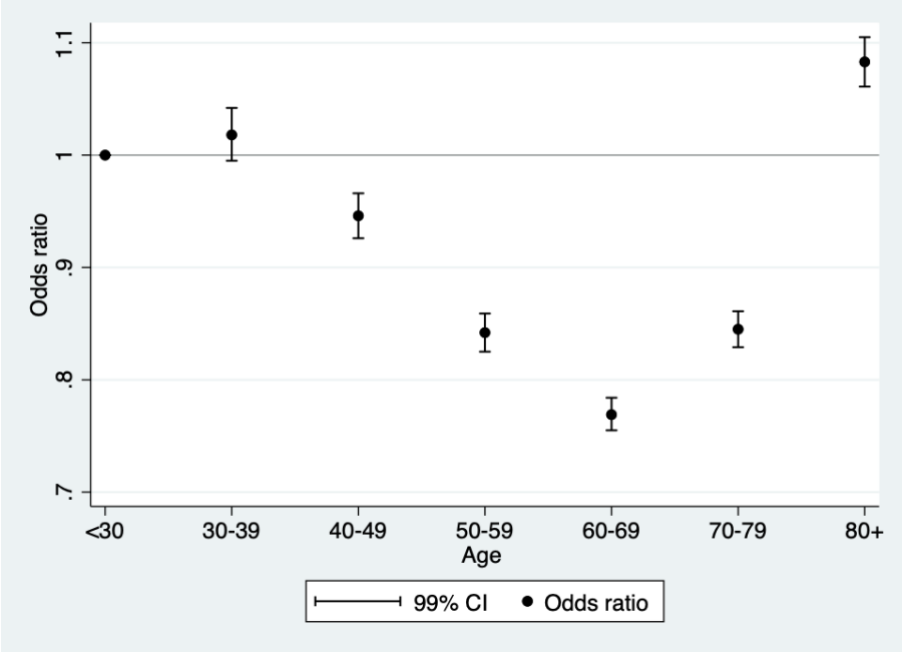


*Figure 2.4.2: Odds ratio of female to male ICU admissions by age group**



*adjusted for APACHE III-J diagnostic category, admission year, hospital type (tertiary, metropolitan, rural/regional or private), geographic region (state of Australia, or New Zealand) and planned vs unplanned ICU admissions

Table 2.3: Multivariable logistic model for female ICU admission

Variable	*N admissions (% female) n=1586076*	*Unadjusted Odds Ratio*	*99% CI*	*Adjusted Odds ratio**	*99% CI*	*Wald chi-square*
Diagnostic category Non-operative						
Cardiovascular	120,883 (40.9)	0.68	0.55-0.84	0.69	0.55-0.85	
Respiratory	171,155 (47.1)	0.87	0.7-1.08	0.88	0.71-1.09	
Gastrointestinal	54,498 (41.4)	0.69	0.56-.086	0.69	0.56-0.86	
Neurological	81,241 (45.2)	0.81	0.65-1.00	0.83	0.67-1.03	
Sepsis	103,390 (45.1)	0.81	0.65-1.00	0.82	0.66-1.03	
Trauma	53,224 (24.9)	0.32	0.26-0.4	0.33	0.26-0.41	
Metabolic	99,302 (54.1)	1.15	0.93-1.43	1.11	0.9-1.38	
Hematologic	7182 (45.4)	0.81	0.65-1.02	0.84	0.67-1.05	
Renal	20,710 (41.1)	0.68	0.55-0.85	0.69	0.56-0.86	
Other	9070 (51.3)	1.03	0.83-1.29	1.01	0.81-1.26	41522 p<0.001
Musculoskeletal	3935 (43.5)	0.75	0.6-0.95	0.75	0.6-0.95	
Operative						
Cardiovascular	301,806 (27.3)	0.37	0.30-0.46	0.39	0.31-0.48	
Respiratory	72,705 (38.5)	0.61	0.50-0.76	0.62	0.5-0.77	
Gastrointestinal	215,902 (46.7)	0.86	0.69-1.06	0.86	0.69-1.06	
Neurological	112,271 (49.2)	0.95	0.77-1.18	0.96	0.77-1.19	
Trauma	25,916 (30.6)	0.43	0.35-0.54	0.43	0.34-0.53	
Renal	32,330 (32.3)	0.47	0.37-0.58	0.48	0.38-0.59	
Musculoskeletal	87,327 (50.3)	0.99	0.80-1.23	0.96	0.77-1.19	
Hematologic	578 (50.5)	Reference		Reference		
Metabolic	12,651 (63.6)	1.71	1.38-2.13	1.73	1.39-2.16	
Age						
<30 years	107,252 (45.2)	Reference		Reference		
30-39 years	104,065 (46.7)	1.06	1.04-1.09	1.02	1.00-1.04	
40-49 years	157,172 (44.4)	0.97	0.95-0.99	0.95	0.93-0.97	5097 p<0.001
50-59 years	246,354 (40.4)	0.82	0.81-0.84	0.84	0.83-0.86	
60-69 years	356,780 (37.4)	0.73	0.71-0.74	0.77	0.76-0.78	
70-79 years	375,028 (39.2)	0.78	0.77-0.8	0.85	0.83-0.86	
80 years & over	239,425 (46.6)	1.06	1.04-1.08	1.08	1.06-1.11	
Hospital type						
Metropolitan	26,504 (46.3)	Reference		Reference		
Tertiary	689,648 (37.9)	0.7	0.70-0.72	0.89	0.88-0.90	1294 p<0.001
Rural	210,833 (45.1)	0.95	0.94-0.97	0.97	0.95-0.98	
Private	424,091 (42.6)	0.86	0.85-0.87	1.03	1.02-.105	

*Odds ratios adjusted for patient age, admission year, hospital type (tertiary, metropolitan, rural/regional or private), geographic region and planned vs unplanned ICU admission. Sex-specific diagnoses were excluded from the model.
p-values refer to the p-value associated with Wald chi-square statistic for each variable.

2.5 DISCUSSION

Key findings

In this comprehensive binational registry-based study we found a substantial sex imbalance in ICU admissions in Australia and New Zealand. Women made up 42.3% of all ICU admissions; nearly a quarter of a million more men than women were admitted to ICU between 2005 and 2018. The sex imbalance was widespread across most diagnostic categories. Cardiovascular diagnoses were the single largest driver of the total sex imbalance.

The percentage of ICU patients who are women increased linearly over time. After adjustment for the pre-specified casemix variables including diagnostic category, age and region, there was a small increase over time in likelihood of an ICU patient being female. Regarding age, the lowest percentage of female patients occurred in the cohorts aged 50-79 years and this pattern persisted in the multivariable model. Admission diagnosis was more strongly associated with sex balance than other variables including age and admission year.

Relationship to previous studies

The percentage of female ICU patients in this study (42.3%) is in the middle of the range reported in previous studies of sex differences in ICU admissions from North America, the UK and Europe (35% to 45% women) (19, 21, 22, 25-27, 105). Most of these studies looked at a modest proportion of ICUs within one or two nations (19, 21, 22, 25-27, 105). Samuelsson and colleagues examined a comprehensive multicenter cohort of 127,254 ICU admissions in Sweden, of whom 43% were women (24). In contrast, our study included the majority of all ICU admissions in Australia and New Zealand across 14 years, with over 5 times the total number of admissions considered in the previous largest study.

Our study is the first to systematically describe sex balance across all diagnostic categories leading to ICU admission. Previous studies reported the casemix for male and female admissions separately rather than reporting sex balance within each diagnostic category (19, 23-25). Other studies examined sex differences within discrete critical illnesses including sepsis and cardiac arrest (27, 59, 112-114).

Our study demonstrates that sepsis – a diagnostic group in which sex differences are relatively well studied – only makes a modest contribution to the overall sex imbalance in ICU admissions. Moreover, the sex imbalance is actually widespread across most diagnostic categories, including diagnoses in which sex differences are not yet well studied.

The preponderance of men among cardiovascular admissions in this study is consistent with previous findings that men have a higher incidence of many cardiovascular diseases including ischemic heart disease and aortic disease (10, 107, 108, 115). Studies from Europe and USA found that between 23.5% and 36.5% of trauma patients admitted to ICU were women and we found a similarly low percentage (26.8%) of female trauma patients (21, 25, 26, 105). In addition, this study found that trauma admissions made a modest contribution to the overall ICU sex imbalance because of the low number of trauma admissions overall.

This study is the first to report a change over time in the sex balance of ICU admissions. Previous studies of sex differences in ICU admissions did not examine changes over time (19, 22, 24-27). The change in sex balance is unlikely to be solely due to changing population demographics: over the study period, the percentage of women in the Australian population increased from 50.3% to 50.4% (116, 117) and in the New Zealand population decreased from 51.0% to 50.8% (118).

Garland and colleagues reported that approximately 80% of the total sex imbalance in ICU admissions in Manitoba, Canada could be attributed to the cohort aged 45-74 (22). Similarly, we found the most prominent sex imbalance in the cohort aged 50-79 years old. Moreover, this persists after adjustment for diagnostic category, suggesting a higher

risk of critical illness *per se* among men in this age group, rather than simply reflecting the varying incidence of diagnoses leading to ICU admission across the lifespan.

Implications of study findings

The finding that sex imbalance exists across most diagnostic categories leading to ICU admission implies a systemic difference in the way that men and women manifest, present with and/or are treated for critical illness resulting from a range of primary organ pathologies. This observation tends to support a broader approach to studying sex differences in critical illness.

Cardiovascular diagnoses were the single largest contributor to the total sex imbalance in ICU admissions, reflecting both the very low percentage of female patients within the cardiovascular diagnostic category and the very high number of cardiovascular admissions. The former can be attributed largely to sex differences in the incidence of cardiovascular disease. However, there are also differences in the way men and women with the same cardiovascular condition are evaluated and treated. For example, women are less likely than men to receive coronary interventions when presenting with acute coronary syndromes and cardiac arrest, and are less likely to be prescribed beta blockers and statins following myocardial infarction (10, 59, 119). Therefore, it is possible that systemic differences in the treatment of men and women with cardiovascular disease also contributed to the observed sex imbalance in ICU admissions.

The percentage of ICU patients who were women increased over time. This increase attenuated in the multivariable model, suggesting that it can be largely attributed to changes in ICU casemix. However, the small increase in adjusted odds of female admission over time suggests that the sex balance is influenced by variables not considered in the model, such as sociocultural factors.

Strengths and weaknesses

This is the largest study of sex differences in ICU admissions to date, drawing from a well-established registry including well over 80% of all ICU admissions in Australia

and New Zealand (111). It is the first to systematically describe the relative contribution of diagnostic groups to the sex imbalance in ICU admissions.

However, this initial descriptive study is limited in scope. We set out to systematically describe the phenomenon of sex imbalance in the ICU patient population particularly focusing on admission diagnosis and change over time and with patient age. We did not consider the denominator of all potential ICU admissions (including aged-based population sex ratios), nor sex differences in illness severity and outcomes – therefore we cannot comment upon equity of access to the ICU. It is possible that the sex imbalance described in this study represents fair and equitable access to the ICU.

We considered sex-specific diagnoses separately in order to assess their impact on the overall sex balance. However, we could not identify all sex-specific conditions because of incomplete diagnostic subcode data. Therefore, some male-specific conditions likely remained in the genitourinary and renal category – for example, cases of prostate cancer coded as 'genitourinary neoplasm' rather than sub coded as 'prostate cancer'. This could have falsely inflated the sex imbalance within the renal and genitourinary category and decreased the size of the 'male-specific' diagnostic category. In addition, there were some male patients with female-designated diagnoses and vice versa (<1% of each category). This could represent coding error or patients whose self-identified gender does not match their biological sex.

2.6 CONCLUSION

Substantially more men than women are admitted to ICU in Australia and New Zealand and a sex imbalance occurs across most diagnostic categories leading to ICU admission. Diagnostic category is a strong predictor of sex balance in ICU admissions. Among the diagnostic categories, cardiovascular diagnoses contribute the most to the overall sex imbalance. The percentage of ICU patients who are women is increasing linearly over time. These findings support further research into sex differences in critical illness and equity of access to the ICU.

Chapter 3. Sex differences in illness severity and mortality in adult intensive care patients: a systematic review and meta-analysis

3.1 ABSTRACT

Purpose: To investigate the association between sex and illness severity and mortality of ICU patients.

Methods: We performed systematic searches of MEDLINE and EMBASE for observational studies of adult ICU patients that explicitly examined the association between sex and illness severity or mortality. We used a random effects model to calculate standardised mean differences in illness severity scores and pooled odds ratios for mortality of women compared to men.

Results: We identified 21 studies with 505,138 participants in total (43.1% women). There was substantial heterogeneity among studies. Only two studies were at low risk of bias overall. At ICU admission, there was a pattern of higher illness severity scores among women (standardised mean difference 0.04, 95% CI -0.01 to 0.09). Women had higher risk-adjusted mortality than men at ICU discharge (OR 1.25 95% CI 1.03 to 1.50) and 1 year (OR 1.08, 95% CI 1.02 to 1.13), however this finding was not robust to sensitivity analysis.

Conclusions: Women tend to have higher illness severity scores at ICU admission. Women also appear to have higher risk-adjusted mortality than men at ICU discharge and at 1 year. Given the heterogeneity and risk of bias in the existing literature, additional studies are needed to confirm or refute these findings.

3.2. INTRODUCTION

Half of the world's population are women, yet women account for only 35-45% of all intensive care unit patients (chapter 2). This raises the important question of whether men and women have equitable access to the ICU. Several studies have addressed this question by examining sex differences in illness severity at ICU admission and survival from critical illness (19, 21, 23, 25, 26, 120), with differing results. Some studies report no difference between the sexes in illness severity at ICU admission (23, 25, 26). Others reported a statistically significant difference in the illness severity of men and women with opposite directions of effect (19, 24). Similarly, while some authors found a higher risk-adjusted mortality for women compared to men (23, 120) other studies found no difference in risk adjusted mortality between the sexes (19, 24). These apparently conflicting findings could reflect methodological differences, or differences in casemix and sociocultural context between studies.

Understanding sex differences in critical illness represents an important opportunity to improve critical care outcomes for both men and women. If sex affects risk of dying from critical illness, intervention thresholds could be tailored specifically for male and female patients. Alternatively, if clinicians unconsciously apply different thresholds for admission of men and women to the ICU, they must be aware of this behaviour in order to attenuate such bias. Understanding the impact of sex on critical illness- for example, the impact of steroid hormones upon host response – may also lead to novel or tailored treatment options.

Accordingly, in this systematic review we aimed to quantify sex differences in illness severity and mortality of adult ICU patients and assess the risk of bias and sources of heterogeneity in the existing literature. We hypothesised that there is no difference between women and men in terms of illness severity at ICU admission or mortality following ICU admission.

3.3 METHODS

The study was conducted according to the Meta-analysis of Observational studies in Epidemiology and the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (121, 122). The study protocol was published prospectively (123). Our study compared female patients (exposure) with male patients (comparator), defined as either sex or gender by the study authors. We adopted this binary approach to defining sex and gender based on the available critical care literature. In addition, we audited whether each study adopted a binary (male/female) or non-binary (>2 sexes) approach to sex or gender. Our outcomes were a) illness severity using any validated illness severity score and b) mortality at any time point reported in the study.

Search strategy and selection criteria

On July 17th, 2020, we undertook a comprehensive database search of MEDLINE (OVID Medline (All)) and EMBASE without language restriction, from the inception of each database – 1946 and 1974 respectively – to the search date. The search strategy used both Medical Subject heading terms and keywords for sex, gender, male and female, and intensive care and critical illness (Figure 3.1). We hand-searched the references of included articles for additional studies to screen.

Figure 3.1: Search strategy; undertaken July 17th, 2020

	OVID Medline (ALL) 1946 to July 15, 2020		EMBASE 1974 to July 15 2020
1	Critical Care/	1	intensive care/
2	Critical Illness/	2	intensive care unit/
3	Intensive Care Units/	3	critical illness/
4	ICU.mp	4	critica* il* .ti.
5	critica* il*.ti.	5	ICU.ti.
6	critical care.ti.	6	critical care.ti.
7	OR/1-6	7	OR/1-6
8	Sex/	8	*sex/ or *sex difference/ or sex ratio/
9	Sex Factors/	9	*gender/ or gender bias/
10	gender.ti.	10	gender.ti.
11	sex.ti.	11	sex.ti.
12	women.ti	12	women.ti
13	men.ti	13	men.ti
14	male.ti	14	male.ti
15	female.ti	15	female.ti
16	or/8-15	16	or/8-15
17	and/7,16	17	and/7,16

We included observational cross-sectional or cohort studies of adult intensive care patients (Figure 3.2 inclusion and exclusion criteria). We included studies that examined the association between sex or gender and at least one of illness severity, mortality or resource use as their explicit primary or secondary objective. Resource use was defined as length of stay in ICU or hospital, use of mechanical ventilation or use of renal replacement therapy. Given the breadth and complexity of our findings, the resource use outcomes are reported separately (Chapter 5). We included studies written in English and available in full text.

We excluded clinical trials because the trial recruitment process may itself confound sex balance in the study population (101). We excluded studies of individual disease or diagnostic cohorts of ICU patients, for example studies of sepsis or trauma patients.

Figure 3.2: Study inclusion and exclusion criteria

Study inclusion criteria

• Observational cross-sectional or cohort studies
• Study participants are adult patients (as defined by study) admitted to an intensive care unit
• Study population is a general ICU population (>1 diagnostic group)
• The study explicitly sets out to examine, as a primary or secondary objective, the association between sex and at least one of:
  ○ illness severity score at ICU admission
  ▪ using a validated illness severity score
  ○ mortality
  ○ resource use:
  ▪ ICU length of stay
  ▪ Hospital length of stay
  ▪ Use of invasive mechanical ventilation
  ▪ Duration of invasive mechanical ventilation
  ▪ Use of renal replacement therapy
• Written in English
• Available in full text

Study Exclusion criteria
• Clinical trials • Study includes paediatric patients and the results for adults and paediatric patients are not reported separately • Study includes non-ICU (coronary care unit patients or general hospital admissions) and the results of ICU patients are not reported separately • Study population is a subset of general ICU population defined by disease or diagnostic group/s • Duplicated cohort. Where the same cohort is reported twice within ten years, we include the study with the most data on sex differences in illness severity, mortality and/or resource use.

Data extraction

Two authors (LM and RV or VA) independently screened the title and abstract of all articles identified in the electronic search. Then the same authors (LM and RV or VA) independently reviewed the full text of potentially eligible articles to confirm eligibility, recording the reason for excluding any article at this stage. For articles published in languages other than English we screened the title and abstract using English translation if available. If there was no full text version published in English, the article was excluded at full text screening. Another author (AH) resolved disagreements arising at either stage of screening. We extracted data independently and in duplicate (LM and RV or VA) and contacted the authors for clarification of data that was not presented suitably for inclusion in the meta-analysis.

Risk of bias assessment

Two reviewers (LM and RV or VA) independently assessed the risk of bias for each selected study using a modified Newcastle-Ottawa scale (Figure 3.3, (124)). This tool quantifies risk of bias (low, high, or unclear) across multiple domains including the representativeness of study population, comparability of exposed and comparator cohorts and outcome bias including the method of ascertaining outcomes and completeness of outcome data. We resolved disagreement between reviewers through discussion.

Figure 3.3: Modified Newcastle-Ottawa Scale – Risk of bias assessment tool for systematic reviews (chapters 3&5)

Selection	
1) Representativeness of the cohort within study population	
Low	Truly representative of the average adult ICU patient: consecutive recruitment of all ICU patients and no major exclusion criteria.
High	Selected group of adult ICU patient. Major exclusion criteria used, for example, excluding some major diagnostic groups
Unclear	No description of the derivation of the cohort
2) Selection of the non-exposed cohort	
Low	Non-exposed (male) cohort drawn from same population as exposed (female) cohort
High	Non-exposed (male) cohort drawn from a different population to exposed cohort
Unclear	No description of populations from which exposed and unexposed patients drawn from
3) Ascertainment of exposure: female patients vs male patients	
Low	Sex or gender ascertained from hospital records or database with clear description of process of recording sex or gender information in this database or record.
High	Inconsistent method of obtaining sex/gender information (for example multiple different methods used)
Unclear	No description or unclear description of how sex or gender ascertained
Comparability of exposed and unexposed cohort	
4) Comparability of cohorts on basis of study design or analysis in assessing mortality:	
Low	mortality estimates (exposed vs unexposed) were adjusted for two or more of age, illness severity, comorbidities or admission diagnosis
High	mortality estimates (exposed vs unexposed) were not adjusted for less than two of age, illness severity, comorbidities or admission diagnostic
Unclear	no description of method to adjust for potential confounders
Outcomes	
5a) Assessment and ascertainment of mortality	
Low	mortality ascertained using a high-quality database* or recorded prospectively from hospital records. If mortality outcome AFTER hospital discharge this is confirmed via registry follow up or personal follow up of patient, next of kin or healthcare provider (e.g. GP).
High	mortality ascertained from database without high quality audit and governance, OR no process described for ascertaining mortality outcomes after hospital discharge (if relevant)
Unclear	no description of how mortality was ascertained or obtained from database with unclear audit and governance
5b) Completion of follow up of cohorts (mortality)	
Low	Complete follow-up or <10% subjects lost **and** appropriate description and treatment of missing data
High	Follow up rate <90% and/or missing data treated in way that is likely to introduce bias (eg. sex ratio in lost to follow up >10% different to sex ratio in study population)

Unclear	No description of loss to follow up or treatment of missing data.

6a) Assessment and ascertainment of illness severity score

Low	validated illness severity score recorded from a high-quality database or prospectively collected from hospital records.
High	unvalidated illness severity score or individual physiologic parameter (e.g. P/F ratio) OR obtained from database without high quality audit or governance
Unclear	no description of how illness severity was scored or obtained from database with unclear audit and governance

6b) Completion of follow up of cohorts (illness severity)

Low	<10% participants had incomplete illness severity data and appropriate description and treatment of missing data
High	>10% patients incomplete illness severity data and/or missing data treated in way that is likely to introduce bias (e.g. sex ratio of those with incomplete illness severity data >10% different to sex ratio in study population)
Unclear	No description of incomplete illness severity data or treatment of missing data.

5a) Ascertainment of treatment (treatment outcomes – chapter 5)

Low	Length of stay, mechanical ventilation and/or RRT use obtained from a database with high quality audit and governance or prospectively collected from hospital record.
High	Length of stay, mechanical ventilation and/or RRT use obtained from database without high quality audit and governance
Unclear	No description of how length of stay, duration of mechanical ventilation or RRT ascertained or obtained from database with unclear audit and governance

5b) Completion of follow up of cohorts (treatment outcomes – chapter 5)

Low	<10% participants had incomplete treatment data and appropriate description and treatment of missing data
High	>10% patients had missing or incomplete treatment data and/or missing data treated in way that is likely to introduce bias
Unclear	No description of incomplete treatment data or approach to missing data.

*Database with high-quality audit and governance defined by at least 3 of:

-transparent data governance arrangements
-data is prospectively collected for registry
-data collectors trained in data collection
-data is verified or audited in a proportion of the registry regularly

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Statistical Analysis

We performed meta-analysis using an inverse variance random effects model. For illness severity scores – continuous variables with differing scales – we calculated the standardised mean difference for women compared to men expressed in units of standard deviation. Therefore, a positive standardised mean difference indicates that women had a higher illness severity score than men. For mortality, we calculated pooled odds ratios for women compared to men (OR <1 indicates that women were less likely to die than men; OR>1 indicates that women were more likely to die than men). We reported 95% confidence intervals (CI) and used a two-sided p-value of <0.05 to indicate statistical significance.

Medians and interquartile ranges were converted to means and standard deviations using the method of Wan and colleagues (125). One study (68) reported data for trauma and non-trauma cohorts separately; these cohorts were combined using the method recommended by the Cochrane collaboration (126). Converted data is denoted within the tables.

We assessed statistical heterogeneity with the I^2 statistic using the following threshold values: > 75% – high statistical heterogeneity; 50-75% – moderate statistical heterogeneity; 25-50% – low statistical heterogeneity. We visually assessed the likelihood of publication bias using a funnel plot.

We pre-specified a sensitivity analysis excluding studies at high risk of bias in one domain or more and the following subgroup analyses: age, diagnostic categories, illness severity score and region of the world. Statistical analysis was performed using Revman 5.4 (Review Manager Version 5.4. The Cochrane Collaboration, 2020).

3.4 RESULTS

Study selection

We identified 3534 unique publications in our searches of Medline and EMBASE. Overall, 3455 publications were excluded at title and abstract screening (Figure 3.4). We assessed the full text of the remaining 79 publications, identifying 21 studies that fulfilled the inclusion criteria. Of these, 20 papers had data suitable for inclusion in meta-analysis.

Characteristics of included studies

Table 3.1 summarises characteristics of the included studies. Ten studies were from Europe (predominantly Western or Northern Europe), 6 from USA, 3 from Canada and 1 each from UK and Taiwan.

The median study population was 2087 (range 241 to 261,255) patients. Eight studies used established national or multi-centre registries, 9 were single centre studies and 5 studies examined data from either two or three ICUs. A single registry-based study from the USA contributed more than half of the total participants (n=261,255(19)).

When referring to the key exposure of patient sex or gender, 6 studies used the term sex, 14 studies used the term gender and one study referred to ‘sex or gender’. No study considered a third or non-binary sex or gender.

Figure 3.4: Study selection

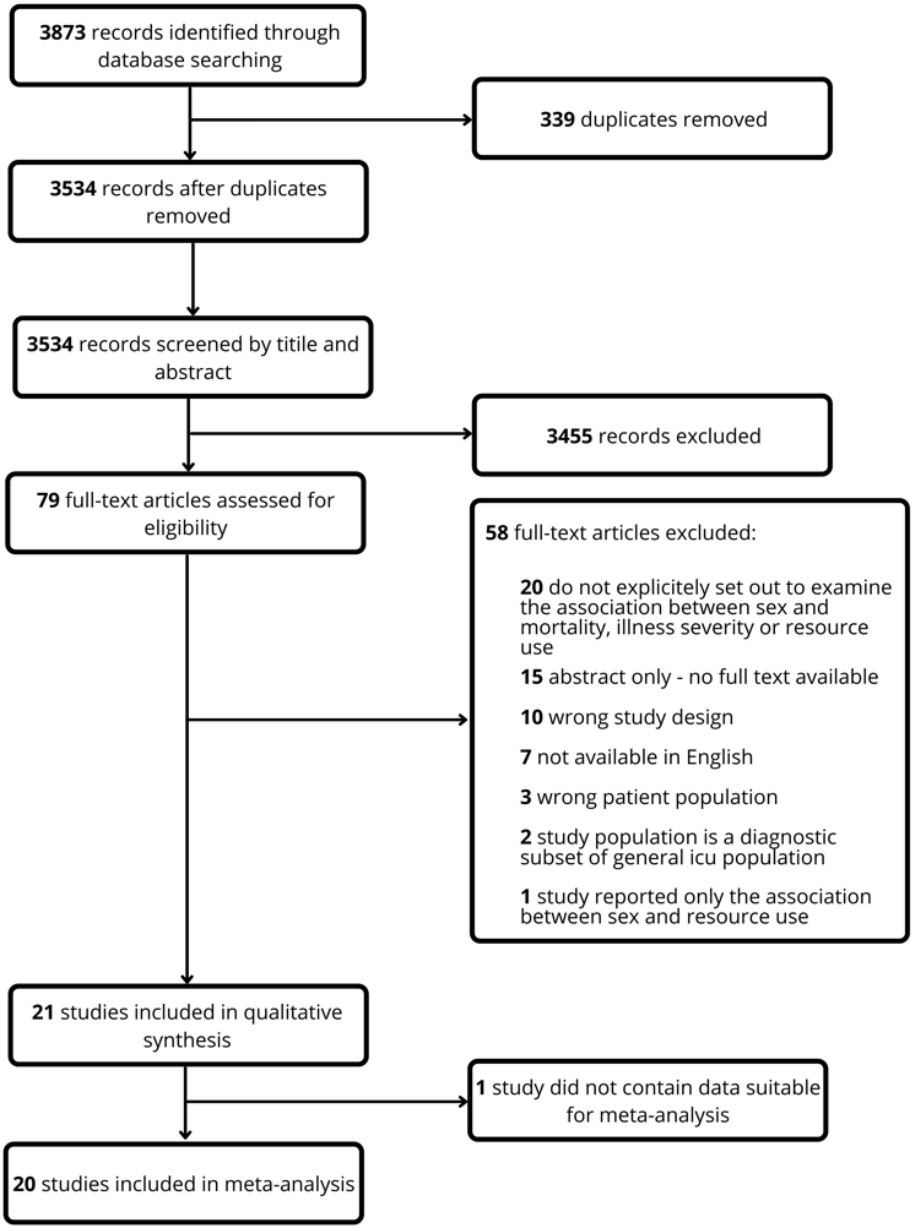


Table 3.1: Characteristics of included studies

Author, year	*Country*	*Exposure term*	*Study design*	*No. of ICUs*	*Study population*	*% women*	*Primary Outcome*
Akgun 2010 (69)	USA	Gender	Prospective	1	309	53.1	Resource use
Combes 2009 (127)	France	Gender	Retrospective	1	1341	34.1	Mortality
Epstein 1999 (128)	USA	Gender	Prospective	1	580	43.1	Mortality
Fowler 2007 (23)	Canada	Sex	Retrospective	13	24778	39.8	Mortality
Girotti 1986 (129)	Canada	Sex	Prospective	1	481	35.1	Mortality
Guidry 2014 (68)	USA	Sex	Prospective	2	2291	34.7[†]	Mortality
Hollinger 2019 (25)	France & Belgium	Gender	Prospective	28	2087	34.8	Mortality
Karlovic 2013[*] (130)	Croatia	Sex	Retrospective	1	288	35.4	Mortality
Kollef 1993 (71)	USA	Gender	Prospective	3	246	31.3	Mortality
Kollef 1997 (70)	USA	Gender	Prospective	2	357	52.9	Mortality
Lipes 2013 (131)	Canada	Sex	Retrospective	2	241	39.0	Mortality
Mahmood 2012 (19)	USA	Gender	Retrospective	Many	261255	44.8	Mortality
Nachtigall 2011 (29)	Germany	Gender	Prospective	3	709	43.6	Mortality
Raine 2002 (27)	UK	Gender	Prospective	91	11704	41.8	Mortality
Reinikainen 2005 (26)	Finland	Gender	Prospective	18	24341	38.3	Mortality
Romo 2004 (120)	Belgium	Sex	Retrospective	1	4420	35.9	Mortality
Samuelsson 2015 (24)	Sweden	Gender	Retrospective	65	127254	43.2	Mortality
Shen 2011 (20)	Taiwan	Gender	Retrospective	Many	5882	36.9	Resource use
Valentin 2003 (21)	Austria	Gender	Prospective	31	25998	41.7	Mortality
Vezzani 2011 (132)	Italy	Gender	Retrospective	1	1978	36.2	Mortality
Zettersten 2020 (105)	Sweden	Sex and gender	Retrospective	1	8598	36.5	Resource use, mortality
TOTAL					**505,138**	**43.1**	

[*]did not contain data suitable for meta-analysis. [†]trauma and non-trauma cohorts combined.

Characteristics of study participants

The 21 studies included a total of 505,138 participants, of whom 43.1% were women. The percentage of the study populations who were women ranged from 31.3% to 53.1%.

Sex-disaggregated age was reported in 18 studies. Women were older than men in 9 of the 10 studies that reported a statistically significant age difference between sexes (Table 3.2). Four studies reported sex disaggregated Charlson Comorbidity Scores and 3 found no statistically significant sex differences in comorbidity (20, 23, 25). Zettersten and colleagues reported that men had slightly higher comorbidity scores than women (105).

Table 3.2: Characteristics of included participants: sex and age

Author, year	*Study population (n)*	*% women*	*Mean age women (SD)*	*Mean age men (SD)*	*p value for age difference*
Akgun 2010[*] (69)	309	53.1	75.6 (8.6)	73.7 (8.2)	0.046
Combes 2009 (127)	1341	34.1	63 (16)	62 (14)	0.22
Epstein 1999 (128)	580	43.1	56 (18)	57 (17)	>0.2
Fowler 2007 (23)	24778	39.8	62.3 (18.5)	61 (17.3)	N/A
Girotti 1986 (129)	481	35.1	55.9 (19.6)	57.6 (16.1)	N/A
Guidry 2014[†] (68)	2291	34.7	52.5 (18.4)	47.6 (18.6)	<0.0001
Hollinger 2019 (25)	2087	34.8	63 (51-75) [‡]	63 (51-74) [‡]	0.590
Karlovic 2013 (130)	288	35.4	N/A	N/A	N/A
Kollef 1993 (71)	246	31.3	56.7 (15.6)	62.4 (12.4)	0.0098
Kollef 1997 (70)	357	52.9	62.9 (16.5	61.6 (17.6)	0.480
Lipes 2013[§](131)	241	39	64.7 (N/A)	67.1 (N/A)	0.380
Mahmood 2012 (19)	261255	44.8	63.1 (N/A)	60.6 (N/A)	<0.0001
Nachtigall 2011 (29)	709	43.6	68 (54-78) [‡]	66 (51-72) [‡]	<0.05
Raine 2002 (27)	11704	41.8	N/A	N/A	N/A
Reinikainen 2005 (26)	24341	38.3	60.4 (19.9)	57.8 (17.9)	<0.001
Romo 2004 (120)	4420	35.9	N/A	N/A	N/A
Samuelsson 2015 (24)	127254	43.2	63 (43 - 75) [‡]	64 (47-74) [‡]	N/A
Shen 2011 (20)	5882	36.9	71 (56-80) [‡]	65 (49-77) [‡]	<0.001
Valentin 2003 (21)	25998	41.7	66 (17.4)	59.3 (16.8)	<0.001
Vezzani 2011(132)	1978	36.2	62 (18)	57 (19)	<0.001
Zettersten 2020 (105)	8598	36.5	61 (41-72) [‡]	59 (40-70) [‡]	<0.001
TOTAL	**505138**	**43.1**			

[*]excluded patients aged <60 years; [†]trauma and non-trauma populations combined using method described in Cochrane handbook (126, 133); [‡]median (IQR); [§]sex ratio provided directly by author

Risk of bias

Only two of 21 studies (9.5%) were considered at low risk of bias across all domains (Table 3.3). 11 studies (52.4%) were at high risk of bias in the representativeness domain due to major exclusion criteria. Two studies (9.5%) used unreliable methods to ascertain mortality including attendance or non-attendance at outpatient clinics. It was unclear how the primary outcome was ascertained in 4 studies (19.0%).

Twelve studies (57.1%) did not adequately describe how the key exposure sex or gender was ascertained. One study described how race and menopausal status were obtained by interviewing the patient or their family but did not describe how information regarding patient sex was ascertained (68). The exposed and comparator cohorts – that is, female and male patients – were drawn from the same population in all studies. Most studies (76.2%) adjusted mortality estimates for at least two important confounders (age, illness severity, comorbidities, or admission diagnosis).

A funnel plot for adjusted mortality was asymmetrical, with no small studies reporting favourable outcomes for women compared to men (Figure 3.5). This suggests possible publication or non-reporting bias.

Figure 3.5: Funnel plot

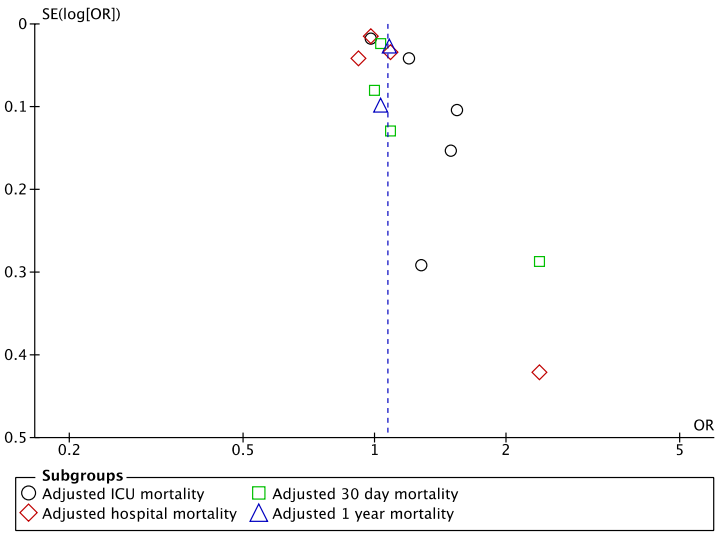


Table 3.3: Risk of bias in 21 included studies

Author, year	*Representative -ness*	*Selection of non-exposed cohort*	*Ascertainment of exposure*	*Comparability of outcome*	*Ascertainment of outcome*	*Follow-up of outcome*
Akgun 2010	High	Low	Unclear	Low	Low	Low
Combes 2009	High	Low	Low	Low	Unclear	Low
Epstein 1999	High	Low	Low	Low	Low	Low
Fowler 2007	Low	Low	Low	Low	Low	High
Girotti 1986	Unclear	Low	Unclear	High	Low	Low
Guidry 2014	High	Low	Unclear	Low	Low	Low
Hollinger 2019	Low	Low	Unclear	Low	Low	Low
Karlovic 2013	High	Low	Unclear	High	High	Low
Kollef 1993	High	Low	Unclear	High	Low	Low
Kollef 1997	Unclear	Low	Low	Low	Unclear	Unclear
Lipes 2013	High	Low	Unclear	Low	High	Unclear
Mahmood 2012	Low	Low	Unclear	Low	Low	Low
Nachtigall 2011	High	Low	Unclear	Low	Low	Low
Raine 2002	High	Low	Unclear	Low	Low	Unclear
Reinikainen 2005	Low	Low	Low	Low	Low	Low
Romo 2004	Low	Low	Low	High	Unclear	Unclear
Samuelsson 2015	Low	Low	Unclear	Low	Low	Low
Shen 2011	High	Low	Low	Low	Low	Low
Valentin 2003	Low	Low	Low	Low	Low	Low
Vezzani 2011	Unclear	Low	Low	High	Low	Low
Zettersten 2020	High	Low	Unclear	Low	Unclear	Unclear

Illness severity

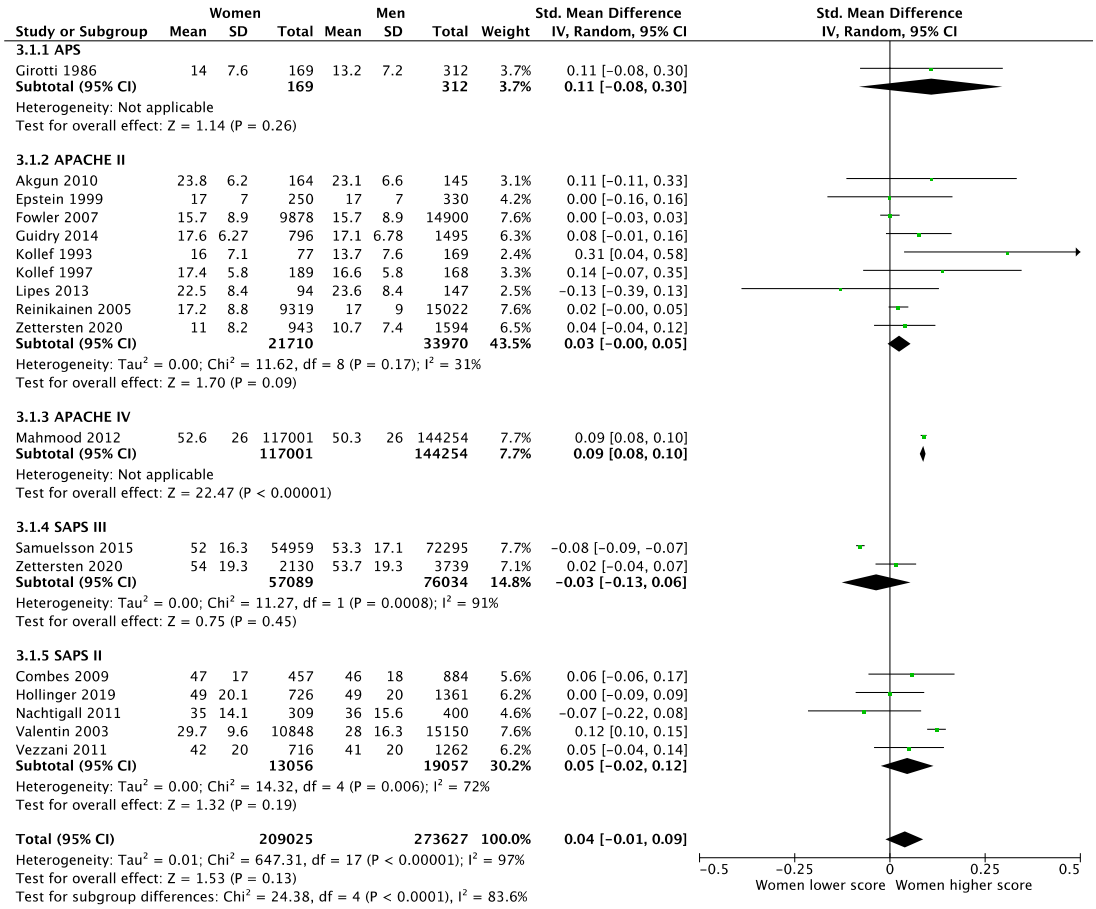
Seventeen studies including 482,652 patients reported sex-disaggregated illness severity at ICU admission. These studies used a variety of illness severity scores including APACHE II, III and IV and SAPS II and III. We treated each of these illness severity scores as subgroups within the meta-analysis.

Figure 3.6 shows the illness severity scores in women relative to men. There was a pattern of increased illness severity scores in women compared to men at ICU admission (standardised mean difference 0.04, 95% CI -0.01 to 0.09).

Heterogeneity was low to moderate within illness severity score subgroups, but high between subgroups (I^2= 83.6%) and overall (I^2=97%). Women had higher illness severity scores than men in most studies. Samuelsson 2015 (n= 127,254) was a notable exception, reporting that women had a statistically significantly lower SAPS III score than men. A post-hoc sensitivity analysis excluding this outlier study decreased the total heterogeneity (I^2=83%) and showed that women had statistically significantly higher illness severity scores than men (Figure 3.7).

In our pre-specified sensitivity analysis excluding studies at high risk of bias in one or more domain, the standardised mean difference in illness severity scores was closer to zero (standardised mean difference 0.03, (95% CI -0.05 to 0.11) Figure 3.8). There were too few studies within each illness severity score to perform sub-group analysis to further explore sources of heterogeneity.

Figure 3.6: Illness severity scores in women relative to men



Fowler, Hollinger, Nachtigall, Valentin: medians and IQR converted to means and SD. Additional data obtained directly from Lipes (% women and men) and Zettersten (total men and women). Zettersten: illness severity score changed from APACHE II to SAPS III during study period, therefore two different scores reported for the early and late cohorts. APS = acute physiology score; SAPS = Simplified acute physiology score; APACHE = acute physiology and chronic health evaluation.

Figure 3.7: Post-hoc sensitivity analysis of illness severity scores excluding outlier study (Samuelsson, 2015)

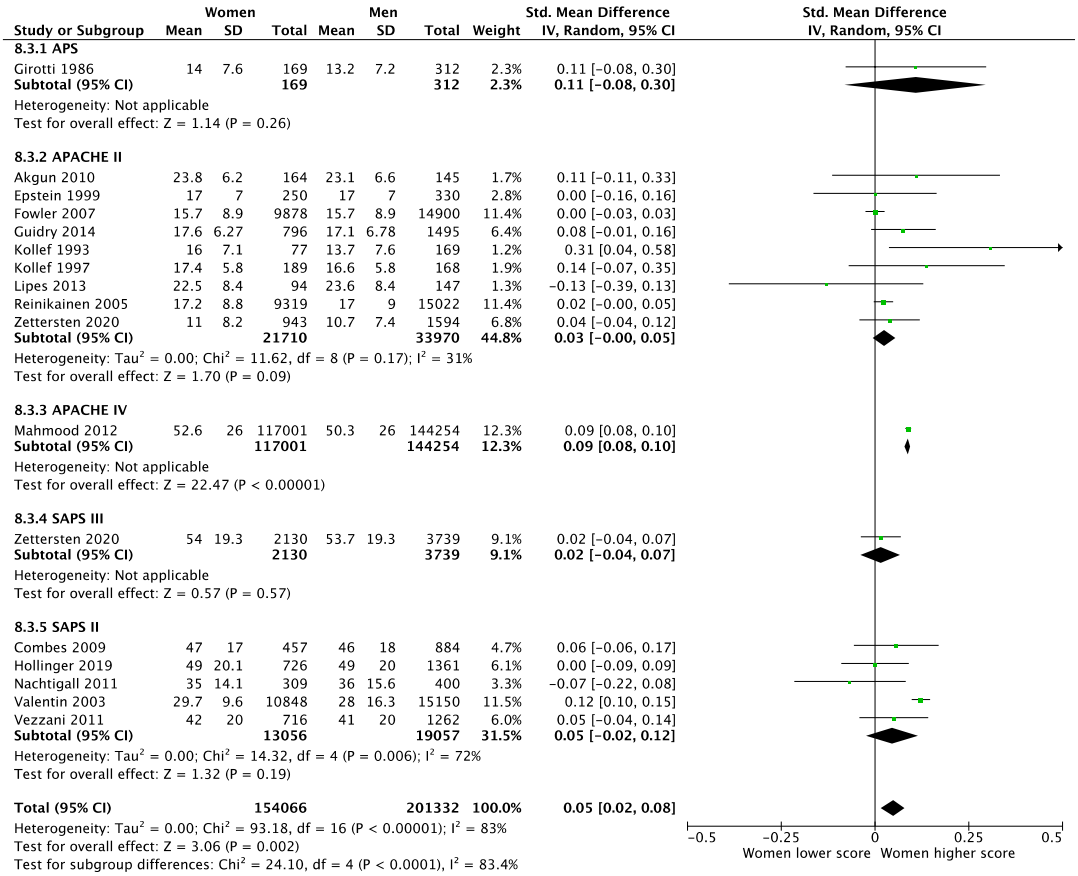
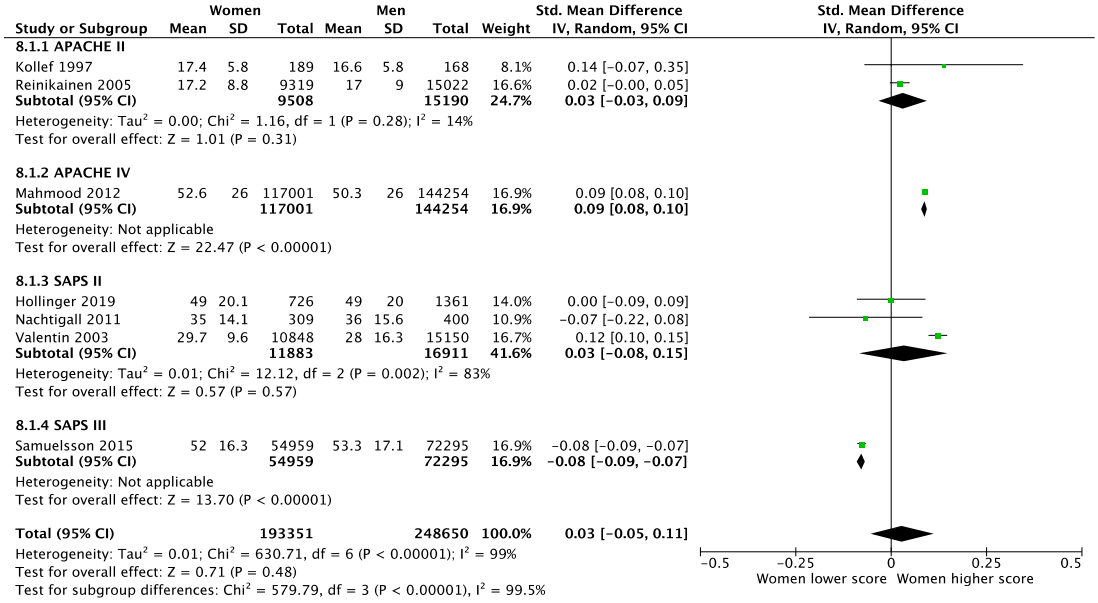


Figure 3.8: Sensitivity analysis excluding studies at high risk of bias: sex differences in illness severity scores



*Excludes studies at high risk of bias in one domain or more: Akgun 2010; Combes 2009; Epstein 1999; Fowler 2007; Guidry 2014; Kollef 1993; Lipes 2013; Vezzani 2011; Zettersten 2020.

Sex differences in mortality

Twenty studies with 501,297 participants reported the unadjusted mortality of male and female participants and 12 studies with 477,826 participants reported adjusted mortality. Mortality was reported at several time points including ICU discharge, hospital discharge, 30 days, 90 days, 1 year and 15 months. These time points were treated as subgroups in the meta-analysis; the 12 month and 15-month outcomes considered as '1 year or more'.

Unadjusted mortality was higher in women compared to men at ICU discharge, although this did not reach statistical significance (ICU mortality OR 1.09, 95% CI 1.00 to 1.18). There was no statistically significant difference between the sexes in unadjusted mortality at other time points (Figure 3.9).

Adjusted mortality (Figure 3.10) was higher in women compared to men at ICU discharge (OR 1.25 95% CI 1.03 to 1.50) and at 1 year or beyond (OR 1.08, 95% CI 1.02 to 1.13). There was no difference in adjusted mortality between men and women at other time points (hospital mortality OR 1.00, 95% CI 0.92 to 1.10; 30-day mortality OR 1.09, 95% 0.93 to 1.28). Statistical heterogeneity was moderate to high at all timepoints.

In the pre-specified sensitivity analysis excluding studies at high risk of bias in one or more domain, there were no statistically significant differences in risk-adjusted mortality between sexes at any time point (6 studies; 441,292 participants, see Figure 3.11). Given the small number of studies reporting adjusted mortality at each timepoint, we did not undertake further subgroup analysis.

Figure 3.9: Unadjusted mortality of women compared to men

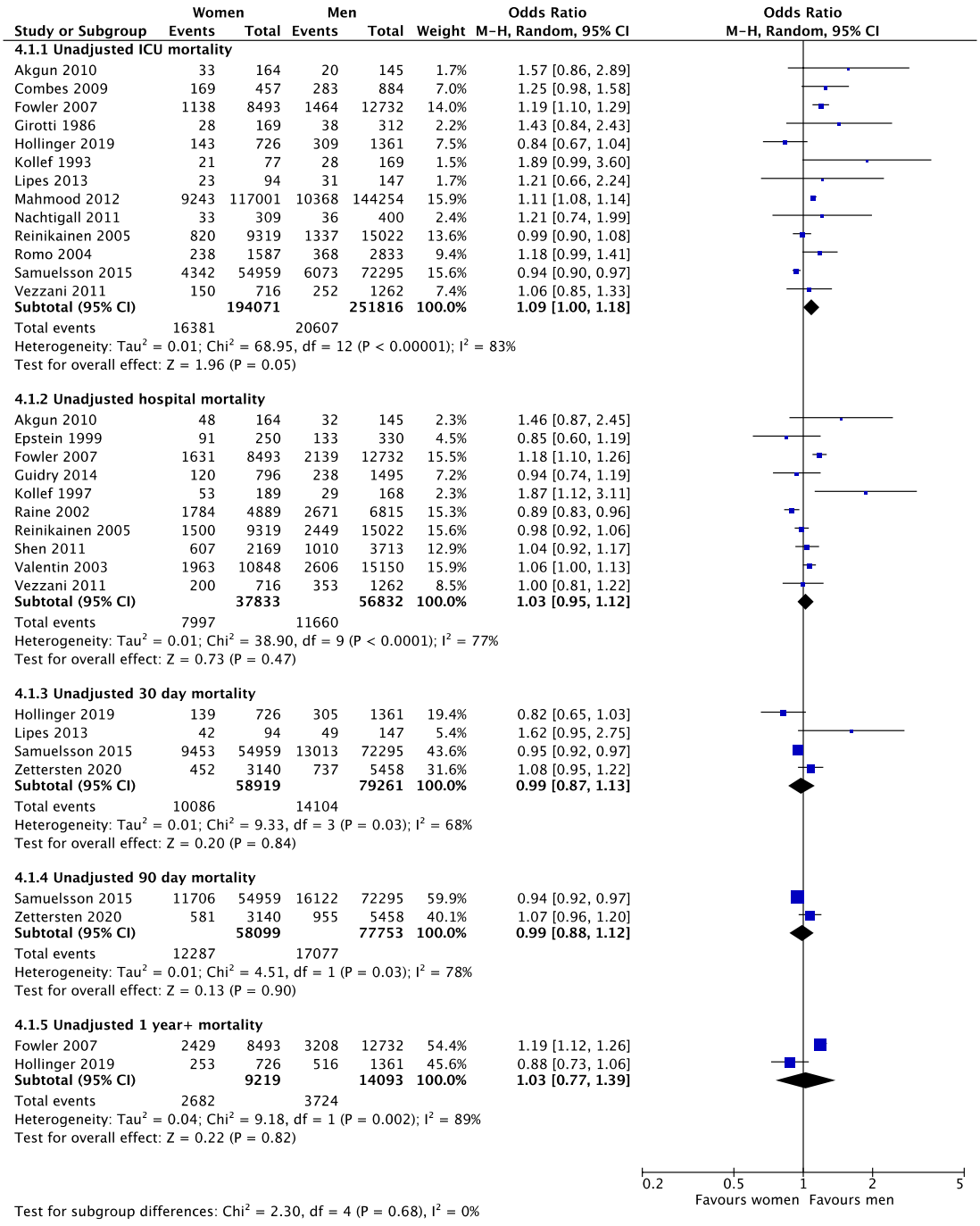
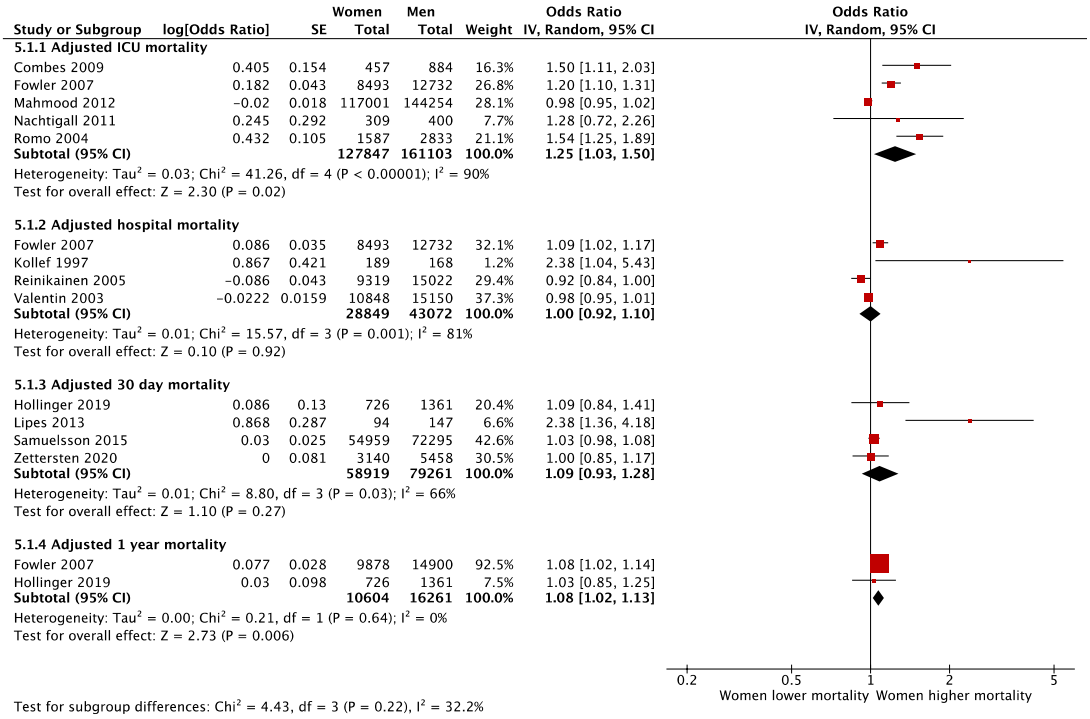
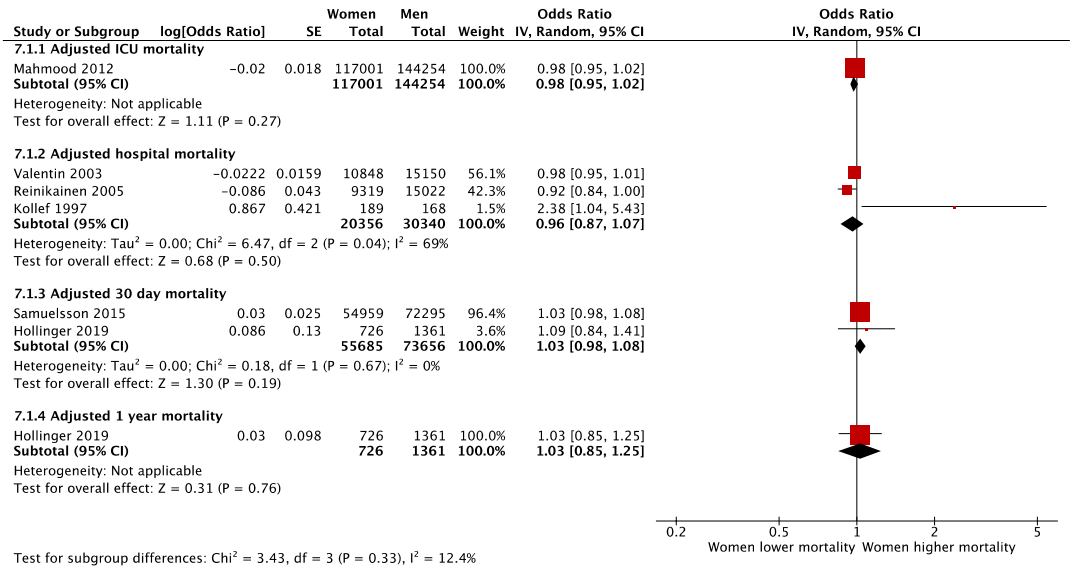


*Figure 3.10: Adjusted mortality of women compared to men**



*each study adjusted mortality for at least one of: illness severity, age, diagnostic group or comorbidities.

Figure 3.11: Sensitivity analysis excluding studies at high risk of bias: adjusted mortality



*excludes studies at high risk of bias in one domain or more: Combes 2009; Fowler 2007; Lipes 2013; Nachtigall 2011; Romo 2004; Zettersten 2020.

3.5 DISCUSSION

In this systematic review of 21 studies with over 500,000 participants, we found that women had a higher risk-adjusted mortality than men at ICU discharge and at 1 year following ICU admission. Additionally, we found a trend towards higher illness severity in women compared to men at ICU admission. However, many studies were considered at high risk of bias and, upon excluding those studies, there were no statistically significant sex differences in illness severity or outcome of ICU patients.

Few studies in this review were at low risk of bias overall. Several small single-centre studies had a poorly representative study sample, some studies did not adequately adjust for confounders and most studies did not define the key exposure (sex or gender). Our review also highlights the substantial clinical and statistical heterogeneity among these studies: illness severity was assessed using different scores, mortality was assessed at a range of time-points and the studies ranged in size from small single-centre studies to large registry-based studies.

To the best of our knowledge, this is the first systematic review and meta-analysis examining sex differences in illness severity and outcomes of a broad cohort of ICU patients. In contrast, previous systematic reviews have considered specific ICU diagnostic groups including out-of-hospital cardiac arrest, sepsis, cardiac surgery and, more recently, severe COVID-19 disease (57, 107, 134, 135).

Implications of study findings

Our finding that women tend to have higher illness severity scores than men at ICU admission raises two possible implications. First, it could reflect the fact that women were actually sicker than men – at higher risk of death – at the time of ICU admission. Our finding that women had higher mortality at ICU discharge than men lends support to this implication. This could indicate that a different threshold may be applied to male and female patients assessed for ICU admission.

Second, this finding could reflect the fact that illness severity scores are not sex-adjusted. Many of the physiological parameters included in the scores have different normal ranges for men and women. For example, the APACHE II score includes mean arterial pressure, creatinine and hematocrit, all of which have different normal ranges for men and women (136-138). This could be remedied by adding sex as an explanatory variable in illness severity models or using sex-adjusted thresholds for each parameter.

The trend towards higher illness severity in women was quite consistent across illness severity score subgroups, with the exception of a Swedish study that reported lower SAPS III scores among women than men (24). This large study (n = 127,254) was judged at low risk of bias overall. Of note, it was the only large registry-based study in which women had a lower median age than men. This highlights the fact that the illness severity scores in this review include an age-based points system, which may explain the tendency for women to have higher illness severity scores overall and is likely related to the finding that the women were older than men on average.

Women had slightly higher pooled odds of risk-adjusted mortality than men at all time points, but this only reached statistical significance at ICU discharge and one year. This aligns with the finding of higher illness severity scores in women and speaks against the possibility that risk of death in women is being overestimated by illness severity scores. However, the sex difference in mortality did not persist after excluding studies at high risk of bias. Therefore, we cannot rule out sex differences in mortality favouring women or men.

We found moderate to high statistical heterogeneity (I^2>50%) among results for adjusted mortality, both within subgroups for each timepoint and between subgroups. There were too few studies at each timepoint to further explore sources of heterogeneity through subgroup analysis or meta-regression. This heterogeneity is likely related to variations in casemix, the proportion of female patients and study methodology (e.g., adjusting mortality for formal illness severity score, comorbidities, age and/or admission diagnosis). In addition, it is possible that men and women have different trajectories of recovery or deterioration following critical illness, leading to true sex differences in mortality at different time points following ICU admission.

An unexpected finding of our review is that most studies did not define their key exposure – sex or gender – nor how it was ascertained. In some studies sex or gender was ascertained from the medical record, which may have been self-reported, reported by family members, or designated by clinical or clerical staff. Overall, these studies effectively used the terms sex and gender interchangeably. All 21 studies used a binary definition of sex and gender (male or female). Therefore, they provide no information about the illness severity and outcomes of transgender or gender non-binary ICU patients. There is a shift towards recording sex and gender separately and allowing multiple gender identity options within national census data and electronic health records (139-141). The large Australia and New Zealand Intensive Care Society Centre for Outcomes and Resource Evaluation Adult Patient Database added a non-binary sex option to their registry in 2016 (43). This will provide important information about the health outcomes of gender non-binary ICU patients.

Our review highlights several important gaps in the existing literature on sex differences in ICU patients. The following issues should be considered priorities for future research: sex differences among ICU patients in low and middle-income countries, the outcomes of ICU patients who are intersex or gender non-binary and the impact of sex on validated illness severity scores used for predicting outcome from critical illness.

Strengths and limitations

The key strengths of our review were our comprehensive search strategy and rigorous approach to assessing bias within studies. We identified studies that explicitly addressed sex differences in a broad intensive care population with a large total number of participants. Where data was not presented in a form suitable for meta-analysis, we were able to obtain data directly from authors in most cases.

However, our review also has limitations. Most studies were from resource-rich countries in Europe and North America so our review in not representative of ICUs in other parts of world, especially low and middle-income countries. This may be partly due to our English-language inclusion criteria. However, our search was undertaken without language restrictions and only 7 studies were excluded due to not being published in English. In addition, there was only one study from the UK, and none from Australia or New Zealand, countries that contribute substantially to critical care research published in English. This suggests a genuine paucity of published research into sex differences in ICUs from many regions of the world. Sociocultural context impacts upon gendered risk-taking and healthcare-seeking behaviour, so it is possible that sex differences in critical illness vary across regions in a way that our study does not capture (142).

We sought studies with a broad cross section of ICU patients and deliberately excluded studies examining sex differences in one diagnostic group of ICU patients. However, many of the included studies had limited casemix due to being single-centre studies. Admission diagnosis is an important predictor of sex balance in ICU admissions, therefore casemix is likely an important source of clinical heterogeneity within our review (chapter 2). For example, studies that include large trauma cohorts are likely to include more young men, which would impact upon sex-specific illness severity findings and outcomes.

3.6 CONCLUSION

Our systematic review and meta-analysis found that women have higher risk-adjusted mortality than men at some, but not all, studied timepoints following admission to ICU. In addition, women tend to have higher illness severity score than men at ICU admission. These findings were not robust to sensitivity analysis therefore further research is needed to establish the relationship between sex, illness severity and outcome in adult ICU patients.

Acknowledgements

We would like to acknowledge the authors of several studies included in this review who generously answered questions about their studies.

Chapter 4. Sex differences in mortality of ICU patients according to diagnosis-related sex balance

4.1 ABSTRACT

Rationale: Women have worse outcomes than men in several conditions more common in men, including cardiac surgery and burns.

Objectives: To describe the relationship between sex balance within each diagnostic group of ICU admissions; defined as the percentage of patients who were women; and hospital mortality of women compared to men with that same diagnosis.

Methods: We studied ICU patients in the Australia and New Zealand Intensive Care Society's Adult Patient Database (2011-2020). We performed mixed effects logistic regression for hospital mortality adjusted for sex, illness severity, ICU lead-time, admission year, and hospital site. We compared sex balance with the adjusted hospital mortality of women compared to men for each diagnosis using weighted linear regression.

Measurements and Main Results: There were 1,450,782 admissions (42.1% women), with no difference in the adjusted hospital mortality of women compared to men overall (odds ratio, 0.99; 99% CI, 0.97 to 1). As the percentage women within each diagnosis increased, the adjusted mortality of women compared to men with that same diagnosis decreased (regression coefficient, -0.015; 99% CI; -0.020 to -0.011; $P < 0.001$) and the illness severity of women compared to men at ICU admission decreased (regression coefficient, -0.0026; 99% CI, -0.0035 to -0.0018; $p<0.001$).

Conclusion: Sex balance in diagnostic groups was inversely associated with both the adjusted mortality and illness severity of women compared to men. In diagnoses with relatively few women, women were more likely to die than men. In diagnoses with fewer men, men were more likely to die than women.

4.2 INTRODUCTION

Women are more likely than men to die following some critical illnesses, including cardiac arrest, cardiac surgery, and burns (17, 57, 107, 143, 144). However, this is not a consistent pattern across all critical illnesses. Considering the intensive care unit (ICU) population overall, women and men appear to have equivalent adjusted hospital or 30-day mortality (21, 24, 25, 89). Moreover, women have lower mortality than men in some critical illnesses, including exacerbation of chronic obstructive pulmonary disease, COVID-19 pneumonia, and spinal surgery (19, 145-148). This variation in the relative outcomes of women and men following different critical illnesses remains unexplained.

Some critical illnesses with higher mortality in women than men also occur less commonly in women than men. For example, only 25% of cardiac surgery patients and 20% of burns patients are women (107, 143, 144). This raises the possibility of a relationship between sex balance within a diagnostic group and the mortality of women compared to men with that diagnosis.

As previously presented in the form of an abstract (149), we hypothesised that among ICU patients, women have relatively better outcomes than men in diagnoses with a higher percentage of patients who are women and men have relatively better outcomes in diagnoses with a higher percentage of patients who are men. Our primary objective was to describe the relationship between the sex balance within each diagnostic group of ICU admissions; defined as the percentage of patients who were women; and the adjusted hospital mortality of women compared to men with that same diagnosis. Our secondary objective was to describe the relationship between sex balance and the relative illness severity of women compared men at ICU admission, by diagnostic group.

4.3 METHODS

Ethics approval

Ethics approval for this study was granted by the Alfred Health Human Research Ethics committee (project number 200/21).

Study design

We conducted a retrospective cross-sectional study of adult patients admitted to ICUs in Australia and New Zealand, as recorded in the Australia and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), one of five clinical quality registry datasets run by the ANZICS Centre for Outcome and Resources Evaluation. The APD records admissions from 90% of ICUs in Australia and New Zealand, including all tertiary hospital ICUs and most metropolitan, regional and private ICUs (150). Each hospital has one ICU that admits both medical and surgical patients under the care of intensive care specialist/s; hospitals that perform cardiac surgery admit post-operative cardiac surgery patients to the hospital's general ICU (150, 151). The APD uses a standardised secure digital data collection tool with automated data validation rules at all sites and a standardised data dictionary. Regular training and accuracy checks are provided for data collectors (150).

We undertook this study in keeping with the STROBE guidelines for cohort observational studies (152).

Study Population

We included patients aged 17 years and over admitted to ICU and reported to the APD between 2011 and 2020. We excluded repeat ICU admissions from within the same hospital visit including those transferred to another ICU, and those with missing diagnosis, outcome, or sex classification. We also excluded patients classified as 'intersex/indeterminate' as this non-binary sex classification was added to the APD in

2017 and accounts for less than 0.1% of ICU admissions each year (43). Given our focus on the sex balance within diagnostic groups we excluded sex-specific diagnoses, defined as diagnoses with less than 1% or greater than 99% women.

Exposure and outcomes

The exposure of interest in this study is sex, defined in the APD data dictionary as the biological distinction between female and male (43). Sex data is obtained from hospital admission details and therefore may be self-reported, reported by family members or determined by hospital staff. There is no gender classification in the APD.

The primary objective of this study was to describe the association between sex balance, defined as the percentage of patients in a diagnostic group who were women, and sex differences in outcome, defined as the adjusted hospital mortality of women compared to men, by ICU admission diagnosis. The ICU admission diagnoses are based on the Acute Physiology and Chronic Health Evaluation III (APACHE III) diagnostic definitions; they are mutually exclusive and reflect the clinical diagnosis during the patient's first 24 hours of ICU admission (non-operative diagnoses) or the operation performed immediately prior to ICU admission (post-operative admissions) (43). We assessed illness severity using the APACHE III score, which does not adjust for patient sex.

Statistical analysis

We reported counts with percentages and means with standard deviation (SD) for normally distributed data and medians with IQR for non-normally distributed data. We used the χ^2- test, Wilcoxon rank-sum or t-test for comparisons as appropriate. To increase the robustness of our findings, we reported 99% confidence intervals (CI) and took $p < 0.01$ to indicate statistical significance. We performed complete case analysis, making no assumptions about missing data. We used STATA 17 for statistical analysis (StataCorp, Texas, USA).

We performed mixed-effects logistic regression analysis for hospital mortality, adjusting for sex, APACHE III score, diagnosis, hours of hospitalisation prior to ICU admission (henceforth ICU lead time), year of admission and hospital site, with site treated as a random effect. We repeated this mixed-effects logistic regression for each of the 111 diagnoses (diagnosis removed from model), reporting the odds ratios (OR) with 99% confidence interval (CI) for adjusted hospital mortality of women compared to men for each diagnosis. Therefore, odds ratios less than one indicate women were less likely to die than men and vice versa. To test the association between sex differences in mortality and sex balance, we performed a frequency-weighted linear regression of the adjusted hospital mortality of women compared to men for each diagnosis (odds ratio), against the sex balance (percentage female patients) within that diagnostic group. Regression results are reported as parameter estimates (99% CI) with a corresponding r-square statistic and a p-value to reflect if the slope differs significantly from 0.

We compared the illness severity of women and men using ratio of female to male mean APACHE III scores (F:M APACHE III). To test the association between sex balance and sex differences in illness severity, we performed weighted linear regression of F:M APACHE III against sex balance for each diagnosis.

Sensitivity analyses

To test the robustness of our findings, we repeated the analysis with the study population divided into groups of hospitals instead of diagnostic groups. Hospitals were ranked into 48 quantiles according to sex balance in admissions. We calculated hospital mortality for each hospital group adjusted for sex, diagnosis, illness severity, ICU lead time and admission year but not hospital site. We then performed weighted linear regression of adjusted hospital mortality against sex balance for each hospital group.

APACHE III components

To examine the association between sex balance and sex differences in elements of the APACHE III score, the APACHE III was broken into its components of physiological derangement, chronic comorbidities and age. We calculated sex differences in

physiological derangement and age using the female to male ratio of mean scores for each admission diagnosis. As the chronic comorbidity score was non-normally distributed, we used the female to male geometric mean ratio of scores. We compared female to male ratios with sex balance by diagnostic group using a weighted linear regression, weighted by the frequency of patients per diagnosis.

Age group

We divided the study population by patient age in years, with a separate category for patients aged over 95 years (78 categories in total). For each age group, we calculated hospital mortality adjusted for sex, diagnosis, the chronic disease and physiological components of APACHE III (i.e., the age component of APACHE III was not included), ICU lead time, admission year and hospital site using mixed effects logistic regression. We used weighted linear regression (weighted by the frequency of patients per age group) to compare adjusted odds ratio for hospital mortality of women compared to men with sex balance for each age group.

Excluding patients with limitation of medical treatment orders

Patients with a limitation of medical treatment or missing LoMT data were excluded. We performed mixed effects logistic regression for hospital mortality adjusted for sex, APACHE III, ICU lead time, admission year and hospital site for each diagnostic group. We then compared the odds ratio for hospital mortality of women compared to men with sex balance for each diagnostic group using weighted linear regression.

ICU lead time

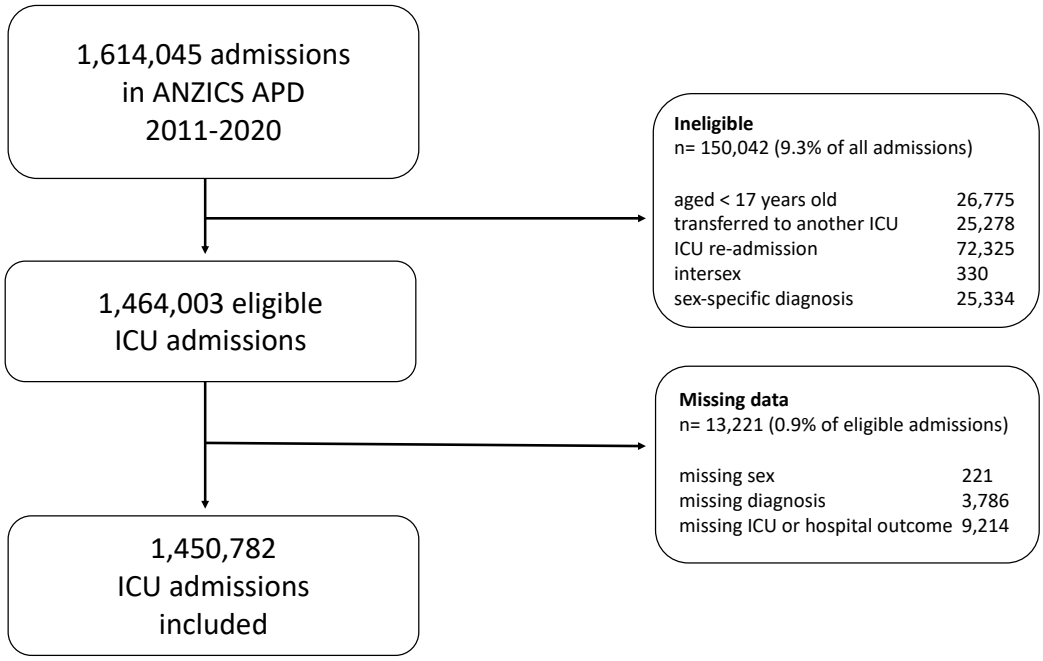
To compare ICU lead time of women and men, we calculated a female to male geometric mean ratio of hours hospitalised prior to ICU admission for each diagnostic group (F:M lead time). We then performed weighted linear regression of F:M lead time against sex balance by diagnostic group.

4.4 RESULTS

Study population and sex differences in mortality

There were 1,614,045 admissions entered into the ANZICS CORE APD between 2011 and 2020, of which 1,450,782 were eligible for this study (Figure 4.1). Complete illness severity data was available for 1,447,135 patients, who were included in the regression models (99.7% of study population).

Figure 4.1: Patient inclusion flow diagram



Overall, 42.1% of the study population were women. On average, women were younger than men and had lower illness severity scores than men (Table 4.1). Women had lower unadjusted hospital mortality than men (8.1% vs 8.6%; $P < 0.001$). After adjustment for APACHE III, diagnosis, ICU lead time, year of admission and hospital site, however, there was no difference in hospital mortality between women and men overall (OR, 0.99; 99% CI, 0.97 to 1.00; $P = 0.05$; Table 4.2).

Table 4.1: Characteristics of women and men admitted to ICU

	*All patients n = 1,450,782**	*Women n = 610,215 (42.1%)*	*Men n = 840,567 (57.9%)*	*p-value for sex difference*
Age, years, mean (SD)	62.3 (17.5)	61.8 (18.3)	62.7(16.9)	<0.001
APACHE III, mean (SD)	52.1 (24.9)	51.3 (24.8)	52.7 (24.9)	<0.001
Pre-ICU time, hours, median [IQR]	9.7 [4.5-28.2]	9.25 [4.5-27.1]	10 [4.6-28.9]	<0.001
Length of stay, days, median [IQR]	1.8 [0.9–25.5]	1.7 [0.9–3.1]	1.8 [0.9–3.3]	<0.001
Admission type				
Elective n (%)	610,729 (42.4)	242,910 (40.1)	367,819(44.1)	<0.001
Non-elective n (%)	829,334 (57.6)	362,852 (59.9)	466,482 (55.9)	<0.001
LOMT n (%)	88,824 (6.3)	41,760 (7.0)	47,064 (5.8)	<0.001

*complete data available for >99% of patients. APACHE = Acute Physiology and Chronic Health Evaluation; LOMT = Limitation of Medical Treatment at the time of admission to ICU

There were significant sex differences in adjusted hospital mortality within five of the nine major diagnostic categories of ICU admissions. Women had lower adjusted hospital mortality than men in three categories: respiratory; sepsis; and the combined metabolic, hematological and renal disorders category (Table 4.2). Women had higher adjusted mortality than men in the cardiac surgery category and other cardiovascular diagnoses category. The most marked sex difference in mortality was observed in the cardiac surgery category, with women significantly more likely to die than men. There was no sex difference in mortality in four categories: neurological; trauma; musculoskeletal, soft tissues and skin diagnoses; and gastrointestinal diagnoses.

Table 4.2: Sex differences in illness severity and hospital mortality by diagnostic category

Diagnostic category	*Patients*			*Illness severity, Female: Male APACHE III* (99% CI)*	*Unadjusted hospital mortality*		*Adjusted hospital mortality of women compared to men, odds ratio (99% CI) †*
	Total, n	*Women, n (%)*	*Men, n (%)*		*Women, n (%)*	*Men, n (%)*	
Cardiovascular‡	186,770	69,282 (37.1)	117,488 (62.9)	0.97 (0.96-0.97)	11,094 (16)	19,277 (16.4)	1.07 (1.02-1.12)
Cardiac surgery	174,425	43,659 (25)	130,766 (75)	1.04 (1.04-1.05)	965 (2.21)	1,612 (1.23)	1.63 (1.45-1.82)
Respiratory	218,252	97,905 (44.9)	120,347 (55.1)	0.98 (0.97-0.99)	9,090 (9.3)	12,700 (10.6)	0.92 (0.88-0.96)
Gastrointestinal	243,174	112,890 (46.4)	130,284 (53.6)	0.96 (0.95-0.96)	7,255 (6.4)	9,344 (7.2)	1.00 (0.95-1.05)
Neurological	184,702	88,754 (48.1)	95,948 (51.9)	0.97 (0.96-0.98)	7,794 (8.8)	9,219 (9.6)	1.00 (0.95-1.05)
Sepsis	105,071	47,316 (45)	57,755 (55)	0.95 (0.94-0.96)	7,369 (15.6)	10,187 (17.6)	0.94 (0.89-0.98)
Trauma	69,381	19,707 (28.4)	49,674 (71.6)	1.09 (1.07-1.11)	1,890 (9.6)	4,463 (8.9)	0.91 (0.83-1.00)
Metabolic, renal hematology	169,059	80,617 (47.7)	88,442 (52.3)	0.96 (0.96-0.97)	2,814 (3.5	3,696 (4.2)	0.87 (0.81-0.94)
Musculoskeletal soft tissue, skin	99,948	50,085 (50.1)	49,863 (49.9)	1.00 (0.99-1.01)	1,205 (2.4)	1,388 (2.8)	0.89 (0.79-1.00)
TOTAL	**1,450,782**	**610,215 (42.1)**	**840,567 (57.9)**	**0.97 (0.97-0.97)**	**49,476 (8.1)**	**71,866 (8.6)**	**0.99 (0.97-1.00)**

APACHE III: Acute Physiology and Chronic Health Evaluation. *Ratio female to male mean APACHE III scores. †Adjusted for APACHE III score, ICU lead time, admission year and hospital site, in addition to sex. ‡excludes cardiac surgery.

Relationship between sex balance and sex differences in mortality

The percentage of patients who were women within each diagnostic group was inversely associated with the adjusted hospital mortality of women relative to men (weighted linear regression coefficient, -0.015; 99% CI; -0.020 to -0.011; $P < 0.001$; $r^2 =$ 38%; Figure 4.2). In diagnostic groups where a lower percentage of the patients were women, the women were relatively more likely to die than the men. Conversely, in diagnostic groups with a higher percentage of female patients, the women were relatively less likely to die than the men. Diagnostic groups containing less than the average percentage female patients (less than 42.1% women), tended to have higher adjusted hospital mortality for women compared to men (OR > 1) and vice versa.

Figure 4.2: Adjusted hospital mortality of women compared to men versus sex balance, by diagnostic group

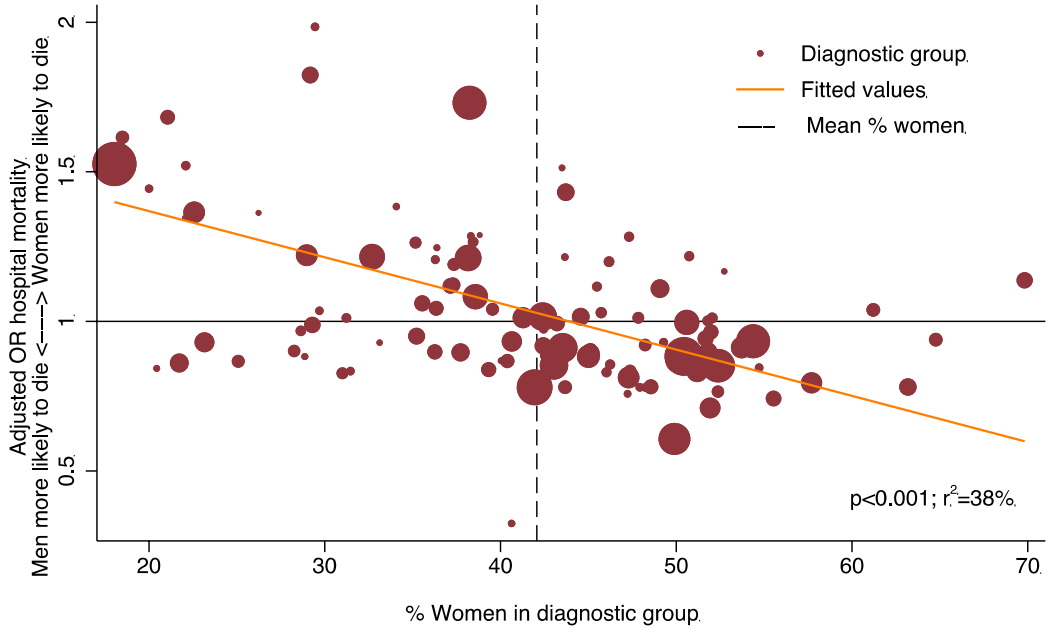


Figure legend: Adjusted hospital mortality of women compared to men versus the percentage of patients who were women by diagnostic group. The weighted regression (fitted values) shows that the adjusted mortality of women compared to men was inversely associated with the percentage of women in the diagnostic groups. As the percentage of female patients within a diagnostic group increased by 10% (for example, from 30% to 40%), the OR for hospital mortality of women compared to men decreased by 0.15, from approximately 1.2 to 1.05 (regression coefficient, -0.015; 99% CI; -0.020 to -0.011; P < 0.001).

Relationship between sex balance and sex difference in illness severity

There was an inverse association between relative illness severity of women compared to men with a diagnosis and the sex balance in that diagnostic group (weighted linear regression coefficient, -0.0026; 99% CI, -0.0035 to -0.0018; $P < 0.001$; r^2=38%; Figure 4.3). In diagnostic groups where a lower percentage of the patients were women, the women had higher illness severity than men at ICU admission and vice versa. A sensitivity analysis examining each component of APACHE III separately found that the association between illness severity and sex balance was driven by the physiological and age components, rather than chronic health conditions (Figure 4.4).

Figure 4.3: Illness severity of women compared to men versus sex balance, by diagnostic group

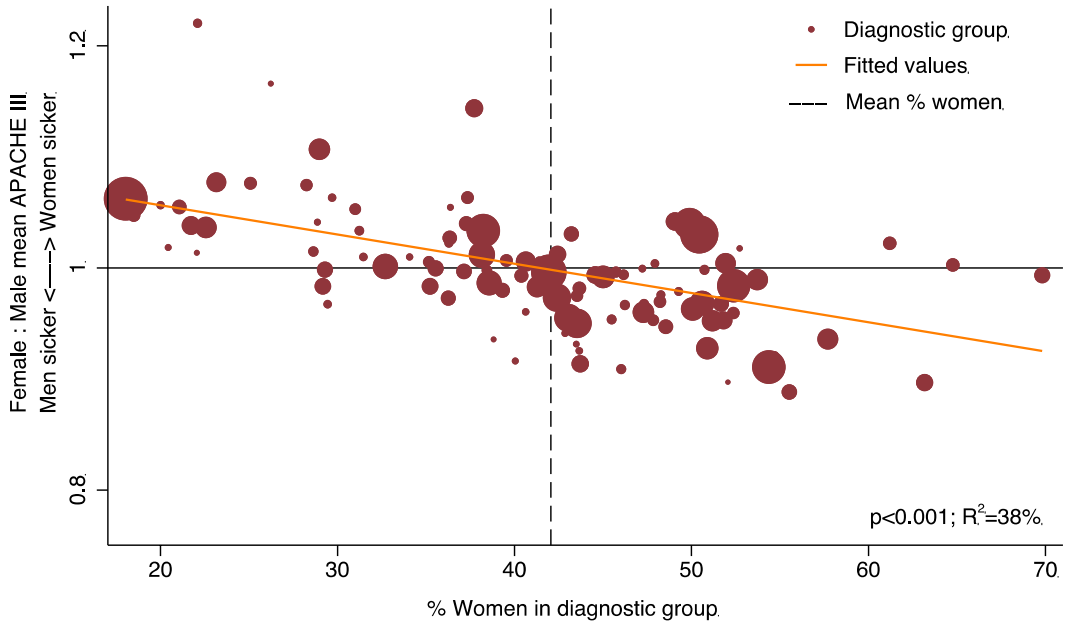


Figure legend: Illness severity of women compared to men versus the percentage of patients who were women by diagnostic group. The weighted regression (fitted values) shows that the illness severity of women compared to men was inversely associated with the percentage of patients who were women in the diagnostic group. An increased percentage of patients who were women within the diagnostic group was associated with lower illness severity of women compared to men at ICU admission: linear regression coefficient, -0.0026; 99% CI, -0.0035 to -0.0018; $P < 0.001$; $r^2 = 38\%$.

Figure 4.4: Sensitivity analysis by components of APACHE III score

Figure 4.4.1: Physiological derangement of women compared to men versus sex balance, by diagnostic group

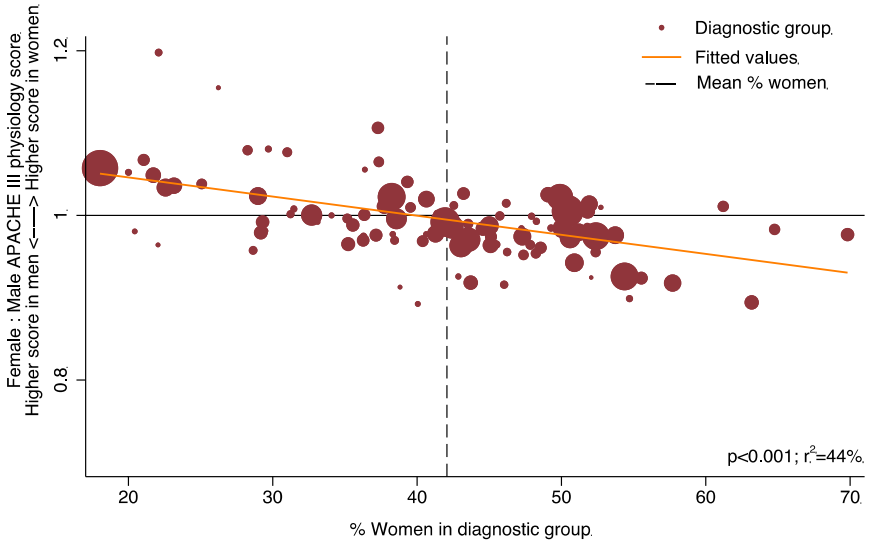


Figure legend: Physiology component of APACHE III score in women compared with men versus sex balance, by diagnostic group. Linear regression coefficient, -0.00232; 99% confidence interval, -0.00233 to -0.00232; $p < 0.001$; $r^2 = 44\%$.

Figure 4.4.2: Age of women compared to men versus sex balance, by diagnostic group

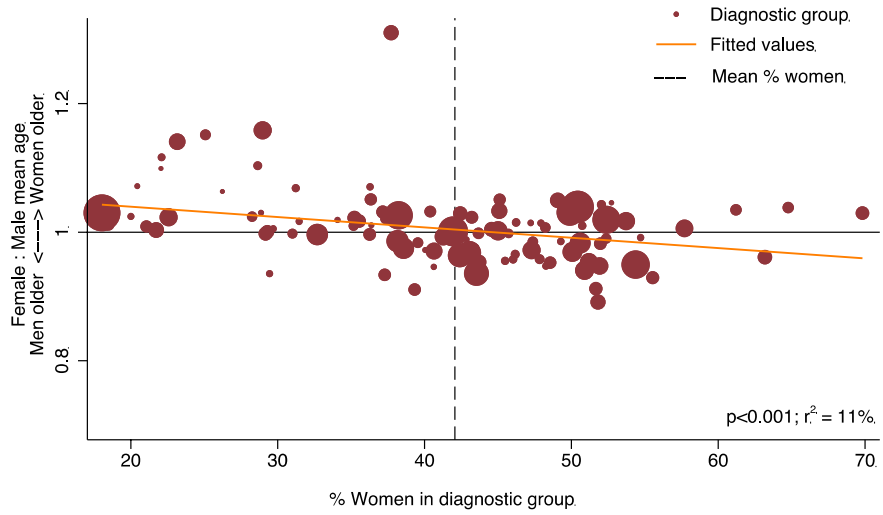


Figure legend: Age component of APACHE III score in women compared with men versus sex balance, by diagnostic group. Linear regression coefficient, -0.00160; 99% confidence interval, -0.00161 to -0.00159; $p<0.001$; $r^2 = 11\%$.

Figure 4.4.3: Chronic comorbidities in women compared to men versus sex balance, by diagnostic group

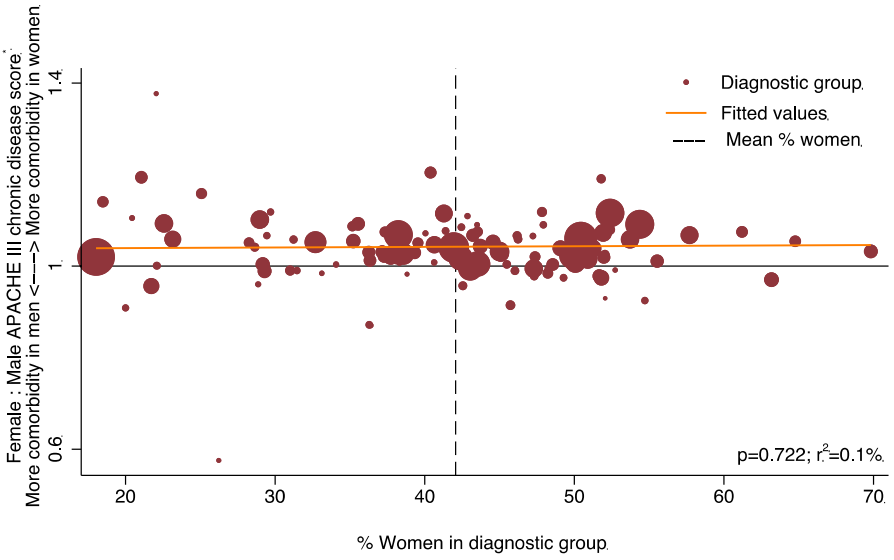


Figure legend: Chronic comorbidity component of APACHE III score in women compared with men versus sex balance, by diagnostic group. Linear regression coefficient, -0.00045; 99% confidence interval, -0.00233 to 0.00145; p = 0.722; r^2 = 0.1%.

Sensitivity analyses

The inverse relationship between mortality and sex balance persisted when the study population were divided by hospitals rather than admission diagnosis (Figure 4.5). However, there was no significant association between mortality and sex balance when the study population were divided according to age (Figure 4.6). A sensitivity analysis that excluded all patients with limitations of medical therapy in place at the time of ICU admission (LoMT) confirmed a significant relationship between sex differences in mortality and sex balance within diagnostic groups (Figure 4.7). Finally, there was a small but significant association between sex difference in ICU lead time and sex balance within diagnostic groups: patients presenting with illnesses less common for their sex spent relatively longer in hospital prior to ICU admission (Figure 4.8).

Figure 4.5: Adjusted hospital mortality of women compared to men versus sex balance, by hospital group

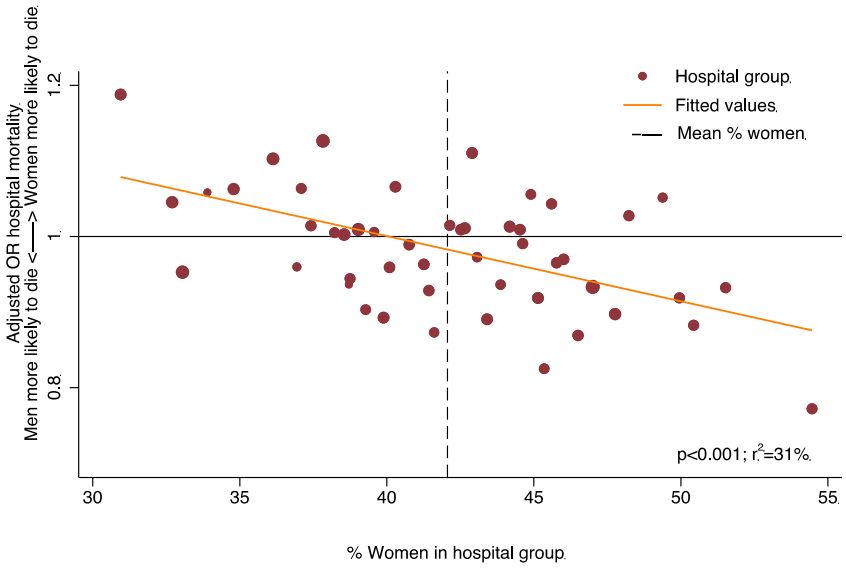


Figure legend: Adjusted hospital mortality of women compared with men versus sex balance, by hospital group. Hospitals were grouped into 48 quantiles based on the percentage of female patients admitted during the study period. Hospital mortality was adjusted for Acute Physiology and Chronic Health Evaluation III score, diagnosis, ICU lead time, and admission year, in addition to sex. As the percentage of female patients increased, the odds ratio (OR) for adjusted hospital mortality of women compared with men decreased (linear regression coefficient, -0.0086; 99% confidence interval, -0.0137 to -0.0035; $p < 0.001$; $r^2 = 31\%$).

Figure 4.6: Adjusted hospital mortality of women compared to men versus sex balance, by age group

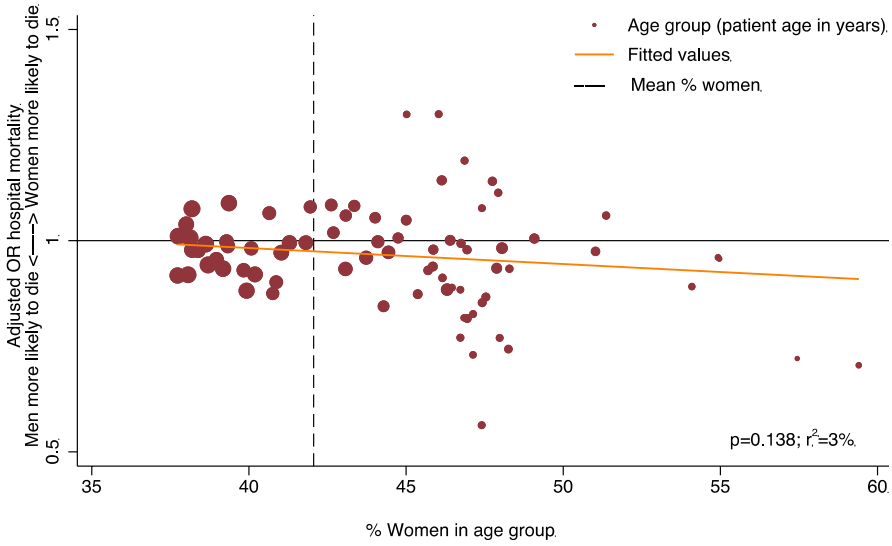


Figure legend: Adjusted hospital mortality of women compared to men versus sex balance, by age in years. Linear regression coefficient, -0.00718; 99% confidence interval, -0.01459 to 0.00023; $p = 0.138$; $r^2 = 3\%$.

Figure 4.7: Adjusted hospital mortality of women compared to men versus sex balance by diagnostic group, excluding patients with limitation of medical treatment

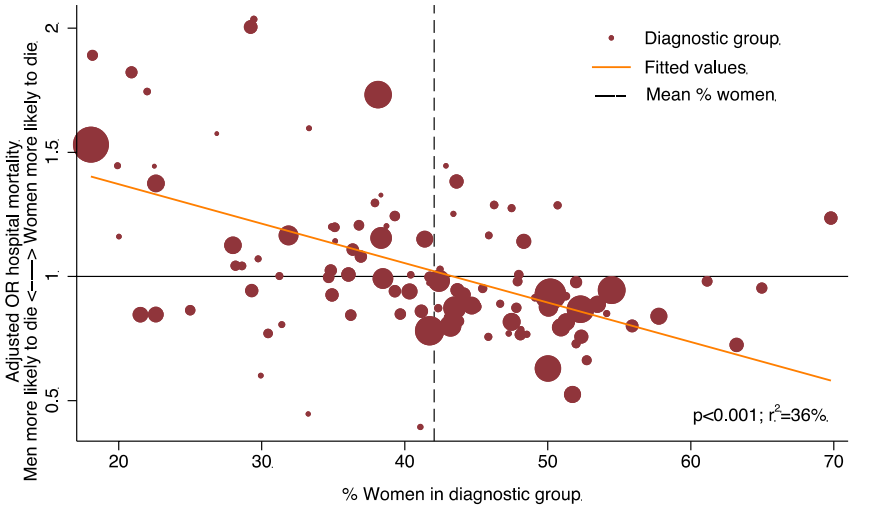


Figure legend: adjusted hospital mortality of women compared to men versus sex balance, by diagnostic group, excluding patients with limitation of medical treatment orders. Linear regression coefficient, -0.01590; 99% confidence interval, -0.01594 to -0.01585; p<0.001; r^2 = 36%.

Figure 4.8: Sex differences in ICU lead time versus sex balance, by diagnostic group

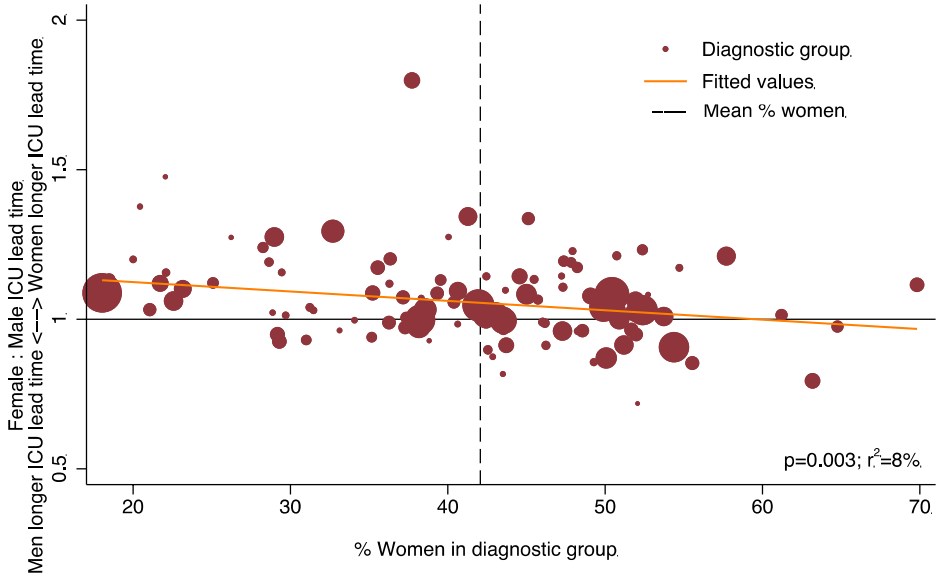


Figure legend: ICU lead time of women compared to men versus sex balance, by diagnostic group. Linear regression coefficient, -0.00398; 99% confidence interval, -0.00724 to -0.00072; p = 0.003; r^2 = 8%.

4.5 DISCUSSION

Key findings

In this study of nearly 1.5 million ICU patients in Australia and New Zealand, women had lower unadjusted hospital mortality and equivalent adjusted hospital mortality compared to men overall. However, there were sex differences in adjusted hospital mortality in 5 of 9 major diagnostic categories of ICU admissions.

We found an inverse relationship between the percentage of patients admitted with a given diagnosis who were women, and the adjusted hospital mortality of women compared to men with that diagnosis. This sex-based minority effect was bidirectional: women were more likely to die if admitted with a diagnosis relatively less common in women (e.g., cardiac surgery) and men were relatively more likely to die if admitted with a diagnosis less common in men (e.g., metabolic disorders). The minority effect persisted across hospitals: patients admitted to ICUs with relatively few patients of their own sex were more likely to die than patients in the majority sex group for that ICU.

There was also an inverse relationship between sex balance and the relative illness severity of women compared to men with the same diagnosis. In diagnostic groups with relatively few women – diagnostic groups in which the percentage of patients who were women was less than the mean of 42.1% – women were admitted to ICU at a higher illness severity than men and vice versa.

Relationship to previous studies

To the best of our knowledge, no previous study has addressed the issue of sex balance and its association with outcome. A meta-analysis of sex differences in outcomes of ICU patients found no difference in the hospital mortality of women and men overall, although there was substantial heterogeneity associated with this result (chapter 3). Similarly, our study found no sex difference in the adjusted hospital mortality of the overall study population. We found significant differences in the outcomes of women

compared to men within most diagnostic categories, suggesting that the heterogeneity in findings of previous studies could be partly due to variations in casemix.

In contrast to most previous studies, the women in our study population were younger and had lower illness severity scores than the men (17, 19-21, 26, 105). This suggests an important difference between the Australian and New Zealand ICU population and those of previous studies of sex differences in ICU patients from Europe, North America, and Taiwan.

Concordant with previous studies, we found that women had higher mortality than men following cardiac surgery (19, 107) and that the cardiac surgery cohort had the most pronounced sex difference in mortality of all the major diagnostic categories of ICU admission.

Implications of study findings

Our key finding that sex balance is associated with the relative outcomes and illness severity of women and men within diagnostic groups has important implications. First, it suggests a type of sex-based volume-outcome relationship. Such volume-outcome relationships are well recognised in critical care (153, 154).

A sex-based volume-outcome effect could be mediated by clinician cognitive bias. Patients may receive more prompt diagnosis and treatment if they present with an illness expected for their sex; a form of ascertainment bias (155). This is supported by our finding that patients were admitted to ICU after a shorter time in hospital and at a lower illness severity if their illness was common in their sex. Availability bias - where the clinician's familiarity or recent experience of treating similar patients affects their diagnosis and treatment –may also contribute to the observed association between sex balance and outcomes (156). Greenwood and colleagues found that female patients with acute myocardial infarction (AMI) had lower mortality if their male physician had recently treated female AMI patients, supporting the theory that a clinician's familiarity with treating male or female patients in a given clinical situation affects the treatment

they provide (157). There is also evidence that the sex balance of the treating team affects sex-based outcomes. This includes both the sex concordance of physician-patient pair and the sex balance within a clinical team (157, 158). Therefore, future studies should examine the impact of the sex balance among ICU clinicians upon the observed sex differences in patient outcomes.

Second, our findings suggest that the exposure of being male or female across the life span may affect both the incidence and outcomes of various critical illness. Biological differences in sex hormones and cytokine response, combined with different patterns of risk-taking behaviour between women and men could contribute to the observed sex differences (7, 68). However, the association between sex balance and mortality persisted across groups of hospitals – after adjusting for admission diagnosis – suggesting that the relationship is driven by system-level rather than simply disease-level factors. Moreover, there was no significant relationship between sex balance and chronic diseases in women and men, which somewhat speaks against the impact of long-term risk-taking behaviours such as smoking or alcohol consumption.

From a clinical perspective, our findings suggest that clinicians should pay heed to patients presenting with illnesses uncommon in their sex. This could be incorporated into clinical warning systems for diseases with a marked female preponderance (for example, metabolic disorders) or marked male preponderance (for example, cardiac surgery). From a research perspective, our findings underscore the importance of obtaining sex-disaggregated data in critical care clinical trials and examining sex as a variable in observational research.

Strengths and limitations

Our study has several strengths. To the best of our knowledge, this is the first to investigate the relationship between sex balance and sex differences in outcomes. We further interrogated the significance of sex balance by examining its relationship with illness severity and performing sensitivity analyses using hospital groups and age cohorts instead of diagnostic cohorts.

We used data obtained from a well-established clinical registry with high quality governance, capturing the vast majority of ICU admissions across Australia and New Zealand (150). Where previous studies focussed on sex differences in either the ICU population overall or selected critical illnesses (17, 19, 24), our very large study comprehensively described sex differences in illness severity and outcomes across diagnoses leading to ICU admission.

The relatively low mortality rate in our study population suggests that our findings are not due to poor clinical performance overall. Furthermore, the equivalent adjusted outcomes of women and men overall speaks against overt sex discrimination affecting our results.

We acknowledge several limitations. We assessed only patients admitted to the ICU rather than all potential ICU patients admitted to hospital. As we did not compare the sex balance and outcomes of the ICU and hospital populations, we cannot comment upon equity of access to the ICU. In comparing mortality of women and men following ICU admission, we are comparing the outcomes of a complex process including treatment received prior to ICU admission. It is possible that both the presumptive diagnosis and the decision for ICU admission were impacted by bias, in turn affecting the observed relationship between sex, diagnosis, and mortality.

Due to the very limited data available on transgender or non-binary ICU patients, we adopted a binary definition of sex. Therefore, we cannot comment upon the outcomes of non-binary ICU patients compared to women or men.

Finally, although our study describes a potentially important relationship between sex balance and sex differences in outcomes, we cannot confirm the mechanism underlying this relationship.

4.6 CONCLUSION

For ICU patients, the hospital mortality of women compared to men is inversely related to the percentage of women admitted within the same diagnostic category: women are more likely to die in diagnostic groups with relatively few women and men are more likely to die in diagnostic groups with fewer men. A similar relationship exists between sex balance and the relative illness severity of women and men: in diagnostic categories with more women, women are admitted at relatively lower illness severity than men. Awareness of this minority effect may allow clinicians to modify their management of patients presenting with illnesses uncommon in their sex.

Chapter 5. Sex differences in treatment of ICU patients: a systematic review and meta-analysis

5.1 ABSTRACT

Objectives: To evaluate and synthesize the available literature on sex differences in the treatment of adult intensive care unit (ICU) patients.

Study selection: Systematic searches were undertaken in MEDLINE and EMBASE. Two reviewers independently screened publications to identify observational studies of adult ICU patients that explicitly examined the association between sex and ICU treatment – specifically, mechanical ventilation, renal replacement therapy, and length of stay.

Data extraction: We extracted data independently and in duplicate: mean age, illness severity, use of mechanical ventilation and renal replacement therapy, and length of stay in ICU and hospital. We assessed risk of bias using the Newcastle-Ottawa Scale. We used a DerSimonian-Laird random effects model to calculate pooled odds ratios and mean differences between women and men.

Data Synthesis: We screened 4,098 publications, identifying 21 eligible studies with 545,538 participants (42.7% women). The study populations ranged from 246 to 261,255 participants (median 4,420). Most studies (76.2%) were at high risk of bias in at least one domain, most commonly representativeness or comparability. Women were less likely than men to receive invasive mechanical ventilation (odds ratio [OR], 0.83; 95% CI, 0.77 to 0.89; $I^2 = 90.4\%$) or renal replacement therapy (OR, 0.79; 95% CI, 0.70 to 0.90; $I^2 = 76.2\%$). ICU length of stay was shorter in women than men (mean difference, –0.24 days; 95% CI, –0.37 to –0.12; $I^2=89.9\%$). These findings persisted in meta-analysis of data adjusted for illness severity and other confounders, and also in sensitivity analysis excluding studies at high risk of bias. There was no significant sex difference in duration of mechanical ventilation or hospital length of stay.

Conclusion: Women were less likely than men to receive mechanical ventilation or renal replacement therapy and had shorter ICU length of stay than men. There is substantial heterogeneity and risk of bias in the literature; however, these findings persisted in sensitivity analyses.

5.2 INTRODUCTION

There is a consistent sex imbalance in the ICU patient population, with fewer women than men admitted to ICUs around the world (19, 20, 22, 27). This observation has spurred increasing research into sex differences in critical illness and admissions to the ICU (17, 24, 89).

Several studies report systematic differences in the treatment women and men receive in the ICU. For example, studies from Europe, North America and Asia all found that women were less likely to receive invasive mechanical ventilation (MV) than men (19-21, 23). Two studies reported that women have lower mean Therapeutic Intervention Scoring System (TISS) scores than men (21, 29). Against this, two studies report that women and men were equally likely to receive MV (25, 127). These inconsistent findings may be due to differences in methodology, study populations or other factors.

The treatment provided to ICU patients should be based upon their physiological requirements and preferences rather than their sex. Therefore, it is important to determine whether sex differences exist in the treatment of ICU patients, and if so, whether they can be attributed to the relative illness severity of women and men in the ICU.

This systematic review and meta-analysis aimed to quantify sex differences in treatment of ICU patients and explore sources of heterogeneity in the literature. We considered three domains of ICU treatment: MV, renal replacement therapy (RRT) and length of stay (LoS). We hypothesised that women received less treatment than men.

5.3 METHODS

We conducted our review in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) and the Meta-Analysis Of Observational Studies in Epidemiology guidelines and published our study protocol prospectively (121-123).

Search Strategy

We searched MEDLINE (OVID Medline (All)) and EMBASE on July 17, 2020, and repeated the search on May 27, 2021, using a carefully piloted search strategy (Figure 3.1). Our search strategy included both keywords and Medical Subject Heading terms for sex, gender, male, female, intensive care, and critical illness and did not use language or date restrictions in our database search. We hand-searched the references of eligible articles for further potentially eligible articles.

Selection Criteria

We included observational cross-sectional or cohort studies of adult ICU patients that examined the association between sex or gender and at least one of illness severity, mortality or treatment as their primary or secondary objective (Figure 3.2). ICU treatment was defined as invasive MV, RRT and LoS. We sought studies of broad populations of ICU patients and excluded studies of individual diagnostic cohorts. We excluded studies that were not available in full text and published in English. Our review yielded extensive findings therefore we reported the illness severity and mortality findings separately (chapter 3).

Selection Process and Risk of Bias Assessment

We screened the title and abstract of each citation identified in our electronic search against selection criteria and examined the full text of articles thus identified to confirm eligibility. All screening was undertaken independently by two authors (LM and either

RV or VA) with another author (AH) resolved disagreements. We recorded the reason for excluding any article at full-text screening.

We used a modified Newcastle-Ottawa Scale to assess risk of bias in six domains: representativeness; selection of cohorts; ascertainment of exposure; and comparability, ascertainment and follow-up of treatment outcome (Figure 3.3, (124)). Two members of the review team (LM and either RV or VA) independently assessed each study for risk of bias and discrepancies were resolved through discussion.

Data Extraction

We extracted data independently and in duplicate using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). If data were not suitable for meta-analysis in their published form, we contacted authors directly for clarification.

Statistical Analysis

We used the DerSimonian-Laird random effects model to calculate pooled odds ratios for dichotomous outcomes and pooled mean differences for continuous outcomes. Throughout the study we compared women to men. Therefore, odds ratios greater than 1 indicate that women were more likely than men to receive the intervention and positive mean differences indicate that women had longer duration of treatment than men. We reported 95% confidence intervals (CI) and took $p < 0.05$ to indicate statistical significance.

Data that were reported as median and interquartile range were converted to mean and standard deviation using the method described by Wan and colleagues (125). Two studies reported data separately for two diagnostic cohorts within the same study population: trauma and non-trauma cohorts (Guidry 2014 (68)), and medical and surgical cohorts (Romo 2004 (120)). We combined data from the two cohorts using the method described by the Cochrane Collaboration (126).

We used the I^2 test to assess statistical heterogeneity with the threshold > 75% taken to indicate high; 50-75%, to indicate moderate; and 25-50%, to indicate low. We calculated separate pooled estimates for unadjusted and adjusted treatment outcomes. The adjusted pooled estimate included data adjusted for two or more of the following important confounders: age, illness severity, comorbidities, and admission diagnosis.
We also performed a pre-specified sensitivity analysis that excluded studies at high risk of bias in any domain. Finally, we explored sources of heterogeneity considering the following variables: continent, diagnostic category, age, illness severity score, year of study (pre-specified); size of study population (number of participants) and percentage female participants (specified post-hoc). We used a funnel plot to visually assess for possible publication bias.

We used Stata/BE 17 (StataCorp Texas, USA) and Review Manager (RevMan) Version 5.4 (The Cochrane Collaboration, 2020) for our statistical analysis.

5.4 RESULTS

Study selection

Our Medline and EMBASE searches identified 4,098 unique publications; 4,007 were excluded on screening the title and abstract. We assessed the full text of the remaining 91 publications and identified 21 studies that met our eligibility criteria (Figure 5.1). Searching the references of included studies did not yield any additional eligible publications.

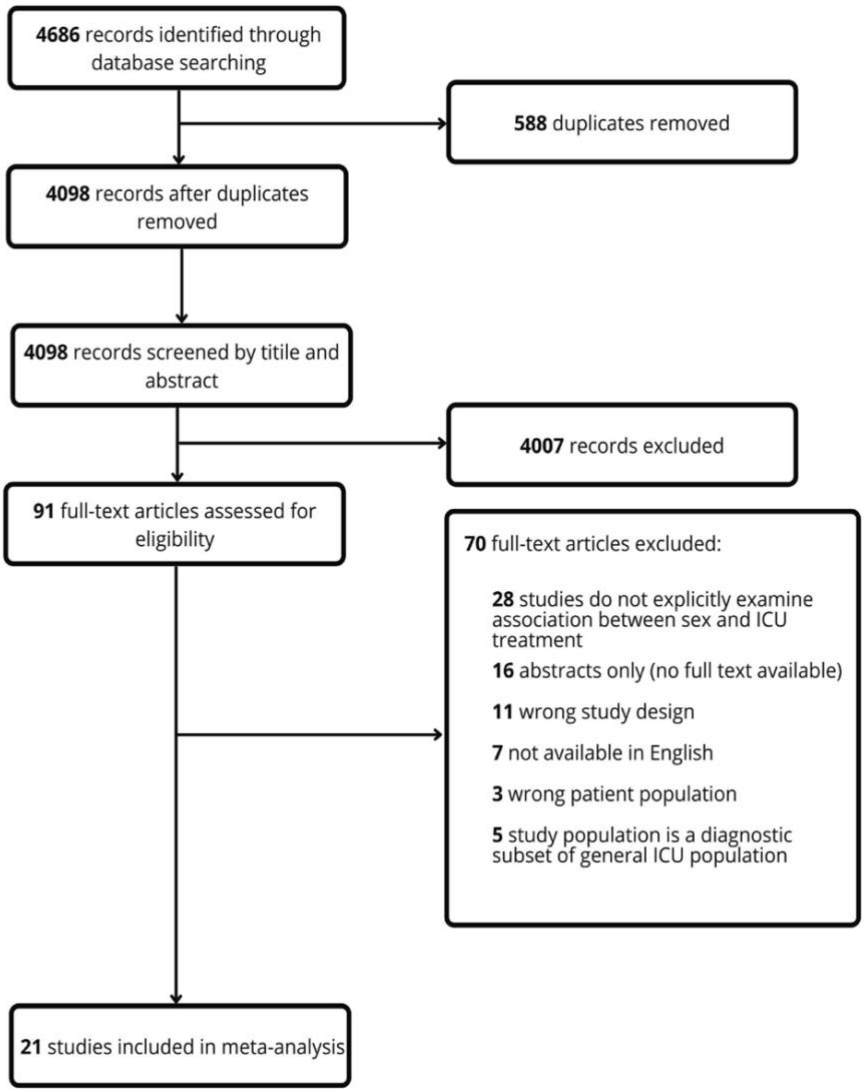
Characteristics of Included Studies

Most studies were from Europe (11 studies) or North America (USA, 7 studies; Canada, 2 studies; Table 5.1). There was one study from Asia (Taiwan) and there were no studies from Africa, South America, or Australasia. Only 5 studies reported sex differences in MV, RRT, or LoS as the primary outcome (20, 69, 89, 105, 159). One study reported sex

differences in use of extra-corporeal membrane oxygenation or tracheostomy as the primary outcome (18); all the other studies examined sex difference in mortality as their primary outcome.

The study populations ranged from 246 to 261,255 participants (median 4420). Eight registry-based studies accounted for approximately 90% of all participants and the largest study (Mahmood 2012 (19)) contributed nearly half of all participants.

Figure 5.1: Flow chart of study selection process



Characteristics of Study Participants

There were 545,538 participants in total, of whom 42.7% were women (range 31.3% to 53.1%). Women were older than men in 11 of the 13 studies that reported a statistically significant age difference between the sexes (range of mean age differences -1 to 6.7 years). The remaining eight studies reported no statistically significant sex difference in age (Table 5.2). Seventeen studies reported sex-disaggregated illness severity scores: nine reported no statistically significant sex difference in illness severity, six reported that women had higher mean illness severity scores and two found that men had higher mean scores.

Table 5.1: Characteristics of Included Studies

Author, year	*Country*	*Study design*	*No. of ICUs*	*Study population*	*% women*	*Treatment outcomes*
Akgun 2010 (69)	USA	prospective	1	309	53.1	MV, RRT, LoS *
Bernard 1993 (159)	USA	retrospective	1	3610	38.6	LoS*
Blecha 2021(18)	Germany	retrospective	6	26,711	35.1	MV, RRT, LoS
Combes 2009 (127)	France	retrospective	1	1341	34.1	MV, RRT, LoS
Epstein 1999 (128)	USA	prospective	1	580	43.1	MV, LoS
Fowler 2007 (23)	Canada	retrospective	13†	24,778	39.8	MV, RRT, LoS,
Guidry 2014(68)	USA	prospective	2	2291‡	34.7	MV, LoS,
Hessey 2020 (89)	Canada	retrospective	17 †	15,238	39.3	MV, RRT*
Hollinger 2019(25)	France, Belgium	prospective	28 †	2087	34.8	MV, RRT, LoS
Kollef 1993 (71)	USA	prospective	3	246	31.3	MV, LoS
Kollef 1997 (70)	USA	prospective	2	357	52.9	MV, LoS
Mahmood 2012 (19)	USA	retrospective	Many†	261,255	44.8	MV, LoS
Nachtigall 2011(29)	Germany	prospective	3	709	43.6	MV, LoS
Reinikainen 2005 (26)	Finland	prospective	18 †	24,341	38.3	LoS
Romo 2004 (120)	Belgium	retrospective	1	4420§	35.9	LoS
Samuelsson 2015 (24)	Sweden	retrospective	65 †	127,254	43.2	LoS
Shen 2011(20)	Taiwan	retrospective	Many†	5882	36.9	MV, LoS*
Valentin 2003 (21)	Austria	prospective	31†	25,998	41.7	MV, RRT, LoS
Vezzani 2011(132)	Italy	retrospective	1	1978	36.2	MV, LoS
Wernly 2020(88)	Europe (21 countries)	prospective	311	7555	47.4	MV, RRT, LoS
Zettersten 2020 (105)	Sweden	retrospective	1	8598	36.5	LoS*
TOTAL				**545,538**	**42.7**	

LoS: length of stay; MV: mechanical ventilation; RRT: renal replacement therapy; *MV, RRT or LoS reported as study's primary outcome; †registry-based studies; ‡trauma and non-trauma cohorts combined using method described by Cochrane (125): §medical and surgical cohorts combined using method described by Cochrane.

Table 5.2: Characteristics of study participants: age, illness severity

Author, year	Mean age Women (SD)	Mean age men (SD)	*p* value	Illness severity score (ISS	Mean ISS, women (SD)	Mean ISS, men (SD)	*p* value
Akgun 2010	75.6 (8.6)	73.7 (8.2)	0.046	APACHE II	23.8 (6.2)	23.1 (6.6)	0.36
Bernard 1993	57.7 (17.4)	55.7 (15.4)	0.13	N/A	N/A	N/A	N/A
Blecha 2021	62.6 (17.0)	61.3 (15.1)	<0.001	SAPS II	32.6 (15.9)	32.3 (15.7)	0.205
Combes 2009	63 (16)	62 (14)	0.22	SAPS II	47 (17)	46 (18)	0.5
Epstein 1999	56 (18)	57 (17)	>0.2	APACHE II	17 (7)	17 (7)	>0.2
Fowler 2007	62.3 (18.5)	61 (17.3)	N/A	APACHE III	52 (36-75)*	52 (36-75)*	N/A
Guidry 2014†	52.5 (18.4)	47.6 (18.6)	<0.001	APACHE II	17.6 (6.27)	17.1 (6.8)	0.013
Hessey 2020	57.3 (17.0)	58.2 (16.4)	0.001	APACHE II	19.0 (8.1)	18.4 (8.1)	<0.001
Hollinger 2019	63 (51-74.8)*	63 (51-74)*	0.590	SAPS II	50 (35-62)*	48 (36-63)*	0.85
Kollef 1993	56.7 (15.6)	62.4 (12.4)	0.0098	APACHE II	16.0 (7.1)	13.7 (7.6)	0.0062
Kollef 1997	62.9 (16.5)	61.6 (17.6)	0.480	APACHE II	17.4 (5.8)	16.6 (5.8)	0.116
Mahmood 2012	63.1 (N/A)	60.6 (N/A)	<0.001	APACHE IV	52.6 (26)	50.3 (26)	<0.001
Nachtigall 2011	68 (54-78) *	66 (51-72)*	<0.05	SAPS II	34 (26-45)*	35 (26-47)*	<0.05
Reinikainen 2005	60.4 (19.9)	57.8 (17.9)	<0.001	APACHE II	17.2 (8.8)	17.0 (9.0)	0.02
Romo 2004	55.5 (19.9)	55.7 (17.7)	0.57	N/A	N/A	N/A	N/A
Samuelsson 2015	63 (43 -75) *	64 (47-74)*	N/A	SAPS III	52 (41-63)*	53 (42-65)*	<0.001
Shen 2011	71 (56-80)*	65 (49-77)*	<0.001	N/A	N/A	N/A	N/A
Valentin 2003	66 (17.4)	59.3 (16.8)	<0.001	SAPS II	28 (20-41)*	26 (18-40)*	<0.01
Vezzani 2011	62 (18)	57 (19)	<0.001	SAPS II	42 (20)	41 (20)	0.388
Wernly 2020	84 (7.4)	83 (7.4)	<0.001	N/A	N/A	N/A	N/A
Zettersten 2020	61 (41-72)*	59 (40-70)*	<0.001	SAPS III	54 (41)	53 (41)	0.52

*median (IQR); †trauma and non-trauma populations combined using method described by Cochrane (125)

Three studies recorded limitations of medical treatment (LoMT) at ICU admission (68, 69, 88). Wernly 2020 found that women were more likely to have LoMT than men; the other two studies reported no difference in LoMT between women and men (88).

Risk of Bias Assessment

Only two studies (9.5%) were considered at low risk of bias across all domains (21, 89) (Table 5.3). An additional 3 studies (16.7%) were rated as low or unclear risk of bias in all domains (18, 24, 26).

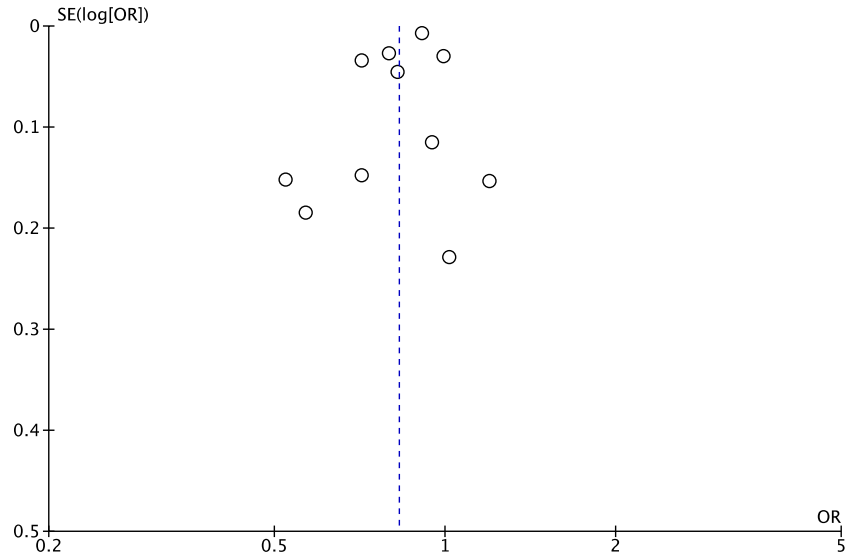
Risk of bias was most often high in the domains of representativeness and comparability. Ten studies (47.6%) were considered poorly representative of the average ICU patient due to being single or dual-centre studies or having major exclusion criteria. Eleven studies (52.4%) did not adjust the treatment outcome for confounders and, therefore, were considered high risk of bias in the comparability domain. These studies often examined treatment as a secondary rather than primary outcome. A funnel plot was reasonably symmetrical, speaking against substantial publication bias (Figure 5.2).

Table 5.3: Risk of bias assessment for included studies

	Study population	*Exposure: women vs men*		*Risk of bias in treatment outcome*		
Author, year	*Representativeness*	*Selection of non-exposed cohort*	*Ascertainment of exposure*	*Comparability*	*Ascertainment of treatment outcome*	*Follow up of treatment outcome*
Akgun 2010 (69)	High	Low	Unclear	High	Low	Low
Bernard 1993	High	Low	Unclear	High	Unclear	Low
Blecha 2021	Low	Low	Unclear	Low	Low	Low
Combes 2009	High	Low	Low	High	High	Low
Epstein 1999	High	Low	Low	High	Low	Low
Fowler 2007	Low	Low	Low	Unclear	Low	High
Guidry 2014	High	Low	Unclear	High	Low	Low
Hessey 2020	Low	Low	Low	Low	Low	Low
Hollinger 2019	Low	Low	Unclear	High	Low	Low
Kollef 1993	High	Low	Unclear	High	Low	Low
Kollef 1997	Unclear	Low	Low	High	Low	Low
Mahmood 2012	Low	Low	Unclear	High	Low	Low
Nachtigall 2011	High	Low	Unclear	Unclear	Low	Low
Reinikainen 2005	Low	Low	Low	Low	Low	Unclear
Romo 2004	Low	Low	Low	High	Unclear	Low
Samuelsson 2015	Low	Low	Unclear	Low	Low	Low
Shen 2011	High	Low	Low	Low	Low	Low
Valentin 2003	Low	Low	Low	Low	Low	Low
Vezzani 2011	Unclear	Low	Low	High	Low	Unclear
Wernly 2020	High	Low	Unclear	Low	Low	Low
Zettersten 2020	High	Low	Unclear	Low	Unclear	Unclear

Criteria for assessment of low risk of bias across each domain (see also figure 3.3)
Representativeness: Truly representative of the average adult ICU patient: consecutive recruitment of all ICU patients and no major exclusion criteria.
Selection of non-exposed cohort: Non-exposed (male) cohort drawn from same population as exposed (female) cohort
Ascertainment of exposure: Sex or gender ascertained from hospital records or database with clear description of process of recording sex or gender information.
Comparability of exposed and unexposed cohorts: treatment outcome adjusted for two or more of age, illness severity, comorbidities or admission diagnosis.
Assessment and ascertainment of treatment outcome: outcome ascertained using a high-quality database or recorded prospectively from hospital records.
Completion of follow up of cohorts: <10% participants had incomplete treatment data and appropriate description and treatment of missing data

Figure 5.2: Funnel plot for use of MV in women compared to men



Sex Differences in MV

Twelve studies including 370,601 participants reported unadjusted MV use in women and men. Women were less likely than men to receive invasive MV on unadjusted analyses (pooled OR, 0.83; 95% CI, 0.77 to 0.89). Heterogeneity in this analysis was high ($I^2 = 90.4\%$; Figure 5.3).

MV use adjusted for at least illness severity and age was reported by six studies with 100,700 participants. Again, women were less likely than men to receive MV and heterogeneity was moderate in this analysis (pooled adjusted OR, 0.89; 95% CI, 0.84 to 0.94, $I^2 = 69.5\%$; Figure 5.4).

Figure 5.3: Unadjusted mechanical ventilation use in women compared to men

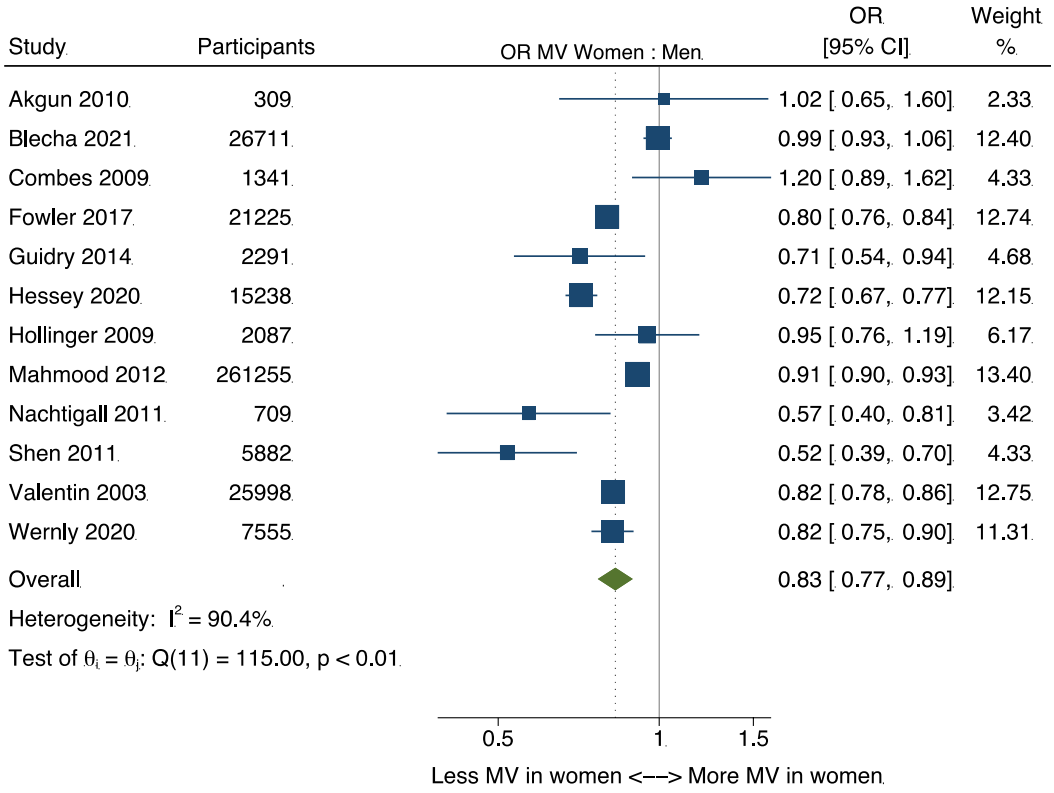
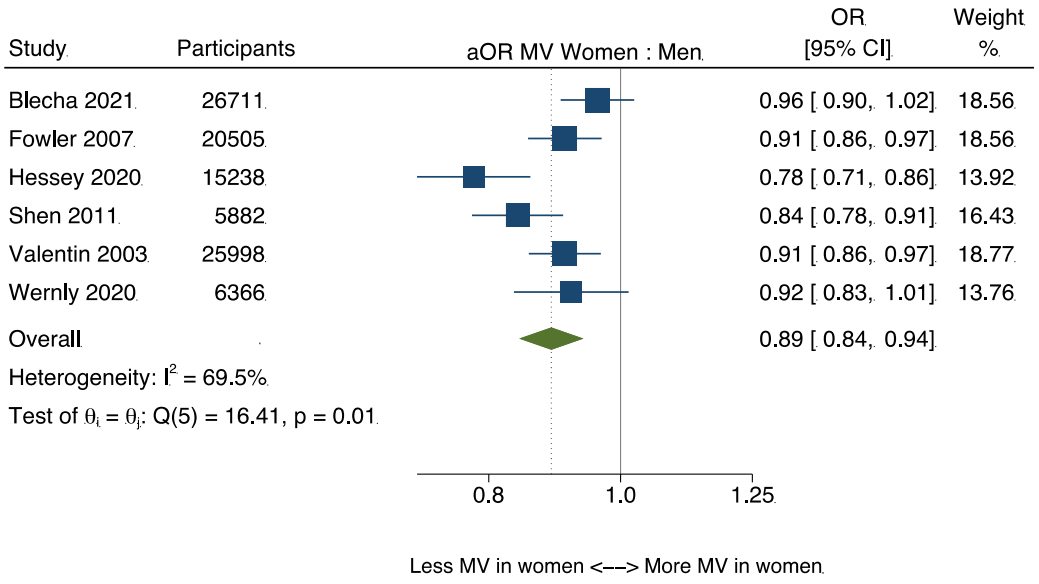


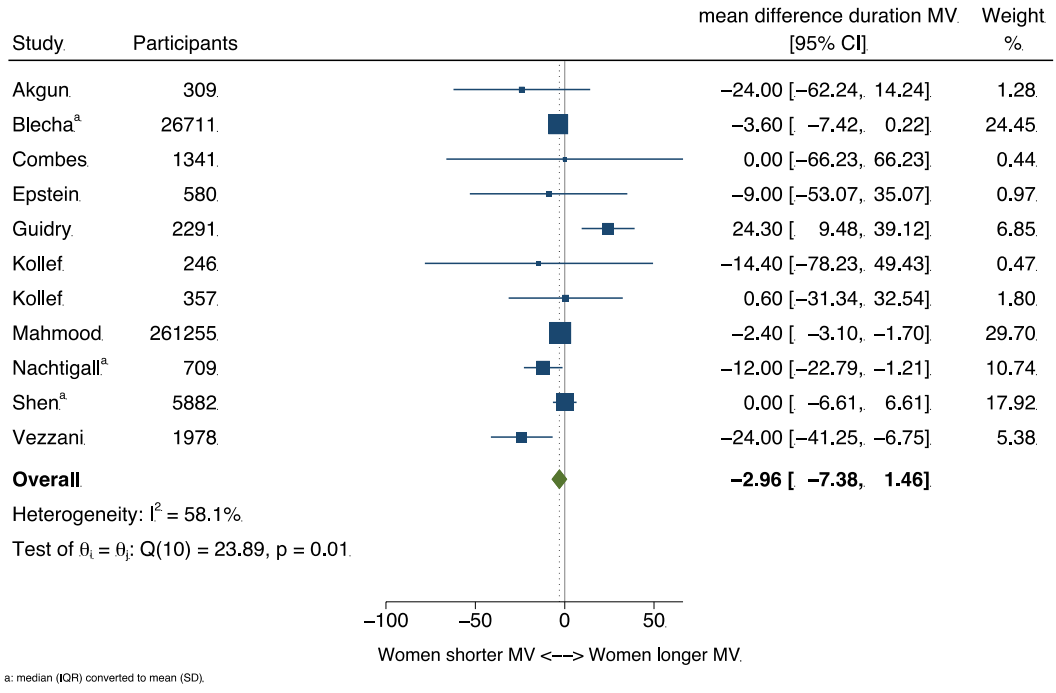
Figure 5.4: Adjusted mechanical ventilation use in women compared to men



*each study adjusted for two or more of age, illness severity, comorbidities or admission diagnosis

Duration of MV was reported in 11 studies with 301,659 participants. There was no statistically significant sex difference in mean duration of MV (pooled mean difference, –2.96 hours; 95% CI, –7.38 to 1.46; $I^2 = 58.1\%$; Figure 5.5).

Figure 5.5: Duration of mechanical ventilation in women compared to men



Sex Differences in RRT

Women were less likely to receive RRT than men in meta-analysis of both unadjusted and adjusted data. Eight studies with 99,744 participants reported unadjusted use of RRT in women compared to men (pooled OR 0.79; 95% CI, 0.70 to 0.90; $I^2 = 76.2\%$; Figure 5.6). Five studies with 94,818 participants reported use of RRT adjusted for at least illness severity and age (pooled adjusted OR = 0.81; 95% CI, 0.73 to 0.89; $I^2 = 57.4\%$; Figure 5.7).

Figure 5.6: Renal replacement therapy in women compared to men (unadjusted)

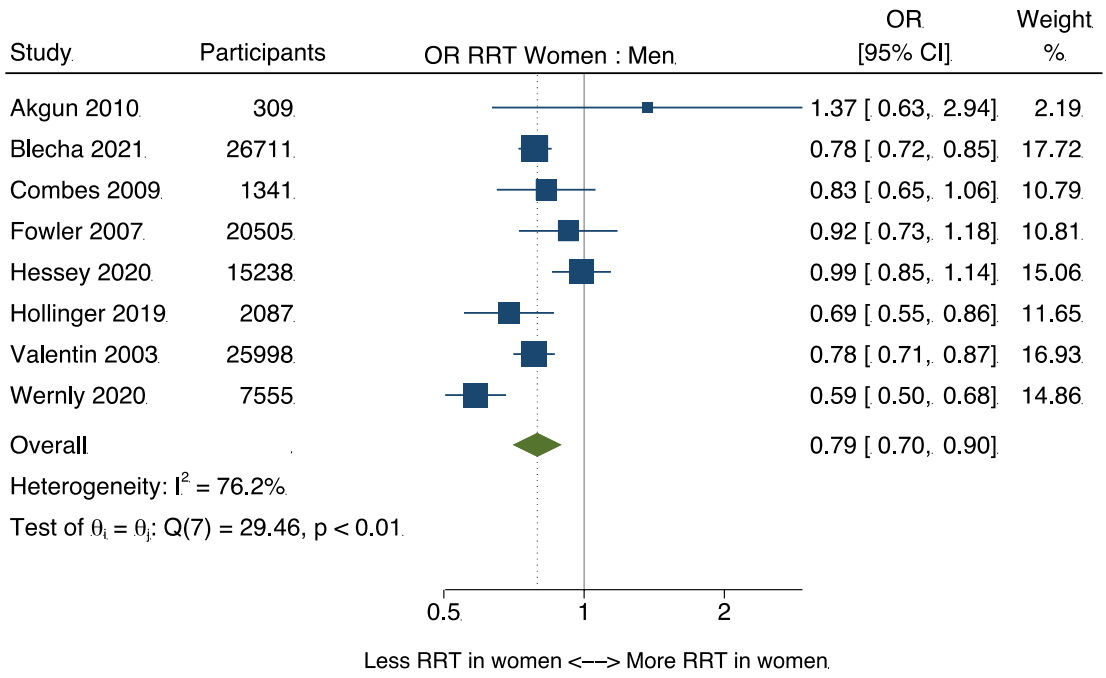
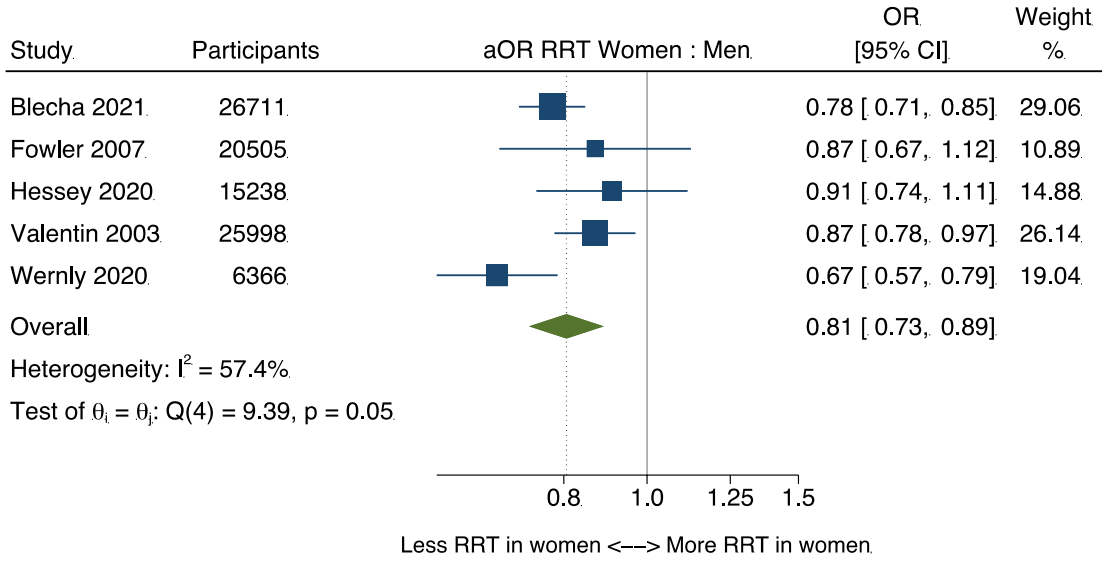


Figure 5.7: Adjusted use of renal replacement therapy in women compared to men



*each study adjusted for two or more of age, illness severity, comorbidities or admission diagnosis

Sex Differences in Length of stay

Unadjusted ICU LoS was reported in 18 studies with 498,796 participants (Figure 5.8). The pooled mean difference in ICU LoS was –0.24 days, (95% CI, –0.37 to –0.12), indicating that women had a shorter ICU LoS than men on average. The heterogeneity in this analysis was high (I^2 = 89.9%).

Three studies (40,494 participants) reported LoS adjusted for at least illness severity and age. Again, women had shorter mean adjusted ICU LoS than men (pooled mean difference, –0.50 days; 95% CI, –0.86 to -0.14; I^2 = 94.1%; Figure 5.9). Two further studies reported that women had shorter adjusted ICU LoS than men however these were not included in the pooled analysis. One study did not present data suitably for pooling (beta coefficient = -0.05, p <0.001,(24) and the other only adjusted for admission diagnosis (mean difference -0.22 days, p<0.001 (159)).

Seven studies with 57,292 participants reported hospital LoS, with no significant difference between women and men on meta-analysis (pooled mean difference, 0.35 days; 95% CI, –0.14 to 0.85; I^2=37.0%; Figure 5.10).

Figure 5.8: ICU Length of stay in women compared to men

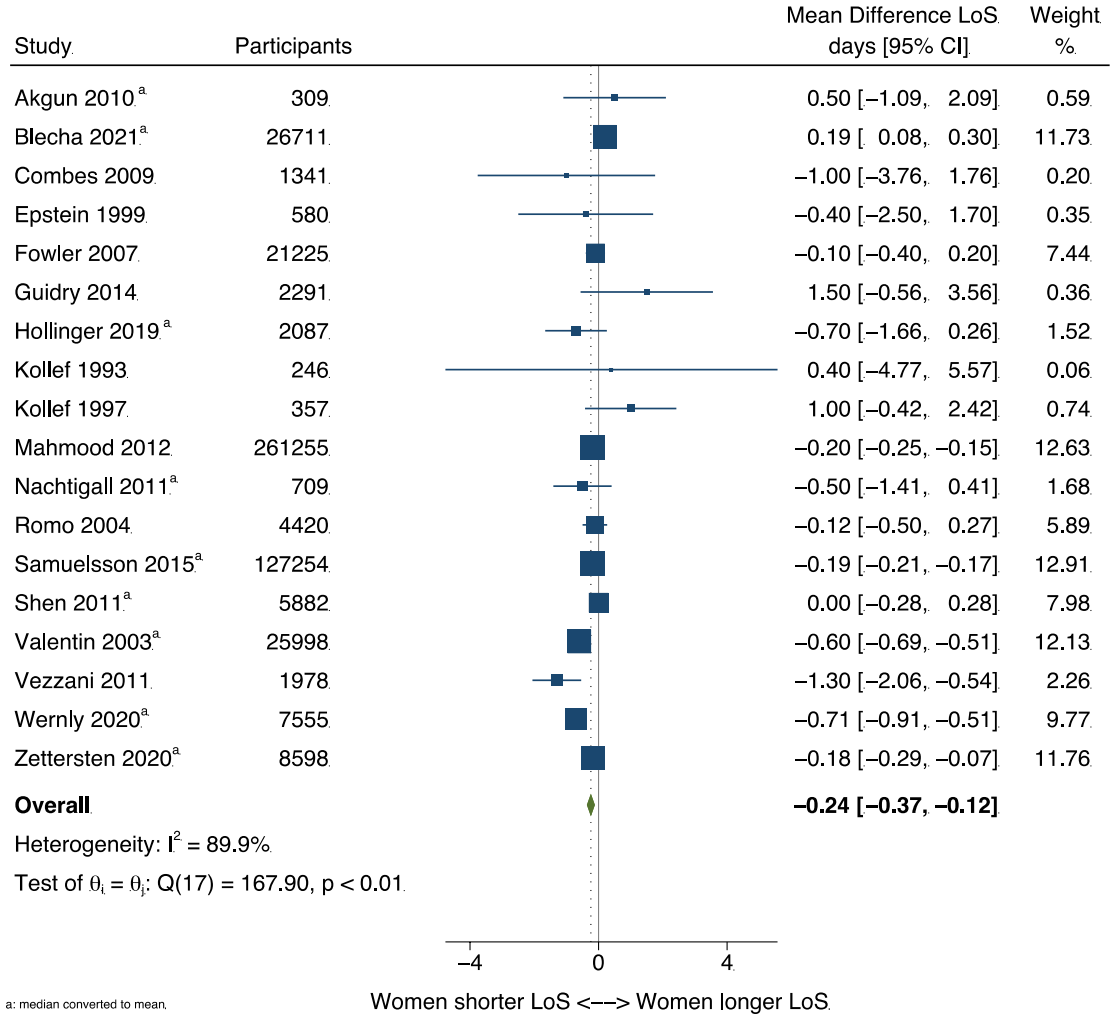


Figure 5.9: Adjusted ICU length of stay in women compared to men

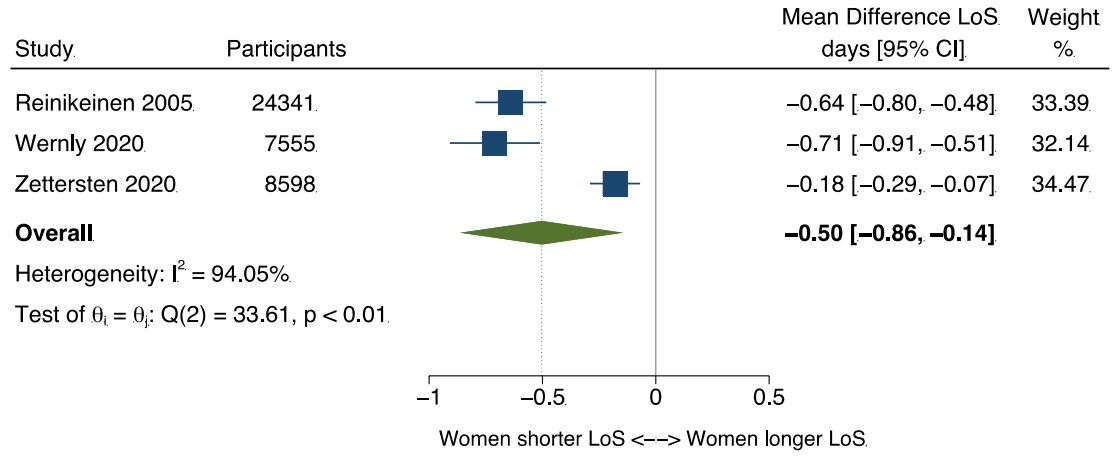
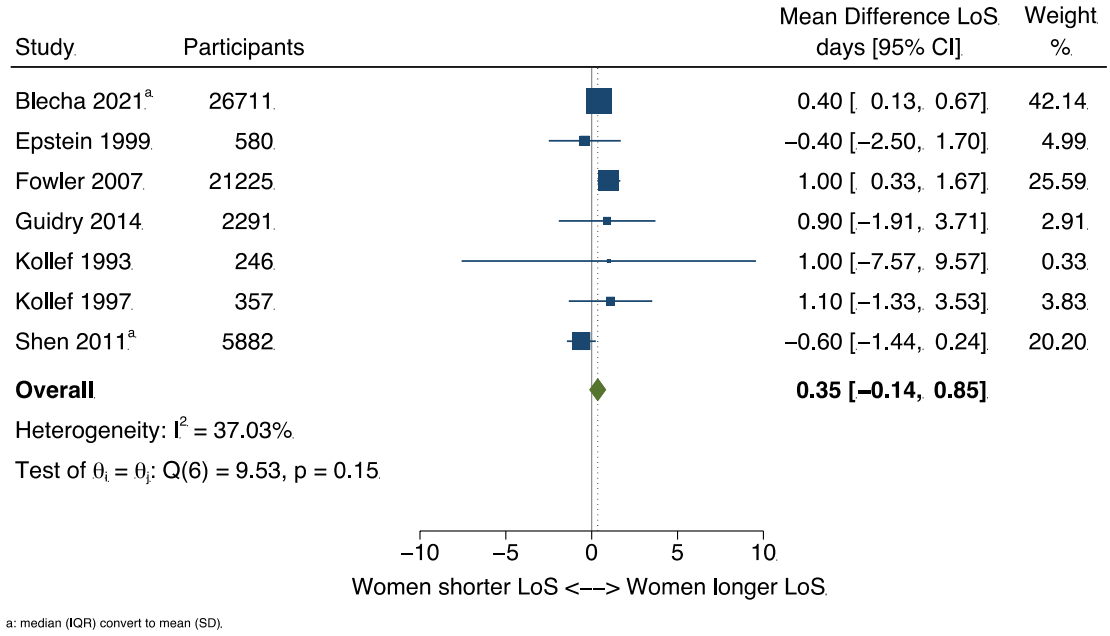


Figure 5.10: Hospital length of stay in women compared to men



Sensitivity and Subgroup Analyses

We performed a pre-specified sensitivity analysis excluding studies considered at high risk of bias in any domain. Three studies with 67,947 participants were included in the sensitivity analyses for MV and RRT use (18, 21, 89). Again, women were less likely than men to receive MV (adjusted OR, 0.89; 95% CI, 0.80 to 0.98; I^2= 84.5%); Figure 5.11) and RRT (adjusted OR, 0.83; 95% CI, 0.76 to 0.92; I^2 = 45.0%; Figure 5.12). We did not perform sensitivity analysis for other outcomes as there was only one eligible study for each (duration MV and hospital LoS: Blecha 2021(18); ICU LoS: Reinikainen 2005 (26)).

We undertook meta-regression to explore heterogeneity in three outcomes: MV use, duration of MV and ICU LoS (Table 5.4). Increasing mean age of the study population modestly amplified the sex difference in duration of MV and ICU LoS: studies with

older populations had relatively shorter duration of MV and ICU LoS in women compared to men (p=0.02 for both; Figure 5.13). Mean age of study population was not associated with sex differences in the use of MV (p=0.88). No other study-level variables significantly contributed to the observed heterogeneity, including mean illness severity score, continent, number of participants and percentage of women (p > 0.05 for all variables; Table 5.4). There were insufficient studies to undertake meta-regression for other outcomes.

Figure 5.11: Adjusted use of mechanical ventilation in women compared to men excluding studies at high risk of bias

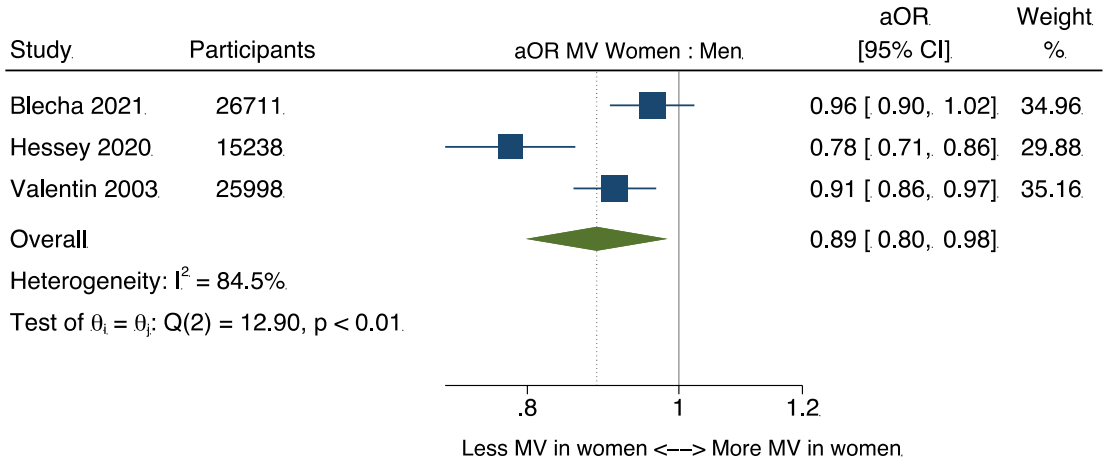


Figure 5.12: Adjusted use of renal replacement therapy in women compared to men excluding studies at high risk of bias

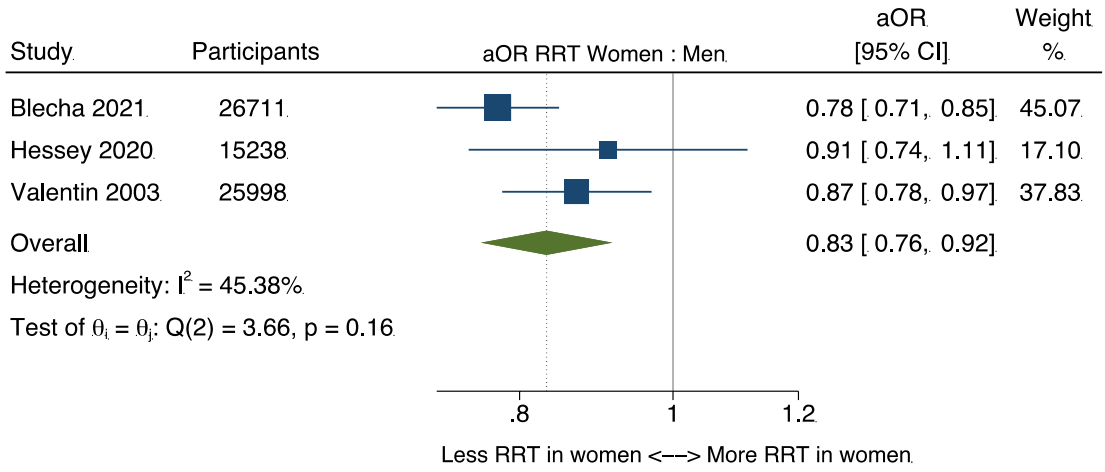


Table 5.4: Meta-regression using a DerSimonian-Laird random effects model

Use of mechanical ventilation in women compared to men (12 studies)

Variable	*Coefficient*	*Standard error*	*p value*
Year	0.001	0.006	0.93
Continent	–0.064	0.078	0.41
Number of participants	<0.001	<0.001	0.36
Percentage women	–0.259	0.926	0.78
Mean age study population	-.001	0.005	0.88
Sex difference in mean illness severity score	0.329	0.924	0.72
Sex difference in mean age	–0.021	0.018	0.23

Duration of mechanical ventilation in women compared to men (11 studies)

Variable	*Coefficient*	*Standard Error*	*p value*
Year	0.289	0.545	0.60
Continent	2.065	4.663	0.66
Number of participants	<0.001	<0.0001	0.87
Percentage women	-61.79	63.46	0.33
Mean age study population	-1.179	0.521	0.02
Sex difference in mean illness severity score	65.84	52.76	0.21
Sex difference in mean age	1.030	1.390	0.46

ICU length of stay of women compared to men (18 studies)

Variable	*coefficient*	*Standard error*	*p value*
Year	0.009	0.009	0.28
Continent	–0.056	0.150	0.71
Number of participants	<0.001	<0.001	0.68
Percentage women	-2.476	1.466	0.09
Mean age study population	-0.021	0.009	0.02
Sex difference in mean illness severity score	-0.592	1.537	0.70
Sex difference in mean age	-0.039	0.032	0.23

Figure 5.13: Meta-regression: Effect of study population age on sex difference in duration of mechanical ventilation

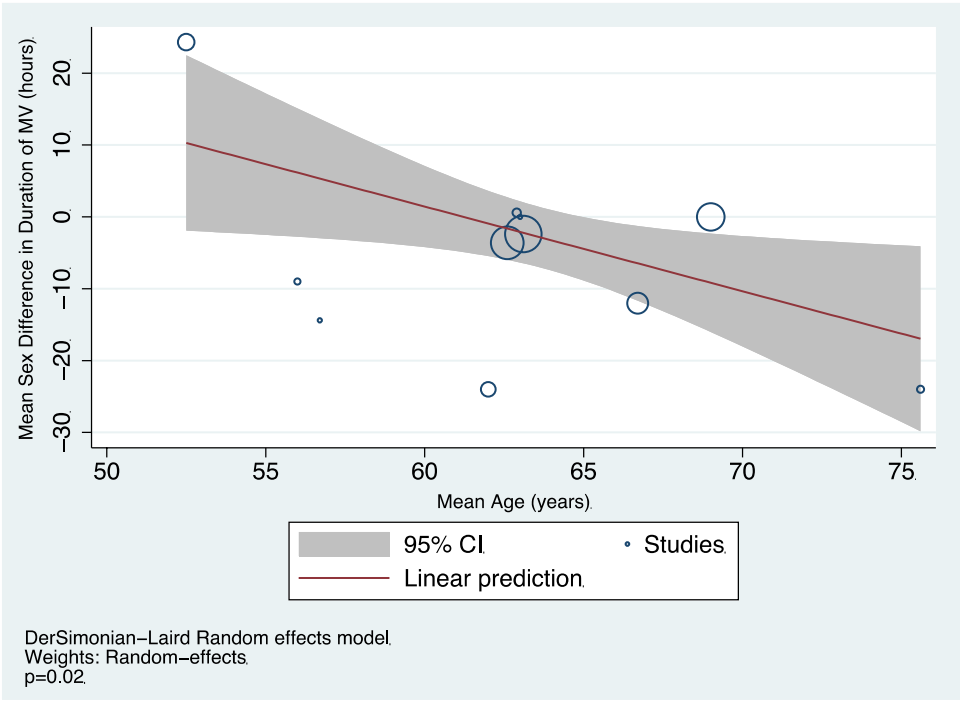
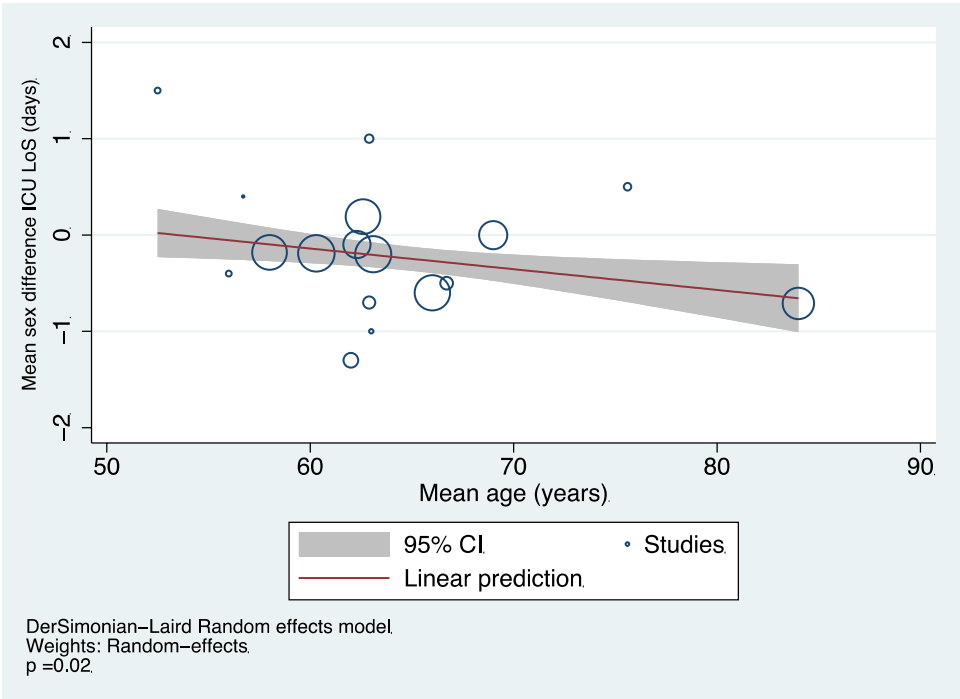


Figure 5.14: Meta-Regression: Effect of study population age on sex difference in ICU length of stay



5.5 DISCUSSION

Key Findings

In this systematic review and meta-analysis, we found that women were less likely than men to receive MV or RRT and had shorter ICU admissions than men. There was no statistically significant difference between the sexes in mean duration of ventilation or hospital LoS. We identified frequent risk of bias and significant heterogeneity within the existing literature. Nonetheless, our key findings were consistent across meta-analysis of adjusted data and unadjusted data, and sensitivity analysis excluding studies at high risk of bias.

Relationship to previous studies

To the best of our knowledge, this is the first systematic review of sex differences in ICU treatment in a general cohort of ICU patients encompassing a broad range of admission diagnoses. A previous systematic review specifically considered sepsis, finding no consistent difference in treatment between men and women (160). In contrast, systematic reviews of the sex differences in cardiac arrest and advanced heart failure found that women received less intensive treatment than men (15, 57). In their recent large study of ICU patients with either cardiovascular or neurovascular diagnoses, Todorov and colleagues also found that women were less likely to receive ICU treatment than men (17). It is possible that sex differences in treatment varies across diagnostic groups of ICU patients.

Our finding that women receive less ICU treatment than men concords with research from other medical specialties. Among patients with chronic kidney disease, fewer women than men receive dialysis (161, 162). This reflects a complex interplay of physiological and sociocultural factors: women have a slower decline in renal function than men and are more likely to refuse dialysis treatment (61, 161). In cardiovascular disease, women are less likely to receive reperfusion therapies after ST-elevation myocardial infarction or cardiac arrest and less likely to receive effective drug

treatments such as anti-platelet therapy or statins (10, 14, 59, 119, 163, 164). This is attributed to sex differences in the efficacy and risk of reperfusion therapies and systemic differences in how clinicians treat women and men (165).

Several studies have reported an interaction between age and sex in ICU treatment and outcomes (17, 20, 23). We found that compared to younger study populations, women in older cohorts spent relatively less time ventilated and in ICU. This may be partly attributed to the withdrawal of invasive support: Block and colleagues described an association between female sex and increasing age of a patient, and the physician's decision to withdraw invasive therapies for that patient (83).

Implications of study findings

We found that women were less likely to receive MV or RRT and spent less time in ICU than men. These interventions – commencing MV, commencing RRT or discharging the patient – are all prescribed by clinicians. There are several plausible reasons why clinicians may be prescribing relatively less ICU treatment for women than men.

First, clinicians could be responding to systemic differences in illness severity between the smaller cohort of women and larger cohort of men admitted to ICU. Our findings make this seem unlikely, as the sex differences persisted when treatment was adjusted for illness severity. Additionally, in 15 of the 17 studies that reported sex-disaggregated illness severity scores, women had similar or higher illness severity score than men.

Second, when deciding whether to intervene with a particular treatment, clinicians often refer to standardized, rather than sex-adjusted, reference parameters. This may promote a tendency to intervene more frequently in men. For example, men have higher serum urea levels than women, which may lead clinicians to prescribe RRT more often in men (166). However, in other instances the sex differences in physiological parameters would tend to support more intensive treatment for women. For example, for most of the lifespan, women have lower blood pressure than men and this would tend to support longer ICU LoS (167).

Third, our findings may reflect the implicit bias of clinicians, who unconsciously provide more intensive treatment for men than women in ICU. A systematic review of 42 studies demonstrated that healthcare professionals hold implicit biases about gender and other variables in a similar manner to the general population, and that these biases can impact upon clinical care (67). Against this, Larsson and colleagues surveyed over 1,000 critical care doctors from 75 countries and found no difference in the approach to ICU triage for hypothetical female and male patients (76). However, it is possible that unconscious bias could manifest when assessing real patients rather than hypothetical patients.

Finally, clinicians could be responding to sex differences in patient preference for treatment. A recent meta-analysis found that women were more likely than men to have limitations to medical treatment (LoMT) at the time of ICU admission (82). However, LoMT provide limited insight into patient treatment preferences, as a minority (5%) of LoMT are made to reflect the patient's own advanced directive (87). The vast majority were made by physicians based on the patient's comorbidities, functional limitations and/or prognosis from their acute illness (87). Therefore, it will be important to establish if women and men have different preferences for treatment in ICU.

Our findings raise an important question for future research: do sex differences in ICU treatment lead to different outcomes for women and men? Our related meta-analysis found that women had slightly higher adjusted ICU mortality than men, but this was not robust to sensitivity analysis (chapter 3). In intensive care, receiving more aggressive treatment does not always lead to a better outcome. For example, RRT can often be safely avoided by taking a conservative approach to its initiation (168). Conversely, delaying intubation may lead to aspiration pneumonia and poorer outcomes overall (169).

Strengths and Limitations

Our study has several strengths. A robust search strategy identified 21 studies with over half a million participants in total, from 4098 potentially eligible publications. We only included studies that focussed specifically on sex differences, rather than simply considering sex as a confounder. Finally, we completed all screening, risk of bias assessment and data extraction independently and in duplicate.

There are also limitations to our review. Most studies reported sex differences in mortality as their primary outcome and sex differences in ICU treatment as a secondary outcome, so did not adjust treatment for important confounders. Therefore, further research specifically dedicated to sex differences in ICU treatment is warranted. We considered only three domains of ICU treatment and did not examine vasoactive medication, extracorporeal circulatory support or other ICU treatments. Finally, duration of mechanical ventilation and length of stay data were not adjusted with death as a competing risk. Our related meta-analysis examining sex differences in ICU mortality found that women had higher risk-adjusted ICU mortality than men (OR 1.25 95% CI 1.03-1.50), therefore, the shorter duration of ICU treatment for women could partly reflect their earlier demise (chapter 3).

There was moderate to high statistical heterogeneity in most analyses in our study. We did not identify significant sources of heterogeneity other than the sex difference in age of study population. Nonetheless, the direction of effect was quite consistent in our analyses.

Finally, most eligible studies were from Europe and North America, so our findings cannot necessarily be generalised to ICU populations elsewhere. Exploring sex differences in the ICU populations of other regions, particularly low and middle-income countries, should be a priority for research.

5.6 CONCLUSION

Our systematic review and meta-analysis found that women received less ICU treatment than men. There is significant heterogeneity and risk of bias in the literature, yet this is a strikingly consistent pattern that warrants further research.

Chapter 6. Sex differences in vital organ support provided to ICU patients

6.1 ABSTRACT

Objective: Critically ill women may receive less vital organ support than men but the mortality impact of this differential treatment remains unclear. We aimed to quantify sex differences in vital organ support provided to adult intensive care unit (ICU) patients and describe the relationship between sex, vital organ support and mortality.

Design: In this retrospective observational study, we examined the provision of invasive ventilation (primary outcome), non-invasive ventilation, vasoactive medication, renal replacement therapy, extra-corporeal membrane support (ECMO), or any one of these five vital organ supports in women compared to men. We performed logistic regression investigating the association of sex with each vital organ support, adjusted for illness severity, diagnosis, pre-existing treatment limitation, year, and hospital. We performed logistic regression for hospital mortality adjusted for the same variables, stratified by vital organ support (secondary outcome).

Setting and Patients: ICU admissions in the Australia and New Zealand Intensive Care Society Adult Patient Database 2018–2021. This registry records admissions from 90% of ICUs in the two nations.

Measurements and Main Results: We examined 699,535 ICU admissions (43.7% women) to 199 ICUs. After adjustment, women were less likely than men to receive invasive ventilation (odds ratio [OR] 0.64 [99% CI 0.63 to 0.65]) and each other organ support except ECMO. Women had lower adjusted hospital mortality overall (OR 0.94, 99% CI 0.91 to 0.97). Among patients who did not receive any organ support, women had significantly lower adjusted hospital mortality (OR 0.82, 99% CI 0.76 to 0.88); among patients who received any organ support women and men were equally likely to die (OR 1.01, 99% CI 0.97 to 1.04).

Conclusion: Women received significantly less vital organ support than men in ICUs in Australia and New Zealand. However, our findings suggest that women may not be harmed by this conservative approach to treatment.

6.2 INTRODUCTION

The provision of vital organ support in the intensive care unit (ICU) should be based upon the patient's physiological derangement and potential to benefit from such treatment. However, there is increasing evidence that a patient's sex, race, and socioeconomic status impact upon treatment they receive in ICU (17, 22, 170, 171).

Regarding patient sex, women appear less likely to receive invasive ventilation, vasoactive medication, renal replacement therapy, extra-corporeal membrane support (ECMO), and tracheostomy than men (17, 18, 90). However, a recent meta-analysis identified significant heterogeneity and risk of bias among existing studies of sex differences in ICU treatment (chapter 5). Many studies did not consider important confounders such as patient illness severity, admission diagnosis, and pre-defined limitations of medical treatment. To understand if the observed sex differences in ICU management represent equitable levels of support, it is important to confirm whether such differences reflect underlying variation in illness severity and treatment limitations, or sex itself.

Accordingly, in this study we aimed to examine sex differences in vital organ support provided to adult ICU patients in Australia and New Zealand. Specifically, we describe sex differences in the use of invasive ventilation, non-invasive ventilation (NIV), vasoactive medication, renal replacement therapy (RRT), ECMO, and any one of these five organ supports. Our primary objective was to test the hypothesis that women would be less likely to receive invasive ventilation than men both before and after adjusting for important confounders. Our secondary objective was to test the hypothesis that there would be a relationship between sex, all forms of vital organ support, and hospital mortality.

6.3 METHODS

Ethics approval

The Alfred Health Human Research Ethics committee granted ethical approval for this study on 1st April 2021 (project number 200/21; 'Sex differences in the outcomes, illness severity and resource use of intensive care patients in Australia and New Zealand'). The project was designed and conducted in accordance with the amended Declaration of Helsinki.

Study design

This is a retrospective observational study of ICU admissions prospectively recorded in the Australia and New Zealand Intensive Care Society's Adult Patient Database (APD). The APD is a clinical registry used for benchmarking of ICUs in Australia and New Zealand. There were 199 contributing ICUs during the study period, representing 90% of all ICUs in the two nations including all tertiary ICUs (8). Data collectors receive regular training and quality assurance review and data is collected using a standardised data dictionary. In addition, regular data checks further ensure the validity of recorded data (150).

Study population

We included ICU admissions recorded in the APD between January 1, 2018, and December 31, 2021. We included patients aged 18 years and over with complete data on sex, use of invasive ventilation, and limitation of medical treatment. If a patient had multiple ICU admissions during the study period only the first ICU admission was included. We excluded patients admitted to ICU for palliative care or consideration of organ donation. We also excluded those classified as intersex, as this group represents less than 0.1% of ICU admissions in Australia and New Zealand (chapter 2).

Explanatory variable: sex

The APD data dictionary defines sex as the biological distinction between men and women; sex data is obtained from medical records. The registry does not record patient gender (43). This reflects current data recording practice in Australian hospital records: patient sex or gender is recorded and it is often unclear which is the intended focus (172). For consistency and readability, in this study we use the term 'sex difference' and compare 'women' and 'men', whilst acknowledging these limitations.

Outcomes: organ support

The primary outcome was sex differences in the provision of invasive ventilation through an artificial airway. Our secondary outcomes were sex differences in the provision of non-invasive ventilation via a mask, vasoactive medication (including inotropes and vasopressors), RRT (including continuous modes and intermittent haemodialysis), ECMO, or the provision of any one of these five vital organ supports.

Statistical analysis

We report counts with percentage (*n* (%)) for categorical variables. We report normally distributed data using means (standard deviation) and compared groups using the Student's t test. For non-parametric data we report median (interquartile range [IQR]) and compared groups using the Wilcoxon rank-sum test. We took $p<0.01$ to indicate statistical significance and report 99% confidence intervals throughout to increase the robustness of our findings.

We performed logistic regression analysis investigating the effect of sex on the provision of invasive ventilation adjusting for Acute Physiology and Chronic Health Evaluation III (APACHE III) score, ICU admission diagnosis, pre-existing limitation of medical treatment (LoMT), admission year, and hospital site. The APACHE III score is an illness severity score that incorporates age; chronic comorbidities including major organ failures, immune disorders and hematological or metastatic malignancy; and

acute physiological derangement. The APACHE III score does not adjust for sex or gender. We adjusted for ICU admission diagnosis based on the ANZICS modification of the APACHE IV diagnosis list, which includes 117 individual diagnoses across both operative and non-operative conditions (43). We repeated this logistic regression analysis for each individual vital organ support, and finally for the provision of any one of the five vital organ supports. Men were the reference sex group, therefore odds ratios (OR) greater than one indicate women were more likely to receive treatment than men. We performed complete case analysis, reporting the total number of patients included in each regression.

To mitigate the survival bias associated with receiving vital organ support at any point during ICU stay, the relationship between mortality and sex was determined separately according to vital organ support status. Therefore, we performed logistic regression for hospital mortality of those who received a vital organ support, and separately, for those who did not receive a vital organ support, adjusted for sex, APACHE III score, admission diagnosis, LoMT, admission year, and hospital site.

To further explore the relationship between illness severity, sex, and vital organ support, we performed subgroup analysis examining two strata of illness severity (below and above the median APACHE III score). We performed a sensitivity analysis excluding patients who received invasive ventilation within 24 hours of ICU admission, to examine patients who deteriorated later in their ICU admission. Similarly, we performed a sensitivity analysis excluding the COVID-19 years 2020 and 2021 as ICU case mix changed in this period. Finally, to estimate the potential impact of unmeasured confounders in this observational study, we calculated E-values for sex differences in the provision of each vital organ support (173) .

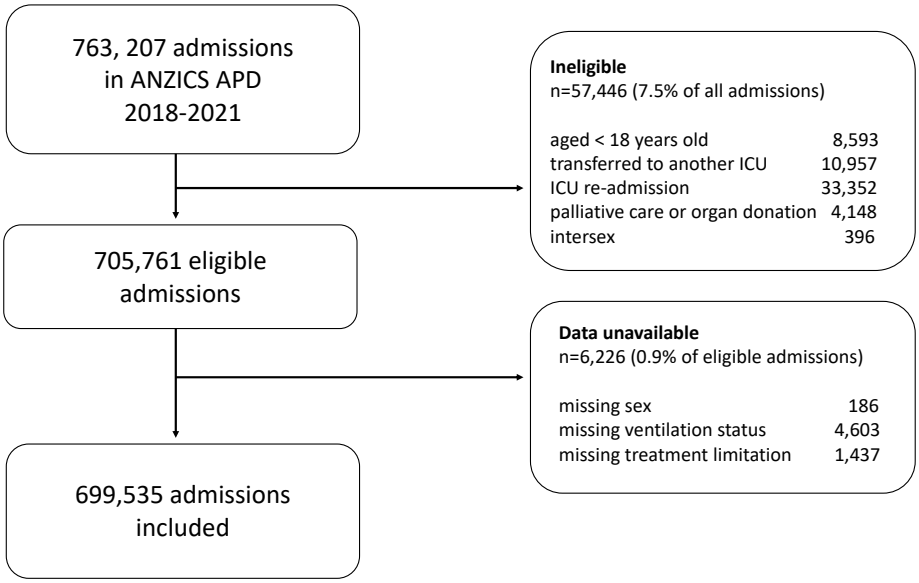
We used STATA/ BE 17 (Statacorp, Texas, USA) for all statistical analysis.

6.4 RESULTS

Study population

There were 763,207 ICU admissions recorded in the binational database during study period. Of these, 57,446 were excluded according to eligibility criteria (Figure 6.1). Data pertaining to patient sex, invasive ventilation, or LoMT were unavailable in 6,226 (0.9%) of eligible admissions. The remaining 699,535 ICU patients were included in our study of whom 305,849 (43.7%) were women.

Figure 6.1: Patient inclusion diagram



Women were younger and had lower illness severity than men (Table 6.1). Despite this, more women than men had a limitation of medical treatment order (LoMT) at ICU admission. Case mix varied between the sexes: women were less likely than men to be admitted due to cardiovascular illness, cardiac surgery, or trauma, and more likely to be admitted with a gastrointestinal, hematological, metabolic, or renal disorder.

Table 6.1: Characteristics of women and men admitted to the intensive care unit

	All patients N=699,535	*Women* n=305,849 (43.7% of all patients)*	*Men* n=393,686 (56.3% of all patients)*
Age, years	62.4 (17.4)	61.4 (18.3)	63.2 (16.6)
APACHE III score	50.1 (23.3)	48.7 (23)	51.2 (23.4)
Admission type			
Elective	275,852 (39.6%)	115,818 (38%)	160,034 (40.8%)
Emergency	420,588 (60.4%)	188,706 (62%)	231,882 (59.2%)
LOMT	53,789 (7.7%)	25,456 (8.3%)	28,333 (7.2%)
Length of ICU stay, hours	41.1 [21.75, 74]	38.4 [21.3, 70.8]	42.8 [22.1, 78,1]
Diagnostic category			
Cardiovascular (excludes cardiac surgery)	92,276 (13.2%)	34,640 (11.4%)	57,636 (14.7%)
Cardiac surgery	70,783 (10.1%)	16,858 (5.5%)	53,925 (13.7%)
Respiratory	99,794 (14.4%)	44,645 (14.6%)	55,149(14%)
Gastrointestinal	116,561(16.7%)	55,979 (18.3%)	60,582 (15.4%)
Neurological	88,014 (12.6%)	42,679 (14%)	45,335 (11.5%)
Trauma	32,155 (4.6%)	9,761 (3.2%)	22,394 (5.7%)
Sepsis	53,285 (7.6%)	23,798 (7.8%)	29,487 (7.5%)
Metabolic, hematological, renal & genitourinary	95,934 (13.7%)	52,099 (17.1%)	43,835 (11.2%)
Musculoskeletal, soft tissue & skin	49,419 (7.1%)	24,732 (8.1%)	24,687 (6.3%)
ICU mortality	30,891 (4.4%)	12,287 (4%)	18,604 (4.7%)
Hospital mortality	48,890 (7%)	19, 679 (6.5%)	29,211 (7.5%)

Data are presented as number and percentage of patients, mean and standard deviation (SD) or median and interquartile range [IQR].* all variables were significantly different between women and men, $p<0.001$; using t-test or Wilcoxon-rank sum as appropriate.

Use of vital organ support

A lower percentage of women than men received each vital organ support (Table 6.2). This sex difference was largest for the provision of invasive ventilation (25.7% women vs. 37.3% men). Moreover, women who received invasive ventilation and vasoactive medication had significantly higher mean APACHE III scores than men who received these treatments. In contrast, women who received NIV or ECMO had lower illness severity scores than men.

After adjustment for illness severity, diagnosis, LoMT, year, and hospital site, women were significantly less likely to receive each vital organ support except for ECMO (Figure 6.2). This sex difference was most pronounced in the provision of invasive ventilation (OR 0.64, 99% CI 0.63 to 0.65; Figure 6.2, Table 6.3). After adjustment for confounders, ECMO was the only vital organ support that women and men were equally likely to receive.

Table 6.2: Vital organ support provided to women and men

	Patients receiving vital organ support	*Women receiving vital organ support*	*Men receiving vital organ support*	*Mean APACHE III of women receiving vital organ support*	*Mean APACHE III of men receiving organ support*	*Absolute difference in mean APACHE III score, women compared to men (99% CI)*
Invasive ventilation (N=697,785)	225,306 (32.2%)	78,510 (25.7%)	146,796 (37.3%)	60.8 (27.3)	58.6 (26.6)	2.2 (1.9 to 2.5)
Non-invasive ventilation (N=583,077)	62,849 (10.8%)	27,221 (10.6%)	35,628 (10.9%)	59 (23.2)	60.1 (23.7)	-1.1 (-1.6 to -0.6)
Vasoactive medication (N=587,709)	214,398 (36.3%)	81,940 (31.7%)	132,458 (39.8%)	62.9 (25.9)	62.5 (25.6)	0.4 (0.05 to 0.6)
Renal replacement therapy (N=575,376)	23,399 (4.1%)	8,688 (3.4%)	14,711 (4.6%)	87 (28.6)	86.9 (27.9)	0.1 (-0.9 to 1.1)
ECMO (N=574,751)	1,580 (0.3%)	549 (0.2%)	1,031 (0.3%)	78.7 (32.5)	84.3 (33.7)	-5.6 (-10.1 to -1)
Any vital organ support (N=609,329)	339,722 (55.1%)	131,493 (49.4%)	208,229 (59.5%)	59.5 (25.2)	59.1 (25.2)	0.4 (0.2 to 0.7)

Data are presented as number and percentage of patients, mean with standard deviation (SD), absolute difference in means (99% CI) or odds ratios (99% CI). N indicates patients with complete data

Figure 6.2: Vital organ support provided to women compared to men, adjusted for confounders

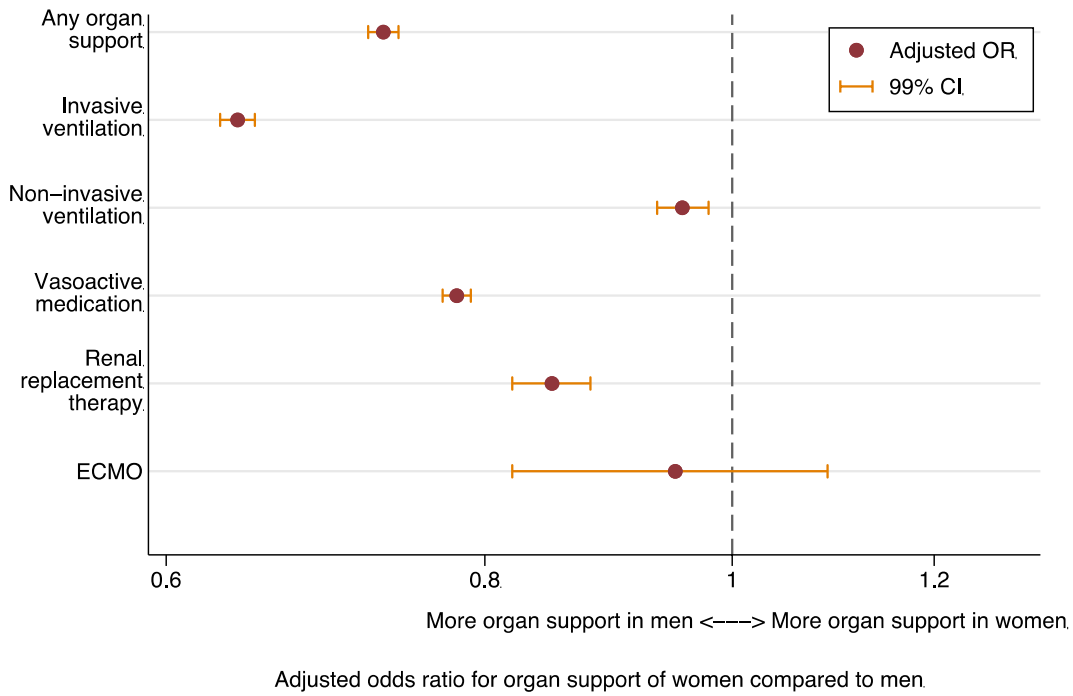


Figure legend: Odds ratio for provision of vital organ support to women compared to men, adjusted for admission diagnosis, APACHE III score, LoMT, admission year, and hospital site. Each red dot represents the adjusted odds ratio for provision of the named organ support to women compared to men. The capped orange line represents the associated 99% confidence interval. The vertical dashed line marks an odds ratio of 1, the point at which women and men were equally likely to receive the organ support.

Sex differences in hospital mortality and their relation to vital organ support

The unadjusted hospital mortality was lower among women than men (6.5% vs. 7.5%, p<0.001). Women also had lower hospital mortality (OR 0.94, 99% CI 0.91 to 0.97) after adjustment for APACHE III score, admission diagnosis, LoMT, admission year, and hospital site.

The lower mortality among women, however, was related to the subgroup of patients who did not receive any vital organ support (Figure 6.3). In contrast, among patients who received one or more vital organ supports, women and men were equally likely to die. Among patients who did not receive invasive ventilation, women were less likely to die than men; among patients who received invasive ventilation, women were more likely to die than men (Figure 6.3).

Figure 6.3: Adjusted hospital mortality of women compared to men, stratified by provision of vital organ support

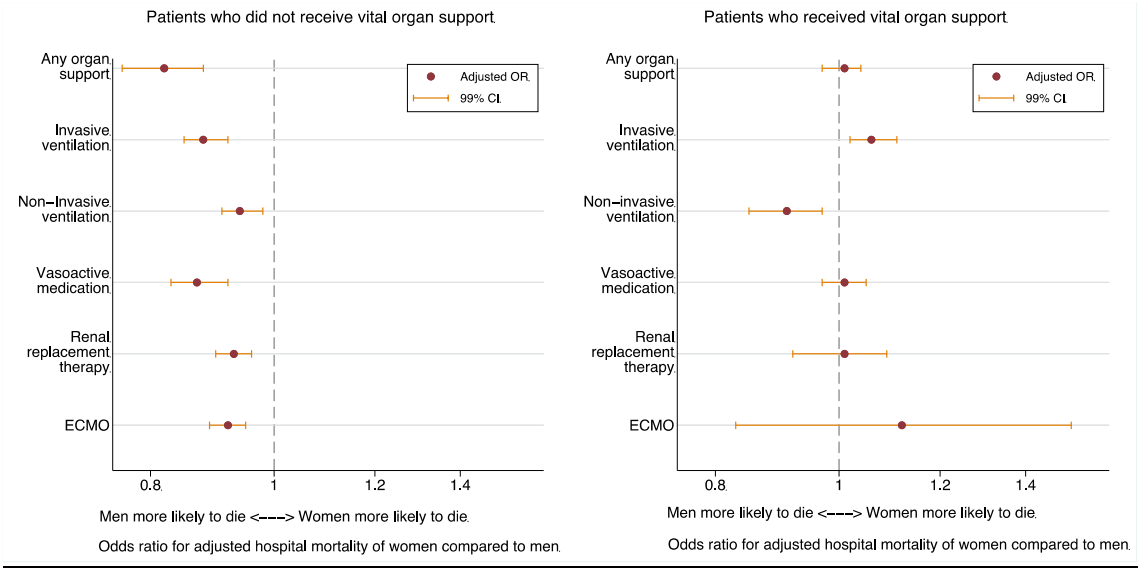


Figure legend: Odds ratio for hospital mortality, adjusted for admission diagnosis, APACHE III score, LoMT, admission year, and hospital site. The analysis is stratified by vital organ support provided: the left-hand figure examines patients who did not receive the named organ support, the right-hand figure examines patients who did receive the named organ support. Each red dot represents the odds ratio for hospital mortality, the associated 99% confidence interval is represented by a capped orange line.

Subgroup and sensitivity analyses

In subgroup analysis according to illness severity (Table 6.4), the higher-risk group showed no overall sex difference in adjusted hospital mortality, yet women were still significantly less likely to receive invasive ventilation after adjustment for confounders. In contrast, in the lower risk group, women had a lower adjusted hospital mortality than men and were much less likely to receive invasive ventilation (Table 6.4). Again, this survival advantage for women was related to patients who did not receive invasive ventilation. Among lower-risk patients who received invasive ventilation, women were more likely to die than men.

On sensitivity analysis that excluded patients ventilated on their first day in ICU, women were still less likely than men to subsequently receive invasive ventilation (adjusted OR 0·68, 99% CI 0·65 to 0·71). Further, during the pre-COVID-19 period (2018 & 2019) women were again less likely to receive invasive ventilation (adjusted OR 0·65, 99% CI 0·64 to 0·67).

Table 6.3: Full regression models

	Hospital Mortality (n=694,857)	*Invasive ventilation (n=697,785)*	*Non-invasive ventilation (n=583,077)*	*Vasoactive medication (n=587,709)*	*Renal Replacement therapy (n=575,376)*	*ECMO (n=574,751)*	*Any treatment (n=609,329)*
Sex: female	0.94 (0.91 to 0.97)	0.64 (0.63 to 0.65)	0.96 (0.93 to 0.98)	0.78 (0.77 to 0.79)	0.85 (0.82 to 0.88)	0.95 (0.82 to 1.09)	0.73 (0.72 to 0.74)
APACHE III risk of death†	1.06 (1.059 to 1.061)	1.024 (1.024 to 1.025)	1.014 (1.014 to 1.015)	1.039 (1.038 to 1.04)	1.045 (1.044 to 1.046)	1.038 (1.036 to 1.041)	1.049 (1.048 to 1.05)
LoMT	3.6 (3.46 to 3.74)	0.29 (0.28 to 0.30)	2.22 (2.14 to 2.29)	0.84 (0.81 to 0.86)	0.48 (0.45 to 0.51)	0.08 (0.04 to 0.14)	0.99 (0.96 to 1.02)
Year‡	0.97 (0.96 to 0.99)	0.97 (0.96 to 0.98)	0.9 (0.89 to 0.91)	1.06 (1.05 to 1.07)	0.99 (0.98 to 1.01)	1.05 (0.98 to 1.11)	0.92 (0.92 to 0.93)

Data are presented as odds ratios with 99% confidence intervals. *excluding odds ratios for individual hospital sites †incorporates APACHE III score and admission diagnosis; the odds ratio represents the increased risk associated with a 1% increase in risk of death. ‡Odds ratio represents annual change in risk over duration of study

Table 6.4: Subgroup analysis according to illness severity

Illness severity category	*Invasive ventilation use, unadjusted*		*Use of invasive ventilation, adjusted OR women compared to men* (99% CI)*	*Hospital mortality, unadjusted*			*Hospital mortality of women compared to men, adjusted OR* (99% CI)*		
	Women	Men		All patients	Women	Men	All patients	Received ventilation	No ventilation
Low† *(n=350,638)*	26,220 (16.2%)	54,053 (28.6%)	0.53 (0.52 to 0.55)	3,294 (0.9%)	1,369 (0.9%)	1,925 (1%)	0.83 (0.75 to 0.91)	1.17 (1.01 to 1.36)	0.72 (0.64 to 0.83)
High (n=348,460)	52,249 (36.3%)	92,644 (45.3%)	0.76 (0.74 to 0.77)	45,539 (13.1%)	18,286 (12.8%)	27,253 (13.4%)	0.97 (0.94 to 1)	1.03 (0.99 to 1.08)	0.93 (0.89 to 0.97)

Data are presented as number with percentages or odds ratios with 99% confidence intervals.
*adjusted for APACHE III score, diagnosis, LoMT, admission year and hospital site. †below median APACHE III score for overall study population

Regarding potential unmeasured confounding, the E-value for the association of sex with invasive ventilation was larger in magnitude than the point estimate odds ratio (E-value 1.81 vs OR 0.64 (inverse OR 1.56); E-value for confidence interval 1.79). Therefore, any unmeasured confounder/s would need a stronger association than that observed between sex and vital organ support to explain away this primary finding. We observed the same pattern in E-values for the association between sex and each other organ support except ECMO (Table 6.5).

Table 6.5: E-values for association between sex and vital organ support

	Odds ratio for sex, Point estimate (99% CI)	*Inverse odds ratio, (99% CI)*	*E-value, (E value associated with confidence interval)*
Invasive ventilation	0.64 (0.63 to 0.65)	1.56 (1.54 to 1.59)	1.81 (1.79)
Non-invasive ventilation	0.96 (0.93 to 0.98)	1.04 (1.02-1.08)	1.17 (1.11)
Vasoactive medication	0.78 (0.77 to 0.79)	1.28 (1.27-1.30)	1.52 (1.5)
Renal replacement therapy	0.85 (0.82 to 0.88)	1.18 (1.14-1.22)	1.63 (1.53)
ECMO	0.95 (0.82 to 1.09)	1.05 (0.92-1.22)	1.29 (1)
Any treatment	0.73 (0.72 to 0.74)	1.37 (1.35-1.39)	1.62 (1.6)

6.5 DISCUSSION

Key findings

In this large retrospective study of patients treated in 199 Australian and New Zealand ICUs, women received less vital organ support than men before and after adjustment for important confounders including diagnosis, illness severity score, treatment limitation (LoMT), year and hospital site. Compared to men, women were less likely to receive invasive ventilation, non-invasive ventilation, vasoactive medication, and renal replacement therapy, but equally likely to receive ECMO.

Despite receiving less vital organ support, women were less likely to die than men, even after adjustment for illness severity and other key confounders. This survival advantage was related to lower mortality among women in the subgroup of patients who did not receive any vital organ support. In contrast, among patients who received one or more vital organ supports, women and men were equally likely to die.

Comparison to other studies

Our finding that women were less likely than men to receive invasive ventilation and other vital organ supports except ECMO is consistent with many previous reports including our 2022 meta-analysis (18, 20, 21, 23, 24, 88-90). Of note, few previous studies have examined sex differences in the provision of ECMO. These had small case cohorts; a shortcoming which also applied to our ECMO cohort (13, 18).

In contrast to previous studies, we examined a comprehensive population of adult ICU patients across two nations with broadly consistent findings across multiple organ supports. Moreover, we adjusted for pre-defined limitations of medical treatment (LoMT), so the observed sex differences cannot be attributed to LoMTs. This is important because women were more likely than men to have a LoMT recorded prior to ICU admission. This disparity in LoMT is consistent with previous studies and may represent another systemic difference in the treatment of women and men (81, 82).

Unlike most previous studies, the women in our study population were younger, had lower illness severity scores and lower adjusted mortality than the men (17, 90). Therefore, we must consider whether the women in our study simply had less need for organ support – or even ICU admission – than men. However, we adjusted for both illness severity and ICU admission diagnosis in our logistic regression model for the provision of each organ support. Furthermore, in the highest-illness severity subgroup of patients, women had equivalent hospital mortality to men yet were significantly less likely to receive invasive ventilation. These observations support a true disparity in treatment provided to women and men.

Implications

There are several possible reasons why women received less vital organ support than men in our study. Clinicians may have underestimated illness severity in women or conversely overestimated illness severity in men. Such disparities in illness recognition are described elsewhere, for example women are more likely to have delayed diagnosis of myocardial infarction and delayed revascularisation (7). However, women were admitted to ICU at lower illness severity than men which suggests that clinicians did not systematically underestimate their illness severity. Admitting women to ICUs at lower illness severity may have facilitated observation and timely non-invasive treatment, averting the need for vital organ support.

Clinicians may believe that women prefer a more conservative approach to treatment than men, or women may choose more conservative treatment for themselves (17). In our study, women had more limitations to treatment *despite* having lower illness severity than men overall. We do not know what proportion of these LoMTs reflected the patients' own advanced directives or were based on the clinician's assessment of prognosis. Previous studies suggest that a minority of LoMTs are based on the patient's directives. Instead, most LoMTs are defined by clinicians based on perceived prognosis and potential to benefit from treatment (81, 87).

Finally, the observed sex differences in vital organ support may be related to the use of standardised rather than sex-adjusted physiologic treatment thresholds. For example, women have lower baseline serum urea levels than men, so a standardised urea threshold for commencing RRT would lead to more men receiving RRT than women. However, this does not readily explain the observed sex differences in the provision of vasoactive medication or ventilation.

In our second key finding, among those patients who did not receive vital organ support, women had lower hospital mortality than men, and, in contrast, equivalent hospital mortality to men among those who did receive vital organ support. This suggests that either the conservative approach to treatment was particularly beneficial

for women (or injurious to men), or that conservative treatment could potentially benefit all patients but was applied to women more frequently.

Avoiding vital organ support may be particularly beneficial to women because these treatments may be poorly tailored for female patients. For example, women intubated for respiratory failure are less likely to receive lung protective ventilation, instead receiving higher weight-adjusted tidal volumes than men (174). This leads to another possible explanation for the sex difference in vital organ support: clinicians may have correctly perceived the relative advantage to women of avoiding vital organ support and deliberately adopted a more conservative approach.

Alternatively, our findings may represent a natural experiment in which a higher treatment threshold was applied to one group of patients – women – with favourable outcomes. This leads to the hypothesis that all patients, including men, could benefit from a more conservative approach to treatment. While this hypothesis cannot be confirmed based on our observational study, there is some evidence from randomised clinical trials supporting a 'less is more' approach to treating critical illness (175-177).

Our study demonstrates that we cannot assume that critical care interventions are applied equally between the sexes, nor that women and men have similar outcomes from these interventions. Therefore, it is vital that critical care trials present sex-disaggregated data with sex-based subgroup analyses.

Strengths and Limitations

This study has several key strengths. It is the largest study of sex differences in the treatment of ICU patients to date, including most adult ICU patients in Australia and New Zealand during the study period. Our results are robust across several types of vital organ support, novel in scope, and carry important implications.

We also acknowledge limitations to our study. As an observational study, we cannot determine the underlying cause for the observed sex differences in vital organ support,

nor the direction of the relationship between sex, vital organ support, and hospital mortality. We examined patients admitted to ICU rather than all critically unwell patients therefore we cannot exclude the possibility that ICU admission collides with the relationship between patient sex and vital organ support, introducing bias. We could not test counterfactuals – for example, what if more men were admitted for observation only? What if more women received vital organ support? – and this necessarily limits our conclusions. Additionally, we did not have data on the time to initiation of vital organ support, which may be an important determinant of outcome following such support.

Whilst we had complete data on provision of invasive ventilation, data on other organ supports was missing for a minority of patients. The impact of data missingness on our findings may be mitigated by the fact that the sex balance among patients with missing data reflected the study population overall.

Another limitation concerns the sex data, which is recorded in the APD from medical records and may have been self-reported or determined by clinicians or clerical staff. In the absence of an accompanying gender variable, the observed differences between 'women' and 'men' likely represent aspects of both biologically affected sex and socially grounded gender. The terms sex and gender are often used interchangeably in critical care research and health research more broadly (172, 178, 179). Sex and gender also interact: the social context of men and women affects their biological differences and vice versa (178). Therefore, the 'sex differences' observed here may be more accurately characterised as 'sex/gender' differences. Furthermore, we considered only a binary definition of sex, so we are unable to comment upon the treatment and outcomes of intersex or non-binary ICU patients. Understanding the characteristics of critical illness in non-binary people is essential to ensuring equitable healthcare.

There is a relatively low illness severity and mortality in our study population compared to other similar studies, which could limit the generalisability of our findings (21, 23). However, our key finding of sex differences in the use of invasive ventilation persisted in the subgroup at highest risk of death. Moreover, the use of invasive ventilation in our

study population (approximately one in three patients) is in keeping with recent large studies of sex differences in ICU treatment (17, 19, 88). Finally, our findings may reflect the sociocultural context of Australia and New Zealand, though they are consistent with previous studies from high-income countries (chapter 5).

6.6 CONCLUSION

Among adult patients admitted to Australian and New Zealand ICUs, women received less vital organ support than men even after adjustment for important confounders including diagnosis, illness severity, and LoMT. Despite receiving less invasive therapy, women were also less likely to die than men. This survival advantage for women was confined to the subgroup of patients who did not receive any vital organ support. In contrast, among patients who received one or more vital organ supports, women and men were equally likely to die.

These observations suggest that critically ill women received more conservative treatment than men, and that, paradoxically, they may not have been harmed by this approach.

Chapter 7. Epidemiology of intensive care patients classified as a third sex

7.1 ABSTRACT

Background: Patient sex affects treatment and outcomes in critical illness. Previous studies of sex differences in critical illness compared female and male patients. In this study we describe the group of patients classified as a third sex admitted to intensive care units (ICUs) in Australia and New Zealand.

Research question: What are the admission characteristics and outcomes of ICU patients classified as belonging to a third sex group, compared to patients classified female or male?

Study design and methods: Retrospective observational study of admissions to 200 ICUs, recorded in the Australia and New Zealand Intensive Care Society's Adult Patient Database 2018–2022. We undertook mixed effect logistic regression to compare hospital mortality across the sex groups, adjusted for illness severity, diagnosis, treatment limitation, year and hospital.

Results: We examined 892,161 admissions, of whom 525 (0.06%) were classified as third sex. Patients classified as third sex were represented across all diagnostic categories, jurisdictions, and hospital types. On average, they were younger than the groups classified as female (59.2+/-20.0 years vs 61.3+/-18.4 years, p=0.02) or male (63.2+/-16.7 years, p<0.001). Patients classified as third sex were more likely to be admitted following orthopedic surgery (10.1% third sex admissions (95% CI 7.7-13.0%) vs 6.2% female (95% CI 6.1-6.3%); 4.8% male (95% CI 4.7-4.9%)) and drug overdose (8.8% third sex admissions (95% CI 6.5-11.5%) vs 4.2% female (95% CI 4.1-4.2%); 3.1% male (95% CI 3.0-3.1%)). There was no difference in the adjusted hospital mortality of patients classified as third sex compared to the other groups.

Interpretation: Patients classified as third sex composed a small minority of adult ICU patients. This group had a different diagnostic casemix, but similar outcomes, to the groups classified as female or male. Further characterizing a third sex group will require improved processes for recording sex and gender in health records.

7.2 BACKGROUND

Patient sex affects illness severity, treatment, and outcomes in critical illness. Female patients are less likely than male patients to receive ventilation, vasoactive medication and renal replacement therapy in the intensive care unit (ICU) (17, 21, 88). There are also significant sex differences in illness severity and hospital mortality within many diagnostic groups of ICU patients (79, 180).

Studies to date on sex differences in critical illness have compared female and male patients; no studies considered a third sex category (chapter 3). This is an important omission. People who have an innate variation in sex characteristics or intersex trait, defined as a variation in sex characteristics or development that differs from medical norms for female or male, are estimated to comprise up to 1.7% of the general population (36, 37). Zeeman and Aranda's 2020 systematic review identified a range of health inequalities encountered by people with innate variations in sex characteristics (181). These inequalities may be amplified by the use of binary sex categories in healthcare and health research (181).

In 2016 the Australia and New Zealand Intensive Care Society's Adult Patient Database (henceforth APD) added a third sex option to the patient sex variable, presenting an opportunity to examine the epidemiology of this group of ICU patients (43). The APD does not record patient gender, therefore the population of people characterized as belonging to a third sex may include transgender and gender-diverse people, including trans men, trans women and non-binary people (people who have a gender that does not fit exclusively into the woman/man gender binary)(182). Nonetheless, describing key characteristics of this group can help to inform future sex and gender-sensitive critical care research and highlight any necessary amendments to the process of recording sex and gender in the hospital medical record and critical care registries.

We undertook a retrospective observational study of adult ICU patients in Australia and New Zealand, describing the epidemiology of patients classified as belonging to a third sex group, compared to the groups classified as female or male. Our primary objective

was to describe the prevalence, characteristics, treatment, and comparative outcomes of adult intensive care patients classified as third sex. We hypothesized that compared to patients classified as female or male, patients classified as third sex would have significantly different admission characteristics, diagnoses, treatments, and outcomes.

7.3 METHODS

Ethics approval

Ethics approval for this research was granted by the Alfred Health Human Research Ethics Committee (project number 200/21).

Study design and population

This is a retrospective study of ICU admissions recorded in the APD. The APD is one of the clinical registry datasets managed by the Australia and New Zealand Intensive Care Society (ANZICS) Centre for Outcomes and Resource Evaluation and is used primarily for bench marking of ICU performance across the two nations. The APD records approximately 98% of all adult intensive care unit admissions in Australia and 67% in New Zealand (150). The registry records admissions to the ICUs in tertiary (major teaching) hospitals, metropolitan (community) hospitals, rural or regional hospitals and private hospitals.

We included patients aged 17 years or older admitted to ICU between 2018 and 2022. We included only the first ICU admission during a hospitalization, excluding ICU re-admissions or transfers from another ICU. We excluded patients with missing sex classification or ICU mortality.

Explanatory variable: patient sex

Patient sex is a mandatory demographic variable in the APD, defined as 'the biological distinction between male and female' (43). Patient sex is recorded in the registry based upon the patient's medical record. Patient gender and innate variations of sex characteristics are not recorded.

In 2016, an 'intersex/indeterminate' option was added, in addition to female, male and unknown sex. Data collection for this amended variable was implemented across contributing sites by 2018. The term 'intersex/indeterminate' was adopted based on government recommendations at the time; this guidance has since changed, in line with intersex community expectations (35, 38). Acknowledging this limitation, we use the term third sex for patients classified as 'intersex/indeterminate' in the registry.

Definitions and Outcomes

We described illness severity using the Acute Physiology and Chronic Health Evaluation III (APACHE III) score. The APACHE III score incorporates patient age, chronic comorbidities and acute physiological derangement and does not include patient sex (183). Regarding treatment in ICU, we examined use of invasive ventilation, vasoactive medication (include inotropes and vasopressors) and renal replacement therapy (including both continuous and intermittent modes).

We compared the diagnostic case mix of the groups in two ways. First, we examined nine broad diagnostic categories: cardiovascular disorders; respiratory disorders; gastrointestinal disorders; neurological disorders; sepsis; trauma; metabolic, endocrine, and hematological disorders; renal, genitourinary and obstetrics disorders; and musculoskeletal, soft tissue and skin disorders. Second, we examined specific admission diagnoses, using the ANZICS modification of the APACHE IV classification of 120 diagnoses including operative and non-operative conditions.

Regarding outcomes following critical illness, we examined ICU and hospital mortality.

Statistical analysis

We used histograms and Q-Q plots to assess continuous data for normality. We compared categorical data using chi-squared test for equal proportions or Fisher's exact test where numbers were small. We compared continuous data using students t-tests for normally distributed data assuming unequal variances, and Wilcoxon rank sum tests for non-normally distributed data. For all hypothesis tests we compared the group classified as third sex with the group classified as female, and separately, with the group classified as male. We adopted this approach due to imbalance in group size: the groups classified as female and male were so much larger than the group classified as intersex that hypothesis tests comparing across all three groups would reflect the difference between the groups classified as female and male, rather than the group classified intersex, our primary focus in this study. We took $p<0.05$ to indicate statistical significance and reported 95% confidence intervals.

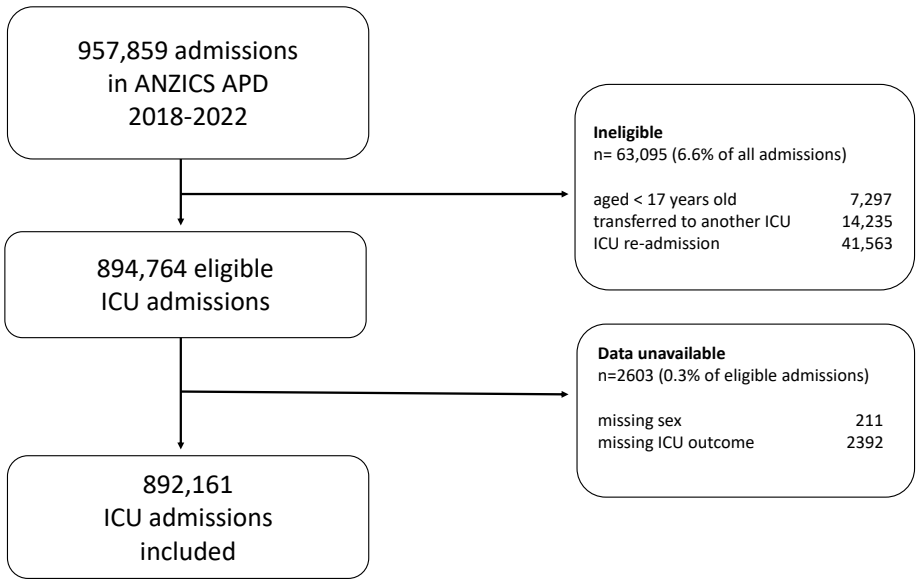
We performed mixed effects logistic regression to assess the association between sex and hospital mortality, APACHE III score, admission diagnosis, admission year and pre-existing limitation of medical treatment order, with hospital site included as a random effect.

All statistical analyses were performed with STATA 17 BE (StataCorp, Texas, USA).

7.4 RESULTS

There were 957,859 admissions to 200 ICUs at 199 hospitals recorded in the APD during the study period; 894,764 (93.4%) were eligible for inclusion. Of these, 2603 admissions had missing sex or mortality data, yielding a final study population of 892,161 patients (Figure 7.1).

Figure 7.1: Patient inclusion flow diagram



A total of 525 patients were classified as third sex, representing 0.06% of the study population. There was no significant difference in the distribution of patients classified as third sex across jurisdictions or years of hospital admission (Table 7.1). Compared to patients classified as female or male, patients classified as third sex were more likely to be admitted to the ICUs of private hospitals and less likely to be admitted to tertiary hospital ICUs.

Table 7.1: Admission year and jurisdiction according to sex group

	Patients classified as third sex n=525	*Patients classified as female n=389,907*	*Patients classified as male n=501,729*	*Total patients n=892,161*
Year of admission, n (% (95% CI))				
2018	95 (0.06 (0.04-0.07))	75,546 (43.8 (43.5-44))	96,999 (56.2 (56-56.4))	172,640
2019	101 (0.06 (0.05-0.07))	79,555 (43.7 (43.4-43.9))	102,554 (56.3 (56.1-56.5))	182,210
2020	110 (0.06 (0.05-0.07))	77,844 (43.4 (43.2-43.7))	101,249 (56.5 (56.3-56.7))	179,203
2021	92 (0.05 (0.04-0.06))	81,049 (44.1 (43.9-44.3))	102,697 (55.9 (55.6-56)	183,838
2022	127 (0.07 (0.06-0.09))	75,913 (43.6 (43.3-43.8))	98,230 (56.4 (56.1-56.6))	174,270
Jurisdiction, n (% (95% CI))				
NSW & ACT	177 (0.06 (0.05-0.07))	139,784 (44.4 (44.2-44.6))	174,939 (55.6 (55.4-55.7))	314,900
SA & NT	57 (0.07 (0.05-0.09))	37,862 (46.4 (46.0-46.7))	43,724 (53.6 (53.2-53.9))	81,643
New Zealand	36 (0.05(0.04-0.07))	28,009 (40.3(40-40.7))	41,379 (59.6 (59.2-60))	69,424
Queensland	97 (0.07 (0.05-0.08))	62,616 (43 (42.7-43.2))	83,075 (57 (56.7-57.2))	145,788
Victoria & Tasmania	118 (0.05 (0.05-0.07))	93,457 (43.4 (43.2-43.6))	121,700 (56.5 (56.3-56.7))	215,275
Western Australia	40 (0.06 (0.04-0.08))	28,179 (43.3 (42.9-43.6))	36,912 (56.7 (56.3-57.1))	65,131

NSW: New South Wales; ACT: Australian Capital Territory; SA: South Australia; NT: Northern Territory (all states or territories in Australia).

On average, patients classified as third sex were younger than patients classified as female or male (Table 7.2). The third sex group had a mean APACHE III score similar to the group classified as female but lower than the group classified as male. This difference in illness severity scores reflected differences in age and physiological derangement, but not level of comorbidity, between the groups. Patients classified as third sex were more frequently admitted to ICU following elective surgery, whereas patients classified as female or male were more frequently admitted following emergency surgery.

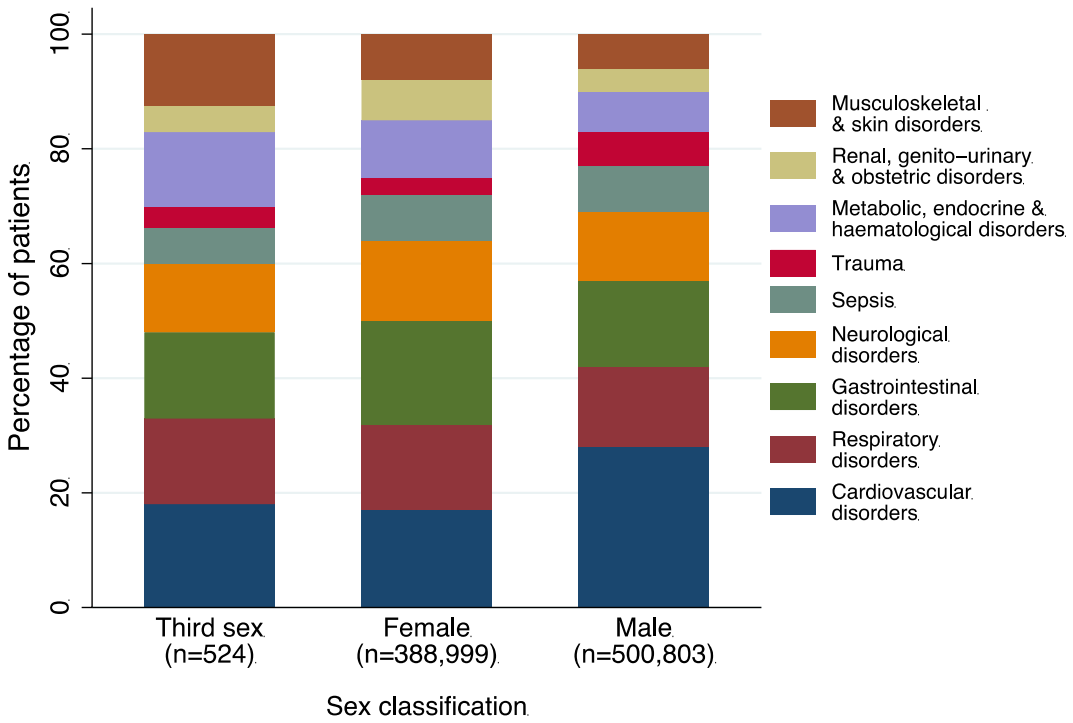
Table 7.2: Characteristics of ICU patients classified as third sex, female and male

	Patients classified as third sex N=525	*Patients classified as female N= 389,907*	*p value (third sex vs female)*	*Patients classified as male N=501,729*	*p value (third sex vs male)*
Age in years, mean (SD)	59.2 (20)	61.3 (18.4)	0.02	63.2 (16.7)	<0.001
APACHE III/IV score, mean (SD)	48.1 (23.9)	49 (23.3)	0.40	51.5 (23.7)	0.01
APACHE III/IV physiological variable component, mean (SD)	37.3 (21.7)	37.8 (20.9)	0.60	39.6 (21.6)	0.02
APACHE III/IV score chronic comorbidity component, Mean (SD)	0.7 (2.8)	0.7 (2.7)	0.81	0.7 (2.7)	0.73
Type of ICU admission, n (%)					
Emergency medical	236 (45)	176,766 (45.6)		218,222 (43.7)	
Emergency surgical	61 (11.6)	65,427 (16.8)	0.001	79,763 (16.0)	0.02
Elective surgical	228 (43.4)	145,725 (37.6)		201,090 (40.3)	
Time in hospital before ICU, Hours, median [IQR]	8.3 [4.5, 24.9]	9.1 [4.8, 25.8]	0.08	9.8 [4.8, 27.9]	0.01
LoMT, n (%)	33 (6.3)	35,733 (9.2)	0.02	40,453 (8.1)	0.14
Hospital classification, n (%)					
Tertiary	124 (23.6)	138,135 (35.4)		212,175 (42.4)	
Metropolitan	89 (17)	63,404 (16.3)	<0.001	69,376 (13.8)	<0.001
Rural/regional	70 (13.3)	55,768 (14.3)		64,879 (12.9)	
Private	242 (46.1)	132,600 (34.0)		154,759 (30.9)	

There were some significant differences in diagnostic case mix across the sex groups (Figure 7.2). Compared to groups classified as female or male, patients classified as third sex were more likely to have an admission diagnosis in the musculoskeletal, soft tissue and skin category or the metabolic, endocrine and hematology category. Patients classified as male were more likely than the other groups to be admitted with a cardiovascular disorder or trauma; patients classified as female were more likely than the other groups to be admitted with a renal, genitourinary or obstetric diagnosis.

However, there were also broad similarities in the casemix of the sex groups. Each sex group recorded a wide variety of admission diagnoses and the commonest admission diagnoses in each group were cardiovascular, respiratory, and gastrointestinal disorders.

Figure 7.2: Admission diagnostic category according to sex classification



Examining individual admission diagnoses, a higher proportion of patients classified as third sex were admitted to ICU following orthopedic surgery, compared to the other groups (10.1% of third sex admissions (95% CI 7.7 to 13.0%) vs. 6.2% female admissions (95% CI 6.1 to 6.3%), 4.8% male admissions (95% CI 4.7 to 4.9%)). Similarly, drug overdoses accounted for a higher proportion of ICU admissions in patients classified third sex than in patients classified as female or male (8.8% of third sex admissions (95% CI 6.5 to 11.5%) vs 4.2% female admissions (95% CI 4.1 to 4.2%) and 3.1% male (95% CI 3.0 to 3.1%)).

The rate of invasive ventilation observed in the group classified as third sex was higher than the group classified female yet lower than the group classified as male (Table 7.3). Patients classified as third sex were less likely to receive vasoactive medication and had shorter length of stay in the ICU and in hospital. Patients classified as third sex were similarly likely to receive renal replacement therapy as the other sex groups (Table 7.3).

The unadjusted hospital mortality of the group classified as third sex (5.5%, 95% CI 3.7 to 7.8%) was closer to the group classified as female (7.1%, 95% CI 7.0 to 7.2%, p=0.16) and significantly lower than the group classified as male (8.1%, 95% CI 8.0 to 8.2%, p=0.03). After multivariable adjustment there was no difference in the hospital mortality of the third sex group compared to either other sex group (Table 7.4).

Table 7.3: Treatment in ICU and outcomes of patients according to sex classification

	Patients classified as third sex (n=525)	*Patients classified as female, (n=389,907)*	*p value female vs 3rd sex*	*Patients classified as male (n=501,729)*	*p-value male vs 3rd sex*
Vital organ supports, n (%; 95% CI)					
Invasive ventilation (n= 887,186)	157 (30.1; 26.2–34.2)	99,951 (25.8; 25.6–25.9)	0.03	186,296 (37.3; 37.2–37.5)	0.001
Vasoactive medication (n=765,817)	126 (27.7; 23.6–32.1)	108,250 (32.4; 32.2–32.5)	0.03	174,139 (41.4; 41.2–41.5)	<0.001
Renal Replacement Therapy (n=749,510)	13 (2.9; 1.6-4.9)	11,384 (3.5; 3.4–3.5)	0.73	19,123 (4.6; 4.5–4.6)	0.20
Length of stay, hours, median [IQR]					
ICU	34.2 [20.6, 66.3]	38.7 [21.3-71.5]	0.06	43.2 [22.2-80.5]	<0.001
Hospital	164.1 [82.3, 291.9]	174.3 [95.3-329.25]	0.03	191.7 [101.5-347.1]	<0.001
Mortality, N (%; 95% CI)					
ICU	17 (3.2; 1.9–5.1)	17,897 (4.6; 4.5–4.7)	0.14	26,537 (5.3; 5.2–5.4)	0.04
Hospital	29 (5.5; 3.7–7.8)	27,640 (7.1; 7.0–7.2)	0.16	40,645 (8.1; 8.0-8.2)	0.03

Table 7.4: Adjusted hospital mortality

Variable	*Odds ratio (95% ci)*	*p-value*
Sex classification		
Third sex	*reference*	
Female	1.25 (0.78-1.99)	0.34
Male	1.35 (0.85-2.15)	0.21
*APACHE III risk of death**	1.06 (1.06-1.06)	<0.001
Limitation of medical treatment order		<0.001
No LOMT	*reference*	
LOMT	4.25 (4.16-4.35)	
Admission year	1.00 (1.00-1.01)	0.304

*APACHE III risk of death calculates a risk of death as a percentage based upon the APACHE III score (age, comorbidities and physiological derangement) and the ICU admission diagnosis

7.5 DISCUSSION

Key findings

People classified as third sex composed a small minority of ICU patients during the study period 2018 to 2022. They were represented across all jurisdictions of Australia and New Zealand and all types of ICUs. Compared to the groups classified as female or male, this third sex group were younger and more likely to be admitted to ICUs in private hospitals following elective surgery.

Patients classified as third sex were admitted with a wide variety of critical illnesses. The group classified as third sex were significantly more likely to be admitted to ICU following orthopedic surgery or drug overdose than the groups classified as female or male.
There was no difference in the adjusted hospital mortality of group classified as third sex compared to either the group classified female or the group classified male.

Comparison to other studies

To the best of our knowledge, there are no previously published studies describing the epidemiology of a third sex group within the critically ill population. Previous studies of sex differences in ICU patients adopted a binary sex definition: patients who might prefer to be categorized in other ways were excluded from the study population or may have been included in binary sex categories (chapter 3).

People classified as third sex made up 0.06% of our study population, far lower than the estimated proportion of people who have innate variations of sex characteristics (1.7%) (36, 37). However, the nature of the group classified as third sex and its relationships to populations of people with innate variations of sex characteristics (intersex/differences of sex development) or people of transgender/gender diverse experience is unclear. Intersex community organizations do not support construction of intersex as a third sex category, and it is likely that many people with innate variations of sex characteristics or intersex variance were classified as female or male upon hospital admission (39).

Conversely, it is likely the group classified as third sex included some transgender and gender-diverse people. This would tend to inflate the size of the group classified as third sex, because transgender and gender diverse people are estimated to compose up to 4.5% of the adult population (184).

We found no difference in the adjusted hospital mortality of the group classified as third sex compared to the groups classified as female or male. This is somewhat surprising as previous research suggests that people with innate variations of sex characteristics have higher rates of disability, previous surgical or medical intervention and mental ill-health, all risk factors for poor outcomes from critical illness (181, 185, 186).

We observed a higher rate of ICU admission for orthopedic conditions among patients classified as third sex compared to the other two groups. In the APACHE diagnostic classification, orthopedic surgery includes major joint replacement, spinal surgery and amputations but excludes traumatic injuries; so this group includes patients with osteoarthritis requiring joint replacement or osteoporosis with spinal degenerative disease (43). Therefore, the higher rate of orthopedic surgery in the group classified as third sex may relate to the impact of innate sex hormone levels and sex hormone therapy on bone density (187). In relation to people with innate variations of sex characteristics, Vena and colleagues observed an increased risk of osteoporotic vertebral fractures in people with Klinefelter syndrome (188). Wiepjes and colleagues (2020) undertook a nation-wide study of fracture risk in transgender people in the Netherlands, reporting a higher risk of fracture among older trans women compared to age-matched controls but no increase in fracture risk in trans men (189). The higher incidence of orthopedic surgery in the third sex group may also be mediated by obesity, as obesity is both a major risk factor for hip and knee osteoarthritis and associated with some innate variations in sex characteristics (190, 191).

We also noted a higher incidence of ICU admission for drug overdose in the group classified as third sex compared to the groups classified as female or male. Most drug overdoses leading to ICU admission are due to intentional overdose, reflecting self-harm or suicidality (192). Therefore, our finding concords with studies reporting

relatively poor mental health among the intersex and transgender populations (65, 181, 186, 193). In a study of people born with atypical sex characteristics in Australia, Jones and colleagues found that the proportion of study participants who had attempted suicide or engaged in self-harm was substantially higher than general population estimates (186). Wanta and colleagues examined the mental health diagnoses of transgender patients in a large electronic health record database, finding that the prevalence of mental health disorders – particularly major depressive disorder – and substance use disorders was higher among transgender patients compared to cisgender patients (193). These poorer mental health outcomes are thought to reflect the stigma, discrimination and violence experienced by the intersex and transgender populations (186, 194).

Implications, strengths, and limitations

Our study shows that patients classified as third sex were admitted to ICUs across Australia and New Zealand with a wide variety of critical illnesses, forming a small but consistent minority in our ICU patient population. Our study also provides an initial overview of the characteristics of this group classified as third sex, including illness severity, treatment, and outcomes.

Our study has limitations, which reflect the uncertainty around the classification of sex, gender, and innate variations of sex characteristics within healthcare data. Most importantly, there is substantial risk of sex misclassification due to terminology and data collection practices (40). Gender and sex are usually not recorded separately in the hospital record; gender is not recorded in the APD registry (43, 172). This conflation of sex, variations of sex characteristics and gender means that there is lack of clarity regarding the composition of the third sex group. It likely includes some endosex transgender or gender-diverse people, and some people with innate variations of sex characteristics, among others (182). Furthermore, the process for recording a patient's sex in the medical record may not engage the patient directly, particularly if the patient is critically ill, with hospital staff guessing or assuming the patient's sex. Alternatively, the data collection process may engage the patient in a non-affirming manner, leading

them to choose an ‘expected’ answer. Of note, we observed that patients classified third sex were more likely to be admitted to ICUs of private hospitals following elective surgery. This is a situation in which the patient is relatively more likely to have completed their own pre-admission paperwork, possibly leading to higher rates of self-identification as third sex.

Sex misclassification undermines sex differences research in important ways. First, it limits understanding of the outcomes for people with innate variations of sex characteristics and transgender and gender-diverse peoples (195). Each of these small minorities are likely to be relatively more affected by misclassification and are at higher risk of poor health outcomes in other settings (40, 181, 194, 196).The conflation of sex, gender and variations of sex characteristics leads to uncertainty as to whether observed ‘sex’ differences arise from innate or acquired biologically-based sex characteristics, experiences of stigmatization and social determinants of health, or some interaction between these variables. Finally, bias due to sex misclassification can obscure or diminish observed differences between all sex groups, including between female and male sex groups (197).

Recording sex, gender, and innate variations of sex characteristics separately could help to mitigate against misclassification in hospital medical records and clinical registries like the APD. The Australian Bureau of Statistics recommends documenting the patient’s sex recorded at birth with the options male, female, or another term (‘please specify’); and gender with options man or male, woman or female, non-binary, another term (‘please-specify’) or prefer not to answer (140). Innate variations of sex characteristics are ascertained in a further question. The USA’s National Academies of Sciences, Engineering and Medicine recommends a very similar approach (36). Engaging consumers from affected minority sex or gender groups can ensure the process of recording sex and gender data in the medical record is affirming and that data collected is less likely to hold assumption and bias.

Finally, this study examined a small minority group within a very large registry-derived population. Therefore, confidence intervals around estimates are wider than for

comparison of larger groups. This is a well-recognized, inherent challenge in studying small minority groups using quantitative methods (198, 199). However, there are also limitations in using solely qualitative or semi-quantitative methods to study minority groups whilst relying mainly on quantitative methods to describe majority populations.

7.6 CONCLUSION

Patients classified as third sex composed a small minority of ICU patients, admitted to ICUs across Australia and New Zealand with a wide variety of critical illnesses. Compared to the groups classified as female or male, patients classified as third sex were more likely to be admitted with orthopedic conditions or drug overdose. The group classified as third sex had illness severity scores and unadjusted mortality rates that were lower than the group classified as male but not significantly different to the group classified as female. There was no difference in the adjusted hospital mortality of the group classified third sex compared to the other two groups.

This work highlights the need to improve hospital and clinical registry systems for recording sex, gender and variations of sex characteristics, to allow better understanding of the health outcomes of sex and gender-based minority groups as well as the impact of sex and gender on critical illness.

Chapter 8. Sex representation in intensive care trials in Australia and New Zealand

This chapter presents a complete report of a study published in an abridged form as a research letter, as cited in the preface and reproduced in Appendix C.

8.1 ABSTRACT

Purpose: We examined sex-based representativeness in critical care trials, comparing the sex balance in study populations and their corresponding target populations.

Methods: We examined randomized controlled trials endorsed by the Australia and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group completed 2014 to 2023. The ANZICS Adult Patient Database (APD) was taken to represent the overall intensive care unit (ICU) patient population. A matched target population was identified for each trial using its own eligibility criteria. We used random effects meta-analysis to calculate pooled differences, reporting the percentage female participants in study populations minus the percentage female patients in target populations. We examined trials according to diagnostic subgroups, year, and consent model.

Results: There were 24 eligible trials with a total of 68,968 participants (36.3% women). Over the trials' cumulative recruitment period, there were 2,017,197 ICU admissions (42.9% women) recorded in the APD. Overall, there was no significant disparity in sex balance between the study populations and matched target populations (pooled arithmetic difference -0.5%, 95% CI -2.2% to 1.2%). However, women were under-represented in cardiac arrest trials (arithmetic difference -5.5% (95% CI -8.6 to -2.4%)) and sepsis trials (arithmetic difference -2.9% (95% CI -5.1% to -0.7%)). No trial recorded a third sex category or patient gender.

Conclusion: Critical care trials in Australia and New Zealand included a representative number of women overall when compared to matched target populations, however they included fewer women than the general ICU patient population. Women appeared under-represented in cardiac arrest and sepsis trials.

8.2 BACKGROUND

When undertaking a clinical trial, there are many advantages to recruiting a study population that reflects the intended target population, or the group of patients affected by the illness in question. Including a representative study population helps to ensure the generalizability of the research findings and increases the likelihood of identifying any heterogeneity of treatment effect between demographic groups (96, 200-202). Such representativeness also helps to ensure fair distribution of the possible benefits and risks of trial participation among affected patients. Finally, it promotes trust in medical research (96, 200, 202).

Notwithstanding these important benefits, clinical trials have historically recruited participants from a limited subset of the target population. Study populations included disproportionate numbers of middle-aged, white, male participants, with under-representation of older adults, women, ethnic minorities and other groups (4, 102, 201-205). Despite significant policy reforms aimed at improving diversity and inclusivity in research, the under-representation of ethnic minorities persists in contemporary clinical trials (103, 206-209). The inclusion of female participants has improved, but women remain under-represented in some fields including oncology and cardiology research (96, 97, 102, 206, 210). Sex and gender-based minorities are largely unrepresented in clinical research (96).

It remains unclear if critical care trials include the sexes in proportions representative of their respective target populations. Accordingly, we compared sex balance in the study populations of RCTs undertaken in Australia and New Zealand ICUs and their corresponding target populations. We hypothesized that the percentage of female participants within each study population was lower than the percentage of female patients in the matched target population, and patients with congenital variations of sex differentiation were not represented in these study populations.

8.3 METHODS

Ethics approval

We obtained ethics approval from the Alfred Health Human Research Ethics committee (Project number 565/23) The study was undertaken in accordance with the ethical standards described in the 1964 Declaration of Helsinki and its later amendments.

Study Design & Data Sources

This retrospective observational study examined published data from RCTs endorsed by the Australia and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). We used the ANZICS Adult Patient Database (APD) to represent the general population of ICU patients in Australia and New Zealand. The APD is one of five clinical registries administered by the ANZICS Centre for Outcomes and Resource Evaluation, it records admissions from 96% ICUs in Australia and 63% ICUs in New Zealand, including all tertiary ICUs (211). Data are collected using a standardized data dictionary by trained data collectors and regular quality assurance reviews help to ensure the reliability of the registry's data (211).

We completed this study in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (152).

Trial Selection Criteria

We included RCTs endorsed by the ANZICS CTG and completed between 2014 and 2023 (211). Trials included examined adult ICU patients, with a study population of 100 or more participants and at least 5 participating ICUs in Australia and New Zealand.

Identifying target populations

For each trial, we identified a target population from the APD, matched according to all possible trial inclusion and exclusion criteria. In this way, we identified a trial's target

population on its own terms. This included matching the trial recruitment period, participating ICUs and clinical eligibility criteria such as diagnosis (e.g., traumatic brain injury) or intervention (e.g., mechanical ventilation). Appendix B presents each trial's eligibility criteria and how these were matched to identify a corresponding target population in the APD.

It was not possible to match each eligibility criteria using data recorded in the APD, due to variables not included in the APD (e.g., the provision of enteral nutrition) or missing data. Therefore, we assessed the quality of matching of each target population across 5 domains: recruitment period, age, diagnostic group, ICU treatments specified in the eligibility criteria (e.g., mechanical ventilation) and participating ICU. According to our pre-specified criteria, a target population was well-matched if the eligibility criteria could be matched in at least 4 domains (212). The quality of matching was assessed by three authors (LM, AB & KT), with disagreements resolved through discussion.

Exposure of interest: patient sex

We examined patient sex, defined in the ANZICS APD data dictionary as the biological distinction between female and male (43). Patient sex is transcribed from the clinical record for both clinical trial demographic data and APD admission data. We did not directly examine patient gender in this study. We recorded whether trials reported patient sex (i.e., relating to their biological characteristics), patient gender (i.e., relating to their personal or social identity), or both.

We initially defined sex balance as the percentage of each population who were female, male, or belonging to a third group including people with innate variations in sex characteristics. However, the included trials recorded only binary participant sex and no trial recorded patient gender. Therefore, our final analysis compared female and male patients, henceforth referred to as 'women' and 'men', with the term 'sex balance' used to describe the percentage of a population who were women.

Statistical Analysis

Categorical variables were reported as counts with percentages to one decimal place. We reported normally distributed data using means with standard deviations and non-parametric data using median with interquartile ranges. Statistical significance was tested at the 5% level.

To compare the sex balance within each study population and the APD-derived target population, we found the arithmetic difference between the percentage of women in each study population and its target population, with an estimated associated 95% confidence interval, using the prtest command in STATA 17 BE (Statacorp, Texas USA). We calculated the percentage of women in each study population minus the percentage of women in its target population, therefore differences greater than zero signified over-representation of women in the study population and differences less than zero signified under-representation of women in the study population. We used restricted maximum likelihood random effects meta-analysis to calculate the pooled arithmetic difference, and 95% confidence interval, in the percentage of women between study populations and target populations. We used the same method to analyse subgroup differences.

We pre-defined three subgroup analyses that examined trials according to their diagnostic group (sepsis, trauma, and multiple diagnostic categories), date of completion (pre- or post-2019) and consent model (consent waived versus any consent process). There were two post-hoc additions to these subgroups: a cardiac arrest subgroup was added to the diagnostic subgroups, and a subgroup of trials in which the consent model varied across jurisdictions was added to the consent subgroups.

We undertook a pre-specified sensitivity analysis including only studies considered well-matched, as defined above. To mitigate the statistical challenge of comparing proportions in two non-independent populations, we performed a post-hoc sensitivity analysis that examined matched APD populations admitted to ICU outside of the trial's own recruitment period. Specifically, target populations were identified using the same

selection criteria, altering only the ICU admission dates to include the period October 2008 - November 2021, excluding the trial's own recruitment period. Finally, we undertook a post-hoc sensitivity analysis examining only studies completed entirely in Australia and New Zealand, excluding multi-national trials.

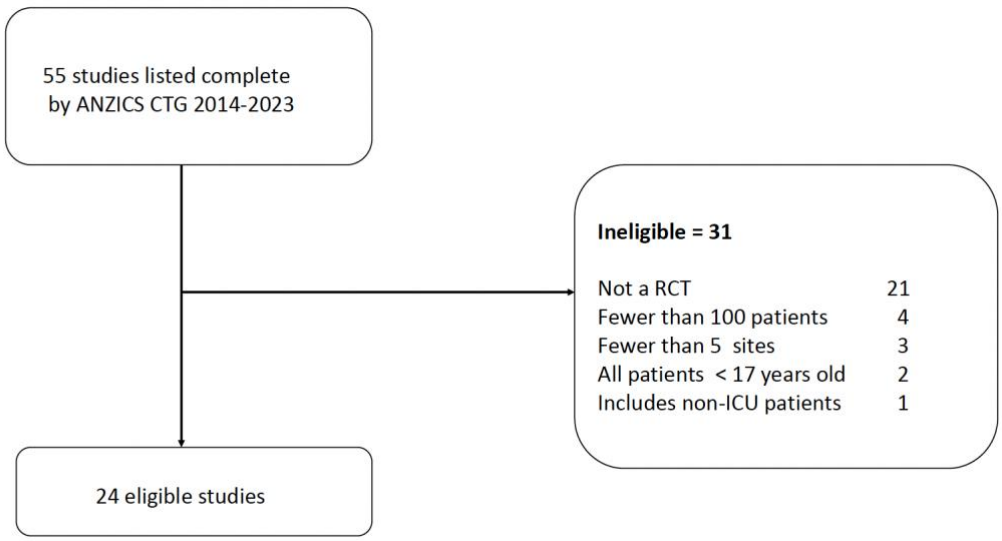
We performed our statistical analyses using STATA 17 BE (Statacorp, Texas USA).

8.4 RESULTS

Characteristics of included trials

A total of 55 CTG-endorsed trials were completed between January 2014 to June 2023. Of these, 24 trials were eligible for inclusion in our study (Figure 8.1). The cumulative recruitment periods of eligible trials ran from October 2008 until November 2021. There were 13 multi-national trials, with additional recruiting sites outside of Australia and New Zealand. The trials studied a range of interventions including enteral nutrition, temperature control, adjunctive corticosteroid use and mechanical ventilation.

Figure 8.1: Trial inclusion flow diagram



The study populations ranged from 112 participants to 26,828 participants (Table 8.1). The sex balance within study populations ranged from 16.7% to 47.8% women. The sex balance of the total study population was 36.3% (25,045 women in 68,966 total participants) and the total target population was 35.6% (152,572 women of 428,697 total patients). All trials recorded patient sex rather than gender, except for the POLAR trial, which referred to men and women (213). No trials recorded a third or non-binary sex group and no trial recorded patient gender.

Characteristics of the general ICU patient population recorded in the APD

Over the cumulative recruitment period of the eligible trials, the APD recorded admissions to 211 different ICUs across Australia and New Zealand. This included all 96 ICUs that participated in the 24 trials examined in our study.

A total of 2,017,197 ICU admissions were recorded in the APD over this time, of whom 864,736 (42.9%) were women. Compared to the pooled study populations, there were substantially fewer women in the general ICU population as represented by the APD (36.3% vs. 42.9%, arithmetic difference -6.6%, 95% CI 6.2% to 6.9%).

Quality of matching

According to our pre-specified criteria for assessing quality of matching, 15 trials (62.5%) had target populations identified that were well-matched overall; the target populations identified for the remaining 9 trials were not well matched (Table 8.2). We were unable to match a target population according to intervention in 14 trials (e.g., provision of enteral nutrition or antibiotics) and according to all participating ICUs for the 13 multi-national trials.

Table 8.1: Characteristics of included trials

Trial	*Trial intervention*	*Participants/patients, n*		*Female participants/patients, n (%)*	
		Study population	*Target population*	*Study population*	*Target population*
PATCH 2023 (214)	Pre-hospital tranexamic acid for severe trauma	1300*	27,710	382 (29.4)	7278 (26.3)
SUDDICU 2023 (215)	Selective decontamination of the digestive tract in mechanically ventilated patients	5982	32,788	2,202 (36.8)	11,719 (35.7)
TAME 2023 (216)	Mild hypercapnia vs normocapnia after out-of-hospital cardiac arrest	1668*	3404	352 (21.1)	953 (28.0)
TEAM 2022 (217)	Early mobilization during mechanical ventilation	741	31,670	274 (37.0)	11066 (35.0)
LUCID 2022 (218)	Liberal glucose control in critically ill patients with pre-existing type 2 diabetes.	419	7913	145 (34.6)	2768 (35.0)
TARGET PROTEIN 2021 (219)	Use of high protein enteral nutrition in mechanically ventilated patients	116	1408	33 (28.4)	456 (32.4)
PLUS 2022 (220)	Plasma-Lyte vs saline for fluid resuscitation	5037	92,618	1948 (38.7)	37,139 (40.1)
STARRT AKI 2020 (176)	Accelerated initiation of renal replacement therapy	2927*	17,587	937 (32.0)	6987 (39.7)
TTM2 2021 (221)	Targeted hypothermia vs normothermia after out of hospital cardiac arrest	1861*	942	384 (20.6)	229 (24.3)
ICU ROX 2020 (222)	Liberal vs conservation oxygen therapy in mechanically ventilated patients	965*	30,289	357 (37.0)	9887 (32.6)
PEPTIC 2020 (223)	Proton pump inhibitor vs histamine-2 receptor blocker for stress ulcer prophylaxis	26828*	47,557	9691 (36.1)	16244 (34.2)
REACTOR 2019 (224)	Active vs usual temperature management	178	2483	60 (33.7)	726 (29.2)
SPICE 2019 (225)	Dexmedetomidine versus usual care sedation	3918*	51,314	1503 (38.4)	17391 (33.9)
POLAR 2018 (213)	Prophylactic hypothermia for traumatic brain injury	500*	2207	99 (20)	439 (19.9)
TARGET, 2018 (226)	Energy dense enteral nutrition	3957	21,724	1464 (37)	7994 (36.8)
ADRENAL 2018(227)	Adjunctive glucocorticoid therapy in septic shock	3713*	11,419	1454 (39.2)	4831 (42.3)
PHARLAP 2019(228)	Open lung ventilation strategy in ARDS	114*	22,559	48 (42.1)	7330 (32.5)
TRANSFUSE 2017(229)	Freshest available red blood cell transfusion	4919*	4656	2350 (47.8)	1982 (42.6)
BLING II 2015(230)	Continuous vs intermittent beta lactam infusion in severe sepsis	432*	4670	167 (38.7)	1886 (40.4)
EPO TBI 2015(231)	Erythropoietin in traumatic brain injury	603*	2490	101(16.7)	502 (20.2)
HEAT, 2015(232)	Permissive hyperthermia through avoidance of paracetamol in likely infection	691	1727	242 (35.0)	661 (38.3)
ARISE, 2014 (233)	Early goal-directed therapy in sepsis	1591	5537	641(40.3)	2548 (46.0)
PROGUARD 2014 (234)	Procalcitonin-guided antibiotic cessation	400	2059	182 (46.2)	898 (43.6)
TARGET feasibility 2014 (235)	Augmented energy delivery enteral feeding	112	1966	29 (25.9)	658 (33.5)

* multinational trials, with participating sites outside of Australia and New Zealand

Table 8.2: Quality of matching assessment for target populations

TRIAL	*Recruit-ment period*	*Age of participants*	*Diagnostic group*	*Intervention*	*Participating units*	*Domains Matched*[*]
SUDDICU [6]	Yes	Yes	Yes	No	Yes	4/5
TEAM [7]	Yes	Yes	Yes	Yes	No[†]	4/5
LUCID [8]	Yes	Yes	No	No	Yes	3/5
TARGET PROTEIN [9]	Yes	Yes	Yes	No	Yes	4/5
PLUS [10]	Yes	Yes	Yes	No	Yes	4/5
STARRT-AKI [11]	Yes	Yes	No	Yes	No[†]	3/5
ICU-ROX [12]	Yes	Yes	Yes	No	No[†]	3/5
PEPTIC [13]	Yes	Yes	Yes	Yes	No[†]	4/5
REACTOR [14]	Yes	Yes	Yes	No	Yes	4/5
SPICE [15]	Yes	Yes	Yes	No	No[†]	3/5
TARGET [16]	Yes	Yes	Yes	No	Yes	4/5
PHARLAP [17]	Yes	Yes	No	Yes	No[†]	3/5
TRANSFUSE [18]	Yes	Yes	Yes	No	No[†]	3/5
TARGET feasibility [19]	Yes	Yes	Yes	No	Yes	4/5
TAME [20]	Yes	Yes	Yes	Yes	No[†]	4/5
TTM2 [21]	Yes	Yes	Yes	Yes	No[†]	4/5
ADRENAL [22]	Yes	Yes	Yes	No	No[†]	3/5
BLING II [23]	Yes	Yes	Yes	No	No[†]	3/5
HEAT [24]	Yes	Yes	Yes	Yes	Yes	4/5
ARISE [25]	Yes	Yes	No	Yes	Yes	4/5
PRO-GUARD [26]	Yes	Yes	Yes	No	Yes	4/5
PATCH [27]	Yes	Yes	Yes	No	No[†]	3/5
POLAR [28]	Yes	Yes	Yes	Yes	No[†]	4/5
EPO-TBI [29]	Yes	Yes	Yes	Yes	No[†]	4/5

[*]According to our pre-specified criteria, a target population was considered well-matched if it could be matched in at least 4 domains [†] multi-national trials with recruitment units outside Australia and New Zealand

Sex balance in study populations compared to matched target populations

The sex balance of the study population was significantly different to the sex balance in the matched target population in 13 trials. In 7 of these trials, the percentage of women was lower in the study population than in the target population; in the other 6 trials the percentage of women was higher in the study population than in the target population (Figure 8.2 and 8.3). There was no significant difference in the sex balance of the study populations and the target populations for the remaining 11 trials. There was no

difference in percentage of women in the overall study and target populations in the pooled analysis (arithmetic difference in percentage women (-0.5, 95% CI -1.2 to 2.3).

The PHARLAP trial had the largest discrepancy in sex balance overall, with more women in the study population compared to the target population (32.5% in target population vs 42.1% in study population). The STARRT AKI trial had the largest discrepancy suggesting the under-recruitment of women (39.7% women in target population vs 32% women in the study population).

Figure 8.2: Forest plot of sex balance of study population compared to target populations

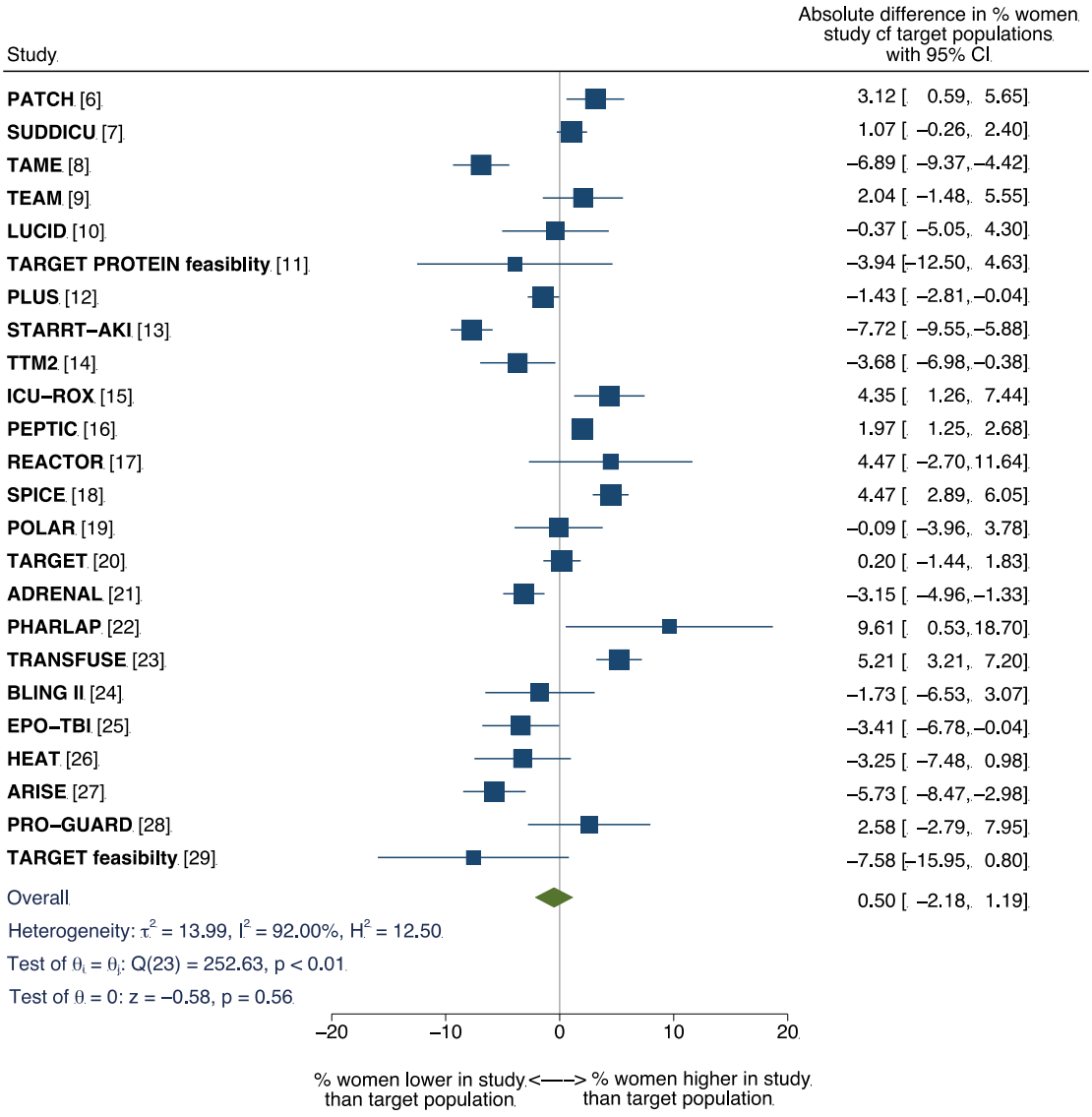


Figure 8.3: Percentage of women in study population compared to target populations

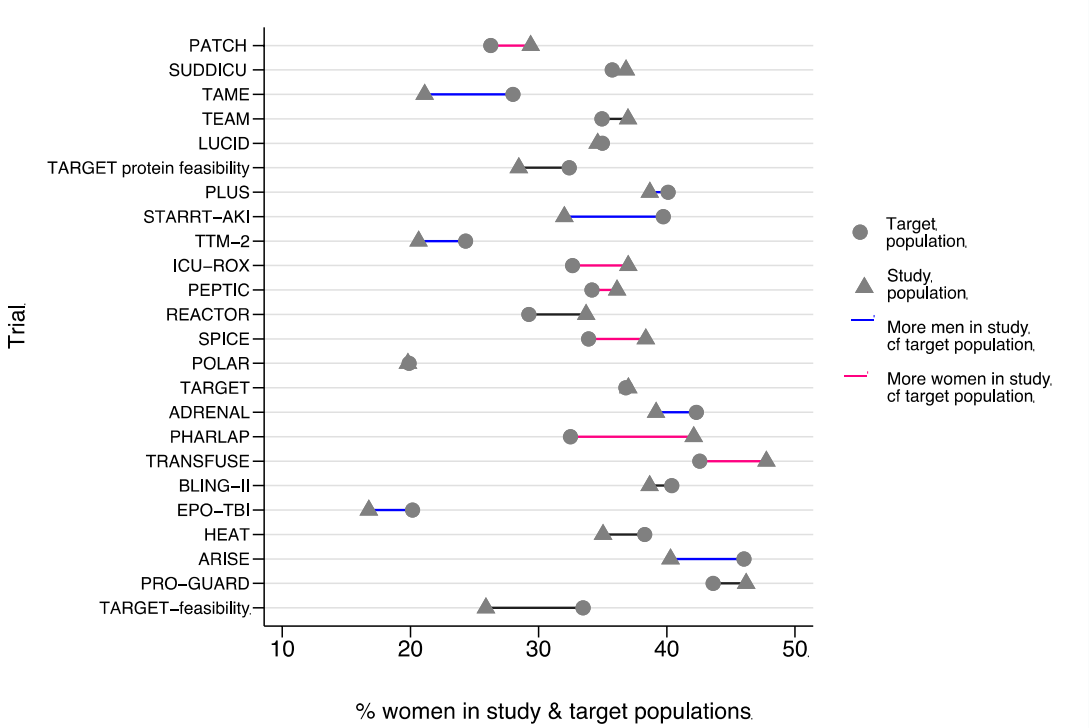


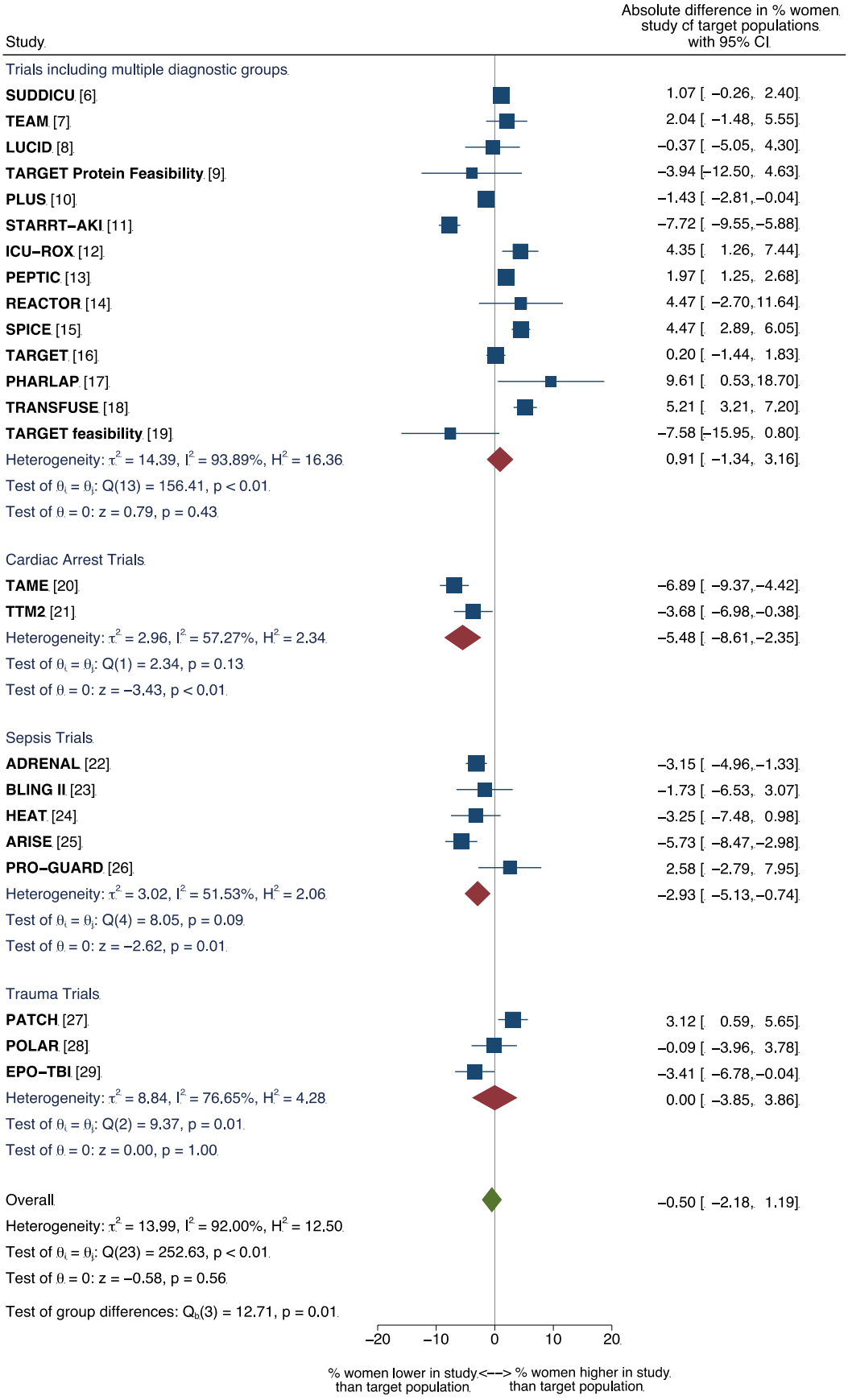
Figure legend: Lines connecting triangles and circles represent the arithmetic difference in the percentage of women in the study population and target population. Pink lines indicate more women in study than target population; blue lines indicate less women in study than target population (adapted from Steinberg et al (97)).

Subgroup analyses

In the subgroup analysis according to diagnostic group, there was a significantly lower percentage of women in the pooled study populations compared to target populations in the sepsis and cardiac arrest trials (Figure 8.4). There was no significant discrepancy in the sex balance of study and target populations in the trauma and 'multiple diagnostic categories' subgroups of trials.

No discrepancy was identified in the sex balance of pooled study and target populations in any of the consent-based subgroups, or in the subgroups of trials completed before 2019 compared with 2019 onward (data not shown).

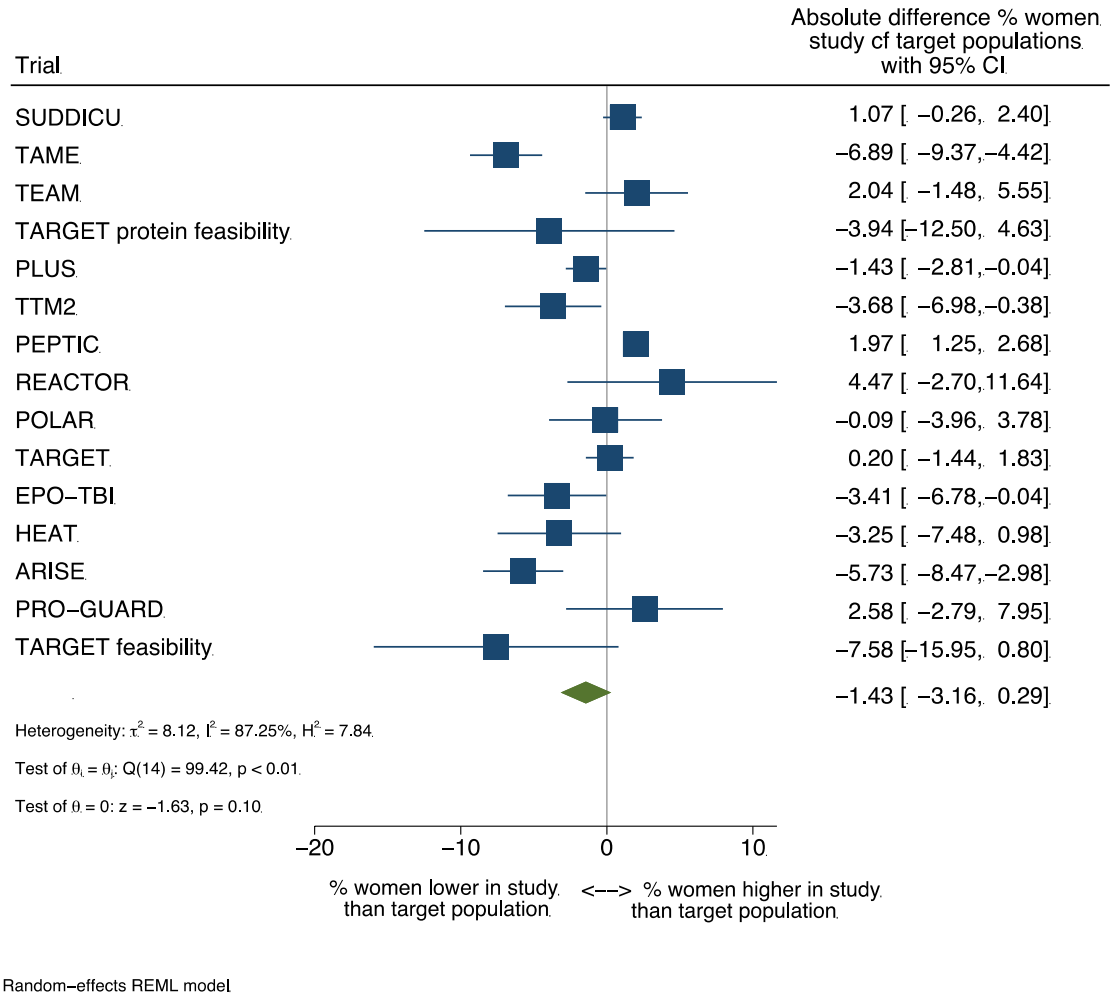
Figure 8.4: Sex balance of study population compared to target populations, by diagnostic subgroup of trials



Sensitivity analyses

In a sensitivity analysis that examined only the trials with well-matched target populations, there was no significant discrepancy in the pooled analysis of sex balance in study versus target populations (Figure 8.5). Our findings were also robust to two further sensitivity analyses: first comparing to target populations of ICU patients admitted outside of each trial's recruitment period (i.e., not overlapping with the study recruitment period), and then excluding trials with participating sites outside of Australia and New Zealand (data not shown).

Figure 8.5: Sensitivity analysis including only well-matched study populations



8.5 DISCUSSION

Key findings

In this study of 24 critical care trials with approximately 70,000 participants completed over a ten-year period in Australia and New Zealand, we found that, overall, study populations included a representative balance of women and men overall. However, women were under-represented in sepsis and cardiac arrest trials. No trial recorded a third sex group of participants with innate variations of sex characteristics or patient gender. Sex-based representation did not change significantly over time, nor according to the trial's consent requirements.

Whilst the sex balance in the pooled study populations reflected that of their intended target populations overall, there was a significant disparity between the sex balance in these study populations and the general population of ICU patients. That is, the percentage of women in the pooled study populations of critical care trials (36.3% women) was substantially lower than the percentage of women in the overall population of ICU admissions recorded in the APD over the trials' cumulative recruitment period 42.9% women).

Comparison to other studies

Steinberg and colleagues completed a comprehensive study of sex representation in research, examining nearly 20,000 clinical trials (97). Of note, they did not examine critical care as a distinct field of research. They found that trials in some fields, including trauma and musculoskeletal disease, tended to over-represent women, whilst trials in other clinical fields, including oncology and neurology, tended to under-represent women. This is consistent with our finding that some critical care trials appeared to have an excess of women and others had a surfeit of men. After adjustment for trial-related factors, they also observed that female participants were most likely to be under-represented in paediatric, cardiology and infectious diseases trials. This concords with our observation that women were under-represented in cardiac arrest and sepsis trials.

Kristensen and colleagues examined intensive care unit (ICU) randomized controlled-trials (RCTs) published in 2011-2012, reporting significantly more male than female participants in 18 of the 25 included trials (101). They reported sex balance in the pooled study populations that was remarkably similar to our findings (36.3% women and 36.4% women, respectively). Our study builds on the previous work by also identifying each trial's target population, in order to assess sex-based representativeness. This is important given that sex balance varies substantially between diagnostic groups of ICU patients, so would be expected to vary between trials examining different critical illnesses (chapter 4).

We found that women appeared to be under-represented in cardiac arrest trials when compared to the eligible populations of patients admitted to ANZ ICUs. This concords with the findings of many studies that women remain under-represented in cardiology trials overall, including trials of interventions for heart failure and acute coronary syndrome (97, 102, 103, 203, 210).

Implications

Our key finding – that critical care trials in Australia and New Zealand recruit women and men in proportions representative of their intended target populations overall – is reassuring. This suggests that the approach to screening and enrolling patients in critical care trials is not biased by patient sex; women and men ICU patients are granted equitable access to participation in trials based on the trial's own eligibility criteria.

However, we observed that the pooled target population of these trials had substantially fewer women than the ICU population in Australia and New Zealand overall. This is an important observation, suggesting that critical care trials are designed to examine populations with relatively more men than the general population of ICU patients. This disparity could emerge due to the study question, participating sites or the eligibility criteria (96). For example, many of the trials in our study examined conditions predominantly affecting men, including trauma or cardiac arrest, rather than conditions

predominantly affecting women, for example subarachnoid hemorrhage or asthma (chapter 4). The participating sites may have a relative preponderance of men, as sex balance varies substantially between individual ICUs (chapter 4). The trial's eligibility criteria may further identify a relatively male-dominated population, for example, by excluding patients who are pregnant, or by including only patients who receive invasive mechanical ventilation – an intervention delivered more commonly to men than women (chapter 5).

Two sub-groups of trials – sepsis and cardiac arrest trials – included a lower percentage of women than observed in their target populations. There are several possible reasons for this. Trials of cardiac arrest include patients who are comatose, so consent is usually obtained from a surrogate decision-maker in the first instance. It may be that in this high-risk situation, surrogate decision makers are more likely to consent to enroll a male family member than a female family member. Older female ICU patients may be less likely to have a readily identifiable surrogate decision-maker, as women are more likely to outlive their spouse than men.

The clinical trials in our study used a binary definition of sex and did not record patient gender in their demographic data. People with innate variations of sex characteristics are estimated to compose approximately 1.7% of the general population. Moreover, approximately 4.5% of the general population are transgender or have gender diverse experiences (36, 184). Therefore, it is possible that some ICU patients with innate variations of sex characteristics or transgender/gender diverse experiences were either misclassified within the binary sex classification or did not participate in the trial. In this way, the current approach to recording patient sex and gender in clinical trials contributes to a paucity of knowledge about critically ill patients from sex and gender-based minority groups.

Strengths and limitations

A key strength of this study is that we were able to identify the target population using a comprehensive clinical registry that included all participating sites for every trial, allowing identification of the local Australia and New Zealand target populations for each trial. Moreover, the trials in this study examined a broad range of critical illnesses and interventions, reflecting the breadth of critical care trials undertaken by ANZICS CTG. Finally, our results were robust to multiple sensitivity analyses.

We acknowledge several limitations. We were unable to match key eligibility criteria for several trials, either because this information is not recorded in the APD (e.g., enteral nutrition), or because there was missing data during the relevant time-period (e.g., diabetes diagnoses). We were also unable to identify matched target populations from participating sites outside of Australia and New Zealand, although our findings remained unchanged in a sensitivity analysis that excluded all multinational trials. We cannot confidently ascertain whether an observed difference between a study population and target population reflects a true difference in the populations or an artefactual difference borne of an imperfect matching process.

For those trials with under-representation of a sex group, we could not identify when the disparity emerged, as the trial screening logs did not routinely record patient sex. Including patient sex data in the screening log would allow analysis of sex balance throughout trial screening, enrolment and follow up.

8.6 CONCLUSION

Critical care trials completed in Australia and New Zealand over a ten-year period included a representative balance of women and men overall when compared to their intended target populations. However, the populations studied in these trials had a significantly lower proportion of women than the general ICU patient population. These findings suggest that trial enrolment was not affected by patient sex, however the trials' conception and design identified relatively male-dominated sections of the ICU population to study.

Chapter 9. Conclusion

9.1 SUMMARY OF FINDINGS

This thesis provides a comprehensive overview of sex differences in the ICU patient population in Australia and New Zealand, spanning differences in diagnostic casemix, illness severity, mortality, treatment, and participation in critical care trials. To summarise the key findings of this research:

- Sex balance among ICU patients varied substantially according to admission diagnosis.
- The sex balance within a diagnostic group was associated with the relative survival of women and men in that group: ICU patients were more likely to survive if admitted with an illness common in their sex.
- Women were less likely to receive vital organ support than men yet were similarly likely to survive their critical illness.
- Critical care trials undertaken in Australia and New Zealand examined male-dominated clinical conditions but recruited a representative proportion of female participants relative to their intended target populations.
- People with innate variations in sex differentiation; and patients with transgender or gender diverse experiences; were not represented in critical care trials.
- Patients classified as belonging to a third sex group composed a small minority of ICU patients in Australia and New Zealand; they had similar outcomes to patients classified as female or male. Compared to the other sex groups, a higher proportion of patients classified as a third sex were admitted after orthopedic surgery or drug overdose.

Sex balance in ICU admissions

Women composed between 42% and 43% of ICU patients in both the Australia and New Zealand ICU patient population and in the pooled population of ICU patients in our meta-analysis. Cardiovascular conditions, particularly those requiring cardiac surgery, accounted for over half of the sex imbalance in ICU admissions in Australia and New Zealand.

Patients classified as belonging to a third sex category composed 0.06% of ICU patients in the Adult Patient Database. This likely represents an underestimate of the true percentage of ICU patients with variations of sex differentiation or transgender experiences, reflecting limitations in the process of recording sex and gender in the hospital medical record. Nonetheless, this third sex category was consistently represented across all regions and hospital types contributing to the APD. We did not identify any previous retrospective studies or clinical trials of ICU patients that examined a third or non-binary sex category.

Illness severity and mortality

In Australia and New Zealand, women were younger and had lower illness severity at the time of ICU admission than men. This contrasts with the findings of most previous studies from Europe and North America, suggesting that Australia and New Zealand may have different ICU admission practices than other high-income countries. In turn, this may relate to diagnostic case mix, overall ICU admission threshold or sex-specific admission thresholds.

Overall, we observed that women and men admitted to ICU had similar hospital mortality in both our meta-analysis and our studies of ICU admissions in Australia and New Zealand. Specifically, our meta-analysis found no difference in risk-adjusted hospital mortality of women and men admitted to ICU. Our meta-analysis found that women had higher risk-adjusted mortality at ICU discharge and one year, but this finding was not robust to sensitivity analysis of studies at low risk of bias. In our study

of women and men admitted to ICUs in Australia and New Zealand, there was no sex difference in hospital mortality after adjustment for illness severity, admission diagnosis, ICU lead time, hospital site and year of admission. Similarly, when we examined the group of ICU patients classified as belonging to a third sex group, there was no significant difference in risk-adjusted hospital mortality between the sex groups.

Of note, we observed a lower adjusted hospital mortality in women compared to men overall in a subsequent study that additionally adjusted for pre-existing limitation of medical treatment orders (chapter 6). This raises the possibility that LoMT orders affect the outcomes of women and men differently. Our studies of ICU patients in Australia and New Zealand demonstrated that women had the highest rate of LoMT orders compared to the other sex groups. This important incidental finding is consistent with the findings of a systematic review of limitations of life sustaining treatments in ICU patients in America (82). Further work is needed to understand the sex difference in incidence of LOMT orders and the association with outcomes within each sex group.

Significance of diagnostic category

We observed that diagnostic case mix varied between the sex groups of ICU patients. The admission diagnoses with the greatest proportion of women were asthma, subarachnoid haemorrhage, and metabolic or endocrine emergencies. Cardiac surgery, aortic surgery and trauma had the highest proportion of male patients. The admission diagnoses with the highest proportion of patients classified as third sex were orthopedic surgery and drug overdose.

There was also large variation in the relative mortality of women compared to men across different diagnostic categories of ICU admissions. Women were significantly more likely to die than men following cardiac surgery and burns. We identified an association between the sex balance within a diagnostic group and sex differences in mortality in that same group. In diagnoses with few women, women were relatively sicker and more likely to die than men. In diagnoses with relatively few men, men were sicker and more likely to die.

Sex differences in vital organ support

Women were less likely to receive vital organ support than men in the ICU, after adjustment for important confounders such as illness severity and LoMT. This is the most consistent finding in this program of research, demonstrated in both our meta-analysis and the analysis of the local APD data. In Australia and New Zealand, ECMO was the only vital organ support applied equally to women and men, although event numbers were relatively low for this organ support.

Despite receiving less aggressive treatment in ICU, women were at least as likely to survive to hospital discharge. Furthermore, there was a clear female survival advantage among ICU patients who avoided vital organ support. This suggests that a more conservative approach to treatment may particularly benefit women. Alternatively, it is possible there is an underlying female survival advantage in critical illness which is ameliorated by the provision of organ support.

There was no consistent pattern in vital organ support provided to patients classified as a third sex compared to the other sex groups. The proportion of patients classified as third sex who received mechanical ventilation was intermediate between the proportion of women and men. The third sex group were equally likely to receive renal replacement therapy compared to women or men, but less likely to receive vasoactive medication compared to the other groups.

Representation of sex and gender-based minorities

People from sex and gender-based minorities are not yet well represented in the critical care literature. All the critical care trials; and all the ICU-population level retrospective studies focussing on sex or gender examined in this thesis; recorded binary sex or gender categories.

This thesis described the characteristics of ICU patients classified as belonging to a third sex category, since the introduction of this category to the APD. We found that

ICU patients classified as belonging to a third sex group were younger on average than those classified as female or male, more likely to be admitted after elective surgery and more likely to be admitted following drug overdose or orthopedic surgery. The third sex group had a similar illness severity to the group classified as female, which was lower than the group classified as male. There was no difference in the adjusted hospital mortality of the third sex group compared to the other sex groups.

The proportion of patients classified as third sex was far lower than expected based on population estimates of either the population of people with innate sex differences or people with transgender and gender diverse experiences. This underscores the significant limitations to current practices of recording sex and gender in the medical record, clinical registries and clinical trials. These limitations not only obscure sex and gender-based minorities admitted to ICU, they also introduce an unquantifiable misclassification bias to binary sex data – a problem affecting this program of research.

Sex representation in clinical trials in Australia and New Zealand

Overall, the proportion of women in the study populations of critical care trials in Australia and New Zealand reflected their intended target populations. Women were under-represented in cardiac arrest and sepsis trials.

Women composed only 36% of the pooled target population of contemporary critical care trials in Australia and New Zealand – significantly lower than the sex balance in the general population of ICU patients. This suggests that these trials examined male-dominated clinical conditions by design, relating to study question, eligibility criteria or participating sites.

9.2 IMPLICATIONS

There are several broad implications from this program of research.

Diagnosis counts

We found that, when considering sex differences in critical illness, diagnosis counts. Sex balance varied substantially between diagnostic groups, as did the relative illness severity and mortality of women and men.

By examining a broad cohort of ICU patients, our research mapped out the diagnostic categories of critical illness with the most and least pronounced sex differences. We confirmed substantial sex differences in the incidence and outcomes of critical illness related to cardiovascular disease. In contrast, we found less pronounced sex differences in sepsis, a critical illness frequently examined in previous sex differences research. These findings could focus future research on diagnostic groups with the most significant sex differences, in both ICU and non-ICU populations.

Implicit bias in the ICU

Two findings from this research particularly suggest that implicit sex or gender bias may affect the treatment of ICU patients. First, the observation that women receive less treatment than men, after adjusting for important confounders such as illness severity or diagnosis. Second, the observation of a ‘minority association’: favourable survival for the predominant sex group within a diagnostic category.

The observation that clinical decisions in the ICU may be affected by implicit or unconscious sex/gender bias is not unexpected, echoing the findings of a systematic review that found implicit bias affects the decision making of healthcare professionals (67). However, it does challenge the ideal of impartial and objective clinical decision making in critical care (67). Our research helps to retrospectively illuminate possible blind spots in clinical decision-making; the next step is to define effective mechanisms for recognising these blind spots in practice. Promising strategies to ameliorate implicit bias in clinical decisions include the use of peer clinician networks to check or

‘challenge’ clinical decisions and ensuring clinicians work with a diversity of colleagues and patients (157, 158).

Less is more: from Yentl syndrome to Achilles syndrome

Our research suggests that ‘Yentl syndrome’ – a tendency to provide less aggressive treatment to women than to men – pervades intensive care units in Australia and New Zealand.

However, the critically ill women in our studies did not so much suffer from Yentl syndrome as thrive with it. Despite receiving less treatment in ICU, women were similarly or more likely to survive. Furthermore, there was a clear female survival advantage among the ICU patients who avoided vital organ support. Therefore, our findings may better describe an ‘Achilles syndrome’: like the Greek warrior masquerading as a woman to avoid dying in the Trojan war, men admitted to ICUs may gain advantage from being treated ‘like a woman’.

Interestingly, this finding that women thrived despite receiving less treatment has been replicated even in situations where there is quite compelling evidence that the intervention improves survival. For example, a Japanese study of over 350,000 patients with out-of- hospital cardiac arrest observed that young women had favourable neurological outcomes despite being less likely to receive bystander cardiopulmonary resuscitation or defibrillation (236).

How to interpret the observation that women received less treatment yet had similar or more favourable outcomes? One aspect is straightforward: women and men were treated differently. The relationship between sex, treatment and outcomes is more difficult to untangle, and the underlying mechanisms cannot be confirmed by our retrospective observational studies.

First, it is possible that female sex conferred a survival advantage, that persisted despite – or was only slightly ameliorated by – receiving less treatment. Second, minimising intervention may be favourable for all patients, and women benefitted from the inequitable application of a conservative treatment strategy. There is certainly

increasing evidence for a ‘less is more’ approach to critical care (175). Recent trials supporting the idea that critically ill patients are best served by receiving ‘just enough’ treatment include studies of nutritional support, renal replacement therapy, oxygenation targets and ventilation strategies (237-240).

Finally, the interventions may be relatively less effective, or even injurious, in women. This may be a true heterogeneity of treatment effect, with sex groups responding differently to the same treatment. Alternatively, the treatment may be applied differently between the sex groups, as with the tendency to provide women with excessive tidal volumes relative to body size during mechanical ventilation (241).

Therefore, it is possible that outcomes in women could be improved even further with better tailored treatment strategies and/or that men could have improved outcomes if they received fewer interventions.

This highlights the challenge of assessing equity in healthcare: observed differences in outcomes between population groups may arise from a combination of biological factors and potential remediable systemic factors. Therefore, equitable treatment sometimes results in unequal outcomes. Conversely, population groups with similar outcomes have not necessarily received similar treatment. Indeed, this thesis found similar hospital mortality for women and men admitted to ICU despite quite substantial differences in vital organ support provided. It is not clear that this likely unwitting differential approach to treatment represents equity. Instead, the relationship between sex, treatment, and outcomes we observed may represent a combination of implicit bias, underling female survival advantage, harm from treatment and heterogeneity of treatment effect. To promote equity and improve outcomes for each sex group, we should provide sex-specific treatment strategies based on demonstrated heterogeneity of treatment effect and avoid differential treatment where there is no such heterogeneity of treatment effect.

9.3 STRENGTHS, LIMITATIONS AND RESEARCH QUESTIONS ARISING FROM THE WORK

This program of research provides the first examination of sex differences in the Australia and New Zealand ICU patient population, the first description of ICU patients classified as a third sex, and the largest study to date of sex differences in mortality of ICU patients. We presented novel findings that address important gaps in the existing literature, quantifying the relative contribution of different critical illnesses to the sex imbalance in ICU admissions; and identifying an association between sex balance and sex differences in mortality within diagnostic groups. Finally, we highlighted some consistent themes emerging from both the international literature and our analysis of local data: women received less vital organ support than men and were more likely to have a limitation of medical treatment defined at ICU admission.

However, there are also important limitations to this research, framed here as questions for subsequent research.

How to study sex and gender in critical illness?

Our research examining the ICU patient population in Australia and New Zealand comprised a series of retrospective observational studies, reporting sex-based associations but unable to establish causal effects. This raises an important question about how to study the impact of patient sex and gender on critical illness most effectively, with a view to improving both equity and outcomes overall. There is likely no single best approach. Instead, complementary strategies of sex and gender-sensitive research are required.

Within major critical care trials, pre-specified sex-based subgroup analyses can illuminate heterogeneity of treatment effect between sex groups, informing a more tailored approach to implementing study findings. This is an important strategy, however it is less likely to identify sex differences in the treatment provided in practice, as the trial structure guides the intervention. Even clinicians' 'usual care' decisions are likely to be affected the knowledge that they are being observed - the Hawthorne effect – which may ameliorate the effect of implicit bias. Therefore, retrospective

observational studies, like the studies in this thesis, remain a useful tool to understand how interventions are applied in practice. In addition, qualitative and mixed-methods research could help to understand clinicians' behaviour, and the possible impact of implicit bias on clinical decision-making.

In some critical illnesses, for example cardiac arrest, women make up such a small minority of the affected target population that even a relatively large trial with a representative study population includes very few women overall, providing little certainty about the effect of the intervention on women. This challenge of understanding heterogeneity of treatment effect in minority populations is only magnified for smaller population groups, such as sex and gender-based minorities groups, or when the minority group is under-represented within the study population, as we observed for the representation of women in cardiac arrest trials.

To address this problem, in some instances it may be justified to over-sample or selectively sample a minority group within a study population, to study the efficacy of an intervention in that group. For example, the Randomised Comparison of the Outcome of Single versus Multiple Arterial Grafts Trial (ROMA) trial, a major multinational trial of different approaches to coronary artery bypass grafting, has a nested sub-trial recruiting only women (ROMA-Woman). The 'ROMA-Woman' trial will be adequately powered to assess the intervention in women, in contrast it is projected that only 15% of the main ROMA study population will be women (242). The importance of this trial is underscored by our finding that women had a substantially higher hospital mortality than men following coronary artery bypass graft surgery.

Similar challenges arise when examining imbalanced group sizes within large data sets, for example comparing a group of transgender patients within a large population group comprising mostly cis-gender women and men. In such class-imbalanced data; that is, where one group within a classification system is far smaller than the majority groups; there will be more uncertainty associated with point estimates for the minority group.(243) This has implications for machine learning models, which tend to have better performance for the majority group or class (e.g. women or men) rather than the minority group (e.g. sex and gender minorities) (244). Strategies to address class

imbalance in machine learning and other AI models include those focussed on data sampling techniques and those focussed on adjusting the algorithm to improve performance in the minority group (245).

How to ensure sex and gender variables are accurately recorded in the health record?

For sex and gender-based minorities, concerns about statistical power are unfortunately secondary to concerns about being represented at all in clinical research. Our systematic reviews (chapter 3 and 5) and review of critical care trials (chapter 8), suggest that people with transgender or gender diverse experience, and people with innate variations in sex differentiation, are not represented in the critical care literature. Our own search strategy had an important limitation: whilst we searched for the terms sex, gender, female, male, man, and woman, we did not include terms relating to transgender or intersex. Therefore, we may have failed to capture studies specifically focussing on the group of patients with innate variations of sex differentiation (or intersex), or studies focussing on patients with transgender experience. Nonetheless, we observed that all studies included our systematic reviews – ICU population-levels studies that examined patient sex or gender as their primary or secondary objective – included only binary sex or gender categories. Similarly, all the ANZICS CTG-endorsed critical care trials examined in chapter 8 recorded patient sex and not gender; and recorded only binary sex categories.

The paucity of research into critical illness in sex and gender-based minorities implies that we do not have evidence to guide personalised critical care for these groups. In this thesis, we were able to present an initial epidemiology of patients classified as third sex (chapter 7). However, there are important conceptual limitations to the 'third sex' categorisation and uncertainty related to the estimated size of the third sex group, which was implausibly low compared to population estimates. To ensure these patients are represented in registry-based retrospective studies and clinical trials, we require reliable and affirming processes for recording sex, gender, and innate variations of sex characteristics in the hospital record.

A related limitation is that this research effectively examined a 'sex/gender' hybrid – referred to throughout as 'patient sex' – reflecting the limited availability of sex and gender information in medical records. This conflation of sex and gender precludes identifying drivers of systemic differences and associated loci for intervention, for example biological targets in the event of a difference related to sex hormones or healthcare system changes for disparities driven by implicit bias. Against this concern, some commentators observe that sex and gender are so inextricably intertwined that untangling them to identify a single cause of an observed health difference between groups is likely to be unrealistic (12). Nonetheless, any such untangling will only be possible if sex and gender are routinely recorded separately, accurately and consistently in the healthcare record.

The Australian state of Victoria made a significant step towards this goal in 2024, requiring all hospitals to record both sex at birth and gender in the medical record (246). The gender options include man, woman, non-binary, another term and 'prefer not to answer'. Sex at birth includes the options male, female, and another term and the associated guidance document includes recommendations for safe and affirming approaches to data collection. Similarly, following well-publicised debate, the Australian Federal Government recently committed to including questions regarding gender and sexual orientation in the next national Census (247). These are both significant changes which will allow much greater understanding of the health needs of transgender and gender diverse people. However, neither the changes to hospital records in Victoria nor the Australian census included a category recording variation in sex characteristics.

Regarding the APD, our research has led to a proposal to amend the APD data dictionary to reflect contemporary terms to describe sex (female, male or another term rather than 'intersex/indeterminate'), and to introduce a gender variable in addition to the existing sex variable.

Does the APACHE III score perform differently between the sex groups? Should patient sex be included in illness severity scores or clinical algorithms?

This program of research used the APACHE III score as the illness severity variable in each of the analyses. There are two limitations associated with this approach. The first relates to the prognostic utility of the APACHE III score, which was derived in 1991 from a cohort of ICU patients in the USA (183). Examining APD data, Paul and colleagues demonstrated deterioration in the calibration of APACHE III in the contemporary Australia and New Zealand ICU context, and therefore developed the Australia and New Zealand Risk of Death (ANZROD) model to more accurately predict outcomes in our local ICU population (248, 249).

We chose the APACHE III score as the key illness severity variable rather than ANZROD in this research, for a few reasons. First, the ANZROD model includes both patient sex and some clinical variables that may be applied inequitably between the sex groups, including limitation of medical treatment orders, time spent in hospital prior to ICU admission and invasive ventilation (248). In contrast, the APACHE III score assesses physiological variables, comorbidities and age, with diagnosis included in the associated risk prediction model (183). This simple structure has the advantage of relative transparency compared to the more complex and unfamiliar ANZROD model. Finally, ANZROD cannot be easily broken apart to interrogate the effect of its component parts, for example, physiological variables.

The second limitation of the APACHE III score is that it may perform differently in women and men. This could partly explain our observation that women were admitted to the ICU with apparently lower illness severity than men yet were similarly likely to die by hospital discharge. Certainly, some risk-prediction models perform differently between sex groups; the performance of these models may be improved by including a patient sex variable or stratifying by sex (49, 50, 250). An analysis of patients admitted to Swiss ICUs with sepsis in 2021 and 2022 found that women had lower SOFA scores on average than men, mainly due to lower scores in the domains of coagulation, renal and liver function (78). Despite these differences, women and men in this study had similar ICU mortality – an observation that echoes our own findings.

This raises a complex question: should patient sex be included in illness severity scores, risk prediction models or clinical algorithms? Unlike a physiological variable like heart rate, patient sex is a complex variable that takes in some biological, behavioural, and systemic characteristics. Therefore, the association between patient sex and outcomes may be mediated by biological factors, such as average muscle mass, or modifiable systemic factors such as unconscious bias affecting the treatment of a sex group. If the latter mechanism predominates, then including patient sex in a clinical algorithm can affect clinical decisions in a way that either perpetuates or ameliorates inequity between sex groups. For this reason, there has been a move to exclude race as a variable in risk prediction models, particularly clinical algorithms used to guide treatment (251, 252).

In their recent *NEJM* review, Goodman and colleagues usefully illustrate this point with the example of cardiac surgery risk models (250). A risk prediction model for valvular cardiac surgery may ascribe a higher risk to a woman than a man with otherwise similar clinical characteristics. In turn, this higher risk estimate may dissuade clinicians from offering surgery to women, leading to delayed surgical intervention in women or stymied efforts to improve cardiac surgery outcomes in women. Alternatively, clinicians may offer closer post-operative monitoring of women undergoing cardiac surgery, which could improve outcomes and ameliorate underlying inequity.

Of note, the possible impacts of including sex in a clinical algorithm are relatively hidden from the user's view and difficult to interrogate retrospectively. Once a variable is included – or buried – in the model it tends to be treated as non-modifiable. In the words of Goodman and colleagues, "If sex-based differences in risk result from biased care or treatment patterns, enshrining those associations in algorithmic predictions is arguably inequitable and possibly unlawful."(250) This program of research found some important sex differences in the treatment of ICU patients. We can only hope to understand these differences and leverage them to improve outcomes if patient sex is overtly examined rather than buried in a model.

Even in instances where sex is prognostically useful due to underlying biological differences, a risk-prediction model may be improved with a more specific variable

rather than the relatively crude sex-based categories. For example, the observation that women are more likely than men to receive excessive tidal volume ventilation is better remedied by routinely adjusting ventilation to individual patient size rather than patient sex. Indeed, consistently adjusting common ICU treatments such as ventilation, vasoactive infusions and antibiotic dosing to patient body size may be a relatively simple way to personalise treatment and avoid the default over-treatment of smaller adults, many of whom are women.

Are different ICU admission or treatment thresholds applied to each sex group? Would sex-specific treatment thresholds improve outcomes?

Related to the issue of sex-specific risk prediction is the question of treatment thresholds: are different ICU admission and treatment thresholds applied to women, men and patients classified as third sex? How does this affect patient outcomes? We examined the population of patients admitted to ICU, rather than the denominator of all critically unwell patients. This limited our assessment of the ICU admission thresholds, beyond comparing the illness severity of each sex group at the time of ICU admission. Similarly, as we did not work with time-stamped data for key interventions such as endotracheal intubation for invasive ventilation, we were unable to define the sex-specific thresholds applied for these supports.

These limitations highlight two important frontiers for equity-focussed research in critical care. First, working with data that includes the denominator of all 'potential intensive care patients', either within a population of hospitalised patients or the general population. For example, Garland and colleagues examined rates of critical illness in the general population in Manitoba, Canada, finding no significant sex discrepancy in rates of ICU admission after considering the population-based denominator of critical illness (22).

Second, working with time-stamped physiological data to describe sex-specific thresholds for key interventions as they are applied in ICU practice. For example, Yarnell and colleagues examined thresholds for endotracheal intubation in patients with respiratory failure, using major critical care databases from Boston, USA and Amsterdam, in the Netherlands (91). The observed threshold to intubate was highly

variable, suggesting unmeasured factors affected the decision. Patient race was associated with the threshold to intubate, but not patient sex. This is notable as it appears to conflict with our finding that women were less likely to receive mechanical ventilation received after adjustment for illness severity and other confounders.

How do other sociodemographic characteristics affect treatment and outcomes from critical illness? How do other sociodemographic characteristics interact with sex?

This program of research focussed on patient sex and did not consider other sociodemographic domains such as race, ethnicity or level of socioeconomic advantage, nor how these may interact. This is an important area for future research. There is substantial body of evidence that these sociodemographic characteristics are associated with access to healthcare, intensity of treatment and outcomes, including in the ICU (171, 253-255). Of note, in Australia there is no requirement to record race or ethnicity, beyond First Nations status, impeding population level research into the association of ethnicity with health outcomes (256). However, it is possible to examine the effect of socioeconomic status at the level of neighbourhood or postcode.

9.4 FUTURE DIRECTIONS

This thesis makes a compelling case for further sex and gender-focussed research in critical care; key areas for future research are summarised here.

First, the work in this thesis can be further extended by defining sex differences in illness severity, treatment, and outcomes of ICU patients with greater nuance. Specifically, it will be important to examine the sex-specific performance of illness severity scores commonly used in critical care trials and critical care benchmarking, such as the APACHE scores. The relationship between patient sex, vital organ support and outcome needs to be further interrogated, using time-stamped data to define sex-specific ICU admission and treatment thresholds, and examined for heterogeneity of treatment effect between the sex groups.

The second key area for further research focusses on ICU patients from sex and gender-based minorities. The new requirement to record patient sex and gender separately for all patients admitted to Victorian hospitals will provide an opportunity to examine the clinical characteristics of ICU patients who identify as transgender or non-binary using more reliable hospital population-level data.

The third key area for future research is the relationship between patient sex and limitation of medical treatment orders. In our studies of patients admitted to ICUs in Australia and New Zealand, women had a higher incidence of LoMT orders than men, despite having lower illness severity at ICU admission. This finding warrants further investigation, examining possible gender differences in patient-defined treatment goals and the perceptions of surrogate decision makers and clinicians. Initially, it will be important to define the extent to which the patient, their surrogate decision maker, critical care and non-critical care doctors each contribute to LoMT decisions in Australian and New Zealand ICUs.

A final key area for further research relates to unconscious gender bias in critical care, an area considered only obliquely in this thesis. Unconscious or implicit bias has been fruitfully examined in other fields of medicine using a variety of research methodologies including simulated patient assessments and implicit association tests (67, 158). A related emerging field of research is the relationship between physician gender and patient outcomes (157). The ANZICS CORE Critical Care Resource registry records the gender composition of the intensive care specialist workforce participating ICUs, making it possible to examine for an association between workforce gender composition and patient outcomes at a unit level (31).

9.5 FINAL REMARKS

This program of research provides a comprehensive overview of sex differences in the population of patients in Australian and New Zealand ICUs. We confirmed that more men than women are admitted to our ICUs, and that cardiovascular disease is the major driver of this sex imbalance. We found that women and men were treated quite differently in the ICU. This striking observation challenges critical care clinicians to abandon the assumption that the treatment they provide is unaffected by patient sex. Further research is clearly needed to delineate the mechanisms underlying this sex difference in treatment, and work towards developing more personalised and equitable treatment for all sex groups admitted to the ICU.

Appendix A. Adult Patient Database (APD) sites

Sites contributing to the Adult Patient Database (APD) during the periods represented in this research:

Albury Base Hospital ICU, Alfred Hospital ICU, Alice Springs Hospital ICU, Allamanda Private Hospital ICU, Angliss Hospital ICU, Armadale Health Service ICU, Ashford Community Hospital ICU, Auckland City Hospital CV ICU, Auckland City Hospital DCCM, Austin Hospital ICU, Ballarat Health Services ICU, Bankstown-Lidcombe Hospital ICU, Bathurst Base Hospital ICU, Bendigo Health Care Group ICU, Blacktown Hospital ICU, Bowral Hospital HDU, Box Hill Hospital ICU, Brisbane Private Hospital ICU, Brisbane Waters Private Hospital ICU, Buderim Private Hospital ICU, Bunbury Regional Hospital ICU, Bundaberg Base Hospital ICU, Caboolture Hospital ICU, Cabrini Hospital ICU, Cairns Hospital ICU, Calvary Bruce Private Hospital HDU, Calvary Hospital (Canberra) ICU, Calvary Hospital (Lenah Valley) ICU, Calvary John James Hospital ICU, Calvary Mater Newcastle ICU, Calvary North Adelaide Hospital ICU, Calvary Wakefield Hospital (Adelaide) ICU, Campbelltown Hospital ICU, Canberra Hospital ICU, Casey Hospital ICU, Central Gippsland Health Service ICU, Christchurch Hospital ICU, Coffs Harbour Health Campus ICU, Concord Hospital (Sydney) ICU, Dandenong Hospital ICU, Dubbo Base Hospital ICU, Dunedin Hospital ICU, Epworth Eastern Private Hospital ICU, Epworth Freemasons Hospital ICU, Epworth Geelong ICU, Epworth Hospital (Richmond) ICU, Fairfield Hospital ICU, Fiona Stanley Hospital ICU, Flinders Medical Centre ICU, Flinders Private Hospital ICU, Footscray Hospital ICU, Frankston Hospital ICU, Fremantle Hospital ICU, Gold Coast Private Hospital ICU, Gold Coast University Hospital ICU, Gosford Hospital ICU, Gosford Private Hospital ICU, Goulburn Base Hospital ICU, Goulburn Valley Health ICU, Grafton Base Hospital ICU. Greenslopes Private Hospital ICU, Griffith Base Hospital ICU, Hawkes Bay Hospital ICU, Hervey Bay Hospital ICU, Hollywood Private Hospital ICU, Holmesglen Private Hospital ICU, Holy Spirit Northside Hospital ICU, Hornsby Ku-ring-gai Hospital ICU, Hurstville Private Hospital ICU, Hutt Hospital ICU, Ipswich Hospital ICU, John Fawkner Hospital ICU, John Flynn Private Hospital ICU, John Hunter Hospital ICU, Joondalup Health Campus ICU, Kareena Private Hospital ICU, Knox Private Hospital ICU, Latrobe Regional Hospital ICU, Launceston General Hospital ICU, Lingard Private Hospital ICU, Lismore Base Hospital ICU, Liverpool Hospital ICU, Logan Hospital ICU, Lyell McEwin Hospital ICU, Mackay Base Hospital ICU, Macquarie University Private Hospital ICU, Maitland Hospital HDU/CCU, Maitland Private Hospital, Manly Hospital & Community Health ICU, Manning Rural Referral Hospital ICU, Maroondah Hospital ICU, Mater Adults Hospital (Brisbane) ICU, Mater Health Services North Queensland ICU, Mater Private Hospital (Brisbane) ICU, Mater Private Hospital (Sydney) ICU, Mater Private Hospital (Townsville) ICU, Melbourne Private Hospital ICU, Middlemore Hospital ICU, Mildura Base Hospital ICU, Modbury Public Hospital ICU, Monash Medical Centre-Clayton Campus ICU, Mount Hospital ICU, Mount Isa Hospital ICU, Nambour General Hospital ICU, National Capital Private Hospital ICU, Nelson Hospital ICU, Nepean

Hospital ICU, Nepean Private Hospital ICU, Newcastle Private Hospital ICU, Noosa Hospital ICU, North Shore Hospital ICU, North Shore Private Hospital ICU, North West Regional Hospital (Burnie) ICU, Northeast Health Wangaratta ICU, Northern Beaches Hospital, Norwest Private Hospital ICU, Orange Base Hospital ICU, Peninsula Private Hospital ICU, Peter MacCallum Cancer Institute ICU, Pindara Private Hospital ICU, Port Macquarie Base Hospital ICU, Prince of Wales Hospital (Sydney) ICU, Prince of Wales Private Hospital (Sydney) ICU, Princess Alexandra Hospital ICU, Queen Elizabeth II Jubilee Hospital ICU, Redcliffe Hospital ICU, Repatriation General Hospital (Adelaide) ICU, Robina Hospital ICU, Rockhampton Hospital ICU, Rockingham General Hospital ICU, Rotorua Hospital ICU, Royal Adelaide Hospital ICU, Royal Brisbane and Women's Hospital ICU, Royal Darwin Hospital ICU, Royal Hobart Hospital ICU, Royal Melbourne Hospital ICU, Royal North Shore Hospital ICU, Royal Perth Hospital ICU, Royal Prince Alfred Hospital ICU, Ryde Hospital & Community Health Services ICU, Shoalhaven Hospital ICU, Sir Charles Gairdner Hospital ICU, South West Healthcare (Warrnambool) ICU, Southern Cross Hospital (Hamilton) ICU, Southern Cross Hospital (Wellington) ICU, St Andrew's Hospital (Adelaide) ICU, St Andrew's Hospital Toowoomba ICU, St Andrew's Private Hospital (Ipswich) ICU, St Andrew's War Memorial Hospital ICU, St George Hospital (Sydney) CICU, St George Hospital (Sydney) ICU, St George Hospital (Sydney) ICU2, St George Private Hospital (Sydney) ICU, St John of God (Berwick) ICU, St John Of God Health Care (Subiaco) ICU, St John Of God Hospital (Ballarat) ICU, St John of God Hospital (Bendigo) ICU, St John Of God Hospital (Geelong) ICU, St John Of God Hospital (Murdoch) ICU, St John of God Midland Public & Private ICU, St Vincent's Hospital (Melbourne) ICU, St Vincent's Hospital (Sydney) ICU, St Vincent's Hospital (Toowoomba) ICU, St Vincent's Private Hospital (Sydney) ICU, St Vincent's Private Hospital Fitzroy ICU, St Vincent’s Private Hospital Northside ICU, Sunnybank Hospital ICU, Sunshine Coast University Hospital ICU, Sunshine Coast University Private Hospital ICU, Sunshine Hospital ICU, Sutherland Hospital & Community Health Services ICU, Sydney Adventist Hospital ICU, Sydney Southwest Private Hospital ICU, Tamworth Base Hospital ICU, Taranaki Health ICU, Tauranga Hospital ICU, The Bays Hospital ICU, The Chris O’Brien Lifehouse ICU, The Memorial Hospital (Adelaide) ICU, The Northern Hospital ICU, The Prince Charles Hospital ICU, The Queen Elizabeth (Adelaide) ICU, The Townsville Hospital ICU, The Valley Private Hospital ICU, The Wesley Hospital ICU, Timaru Hospital ICU, Toowoomba Hospital ICU, Tweed Heads District Hospital ICU, University Hospital Geelong ICU, Wagga Wagga Base Hospital & District Health ICU, Waikato Hospital ICU, Warringal Private Hospital ICU, Wellington Hospital ICU, Werribee Mercy Hospital ICU, Western District Health Service (Hamilton) ICU, Western Hospital (SA) ICU, Western Private Hospital ICU, Westmead Hospital ICU, Westmead Private Hospital ICU, Whakatane Hospital ICU, Whangarei Area Hospital, Northland Health Ltd ICU, Grampians Health Horsham ICU, Wollongong Hospital ICU, Wollongong Private Hospital ICU, Women's and Children's Hospital PICU, Wyong Hospital ICU

Appendix B. Trial eligibility criteria and matching of target populations (chapter 8)

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
PATCH July 2014 – Sept 2021 *Multinational*	Age ≥ 18 years	Age ≥ 18 years	From facility for older persons	Hospital source is nursing home, or chronic care facility
	Suspected severe traumatic injuries	Any trauma ICU admission diagnosis		
	High risk trauma-induced coagulopathy	Not matched	Known or suspected pregnancy	Pregnant
	First dose of tranexamic acid given within 3 hours injury and before hospital admission	Not matched		
SUDDICU May 2017-Nov 2021 *Australia and New Zealand only*	Mechanical ventilation via ETT at admission and predicted to continue ventilation > 48 hours	Invasively ventilated & duration of ventilation > 48 hours *Ventilation hours missing for 28.5% admissions during study period. We included all ventilated patients with missing ventilation hours. This criterion judged poorly matched.*	Age less than 16 years in New Zealand	Age<16 years & admitted to ICU in New Zealand
			Not expected to survive 12 hours	Palliative care of the dying patient or potential organ donor
			Known or suspected pregnancy	Pregnant
			Enrolled in interacting clinical trial	Not matched
			Allergy or interaction with trial drugs	Not matched
TAME Mar 2018 – Sept 2021 *Multinational*	Age ≥ 18 years	Age ≥ 18 years	Time from ROSC to screening >180 minutes	Not matched
	Coma following OOHCA	Cardiac arrest diagnosis AND admitted to ICU from ED	Limitation of treatment	Pre-existing treatment limitation, or admitted for palliative care or potential organ donation
	Sustained ROSC >20 minutes	Implied	Unwitnessed cardiac arrest with initial asystole	Not matched
TEAM Feb 2018 – Nov 2021 *Multinational*	Age ≥ 18 years	Age ≥ 18 years	Spinal cord or brain injury	Admission diagnosis includes spinal injury or head injury
	Condition sufficiently stable for mobilization	Not matched	Rest-in-bed orders	Not matched
	Predicted to remain ventilated until day after tomorrow	Invasively ventilated> 48 hours *Ventilation hours missing for 20.3% admissions during study. all ventilated patients with missing ventilation hours; this criterion judged poorly matched.*	Dependency in any activity of daily living in the month before hospitalization	Moderately or more frail (clinical frailty score ≥ 5 and not missing)

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
LUCID May 2017 – Nov 2020 *Australia and New Zealand only*	Age ≥ 18 years	Age ≥ 18 years	Death during ICU inevitable	Palliative care of dying patient or potential organ donor
	Likely to remain in ICU until day after tomorrow	ICU length of stay > 48 hours	Diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome	Admission diagnosis diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome
	Arterial line or central line in situ	Not matched	Juvenile type 1 diabetes	Type 1 diabetes
	Type II diabetes	Type 2 diabetes *Diabetes status missing for 35% of APD admissions during study period. We included only patients with recorded type 2 diabetes & this criterion judged poorly matched.*	Specific blood glucose target required	Not matched
			Pregnancy or suspected pregnancy	Pregnant
			Cannot provide informed consent	Not matched
			In ICU ≥ 24 hours before randomized	Not matched
			Previously enrolled	ICU re-admissions
	Likelihood of blood glucose level ≥10mmol/L during ICU admission	Not matched		
TARGET protein feasibility April 2019 – July 2019 *Australia and New Zealand only*	Age ≥ 18 years	Age ≥ 18 years	Expected to be receiving oral nutrition before the calendar day after randomization	Not matched
	Receiving mechanical ventilation	Invasive ventilation	Receive any EN or PN for >12 hours during the current ICU admission	Not matched
	About to commence enteral nutrition (EN)	Not matched	Treating clinician considered the trial EN or rate of delivery to be clinically contraindicated	Not matched
	Expected to be receiving enteral nutrition in the ICU until at least the calendar day after randomization.	ICU admission >48 hours	Patient had been previously enrolled in the trial	ICU re-admissions
			Death was deemed imminent or inevitable	Palliative care of dying patient or potential organ donor
			Survival to day 90 was considered unlikely	Not matched

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
PLUS Sep 2017 – Dec 2020 *Australia and New Zealand only*	Requires a fluid bolus	Not matched	Age < 18 years	Age< 18 years
	In ICU until the day after tomorrow	ICU hours>48	Already received more than 500mL fluid	Not matched
	Arterial line or central line in situ	Not matched	Contra-indication to study fluid	Not matched
	Plasmalyte 148 and normal saline equally appropriate	Not matched	Patient with burns, liver transplant, correction of specific electrolyte abnormalities	Admission diagnosis burns, liver transplant, metabolic coma, diabetic ketoacidosis, other metabolic disorders
	At least 1 prespecified clinical sign indicating need for fluid resuscitation: 1. Heart rate > 90 2. Systolic BP< 100mmHg 3. MAP < 75mmHg 4. CVP < 10mmHg 5. Pulmonary artery wedge pressure < 12 mmHg 6. Capillary refill time > 1 second 7. Urine output < 0.5 ml/kg for at least one hour	Heart rate >90 or MAP <75 mmHg or Urine output <936mL over 24 hrs (women) OR <1058mL over 24 hours (men)	Traumatic brain injury or risk of cerebral edema	Admission diagnosis head trauma
			Death imminent or inevitable	Palliative care of dying patient or potential organ donor
			Life expectancy < 90 days	Not matched
			Unlikely to be able to ascertain primary outcome	Not matched
			Known or suspected pregnancy	Pregnant
	Not well enough to eat tomorrow	Not matched	Previously enrolled	ICU re-admissions
STARRT-AKI Oct 2015 – Sep 2019 *Multinational trial*	Age ≥ 18 years	Age≥ 18 years	Clinician has no equipoise for timing of RRT	Not matched
	Serum creatinine ≥100 (women) and ≥130 (men) AND one of the following 2-fold increase in serum creatinine from baseline; serum creatinine ≥354 with an increase of 27; Urine output <6mL/kg over 12 hours	Creatinine ≥100 (women) and creatinine ≥130 (men) *and one of* 2-fold increase in serum creatinine from baseline; serum creatinine ≥354 with an increase of 27; Urine output <936mL in 24 hours (women) or urine output <1058mL/ 24 hours (men) *Only assessed in first 24 hours, this criterion judged poorly matched*	Drug intoxication requiring RRT	Diagnosis of drug overdose
			Lack of commitment to provide RRT as part of ongoing treatment	Treatment limitation or palliative care or potential organ done
			Acute kidney injury resulting from treatable etiology	Not matched
			History of pre-existing kidney disease (renal replacement therapy in last 2 months, renal transplant last 12 months, known advanced chronic kidney disease)	Pre-existing chronic kidney disease requiring long-term dialysis

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
TTM-2 Nov 2017 – Jan 2020 *Multinational trial*	Out of hospital cardiac arrest, presumed cardiac or unknown cause	Cardiac arrest admission diagnosis AND admitted from ED	Unwitnessed cardiac arrest with initial rhythm asystole	Not matched
			On ECMO prior to ROSC	Received ECMO
	Sustained ROSC	Implied	Temperature on admission < 30° Celsius	Lowest temperature <30° Celsius in first 24 hours
	Unconscious	Ventilated	Obvious or suspected pregnancy	Currently pregnant or post-partum
	Eligible for ICU admission with no limitation	Full treatment or missing treatment limitation	Intracranial bleeding	Admission diagnosis ICH
			COPD with home oxygen	Chronic respiratory disease as comorbidity
ICU ROX Sep 2015 – May 2018 *Multinational trial*	≥ 18 years	Age ≥ 18 years	More than 2 hours of invasive mechanical ventilation	Not matched
			Enrolled in other trial of targeted oxygen therapy	Not matched
			Enrolment not in patient's best interests	Not matched
	Expected to receive ventilation until day after recruitment	Invasive ventilation & Ventilated > 48 hours *Ventilation hours missing for 85% admissions during study period. We included all ventilated patients with missing ventilation hours. This criterion judged poorly matched.*	Hyperoxia *OR* Avoidance of hyperoxia clinically indicated	Not matched
			Pregnancy	Pregnant
			Death inevitable and not committed to full active treatment	Treatment limitation, palliative care or potential organ donor
			Life expectancy < 90 days	Not matched
			Drug overdose	Drug overdose diagnosis
			Long term ventilation dependence	Not matched
			GBS, cervical cord injury above C5, muscular dystrophy, MND	GBS, any spinal cord injury, muscular dystrophy, MND
			Previously enrolled in ICU ROX	Re-admissions

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
PEPTIC Aug 2016 – Jan 2019 *Multi-national*	≥18 years	Age ≥ 18 years	Admission diagnosis upper GI bleeding	Variceal bleeding, GI bleeding ulcer/laceration,
	Mechanical ventilation	Mechanical ventilation	Previous ICU admission	ICU re-admission
REACTOR Nov 2016 – Mar 2019 *Australia and New Zealand only*	≥18 years	Age≥18 years	Acute brain pathology	Admission diagnosis TBI, ICH, subarachnoid hemorrhage, stroke
	Mechanical ventilation beyond day after randomization	Invasive ventilation & ventilated > 48 hours *Ventilation hours missing for 54% admissions during study period. We included all ventilated patients with missing ventilation hours. This criterion judged poorly matched.*	Confirmed or suspected HIE	Admission diagnosis cardiac arrest or respiratory arrest
			Burns ≥20%	Admission diagnosis burns
			Death inevitable	Palliative care of dying patient or potential organ donor
			Fulfilled all criteria 24 hours ago	Not matched
			Life expectancy < 90 days	Not matched
	Documented fever ≥37.8 ° Celsius in previous 12 hours	Temperature ≥37.8 ° Celsius in first 24 hours	Previously enrolled	ICU re-admission
	Deeply sedated	Not matched	Fulfilled all criteria 24 hours ago	Not matched
SPICE III Nov 2013 – Feb 2018 *Multi-national trial*	Intubated and receiving mechanical ventilation Will remain intubated until day after tomorrow	Invasive ventilation & ventilated > 48 hours *Ventilation hours missing for 93% admissions during study period. We included all ventilated patients with missing ventilation hours, this criterion judged poorly matched.*	≤ 18 years	≤ 18 years
			Pregnant or lactating	Pregnant or post-partum
			Intubated ≥12 hours in ICU pre-randomization	Not matched
			Proven or suspected TBI, ICH, stroke, hypoxic brain injury, spinal cord injury, drug overdose, burns acute hepatic failure	Admission diagnosis TBI, stroke, ICH, spinal cord injury, burns, acute liver failure
	Requires ongoing sedation	Not matched	Ongoing neuromuscular blockade	Not matched
			MAP <50 mmHg	MAP <50mmHg in first 24 hour
			HR <55bpm	HR <55 first 24 hours
			Known sensitivity to study drug	Not matched
			Lives in full time residential care	Admitted from nursing home
			Death deemed imminent, survival to 90 days unlikely	Palliative care/potential organ donor
			Previously enrolled in SPICE	ICU re-admission

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
POLAR Dec 2010 – Nov 2017 *Multinational trial*	Non–penetrating severe TBI (i.e., Glasgow Coma Scale (GCS) ≤ 8)	Admission diagnosis TBI and GCS < 9	Pre-intubation airway reflexes are absent	Not matched
	Estimated age ≥ 15 and < 60 years of age	Age ≥ 15 & < 60 years	Pre-intubation HR <120 bpm or systolic BP < 90mmHg	Not matched
	Injury estimated to have occurred within 2 hours of paramedic arrival	Not matched	Pre-intubation GCS 3 with unreactive pupils	Palliative care of dying patient or potential organ donor
			Penetrating neck/torso injury	Not matched
	The patient is intubated	Intubated	Receiving hospital not a study site	Included only admissions to participating sites
			Obvious pregnancy	Currently pregnant or post-partum
			Warfarin treatment	Not matched
TARGET Jun 2016 – Nov 2017 *Australia and New Zealand only*	≥18 years	Age ≥ 18 years	Any enteral or parenteral nutrition received for > 12 hours in this ICU admission	Not matched
	Intubated and receiving mechanical ventilation	Received invasive ventilation in ICU	Treating clinician considers the enteral nutrition goal rate of 1 ml per kg ideal body weight per hour to be clinically contraindicated	Not matched
	About to commence enteral nutrition or enteral nutrition commenced within the previous 12 hours	Not matched	Requirement for specific nutritional therapy as determined by the treating doctor or dietitian	Not matched
	Expected to be receiving enteral nutrition in ICU until at least the day after tomorrow	ICU length of stay > 48 hours	Death is deemed to be imminent or inevitable; survival to 90 days unlikely	Palliative care of dying patient or potential organ donor
			≥ 15% acute burns	Admission diagnosis burns
			Previously enrolled	ICU re-admission

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
ADRENAL Mar 2013 – Apr 2017 *Multinational trial*	≥ 18 years	≥ 18 years	Met all inclusion criteria < 24 hours ago	Not matched
	Documented site of infection, or strong suspicion of infection	Admission diagnosis is an infection	Clinician expects to prescribe corticosteroids for an indication other than septic shock	Not specifically matched – non-infection admission diagnoses excluded by default
	Two of the four clinical signs of inflammation	2 or more of: temp >38° or <36° Celsius; heart rate >90; respiratory rate >20 or PaCO2< 32 mmHg; white cell count >12×10^9/Litre	Patients treated with etomidate	Not matched
			Patients receiving treatment with Amphotericin B	Admission diagnosis fungal pneumonia
			Previously enrolled	ICU re-admission
	Being treated with mechanical ventilation	Ventilated in ICU	Patients with cerebral malaria or strongyloides	Not matched
	Administration of vasopressors or inotropes for ≥ 4 hours and present at time of randomization	Not matched	Death is deemed inevitable or imminent during admission	Palliative care of dying patient or potential organ donor
			Death from underlying disease is likely within 90 days	Not matched
PHARLAP Oct 2012 – Sep 2017 *Multinational trial*	Intubated and receiving mechanical ventilation;	Received invasive ventilation in ICU	< 16 years age	< 16 years
			>72 hours since ARDS onset	Not matched
	Within 72 hours of mechanical ventilation for a diagnosis of moderate to severe acute respiratory distress syndrome (ARDS)	Not matched	>10 days ventilation	Not matched
			Clinical suspicion of significant restrictive lung disease	restrictive lung disease OR severe pre-existing chronic lung disease
			Barotrauma is present	Admission dx pneumothorax
	Has a respiratory failure not fully explained by cardiac failure or fluid overload	Exclude admission diagnosis cardiac failure	Significant chest trauma	Admission diagnosis chest trauma
			ECMO	ECMO
			Active bronchospasm or significant chronic obstructive pulmonary disease or asthma	Admission diagnosis asthma OR Severe pre-existing chronic lung disease
	Has an arterial partial pressure of oxygen/fraction of inspired oxygen (P/F) ratio< 200 & PEEP≥ 5 cmH2O	In first 24 hours, worst P/F ratio <200 PEEP not matched	Moderate or severe TBI	Admission diagnosis TBI
			Unstable cardiovascular status	MAP < 50mmHg
			Pregnancy	Currently pregnant
			HFOV	Not matched
			Death is deemed imminent and inevitable	Palliative care or potential organ donor

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
TRANSFUSE Nov 2012 – Dec 2016 *Multi-national trial*	Decision to transfuse one red blood cells unit	Haematocrit < 21%	Age <18 years	Age < 18 years
	Anticipated ICU length of stay greater than 24 hours	ICU length of stay > 24 hours	Previous RBC transfusion during the current hospital admission	Not matched
			Diagnosis of transplantation or hematologic malignancy	Leukaemia; heart, lung, liver or kidney transplant admission dx
			Receiving palliative or supportive treatment	Palliative treatment or potential organ donor
			Pregnancy	Pregnant
			Cardiac surgery during the present hospital admission	Cardiac surgery admission diagnosis
			Expected to die imminently (<24 hours)	Palliative care of dying patient or potential organ donor
			The treating physician believes it is not in the patient's best interest	Not matched
			Known objection to the administration of blood products	Not matched
			Participation in a competing study	Not matched
BLING II Jul 2012 – Apr 2014 *Multi-national trial*	Severe sepsis with new organ dysfunction	Admission diagnosis is infection and sequential organ failure assessment (SOFA) score ≥ 1	Receipt of any potential study drug for > 24 hours during ICU admission	Not matched
	Treating clinician has chosen meropenem or piperacillin-tazobactam to treat infection	Not matched	<18 years	<18 years
			Underlying process likely to result in death within 90 days	Not matched
	Treating clinician uncertain if infusion or bolus is superior	Not matched	Allergy or potential allergy to study medications	Not matched
	Expected to remain in ICU beyond next calendar day	ICU length of stay > 48 hours	Pregnancy	Pregnant
			No central venous access	Not matched
			Receiving palliative or supportive treatment; death imminent	Palliative care of dying patient or potential organ donor
			Not committed to advanced life support for at least 48 hours	Any treatment limitation, admitted for palliative care

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
EPO-TBI May 2010 – Nov 2014 *Multinational trial*	Between 15 and 65 years of age	Age > 14 years & < 66 years	GCS 3 and fixed dilated pupils	Not matched
	Non-penetrating moderate (GCS 9-12) or severe (GCS 3-8) traumatic brain injury less than 24 hours since traumatic injury	Admission diagnosis is traumatic brain injury and & GCS < 13	History of deep vein thrombosis, pulmonary embolism or other thromboembolic event	Not matched
	Anticipated intensive care unit length of stay at least 48 hours	ICU length of stay > 48 hours	A chronic hypercoagulable disorder, including known malignancy	Lymphoma, leukaemia or metastatic malignancy as comorbidity
	Haemoglobin concentration below the upper limit of normal	Peak haematocrit <0.50	Treatment with erythropoietin in the past 30 days	Chronic kidney disease requiring long-term dialysis as comorbidity
	Provision of valid consent	Not matched	First dose of study drug unable to be given within 24 hours of primary injury	Not matched
			Pregnancy or lactation or 3 months post-partum	Currently pregnant or post-partum
			Uncontrolled hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg)	MAP > 140mmHg
			Acute myocardial infarct within the past 12 months	Not matched
			Past history of epilepsy with seizures in past 3 months	Not matched
			Expected to die imminently	Admitted to ICU for palliative care or organ donation

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
HEAT Feb 2013 – Jul 2014 *Australia and New Zealand only*	16 years of age or older	Age ≥ 16 years	AST or ALT more than 5 times upper limit of normal, or bilirubin more than 5 times upper limit of normal, or any contraindication to 4 g acetaminophen per day	Bilirubin >42 micromol/Litre Liver failure Cirrhosis
	Temperature of 38° Celsius or higher within 12 hours before enrolment and receiving antimicrobial therapy for a known or suspected infection	Admission diagnosis is an infection Temp ≥ 38° Celsius	Requirement for ongoing use of non-steroidal anti-inflammatories	Not matched
			Admission to ICU following a cardiac arrest which is currently being treated with therapeutic hypothermia or where a need for therapeutic hypothermia is anticipated	Admitted following cardiac or respiratory arrest
			Acute brain injury	Traumatic brain injury dx
			Hyperthermic syndromes including heat stroke; malignant hyperthermia, neuroleptic malignant syndrome, or other drug-induced hyperthermia	Admitted with a hyperthermic syndrome
			Current biochemical evidence of thyrotoxicosis	Not matched
			Limitation of therapy order	Any limitation of medical treatment
			Moribund; death is perceived to be imminent	Admitted for palliative care or organ donor
			Clinically significant rhabdomyolysis	Admission diagnosis rhabdomyolysis
			Transferred from another ICU where they spent > 12 hours and fulfilled all inclusion criteria while there	Transferred from another ICU
			Pregnancy	Pregnant
			Previously enrolled	ICU re-admissions

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
ARISE Oct 2008 – Apr 2014 *Australia and New Zealand only*	≥ 18 years	Age ≥ 18 years	Age < 18 years	Age < 18 years
	Met criteria within 6 hours of arrival in the emergency department	Admitted to ICU from the emergency department	Contraindication to central venous catheter insertion in the superior vena cava	Not matched
	Suspected or confirmed infection	Admission diagnosis is infection	Confirmed or suspected pregnancy	Pregnant
	Two or more SIRS criteria	SIRS score ≥ 2	Contraindication to receiving blood products	Not matched
	Evidence of refractory hypotension or hypoperfusion	MAP < 65 mmHg Lactate not matched as data not available in APD during study period.	Hemodynamic instability due to active bleeding	Not matched
			Underlying disease process with a life expectancy < 90 days	Not matched
			Death deemed imminent and inevitable	Palliative care of dying patient or potential organ donor
			Documented limitation of therapy order restricting implementation of the study protocol or aggressive care deemed unsuitable by the treating clinician	Any treatment limitation
			In-patient transfer from another acute health care facility	Hospital source is another hospital, ICU or ED
			Inability to commence early goal-directed therapy (EGDT) within one hour of randomization or deliver EGDT for 6 hours	Not matched

Study & recruitment period	Inclusion criteria	Method of matching inclusion criteria	Exclusion criteria	Method of matching exclusion criteria
PROGUARD Mar 2011 – Dec 2012 *Australia and New Zealand only*	Age ≥18 years	Age ≥18	Prophylactic antibiotics e.g., surgical	Not matched
	Receiving antibiotics for suspected bacterial infection with 2 or more SIRS criteria	Admission diagnosis is infection with two or more SIRS criteria in first 24 hours	Planned antibiotics for three weeks or more	Admission diagnosis endocarditis, septic arthritis, neurologic abscess
	Anticipated ICU stay >24 hours	ICU length of stay > 24 hours	Fungal or viral infection	Admission diagnosis fungal pneumonia, viral pneumonia, viral myositis
			Trauma	Any trauma admission diagnosis
			Medullary thyroid cancer or small cell lung cancer	Admitted following surgery for thyroid or lung malignancy
			Known pregnancy	Pregnant
			Not anticipated to survive hospital discharge	Palliative care of dying patient or potential organ donor
			Neutropenia	Admission diagnosis neutropenia
			Immunosuppressive agents	Immunosuppression within 4 weeks prior to ICU admission
			Cardiac surgery	Admitted following cardiac surgery including coronary artery grafts or valvular surgery
			Heat stroke	Admission diagnosis heat stroke
TARGET FEASIBILITY Jan 2013 – May 2013 *Australia and New Zealand only*	≥18 years	Age ≥ 18 years	Received > 12 hours EN or PN during ICU stay	Not matched
	Invasive mechanical ventilation	Received invasive ventilation during ICU admission	EN study goal rate contra-indicated	Not matched
	Expected to receive enteral nutrition for ≥2 days	Not matched	Requirement for specific EN solution	Not matched

Table legend: ALT denotes alanine transferase, AST aspartate aminotransferase, Dx diagnosis ECMO extra-corporeal membrane oxygenation, ED emergency department, EN enteral nutrition, GBS Guillain-Barre Syndrome, GCS Glasgow Coma Score, ICH intracranial haemorrhage, MAP mean arterial pressure, MND motor neurone disease, PEEP positive end-expiratory pressure, PN parenteral nutrition, SIRS systemic inflammatory response syndrome, TBI traumatic brain injury

Appendix C. Research Letter: Sex representation within intensive care trials in Australia and New Zealand

Modra L, Bone A, Pilcher D, Woodward M, Thompson K. Sex representation in intensive care trials in Australia and New Zealand. *Intensive Care Med* **50**, 1529–1531 (2024). https://doi.org/10.1007/s00134-024-07541-1

Dear Editor,

Recruiting a representative study population helps to ensure the generalizability of a trial's findings across demographic groups. It also promotes trust and fair access to trial participation among the target population of affected patients [1]. Nonetheless, women remain under-represented in some fields including oncology, cardiology and infectious diseases trials [2,3]. Regarding critical care trials, Kristensen and colleagues found that a minority of participants were women, however they did not compare sex balance between study populations and their respective target populations [4].

We examined sex-based representativeness in randomized controlled trials (RCTs) endorsed by the Australia and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group and completed 2014–2023 (supplement Fig. 1). The ANZICS Adult Patient Database (APD) was taken to represent the general population of intensive care unit (ICU) patients, as it captures 90% of ICU admissions in Australia and New Zealand [5]. The database records patient sex – the focus of our study – defined as the biological distinction between female and male [5].

For each trial, the study population was compared with a matched target population identified from the APD using the trial's own eligibility criteria (supplement Table 1). Quality of matching was assessed using pre-specified criteria; target populations were considered well-matched if matched in at least 4 of 5 domains (supplement Table 2). We calculated the arithmetic difference between the percentage of women in each study population minus the percentage women in each target population, with estimated 95% confidence interval. We used random effects meta-analysis to calculate pooled differences, using STATA 17 BE (Statacorp, Texas USA) for all analyses.

There were 24 eligible trials with 68,968 participants in total (36.3% women). The sex balance ranged from 16.7% to 47.8% women (Figure 1a). Each trial recorded patient sex but not gender and no trial included a third sex category, e.g., intersex. Therefore, sex and gender-based minorities were not represented.

There were 2,017,197 admissions (42.9% women) recorded in the APD during the trials' cumulative recruitment period October 2008 to November 2021. There were substantially fewer women in the pooled study population than the general ICU population represented by the APD (arithmetic difference -6.6%, 95% CI -6.2% to -6.9%).

When compared to matched target populations, there was no significant disparity in sex balance between the study populations and target populations overall (pooled arithmetic difference -0.5%, 95% CI -2.2% to 1.2%; Fig. 1b). This finding was robust to sensitivity analysis including only trials with well-matched target populations (supplement Fig 2).

On diagnostic subgroup analysis, women were under-represented in cardiac arrest trials (arithmetic difference -5.5% (95% CI -8.6 to -2.4%)) and sepsis trials (arithmetic difference -2.9%
(95% CI -5.1% to -0.7%)), compared to the target populations of ICU patients with these diagnoses. There was no sex-based disparity in trauma trials or trials including multiple diagnostic categories (supplement Fig. 3).

We found critical care trials in Australia and New Zealand recruited representative proportions of women and men overall, when compared to target populations defined by their own eligibility criteria, suggesting that screening and enrolment of participants was not affected by patient sex. However, the pooled study population had substantially fewer women than the general population of ICU patients in Australia and New Zealand. This suggests the trials examined relatively male-dominated groups of ICU patients by design, related to study question, participating sites or eligibility criteria. Many trials examined conditions predominantly affecting men, including trauma or cardiac arrest, rather than female-dominated conditions such as subarachnoid hemorrhage or asthma [5].

Concordant with previous research, women were under-represented in cardiac arrest and sepsis trials [2]. This may relate to the decision-making of surrogate decision-makers or clinicians in high-risk situations. Further research is needed to identify effective strategies for improving sex-based representation in these trials.

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Ethics statement

Ethics approval was obtained from Alfred Health Human Research Ethics Committee.

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Fig 1a. Percentage of women in study population compared to target populations

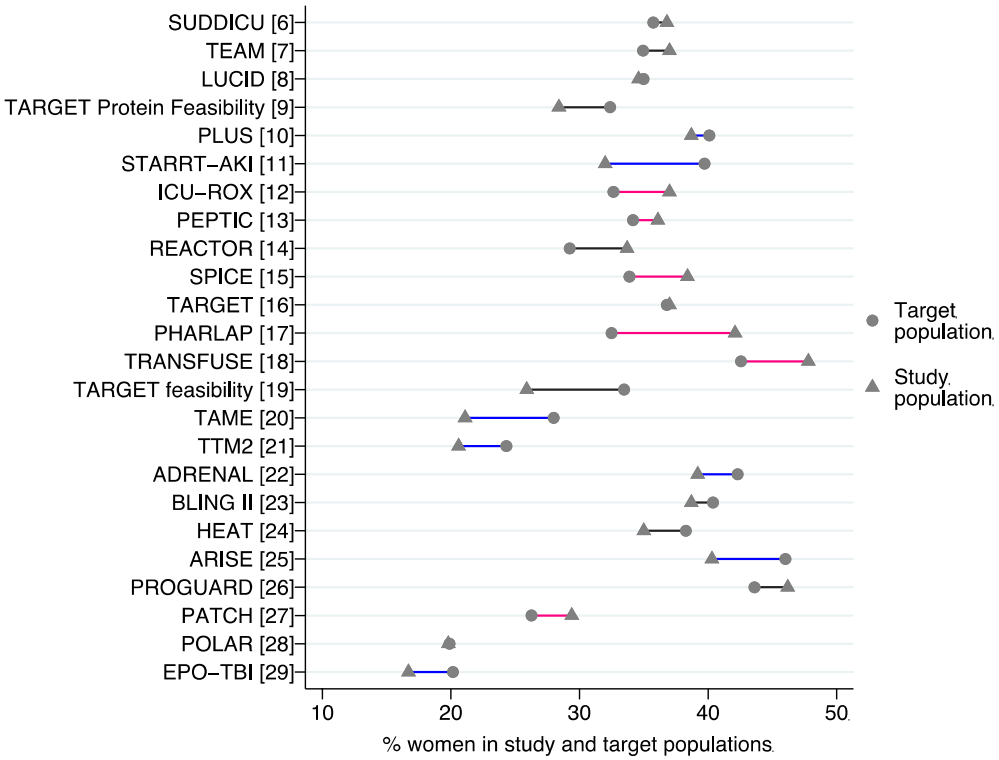
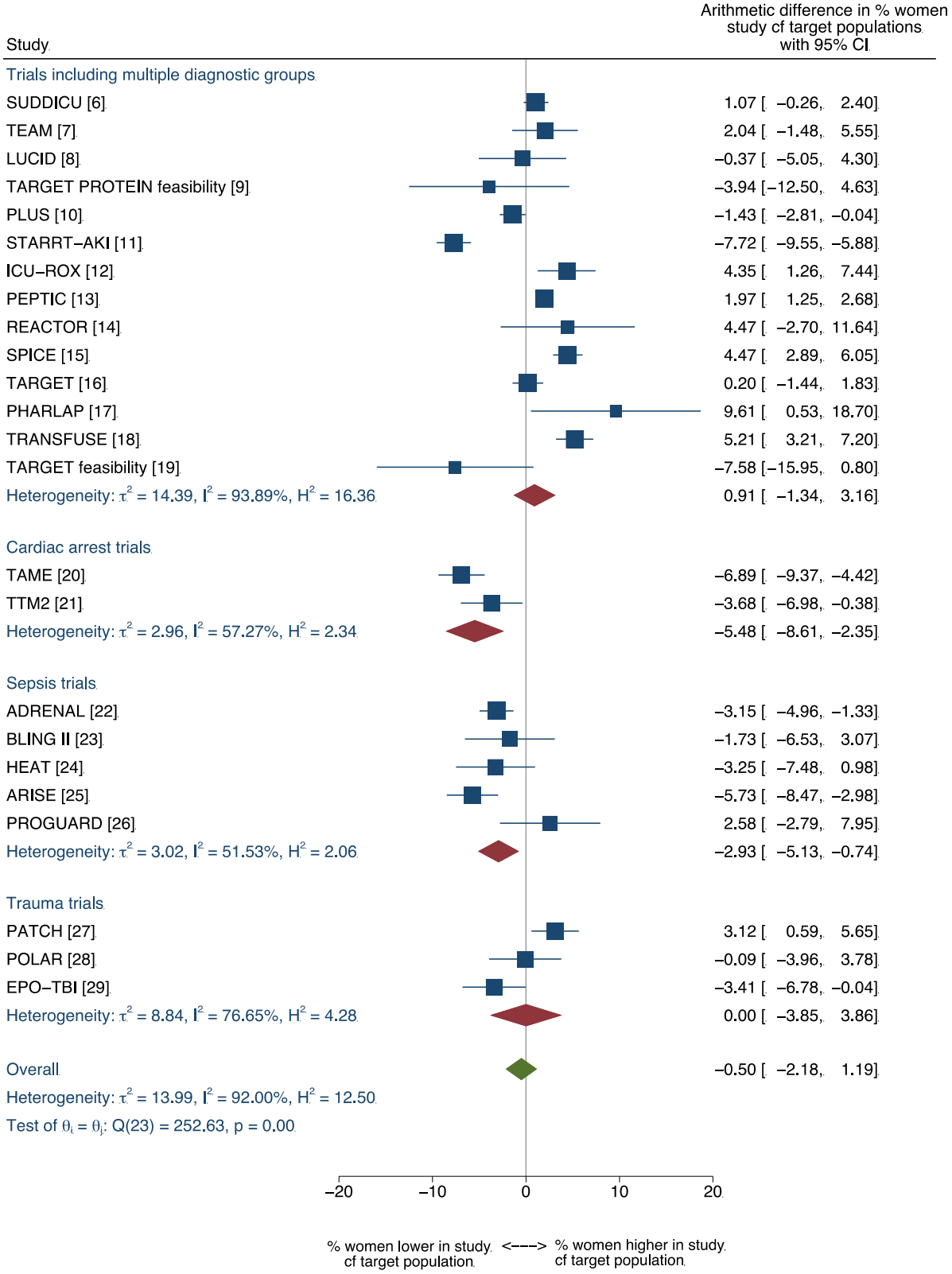


Figure legend: Lines connecting triangles and circles represent the arithmetic difference in the percentage of women in the study population and target population. Pink lines indicate more women in study than target population; blue lines indicate less women in study than target population (adapted from Steinberg et al [2]). References 6-29 are provided in supplement.

Fig 1b. Forest plot of sex balance in study population compared to target populations



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