Interrogating disease clusters, multimorbidity and adverse outcomes in chronic kidney disease

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Abstract

Background

Chronic kidney disease (CKD) is common amongst adults and it often co-exists with other chronic conditions. Compared to people with normal kidney function, people with CKD are at increased risk of kidney-specific outcomes like the need for dialysis, and other outcomes like cardiovascular events. As people age, chronic conditions including CKD become more common, and the risk of adverse outcomes increases. However, little is known about the ways in which CKD and multimorbidity relate to the risk of adverse outcomes.

Multimorbidity is the presence of two or more chronic conditions in an individual. It affects more than half of people over the age of 65 and it is closely linked to frailty, socioeconomic deprivation, and reduced quality of life. However, it is not known if the associations between multimorbidity and adverse outcomes are dependent on particular combinations, or “clusters” of conditions.

Methods and Results

The overall hypothesis was that multimorbidity and clusters of chronic conditions are associated with adverse outcomes in populations with CKD.

A systematic review and meta-analysis was followed by four quantitative studies. Four datasets were used:

1. UK Biobank: a prospective research study.
2. The Secure Anonymised Information Linkage Databank (SAIL): a primary care database for the population of Wales.
3. The Stockholm Creatinine Measurement project (SCREAM): a routine care database for the population of Stockholm, Sweden.
4. The International Severe Acute Respiratory and emerging Infection Consortium study (ISARIC): a prospective cohort study of patients hospitalised with COVID-19 in the UK.

Associations between risk factors and adverse outcomes were studied. The main risk factors studied were the number of chronic conditions, type of chronic conditions, and combinations of conditions. The adverse outcomes were: mortality, hospitalisation, cardiovascular events, acute kidney injury, and major adverse kidney

events. Finally, clustering statistical techniques were used to identify clusters of conditions and the associations between clusters and adverse outcomes were scrutinised.

The research questions and the respective results were:

1. What are the associations between multimorbidity, CKD, and risk of adverse outcomes?

   A systematic review showed that amongst patients with CKD, there are associations between multimorbidity and mortality. However, most studies were in patients with advanced CKD and there was a paucity of research involving mild to moderate CKD or adverse outcomes other than mortality.

2. What are the associations between multimorbidity and risk of major adverse kidney events?

   The risk of major adverse kidney events increases as the number of chronic conditions increases, even amongst people with normal kidney function at baseline. Specific combinations of conditions are at particularly high risk, especially those including cardiometabolic conditions.

3. What are the associations between multimorbidity, CKD, and risk of hospitalisations?

   Multimorbidity is associated with an increased risk of emergency hospitalisations and the risk of hospitalisation is particularly high when CKD is one of the chronic conditions. Patients with CKD plus multiple cardiometabolic conditions, conditions affecting multiple systems of the body, and physical and mental health conditions are at heightened risk of hospitalisation.

4. What are the risk factors for acute kidney injury in COVID-19 and what is the association with mortality?

   Amongst patients hospitalised with COVID-19, risk factors for acute kidney injury are chronic conditions such as CKD and diabetes mellitus, black ethnicity, and severe COVID-19 illness on admission. AKI rates reduced as the pandemic progressed, but AKI remained a key risk factor for mortality.

5. Amongst patients with CKD, what clusters of chronic conditions are associated with the highest risk of adverse outcomes?

    Cardiovascular conditions cluster together, particularly in advanced CKD. Chronic pain and depression are important components of multimorbidity, and when combined with cardiometabolic conditions, are associated with adverse outcomes. The management of people with multimorbidity may be targeted based on clusters of conditions refined by kidney function.

Conclusion

Multimorbidity is common amongst people with CKD and it is an important risk factor for adverse outcomes. The risk of kidney events, cardiovascular events, hospitalisation, and mortality increases with the number of chronic conditions and with specific combinations of conditions. People with multiple cardiometabolic conditions are particularly likely to experience these adverse outcomes and these conditions cluster together amongst people with advanced CKD.

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Other publications arising from this thesis

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Scientific presentations and abstracts

American Society of Nephrology Kidney Week

2021. Poster Presentation. "*Patients with chronic kidney disease and multiple chronic conditions are at increased risk of cardiovascular events*"

North American Primary Care Research Group Annual Meeting

2021. Oral Presentation. "*Acute kidney injury in COVID-19 in the UK: A prospective, multicentre cohort study*"

European Renal Association Annual Congress

2021. Mini-oral presentation. "*Hospitalisation events in people with chronic kidney disease and multiple long-term conditions*"
2022. Oral presentation. "*The race-free eGFR equation, the kidney failure risk equation and referrals to specialist renal clinics*"
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UK Kidney Week

2020. Poster presentation. "*Multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: findings from the UK Biobank Cohort*"
2022. Oral presentation. "*The impact of KFRE and the 2021 CKD-EPI eGFR equation on potential referrals from primary care to renal clinics*"
2022. Moderated poster presentation. "*Clusters of conditions in chronic kidney disease: A Welsh population study*"

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2021. Poster presentation. "*What is the relationship between chronic kidney disease, multiple long-term conditions and the risk of hospitalisation?*"
2022. Oral presentation. "*Optimising referrals from primary care to renal clinics. Findings from a Welsh population study*"

Scottish Renal Association Virtual Conference

2020. Oral presentation. "*Multimorbidity and the risk of major adverse renal events: findings from the UK Biobank cohort*"

2021. Poster presentation. "*The impact of multimorbidity on cardiovascular events in 173,388 patients with CKD*"

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Author’s declaration

The work presented in this thesis was conducted by me, unless explicitly stated otherwise. The contribution of other researchers is detailed in each chapter under the title ‘Authors contributions’, with key contributions summarised below. This thesis, including statistical analysis and presentation of results, has been prepared by myself and is a record of work performed by myself. It has not previously been submitted for a higher degree.

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Abbreviations

ACM	All-cause mortality
ADR	Adverse drug reaction
AKI	Acute kidney injury
ANOVA	Analysis of variance
AUC	Area under the receiver operating characteristic curve
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
ARDS	Acute respiratory distress syndrome
BSA	Body surface area
BMI	Body mass index
CCI	Charlson comorbidity index
CCP	Clinical characterisation protocol
CI	Confidence interval
CKD	Chronic kidney disease
CKD-PC	Chronic kidney disease prognosis consortium
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CSS	Comorbidity severity score
eGFR	Estimated glomerular filtration rate
GP	General practitioner
HD	Haemodialysis
HES	Hospital Episode Statistics
HIFNT	High intercept and fast negative trajectory
HIPT	High intercept and positive trajectory
HR	Hazard ratio
IIMNT	Intermediate intercept and mild negative trajectory
ISARIC	International Severe Acute Respiratory emerging Infection Consortium
KRT	Kidney replacement therapy
HIV	Human immunodeficiency virus
ICD	International Classification of Diseases
IDMS	Isotope dilution mass spectrometry
IMD	Index of Multiple Deprivation
IQI	Interquartile interval
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
LMIC	Low- and middle-income country
LIFNT	Low intercept and fast negative trajectory
LTC	Long-term condition
MACE	Major adverse cardiovascular event
MAKE	Major adverse kidney event
MAR	Missing at random
MCAR	Missing completely at random

MNAR	Missing not at random
MRC	Medical Research Council
NICE	The National Institute for Health and Care Excellence
NOS	Newcastle Ottawa scale
O/E	Observed/expected
OR	Odds ratio
PD	Peritoneal dialysis
PEDW	Patient Episode Database for Wales
PRISMA-P	Preferred reporting items for systematic review meta-analysis protocols
RAS	Renin-angiotensin system
RCT	Randomised controlled trial
RR	Risk ratio
RQ	Research question
RR	Respiratory rate
RRT	Renal replacement therapy
SAIL	Secure Anonymised Information Linkage Databank
SCREAM	Stockholm Creatinine Measurement project
SDH	Subdistribution hazards
SGLT2	Sodium-glucose co-transporter-2
sHR	Subhazard ratio
SMR	Scottish Morbidity Records
SpO2	Oxygen saturations
TIA	Transient ischaemic attack
uACR	Urine albumin-creatinine ratio
WHO	World Health Organization
WIMD	Welsh Index of Multiple Deprivation

Chapter: 1 Overview

1.1 Chapter summary

In this chapter, a general overview of the thesis is provided. The subject area is introduced, with an explanation of why the project was deemed important. The central hypothesis is described, followed by the research questions and an outline of the chapters.

1.2 Introduction

In this section, the concept of multimorbidity is introduced, with a description of how patients with chronic kidney disease (CKD) are affected. The potential impact of these problems on patients' lives and how they can influence clinical management is presented. Possible ways this research may lead to improvements in patients' care are proposed.

Multimorbidity is commonly defined as the presence of two or more chronic conditions in an individual.[1] This definition and the ways in which chronic conditions can occur together are discussed in further detail in the next chapter. People with multimorbidity often deal with numerous symptoms. They must also balance complex treatment regimens, and sometimes attend multiple hospital specialists.[2] Chronic conditions accumulate with advancing age, just as kidney function can decline as we get older. This partly explains why multimorbidity is very common in CKD and why patients who attend nephrologists have more chronic conditions and take more medications than patients attending many other specialists.[3,4]

CKD and additional chronic conditions can impact patients' quality of life while also putting them at higher risk of adverse outcomes including early mortality.[1,5,6] Multimorbidity is common in patients who come in contact with medical services. A UK study found that 53% of consultations with general practitioners were with patients with multimorbidity.[7] Clinicians are therefore accustomed to managing these patients, although the evidence on how to do so well is sparse. Clinical guidelines typically focus on individual conditions, even though in practice, patients have combinations of conditions which adds to the complexity of managing the overall patient.

Given there are dozens of chronic conditions which can accompany CKD, there are **many** possible combinations of these conditions. Although clinicians will recognise which conditions co-exist in the patients they see, it is difficult to know if this is a true reflection of the general population. Moreover, it is poorly understood how patterns of multimorbidity change at different levels of kidney function and how they relate to outcomes. Information about common and meaningful combinations of conditions

and their impact on outcomes may be helpful for clinicians treating these patients and healthcare service planning.

Understanding how multimorbidity relates to adverse outcomes is key to exploring these issues. Modern data-driven approaches can be used to identify common combinations of conditions. Patients with multimorbidity are challenging to study because they are often excluded from clinical trials.[8] Observational studies are better placed to investigate this area at present, and so the thesis presented here relies on this type of study.

Once combinations of conditions – sometimes termed clusters – have been identified, they may be used to advance the management of patients in a number of ways. First, if they can effectively predict adverse outcomes, they may be used for improving **risk stratification** and targeting treatments. For example, if a cluster is at heightened risk of cardiovascular events, these patients may be targeted with risk reduction strategies, such as lipid lowering therapies.[9] Second, by understanding which combinations of conditions are common, healthcare services may be able to plan **preventative measures**, such as by addressing common risk factors. Third, **clinical guideline** developers may be able to incorporate clusters into guidelines, thereby helping clinicians take account of multimorbidity when treating their patients.[10]

This PhD started in August 2019 and so the COVID-19 pandemic impacted on my studies from an early stage. In the first wave of the pandemic, there was widespread concern about the National Health Service in the UK becoming overwhelmed. I therefore suspended my studies for three months while I performed clinical work full time. I also re-considered the focus of my studies within the context of the pandemic. It became clear that acute kidney injury was one of the major adverse outcomes associated with COVID-19 and that people with multiple chronic conditions were particularly vulnerable to dying from the illness. I therefore added a research question to my original PhD plan, which focused on acute kidney injury in COVID-19 (research question 4).

1.3 Hypothesis

In this thesis, the following hypothesis is tested:

> *Multimorbidity and clusters of chronic conditions are associated with adverse outcomes in populations with chronic kidney disease*.

The adverse outcomes of interest are:

- Mortality
- Hospitalisation
- Cardiovascular events
- Acute kidney injury
- Major adverse kidney events

1.4 Research questions

Below are outlined the five research questions to be addressed in this thesis.

Research question 1 (RQ1):
What are the associations between multimorbidity, chronic kidney disease, and risk of adverse outcomes?

Research question 2 (RQ2):
What are the associations between multimorbidity and risk of major adverse kidney events?

Research question 3 (RQ3):
What are the associations between multimorbidity, chronic kidney disease, and risk of hospitalisations?

Research question 4 (RQ4):
What are the risk factors for acute kidney injury in COVID-19 and what is the association with mortality?

Research question 5 (RQ5):
Amongst patients with chronic kidney disease, what clusters of chronic conditions are associated with the highest risk of adverse outcomes?

1.5 Outline of chapters

Chapter 2 provides a background of the existing literature on chronic kidney disease, multimorbidity, and how these problems are connected.

Chapter 3 summarises the methods used in the project and the data sources.

Chapter 4 provides the findings of a systematic review of multimorbidity, chronic kidney disease, and adverse outcomes (RQ1).

Chapter 5 provides the findings of a study of the association between multimorbidity and major adverse kidney events in the UK Biobank cohort (RQ2).

Chapter 6 provides the findings of a study of the association between multimorbidity and hospitalisations in the UK Biobank cohort and Secure Anonymised Information Linkage Databank (SAIL) (RQ3).

Chapter 7 provides the findings of a study of acute kidney injury in COVID-19 (RQ4).

Chapter 8 provides the findings of analyses in SAIL and the Stockholm CREAtinine Measurement project (SCREAM) which identify clusters of conditions stratified by kidney function (RQ5).

Chapter 9 summarises the overall findings of the thesis, compares it to the existing literature, considers the strengths and limitations as well as possible implications of the findings for clinical practice and directions for future research.

Chapter: 2 Background

2.1 Chapter summary

There are three sections in this chapter. The first section is an overview of chronic kidney disease, with information on epidemiology and complications. The second section is a description of the current understanding of multimorbidity, including which patterns of chronic conditions have previously been identified, and how it relates to quality of life, deprivation, and frailty. The third section explains how the lives of people with chronic kidney disease may be affected by multimorbidity.

2.2 Chronic kidney disease

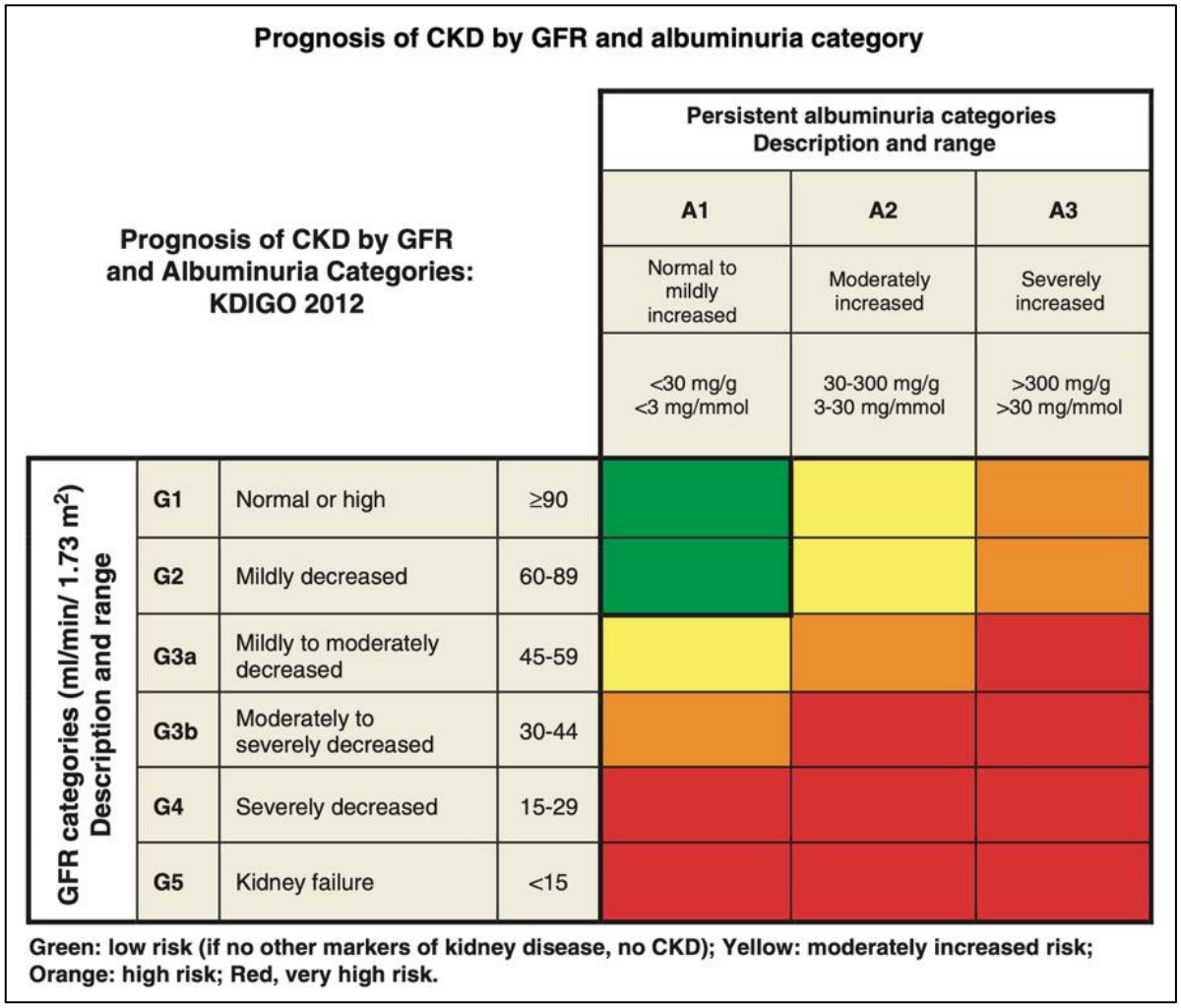
2.2.1 Chronic kidney disease definitions

Chronic kidney disease (CKD) is defined as a *persistent and irreversible reduction in kidney function*.[11] The most common approach to diagnosis is by using estimated glomerular filtration rate (eGFR) derived from serum creatinine. CKD is indicated by two or more values of less than 60mL/min/1.73m^2 at least three months apart.[12] Other diagnostic criteria include:

- urinary abnormalities (principally albuminuria)
- structural abnormalities (e.g. kidney hypoplasia)
- serum electrolyte abnormalities (e.g. Fanconi syndrome)
- histological abnormalities (e.g. IgA nephropathy)
- previous kidney transplantation

A diagnosis of CKD helps clinicians with clinical management (e.g. drug dosing) and informs the risk of adverse outcomes. Classification of CKD incorporates eGFR and urine albumin-creatinine ratio (uACR) (Figure 2-1).[11] The stages of eGFR range from G1 (normal) to G5 (kidney failure) and the stages of uACR range from A1 (normal) to A3 (severely increased). Although stages G1-G5 exist, only stages G3-G5 are routinely identified in clinical care, unless accompanied by significant albuminuria. People with low eGFRs and people with high uACRs are more likely to experience adverse outcomes than those with normal kidney function. The adverse outcomes which CKD typically helps prognosticate for are mortality, progressive CKD including kidney failure requiring treatment (dialysis or transplantation), acute kidney injury, and cardiovascular events. Combining uACR with eGFR improves risk stratification of these adverse outcomes over eGFR alone.[13]

Figure 2-1. Classification of CKD using eGFR and uACR with risk of adverse outcomes (mortality, cardiovascular mortality, kidney failure, AKI, and progressive CKD).



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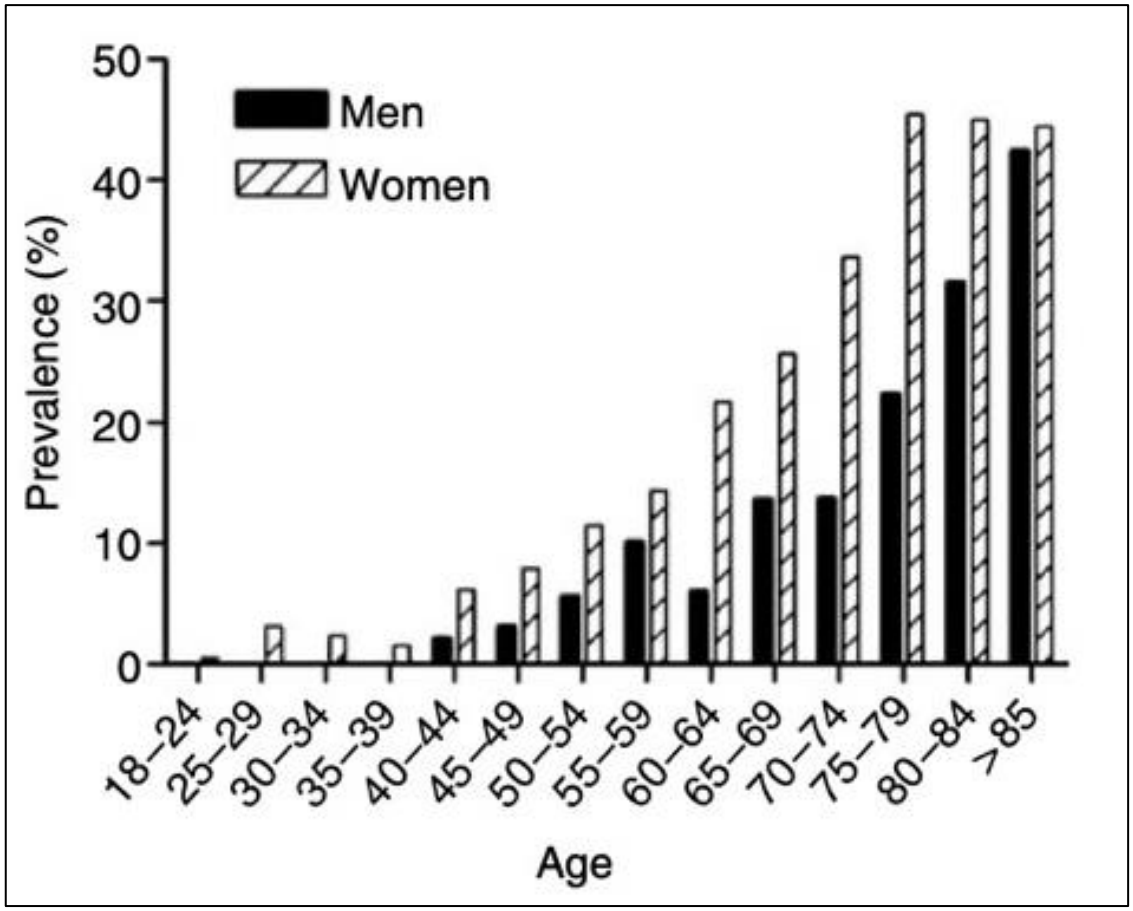
2.2.2 Epidemiology of chronic kidney disease

Estimates of the global prevalence of CKD amongst adults are between 4% and 11%.[15] In the UK, CKD stages G3-G5 affect approximately 14% of people over the age of 60.[16] Estimates of CKD prevalence in low- and middle-income countries (LMICs) vary. In a meta-analysis of studies involving people living in Africa, the prevalence of CKD stages G3-G5 was estimated to be 3-6%.[17] However, a subsequent study of people living in Malawi, Uganda, and South Africa demonstrated that standard tests of kidney function are inaccurate in these countries and that the rates of CKD stages G3-G5 are much higher (14-23%).[18]

Diabetes mellitus and hypertension are the leading causes of CKD. In the UK, diabetes mellitus is the underlying cause of CKD in approximately 30% of adults starting kidney replacement therapy (KRT: dialysis or kidney transplantation).[19] Specific kidney diseases such as glomerulonephritis and polycystic kidney disease are the underlying cause of CKD in approximately 20% of adults starting KRT. Amongst patients with less severe CKD i.e., those not requiring dialysis or transplantation, the causes are more varied. Many patients who develop CKD as older adults have multiple causes underpinning the development of CKD including reduced nephron mass as part of a normal ageing process and vascular disease. In an Australian study of adults attending a nephrology service, 45% of participants had multifactorial CKD and 38% had hypertension and vascular disease contributing to their CKD.[20] As people age, kidney function often declines. This is reflected in the equations which calculate eGFR from serum creatinine, age, sex, and ethnicity.[21] As a result, over 40% of people over the age of 85 are categorised as having CKD (Figure 2-2).[22]

Figure 2-2. Prevalence of CKD stratified by age and sex.



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CKD has a bigger impact on women than on men. In a study of adults living in England, the prevalence of CKD stages G3-G5 was 10.6% in women and 5.8% in men.[23] Kidney function is partly determined by kidney size, which is related to body surface area (BSA). As women tend to have smaller BSAs, their kidneys tend to be smaller, leading to comparatively reduced kidney function.[24] In general, women live longer than men, and so the overall female population at risk of CKD is larger. Women are also disproportionately affected by symptoms related to CKD: in an American study on health-related quality of life, women were more likely to report symptoms related to CKD than men at a similar level of kidney function.[25]

Ethnicity has a significant impact on the rates of CKD. Compared to white people, **the prevalence of kidney failure in the USA is 57% higher in Asian people and 428% higher in black people**.[26] This is partly explained by high rates of diabetes mellitus and hypertension in non-white patients.[27] Amongst black patients, hypertension-related kidney disease is particularly common. Of those developing kidney failure in the USA, hypertension is the underlying cause in 39% of black patients, compared to 25% of white patients.[26] High-risk alleles in the gene APOL1 partly explains this susceptibility amongst black patients.[28]

Socioeconomic deprivation is likely to contribute to the elevated risk of CKD amongst non-white ethnic groups[29] as it has been shown in an English study to be associated with progressive CKD.[30] The association between CKD and deprivation is likely to be multifactorial.[31] People living in socioeconomically deprived areas are disproportionately exposed to risk factors for CKD such as diabetes mellitus,[32] cardiovascular disease,[33] and hypertension.[34] Deprivation also has an impact on CKD treatment, with studies from the UK,[35] Netherlands[36] and USA[37] demonstrating that those from the most deprived areas are less likely to receive a kidney transplant from a living donor, which is often regarded as the best form of treatment for kidney failure.

2.2.3 Chronic kidney disease in primary care

General practitioners (GPs) in the UK care for most patients with CKD, with a minority of patients attending specialist nephrology clinics. In a study of 2.7 million

UK residents, **95% of those with CKD had stage G3**, most of whom were cared for in primary care.[38] Although very few of these patients will progress to kidney failure requiring treatment, clinical guidelines suggest that these patients should have blood tests one to three times per year (more frequently if they have albuminuria).[11] By monitoring eGFR via blood tests, GPs should be able to detect patients whose CKD is progressing. Guidelines from The National Institute for Health and Care Excellence (NICE) also say that CKD monitoring should be tailored to individual patients' conditions, treatments, acute illnesses and eGFR decline,[39] which makes it a complex task to perform.

GPs are expected to treat hypertension in these patients and ensure they are on the correct doses of appropriate medications while balancing the management of other chronic conditions. This constitutes a significant workload for GPs, many of whom lack the resources to carefully manage all their patients with CKD. There is a national shortage of GPs in the UK, with approximately 14% of GP posts vacant.[40] Many GPs are kept extremely busy treating patients for acute problems and they sometimes have inadequate time to focus on monitoring chronic diseases like CKD.

2.2.4 Symptom burden in chronic kidney disease

CKD is asymptomatic in most patients until it progresses to the advanced stages. As eGFR declines, complications such as anaemia and acidosis occur and toxic molecules accumulate. If untreated, patients eventually develop uraemic symptoms: nausea, pruritus, restless legs, and sleep disturbances. Some individuals experience these symptoms when the urea level is greater than 20mmol/L, while others remain asymptomatic even when the urea is greater than 40mmol/L. Although CKD is common in the general population, as most patients have stage G3 (eGFR 30-59mL/min/1.73m^2), it is uncommon for these patients to develop symptoms.
For those with advanced CKD, some of the symptoms can be helped by medications and/or effective KRT.

Anaemia in CKD becomes more common as eGFR declines below 30mL/min/1.73m^2. In an American study, the prevalence of anaemia in those with eGFR 30-59mL/min/1.73m^2 was just 5% and at eGFR 15-29mL/min/1.73m^2, it was

higher at 44%.[41] Anaemia often causes lethargy, which is a non-specific symptom which can be caused by many different conditions and treatments.[42] Renal anaemia can be treated with the replacement of haematinics (primarily iron), recombinant erythropoietin, management of metabolic bone disease, effective KRT, and sometimes blood transfusions. However, treatment of renal anaemia can sometimes leave patients still feeling lethargic, because the aetiology of lethargy is often multifactorial. With the overlap in symptoms between CKD and other chronic conditions, it can be challenging to determine what is causing particular symptoms and this often results in patients receiving a range of treatments. These issues of complexity are particularly problematic for patients with CKD and **multiple** chronic conditions.

2.2.5 Significance of diagnosis of chronic kidney disease

As CKD is asymptomatic until the advanced stages, 40% to 90% of patients with CKD are unaware they have the condition.[43,44] Because the diagnosis of CKD usually depends on blood tests, it can be undiagnosed in people who do not have blood tests because they are not in regular contact with healthcare services. A study of patients aged over 60 in the UK estimated that 44% of those with CKD were undiagnosed.[16] As kidney function declines with advancing age, some have suggested that early “chronic kidney disease” in the elderly is part of the normal ageing process and it is not a disease.[45] For example, those over the age of 65 with eGFR 45-59mL/min/1.73m^2 and no other abnormalities might be categorised as having normal kidney function for their age.[46] There are various problems with labelling a person with a disease when they are asymptomatic and their risk of adverse outcomes is very low.[47] For healthcare services, chronic disease monitoring is costly. For individual patients, they may undergo potentially unnecessary tests and treatments and may be worried about the label “disease”.[48] Concerns about the overdiagnosis of CKD are balanced by its importance in cardiovascular risk stratification. Given its well documented links to cardiovascular risk, there is an argument for CKD screening, such as via routine blood tests which take place via the NHS Health Check for people over the age of 40 in England.[49] However, screening is most likely to be effective if targeted at people at elevated risk of CKD, such as those with diabetes mellitus and/or hypertension.[50]

2.2.6 Kidney-related adverse outcomes

Kidney function declines in just 1-4% of patients with CKD such that they require KRT.[13,51] These patients require careful planning of treatment for kidney failure, which usually involves numerous attendances at hospital. Preparation for dialysis and transplantation require various treatments (e.g. hepatitis B immunisation), investigations (e.g. cardiac stress testing for transplantation) and procedures (e.g. arteriovenous fistula creation). Dialysis can also have a negative impact on an individual's quality of life, such as by limiting the time they can do paid work or the time they can spend with loved ones.[52] Most dialysis patients in the UK are on haemodialysis, which usually involves thrice-weekly hospital attendances and can leave them feeling tired afterwards.[53]

Patients with conditions like diabetes mellitus and cardiovascular disease are more likely to start dialysis earlier than patients without these conditions.[54] This may be because they are more likely to develop problems like fluid overload at an early stage, or they may become symptomatic of uraemia earlier than patients with fewer chronic conditions. Some patients who develop kidney failure will choose conservative care instead of dialysis or transplantation, and the decisions around if and when to start KRT are unique to each individual. Unfortunately, there are significant variations globally regarding access to KRT. Patients in some LMICs cannot access KRT when it is needed, and this problem is increasingly common globally.[55]

Besides the risk of CKD progression, patients with CKD are also at heightened risk of acute kidney injury (AKI). This risk is independent of other risk factors like diabetes mellitus and it exists even for those with early CKD i.e., CKD stage G3.[56]

2.2.7 Kidney function trajectories

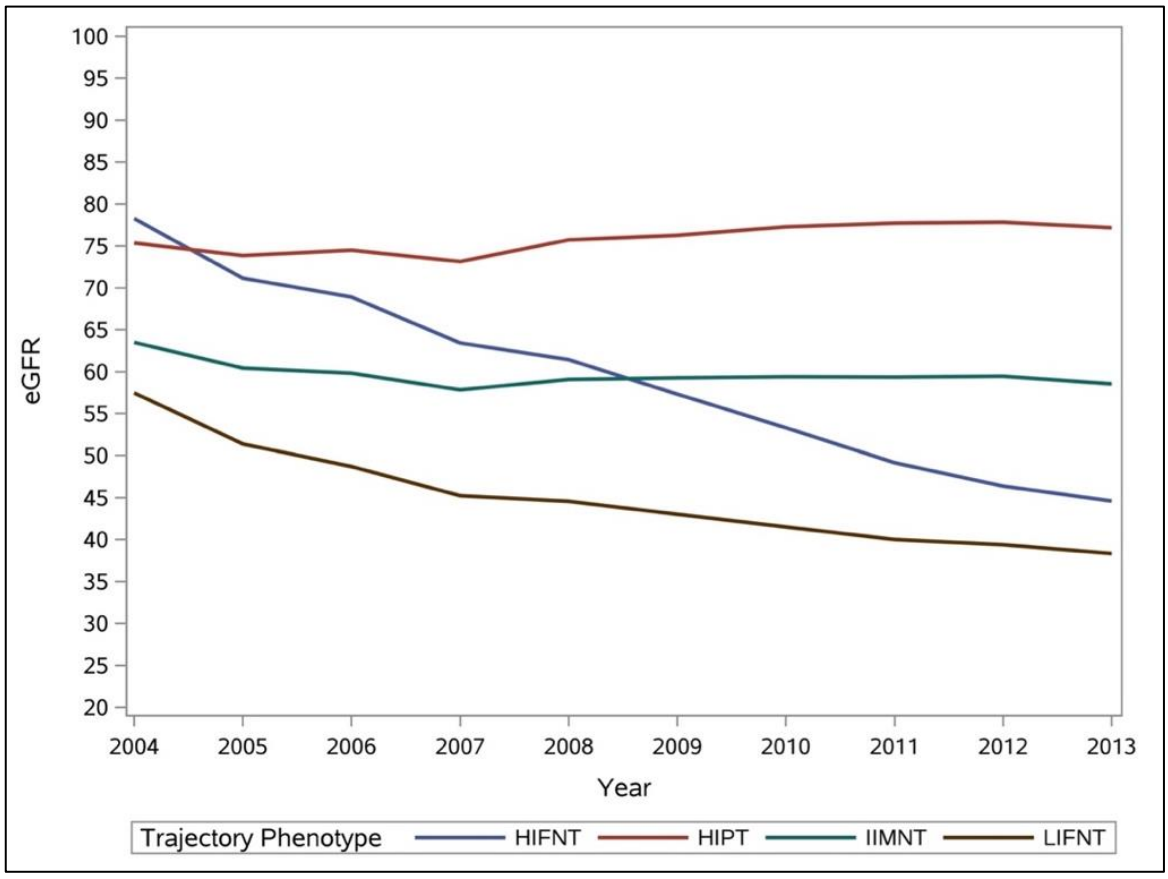
Kidney function can follow a number of trajectories over time. Although these are not always followed closely in routine clinical practice, an American research team identified four common trajectory phenotypes (Figure 2-3):[57]

- The eGFR can **start high and deteriorate quickly**, as may be seen in those with heavy albuminuria (HIFNT, high intercept and fast negative trajectory).

- The eGFR can **start high and stay stable or even increase** (HIPT, high intercept and positive trajectory).
- The eGFR can be **slightly reduced with a slow decline**, such as in older adults with hypertension and/or vascular disease (IIMNT, intermediate intercept and mild negative trajectory).
- The eGFR can **start low and decline at a fast rate** (LIFNT, low intercept and fast negative trajectory).

A patient's age, what chronic conditions they have, and the trajectory of their kidney function will influence what clinical care is appropriate for them. Older adults with life-limiting conditions and stable CKD are unlikely to require KRT. Performing KRT planning for them might be unnecessary while exposing them to various risks, such as vascular access surgery. Chronic conditions other than CKD may exist before an individual has established CKD, or conditions may develop as kidney function declines.

Figure 2-3. Possible kidney function trajectory phenotypes, as described by Xie et al[57].



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2.2.8 Non-kidney related adverse outcomes

Although patients with CKD and clinicians worry about deteriorations in kidney function, their risk of **non-kidney** adverse outcomes is greater. An American study investigated 10,940 participants with hypertension and the relationship between serum creatinine and adverse outcomes. Amongst participants with a serum creatinine greater than 150μmol/L at baseline, participants were more likely to die during follow-up than have declines in their kidney function.[58]

This risk of **mortality** increases with falling eGFR. A meta-analysis of 10 cohorts including 266,975 patients with diabetes mellitus, hypertension or cardiovascular disease studied the relationship between eGFR, uACR, and mortality.[59] It found that the risk of all-cause mortality rose once eGFR fell below 60mL/min/1.73m^2, independent of traditional risk factors. This risk of mortality increased once uACR rose above 10mg/g, and there was a multiplicative effect with both reduced eGFR **and** elevated uACR. These findings indicate that even early CKD is a key risk factor for mortality, independent of traditional risk factors.

This heightened risk is mainly driven by **cardiovascular disease**. In a meta-analysis of 105,872 patients from 14 cohorts, cardiovascular mortality risk was **three times higher** amongst those with an eGFR of 15mL/min/1.73m^2 compared to those without CKD.[60] Although patients with CKD and cardiovascular disease share risk factors like diabetes mellitus, smoking, and obesity, **low eGFR and (to a greater extent) elevated uACR are independent predictors of cardiovascular events**. In a meta-analysis including 637,315 patients without cardiovascular disease, the performance of models predicting cardiovascular events improved with the addition of both eGFR and uACR.[61] CKD has therefore been incorporated into cardiovascular risk calculators such as QRISK.[62]

There are several factors which help explain why patients with CKD are at heightened risk of cardiovascular disease. They are disproportionately affected by

chronic inflammation, metabolic bone disease, left ventricular hypertrophy, and stiffening and calcification of their arteries.[63] In advanced CKD, electrolyte imbalance and excessive salt and water make patients vulnerable to fluid overload, which is sometimes labelled as “heart failure”.

A further risk faced by patients with CKD is unplanned admissions to hospital. They are disproportionately at risk of problems like AKI, heart failure, and infections.[64] The harm associated with these admissions extends beyond the symptoms they experience. Patients and their carers face isolation, anxiety, and sometimes complications while in hospital, such as healthcare-associated infections.

2.2.9 Comorbidities in CKD

Patients with CKD usually have multiple chronic conditions and their treatment is often complex.[65] A large Canadian study found that compared to patients seeing a range of other specialists, those seeing nephrologists had more chronic conditions, took more medications, and were more likely to die during follow-up.[3] The treatment of chronic conditions can differ in patients with CKD compared to those without CKD. For example, the identification of depression in patients with CKD can be challenging, and antidepressants often do not work as well as they do in patients without CKD.[66] Part of the challenge in the treatment of patients with CKD is that they are systematically excluded from drug trials, so the evidence base on treating them is limited.[67,68]

2.2.10 Summary

CKD is therefore a common problem which is linked to a range of adverse clinical outcomes. It becomes more common as people age, and the diagnosis usually relies on blood tests. Severely reduced kidney function i.e. eGFR less than 30mL/min/1.73m^2 can cause symptoms and complications, but this represents the tip of the iceberg of CKD. Most patients with CKD develop a slight reduction in eGFR as they get older, and the clinical significance of this remains unclear, especially what its significance is in the context of other chronic conditions.

2.3 Multimorbidity

2.3.1 Multimorbidity definitions

Multimorbidity has been described in a number of ways, but the most widely used definition is the presence of **two or more chronic conditions** in an individual.[69] Other definitions incorporate factors which may influence health besides chronic conditions such as this definition from Le Reste et al[70]:

> *"any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor"*.

Using this definition, symptoms and risk factors such as pain and alcohol misuse are sometimes included in measures of multimorbidity.

The chronic conditions which contribute to multimorbidity may be physical or mental, infectious or non-communicable, and are not defined by an index condition. By comparison, "comorbidities" are chronic conditions additional to an index condition.[71] A clinician in the nephrology clinic may therefore view kidney disease as the index condition with diabetes mellitus, heart disease, and cancer as **comorbidities**.[72] **Multimorbidity** reflects a more generalist view of patients' health conditions by focusing on the overall patient rather than individual conditions.

2.3.2 Epidemiology of multimorbidity

The prevalence of multimorbidity varies by country, age group, and the methods used to define chronic conditions. In a landmark study of 1.8 million people living in Scotland, 23% of people had two or more chronic conditions and **most people over the age of 65 had multimorbidity**.[1] In a study of 403,985 adults in England, 27% of people had multimorbidity.[7] Most patients who had appointments with their GP and most patients admitted to hospital had multimorbidity. For healthcare professionals caring for patients in the UK, it has become unusual to go through a working day **without** seeing a patient with multimorbidity.

Despite inconsistencies in the recording and reporting of chronic conditions in LMICs, multimorbidity is also becoming more common in these countries. One study found the prevalence of multimorbidity to vary between 20% and 35% in different

LMICs.[73] However, greater variability in multimorbidity estimates was found in a systematic review of 39 studies, which found the prevalence to range between 13% and 95%.[74] Although historically patients in many LMICs required treatment for infectious diseases, the burden of non-communicable diseases in these countries is rising.[73]

2.3.3 Measurement of multimorbidity

The chronic conditions included in the study of multimorbidity have not been standardised.[75] Many studies define chronic conditions from health care records, and up to 300 chronic conditions have been used.[76] Studies which include more diagnostic codes and/or more conditions will report higher rates of multimorbidity. A systematic review of multimorbidity studies found significant variation in the chronic conditions included, with as many as 13% of studies not reporting which conditions they included.[77] Despite these variations in reporting, there is consensus that **multimorbidity is common** and that with ageing populations, it is becoming a more widespread problem.[78]

Although many studies report multimorbidity counts i.e., counts of the numbers of chronic conditions, other studies use weighted counts e.g. Charlson comorbidity index.[79] These indices assign greater weight to certain chronic conditions, often if they are associated with an outcome of interest such as mortality. Many multimorbidity measures have been developed, with systematic reviews describing up to 35 measures.[80,81,82] A meta-review concluded that both multimorbidity counts and weighted scores have their roles, and that researchers should use the measure best suited to their study.[83]

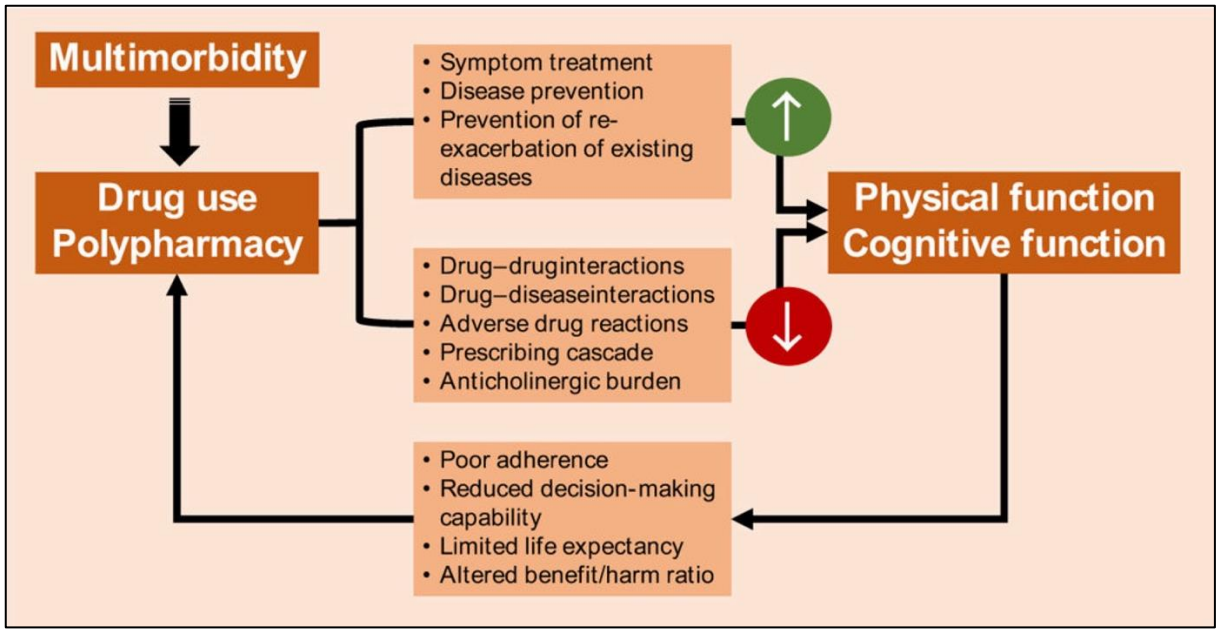
2.3.4 Impact of multimorbidity

Multimorbidity has a negative impact on the lives of patients and carers. Symptom burden is well recognised i.e., the symptoms caused by conditions. An additional impact is treatment burden i.e., the work patients and carers must do to manage their conditions.[84] This means taking multiple treatments at the correct times, performing self-management (dietary measures, monitoring symptoms, exercises), and navigating complex healthcare systems i.e., travelling to appointments or using

telephones or computers to access care remotely. The demands placed on patients are particularly challenging for those with communication difficulties and for those who do not speak the local language. Patients can also be disadvantaged if they have limited health literacy or if they have insufficient skills e.g. reading, computing, and the ability to complete practical tasks such as checking and interpreting capillary blood glucose levels.

There is a bidirectional relationship between functional impairments and multimorbidity.[85] Chronic conditions may cause reductions in a person's ability to perform everyday tasks, while physical and cognitive impairments can inhibit a person's ability to look after themselves and manage treatment burden. Polypharmacy contributes to a vicious cycle whereby as medications are added to an individual's prescription, they are at increased risk of side effects and drug interactions, leading to reduced adherence (Figure 2-4). Often, carers help patients to ensure they take their medications as prescribed, attend appointments, and follow lifestyle measures. Studies from LMICs show that carers must work particularly hard to ensure their loved ones access healthcare when services are poorly integrated, especially when families must pay for expensive treatments like dialysis.[86]

Figure 2-4. Bidirectional relationship between multimorbidity and functional impairments.



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Overall, multimorbidity leads to reduced quality of life, with one systematic review reporting disproportionate effects in young patients and in women.[87] Multimorbidity is also a clear risk factor for mortality, with a systematic review reporting a 1.2-fold increase in all-cause mortality risk for each additional chronic condition.[88] In a UK Biobank study, multimorbidity was a risk factor for mortality from any cause, but also cancer- and vascular-mortality, with heightened risk particularly in those with cardiometabolic conditions.[89]

2.3.5 Frailty and multimorbidity

Although frailty and multimorbidity are different concepts, they often co-exist and they are linked.[90] Frailty refers to a decline in function and a lack of physiological reserve which makes individuals vulnerable to stressors.[91] It can be quantified by tools such as the Rockwood index[92] and the Fried frailty phenotype.[93] Although chronic conditions can have an impact on how frail an individual is, these tools are distinct from multimorbidity as they incorporate symptoms and what activities a person can do.

Frailty becomes more common as adults age and as they accumulate chronic conditions. In a study of 38,027 adults living in Norway, 62% of people had multimorbidity and at least one frailty dimension.[94] Although frailty affected a larger **proportion** of older adults, there were overall **more people** under the age of 65 with multimorbidity and frailty than those over the age of 65. A UK Biobank study of 20,566 middle aged adults with type 2 diabetes mellitus showed that the concepts of frailty and multimorbidity are **both** helpful in identifying patients at increased risk of harm such as hospitalisations, falls, cardiovascular events, and hypoglycaemic events.[95]

2.3.6 Socioeconomic status and multimorbidity

Multimorbidity disproportionately affects people who live in socioeconomically deprived areas. In Barnett and colleagues' study, multimorbidity occurred 10 to 15 years earlier in people from the most deprived areas compared to the least deprived areas.[1] Mental health conditions were particularly common in more deprived areas. Unhealthy lifestyles (smoking, physical inactivity, obesity, alcohol use, and poor nutrition) contribute to this trend, but these factors do not fully explain the role of

deprivation in the accumulation of chronic conditions.[96] In a study of 119,084 adults living in Finland and the UK, low socioeconomic status was associated with the development of 18 chronic conditions, after adjustment for lifestyle factors.[97] In deprived areas, conditions related to mental health and substance misuse were often precursors to the development of conditions affecting the kidneys, heart, liver, and central nervous system. These trends were not witnessed in people from less deprived areas, suggesting that mental health problems and substance misuse may mediate the role socioeconomic status has in the development of multimorbidity.

2.3.7 Multimorbidity patterns

Beyond the number of chronic conditions, another key consideration is the **type** of conditions. One way to categorise conditions is whether they are physical or mental. Mental health conditions include mood disorders like depression and schizophrenia, and may also include the misuse of substances like alcohol or illicit drugs. These conditions are particularly important when combined with physical conditions. There is a complex relationship between physical and mental health conditions, as they may share risk factors and influence one another.[98] For example, some mental health conditions contribute to sedentary lifestyles, which in turn put patients at risk of diabetes mellitus and heart disease. Conversely, physical conditions may lead to pain and social isolation, which can contribute to anxiety and depression. The combined effect is of **reduced quality of life** and **increased risk of adverse outcomes** like hospitalisation[99] and mortality.[100]

Chronic conditions may also be categorised as **concordant or discordant**. Concordant conditions share common risk factors and may share common management strategies, whereas discordant conditions are unrelated.[101] This concept can be helpful, but the process of allocating concordance or discordance is subjective. For example, although obesity can lead to diabetes mellitus and osteoarthritis, these conditions could be categorised as discordant as different risk factors exist for each and the management of each condition usually differs.

Cardiometabolic conditions are a further type of condition. These may include ischaemic heart disease, heart failure, atrial fibrillation, peripheral vascular disease,

cerebrovascular disease, and diabetes mellitus. This group of conditions is thought to be important because the risk of mortality is particularly high if any of them are present, with amplified risk in those with **multiple** cardiometabolic conditions.[102]

Patients and their treatment typically become more complicated as they accumulate more conditions affecting different parts of the body. The term "**complex multimorbidity**" describes patients with three or more chronic conditions affecting different body systems.[103] A Norwegian study showed that patients with complex multimorbidity are at high risk of mortality and of requiring assistance with activities of daily living.[104] A study of adults in England showed that while the prevalence of multimorbidity rose by 12% between 2002 and 2015, the prevalence of complex multimorbidity rose by 73% in the same time frame.[105] Patients with a high level of medical complexity are therefore becoming more prevalent, and the medical community must learn more about these patients and adapt to maintain high standards of care.

2.3.8 Multimorbidity clusters

The concept of "clusters" of conditions has been developed from the observation that some conditions occur together frequently.[106] Clusters may exist if conditions share risk factors. For example, smoking may cause cancers and respiratory diseases, so these conditions may be seen in a cluster. Conditions may also commonly co-exist if each of them are highly prevalent. For example, hypertension and diabetes mellitus are common in older adults and so patients with one often have the other. It is possible that identifying clusters of conditions could potentially improve clinical care in three ways:

- **Preventative strategies** might be developed for clusters with common risk factors.
- Clusters might be used for **risk stratification** of adverse outcomes and may therefore be used to target risk reduction strategies.
- Clusters might be highlighted in **clinical guidelines** if clinicians frequently find it challenging to manage these patients.

Several researchers have used observational studies to identify clusters of conditions. In a UK Biobank study, three main clusters were identified: one with cardiovascular diseases, one with diabetes, and one with several conditions (hypertension, asthma, depression, and cancer).[107] Other studies have linked clusters to adverse outcomes, such as a study of 113,211 adults living in England which studied the relationship between clusters and the risks of mortality and health service use.[108] They found that the clusters most closely associated with adverse outcomes depended on the age of participants. In those under the age of 65, clusters of mental health conditions were the highest risk; in those aged 65-84, a cluster of depression and cardiovascular disease was the highest risk; and in those aged over 85, a cluster of cardiovascular diseases was at highest risk.

However, not all research into the concept of multimorbidity "clusters" has found it to be useful. A study of over eight million people living in England admitted to hospital identified clusters of conditions, examining the associated financial costs to the healthcare system.[109] They did not find any clusters linked to elevated costs and concluded that clusters could therefore not be targeted by interventions to prevent hospitalisations. These findings suggest that in some settings, the identification of clusters may be more helpful for the development of preventative strategies than for targeting treatments once multimorbidity is established. However, much more work is needed to understand clusters and how they can be used to improve patient care.

2.3.9 Interventions for patients with multimorbidity

Clinical guidelines usually focus on individual conditions. For patients with multiple conditions, **following guidelines for each individual condition can be difficult,**[110] **or even impossible** if the guidelines contradict each other.[111] For clinicians looking after patients with multimorbidity, it is difficult to apply these guidelines in clinical practice and treatment may become sub-optimal.[112] Conventional undergraduate medical teaching focuses on individual organs and conditions, rather than encompassing the overall patient. Patients with multiple conditions are also poorly represented in clinical trials.[8] This makes it challenging to write clinical guidelines while incorporating multimorbidity and helping clinicians treat these complex patients.

Modern medicine is therefore faced by the challenge of increasing numbers of patients with multimorbidity, without the evidence or tools to treat them well. Health care services would be better prepared if they were patient-focused rather than disease-focused, although delivering clinical care like this is challenging.[113] In a randomised controlled trial in primary care in the UK, routine care (annual reviews of individual conditions) was compared to more frequent holistic reviews with support from nurses and pharmacists.[114] After 15 months of the intervention, there were only small improvements in quality of life, which were not statistically significant or cost-effective. A systematic review of telemedicine interventions in patients with multimorbidity found that although improvements in disease control measures could be achieved (e.g. glycated haemoglobin), there were no improvements in patient-reported outcomes.[115] A further systematic review suggested that system-level interventions (those which alter how healthcare is organised and delivered) may be able to reduce treatment burden, although the evidence base was small and heterogenous.[116]

These examples of interventions demonstrate how difficult it is to improve the care of patients with multimorbidity. In a Cochrane review of interventions for patients with multimorbidity, only 17 clinical trials were found and the conclusions were mixed.[117] Most of the trials focused on the logistics of care, such as nurse specialists helping to deliver care. There was little evidence that health service use or clinical outcomes improved and the best evidence existed for interventions targeted at improving mental health. For example, a cluster randomised trial amongst patients with diabetes mellitus, cardiovascular disease, and depressive symptoms living in England assessed the effect of psychological therapy and integrated treatment from practice nurses.[118] In a deprived population with physical and mental multimorbidity, they reported reductions in depressive symptoms with the intervention.

2.3.10 Summary

Multimorbidity is therefore a common problem which has significant effects on patients' lives. It is closely linked to polypharmacy, frailty, and socioeconomic deprivation. However, it is unclear whether knowing about multimorbidity clusters can help improve patient care.

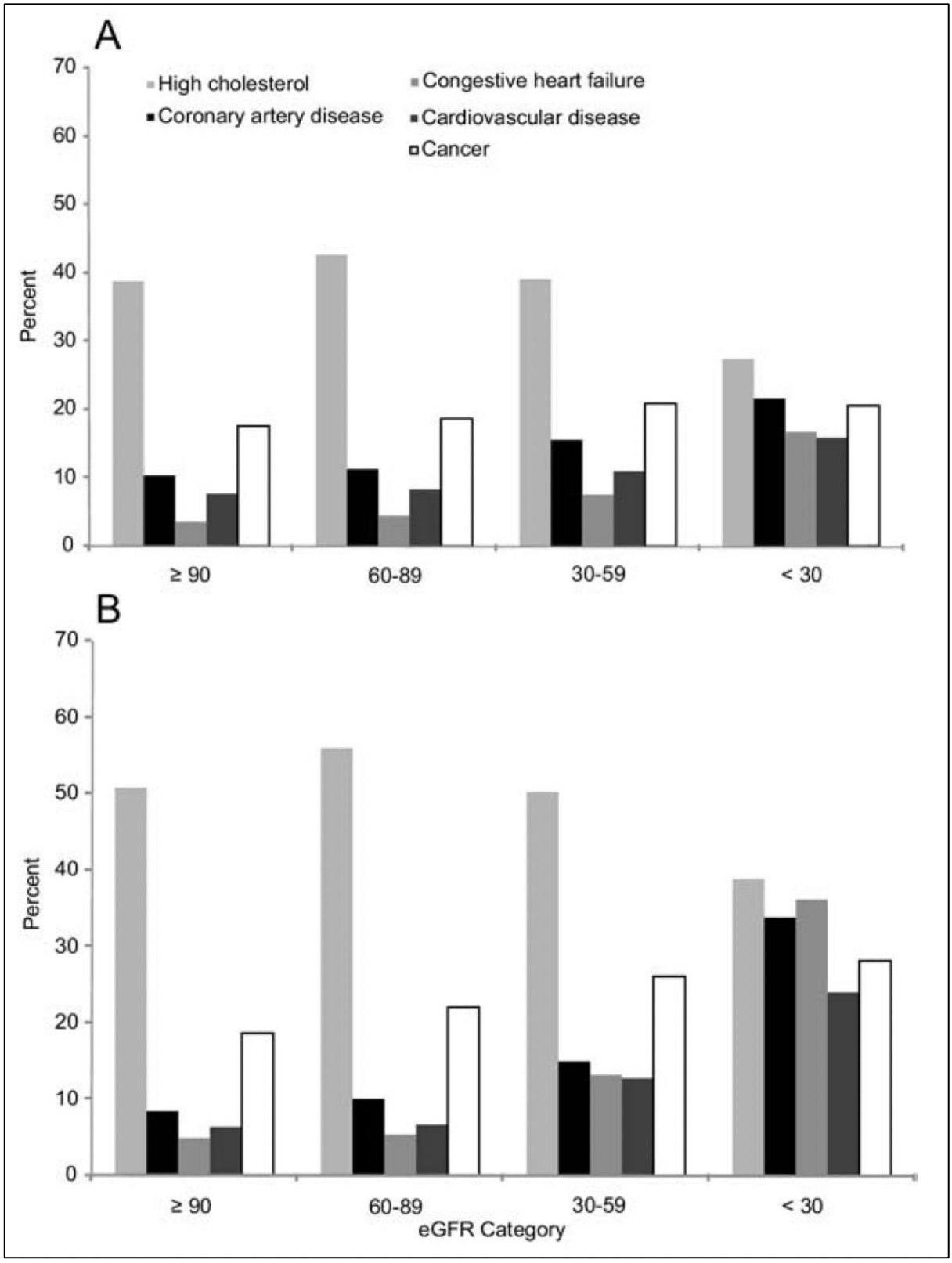
2.4 Multimorbidity in chronic kidney disease

2.4.1 Multimorbidity prevalence in chronic kidney disease

Patients with CKD and any additional chronic conditions have, by definition, multimorbidity. In a UK study of 1,741 adults with CKD stage G3 (mean age 73 years), only 4% of participants had CKD with no other chronic conditions.[119] 40% of participants had CKD plus three or more chronic conditions and 59% of participants were taking five or more medications. The commonest chronic condition was hypertension (88%), followed by painful conditions (30%). By comparison, in a retrospective Canadian study of 530,771 adults with CKD stages G1-G5 (median age 56 years), 29% of participants had CKD with no other chronic conditions.[120] The commonest chronic condition was hypertension (47%), followed by diabetes mellitus (18%). Therefore, although the rates of multimorbidity vary depending on the population studied, **multimorbidity affects most patients with CKD**.

The rates of some chronic conditions vary at different levels of kidney function. In two American studies (Kidney Early Evaluation Program and the National Health and Nutrition Examination Survey), cardiovascular conditions and cancer became more prevalent as eGFR declined, but hypercholesterolaemia became less prevalent (Figure 2-5).[121] Although the rates of these **particular** conditions change depending on eGFR, **it is unclear how multimorbidity overall changes as kidney function declines**.

Figure 2-5. Prevalence of selected chronic conditions stratified by eGFR category. A. Kidney Early Evaluation Program. B. National Health and Nutrition Examination Survey.



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2.4.2 Polypharmacy in chronic kidney disease

Polypharmacy – the use of multiple medications – is common amongst patients with CKD, which is related to the high prevalence of multimorbidity. In an international cohort study of 1,317 people over the age of 65 with an eGFR of less than 20mL/min/1.73m^2, 91% of participants were affected by polypharmacy.[122] In a Dutch study of 27,573 adults with CKD, the median number of medications prescribed was 10, compared to a median of one medication amongst a control population without CKD matched on age, sex, and socioeconomic deprivation.[123] Medications may be directly related to CKD (e.g. sodium bicarbonate, erythropoiesis stimulating agents) or patients may take them for other conditions (e.g. insulin, painkillers). Adverse drug reactions (ADRs) are common in CKD, particularly in those with low eGFRs. In a study of 3,033 patients attending nephrology clinics in France, 18% of participants had an ADR during two years of follow-up and ADRs were twice as common in those with eGFRs less than 30mL/min/1.73m^2 compared to those with eGFRs 30-59mL/min/1.73m^2.[124]

2.4.3 Impact of chronic kidney disease on care of other conditions

Clinical management can be complex when CKD is present, and care sometimes differs to when kidney function is normal. In CKD, certain medications are contraindicated because they can cause kidney damage. For example, cisplatin is an effective chemotherapy agent, but it causes kidney damage.[125] Patients with CKD and cancer may need alternative chemotherapy agents to those without CKD, which could affect their outcomes.[126] Other medications are not licensed in CKD because they have not been adequately tested amongst people with CKD.[67] For example, some medications used for treating COVID-19 were not licensed for people with renal impairment, despite a concern that CKD is a key risk factor for adverse outcomes like mortality.[127] Patients with renal impairment may not have had access to the medications remdesivir and nirmatrelvir–ritonavir because they were poorly represented in clinical trials, although the safety profiles of these medications are likely to be similar in those with and without renal impairment.[128,129]

Procedures such as coronary angiography and investigations such as contrast-enhanced scans are sometimes delayed or not performed if a person has CKD. An

American study of acute myocardial infarction found that 25% of patients with CKD had a coronary angiogram compared to 47% of those without CKD, despite the indications for angiography being similar in both groups.[130] Observations like this have given rise to the concept of “renalism”, whereby clinical care is **inappropriately** altered because of the presence of CKD.[131]

2.4.4 Impact of multimorbidity on chronic kidney disease care

As a patient’s kidney function declines (particularly to eGFR less than 15mL/min/1.73m^2), clinicians plan whether to pursue KRT or not and which treatment option(s) to choose. In a UK study of patients with pre-dialysis CKD, factors which influenced treatment choices were age, social and lifestyle factors, and the number of chronic conditions.[132] Older adults and those with more chronic conditions were more likely to choose conservative care instead of dialysis. Conservative care is where clinicians provide management of kidney failure without dialysis or transplantation e.g. management of renal anaemia and symptom control. Dialysis is likely to only improve life expectancy by a small amount in frail older adults[133] and it remains unclear how the choice of dialysis or conservative care impacts on quality of life.[134]

A survey of 67 renal units in the UK in 2015 found that all but one unit provided conservative care for older adults with advanced CKD.[135] They reported that the most important factors which influenced decision-making regarding conservative care were:

1. Patient preference
2. Extent and severity of comorbidities
3. Frailty
4. Functional status
5. Current quality of life

However, it is worth considering that many patients with advanced CKD and multimorbidity are young. Conservative care may not be a reasonable treatment choice for these patients or for non-frail older adults. There is good evidence that quality of life[136] and life expectancy[137,138] are better for most kidney transplant recipients compared to those on dialysis. However, the process of assessment for

kidney transplantation is rigorous, and patients must be deemed fit enough to undergo surgery. Those with cardiometabolic conditions are less likely to gain access to transplantation than those without these conditions.[139,140] However, it is unclear whether patients with non-cardiometabolic multimorbidity are also disadvantaged when it comes to transplant listing.

2.4.5 Treatment burden in chronic kidney disease

Treatment burden is significant for many patients with CKD and it changes as CKD progresses.[141] The challenges faced by patients are often different for patients not on KRT, for those on dialysis, and for kidney transplant recipients.

For patients with mild to moderate CKD, treatment burden may be primarily influenced by risk reduction strategies and priorities related to comorbid conditions.[65,142] In a qualitative study of patients with CKD not requiring KRT living in England, those with CKD stage G3 reported difficulties keeping track of multiple medications and poor communication between different healthcare teams causing fragmented care.[143] Patients who attend multiple hospital specialists are sometimes given conflicting advice from different medical teams. Some patients' GPs co-ordinate their care, but for others, there is no single co-ordinator of care and they can be left unsure about whose advice they should follow. This problem is compounded if they see different doctors each time they attend the GP surgery or hospital clinic.[144]

For patients who attend hospital for haemodialysis, they spend long hours at dialysis units and additional time travelling. There is little flexibility in when they attend, and so appointments for other conditions must be fit in around their dialysis schedule. Their availability to do paid work is limited and resulting financial difficulties may reduce their capacity to manage treatment burden. For most patients on home-based KRT (peritoneal dialysis and home haemodialysis), they and their carers usually must develop advanced skills to perform the dialysis while closely monitoring their condition.

2.5 Conclusion

CKD and multimorbidity pose significant challenges for patients and healthcare services. It is clear that both problems are common amongst adults, they contribute to significant treatment burden for patients, and clinical management of these patients is often complex.

However, there are notable evidence gaps surrounding CKD and multimorbidity. We can anticipate which adverse outcomes patients with CKD and multiple chronic conditions will be at heightened risk of (e.g. cardiovascular events) but evidence on the impact other adverse outcomes remains unclear (e.g. hospitalisation). It is also unclear which chronic conditions are most closely associated with adverse outcomes and if the type of condition is important. We do not know if type of comorbid chronic conditions among CKD patients changes at different stages of CKD. Clustering of chronic conditions has been proposed to identify common or previously unknown combinations of conditions. Improving understanding of multimorbidity amongst patients with CKD may improve the approach to disease prevention or to clinical management once multimorbidity has developed.

In this thesis, the underlying hypothesis is that multimorbidity and clusters of chronic conditions are associated with adverse outcomes in populations with chronic kidney disease. This hypothesis is explored using a data-driven approach in four patient cohorts. In the next chapter, these cohorts and the methods used to analyse them are discussed in detail.

Chapter: 3 Methods

3.1 Chapter summary

In this chapter, the methods for the thesis are described in detail. These methods were chosen after my supervisors and I considered a range of approaches and their relative merits.

The approach to **systematic review** is outlined, with descriptions of the techniques chosen. The **datasets** employed for the quantitative work and their potential strengths and weaknesses are described. The different ways to **assess kidney function** and **chronic conditions** from the datasets are discussed, with justification of the methods chosen. In the final section of the chapter, the various **statistical techniques** used are explained.

3.2 Systematic review and meta-analysis

The first task in understanding the interface between multimorbidity and chronic kidney disease (CKD) was to study the existing literature on the subject. A systematic review with meta-analysis was used to identify knowledge gaps and to put the rest of the thesis in the context of existing evidence.

3.2.1 Review planning

The review was planned after consulting the *Preferred reporting items for systematic review and meta-analysis protocols* (PRISMA-P)[145] and Cochrane[146] guidelines. A protocol was developed and registered on PROSPERO, the International Prospective Register of Systematic Reviews http://www.crd.york.ac.uk/PROSPERO (CRD42019147424). The protocol is included in the Appendix.

3.2.2 Eligibility criteria

Quantitative studies from 1946 to the date of the search (29/08/2019) were sought which investigated multimorbidity amongst patients with CKD. The following criteria were used:

Population

We included studies of patients with CKD i.e. those on kidney replacement therapy (KRT: dialysis or kidney transplantation) and those with CKD not on KRT. This ensured patients with a range of CKD stages were included.

Exposure

Studies needed to provide counts of chronic conditions: simple or weighted.

Comparator

There needed to be a comparator group of patients without multimorbidity. Multimorbidity was defined as two or more chronic conditions.

Outcomes

Studies which reported adverse clinical outcomes were included (all-cause mortality, cardiovascular events, kidney events, and hospitalisations). The associations between chronic conditions and outcomes needed to be quantified.

Because all patients in the selected studies had CKD, I considered chronic conditions **additional** to CKD. An alternative approach would have been to study patients both with CKD and without CKD. In this way, one could study the association between CKD and the risk of adverse outcomes. However, CKD is an established risk factor for the adverse clinical outcomes under investigation, and the focus of the review was to examine the impact of multimorbidity amongst patients with CKD.

Exclusion criteria

Qualitative studies and review articles were excluded because they would not quantify the associations between multimorbidity and adverse outcomes. Drug intervention studies were excluded because I was not reporting on the impact of interventions on outcomes. Studies which included children under the age of 18 were excluded because children with CKD are a different population to adults with CKD and so it is inappropriate to compare studies including adults and studies including children. I did not focus on patient reported outcome measures because a preliminary literature search showed very few studies which reported these outcomes.

3.2.3 Literature search

A search strategy was developed with a librarian who has expertise in medical literature (Figure 3-1). Medical subject headings and text words were used to identify studies which referenced both multimorbidity and CKD.

Figure 3-1. Systematic review search strategy.

1.	kidney failure/ or chronic kidney failure/ or end stage renal disease/ or mild renal impairment/ or moderate renal impairment/ or renal replacement therapy-dependent renal disease/ or severe renal impairment/ or subclinical renal impairment/
2.	kidney disease/ or kidney dysfunction/
3.	renal replacement therapy/ or hemodiafiltration/ or hemodialysis/ or hemofiltration/ or peritoneal dialysis/
4.	continuous ambulatory peritoneal dialysis/
5.	kidney transplantation/ or kidney graft/
6.	(chronic renal or chronic kidney).tw.
7.	(renal failure or kidney failure).tw.
8.	kidney disease.tw.
9.	renal insufficienc*.tw.
10.	(CKD or CKF or CRD or CRF).tw.
11.	(predialysis or pre-dialysis).tw.
12.	(endstage renal or endstage kidney).tw.
13.	(hemodialysis or haemodialysis).tw.
14.	(hemodiafiltration or haemodiafiltration).tw.
15.	dialysis.tw.
16.	peritoneal dialysis.tw.
17.	(CAPD or CCPD or APD or PD).tw.
18.	(kidney transplant* or renal transplant*).tw.
19.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20.	multiple chronic conditions/
21.	(multimorbid* or multi morbid*).tw.
22.	(multiple condition* or multi condition* or multicondition*).tw.
23.	(multiple disease* or multi disease* or multidisease*).tw.
24.	(multiple disorder* or multi disorder* or multidisorder*).tw.
25.	(multiple comorbidities or multiple co morbidities).tw.
26.	(discordant comorbidities or concordant comorbidities).tw.
27.	condition count*.tw.
28.	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29.	exp adult/
30.	(adult* or aged* or elderly).tw.
31.	29 or 30
32.	human/
33.	19 and 28 and 31 and 32

Five databases were searched (*Medline*, *Embase*, *Cinahl*, *Cochrane*, and *Scopus*) and the results were collated using referencing software *Endnote* (Clarivate Analytics, Philadelphia, USA). Using several databases reduced the likelihood of articles being missed. Reference lists of review articles and included studies were screened for additional studies.

3.2.4 Study screening

Another reviewer and I screened studies using the software *DistillerSR* (Evidence Partners, Ottawa, Canada). In the first stage, titles were screened and studies advanced if both reviewers agreed. In the second stage, abstracts were reviewed; and in the third stage, full papers were reviewed. Disagreements between the reviewers at each stage were discussed with a third reviewer. This independent screening process led to studies being selected in a reliable manner.

3.2.5 Data collection

The following information was extracted from each study:

- Country
- Sample size
- Setting
    - Dialysis, kidney transplant, non-KRT CKD, conservative care
- Duration of follow-up
- Multimorbidity measurements
    - Conditions included
    - Simple or weighted counts
    - Multimorbidity considered as a continuous or a categorical variable
- Outcomes reported
- Effect sizes
    - Type i.e. hazard ratio, rate ratio
    - Values

3.2.6 Quality appraisal

The Newcastle-Ottawa Scale (NOS) was used to identify bias in studies and to assess their quality.[147] This approach was chosen as the Cochrane handbook recommends it for its simplicity and effectiveness.[146] Although the NOS often needs to be adjusted for specific reviews, it is thought to be better than other tools, such as the Downs and Black instrument.[148] Use of the Downs and Black instrument requires extensive epidemiological training and only some of the questions are helpful.[149] As quality appraisal is a subjective process, two reviewers used the NOS independently and ensured the assessments were identical. The NOS was adjusted for our review, such as by specifying the exposed populations (CKD with multimorbidity) and non-exposed populations (CKD without multimorbidity) (see adjusted NOS, Supplementary figure 4-1).

3.2.7 Meta-analysis

Quantitative results related to the most commonly reported outcome, mortality, were synthesised using meta-analysis. Methodological heterogeneity of the studies made this challenging. A range of multimorbidity measurements were used (Charlson comorbidity index, condition count etc.), and multimorbidity was expressed as a continuous variable in some studies and a categorical variable in others. After discussion with my supervisors, meta-analysis was restricted to studies which used **the same multimorbidity measure in the same way and reported the same effect size** i.e. hazard ratio or rate ratio. As a result, only 10 of 26 studies could be included, meaning that the meta-analysis excluded results from most of the studies in the review. An alternative approach would have been to not perform meta-analysis, but to summarise the results with narrative descriptions only. Some studies could not be included in the meta-analysis because the necessary data were not published. I contacted the authors of five studies by e-mail to request data. One author replied and these data were included. Had more authors replied, the meta-analysis would have been more inclusive.

Fixed effects models were used instead of random effects models, on the assumption that presence of multimorbidity would be associated with an increased risk of mortality. Studies in non-CKD populations have consistently shown this

association,[88] so it was assumed that similar associations would be found in CKD populations. Sensitivity analyses using random effects models were performed.

Two meta-analysis methods were used. The **generic inverse variance method** was used to pool the effect sizes from studies using the Charlson comorbidity index as a continuous variable. This is a simple technique when hazard ratios are available.[146] For studies which presented multimorbidity as a categorical variable and reported risk ratios, the **Mantel-Haenszel method** was used as it can combine risk ratios effectively.[146] The proportion of variability attributable to between-study heterogeneity was estimated using the I^2 test, which compares the effect sizes and confidence intervals from different studies. A value of greater than 50% is suggestive of substantial statistical heterogeneity.[146] *RevMan V.5.3* software was used for these analyses (Cochrane Collaboration, Copenhagen, Denmark).

3.3 Description of datasets

Four datasets were chosen, based partly on their qualities and partly on their ease of availability. They are described in this section, with a focus on their respective strengths and weaknesses.

3.3.1 UK Biobank

3.3.1.1 Overview

UK Biobank is a prospective research study which was developed with the aim of investigating risk factors for health-related outcomes.[150] Planning for the study began in 1999, with the aim of recruiting a population at risk of adverse outcomes over the next 20 years. People living within 25 miles of 22 assessment centres in England, Scotland, and Wales were invited to take part (Figure 3-2). 502,503 participants aged 37 to 73 years were enrolled between 2006 and 2010 and have been followed up since.

Figure 3-2. Locations of UK Biobank assessment centres. Reproduced with permission from UK Biobank

Participants had multimodal assessments at baseline including demographics, health and lifestyle information, physical measurements, and laboratory tests. Chronic conditions were taken from self-report, which as an approach is discussed in a section below. Linkage to health records (death registers, hospital records etc.) allows researchers to study a range of outcomes.

3.3.1.2 Strengths

The main strengths of UK Biobank are its **large sample size and detailed baseline assessments**. Certain demographic, lifestyle related, and biochemical measurements available in UK Biobank are often poorly recorded in routine care databases e.g. ethnicity, physical activity levels, and urinary albumin-creatinine ratio (uACR). The availability of this information reduces selection bias when studying risk factors for adverse outcomes because most participants have these variables recorded, rather than just high-risk individuals whose data are typically available in some other observational studies. Survival analysis using UK Biobank benefits from a long duration of follow-up (over 10 years) and the ability to include key cofounding variables in statistical models. The prospective nature of UK Biobank is a key strength because assessments for risk factors were performed before they were influenced by ill health or treatments.[151]

Kidney function was measured in UK Biobank using reliable techniques. Serum creatinine values were measured using a Beckman Coulter AU5400 analyser at a central laboratory.[152] The enzymatic, isotope dilution mass spectrometry (IDMS)-traceable method which was used is reliable.[153] This is important because some observational studies report data from different laboratories with different techniques, some of which may not be standardised.

3.3.1.3 Limitations

UK Biobank is mainly limited by **participatory selection bias**. Only 5% of the people invited to take part did so, which leads to **healthy volunteer bias**.[154] In a study comparing UK Biobank participants to the general population, study participants overall had fewer chronic conditions, lived in less socioeconomically deprived areas, and had healthier lifestyles than the general population i.e. low rates of smoking, alcohol misuse, and obesity.[154] Ethnicity in UK Biobank is 95% white, which is greater than the UK estimate of 87% from the 2011 census.[155] These factors may limit the generalisability of results from UK Biobank to the general population, or to populations in different countries. However, a further study comparing UK Biobank to studies in the general population showed that although fewer UK Biobank participants died during follow-up and the prevalence of risk factors was lower than in general population studies, **the strengths of association between risk factors and outcomes were similar**.[156] A subsequent study compared people with multimorbidity in UK Biobank and SAIL, and their risk of adverse outcomes (mortality, hospitalisations, and cardiovascular events).[157] Crucially, it found that although UK Biobank participants had fewer chronic conditions than people in the SAIL Databank, associations between multimorbidity and adverse outcomes were similar between the two datasets. These studies indicate that UK Biobank is a valuable tool for studying risk factors for adverse outcomes.

Although linkage to mortality registers and hospital records allows for accurate ascertainment of some outcomes (e.g. all-cause mortality, cardiovascular events, hospitalisations), the identification of kidney events in UK Biobank is less reliable. Only 4% of participants had follow-up blood tests via UK Biobank. Primary care records were linked for 46% of participants, but only 25% of these had blood tests to

quantify kidney function. When assessing follow-up blood tests, there is therefore **significant selection bias**. As UK Biobank is not linked to renal registries (which hold reliable information about people starting long-term dialysis or receiving kidney transplants), the ascertainment of kidney failure requiring treatment may be inaccurate. An algorithm using hospital records was developed by UK Biobank collaborators to optimise the identification of participants starting KRT.[158] This was based on an approach taken from a previous UK study.[159] Therefore, although methods exist to identify kidney events in UK Biobank, they are prone to selection bias and they are not as accurate as if there was linkage to renal registries.

Acknowledging these potential limitations of UK Biobank, its qualities made it an invaluable dataset for my studies.

3.3.2 Secure Anonymised Information Linkage (SAIL) Databank

3.3.2.1 Overview

SAIL is a routine care database which holds anonymised health care data for people living in Wales. It was developed at Swansea University in 2006 to facilitate research projects.[160] Each individual has a unique identifier, which is used to link several electronic records:

- Demographics
- Primary care records (including prescribing)
- Hospital inpatient records
- Hospital outpatient records
- Mortality records

Researchers have access to these records via a remote desktop. SAIL is therefore a safe and convenient way for researchers to perform studies without having patient data on their personal computers. This became particularly important during the COVID-19 pandemic, when travel was restricted and many people living in the UK worked from home.

3.3.2.2 Strengths

SAIL is useful for healthcare research because it holds information for **a large number of real-world patients**. It is estimated that GP records for 79% of the Welsh population are available.[161] At any one time, the population of Wales is approximately 3.1 million,[162] so large sample sizes can therefore be studied. Data come from the routine care of patients in contact with GPs and hospitals in Wales. Findings from research using SAIL are therefore generalisable to patients in the UK in contact with healthcare services. Laboratory results are only available from primary care records, which means that blood results are less likely to be from episodes of acute illness than if hospital records were also included. This is helpful when studying long-term kidney function.

3.3.2.3 Limitations

Ethnicity for the Welsh population is approximately 96% white.[162] Studies using SAIL may therefore not be generalisable to populations with greater ethnic diversity. Given ethnicity is not always recorded in GP records, it is not possible to reliably report ethnicity from SAIL. In my project, I made a specific request to the SAIL team at Swansea University to report ethnicity, although this information was missing for 55% of patients.

Studies using routine care databases can be susceptible to **inconsistent recording of data**. Researchers using SAIL must extract data using codes for diagnoses, investigations, and treatments. Although code browsers exist (including one which can be accessed in the SAIL platform), the use of codes for electronic health records research has not been standardised. Different versions of code lists exist and numerous codes exist for individual variables. Variability regarding coding practices during routine clinical care can lead to inaccurate data. Researchers must search for several codes to extract data for each variable, but it is challenging to account for missing codes or inaccurate use of codes. In a study of diabetes records in primary care in the UK, there were coding errors in 40% of patients with diabetes, most commonly diabetes being recorded when the patient did not have the diagnosis.[163] These problems are not unique to SAIL, but they are important to consider when performing research using electronic health records.

Laboratory results from routine care databases rely on what tests have been performed and the accuracy of the tests. Given blood and urine tests are performed for specific reasons, the patients with results are likely to be different to those who have not had tests. An example is urine tests for albumin to creatinine ratio. This test is more often performed in patients with diabetes than in patients without diabetes: in an audit of CKD in England and Wales in 2017, uACR results were only available for 31% of patients with CKD.[164] Given albuminuria is a key risk factor for adverse outcomes (kidney, cardiac, and mortality[59]), the poor availability of this information in SAIL is a notable limitation.

Kidney function is often measured as a component of routine blood tests, but there are many patients who never have blood tests performed. Given two or more tests are required to ascertain a patient's CKD status, my studies do not include patients with one or no blood results, which is a potential limitation. When comparing patients with CKD to patients without CKD, a possible alternative approach is to assume that those without blood tests do not have CKD. This comprises a sensitivity analysis in Chapter 6. An additional approach would have been to allow the inclusion of patients with single blood tests (as in my UK Biobank analyses). However, this would assume kidney function is stable when a patient has a blood test with their GP and it would counter international clinical guidelines which suggest using two blood tests.[165]

Serum creatinine is used to estimate kidney function and it is measured using different analysers in different laboratories. It is not possible to know if the analysers used throughout Wales are validated with an IDMS-traceable approach.[153] Based on discussions with one of my collaborators (Dorothea Nitsch, London School of Hygiene and Tropical Medicine), validated analysers were likely to be in widespread use from 2013 onwards. One potential limitation of SAIL is therefore that blood results from before 2013 may be unreliable.

Acknowledging the potential pitfalls of using primary care databases (including missing data), SAIL's qualities (large sample and population level coverage) made it a valuable resource. It allowed me to extend my studies from a research setting in UK Biobank to the general population, which is a practice recommended by a 2022 study on multimorbidity.[157]

3.3.3 Stockholm CREAtinine Measurement project (SCREAM)

3.3.3.1 Overview

SCREAM is a routine care database which holds anonymised health care data for people living in Stockholm, Sweden. It was developed in 2010 at the *Karolinska Institutet* to study CKD amongst 1.8 million people with kidney function tests.[166] Each individual's identification number is used to link the following records:

- Administrative data
- Healthcare records
- Laboratory results
- Prescribed drug register
- Renal register
- Death register

3.3.3.2 Strengths

As with SAIL, the usefulness of SCREAM relates to it being a **large study of the general population**. It was helpful in my studies because it is from a country outside of the UK with different genetics, lifestyles, and healthcare practices. This allowed me to investigate whether findings in SAIL were replicable in a non-UK population. Although both SAIL and SCREAM are from Northern Europe with predominantly white populations, using SCREAM strengthened the generalisability of my findings beyond the UK. The alternative to using SCREAM would have been to use a dataset from a non-European population with greater ethnic diversity. However, SCREAM was attractive to use because it holds detailed information about patients, and like in the UK, Sweden has universal health coverage, which helps with outcome ascertainment.

3.3.3.3 Limitations

The limitations of SCREAM relate to it being from routine patient care. A number of problems are therefore shared with SAIL i.e. potential miscoding of diagnoses, availability of test results etc.

Access to SCREAM data during my PhD presented an unexpected problem. In my original PhD plan, I hoped to travel to Stockholm for a period of time to perform data analysis. Unfortunately, travel restrictions during the COVID-19 pandemic meant this was not possible. Fortunately, I was able to work with a data scientist – Dr Alessandro Gasparini – who could run the analysis using SCREAM data on my behalf.

3.3.4 International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterisation Protocol (CCP-UK)

3.3.4.1 Overview

The ISARIC study is a prospective cohort study.[167] It was planned in 2012 to investigate any emergent infectious disease. Its protocol was activated in the UK in January 2020, when the COVID-19 pandemic began. Research nurses and medical students collected detailed information about patients hospitalised with COVID-19. When I performed my analysis, data were available for approximately 100,000 patients and the opportunity arose for me to study acute kidney injury (AKI).

In the early days of what was an unprecedented pandemic, there were reports that up to 14% of hospitalised patients required dialysis for AKI.[168] There were therefore concerns about the ability of healthcare services to care for all affected patients and there was a pressing need to understand the impact of COVID-19 on kidney outcomes.[169] Although this study was not included in my original PhD plan, studying risk factors for kidney outcomes in COVID-19 – many of which are chronic conditions – represented a good opportunity. The analysis became the largest study of AKI in COVID-19 globally.

3.3.4.2 Strengths

The use of ISARIC was attractive because it holds **detailed information for a large number of patients with COVID-19**. Enrollment to the study began as the first patients with COVID-19 were admitted to UK hospitals and it continued throughout the pandemic. It includes information on patients before and after COVID-specific therapies were in use, such as dexamethasone. It was therefore possible to study

changes as the pandemic progressed and as these treatments were incorporated into clinical practice.

3.3.4.3 Limitations

The main limitation of the study was the **absence of baseline data**, in particular kidney function. The vast majority of patients with AKI have this detected via blood tests (rises in serum creatinine). It was therefore only possible to detect AKI in patients with two or more blood tests i.e. when serum creatinine rose or fell while in hospital. Many patients therefore had to be excluded from the analysis and some cases of AKI may have been missed or misclassified. Given data were collected in real time and during an unprecedented pandemic, some blood results may not have been recorded in the study, which may have had an additional impact on AKI detection and classification.

In the early months of the COVID-19 pandemic, there was limited access to SARS-Cov-2 testing, even in hospitals. Some patients recruited in the early weeks of the study were included when the infection was highly suspected, but it was not proven via a test. Some of the patients included may therefore have had illnesses other than COVID-19, with similar symptoms and signs e.g. pneumonia.

Therefore, despite the limitations of ISARIC and the fact that COVID-19 was not known about when I planned my PhD, it was a valuable dataset which allowed me to perform a study of public health importance.

3.4 Assessment of kidney function

In each dataset described above, kidney function was quantified using serum or plasma creatinine and estimated glomerular filtration rate (eGFR) values. Depending on the type of the analysis and data availability, four different methods and their respective assumptions/limitations are discussed here, as applicable.

1. **Creatinine**

   This was used when AKI was the outcome in ISARIC data, in Chapter 7. Creatinine is preferred to eGFR in the identification of AKI because small rises in creatinine can be detected before eGFR starts to decline. The alternative

way to identify AKI is via changes in urine output, but unfortunately this information was not available.

2. **Single eGFR**

   In UK Biobank, only one blood sample was processed per person at baseline. Using a single eGFR value is a simple and convenient approach, although clinical guidelines suggest that two eGFR values, three months apart, should be used to quantify long-term kidney function.[11] I assumed that in UK Biobank, single blood results were reliable estimations of long-term kidney function. I assumed that participants were in a stable state of health when they attended for assessment, although it is possible that their eGFR may have been temporarily below or above its usual level on the day of blood sampling.

3. **Two eGFRs more than three months apart**

   This is the approach recommended by clinical guidelines.[11] It has the advantage of being clinically relevant: clinicians can review a patient's blood results and, in most cases, easily assess their kidney function. The limitation of this approach is that if there is lots of variability between blood results, or if the results are separated by a long period of time, it can be challenging to assess an individual's kidney function at any one time. It is also possible for kidney function to decline temporarily, and this approach does not always ensure changes are sustained in the long-term.

4. **Interpolation of eGFRs**

   This approach uses all available eGFRs to estimate the date a patient's eGFR goes from above to below a threshold e.g. 60mL/min/1.73m^2. Each patient's eGFR values are plotted over time and a linear mixed effects model is used to interpolate the date thresholds are crossed. This overcomes the problem of variability in eGFRs and ensures that eGFR changes are sustained in the long-term. It provides a date when kidney function is estimated to be at a threshold, which provides a date to ascertain variables and to begin a period of follow-up. A disadvantage of this approach is that it is computationally intense and therefore can only be used in research settings and not by clinicians. It also excludes participants whose kidney function does not change over time.

3.5 Defining chronic conditions

I used simple counts of conditions in this thesis instead of weighted counts. These were favoured because they offer flexibility when studying a range of datasets, outcomes, and combinations of conditions. The conditions which were included were based on two considerations:

1. The seminal multimorbidity paper by Barnett et al included 40 chronic conditions i.e. CKD plus 39 other conditions.[1] This list of conditions has been used for numerous multimorbidity studies since.
2. Each dataset studied included different information regarding chronic conditions. For example, chronic conditions in SCREAM are defined using International Classification of Diseases (ICD-10) codes, so in Chapter 8 I focused on conditions which could be reliably identified using these codes using a pre-existing algorithm.[170]

Each approach to identifying chronic conditions from datasets has advantages and disadvantages. In this section, I discuss each approach.

3.5.1 Self-report

In UK Biobank, information was collected from participants via a combination of a touchscreen questionnaire and a nurse-led interview. Nurses supported participants with particular questions, such as those about medications.

Self-report may be unreliable if chronic conditions were diagnosed a long time before the assessment date (**recall bias**), or if participants have not had their health fully explained to them by healthcare professionals. The accuracy of self-report for a given condition is likely to depend on the population and the condition. An American study in the 1980s found that self-report for particular conditions led to only a small number of false positives e.g. less than 10% for cancer.[171] However, 40% of myocardial infarction cases were false positives, perhaps because participants had other cardiovascular conditions like angina. In a systematic review, self-report for stroke performed variably in different settings.[172] In populations with low stroke prevalence, around 30% of self-reported strokes were false positives. The authors concluded that a confirmatory information source would improve the accuracy of self-

report. Although research nurses in UK Biobank provided support to participants, the nurses did not have access to healthcare records and the support may have been variable between participants. This contrasts to ISARIC, where research nurses could combine medical records with self-report (assuming patients were well enough to discuss their medical history).

Therefore, the accuracy of self-report is variable, depending on the population, the condition, and if additional information sources are available.

3.5.2 Diagnostic codes

In routine care databases – such as SAIL and SCREAM – chronic conditions are primarily identified by diagnostic codes. The process of recording codes during routine clinical care can be **time-consuming and subjective**, which impacts on its reliability.

In primary care in the UK, Read Codes are added to patients' electronic health records by GPs, nurses or administrators.[173] The diagnoses recorded by resource-limited staff may not always be reliable. In a systematic review of studies using the UK-based dataset CPRD (Clinical Practice Research Datalink), Read Codes which were recorded were generally accurate, but diagnoses were occasionally missing.[174] Conditions may be missing from primary care records for a variety of reasons: if "free text" diagnoses are used; if patients do not present to their GP and information is not communicated effectively from other healthcare providers to the GP; or if GP staff lack the resources to enter every code for their patients. In a previous study using SAIL to define chronic conditions, diagnostic codes and prescribing data were found to be incomplete before 2011.[8] In my use of SAIL, I therefore focused on data from 2011 onwards.

In secondary care, ICD codes are used to document diagnoses. In the UK, these are recorded when a patient is discharged from hospital. This is usually performed by a team of coders who examine clinical notes and discharge letters. Diagnostic codes are stored in country-specific locations:

- Scotland: Scottish Morbidity Records (SMR)

- Wales: Patient Episode Database for Wales (PEDW)
- England: Hospital Episode Statistics (HES)

The team of coders are seldom involved in patient care. The accuracy of coding therefore relies on coding staff being adequately trained and clinical notes being clear and detailed enough. An audit of HES in 2014 found that chronic conditions were often under-reported, usually because of clinical notes were often incomplete and coders relied on discharge summaries which were often brief.[175]

Therefore, diagnostic codes are a helpful way to identify chronic conditions from routine care databases, although the recording of codes relies on busy healthcare teams and under-recording is problematic.

3.5.3 Prescribing data

Prescribing data can be used either to identify conditions or to validate diagnoses identified from other information sources. Some conditions – such as chronic pain – may be poorly recorded because they lack specific diagnostic codes, and so prescribing data can be helpful.[176] For some conditions which may cease to be active – such as asthma or eczema – prescription data can be used to validate they are an ongoing problem. Because medications can be used for different purposes – such as gabapentin for epilepsy and pain – the use of prescription data in this thesis was carefully considered. It was guided by my supervisors and a previous study.[8]

3.6 Choice of statistical techniques

Prior to each analysis, I discussed with my supervisors the possible statistical techniques. The approaches used and their potential limitations are described below.

3.6.1 Adverse outcome analyses

In the course of this thesis, five adverse outcomes are studied:

- Acute kidney injury
- Major adverse kidney events
- Major adverse cardiovascular events
- Number of hospitalisations

- All-cause mortality

The definitions of these outcomes are provided in the relevant chapters.

The participants of each study (UK Biobank, SAIL, SCREAM, and ISARIC) live in the UK and Sweden, where health services are universally available. This was a strength of the datasets because most adverse outcomes are likely to be captured. However, it is possible that some events may not be identified if participants used private healthcare services or if they moved outside the area of study, either temporarily or permanently.

3.6.1.1 Cox proportional hazards models

This technique was used when time-to-event data were available and a binary outcome was being studied e.g. mortality. The main limitation of Cox models is the assumption that hazard ratios are constant throughout time. In this thesis, the proportionality of data was checked using Schoenfeld residuals. On one occasion, the proportional hazards assumption was violated: in Chapter 5. The hazard ratio related to age rose as follow-up progressed. To mitigate this, I used age as the time variable instead of as a confounder.

3.6.1.2 Logistic regression models

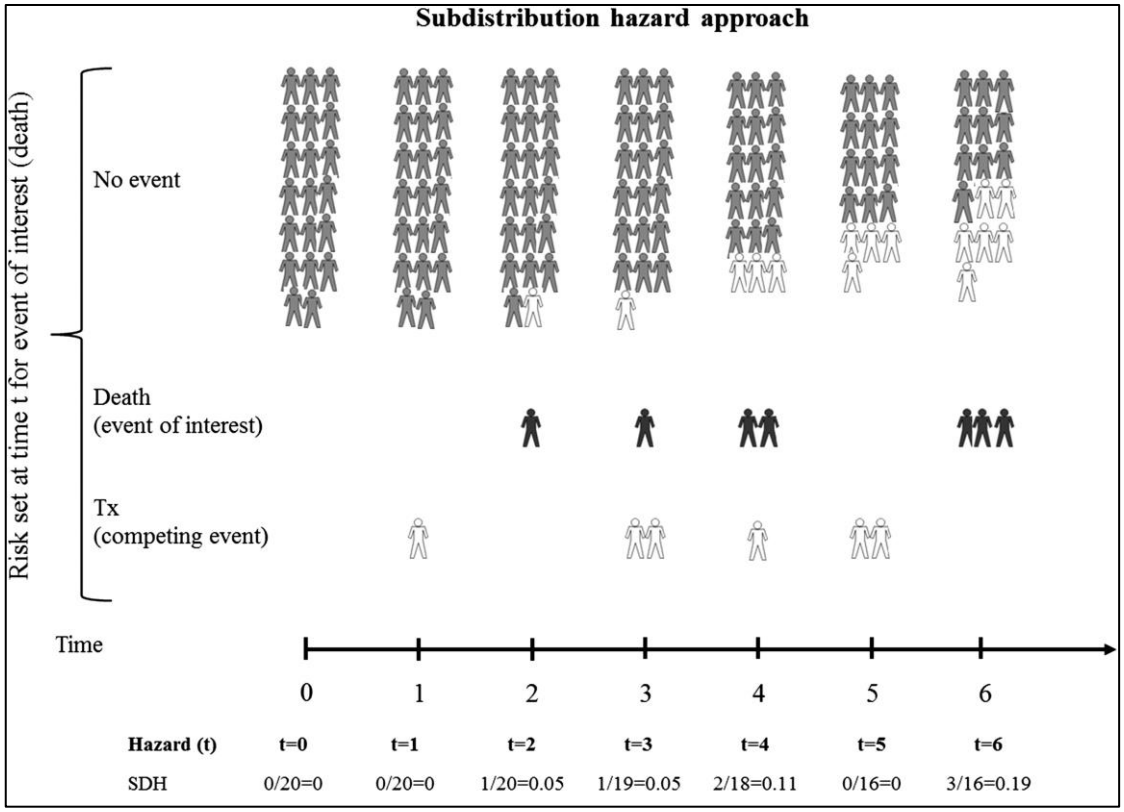
This technique was used when a binary outcome was being studied, but **no time-to-event data were available**. In Chapter 7, logistic regression was used because information on whether patients required kidney replacement therapy was available, but not the date of treatment. For multivariable analysis, at least 10 events should occur for each confounding variable, to ensure model stability.[177] There were sufficient events in my analyses that this did not limit the use of confounding variables.

3.6.1.3 Competing risks models

This technique was used when **the likelihood of an outcome occurring was altered by another "competing" outcome**.[178] In Chapter 5, patients were more likely to die during follow-up than to experience a kidney event. Fine-Gray models can be used to account for such competing events. The individuals who experience

the competing event are “left in” the risk set (Figure 3-3: the individuals in white experience the competing event but remain in the risk set). The alternative to this approach is to use cause-specific hazards models, where a patient who experiences a competing event is censored.

Figure 3-3. Graphical representation of calculating subdistribution hazards (SDH) using a Fine-Gray model.



Tx, kidney transplant. Reproduced with permission[179]

3.6.1.4 Propensity score matching

This technique was used when assessing the relationship between treatments and outcomes.[180] It matches patients in theoretical treatment and non-treatment arms, based on specified variables. In Chapter 7, I compared the risk of AKI in patients with COVID-19 treated with and without dexamethasone and with and without remdesivir. Propensity score matching is an alternative to adjusting for covariates in multivariable models, and in theory it reduces selection bias when estimating **causal relationships**.[181] One of the challenges with this technique is adequately matching treatment groups, and although it attempts to simulate a clinical trial, it is not as

effective as randomisation. This means that **residual confounding** can exist (see section below).

3.6.1.5 Negative binomial models

This technique was used when a **count-based** outcome was being studied. In Chapter 6, hospitalisations were the outcome of interest. Negative binomial models can be used instead of standard Poisson models when data are **overdispersed** i.e. when there is more variability in the data than is expected in a standard model. In a similar way to Poisson models, negative binomial models assume there is a linear relationship between exposures and log event rates.

A possible alternative to negative binomial models is the use of zero-inflated models. These models can be used when there are excessive zeroes i.e. when more patients have zero events than is expected in a standard model. This might happen if patients are **unable** to have an event and so their number of events will always be zero e.g. in some countries, certain populations have poor access to healthcare and so are unlikely to ever be admitted to hospital. It is possible to compare the suitability of standard and zero-inflated models using Vuong tests.[182]

3.6.1.6 Landmark analysis

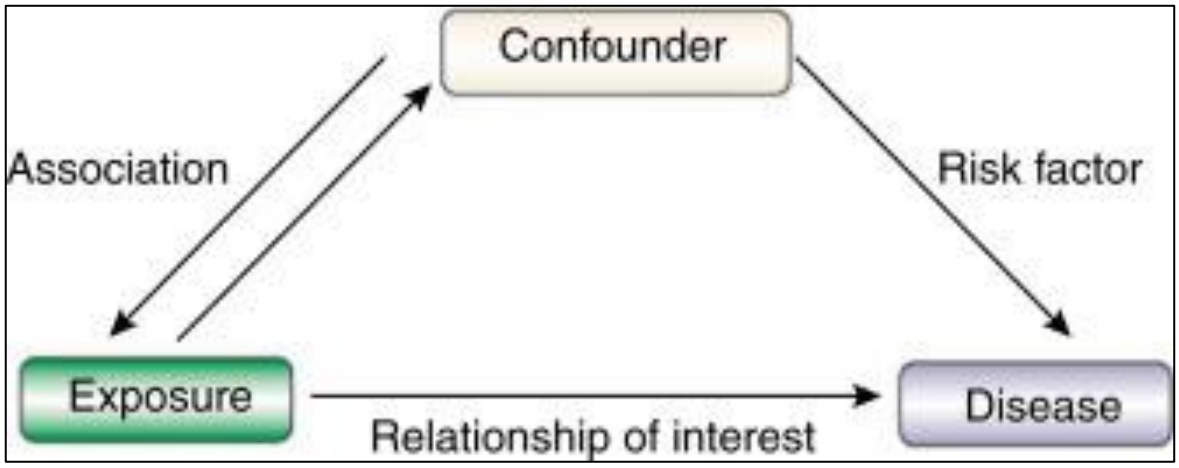
This technique was used when there was the possibility that adverse outcomes could be imminent at the beginning of follow-up. In a landmark analysis, participants who are unstable at the beginning of follow-up are excluded by starting follow-up a pre-specified period of time after study enrollment.[183] In Chapter 5, participants may have been very close to starting dialysis when they were recruited to the study. One limitation of this approach is the need to choose a clinically meaningful time period, which is not always obvious.

3.6.1.7 Confounding variables

When studying risk factors for adverse outcomes, it is key to account for confounding variables. These variables “obscure” the real effect of a risk factor and researchers therefore try to **eliminate** the potential effect of confounding variables. They must first be identified, and then in multivariable models, adjustments can be made.

Confounding variables can be difficult to identify. First, they need to be risk factors for the outcome (Figure 3-4).[184] Second, they should be **associated** with the risk factor being studied, without being a **direct effect** of this risk factor.

Figure 3-4. Flow diagram demonstrating the interaction between exposures, confounding variables, and diseases.



Reproduced with permission[184]

The appropriate use of confounding variables is one of the key challenges when using observational studies. Adjustments can only be made for variables which are available in datasets, which can be limited in routine care databases. There can always be **residual confounding**, when adjustment is incomplete, or when information is not available, so not all confounders can be included.

3.6.2 Missing data

Missing data are a problem in all studies, and they can have an impact on statistical analysis. In research studies with detailed data collection (such as UK Biobank), this tends to be a less significant problem than in routine care databases. For example, in UK Biobank most baseline information is available for most participants (including demographics and laboratory results). When performing multivariable statistical models, all variables must be available for a participant to be included: the exposure of interest, all confounding variables, and the outcome. For UK Biobank, **complete case analysis** is a good option for most analyses i.e. only a small number of participants have missing data and are therefore excluded.

For routine care databases, rates of missingness are often high for many variables: demographics e.g. ethnicity, and laboratory results e.g. uACR. There are three simple ways to handle missing data:

1. Omit the missing variable from the analysis
2. Omit participants with missing data (complete case analysis)
3. Impute the missing data

The advantage of imputing missing data over the other options is that a greater number of participants can be included in the analysis. This is balanced against making possibly flawed assumptions about missing data. Imputation is valid only when the number of participants with missing data is low and when missing values are predictable from the available data. Although there is no rate of missingness which precludes imputation, the process becomes problematic at a rate of greater than 30%.[185]

A common way to impute missing data is using multiple imputation by chained equations.[186] Before doing this, it is important to ensure that data are either missing completely at random (MCAR) or missing at random (MAR) instead of missing not at random (MNAR) i.e. data may be missing related to known characteristics of participants, but the specific values that are missing are random.[185] In practice, the only way to differentiate between MCAR, MAR, and MNAR is to obtain some of the missing data and study it, which is seldom possible.

Multiple imputation was used in Chapter 6 (**for smoking status and deprivation status**) and Chapter 7 (**for ethnicity, deprivation status, chronic conditions, respiratory rate and oxygen saturations**). Assumptions were made about the patterns of missing data, and complete case sensitivity analyses were performed on each occasion.

3.6.3 Clustering analysis

Clustering techniques can identify **patterns** within datasets and describe **phenotypes** of patients. They were used to study combinations of chronic conditions in Chapter 8. The hypothesis was that unknown patterns of multimorbidity exist and

they may change at different levels of kidney function. The research question here (RQ5) was:

> *Amongst patients with chronic kidney disease, what clusters of chronic conditions are associated with the highest risk of adverse outcomes?*

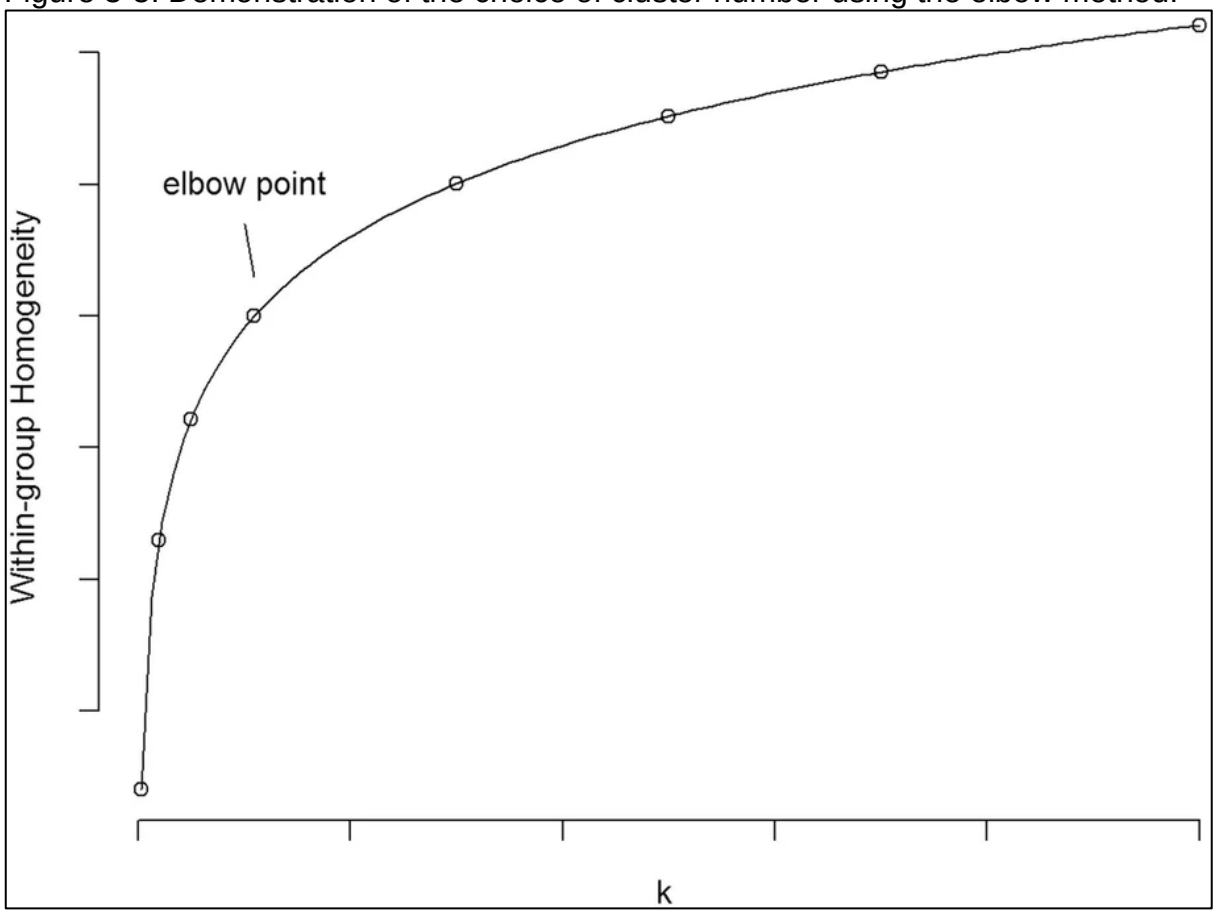
Clustering techniques – or algorithms – are examples of unsupervised machine learning, which means the results come from structures found in baseline variables, rather than tied to an outcome. These techniques organise data into groups, where data points **within** groups are **similar**, and data points in **different** groups are **dissimilar**. Numerous algorithms exist. I considered using the following clustering algorithms:

- **Kmeans**

  This is one of the simplest and most frequently used clustering algorithms, which divides data into a number of clusters (*k*).[187] It is based on the "distance" between data points, most commonly the Euclidean distance. The algorithm assigns *k* centroids to random values, allocating each data point to a centroid and then iterating until the data points cluster around the centroids.

  Because the "distances" are from numeric values, kmeans can only be used with continuous variables. Another limitation of kmeans is that one must choose the number for *k* before running the algorithm. However, it is possible to run the algorithm with various values of *k* and then select the **best** algorithm using "the elbow technique". This technique involves calculating the mean distance between data points and the centroid (within-cluster distance). A line chart is plotted with these values and the optimal *k* should become obvious at the "elbow" i.e. where increasing the number of clusters leads to a marginal decrease in the within-cluster distance (Figure 3-5).

Figure 3-5. Demonstration of the choice of cluster number using the elbow method.



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Despite the option to use the elbow technique, the need to choose *k* is a limitation of k-means.

A study which used k-means to identify multimorbidity clusters used primary care data for people living in England to compare clusters amongst those with and without severe mental illness.[189] The authors found similar clusters in the two groups but noted that patients with severe mental illness had more physical conditions than those without, especially amongst young patients.

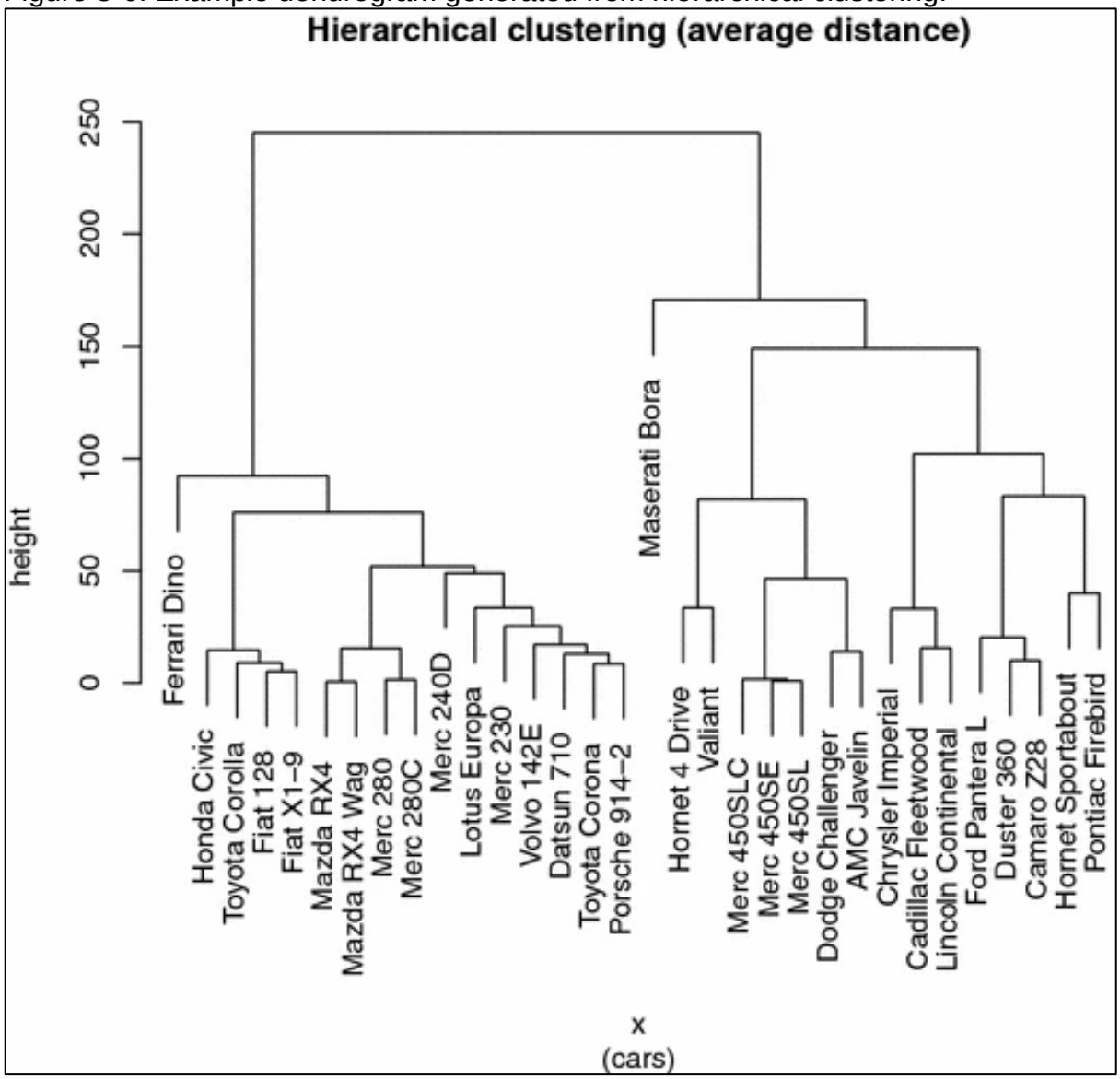
- **Hierarchical clustering**

  This algorithm is also based on the “distance” between data points. It starts by dividing each data point into individual clusters and calculates the “distance” between each cluster. Clusters which are close together by distance are

grouped together to create new clusters. This process is repeated until all data points are grouped together in the same cluster.

A dendrogram is created and the optimal number of clusters can be chosen (Figure 3-6).

Figure 3-6. Example dendrogram generated from hierarchical clustering.



Reproduced with permission[190]

One limitation of hierarchical clustering is that dendrograms created using large datasets are complex and it can be challenging to choose the optimal number of clusters.

A study which used hierarchical clustering to identify multimorbidity clusters studied adults living in inner London.[191] The authors identified five clusters, including one with cardiometabolic conditions and chronic pain.

- **Latent class analysis**

  This technique identifies "latent", or hidden, "classes" within populations.[192] The algorithm analyses the overall pattern of pre-specified variables and assigns each individual a probability of being in each class. It uses **statistical models** to differentiate classes, instead of the distances used in k-means and hierarchical clustering. It can handle both continuous and categorical variables. Using metrics from statistical models to choose the number of classes is a more objective approach than that used for k-means or hierarchical clustering. One of the limitations of latent class analysis is that the algorithm provides a probability of each individual belonging to a class, rather than allocating individuals to specific classes.[193] If the probabilities are low for all classes, some individuals may be poorly allocated.

  A study which used latent class analysis in multimorbidity research studied elderly people admitted to hospital in Denmark.[194] Five patterns of multimorbidity were identified and these were differentially associated with future use of healthcare services.

I considered which clustering technique to use, and discussed this with a statistician with expertise on clustering (Craig Anderson, School of Mathematics, University of Glasgow). We agreed to use k-means for several reasons:

- It has been used extensively by researchers and it is effective.[195]
- It can be used to analyse large datasets.[196]
- It is computationally less intensive than other techniques.[197,198] This was important because numerous chronic conditions were entered into the algorithm and there were many patients.

K-means can be adapted to handle categorical variables with the algorithm **k-modes**,[199] so this was used. Instead of using means – as with k-means – **modes** are used. Instead of measuring **distances** between data points, the algorithm assigns

individuals to clusters based on **matches** between categorical variables. In Chapter 8, I used chronic conditions as the categorical variables i.e. condition absent or present. K-modes therefore identifies clusters of individuals who have **many of the same chronic conditions**.

3.7 Conclusion

A range of methods and approaches were utilised to study the risk of adverse clinical outcomes associated with CKD and multimorbidity. These methods and the datasets chosen have been described in detail in this chapter, with discussions of the potential limitations of each.

In the next five chapters, peer-reviewed publications present the findings from these methods. The next chapter, Chapter 4, is the systematic review and meta-analysis.

Chapter: 4 Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis

4.1 Reference

Sullivan, M. K., Rankin, A. J., Jani, B. D., Mair, F. S., & Mark, P. B. (2020). Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *BMJ Open*, *10*(6), e038401. https://doi.org/10.1136/bmjopen-2020-038401

4.2 Chapter summary

In this chapter, the associations between multimorbidity, chronic kidney disease, and adverse outcomes is explored through a systematic review of the literature.

4.3 Manuscript

Abstract

Objective To systematically review the literature exploring the associations between multimorbidity (the presence of two or more long-term conditions (LTCs)) and adverse clinical outcomes in patients with chronic kidney disease (CKD).

Design Systematic review and meta-analysis.

Data sources MEDLINE, EMBASE, CINAHL, Cochrane Library and SCOPUS (1946–2019). The main search terms were 'Chronic Kidney Failure' and 'Multimorbid*'.

Eligibility criteria Observational studies of adults over the age of 18 with CKD stages 3–5, that is, estimated glomerular filtration rate less than 60 mL/min/1.73 m^2. The exposure was multimorbidity quantified by measures and the outcomes were all-cause mortality, renal progression, hospitalisation and cardiovascular events. We did not consider CKD as a comorbid LTC.

Data extraction and synthesis Newcastle-Ottawa Scale for quality appraisal and risk of bias assessment and fixed effects meta-analysis for data synthesis.

Results Of 1852 papers identified, 26 met the inclusion criteria. 21 papers involved patients with advanced CKD and no studies were from low or middle-income countries. All-cause mortality was an outcome in all studies. Patients with multimorbidity were at higher risk of mortality compared with patients without multimorbidity (total risk ratio 2.28 (95% CI 1.81 to 2.88)). The risk of mortality was higher with increasing multimorbidity (total HR 1.31 (95% CI 1.27 to 1.36)) and both concordant and discordant LTCs were associated with heightened risk. Multimorbidity was associated with renal progression in four studies, hospitalisation in five studies and cardiovascular events in two studies.

Limitations Meta-analysis could only include 10 of 26 papers as the methodologies of studies were heterogeneous.

Conclusions There are associations between multimorbidity and adverse clinical outcomes in patients with CKD. However, most data relate to mortality risk in patients with advanced CKD. There is limited evidence regarding patients with mild to moderate CKD, outcomes such as cardiovascular events, types of LTCs and regarding patients from low or middle-income countries.

PROSPERO registration number CRD42019147424

Strengths and limitations of this study

- This review is the first to synthesise the existing evidence on multimorbidity in patients with chronic kidney disease and it included a range of settings.
- The outcomes of interest were chosen by researchers and these do not include all outcomes that are important to patients, for example, quality of life.
- Two authors independently performed paper selection, data extraction and quality appraisal.
- Meta-analysis was performed, but only included selected papers because of methodological heterogeneity of papers.

Introduction

Multimorbidity is the presence of two or more long-term conditions (LTC).[200] In a Scottish study of 1.8 million patients, it was found to affect 23% of the whole population and in particular those from areas of lower socioeconomic status.[1] It is a problem for individual patients because it is associated with complex treatment regimens that result in a high burden of treatment and reduced quality of life.[201] For clinicians and health services, caring for these individuals represents a huge workload and equates to approximately two-thirds of healthcare spending.[113] The current disease-orientated approaches of guidelines and healthcare are inadequate for patients with multiple LTCs and complex needs.[84]

Multimorbidity is more common in patients with chronic kidney disease (CKD) than any other LTC: for example, among 2.5 million Canadians, patients with CKD had more comorbid LTCs than patients with lung disease (mean 4.2 LTCs vs 2.8).[3] The prevalence of CKD is around 12%[202] and as this rises globally, the adverse effects of CKD and multimorbidity on quality of life are increasing.[203] The leading cause of death in patients with CKD is cardiovascular disease and although this is partly related to risk factors common to both conditions, low estimated glomerular filtration rate (eGFR) and proteinuria are predictors of cardiovascular mortality.[59,61] The higher cardiovascular risk observed among patients with CKD is independent of traditional atherosclerotic risk factors such as hypertension and dyslipidaemia, but the reasons for this and the influence of multimorbidity on CKD are incompletely understood. CKD and multimorbidity therefore occur together frequently and there are a number of issues common to both problems such as polypharmacy and significant treatment burden.[65]

We undertook this systematic review to establish the current evidence concerning associations between multimorbidity and adverse clinical outcomes in patients with CKD.

Materials and methods

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines were followed[145] and this review was registered with the International Prospective Register of Systematic Reviews.

Literature search

A comprehensive search strategy identified studies of patients with CKD that investigated the associations between multimorbidity and adverse clinical outcomes (see supplementary table 4-1 for search terms). We included observational studies; in particular those using electronic healthcare records. There was no restriction on sample size. The databases searched included studies from 1946 to 2019. The search was limited to papers published in English. Databases searched were MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL Complete (EBSCO interface), the Cochrane Library (OVID interface) and SCOPUS. Selected Medical Subject Headings were combined with keywords relating to multimorbidity and CKD to create a search strategy which was produced for use in MEDLINE and amended for use in the other databases, using controlled vocabulary, Boolean operators and search symbols. The search was carried out to include literature published up to 29 August 2019. The results were supplemented with searches of reference lists of included studies. Search data were stored and merged using Endnote X9 (Clarivate Analytics, Philadelphia, USA) and papers were shared and assessed using DistillerSR (Evidence Partners, Ottawa, Canada).

Supplementary Table 4-1. Systematic review database search terms.

Subject headings	Chronic Kidney Failure Kidney Failure Chronic Renal Insufficiency Renal Insufficiency Kidney Disease Kidney Dysfunction Mild renal Impairment Moderate renal Impairment Severe renal Impairment Subclinical renal Impairment Renal replacement therapy Hemodialysis Peritoneal Dialysis Continuous Ambulatory Peritoneal Dialysis Kidney transplantation Kidney graft	Multimorbidity Multiple Chronic Conditions	Humans Adult
Textwords	Chronic kidney or chronic renal CKF, CKD, CRF or CRD Predialysis or pre-dialysis Renal failure or kidney failure Kidney disease Renal insufficienc* Hemodialysis or Haemodialysis Hemodiafiltration or haemodiafiltration Dialysis Endstage renal or endstage kidney Peritoneal dialysis CAPD or APD or CCPD or PD Kidney Transplant	Multimorbid* or multi morbid Condition count Multiple condition or multicondition or multi condition Multiple disease or multidisease or multi disease Multiple disorder or multidisorder or multi disorder Multiple comorbidities or multiple co morbidities Discordant comorbidities or concordant comorbidities	Adult* or aged* or elderly

Inclusion criteria

We included empirical quantitative studies that contained data on associations between multimorbidity measures and all-cause mortality or additional outcomes in adults with CKD. We accepted any multimorbidity measure, which included simple counts of LTCs and comorbidity scoring systems. We did not consider CKD as a comorbid LTC because all of the patients in our papers had CKD. Additional outcomes were hospitalisation, cardiovascular events, cardiovascular deaths, heart failure hospitalisations and renal progression (40% reduction in eGFR, doubling of serum creatinine or initiation of renal replacement therapy (RRT)). Studies that analysed the relationship between a multimorbidity measure and any of our outcomes of interest were included in adults over the age of 18 with CKD stages 3–5, that is, eGFR less than 60 mL/min/1.73 m^2 including those requiring RRT, that is, haemodialysis (HD), peritoneal dialysis (PD) or renal transplantation.

Exclusion criteria

Review articles, drug intervention studies, qualitative studies, case reports and conference abstracts were excluded. Studies with children or adolescents aged 18 or under, animals and individuals without CKD were excluded. The study selection process was conducted by two reviewers (MS, AR). Title screening was followed by abstract and full paper review, where necessary. Any inter-reviewer disagreements were resolved by a third reviewer (PM).

Data extraction

As recommended by the Cochrane Handbook,[146] data were extracted in a Population, Exposure, Comparator, Outcomes approach:

Population: We extracted data on the characteristics of study populations: country, sample size, follow-up time and setting, that is, CKD, HD, PD, renal transplant and conservative care.

Exposure: We extracted the multimorbidity measure used in each study and whether LTCs were categorised into different types for analysis.

Comparator: We extracted the details provided of comparator groups, that is, patients with CKD with less than two LTCs. We did not count CKD as an LTC.

Outcomes: We extracted details of the statistical analyses employed to evaluate the relationship between multimorbidity measure and outcomes. Risks were expressed as effect sizes with 95% confidence intervals (CIs), where available.

Data synthesis and analysis

Results were presented in a narrative format. Where possible, fixed effects meta-analysis was performed for the primary outcome, all-cause mortality. Previous systematic reviews including patients from the general population have demonstrated consistent associations between multimorbidity and mortality.[88] We assumed the direction of effect of multimorbidity on mortality would be consistent across our studies, barring sampling errors and differences in sample size, and so we applied fixed effects models. However, random effects models were also performed as sensitivity analysis, as this approach would be more helpful if the participants in the included studies were inherently different. The generic inverse variance method was used where multimorbidity was expressed as a continuous variable and the Mantel-Haenszel method was used where multimorbidity was expressed as a categorical variable. Quantification of statistical heterogeneity was assessed by means of I^2, which shows the percentage of total variation across studies due to heterogeneity.[146] These analyses were carried out using RevMan V.5.3 (Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis was limited by heterogeneous methodologies: variable multimorbidity measures, use of effect sizes (hazard ratios (HRs), risk ratios (RR), Kaplan-Meier curves) and the use of multimorbidity as a continuous and categorical variable. We therefore performed meta-analysis where several studies used similar methodologies. Data on numbers of deceased patients were not available for all studies and so we contacted study authors for their primary data. For meta-analysis and where necessary and possible, we calculated RRs for studies, comparing patients with multimorbidity to those without multimorbidity. HRs could not be calculated as there were no individual time-to-event data.

Quality appraisal

Two researchers conducted quality appraisal independently (MS, AR). Studies were assessed using an adapted Newcastle-Ottawa Scale (NOS) for quality assessment, as informed by the Cochrane Handbook[146] (see supplementary figure 4-1). Studies were not excluded based on quality appraisal.

Supplementary figure 4-1. Newcastle-Ottawa Quality Assessment Scale.

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort ie chronic kidney disease (CKD) with multimorbidity (MM)
   a) truly representative of the average CKD/MM population in the community *
   b) somewhat representative of the average CKD/MM population in the community *
   c) selected group of users eg only one disease group
   d) no description of the derivation of the cohort

2) Selection of the unexposed cohort ie CKD without MM
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
   d) no control group

3) Ascertainment of CKD/MM status
   a) secure record (eg medical records) *
   b) structured interview *
   c) written self report
   d) no description

4) Demonstration that outcomes were not present at start of study
   a) yes *
   b) no

Comparability

1) Comparability of cohorts on the basis of the design ie are exposed/non-exposed individuals matched or do the authors actively control for confounding factors?
   a) study controls for ischaemic heart disease *
   b) study controls for additional factor(s) *
   Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Outcomes

1) Assessment of outcome(s)
   a) independent blind assessment *
   b) record linkage *
   c) self report
   d) no description

2) Was follow-up long enough ie > 1 year
   a) yes *
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for *
   b) subjects lost to follow up unlikely to introduce bias - small number lost to follow up, or description provided of those lost) *
   c) high lost to follow up rate and no description of those lost
   d) no statement

Total stars /8

Patient and public involvement

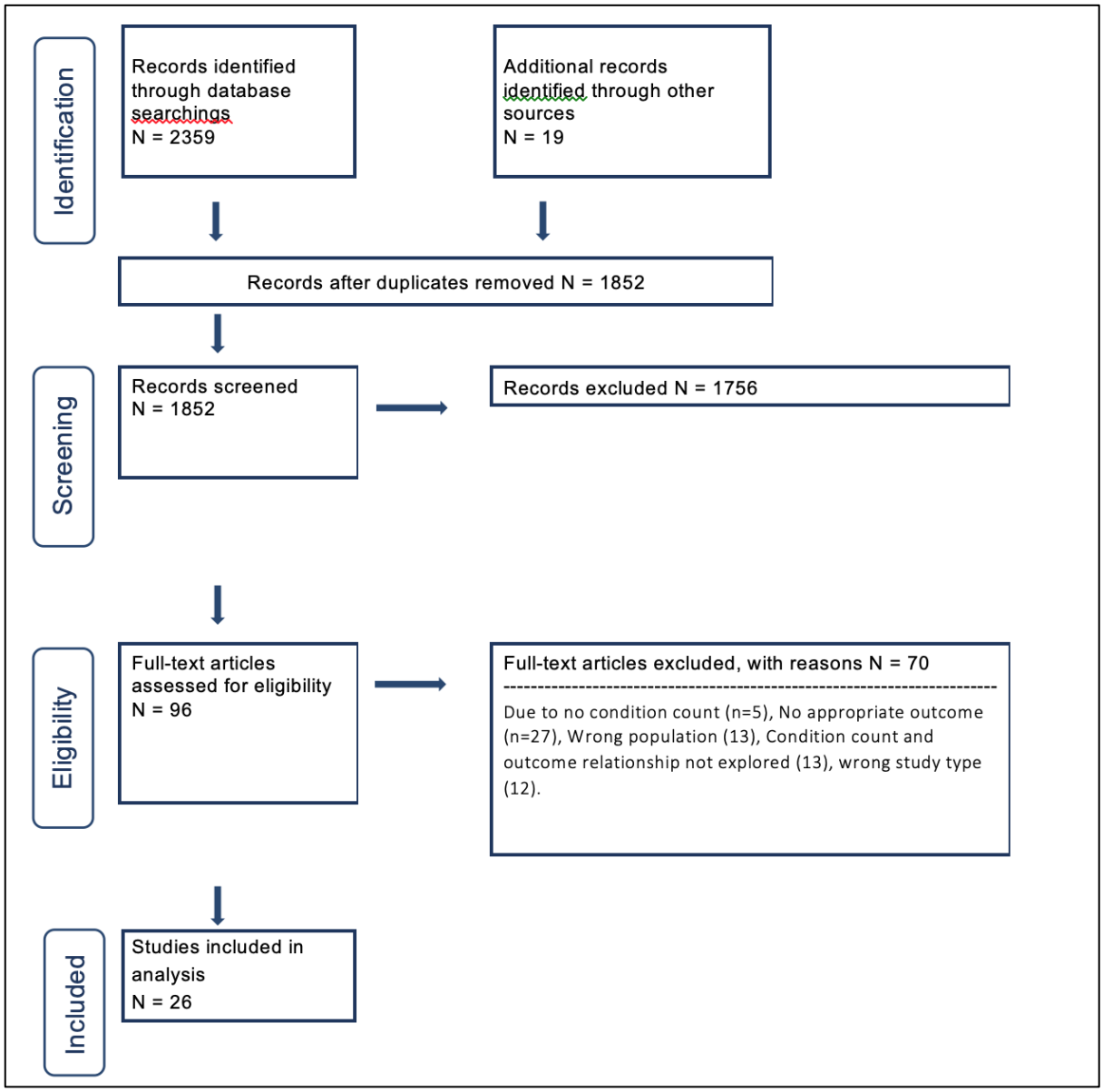
No patients were involved.

Results

Search results

Figure 4-1 demonstrates the literature search flow. After the removal of duplicate papers, 1852 papers were identified. A total of 1756 papers were excluded as they were not relevant and so 96 full papers were screened and 26 papers met our eligibility criteria and were included in the review.[119,120,204–227]

Figure 4-1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.



Study characteristics

Table 4-1 lists the characteristics of the 26 included studies. The studies were published between 1995 and 2019 and all used a cohort design. The size of populations was between 69 and 821 334. Fourteen studies examined the subjects predominantly on dialysis[204,206–211,213,215,218,221,223,227]; five included patients with CKD stages 3–5[119,120,205,222] including two with mild CKD[119,222]; two involved patients with CKD stage 5 including those not on RRT or conservative care[217,219]; two included those receiving conservative care[212,225]; three included renal transplant recipients.[214,220,226]

Table 4-1. Study characteristics.

Reference	Country	Setting	Sample size	Average follow-up (months)	Outcome(s)	
					Mortality	Others
DIALYSIS						
Beddhu 2000	USA	HD/PD	268	13.1	✓	Hospitalisation
Chae 2010	South Korea	HD	456	40.6	✓	
Chandna 1999	UK	HD/PD	292	63	✓	Hospitalisation
Chandna 2010	UK	CC/RRT	844	58.7*	✓	
Davies 1995	UK	PD	97	30	✓	
Davies 2002	UK	PD	303	72.0*	✓	
Di Iorio 2004	Italy	HD	515	15	✓	
Fried 2001	USA	PD	268	16.9	✓	
Hemmelgarn 2003	Canada	HD/PD	237	26.3	✓	
Park 2015	South Korea	HD	24738	47.7	✓	
Rattanasompattikul 2012	USA	HD	893	72	✓	
Shum 2013	China	PD/CC	157	23.5	✓	Hospitalisation
van Manen 2002	Netherlands	HD/PD	589	NK	✓	
Wu 2013	Taiwan	HD/PD	79645	NK	✓	
NON-RRT CKD						
Bowling 2016	USA	CKD 3-5	821334	81.6	✓	
Fraser 2015	UK	CKD 3	1741	43.2	✓	

Lee 2018	Taiwan	CKD 3-5	1463	76.7	✓	Renal progression
Lhotta 2003	Austria	CKD 5	75	48	✓	
Ritchie 2009	USA	CKD/Heart failure	1974	32.6	✓	Hospitalisation, HF hospitalisation, CV death
Tonelli 2015	Canada	CKD 3-5	530771	48	✓	Hospitalisation, Myocardial Infarction
TRANSPLANT						
Fernandez 2019	USA	Tx assessment	2086	NK	✓	
Grosso 2012	Italy	Tx recipients	223	NK	✓	Renal Progression
Pieloch 2015	USA	Tx recipients	100261	36	✓	Renal Progression
Wu 2005	USA	Tx recipients	715	40.2	✓	Renal Progression
CONSERVATIVE CARE						
Ellam 2008	UK	CC	69	21*	✓	
Wong 2007	UK	CC	73	23.4*	✓	

HD, haemodialysis; PD, peritoneal dialysis; CKD, chronic kidney disease; RRT, renal replacement therapy; CC, conservative care; Tx, transplant; NK, Not Known. *Median survival

Table 4-2 shows the number of studies using each multimorbidity measure and how the corresponding effect sizes were presented: as a categorical or a continuous variable. In addition to these, three studies examined more than one multimorbidity measure: comparing how effectively each measure predicted outcomes.[211,215,224] Ten studies used the Charlson Comorbidity Index (CCI) or a modification of this scale (modified CCI).[204,206,213,214,218,219,221,223,226,227] Seven studies used the number of LTCs, that is, condition count.[119,120,205,212,216,217,225] Two studies used the Stoke comorbidity grade, which uses condition count to divide patients into low, intermediate and high grades.[209,210] Two studies used the comorbidity severity score.[207,208] One study compared those with CKD, diabetes and heart failure to those with just CKD and heart failure.[222] One study used the Kidney Transplant Morbidity Index.[220]

Table 4-2. Studies using each Multimorbidity measure.

Variable Type	Multimorbidity Measure: number of studies				
	CCI	Condition Count	CSS	KTMI	Heart failure and CKD versus Heart failure, CKD and diabetes
Categorical	6	4	1	1	1
Continuous	6	4	1	0	0

CCI, Charlson Comorbidity Index; CSS, Comorbidity Severity Score; KTMI, Kidney Transplant Morbidity Index.

All studies reported the effect of multimorbidity on all-cause mortality. Five studies reported the effect of multimorbidity on hospitalisation[120,204,208,222,223] and four on renal progression.[214,216,220,226] One study reported the effect of multimorbidity on heart failure hospitalisation and cardiovascular death[222] and one study reported the effect of multimorbidity on myocardial infarction.[120] Twelve studies expressed effect sizes using multimorbidity as a categorical variable,[119,120,205–207,214,220–222,226,227] nine as a continuous variable[204,208–210,213,217,218,223,225] and one as both.[219] One study gave a narrative comparison of groups[212] and two used Kaplan-Meier curves.[215,224] Two studies categorised LTCs into types: both used concordant and discordant as types and one also specified mental health and chronic pain LTCs.[120,205]

Main findings

Mortality

The results of the included studies are summarised in supplementary table 4-2. Some papers did not provide adjusted HRs. To make it easier to compare the studies, we therefore quoted unadjusted HRs. Where multimorbidity was used as a categorical variable, 12 of 13 studies found that patients with multimorbidity had higher rates of mortality than patients without multimorbidity. In the one study that did not detect a difference, Lee et al's primary outcome was renal progression.[216] For all-cause mortality, the authors provided event rates and Kaplan-Meier curves but there were no HRs with adjustments for confounding variables.

Where multimorbidity was used as a continuous variable, 10 of 11 studies found that with each increase in multimorbidity measure, all-cause mortality was higher. In the one study to not detect a difference, Ellam et al was a study of just 69 conservatively managed patients.[212]

Non-mortality outcomes

Of the four studies that reported renal progression, three were in renal transplant recipients.[214,219,220] All four studies demonstrated higher rates of renal progression in patients with multimorbidity (HRs from each study 2.97 (95% CI 1.53 to 5.76), 2.44 (95% CI 1.19 to 5.02), 3.11 (95% CI 2.55 to 3.80), 1.42 (95% CI 1.02 to 1.97)). Renal progression was defined by graft loss or RRT initiation and one paper reported significant annual reductions in eGFR by increasing number of LTCs.[216] Five studies reported rates of hospitalisation and all of these identified an association between multimorbidity and hospitalisation.[120,204,208,222,223]

One paper reported rates of heart failure hospitalisation and cardiovascular death[222]: patients with multimorbidity had higher rates of both outcomes than patients without multimorbidity. One paper reported higher rates of myocardial infarction in patients with multimorbidity.[120]

Type of conditions

Two papers described the influence of concordant and discordant LTCs on adverse outcomes.[120,205] These papers found that both types of LTC were associated with higher rates of mortality. One paper found that the rates of outcomes were higher in patients with at least one discordant LTC compared with patients with only concordant LTCs.[205] No association was identified between mental health and chronic pain LTCs and myocardial infarction.[112]

Supplementary Table 4-2. Results from mortality analyses of included studies

Reference	Effect size	CCI groups	Effect size (95% Confidence Interval)
CATEGORICAL PRESENTATION OF EFFECT SIZE			
Chae 2010	HRs	**A. Standard CCI variables**	
		Quartile 1 (CCI 2)	Ref
		Quartile 2 (CCI 4-5)	9.22 (3.29-25.84)
		Quartile 3 (CCI 6)	16.77 (5.97-47.11)
		Quartile 4 (CCI 7-11)	22.37 (8.08-61.93)
		B. CCI excluding age and diabetes	
		Tertile 1 (CCI 2)	Ref
		Tertile 2 (CCI 3)	1.39 (1.01-2.05)
		Tertile 3 (CCI 4-8)	1.98 (1.25-3.14)
Wu 2005	HRs	**CCI excluding age**	
		CCI < 5	Ref
		CCI ≥ 5	2.88 (1.90-4.37)
Grosso 2012	HRs	**Modified CCI** 1 point: myocardial infarction, heart failure, peripheral vascular disease, COPD, connective tissue disease or mild liver disease 2 points: diabetes mellitus, cerebrovascular accident, solid tumour or leukaemia	
		CCI ≤ 1	Ref
		CCI > 1	3.87 (1.06-14.06)
Rattanasompattikul 2012	HRs	**CCI excluding age and renal disease**	
		Quartile 1 (CCI 0)	Ref
		Quartile 2 (CCI 1-2)	1.72 (1.26-2.36)
		Quartile 3 (CCI 3)	2.60 (1.13-3.26)
		Quartile 4 (CCI 4-9)	3.40 (2.41-4.79)
Wu 2013	HRs	**CCI excluding age**	
		CCI ≤ 3	Ref
		CCI 4-6	2.49 (2.35-2.63)
		CCI 7-9	3.53 (3.34-3.73)
		CCI 10-12	3.66 (3.45-3.88)
		CCI 13-15	4.12 (3.84-4.42)
		CCI > 15	4.42 (4.02-4.86)

CONTINUOUS PRESENTATION OF EFFECT SIZES			
Beddhu 2000	HRs	**Modified CCI** 1 point: coronary artery disease, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, diabetes 2 points: hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, any tumour, leukaemia, lymphoma 3 points: moderate or severe liver disease 6 points: metastatic solid tumour, AIDS	
		Each increase in CCI	1.24 (1.11-1.39)
Fried 2001	Relative risk	**Standard CCI variables**	
		Each increase in CCI	1.54 (1.36-1.74)
Park 2015	HRs	**A. Standard CCI variables**	
		Each increase in CCI	1.42 (1.39-1.45)
		B. Modified CCI in incident haemodialysis patients Details not provided	
		Each increase in CCI	1.72 (1.66-1.78)
Shum 2013	HRs	**ESRD Modified CCI**	
		Each increase in CCI (PD group only)	1.36 (1.18-1.56)
CONTINUOUS AND CATEGORICAL PRESENTATION OF EFFECT SIZES			
Fernandez 2019	HRs	**ESRD Modified CCI**	
		Each increase in CCI	1.08 (1.03-1.13)
		Low comorbidity burden CCI 0-1	Ref
		High comorbidity burden CCI ≥ 2	1.38 (1.01-1.89)

Results from studies using Charlson Comorbidity Index (CCI) as Multimorbidity Measure. HR; hazard ratio. COPD; Chronic Obstructive Pulmonary Disease. AIDS; Acquired Immune Deficiency Syndrome. PD; peritoneal dialysis.

Reference	Effect size	Conditions and groups	Effect size (95% Confidence Interval)
CATEGORICAL PRESENTATION OF EFFECT SIZE			
Bowling 2016	HRs	22 conditions: hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation, heart failure, peripheral arterial disease, arthritis, osteoporosis, gout, diabetes, hypothyroidism, cancer, prostate cancer, anaemia, cerebrovascular disease, depression, dementia, epilepsy, Parkinson's disease, gastroesophageal reflux disease/peptic ulcer disease, benign prostatic hypertrophy and COPD/asthma	
		1	Ref
		2	0.95 (0.93-0.97)
		3	1.03 (1.01-1.05)
		4	1.24 (1.21-1.26)
		5	1.43 (1.39-1.47)

		≥ 6	1.72 (1.64-1.80)
Fraser 2015	HRs	11 conditions: hypertension, diabetes, ischaemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, chronic respiratory disorder, depression, chronic painful condition, thyroid disorder and anaemia	
		0-1	Ref
		2	2.31 (1.36-3.94)
		≥ 3	4.58 (2.85-7.38)
Lee 2018	10-year survival rates	12 conditions: diabetes, hypertension, gout, heart failure, ischemic heart disease, cerebrovascular disease, liver disease, malignancy, tuberculosis, hyperlipidaemia, anaemia and connective tissue disease	
		0	93.7%
		1	94.3%
		2	92.9%
		≥ 3	92.7%
Tonelli 2015	HRs	29 conditions: alcohol misuse, asthma, atrial fibrillation, lymphoma, non-metastatic cancer, metastatic cancer, heart failure, chronic pain, COPD, chronic hepatitis B, cirrhosis, severe constipation, dementia, depression, diabetes, epilepsy, hypertension, hypothyroidism, inflammatory bowel disease, irritable bowel syndrome, multiple sclerosis, myocardial infarction, Parkinson's disease, peptic ulcer disease, peripheral vascular disease, psoriasis, rheumatoid arthritis, schizophrenia, and stroke or transient ischemic attack	
		0	Ref
		1	1.57 (1.50-1.63)
		2	2.34 (2.24-2.44)
		3	3.43 (3.29-3.58)
		4	4.81 (4.60-5.02)
		≥ 5	7.74 (7.43-8.07)
CONTINUOUS PRESENTATION OF EFFECT SIZES			
Davies 1995	HRs	**Development of the Stoke Comorbidity Grade** 11 conditions: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease, COPD, pulmonary fibrosis, pulmonary tuberculosis, asthma and cirrhosis Low grade: 0 conditions Intermediate grade: 1-2 conditions High grade: ≥ 3 conditions	
		Each increase in grade	2.66 (1.55-4.55)
Davies 2002	Relative risk	**Stoke Comorbidity Grade**	
		Each increase in grade	2.4 (1.4-4.1)
Ellam 2008	Narrative	**Stoke Comorbidity Grade**	"No statistically significant effect on survival"
Wong 2007	HRs	**Stoke Comorbidity Grade**	
		Each increase in grade	2.53 (1.32-4.83)

Lhotta 2003	HRs	Five conditions: diabetes, heart failure, coronary artery disease, cerebrovascular disease and peripheral vascular disease	
		Each increase in comorbidity score	1.78 (1.32-2.40)

Results from studies using Condition Count as Multimorbidity Measure. COPD; chronic obstructive pulmonary disease. HR; hazard ratio.

Reference	Effect size measure	Multimorbidity measure and groups	Effect size (95% Confidence Interval)
Chandna 1999	HRs	**Comorbidity severity score (CSS)** Cardiac score, according to New York Heart Association, respiratory disease score (1-4), cerebrovascular disease score (1-4), peripheral vascular disease score (1-4), cirrhosis (4), and malignancy score (1-4)	
		Each increase in CSS	1.238 (1.145-1.338)
Chandna 2010	HRs	**Comorbidity severity score**	
		Low comorbidity (CSS ≤ 4)	Ref
		High comorbidity (CSS > 4)	1.823 (1.255-2.650)
Pieloch 2015	HRs	**Kidney Transplant Morbidity Index**	
		0	Ref
		1	1.85 (1.45-2.36)
		2	3.11 (2.46-3.94)
		3	5.00 (3.96-6.31)
		4	7.37 (5.83-9.32)
		5	9.41 (7.41-11.94)
		6	12.15 (9.45-15.63)
		≥ 7	13.03 (9.68-17.54)
Ritchie 2009	HRs	**Heart failure, CKD and diabetes**	
		Heart failure and CKD	Ref
		Heart failure, CKD and diabetes	1.25 (1.07-1.46)

Results from studies using other Multimorbidity Measures. HR; hazard ratio. CKD; chronic kidney disease.

Reference	Scores studied	Presentation of effect size
Hemmelgarn 2003	CCI Development of ESRD modified CCI	Kaplan-Meier curves
Di Iorio 2004	CCI Development of CCI modified for haemodialysis patients	Relative risk, 5.5 for CCI
van Manen 2002	CCI Khan index Davies index Development of a new index	Kaplan-Meier curves

Studies that analyse different Multimorbidity Measures. CCI; Charlson Comorbidity Index

Meta-analysis

Data synthesis was problematic because each study reported different effect sizes for different categorical groups. We therefore performed meta-analysis for all-cause mortality where several studies used comparable methodologies. Figure 4-2 included studies that used CCI as a continuous variable, demonstrating that with each increase in CCI, the risk of mortality was higher (total HR 1.31 (95% CI 1.27 to 1.36)). All studies included in this meta-analysis had HRs available.

Figure 4-2. Mortality risk for each increase in Charlson Comorbidity Index (Generic Inverse Variance Method, Fixed Effects Model).

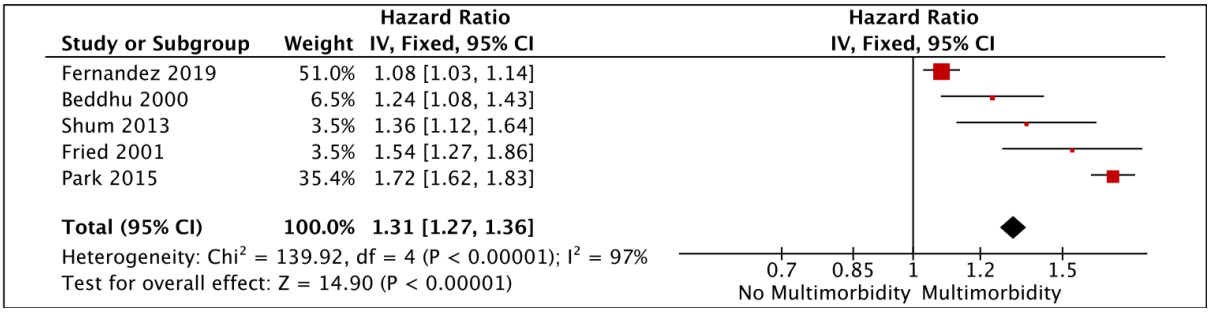
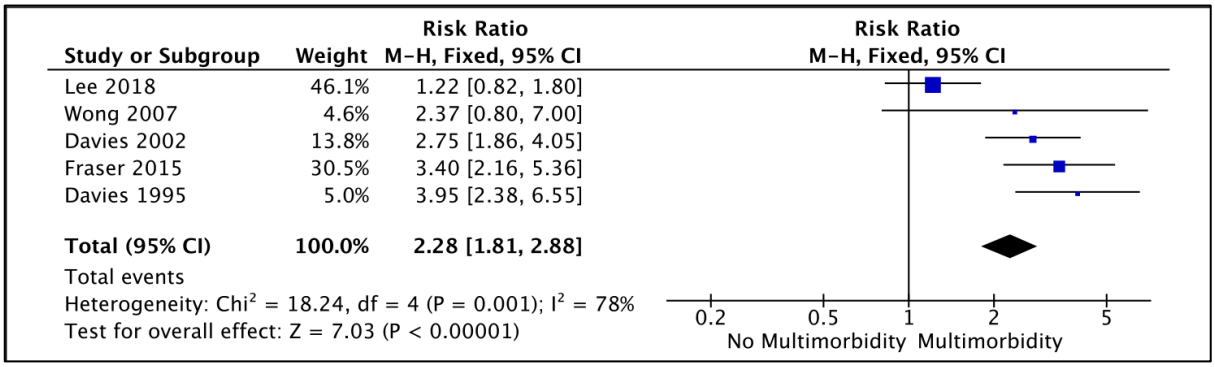


Figure 4-3 included studies that used condition count as a categorical variable: demonstrating that patients with multimorbidity were at higher risk of mortality compared with patients without multimorbidity (total RR 2.28 (95% CI 1.81 to 2.88)). RR was used here because time-to- event data were not available for all these studies and so HRs could not be calculated.

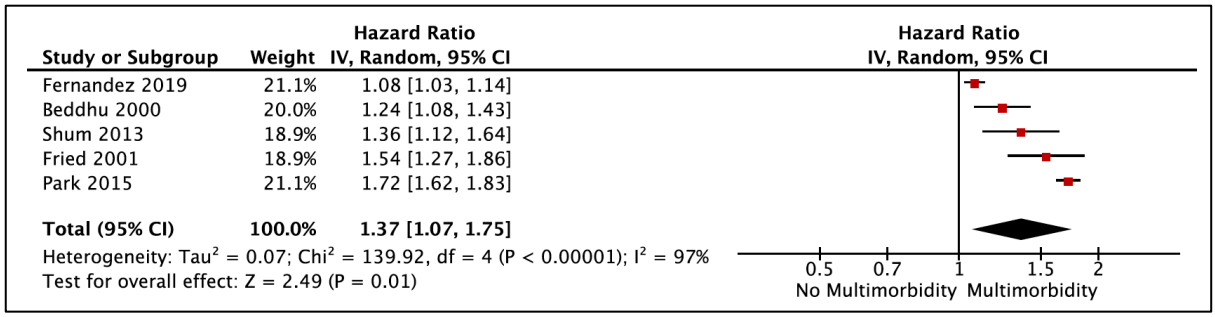
Figure 4-3. Mortality risk for patients with multimorbidity (Mantel-Haenszel Method, Fixed Effects Model).



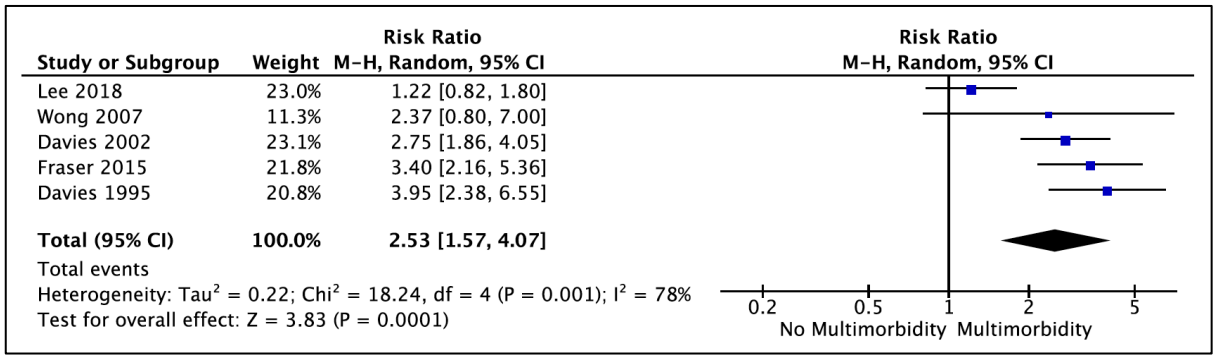
There was considerable statistical heterogeneity in the studies included in each meta-analysis (I^2 97% in figure 4-2 and 78% in figure 4-3). Subgroup analyses were not possible such as for patients with mild to moderate CKD because there were inadequate studies. Where random effects models were fitted, there remained significant associations between multimorbidity and all-cause mortality (supplementary figures 4-2A and 4-2B). For studies that used CCI as a continuous variable, the risk of mortality was higher for each increase in CCI (total HR 1.37 (95% CI 1.07 to 1.75)). For studies that used condition count as a categorical variable, patients with multimorbidity were at higher risk of mortality compared with patients without multimorbidity (total RR 2.53 (95% CI 1.57 to 4.07)).

Supplementary Figures 4-2. Meta-analysis with random effects models

A. Mortality risk for Charlson Comorbidity Index as a continuous variable (Random Effects Model)



B. Mortality risk for patients with multimorbidity (Random Effects Model)



Risk of bias

All studies selected patients with and without multimorbidity from the same cohort and used either secure medical records or structured interviews to collect data. Most studies included just one group of patients with CKD such as patients receiving HD and only three studies included patients with a true range of mild to severe CKD.[120,205,217] All but two studies controlled for factors such as ischaemic heart disease, age or diabetes.[207,212] Only one study made a statement about subjects who were lost to follow-up.[215] However, as all the studies were based on healthcare databases, it is reasonable to assume complete or near-complete follow-up. All studies followed up patients for more than 1 year, but there was variation in the average length of follow-up (from 13.1 to 81.6 months). Four studies did not specify the average follow-up time but from their survival analyses, it was clear that patients were followed up for at least 1 year.[214,219,224,227]

The NOS score evaluation of each study was between five and seven stars (see online supplementary table 4-3). The two studies that did not control for confounding factors were ‘poor’ quality as per the Agency for Healthcare Research and Quality standards.[207,212,228] The remainder were ‘good’ quality.[119,120,204–206,208–211,213–227]

Supplementary table 4-3. Risk of bias: Results from Newcastle Ottawa Scale.

Reference	Selection				Comparability	Outcome assessment			Quality score
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Beddhu 2000		✵	✵	✵	✵	✵	✵		6
Bowling 2016	✵	✵	✵	✵	✵	✵	✵		7
Chae 2010		✵	✵	✵	✵	✵	✵		6
Chandna 1999		✵	✵	✵	✵	✵	✵		6
Chandna 2010		✵	✵	✵		✵	✵		5
Davies 1995		✵	✵	✵	✵	✵	✵		6
Davies 2002		✵	✵	✵	✵	✵	✵		6
Di Iorio 2004		✵	✵	✵	✵	✵	✵		6
Ellam 2008		✵	✵	✵		✵	✵		5
Fernandez 2019		✵	✵	✵	✵	✵	✵		6
Fraser 2015		✵	✵	✵	✵	✵	✵		6
Fried 2001		✵	✵	✵	✵	✵	✵		6
Grosso 2012		✵	✵	✵	✵	✵	✵		6
Hemmelgarn 2003		✵	✵	✵	✵	✵	✵	✵	7
Lee 2018	✵	✵	✵	✵	✵	✵	✵		7
Lhotta 2003		✵	✵	✵	✵	✵	✵		6
Park 2015		✵	✵	✵	✵	✵	✵		6
Pieloch 2015		✵	✵	✵	✵	✵	✵		6
Rattanasompattikul 2012		✵	✵	✵	✵	✵	✵		6
Ritchie 2009		✵	✵	✵	✵	✵	✵		6
Shum 2013		✵	✵	✵	✵	✵	✵		6
Tonelli 2015	✵	✵	✵	✵	✵	✵	✵		7
van Manen 2002		✵	✵	✵	✵	✵	✵		6
Wong 2007		✵	✵	✵	✵	✵	✵		6
Wu 2005		✵	✵	✵	✵	✵	✵		6
Wu 2013		✵	✵	✵	✵	✵	✵		6

1. Representativeness of the exposed cohort. 2. Selection of the non-exposed cohort. 3. Ascertainment of chronic kidney disease/multimorbidity status. 4. Demonstration that outcomes were not present at start of study. 5. Comparability of cohorts on the basis of the design. 6. Assessment of outcome(s). 7. Was follow-up long enough. 8. Adequacy of follow up of cohort.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to synthesise the existing evidence on the associations between multimorbidity and outcomes specific to patients with CKD. It is increasingly recognised that multimorbidity and the management of patients with disease clusters are challenging problems.[229] The medical profession has been given a mandate to improve the care of patients affected by multimorbidity and to do so, improving our understanding of the issues will be fundamental. Multimorbidity has been studied in the general population, with clear associations reported between it and high rates of mortality.[89] It is time for researchers to build a body of evidence about patients with kidney disease. Our review demonstrates that for patients with CKD, multimorbidity is associated with high rates of mortality, and the risk is higher with increasing numbers of LTCs. Unfortunately, the literature provides little detail beyond this association. Of the papers in the review, only two categorised LTCs and studied whether the type of LTCs influenced outcomes. Tonelli et al and Bowling et al found that concordant LTCs such as diabetes were associated with high rates of mortality, but so were discordant or unrelated LTCs like cancer and depression.[120,205] Bowling et al found that the presence of one or more discordant LTCs conferred higher risk compared with patients with only concordant LTCs. This suggests that there are groups of patients in whom it is the number and the type of LTCs that put them at elevated risk. Further research is needed into what patterns or clusters of disease exist to help clinicians understand the risks faced by patients with CKD and multimorbidity.

Patients require clinicians to help with their overall health and quality of life, not just the status of individual LTCs. As seen in the Standardized Outcomes in Nephrology-Hemodialysis initiative, patients usually wish to understand the risks they face. However, there is often a mismatch between the outcomes regarded as important by patients to those emphasised in clinical guidelines.[230,231] It is therefore imperative that we consider patient-oriented outcomes when studying multimorbidity and ensure that research leads to improvements in care for patients. A limitation of our review is that we did not summarise outcomes prioritised by patients. The merit in investigating multimorbidity in patients with CKD will be that patients and clinicians will have an improved understanding of the risks they face. They will therefore be

able to prioritise particular interventions such as cardiovascular risk factor modification and vascular access creation.

Despite the methodological and clinical heterogeneity of the studies in our review, the findings are consistent with existing literature.[65] We have confirmed associations between multimorbidity and adverse clinical outcomes in RRT and non-RRT settings, and in a range of countries. Twenty-one of 26 studies included patients with advanced CKD including those on RRT. However, it should be noted that there was no information available from low or middle-income countries. Mild to moderate CKD was also under-represented, despite this constituting 99% of the patients with CKD.[232] Multimorbidity in patients with CKD from low and middle-income countries and in those with mild to moderate CKD should therefore be targets for future research. Only two studies assessed the influence of multimorbidity on cardiovascular outcomes.[120,222] Cardiovascular morbidity and mortality is the most significant risk for patients with CKD and many of the LTCs that occur in patients with CKD are risk factors for cardiovascular events.[61] Further research is therefore needed to explore how multimorbidity influences cardiovascular events in patients with CKD. Of the four studies that examined the influence of multimorbidity on renal progression, all but one were in patients with renal transplants. The study in non-transplant patients identified an association between multimorbidity and renal progression.[216] This risk is a significant one, particularly for the patients who develop the need for RRT. Many patient cohorts around the world have ample follow-up data and so the influence of multimorbidity on renal progression in non-transplant cohorts should be studied in greater detail.

The studies included in our review are heterogeneous. Clinical heterogeneity is evident in the range of populations studied: stage 3 CKD, HD, PD, transplant and conservative care. There are high levels of methodological and statistical heterogeneity. There is no consensus as to which multimorbidity measure should be used, and which measure is the most effective at predicting adverse outcomes.[80] CCI was the most commonly used measure, although a number of modifications have been made for use in populations with CKD. Three studies included in this review compared different multimorbidity measures. CCI was found to effectively predict mortality risk, with other scoring systems performing comparably and none

superior to the rest. Although our work demonstrates that various multimorbidity measures are associated with adverse clinical outcomes, we have not identified the best multimorbidity measure for risk prediction.

It has been recognised that there are fewer randomised controlled trials (RCTs) to assess the efficacy of interventions in patients with CKD than in other medical specialties and that patients with CKD are often excluded from RCTs.[67,68] Furthermore, patients with advanced CKD that are included in RCTs are not representative of the wider population of those with CKD.[233] Similar observations have been made in other fields, whereby subjects with multimorbidity are under-represented in trials of novel interventions.[8] Therefore, to improve outcomes for patients with CKD, both epidemiological studies and RCTs need to account for the range of multimorbidity in patients with CKD. A strength of our review is that it brings together information about the effects of multimorbidity in patients with CKD from various settings to create a comprehensive picture of the effects on different outcomes. Although the studies are challenging to summarise given the heterogeneity, the data are ample and clinically acceptable and therefore likely to be correct. Meta-analysis was performed with data from only 10 studies. The data from 16 studies, including those with large sample sizes, therefore did not contribute to full data analysis. If a uniform multimorbidity measure were agreed and established in guidelines, the comparability and synthesis of data in future would be improved. The evaluation of the effects of types of LTCs on outcomes was limited because only two studies examined this issue. A key focus of future research should therefore be what patterns of multimorbidity or disease clusters exist in groups of patients with CKD.

In conclusion, this review provides evidence of associations between multimorbidity and heightened risk of adverse clinical outcomes in patients with CKD. Our findings emphasise the need for further research into the details of how multimorbidity influences different outcomes. In particular, evidence gaps exist for patients with mild to moderate CKD, for outcomes other than mortality such as renal progression and cardiovascular events, for patients with CKD from low and middle-income countries and for the patterns of multimorbidity that contribute to heightened risk.

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Chapter: 5 Multimorbidity and the risk of major adverse kidney events: findings from the UK Biobank cohort

5.1 Reference

Sullivan, M. K., Jani, B. D., Lees, J. S., Welsh, C. E., McConnachie, A., Stanley, B., Welsh, P., Nicholl, B. I., Lyall, D. M., Carrero, J.-J., Nitsch, D., Sattar, N., Mair, F. S., & Mark, P. B. (2021). Multimorbidity and the risk of major adverse kidney events: findings from the UK Biobank cohort. *Clinical Kidney Journal*, *14*(11), 2409–2419. https://doi.org/10.1093/CKJ/SFAB079

5.2 Chapter summary

In this chapter, the relationship between multimorbidity and kidney events is studied using the UK Biobank cohort.

5.3 Manuscript

Abstract

Background. Multimorbidity (the presence of two or more long-term conditions) is associated with a heightened risk of mortality, but little is known about its relationship with the risk of kidney events.

Methods. Associations between multimorbidity and major adverse kidney events (MAKE: the need for long-term kidney replacement therapy, doubling of serum creatinine, fall of estimated glomerular filtration rate (eGFR) to <15 ml/min/1.73m^2 or 30% decline in eGFR) were studied in 68,505 participants from the UK Biobank cohort. Participants were enrolled in the study between 2006 and 2010. Associations between long-term condition counts and MAKE were tested using survival analyses accounting for the competing risk of death.

Results. Over a median follow-up period of 12.0 years, 2,963 participants (4.3%) had MAKE. There were associations between long-term condition count categories and the risk of MAKE (one long-term condition adjusted subhazard ratio (sHR) 1.29 (95% Confidence Interval 1.15-1.45), 2 long-term conditions sHR 1.74 (1.55-1.96), three or more long-term conditions sHR 2.41 (2.14-2.71)). This finding was more pronounced when only cardiometabolic long-term conditions were considered (one long-term condition sHR 1.58 (1.45-1.73), two long-term conditions sHR 3.17 (2.80-3.59), three or more long-term conditions sHR 5.24 (4.34-6.33)). Combinations of long-term conditions associated with MAKE were identified. Diabetes, hypertension and coronary heart disease featured most commonly in high-risk combinations.

Conclusions. Multimorbidity, and in particular cardiometabolic multimorbidity, is a risk factor for MAKE. Future research should study groups of patients who are at high risk of progressive kidney disease based on the number and type of long-term conditions.

Key Learning Points

What is already known about this subject?

- Patients with chronic kidney disease are at risk of kidney events (deterioration of kidney function and/or the need for kidney replacement therapy).
- Multimorbidity is associated with an increased risk of adverse events such as mortality.

What this study adds?

- Multimorbidity is a risk factor for kidney events, whether or not chronic kidney disease is present at baseline.
- Cardiometabolic multimorbidity and certain combinations of long-term conditions are important risk factors for the development of kidney events.

What impact this may have on practice or policy?

- Clinical guidelines should highlight the importance of monitoring kidney function for at-risk patients with multimorbidity, even in the absence of chronic kidney disease.

Keywords. Multimorbidity, Comorbidity, Kidney outcomes, Cardiometabolic, Mortality, Condition clusters

Introduction

Multimorbidity (the presence of two or more long-term conditions (LTCs)) is a mounting problem worldwide [69,234]. It is associated with polypharmacy[235], increased treatment burden[84] and patients often experience poor quality of life[236]. Patients with multimorbidity are at increased risk of mortality[88,89] and there is growing recognition that patterns of multimorbidity, or the types of LTCs, are linked to adverse outcomes[89]. Although studies have investigated the associations between multimorbidity and mortality, less is known about how the presence of multimorbidity relates to major adverse kidney events (MAKE).

With reductions in estimated glomerular filtration rate (eGFR), the risks of death, cardiovascular events and hospitalisation rise[237,59]. Tools such as the Kidney Failure Risk Equation can help predict which patients are at highest risk of needing kidney replacement therapy (KRT)[238]. However, the risk of kidney failure is likely to be more complex than that simply defined by biochemical serum and urinary measurements[65]. Many LTCs and their treatments cause reductions in eGFR, while others develop as complications of chronic kidney disease (CKD)[239]. Reduced eGFR limits which tests and treatments can be used for comorbid LTCs such as the use of contrast studies for coronary angiography, and there are often conflicts between disease-specific guidelines.

Cardiometabolic LTCs (hypertension, coronary heart disease, peripheral vascular disease, atrial fibrillation, diabetes, heart failure and stroke) are particularly associated with adverse outcomes[240]. Patients with two or more cardiometabolic LTCs (cardiometabolic multimorbidity) are at high risk of death[89,102]. Diabetes and hypertension are the two leading causes of and/or risk factors for MAKE in industrialised nations[239,241,242]. However, the impact of the *cumulative* influence of cardiometabolic multimorbidity, rather than *individual* cardiometabolic conditions, on MAKE is not well described.

UK Biobank is a large, prospective, community-based cohort of participants with extensive phenotyping and biochemical testing. We hypothesised that in a large population study we would observe an association between LTC counts and the future risk of MAKE. We further hypothesised that there may be specific combinations of LTCs that are associated with higher risk of developing MAKE.

Materials and Methods

Study Design

UK Biobank recruited 502,503 participants aged 37 to 73 between 2006 and 2010. Biological data and detailed sociodemographic, lifestyle and medical information were collected at 22 assessment centres. Ethical approval was provided by the NHS National Research Ethics Service (16/NW/0274) and all participants provided written, informed consent for data use and linkage of General Practice (GP), hospital episode and national mortality records. This study is part of UK Biobank project 14151.

Assessments

Blood and urine samples were collected at baseline: serum creatinine, total cholesterol and urine albumin to creatinine ratio (uACR) were measured at a centralised laboratory. The biochemistry sampling, handling and quality control protocol has been detailed previously[152]. Serum creatinine was measured using an enzymatic, IDMS-traceable method on a Beckman Coulter AU5400 instrument[243] and the CKD–EPI formula was used to calculate eGFR[244].

Participants self-reported their health conditions, medications and health-related behaviours at baseline. Forty three LTCs were considered, as described in previous literature on multimorbidity in UK Biobank (see list of LTCs, Supplementary Table 5-1)[89]. All LTCs were taken from self-report, other than CKD (stages 3-5), which was defined by eGFR of less than 60 ml per min. per 1.73 m^2 at baseline. A single blood test was used because all participants were not acutely unwell at the time of sampling. LTC counts were categorised into zero LTCs, one LTC, two LTCs and three or more LTCs. The category “Three or more LTCs” was chosen as the maximum category because the proportion of participants with more than four LTCs was small. Cardiometabolic LTCs were categorised in the same way.

Supplementary Table 5-1. List of long-term conditions (LTCs) considered.

Cardiometabolic LTCs	**Non-Cardiometabolic LTCs**
Hypertension	Depression
Coronary Heart Disease	Painful conditions
Diabetes Mellitus	Asthma
Stroke or transient ischaemic attack	Treated Dyspepsia
Atrial Fibrillation	Thyroid Disorders
Peripheral Vascular Disease	Connective tissue disorders
Heart Failure	Hearing loss
	Chronic Obstructive Pulmonary Disease
	Anxiety & other neurotic, stress related & somatoform disorders
	Irritable Bowel Syndrome
	Cancer
	Alcohol Problems
	Psychoactive substance misuse
	Treated Constipation
	Chronic Kidney Disease (eGFR < 60ml/min/1.73m^2 at baseline assessment)
	Diverticular Disease
	Prostate Disorders
	Glaucoma
	Treated Epilepsy
	Dementia
	Schizophrenia or Bipolar Disorder
	Psoriasis or Eczema
	Inflammatory Bowel Disease
	Migraine
	Chronic Sinusitis
	Anorexia Nervosa or Bulimia
	Parkinson's Disease
	Multiple Sclerosis
	Viral Hepatitis
	Chronic Liver Disease
	Polycystic Ovarian Syndrome
	Pernicious Anaemia
	Meniere's Disease
	Endometriosis
	Chronic Fatigue Syndrome
	Osteoporosis

Smoking status was divided into three categories: never, current or previous. Body mass index (BMI) was ascertained at initial assessment and used as a continuous variable. Ethnicity was coded as White, Asian, Black, Chinese, mixed or other (including Latin American). Townsend score was used to classify socioeconomic status and used as a continuous variable (a higher score suggests higher levels of deprivation)[245]. The frequency of alcohol consumption was categorised as: never, special occasions only, one to three times a month, one to four times a week and daily or almost daily. Physical activity was categorised as none (no physical activity in the last four weeks), low (light 'do it yourself' activity only in the last four weeks), medium (heavy 'do it yourself' and/or walking and/or other exercises for pleasure in the last four weeks) and high (vigorous sports in the last four weeks)[246].

Follow up kidney function

Serum creatinine values were taken from UK Biobank follow-up testing and linked GP records. We assumed that all UK laboratories report IDMS-traceable creatinine. For individuals with more than one creatinine value, the value corresponding to the latest testing date was used. Creatinine values were identified from GP read codes (Appendix Table 1)[247]. Values were excluded if the participant had an emergency admission to hospital within five days of sampling, as the results would be more likely to be during a period of acute kidney injury (admissions identified from GP read codes: Appendix Table 1)[248].

Inclusion Criteria

We included participants with creatinine values at baseline and at follow-up. We included participants with an eGFR of >15 ml per min per 1.73 m^2 and not receiving KRT at baseline. KRT was defined using hospital admission codes, according to a pre-specified algorithm[158].

Study Outcomes

The primary outcome was MAKE[249]: the first of the following endpoints to occur: the need to receive long-term KRT, doubling of serum creatinine, fall of eGFR to <15 ml per min per 1.73 m^2 or 30% decline in eGFR from baseline. This

definition is based on previous work from the Chronic Kidney Disease Prognosis Consortium (CKD-PC)[250,251]. All-cause mortality before MAKE was considered as a competing risk (an event which prevents the primary outcome from occurring)[179, 252]. We excluded participants who died or who had MAKE in the first 12 months of follow-up. This landmark analysis sought to exclude participants whose condition was deteriorating rapidly at recruitment[183]. The follow-up period started 12 months after the date of first assessment and ended with the date of death, date of MAKE, or end of data collection (26/04/2020), whichever occurred first.

Statistical Analysis

Demographic, physiological, prescribing and laboratory characteristics were described across LTC count categories, using medians and interquartile ranges for continuous variables and percentages for categorical variables. Differences in the distribution of these characteristics were tested using analysis of variance for continuous variables and chi-squared tests for categorical variables. The characteristics of participants who had MAKE were compared to those who did not. The characteristics of participants were compared based on the availability of follow-up data: those with and without creatinine results, those with and without linked GP data, those with linked GP data with and without creatinine results and those with and without creatinine results via UK Biobank.

Cumulative event incidence plots and Fine and Gray subdistribution hazard models were used to examine the relationship between LTC count categories and outcomes, with all-cause mortality the competing event[179, 252]. A competing risks approach was chosen over a Cox model as the preferred approach for prognostication of kidney function in the presence of a competing event such as the risk of death before MAKE[179,253]. Participants with zero LTCs were used as the reference group. Subdistribution hazard models generated subhazard ratios, with adjustments for confounding variables and 95% confidence intervals. Confounding variables in the standard model were age, sex, baseline eGFR, uACR, ethnicity, total cholesterol, BMI, smoking status and physical activity levels. These variables were chosen because there are associations with MAKE[239]. The proportional hazards assumption was tested using

Schoenfeld residuals. Complete cases were used, which was acceptable because the proportion of participants with missing data was less than 5%. Analyses were repeated using cardiometabolic LTC counts. Additional analyses were performed adding adjustments for blood pressure and alcohol use. Blood pressure and alcohol use were not included in the standard model because hypertension and alcohol problems were included as self-reported LTCs. Adjustments were not made for the use of medications such as Renin–angiotensin–aldosterone system blockers because of the risks of indication bias. A sensitivity analysis was performed using event plots and proportional hazard Cox models with participants censored at their date of death. These analyses were performed for total LTC counts and for cardiometabolic LTC counts with adjustments as in the standard model above.

Combinations of LTCs were identified and the associations between different LTC combinations and MAKE were studied. Competing risks models were used to identify which individual LTCs were associated with MAKE and these were used to identify all possible combinations of LTCs. To reduce the risk of multiple comparisons, we restricted our analysis to individual conditions and combinations of conditions present in more than 0.1% of the cohort (i.e. >68 subjects). This technique was performed for the LTC count categories two LTCs and three or more LTCs. All models were adjusted as in the standard model above. Participants with zero LTCs were used as the reference group. We reported event numbers and subhazard ratios with 95% confidence intervals for individual LTCs and LTC combinations associated with MAKE.

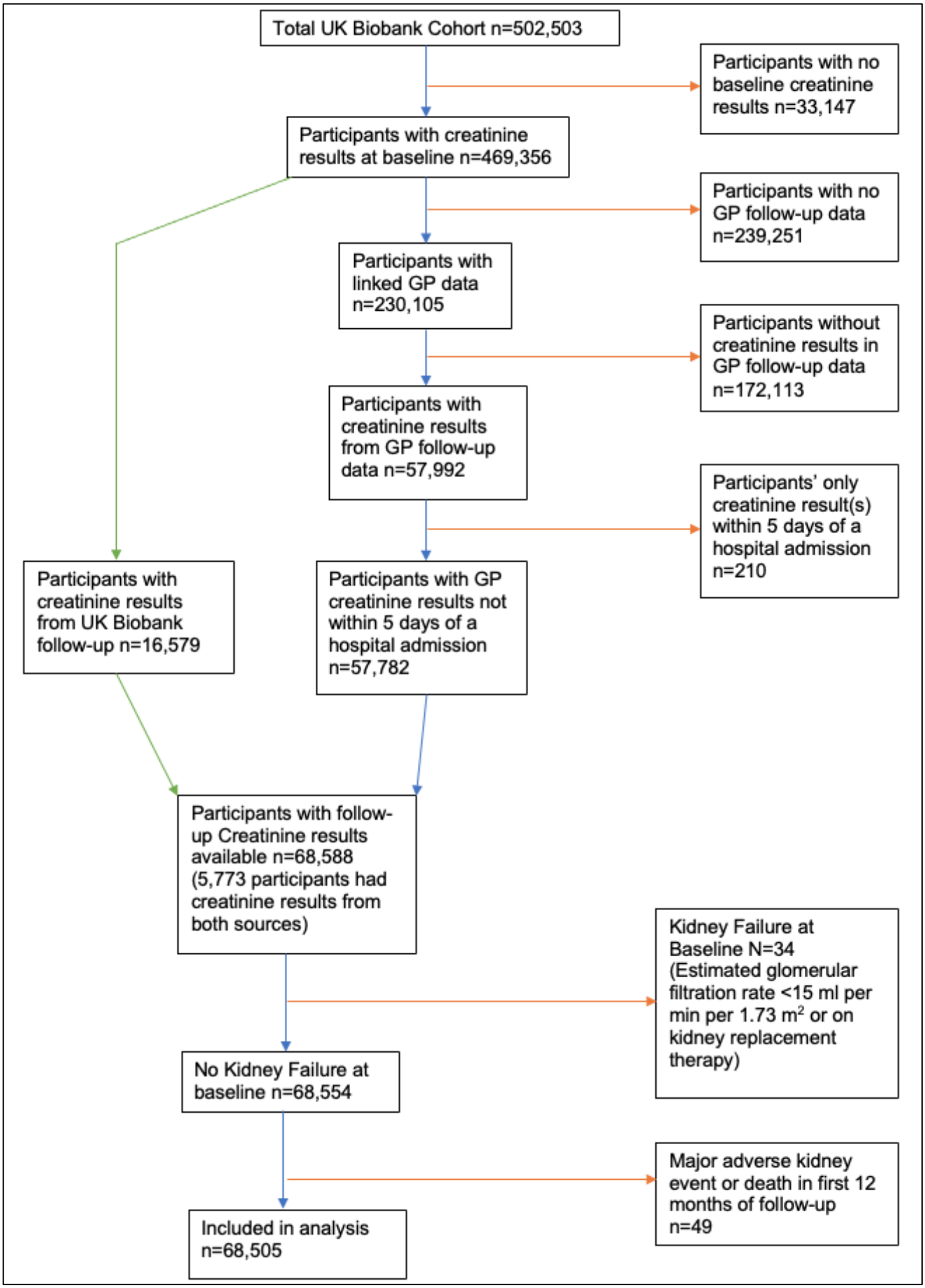
All analysis was conducted using R software version 3.6.0.

Results

Participant Inclusion

68,505 participants met the inclusion criteria (see participant flow chart, Supplementary Figure 5-1). From the original UK Biobank cohort, 469,356 of 502,503 participants had a creatinine result at baseline. Of the 230,105 participants with linked GP data, 57,992 had one or more creatinine result during the follow-up period. 16,579 participants had follow-up creatinine values recorded through UK Biobank. A total of 580,387 follow-up creatinine measurements were available. 34 participants were excluded because their eGFR was <15 ml per min per 1.73m^2 or they were on KRT at baseline. 49 participants were excluded because they died or had MAKE in the first twelve months of follow-up.

Supplementary Figure 5-1. Participant inclusion flow.



Baseline Characteristics

Table 5-1 demonstrates the baseline characteristics of the included participants by LTC count categories. Compared to participants with zero LTCs, those with more LTCs tended to be older, female, of white ethnicity, residing in areas of greater socioeconomic deprivation, smokers, with less alcohol consumption, lower physical activity levels, higher BMI, higher systolic blood pressure, higher uACR, lower total cholesterol, lower eGFR and more were prescribed antihypertensives and statins.

Table 5-1. Baseline characteristics by long-term condition count category.

Baseline Characteristics		**0 LTCs** N=22348 (32.6%)	**1 LTC** N=22594 (33.0%)	**2 LTCs** N=13395 (19.6%)	**3 or more LTCs** N=10168 (14.8%)	**Total** N=68505
Age	Median (IQR)	55.0 (48.0 to 61.0)	58.0 (51.0 to 63.0)	60.0 (54.0 to 64.0)	61.0 (56.0 to 65.0)	58.0 (51.0 to 63.0)
Sex	Female	11783 (52.7)	12072 (53.4)	7170 (53.5)	5810 (57.1)	36835 (53.8)
	Male	10565 (47.3)	10522 (46.6)	6225 (46.5)	4358 (42.9)	31670 (46.2)
Ethnicity (%) Missing values n= 217 (0.3%)	White	21450 (96.0)	21860 (96.8)	13010 (97.1)	9858 (97.0)	66178 (96.6)
	Asian	293 (1.3)	242 (1.1)	132 (1.0)	110 (1.1)	777 (1.1)
	Black	162 (0.7)	155 (0.7)	71 (0.5)	53 (0.5)	441 (0.6)
	Mixed	130 (0.6)	101 (0.4)	59 (0.4)	48 (0.5)	338 (0.5)
	Chinese	97 (0.4)	56 (0.2)	29 (0.2)	9 (0.1)	191 (0.3)
	Other	143 (0.6)	105 (0.5)	63 (0.5)	52 (0.5)	363 (0.5)
Socioeconomic status based on Townsend Score Missing values n= 89 (0.1%)	Median (IQR)	-2.5 (-3.8 to -0.2)	-2.4 (-3.8 to 0.0)	-2.2 (-3.7 to 0.4)	-1.7 (-3.4 to 1.5)	-2.3 (-3.7 to 0.2)
Frequency of alcohol consumption (%) Missing values n= 96 (0.1%)	Never	1246 (5.6)	1510 (6.7)	1136 (8.5)	1360 (13.4)	5252 (7.7)
	Special occasions only	1921 (8.6)	2436 (10.8)	1648 (12.3)	1714 (16.9)	7719 (11.3)
	One to three times a month	2388 (10.7)	2508 (11.1)	1537 (11.5)	1234 (12.1)	7667 (11.2)
	Once or twice a week	6336 (28.4)	5899 (26.1)	3406 (25.4)	2390 (23.5)	18031 (26.3)
	Three or four times a week	5912 (26.5)	5531 (24.5)	2947 (22.0)	1750 (17.2)	16140 (23.6)
	Daily or almost daily	4515 (20.2)	4679 (20.7)	2706 (20.2)	1700 (16.7)	13600 (19.9)
Physical Activity (%) Missing values n= 337 (0.5%)	None	1072 (4.8)	1325 (5.9)	1069 (8.0)	1374 (13.5)	4840 (7.1)
	Low	608 (2.7)	758 (3.4)	587 (4.4)	628 (6.2)	2581 (3.8)
	Medium	17314 (77.5)	18202 (80.6)	10782 (80.5)	7667 (75.4)	53965 (78.8)
	High	3292 (14.7)	2255 (10.0)	879 (6.6)	356 (3.5)	6782 (9.9)
Smoking status	Never	13484 (60.3)	12656 (56.0)	6996 (52.2)	4713 (46.4)	37849 (55.2)

Missing values n= 258 (0.4%)	Current	2180 (9.8)	2271 (10.1)	1338 (10.0)	1219 (12.0)	7008 (10.2)
	Previous	6617 (29.6)	7582 (33.6)	5008 (37.4)	4181 (41.1)	23388 (34.1)
Body Mass Index (kg/m^2) Missing values n= 217 (0.3%)	Median (IQR)	25.8 (23.5 to 28.6)	26.7 (24.2 to 29.7)	27.6 (24.9 to 31.0)	28.9 (25.8 to 32.7)	26.9 (24.3 to 30.1)
Systolic Blood Pressure (mmHg); Missing values n=3408 (5.0%)	Median (IQR)	134.0 (123.0 to 146.0)	138.0 (126.0 to 152.0)	140.0 (129.0 to 153.0)	141.0 (129.0 to 153.0)	138.0 (126.0 to 151.0)
Chronic Kidney Disease (eGFR <60ml/min/1.73m^2; %)		0 (0.0)	225 (1.0)	363 (2.7)	893 (8.8)	1481 (2.2)
Diabetes Mellitus (%)		0 (0.0)	457 (2.0)	1097 (8.2)	1870 (18.4)	3424 (5.0)
Hypertension (%)		0 (0.0)	6409 (28.4)	6484 (48.4)	6572 (64.6)	19465 (28.4)
Baseline eGFR (ml per min. per 1.73 m^2)	Median (IQR)	94.6 (86.1 to 101.5)	93.0 (83.6 to 99.8)	91.8 (81.7 to 98.5)	90.1 (77.4 to 97.5)	92.9 (83.2 to 99.8)
Urine ACR (mg mmol^{-1}) Missing values n=1612 (2.4%)	Median (IQR)	0.0 (0.0 to 0.4)	0.0 (0.0 to 0.6)	0.0 (0.0 to 0.7)	0.0 (0.0 to 0.9)	0.0 (0.0 to 0.6)
Total Cholesterol (mmol l^{-1}) Missing values n= 15 (0.02%)	Median (IQR)	5.8 (5.1 to 6.5)	5.7 (5.0 to 6.5)	5.5 (4.7 to 6.4)	5.3 (4.4 to 6.2)	5.6 (4.9 to 6.4)
Prescribed antihypertensives (%)		221 (1.0)	5072 (22.4)	5409 (40.4)	5818 (57.2)	16520 (24.1)
Prescribed statins (%)		1012 (4.5)	3315 (14.7)	3540 (26.4)	4110 (40.4)	11977 (17.5)

LTC, long-term condition. eGFR, estimated glomerular filtration rate. ACR, albumin-creatinine ratio. IQR, interquartile range. P-values <.001 for all variables (Kruskal-Wallis test for continuous variables and chi-squared tests for categorical variables).

The participants with and without linked GP data and those with and without follow-up data from UK Biobank and GP records were similar (Supplementary Tables 5-2 to 5-5). In those with and without follow-up data, participants had similar numbers of LTCs and the prevalence of diabetes was similar. Participants of Black and Asian ethnicities were under-represented and those with hypertension were over-represented.

Supplementary Table 5-2. Baseline characteristics by availability of follow-up data.

Baseline Characteristics		**No follow-up renal data** N= 433705 (86.4%)	**Included participants** N=68505 (13.6%)	**p-value**
Age	Median (IQR)	58.0 (50.0 to 63.0)	58.0 (51.0 to 63.0)	<.001
Sex (%)	Female	236548 (54.5)	36835 (53.8)	<.001
	Male	197450 (45.5)	31670 (46.2)	
Ethnicity (%) Missing = 2,776 (0.6%)	White	406516 (93.7)	66178 (96.6)	<.001
	Asian	9105 (2.1)	777 (1.1)	
	Black	7620 (1.8)	441 (0.6)	
	Chinese	1383 (0.3)	191 (0.3)	
	Mixed	2620 (0.6)	338 (0.5)	
	Other	4195 (1.0)	363 (0.5)	
Socioeconomic status based on Townsend Score Missing = 623 (0.1%)	Median (IQR)	-2.1 (-3.6 to 0.6)	-2.3 (-3.7 to 0.2)	<.001
Frequency of alcohol consumption (%) Missing = 1501 (0.3%)	Never	35389 (8.2)	5252 (7.7)	<.001
	Special occasions only	50290 (11.6)	7719 (11.3)	
	One to three times a month	48188 (11.1)	7667 (11.2)	
	Once or twice a week	111260 (25.6)	18031 (26.3)	
	Three or four times a week	99299 (22.9)	16140 (23.6)	
	Daily or almost daily	88167 (20.3)	13600 (19.9)	
Physical Activity (%) Missing = 7150 (1.4%)	None	28008 (6.5)	4840 (7.1)	<.001
	Low	16357 (3.8)	2581 (3.8)	
	Medium	339534 (78.2)	53965 (78.8)	
	High	43286 (10.0)	6782 (9.9)	
Smoking status (%) Missing = 2948 (0.6%)	Never	235667 (54.3)	37849 (55.3)	<.001
	Current	45967 (10.6)	7008 (10.2)	
	Previous	149663 (34.5)	23388 (34.1)	
Body Mass Index (kg/m^2) Missing = 3105 (0.6%)	Median (IQR)	26.7 (24.1 to 29.9)	26.9 (24.3 to 30.1)	<.001
Systolic Blood Pressure (mmHg) Missing = 16839 (3.4%)	Median (IQR)	136.0 (125.0 to 149.0)	138.0 (126.0 to 151.0)	<.001
Diabetes Mellitus (%)		22073 (5.1)	3424 (5.0)	.331
Hypertension (%)		113825 (26.2)	19465 (28.4)	<.001
Baseline eGFR (ml per min per 1.73 m^2) Missing = 33147 (6.6%)	Median (IQR)	92.8 (82.9 to 100.0)	92.8 (82.9 to 100.0)	.64
uACR (mg mmol^{-1}) Missing = 18217 (3.6%)	Median (IQR)	0.0 (0.0 to 0.6)	0.0 (0.0 to 0.6)	.29
Total Cholesterol (mmol l^{-1}) Missing = 32915 (6.6%)	Median (IQR)	5.7 (4.9 to 6.4)	5.6 (4.9 to 6.4)	.02
Antihypertensives prescribed (%)		96984 (22.3)	16520 (24.1)	<.001
Statin prescribed (%)		69972 (16.1)	11977 (17.5)	<.001
LTCs (%)	0	134397 (31.0)	20229 (29.5)	<.001
	1	131326 (30.3)	21180 (30.9)	
	2	83529 (19.2)	13693 (20.0)	
	3 or more	84735 (19.5)	13403 (19.6)	

LTCs, long-term conditions. eGFR, estimated glomerular filtration rate. uACR, urine albumin-creatinine ratio. IQR, interquartile range. P-values: Kruskal-Wallis test for continuous variables and chi-squared tests for categorical variables.

Supplementary Table 5-3. Baseline characteristics by linkage of data from General Practice (GP) data.

Baseline Characteristics		**GP data not linked** N= 272406 (54.2%)	**GP data linked** N=230097 (45.8%)	**p-value**
Age	Median (IQR)	58.0 (50.0 to 63.0)	58.0 (50.0 to 63.0)	.049
Sex (%)	Female	147600 (54.2)	125783 (54.7)	.001
	Male	124806 (45.8)	104314 (45.3)	
Ethnicity (%) Missing = 2,776 (0.6%)	White	254345 (93.4)	218349 (94.9)	<.001
	Asian	5174 (1.9)	4708 (2.0)	
	Black	5552 (2.0)	2509 (1.1)	
	Chinese	974 (0.4)	600 (0.3)	
	Mixed	1791 (0.7)	1167 (0.5)	
	Other	2872 (1.1)	1686 (0.7)	
LTCs (%)	0	84912 (31.2)	69714 (30.3)	<.001
	1	82648 (30.3)	69858 (30.4)	
	2	52406 (19.2)	44816 (19.5)	
	3 or more	52433 (19.3)	45705 (19.9)	
Socioeconomic status based on Townsend Score Missing = 623 (0.1%)	Median (IQR)	-2.1 (-3.6 to 0.6)	-2.1 (-3.6 to 0.5)	.001
Frequency of alcohol consumption (%) Missing = 1501 (0.3%)	Never	21738 (8.0)	18903 (8.2)	<.001
	Special occasions only	31782 (11.7)	26227 (11.4)	
	One to three times a month	29925 (11.0)	25930 (11.3)	
	Once or twice a week	68897 (25.3)	60394 (26.2)	
	Three or four times a week	62545 (23.0)	52894 (23.0)	
	Daily or almost daily	56596 (20.8)	45171 (19.6)	
Physical Activity (%) Missing = 7150 (1.4%)	None	17368 (6.4)	15480 (6.7)	<.001
	Low	10205 (3.7)	8733 (3.8)	
	Medium	212024 (77.8)	181475 (78.9)	
	High	27319 (10.0)	22749 (9.9)	
Smoking status (%) Missing = 2948 (0.6%)	Never	147780 (54.3)	125736 (54.6)	<.001
	Current	28789 (10.6)	24186 (10.5)	
	Previous	94094 (34.5)	78957 (34.3)	
Body Mass Index (kg/m^2) Missing = 3105 (0.6%)	Median (IQR)	26.7 (24.1 to 29.8)	26.8 (24.2 to 30.0)	<.001
Systolic Blood Pressure (mmHg) Missing = 16839 (3.4%)	Median (IQR)	136.0 (125.0 to 149.0)	137.0 (125.0 to 150.0)	<.001
Diabetes Mellitus		13951 (5.1)	11546 (5.0)	.096
Hypertension		72054 (26.5)	61236 (26.6)	.20
Baseline eGFR (ml per min per 1.73 m^2) Missing = 33147 (6.6%)	Median (IQR)	92.8 (82.9 to 100.0)	92.8 (82.9 to 100.0)	.64
uACR (mg mmol^{-1}) Missing = 18217 (3.6%)	Median (IQR)	0.0 (0.0 to 0.6)	0.0 (0.0 to 0.6)	.85
Total Cholesterol (mmol l^{-1}) Missing = 32915 (6.6%)	Median (IQR)	5.6 (4.9 to 6.4)	5.7 (4.9 to 6.4)	<.001
Prescribed Antihypertensives		60962 (22.4)	52542 (22.8)	<.001
Prescribed statins		43976 (16.1)	37973 (16.5)	.001

LTCs, long-term conditions. eGFR, estimated glomerular filtration rate. uACR, urine albumin-creatinine ratio. IQR, interquartile range. P-values: Kruskal-Wallis test for continuous variables and chi-squared tests for categorical variables.

Supplementary Table 5-4. Baseline characteristics by availability of creatinine results in linked General Practice data.

Baseline Characteristics		**No creatinine result in linked GP data** N= 172107 (74.8%)	**Creatinine result(s) in linked GP data** N=57990 (25.2%)	**p-value**
Age	Median (IQR)	58.0 (50.0 to 63.0)	58.0 (51.0 to 63.0)	<.001
Sex (%)	Female	93805 (54.5)	31978 (55.1)	.007
	Male	78302 (45.5)	26012 (44.9)	
Ethnicity (%) Missing = 1078 (0.5%)	White	162570 (94.5)	55779 (96.2)	<.001
	Black	2088 (1.2)	421 (0.7)	
	Asian	3977 (2.3)	731 (1.3)	
	Chinese	425 (0.2)	175 (0.3)	
	Mixed	857 (0.5)	310 (0.5)	
	Other	1352 (0.8)	334 (0.6)	
LTCs (%)	0	52750 (30.6)	16964 (29.3)	<.001
	1	51984 (30.2)	17874 (30.8)	
	2	33265 (19.3)	11551 (19.9)	
	3 or more	34105 (19.8)	11600 (20.1)	
Socioeconomic status based on Townsend Score Missing = 343 (0.1%)	Median (IQR)	-2.1 (-3.6 to 0.5)	-2.2 (-3.7 to 0.5)	<.001
Frequency of alcohol consumption (%) Missing = 578 (0.3%)	Never	14075 (8.2)	4828 (8.3)	<.001
	Special occasions only	19288 (11.2)	6939 (12.0)	
	One to three times a month	19318 (11.2)	6612 (11.4)	
	Once or twice a week	44941 (26.1)	15453 (26.6)	
	Three or four times a week	39869 (23.2)	13025 (22.5)	
	Daily or almost daily	34174 (19.9)	10997 (19.0)	
Physical Activity (%) Missing = 1660 (0.7%)	None	10801 (6.3)	4679 (8.1)	<.001
	Low	6378 (3.7)	2355 (4.1)	
	Medium	136369 (79.2)	45106 (77.8)	
	High	17324 (10.1)	5425 (9.4)	
Smoking status (%) Missing = 1212 (0.5%)	Never	94273 (54.8)	31463 (54.3)	<.001
	Previous	59284 (34.4)	19673 (33.9)	
	Current	17618 (10.2)	6568 (11.3)	
Body Mass Index (kg/m^2) Missing = 1406 (0.6%)	Median (IQR)	26.8 (24.2 to 29.9)	27.0 (24.4 to 30.3)	<.001
Systolic Blood Pressure (mmHg) Missing = 7975 (3.5%)	Median (IQR)	137.0 (125.0 to 150.0)	138.0 (126.0 to 151.0)	<.001
Diabetes Mellitus		8479 (4.9)	3067 (5.3)	.001
Hypertension		44255 (25.7)	16981 (29.3)	<.001
Baseline eGFR (ml per min per 1.73 m^2) Missing = 13806 (6.0%)	Median (IQR)	92.7 (82.7 to 100.0)	93.1 (83.3 to 100.1)	<.001
uACR (mg mmol^{-1}) Missing = 7616 (3.3%)	Median (IQR)	0.0 (0.0 to 0.6)	0.0 (0.0 to 0.6)	<.001
Total Cholesterol (mmol l^{-1}) Missing = 13700 (6.0%)	Median (IQR)	5.7 (4.9 to 6.4)	5.7 (4.9 to 6.4)	.012
Prescribed Antihypertensives		38143 (22.2)	14399 (24.8)	<.001
Prescribed statins		27673 (16.1)	10300 (17.8)	<.001

LTCs, long-term conditions. eGFR, estimated glomerular filtration rate. uACR, urine albumin-creatinine ratio. IQR, interquartile range. P-values: Kruskal-Wallis test for continuous variables and chi-squared tests for categorical variables.

Supplementary Table 5-5. Baseline characteristics by availability of creatinine results in UK Biobank data.

Baseline Characteristics		**No UK Biobank creatinine result available** N=484660 (96.4%)	**UK Biobank creatinine result available** N=17843 (3.6%)	**p-value**
Age	Median (IQR)	58.0 (50.0 to 63.0)	59.0 (52.0 to 63.0)	<.001
Sex (%)	Female	264505 (54.6)	8878 (49.8)	<.001
	Male	220155 (45.4)	8965 (50.2)	
Ethnicity (%) Missing = 2,776 (0.6%)	White	455282 (93.9)	17412 (97.6)	<.001
	Black	7982 (1.6)	79 (0.4)	
	Asian	9761 (2.0)	121 (0.7)	
	Chinese	1532 (0.3)	42 (0.2)	
	Mixed	2894 (0.6)	64 (0.4)	
	Other	4476 (0.9)	82 (0.5)	
LTCs (%)	0	148931 (30.7)	5695 (31.9)	<.001
	1	146920 (30.3)	5586 (31.3)	
	2	93797 (19.4)	3425 (19.2)	
	3 or more	95001 (19.6)	3137 (17.6)	
Socioeconomic status based on Townsend Score Missing = 623 (0.1%)	Median (IQR)	-2.1 (-3.6 to 0.6)	-2.7 (-4.0 to -0.8)	<.001
Frequency of alcohol consumption (%) Missing = 1501 (0.3%)	Never	39650 (8.2)	991 (5.6)	<.001
	Special occasions only	56389 (11.6)	1620 (9.1)	
	One to three times a month	53984 (11.1)	1871 (10.5)	
	Once or twice a week	124775 (25.7)	4516 (25.3)	
	Three or four times a week	110605 (22.8)	4834 (27.1)	
	Daily or almost daily	97765 (20.2)	4002 (22.4)	
Physical Activity (%) Missing = 7150 (1.4%)	None	32147 (6.6)	701 (3.9)	<.001
	Low	18459 (3.8)	479 (2.7)	
	Medium	379341 (78.3)	14158 (79.3)	
	High	48006 (9.9)	2062 (11.6)	
Smoking status (%) Missing = 2948 (0.6%)	Current	51823 (10.7)	1152 (6.5)	<.001
	Never	262996 (54.3)	10520 (59.0)	
	Previous	166924 (34.4)	6127 (34.3)	
Body Mass Index (kg/m^2) Missing = 3105 (0.6%)	Median (IQR)	26.8 (24.2 to 29.9)	26.3 (23.8 to 29.2)	<.001
Systolic Blood Pressure (mmHg) Missing = 16839 (3.4%)	Median (IQR)	137.0 (125.0 to 150.0)	137.0 (125.0 to 149.0)	.61
Diabetes Mellitus		24794 (5.1)	703 (3.9)	<.001
Hypertension		128999 (26.6)	4291 (24.0)	<.001
Baseline eGFR (ml per min per 1.73 m^2) Missing = 33147 (6.6%)	Median (IQR)	92.8 (82.9 to 100.1)	92.5 (83.0 to 99.0)	<.001
uACR (mg mmol^{-1}) Missing = 18217 (3.6%)	Median (IQR)	0.0 (0.0 to 0.6)	0.0 (0.0 to 0.4)	<.001
Total Cholesterol (mmol l^{-1}) Missing = 32915 (6.6%)	Median (IQR)	5.7 (4.9 to 6.4)	5.6 (4.9 to 6.4)	.004
Prescribed Antihypertensives		109876 (22.7)	3628 (20.3)	<.001
Prescribed statins		79167 (16.3)	2782 (15.6)	.008

LTCs, long-term conditions. eGFR, estimated glomerular filtration rate. uACR, urine albumin-creatinine ratio. IQR, interquartile range. P-values: Kruskal-Wallis test for continuous variables and chi-squared tests for categorical variables.

Outcomes

During a median follow-up period of 12.0 years (interquartile range 11.2 to 12.3 years), 2,963 participants had a MAKE event and 3,338 died. Those with MAKE had more LTCs and more cardiometabolic LTCs (Table 5-2). Those with MAKE were more likely to be older, smokers, from areas of greater socioeconomic deprivation, with lower consumption of alcohol, lower physical activity levels, higher BMI, higher systolic blood pressure, higher uACR, lower baseline eGFR, lower total cholesterol and proportionally more were prescribed antihypertensives and statins.

Table 5-2. Baseline Characteristics by major adverse kidney events

Baseline Characteristics		**No MAKE** N= 65542 (95.7%)	**MAKE** N=2963 (4.3%)
Age	Median (IQR)	58.0 (51.0 to 63.0)	61.0 (55.0 to 66.0)
Sex (%)	Female	35215 (53.7)	1620 (54.7)
	Male	30327 (46.3)	1343 (45.3)
Ethnicity	White	63339 (96.6)	2839 (95.8)
	Asian	727 (1.1)	50 (1.7)
	Black	418 (0.6)	23 (0.8)
	Mixed	326 (0.5)	12 (0.4)
	Chinese	182 (0.3)	9 (0.3)
	Other	342 (0.5)	21 (0.7)
Socioeconomic status based on Townsend Score	Median (IQR)	-2.3 (-3.8 to 0.1)	-2.0 (-3.6 to 1.0)
Frequency of alcohol consumption (%)	Never	4904 (7.5)	348 (11.7)
	Special occasions only	7229 (11.0)	490 (16.5)
	One to three times a month	7340 (11.2)	327 (11.0)
	Once or twice a week	17239 (26.3)	792 (26.7)
	Three or four times a week	15612 (23.8)	528 (17.8)
	Daily or almost daily	13129 (20.0)	471 (15.9)
Physical Activity (%)	None	4485 (6.8)	355 (12.0)
	Low	2410 (3.7)	171 (5.8)
	Medium	51719 (78.9)	2246 (75.8)
	High	6624 (10.1)	158 (5.3)
Smoking status (%)	Never	36437 (55.6)	1412 (47.7)
	Current	6587 (10.1)	421 (14.2)
	Previous	22278 (34.0)	1110 (37.5)
Body Mass Index (kg/m^2)	Median (IQR)	26.8 (24.2 to 30.0)	28.3 (25.3 to 32.2)
Systolic Blood Pressure (mmHg)	Median (IQR)	137.0 (126.0 to 150.0)	143.0 (131.0 to 157.0)
Chronic Kidney Disease (%) (eGFR <60ml/min/1.73m^2; %)		1264 (1.9)	217 (7.3)
Diabetes Mellitus		2817 (4.3)	607 (20.5)
Hypertension		18023 (27.5)	1442 (48.7)
LTCs	0	21839 (33.3)	509 (17.2)
	1	21809 (33.3)	785 (26.5)
	2	12657 (19.3)	738 (24.9)
	3 or more	9237 (14.1)	931 (31.4)
Cardiometabolic LTCs	0	44439 (67.8)	1267 (42.8)
	1	17062 (26.0)	1002 (33.8)
	2	3487 (5.3)	522 (17.6)
	3 or more	554 (0.8)	172 (5.8)
Baseline eGFR (ml per min. per 1.73 m^2)	Median (IQR)	93.0 (83.4 to 99.9)	90.1 (79.6 to 96.6)
Urine ACR (mg mmol^{-1})	Median (IQR)	0.0 (0.0 to 0.6)	0.0 (0.0 to 1.5)
Total Cholesterol (mmol l^{-1})	Median (IQR)	5.7 (4.9 to 6.4)	5.4 (4.5 to 6.2)
Antihypertensives prescribed (%)		15154 (23.1)	1366 (46.1)
Statin prescribed (%)		10955 (16.7)	1022 (34.5)

MAKE, major adverse kidney events. eGFR, estimated glomerular filtration rate. ACR, albumin-creatinine ratio. IQR, interquartile range. LTCs, long-term conditions. P-values <.001 for all variables apart from Sex (0.31) and ethnicity (0.065) (Kruskal-Wallis test for continuous variables and chi-squared tests for categorical variables).

Of the 2963 participants developing MAKE, 67 (2.3%) initiated KRT, 214 (7.2%) had a doubling of creatinine, 59 (2.0%) had eGFR fall to <15mL/min/1.73m^2 and (99.1%) had a 30% or greater decline in eGFR. Cumulative incidences of MAKE and mortality were higher in participants with more LTCs (Figure 5-1). At the end of the follow-up period, 509 participants (2.3%) in the zero LTC category had MAKE, compared to 785 participants (3.5%) in the one LTC category, 738 participants (5.5%) in the two LTCs category and 931 participants (9.2%) in the three or more LTCs category. When only cardiometabolic LTCs were considered, 1,267 participants (2.8%) in the zero LTC category had MAKE, compared with 1,002 participants (5.5%) in the one LTC category, 522 participants (13.0%) in the two LTC category and 172 participants (23.7%) in the three or more LTC category (Figure 5-2).

Figure 5-1. Cumulative incidence of outcomes by long-term condition (LTC) count category

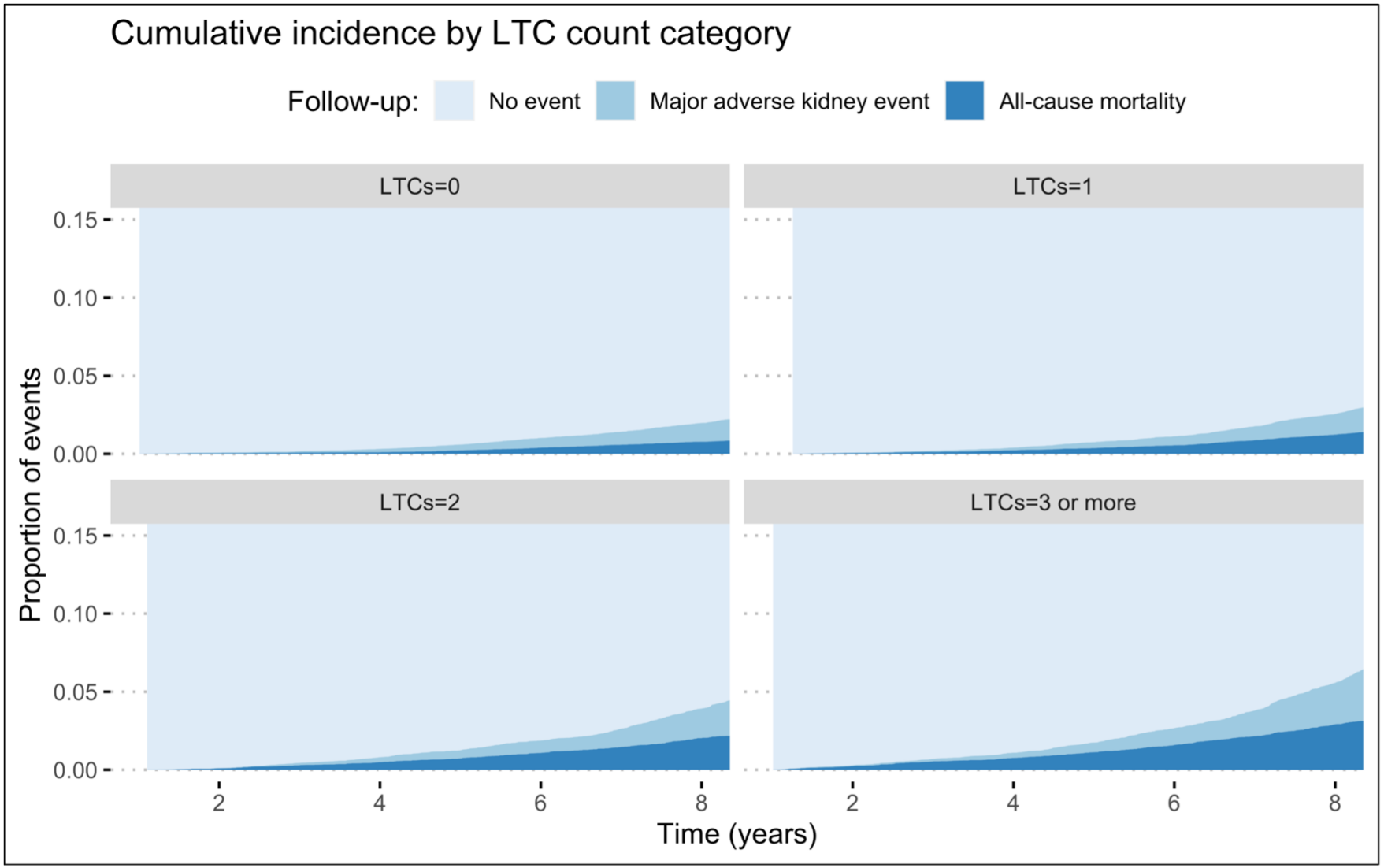
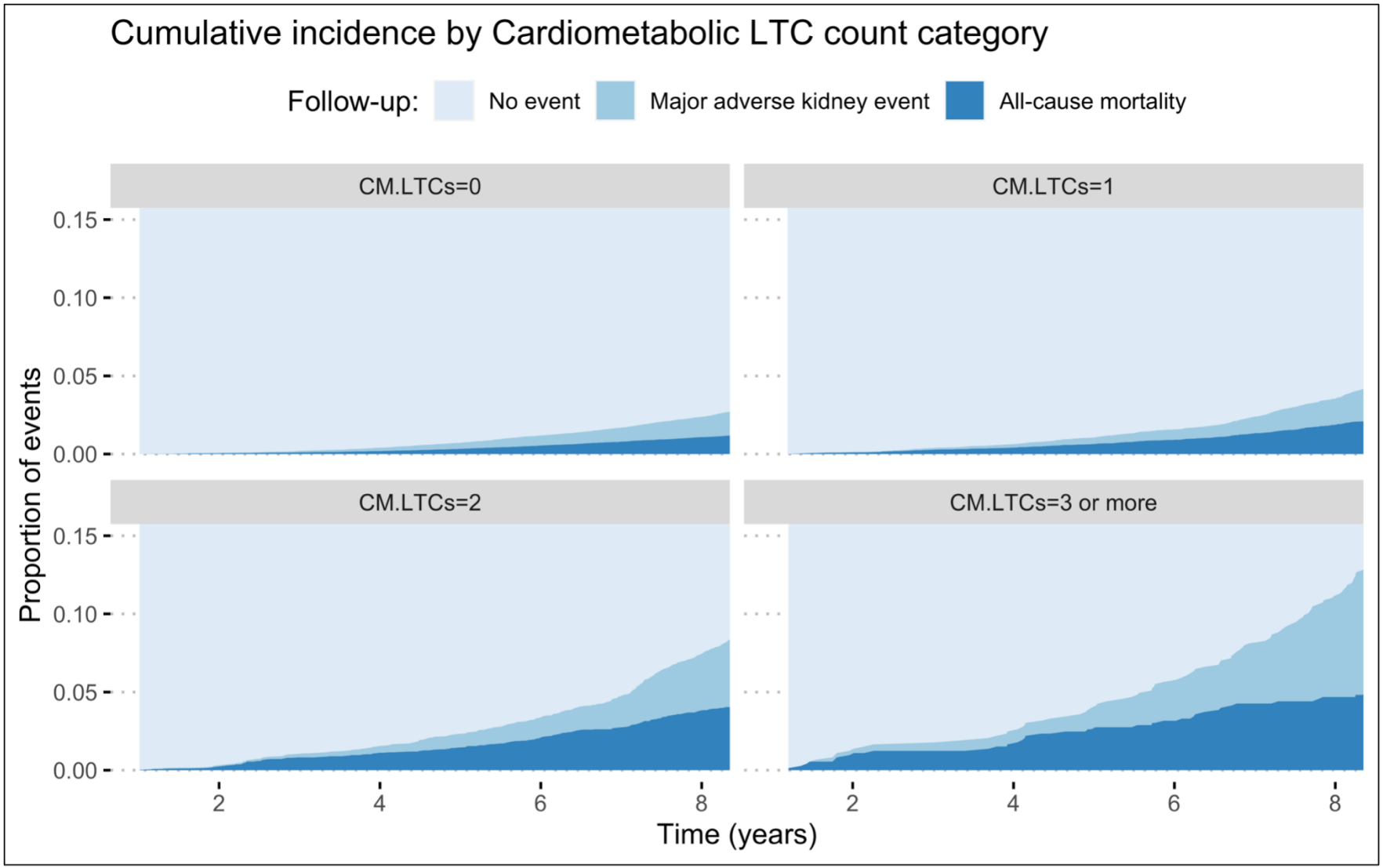


Figure 5-2. Cumulative incidence of outcomes by cardiometabolic long-term condition (CM.LTC) count category



Competing Risks Analysis

The proportional hazards assumption was upheld. Associations were observed between LTC count categories and the risk of MAKE over the follow-up period (Table 5-3). A dose-response relationship was seen in both unadjusted and adjusted competing risks analyses. In the standard model, participants with three or more LTCs were more than twice as likely to develop MAKE than those with zero LTCs (subhazard ratio (sHR) 2.41 (95% Confidence Interval (CI) 2.14 to 2.71). For participants with three or more cardiometabolic LTCs, the risk was more than five times greater than those with zero LTCs (standard model sHR 5.24 (95% CI 4.34 to 6.33)). The relationship between the number of conditions and MAKE appeared to be cumulative, whether all LTCs or just cardiometabolic LTCs were considered.

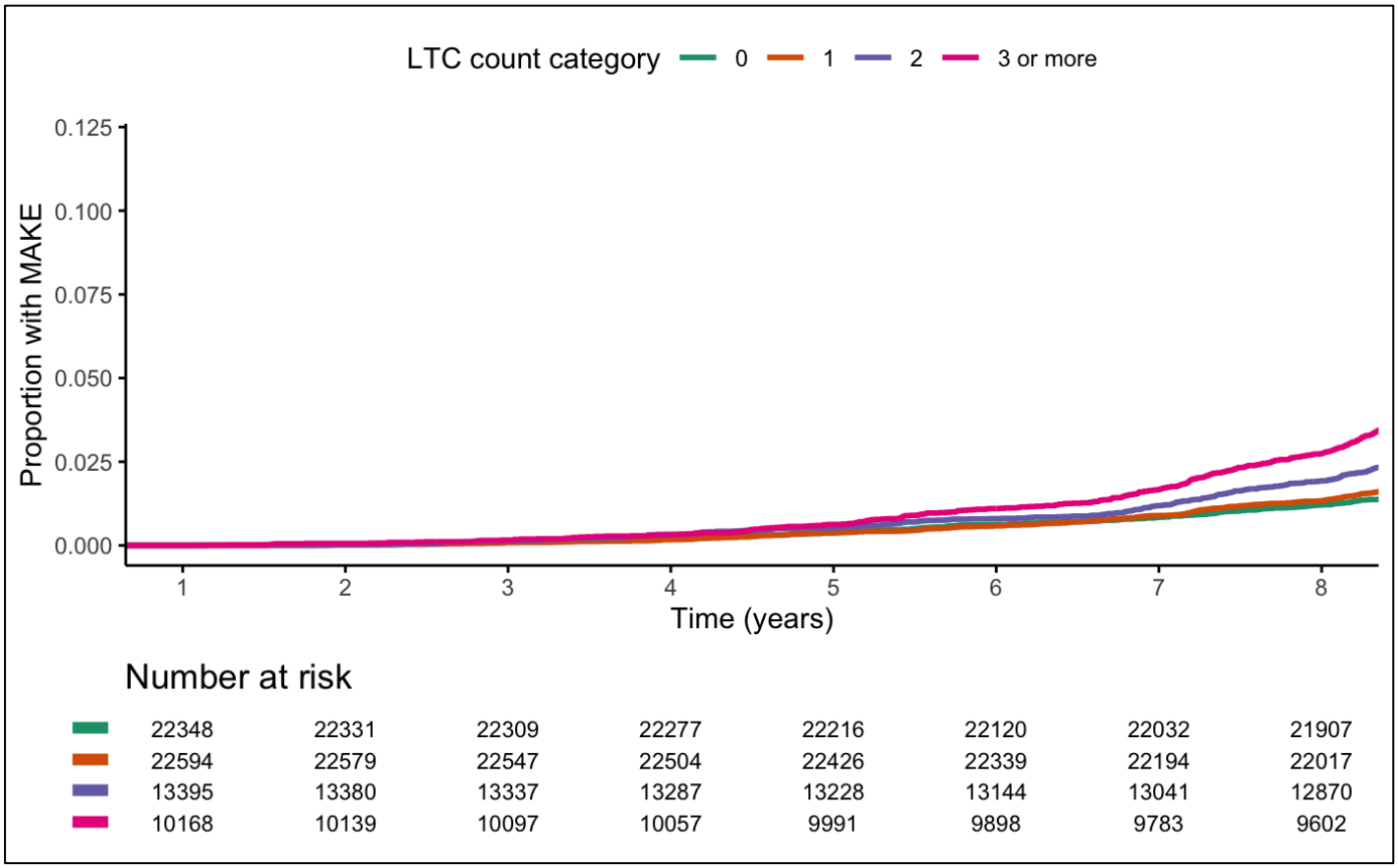
Table 5-3. Major adverse kidney events by long-term condition count category: events and competing risks analysis.

		n	MAKE (%)	Unadjusted model (sHR)	95% CI	Standard model (sHR)[a] Missing values n=2433 (3.6%)	95% CI	Additional model (sHR)[b] Missing values n=5680 (8.3%)	95% CI
LTCs	0	22348	509 (2.3)	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
	1	22594	785 (3.5)	1.53	1.37 to 1.71	1.29	1.15 to 1.45	1.28	1.13 to 1.44
	2	13395	738 (5.5)	2.45	2.19 to 2.74	1.74	1.55 to 1.96	1.74	1.54 to 1.96
	3 or more	10168	931 (9.2)	4.13	3.71 to 4.61	2.41	2.14 to 2.71	2.40	2.12 to 2.71
Cardiometabolic LTCs	0	45706	1,267 (2.8)	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
	1	18064	1,002 (5.5)	2.02	1.86 to 2.20	1.58	1.45 to 1.73	1.51	1.37 to 1.66
	2	4009	522 (13.0)	4.90	4.43 to 5.42	3.17	2.80 to 3.59	3.10	2.72 to 3.52
	3 or more	726	172 (23.7)	9.31	7.97 to 10.87	5.24	4.34 to 6.33	5.25	4.32 to 6.37

MAKE, Major adverse kidney events. LTC, Long-term condition. sHR, subhazard ratio. [a]Adjusted for age, baseline estimated glomerular filtration rate, uACR, sex, ethnicity, cholesterol, BMI, smoking status & physical activity levels. [b]Adjusted for age, baseline estimated glomerular filtration rate, uACR, sex, ethnicity, cholesterol, BMI, smoking status, physical activity levels & systolic blood pressure. P-values <.001 for all sub-categories.

Results were similar when Cox proportional hazards models were fitted, but with smaller effect sizes, including for cardiometabolic LTCs (Supplementary Figures 5-2 and 5-3 and Supplementary Tables 5-6 and 5-7).

Supplementary Figure 5-2. Event plot for major adverse kidney events (MAKE) by long-term condition (LTC) count category

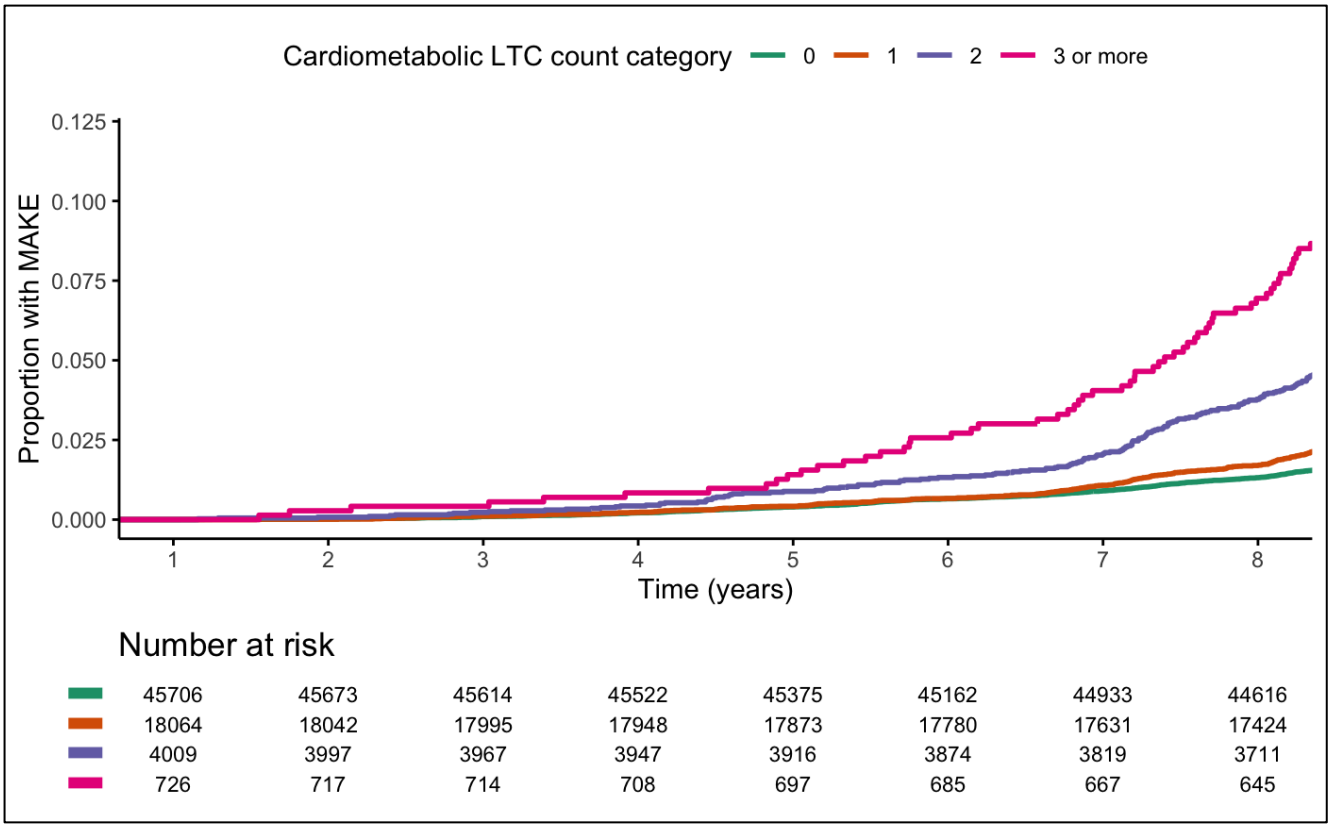


Supplementary Table 5-6. Proportional hazards cox regression for major adverse kidney events.

		Unadjusted model (HR)	95% CI	p-value	Standard model (HR)*	95% CI	p-value	Additional model (HR)**	95% CI	p-value
LTCs	0	1.0 (ref.)			1.0 (ref.)			1.0 (ref.)		
	1	1.20	1.08 to 1.35	.001	1.08	0.96 to 1.21	.21	1.07	0.95 to 1.21	.26
	2	1.67	1.49 to 1.87	<.001	1.33	1.18 to 1.50	<.001	1.34	1.19 to 1.52	<.001
	3 or more	2.39	2.15 to 2.67	<.001	1.70	1.51 to 1.92	<.001	1.71	1.51 to 1.93	<.001

*Adjusted for age, baseline eGFR, uACR, sex, ethnicity, cholesterol, BMI, smoking status & physical activity levels. **Adjusted for age, baseline eGFR, uACR, sex, ethnicity, cholesterol, BMI, smoking status, physical activity levels & systolic blood pressure.

Supplementary Figure 5-3. Event plot for major adverse kidney events (MAKE) by cardiometabolic long-term condition (LTC) count category.



Supplementary Table 5-7. Proportional hazards cox regression for major adverse kidney events by cardiometabolic long-term condition (LTC) count category.

		Unadjusted model (HR)	95% CI	p-value	Standard model (HR)*	95% CI	p-value	Additional model (HR)**	95% CI	p-value
LTCs	0	1.0 (ref.)			1.0 (ref.)			1.0 (ref.)		
	1	1.36	1.25 to 1.48	<.001	1.16	1.06 to 1.27	<.001	1.14	1.04 to 1.26	.005
	2	2.57	2.32 to 2.85	<.001	1.98	1.75 to 2.23	<.001	1.98	1.75 to 2.25	<.001
	3 or more	4.18	3.56 to 4.91	<.001	3.05	2.54 to 3.67	<.001	3.09	2.56 to 3.73	<.001

*Adjusted for age, baseline eGFR, uACR, sex, ethnicity, cholesterol, BMI, smoking status & physical activity levels. **Adjusted for age, baseline eGFR, uACR, sex, ethnicity, cholesterol, BMI, smoking status, physical activity levels & systolic blood pressure.

Results were similar when frequency of alcohol use was added as a covariable of interest (Supplementary Table 5-8). Most MAKE events were related to a 30% or more decline in eGFR with 67 participants needing to initiate KRT (Supplementary Table 5-9). Competing risks analysis of each component of the MAKE definition confirmed associations between increasing LTC count category and each component, except KRT initiation (perhaps because of small event numbers). 65.9% of those with MAKE defined from biochemical changes had blood samples which confirmed the decline in kidney function was sustained

Supplementary Table 5-8. Major adverse kidney events by long-term condition count category with added adjustment for alcohol frequency.

		Adjusted Subhazard Ratio*
LTCs	0	-
	1	1.29 (1.15-1.44, p<0.001)
	2	1.73 (1.53-1.94, p<0.001)
	3 or more	2.32 (2.06-2.62, p<0.001)
Cardiometabolic LTCs	0	-
	1	1.59 (1.45-1.74, p<0.001)
	2	3.12 (2.76-3.53, p<0.001)
	3 or more	4.98 (4.12-6.02, p<0.001)

*Adjusted for age, baseline estimated glomerular filtration rate, uACR, sex, ethnicity, cholesterol, BMI, smoking status, physical activity levels & alcohol frequency

Supplementary Table 5-9. Major adverse kidney events (MAKE) by long-term condition (LTC) count category: events and competing risks analysis divided by each component of the primary outcome.

MAKE Component	LTCs	Unadjusted sHR	Adjusted sHR*
KRT initiation N=67	0	-	-
	1	0.99 (0.35-2.83, p=.990)	0.81 (0.29-2.30, p=.690)
	2	4.56 (1.92-10.86, p=.001)	1.63 (0.66-4.00, p=.290)
	3 or more	9.65 (4.24-21.97, p<.001)	2.05 (0.78-5.41, p=.150)
Doubling Creatinine N=214	0	-	-
	1	2.60 (1.46-4.63, p=.001)	2.09 (1.17-3.74, p=.013)
	2	5.47 (3.12-9.58, p<.001)	3.37 (1.92-5.93, p<.001)
	3 or more	12.84 (7.55-21.85, p<.001)	5.71 (3.27-9.97, p<.001)
eGFR fall <15ml/min/1.73m^2 N=59	0	-	-
	1	1.74 (0.51-5.93, p=.380)	1.36 (0.40-4.58, p=.620)
	2	5.46 (1.78-16.76, p=.003)	2.14 (0.71-6.47, p=.180)
	3 or more	17.45 (6.16-49.45, p<.001)	4.15 (1.38-12.44, p=.011)
30% or greater fall in eGFR N=2936	0	-	-
	1	1.54 (1.37-1.72, p<.001)	1.29 (1.15-1.45, p<.001)
	2	2.43 (2.16-2.73, p<.001)	1.73 (1.53-1.94, p<.001)
	3 or more	4.11 (3.68-4.59, p<.001)	2.38 (2.12-2.69, p<.001)

KRT, Kidney Replacement Therapy; eGFR, estimated glomerular filtration rate; sHR, Subhazard Ratio; *Adjusted for age, baseline eGFR, urine albumin-creatinine ratio, sex, ethnicity, cholesterol, body mass index, smoking status and physical activity levels

Combinations of LTCs

14 LTCs were present in greater than 0.1% of the cohort and had associations with MAKE and so were considered for potential combinations of LTCs (Table 4). For participants with two LTCs, 10 different combinations of the 14 individual LTCs were present in greater than 0.1% of the cohort and six had associations with MAKE (Table 5-4). For participants with three or more LTCs, 29 different combinations individual LTCs had individual associations with MAKE and 20 of these were present in greater than 0.1% of the cohort (Table 5-4). For participants with two LTCs, hypertension featured in all of the combinations and for those with three or more LTCs, hypertension, diabetes, coronary heart disease and treated dyspepsia featured most commonly.

Table 5-4. Long-term conditions and combinations of conditions that associate with major adverse kidney events.

Adjusted subhazard ratios for MAKE, when compared to reference group 0 LTCs* (95% confidence intervals)						
Individual LTCs		Category LTC count = 2 N=13395; total number with Major adverse kidney events N = 738		Category LTC count = 3 or more N= 10168; total number with Major adverse kidney events N = 931		
				Index LTCs	Third LTC	
Diabetes N=607 events	3.47 (3.11 – 3.88)	Hypertension & CKD N=37 events	6.65 (4.26 – 10.38)	**Hypertension, Diabetes**	Stroke or TIA N=36 events	11.17 (7.16 – 17.43)
Schizophrenia or Bipolar Disorder N=34 events	2.88 (2.04 – 4.07)	Hypertension & Diabetes N=119 events	4.91 (3.72 – 6.48)		CKD N=51 events	9.42 (5.73 – 15.51)
Heart failure N=19 events	2.57 (1.53 – 4.32)	Hypertension & Stroke or TIA N=14 events	2.89 (1.68 – 4.97)		Cancer N=54 events	8.24 (5.75 – 11.82)
Chronic liver disease N=12 events	1.90 (1.04 – 3.47)	Hypertension & Cancer N=38 events	2.42 (1.72 – 3.4)		Treated Dyspepsia N=60 events	8.18 (5.79 – 11.55)
CKD (stages 3-5: eGFR < 60ml/min/1.73m^2 at baseline assessment) N=217 events	1.84 (1.54 – 2.21)	Hypertension & Coronary Heart Disease N=32 events	2.17 (1.47 – 3.19)		Psoriasis or Eczema N=20 events	7.95 (4.86 – 13.03)
Hypertension N=1442 events	1.66 (1.53 – 1.79)	Hypertension & Treated Dyspepsia N=23 events	1.94 (1.27 – 2.97)		Coronary Heart Disease N=105 events	7.38 (5.4 – 10.11)
Stroke or transient ischaemic attack N=136 events	1.62 (1.35 – 1.95)				Connective Tissue Disease N=16 events	6.91 (3.95 – 12.1);
Atrial fibrillation N=45 events	1.45 (1.07 – 1.97)			**Hypertension, CKD**	Cancer N=26 events	6.28 (3.73 – 10.58)
Inflammatory bowel disease N=43 events	1.42 (1.01 – 2.01)				Coronary Heart Disease N=31 events	5.99 (3.57 – 10.05)

Coronary Heart Disease N=320 events	1.35 (1.18 – 1.54)				Stroke or TIA N= 14 events	5.42 (2.67 – 10.99)
Cancer N=324 events	1.35 (1.20 – 1.53)				Treated Dyspepsia N=16 events	4.64 (2.44 – 8.83)
Connective Tissue Disease N=110 events	1.30 (1.07 – 1.59)			**Hypertension, Coronary Heart Disease**	Psoriasis or Eczema N=10 events	HR 5.09 (2.63 – 9.87)
Psoriasis or Eczema N=127 events	1.26 (1.06 – 1.5)				Connective Tissue Disease N=13 events	HR 4.74 (2.64 – 8.52)
Treated Dyspepsia N=332 events	1.15 (1.02 – 1.29)				Stroke or TIA N=22 events	4.61 (2.79 – 7.63)
					Treated Dyspepsia N=47 events	4.58 (3.18 – 6.58)
					Cancer N=22 events	3.71 (2.33 – 5.92)
				Hypertension, Treated Dyspepsia	Connective Tissue Disease N=13 events	4.56 (2.57 – 8.09)
					Stroke or TIA N=11 events	4.26 (2.23 – 8.15)
					Psoriasis or Eczema N=11 events	HR 3.55 (1.99 – 6.33)
					Cancer N=20 events	3.16 (1.98 – 5.06)

LTCs, Long-term conditions. MAKE, major adverse kidney events. TIA, transient ischaemic attack. CKD, chronic kidney disease (stages 3-5).
*Adjusted for age, baseline estimated glomerular filtration rate, uACR, sex, ethnicity, cholesterol, BMI, smoking status & physical activity levels.

Discussion

In this study of 68,505 UK Biobank participants, we found an association between increasing LTC counts and the risk of MAKE. This finding was consistent for all LTCs, and the association with cardiometabolic multimorbidity was observed to have higher effect sizes. We identified combinations of LTCs which were associated with extremely high-risk of MAKE. Diabetes and hypertension predominate in these high-risk groups, and this is not an unexpected finding. However, the substantial cumulative link and the magnitude of the association between combinations of cardiometabolic LTCs and MAKE has not been investigated in this easily understood manner before and it is more descriptive of the clinical problem faced by clinicians caring for at-risk patients.

Our study findings are consistent with a previous study in which increasing LTC counts were associated with the need for dialysis in patients with CKD[216]. However, our approach was more comprehensive, including participants with normal and abnormal kidney function at baseline. Notably, more than 90% of participants who developed MAKE did not have CKD at baseline. We have therefore shown that cardiometabolic multimorbidity is a risk factor for MAKE, even in the absence of CKD at baseline. Our definition of MAKE included a 30% fall of eGFR, which is an approach consistent with recommendations emerging from National Kidney Foundation and the US Food and Drug Administration workshops[250,251]. This surrogate end point for the development of kidney failure is important because it identifies patients before the late outcome of KRT. Studies by Bowling *et al*[205] and Tonelli *et al*[120] have shown that the pattern of LTCs is a risk factor in the association between multimorbidity and death in patients with CKD. Our analysis meaningfully extends this work by demonstrating that the pattern of LTCs is also linked to MAKE.

As expected, cardiometabolic LTCs and CKD were associated with MAKE. There were also associations with schizophrenia and bipolar disorder, but there were insufficient participants with these conditions for them to feature in the

high-risk combinations of LTCs. It is likely that patients with mental health conditions are under-represented in UK Biobank. If a similar study was performed in the general population, high-risk groups of patients with combinations of physical and mental health problems may be identified. Some non-cardiometabolic LTCs were identified in the high-risk combinations: dyspepsia, cancer and psoriasis or eczema. Medications used in these conditions may explain the link, or other, unidentified mechanisms could be responsible. Dyspepsia has been identified in high-risk combinations of LTCs in a similar analysis studying mortality risk in patients with diabetes[254]. Although some associations with proton-pump inhibitor used and future risk of CKD have been described[255], it is unclear why these associations exist.

An important strength of our study was the inclusion of many participants with extensive phenotyping and a follow-up period which was adequate to observe the development of MAKE. The use of competing risks analysis is appropriate for studying the prognostication of kidney function, where death is a more frequent event than the kidney outcomes of interest[179].

Our study has some limitations. A large proportion of UK Biobank participants were healthy volunteers and there was under-representation of non-White and socioeconomically deprived populations[154]. Analysis in a cohort with greater ethnic diversity may be necessary to confirm the generalisability of our findings to other countries. LTCs and covariates were only taken at baseline and we have not taken into account changes during follow-up because we sought to estimate the risk of progressive kidney disease from a single point in time. Our study used a select population because GP data were not available for 51.0% of participants and only 14.6% of participants with baseline data had follow-up biochemistry available. Although there was a risk of selection bias (survival and ascertainment), we showed that the populations with and without follow-up biochemistry had similar characteristics. Single blood tests were used to quantify eGFR without confirmatory testing, which was deemed to be acceptable because participants were assumed to be stable at baseline assessment. Follow-up results were excluded if they were taken close to hospital admissions, but it is possible that we were unable to detect all cases of

acute kidney injury. The use of self-reported LTCs is a potential limitation. However, participants were supported by a nurse in the assessment process to improve accuracy, and self-report has been found to be a valid method[256]ir risk can be reduced. Clinical leaders have highlighted that multimorbidity, rather than comorbidity, is a major global health issue and suggest that identifying clusters of conditions with clinical impacts is a research priority that could help improve the treatment of these complex patients[69, 234, 229]. Clinical guidelines should emphasise the importance of monitoring kidney function for patients with cardiometabolic multimorbidity, including those with normal kidney function. Potential interventions in these patients are intensive blood pressure and glycaemic control, lifestyle modification or planning of KRT. These interventions must always consider the priorities of patients, acknowledging their treatment burdens which may already be significant.

Our study has demonstrated that multimorbidity, and in particular cardiometabolic multimorbidity, is a risk factor for MAKE, even in the absence of CKD. We have highlighted combinations of LTCs that are associated with high-risk of MAKE in whom more research is necessary to understand how risk reduction can be improved.

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Conflicts of interest
The results presented in this paper have not been published previously in whole or part.
NS reports personal fees from Amgen, personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, personal fees from Eli Lilly, personal fees from Merck Sharp & Dohme, personal fees from Novo Nordisk, personal fees from Pfizer, personal fees from Sanofi, outside the submitted work;
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JL reports personal fees from Pfizer, personal fees from Astra Zeneca, personal fees from Bristol Myers Squibb, outside the submitted work;
MS, AM, BS, BJ, CW, DL, JC, BN, FM and JL have nothing to disclose

Authors Contributions
The aim of this research was developed by MS, PM, BJ and FM. The analysis was conducted by MS and BJ. All authors (MS, BJ, JS, CW, AM, BS, PW, BN, DL, JC, DN, NS, FM and PM) contributed to the design and interpretation of the analysis and to the direction of the discussion. MS wrote the first draft of this manuscript; PM contributed to writing and led on the manuscript development. All authors (MS, BJ, JS, CW, AM, BS, PW, BN, DL, JC, DN, NS, FM and PM) reviewed, edited, and commented on drafts of the manuscript and approved the final manuscript.

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Ethics approval
UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274).

Data Availability
The data that support the findings of this study are available from UK Biobank project site, subject to successful registration and application process. Further details can be found at https://www.ukbiobank.ac.uk/.

Chapter: 6 Hospitalisation events in people with chronic kidney disease as a component of multimorbidity: parallel cohort studies in research and routine care settings

6.1 Reference

Sullivan, M. K., Jani, B. D., McConnachie, A., Hanlon, P., McLoone, P., Nicholl, B. I., Carrero, J.-J., Nitsch, D., McAllister, D., Mair, F. S., & Mark, P. B. (2021). Hospitalisation events in people with chronic kidney disease as a component of multimorbidity: parallel cohort studies in research and routine care settings. *BMC Medicine*, *19*(1), 278. https://doi.org/10.1186/s12916-021-02147-6

6.2 Chapter summary

In this chapter, the relationship between multimorbidity, chronic kidney disease and emergency hospitalisations is studied using UK Biobank and SAIL.

6.3 Manuscript

Abstract

Background*:* Chronic Kidney Disease (CKD) typically co-exists with multimorbidity (presence of 2 or more long-term conditions: LTCs). The associations between CKD, multimorbidity and hospitalisation rates are not known. The aim of this study was to examine hospitalisation rates in people with multimorbidity with and without CKD. Amongst people with CKD, the aim was to identify risk factors for hospitalisation.

Methods*:* Two cohorts were studied in parallel: UK Biobank (a prospective research study: 2006-2020) and Secure Anonymised Information Linkage Databank (SAIL: a routine care database, Wales, UK: 2011-2018). Adults were included if their kidney function was measured at baseline. Nine categories of participants were used: zero LTCs; one, two, three and four or more LTCs excluding CKD; and one, two, three and four or more LTCs including CKD. Emergency hospitalisation events were obtained from linked hospital records.

Results: Among 469,339 UK Biobank participants, those without CKD had a median of 1 LTC and those with CKD had a median of 3 LTCs. Among 1,620,490 SAIL participants, those without CKD had a median of 1 LTC and those with CKD had a median of 5 LTCs. Compared to those with zero LTCs, participants with four or more LTCs (excluding CKD) had high event rates: Rate Ratios 4.95 (95% confidence interval 4.82-5.08)/3.77 (3.71-3.82) with higher rates if CKD was one of the LTCs: Rate Ratios 7.83 (7.42-8.25)/9.92 (9.75-10.09). Amongst people with CKD, risk factors for hospitalisation were advanced CKD, age over 60, multiple cardiometabolic LTCs, combined physical and mental LTCs and complex patterns of multimorbidity (LTCs in three or more body systems).

Conclusions*:* People with multimorbidity have high rates of hospitalisation. Importantly, the rates are two to three times higher when CKD is one of the multimorbid conditions. Further research is needed into the mechanism underpinning this to inform strategies to prevent hospitalisation in this very high-risk group.

Keywords

Chronic Kidney Disease, Multimorbidity, Comorbidity, Clinical Epidemiology

Background

Chronic Kidney Disease (CKD) is a global health problem and is closely linked to adverse outcomes.[257] Compared to those without CKD, people with CKD are more likely to be hospitalised[237], develop complications while in hospital[258] and be re-admitted.[259] They have frequent contacts with health care services: clinic visits, blood tests, procedures and in the case of advanced CKD, the need for dialysis and/or kidney transplantation. Unplanned hospitalisations are additional, undesirable events with heightened anxiety, particularly when admissions are via emergency services. CKD is typically accompanied by multimorbidity (the co-occurrence of two or more long-term conditions: LTCs), which may have caused CKD, developed as direct or indirect complications of CKD or are unrelated.[119] Multimorbidity has been identified by the medical community as a major challenge which should be made a research priority.[229] Polypharmacy and high treatment burden are frequently experienced by these people, which reduce their quality of life.[65, 84] Hospital admissions may be directly linked to CKD (fluid overload, vascular access surgery) or other illnesses which occur in excess in CKD (infections, cardiovascular events[237]). In addition to therapeutic intervention, people are exposed to the risk of the healthcare environment (e.g. nosocomial infection and isolation). However, there is a paucity of evidence about the implications of multimorbidity and CKD in those with mild to moderate CKD nor do we know the relationship between different types of LTCs and CKD.[260]

In this study, we sought to fill this evidence gap and to examine the associations between CKD, multimorbidity and emergency admissions to hospital. We hypothesised that people with multimorbidity would have high rates of emergency hospitalisation, and that the rates would be higher when CKD was one of the LTCs. We also hypothesised that amongst those with CKD, subgroups with proven susceptibilities to adverse outcomes would be high risk: those with advanced CKD[237], those living in socioeconomically deprived areas[261] and those with low body weight.[262] A 2021 National Institute for Health Research policy paper on multimorbidity states that improving our understanding of combinations of conditions, or clusters, may help develop strategies to prevent ill health.[263] We therefore explored the associations between hospitalisation and combinations of conditions

which have been shown to be associated with increased risk of adverse outcomes: multiple cardiometabolic conditions[102] (i.e. heart failure, hypertension, coronary heart disease, peripheral vascular disease, atrial fibrillation, diabetes and stroke), complex LTCs[103] (three or more conditions from three or more body systems) and mixed physical and mental conditions.[264]

Two different types of cohort were studied: first, a prospective cohort study was used because it has extensive clinical phenotyping and there is extensive published data demonstrating its utility for studying multimorbidity.[89 265 254 266 267] Second, because healthy volunteer bias can occur in research studies, a nationally representative primary care cohort generated from routine care records was used. This approach allowed us to confirm the generalisability of our findings to the general population.

Methods

Study design & Setting

UK Biobank is a prospective research cohort with participants from England, Scotland and Wales. It enrolled volunteer participants aged 37 to 73 between 2006 and 2010 and they have been followed up since enrolment.[150] Individuals living within 25 miles of a UK Biobank assessment centre were invited to participate and there was a 5% response rate. Each participant provided a detailed account of sociodemographic, lifestyle and medical information via a nurse-led interview and touchscreen questionnaire.

The Secure Anonymised Information Linkage Databank (SAIL) is a routine care database which holds anonymised primary care data for 79% of the population of Wales.[160] Our study included participants aged 18 to 108 with data after January 1st, 2011. This date was chosen because recording of information before this date is incomplete.[8] Each participant has a random identifier which maintains confidentiality and ensures their identity stays the same if they relocate within Wales.

Inclusion Criteria

UK Biobank participants were included if their kidney function was measured at baseline. Adults over the age of 18 in SAIL were included if their kidney function was measured.

Kidney Function

The participants in each cohort were categorised into CKD (Stages 3-5: estimated glomerular filtration rate: eGFR (using the CKD-EPI formula[244]) less than 60ml/min/1.73m^2) and non-CKD (eGFR greater than 60ml/min/1.73m^2). UK Biobank participants were assumed to be well and in a stable state of health when attending for assessment. Therefore, a single eGFR measured at the baseline assessment was used. Because results in SAIL are from routine care, we cannot assume a single eGFR result is during a stable state of health. To ensure reduced eGFRs reflect a chronic state, two results at least three months apart were used, in keeping with Kidney Disease: Improving Global Outcomes recommendations.[239] An alternative approach would have been to categorise participants without eGFR measurements

as non-CKD.[268] This approach was included as a sensitivity analysis. Albuminuria was seldom recorded in SAIL, so it could not be used for the definition of CKD. Given albuminuria data were available in UK Biobank, we performed a sensitivity analysis by categorising participants with a urine albumin to creatinine ratio (uACR) greater than 30mg/g as having CKD (Kidney Disease: Improving Global Outcomes (KDIGO) A2 or worse[165]).

The UK Biobank biochemistry testing protocol has been detailed previously and calibrated analysers were used.[152, 243] Serum creatinine values for SAIL were taken from primary care data (Read codes, Appendix Table 2). Given many different laboratories were used, creatinine values were multiplied by 0.95 to account for possible lack of calibration.[21 64]

Primary Analysis

Consistent with previous literature on LTCs in UK Biobank, 42 conditions additional to CKD were captured in both cohorts and limited to conditions present before cohort entry (Table 6-1).[89] In UK Biobank, participants self-reported conditions and they entered the cohort on the date of baseline assessment. In SAIL, primary care Read codes (codes of clinical terms) were used to identify LTCs with prescription data confirming active treatment for some conditions (Appendix Table 3).[1] Participants in SAIL entered the cohort on the date of blood sampling (single sample for non-CKD and second, confirmatory sample for CKD). Participants were divided into nine categories. “Zero LTCs” was the reference category. Those without CKD were categorised as one LTC, two LTCs, three LTCs or four or more LTCs. Those with CKD were categorised as one LTC (i.e. CKD), two LTCs (i.e. CKD plus one other), three LTCs and four or more LTCs.

Table 6-1. Long-term conditions included. [m]Mental health conditions

Hypertension	Peripheral Vascular Disease	Multiple Sclerosis
Depression[m]	Atrial Fibrillation	Parkinson's Disease
Asthma	Heart Failure	Viral Hepatitis
Coronary Heart Disease	Prostate Disorders	Chronic Liver Disease
Diabetes Mellitus	Glaucoma	Diverticular Disease
Thyroid Disease	Epilepsy	Osteoporosis
Connective Tissue Disease	Dementia[m]	Pernicious Anaemia
Chronic Obstructive Pulmonary Disease	Schizophrenia or Bipolar Affective Disorder[m]	Endometriosis
Anxiety[m]	Psoriasis or Eczema	Chronic Fatigue Syndrome
Irritable Bowel Syndrome	Inflammatory Bowel Disease	Polycystic Ovarian Syndrome
Cancer	Painful Condition	Meniere's Disease
Alcohol Problems[m]	Chronic Sinusitis	Treated Constipation
Psychoactive Substance Misuse[m]	Anorexia Nervosa or Bulimia[m]	Treated Dyspepsia
Stroke or Transient Ischaemic Attack	Bronchiectasis	Migraine

Types of Condition

Conditions were categorised based on high-risk constellations of clinical disease groups[102, 103, 264]:

1. Cardiometabolic conditions
2. Complex pattern of conditions
    - This was defined as the involvement of three or more body systems. Body systems were categorised using ICD-10 codes (Infections, Neoplasms, Haematological, Endocrine/Metabolic, Mental, Neurological, Ophthalmological, Otological, Circulatory, Respiratory, Gastrointestinal, Dermatological, Musculoskeletal, Genitourinary and Other).
3. Physical and mental conditions
    - Mental health conditions are labelled in Table 6-1.

Covariates

Ethnicity was categorised as White, Black, Asian, Mixed or Other. Socioeconomic status was quantified via deprivation scores and used as a continuous variable: Townsend[245] in UK Biobank and Welsh Index of Multiple Deprivation[269] (WIMD) in

SAIL. Smoking status was categorised as never, current or previous. Body Mass Index (BMI), uACR and blood pressure were measured at baseline for UK Biobank. In SAIL, covariates were extracted using Read codes within 12 months of cohort entry (Appendix Table 2).

Outcomes

Emergency hospitalisation events i.e. admissions to hospital, following the date of cohort entry were identified using linked hospital records. They were limited to emergencies by method of admission codes (Appendix Table 4).[270] Primary diagnoses were divided into systems of the body using Clinical Classification System categories.[271] Follow-up started on the date of baseline assessment for UK Biobank and the date of blood sampling for SAIL. Follow-up ended on 31/03/2020 for UK Biobank in Scotland and England; 28/02/2018 for UK Biobank in Wales; 31/05/2018 for SAIL; or on the date of death if this occurred earlier.

Statistical Analysis

Baseline characteristics were described for the CKD and non-CKD groups using medians and interquartile ranges for continuous variables and percentages for categorical variables. Differences in the distribution of these characteristics were tested using chi-squared tests for categorical variables and Kruskal-Wallis tests for continuous variables. Variables were also compared across LTC count categories.

Event rates were calculated by summing events for participants within each category over 100 years of follow-up and provided as per 100 person years. Rate ratios were calculated using negative binomial regression models. The linearity of the relationship between LTC counts and events was studied by plotting residuals against fitted values. Negative binomial models accounted for overdispersion.[272] Standard and zero-inflated models were compared to assess for excess zeroes using Vuong tests.[182] The log of duration of follow-up was included as an offset term. Adjustments were made for age, sex, smoking status and deprivation status as these variables have previously been linked to the risk of hospitalisation.[64] Given the risk of immortal time bias in SAIL for those with CKD, we built Cox proportional hazards models using CKD diagnosis as a time-varying covariate.[273] Interactions between CKD status and LTC counts were tested by the addition of an interaction term to the

models and the application of analysis of variance (ANOVA) tests between these and the standard models. Interactions were considered significant if p-values were <0.01.

Complete case analysis was deemed appropriate for UK Biobank as greater than 95% of the cohort had complete data. Multivariate Imputation by Chained Equations[186] was performed in SAIL for smoking status and socioeconomic deprivation status with ten sets, each with ten iterations, assuming that these data were missing at random. Complete case sensitivity analysis was performed and these results were compared to the primary analysis.

CKD participants: Subgroup Analysis

Among participants with CKD, the following subgroups were studied:

- Men and women
- CKD stages (3A, 3B and 4/5)[239]
- Age (<50, 50-60, 60-70, 70-80* and >80* years, *only available in SAIL)
- Deprivation quintiles (defined by distribution in the general cohort)
- BMI (<25, 25-30 and >30kg/m^2)

Event rates were compared to identify the subgroups most vulnerable to emergency hospitalisation. Rate ratios for each increase in LTC count were used to estimate the strength of association between increasing LTC count and hospitalisation.

Type of condition

Among participants with CKD, the relationship between the type of LTC and hospitalisation was studied. The reference group was participants with zero or one LTC (excluding CKD as all participants in this part of the analysis had CKD). This was also performed for the non-CKD participants: the reference group was participants with zero or one LTC. This allowed us to compare the impact of type of LTC in people with and without CKD.

Statistical analyses were conducted using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, AUT) with the tidyverse, MASS, pubh, survival, finalfit and forestplot packages.

Results

*Participant*s

469,339 of 502,485 UK Biobank participants (93.4%) met the inclusion criteria and 10,767 (2.3%) of these had CKD. 1,620,490 of 2,611,238 adults in SAIL (62.1%) met the inclusion criteria and 173,388 (10.7%) of these had CKD. In SAIL, compared to those excluded from the analysis, those included tended to be older and had more LTCs (Supplementary Table 6-1).

Supplementary Table 6-1. Baseline characteristics in SAIL by study inclusion.

SAIL		Excluded i.e. no kidney function available N=990748	Included i.e. kidney function available N=1620490
Age (years)	Median (IQR)	30 (20-45)	50 (35-65)
Sex (%)	Female	449800 (45.4)	857305(54.7)
Ethnicity (%) Missing values 1474539 (56.5%)	White	392704 (86.1)	645205 (94.8)
	Black	8665 (1.9)	6125 (0.9)
	Asian	23261 (5.1)	16334 (2.4)
	Mixed	6385 (1.4)	3403 (0.5)
	Other	25085 (5.5)	9528 (1.4)
WIMD score Missing values 765231 (29.3%)	Median (IQR)	17.8 (10.8-30.1)	18.0 (10.8-29.8)
Smoking (%) Missing values 1035418 (39.7%)	Never	313633 (61.6)	516300 (48.4)
	Ex	61097 (12.0)	277351 (26.0)
	Current	134414 (26.4)	274151 (25.7)
Body mass index Missing values 2452490 (93.9%)	Median (IQR)	24 (21-28)	28 (24-33)
Systolic blood pressure Missing values 1220472 (46.7%)	Median (IQR)	120 (110-131)	130 (120-142)
Long-term conditions	Median (IQR)	0 (0-1)	2 (0-3)

IQR, interquartile range, WIMD Welsh Index of Multiple Deprivation

Baseline Characteristics

UK Biobank

Compared to those without CKD, the participants with CKD had more LTCs, were older, were more likely to be ex-smokers and had higher BMI and higher systolic blood pressure (Table 6-2). Participants with more LTCs (whether CKD was included or excluded) were older, were more likely to be current or ex-smokers, lived in more deprived areas, with higher BMI, higher systolic blood pressure, higher uACR and lower eGFR (Supplementary Table 6-2).

		UK Biobank			SAIL		
		No CKD n=458 572 (97.7%)	CKD n=10 767 (2.3%)	P-value	No CKD n=1 447 102 (89.3%)	CKD n=173 388 (10.7%)	P-value
Age (years)	Median (IQR)	58 (50 to 63)	64 (60 to 67)	<0.001	50 (36 to 63)	79 (72 to 85)	<0.001
Sex (%)	Female	248 751 (54.2)	5 746 (53.4)	0.072	788 725 (54.5)	98 782 (57.0)	<0.001
	Male	209 821 (45.8)	5 021 (46.6)		658 377 (45.5)	74 606 (43.0)	
Ethnicity (%)	White	432 151 (94.7)	10 202 (95.3)	0.008	622 324 (94.5)	71 424 (98.6)	<0.001
	Black	7 173 (1.6)	128 (1.2)		6 032 (0.9)	129 (0.2)	
	Asian	10 311 (2.3)	235 (2.2)		16 499 (2.5)	335 (0.7)	
	Mixed	2 705 (0.6)	48 (0.4)		3 806 (0.6)	105 (0.1)	
	Other	4 085 (0.9)	96 (0.9)		10 061 (1.5)	222 (0.3)	
	Missing values	2 205 (0.5%)			889 353 (54.9)		
Deprivation Score[a]	Median (IQR)	-2.2 (-3.7 to 0.5)	-2.0 (-3.5 to 0.9)	<0.001	18.0 (10.8 to 30.0)	17.6 (11.0 to 28.3)	<0.001
	Missing values	577 (0.1 %)			302 952 (18.7%)		
Smoking status (%)	Never	250 304 (54.9)	5 261 (49.3)	<0.001	516 728 (48.4)	65 132 (47.4)	<0.001
	Previous	157 573 (34.5)	4 558 (42.7)		273 908 (25.7)	58 190 (42.4)	
	Current	48 402 (10.6)	862 (8.1)		276 545 (25.9)	13 962 (10.2)	
	Missing values	2 379 (0.5%)			416 025 (25.7%)		
Body Mass Index (kg/m^2)	Median (IQR)	27 (24 to 30)	29 (26 to 32)	<0.001	29 (24 to 33)	29 (25 to 32)	0.394
	Missing values	1 873 (0.4%)			1 472 240 (90.9%)		
Systolic Blood Pressure (mmHg)	Median (IQR)	136 (125 to 150)	139 (127 to 152)	<0.001	130 (120 to 141)	134 (122 to 144)	<0.001
	Missing values	14 639 (3.1%)			287 529 (17.7%)		
Estimated Glomerular Filtration Rate (ml/min/1.73m^2)	Median (IQR)	93.1 (83.8 to 100.2)	54.1 (48.1 to 57.6)	<0.001	97.1 (85.4 to 109.4)	51.2 (42.9 to 56.2)	<0.001
Urine Albumin-Creatinine Ratio (mg/mmol)	Median (IQR)	0.0 (0.0 to 0.6)	0.4 (0.0 to 1.9)	<0.001	0.9 (0.5 to 2.1)	1.8 (0.8 to 5.7)	<0.001
	Missing values	13 406 (2.9%)			1 453 186 (89.7%)		
Long-term Condition Count (Excluding CKD)	Median (IQR)	1 (0 to 2)	2 (1 to 3)	<0.001	1 (0 to 2)	4 (2 to 5)	<0.001

Table 6-2. Baseline Characteristics by chronic kidney disease (CKD) status.

Interquartile range (IQR). P-values: Kruskal-Wallis test for continuous variables and chi-squared tests for categorical variables. [a]Townsend score for UK Biobank: Higher scores suggest higher levels of deprivation. Welsh Index of Multiple Deprivation Rank for SAIL: Lower ranks suggest higher levels of deprivation

Supplementary Table 6-2. Baseline characteristics by chronic kidney disease (CKD) status and number of long-term conditions (LTCs) for UK Biobank.

UK Biobank		**No CKD, No LTCs n=159642 (34.0%)**	**No CKD, 1 LTC n=151149 (32.2%)**	**No CKD, 2 LTCs n=86731 (18.5%)**	**No CKD, 3 LTCs n=38556 (8.2%)**	**No CKD, 4 or more LTCs n=22494 (4.8%)**	**CKD, No additional LTCs n=1540 (0.3%)**	**CKD, 1 additional LTC n=2696 (0.6%)**	**CKD, 2 additional LTCs n=2808 (0.6%)**	**CKD, 3 or more additional LTCs n=3723 (0.8%)**	**p-value**
Age (years)	Median (IQR)	54 (47 to 61)	58 (50 to 63)	60 (53 to 64)	61 (55 to 65)	62 (56 to 65)	62 (57 to 66)	64 (59 to 67)	65 (61 to 67)	65 (61 to 67)	<.001
Sex (%)	Female	85417 (53.5)	81437 (53.9)	47023 (54.2)	21487 (55.7)	13387 (59.5)	947 (61.5)	1448 (53.7)	1453 (51.7)	1898 (51.0)	<.001
	Male	74225 (46.5)	69712 (46.1)	39708 (45.8)	17069 (44.3)	9107 (40.5)	593 (38.5)	1248 (46.3)	1355 (48.3)	1825 (49.0)	
Ethnicity (%)	White	149679 (94.2)	142566 (94.8)	82047 (95.0)	36503 (95.2)	21356 (95.5)	1480 (96.5)	2565 (95.7)	2638 (94.5)	3519 (95.0)	<.001
	Black	2646 (1.7)	2423 (1.6)	1302 (1.5)	538 (1.4)	264 (1.2)	7 (0.5)	30 (1.1)	41 (1.5)	50 (1.3)	
	Asian	3925 (2.5)	3266 (2.2)	1862 (2.2)	805 (2.1)	453 (2.0)	19 (1.2)	59 (2.2)	69 (2.5)	88 (2.4)	
	Mixed	1028 (0.6)	878 (0.6)	486 (0.6)	191 (0.5)	122 (0.5)	9 (0.6)	7 (0.3)	17 (0.6)	15 (0.4)	
	Other	1607 (1.0)	1327 (0.9)	669 (0.8)	307 (0.8)	175 (0.8)	18 (1.2)	18 (0.7)	28 (1.0)	32 (0.9)	
Townsend Deprivation Score	Median (IQR)	-2.3 (-3.7 to 0.2)	-2.2 (-3.7 to 0.3)	-2.1 (-3.6 to 0.7)	-1.8 (-3.4 to 1.2)	-1.2 (-3.2 to 2.2)	-2.5 (-3.8 to -0.1)	-2.3 (-3.7 to 0.1)	-2.0 (-3.5 to 0.7)	-1.5 (-3.2 to 1.8)	<.001
Smoking status (%)	Never	94815 (59.7)	83235 (55.3)	44291 (51.3)	18274 (47.7)	9689 (43.4)	893 (58.3)	1425 (53.3)	1374 (49.3)	1569 (42.5)	<.001
	Previous	47508 (29.9)	51671 (34.3)	33002 (38.3)	15708 (41.0)	9684 (43.4)	531 (34.7)	1045 (39.1)	1181 (42.4)	1801 (48.8)	
	Current	16621 (10.5)	15530 (10.3)	8979 (10.4)	4326 (11.3)	2946 (13.2)	108 (7.0)	202 (7.6)	230 (8.3)	322 (8.7)	
Body Mass Index (kg/m^2)	Median (IQR)	25.8 (23.5 to 28.5)	26.6 (24.1 to 29.6)	27.5 (24.8 to 30.8)	28.3 (25.4 to 32.0)	29.4 (26.1 to 33.6)	26.7 (24.4 to 29.4)	27.6 (25.0 to 30.7)	28.5 (25.9 to 31.9)	30.0 (26.8 to 33.8)	<.001
Systolic Blood Pressure (mmHg)	Median (IQR)	133 (122 to 145)	137 (125 to 150)	140 (128 to 153)	140 (129 to 153)	140 (128 to 153)	137 (126 to 149)	139 (127 to 152)	140 (128 to 153)	139 (126 to 153)	<.001
Estimated Glomerular Filtration Rate ($ml/min/1.73m^2$)	Median (IQR)	94.6 (85.8 to 101.9)	93.0 (83.8 to 100.1)	92.0 (82.2 to 98.7)	91.4 (81.1 to 98.1)	90.9 (79.8 to 97.7)	56.0 (52.7 to 58.3)	54.9 (49.7 to 57.8)	53.7 (47.4 to 57.5)	52.3 (45.1 to 56.8)	<.001
Urine Albumin-Creatinine Ratio (mg/mmol)	Median (IQR)	0.0 (0.0 to 0.4)	0.0 (0.0 to 0.6)	0.0 (0.0 to 0.7)	0.0 (0.0 to 0.9)	0.0 (0.0 to 1.1)	0.0 (0.0 to 0.7)	0.0 (0.0 to 1.4)	0.5 (0.0 to 2.2)	0.7 (0.0 to 2.9)	<.001

IQR, interquartile range

SAIL

Compared to those without CKD, participants with CKD had more LTCs, were older, there were proportionally more women and proportionally fewer non-White people and they were more likely to be ex-smokers with higher systolic blood pressure (Table 6-1). Participants with more LTCs (whether CKD was included or excluded) were older, were more likely to be ex-smokers, lived in less deprived areas, with higher BMI, higher systolic blood pressure, higher uACR and lower eGFR (Supplementary Table 6-3).

Supplementary Table 6-3. Baseline characteristics by chronic kidney disease (CKD) status and number of long-term conditions (LTCs) for SAIL.

SAIL		**No CKD, No LTCs n=442601 (27.3%)**	**No CKD, 1 LTC n=375376 (23.2%)**	**No CKD, 2 LTCs n=290614 (17.9%)**	**No CKD, 3 LTCs n=169272 (10.4%)**	**No CKD, 4 or more LTCs n=169239 (10.4%)**	**CKD, No additional LTCs n=4311 (0.3%)**	**CKD, 1 additional LTC n=17460 (1.1%)**	**CKD, 2 additional LTCs n=29539 (1.8%)**	**CKD, 3 or more additional LTCs n=122078 (7.5%)**	**P-value**
Age (years)	Median (IQR)	43 (29 to 55)	50 (37 to 62)	52 (39 to 64)	56 (43 to 67)	62 (50 to 72)	76 (69 to 84)	77 (70 to 84)	78 (71 to 84)	79 (72 to 85)	<.001
Sex (%)	Female	218064 (49.3)	199814 (53.2)	169345 (58.3)	100293 (59.2)	101209 (59.8)	2374 (55.1)	9577 (54.9)	16348 (55.3)	70483 (57.7)	<.001
	Male	224537 (50.7)	175562 (46.8)	121269 (41.7)	68979 (40.8)	68030 (40.2)	1937 (44.9)	7883 (45.1)	13191 (44.7)	51595 (42.3)	
Ethnicity (%)	White	174878 (89.6)	158847 (94.9)	130368 (96.8)	78060 (97.7)	80171 (98.3)	1465 (98.0)	6480 (98.4)	11441 (98.5)	52038 (98.7)	<.001
	Black	3355 (1.7)	1412 (0.8)	723 (0.5)	303 (0.4)	239 (0.3)	<15	<15	25 (0.2)	88 (0.2)	
	Asian	9195 (4.7)	3951 (2.4)	1925 (1.4)	797 (1.0)	631 (0.8)	18 (1.2)	50 (0.8)	97 (0.8)	370 (0.7)	
	Mixed	1835 (0.9)	973 (0.6)	593 (0.4)	233 (0.3)	172 (0.2)	<15	<15	<15	77 (0.1)	
	Other	5961 (3.1)	2282 (1.4)	1033 (0.8)	467 (0.6)	318 (0.4)	<15	32 (0.5)	42 (0.4)	142 (0.3)	
Welsh Index of Multiple Deprivation Rank	Median (IQR)	17.1 (10.4 to 27.7)	17.3 (10.5 to 28.4)	18.4 (11.0 to 30.6)	19.3 (11.4 to 31.9)	20.4 (12.2 to 34.1)	16.8 (10.5 to 26.9)	16.8 (10.5 to 26.7)	17.1 (10.8 to 27.0)	18.0 (11.2 to 29.0)	<.001
Smoking Status (%)	Never	169456 (57.5)	139770 (51.1)	99381 (44.8)	55789 (41.4)	52332 (36.9)	1601 (54.7)	7139 (54.0)	11805 (51.1)	44587 (45.5)	<.001
	Previous	57520 (19.5)	67446 (24.6)	61184 (27.6)	40334 (29.9)	47424 (33.4)	988 (33.7)	4649 (35.2)	8992 (38.9)	43561 (44.4)	
	Current	67861 (23.0)	66492 (24.3)	61287 (27.6)	38711 (28.7)	42194 (29.7)	340 (11.6)	1426 (10.8)	2311 (10.0)	9885 (10.1)	
Body Mass Index	Median (IQR)	27 (23 to 31)	28 (24 to 32)	29 (25 to 33)	29 (25 to 34)	30 (25 to 34)	27 (24 to 30)	28 (24 to 31)	28 (25 to 32)	29 (25 to 32)	<.001
Systolic Blood Pressure (mmHg)	Median (IQR)	128 (118 to 140)	130 (120 to 142)	130 (120 to 142)	131 (120 to 142)	132 (120 to 143)	136 (124 to 144)	136 (126 to 146)	136 (125 to 145)	133 (120 to 143)	<.001
Estimated Glomerular Filtration Rate (ml/min/1.73m2)	Median (IQR)	102.7 (90.7 to 115.4)	97.3 (85.9 to 109.2)	95.9 (84.4 to 107.7)	93.3 (82.3 to 104.7)	89.6 (79.2 to 100.3)	52.4 (45.7 to 56.6)	52.2 (44.9 to 56.6)	51.9 (44.0 to 56.5)	50.8 (42.2 to 56.1)	<.001
Albumin-Creatinine Ratio (mg/mmol)	Median (IQR)	0.8 (0.5 to 1.7)	0.8 (0.5 to 1.7)	0.9 (0.5 to 2.0)	0.9 (0.5 to 2.1)	1.1 (0.6 to 2.6)	1.1 (0.6 to 3.3)	1.3 (0.7 to 3.6)	1.5 (0.7 to 4.7)	1.9 (0.8 to 6.2)	<.001

IQR, interquartile range

Primary Analysis

Median follow-up time in UK Biobank was 11.2 years (interquartile range (IQR) 10.5-11.9) and in SAIL it was 8.0 years (IQR 6.5-8.2). There was a dose-response relationship between the number of LTCs and event rates in participants with and without CKD in both cohorts (Supplementary Table 6-4). Event rates were higher when CKD was included as an LTC, particularly in SAIL. The most common cause of hospitalisation was circulatory, especially in those with CKD (Supplementary Table 6-5).

Supplementary Table 6-4. Hospitalisation Events by Chronic Kidney Disease (CKD) status and number of long-term conditions (LTCs).

LTCs	UK Biobank										SAIL									
	No CKD					CKD					No CKD					CKD				
	Events per 100 person years	Unadjusted		Adjusted*		Events per 100 person years	Unadjusted		Adjusted*		Events per 100 person years	Unadjusted		Adjusted*		Events per 100 person years	Unadjusted*		Adjusted*	
		Rate Ratio	P-value	Rate Ratio	P-value		Rate ratio	P-value	Rate ratio	P-value		Rate Ratio	P-value	Rate Ratio	P-value		Rate Ratio	P-value	Rate Ratio	P-value
0	2.45	1.00 (ref.)		1.00 (ref.)							3.02	1.00 (ref.)		1.00 (ref.)						
1	2.96	1.47 (1.45-1.49)	<.001	1.47 (1.45-1.49)	<.001	2.76	1.34 (1.22-1.47)	<.001	1.36 (1.23-1.52)	<.001	3.36	1.52 (1.51-1.54)	<.001	1.27 (1.25-1.29)	<.001	6.45	3.28 (3.12-3.46)	<.001	3.34 (3.11-3.60)	<.001
2	3.50	2.08 (2.05-2.11)	<.001	2.09 (2.05-2.12)	<.001	3.61	2.59 (2.42-2.77)	<.001	2.75 (2.55-2.96)	<.001	3.88	2.15 (2.13-2.17)	<.001	1.70 (1.67-1.72)	<.001	6.50	3.71 (3.62-3.81)	<.001	3.54 (3.42-3.67)	<.001
3	4.09	3.02 (2.96-3.08)	<.001	3.02 (2.96-3.08)	<.001	4.49	3.90 (3.69-4.12)	<.001	4.43 (4.14-4.74)	<.001	4.38	2.99 (2.95-3.03)	<.001	2.23 (2.20-2.27)	<.001	7.23	4.46 (4.38-4.54)	<.001	4.57 (4.45-4.70)	<.001
4 or more	4.81	4.78 (4.67, 4.89)	<.001	4.95 (4.82-5.06)	<.001	5.23	6.40 (6.13-6.69)	<.001	7.83 (7.42-8.25)	<.001	5.38	4.96 (4.91-5.02)	<.001	3.77 (3.71-3.82)	<.001	10.16	7.54 (7.46-7.62)	<.001	9.92 (9.75-10.09)	<.001

*Adjusted for age, sex, deprivation status and smoking status

Supplementary Table 6-5.

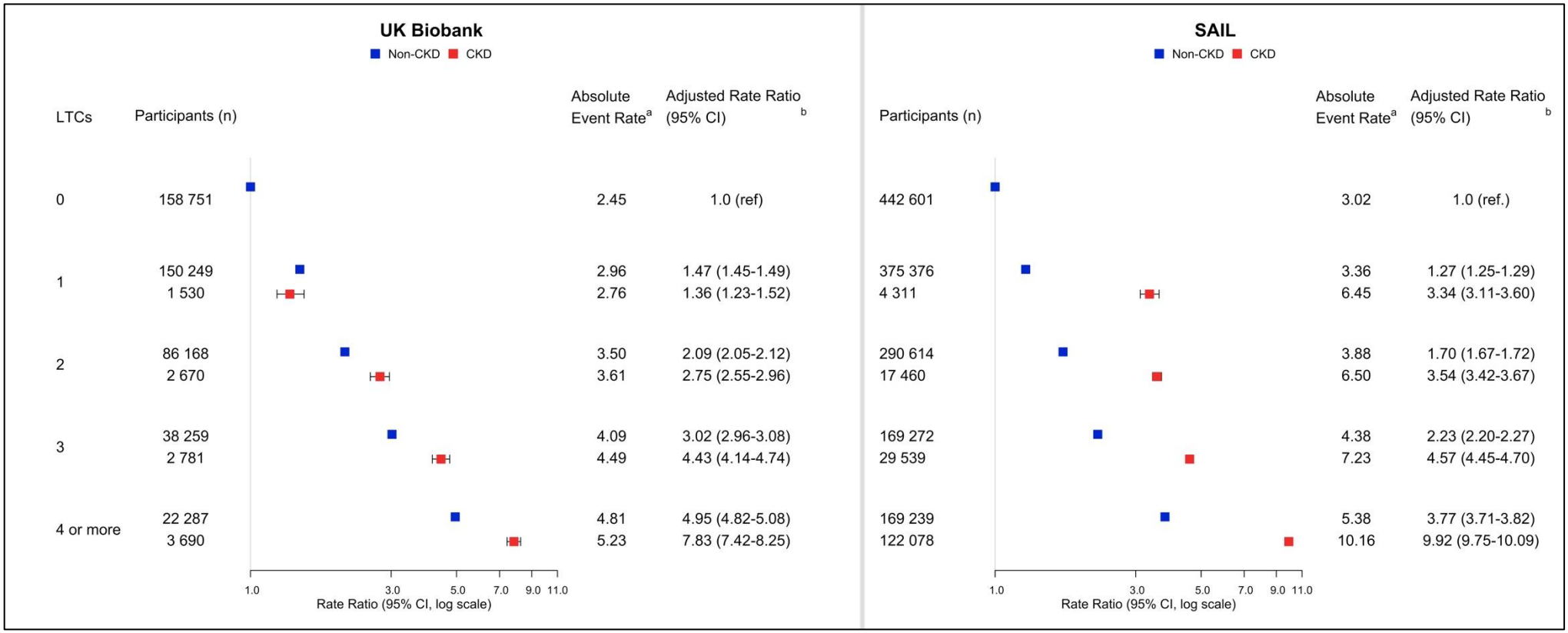
Body System	Hospitalisation Events (%)					
	UK Biobank			SAIL		
	No CKD	CKD	P-value	No CKD	CKD	P-value
Circulatory	98 522 (18.1)	6 696 (22.4)	<.001	211 594 (15.5)	116 788 (23.7)	<.001
Metabolic	5 535 (1.0)	903 (3.0)		164 486 (12.0)	119 920 (24.3)	
Gastrointestinal	49 531 (9.1)	2 685 (9.0)		88 582 (6.5)	22 401 (4.5)	
Respiratory	29 655 (5.5)	1 988 (6.7)		74 240 (5.4)	14 600 (3.0)	
Injuries	64 076 (11.8)	2 794 (9.4)		37 103 (2.7)	4 118 (0.8)	
Genitourinary	19 593 (3.6)	2 160 (7.2)		30 344 (2.2)	9 399 (1.9)	
Neoplasms	15 920 (2.9)	834 (2.8)		90 045 (6.6)	31 216 (6.3)	
Musculoskeletal	23 878 (4.4)	1 259 (4.2)		27 934 (2.0)	6 757 (1.4)	
Neurological	18 916 (3.5)	706 (2.4)		54 356 (4.0)	12 551 (2.5)	
Infections	5 701 (1.0)	434 (1.5)		25 556 (1.9)	9 114 (1.8)	
Dermatological	13 063 (2.4)	713 (2.4)		20 016 (1.5)	4 697 (1.0)	
Haematological	2 910 (0.5)	338 (1.1)		34 224 (2.5)	23 501 (4.8)	
Congenital Abnormalities	287 (0.1)	74 (0.2)		805 (0.1)	98 (0.0)	
Other	71 022 (13.1)	1 760 (5.9)		248 869 (18.2)	36 497 (7.4)	
Missing	125 372 (23.0)	6 487 (21.7)		258 009 (18.9)	81 923 (16.6)	

Causes of Hospitalisation. CKD, chronic kidney disease

A linear relationship was identified between LTC counts and log event rates in both cohorts whether CKD was included or not. Vuong tests demonstrated that standard models were superior to zero-inflated models ($p<0.001$ in both cohorts).

In both cohorts, event rates and rate ratios were highest in those with more LTCs (Figure 6-1). For UK Biobank participants with one LTC, the rate ratios were similar for those with and without CKD. For SAIL participants with one LTC, the rate ratio was higher in those with CKD compared to those without CKD. With increasing numbers of LTCs in both cohorts, the rate ratios were higher, especially in those with CKD.

Figure 6-1. Hospitalisation Events by Chronic Kidney Disease (CKD) status and number of long-term conditions (LTCs).



[a]Events per 100 patient years. [b]Adjusted for age, sex, deprivation status and smoking status. P-values for all categories <0.001

UK Biobank sensitivity analysis

Compared to the primary analysis, effect sizes were very similar when participants with albuminuria were categorised as having CKD (Supplementary Table 6-6).

Supplementary Table 6-6. UK Biobank Sensitivity analysis. Analysis categorising participants with albuminuria as Chronic Kidney Disease (CKD). Hospitalisation Events by CKD status and number of long-term conditions (LTCs)**.**

LTCs	No CKD			CKD		
	Events per 100 participant years	Unadjusted Rate Ratio	Adjusted* Rate Ratio	Events per 100 participant years	Unadjusted Rate Ratio	Adjusted* Rate Ratio
0	2.45	1.0 (re.)	1.0 (ref.)			
1	2.96	1.46 (1.44, 1.48)	1.47 (1.45, 1.49)	2.85	1.40 (1.28, 1.53)	1.41 (1.29, 1.55)
2	3.50	2.07 (2.04, 2.11)	2.08 (2.05, 2.12)	3.62	2.61 (2.45, 2.77)	2.75 (2.56, 2.94)
3	4.08	3.00 (2.95, 3.06)	3.00 (2.94, 3.07)	4.50	3.89 (3.7, 4.1)	4.38 (4.12, 4.67)
4 or more	4.80	4.76 (4.65, 4.87)	4.92 (4.79, 5.06)	5.27	6.4 (6.14, 6.67)	7.76 (7.38, 8.16)

*Adjusted for age, sex, Welsh Index of Multiple Deprivation and smoking status. P-values <.001 for all comparisons

SAIL sensitivity analyses

Compared to the primary analysis, effect sizes were higher for CKD participants when categorising those without biochemistry as non-CKD (Supplementary Table 6-7), but similar when using CKD diagnosis as a time-varying covariate (Supplementary Table 6-8) and in complete case analysis (Supplementary Table 6-9). There was evidence of multiplicative interactions between CKD status and the number of LTCs ($p<0.01$ in both cohorts).

Supplementary Table 6-7. SAIL Sensitivity analysis 1. Analysis including participants without biochemistry categorised as no Chronic Kidney Disease (CKD). Hospitalisation Events by CKD status and number of long-term conditions (LTCs).

LTCs	No CKD			CKD		
	Events per 100 participant years	Unadjusted Rate Ratio	Adjusted* Rate Ratio	Events per 100 participant years	Unadjusted Rate Ratio	Adjusted* Rate Ratio
0	1.57	1.0 (ref.)	1.0 (ref.)			
1	2.08	1.75 (1.73-1.77)	1.43 (1.42-1.45)	6.45	4.88 (4.64-5.14)	7.06 (6.63-7.52)
2	2.47	2.43 (2.40-2.46)	1.89 (1.87-1.91)	6.50	5.52 (5.39-5.66)	7.42 (7.19-7.66)
3	2.95	3.36 (3.32-3.39)	2.53 (2.51-2.56)	7.23	6.63 (6.51-6.75)	9.62 (9.39-9.86)
4 or more	3.97	5.79 (5.74-5.85)	4.61 (4.56-4.66)	10.16	11.22 (11.11-11.32)	21.20 (20.87-21.50)

*Adjusted for age, sex, Welsh Index of Multiple Deprivation and smoking status. P-values <.001 for all comparisons

Supplementary Table 6-8. SAIL Sensitivity analysis 2. Analysis using chronic kidney disease (CKD) diagnosis as a time-varying covariate. Hospitalisation Events by CKD status and number of long-term conditions (LTCs).

LTCs	No CKD	CKD
	Hazard Ratio*	Hazard Ratio*
0	1.0 (ref.)	
1	1.35 (1.33-1.36)	3.56 (3.42-3.76)
2	1.62 (1.61-1.64)	4.00 (3.91-4.10)
3	1.92 (1.91-1.94)	4.87 (4.78-4.96)
4 or more	2.54 (2.52-2.57)	8.19 (8.10-8.29)

*Adjusted for age, sex, Welsh Index of Multiple Deprivation and smoking status. P-values <.001 for all comparisons

Supplementary Table 6-9. SAIL Sensitivity analysis 3. Complete case analysis: Hospitalisation Events by Chronic Kidney Disease (CKD) status and number of long-term conditions (LTCs).

LTCs	No CKD	CKD
	Rate Ratio*	Rate Ratio*
0	1.00 (ref.)	
1	1.27 (1.25-1.29)	3.34 (3.09-3.61)
2	1.70 (1.67-1.72)	3.54 (3.41-3.68)
3	2.23 (2.19-2.27)	4.57 (4.43-4.72)
4 or more	3.77 (3.70-3.83)	9.92 (9.71-10.13)

*Adjusted for age, sex, Welsh Index of Multiple Deprivation and smoking status. P-values <.001 for all comparisons

CKD participants: Subgroup Analysis

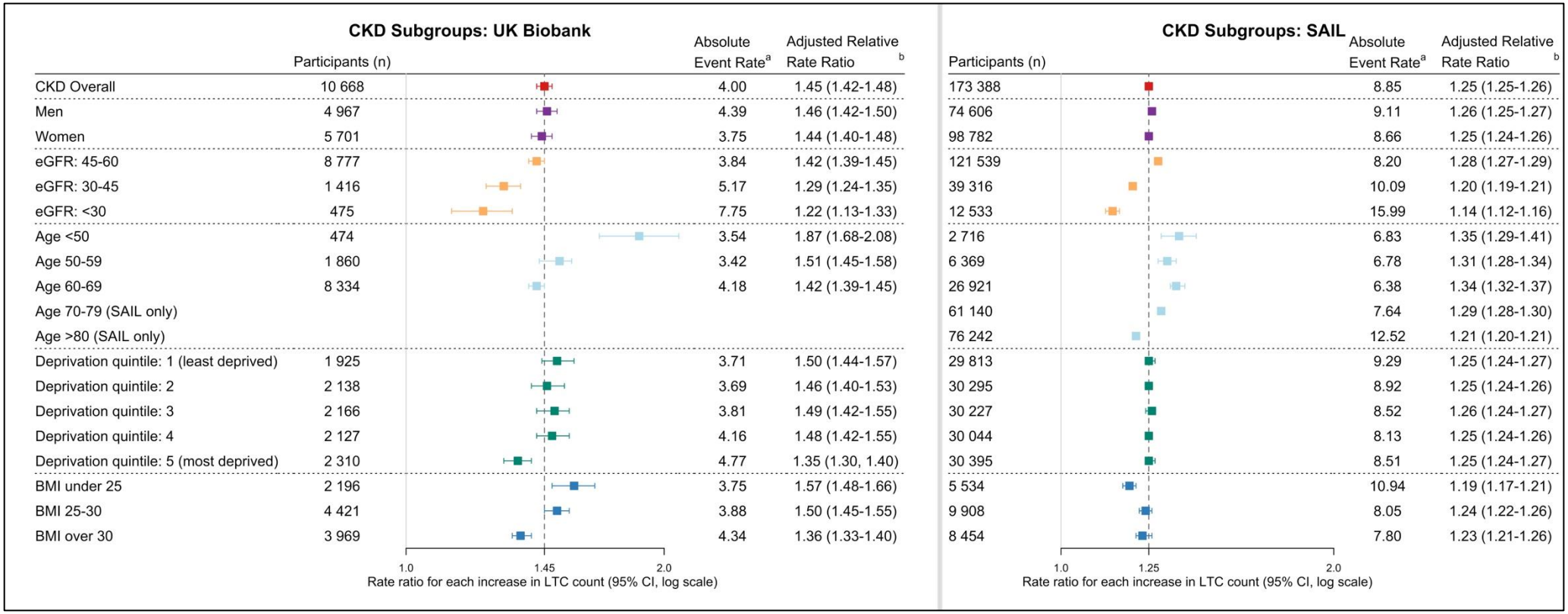
Event rates in subgroups with CKD *(Figure 6-2)*

Among those with CKD, event rates were similar for men and women. In both cohorts, participants over the age of 60 and participants with eGFRs less than 30ml/min/1.73m^2 had high event rates. In UK Biobank, event rates were highest in those living in the most deprived areas, but this was not the case in SAIL. In UK Biobank, participants with low BMIs had lower event rates than those with higher BMIs. The opposite trend was seen in SAIL, although proportionally few SAIL participants had BMI recorded and could be included in this part of the analysis.

Rate ratios in subgroups with CKD *(Figure 6-2)*

The importance of increasing LTC count as a risk factor was assessed via adjusted rate ratios for each increase in LTC. In both cohorts, adjusted rate ratios were similar for men and women and for participants from different deprivation quintiles. Adjusted rate ratios were higher in those under the age of 50 and those with eGFRs 45-60ml/min/1.73m^2 compared to older participants and those with lower eGFRs. In UK Biobank, the adjusted rate ratio was higher for those with BMI less than 25kg/m^2 than for those with higher BMI, but this trend was not seen in SAIL.

Figure 6-2. Risk of Hospitalisation Events in Chronic Kidney Disease (CKD) participants with number of long-term conditions (LTCs) by sub-group.



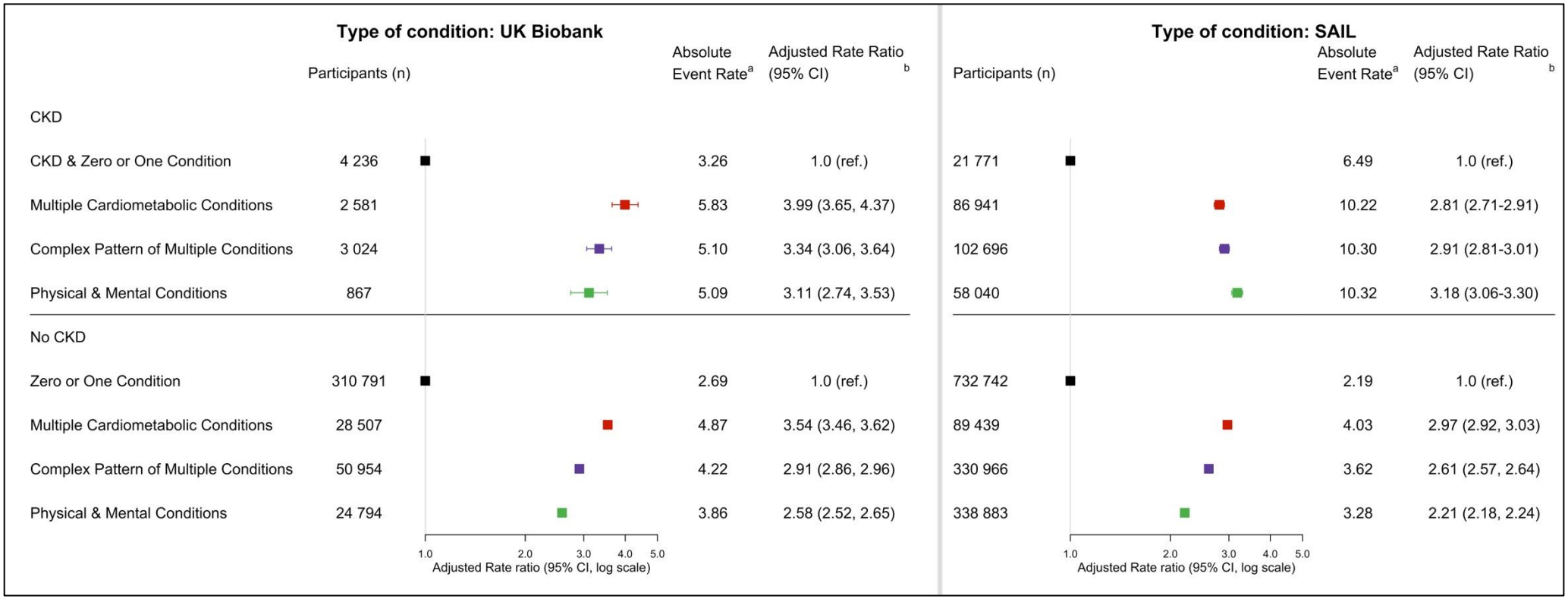
eGFR, Estimate glomerular filtration rate. BMI, Body mass index. [a]Events per 100 patient years. [b]Adjusted for age, sex, deprivation status and smoking status. P-values for all categories <0.001

Type of condition *(Figure 6-3)*

In both cohorts, participants with CKD and multiple cardiometabolic conditions were three to four times more likely to have events than those with CKD and zero or one LTC. Event rates for those with CKD and complex LTCs were approximately three times the rate of those with CKD and zero or one LTC. Participants with CKD, physical and mental health LTCs were approximately three times more likely to have events than those with CKD and zero or one LTC.

In both cohorts, similar trends were seen for the non-CKD participants, but with lower effect sizes compared to the CKD participants (except for cardiometabolic LTCs in SAIL). In SAIL, combined physical and mental conditions was a more significant risk factor in CKD participants (adjusted rate ratio 3.18: 3.06-3.30) compared to non-CKD participants (adjusted rate ratio 2.21: 2.18-2.24).

Figure 6-3. Hospitalisation Events by type of condition.



[a]Events per 100 patient years. [b]Adjusted for age, sex, deprivation status and smoking status. P-values for all categories <0.001

Discussion

We have studied emergency hospitalisations in a combined 2.1 million individuals from a prospective research study and a routine care database. Those with more LTCs had high rates of emergency hospitalisation and the risk was substantially increased by two to threefold in those with CKD (depending on the cohort). We also showed that the type of LTCs was important: those with CKD plus multiple cardiometabolic conditions, complex LTCs and physical and mental health LTCs were at heightened risk of hospitalisation.

Previous studies have identified a relationship between reduced eGFR and hospitalisation.[237, 274] Others have examined cohorts of patients with CKD and demonstrated that patients with LTCs are at high risk of hospitalisation.[120] What has not been studied before is how CKD relates to hospitalisation compared to, or in combination with, other LTCs. We have demonstrated that CKD is not equivalent to other LTCs as part of a multimorbidity count, but rather that individuals with CKD as one of the LTCs are particularly vulnerable to hospitalisation. In our study, people with CKD were frequently admitted with cardiovascular problems. This vulnerability to cardiovascular problems amongst people with CKD is well known, and it undoubtedly contributed to the overall high rates of hospitalisation in our study. The use of sodium-glucose cotransporter-2 inhibitors may prevent a proportion of these admissions in future.[275] Because numerous multimorbidity measures exist, researchers are encouraged to use a measure which suits their purpose.[80] Our study supports this message, emphasising that CKD is a critical condition in these measures and its significance should not be overlooked.

Amongst those with CKD, we found low eGFR and advanced age to be associated with high hospitalisation rates. However, regression analyses showed there was a disproportionately strong association between the number of LTCs and hospitalisation in those under the age of 50. We had hypothesised that the link between LTCs and hospitalisation would be strongest in those with more advanced CKD. We were surprised to find that the association between the number of LTCs and hospitalisation was less strong than the same association in those with mild to moderate CKD. It may be that because people with advanced CKD are primarily

elderly, most of them have multiple LTCs and they have such a high baseline rate of hospitalisation, the influence of additional LTCs is attenuated. A previous study in 530,771 Canadians with CKD studied the link between the type of LTC and adverse outcomes.[120] As in our study, they found associations between LTCs and hospitalisation. In their study, this relationship was not unique to concordant LTCs, with associations also seen for discordant and mental health conditions. We have meaningfully extended this subject area by finding that certain combinations of LTCs were associated with heightened risk of hospitalisation (cardiometabolic, complex and physical/mental LTCs).

These findings are important for patients, carers, healthcare professionals and policy makers. As people with CKD and LTCs are known to be high-risk, clinicians caring for them should provide targeted monitoring. This does not mean monitoring of blood tests in isolation, as people with CKD and multimorbidity should have regular, thorough reviews of their clinical status, medications and preferences. CKD is common in the general population and although asymptomatic in the early stages, knowing which people have CKD may be helpful for healthcare planning. Combined physical and mental health conditions was a risk factor for hospitalisation in our study. Although we cannot assume that mental health support would prevent hospitalisations, people with mental and physical conditions are in need of psychological support,[276] which has been proven to reduce depression and improve self-management. [118]

Alternative strategies to hospitalisation exist, with improvements in quality of life for patients and cost reductions for healthcare systems.[277] Safe and effective care can be provided for outpatient management of illnesses such as pneumonia.[278] Alternatively, some people may not wish to be hospitalised and “Hospital at Home” services[279] and/or anticipatory care planning[280] may be better for some people. Clinicians should be mindful of these strategies when seeing people with multiple health conditions, and they should discuss the options during routine appointments, so their patients know what alternatives to emergency admission exist. Care models like these are not appropriate for all people or all illnesses, but when they are used, they can be beneficial for patients and less costly for healthcare systems. Structured

interventions are, however, not always successful[281], and incentivisation may be necessary to reduce admissions.[282]

Our study has several strengths. Using two large cohorts, we have expanded from a research setting with healthy volunteer bias[154] to a routine care database to confirm the generalisability of our findings in the general population. The use of linked healthcare records with universal coverage in the UK ensures we have identified most hospitalisations.[283] UK Biobank has been used extensively to study risk factors for health outcomes, but it sometimes draws criticism for not being representative of the general population.[154] Although event rates were higher in SAIL and the general population were older with more LTCs, the trends identified in UK Biobank were similar in SAIL.

Our study has some limitations. Although we have adjusted for age in our regression models, there is still a possibility of residual confounding. Some risk factors are undoubtedly on the causal pathways to our exposures and our outcome (e.g. obesity, alcohol use). It has not been possible in this study to unravel the complex relationships between all risk factors, exposures and the outcome. The relative lack of ethnic diversity in these particular UK cohorts means that the study should be replicated in other contexts. The eGFR equation we used (CKD-EPI) incorporates ethnicity, and there is not yet consensus in the medical community about whether this is appropriate.[284] LTCs in UK Biobank were self-reported and this risks the introduction of error. Although self-report may be less accurate for some conditions such as heart failure[285], it has been found to be a valid approach.[256, 172] CKD status, LTCs and covariates were only taken at baseline and we have not taken into account changes during follow-up. Data about severity of conditions would have been informative (particularly for some conditions such as heart failure and chronic obstructive pulmonary disease), but this was not available. Regardless, it would have been difficult to synthesise such information for 42 conditions. We employed counts of conditions rather than an index which assigns scores to conditions associated with greater morbidity. The evidence regarding whether simple counts or weighted measures are preferable is mixed[82] with some systematic reviews concluding that both are equally effective at predicting most outcomes.[81] A meta-review of six systematic reviews on this topic concluded there is a lack of a clear consensus and it

suggested selection of measures should depend on the purpose of any given study.[83] Our finding that CKD is linked to a heightened risk of hospitalisation may be transferable to other specific conditions, but we have not repeated it for each condition. We excluded 37.9% of the SAIL population without biochemistry data, who tended to be younger with fewer additional LTCs than those included. Sensitivity analysis showed that the difference in hospitalisation rates between non-CKD and CKD groups widened when participants without biochemistry were categorised as non-CKD. SAIL participants were lost to follow-up if they move away from Wales, which means some hospitalisation events may have not been recorded. The rates of missing data were high for some variables in SAIL. Multiple imputation was used, with similar results obtained in complete case analysis.

Conclusions

People with increasing multimorbidity count are therefore at high risk of emergency hospitalisation, and the rates are two to threefold higher when CKD is present. People with CKD at heightened risk of hospitalisation should be targeted by research aimed at addressing emergency hospital admissions.

Declarations

Ethics approval and consent to participate

For UK Biobank, participants provided written, informed consent, including for linkage to hospital records. The NHS National Research Ethics Service provided ethical approval for this study as part of project 14151 (16/NW/0274). For SAIL, Swansea University's Health Information Research Unit Information Governance Review Panel granted approval for this study as part of project 0830.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from UK Biobank and SAIL, subject to successful registration and application process. Further details can be found at ukbiobank.ac.uk and saildatabank.com.

Competing interests

DN reports fees from GSK, outside the submitted work; PM2 reports personal fees and non-financial support from Vifor, personal fees from Astrazeneca, Astellas, Novartis and Janssen grants from Boehringer Ingelheim, personal fees and non-financial support from Pharmacosmos, personal fees and non-financial support from Napp, outside the submitted work; MS, AM, BJ, JC, BN, FM, PH, PM1 and DM have nothing to disclose.

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Authors' contributions

The aim of this research was developed by MS, PM2, BJ and FM. The analysis was conducted by MS and PH. MS, BJ, AM, PH, PM1, BN, JJC, DN, DM, FM and PM2 contributed to the design and interpretation of the analysis and to the direction of the discussion. MS wrote the first draft of this manuscript; PM2 contributed to writing and led on the manuscript development. MS, BJ, AM, PH, PM1, BN, JJC, DN, DM, FM and PM2 reviewed, edited, and commented on drafts of the manuscript and approved the final manuscript.

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Chapter: 7 Acute kidney injury in patients hospitalised with COVID-19 from the ISARIC WHO CCP-UK Study: a prospective, multicentre cohort study

7.1 Reference

Sullivan, M. K., Lees, J. S., Drake, T. M., Docherty, A. B., Oates, G., Hardwick, H. E., Russell, C. D., Merson, L., Dunning, J., Nguyen-Van-Tam, J. S., Openshaw, P., Harrison, E. M., Baillie, J. K., Investigators, I., Semple, M. G., Ho, A., Mark, P. B. (2022). Acute kidney injury in patients hospitalized with COVID-19 from the ISARIC WHO CCP-UK Study: a prospective, multicentre cohort study. *Nephrology Dialysis Transplantation*, *37*(2), 271–284. https://doi.org/10.1093/NDT/GFAB303

7.2 Chapter summary

In this chapter, acute kidney injury related to COVID-19 was studied, with a focus on risk factors and the relationship with mortality.

7.3 Manuscript

Abstract

Background: Acute kidney injury (AKI) is common in COVID-19. This study investigated adults hospitalised with COVID-19 and hypothesised that risk factors for AKI would include co-morbidities and non-white race.

Methods: A prospective multicentre cohort study was performed using patients admitted to 254 UK hospitals with COVID-19 between January 17th 2020 and December 5th 2020.

Results: Of 85,687 patients, 2,198 (2.6%) received acute kidney replacement therapy (KRT). Of 41,294 patients with biochemistry data, 13,000 (31.5%) had biochemical AKI: 8,562 stage 1 (65.9%), 2,609 stage 2 (20.1%) and 1,829 stage 3 (14.1%). The main risk factors for KRT were chronic kidney disease (CKD: Adjusted odds ratio (aOR) 3.41: 95% confidence interval 3.06-3.81), male sex (aOR 2.43: 2.18-2.71) and black race (aOR 2.17: 1.79-2.63). The main risk factors for biochemical AKI were admission respiratory rate >30 breaths per minute (aOR 1.68: 1.56-1.81), CKD (aOR 1.66: 1.57-1.76) and black race (aOR 1.44: 1.28-1.61). There was a gradated rise in the risk of 28-day mortality by increasing severity of AKI: stage 1 aOR 1.58 (1.49-1.67); stage 2 aOR 2.41 (2.20-2.64); stage 3 aOR 3.50 (3.14-3.91); KRT aOR 3.06 (2.75-3.39). AKI rates peaked in April 2020 and the subsequent fall in rates could not be explained by the use of dexamethasone or remdesivir.

Conclusions: AKI is common in adults hospitalised with COVID-19 and it is associated with a heightened risk of mortality. Although the rates of AKI have fallen from the early months of the pandemic, high-risk patients should have their kidney function and fluid status monitored closely.

Study registration ISRCTN66726260. The ISARIC WHO CCP-UK study was registered at https://www.isrctn.com/ISRCTN66726260 and designated an Urgent Public Health Research Study by NIHR.

KEY LEARNING POINTS

What is already known about this subject.

- Acute kidney injury is the commonest complication in COVID-19 and it is associated with an increased risk of mortality.
- Studies from early in the pandemic identified risk factors for COVID-AKI: male sex, older age, black race, diabetes, chronic kidney disease, hypertension, heart disease and obesity.
- This is the largest prospective cohort study of kidney outcomes in patients hospitalised with COVID-19 with data over the course of 2020 and it includes valuable information on illness severity, race and COVID-19 specific medications.

What this study adds.

- Patients from minority ethnic backgrounds are at heightened risk of COVID-AKI and co-morbidities like diabetes and chronic kidney disease play important roles in their risk profiles.
- COVID-AKI has become less common since the first wave of the pandemic, but this is not linked to the use of Dexamethasone or Remdesivir.

What impact this may have on practice or policy.

- Although the rates of COVID-AKI have fallen from the first wave of the pandemic, it remains common, particularly in patients with chronic kidney disease, patients with severe COVID-19 illness and patients of black race.
- Given the link between COVID-AKI and mortality, clinicians should monitor the fluid balance and kidney function of patients with COVID-19 and intervene early if acute kidney injury occurs.

Keywords: Acute kidney injury, Dialysis, Renal failure, SARS-CoV-2, COVID-19

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a major impact on global health. Although COVID-19 produces primarily pulmonary damage (acute respiratory distress syndrome – ARDS), acute kidney injury (AKI) is common,[286] ranging from minor biochemical changes in serum creatinine to requirement for kidney replacement therapy (KRT: dialysis or haemofiltration).

As infection rates accelerated in New York in March 2020, there were reports of AKI in 37% of hospitalised patients[287 288 168], substantially higher than reports from China (<5%).[289 290] Given KRT resources are finite, additional strategies were planned in some areas[291], including acute peritoneal dialysis.[292] However, AKI rates among patients with COVID-19 have fallen as the pandemic has unfolded, perhaps due to improvements in treatment, changes in practice, or some other factors. Several mechanisms of AKI in COVID-19 have been postulated, including systemic inflammation[293]; kidney tropism and direct damage[294295]; collapsing glomerulopathy[296]; complement activation[297]; and organ crosstalk; although it seems likely from case series that acute tubular necrosis is the predominant renal pathology.[298 299] AKI is common in all patients treated in critical care environments, so it may be that AKI in COVID-19 is merely an indicator of severe illness.

Studies of AKI from the early months of the pandemic have not been verified and updated via comprehensive studies. The International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) World Health Organization (WHO) Clinical Characterisation Protocol UK (CCP-UK) for Severe Emerging Infections was planned in 2012 to capture clinical information on any emerging infectious disease. It was activated in the UK on January 17th, 2020 in response to the COVID-19 pandemic and has collected data since. It is one of the largest global cohorts of patients hospitalised with COVID-19 and it has demonstrated that renal complications are more frequent than in any other body system.[300] This study investigates AKI in detail, refining the estimates of risk factors and mortality and focusing on the potential relationships between AKI and race, illness severity and pharmaceutical intervention.

Materials and Methods

Study Design and Patients

Adults over the age of 18 hospitalised between January 17th 2020 and December 5th 2020 with confirmed or highly suspected SARS-CoV-2 infection leading to COVID-19 were recruited at 254 sites in England, Scotland and Wales. Data were entered into a standardised Research Electronic Data Capture secure online database.[301] Study information and materials are available online.[167] Confirmation of SARS-CoV-2 was performed using reverse-transcriptase polymerase chain reaction. Highly suspected cases were eligible for inclusion because SARS-CoV-2 was an emergent pathogen at the time of protocol activation. Exclusion criteria were long-term dialysis, nosocomial infection and readmission to hospital (i.e. only the first admission was included for each patient).[302] Two analyses were performed:

- KRT analysis: patients with information on the need for acute KRT were included.
- Biochemical AKI analysis: patients with two or more serum creatinine results were included.

Outcomes

The primary outcome was the use of acute KRT. The secondary outcome was biochemical AKI. We used biochemical AKI definitions based on the National Health Service AKI e-alert algorithms[303] and AKI severity was graded using KDIGO stages[304]:

- Stage 1
    - Serum creatinine >26 µmol/L higher than the lowest creatinine within 48 hours
    - Serum creatinine ≥1.5-1.9 times higher than the lowest creatinine within seven days
    - Serum creatinine ≥1.5-1.9 times higher than the median of all creatinine values eight to 365 days ago
- Stage 2
    - Serum creatinine ≥2-2.9 times higher than the lowest creatinine within seven days

    - Serum creatinine ≥2-2.9 times higher than the median of all creatinine values eight to 365 days ago
- Stage 3 Biochemical
    - Serum creatinine ≥3 times higher than the lowest creatinine within seven days
    - Serum creatinine ≥3 times higher than the median of all creatinine values eight to 365 days ago

Covariates

Race was categorised as white, black, south Asian, east Asian and other. Socioeconomic deprivation was quantified using Index of Multiple Deprivation (IMD) scores. Smoking status was categorised as “Never”, “Previous” and “Current”. Health conditions and long-term use of medications before admission were captured from available health care records by research nurses and volunteer medical students. Illness severity on admission was estimated using oxygen saturation on air and respiratory rate.

Statistical Methods

Patient characteristics were described for those who received and did not receive KRT, for those with each stage of biochemical AKI and for those from the overall cohort with and without biochemistry data. Medians and interquartile ranges were used to describe continuous variables and percentages for categorical variables.

Logistic regression was performed to study the associations between risk factors and KRT, biochemical AKI and each stage of AKI. Adjustments were made for age, sex, race, diabetes, heart disease, chronic kidney disease (CKD), use of renin-angiotensin system blockers (RAS-blockers) before admission and socioeconomic deprivation status (as these variables have previously been associated with AKI[304]), oxygen saturation on air and respiratory rate on admission (as indicators of illness severity, both as continuous variables). Age as a confounder was treated as a continuous variable and as a risk factor as a categorical variable. The missingness patterns of race, deprivation, diabetes, heart disease, CKD, and admission respiratory rate and oxygen saturations were explored, and these variables were found to be missing at random. Multiple imputation using chained equations[305] was

used for these variables using ten sets, each with ten iterations and Rubin's rules were used to combine the results.[306] Complete case sensitivity analysis was performed and the results compared to those from multiple imputation. Prespecified interaction analyses were performed for the relationship between race and each of KRT and biochemical AKI and considered significant if p-values <0.01. Race was studied with interaction analyses given the high rates of adverse outcomes seen amongst non-white groups with COVID-19.

The relationship between AKI and 28-day mortality was described using a Kaplan-Meier survival curve. Follow-up started on the date of symptom onset or – where this was not available – the date of hospitalisation. Follow-up ended on the date of death or discharge (whichever occurred first); or 28 days following hospitalisation if neither event occurred. Patients were categorised by the highest stage of AKI they reached. Logistic regression was performed for 28-day mortality using the same confounders and multiple imputation approach as in the AKI analyses. These analyses were stratified by AKI stage and critical care status.

AKI rates in each month in 2020 were compared by calculating the proportion of patients with each stage of AKI. 95% confidence intervals were calculated using Wilson Score Intervals.[307] Severity of COVID-19 illness was compared using median admission 4C Mortality Scores per month.[308]

The median number of days from both symptom onset and hospitalisation to identification of AKI was compared per month. The proportion of patients whose AKI had resolved by the end of follow-up was calculated.

The risk of AKI in patients receiving dexamethasone was compared to patients not receiving dexamethasone using propensity score matching. Propensity score matching was used for this part of the study as a method for evaluating treatment effects using observational data.[181] Only patients receiving supplemental oxygen and admitted to hospital after 31/05/2020 were included because dexamethasone became the standard of care for patients with COVID-19 requiring oxygen from June 2020 onwards.[309] Patients with AKI on the day of admission were excluded from this part of the analysis because the influence of dexamethasone on AKI could not be

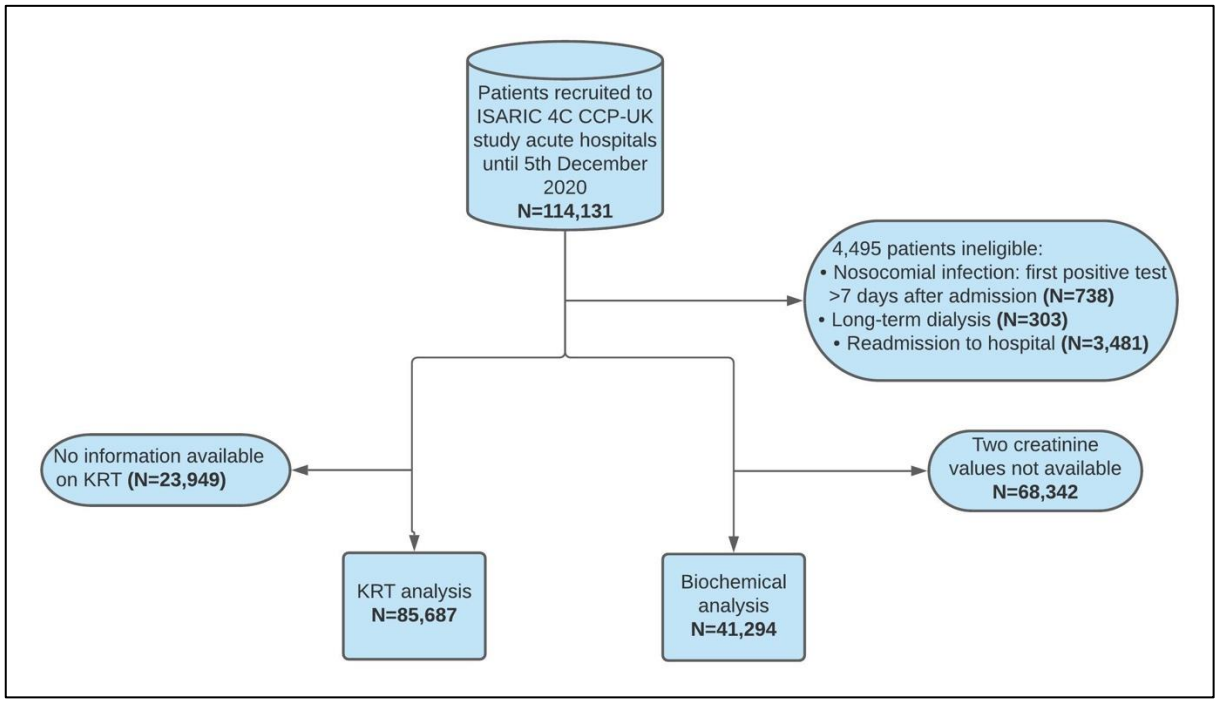
determined for them. Exact matching was performed for month of admission with nearest neighbour matching for age, sex, race, IMD deprivation quintile, diabetes, heart disease, CKD, RAS-blockers and oxygen saturations on air and respiratory rate on admission. The same analysis was performed for remdesivir, but in addition patients needed satisfactory kidney and liver function on admission to be included, based on UK prescribing guidelines for remdesivir (estimated glomerular filtration rate greater than 30ml/min/1.73m^2 and alanine aminotransferase less than five times the upper limit of normal). The characteristics of the patients receiving dexamethasone and/or remdesivir were compared to those not receiving the medications. Analyses were not performed for tocilizumab because insufficient patients in the cohort received the drug.

Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, AUT): *tidyverse, finalfit, survival, survminer, nephro, mice, MatchIt* and *forestplot* packages.

Results

Of 114,131 patients with data available at the time of the analysis, 85,687 were studied in the KRT analysis and 41,294 in the biochemical AKI analysis (Supplementary Figure 7-1). 2,198 patients (2.6%) received acute KRT and 13,000 (31.5%) had biochemical AKI: 8,562 stage 1 (65.9%), 2,609 stage 2 (20.1%) and 1,829 stage 3 (14.1%).

Supplementary Figure 7-1. Consort Diagram.



KRT, kidney replacement therapy

Patient Characteristics

Patient characteristics are presented by KRT status (table 7-1) and stage of biochemical AKI (table 7-2). Of the 85,687 patients in the KRT analysis, 63,021 (73.5%) had confirmed infection and 22,666 (26.5%) had highly suspected infection.

Table 7-1. Patient characteristics by kidney replacement therapy status.

		No KRT N=83489	**KRT N=2198**
Age (years)	Median (IQR)	74 (58 to 83)	62 (54 to 70)
Sex (%) Not specified 202 (0.2%)	Female	37339 (44.7)	528 (24.0)
	Male	45954 (55.0)	1664 (75.7)
Race (%) Missing values 9718 (11.3%)	White	61266 (82.7)	1204 (63.8)
	Black	2642 (3.6)	179 (9.5)
	South Asian	4407 (5.9)	245 (13.0)
	East Asian	543 (0.7)	25 (1.3)
	Other	5224 (7.1)	234 (12.4)
IMD quintile (%) Missing values 3183 (3.7%)	1	16228 (20.2)	436 (20.7)
	2	16610 (20.7)	457 (21.7)
	3	15836 (19.7)	362 (17.2)
	4	15988 (19.9)	414 (19.7)
	5	15739 (19.6)	434 (20.6)
Smoking (%) Missing values 34413 (40.2%)	Never	27733 (55.7)	899 (61.0)
	Current	4390 (8.8)	86 (5.8)
	Former	17678 (35.5)	488 (33.1)
Hypertension (%) Missing values 8990 (10.5%)		40304 (53.9)	1164 (62.1)
Diabetes (%) Missing values 6952 (8.1%)		16753 (21.8)	742 (36.9)
Chronic kidney disease (%) Missing values 3991 (4.7%)		12944 (16.3)	648 (31.1)
Heart disease (%) Missing values 3601 (4.2%)		25507 (31.9)	485 (23.6)
Lung disease (not asthma) (%) Missing values 3767 (4.4%)		13808 (17.3)	175 (8.5)
Asthma (%) Missing values 3954 (4.6%)		10848 (13.6)	306 (14.9)
Chronic liver disease (%) Missing values 4479 (5.2%)		2659 (3.4)	67 (3.3)
Neurological disease (%) Missing values 4274 (5.0%)		9917 (12.5)	117 (5.7)
Cancer (%) Missing values 4412 (5.1%)		8095 (10.2)	118 (5.8)
Haematological disease (%) Missing values 4442 (5.2%)		3435 (4.3)	86 (4.2)
Human immunodeficiency virus (%)		288 (0.4)	23 (1.1)

Missing values 5689 (6.6%)		
Obesity (%) Missing values 12413 (14.5%)	8602 (12.1)	510 (26.6)
Rheumatological disease (%) Missing values 4650 (5.4%)	9247 (11.7)	153 (7.6)
Dementia (%) Missing values 4242 (5.0%)	12386 (15.6)	23 (1.1)
RAS-blockers (%) Missing values 9926 (11.6%)	20603 (27.9)	618 (33.6)
Calcium channel blockers (%) Missing values 9926 (11.6%)	15794 (21.4)	594 (32.3)
Beta-blockers (%) Missing values 9926 (11.6%)	22349 (30.2)	602 (32.8)
Diuretics (%) Missing values 9926 (11.6%)	18165 (24.6)	383 (20.8)
Statins (%) Missing values 9926 (11.6%)	30843 (41.7)	858 (46.7)
Systemic corticosteroids (%) Missing values 9926 (11.6%)	8368 (11.3)	230 (12.5)
Immunosuppressants (%) Missing values 9926 (11.6%)	1871 (2.5)	84 (4.6)
Proton pump inhibitors (%) Missing values 9926 (11.6%)	32347 (43.8)	771 (41.9)
Nonsteroidal anti-inflammatory drugs (%) Missing values 9926 (11.6%)	2710 (3.7)	74 (4.0)
Aspirin (%) Missing values 9926 (11.6%)	22254 (30.1)	586 (31.9)
Any supplemental oxygen (%) Missing values 281 (0.3%)	60640 (72.9)	2091 (95.4)
Any critical care admission (%) Missing values 47 (0.1%)	10603 (12.7)	1752 (79.7)
Any invasive ventilation (%) Missing values 39 (0.0%)	4872 (5.8)	1613 (73.5)
Any non-invasive ventilation (%) Missing values 242 (0.3%)	11709 (14.1)	1040 (47.5)

All medications were those in use before hospitalisation.

Table 7-2. Patient Characteristics by biochemical acute kidney injury stage.

		No AKI N=28294	**Stage 1 N=8562**	**Stage 2 N=2609**	**Stage 3 N=1829**
Age (years)	Median (IQR)	73 (58 to 83)	73 (61 to 83)	71 (60 to 80)	65 (57 to 75)
Sex (%) Not specified 151 (0.4%)	Female	12105 (42.8)	3085 (36.0)	960 (36.8)	586 (32.0)
	Male	16096 (56.9)	5441 (63.5)	1637 (62.7)	1233 (67.4)
Race (%) Missing values 4543 (11.0%)	White	20689 (82.2)	6183 (80.6)	1800 (78.3)	1147 (70.9)
	Black	953 (3.8)	395 (5.1)	134 (5.8)	125 (7.7)
	South Asian	1315 (5.2)	421 (5.5)	137 (6.0)	136 (8.4)
	East Asian	214 (0.9)	68 (0.9)	16 (0.7)	20 (1.2)
	Other	1989 (7.9)	608 (7.9)	211 (9.2)	190 (11.7)
IMD quintile (%) Missing values 1734 (4.2%)	1	5022 (18.5)	1616 (19.7)	487 (19.5)	348 (19.9)
	2	5245 (19.3)	1672 (20.4)	569 (22.8)	373 (21.4)
	3	5294 (19.5)	1610 (19.7)	510 (20.4)	319 (18.3)
	4	5470 (20.2)	1605 (19.6)	448 (17.9)	324 (18.5)
	5	6092 (22.5)	1689 (20.6)	484 (19.4)	383 (21.9)
Smoking (%) Missing values 15,327 (37.1%)	Never	9972 (55.9)	2828 (53.2)	862 (54.9)	726 (58.3)
	Current	1485 (8.3)	414 (7.8)	115 (7.3)	83 (6.7)
	Former	6381 (35.8)	2073 (39.0)	592 (37.7)	436 (35.0)
Hypertension (%) Missing values 3620 (8.8%)		13681 (53.1)	4795 (60.4)	1428 (59.8)	941 (59.0)
Diabetes (%) Missing values 3378 (8.2%)		5872 (22.6)	2261 (28.9)	702 (29.7)	510 (29.9)
Chronic kidney disease (%) Missing values 2273 (5.5%)		4040 (15.1)	2043 (25.2)	487 (19.9)	240 (13.9)
Heart disease (%) Missing values 1997 (4.8%)		8367 (31.0)	2805 (34.4)	714 (29.2)	381 (22.0)
Lung disease (not asthma) (%) Missing values 2164 (5.2%)		4706 (17.5)	1471 (18.1)	416 (17.0)	197 (11.4)
Asthma (%) Missing values 2285 (5.5%)		3919 (14.6)	988 (12.2)	321 (13.1)	237 (13.7)
Chronic liver disease (%) Missing values 2583 (6.3%)		1002 (3.8)	282 (3.5)	90 (3.7)	48 (2.8)
Neurological disease (%) Missing values 2476 (6.0%)		3095 (11.6)	948 (11.8)	259 (10.7)	137 (8.0)

Cancer (%) Missing values 2523 (6.1%)	2812 (10.6)	835 (10.4)	246 (10.1)	120 (7.0)
Haematological disease (%) Missing values 2559 (6.2%)	1219 (4.6)	396 (4.9)	112 (4.6)	46 (2.7)
Human immunodeficiency virus (%) Missing values 3190 (7.7%)	102 (0.4)	36 (0.5)	<15 (0.3)	<15 (0.9)
Obesity (%) Missing values 6081 (14.7%)	3183 (13.2)	1086 (14.8)	408 (18.5)	348 (21.7)
Rheumatological disease (%) Missing values 2660 (6.4%)	3163 (11.9)	878 (11.0)	258 (10.7)	141 (8.2)
Dementia (%) Missing values 2395 (5.8%)	3498 (13.1)	1234 (15.3)	328 (13.5)	136 (7.9)
RAS-blockers (%) Missing values 3946 (9.6%)	6895 (27.0)	2529 (32.2)	830 (35.0)	542 (34.3)
Calcium channel blockers (%) Missing values 3946 (9.6%)	5495 (21.5)	2003 (25.5)	665 (28.1)	433 (27.4)
Beta-blockers (%) Missing values 3946 (9.6%)	7457 (29.2)	2666 (34.0)	773 (32.6)	433 (27.4)
Diuretics (%) Missing values 3946 (9.6%)	6079 (23.8)	2201 (28.1)	599 (25.3)	336 (21.2)
Statins (%) Missing values 3946 (9.6%)	10638 (41.6)	3669 (46.8)	1057 (44.6)	666 (42.1)
Systemic corticosteroids (%) Missing values 3946 (9.6%)	3042 (11.9)	914 (11.7)	259 (10.9)	153 (9.7)
Immunosuppressants (%) Missing values 3946 (9.6%)	776 (3.0)	296 (3.8)	66 (2.8)	47 (3.0)
Proton pump inhibitors (%) Missing values 3946 (9.6%)	11349 (44.4)	3440 (43.8)	1010 (42.6)	607 (38.4)
Nonsteroidal anti-inflammatory drugs (%) Missing values 3946 (9.6%)	894 (3.5)	235 (3.0)	91 (3.8)	89 (5.6)
Aspirin (%) Missing values 3946 (9.6%)	7400 (29.0)	2618 (33.4)	734 (31.0)	386 (24.4)
Any supplemental oxygen (%) Missing values 402 (1.0%)	22623 (80.8)	7464 (88.0)	2333 (90.0)	1696 (93.8)
Any critical care admission (%) Missing values 163 (0.4%)	4838 (17.2)	2616 (30.7)	1240 (47.7)	1275 (70.0)
Any invasive ventilation (%) Missing values 601 (1.5%)	2184 (7.8)	1615 (19.1)	1001 (38.8)	1147 (63.7)
Any non-invasive ventilation (%) Missing values 686 (1.7%)	5232 (18.8)	2405 (28.5)	928 (36.0)	785 (43.7)

All medications were those in use before hospitalisation

The characteristics of patients with biochemistry data were slightly different to patients without biochemistry data (Supplementary Table 7-1). A number of comorbidities were more common in patients with biochemistry data compared to those without biochemistry data, including diabetes (24.7% vs. 20.3%), CKD (17.5 vs. 16.2%) and obesity (14.2 vs. 10.9%).

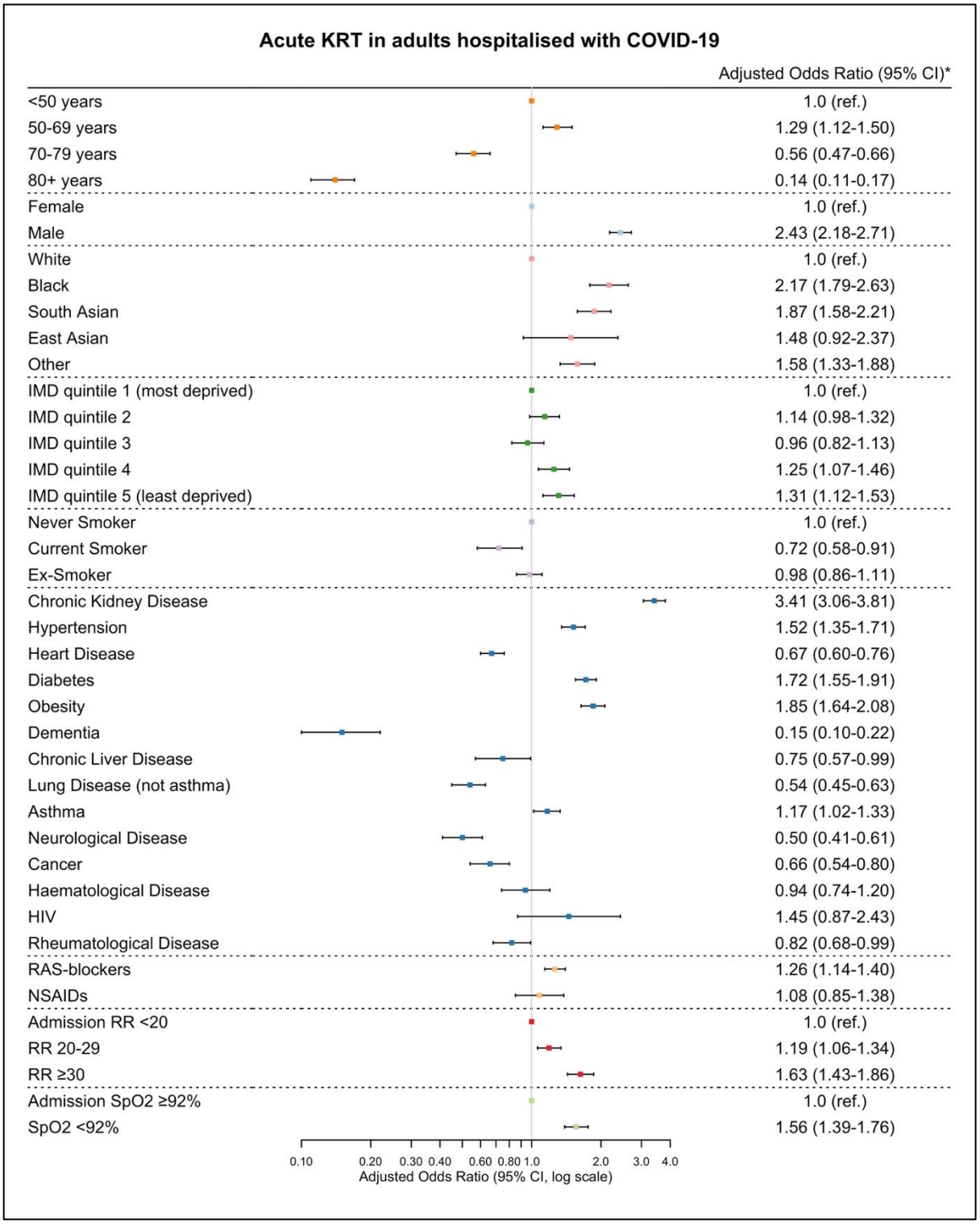
Supplementary Table 7-1. Baseline characteristics by availability of biochemistry.

		Biochemistry available N=41294	**No biochemistry available N=68342**
Age (years)	Median (IQR)	72 (59 to 82)	74 (57 to 84)
Sex	Female	16896 (40.7)	29277 (46.8)
	Male	24587 (59.3)	33251 (53.2)
Race	White	30099 (81.2)	45066 (83.5)
	Black	1613 (4.4)	1596 (3.0)
	South Asian	2021 (5.5)	3554 (6.6)
	East Asian	318 (0.9)	335 (0.6)
	Other	3008 (8.1)	3422 (6.3)
IMD quintile	1	7508 (18.8)	12590 (20.8)
	2	7920 (19.9)	12634 (20.9)
	3	7812 (19.6)	12054 (19.9)
	4	7933 (19.9)	12354 (20.4)
	5	8716 (21.9)	10852 (17.9)
Smoking	Current	2129 (8.1)	2882 (9.5)
	Former	9567 (36.5)	10618 (35.0)
	Never	14487 (55.3)	16878 (55.6)
Hypertension		21033 (55.3)	28646 (53.9)
Diabetes		9423 (24.7)	9968 (20.3)
Chronic kidney disease		6893 (17.5)	8329 (16.2)
Heart disease		12404 (31.3)	16589 (32.1)
Lung disease (not asthma)		6867 (17.4)	8879 (17.2)
Asthma		5520 (14.0)	6999 (13.6)
Chronic liver disease		1439 (3.7)	1642 (3.2)
Neurological disease		4501 (11.5)	6621 (12.9)
Cancer		4058 (10.4)	5121 (10.0)
Haematological disease		1789 (4.6)	2044 (4.0)
Human immunodeficiency virus		161 (0.4)	185 (0.4)
Obesity		5053 (14.2)	4964 (10.9)
Rheumatological disease		4497 (11.5)	5976 (11.7)
Dementia		5263 (13.4)	8549 (16.7)
RAS-blockers		10885 (28.9)	14489 (27.8)
Calcium channel blockers		8655 (23.0)	10897 (20.9)
Beta-blockers		11447 (30.4)	15958 (30.6)
Diuretics		9318 (24.7)	12773 (24.5)
Statins		16165 (42.9)	21707 (41.6)
Systemic corticosteroids		4403 (11.7)	5810 (11.1)
Immunosuppressants		1191 (3.2)	1137 (2.2)
Proton pump inhibitors		16563 (44.0)	23007 (44.1)
Non-steroidal anti-inflammatory drugs		1319 (3.5)	2046 (3.9)
Aspirin		11254 (29.9)	15982 (30.6)

Clinical variables associated with KRT (Figure 7-1)

Risk factors strongly positively associated with KRT were CKD (Adjusted odds ratio (aOR) 3.41: 95% confidence interval 3.06-3.81), male sex (aOR 2.43: 2.18-2.71) and black race (aOR 2.17: 1.79-2.63). Indicators of severe illness on admission associated with KRT were: admission respiratory rate greater than 30 breaths per minute (aOR 1.63: 1.43-1.86) and admission oxygen saturation less than 92% on air (aOR 1.56: 1.39-1.76). Age over 80 (aOR 0.14: 0.11-0.17) and dementia (aOR 0.15: 0.10-0.22) were negatively associated with KRT. aORs were similar for complete case sensitivity analysis (Supplementary Table 7-2).

Figure 7-1. Associations between risk factors and acute kidney replacement therapy.



*Adjusted for age, sex, race, deprivation quintile, chronic kidney disease, heart disease, diabetes, admission oxygen saturations on air and admission respiratory rate. HIV, Human immunodeficiency virus; RR, respiratory rate; SpO2, oxygen saturations. Error bars are 95% confidence intervals (CI)

Supplementary Table 7-2. Complete case sensitivity analysis for kidney replacement therapy.

		Odds ratio (univariable)	Odds ratio* (multivariable)
Race	White	-	-
	Black	3.45 (2.92-4.04, p<0.001)	1.83 (1.31-2.52, p<0.001)
	South Asian	2.83 (2.45-3.25, p<0.001)	2.14 (1.64-2.76, p<0.001)
	East Asian	2.34 (1.52-3.43, p<0.001)	1.42 (0.59-2.87, p=0.377)
	Other	2.28 (1.97-2.62, p<0.001)	1.29 (0.94-1.72, p=0.101)
Sex	Male	2.56 (2.32-2.83, p<0.001)	2.35 (1.96-2.84, p<0.001)
IMD quintile	1	-	-
	2	1.02 (0.90-1.17, p=0.726)	1.10 (0.86-1.41, p=0.453)
	3	0.85 (0.74-0.98, p=0.025)	0.85 (0.65-1.11, p=0.243)
	4	0.96 (0.84-1.10, p=0.596)	1.15 (0.89-1.48, p=0.299)
	5	1.03 (0.90-1.17, p=0.705)	1.37 (1.07-1.77, p=0.014)
Age (years)	<50	-	-
	50-69	1.85 (1.64-2.10, p<0.001)	1.17 (0.92-1.49, p=0.201)
	70-79	0.80 (0.69-0.92, p=0.002)	0.44 (0.33-0.59, p<0.001)
	80+	0.14 (0.12-0.18, p<0.001)	0.09 (0.07-0.13, p<0.001)
Respiratory rate**	<20	-	-
	20-29	1.44 (1.30-1.60, p<0.001)	1.04 (0.85-1.25, p=0.719)
	>30	2.54 (2.27-2.83, p<0.001)	1.33 (1.05-1.66, p=0.015)
Oxygen saturation (%)**	>=92	-	-
	<92	3.00 (2.64-3.42, p<0.001)	2.54 (2.11-3.04, p<0.001)
Smoking	Never	-	-
	Current	0.60 (0.48-0.75, p<0.001)	0.46 (0.27-0.72, p=0.001)
	Former	0.85 (0.76-0.95, p=0.005)	0.84 (0.66-1.05, p=0.125)
Chronic kidney disease		2.33 (2.12-2.56, p<0.001)	4.98 (4.15-5.98, p<0.001)
Heart disease		0.66 (0.60-0.73, p<0.001)	0.82 (0.67-0.99, p=0.039)
Diabetes		2.09 (1.91-2.29, p<0.001)	1.79 (1.50-2.13, p<0.001)
Hypertension		1.40 (1.28-1.54, p<0.001)	1.78 (1.45-2.18, p<0.001)
Chronic liver disease		0.98 (0.76-1.25, p=0.883)	0.96 (0.64-1.40, p=0.845)
Lung disease (not asthma)		0.45 (0.38-0.52, p<0.001)	0.64 (0.49-0.83, p=0.001)
Asthma		1.11 (0.98-1.25, p=0.096)	1.24 (0.98-1.54, p=0.065)
Neurological disease		0.43 (0.35-0.51, p<0.001)	0.47 (0.33-0.65, p<0.001)
Cancer		0.54 (0.45-0.65, p<0.001)	0.56 (0.39-0.78, p=0.001)
Haematological disease		0.97 (0.77-1.20, p=0.791)	0.87 (0.58-1.27, p=0.504)
Human immunodeficiency virus		3.11 (1.97-4.66, p<0.001)	1.97 (0.79-4.18, p=0.104)
Obesity		2.64 (2.38-2.93, p<0.001)	1.99 (1.62-2.45, p<0.001)
Rheumatological disease		0.62 (0.52-0.73, p<0.001)	0.68 (0.49-0.92, p=0.017)
Dementia		0.06 (0.04-0.09, p<0.001)	0.11 (0.05-0.21, p<0.001)
RAS-blockers		1.31 (1.19-1.45, p<0.001)	1.13 (0.94-1.36, p=0.184)
Non-steroidal anti-inflammatory drugs		1.10 (0.86-1.38, p=0.418)	0.67 (0.39-1.09, p=0.133)

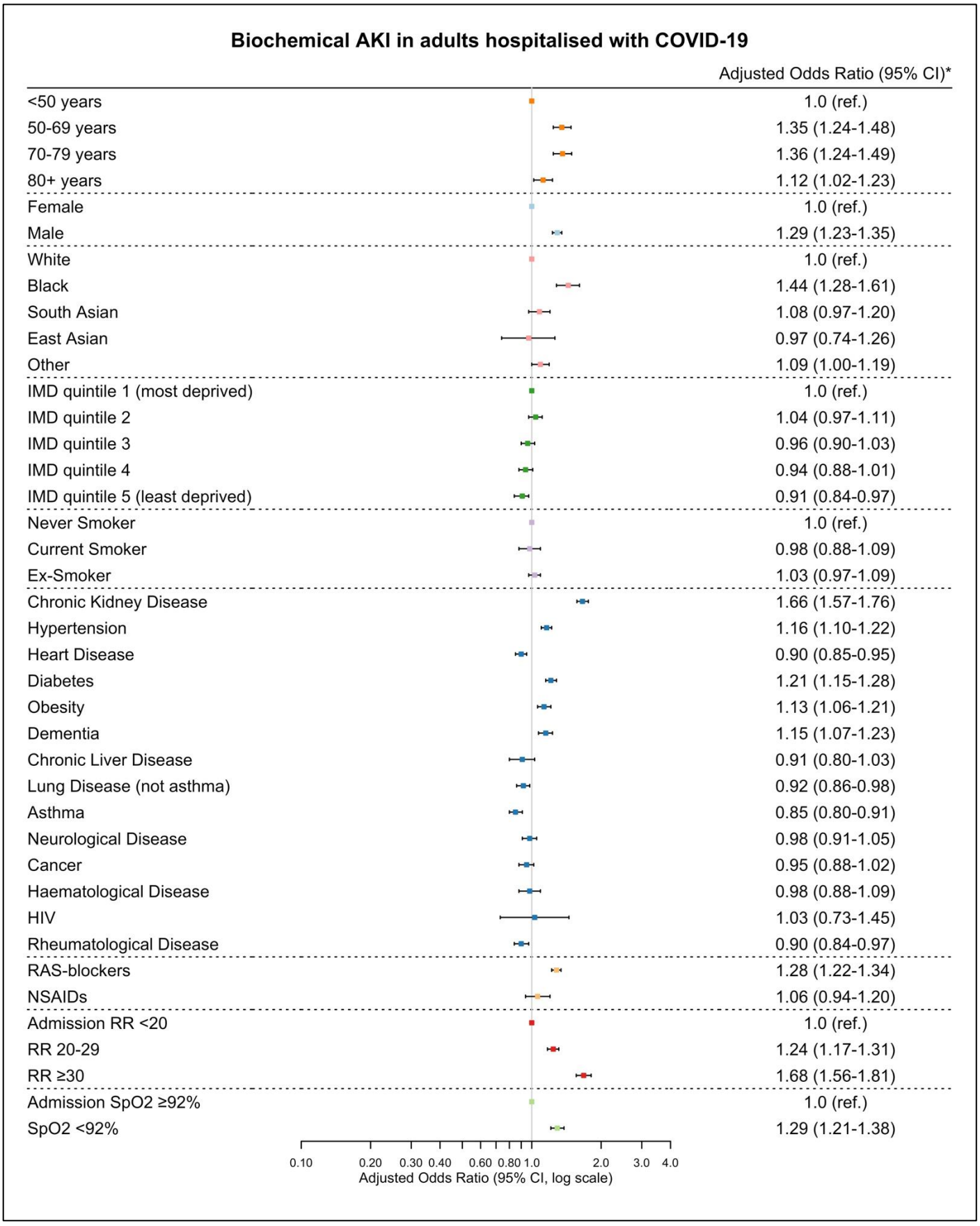
*Adjusted for age, sex, race, deprivation quintile, chronic kidney disease, heart disease, diabetes, admission oxygen saturations on air and admission respiratory rate.

**On admission

Clinical variables associated with biochemical AKI (Figure 7-2)

Risk factors with strongly positive associations with biochemical AKI were admission respiratory rate greater than 30 breaths per minute (aOR 1.68: 1.56-1.81), CKD (aOR 1.66: 1.57-1.76) and black race (aOR 1.44: 1.28-1.61). aORs were similar for complete case sensitivity analysis (Supplementary Table 7-3). Analysis of each stage of AKI showed similar risk factors (Supplementary Table 7-4). Patients of south Asian and other race and those on non-steroidal anti-inflammatory drugs were at increased risk of stages 2 and 3 AKI, but not stage 1.

Figure 7-2. Associations between risk factors and biochemical acute kidney injury.



*Adjusted for age, sex, race, deprivation quintile, chronic kidney disease, heart disease, diabetes, admission oxygen saturations on air and admission respiratory rate. HIV, Human immunodeficiency virus; RR, respiratory rate; SpO2, oxygen saturations. Error bars are 95% confidence intervals (CI)

Supplementary Table 7-3. Complete case sensitivity analysis for biochemical acute kidney injury.

		Odds Ratio (univariable)	**Odds Ratio* (multivariable)**
Race	White	-	-
	Black	1.56 (1.40-1.72, p<0.001)	1.58 (1.34-1.87, p<0.001)
	South Asian	1.20 (1.09-1.31, p<0.001)	1.04 (0.89-1.22, p=0.602)
	East Asian	1.10 (0.87-1.39, p=0.422)	0.91 (0.61-1.33, p=0.618)
	Other	1.15 (1.06-1.24, p=0.001)	1.10 (0.96-1.26, p=0.155)
Sex	Male	1.35 (1.29-1.41, p<0.001)	1.27 (1.18-1.36, p<0.001)
IMD quintile	1	-	-
	2	1.02 (0.95-1.09, p=0.542)	0.97 (0.87-1.08, p=0.560)
	3	0.94 (0.88-1.01, p=0.097)	0.98 (0.88-1.09, p=0.751)
	4	0.89 (0.83-0.95, p=0.001)	0.88 (0.79-0.98, p=0.017)
	5	0.86 (0.80-0.92, p<0.001)	0.91 (0.82-1.01, p=0.083)
Age (years)	<50	-	-
	50-69	1.60 (1.48-1.72, p<0.001)	1.46 (1.28-1.67, p<0.001)
	70-79	1.58 (1.46-1.71, p<0.001)	1.56 (1.35-1.79, p<0.001)
	80+	1.23 (1.14-1.33, p<0.001)	1.34 (1.16-1.54, p<0.001)
Respiratory rate**	<20	-	-
	20-29	1.29 (1.23-1.35, p<0.001)	1.13 (1.05-1.22, p=0.001)
	>30	1.87 (1.76-1.98, p<0.001)	1.39 (1.25-1.55, p<0.001)
Oxygen saturation (%)**	>=92	-	-
	<92	1.71 (1.61-1.82, p<0.001)	1.48 (1.37-1.61, p<0.001)
Smoking	Never	-	-
	Current	0.93 (0.84-1.03, p=0.161)	1.00 (0.85-1.18, p=0.982)
	Former	1.10 (1.04-1.16, p=0.001)	1.04 (0.95-1.15, p=0.382)
Chronic kidney disease		1.63 (1.55-1.73, p<0.001)	1.80 (1.66-1.96, p<0.001)
Heart disease		1.03 (0.98-1.08, p=0.258)	0.95 (0.88-1.03, p=0.217)
Diabetes		1.41 (1.35-1.49, p<0.001)	1.25 (1.16-1.35, p<0.001)
Hypertension		1.33 (1.27-1.39, p<0.001)	1.12 (1.04-1.21, p=0.004)
Chronic liver disease		0.91 (0.81-1.02, p=0.121)	1.11 (0.94-1.30, p=0.228)
Lung disease (not asthma)		0.96 (0.91-1.01, p=0.138)	0.92 (0.84-1.00, p=0.064)
Asthma		0.84 (0.79-0.90, p<0.001)	0.83 (0.75-0.92, p<0.001)
Neurological disease		0.94 (0.88-1.01, p=0.083)	0.92 (0.83-1.02, p=0.118)
Cancer		0.92 (0.86-0.99, p=0.031)	1.04 (0.93-1.15, p=0.517)
Haematological disease		0.99 (0.89-1.10, p=0.877)	1.04 (0.89-1.21, p=0.601)
Human immunodeficiency virus		1.26 (0.91-1.73, p=0.159)	1.12 (0.65-1.88, p=0.662)
Obesity		1.30 (1.22-1.38, p<0.001)	1.02 (0.91-1.14, p=0.726)
Rheumatological disease		0.87 (0.81-0.93, p<0.001)	0.89 (0.80-0.98, p=0.025)
Dementia		1.07 (1.00-1.13, p=0.043)	1.20 (1.09-1.32, p<0.001)
RAS-blockers		1.34 (1.27-1.40, p<0.001)	1.29 (1.20-1.39, p<0.001)
Nonsteroidal anti-inflammatory drugs		1.01 (0.89-1.13, p=0.926)	0.88 (0.72-1.07, p=0.200)

*Adjusted for age, sex, race, deprivation quintile, chronic kidney disease, heart disease, diabetes, admission oxygen saturations on air and admission respiratory rate.

**On admission

Supplementary Table 7-4. Associations between risk factors and each stage of acute kidney injury

		Stage 1. Odds ratio*	Stage 2. Odds Ratio*	Stage 3. Odds Ratio*
Race	White	NA	NA	NA
	Black	1.44 (1.28-1.61, p<0.001)	1.49 (1.28-1.74, p<0.001)	1.64 (1.32-2.02, p<0.001)
	South Asian	1.08 (0.97-1.20, p=0.168)	1.18 (1.02-1.36, p=0.029)	1.37 (1.12-1.68, p=0.003)
	East Asian	0.97 (0.74-1.26, p=0.807)	0.84 (0.56-1.28, p=0.422)	1.12 (0.65-1.95, p=0.676)
	Other	1.09 (1.00-1.19, p=0.061)	1.17 (1.03-1.32, p=0.016)	1.26 (1.06-1.51, p=0.011)
Sex	Male	1.29 (1.23-1.35, p<0.001)	1.23 (1.15-1.32, p<0.001)	1.34 (1.21-1.50, p<0.001)
IMD quintile	1	NA	NA	NA
	2	1.04 (0.97-1.11, p=0.309)	1.10 (0.99-1.22, p=0.088)	1.04 (0.88-1.23, p=0.667)
	3	0.96 (0.90-1.03, p=0.301)	1.01 (0.91-1.13, p=0.806)	0.98 (0.82-1.16, p=0.783)
	4	0.94 (0.88-1.01, p=0.115)	0.96 (0.85-1.07, p=0.419)	0.99 (0.84-1.18, p=0.937)
	5	0.91 (0.84-0.97, p=0.007)	0.97 (0.87-1.08, p=0.556)	1.06 (0.90-1.25, p=0.483)
Age (years)	<50	NA	NA	NA
	50-69	1.35 (1.24-1.48, p<0.001)	1.46 (1.28-1.66, p<0.001)	1.46 (1.22-1.75, p<0.001)
	70-79	1.36 (1.24-1.49, p<0.001)	1.27 (1.11-1.45, p=0.001)	1.08 (0.88-1.31, p=0.475)
	80+	1.12 (1.02-1.23, p=0.014)	0.86 (0.75-1.00, p=0.044)	0.62 (0.50-0.76, p<0.001)
Respiratory rate**	<20	NA	NA	NA
	20-29	1.24 (1.17-1.31, p<0.001)	1.28 (1.18-1.38, p<0.001)	1.31 (1.16-1.48, p<0.001)
	>30	1.68 (1.56-1.81, p<0.001)	1.88 (1.70-2.07, p<0.001)	1.97 (1.71-2.26, p<0.001)
Oxygen saturation(%)**	>=92	NA	NA	NA
	<92	1.29 (1.21-1.38, p<0.001)	1.37 (1.24-1.51, p<0.001)	1.44 (1.21-1.70, p<0.001)
Smoking	Never	NA	NA	NA
	Current	0.98 (0.88-1.09, p=0.658)	0.91 (0.77-1.07, p=0.265)	0.90 (0.73-1.12, p=0.338)
	Former	1.03 (0.97-1.09, p=0.338)	1.01 (0.92-1.10, p=0.873)	1.03 (0.89-1.18, p=0.688)
Chronic kidney disease		1.66 (1.57-1.76, p<0.001)	1.12 (1.03-1.23, p=0.011)	0.96 (0.83-1.11, p=0.600)
Heart disease		0.90 (0.85-0.95, p<0.001)	0.79 (0.73-0.85, p<0.001)	0.71 (0.62-0.81, p<0.001)
Diabetes		1.21 (1.15-1.28, p<0.001)	1.22 (1.13-1.32, p<0.001)	1.25 (1.11-1.41, p<0.001)
Hypertension		1.16 (1.10-1.22, p<0.001)	1.16 (1.07-1.25, p<0.001)	1.24 (1.09-1.40, p=0.001)
Chronic liver disease		0.91 (0.80-1.03, p=0.141)	0.89 (0.74-1.08, p=0.234)	0.74 (0.54-1.01, p=0.055)
Lung disease (not asthma)		0.92 (0.86-0.98, p=0.008)	0.86 (0.78-0.94, p=0.002)	0.73 (0.62-0.86, p<0.001)

Asthma	0.85 (0.80-0.91, p<0.001)	0.92 (0.84-1.02, p=0.113)	0.97 (0.84-1.12, p=0.673)
Neurological disease	0.98 (0.91-1.05, p=0.506)	0.91 (0.81-1.01, p=0.084)	0.80 (0.67-0.97, p=0.021)
Cancer	0.95 (0.88-1.02, p=0.163)	0.94 (0.84-1.05, p=0.288)	0.80 (0.66-0.97, p=0.026)
Haematological disease	0.98 (0.88-1.09, p=0.715)	0.88 (0.73-1.05, p=0.141)	0.64 (0.47-0.87, p=0.004)
Human immunodeficiency virus	1.03 (0.73-1.45, p=0.858)	1.07 (0.67-1.73, p=0.775)	1.57 (0.87-2.82, p=0.130)
Obesity	1.13 (1.06-1.21, p<0.001)	1.25 (1.14-1.38, p<0.001)	1.29 (1.12-1.49, p<0.001)
Rheumatological disease	0.90 (0.84-0.97, p=0.004)	0.91 (0.81-1.02, p=0.097)	0.82 (0.69-0.99, p=0.038)
Dementia	1.15 (1.07-1.23, p<0.001)	1.01 (0.90-1.13, p=0.853)	0.80 (0.66-0.96, p=0.020)
RAS-blockers	1.28 (1.22-1.34, p<0.001)	1.34 (1.24-1.44, p<0.001)	1.30 (1.16-1.45, p<0.001)
Nonsteroidal anti-inflammatory drugs	1.06 (0.94-1.20, p=0.325)	1.33 (1.13-1.57, p=0.001)	1.58 (1.26-1.98, p<0.001)

*Adjusted for age, sex, race, deprivation quintile, chronic kidney disease, heart disease, diabetes, admission oxygen saturations on air and admission respiratory rate

**On admission

Race analyses (Supplementary Table 7-5, 7-6)

Race was chosen for interaction analyses to investigate potential reasons for the high rates of adverse outcomes being seen in non-white populations. For the KRT analysis, there were interactions between south Asian race and each of: age, male sex, CKD and hypertension; there was an interaction between black race and CKD; and there was an interaction between other race and each of: age and CKD (p-values all <0.01). For the biochemical AKI analysis, there was an interaction between south Asian race and each of CKD and diabetes; and there was an interaction between black race and CKD (p-values all <0.01). Compared to white patients, those from minority race groups in the analysis were younger and proportionally more of them were admitted to critical care (Table S7). CKD was more common in white patients (17.6%) than those from minority race groups: black (15.7%), south Asian (14.5%), east Asian (9.5%) and other (12.6%).

Supplementary Table 7-5. Interactions between race and other risk factors in kidney replacement therapy logistic regression model.

Interaction	Coefficient
ethnicityBlack:ckdYes	0.54 (0.16-0.91, p=0.005)
ethnicityEast Asian:ckdYes	0.52 (-0.53-1.57, p=0.332)
ethnicityOther:ckdYes	0.59 (0.24-0.93, p=0.001)
ethnicitySouth Asian:ckdYes	0.82 (0.51-1.14, p<0.001)
ethnicityBlack:diabetesYes	0.19 (-0.20-0.59, p=0.333)
ethnicityEast Asian:diabetesYes	-0.55 (-1.60-0.50, p=0.303)
ethnicityOther:diabetesYes	0.15 (-0.18-0.47, p=0.373)
ethnicitySouth Asian:diabetesYes	0.33 (0.02-0.65, p=0.038)
ethnicityBlack:hypertensionYes	0.21 (-0.18-0.60, p=0.281)
ethnicityEast Asian:hypertensionYes	0.08 (-0.89-1.04, p=0.877)
ethnicityOther:hypertensionYes	0.15 (-0.17-0.46, p=0.358)
ethnicitySouth Asian:hypertensionYes	0.56 (0.24-0.89, p=0.001)
ethnicityBlack:sexMale	-0.10 (-0.51-0.31, p=0.631)
ethnicityEast Asian:sexMale	-1.10 (-2.03–0.18, p=0.020)
ethnicityOther:sexMale	-0.21 (-0.57-0.16, p=0.265)
ethnicitySouth Asian:sexMale	-0.46 (-0.79–0.13, p=0.006)
ethnicityBlack:RASBYes	0.08 (-0.30-0.47, p=0.677)
ethnicityEast Asian: RASBYes	-0.09 (-1.07-0.89, p=0.864)
ethnicityOther: RASBYes	-0.11 (-0.47-0.25, p=0.543)
ethnicitySouth Asian: RASBYes	0.19 (-0.13-0.51, p=0.246)
ethnicityBlack:obesityYes	-0.31 (-0.79-0.18, p=0.212)
ethnicityEast Asian:obesityYes	-0.40 (-1.74-0.94, p=0.560)
ethnicityOther:obesityYes	-0.13 (-0.51-0.25, p=0.513)
ethnicitySouth Asian:obesityYes	-0.13 (-0.51-0.24, p=0.483)
ethnicityBlack:asthmaYes	-0.28 (-0.88-0.33, p=0.372)
ethnicityEast Asian:asthmaYes	-0.29 (-1.76-1.18, p=0.699)
ethnicityOther:asthmaYes	-0.17 (-0.60-0.26, p=0.439)
ethnicitySouth Asian:asthmaYes	-0.34 (-0.75-0.06, p=0.096)
ethnicityBlack:age	0.01 (0.00-0.02, p=0.010)
ethnicityEast Asian:age	0.02 (-0.00-0.05, p=0.093)
ethnicityOther:age	0.01 (0.01-0.02, p<0.001)
ethnicitySouth Asian:age	0.02 (0.01-0.03, p<0.001)
ethnicityBlack:imd_quintile2	-0.06 (-0.52-0.41, p=0.817)
ethnicityEast Asian:imd_quintile2	0.48 (-0.93-1.88, p=0.504)
ethnicityOther:imd_quintile2	-0.44 (-0.92-0.03, p=0.069)
ethnicitySouth Asian:imd_quintile2	-0.26 (-0.71-0.18, p=0.248)
ethnicityBlack:imd_quintile3	0.04 (-0.54-0.62, p=0.891)

ethnicityEast Asian:imd_quintile3	-0.51 (-2.23-1.21, p=0.560)
ethnicityOther:imd_quintile3	-0.26 (-0.76-0.24, p=0.303)
ethnicitySouth Asian:imd_quintile3	0.13 (-0.35-0.62, p=0.585)
ethnicityBlack:imd_quintile4	-0.23 (-0.84-0.39, p=0.469)
ethnicityEast Asian:imd_quintile4	-0.62 (-2.47-1.23, p=0.509)
ethnicityOther:imd_quintile4	-0.62 (-1.16–0.08, p=0.024)
ethnicitySouth Asian:imd_quintile4	-0.10 (-0.65-0.46, p=0.734)
ethnicityBlack:imd_quintile5	-0.47 (-1.16-0.22, p=0.178)
ethnicityEast Asian:imd_quintile5	0.09 (-1.41-1.59, p=0.906)
ethnicityOther:imd_quintile5	-0.32 (-0.81-0.17, p=0.200)
ethnicitySouth Asian:imd_quintile5	0.08 (-0.46-0.62, p=0.768)
ethnicityBlack:resp_rate20-29	-0.07 (-0.47-0.33, p=0.739)
ethnicityEast Asian:resp_rate20-29	0.45 (-0.93-1.82, p=0.522)
ethnicityOther:resp_rate20-29	0.03 (-0.34-0.39, p=0.880)
ethnicitySouth Asian:resp_rate20-29	-0.27 (-0.65-0.10, p=0.155)
ethnicityBlack:resp_rate>30	-0.57 (-1.04–0.10, p=0.018)
ethnicityEast Asian:resp_rate>30	0.24 (-1.08-1.57, p=0.718)
ethnicityOther:resp_rate>30	-0.16 (-0.56-0.25, p=0.448)
ethnicitySouth Asian:resp_rate>30	-0.28 (-0.67-0.11, p=0.161)
ethnicityBlack:oxy_sats<92	-0.36 (-0.80-0.08, p=0.108)
ethnicityEast Asian:oxy_sats<92	-0.32 (-1.62-0.98, p=0.624)
ethnicityOther:oxy_sats<92	-0.19 (-0.61-0.23, p=0.369)
ethnicitySouth Asian:oxy_sats<92	-0.27 (-0.74-0.20, p=0.256)

Supplementary Table 7-6. Interactions between race and other risk factors in biochemical acute kidney injury logistic regression model.

Interaction	Coeffiecient
ethnicityBlack:ckdYes	0.38 (0.11-0.66, p=0.007)
ethnicityEast Asian:ckdYes	0.46 (-0.30-1.23, p=0.235)
ethnicityOther:ckdYes	0.23 (0.00-0.46, p=0.049)
ethnicitySouth Asian:ckdYes	0.52 (0.26-0.77, p<0.001)
ethnicityBlack:diabetesYes	0.31 (0.06-0.56, p=0.016)
ethnicityEast Asian:diabetesYes	0.10 (-0.48-0.67, p=0.743)
ethnicityOther:diabetesYes	0.08 (-0.11-0.27, p=0.415)
ethnicitySouth Asian:diabetesYes	0.30 (0.08-0.52, p=0.007)
ethnicityBlack:hypertensionYes	0.15 (-0.09-0.40, p=0.218)
ethnicityEast Asian:hypertensionYes	-0.11 (-0.67-0.45, p=0.695)
ethnicityOther:hypertensionYes	0.16 (-0.02-0.35, p=0.085)
ethnicitySouth Asian:hypertensionYes	0.12 (-0.09-0.32, p=0.278)
ethnicityBlack:sexMale	-0.00 (-0.24-0.23, p=0.968)

ethnicityEast Asian:sexMale	-0.22 (-0.76-0.31, p=0.411)
ethnicityOther:sexMale	0.11 (-0.07-0.29, p=0.249)
ethnicitySouth Asian:sexMale	0.06 (-0.15-0.27, p=0.597)
ethnicityBlack: RASBYes	0.09 (-0.15-0.34, p=0.454)
ethnicityEast Asian: RASBYes	-0.39 (-0.93-0.15, p=0.157)
ethnicityOther: RASBYes	-0.04 (-0.23-0.15, p=0.669)
ethnicitySouth Asian: RASBYes	-0.00 (-0.21-0.21, p=0.984)
ethnicityBlack:obesityYes	0.26 (-0.05-0.57, p=0.101)
ethnicityEast Asian:obesityYes	-0.05 (-0.92-0.82, p=0.906)
ethnicityOther:obesityYes	0.22 (-0.03-0.47, p=0.088)
ethnicitySouth Asian:obesityYes	0.02 (-0.26-0.29, p=0.907)
ethnicityBlack:dementiaYes	0.01 (-0.42-0.44, p=0.951)
ethnicityEast Asian:dementiaYes	0.71 (-0.29-1.70, p=0.163)
ethnicityOther:dementiaYes	-0.05 (-0.36-0.26, p=0.738)
ethnicitySouth Asian:dementiaYes	0.10 (-0.40-0.59, p=0.701)
ethnicityBlack:age	0.01 (0.00-0.02, p=0.016)
ethnicityEast Asian:age	0.01 (-0.01-0.02, p=0.479)
ethnicityOther:age	0.00 (-0.00-0.01, p=0.140)
ethnicitySouth Asian:age	0.01 (0.00-0.01, p=0.020)
ethnicityBlack:imd_quintile2	-0.23 (-0.53-0.06, p=0.120)
ethnicityEast Asian:imd_quintile2	-0.23 (-1.04-0.58, p=0.576)
ethnicityOther:imd_quintile2	0.03 (-0.24-0.30, p=0.833)
ethnicitySouth Asian:imd_quintile2	0.10 (-0.19-0.39, p=0.497)
ethnicityBlack:imd_quintile3	0.01 (-0.35-0.37, p=0.952)
ethnicityEast Asian:imd_quintile3	-0.26 (-1.08-0.56, p=0.538)
ethnicityOther:imd_quintile3	0.02 (-0.26-0.30, p=0.898)
ethnicitySouth Asian:imd_quintile3	0.13 (-0.15-0.41, p=0.372)
ethnicityBlack:imd_quintile4	-0.30 (-0.67-0.08, p=0.125)
ethnicityEast Asian:imd_quintile4	-0.60 (-1.46-0.26, p=0.168)
ethnicityOther:imd_quintile4	-0.16 (-0.45-0.13, p=0.272)
ethnicitySouth Asian:imd_quintile4	0.24 (-0.10-0.59, p=0.164)
ethnicityBlack:imd_quintile5	-0.24 (-0.64-0.17, p=0.252)
ethnicityEast Asian:imd_quintile5	-0.86 (-1.77-0.05, p=0.065)
ethnicityOther:imd_quintile5	0.01 (-0.27-0.28, p=0.957)
ethnicitySouth Asian:imd_quintile5	0.10 (-0.24-0.45, p=0.553)
ethnicityBlack:resp_rate20-29	0.04 (-0.23-0.30, p=0.786)
ethnicityEast Asian:resp_rate20-29	0.15 (-0.53-0.82, p=0.664)
ethnicityOther:resp_rate20-29	-0.17 (-0.37-0.03, p=0.096)
ethnicitySouth Asian:resp_rate20-29	-0.30 (-0.53–0.06, p=0.014)
ethnicityBlack:resp_rate>30	-0.21 (-0.53-0.11, p=0.207)
ethnicityEast Asian:resp_rate>30	-0.12 (-0.83-0.59, p=0.744)

ethnicityOther:resp_rate>30	-0.21 (-0.43-0.02, p=0.075)
ethnicitySouth Asian:resp_rate>30	-0.21 (-0.47-0.06, p=0.122)
ethnicityBlack:oxy_sats<92	-0.02 (-0.34-0.30, p=0.899)
ethnicityEast Asian:oxy_sats<92	-0.21 (-0.87-0.44, p=0.515)
ethnicityOther:oxy_sats<92	0.05 (-0.18-0.27, p=0.671)
ethnicitySouth Asian:oxy_sats<92	0.06 (-0.21-0.33, p=0.670)

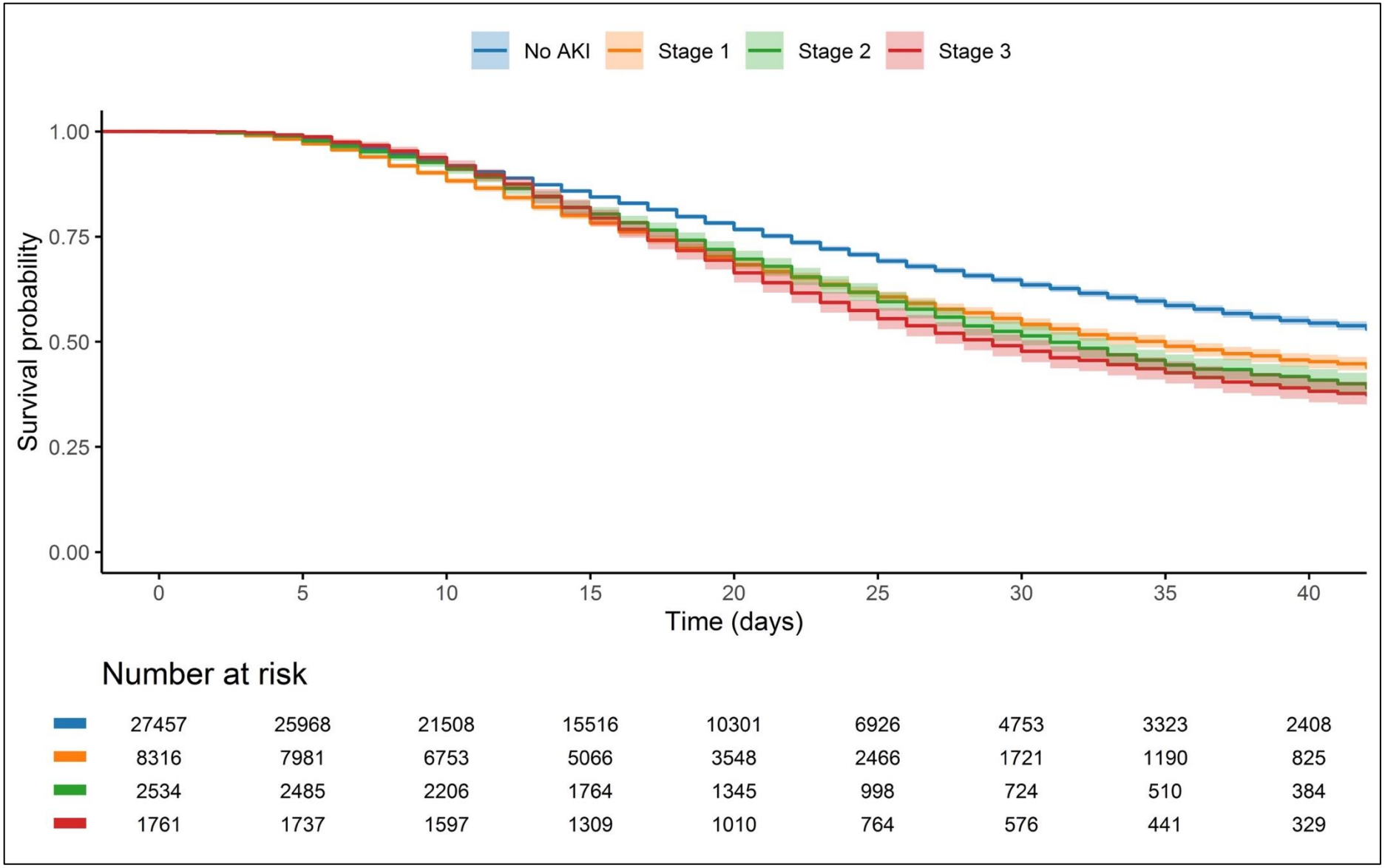
Supplementary Table 7-7. Patient characteristics by race.

		White	**Black**	**East Asian**	**Other**	**South Asian**
Age (years)	Median (IQR)	76 (62 to 84)	58 (46 to 74)	60 (46 to 75)	60 (46 to 76)	59 (43 to 72)
Sex	Female	28118 (45.0)	1268 (44.9)	228 (40.1)	2295 (42.0)	1954 (42.0)
	Male	34259 (54.8)	1551 (55.0)	339 (59.7)	3155 (57.8)	2692 (57.9)
Smoking	Never	18958 (50.8)	1424 (79.9)	302 (79.3)	2427 (69.4)	2444 (81.2)
	Current	3465 (9.3)	80 (4.5)	17 (4.5)	251 (7.2)	164 (5.5)
	Former	14920 (40.0)	278 (15.6)	62 (16.3)	820 (23.4)	400 (13.3)
Hypertension		31227 (54.2)	1406 (60.6)	271 (59.6)	2265 (50.5)	2108 (54.7)
Diabetes		12224 (21.1)	806 (31.0)	138 (25.7)	1259 (25.2)	1447 (34.4)
Chronic kidney disease		10589 (17.6)	427 (15.7)	52 (9.5)	655 (12.6)	649 (14.5)
Heart disease		21011 (34.8)	434 (16.0)	98 (17.8)	1073 (20.7)	1060 (23.6)
Obesity		6613 (12.3)	383 (15.3)	45 (9.0)	626 (13.2)	569 (14.2)
RAS-blockers		15782 (27.6)	651 (29.0)	147 (33.4)	1245 (28.3)	1224 (32.8)
Oxygen saturation	Median (IQR)	96 (93 to 97)	96 (92 to 98)	95 (92 to 98)	96 (93 to 98)	96 (93 to 98)
Respiratory rate	Median (IQR)	20 (18 to 25)	22 (18 to 28)	23 (19 to 30)	22 (18 to 28)	22 (19 to 28)
Any supplemental oxygen		45901 (73.7)	2123 (75.5)	433 (76.5)	4139 (76.1)	3275 (70.6)
Any critical care admission		7508 (12.0)	708 (25.1)	158 (27.8)	1217 (22.3)	1171 (25.2)
Any invasive ventilation		3688 (5.9)	449 (15.9)	111 (19.5)	772 (14.2)	549 (11.8)
Any non-invasive ventilation		8761 (14.1)	545 (19.3)	119 (21.0)	1044 (19.2)	936 (20.2)

28-day Mortality risk (Figures 7-3, 7-4)

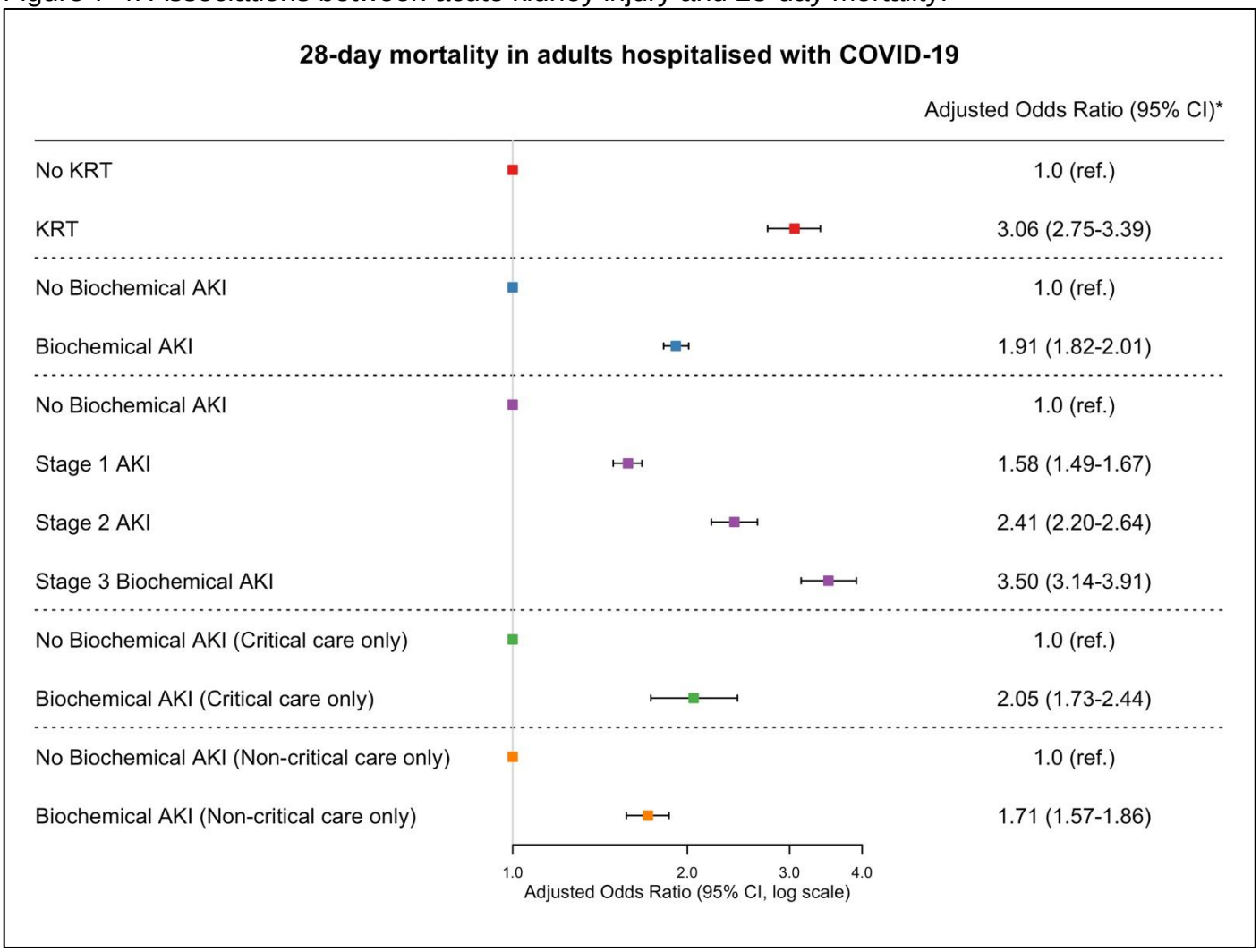
There was an increased risk of mortality for those requiring KRT (aOR 3.06: 2.75-3.39) and those with biochemical AKI (aOR 1.91: 1.82-2.01). The associations for biochemical AKI were present in patients treated within and out with critical care and mortality risk was higher in those with stage 3 than less severe stages (aOR 3.50: 3.14-3.91).

Figure 7-3. Kaplan Meier plot of 28-day mortality by biochemical acute kidney injury status. Time can exceed 28 days as it is after symptom onset and 28-day mortality is from the day of hospitalisation.



Shaded area represents 95% confidence intervals

Figure 7-4. Associations between acute kidney injury and 28-day mortality.

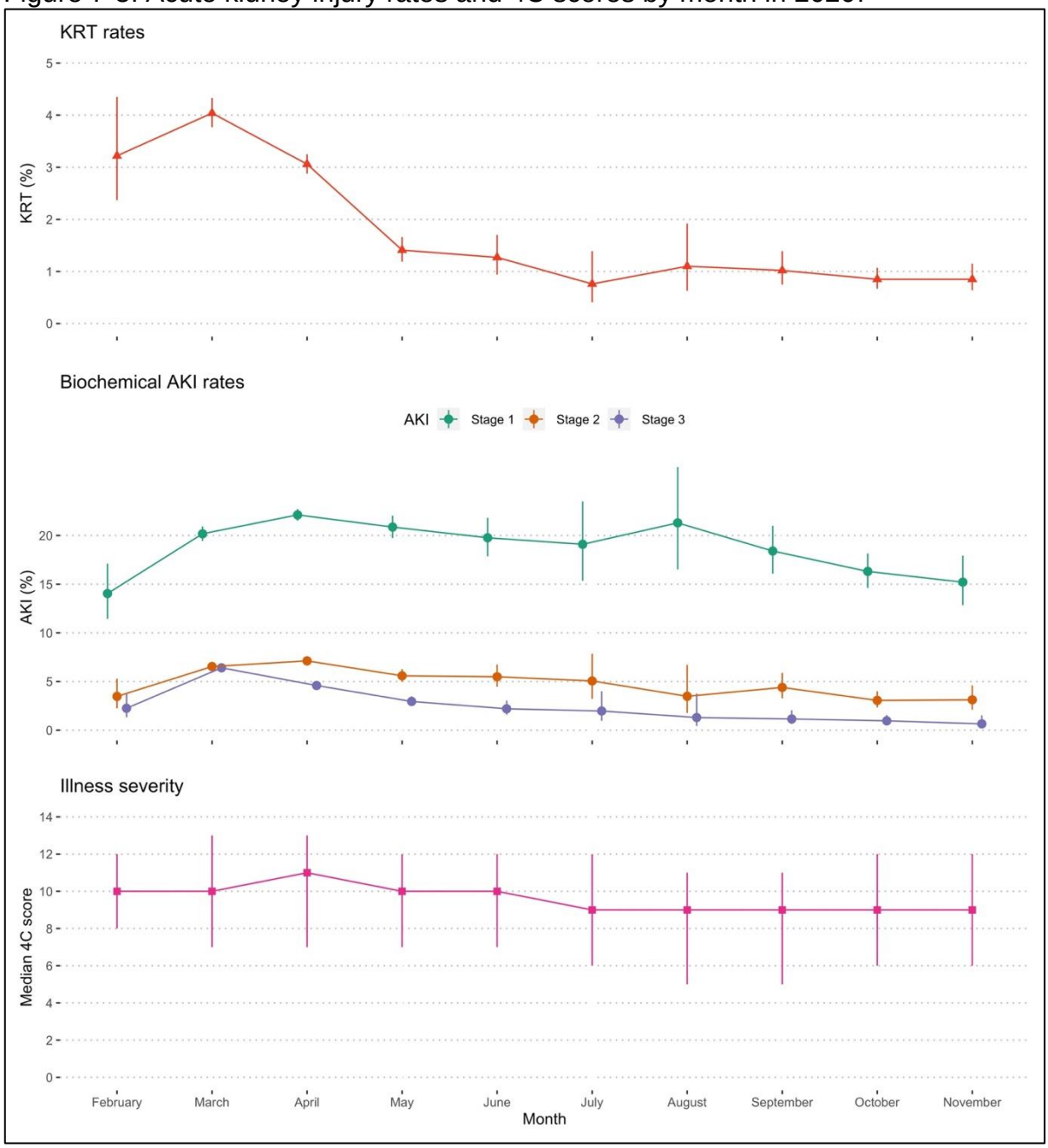


CI, confidence interval. P-values for all groups <0.001. *Adjusted for age, sex, race, deprivation quintile, chronic kidney disease, heart disease, diabetes, admission oxygen saturations on air and admission respiratory rate. Error bars are 95% confidence intervals

AKI rates by month (Figure 7-5)

KRT rates peaked in March 2020 at 4.0% and biochemical AKI in April 2020 at 33.8%. After June 2020, there was a marginal reduction in 4C Mortality Scores: median score 11 (interquartile range (IQR) 7-13) in April 2020 and 9 (IQR 6-12) from July 2020 onwards.

Figure 7-5. Acute kidney injury rates and 4C scores by month in 2020.



Error bars represent 95% confidence intervals for KRT and biochemical AKI rates and interquartile ranges for Illness severity

Timing of AKI

Amongst patients with AKI, the median time from symptom onset to AKI was 6 days (IQR 2-11). Amongst patients with AKI, 7,123 of 13,000 (54.8%) had it on the day of admission and the median time from admission to AKI was 0 days (IQR 0-3). There was no trend in the timing of AKI throughout the months of 2020 (Supplementary Table 7-8). At the end of follow-up, AKI had resolved in 9,758/13,000 (75.1%) of patients.

Supplementary Table 7-8. Time to AKI per month in 2020.

	February	**March**	**April**	**May**	**June**	**July**	**August**	**September**	**October**	**November**
Median days from symptom onset to AKI (IQR)	3 (2 to 9)	7 (3 to 12)	6 (2 to 11)	4 (1 to 0)	5 (1 to 9)	5 (2 to 9)	6 (4 to 10)	6 (3 to 10)	7 (3 to 10)	7 (4 to 12)
Median days from admission to AKI (IQR)	2 (0 to 13)	2 (0 to 5)	0 (0 to 2)	0 (0 to 2)	0 (0 to 2)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)

IQR, interquartile range

Dexamethasone / Remdesivir (Supplementary Table 7-9a to 7-9d)
Compared to the patients not receiving these medications, those receiving dexamethasone and/or remdesivir were on average six years younger and had higher rates of antimicrobial use and treatment in critical care (Supplementary Table 7-10 and 7-11). The use of dexamethasone was positively associated with KRT (Odds ratio (OR) 2.23: 1.09-4.80) and there was no relationship between dexamethasone and biochemical AKI (OR 0.90: 0.51-1.56). There was no relationship between the use of remdesivir and KRT (OR 1.09: 0.38-2.72) or biochemical AKI (OR 0.84: 0.52-1.34).

Supplementary Table 7-9. Medication propensity score matching results

Only patients receiving supplemental oxygen, admitted to hospital after 31/05/2020 and without biochemical acute kidney injury on the day of hospital admission were included. For remdesivir, patients also needed satisfactory kidney and liver function on admission to be included (estimated glomerular filtration rate greater than 30ml/min/1.73m^2 and alanine aminotransferase less than five times the upper limit of normal).

Exact matching month of admission with nearest neighbour matching for age, sex, race, IMD deprivation quintile, diabetes, heart disease, CKD, RAS-blockers and oxygen saturations on air and respiratory rate on admission. Matching ratio 3:1 where sample size allowed.

a. Dexamethasone Propensity Score Matching

	No biochemical acute kidney injury	**Biochemical acute kidney injury**	**Odds ratio**
No dexamethasone (%)	288 (89.7)	33 (10.3)	-
Dexamethasone (%)	224 (90.7)	23 (9.3)	0.90 (0.51-1.56, p=0.701)

b.

	No kidney replacement therapy	**Kidney replacement therapy**	**Odds ratio**
No dexamethasone (%)	1775 (99.4)	11 (0.6)	-
Dexamethasone (%)	1522 (98.6)	21 (1.4)	2.23 (1.09-4.80, p=0.032)

c. Remdesivir Propensity Score Matching

	No biochemical acute kidney injury	**Biochemical acute kidney injury**	**Odds ratio**
No remdesivir (%)	478 (91.0)	47 (9.0)	-
Remdesivir (%)	376 (92.4)	31 (7.6)	0.84 (0.52-1.34, p=0.466)

d.

	No kidney replacement therapy	**Kidney replacement therapy**	**Odds ratio**
No remdesivir (%)	1635 (99.2)	14 (0.8)	-
Remdesivir (%)	645 (99.1)	6 (0.9)	1.09 (0.38-2.72, p=0.866)

Supplementary Table 7-10. Patient characteristics by administration of dexamethasone status.

		No Dexamethasone N=1473	Dexamethasone N=2403
Age	Median (IQR)	70 (54 to 82)	64 (53 to 76)
Sex (%)	Female	721 (48.9)	895 (37.2)
	Male	752 (51.1)	1500 (62.4)
Ethnicity (%)	White	1066 (82.6)	1567 (74.4)
	Black	34 (2.6)	97 (4.6)
	East Asian	5 (0.4)	25 (1.2)
	Other	105 (8.1)	171 (8.1)
	South Asian	80 (6.2)	246 (11.7)
IMD quintile (%)	1	281 (19.4)	721 (31.0)
	2	295 (20.4)	504 (21.7)
	3	293 (20.2)	376 (16.2)
	4	262 (18.1)	399 (17.2)
	5	317 (21.9)	325 (14.0)
Smoking (%)	Never	456 (53.5)	812 (54.1)
	Current	108 (12.7)	104 (6.9)
	Former	288 (33.8)	585 (39.0)
Hypertension (%)		660 (50.1)	1124 (54.4)
Diabetes (%)		263 (19.3)	448 (20.4)
Chronic kidney disease (%)		218 (15.4)	263 (11.3)
Heart disease (%)		455 (31.9)	548 (23.5)
Lung disease (not asthma) (%)		234 (16.5)	355 (15.2)
Asthma (%)		201 (14.1)	397 (17.0)
Chronic liver disease (%)		65 (4.6)	64 (2.8)
Neurological disease (%)		139 (9.8)	170 (7.3)
Cancer (%)		161 (11.4)	168 (7.3)
Haematological disease (%)		73 (5.2)	75 (3.2)
Human immunodeficiency virus (%)		<10 (0.4)	15 (0.7)
Obesity (%)		154 (12.1)	486 (22.8)
Rheumatological disease (%)		185 (13.1)	265 (11.4)
Dementia (%)		165 (11.7)	95 (4.1)
Treatment before admission			
RAS-blockers (%)		344 (26.5)	693 (34.3)
NSAIDs (%)		67 (5.2)	93 (4.6)
Treatment during admission			
Antibiotics (%)		1059 (72.7)	2214 (93.0)
Antifungals (%)		55 (3.8)	179 (7.8)
Critical care admission (%)		156 (10.6)	1021 (42.5)
Vasoactive drugs (%)		35 (2.4)	213 (9.3)
Invasive ventilation (%)		61 (4.2)	336 (14.1)
Non-invasive ventilation (%)		123 (8.4)	985 (41.2)

Supplementary Table 7-11. Patient characteristics by administration of remdesivir status.

		No Remdesivir N=2719	Remdesivir N=1611
Age (%)	Median (IQR)	69 (54 to 80)	63 (53 to 74)
Sex (%)	Female	1227 (45.1)	585 (36.3)
	Male	1484 (54.6)	1021 (63.4)
Ethnicity (%)	White	1922 (80.7)	1035 (73.6)
	Black	75 (3.1)	62 (4.4)
	East Asian	15 (0.6)	18 (1.3)
	Other	173 (7.3)	134 (9.5)
	South Asian	198 (8.3)	157 (11.2)
IMD quintile (%)	1	596 (22.6)	504 (32.1)
	2	550 (20.8)	345 (22.0)
	3	516 (19.5)	248 (15.8)
	4	466 (17.7)	272 (17.3)
	5	512 (19.4)	202 (12.9)
Smoking (%)	Never	799 (53.1)	563 (53.8)
	Current	178 (11.8)	66 (6.3)
	Former	529 (35.1)	417 (39.9)
Hypertension (%)		1281 (53.4)	716 (52.4)
Diabetes (%)		503 (20.2)	292 (19.8)
Chronic kidney disease (%)		420 (16.2)	120 (7.7)
Heart disease (%)		794 (30.5)	331 (21.1)
Lung disease (not asthma) (%)		414 (16.0)	260 (16.6)
Asthma (%)		386 (14.9)	279 (17.8)
Chronic liver disease (%)		103 (4.0)	42 (2.7)
Neurological disease (%)		256 (9.9)	99 (6.3)
Cancer (%)		280 (10.9)	102 (6.5)
Haematological disease (%)		123 (4.8)	42 (2.7)
Human immunodeficiency virus (%)		12 (0.5)	11 (0.7)
Obesity (%)		332 (14.3)	363 (25.2)
Rheumatological disease (%)		364 (14.1)	139 (8.9)
Dementia (%)		248 (9.6)	51 (3.2)
Treatment before admission			
RAS-blockers (%)		693 (29.6)	453 (33.8)
NSAIDs (%)		105 (4.5)	72 (5.4)
Treatment during admission			
Antibiotics (%)		1992 (79.8)	1477 (93.4)
Antifungals (%)		115 (4.8)	131 (8.5)
Critical care admission (%)		612 (22.6)	730 (45.3)
Vasoactive drugs (%)		107 (4.3)	147 (9.7)
Invasive ventilation (%)		189 (7.1)	243 (15.2)
Non-invasive ventilation (%)		453 (16.9)	758 (47.3)

Discussion

In this prospective, multicentre study of up to 85,687 patients hospitalised with COVID-19, we have described risk factors and associations for COVID-19 induced AKI and related mortality. Men, patients with CKD, diabetes, hypertension and obesity, patients from minority race backgrounds and those with severe COVID-19 on admission were at highest risk of AKI related to COVID-19. All stages of AKI were associated with an increased risk of mortality and there was a graded rise in mortality risk by increasing AKI severity. Rates of AKI peaked in April 2020 and although they fell following the first wave of the pandemic, improvements in COVID-19 treatment via pharmaceutical developments were not associated with risk reductions.

The rate of AKI in our study was 31.5%, matching reports from the US.[287 310] The KRT rate in our study was 2.6%, lower than in some others (14-15%).[168 311] However, these were single centre studies and clinical practice such as eligibility criteria for critical care treatment may have influenced KRT rates. Declines in AKI rates following the first wave of the pandemic have been reported elsewhere[310 312], but the reasons for this have not been evaluated. Our findings suggest that improvements in treatment of COVID-19 with dexamethasone and remdesivir did not directly account for the falls in AKI rates. By comparison, the RECOVERY randomised controlled trial found that fewer patients randomised to dexamethasone needed KRT.[313] This may be because after the end of May 2020, these medications were given to the most unwell patients with COVID-19 in the hospital. Although we adjusted for several confounding variables including illness severity, there is likely to be residual confounding which could affect the results.

Beyond pharmaceutical developments, the management of COVID-19 patients changed significantly during 2020. National Institute for Health and Care Excellence guidelines in the UK encouraged maintenance of euvolaemia in COVID-19.[314] However, some clinicians employed conservative fluid resuscitation strategies in the early months of the pandemic. This approach originated from the treatment of patients with non-COVID-19 ARDS and was advocated in the COVID-19 Surviving

Sepsis Guideline.[315] We postulate that conservative fluid strategies may have inadvertently contributed to the development of AKI in some patients in the early months of the pandemic, such as in those with precarious oxygenation and fluid losses. As previously reported from the ISARIC WHO CCP-UK study, the use of invasive mechanical ventilation in patients with COVID-19 fell significantly as the pandemic unfolded.[316] This change in practice may have had an additional impact on AKI. We found the risk of biochemical AKI was lower in the oldest adults (over 80 years) compared to other age groups (50 to 79 years). This was not associated with reduced frequency of blood tests in the oldest adults, hence the reasons for this trend are unclear. The declining rates of AKI over time may in part be due to increasing clinician awareness of AKI in COVID-19, prompting them to monitor their patients' fluid status and blood tests more closely, as well as decreasing illness severity.[316]

We have verified findings from smaller studies from the first wave of the pandemic, including the role of AKI as a risk factor for mortality in COVID-19. 40.4% of patients with biochemical AKI in our study died, which is between the 34%[287 310 290] and 51.8%[317] reported in previous studies. Even patients with minor biochemical changes (stage 1 AKI) were at increased risk of dying, highlighting that all patients with COVID-19 and AKI should have targeted monitoring and optimisation of their fluid status. Although we have confirmed that mortality risk rose with increasing stage of AKI, our odds ratios are lower than in previous studies. [290 310 318] This may be because the patients in our "no AKI" reference group were more co-morbid than the rest of the cohort, with high rates of diabetes and CKD.

The AKI risk factors we identified were similar to those reported previously.[287, 310] We have confirmed a particularly high risk of AKI in patients from minority race backgrounds and our findings suggest this is contributed to by comorbidities.[319] A study of 1,737 patients with COVID-19 in East London (60% non-white) demonstrated an increased risk of mortality in black and Asian patients, independent of comorbidities.[320] Several factors are postulated to contribute to this increased risk, including higher prevalence of comorbidities that are associated with greater COVID-19 disease severity, cultural factors, host genetics, cultural and lifestyle factors, and inequality.[321] We found that non-white patients admitted to hospital with COVID-19

were younger and more likely to be admitted to critical care than their white counterparts. This may explain to a large extent their increased risk of requiring KRT. South Asian race was a predictor of stages 2 and 3 AKI, and our interaction analysis suggests this was contributed to by CKD and diabetes. Our results suggest that the increased risk of biochemical AKI in black patients is contributed to by CKD, even though the proportion of black patients with CKD was less than in white patients. It is possible that prior CKD was infrequently recorded in patients of black race.[322] In addition to multiple socioeconomic and health risk factors associated with adverse outcomes in people of black race in COVID-19,[323] AKI-specific risk may in some part be attributable to the possession of high-risk APOL1 genotypes [324], which are present in people of west African ancestry. These alleles are associated with greatly increased risk of CKD in people of black race in North America[28] and have been implicated in COVID-19-related glomerular disease.[325]

Our study has some notable strengths. To our knowledge, it is the largest study of AKI in COVID-19 to date. Our cohort comprised patients from 254 acute hospital sites spanning most of 2020, allowing us to evaluate the temporal variations in AKI and KRT rates over the first wave and part of the second wave of the pandemic. Our cohort included a significant number of patients that were prescribed dexamethasone and remdesivir, thus allowing us to assess the relationship between the use of these medications and AKI. We have explored additional crucial areas: the relationship between race and AKI and illness severity as a key risk factor for AKI.

Our study has some limitations. 26.5% of the patients were identified as having COVID-19 before testing for SARS-CoV-2 was universally available. Some of these patients may therefore have had illnesses other than COVID-19. In our biochemical AKI analysis, we excluded patients without two or more recorded creatinine values, risking the introduction of selection bias. Despite slightly higher rates of co-morbidities such as CKD in those included in the study, the patients without biochemistry data were very similar. Some blood results during an individual's admission may not have been available if they were not recorded in the database. This could have an impact on AKI detection and accurate categorisation of AKI stage. The execution of separate KRT and biochemical AKI analyses was

appropriate for two reasons. First, the use of acute KRT in an individual is considerably linked to illness severity and whether clinicians decide it is appropriate to care for them in a critical care environment or a ward (which may depend on pre-morbid health status). Second, due to the challenges of real-time data collection during a pandemic, creatinine results were available for relatively few patients and we sought to study as many patients as possible. We did not have access to baseline kidney function, therefore we may have missed some AKI events and we were unable to stratify risk by severity of baseline CKD. Although most cases of AKI had resolved by the end of in-hospital follow-up, we did not have access to kidney function following discharge and so we were unable to study long-term recovery following AKI. We did not have data on urine output or fluid resuscitation regimens, although it is difficult reliably to record this information outside of critical care settings.

In conclusion, AKI was common in patients hospitalised with COVID-19 and these patients were at high risk of death. The patients at highest risk of AKI were typically men, black, with CKD and had severe COVID-19 illness on admission. AKI rates have fallen since the early months of the pandemic, despite no observed influence of pharmaceutical developments. This may reflect changes in attitudes towards fluid balance. Clinicians should monitor the kidney function and fluid status of patients with COVID-19 closely and intervene early if AKI develops.

Conflict of Interest Statement

All authors declare support from the National Institute for Health Research (NIHR), the Medical Research Council (MRC), the NIHR Health Protection Research Unit (HPRU) in Emerging and Zoonotic Infections at University of Liverpool, NIHR HPRU in Respiratory Infections at Imperial College London, NIHR Biomedical Research Centre at Imperial College London, and NIHR Clinical Research Network for the submitted work; ABD reports grants from Department of Health and Social Care (DHSC), during the conduct of the study, grants from Wellcome Trust, outside the submitted work; PO reports personal fees from consultancies and from European Respiratory Society, grants from MRC, MRC Global Challenge Research Fund, EU, NIHR BRC, MRC/GSK, Wellcome Trust, NIHR (Health Protection Research Unit (HPRU) in Respiratory Infection), and is NIHR senior investigator outside the submitted work; his role as President of the British Society for Immunology was unpaid but travel and accommodation at some meetings was provided by the Society; JKB reports grants from MRC UK; MGS reports grants from DHSC NIHR UK, grants from MRC UK, grants from HPRU in Emerging and Zoonotic Infections, University of Liverpool, during the conduct of the study, other from Integrum Scientific LLC, Greensboro, NC, USA, outside the submitted work. The remaining authors all declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Author Contributions

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MKS is guarantor and corresponding author for this work, and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data Availability Statement

This work uses data provided by patients and collected by the NHS as part of their care and support #DataSavesLives. The CO-CIN data was collated by ISARIC4C Investigators. ISARIC4C welcomes applications for data and material access through our Independent Data and Material Access Committee (https://isaric4c.net).

Ethical Approval

Ethical approval was provided by the South Central – Oxford C Research Ethics Committee in England (Ref. 13/SC/0149), and by the Scotland A Research Ethics Committee (Ref. 20/SS/002

Chapter: 8 The presence and impact of multimorbidity clusters on adverse outcomes across the spectrum of kidney function

8.1 Reference

Sullivan, M. K., Carrero, J.-J., Jani, B.D., Anderson, C., McConnachie, A., Hanlon, P., Nitsch, D., McAllister, D.A., Mair, F.S., Mark, P. B., Gasparini, A. (2022). *BMC Medicine*, *20*(1), 1–13. https://doi.org/10.1186/s12916-022-02628-2

8.2 Chapter summary

In this chapter, clusters of chronic conditions were identified in patients at different levels of kidney function. The associations between clusters and adverse outcomes (mortality and cardiovascular events) were then investigated.

Abstract

Background: Multimorbidity (the presence of two or more chronic conditions) is common amongst people with chronic kidney disease, but it is unclear which conditions cluster together and if this changes as kidney function declines. We explored which clusters of conditions are associated with different estimated glomerular filtration rates (eGFRs) and studied associations between these clusters and adverse outcomes.

Methods: Two population-based cohort studies were used: Stockholm Creatinine Measurements project (SCREAM, Sweden, 2006-2018) and Secure Anonymised Information Linkage Databank (SAIL, Wales, 2006-2021). We studied participants in SCREAM (404,681 adults) and SAIL (533,362) whose eGFR declined lower than thresholds (90, 75, 60, 45, 30 and 15 ml/min/1.73m^2). Clusters based on 27 chronic conditions were identified. We described the most common chronic condition(s) in each cluster and studied their association with adverse outcomes using Cox proportional hazards models (all-cause mortality: ACM; and major adverse cardiovascular events: MACE).

Results: Chronic conditions became more common and clustered differently across lower eGFR categories. At eGFR 90, 75, and 60mL/min/1.73m^2, most participants were in large clusters with no prominent conditions. At eGFR 15 and 30mL/min/1.73m^2, clusters involving cardiovascular conditions were larger and were at the highest risk of adverse outcomes. At eGFR 30mL/min/1.73m^2: Heart Failure, Peripheral Vascular Disease & Diabetes cluster in SCREAM; ACM hazard ratio (HR) 2.66 (95% confidence interval (CI) 2.31-3.07), MACE HR 4.18 (CI 3.65-4.78); Heart Failure & Atrial Fibrillation cluster in SAIL; ACM HR 2.23 (CI 2.04 to 2.44), MACE HR 3.43 (CI 3.22-3.64). Chronic pain and depression were common and associated with adverse outcomes when combined with physical conditions. At eGFR 30mL/min/1.73m^2: Chronic Pain, Heart Failure & Myocardial Infarction cluster in SCREAM; ACM HR 2.00 (CI 1.62-2.46), MACE HR 4.09 (CI 3.39-4.93); Depression, Chronic Pain & Stroke cluster in SAIL; ACM HR 1.38 (CI 1.18-1.61), MACE HR 1.58 (CI 1.42-1.76).

Conclusions: Patterns of multimorbidity and corresponding risk of adverse outcomes varied with declining eGFR. While diabetes and cardiovascular disease are known

high-risk conditions, chronic pain and depression emerged as important conditions and associated with adverse outcomes when combined with physical conditions.

Keywords: Multimorbidity, Chronic conditions, Chronic kidney disease, Clustering analysis

Background

As the world's population lives longer, an increasing number of people are living with multiple chronic conditions (multimorbidity).[1] These people suffer from high treatment burden as they often must cope with numerous medications and attend multiple specialists.[84] Multimorbidity is a leading challenge facing 21st century medicine, and the optimal management of people with several complex medical conditions is yet to be established.[229,69]

Chronic kidney disease (CKD), defined as a persistent and irreversible degradation of kidney function, affects around 10% of the world's population.[202,239] Its multifactorial nature, progressive trajectory which is often associated with complications, and the development of cardiometabolic conditions means that CKD is usually linked to multimorbidity. The care of people with CKD has been reported to be more complex than that of patients attending any other specialist[3] and they are disproportionately susceptible to adverse outcomes such as hospitalisation[326] and cardiovascular events.[59] Research into people with multiple chronic conditions has primarily focused on the number of conditions, and there has been less focus on clusters of conditions, particularly amongst people with CKD. Identifying clusters of conditions may help to improve the management of these people by informing preventative strategies, targeted treatments and health service organisation.[263] Some conditions may cluster together in clinically meaningful ways, such as if cluster membership tells us about common risk factors or if it helps stratify the risk of subsequent adverse events.[327]

How multimorbidity changes with declining kidney function and how this contributes to poor outcomes is not known. Clustering techniques can be used to uncover unknown patterns within data and are used in this study to identify clusters of conditions in two geographically distinct population-based cohorts. We identified these clusters in people at different levels of kidney function (including estimated glomerular filtration rate (eGFR) >60mL/min/1.73m^2) and studied the associated risk of mortality and major adverse cardiovascular events (MACE).

Methods

Study populations

We used two databases with anonymised health and administrative data: the Stockholm Creatinine Measurements project (SCREAM) covers the entire region of Stockholm, Sweden (approximately 2.9 million people during the study period);[328] and the Secure Anonymised Information Linkage Databank (SAIL) covers 79% of the population of Wales (approximately 3.4 million people during the study period).[160] In both cohorts, primary care, secondary care, prescribing, and mortality data were linked. We included adults with outpatient serum/plasma creatinine values after 1st January 2006. Calibrated laboratory analysers for creatinine were used in SCREAM; in SAIL, non-calibrated analysers may have been used and so creatinine values were multiplied by 0.95 to account for possible lack of calibration.[21] Participants were lost to follow-up if they permanently left the region for SCREAM, or if they left a participating GP practice or the country for SAIL. Participants were followed up until 31st December 2018 in SCREAM and 1st June 2021 in SAIL.

Selection of patients and kidney function thresholds

EGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation, but without considering the race coefficient.[244] We studied all adults with at least two eGFR values whose eGFR crossed one or more threshold during follow-up: 90, 75, 60, 45, 30 and 15 mL/min/1.73m^2. All eGFR values were used to fit a linear fixed effects model, and this procedure is described in more detail in the supplementary material. By estimating the dates at which participants crossed these thresholds, we could define study covariates at these dates and outcomes thereafter. Participants could cross more than one eGFR threshold and could therefore be included in more than one eGFR category for subsequent analysis. Flow charts of included individuals are depicted in Supplementary figures 8-1A and 8-1B.

Supplementary Material: Interpolation of kidney function

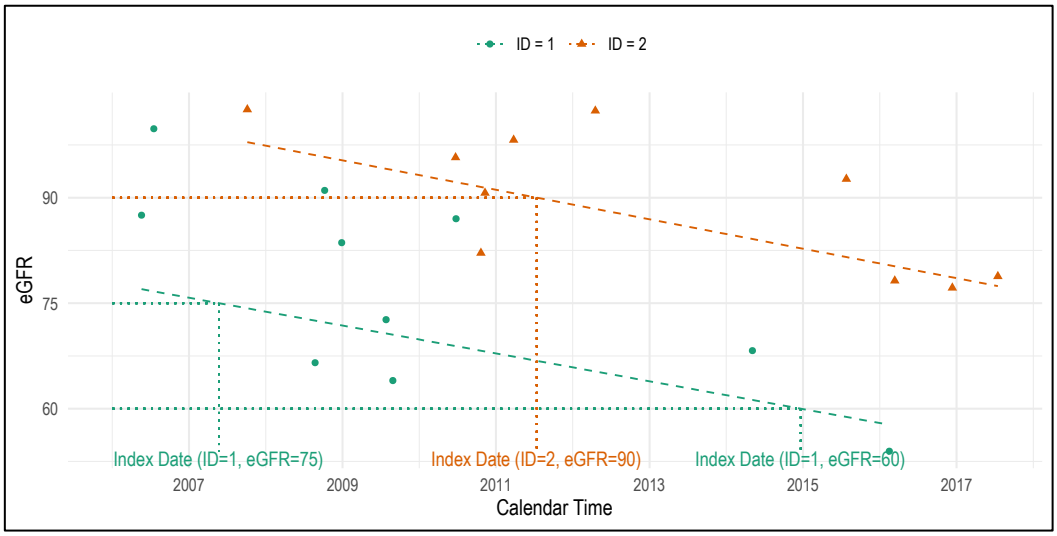
We selected our cohorts through evaluation of linear trajectories of estimated glomerular filtration rate (eGFR) decline using all available creatinine measurements per participant. This aimed to reduce outcome misclassification bias owing to intrinsic eGFR variability, and to confirm whether eGFR declines were sustained over time. To that end, we fitted a linear mixed effects model with a random intercept and slope of time to interpolate the date at which each participant reached the following eGFR thresholds: 90, 75, 60, 45, 30 and 15 mL/min/1.73m^2.[367] The model included only time as a covariate, assuming linearity; furthermore, we assumed an unstructured variance-covariance matrix for the random effects. The model equation for the ith participant is therefore:

$$eGFR_i = \beta_0 + b_{0i} + (\beta_1 + b_{1i})time_i$$

Using the fitted model coefficients and the predicted random effects for each participant, we can estimate the time at which a given eGFR threshold (named (eGFR$_T$) was reached using the following equation:

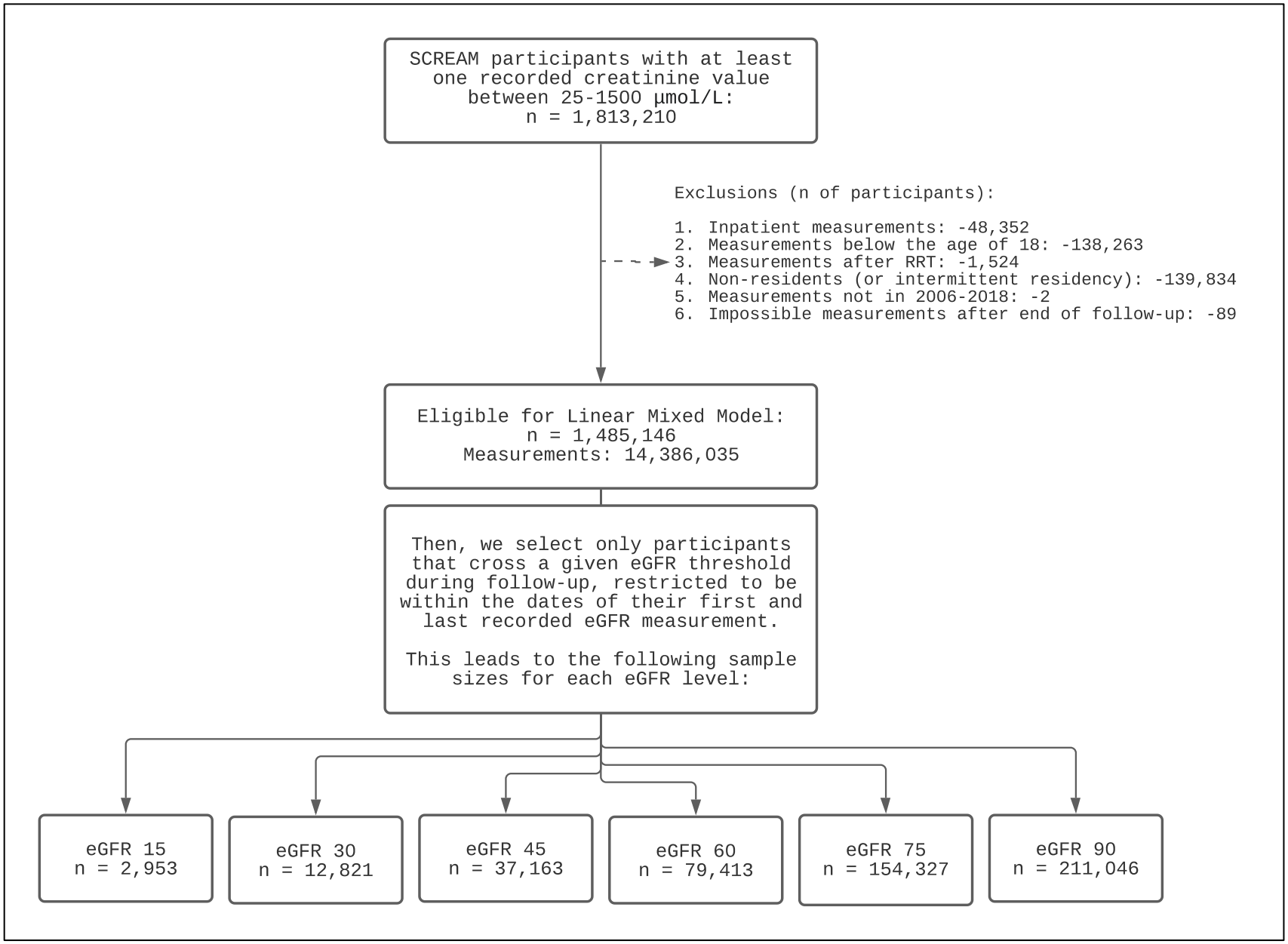
$$time_i = \frac{eGFR_T - \beta_0 - b_{0i}}{\beta_1 + b_{1i}}$$

The plot below illustrates the interpolation procedure in practice: according to our procedure, participant with ID = 1 will be included for the analysis at the eGFR = 60 and eGFR = 75 levels, while participant with ID = 2 will be included for the eGFR = 90 analysis, with corresponding index dates based on the results of the mixed modelling analysis (e.g., the subject-specific dashed lines).

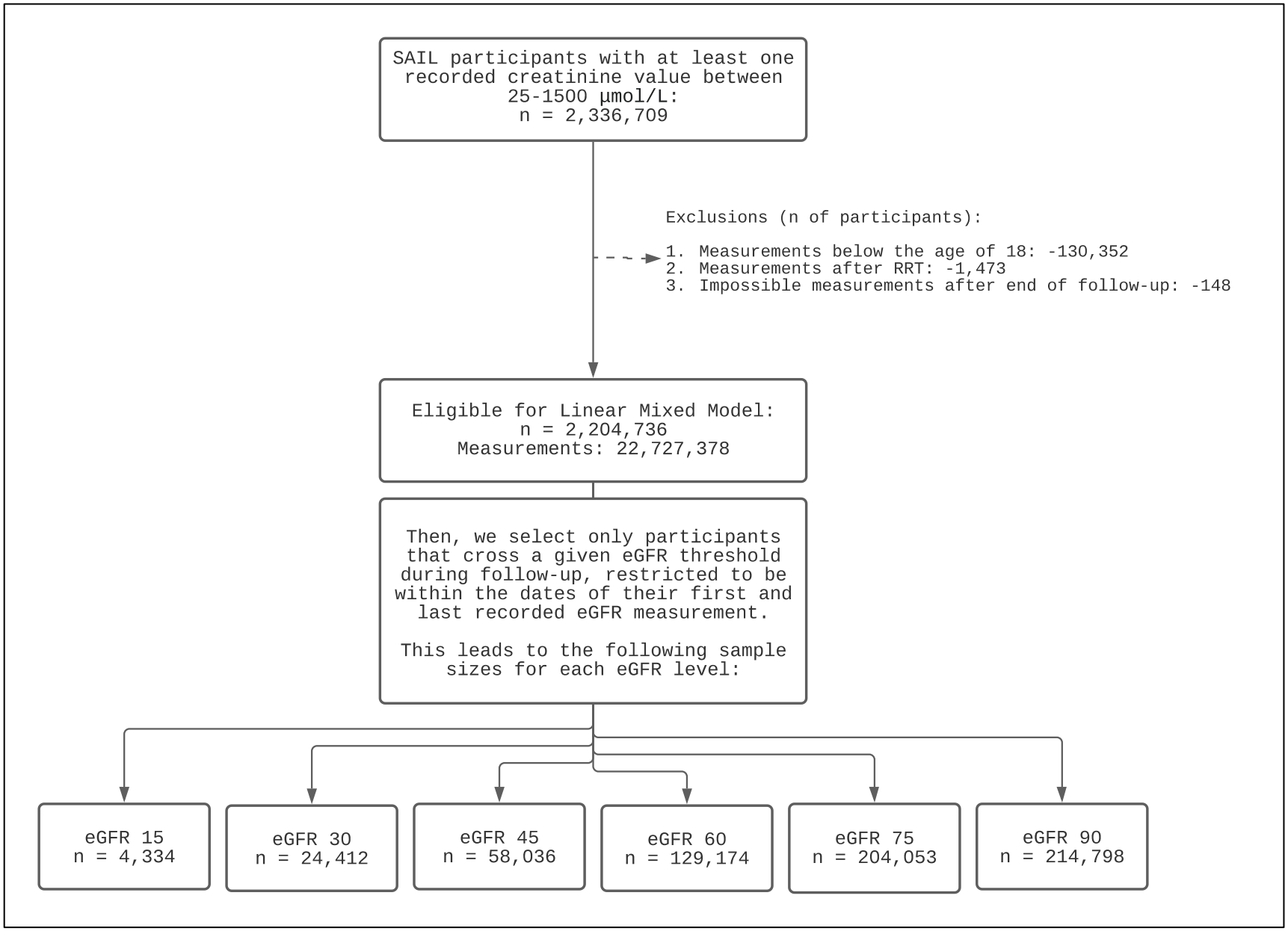


We note that participants could be included in more than one eGFR category through their disease course and extent of follow up. In this design, participants undergoing long-term kidney replacement therapy were excluded after it began, as were participants with stable eGFR that did not cross any of the abovementioned thresholds.

Supplementary figure 8-1A. SCREAM participant inclusion flow chart. RRT, renal replacement therapy.



Supplementary figure 8-1B. SAIL participant inclusion flow chart. RRT, renal replacement therapy.



Chronic conditions

For each participant, and at each eGFR threshold, we evaluated the presence of 27 different chronic conditions. In SCREAM, ICD-10 codes recorded in primary and secondary care records were used. In SAIL, ICD-10 codes were used for secondary care records with separate primary care read codes used, as previously described.[326] These conditions were ascertained using a validated algorithm[170] with some modifications: we excluded CKD as it was our exposure, and we used a single cancer definition (excluding non-melanoma skin cancer); combining lymphoma, metastatic cancer and non-metastatic cancer. Conditions were defined for each participant at the estimated date of crossing eGFR thresholds and time windows were applied as per the algorithm in use.[170] The cause of CKD was not incorporated as it is rarely possible to determine this from population-level data. As depression and chronic pain are poorly recorded in healthcare records, we enriched the definitions of these conditions with prescription data, as previously described.[1,326] In brief, a participant was assigned to have depression if they had four or more antidepressant prescriptions within a year and chronic pain if they had four or more prescriptions for painkillers within a year (including antiepileptic medications such as gabapentin, so long as the participant did not have epilepsy). Four or more prescriptions was used on the assumption that medications were being used for more than three months and the problem was therefore chronic.

Outcomes

After identifying clusters of conditions, we studied associations between cluster membership and subsequent adverse outcomes. Outcomes were identified from death and secondary care records: all-cause mortality, MACE (myocardial infarction, stroke or cardiovascular death, denoted as MACE3) and MACE plus heart failure hospitalisation (denoted as MACE4). Relevant ICD-10 codes are available in supplementary table 8-1. To capture as many events as possible in both cohorts, the secondary care records used were from hospitals in Sweden and Wales that provide universal coverage.

Supplementary table 8-1. ICD-10 codes for major adverse cardiovascular events (MACE)

Outcome	Diagnosis	ICD-10 codes
MACE3	Cardiovascular death	Death attributed to G45-G46, H341, I*
	Hospitalisation attributed to myocardial infarction	I21, I22, I23
	Hospitalisation attributed to stroke	H341, G45, G46, I60, I61, I63, I64
MACE4	Cardiovascular death	Death attributed to G45-G46, H341, I*
	Hospitalisation attributed to myocardial infarction	I21, I22, I23
	Hospitalisation attributed to stroke	H341, G45, G46, I60, I61, I63, I64
	Hospitalisation attributed to heart failure	I099, I110, I130, I132, I255, I420, I425-429, I43, I50

Statistical analysis

Baseline characteristics including the prevalence of chronic conditions were compared between participants in each eGFR category. Categorical variables were expressed as frequencies with percentages and continuous variables as medians with interquartile intervals (IQI). We compared the participants with available eGFRs who were included in the analysis to those with available eGFRs not included in terms of their birth dates, sex, and number of eGFR measurements.

We applied a k-modes algorithm within each eGFR category to identify clusters of conditions.[199] This clustering technique identifies clusters of participants with similar combinations of covariates, in our case the 27 chronic conditions, maximising homogeneity within clusters and heterogeneity between clusters. We chose to use this algorithm as it can perform clustering with categorical data and is computationally efficient (given our large sample sizes). We ran the algorithm for two to 10 possible clusters, as we deemed a larger number of clusters not clinically useful. We allowed for a maximum of 20 iterations of the algorithm. The optimal

number of clusters was selected using the elbow method, to minimise the within-cluster distance while selecting a parsimonious number of clusters.[329] We plotted gradients of the elbow plots to ease the choice, as gradients approach zero when the elbow plots flatten. The k-modes algorithm was repeated with participants stratified by age (< and ≥65 years).

The prevalence of chronic conditions in each cluster was compared to their prevalence in the overall eGFR category. Observed/expected (O/E) ratios were calculated by dividing condition prevalence in a cluster by the prevalence in each eGFR category. Prominent conditions for each cluster were identified as conditions which were common (≥20% prevalence) and more common than the overall eGFR category (O/E ratio ≥2).[330] To prevent cluster descriptions becoming protracted, a maximum of three prominent conditions were selected as the defining condition(s) for each cluster, with the most prevalent conditions used if more than three were identified. To help compare the prominent conditions, the clusters were further categorised using the single most prevalent condition in each cluster, using that condition's body system: cancer, cardiovascular, dermatological, endocrine, gastrointestinal, mental health and pain, neurological, respiratory, rheumatological, and non-specific. We then compared the proportion of participants in clusters in each eGFR category.

Cluster allocation for all participants was fully determined prior to analysing the outcome data. We calculated crude rates of incident adverse events per cluster, and expressed them per 1000 person-years at risk. Then, relationships between cluster membership and outcomes were assessed using Cox proportional hazard models, adjusting for age and sex. For the MACE analyses, participants were censored on the date of death. The reference groups were participants in clusters with no prominent conditions (based on prevalence). If there was more than one cluster with no prominent condition, the cluster with the highest number of participants was selected as the reference group. For each model, we tested the statistical significance of the clustering variable using Wald tests and produced standardised survival curves (using regression standardisation[331]) to quantify absolute risks for

each cluster at each eGFR level considered in the study. We assessed the prediction of outcomes via internal validation of our models using time-varying area under the receiver operating characteristic curve (AUC) and Brier scores over the duration of follow-up; non-parametric bootstrap with 100 resamples was used to calculate standard errors for each metric. Models with age and sex only were compared to models which added cluster membership and models which added the number of chronic conditions.

Statistical analyses were conducted using R version 4.0.5 or later[332] with the tidyverse, nephro, lme4, SCREAM, klaR, glue, formattable, survival, broom, aod, ggalluvial, matrixStats, ggrepel, stdReg, ggtext, hrbrthemes, knitr, patchwork, readxl, riskRegression, and cowplot packages. Code is available on Github for others to replicate our analysis: https://github.com/ellessenne/multimorbidity-ckd-clustering.

Results

Baseline characteristics

The SCREAM cohort consisted of 404,681 unique participants (53.5% women). Median age was lowest in the eGFR 90 category (58.8 years, IQI: 49.3-66.2) and highest in the eGFR 30 category (82.5 years, IQI: 73.7-88.4) (Table 8-1A). The SAIL cohort consisted of 533,362 unique participants (55.3% women). Median age was lowest in the eGFR 90 category (55.5 years, IQI: 46.6-63.5) and highest in the eGFR 30 category (80.8 years, IQI: 73.1-86.5) (Table 8-1B). Comparing both tables shows that SAIL participants in this study have a higher multimorbidity count when compared to their Swedish counterparts.

Participants in the low eGFR categories had the highest number of chronic conditions, particularly in those aged over 65 years (Figure 8-1). Participants included in the analysis tended to be born at earlier dates and have more eGFR measurements than those excluded (Supplementary figures 8-2A and 8-2B). The proportions of females and males included were similar, except at eGFR 15mL/min/1.73m^2, where proportionally fewer women were included.

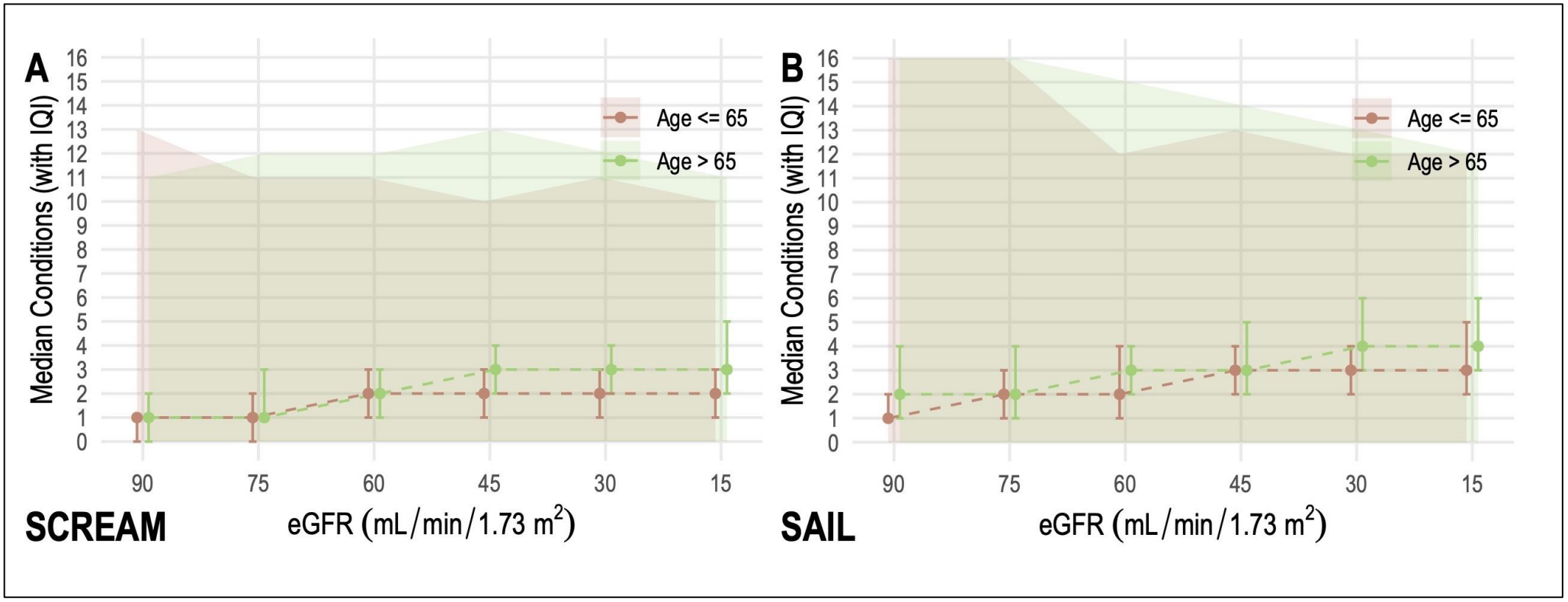
Table 8-1A. SCREAM baseline characteristics by eGFR category.

		Estimated glomerular filtration rate (eGFR) category (mL/min/1.73m^2)					
		90	75	60	45	30	15
Number of participants		211,046	154,327	79,413	37,163	12,821	2,953
Age (years)	Median (IQI)	58.8 (49.3 to 66.2)	68.7 (60.9 to 75.8)	76.7 (69.8 to 83.1)	81.4 (74.2 to 87.1)	82.5 (73.7 to 88.4)	74.7 (64.0 to 83.9)
Sex	Female (%)	107,965 (51.2)	83,321 (54.0)	44,061 (55.5)	20,497 (55.2)	6,500 (50.7)	1,172 (39.7)
Chronic condition count (% for eGFR category)	0	88,122 (41.8)	43,897 (28.4)	11,684 (14.7)	2,858 (7.7)	591 (4.6)	70 (2.4)
	1	63,136 (29.9)	44,508 (28.8)	18,334 (23.1)	5,903 (15.9)	1,361 (10.6)	231 (7.8)
	2	34,152 (16.2)	31,654 (20.5)	18,645 (23.5)	7,852 (21.1)	2,048 (16.0)	461 (15.6)
	3	15,289 (7.2)	18,202 (11.8)	13,784 (17.4)	7,493 (20.2)	2,387 (18.6)	523 (17.7)
	4+	10,347 (4.9)	16,066 (10.4)	16,966 (21.4)	13,057 (35.1)	6,434 (50.2)	1,668 (56.5)

Table 8-1B. SAIL baseline characteristics by eGFR category.

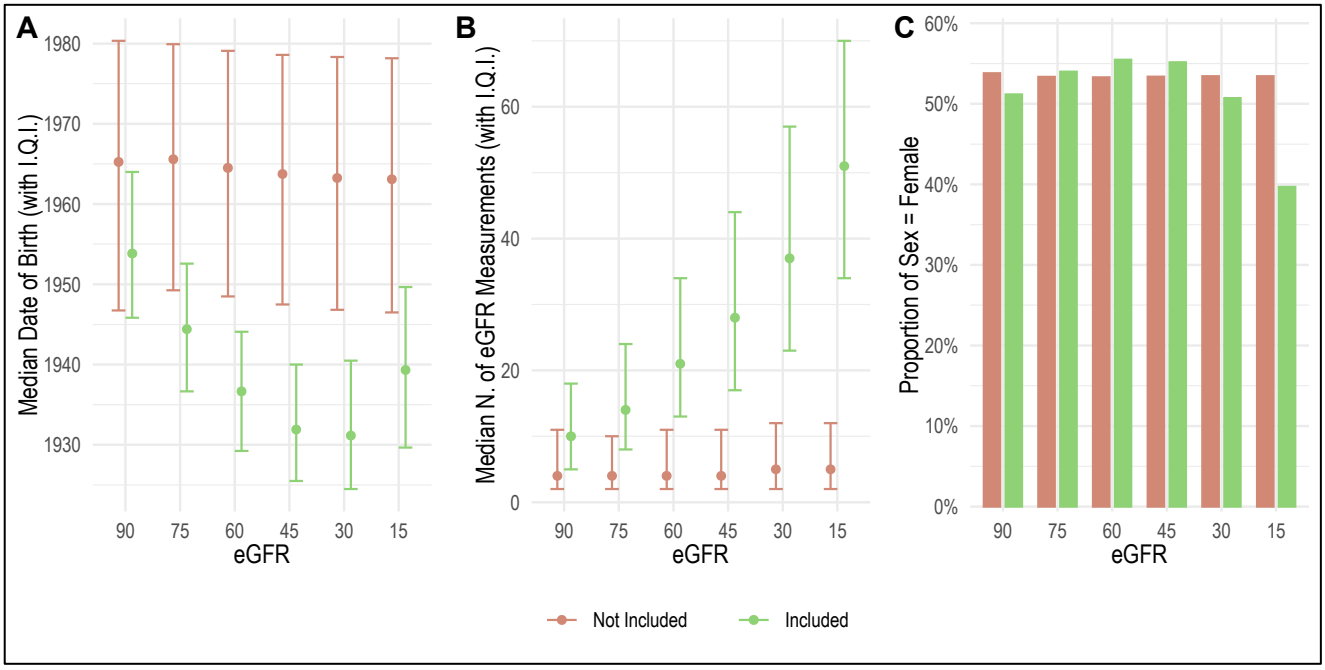
		Estimated glomerular filtration rate (eGFR) category (mL/min/1.73m^2)					
		90	75	60	45	30	15
Number of participants		214,798	204,053	129,174	68,036	24,412	4,334
Age (years)	Median (IQI)	55.5 (46.6 to 63.5)	66.6 (58.5 to 73.8)	74.2 (67.5 to 80.5)	79.0 (72.4 to 84.6)	80.8 (73.1 to 86.5)	76.0 (65.9 to 83.8)
Sex	Female (%)	117,993 (54.9)	110,615 (54.2)	70,649 (54.7)	37,082 (54.5)	12,702 (52.0)	1,870 (43.1)
Chronic condition count (% for eGFR category)	0	45,135 (21.0)	27,180 (13.3)	8,085 (6.3)	1,721 (2.5)	379 (1.6)	60 (1.4)
	1	61,264 (28.5)	47,732 (23.4)	21,402 (16.6)	7,472 (11.0)	1,895 (7.8)	307 (7.1)
	2	46,572 (21.7)	45,869 (22.5)	27,560 (21.3)	12,447 (18.3)	3,578 (14.7)	624 (14.4)
	3	28,807 (13.4)	34,165 (16.7)	25,475 (19.7)	13,528 (19.9)	4,579 (18.8)	824 (19.0)
	4+	33,020 (15.4)	49,107 (24.1)	46,652 (36.1)	32,868 (48.3)	13,981 (57.3)	2,519 (58.1)

Figure 8-1. Median number of chronic conditions by cohort and eGFR category: A SCREAM, B SAIL.

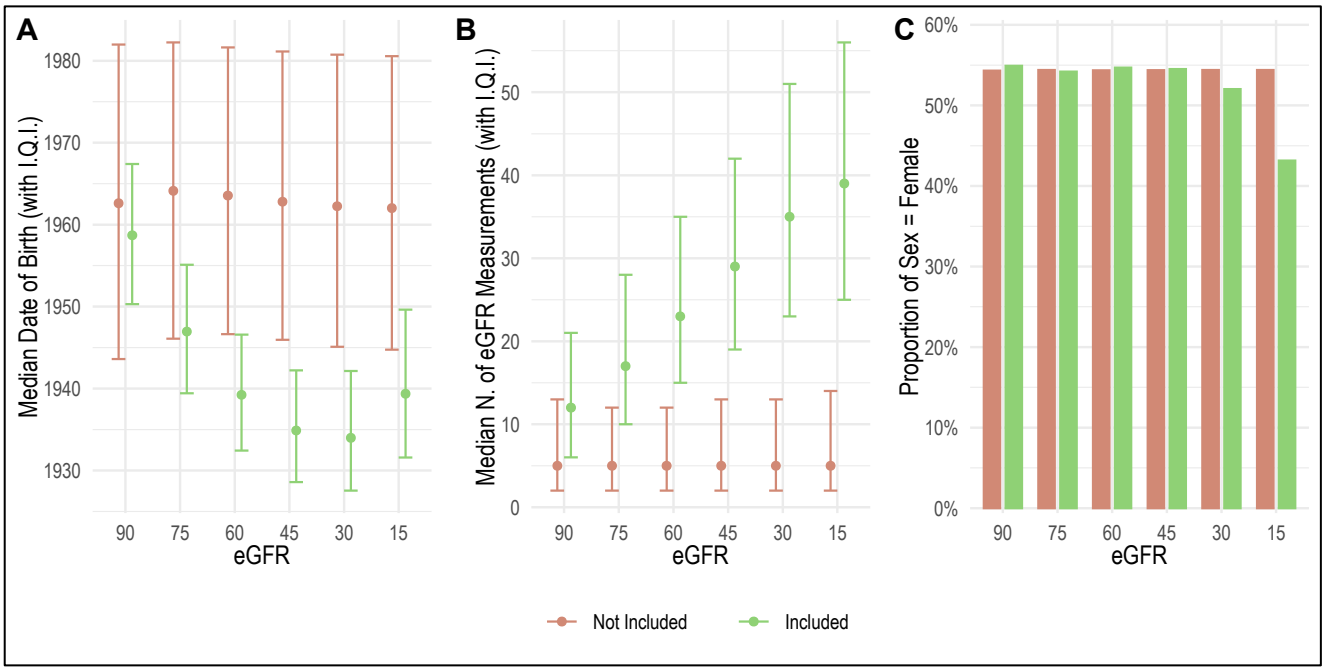


Error bars represent IQIs and the shaded areas minimum and maximum counts.

Supplementary figure 8-2A. Comparison of SCREAM participants included and excluded from the analysis. A Birth dates; B Number of eGFR measurements; C Proportion female sex



Supplementary figure 8-2B. Comparison of SAIL participants included and excluded from the analysis. A Birth dates; B Number of eGFR measurements; C Proportion female sex

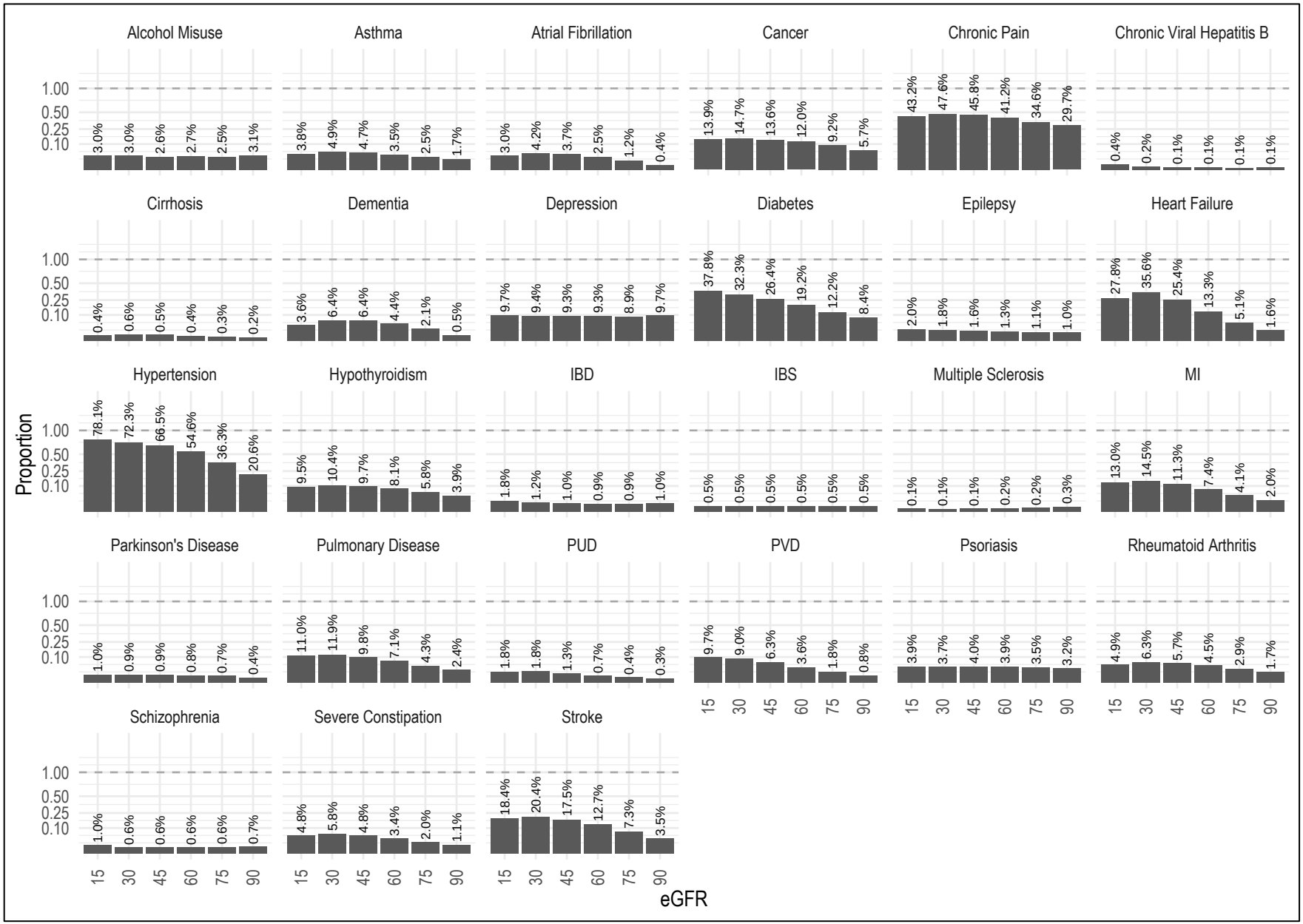


Prevalence of chronic conditions by eGFR

The prevalence of most chronic conditions increased in lower eGFR categories (Supplementary figures 8-3A and 8-3B). For example, in SAIL, the prevalence of cancer at eGFR 90 was 9.3% and at eGFR 15 25.7%.

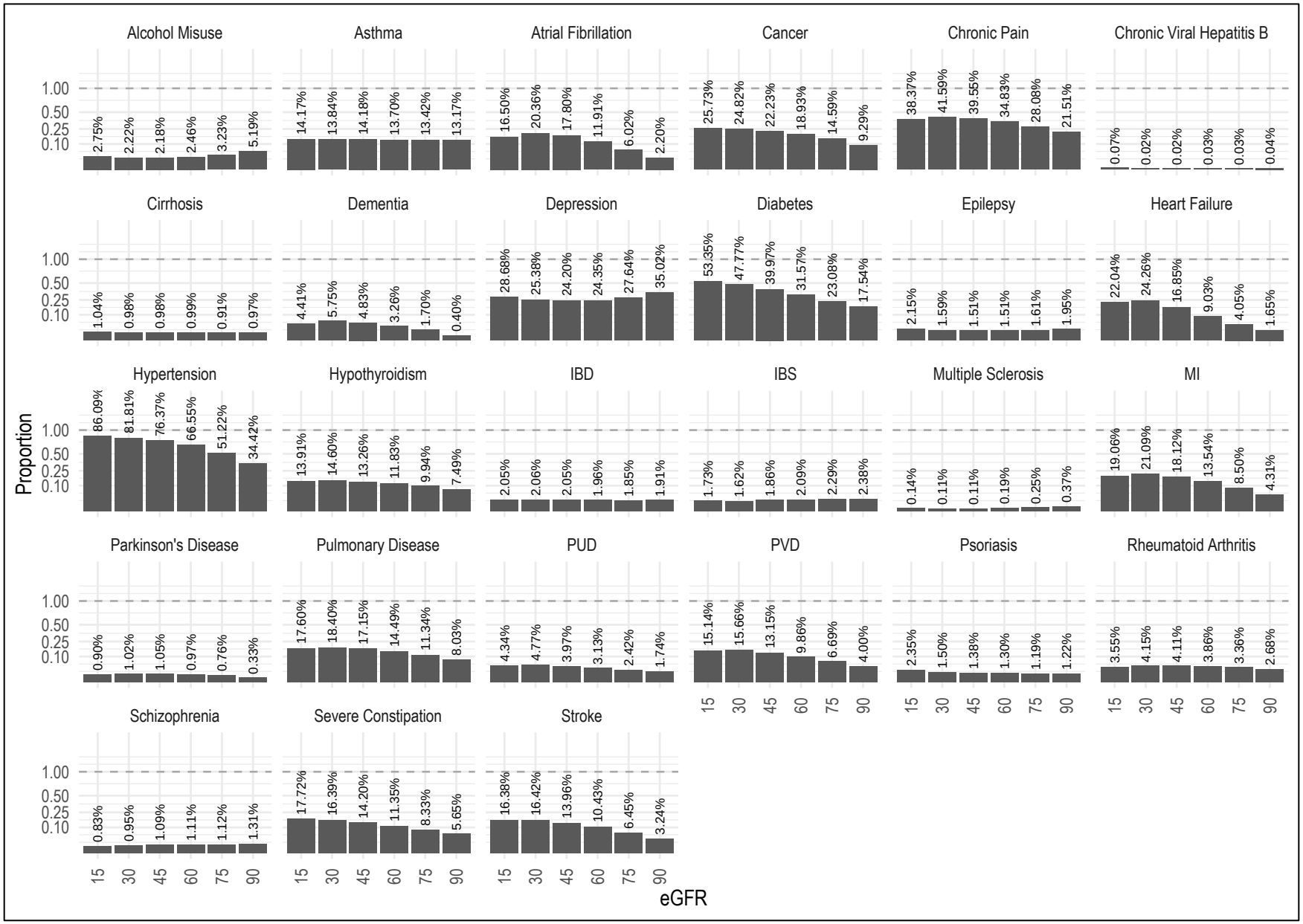
The most frequently recorded chronic condition in SCREAM was hypertension, which ranged from 20.6% in the eGFR 90 group to 78.1% in eGFR 15. Analogously, chronic pain ranged from 29.7% in the eGFR 90 group to 43.2% in eGFR 15; diabetes ranged from 8.4% to 37.8% for eGFR 90 and 15; and heart failure ranged from 1.6% to 27.8% for eGFR 90 and 15.

Supplementary figure 8-3A. Proportion of conditions by eGFR category in SCREAM.



The most frequently recorded chronic condition in SAIL was also hypertension, which ranged from 34.4% to 86.1% for eGFR 90 and 15, respectively. Analogously; chronic pain ranged from 21.5% for eGFR 90 and 38.4% for eGFR 15; diabetes ranged from 17.5% to 53.4% for eGFR 90 and 15. The proportion of participants with depression ranged from 35.0% for eGFR 90 to 28.7% for eGFR 15.

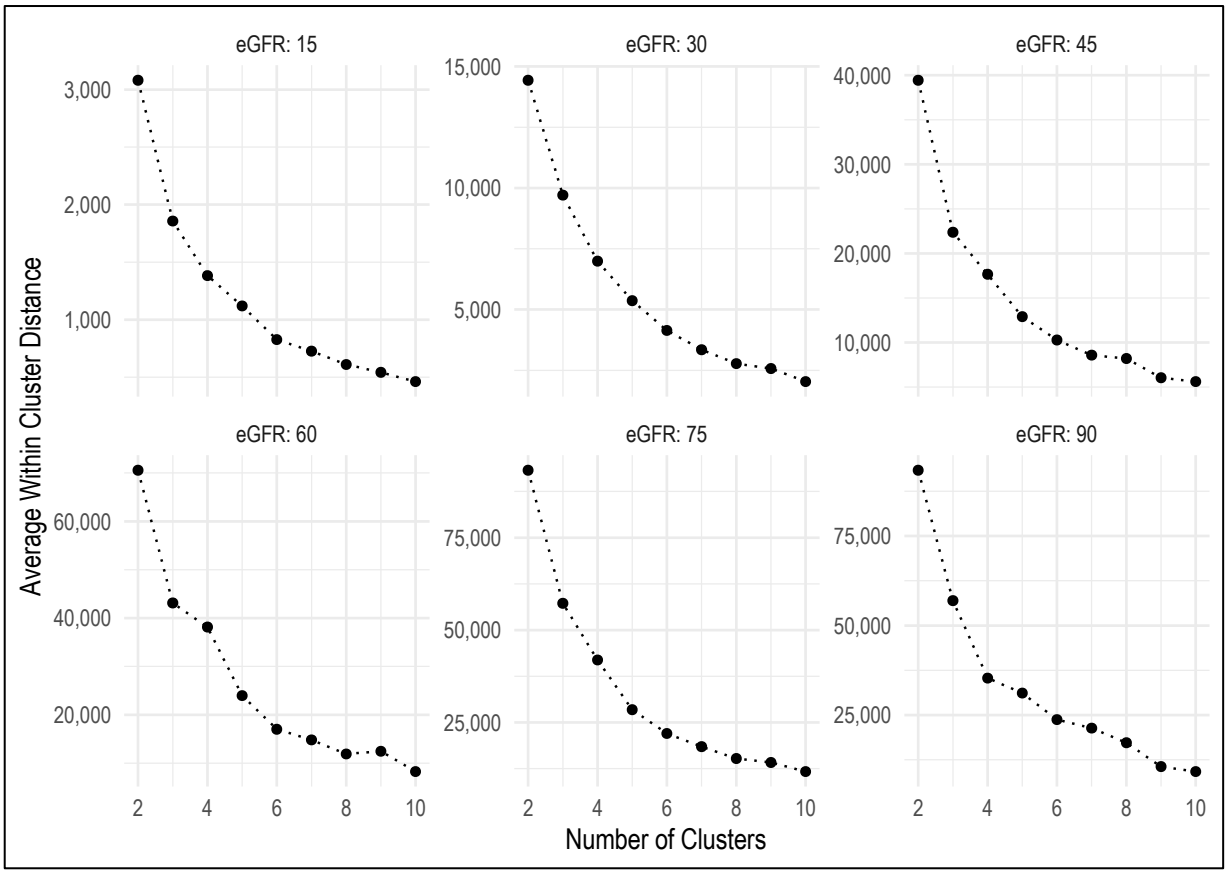
Supplementary figure 8-3B. Proportion of conditions by eGFR category in SAIL.



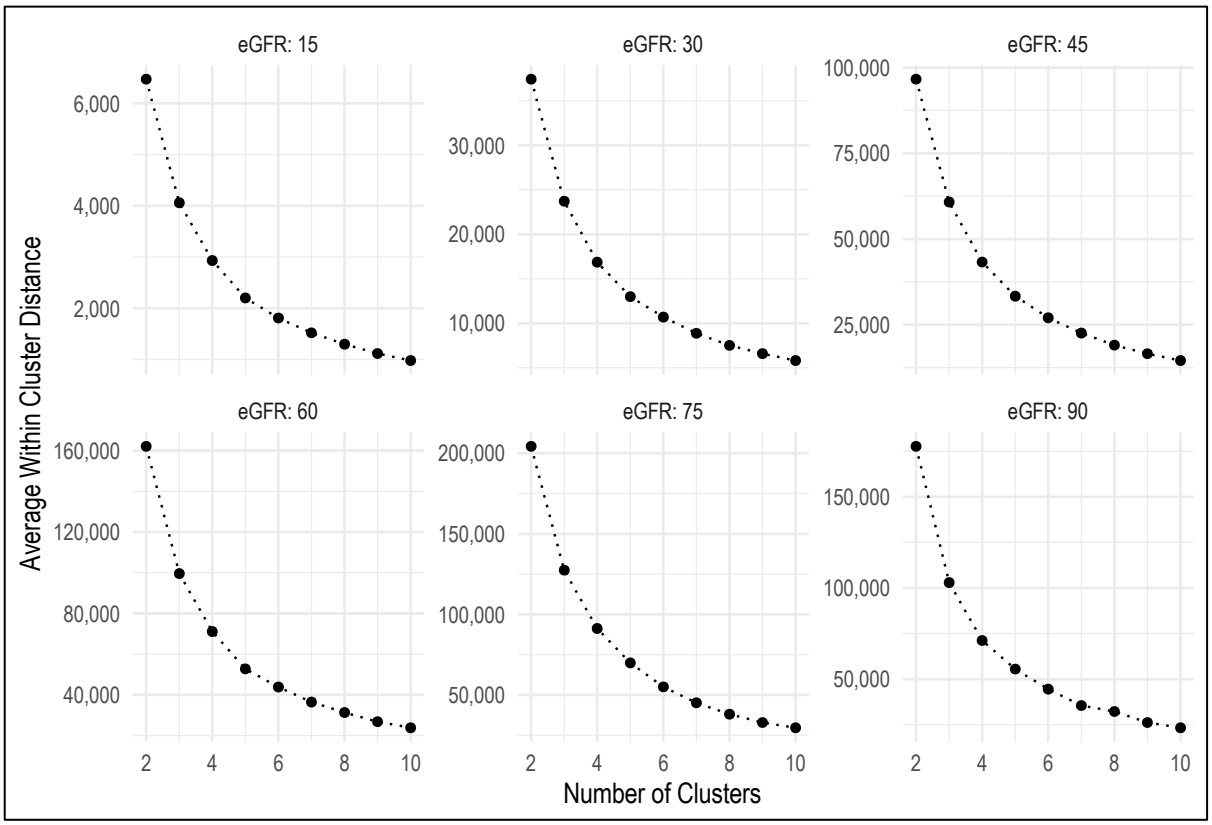
The optimal number of clusters varied at each eGFR level. Elbow plots (Supplementary figures 8-4A and 8-4B) and gradient plots (Supplementary figures 8-5A and 8-5B) suggested that the model fitness stabilised in each eGFR level at between five and nine clusters, i.e., using more clusters did not significantly improve the goodness of fit. Overall, the optimal number of clusters was highest at eGFRs 15 and 30mL/min/1.73m^2.

Supplementary figure 8-4. Elbow plots by eGFR category. These plots help choose the optimal number of clusters. The optimal number of clusters is where the line flattens i.e. where increasing the number of clusters leads to an only marginal reduction in the within-cluster distance.

A. SCREAM

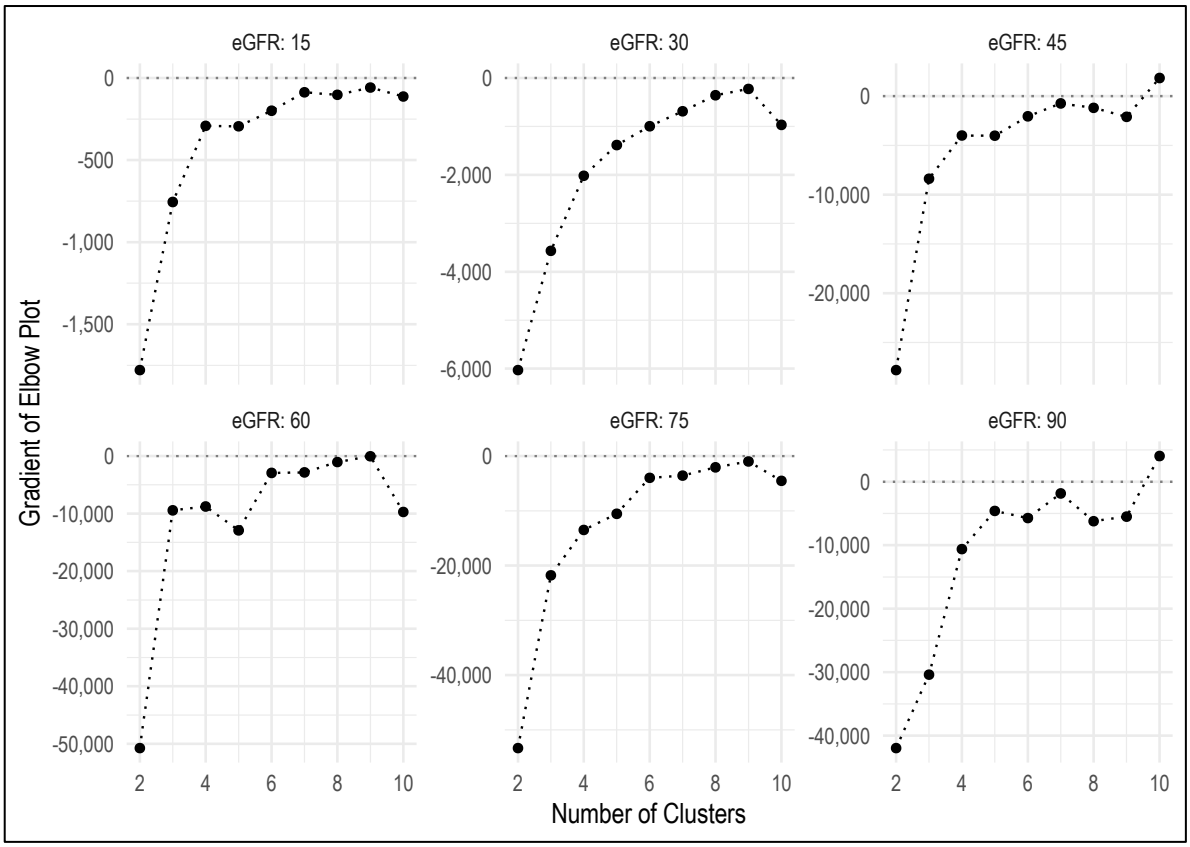


B. SAIL

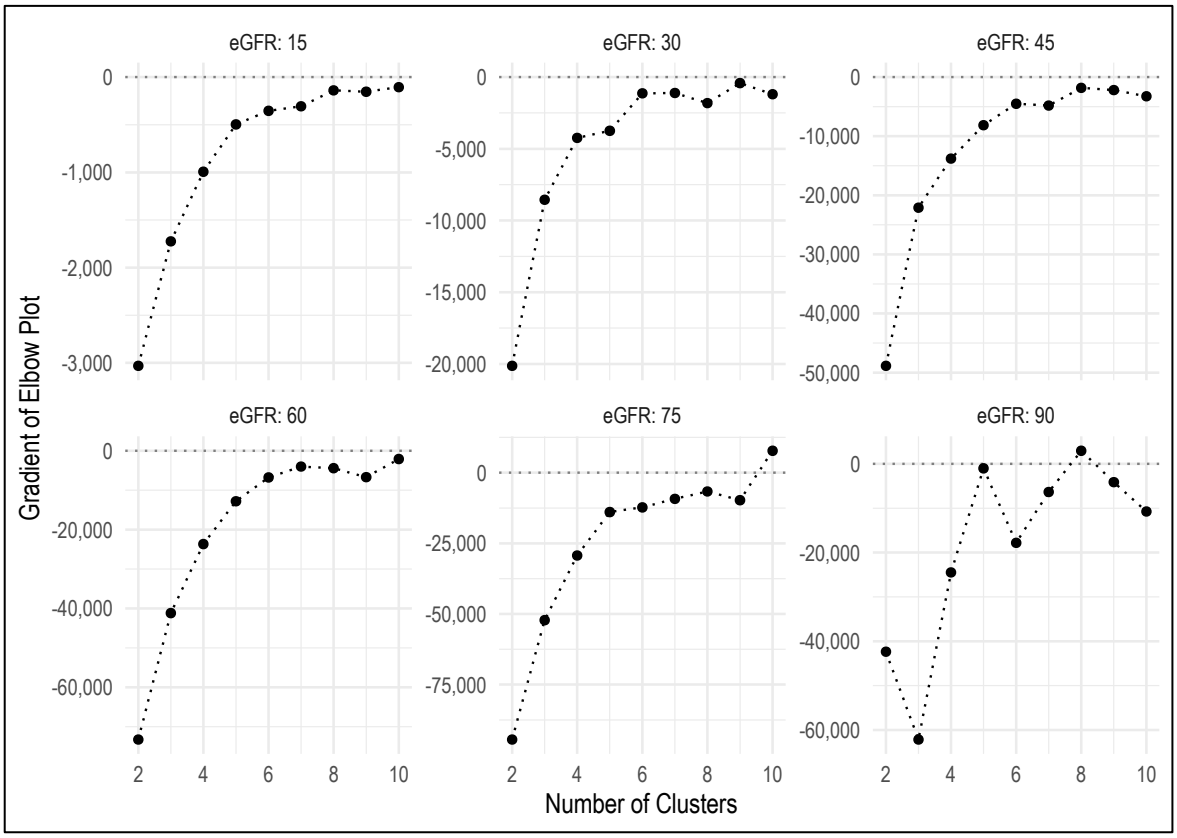


Supplementary figure 8-5. Gradient plots derived from goodness of fit elbow plots by eGFR category. These plots are an alternative way to display the data in supplementary figure 8-4, which may be simpler to interpret. The optimal number of clusters is where the line approaches 0.

A. SCREAM



B. SAIL



Prevalence of conditions by cluster

Supplementary tables 8-2A and 8-2B show the prevalence of chronic conditions in each cluster, simplified graphically in heatmaps (Figures 8-2A and 8-2B). Hypertension, diabetes, and chronic pain were common in many clusters.

Supplementary table 8-2A. Condition prevalence by cluster in SCREAM.

eGFR	Condition	Cluster_1	Cluster_2	Cluster_3	Cluster_4	Cluster_5	Cluster_6	Cluster_7	Cluster_8	Cluster_9
15	n	790	1,383	212	74	354	77	63	NA	NA
15	Age	75.4	70	77.06	73.34	70.23	78.91	74.1	NA	NA
15	Gender = Female	48.23%	34.85%	33.96%	75.68%	40.11%	29.87%	25.40%	NA	NA
15	Alcohol Misuse	3.16%	2.31%	3.77%	1.35%	5.65%	2.60%	1.59%	NA	NA
15	Asthma	7.09%	1.52%	4.25%	9.46%	3.67%	5.19%	1.59%	NA	NA
15	Atrial Fibrillation	5.57%	1.45%	2.83%	0.00%	1.98%	10.39%	4.76%	NA	NA
15	Cancer	10.38%	12.15%	17.92%	14.86%	16.67%	64.94%	4.76%	NA	NA
15	CKD	94.81%	81.49%	89.62%	91.89%	86.16%	97.40%	95.24%	NA	NA
15	Chronic Pain	86.96%	0.00%	68.87%	90.54%	100.00%	28.57%	0.00%	NA	NA
15	Chronic Viral Hepatitis B	0.38%	0.43%	0.47%	1.35%	0.56%	0.00%	0.00%	NA	NA
15	Cirrhosis	1.27%	0.07%	0.00%	0.00%	0.28%	0.00%	0.00%	NA	NA
15	Dementia	2.91%	3.90%	8.02%	0.00%	2.26%	2.60%	4.76%	NA	NA
15	Depression	11.77%	6.94%	10.85%	18.92%	13.56%	7.79%	11.11%	NA	NA
15	Diabetes	76.58%	19.74%	59.43%	5.41%	0.00%	84.42%	66.67%	NA	NA
15	Epilepsy	2.41%	1.30%	3.77%	0.00%	2.82%	1.30%	4.76%	NA	NA
15	Heart Failure	65.95%	14.61%	0.00%	9.46%	0.00%	90.91%	34.92%	NA	NA
15	Hypertension	88.61%	69.78%	90.09%	85.14%	73.16%	92.21%	88.89%	NA	NA
15	Hypothyroidism	13.04%	6.65%	11.79%	60.81%	0.00%	14.29%	6.35%	NA	NA
15	IBD	1.52%	1.66%	0.94%	1.35%	3.67%	0.00%	1.59%	NA	NA
15	IBS	0.76%	0.43%	0.47%	1.35%	0.00%	0.00%	0.00%	NA	NA
15	Multiple Sclerosis	0.25%	0.07%	0.00%	0.00%	0.28%	0.00%	0.00%	NA	NA
15	MI	16.08%	5.86%	8.49%	4.05%	6.21%	90.91%	100.00%	NA	NA
15	Parkinson's Disease	1.90%	0.87%	0.47%	0.00%	0.28%	0.00%	0.00%	NA	NA
15	Pulmonary Disease	17.97%	7.16%	9.91%	8.11%	10.45%	20.78%	4.76%	NA	NA
15	PUD	2.15%	1.01%	4.25%	1.35%	2.26%	2.60%	1.59%	NA	NA
15	PVD	15.57%	5.42%	13.21%	4.05%	7.34%	22.08%	23.81%	NA	NA
15	Psoriasis	5.57%	2.39%	4.25%	2.70%	6.21%	3.90%	1.59%	NA	NA
15	Rheumatoid Arthritis	5.70%	2.68%	4.72%	62.16%	0.00%	6.49%	1.59%	NA	NA
15	Schizophrenia	0.89%	1.30%	0.00%	0.00%	1.13%	1.30%	0.00%	NA	NA
15	Severe Constipation	8.23%	1.95%	7.55%	9.46%	5.65%	5.19%	6.35%	NA	NA
15	Stroke	17.22%	9.91%	100.00%	4.05%	0.00%	11.69%	71.43%	NA	NA
30	n	2,582	3,455	150	3,259	1,338	453	967	314	303
30	Age	76.94	79.4	80.42	79.13	85.91	77.31	82.23	77.38	81.13
30	Gender = Female	47.79%	48.05%	64.00%	53.30%	59.42%	43.71%	50.78%	57.64%	35.64%
30	Alcohol Misuse	3.18%	3.24%	5.33%	2.45%	2.62%	1.77%	3.00%	7.96%	2.31%
30	Asthma	2.01%	5.38%	69.33%	3.07%	7.55%	4.19%	4.96%	2.55%	3.96%
30	Atrial Fibrillation	0.93%	4.95%	11.33%	2.79%	9.79%	1.55%	6.62%	6.69%	5.61%
30	Cancer	9.14%	11.81%	13.33%	15.83%	15.47%	70.86%	12.00%	6.37%	14.85%
30	CKD	29.74%	54.56%	70.00%	40.01%	55.16%	54.30%	56.05%	61.46%	67.99%
30	Chronic Pain	21.26%	33.43%	96.67%	37.62%	100.00%	95.14%	88.31%	98.41%	33.66%
30	Chronic Viral Hepatitis B	0.12%	0.23%	0.67%	0.12%	0.15%	0.44%	0.21%	0.64%	0.00%
30	Cirrhosis	0.54%	0.93%	0.00%	0.21%	0.67%	0.66%	0.41%	1.27%	0.00%
30	Dementia	6.27%	5.67%	6.67%	6.63%	7.17%	3.97%	9.00%	7.01%	6.27%
30	Depression	8.25%	4.69%	65.33%	7.70%	6.80%	7.06%	11.17%	71.02%	7.59%
30	Diabetes	9.99%	77.08%	55.33%	0.00%	0.00%	70.42%	31.23%	86.62%	82.18%
30	Epilepsy	1.51%	1.19%	2.67%	1.66%	1.79%	1.99%	4.45%	2.87%	0.66%

30	Heart Failure	15.49%	57.34%	82.67%	0.00%	100.00%	3.75%	22.34%	71.97%	87.46%
30	Hypertension	0.00%	97.22%	91.33%	100.00%	76.98%	27.81%	96.79%	43.31%	93.40%
30	Hypothyroidism	6.24%	11.78%	14.67%	9.91%	13.75%	9.49%	12.10%	12.42%	11.55%
30	IBD	1.36%	1.04%	3.33%	1.20%	1.12%	0.88%	1.14%	1.91%	0.99%
30	IBS	0.23%	0.43%	2.00%	0.43%	1.12%	0.00%	0.52%	1.27%	0.33%
30	Multiple Sclerosis	0.12%	0.12%	0.00%	0.15%	0.07%	0.22%	0.10%	0.32%	0.00%
30	MI	6.74%	12.42%	76.00%	3.68%	17.34%	6.84%	54.29%	9.87%	66.01%
30	Parkinson's Disease	1.12%	0.81%	1.33%	0.80%	1.05%	0.88%	0.72%	1.91%	0.99%
30	Pulmonary Disease	7.59%	14.18%	40.00%	6.72%	20.48%	7.73%	13.34%	17.83%	21.78%
30	PUD	1.12%	1.68%	2.67%	1.53%	3.51%	0.44%	2.28%	3.50%	4.62%
30	PVD	3.64%	7.87%	16.00%	6.01%	9.49%	4.42%	11.79%	12.74%	86.47%
30	Psoriasis	3.02%	3.82%	3.33%	3.59%	4.71%	4.19%	3.72%	4.78%	3.30%
30	Rheumatoid Arthritis	4.69%	5.35%	13.33%	5.86%	10.09%	8.61%	7.34%	8.28%	4.62%
30	Schizophrenia	1.39%	0.52%	0.00%	0.43%	0.15%	1.10%	0.10%	0.64%	0.00%
30	Severe Constipation	3.72%	5.35%	15.33%	4.36%	10.76%	2.43%	8.27%	11.46%	8.91%
30	Stroke	12.01%	15.28%	16.67%	12.18%	19.58%	10.82%	82.01%	17.20%	67.00%
45	n	13,421	4,837	3,854	7,426	5,897	1,576	152	NA	NA
45	Age	77.67	82.96	82.85	80.12	78.21	82	81.7	NA	NA
45	Gender = Female	50.12%	59.95%	53.87%	68.07%	49.26%	48.67%	44.74%	NA	NA
45	Alcohol Misuse	2.85%	3.18%	2.57%	2.18%	2.31%	3.05%	1.97%	NA	NA
45	Asthma	3.76%	9.63%	4.13%	4.59%	2.07%	8.25%	7.24%	NA	NA
45	Atrial Fibrillation	2.24%	7.90%	3.79%	3.22%	0.76%	8.12%	100.00%	NA	NA
45	Cancer	12.47%	15.71%	13.31%	15.62%	11.85%	13.20%	19.74%	NA	NA
45	CKD	18.33%	25.22%	15.10%	15.46%	10.21%	27.28%	30.26%	NA	NA
45	Chronic Pain	23.42%	78.97%	36.30%	100.00%	0.00%	79.06%	0.00%	NA	NA
45	Chronic Viral Hepatitis B	0.14%	0.14%	0.03%	0.12%	0.07%	0.38%	0.00%	NA	NA
45	Cirrhosis	0.76%	0.33%	0.13%	0.54%	0.53%	0.44%	0.66%	NA	NA
45	Dementia	5.15%	7.26%	10.51%	6.29%	6.26%	5.33%	3.95%	NA	NA
45	Depression	7.74%	10.92%	11.57%	12.44%	5.78%	10.91%	9.21%	NA	NA
45	Diabetes	60.00%	25.26%	0.00%	0.00%	0.00%	32.93%	14.47%	NA	NA
45	Epilepsy	1.27%	1.96%	3.68%	1.28%	0.70%	2.22%	1.97%	NA	NA
45	Heart Failure	9.74%	100.00%	18.06%	0.00%	15.30%	100.00%	89.47%	NA	NA
45	Hypertension	86.60%	81.06%	76.05%	64.06%	0.00%	84.71%	94.74%	NA	NA
45	Hypothyroidism	8.52%	13.19%	10.92%	11.61%	5.10%	13.77%	9.87%	NA	NA
45	IBD	1.01%	0.87%	0.78%	1.39%	1.05%	0.76%	0.00%	NA	NA
45	IBS	0.29%	0.91%	0.42%	0.61%	0.24%	0.76%	0.00%	NA	NA
45	Multiple Sclerosis	0.14%	0.19%	0.08%	0.15%	0.12%	0.19%	0.00%	NA	NA
45	MI	10.02%	0.00%	11.16%	5.91%	5.56%	100.00%	51.97%	NA	NA
45	Parkinson's Disease	0.65%	1.24%	1.61%	0.93%	0.95%	1.02%	0.66%	NA	NA
45	Pulmonary Disease	7.21%	20.26%	8.93%	8.34%	6.10%	21.83%	19.74%	NA	NA
45	PUD	1.11%	1.94%	1.48%	1.16%	0.64%	2.54%	3.95%	NA	NA
45	PVD	6.90%	9.10%	6.49%	4.71%	2.31%	14.53%	9.87%	NA	NA
45	Psoriasis	4.03%	4.47%	3.76%	4.77%	2.36%	4.70%	1.32%	NA	NA
45	Rheumatoid Arthritis	4.00%	8.17%	5.60%	8.40%	2.78%	10.53%	5.92%	NA	NA
45	Schizophrenia	0.60%	0.29%	0.29%	0.54%	0.93%	0.32%	0.66%	NA	NA
45	Severe Constipation	3.32%	9.49%	5.94%	5.17%	1.95%	9.07%	8.55%	NA	NA
45	Stroke	10.80%	17.92%	100.00%	0.00%	0.00%	21.32%	8.55%	NA	NA
60	n	26,463	22,991	4,667	2,151	22,182	959	NA	NA	NA
60	Age	76.13	76.21	79.57	76.22	74.28	75.35	NA	NA	NA
60	Gender = Female	64.22%	49.50%	57.62%	82.29%	49.00%	37.23%	NA	NA	NA

60	Alcohol Misuse	2.96%	2.93%	3.77%	1.81%	1.94%	5.32%	NA	NA	NA
60	Asthma	5.13%	2.84%	6.73%	5.11%	1.50%	5.32%	NA	NA	NA
60	Atrial Fibrillation	3.38%	2.34%	5.49%	2.05%	0.89%	3.65%	NA	NA	NA
60	Cancer	14.03%	11.57%	13.09%	12.74%	9.76%	11.68%	NA	NA	NA
60	CKD	8.92%	6.60%	10.56%	6.56%	4.52%	15.02%	NA	NA	NA
60	Chronic Pain	100.00%	0.00%	100.00%	46.63%	0.00%	61.21%	NA	NA	NA
60	Chronic Viral Hepatitis B	0.14%	0.05%	0.11%	0.00%	0.07%	0.21%	NA	NA	NA
60	Cirrhosis	0.46%	0.34%	0.28%	0.19%	0.38%	0.31%	NA	NA	NA
60	Dementia	4.18%	4.15%	7.67%	6.32%	4.01%	5.01%	NA	NA	NA
60	Depression	12.59%	6.53%	15.92%	15.02%	6.10%	11.37%	NA	NA	NA
60	Diabetes	19.91%	23.84%	23.27%	11.90%	9.94%	100.00%	NA	NA	NA
60	Epilepsy	1.00%	1.44%	4.07%	1.07%	0.82%	2.40%	NA	NA	NA
60	Heart Failure	14.63%	13.56%	24.49%	13.02%	8.10%	33.47%	NA	NA	NA
60	Hypertension	60.37%	100.00%	75.66%	0.00%	0.00%	91.14%	NA	NA	NA
60	Hypothyroidism	6.92%	7.88%	12.19%	100.00%	0.00%	8.76%	NA	NA	NA
60	IBD	1.18%	0.68%	0.99%	1.02%	0.83%	0.73%	NA	NA	NA
60	IBS	0.79%	0.34%	0.90%	0.65%	0.27%	0.52%	NA	NA	NA
60	Multiple Sclerosis	0.20%	0.10%	0.17%	0.23%	0.17%	0.00%	NA	NA	NA
60	MI	7.47%	9.31%	12.41%	4.56%	4.04%	22.11%	NA	NA	NA
60	Parkinson's Disease	0.91%	0.67%	1.48%	1.21%	0.69%	0.63%	NA	NA	NA
60	Pulmonary Disease	9.27%	6.34%	11.33%	8.32%	4.00%	15.85%	NA	NA	NA
60	PUD	0.82%	0.67%	1.44%	0.60%	0.39%	1.67%	NA	NA	NA
60	PVD	2.82%	2.45%	4.78%	2.14%	1.47%	100.00%	NA	NA	NA
60	Psoriasis	4.85%	3.60%	4.97%	3.81%	2.67%	6.99%	NA	NA	NA
60	Rheumatoid Arthritis	7.15%	2.83%	7.91%	6.09%	2.23%	5.21%	NA	NA	NA
60	Schizophrenia	0.45%	0.37%	0.41%	1.67%	0.91%	0.52%	NA	NA	NA
60	Severe Constipation	4.64%	2.40%	8.29%	5.67%	1.73%	4.69%	NA	NA	NA
60	Stroke	0.00%	16.06%	100.00%	3.77%	6.40%	24.61%	NA	NA	NA
75	n	42,753	32,312	2,446	5,961	65,668	5,187	NA	NA	NA
75	Age	68.02	70.92	73.1	75.32	65.06	71.6	NA	NA	NA
75	Gender = Female	64.92%	47.09%	41.17%	53.04%	50.51%	58.07%	NA	NA	NA
75	Alcohol Misuse	3.08%	2.74%	3.64%	6.79%	1.60%	2.95%	NA	NA	NA
75	Asthma	3.81%	2.28%	2.04%	7.87%	1.01%	5.24%	NA	NA	NA
75	Atrial Fibrillation	1.45%	1.55%	1.47%	5.96%	0.43%	2.12%	NA	NA	NA
75	Cancer	0.00%	10.19%	8.87%	12.40%	7.16%	100.00%	NA	NA	NA
75	CKD	4.10%	3.83%	4.13%	9.08%	2.25%	7.00%	NA	NA	NA
75	Chronic Pain	100.00%	0.00%	0.00%	92.28%	0.00%	100.00%	NA	NA	NA
75	Chronic Viral Hepatitis B	0.10%	0.06%	0.08%	0.13%	0.05%	0.10%	NA	NA	NA
75	Cirrhosis	0.29%	0.23%	0.29%	0.47%	0.21%	0.29%	NA	NA	NA
75	Dementia	2.29%	2.28%	5.85%	5.69%	1.49%	2.06%	NA	NA	NA
75	Depression	14.06%	6.00%	8.99%	16.32%	5.82%	14.27%	NA	NA	NA
75	Diabetes	13.08%	20.70%	9.48%	30.28%	5.96%	12.80%	NA	NA	NA
75	Epilepsy	1.09%	1.23%	5.11%	4.55%	0.50%	1.06%	NA	NA	NA
75	Heart Failure	2.08%	5.77%	9.93%	53.92%	2.33%	2.53%	NA	NA	NA
75	Hypertension	36.88%	100.00%	0.00%	97.11%	0.00%	41.97%	NA	NA	NA
75	Hypothyroidism	7.77%	6.15%	5.23%	10.80%	3.69%	9.08%	NA	NA	NA
75	IBD	1.12%	0.65%	0.86%	1.06%	0.85%	1.06%	NA	NA	NA
75	IBS	0.90%	0.29%	0.20%	0.79%	0.27%	0.60%	NA	NA	NA
75	Multiple Sclerosis	0.37%	0.13%	0.33%	0.17%	0.19%	0.29%	NA	NA	NA

75	MI	3.58%	6.66%	5.15%	16.79%	1.98%	3.72%	NA	NA	NA
75	Parkinson's Disease	0.93%	0.60%	0.98%	1.61%	0.47%	0.79%	NA	NA	NA
75	Pulmonary Disease	5.50%	4.51%	5.40%	15.70%	2.11%	6.96%	NA	NA	NA
75	PUD	0.58%	0.46%	0.78%	1.80%	0.21%	0.67%	NA	NA	NA
75	PVD	2.18%	2.42%	2.45%	7.62%	0.59%	2.35%	NA	NA	NA
75	Psoriasis	4.43%	3.44%	2.74%	5.40%	2.64%	4.67%	NA	NA	NA
75	Rheumatoid Arthritis	4.87%	1.98%	2.33%	6.88%	1.50%	4.97%	NA	NA	NA
75	Schizophrenia	0.58%	0.39%	0.70%	0.42%	0.79%	0.25%	NA	NA	NA
75	Severe Constipation	3.03%	1.59%	2.41%	7.92%	0.91%	1.95%	NA	NA	NA
75	Stroke	2.92%	10.67%	100.00%	66.00%	0.00%	3.74%	NA	NA	NA
90	n	26,586	1,440	165,836	2,503	14,681	NA	NA	NA	NA
90	Age	63.3	67.25	55.59	66.72	63.47	NA	NA	NA	NA
90	Gender = Female	43.96%	41.94%	51.72%	60.85%	57.09%	NA	NA	NA	NA
90	Alcohol Misuse	4.15%	7.92%	2.47%	13.66%	5.50%	NA	NA	NA	NA
90	Asthma	1.82%	6.25%	1.20%	17.18%	4.27%	NA	NA	NA	NA
90	Atrial Fibrillation	0.67%	2.01%	0.20%	2.08%	1.55%	NA	NA	NA	NA
90	Cancer	7.06%	59.79%	4.81%	10.91%	6.38%	NA	NA	NA	NA
90	CKD	2.58%	7.92%	1.95%	6.15%	4.27%	NA	NA	NA	NA
90	Chronic Pain	0.00%	95.49%	26.66%	100.00%	100.00%	NA	NA	NA	NA
90	Chronic Viral Hepatitis B	0.06%	0.35%	0.08%	0.36%	0.16%	NA	NA	NA	NA
90	Cirrhosis	0.21%	0.76%	0.14%	0.72%	0.32%	NA	NA	NA	NA
90	Dementia	0.75%	2.57%	0.39%	2.20%	0.91%	NA	NA	NA	NA
90	Depression	6.94%	17.36%	9.30%	22.13%	15.64%	NA	NA	NA	NA
90	Diabetes	20.24%	85.49%	4.65%	16.78%	20.69%	NA	NA	NA	NA
90	Epilepsy	1.37%	6.32%	0.82%	3.16%	1.68%	NA	NA	NA	NA
90	Heart Failure	3.41%	11.04%	0.88%	12.74%	4.24%	NA	NA	NA	NA
90	Hypertension	100.00%	73.12%	0.00%	45.11%	100.00%	NA	NA	NA	NA
90	Hypothyroidism	4.68%	7.71%	3.40%	8.35%	7.43%	NA	NA	NA	NA
90	IBD	0.76%	1.39%	1.06%	2.12%	1.16%	NA	NA	NA	NA
90	IBS	0.27%	0.83%	0.49%	1.00%	1.03%	NA	NA	NA	NA
90	Multiple Sclerosis	0.20%	0.28%	0.36%	0.44%	0.46%	NA	NA	NA	NA
90	MI	5.08%	9.51%	1.11%	7.03%	5.42%	NA	NA	NA	NA
90	Parkinson's Disease	0.30%	1.39%	0.33%	0.84%	0.73%	NA	NA	NA	NA
90	Pulmonary Disease	3.54%	8.61%	0.89%	100.00%	0.00%	NA	NA	NA	NA
90	PUD	0.36%	1.18%	0.21%	1.08%	0.87%	NA	NA	NA	NA
90	PVD	1.63%	5.62%	0.41%	5.07%	2.38%	NA	NA	NA	NA
90	Psoriasis	3.83%	5.62%	2.77%	7.11%	5.27%	NA	NA	NA	NA
90	Rheumatoid Arthritis	1.19%	3.33%	1.47%	5.43%	3.98%	NA	NA	NA	NA
90	Schizophrenia	0.39%	1.04%	0.72%	1.32%	0.46%	NA	NA	NA	NA
90	Severe Constipation	1.00%	3.75%	0.89%	5.95%	2.55%	NA	NA	NA	NA
90	Stroke	8.04%	62.92%	1.86%	8.15%	6.64%	NA	NA	NA	NA

Supplementary table 8-2B. Condition prevalence by cluster in SAIL.

eGFR	Condition	Cluster_1	Cluster_2	Cluster_3	Cluster_4	Cluster_5	Cluster_6	Cluster_7	Cluster_8
15	n	1,656	452	294	357	608	289	159	519
15	Age	72.74	78.06	79.02	78.9	67.14	72.88	75.43	72.82
15	GENDER = Female	46.07%	33.85%	42.52%	35.85%	50.66%	42.91%	49.06%	36.80%
15	Alcohol Misuse	2.29%	2.43%	2.72%	1.96%	5.59%	3.81%	<3%	1.54%
15	Asthma	13.59%	10.84%	26.87%	13.73%	14.97%	18.34%	15.09%	8.48%
15	Atrial Fibrillation	11.29%	18.36%	73.47%	17.93%	11.51%	9.00%	12.58%	9.44%
15	Cancer	10.75%	100.00%	21.77%	100.00%	0.00%	15.22%	12.58%	0.00%
15	Heart Failure	13.29%	19.91%	91.84%	14.57%	18.42%	14.53%	84.91%	6.55%
15	Chronic Pain	55.50%	29.87%	59.18%	0.00%	22.86%	70.93%	57.23%	0.00%
15	Pulmonary Disease	15.22%	14.38%	63.61%	17.93%	14.64%	14.53%	11.32%	8.86%
15	Chronic Viral Hepatitis B	<3%	0.00%	<3%	0.00%	0.00%	0.00%	0.00%	0.00%
15	Cirrhosis	0.91%	<3%	<3%	<3%	<3%	<3%	<3%	1.73%
15	Dementia	3.68%	3.32%	4.42%	4.48%	6.09%	8.30%	9.43%	1.93%
15	Depression	14.61%	23.23%	22.45%	19.33%	100.00%	33.56%	35.22%	0.00%
15	Diabetes	14.49%	100.00%	90.14%	0.00%	67.27%	100.00%	86.79%	100.00%
15	Epilepsy	2.17%	<3%	<3%	<3%	2.30%	4.50%	5.66%	1.54%
15	Hypertension	83.94%	86.73%	92.52%	80.39%	85.69%	88.58%	91.82%	89.98%
15	Hypothyroidism	13.53%	14.38%	15.65%	12.61%	15.30%	11.42%	15.09%	14.07%
15	IBD	2.36%	1.55%	2.72%	1.96%	1.97%	<3%	3.77%	1.35%
15	IBS	1.57%	2.21%	<3%	1.68%	1.64%	2.77%	<3%	1.16%
15	Multiple Sclerosis	<3%	0.00%	0.00%	0.00%	<3%	0.00%	<3%	<3%
15	MI	14.07%	17.92%	36.05%	16.53%	14.47%	21.11%	87.42%	11.37%
15	Parkinson's Disease	0.91%	<3%	<3%	<3%	<3%	<3%	<3%	<3%
15	PUD	3.56%	3.98%	7.82%	3.36%	3.78%	6.92%	7.55%	4.05%
15	PVD	13.41%	15.93%	21.09%	12.04%	13.98%	18.34%	21.38%	16.38%
15	Psoriasis	2.17%	2.88%	3.74%	3.08%	2.30%	2.77%	3.77%	<3%
15	Rheumatoid Arthritis	4.59%	2.88%	4.42%	2.24%	2.47%	4.50%	5.03%	1.54%
15	Schizophrenia	0.66%	0.00%	<3%	<3%	1.81%	2.42%	0.00%	<3%
15	Severe Constipation	14.61%	10.18%	24.15%	10.08%	11.18%	100.00%	10.06%	0.00%
15	Stroke	13.16%	11.73%	14.97%	16.81%	16.78%	20.42%	71.70%	11.56%
30	n	3,212	5,197	5,452	7,065	2,614	872	NA	NA
30	Age	80.77	78.43	76.22	77.79	80.65	81.02	NA	NA
30	GENDER = Female	50.34%	64.08%	42.90%	49.60%	52.68%	61.35%	NA	NA
30	Alcohol Misuse	2.05%	2.21%	2.20%	2.01%	2.45%	3.90%	NA	NA
30	Asthma	17.75%	15.39%	11.67%	10.54%	18.67%	15.94%	NA	NA
30	Atrial Fibrillation	14.32%	4.62%	11.46%	15.47%	80.64%	50.92%	NA	NA
30	Cancer	25.06%	25.51%	22.76%	25.24%	25.40%	27.64%	NA	NA
30	Heart Failure	69.15%	0.00%	9.57%	12.89%	83.24%	10.67%	NA	NA
30	Chronic Pain	70.05%	100.00%	0.00%	0.00%	73.95%	88.76%	NA	NA
30	Pulmonary Disease	26.46%	17.11%	14.82%	14.55%	27.77%	21.90%	NA	NA
30	Chronic Viral Hepatitis B	<3%	0.00%	0.00%	<3%	<3%	0.00%	NA	NA
30	Cirrhosis	0.78%	1.12%	1.23%	0.69%	1.34%	<3%	NA	NA
30	Dementia	5.17%	6.41%	4.90%	4.87%	5.59%	16.86%	NA	NA
30	Depression	26.40%	26.67%	21.99%	17.75%	27.70%	90.02%	NA	NA
30	Diabetes	41.72%	44.33%	100.00%	0.00%	86.53%	34.86%	NA	NA
30	Epilepsy	1.74%	1.46%	1.17%	1.57%	1.38%	5.28%	NA	NA
30	Hypertension	84.87%	81.95%	84.26%	76.53%	85.27%	86.70%	NA	NA
30	Hypothyroidism	17.90%	14.57%	12.97%	12.67%	18.17%	17.78%	NA	NA
30	IBD	1.99%	2.41%	1.80%	2.17%	1.72%	2.06%	NA	NA
30	IBS	2.12%	2.33%	0.92%	1.22%	1.80%	2.75%	NA	NA
30	Multiple Sclerosis	<3%	<3%	0.18%	<3%	<3%	<3%	NA	NA
30	MI	87.30%	0.00%	15.06%	9.77%	25.02%	20.64%	NA	NA
30	Parkinson's Disease	1.25%	1.17%	0.99%	0.61%	1.22%	2.29%	NA	NA
30	PUD	6.20%	4.58%	4.38%	3.75%	5.62%	8.83%	NA	NA
30	PVD	20.36%	15.07%	15.17%	12.61%	19.66%	17.66%	NA	NA
30	Psoriasis	1.31%	1.69%	1.43%	1.19%	1.95%	2.75%	NA	NA
30	Rheumatoid Arthritis	5.54%	6.16%	2.16%	3.01%	5.13%	5.73%	NA	NA
30	Schizophrenia	0.47%	1.06%	1.01%	1.13%	0.69%	0.92%	NA	NA
30	Severe Constipation	23.29%	21.80%	10.18%	9.94%	22.49%	31.54%	NA	NA
30	Stroke	15.35%	9.76%	15.15%	13.45%	18.13%	86.93%	NA	NA
45	n	10,056	40,000	6,990	5,391	3,123	2,476	NA	NA
45	Age	78.52	76.96	77.56	77.3	81.14	80.29	NA	NA

45	GENDER = Female	54.62%	52.65%	58.33%	52.49%	62.02%	68.05%	NA	NA
45	Alcohol Misuse	2.00%	1.81%	3.03%	3.36%	2.56%	3.47%	NA	NA
45	Asthma	9.95%	5.15%	81.97%	7.12%	3.14%	15.11%	NA	NA
45	Atrial Fibrillation	14.86%	12.07%	18.76%	67.95%	14.86%	14.14%	NA	NA
45	Cancer	68.07%	14.62%	12.29%	13.69%	10.12%	20.96%	NA	NA
45	Heart Failure	11.51%	9.46%	20.99%	64.51%	7.30%	54.36%	NA	NA
45	Chronic Pain	77.83%	14.29%	68.45%	68.24%	82.64%	93.70%	NA	NA
45	Pulmonary Disease	13.47%	7.49%	83.56%	13.93%	6.05%	21.73%	NA	NA
45	Chronic Viral Hepatitis B	<3%	0.02%	<3%	<3%	0.00%	0.00%	NA	NA
45	Cirrhosis	0.98%	0.84%	1.20%	1.67%	0.93%	1.29%	NA	NA
45	Dementia	4.70%	3.83%	4.38%	5.90%	10.05%	13.69%	NA	NA
45	Depression	21.95%	16.40%	27.80%	58.12%	19.12%	81.79%	NA	NA
45	Diabetes	32.62%	36.11%	43.30%	85.33%	33.53%	32.11%	NA	NA
45	Epilepsy	1.65%	1.17%	1.49%	1.58%	3.97%	3.15%	NA	NA
45	Hypertension	33.51%	81.48%	87.91%	90.54%	94.72%	81.30%	NA	NA
45	Hypothyroidism	13.07%	12.13%	15.89%	15.62%	15.08%	17.37%	NA	NA
45	IBD	2.71%	1.70%	3.15%	1.95%	1.92%	2.42%	NA	NA
45	IBS	2.23%	1.23%	2.78%	2.30%	2.72%	5.86%	NA	NA
45	Multiple Sclerosis	0.18%	0.09%	0.10%	0.13%	0.19%	<3%	NA	NA
45	MI	15.54%	15.00%	23.75%	33.67%	18.38%	28.88%	NA	NA
45	Parkinson's Disease	1.09%	0.82%	1.04%	1.34%	2.08%	2.58%	NA	NA
45	PUD	3.96%	3.12%	5.71%	5.40%	6.12%	6.87%	NA	NA
45	PVD	13.11%	11.53%	16.19%	19.33%	14.47%	15.63%	NA	NA
45	Psoriasis	1.58%	1.16%	1.87%	1.84%	1.44%	1.62%	NA	NA
45	Rheumatoid Arthritis	4.95%	3.05%	6.60%	4.47%	5.73%	7.84%	NA	NA
45	Schizophrenia	1.01%	1.08%	0.80%	0.82%	1.12%	2.87%	NA	NA
45	Severe Constipation	12.24%	5.83%	15.84%	9.59%	72.53%	89.22%	NA	NA
45	Stroke	11.36%	9.44%	15.45%	20.22%	70.73%	8.20%	NA	NA
60	n	29,274	12,383	66,079	8,486	7,918	2,310	2,724	NA
60	Age	75.64	74.19	73.04	68.68	70.49	73.62	77.94	NA
60	GENDER = Female	63.18%	51.51%	49.74%	71.02%	56.11%	62.25%	36.67%	NA
60	Alcohol Misuse	2.06%	3.31%	1.72%	4.96%	4.53%	6.54%	3.67%	NA
60	Asthma	7.39%	78.13%	4.84%	14.44%	6.02%	30.78%	9.21%	NA
60	Atrial Fibrillation	10.51%	14.90%	8.89%	6.92%	12.00%	13.98%	100.00%	NA
60	Cancer	20.27%	19.97%	18.07%	17.55%	19.02%	20.65%	23.09%	NA
60	Heart Failure	9.22%	17.39%	5.87%	5.94%	11.35%	15.67%	42.58%	NA
60	Chronic Pain	100.00%	55.29%	0.00%	50.34%	36.95%	28.23%	37.37%	NA
60	Pulmonary Disease	6.01%	79.59%	4.67%	10.08%	5.99%	100.00%	13.51%	NA
60	Chronic Viral Hepatitis B	0.03%	0.06%	0.02%	<3%	<3%	0.00%	<3%	NA
60	Cirrhosis	0.89%	1.49%	0.73%	1.37%	2.36%	0.91%	0.88%	NA
60	Dementia	3.70%	2.72%	2.31%	5.72%	6.37%	6.58%	4.33%	NA
60	Depression	15.18%	23.09%	7.75%	100.00%	100.00%	100.00%	11.67%	NA
60	Diabetes	24.48%	65.73%	23.75%	12.02%	100.00%	0.00%	31.20%	NA
60	Epilepsy	1.63%	2.04%	1.17%	2.20%	2.05%	2.21%	1.98%	NA
60	Hypertension	75.97%	77.91%	66.02%	0.00%	83.25%	71.86%	80.91%	NA
60	Hypothyroidism	13.16%	13.17%	10.06%	15.61%	14.40%	14.68%	13.00%	NA
60	IBD	2.06%	2.75%	1.60%	2.73%	2.11%	3.12%	2.09%	NA
60	IBS	2.81%	2.92%	1.22%	3.72%	3.31%	3.64%	1.76%	NA
60	Multiple Sclerosis	0.24%	0.15%	0.12%	0.49%	0.28%	0.30%	<3%	NA
60	MI	12.48%	20.24%	9.37%	7.71%	17.02%	18.05%	100.00%	NA
60	Parkinson's Disease	1.20%	0.84%	0.71%	1.63%	1.62%	1.47%	1.21%	NA
60	PUD	3.96%	4.85%	2.21%	3.25%	3.95%	4.94%	4.26%	NA
60	PVD	11.41%	13.71%	8.14%	7.54%	11.87%	14.24%	15.09%	NA
60	Psoriasis	1.43%	2.05%	0.97%	1.46%	2.18%	1.56%	1.28%	NA
60	Rheumatoid Arthritis	6.53%	5.85%	2.24%	4.38%	3.33%	4.81%	4.30%	NA
60	Schizophrenia	0.64%	0.76%	0.66%	4.74%	2.98%	2.86%	0.37%	NA
60	Severe Constipation	18.01%	16.54%	6.03%	16.23%	14.57%	17.19%	15.57%	NA
60	Stroke	11.97%	13.13%	8.48%	7.60%	14.86%	16.06%	20.19%	NA
75	n	95,957	84,041	3,754	9,023	11,278	NA	NA	NA
75	Age	68.55	61.65	73.4	69.02	67.36	NA	NA	NA
75	GENDER = Female	51.70%	56.60%	47.79%	58.86%	56.13%	NA	NA	NA
75	Alcohol Misuse	3.22%	2.94%	5.57%	6.01%	2.46%	NA	NA	NA
75	Asthma	9.40%	9.72%	39.61%	86.68%	7.97%	NA	NA	NA
75	Atrial Fibrillation	7.74%	3.39%	12.79%	10.73%	4.97%	NA	NA	NA
75	Cancer	14.74%	0.00%	100.00%	6.61%	100.00%	NA	NA	NA

75	Heart Failure	4.98%	2.08%	9.83%	12.04%	2.57%	NA	NA	NA
75	Chronic Pain	29.56%	19.94%	41.26%	87.32%	24.42%	NA	NA	NA
75	Pulmonary Disease	6.84%	6.87%	100.00%	78.04%	0.00%	NA	NA	NA
75	Chronic Viral Hepatitis B	0.02%	0.03%	<3%	<3%	<3%	NA	NA	NA
75	Cirrhosis	1.01%	0.74%	0.93%	1.60%	0.75%	NA	NA	NA
75	Dementia	2.01%	1.20%	3.14%	2.34%	1.79%	NA	NA	NA
75	Depression	24.85%	28.75%	32.79%	44.63%	27.69%	NA	NA	NA
75	Diabetes	28.45%	13.28%	23.04%	67.88%	14.69%	NA	NA	NA
75	Epilepsy	1.49%	1.57%	1.86%	3.04%	1.68%	NA	NA	NA
75	Hypertension	100.00%	0.00%	62.20%	68.99%	0.00%	NA	NA	NA
75	Hypothyroidism	9.63%	9.79%	11.08%	14.05%	10.12%	NA	NA	NA
75	IBD	1.68%	1.81%	2.72%	2.55%	2.76%	NA	NA	NA
75	IBS	2.19%	2.05%	3.14%	5.25%	2.28%	NA	NA	NA
75	Multiple Sclerosis	0.24%	0.26%	0.16%	0.25%	0.21%	NA	NA	NA
75	MI	11.28%	4.45%	14.52%	18.48%	5.05%	NA	NA	NA
75	Parkinson's Disease	0.83%	0.59%	1.41%	1.12%	0.98%	NA	NA	NA
75	PUD	2.64%	1.80%	4.79%	5.29%	2.20%	NA	NA	NA
75	PVD	7.78%	4.72%	12.52%	11.89%	5.91%	NA	NA	NA
75	Psoriasis	1.28%	0.97%	1.60%	2.11%	1.19%	NA	NA	NA
75	Rheumatoid Arthritis	3.47%	2.78%	5.97%	6.84%	3.12%	NA	NA	NA
75	Schizophrenia	0.73%	1.53%	0.75%	1.60%	1.06%	NA	NA	NA
75	Severe Constipation	9.03%	5.95%	16.78%	19.00%	8.78%	NA	NA	NA
75	Stroke	8.69%	3.37%	10.90%	11.95%	4.54%	NA	NA	NA
90	n	136,801	16,909	2,149	54,820	4,119	NA	NA	NA
90	Age	51.09	59.51	63.42	60.07	61.47	NA	NA	NA
90	GENDER = Female	59.06%	53.95%	53.00%	44.57%	60.69%	NA	NA	NA
90	Alcohol Misuse	4.54%	9.89%	14.47%	4.68%	9.57%	NA	NA	NA
90	Asthma	11.71%	24.68%	22.94%	11.97%	25.01%	NA	NA	NA
90	Atrial Fibrillation	1.21%	4.28%	8.24%	3.59%	4.73%	NA	NA	NA
90	Cancer	7.03%	0.00%	14.43%	10.77%	100.00%	NA	NA	NA
90	Heart Failure	0.80%	5.10%	5.72%	2.34%	4.78%	NA	NA	NA
90	Chronic Pain	15.37%	78.66%	72.87%	12.72%	81.33%	NA	NA	NA
90	Pulmonary Disease	6.08%	16.88%	22.94%	8.62%	21.10%	NA	NA	NA
90	Chronic Viral Hepatitis B	0.04%	0.07%	<3%	0.04%	<3%	NA	NA	NA
90	Cirrhosis	0.67%	2.70%	1.26%	1.05%	2.52%	NA	NA	NA
90	Dementia	0.25%	1.05%	4.14%	0.38%	1.21%	NA	NA	NA
90	Depression	34.88%	79.06%	73.20%	16.72%	82.57%	NA	NA	NA
90	Diabetes	9.55%	71.84%	0.00%	18.63%	54.67%	NA	NA	NA
90	Epilepsy	1.81%	3.14%	9.59%	1.52%	3.64%	NA	NA	NA
90	Hypertension	0.00%	89.52%	80.78%	100.00%	54.33%	NA	NA	NA
90	Hypothyroidism	7.26%	10.79%	10.10%	6.59%	11.97%	NA	NA	NA
90	IBD	1.96%	2.22%	2.70%	1.55%	3.69%	NA	NA	NA
90	IBS	2.15%	5.26%	4.70%	1.72%	5.56%	NA	NA	NA
90	Multiple Sclerosis	0.38%	0.59%	0.79%	0.24%	0.70%	NA	NA	NA
90	MI	2.00%	12.31%	11.17%	6.99%	9.10%	NA	NA	NA
90	Parkinson's Disease	0.23%	0.72%	1.81%	0.33%	1.19%	NA	NA	NA
90	PUD	1.34%	3.65%	4.84%	1.82%	4.22%	NA	NA	NA
90	PVD	2.99%	7.85%	9.91%	4.83%	7.53%	NA	NA	NA
90	Psoriasis	1.01%	2.17%	2.23%	1.32%	2.33%	NA	NA	NA
90	Rheumatoid Arthritis	2.28%	5.25%	6.47%	2.49%	6.26%	NA	NA	NA
90	Schizophrenia	1.45%	2.32%	1.63%	0.57%	2.14%	NA	NA	NA
90	Severe Constipation	4.51%	13.82%	20.10%	4.45%	18.31%	NA	NA	NA
90	Stroke	1.42%	5.67%	100.00%	3.13%	4.71%	NA	NA	NA

Figure 8-2. Heatmaps of chronic condition prevalence by cluster and eGFR category. A SCREAM, B SAIL.

IBD, inflammatory bowel disease, IBS, irritable bowel syndrome, MI, myocardial infarction, PUD, peptic ulcer disease, PVD, peripheral vascular disease

Prominent conditions (based on prevalence)

Supplementary figures 8-6A and 8-6B depict how prominent conditions were identified within each cluster. Although hypertension was the commonest condition in each eGFR category, it could not be a prominent condition in most of the clusters because the background prevalence was >50% and the O/E ratio could not be ≥2.

Supplementary figure 8-6. Identification of prominent condition(s) by cluster and eGFR category.

The red marks indicate which conditions have a prevalence of ≥20% and an O/E ratio of ≥2.

A. SCREAM

B. SAIL

Table 8-2 summarises the number of participants and the prominent condition(s) in each cluster. Some clusters in the same eGFR category share the same description, but are distinct because there are differences between the conditions separate to the “prominent” conditions. For example, at eGFR 15 in SAIL, there were two “Cancer” clusters, but in one cluster all participants had diabetes and in the other no participants had diabetes.

Table 8-2A. Prominent conditions by cluster in SCREAM.

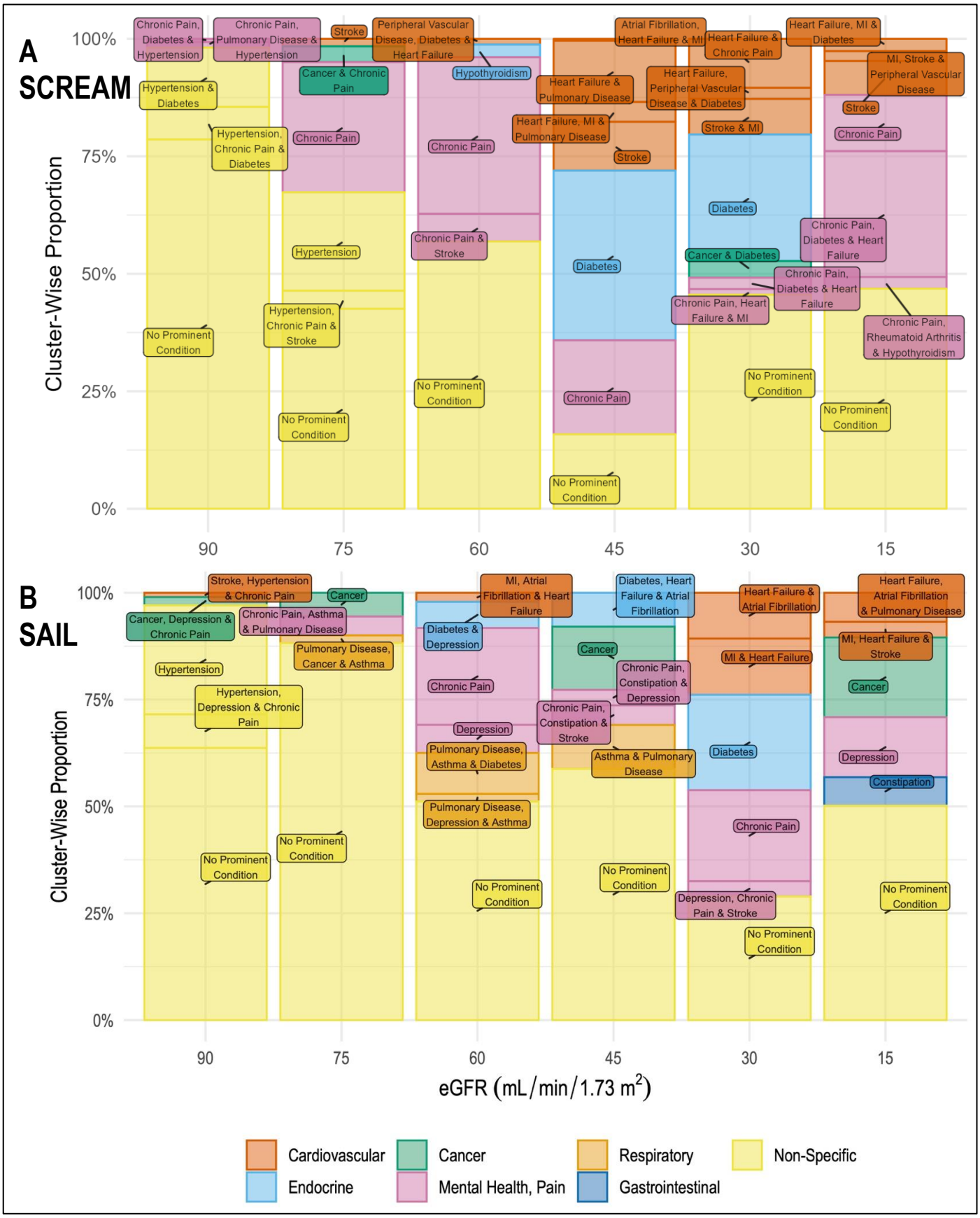
SCREAM				
eGFR category	**Cluster number**	**n**	**% of eGFR category**	**Cluster (defined via prominent condition(s))**
15	2	1,383	46.8	No Prominent Condition
	1	790	26.8	Chronic Pain, Diabetes & Heart Failure
	5	354	12.0	Chronic Pain
	3	212	7.2	Stroke
	6	77	2.6	Heart Failure, MI & Diabetes
	4	74	2.5	Chronic Pain, Rheumatoid Arthritis & Hypothyroidism
	7	63	2.1	MI, Stroke & Peripheral Vascular Disease
30	2	3,455	26.9	Diabetes
	4	3,259	25.4	No Prominent Condition
	1	2,582	20.1	No Prominent Condition
	5	1,338	10.4	Heart Failure & Chronic Pain
	7	968	7.6	Stroke & MI
	6	453	3.5	Cancer & Diabetes
	8	314	2.4	Chronic Pain, Diabetes & Heart Failure
	9	303	2.4	Heart Failure, Peripheral Vascular Disease & Diabetes
	3	150	1.2	Chronic Pain, Heart Failure & MI
45	1	13,421	36.1	Diabetes
	4	7,426	20.0	Chronic Pain
	5	5,897	15.9	No Prominent Condition
	2	4,837	13.0	Heart Failure & Pulmonary Disease
	3	3,855	10.4	Stroke
	6	1,576	4.2	Heart Failure, MI & Pulmonary Disease
	7	152	0.4	Atrial Fibrillation, Heart Failure & MI
60	1	26,463	33.3	Chronic Pain
	2	22,992	29.0	No Prominent Condition
	5	22,182	27.9	No Prominent Condition
	3	4,667	5.9	Chronic Pain & Stroke
	4	2,151	2.7	Hypothyroidism
	6	959	1.2	Peripheral Vascular Disease, Diabetes & Heart Failure
75	5	65,668	42.6	No Prominent Condition
	1	42,753	27.7	Chronic Pain
	2	32,312	20.9	Hypertension
	4	5,961	3.9	Hypertension, Chronic Pain & Stroke
	6	5,187	3.4	Cancer & Chronic Pain
	3	2,447	1.6	Stroke
90	3	165,836	78.6	No Prominent Condition
	1	26,586	12.6	Hypertension & Diabetes
	5	14,681	7.0	Hypertension, Chronic Pain & Diabetes
	4	2,503	1.2	Chronic Pain, Pulmonary Disease & Hypertension
	2	1,440	0.7	Chronic Pain, Diabetes & Hypertension

Table 8-2B. Prominent conditions by cluster in SAIL

SAIL				
eGFR category	**Cluster number**	**n**	**% of eGFR category**	**Cluster (defined via prominent condition(s))**
15	1	1,656	38.2	No Prominent condition
	5	608	14.0	Depression
	8	519	12.0	No Prominent condition
	2	452	10.4	Cancer
	4	357	8.2	Cancer
	3	294	6.8	Heart failure, atrial fibrillation & pulmonary disease
	6	289	6.7	Constipation
	7	159	3.7	MI, heart failure & stroke
30	4	7,065	28.9	No Prominent condition
	3	5,452	22.3	Diabetes
	2	5,197	21.3	Chronic pain
	1	3,212	13.2	MI & heart failure
	5	2,614	10.7	Heart failure & atrial fibrillation
	6	872	3.6	Depression, chronic pain & stroke
45	2	40,000	58.8	No Prominent condition
	1	10,056	14.8	Cancer
	3	6,990	10.3	Asthma & pulmonary disease
	4	5,391	7.9	Diabetes, heart failure & atrial fibrillation
	5	3,123	4.6	Chronic pain, constipation & stroke
	6	2,476	3.6	Chronic pain, constipation & depression
60	3	66,079	51.2	No Prominent condition
	1	29,274	22.7	Chronic pain
	2	12,383	9.6	Pulmonary disease, asthma & diabetes
	4	8,486	6.6	Depression
	5	7,918	6.1	Diabetes & depression
	6	2,310	1.8	Pulmonary disease, depression & asthma
	7	2,724	2.1	MI, atrial fibrillation & heart failure
75	1	99,957	47.0	No Prominent condition
	2	84,041	41.2	No Prominent condition
	5	11,278	5.5	Cancer
	4	9,023	4.4	Chronic pain, asthma & pulmonary disease
	3	3,754	1.8	Pulmonary disease, cancer & asthma
90	1	136,801	63.7	No Prominent condition
	4	54,820	25.5	Hypertension
	2	16,909	7.9	Hypertension, depression & chronic pain
	5	4,119	1.9	Cancer, depression & chronic pain
	3	2,149	1.0	Stroke, hypertension & chronic pain

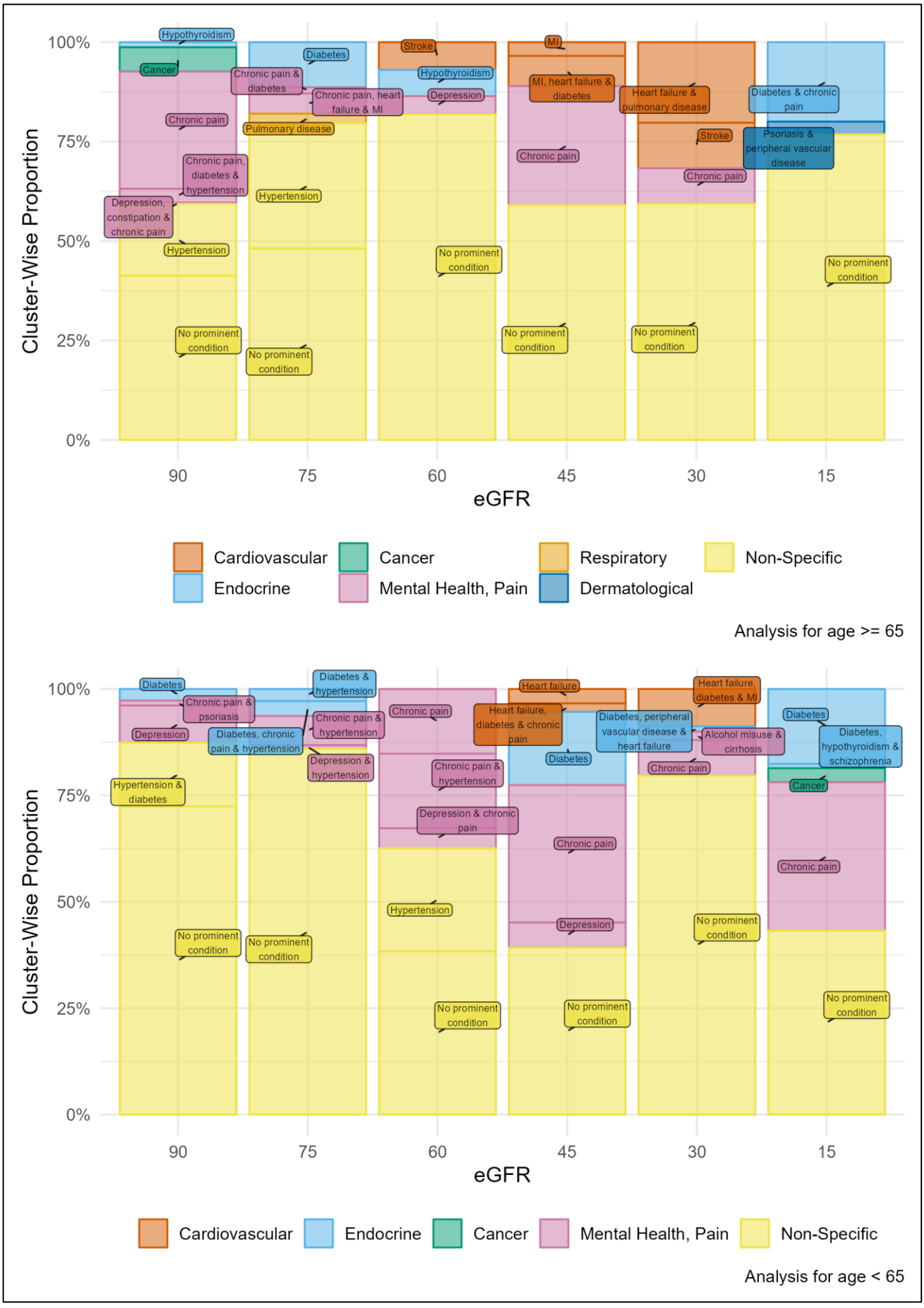
Figure 8-3 shows the proportion of participants in each cluster by eGFR category. In both cohorts, most participants were included in one or two clusters with no system-specific prominent conditions i.e., there was either no prominent condition or hypertension was the most prominent condition. The cluster-wise proportion of participants with no prominent condition, however, decreased as kidney function declined. As expected, diabetes and cardiovascular conditions featured more prominently as eGFR worsened. Chronic pain and in SAIL, depression, featured in clusters across the spectrum of kidney function.

Figure 8-3. Proportion of patients in clusters by prominent conditions and body system. A SCREAM. B. SAIL

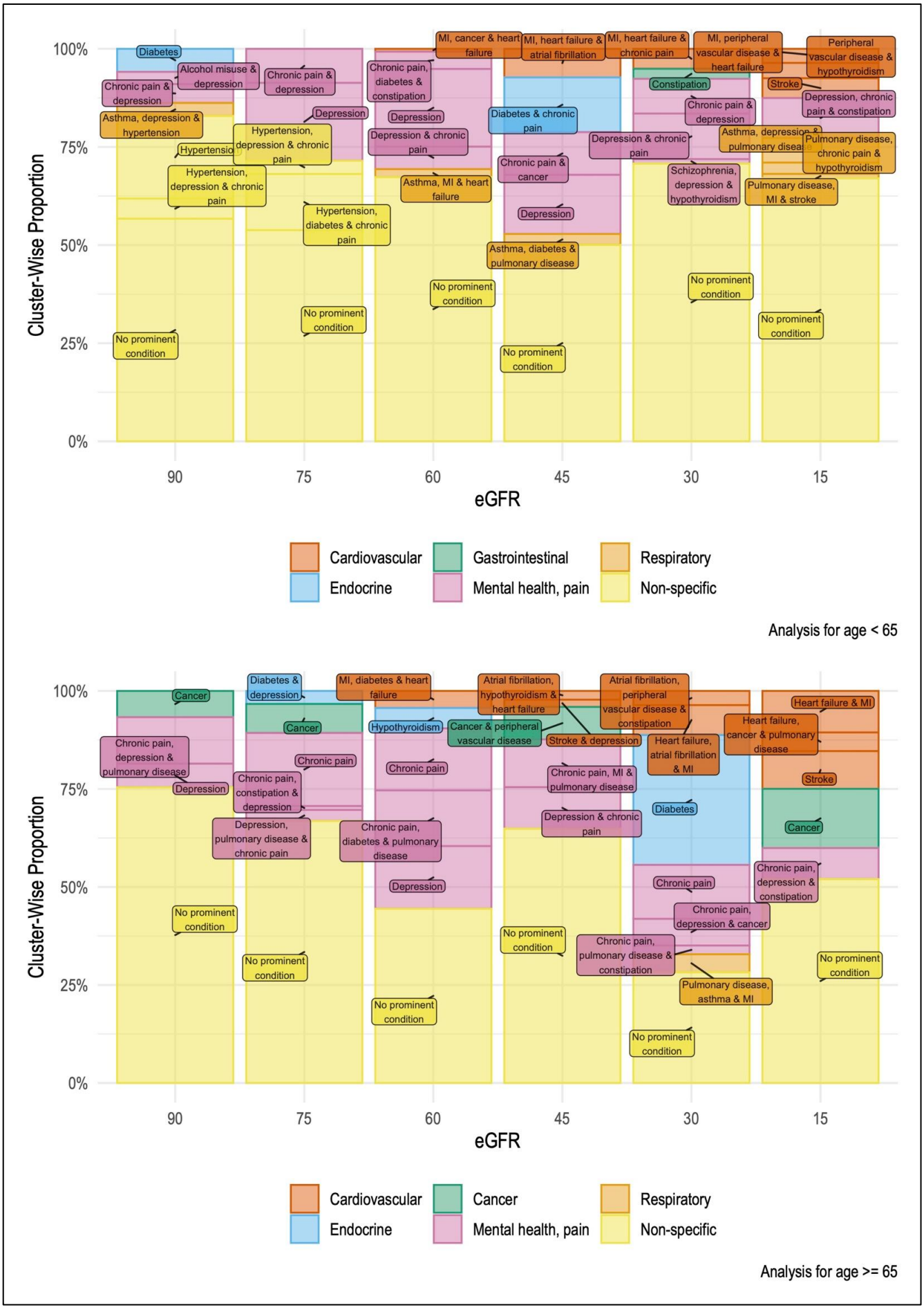


When clustering was stratified by age, proportionally more participants aged over 65 years were in clusters with prominent conditions (based on prevalence) compared to those under 65 years (Supplementary figures 8-7A and 8-7B). Clusters which featured Heart Failure and Myocardial Infarction existed at eGFRs 30 and 45 in both cohorts and in all age groups, but these were proportionally larger in those over the age of 65 than under 65. In SAIL, cancer featured in more clusters in those over the age of 65 than under 65.

Supplementary figure 8-7A. Age-stratified prominent conditions in SCREAM (≥65 and <65 years).



Supplementary figure 8-7B. Age-stratified prominent conditions in SAIL (<65 and ≥65 years).



Outcomes

In SCREAM, median follow-up time ranged from 1.94 years (IQI 1.87-2.03) at eGFR 15 to 6.32 years (IQI 6.30-6.34) at eGFR 90 (Supplementary table 8-3A). In SAIL, median follow-up time ranged from 5.51 years (IQI 5.32-5.68) at eGFR 15 to 7.45 years (IQI 7.42-7.47) at eGFR 90 (Supplementary table 8-3B). In both cohorts, crude event rates were higher at lower eGFR categories compared to higher eGFR (Supplementary figures 8-8A and 8-8B). Event rates were lowest in clusters with no prominent condition.

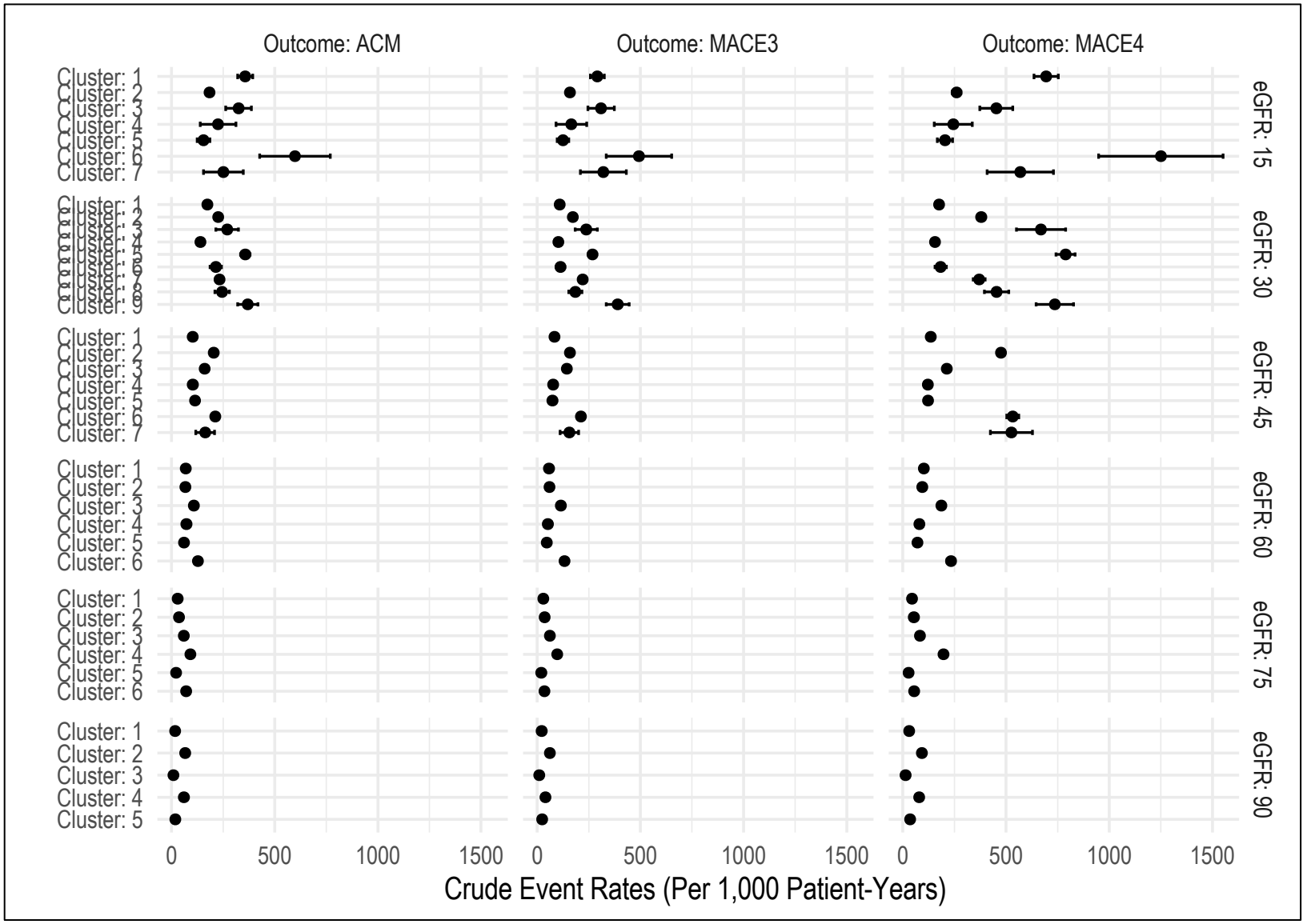
Supplementary table 8-3A. Median follow-up time in SCREAM.

eGFR category	**Median follow-up time (years: interquartile interval)**
15	1.94 (1.87-2.03)
30	4.21 (4.11-4.32)
45	5.10 (5.04-5.15)
60	5.44 (5.40-5.48)
75	5.70 (5.67-5.73)
90	6.32 (6.30-6.34)

Supplementary table 8-3B. Median follow-up time in SAIL.

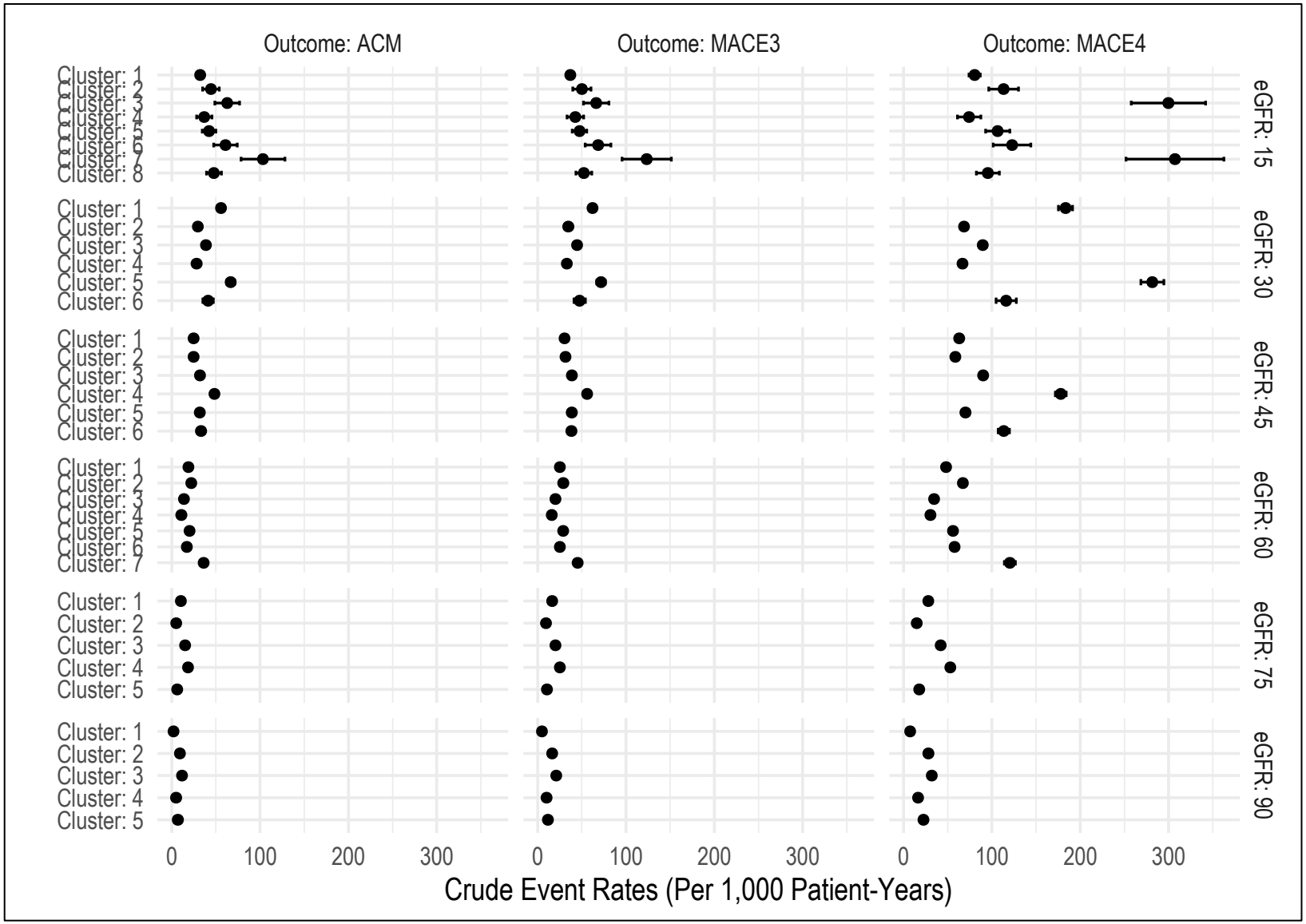
eGFR category	**Median follow-up time (years: interquartile interval)**
15	5.51 (5.32-5.68)
30	6.68 (6.60-6.77)
45	7.55 (7.50-7.60)
60	8.22 (8.18-8.26)
75	8.14 (8.11-8.17)
90	7.45 (7.42-7.47)

Supplementary figure 8-8A. Adverse event rates by cluster in SCREAM.



Error bars represent 95% confidence intervals

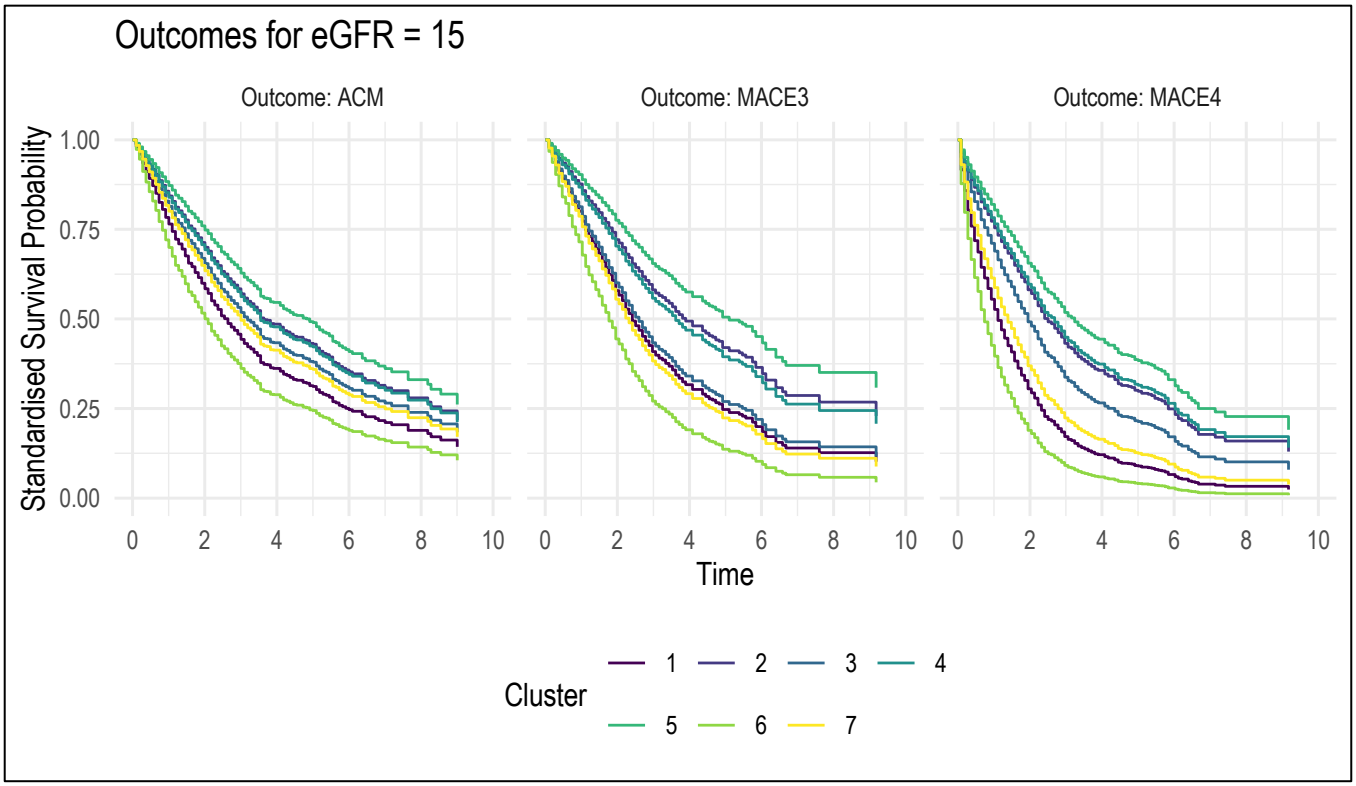
Supplementary figure 8-8B. Adverse event rates by cluster in SAIL.



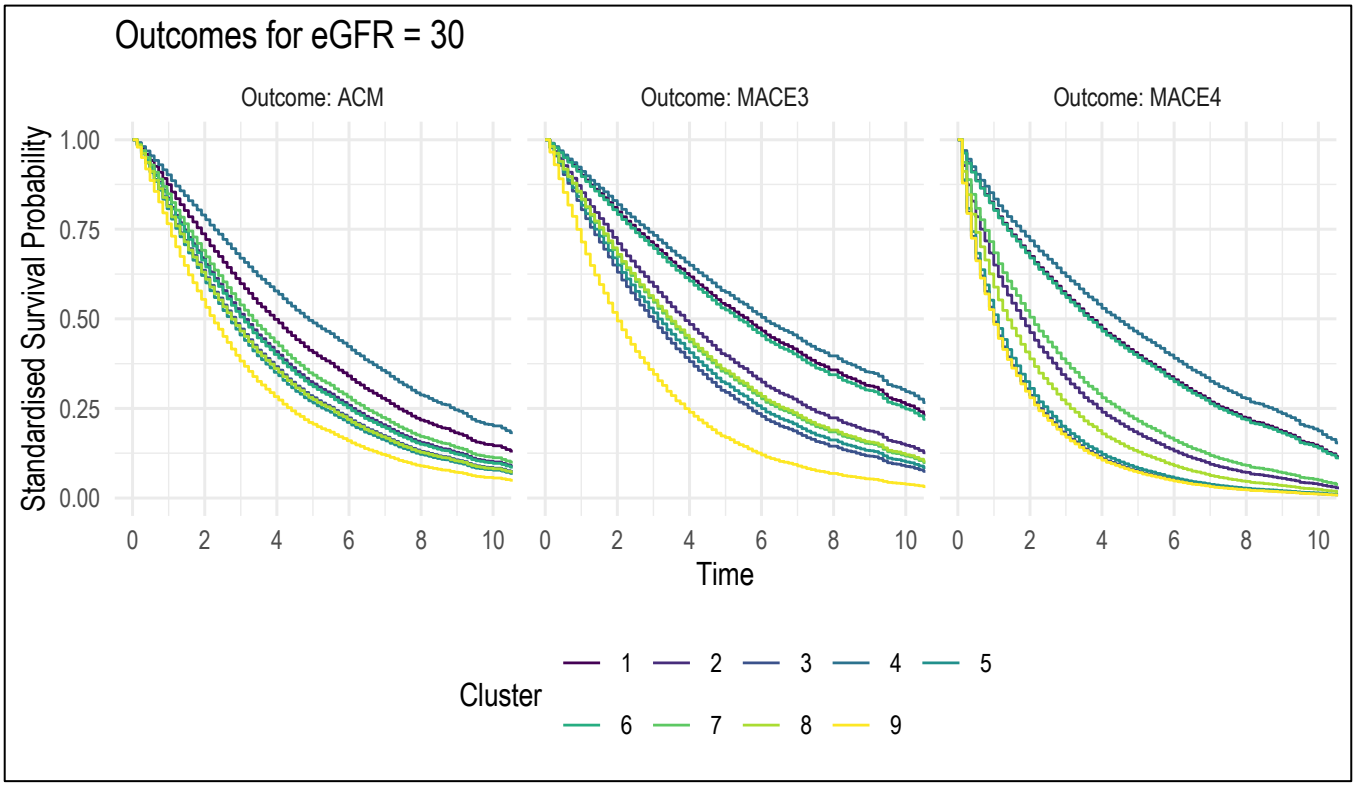
Error bars represent 95% confidence intervals

Clustering membership was significantly associated with event rates for each outcome (Wald test p-values <0.001 in all eGFR categories, adjusted for age and sex). This was reflected in the standardised survival curves at every eGFR level (Supplementary figures 8-9A1 to 8-9A6 and 8-9B1 to 8-9B6).

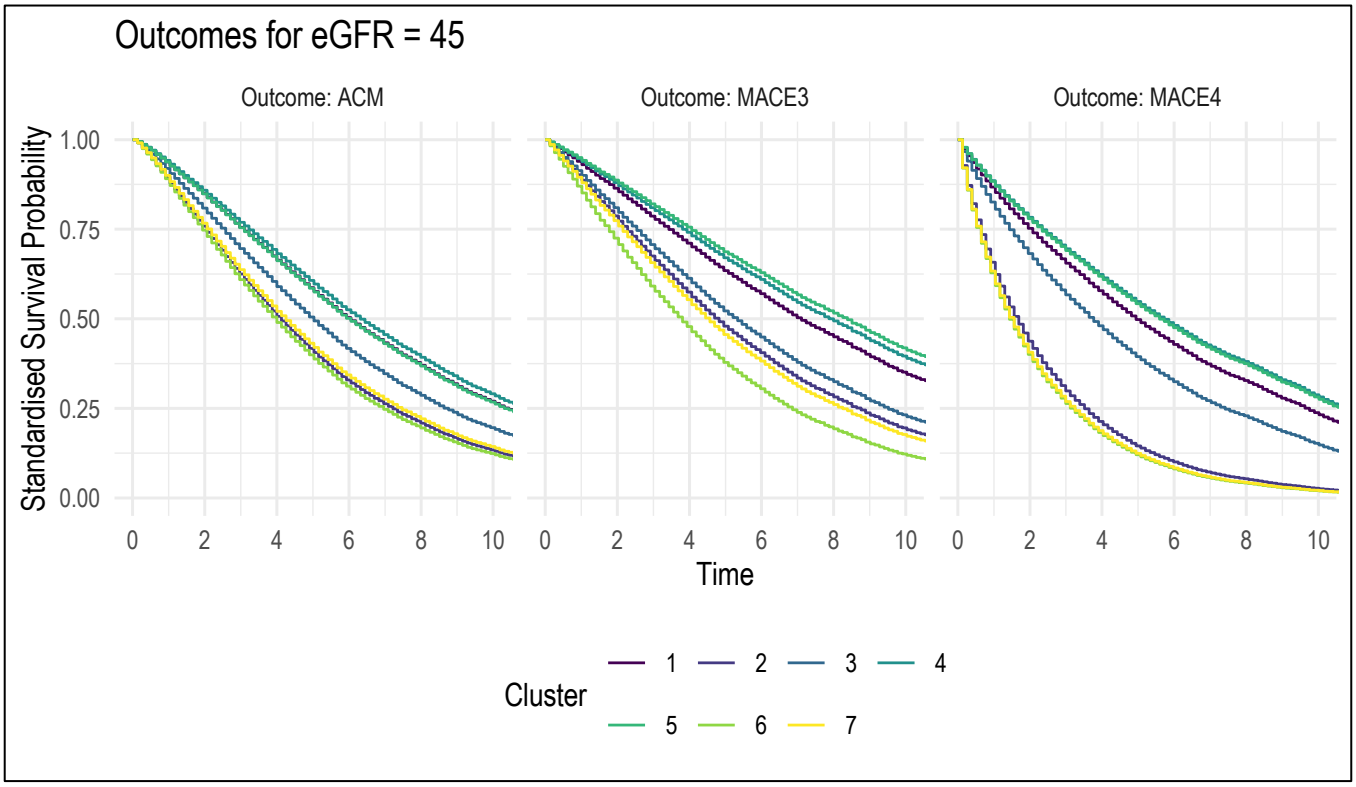
Supplementary figure 8-9A1. Standardised regression survival curves in eGFR 15 category in SCREAM.



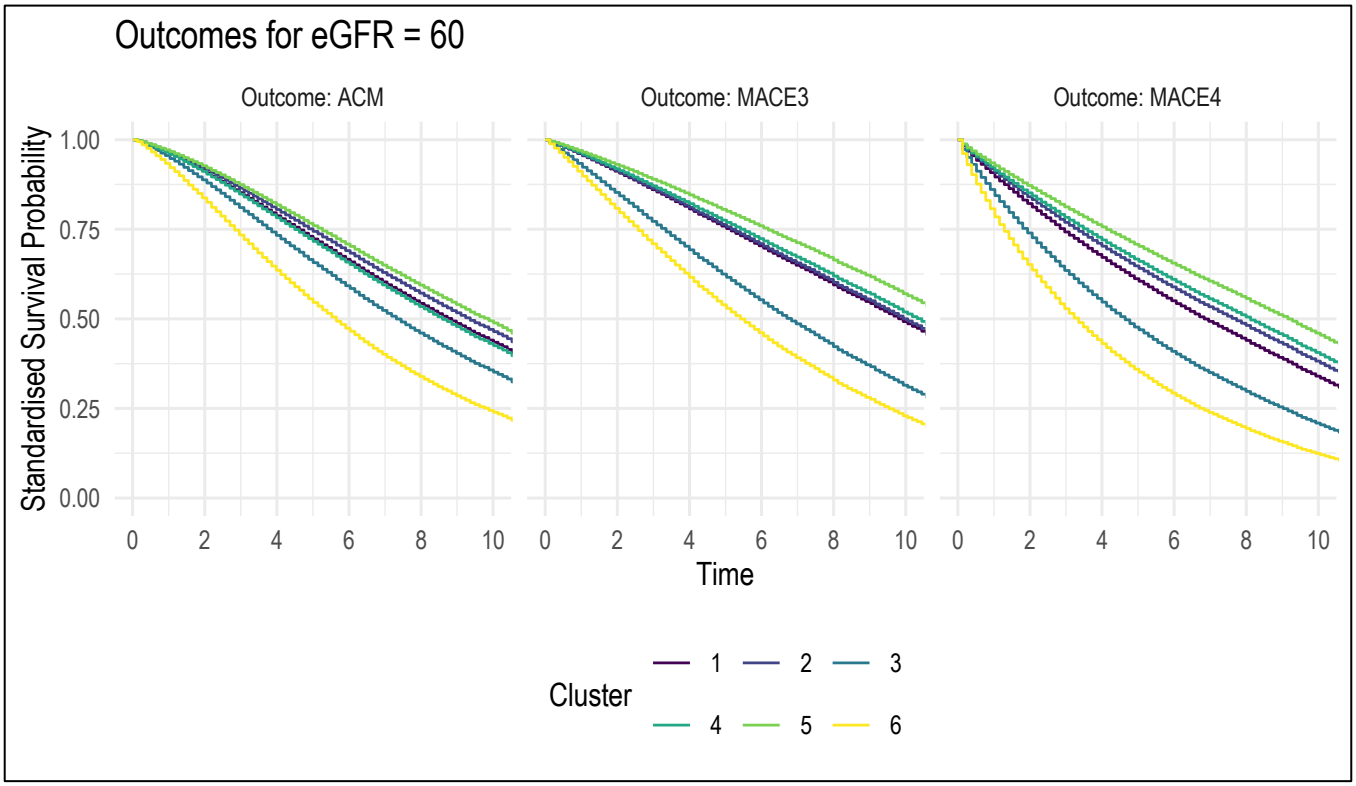
Supplementary figure 8-9A2. Standardised regression survival curves in eGFR 30 category in SCREAM.



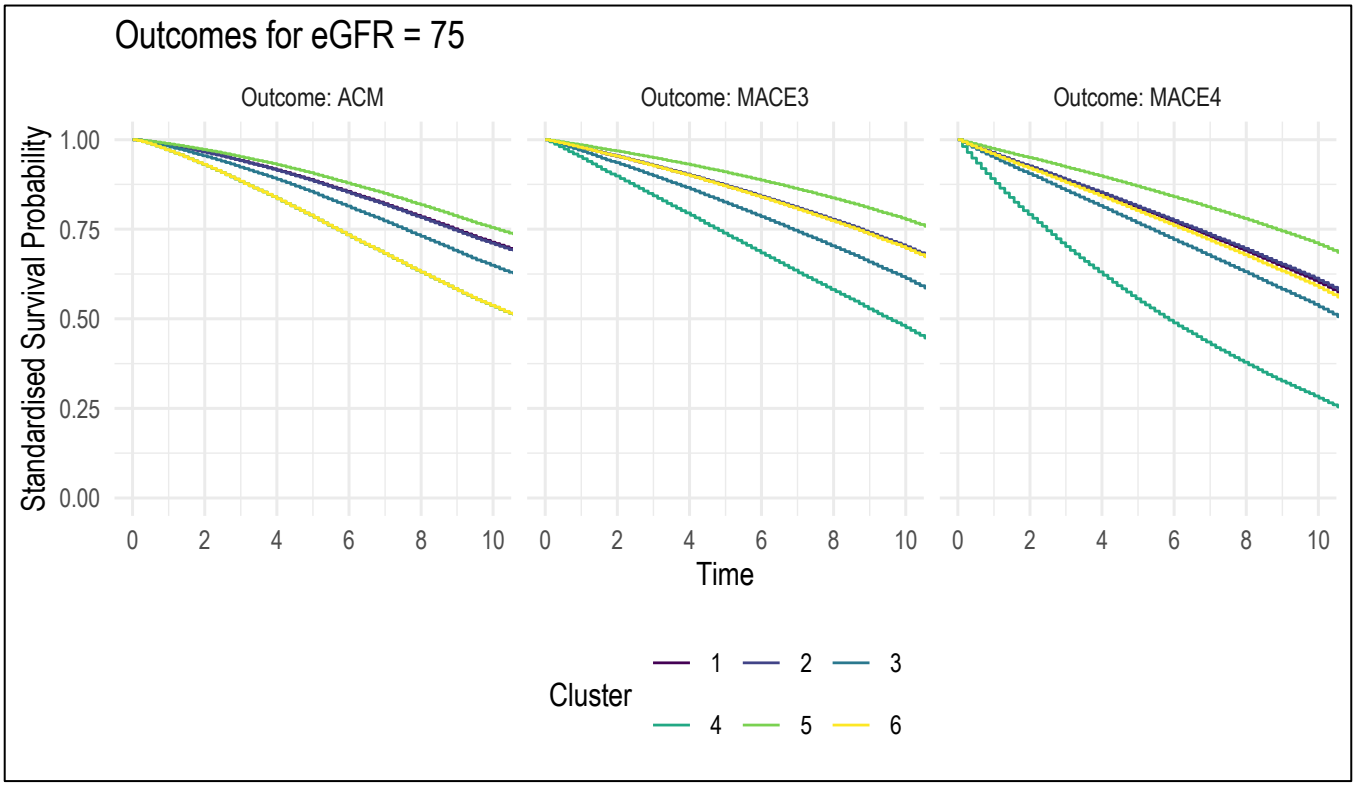
Supplementary figure 8-9A3. Standardised regression survival curves in eGFR 45 category in SCREAM.



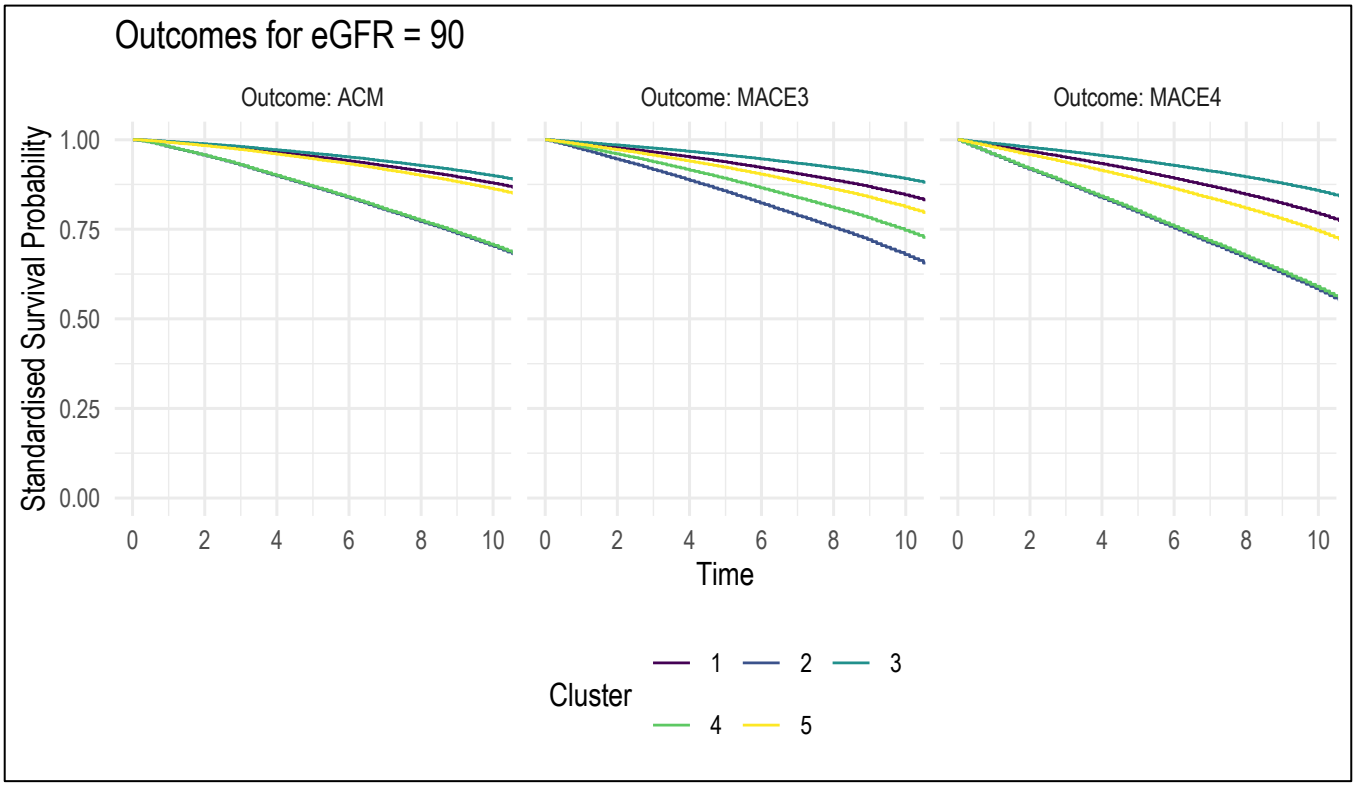
Supplementary figure 8-9A4. Standardised regression survival curves in eGFR 60 category in SCREAM.



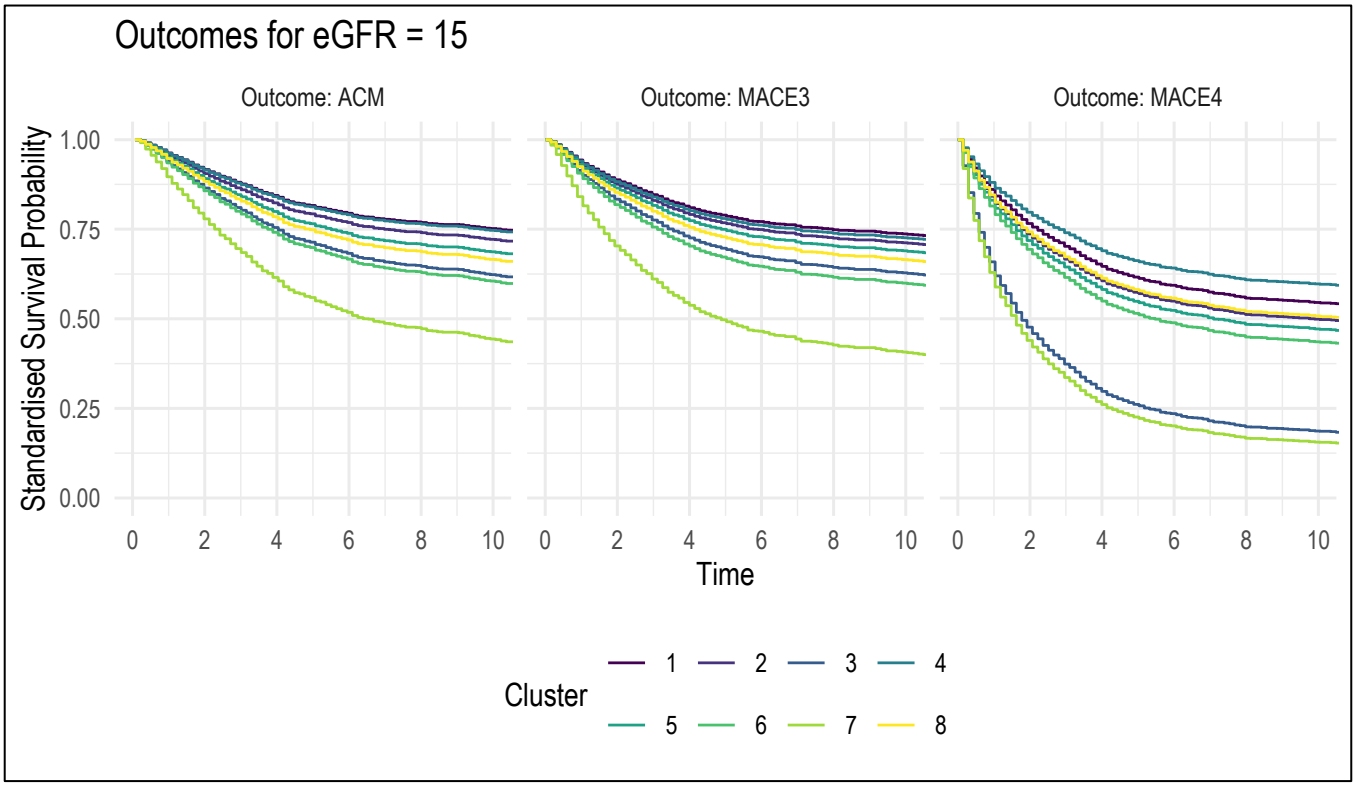
Supplementary figure 8-9A5. Standardised regression survival curves in eGFR 75 category in SCREAM.



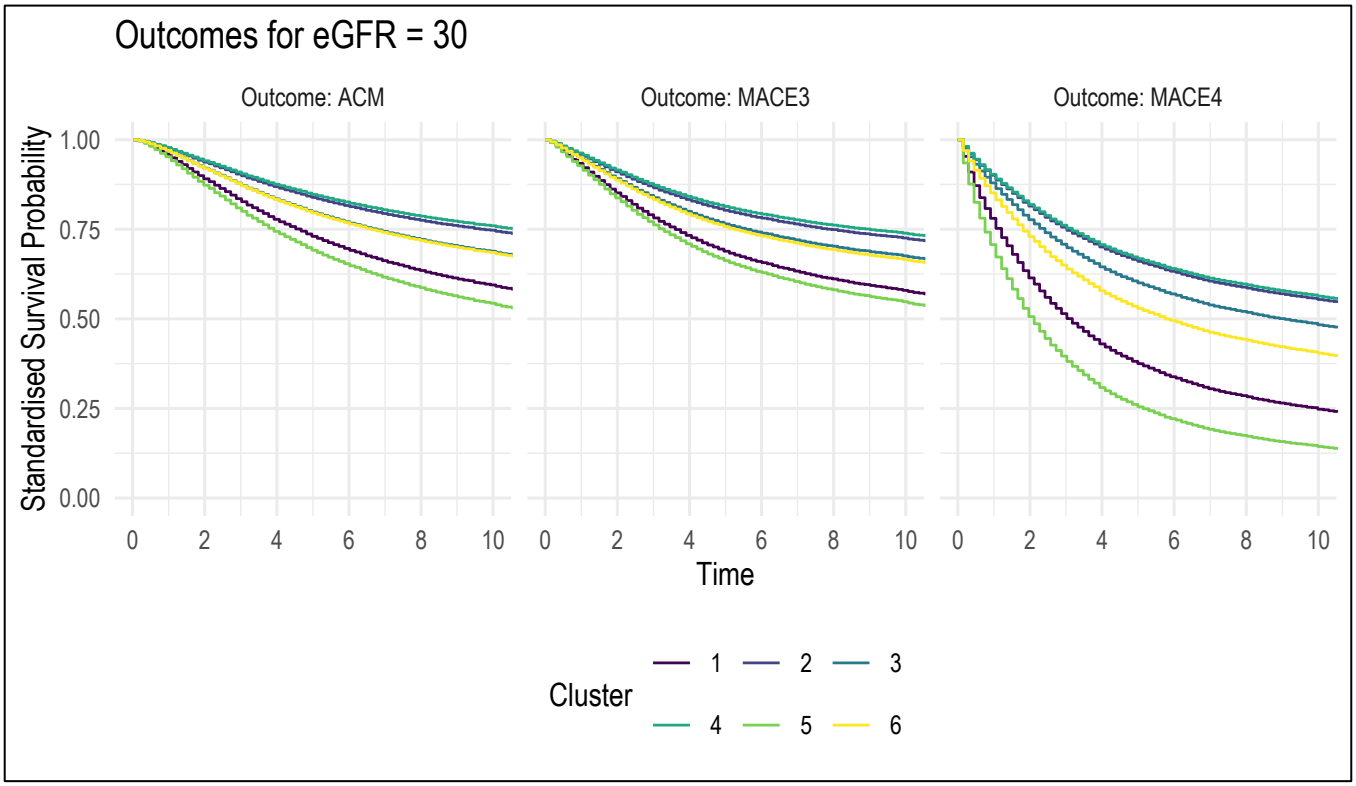
Supplementary figure 8-9A6. Standardised regression survival curves in eGFR 90 category in SCREAM.



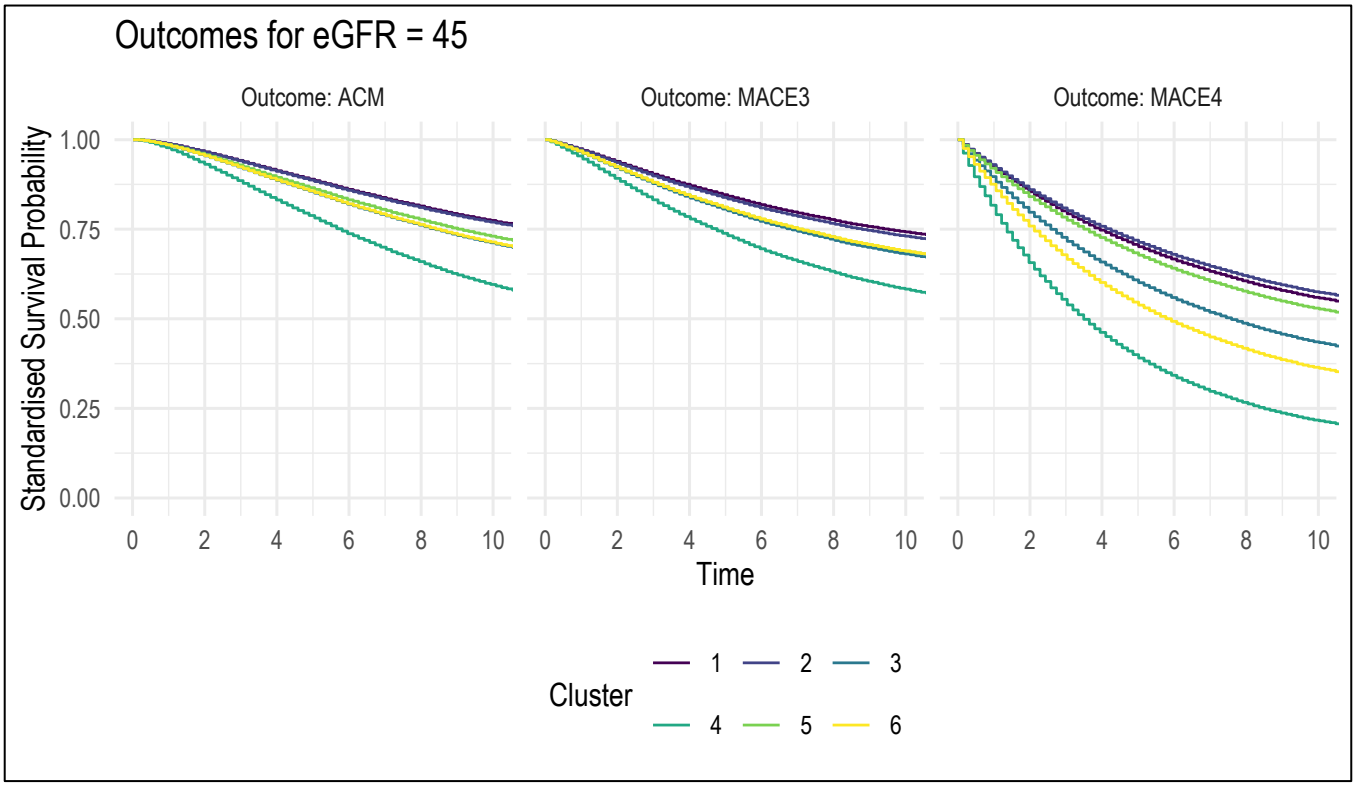
Supplementary figure 8-9B1. Standardised regression survival curves in eGFR 15 category in SAIL.



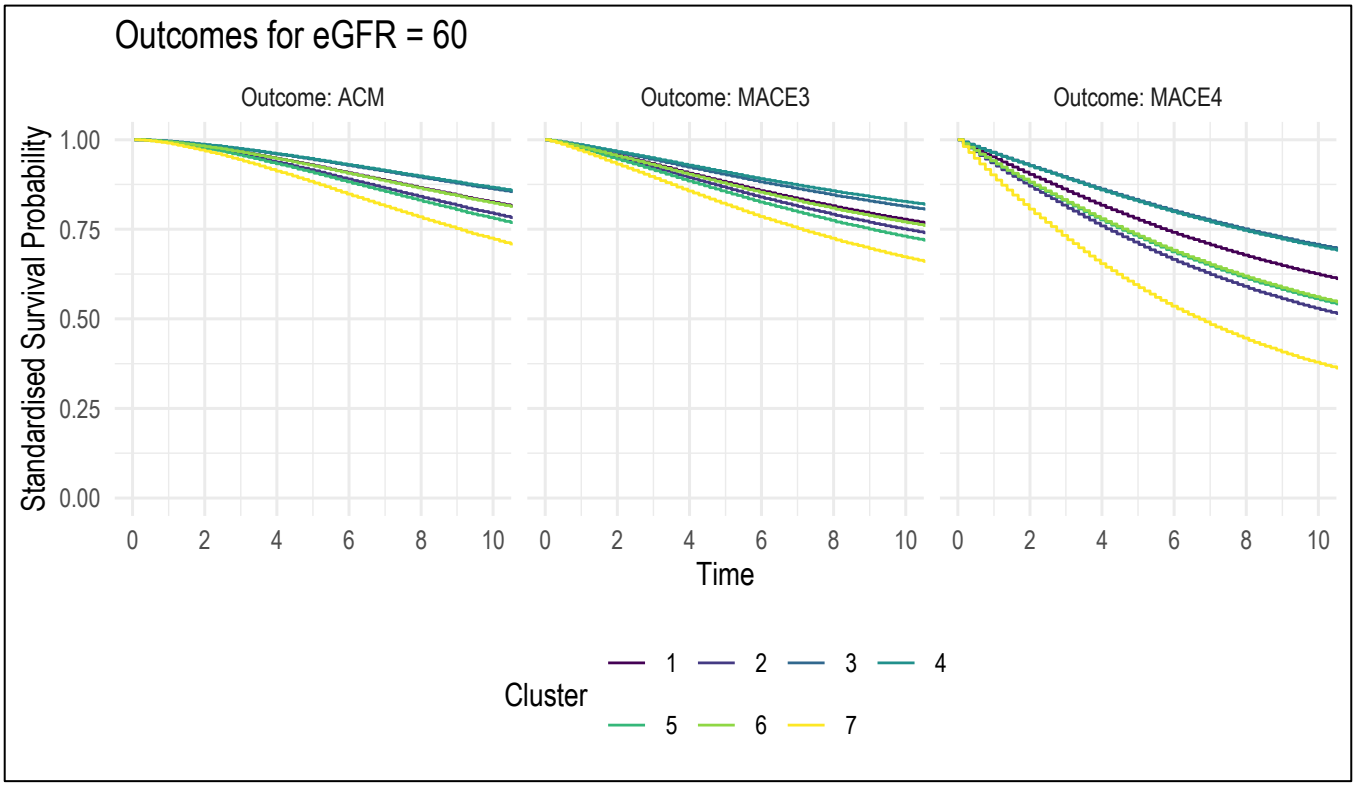
Supplementary figure 8-9B2. Standardised regression survival curves in eGFR 30 category in SAIL.



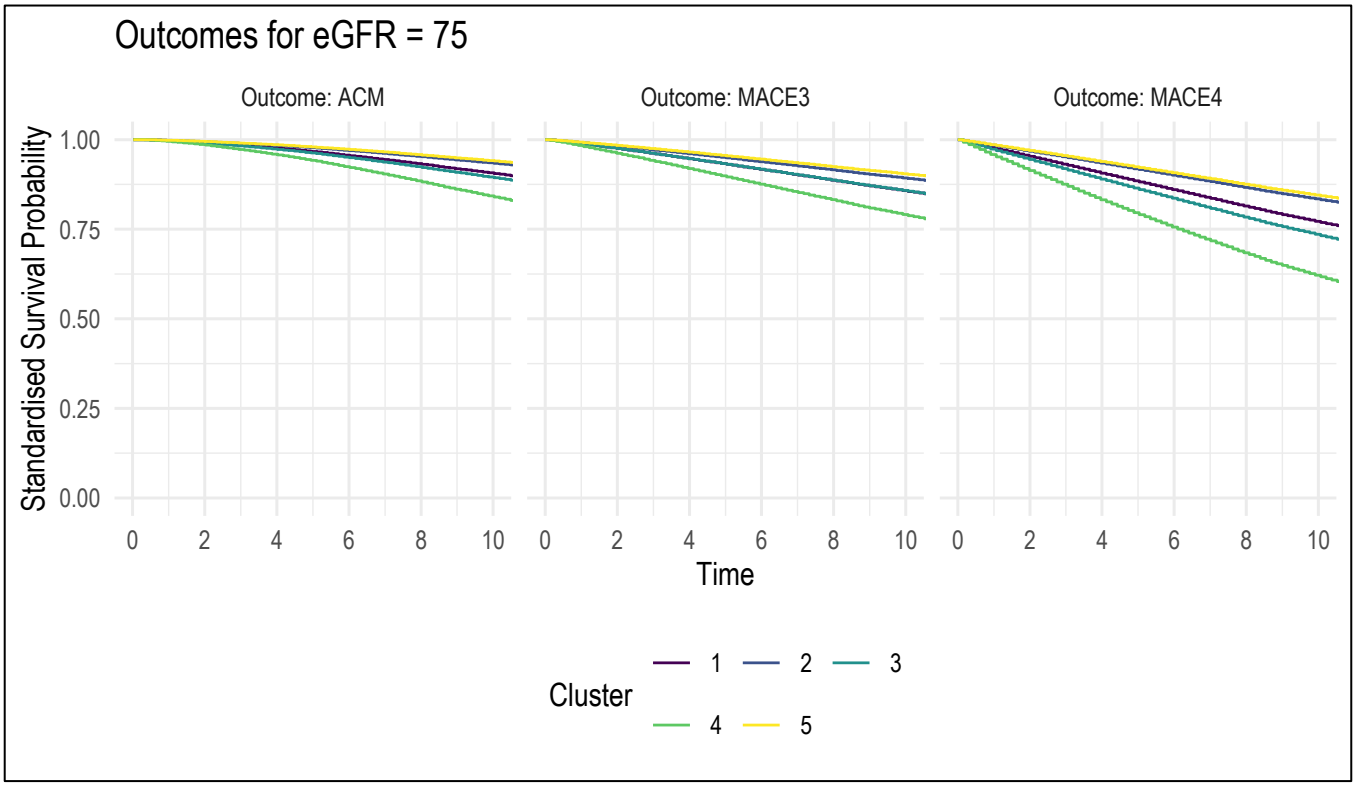
Supplementary figure 8-9B3. Standardised regression survival curves in eGFR 45 category in SAIL.



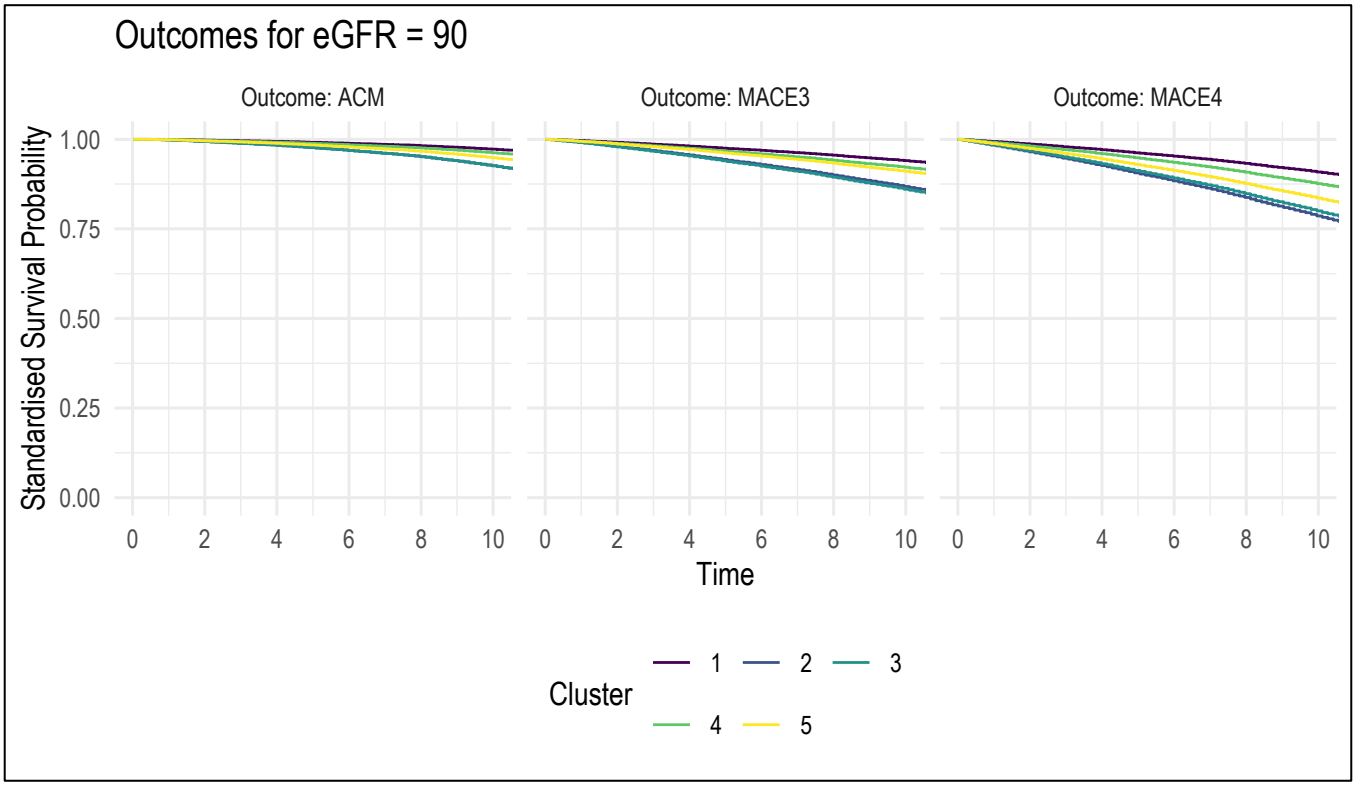
Supplementary figure 8-9B4. Standardised regression survival curves in eGFR 60 category in SAIL.



Supplementary figure 8-9B5. Standardised regression survival curves in eGFR 75 category in SAIL.

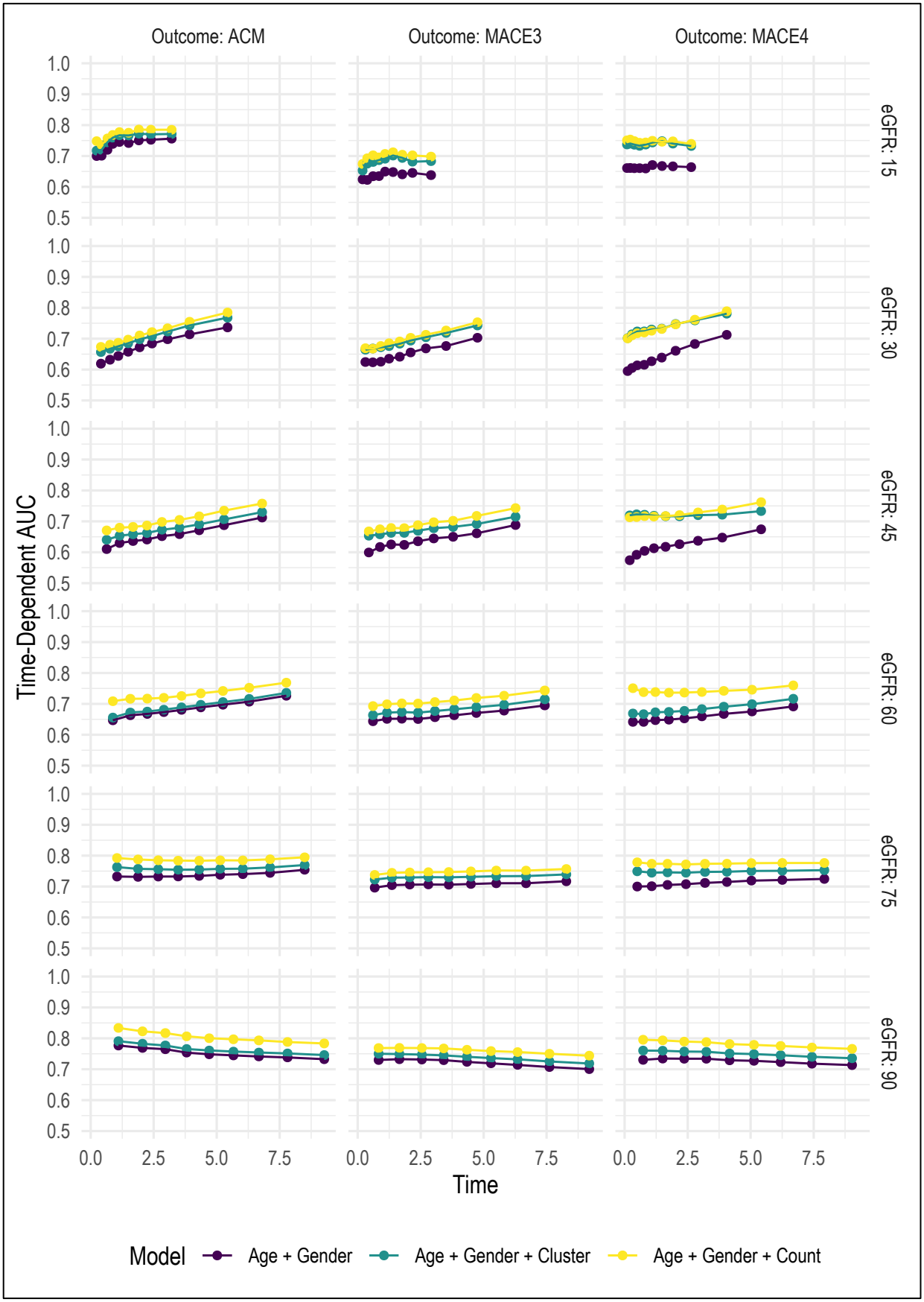


Supplementary figure 8-9B6. Standardised regression survival curves in eGFR 90 category in SAIL.



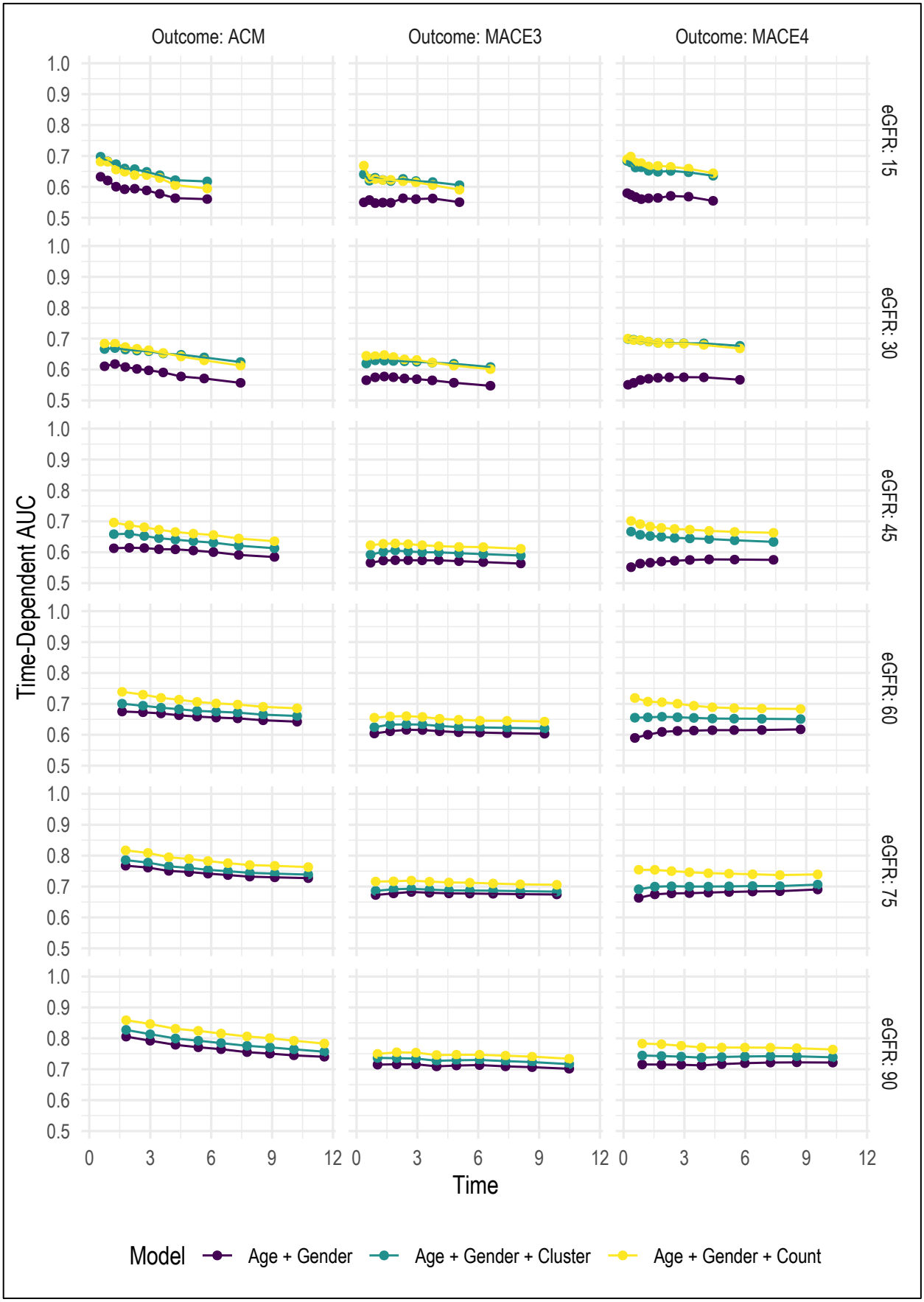
Finally, the predictive performance (of predicting adverse outcomes) of cluster membership information was, overall, similar to that of using the number of conditions (AUCs displayed in supplementary figures 8-10A and 8-10B and Brier scores in supplementary figures 8-11A and 8-11B).

Supplementary figure 8-10A. Predictive performance of clusters for adverse outcomes in SCREAM using area under curve (AUC).



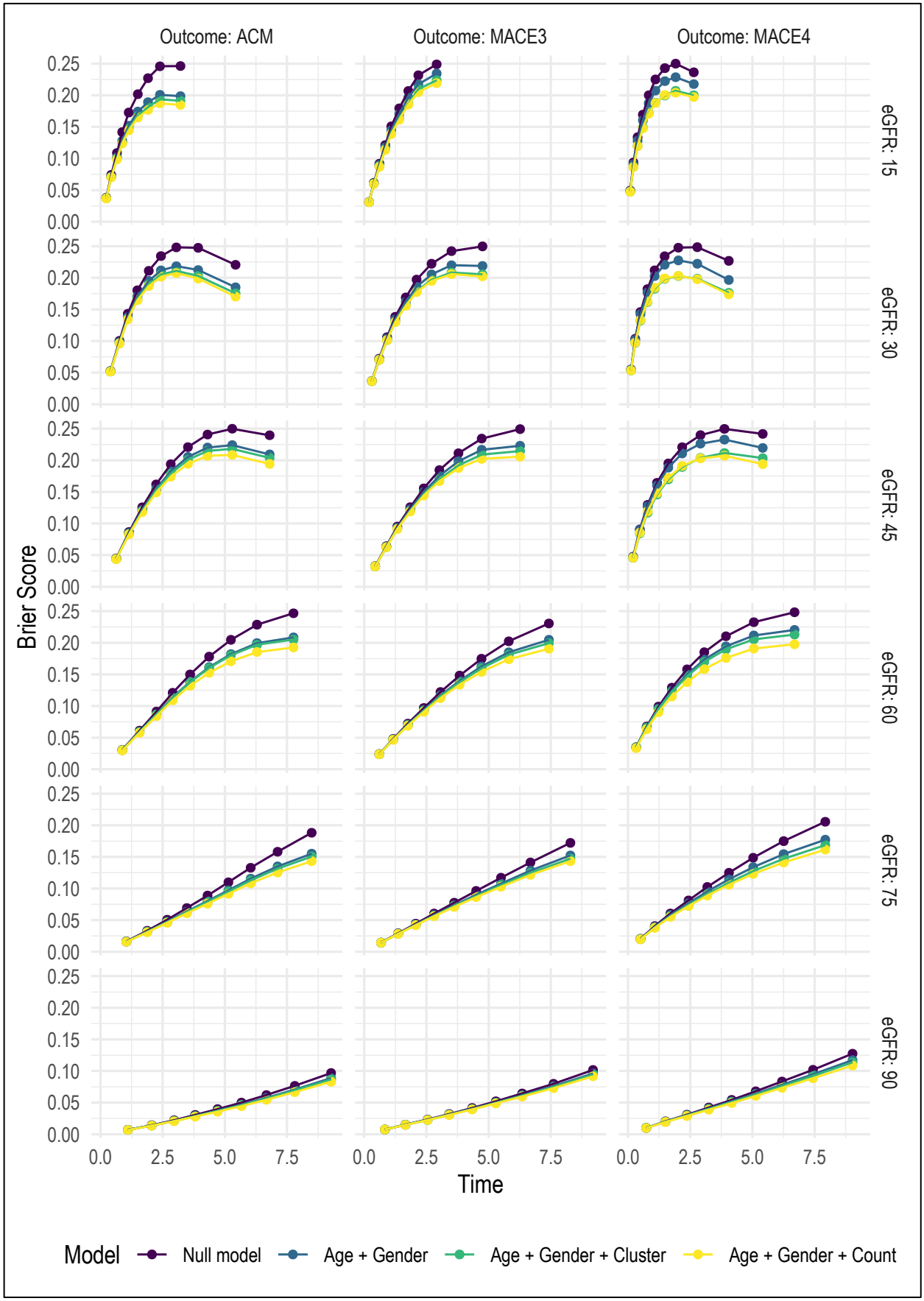
ACM, all-cause mortality. MACE3, major adverse cardiovascular events (myocardial infarction, stroke, cardiovascular death), MACE4, (myocardial infarction, stroke, cardiovascular death, heart failure hospitalisation). Time is measured in years

Supplementary figure 8-10B. Predictive performance of clusters for adverse outcomes in SAIL using area under curve (AUC).



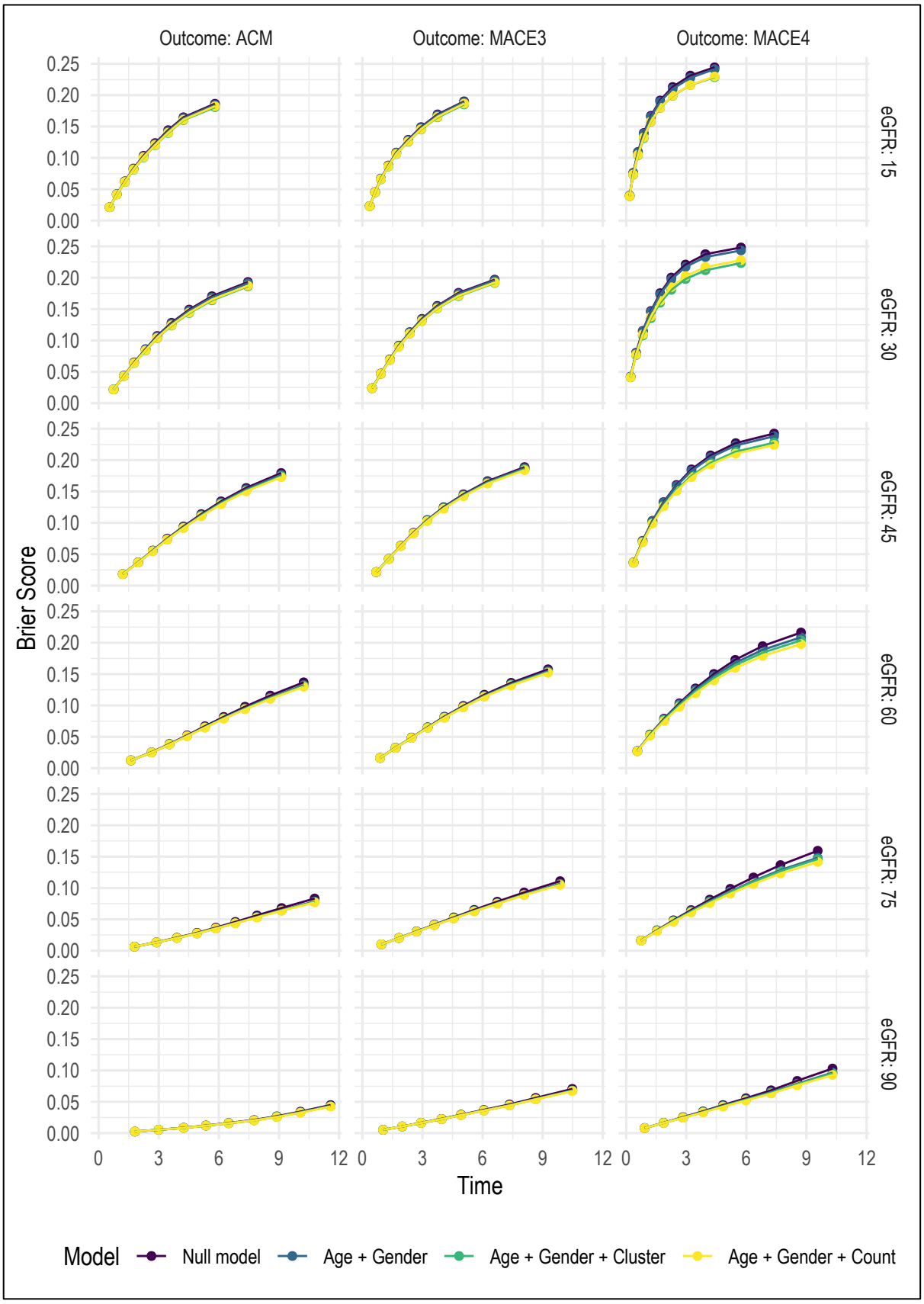
ACM, all-cause mortality. MACE3, major adverse cardiovascular events (myocardial infarction, stroke, cardiovascular death), MACE4, (myocardial infarction, stroke, cardiovascular death, heart failure hospitalisation). Time is measured in years

Supplemetary figure 8-11A. Predictive performance of clusters for adverse outcomes in SCREAM using Brier score.



ACM, all-cause mortality. MACE3, major adverse cardiovascular events (myocardial infarction, stroke, cardiovascular death), MACE4, (myocardial infarction, stroke, cardiovascular death, heart failure hospitalisation). Time is measured in years

Supplementary figure 8-11B. Predictive performance of clusters for adverse outcomes in SAIL using Brier score.



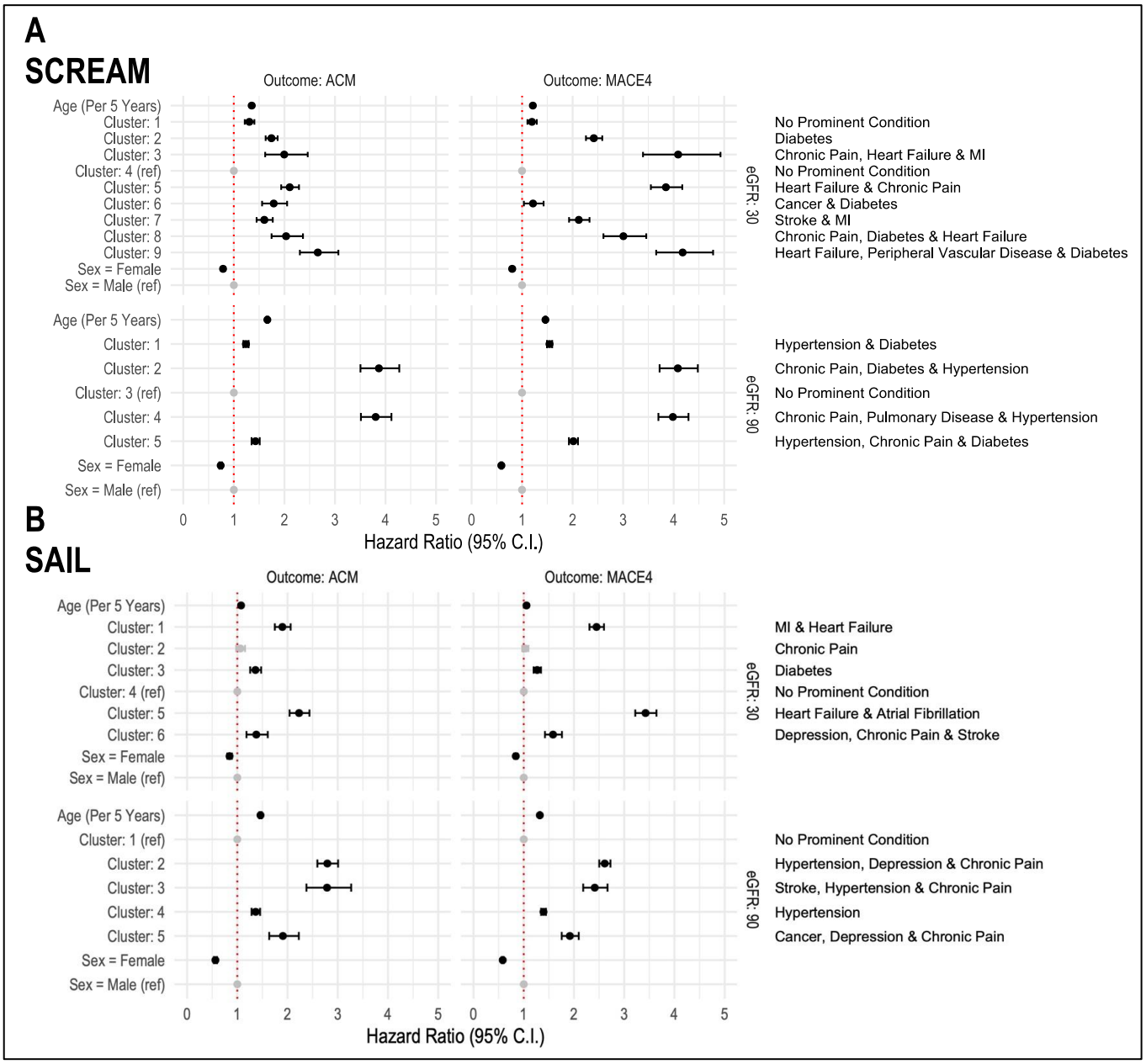
ACM, all-cause mortality. MACE3, major adverse cardiovascular events (myocardial infarction, stroke, cardiovascular death), MACE4, (myocardial infarction, stroke, cardiovascular death, heart failure hospitalisation). Time is measured in years

The relative rates of all-cause mortality and MACE were highest in the clusters with cardiometabolic prominent conditions (Supplementary figure 8-12, supplementary table 8-4). Figure 8-4 features results from low (30) and high (90) eGFR categories. In SAIL at eGFR 30, cluster 5 (Heart Failure & Atrial Fibrillation) showed a hazard ratio (HR) for all-cause mortality of 2.23 (95% confidence interval (CI) 2.04-2.44), and for MACE HR 3.43 (CI 3.22-3.64).

Hazard ratios tended to be higher when cardiometabolic conditions were combined with chronic pain or depression. In SCREAM at eGFR 90, cluster 1 (Hypertension & Diabetes) showed an HR for all-cause mortality of 1.24 (CI 1.19-1.29), and for MACE HR 1.54 (CI 1.49-1.60). Also at eGFR 90 in SCREAM, cluster 2 (in which Chronic Pain was prominent in addition to Hypertension & Diabetes), the HR for all-cause mortality was 3.87 (CI 3.51-4.27) and MACE 4.08 (CI 3.72-4.48).

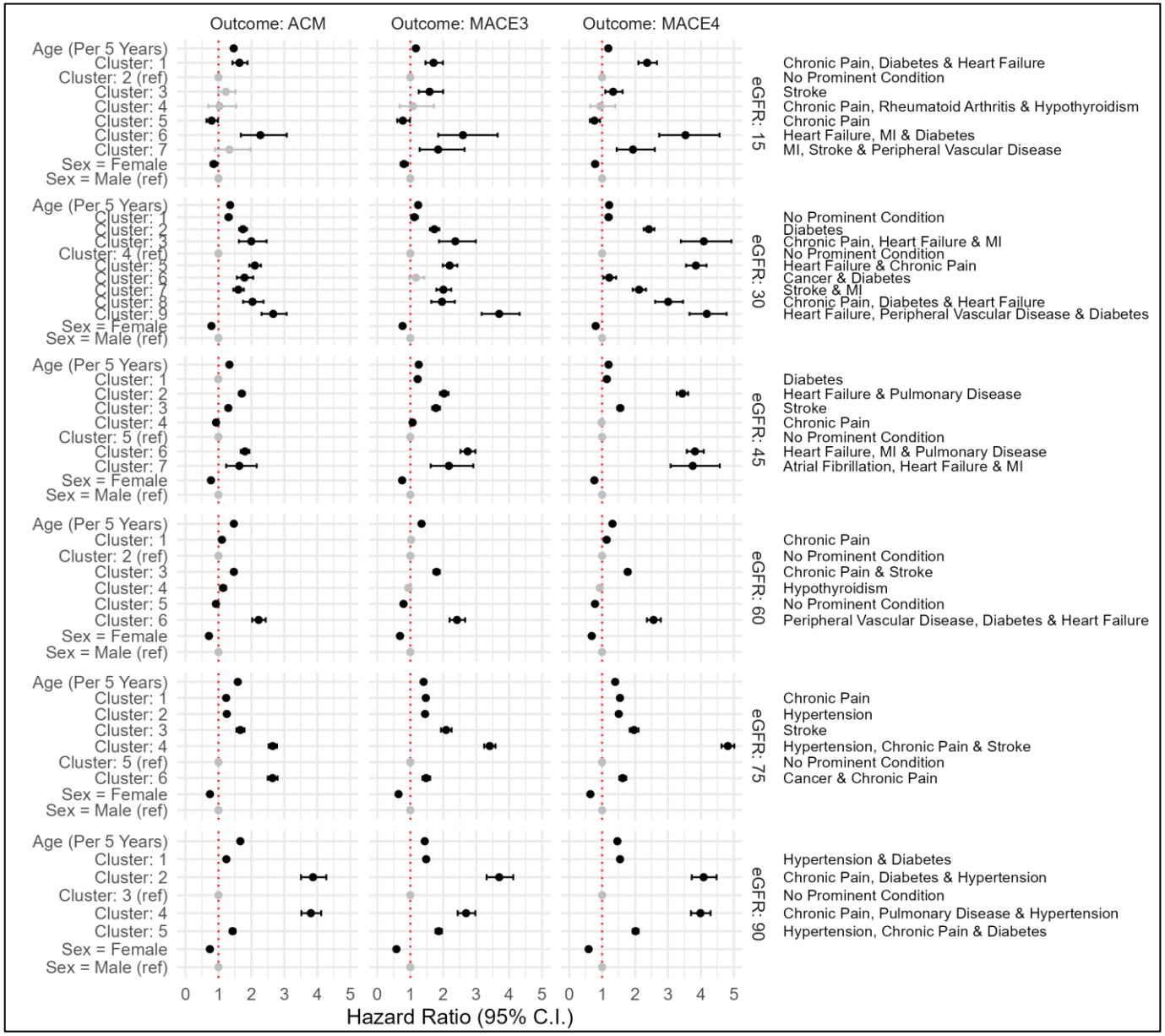
However, when chronic pain or depression were the sole prominent condition, these clusters were either not at increased risk of adverse outcomes or the increased risk was minimal. For example in SCREAM at eGFR 60, cluster 1 (Chronic Pain) all-cause mortality HR 1.11 (CI 1.07-1.14) and MACE HR 1.14 (CI 1.11-1.17). In SAIL at eGFR 60, cluster 4 (Depression) all-cause mortality HR 0.97 (CI 0.89-1.05), MACE HR 1.02 (CI 0.97-1.07).

Figure 8-4. Forest plot showing the risk of all-cause mortality (ACM) and MACE by cluster allocation. A. SCREAM. B. SAIL.



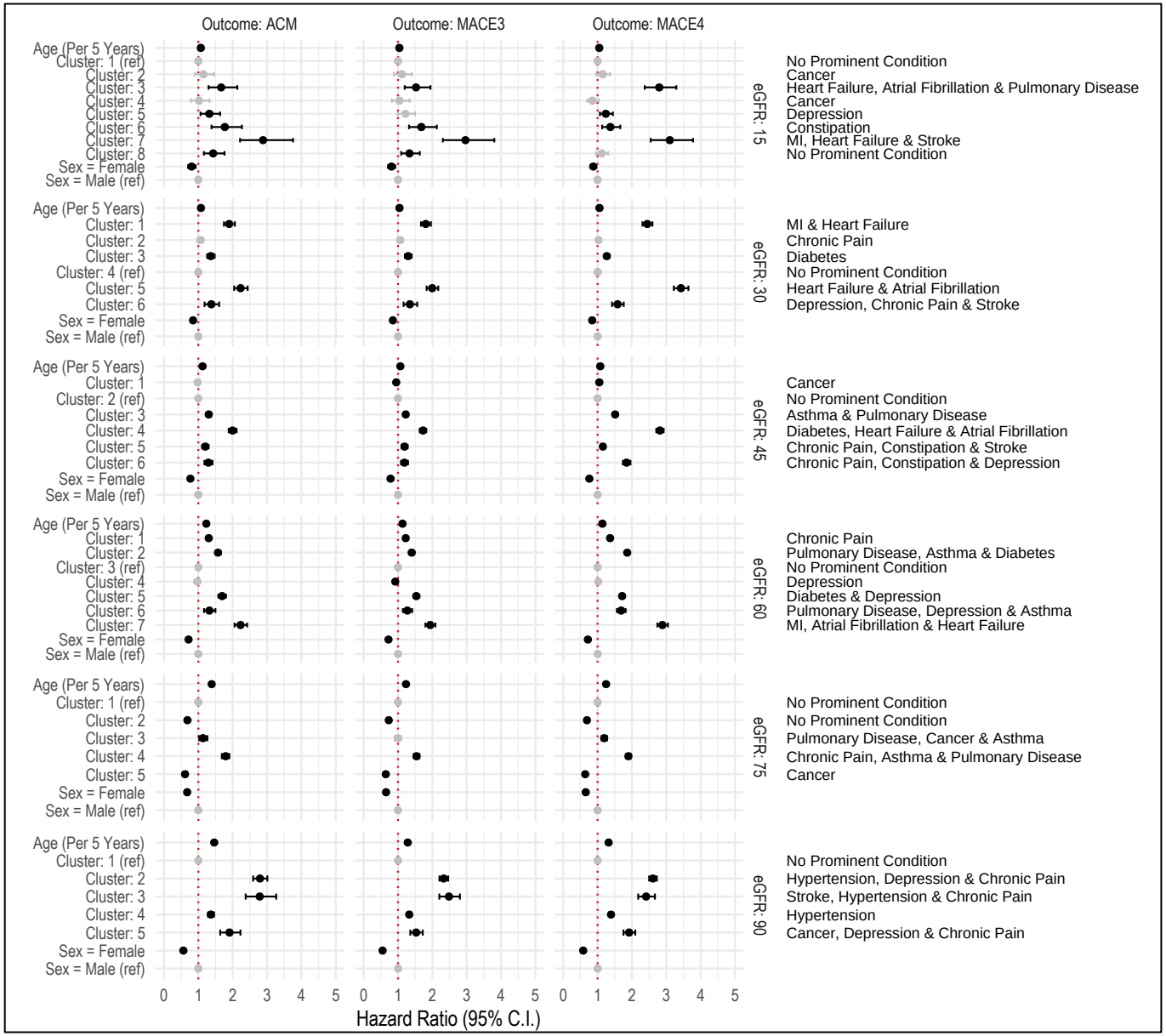
Hazard ratios are adjusted for sex and age, and on the right side the prominent condition of each cluster is listed.

Supplementary figure 8-12A. Forest plot showing the risk of all-cause mortality (ACM) and MACE by cluster allocation in SCREAM.



Hazard ratios are adjusted for sex and age

Supplementary figure 8-12B. Forest plot showing the risk of all-cause mortality (ACM) and MACE by cluster allocation in SAIL.



Hazard ratios are adjusted for sex and age

Supplementary fable 8-4A. Risk of adverse outcomes by cluster in SCREAM.

Cox models adjusted for age and sex. ACM, all-cause mortality, MACE3, major adverse cardiovascular events (myocardial infarction, stroke, cardiovascular death), MACE4, (myocardial infarction, stroke, cardiovascular death, heart failure hospitalisation)

eGFR 15	**ACM**	**MACE3**	**MACE4**
Age (Per 5 Years)	1.462 (1.418-1.509)	1.170 (1.138-1.202)	1.188 (1.162-1.214)
Cluster: 1	1.638 (1.425-1.881)	1.706 (1.460-1.993)	2.366 (2.101-2.664)
Cluster: 2 (ref)	---	---	---
Cluster: 3	1.225 (0.991-1.515)	1.585 (1.257-1.998)	1.334 (1.097-1.622)
Cluster: 4	1.031 (0.691-1.538)	1.080 (0.678-1.719)	0.948 (0.642-1.399)
Cluster: 5	0.791 (0.637-0.984)	0.773 (0.605-0.988)	0.767 (0.630-0.935)
Cluster: 6	2.272 (1.680-3.074)	2.599 (1.850-3.651)	3.532 (2.733-4.565)
Cluster: 7	1.332 (0.897-1.978)	1.845 (1.286-2.648)	1.937 (1.443-2.601)
Sex = Female	0.855 (0.758-0.965)	0.808 (0.706-0.924)	0.788 (0.709-0.875)
Sex = Male (ref)	---	---	---
eGFR 30			
Age (Per 5 Years)	1.353 (1.335-1.372)	1.238 (1.219-1.257)	1.213 (1.199-1.228)
Cluster: 1	1.307 (1.215-1.406)	1.125 (1.026-1.233)	1.195 (1.107-1.291)
Cluster: 2	1.743 (1.628-1.866)	1.731 (1.594-1.878)	2.420 (2.263-2.588)
Cluster: 3	1.998 (1.621-2.462)	2.366 (1.873-2.990)	4.088 (3.393-4.926)
Cluster: 4 (ref)	---	---	---
Cluster: 5	2.106 (1.938-2.288)	2.196 (1.986-2.427)	3.847 (3.549-4.170)
Cluster: 6	1.789 (1.558-2.054)	1.172 (0.966-1.422)	1.216 (1.036-1.427)
Cluster: 7	1.602 (1.452-1.769)	2.004 (1.792-2.241)	2.122 (1.929-2.334)
Cluster: 8	2.034 (1.747-2.367)	1.963 (1.637-2.353)	3.005 (2.611-3.458)
Cluster: 9	2.661 (2.307-3.070)	3.698 (3.166-4.319)	4.179 (3.653-4.779)
Sex = Female	0.787 (0.750-0.825)	0.765 (0.723-0.811)	0.805 (0.768-0.843)
Sex = Male (ref)	---	---	---
eGFR 45			
Age (Per 5 Years)	1.333 (1.320-1.346)	1.256 (1.243-1.270)	1.196 (1.186-1.206)
Cluster: 1	0.994 (0.950-1.039)	1.223 (1.156-1.293)	1.145 (1.093-1.199)
Cluster: 2	1.708 (1.622-1.799)	2.026 (1.900-2.160)	3.434 (3.264-3.613)
Cluster: 3	1.298 (1.228-1.373)	1.779 (1.663-1.902)	1.550 (1.464-1.641)
Cluster: 4	0.926 (0.878-0.976)	1.071 (1.002-1.143)	0.981 (0.929-1.036)
Cluster: 5 (ref)	---	---	---
Cluster: 6	1.803 (1.676-1.940)	2.740 (2.523-2.976)	3.820 (3.571-4.086)
Cluster: 7	1.633 (1.235-2.161)	2.172 (1.620-2.912)	3.753 (3.081-4.572)
Sex = Female	0.772 (0.748-0.796)	0.753 (0.726-0.781)	0.764 (0.742-0.787)
Sex = Male (ref)	---	---	---
eGFR: 60			
Age (Per 5 Years)	1.467 (1.455-1.479)	1.342 (1.330-1.354)	1.315 (1.306-1.324)
Cluster: 1	1.105 (1.070-1.142)	1.025 (0.989-1.064)	1.139 (1.106-1.173)
Cluster: 2 (ref)	---	---	---
Cluster: 3	1.468 (1.394-1.545)	1.797 (1.702-1.897)	1.777 (1.698-1.860)
Cluster: 4	1.140 (1.054-1.234)	0.939 (0.854-1.034)	0.928 (0.857-1.005)
Cluster: 5	0.923 (0.893-0.953)	0.794 (0.764-0.824)	0.785 (0.761-0.810)
Cluster: 6	2.218 (2.023-2.433)	2.418 (2.193-2.666)	2.562 (2.361-2.781)
Sex = Female	0.710 (0.692-0.728)	0.688 (0.668-0.708)	0.685 (0.669-0.702)
Sex = Male (ref)	---	---	---
eGFR: 75			
Age (Per 5 Years)	1.586 (1.575-1.597)	1.403 (1.393-1.414)	1.397 (1.388-1.405)
Cluster: 1	1.234 (1.192-1.276)	1.471 (1.420-1.524)	1.542 (1.497-1.589)
Cluster: 2	1.254 (1.213-1.295)	1.449 (1.400-1.499)	1.505 (1.462-1.549)
Cluster: 3	1.663 (1.545-1.790)	2.087 (1.932-2.254)	1.967 (1.838-2.106)
Cluster: 4	2.646 (2.523-2.776)	3.410 (3.244-3.586)	4.816 (4.625-5.015)
Cluster: 5 (ref)	---	---	---
Cluster: 6	2.641 (2.497-2.794)	1.481 (1.368-1.603)	1.624 (1.522-1.733)
Sex = Female	0.742 (0.723-0.761)	0.643 (0.626-0.660)	0.644 (0.630-0.659)
Sex = Male (ref)	---	---	---
eGFR 90			
Age (Per 5 Years)	1.663 (1.647-1.680)	1.438 (1.425-1.451)	1.463 (1.451-1.474)
Cluster: 1	1.239 (1.189-1.291)	1.482 (1.425-1.541)	1.543 (1.492-1.596)
Cluster: 2	3.870 (3.505-4.272)	3.699 (3.317-4.125)	4.083 (3.722-4.478)
Cluster: 3 (ref)	---	---	---
Cluster: 4	3.805 (3.516-4.119)	2.694 (2.439-2.974)	3.985 (3.699-4.293)
Cluster: 5	1.429 (1.350-1.512)	1.862 (1.768-1.962)	2.016 (1.929-2.106)
Sex = Female	0.739 (0.716-0.764)	0.579 (0.560-0.598)	0.591 (0.575-0.608)
Sex = Male (ref)	---	---	---

Supplementary table 8-4B. Risk of adverse outcomes by cluster in SAIL.

eGFR 15	ACM	MACE3	MACE4
Age (Per 5 Years)	1.072 (1.045-1.100)	1.041 (1.017-1.066)	1.047 (1.029-1.066)
Cluster: 1 (ref)	—	—	—
Cluster: 2	1.145 (0.899-1.458)	1.113 (0.884-1.402)	1.148 (0.968-1.362)
Cluster: 3	1.665 (1.297-2.137)	1.526 (1.196-1.947)	2.796 (2.375-3.293)
Cluster: 4	1.023 (0.789-1.326)	1.049 (0.820-1.341)	0.850 (0.699-1.034)
Cluster: 5	1.320 (1.065-1.635)	1.219 (0.993-1.496)	1.241 (1.067-1.445)
Cluster: 6	1.770 (1.382-2.267)	1.680 (1.325-2.130)	1.374 (1.135-1.662)
Cluster: 7	2.884 (2.213-3.757)	2.962 (2.307-3.805)	3.103 (2.546-3.781)
Cluster: 8	1.430 (1.162-1.761)	1.337 (1.093-1.634)	1.119 (0.955-1.312)
Sex = Female	0.804 (0.704-0.919)	0.810 (0.713-0.920)	0.874 (0.794-0.961)
Sex = Male (ref)	—	—	—
eGFR 30			
Age (Per 5 Years)	1.075 (1.061-1.089)	1.045 (1.033-1.057)	1.055 (1.045-1.064)
Cluster: 1	1.898 (1.747-2.062)	1.809 (1.671-1.958)	2.448 (2.308-2.597)
Cluster: 2	1.061 (0.976-1.154)	1.062 (0.982-1.150)	1.029 (0.968-1.093)
Cluster: 3	1.361 (1.257-1.474)	1.297 (1.203-1.399)	1.268 (1.197-1.343)
Cluster: 4 (ref)	—	—	—
Cluster: 5	2.230 (2.041-2.436)	1.997 (1.833-2.175)	3.425 (3.220-3.642)
Cluster: 6	1.378 (1.182-1.606)	1.348 (1.165-1.560)	1.583 (1.423-1.761)
Sex = Female	0.846 (0.801-0.893)	0.852 (0.809-0.897)	0.841 (0.810-0.874)
Sex = Male (ref)	—	—	—
eGFR 45			
Age (Per 5 Years)	1.123 (1.112-1.134)	1.070 (1.061-1.079)	1.078 (1.071-1.085)
Cluster: 1	0.978 (0.927-1.032)	0.950 (0.904-0.998)	1.051 (1.013-1.091)
Cluster: 2 (ref)	—	—	—
Cluster: 3	1.302 (1.230-1.377)	1.226 (1.164-1.292)	1.512 (1.454-1.572)
Cluster: 4	1.995 (1.885-2.112)	1.727 (1.637-1.822)	2.815 (2.709-2.924)
Cluster: 5	1.202 (1.111-1.300)	1.191 (1.107-1.281)	1.154 (1.089-1.223)
Cluster: 6	1.290 (1.179-1.412)	1.187 (1.090-1.292)	1.844 (1.739-1.956)
Sex = Female	0.767 (0.741-0.795)	0.784 (0.759-0.810)	0.760 (0.741-0.779)
Sex = Male (ref)	—	—	—
eGFR 60			
Age (Per 5 Years)	1.232 (1.221-1.243)	1.132 (1.123-1.140)	1.140 (1.134-1.147)
Cluster: 1	1.303 (1.254-1.354)	1.226 (1.186-1.267)	1.364 (1.330-1.400)
Cluster: 2	1.571 (1.494-1.653)	1.400 (1.339-1.463)	1.863 (1.803-1.924)
Cluster: 3 (ref)	—	—	—
Cluster: 4	0.969 (0.894-1.050)	0.921 (0.861-0.986)	1.020 (0.970-1.074)
Cluster: 5	1.691 (1.584-1.806)	1.534 (1.451-1.622)	1.715 (1.643-1.790)
Cluster: 6	1.320 (1.165-1.496)	1.272 (1.145-1.413)	1.686 (1.564-1.817)
Cluster: 7	2.230 (2.056-2.419)	1.940 (1.801-2.090)	2.889 (2.738-3.048)
Sex = Female	0.714 (0.692-0.737)	0.724 (0.705-0.744)	0.716 (0.701-0.731)
Sex = Male (ref)	—	—	—
eGFR 75			
Age (Per 5 Years)	1.388 (1.375-1.400)	1.234 (1.226-1.242)	1.247 (1.240-1.254)
Cluster: 1 (ref)	—	—	—
Cluster: 2	0.684 (0.656-0.712)	0.732 (0.709-0.755)	0.691 (0.674-0.708)
Cluster: 3	1.137 (1.024-1.262)	0.995 (0.909-1.090)	1.194 (1.117-1.277)
Cluster: 4	1.792 (1.686-1.904)	1.542 (1.463-1.625)	1.897 (1.824-1.972)
Cluster: 5	0.612 (0.559-0.670)	0.647 (0.602-0.694)	0.641 (0.606-0.677)
Sex = Female	0.676 (0.653-0.700)	0.653 (0.636-0.672)	0.657 (0.643-0.671)
Sex = Male (ref)	—	—	—
eGFR 90			
Age (Per 5 Years)	1.462 (1.441-1.483)	1.284 (1.272-1.297)	1.320 (1.310-1.330)
Cluster: 1 (ref)	—	—	—
Cluster: 2	2.793 (2.594-3.007)	2.331 (2.209-2.460)	2.612 (2.503-2.726)
Cluster: 3	2.787 (2.377-3.267)	2.485 (2.202-2.804)	2.414 (2.184-2.668)
Cluster: 4	1.366 (1.284-1.454)	1.327 (1.271-1.385)	1.393 (1.346-1.442)
Cluster: 5	1.908 (1.636-2.225)	1.529 (1.357-1.722)	1.918 (1.756-2.095)
Sex = Female	0.564 (0.534-0.596)	0.551 (0.530-0.573)	0.581 (0.564-0.599)
Sex = Male (ref)	—	—	—

Cox models adjusted for age and sex. ACM, all-cause mortality, MACE3, major adverse cardiovascular events (myocardial infarction, stroke, cardiovascular death), MACE4, (myocardial infarction, stroke, cardiovascular death, heart failure hospitalisation)

Discussion

In two geographically distinct health systems we report the following findings: *1)* low eGFR is accompanied by increasing age and increasing prevalence of chronic conditions; *2)* these chronic conditions often cluster, with differential patterns across the eGFR spectrum, and show strong associations with the risk of adverse outcomes; *3)* clusters with cardiovascular conditions were more prominent at low eGFR; *4)* chronic pain and depression were common and when combined with physical conditions, were associated with adverse outcomes; *5)* clustering information could predict the risk of adverse outcomes in a similar way to the number of chronic conditions, with the advantage of being more clinically relevant. Collectively, these findings illustrate the complexity of medical conditions for people with CKD and have practical implications for service delivery, by supporting a move away from healthcare for individual diseases towards the development of clinical guidelines for common clusters of conditions.

In both cohorts, there was a dichotomy between low-risk clusters with low rates of chronic conditions and high-risk clusters featuring cardiovascular conditions. This agrees with an analysis of people with CKD in the Chronic Renal Insufficiency Cohort Study which found one large cluster with relatively healthy individuals[333] and a longitudinal study which found that as clusters were compared over follow-up, cardiovascular conditions became prominent as the participants aged.[334] Our finding that cardiovascular clusters became more dominant at eGFR 30 and 15mL/min/1.73m^2 was not surprising, as people with CKD, diabetes, and heart disease are a well-recognised group with consistently poor outcomes.[335] This group of patients may benefit from integrated clinics, where multiple specialties see patients together. For example, clinics with cardiology, nephrology and endocrinology have been found to be effective at optimising treatment (e.g. improving glycated haemoglobin levels and commencing sodium-glucose co-transporter-2 inhibitors).[336] There is evidence that integrated clinics may help address some of the problems associated with attending hospital clinics, such as by reducing the number of appointments patients must attend and by improved continuity of care.[337] However, the impact on quality of life is less clear[338] and further work is required to determine if these models of care work well. As these clusters in

our study were at heightened risk of adverse events, they may benefit from targeted evidence-based interventions such as statins,[9] renin-angiotensin system inhibitors,[339,340,341,342] sodium-glucose co-transporter-2-inhibitors,[275,343] and smoking cessation support.[11]

Chronic pain was common in both cohorts, particularly at low eGFR, and identified in many clusters. This agrees with a recent systematic review reporting that chronic pain was common in people with CKD.[344] The systematic review reported a higher prevalence of chronic pain (48%)[344] compared to our cohorts, perhaps because estimates were based on clinical studies with assessment of pain scales, and our estimates may be affected by poor recognition of pain by health professionals. We in part used prescribing data to identify chronic pain and depression, and a reluctance amongst clinicians to prescribe nephrotoxic medication may have led some patients with chronic pain to go undetected. It also agrees with a clustering analysis of people with multimorbidity in England that found chronic pain to feature in 13 of 20 clusters and to be associated with frequent health service use.[108] We similarly found that adverse outcome rates were higher when chronic pain featured in clusters alongside physical conditions, but not on its own. Management of chronic pain is challenging, especially in people with CKD. Prescribers often avoid non-steroidal anti-inflammatory drugs because of nephrotoxic effects, and both these medications and opioids are associated with significant harm.[345] Previous studies of multimorbidity in people with CKD have not explored the importance of chronic pain.[346,347] More research must therefore be done to understand why its prevalence in CKD is so high and what can be done to improve its management.

Depression featured in clusters in SAIL, often alongside physical conditions. Mental and physical conditions are known to occur together frequently, but treatment in these people can be challenging. Clusters in our study which featured depression in combination with physical conditions were associated with increased risk of adverse outcomes, which is consistent with previous studies.[348] Depression in people with CKD is currently under-recognised and under-treated, and antidepressant medications do not work as well as when kidney function is normal.[66] In a systematic

review of interventions for people with multimorbidity, those targeting depression were the most effective, particularly alterations to care delivery, such as nurses and psychologists setting goals with patients.[117] Interventions like these therefore warrant investigation in people with CKD and multimorbidity.

We found that clustering conditions did not significantly improve the prediction of outcomes over counting conditions. This is consistent with a study of over 8 million English people, which could not identify any clusters which could be targeted to reduce emergency hospitalisations.[109] However, our study was not aimed at developing a prediction model for the risk of adverse outcomes and metrics were only internally validated, thus limiting our conclusions with regards to the predictive ability of clusters versus condition counts. Rather than being incorporated into risk stratification, clusters of conditions may be more helpful in informing clinical guidelines and preventative measures. Clinical guidelines could be developed to help clinicians treat chronic pain amongst people with CKD and cardiometabolic conditions. Public health measures might encourage healthy lifestyles to reduce the numbers of people in high-risk clusters e.g., those with CKD, diabetes, and heart disease. It is possible that risk for cardiometabolic conditions starts being accrued early in life, perhaps even in the prenatal period,[349] and that interventions in childhood could have long-lasting effects.

The strengths of this study are its state-of-the art methods and its unrivalled sample size in researching multimorbidity and CKD. Observing similarities across two distinct cohorts does increase generalisability, but we did not expect results to be identical given differences in the frequency of blood tests, lifestyles, genetic background, and variation of timely diagnoses of conditions such as pulmonary disease or heart failure, which can be challenging especially in inactive patients. For example, respiratory conditions were more common in SAIL than in SCREAM, which is consistent with the high rates of these conditions in Wales compared to Sweden.[350] Our analyses were restricted to participants whose eGFR crossed thresholds, and future work should consider clustering analyses in other populations e.g. people with stable kidney function, people on dialysis. We openly provide the

statistical code that we used for this work, and encourage other researchers to replicate this analysis in their settings. Given age and kidney function are closely linked,[351] the conditions prominent in each eGFR strata will have been largely influenced by age. It is unclear to what extent changes in clusters as eGFR declines is explained by advancing age rather than being specific to changes in kidney function. There are inherent limitations of health records research in that they rely on routine coding, a subjective process that if incomplete, can lead to misclassification of clusters identified. We tried to improve the sensitivity of our ascertainment of chronic conditions by using previously validated algorithms,[170] supplemented in some cases with medication data. We chose to enrich the definitions of depression and chronic pain with prescribing data, which will have increased the prevalence of these conditions and contributed to them featuring clusters. Other conditions may have featured more prominently in the clusters if we had used prescribing data to define them, also. Our analysis included people with a relative abundance of blood tests and who were older than those excluded, which results in a degree of selection bias. This limits its generalisability to younger adults and those who seldom have blood tests. We studied patients across the range of eGFR, without considering proteinuria data. Many of the patients in the eGFR categories 75 and 90 were therefore unlikely to have CKD and instead, their inclusion allowed us to study clusters of conditions in people with good kidney function. Some of the follow-up period in SAIL was during the Covid-19 pandemic, when blood tests and recording of chronic conditions may have been inconsistent. However, this was a small proportion of the follow-up period and results were, overall, similar to SCREAM. We used k-modes as the clustering method, whereas other studies have used alternative techniques such as hierarchical clustering,[107] latent class analysis,[108] and consensus clustering.[333] This may limit our capacity to compare findings across studies. Finally, we did not account for the severity of chronic conditions. Such information may have been useful, but with a heterogenous list of conditions, this would have been challenging to ascertain for each condition or to include in the analysis.

Conclusions

In summary, our study shows that there are clinically meaningful clusters of conditions which vary with declining kidney function. Cardiovascular conditions are prominent at low eGFR and associated with adverse outcomes and hence cardiovascular risk assessment and management should be included in the management of these patients. Importantly, chronic pain and depression are also common across the spectrum of kidney function but these conditions currently receive less attention or have fewer available treatment options in CKD. These data illustrate that CKD is not simply a biochemical ‘diagnosis’ but exists as part of the complex interactions between multiple chronic conditions. Health services need to improve the treatment they provide for people with multimorbidity, and adapting how care is organised and delivered may help achieve this. Identification and awareness of clusters of conditions may inform public health initiatives and permit health professionals to provide targeted interventions for patients with CKD.

Ethical approval

For SCREAM, the Regional Ethics Review Board in Stockholm approved the study; informed participant consent was not deemed necessary since all data were de-identified at the Swedish Board of Health and Welfare. For SAIL, Swansea University's Health Information Research Unit Information Governance Review Panel granted approval for this study as part of project 0830.

Competing interests

DN reports fees from GSK, outside the submitted work; PBM reports personal fees and non-financial support from Vifor, personal fees from Astrazeneca, Astellas, Novartis and Janssen grants from Boehringer Ingelheim, personal fees and non-financial support from Pharmacosmos, personal fees and non-financial support from Napp, outside the submitted work; MKS, AM, BDJ, JJC, FSM, PH, AG, CA, and DAM have nothing to disclose.

Availability of data

The data that support the findings of this study are available from SCREAM and SAIL, for collaborative research projects subject to successful application processes and fulfillment of ethics and GDPR regulations. Further details can be found by contacting juan.jesus.carrero@ki.se for SCREAM and at www.saildatabank.com for SAIL.

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Authors' contributions

MKS, PBM, JJC, AG, FSM, BDJ, CA, DAM, and AMC initiated the study. AG had full access to the SCREAM data and MKS had full access to the SAIL data and each of them did the data analysis. MKS drafted the manuscript. All authors contributed to the design of the study; analysis, and interpretation of data; and the critical revision of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Transparency

The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Patient and public involvement and engagement

Ewen Maclean (Patient Support and Advocacy Officer from the charity Kidney Care UK) contributed to the planning of this study and interpretation of the results.

Chapter: 9 Discussion

9.1 Chapter summary

In this chapter, the key findings of the thesis and its potential implications are described. The strengths and limitations of the overall work are discussed, followed by future research planning.

9.2 Key findings

9.2.1 Adverse outcomes amongst people with multimorbidity

Most people with CKD have multiple chronic conditions. People with CKD in SAIL had a median of four chronic conditions in addition to CKD (Chapter 6). The rates of each adverse outcome studied increased with the number of chronic conditions, and there was considerable variation in the observed risk depending on the pattern of conditions. For example, cardiovascular conditions clustered together, particularly amongst patients with low eGFR and these clusters were at the highest risk of cardiovascular events and mortality.

Amongst 68,505 UK Biobank participants, the risk of major adverse kidney events rose with increasing numbers of chronic conditions (Chapter 5). This agreed with a study of 1,463 people with CKD living in Taiwan.[216] By studying a much larger number of people, I could investigate the relationship between multimorbidity and kidney events in greater detail than this previous study. In studying people with and without CKD, I showed that multimorbidity is not just an important risk factor for kidney events for people with pre-existing CKD, but also for people with normal kidney function at baseline. I was also able to study the variation in risk of kidney events with different **combinations** of chronic conditions. It is already known that diabetes mellitus, heart disease, and hypertension are each associated with progressive kidney disease.[352] My study showed that although people with these conditions were at increased risk of kidney events, those with **combinations of conditions** were at much greater risk. This was particularly true for people with multiple **cardiometabolic** conditions. I also found that people with schizophrenia and

bipolar affective disorder were at elevated risk of kidney events. This fits with a previous study which showed that severe mental illness is a risk factor for kidney disease, even amongst those **not** treated with lithium.[353] Overall, these findings suggest that people with multimorbidity – including those **without CKD** – may benefit from their kidney function being monitored to identify kidney dysfunction early.

People with certain chronic conditions are at elevated risk of acute kidney injury (AKI): CKD, diabetes mellitus, hypertension, and heart disease.[354,355] At the beginning of the COVID-19 pandemic, it became clear that these conditions were also risk factors for AKI related to COVID-19.[287,310] I used the ISARIC study to investigate risk factors for AKI in COVID-19 on a larger scale than had been performed previously (Chapter 7). Findings from ISARIC confirmed that **CKD** is the most important risk factor for AKI in people with COVID-19 and other risk factors included hypertension, obesity, diabetes mellitus, and dementia. The study also showed that the high burden of **chronic conditions** amongst **non-white people** put them at heightened risk of AKI and associated mortality when unwell with COVID-19. These findings were consistent with a subsequent study which showed that non-white people and those with cardiometabolic multimorbidity were at the highest risk of cardiovascular complications and death related to COVID-19.[356]

People with CKD and multimorbidity were at heightened risk of emergency hospitalisation long before the COVID-19 pandemic, as shown in Chapter 6. My findings were consistent with a study of 530,771 people with CKD living in Canada.[120] I built on this previous work by comparing people with and without CKD and by showing that **CKD is a key component of multimorbidity** and is associated with an elevated risk of hospitalisation. I also identified **high-risk patterns** of chronic conditions with elevated hospitalisation risk:

- **Cardiometabolic conditions** are known to be associated with an increased risk of mortality,[102] and I demonstrated they were also associated with higher hospitalisation.
- People with **combined physical and mental conditions** are known to be at elevated risk of hospitalisations,[99] and I found this was true amongst people with CKD.

- The concept of **complex multimorbidity** has not been studied frequently before,[104] but I found that people with chronic conditions affecting three or more body systems to be at increased risk of hospitalisation.

These findings may help clinicians appropriately risk assess and potentially prevent hospitalisations, if they can monitor people with CKD and multimorbidity closely and provide treatment for illnesses **before** admission to hospital becomes necessary.

9.2.2 Clusters of chronic conditions

To identify **novel** patterns of chronic conditions, I used statistical clustering techniques (Chapter 8). Many of the clusters I identified were not novel e.g. cardiovascular conditions amongst people with poor kidney function. Cardiometabolic conditions are likely to have common modifiable risk factors such as smoking, sedentary lifestyles, and unhealthy diets. **Preventative strategies** highlighted by my findings (such as public health initiatives to promote healthy eating) are therefore important, but they are well-recognised and these suggestions are not novel.[357] To my knowledge, clustering techniques used elsewhere in healthcare research have similarly failed to identify novel combinations of conditions.

Clustering techniques have been more successfully used to help **risk stratify** patients. They have been used to describe different phenotypes of patients with diabetes mellitus.[358] This approach categorises patients in terms of their risk of diabetic complications, and provides clinicians with the opportunity to provide targeted treatments early. Using chronic conditions for clustering, one study identified clusters at the highest risk of mortality and those associated with greatest healthcare service use.[108] However, not all studies using clustering for risk stratification have shown this approach to be effective. In a study of eight million people living in England, a clusters-based approach of classifying multimorbidity could not identify ways to reduce secondary care costs.[109] In my study, clusters of conditions were associated with cardiovascular events and mortality, but **the number of conditions was equally helpful** at predicting these outcomes. The usefulness of clustering techniques for risk stratification was therefore equivocal.

The final way in which clusters might impact on patient care is by highlighting important patterns of multimorbidity to clinical guideline developers. This is likely to be the most helpful way to inform clinical practice and it is discussed in greater detail in the “Clinicians” section below.

9.3 Implications from findings

9.3.1 Patients and carers

For patients with CKD, the findings from this thesis show how important other chronic conditions are in addition to their kidney disease. Many patients are well-informed about their medical problems and the treatments they take. For others who are not and who want to know more about their health, it may be helpful for them to ask clinicians about their conditions and the treatments they require.

For patients with multimorbidity, it may be helpful for them to know about their kidney function. Given CKD is asymptomatic until the late stages, patients usually only know they have CKD if they are informed by a health professional. Not all patients or their carers will want to know about their kidney function, so research would be required to ascertain what proportion of patients **do** want to know this information. It would also be possible to research whether targeting knowledge of kidney disease improves patient engagement with health care, such as home blood pressure monitoring.

Beyond patients being informed about their health conditions, health literacy is required to allow patients to understand and critique new information given to them. With limited health literacy, patients and carers can find it challenging and even stressful when trying to act on new information provided by healthcare professionals. However, these are skills that can be improved, helping patients’ capacity to do self-management and deal with treatment burden. Improving engagement with chronic disease management has the potential to improve patients’ experiences of health care, but might also assist health care teams. Patients are often the conduit of information between different teams and this could be developed further such as by

patients carrying their electronic health records, as in France with the *Carte Vitale* electronic card.[359]

The findings included in this thesis have been disseminated to patients and carers in a number of ways:

- Via a newly-created patient and public involvement and engagement group for people with kidney disease in the West of Scotland.
- In an interview in the patient-facing magazine Kidney Matters: see https://www.kidneycareuk.org/about-kidney-health/kidney-matters/kidney-matters-issue-18/ .
- Via a short animation which has been shared with patients online.

9.3.2 Policymakers and health care services

Although many people with CKD and multimorbidity are frequently in contact with healthcare services, these services do not always deliver high standards of care. In particular, secondary care services are usually focused on individual conditions, which can make care fragmented. Services might consider improving the treatment of people with multimorbidity by adapting current models and/or by developing new models:

Adapting current care models

- Medical professionals do not always communicate effectively with each other and with patients and carers. Sometimes there are long delays between clinicians reviewing patients and changes to their clinical management being communicated to the wider healthcare team. Improving communication and access to healthcare services for patients may lead to improvements in care and reductions in treatment burden. One option would be agreeing a dedicated healthcare professional who acts as the main bridge between the multi-disciplinary team and the patient or between primary and secondary care.[360]
- Medical training should be adapted to ensure that generalist skills are developed alongside specialist training. For example, renal physicians may be

provided with more training on multimorbidity and treatment strategies for common problems like pain.

Developing new care models

- Given the high complexity of patients with CKD and multimorbidity, GPs might run new clinics with longer appointment times to allow them to explore problems in greater detail than current clinics allow. Inter-disciplinary clinics may also be developed, where two or more specialists review patients together, or GPs work alongside specialists in the same clinic.
- New interventions may be required, such as nurse specialists providing integrated care for patients with multimorbidity.[117]

Making improvements to healthcare is often costly for healthcare services, who usually lack the resources to provide optimal care for all their patients. However, if healthcare services do not adapt to take account of multimorbidity, the onus will remain on patients and their carers to ensure effective management of all their chronic conditions.

Given the challenges of managing patients with multimorbidity once it has developed, there should be a greater emphasis on **preventing** people developing multiple chronic conditions. This should include the prevention of symptoms such as pain and low mood, which have significant impacts on quality of life. The patients at greatest risk of adverse outcomes have cardiometabolic conditions, so public health initiatives should focus on modifiable risk factors for these conditions e.g. cigarette smoking, poor diets, obesity. One of the root causes of these risk factors is socioeconomic deprivation. Addressing inequalities at a societal level may therefore have the greatest impact on preventing multimorbidity. As populations age globally and as multimorbidity becomes more prevalent, healthcare services should prioritise public health measures while planning for how to deliver high standards of care for patients who do develop multimorbidity.

9.3.3 Clinicians

By knowing that people with CKD and multimorbidity are at high risk of adverse outcomes, clinicians should adapt their approaches to caring for these people. For

example, if a patient with CKD and multimorbidity develops symptoms of an infection, prompt review by a clinician and early treatment may make them less likely to require hospitalisation. Although preventing outcomes like cardiovascular events and mortality can be more difficult, recognising at-risk patient groups may help clinicians target them with risk reduction strategies, such as lipid-lowering therapies,[9] renin-angiotensin system inhibitors,[339] sodium-glucose co-transporter-2 (SGLT2) inhibitors,[275] and support to stop smoking.[11] However, it is unclear whether close monitoring or targeted treatments in high-risk clusters would in fact lead to fewer adverse outcomes.

As multimorbidity affects most people with CKD, issues such as polypharmacy and high treatment burden are commonplace. Clinicians treating patients with CKD may be able to deliver better care if multimorbidity is incorporated into clinical guidelines. Three specific findings from this thesis are:

- Patients with CKD and multimorbidity are at high risk of various adverse outcomes. Clinicians should be aware of the vulnerability of these patients and they should have a low threshold for doing clinical reviews.
- Patients with cardiometabolic multimorbidity are at high risk of their kidney function deteriorating. These patients may benefit from having their kidney function monitored, even in the absence of CKD.
- Chronic pain is common in CKD, and when combined with physical conditions it is associated with adverse outcomes. Guidelines should provide clinicians with advice on how to alter the management of chronic pain in the presence of CKD and multimorbidity.

The main international CKD guidelines are provided by KDIGO (Kidney Disease: Improving Global Outcomes).[11] In February 2022, my supervisor Professor Mark and I contacted KDIGO about the upcoming 2022 CKD management guideline. We identified areas in the guideline in which multimorbidity should be taken into account.

9.3.4 Researchers

The findings in this thesis show that in the context of multimorbidity, CKD is a key condition. It is important that **multimorbidity researchers include CKD** as one of

the chronic conditions they study. Only 10% to 60% of people with CKD know that they have it,[43,44] so self-report is not a reliable tool for identifying CKD. A study using English primary care data showed that only 14% of patients with incident CKD had the condition coded in their medical records within a year.[361] Diagnoses of CKD should therefore be derived from blood and urine tests, rather than self-report or codes from medical records.

SGLT2-inhibitor medications have been shown to prevent adverse outcomes in people with proteinuric kidney disease.[343] They have been extensively investigated amongst people with diabetes mellitus and heart failure, but **it is unclear if they are effective and safe in people with multiple chronic conditions**. In the Dapa-CKD trial which investigated the use of dapagliflozin to prevent kidney failure, the mean age was 62 years and 37% of participants had cardiovascular disease.[275] It is not known if SGLT2-inhibitors are effective in older adults and/or people with multimorbidity and if the rates of adverse effects are acceptable e.g. genitourinary infections, ketoacidosis.

Although CKD is a condition which often affects older adults, there is a group of **young patients** who have CKD and multimorbidity, for example people with diabetes and numerous complications. Their lifetime risk of adverse outcomes is significant, and they may have more to gain from improvements in care than older adults. Young people with multimorbidity should therefore be a focus of future research, including into the use of SGLT2-inhibitors.

9.4 Strengths and limitations

The work presented in this thesis has a number of strengths and limitations, which are discussed here.

9.4.1 Strengths

Multiple large datasets from the UK and one from Sweden were used in this thesis. The cohorts have high quality data and they each have diverse characteristics. A recent study using UK Biobank and SAIL suggested that combining information-rich research cohorts and representative routine data is the best way to study

multimorbidity.[157] By comparing findings in different datasets and by using general population cohorts, I was able to comment on the generalisability of my findings to the wider population.

Detailed information was available in the datasets e.g. medications used to treat COVID-19 in ISARIC and numerous blood results for individual patients in SAIL and SCREAM. Rather than just focusing on one adverse outcome, a range of outcomes were studied. Advanced statistical and complex data science techniques were used to perform the analyses. The merits of these techniques were considered carefully and sensitivity analyses were performed, where relevant.

9.4.2 Limitations

The populations studied were based in Northern Europe and were therefore predominantly of white ethnicity. The project may have been improved by using one dataset from a low or middle income country, although it is challenging to find datasets from these settings with the required granularity. Selection bias was introduced because blood tests were required to ascertain exposures (CKD) and outcomes (AKI, kidney events). Observational studies are often hindered by residual confounding, although I made attempts to adjust for the main confounding variables. I investigated how important CKD was as part of a multimorbidity count, but I did not compare this to other specific conditions. Similar associations may have been found if analyses were replicated for conditions such as diabetes mellitus or heart failure. Individual patients' chronic conditions were defined at a single point in time, without accounting for them changing. It would have been interesting to study how conditions evolved over time, but this would have been challenging. The clustering analysis was limited to chronic conditions, without incorporating other variables such as deprivation or body mass index. Factoring in these additional variables may have been informative, but it would have made the analysis and interpretation of the results much more complicated.

9.5 Future directions

9.5.1 Trajectories for patients with CKD and multimorbidity

In this thesis, I have not explored how chronic conditions change over time for individual people with CKD. I would therefore like to study how chronic conditions change in individual patients, particularly as their kidney function declines. I would include patients as they commence dialysis or have a kidney transplant, to determine how multimorbidity changes following these transitions. It may be possible to identify time periods where healthcare teams may be able to intervene to prevent the harms related to multimorbidity.

In a similar way, it would be interesting to study how cluster membership for individual patients changes over time or as their kidney function declines. The potential impact of clusters could also be studied from a health economics perspective, to establish which clusters are associated with the greatest costs to healthcare systems.

9.5.2 Interventions targeted at multimorbidity in CKD patients

Although this thesis describes the vulnerability of people with CKD and multimorbidity to adverse outcomes, intervening to improve care is a greater challenge. A systematic review of multimorbidity interventions demonstrated that the most effective interventions were designed to address depressive symptoms.[117] Given my work has shown that people with CKD, mental health problems, and cardiometabolic conditions are an at-risk group, **these interventions should be trialled in populations with CKD**.

I would propose a randomised controlled trial of a complex intervention targeted at the treatment of depression amongst people with CKD and cardiometabolic conditions. This would require intervention development work,[362] but in theory patients would be randomised into two treatment arms:

1. Usual primary care management of depression i.e. antidepressants, referral for talking therapies.

2. Personalised management of depression, delivered by nurse specialists. These nurses would meet with patients to identify which problems have a negative impact on patients' mental health and make treatment plans to manage these problems. For example, the nurses may support patients to attend social clubs or exercise classes, or refer patients with low appetites for help with their diet.

Possible outcome measures to discuss with patient and public partners would be:

1. The Patient Health Questionnaire (PHQ-9)[363]
2. Healthcare use
    a. Emergency hospitalisations
    b. GP visits

In this way, it may be possible to determine whether providing a targeted intervention could lead to reductions in depressive symptoms and/or healthcare use.

An additional evidence gap is the management of chronic pain amongst people with CKD. More research is required to understand why chronic pain is so highly prevalent in CKD populations and how treatment strategies can be improved. Given current painkiller medications have numerous side effects, there is a pressing need for better treatment options.

9.5.3 Kidney failure risk

A small proportion of people with CKD are at risk of kidney failure requiring treatment (dialysis or transplantation), but identifying these people can be difficult. The **kidney failure risk equation (KFRE)** uses an individual's age, sex, estimated glomerular filtration rate, and urine albumin-creatinine ratio to estimate their risk at two- and five-years.[364] It has been incorporated into clinical guidelines in the UK, which stipulate that GPs should refer to nephrology clinics if the five-year risk of kidney failure is greater than 5%.[39]

It is unclear how effectively this recommendation will be implemented in clinical practice, especially as uACR testing is not always routinely performed.[164] I performed a study using SAIL data, which showed that annual uACR testing rates

were 30% or less amongst people with CKD.[365] Through this paper and other engagement activities with GPs, awareness of albuminuria testing and KFRE will hopefully improve.

Another key factor which may influence the usefulness of KFRE is multimorbidity. KFRE has not been validated in the context of multimorbidity, and its performance may vary depending on the number of chronic conditions or in different patient clusters. Further research is therefore planned to study the tool's validity in the presence of multimorbidity.

9.5.4 Quality of life and treatment burden

This thesis reports on a range of adverse outcomes, but not on patient-reported outcomes, such as health-related quality of life. This can be quantified by tools such as the EQ-5D questionnaire.[366] Future work including these outcomes are planned, which hope to reflect the "patient voice" regarding the reality of living with CKD and multimorbidity. This work will include qualitative approaches, which will assess treatment burden and may identify how care can be improved.

When patients with frailty and multimorbidity are making decisions about their care such as whether they wish to undergo dialysis, treatment burden is a key factor.[143] Future studies should therefore study the relationship between treatment burden, treatment for kidney disease, and quality of life. It is always challenging to reduce treatment burden and improve quality of life, but these ambitious goals should be prioritised in this patient group.

9.6 Conclusion

Multimorbidity is common amongst people with CKD and it is an important risk factor for adverse outcomes. The risk of kidney events, cardiovascular events, hospitalisation, and mortality increases with the number of chronic conditions and varies with specific combinations of conditions. People with multiple **cardiometabolic** conditions are particularly likely to experience these adverse outcomes and these conditions cluster together amongst people with advanced

CKD. Although clusters of conditions were identified in this thesis, they have not revealed novel patterns of multimorbidity and they do not improve risk stratification above counts of conditions.

The clinical management of people with CKD and multimorbidity can be challenging. Efforts to prevent the development of multimorbidity should be prioritised, especially for cardiometabolic conditions. For people with one cardiometabolic condition, it would be useful to know how to prevent them accumulating additional cardiometabolic conditions. For people who have already developed multimorbidity, care models must be improved to account for the complexity of their care, rather than following traditional health care models which focus on individual conditions. Clinical guidelines should specify how treatment should be adapted in the presence of multimorbidity, to help clinicians deliver high standards of care. Chronic pain and depression are common in people with CKD and when combined with physical conditions, are associated with adverse outcomes. Given the evidence gaps which exist in the treatment of chronic pain and depression, researchers and health care services should target these gaps in knowledge and care.

As populations age globally, multimorbidity has become the norm and yet we have not successfully adapted to provide high standards of care for patients and carers.[229] Treating patients with CKD and multimorbidity may be complicated, but if we do not rise to this challenge, we will fail our patients.

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Appendix

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

A list of fields that can be edited in an update can be found here

1 [1 change]. * Review title.

Give the title of the review in English

Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis 2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title. 3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

12/08/2019 4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

12/11/2019 5 [4 changes]. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: No

Review stage	Started	Completed

Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Michael Sullivan Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Sullivan 7. * Named

contact email.

Give the electronic email address of the named contact.

michael.sullivan@glasgow.ac.uk

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

University of Glasgow, Institute of Cardiovascular and medical sciences, BHF Glasgow Cardiovascular Research Centre (GCRC), 126 University Place, Glasgow G12 8TA 9.

Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

07393403276 10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Glasgow
Organisation web address:
https://www.gla.ac.uk/researchinstitutes/icams/ 1 [1 change]. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Michael Sullivan. University of Glasgow
Professor Patrick Mark. University of Glasgow
Dr Bhautesh Jani. University of Glasgow
Professor Frances Mair. University of Glasgow
Dr Alastair Rankin. University of Glasgow 12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None.

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What is the association between multimorbidity and all-cause mortality in people with chronic kidney disease?If the data allow, the review will also assess - in people with chronic kidney disease - the association between multimorbidity and adverse clinical outcomes such as cardiovascular events.

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We will search the following electronic databases: MEDLINE (OVID), EMBASE (OVID), CINAHL Complete (The search strategy will include only terms relating to or describing the review question.EBSCO), The Cochrane Library (OVID), and Scopus.

We shall adapt the entry of the search terms for each of the electronic databases.

Searches will be limited to Human empirical studies, studying adults over the age of 18 in English with no restriction on publication date.

We will supplement our results with searches of reference lists of included studies. 17.

URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

https://www.crd.york.ac.uk/PROSPEROFILES/147424_STRATEGY_20190917.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available 18.

* Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Chronic kidney disease (CKD) is the term used to describe a reduction in kidney function lasting more than three months, that may be caused by a range of conditions. It typically exists in individuals with long-term medical conditions (LTCs) and those with two or more conditions are described to be multi-morbid. CKD and many of the LTCs put individuals at high risk of death, cardiovascular events, hospitalisation for heart failure, progression of renal failure and the need to commence renal replacement therapy (RRT). RRT is defined as renal transplantation or dialysis. 19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria: adults over the age of 18 with chronic kidney disease stages three to five i.e. their estimated glomerular filtration rate is less than 60ml/minute including those requiring renal replacement therapy i.e. haemodialysis, peritoneal dialysis or renal transplantation.Exclusion criteria: children or adolescents aged 18 or under, animal studies and individuals without chronic kidney disease. 20 [1 change]. *

Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Our primary exposure of interest will be multi-morbidity (MM) count i.e. the co-occurrence of ?2 chronic conditions. We will accept any type of MM count, which may include a list of chronic conditions from a range of datasets. Studies that analyse the relationship between a numerical count of MM and our outcomes of interest will be included. Chronic kidney disease itself will not count as a co-morbidity i.e. MM will be CKD plus two or more additional conditions. 2 [1 change]. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

The control group will be people with chronic kidney disease with no chronic conditions or just one comorbidity. A control group must be present for comparison. 22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will include all quantitative empirical studies.

Our focus of interest will be large-scale observational studies, in particular, those derived from electronic health care records and administrative databases sources of patient data.

Review articles, drug intervention studies, qualitative studies, case reports and conference abstracts will be excluded. 23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

All-cause mortality.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Outcomes taken at any time after commencement of observation will be included. 25.

* Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

Cardiovascular deaths, cardiovascular events, heart failure hospitalisations, 40% reduction in eGFR, doubling of serum creatinine or initiation of renal replacement therapy.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Outcomes taken at any time after commencement of observation will be included. 26.

* Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Two of our review authors shall independently screen the titles of studies retrieved using the search strategy to identify studies that potentially meet the inclusion criteria outlined above. Two members of the team will

independently screen abstracts for studies that potentially meet the inclusion and exclusion criteria. Full paper screening, data extraction and analysis will be carried out by two reviewers. Any inter-reviewer disagreements will be discussed and resolved by a third reviewer. 27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Two reviewers will independently assess the risk of bias (quality) in All studies will be assessed using the Newcastle-Ottawa quality assessment scale. The choice of this toolach of the included studies.

was informed by recommendations from the Cochrane Handbook on assessing the quality of nonrandomised studies.

Any inter-reviewer disagreements will be discussed and resolved by a third reviewer. 28.

* Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If metaanalysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

We will conduct a narrative synthesis of findings, detailing the association between CKD, MM count, MM type and our outcomes. We anticipate that outcomes will be expressed as hazard or odds ratios and if possible, we will use Cox regression to analyse the data. Tests for publication bias and heterogeneity will be conducted. If the included studies are sufficiently homogenous in terms of study design, study population, outcomes and data analysis, a meta-analysis will be considered. 29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach. This will depend on the results found. If appropriate data is available, separate analysis will be conducted for age/gender, number and type of chronic conditions. 30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

Yes
Individual patient data (IPD) meta-analysis

No

Intervention

No

Living systematic review

No

Meta-analysis

No

Methodology

No

Narrative synthesis

Yes

Network meta-analysis

No

Pre-clinical

No

Prevention

No

Prognostic

Yes

Prospective meta-analysis (PMA)

No

Review of reviews

No

Service delivery

No

Synthesis of qualitative studies

No

Systematic review

Yes

Other

No

Health area of the review

Alcohol/substance misuse/abuse

No

Blood and immune system

No

Cancer

No

Cardiovascular

Yes

Care of the elderly

No

Child health

No

Complementary therapies

No

COVID-19

No

Crime and justice

No

Dental

No

Digestive system

No

Ear, nose and throat

No

Education

No

Endocrine and metabolic disorders

No

Eye disorders

No

General interest

No

Genetics

No

Health inequalities/health equity

No

Infections and infestations

No

International development

No

Mental health and behavioural conditions

No

Musculoskeletal

No

Neurological

No

Nursing

No

Obstetrics and gynaecology

No

Oral health

No

Palliative care

No

Perioperative care

No

Physiotherapy

No

Pregnancy and childbirth

No

Public health (including social determinants of health)

No

Rehabilitation

No

Respiratory disorders

No

Service delivery

No

Skin disorders

No

Social care

No

Surgery

No

Tropical Medicine

No

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary 32.

* Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved. Scotland

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank. 34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36 [1 change].

Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

chronic kidney disease, dialysis, comorbid, multimorbidity, diabetes, cardiovascular 37.

Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available. 38 [4 changes]. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission. Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

Work is being undertaken as part of Michael Sullivan's PhD. 40 [1 change]. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Published in BMJ Open 30.06.20

Give the link to the published review or preprint.

https://bmjopen.bmj.com/content/10/6/e038401

Appendix Table 1. Read codes to define kidney function and. outcomes

Variable	**Read codes**
GP data Creatinine Values	44J3, 44JF, 44JD, 44JC and 4Q40
GP data emergency hospital admissions	8H2., 8H2R, 8H2F, 8H28, 8H2S, 8H24, 8H2K, h8H2, 8H2B, 8H29, 8H2, |8H21, 8H2V, 8H230, 8H2J, 8H2O, 8H2D, 8H26, 8H2T, 8H2M, 8H2G, 8H2H, 8H2X, 8H2N, 8H2C, 8H2E, 8H2L, 8H27, 8H2A, 8Hb., 8Hd1, 8Hd5, 8Hd3 and 8Hd6
ICD-10 Kidney Replacement Therapy	E85.3, N16.5, N18.0, N18.5, Q60.1, T82.4, T86.1, Y60.2, Y61.2, Y62.2, Y84.1, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2, N18.0, N18.5
OPCS4 Kidney Replacement Therapy	L74.1, L74.2, L74.3, L74.4, L74.5, L74.6, L74.8, L74.9, M01.2, M01.3, M01.4, M01.5, M01.8, M01.9, M02.3, M08.4, M17.2, M17.4, M17.8, M17.9, X40.1, X40.2, X40.3, X40.4, X40.5, X40.6, X40.7, X40.8, X40.9, X41.1, X41.2, X41.8, X41.9, X42.1, X42.8, X42.9, X43.1

Appendix Table 2. Read codes to define laboratory variables and risk factors

Variable	Read Code(s)
Laboratory	
Serum Creatinine	44J33, 44J30, 44J3Z, 44J3., EMISREQ|44J3, 44JF., 44J32, 44JC., 44JD., 44J31, 4Q40.
Total Cholesterol	44P.., 44OE., 44PH., 44PJ., 44PK., 662a., 6879., 44PF., 44PZ., 44P9.
Urine albumin:creatinine ratio	46TC., 44J7.
Smoking	
Never-Smoker	1371., 137L.
Ex-Smoker	1377., 1378., 1379., 137A., 137B., 137F., 137j., 137K., 137l., 137N., 137O., 137S., 9km..
Smoker	137.., 1372., 1373., 1374., 1375., 1376., 137a., 137H., 137J., 137P., 137Q., 137R., 137X., 137Y., 137Z., 9ko..
Body Measurements	
Weight	22A..
Height	229..
Systolic blood pressure	2469., 246N., 246Q., 246S., 246b., 246d., 246e., 246W., 246Y., 246l., 246..

Appendix Table 3. Long-term conditions considered and read code definitions used in Secure Anonymised Information Linkage Databank.

[m]Mental health condition

Long-term condition	Condition Read Codes	Additional Requirements
Hypertension	662G., 662O., 662P., 662q., 662r., 8B26., 8BL0., 8CR4., F4042, F4213, F4504, G2..., G20.., G200., G201., G202., G203., G20z., G21.., G210., G2100, G2101, G210z, G211., G2110, G2111, G211z, G21z., G21z0, G21z1, G21zz, G22.., G220., G221., G222., G22z., G23.., G230., G231., G232., G233., G234., G23z., G24.., G240., G2400, G240z, G241., G2410, G241z, G244., G24z., G24z0, G24z1, G24zz, G2y.., G2z.., G672., Gyu2., Gyu20, Gyu21	
Depression[m]	1B17., 1B1U., 1BT.., 2257, 62T1., 66590, 6G00., 8CAa., 8HHq., 9H90., 9H91., 9H92., 9HA0., E0013, E002., E0021, E002z, E0043, E02y3, E112., E1120, E1121, E1122, E1123, E1124, E1125, E1126, E112z, E113., E1130, E1131, E1132, E1133, E1134, E1135, E1136, E1137, E113z, E118., E11y2, E11z2, E130., E135., E204., E2003, E290., E290z, E291., E2B.., E2B0., E2B1., Eu204, Eu251, Eu32., Eu320, Eu321, Eu322, Eu323, Eu324, Eu325, Eu326, Eu327, Eu328, Eu329, Eu32A, Eu32y, Eu32z, Eu33., Eu330, Eu331, Eu332,	OR Four or more prescriptions for antidepressants issued per year. Medication read Codes: d8... , daD.. , daD1. , daD2. , du61. , du6z. , da9.. , da91. , da92. , da93. , da94. , da95. , da96. , da97. , da98. , da99. , da9A. , da9z. , gde3. , gde4. , gdew. , gdex. , daC.. , daC1. , daC2. , daC3. , daC4. , daC5. , daC6. , daC7. , daC8. , daC9. , daCA. , da4.. , da41. , da42. , da43. , da44. , da45. , da46. , da47. , da48. , da49. , da4A. , da4B. , da4C. , da3.. , da31. , da32. , da33. , da34. , d82.. , d821. , d822. , d82y. , d82z. , d83.. , d831. , d83z. , d7b.. , d7b1. , d7b2. , d7b3. ,

	Eu333, Eu334, Eu33y, Eu33z, Eu341, Eu412, Eu920, ZN120, ZN121, ZN123, ZN124, ZN125	d7b4. , d7b5. , d7b6. , d7b7. , d7b8. , d7b9. , daB.. , daB1. , daB2. , daB3. , daB4. , daB5. , daB6. , daB7. , daB8. , daBy. , daBz. , d85.. , d851. , d852. , d853. , d854. , da8.. , da81. , da82. , da83. , da84. , da85. , da86. , da6.. , da61. , da62. , da63. , da64. , da65. , da66. , da67. , da68. , d81.. , d811. , d81z. , daA.. , daA1. , daA2. , da5.. , da51. , da52. , da53. , da54. , d84.. , d841. , d84z. , d7e.. , d7e1. , d7e2. , d7e3. , d7e4. , d7e5. , d7e6. , d7e7. , d7ew. , d7ex. , d7ez. , da2.. , da21. , da22. , da23. , da24. , da2y. , da2z. , da7.. , da71. , da72. , da73. , da74. , da75. , da76. , da77. , da78. , da79. , da7a. , da7A. , da7b. , da7B. , da7c. , da7C. , da7d. , da7D. , da7e. , da7E. , da7f. , da7F. , da7g. , da7G. , da7h. , da7H. , da7i. , da7I. , da7j. , da7J. , da7k. , da7K. , da7l. , da7L. , da7m. , da7M. , da7n. , da7N. , da7o. , da7O. , da7p. , da7P. , da7q. , da7Q. , da7r. , da7R. , da7s. , da7S. , da7T. , da7U. , da7V. , da7W. , da7X. , da7Y. , da7Z. , d7g.. , d7g1. , d7gz. , daE.. , daE2. , daE4. , daE6.
Asthma	173A., 173c., 173d., 1780, 1O2.., 663d., 663e., 6.63E+02, 6.63E+03, 663f., 663h., 663j., 663m., 663n., 663N., 663N0, 663N1, 663N2, 663O., 663O0, 663p., 663P., 663q., 663Q., 663r., 663s., 663t., 663u., 663U., 663v., 663V., 663P., 663q., 663r., 663u., 663v., 663V0, 663V1, 663V2, 663V3, 663w., 663W., 663x., 663y.,	AND Four or more prescriptions for asthma medication issued per year. Medication read codes: c1... , c3... , c4... , cA... , cl... , c34.. , c341. , c342. , c41.. , c411. , c412. , c413. , c414. , c415. , c416. , c417. , c418. , c41a. , c41A. , c41b. , c41B. , c41c. , c41C. , c41d. , c41e. , c41f. , c41g. , c41h. , c41i. , c41j. , c41k. , c41m. , c1B.. ,

	66Y5., 66Y9., 66YA., 66YC., 66YE., 66YJ., 66YK., 66YP., 66YQ., 66YR., 8793, 8794, 8795, 8796, 8797, 8798, 8B3j., 8CR0., 8791, 9hA.., H3120, H33.., H330., H3300, H3301, H330z, H331., H3310, H3311, H331z, H332., H333., H334., H33z., H33z0, H33z1, H33z2, H33zz, H35y6, H35y7, H47y0	c1B1. , c1B2. , c1B3. , c1B4. , c61.. , c611. , c612. , c613. , c614. , c616. , c617. , c619. , c61a. , c61A. , c61b. , c61B. , c61c. , c61C. , c61d. , c61D. , c61e. , c61E. , c61f. , c61F. , c61g. , c61G. , c61h. , c61H. , c61i. , c61j. , c61J. , c61k. , c61K. , c61l. , c61L. , c61m. , c61M. , c61n. , c61N. , c61O. , c61p. , c61P. , c61q. , c61Q. , c61r. , c61R. , c61s. , c61S. , c61t. , c61T. , c61u. , c61v. , c61V. , c61w. , c61W. , c61x. , c61X. , c61y. , c61Y. , c61z. , c61Z. , c66.. , c661. , c662. , c663. , c664. , c665. , c666. , c667. , c668. , c669. , c66a. , c66A. , c66b. , c66B. , c66c. , c66C. , c66d. , c66D. , c66e. , c66E. , c66f. , c66F. , c66g. , c66G. , c66h. , c66H. , c66I. , c66J. , c66K. , c66L. , c66M. , c66N. , c66P. , c66Q. , c66R. , c66S. , c66T. , c66U. , c66V. , c66W. , c66X. , c66Y. , c66Z. , c63.. , c631. , c63z. , c64.. , c641. , c642. , c643. , c644. , c645. , c647. , c648. , c649. , c64a. , c64A. , c64b. , c64B. , c64c. , c64C. , c64d. , c64D. , c64e. , c64E. , c64F. , c64g. , c64G. , c64h. , c64H. , c64i. , c64I. , c64j. , c64J. , c64k. , c64K. , c64l. , c64L. , c64m. , c64M. , c64n. , c64N. , c64o. , c64p. , c64u. , c64v. , c64w. , c64x. , c64y. , c64z. , c42.. , c421. , c422. , c423. , c424. , c42w. , c42x. , c42y. , c42z. , c69.. , c691. , c692. , c69y. , c69z. , c71.. , c711. , c712. , c713. , c714. , c715. , c716. , c717. , c718. , c719. , c71a. , c71b. , c71c. , c71d. , c71e. , c71f. , c71g. , c71h. , c71i. ,

		c71j. , c71k. , c22.. , c221. , c222. , c223. , c224. , c225. , c226. , c227. , c21.. , c213. , c216. , c15.. , c151. , c152. , c153. , c154. , c15y. , c15z. , c51A. , c51B. , c51i. , c51v. , c51w. , c51x. , c65.. , c651. , c652. , c653. , c654. , c655. , c656. , c657. , c658. , c659. , c65a. , c65A. , c65b. , c65B. , c65c. , c65C. , c65d. , c65D. , c65e. , c65E. , c65f. , c65F. , c65g. , c65G. , c65H. , c65I. , c65J. , c65K. , c65L. , c65M. , c65N. , c65O. , c65P. , c65Q. , c65R. , c65S. , c65T. , c65U. , c65V. , c65W. , c65X. , c65Y. , c65Z. , c1C.. , c1C1. , c1C2. , c1C3. , c1C4. , c1C5. , c1C6. , c1C7. , c1C8. , c1Cy. , c1Cz. , c1c.. , c1c1. , c1c2. , c1c3. , c1cx. , c1cy. , c1cz. , c67.. , c671. , c672. , c673. , c67x. , c67y. , c67z. , c6A.. , c6A1. , c6Az. , o323. , o324. , c1b.. , c1b1. , c1b2. , c1b3. , c1b4. , c31.. , c311. , c312. , c313. , c314. , c315. , c316. , c317. , c318. , c319. , c31A. , c31B. , c31C. , c31D. , c31E. , c31F. , c31G. , c31t. , c31u. , c31v. , c31w. , c31x. , c31y. , c31z. , c23.. , c231. , c23z. , c24.. , c243. , c245. , c246. , c24x. , c24y. , c24z. , c75.. , c752. , c68.. , c681. , c682. , c683. , c684. , cA1.. , cA11. , cA12. , cA13. , cA14. , cA15. , cA16. , cA1y. , cA1z. , c74.. , c741. , c742. , c743. , c744. , c745. , c746. , c747. , c1d.. , c1d2. , ck1.. , ck11. , ck12. , ck13. , ck14. , ck15. , ck16. , c251. , c252. , c254. , c255. , c25v. , c25w. , c25y. , c25z. , c32.. , c321. , c322. , c323. , c324. ,

		c16.. , c161. , c162. , c163. , c164. , c16w. , c16x. , c16y. , c16z. , c17.. , c173. , c17y. , c18.. , c181. , c182. , c183. , c184. , c18y. , c18z. , cl1.. , cl11. , cl1z. , c11.. , c111. , c112. , c113. , c114. , c115. , c116. , c118. , c119. , c11a. , c11b. , c11c. , c11d. , c11D. , c11e. , c11f. , c11g. , c11h. , c11i. , c11j. , c11k. , c11m. , c11n. , c11o. , c11p. , c11q. , c11v. , c11x. , c11y. , c11z. , c12.. , c121. , c122. , c123. , c124. , c125. , c126. , c12w. , c12x. , c12y. , c12z. , c13.. , c131. , c132. , c133. , c134. , c135. , c136. , c137. , c139. , c13a. , c13A. , c13B. , c13C. , c13d. , c13D. , c13e. , c13E. , c13f. , c13F. , c13g. , c13G. , c13h. , c13H. , c13i. , c13I. , c13j. , c13J. , c13K. , c13l. , c13L. , c13m. , c13M. , c13n. , c13N. , c13o. , c13O. , c13p. , c13P. , c13q. , c13Q. , c13r. , c13R. , c13S. , c13T. , c13U. , c13v. , c13V. , c13w. , c13W. , c13x. , c13X. , c13y. , c13Y. , c13z. , c13Z. , c1E.. , c1E1. , c1E2. , c1E3. , c1E4. , c1E5. , c1E6. , c1E7. , c1E8. , c1E9. , c1EA. , c1EB. , c1EC. , c1ED. , c1EE. , c51C. , c51D. , c51E. , c51F. , c51G. , c51H. , c531. , c722. , c723. , c72y. , c72z. , c19.. , c191. , c192. , c193. , c194. , c195. , c196. , c197. , c198. , c199. , c19A. , c19B. , c19z. , c1D.. , c1D1. , c1D2. , c1D3. , c1D4. , c1D5. , c1D6. , c1Du. , c1Dv. , c1Dw. , c1Dx. , c1Dy. , c1Dz. , c14.. , c141. , c142. , c143. , c144. , c145. , c146. , c147. , c148. , c149. , c14a. , c14b. ,

		c14c. , c14e. , c14f. , c14g. , c14h. , c14i. , c14j. , c14k. , c14r. , c14s. , c14t. , c14u. , c14v. , c14w. , c14x. , c14y. , c14z. , c43.. , c431. , c432. , c433. , c434. , c435. , c436. , c437. , c438. , c439. , c43a. , c43A. , c43b. , c43B. , c43c. , c43d. , c43e. , c43f. , c43g. , c43h. , c43i. , c43j. , c43k. , c43m. , c43n. , c43o. , c43p. , c43q. , c43r. , c43s. , c43t. , c43u. , c43v. , c43w. , c43x. , c43y. , c43z. , c51t. , c51u. , c33.. , c331. , c332. , c333. , c33x. , c33y. , c33z. , c1a.. , c1a1. , c1a2. , c1a3. , c1a4. , c1a5. , cA2.. , cA21. , cA22.
Coronary Heart Disease	14AL., G3..., G30B., G31.., G310., G3110, G312., G31y., G31y0, G31y1, G31y2, G31y3, G31yz, G32.., G33z., G33z0, G33z1, G33z2, G33z3, G33z4, G33z5, G33z6, G33z7, G33zz, G34.., G340., G3400, G3401, G34.., G340., G3400, G3401, G3412, G342., G343., G344., G34y., G34y0, G34y1, G34yz, G34z., G34z0, G35.., G350., G351., G353., G35X., G36.., G360., G361., G362., G363., G364., G365., G366., G38.., G380., G381., G382., G383., G384., G38z., G3y.., G3z.., G501., G5y2., Gyu3., Gyu31, Gyu32, Gyu33, Gyu35, Gyu36	
Diabetes Mellitus	13AB., 13AC., 13B1., 1434, 14F4., 2BBF., 2BBk., 2BBL., 2BBl., 2BBo., 2BBP., 2BBQ., 2BBR., 2BBr., 2BBS., 2BBT., 2BBV., 2BBW., 2BBX., 2G510, 2G5A., 2G5B.,	

	2G5C., 2G5E., 2G5F., 2G5G., 2G5H., 2G5I., 2G5J., 2G5K., 2G5L., 2G5V., 2G5W., 3881, 3882, 3883, 42c.., 42c0., 42c1., 42c2., 42W.., 42W1., 42W2., 42W3., 42WZ., 44V3., 66A.., 66A1., 66A2., 66A3., 66A4., 66A5., 66A6., 66A7., 66A70, 66A71, 66A8., 66A9., 66Aa., 66AA., 66Ab., 66AB., 66Ac., 66AC., 66Ad., 66AD., 66Ae., 66Af., 66Ag., 66Ah., 66AH., 66AH0, 66Ai., 66AI., 66Aj., 66AJ., 66AJ0, 66AJ1, 66AJ2, 66AJ3, 66AJz, 66Ak., 66AK., 66Al., 66AL., 66Am., 66AM., 66An., 66AN., 66Ao., 66Ap., 66AP., 66Aq., 66AQ., 66AR., 66AS., 66AT., 66AU., 66AV., 66AW., 66AX., 66AY., 66AZ., 6761, 7L198, 8A12., 8A13., 8A17., 8A19., 8B3l., 8CA41, 8CP2., 8CR2., 8CS0., C10.., C100., C1000, C1001, C100z, C101., C1010, C1011, C101y, C101z, C102., C1020, C1021, C102z, C103., C1030, C1031, C103y, C103z, C104., C1040, C1041, C104y, C104z, C105., C1050, C1051, C105y, C105z, C106., C1060, C1061, C106y, C106z, C107., C1070, C1071, C1072, C1073, C1074, C107y, C107z, C108., C1080, C1081, C1082, C1083, C1084, C1085, C1086, C1087, C1088, C1089, C108A, C108B, C108C, C108D, C108E, C108F, C108G, C108H, C108J, C108y, C108z, C109., C1090, C1091, C1092, C1093, C1094, C1095, C1096, C1097,	

	C1099, C109A, C109B, C109C, C109D, C109E, C109F, C109G, C109H, C109J, C109K, C10A., C10A0, C10A1, C10A2, C10A3, C10A4, C10A5, C10A6, C10A7, C10AW, C10AX, C10B., C10B0, C10C., C10D., C10E., C10E0, C10E1, C10E2, C10E3, C10E4, C10E5, C10E6, C10E7, C10E8, C10E9, C10EA, C10EB, C10EC, C10ED, C10EE, C10EF, C10EG, C10EH, C10EJ, C10EK, C10EL, C10EM, C10EN, C10EP, C10EQ, C10ER, C10F., C10F0, C10F1, C10F2, C10F3, C10F4, C10F5, C10F6, C10F7, C10F9, C10FA, C10FB, C10FC, C10FD, C10FE, C10FF, C10FG, C10FH, C10FJ, C10FK, C10FL, C10FM, C10FN, C10FP, C10FQ, C10FR, C10FS, C10G., C10G0, C10H., C10H0, C10M., C10M0, C10N., C10N0, C10N1, C10y., C10y0, C10y1, C10yy, C10yz, C10z., C10z0, C10z1, C10zy, C10zz, C11y0, Cyu2., Cyu20, Cyu21, Cyu22, Cyu23, F1711, F3450, F35z0, F372., F3720, F3721, F3722, F3813, F3y0., F420., F4200, F4201, F4202, F4203, F4204, F4205, F4206, F4207, F4208, F420z, F4407, F4640, G73y0, K01x1, L1805, L1806, L1807, L180X, Lyu29, M0372, M2710, M2711, M2712, N0300, N0301, Q441., R0542, R0543	

Thyroid Disease	22H2., 22H3., 22H4., 66B.., 66B1., 66B2., 66B3., 66B4., 66B5., 66B7., 66B8., 66B9., 66BB., 66BZ., 8CR5., C0..., C00.., C000., C00z., C01.., C010., C011., C01z., C03.., C03y., C03y0, C03y1, C03z., C04.., C040., C041., C0410, C041z, C042., C043., C0430, C0431, C0432, C043z, C044., C047., C04y., C04z., C04z0, C04z1, C05.., C050., C0500, C0501, C0502, C050z, C051., C052., C053., C054., C05y., C05y4, C05z., C06.., C060., C061., C062., C063., C0630, C0631, C063z, C06y., C06y0, C06y1, C06yz, C06z., C0A.., C0A0., C0A1., C0A2., C0A3., C0A4., C0A5., C0AX., C1343, C3A.., Cyu1., Cyu10, Cyu11, Cyu12, Cyu14, Cyu15, Cyu4J, F11x5, F1441, F3814, L1810, PK251, Q4337	
Connective Tissue Disease	14G1., 669.., 6691, 6692, 6693, 6697, 6699, 669Z., 66c0., AD61., C34.., C340., C341., C3410, C3411, C341z, C342., C343., C344., C345., C34y., C34y0, C34y1, C34y2, C34y3, C34y4, C34y5, C34yz, C34z., C394., F371., F3710, F3711, F3712, F371z, F3961, F3963, F3964, F3966, F3967, F4A32, G5573, G5yA., G5y8., G75.., G750., G751., G7510, G751z, G752., G7520, G752z, G753., G754., G755., G7550, G7551, G7552, G755z, G756., G7560, G7561, G756z, G757., G758., G759., G75X., G75z., H570., H572., H57y1,	

	H57y3, H57y4, K01x3, K01x4, K0B40, M1601, M1602, N00.., N000., N0000, N0001, N0002, N0003, N0004, N0005, N000z, N001., N0010, N0011, N0012, N002., N003., N0030, N0031, N003X, N004., N005., N00y., N00y0, N00y1, N00z., N012., N0120, N0121, N0122, N0123, N0124, N0125, N0126, N0127, N012x, N012y, N012z, N02.., N020., N0200, N0201, N0202, N0203, N0204, N0205, N0206, N0207, N020x, N020y, N020z, N021., N0210, N0211, N0212, N0213, N0214, N0215, N0216, N0217, N021x, N021y, N021z, N022., N0220, N0221, N0222, N0223, N0224, N0225, N0226, N0227, N022x, N022y, N022z, N023., N0230, N0231, N0232, N0233, N0234, N0235, N0236, N0237, N0238, N023x, N023y, N023z, N024., N02y., N02y0, N02y1, N02y2, N02y3, N02y4, N02y5, N02y6, N02y7, N02y8, N02yx, N02yy, N02yz, N02z., N02z0, N02z1, N02z2, N02z3, N02z4, N02z5, N02z6, N02z7, N02z8, N02z9, N02zA, N02zB, N02zC, N02zD, N02zE, N02zF, N02zG, N02zH, N02zJ, N02zK, N02zL, N02zM, N02zN, N02zP, N02zQ, N02zR, N02zS, N02zT, N02zx, N02zy, N02zz, N03.., N030., N0302, N031., N032., N036., N03x., N03x0, N03x1, N03x2, N03x3, N03x4, N03x5, N03x6, N03x7, N03x8, N03x9, N03xA, N03xB, N03xC, N03xD, N03xE,	

	N03xF, N03xG, N03xH, N03xJ, N03xK, N03y., N03z., N0237, N0238, N023x, N023y, N023z, N024., N02y., N02y0, N02y1, N02y2, N02y3, N02y4, N02y5, N02y6, N02y7, N02y8, N02yx, N02yy, N02yz, N02z., N02z0, N02z1, N02z2, N02z3, N02z4, N02z5, N02z6, N02z7, N02z8, N02z9, N02zA, N02zB, N02zC, N02zD, N02zE, N02zF, N02zG, N02zH, N02zJ, N02zK, N02zL, N02zM, N02zN, N02zP, N02zQ, N02zR, N02zS, N02zT, N02zx, N02zy, N02zz, N03.., N030., N0302, N031., N032., N036., N03x., N03x0, N03x1, N03x2, N03x3, N03x4, N03x5, N03x6, N03x7, N03x8, N03x9, N03xA, N03xB, N03xC, N03xD, N03xE, N03xF, N03xG, N03xH, N03xJ, N03xK, N03y., N03z., N023x, N04.., N040., N0400, N0401, N0402, N0403, N0404, N0405, N0406, N0407, N0408, N0409, N040A, N040B, N040C, N040D, N040E, N040F, N040G, N040H, N040J, N040K, N040L, N040M, N040N, N040P, N040Q, N040R, N040S, N040T, N041., N042., N0420, N0421, N0422, N042z, N043., N0430, N0431, N0432, N0433, N043z, N0451, N0452, N0453, N0454, N0455, N0456, N047., N04X., N04y., N04y2, N04y3, N04yz, N04z., N0505, N060., N0600, N0601, N0602, N0603, N0604, N0605, N0606, N0607, N0608, N0609, N060z, N062., N0620, N0621, N0622, N0623,	

	N0624, N0625, N0626, N0627, N0628, N0629, N062z, N063., N0630, N0631, N0632, N0633, N0634, N0635, N0636, N0637, N0638, N0639, N063z, N065., N0650, N0651, N0652, N0653, N0654, N0655, N0656, N0657, N0658, N0659, N065A, N065z, N068., N069., N06y., N06y0, N06y1, N06y2, N06y3, N06y4, N06y5, N06y6, N06y7, N06y8, N06y9, N06yz, N06zA, N06zB, N06zz, N090W, N092., N0920, N0921, N0922, N0923, N0924, N0925, N0926, N0927, N0928, N0929, N092A, N092B, N092C, N092D, N092E, N092F, N092G, N092H, N092J, N092K, N092L, N092M, N092N, N092P, N092Q, N092R, N092S, N092T, N092U, N092V, N092z, N093., N0930, N0931, N0932, N0933, N0934, N0935, N0936, N0937, N0938, N0939, N093z, N0y.., N0z.., N20.., N200., N2208, N235., N2432, Nyu00, Nyu1., Nyu10, Nyu11, Nyu12, Nyu13, Nyu14, Nyu15, Nyu16, Nyu17, Nyu18, Nyu19, Nyu1A, Nyu1B, Nyu1C, Nyu1D, Nyu1E, Nyu1F, Nyu1G, Nyu4., Nyu40, Nyu41, Nyu42, Nyu43, Nyu44, Nyu45, Nyu46, Nyu47, Nyu48, Nyu49, Nyu4A, Nyu4B, Nyu4C, Nyu4D, Nyu4E, Nyu4F	
Chronic Obstructive Pulmonary Disease	66YB., 66Yd., 66YD., 66Ye., 66Yf., 66Yg., 66Yh., 66Yi., 66YI., 66YL., 66YM., 66YS., 66YT., 8CR1., H3..., H30.., H300., H301., H302., H30z., H31.., H310., H3100,	

	H3101, H310z, H311., H3110, H3111, H311z, H312., H3120, H3121, H3122, H312z, H313., H31y., H31y0, H31y1, H31yz, H31z., H32.., H320., H3200, H3201, H3202, H3203, H320z, H321., H322., H32y., H32y0, H32y1, H32y2, H32yz, H32z., H36.., H37.., H38.., H39.., H3y.., H3y0., H3y1., H3z.., H4640, H4641, Hyu3., Hyu30, Hyu31	
Anxiety[m]	285.., 286.., 1466, 1B13., 225J., 8G94., E2..., E20.., E200., E2000, E2001, E2002, E2003, E2004, E2005, E200z, E201., E2010, E2011, E2012, E2013, E2014, E2015, E2016, E2017, E2018, E2019, E201A, E201B, E201C, E201z, E202., E2020, E2021, E2022, E2023, E2024, E2025, E2026, E2027, E2028, E2029, E202A, E202B, E202C, E202D, E202E, E202z, E203., E2030, E2031, E203z, E204., E205., E206., E207., E20y., E20y0, E20y1, E20y2, E20y3, E20yz, E20z., E21.., E210., E211., E2110, E2111, E2112, E2113, E211z, E212., E2120, E2121, E2122, E212z, E213., E214., E2140, E2141, E214z, E215., E2150, E2151, E2152, E2153, E215z, E216., E217., E21y., E21y0, E21y1, E21y2, E21y3, E21y4, E21y5, E21y6, E21y7, E21yz, E21z., E26.., E260., E2600, E2601, E260z, E261., E2610, E2611, E2612, E2613, E2614, E2615, E261z,	OR Four or more prescriptions for anxiolytics issued per year. Medication read codes: d2... , d22.. , d221. , d222. , d22y. , d22z. , d23.. , d231. , d232. , d23y. , d23z. , d2f.. , d2f1. , d2f2. , d2f3. , d2f4. , d2f5. , d24.. , d241. , d242. , d243. , d244. , d245. , d246. , d247. , d248. , d249. , d24a. , d24b. , d24c. , d24d. , d24e. , d24f. , d24g. , d24h. , d24i. , d24j. , d26.. , d261. , d262. , d263. , d264. , d265. , d266. , d267. , d268. , d21.. , d211. , d212. , d213. , d214. , d215. , d216. , d217. , d218. , d219. , d21a. , d21A. , d21b. , d21B. , d21c. , d21C. , d21d. , d21D. , d21e. , d21E. , d21f. , d21F. , d21g. , d21G. , d21h. , d21J. , d21k. , d21l. , d21m. , d21n. , d21o. , d21p. , d21q. , d21r. , d21s. , d21t. , d21u. , d21v. , d21y. , d21z. , o53.. , o531. , o532. , o533. , o534. , o535. , d28.. , d281. , d282. , d283. , d284. , d285. , d28x. , d28y. , d28z. , d29.. , d291. , d292. , d29y. , d29z. , d2a.. , d2a1. , d2a2. , d2a3. , d2a4. , d2a5. ,

	E262., E2620, E2621, E2622, E2623, E262z, E263., E2630, E263z, E264., E2640, E2642, E2643, E2644, E2645, E264z, E265., E2650, E2651, E2652, E2653, E265z, E266., E267., E26y., E26y0, E26yz, E26z., E278., E2780, E2781, E2782, E278z, E28.., E280., E281., E282., E283., E2830, E2831, E283z, E284., E28z., E29.., E2900, E2920, E2921, E2922, E2923, E2924, E2925, E292y, E292z, E293., E2930, E2931, E2932, E293z, E294., E29y., E29y0, E29y1, E29y2, E29y3, E29y4, E29y5, E29yz, E29z., E292., Eu054, Eu4.., Eu40., Eu400, Eu401, Eu402, Eu403, Eu40y, Eu40z, Eu41., Eu410, Eu411, Eu412, Eu413, Eu41y, Eu41z, Eu42., Eu420, Eu421, Eu422, Eu42y, Eu42z, Eu43., Eu430, Eu431, Eu432, Eu43y, Eu43z, Eu44., Eu440, Eu441, Eu442, Eu443, Eu444, Eu445, Eu446, Eu447, Eu44y, Eu44z, Eu45., Eu450, Eu451, Eu452, Eu453, Eu454, Eu455, Eu45y, Eu45z, Eu46., Eu460, Eu461, Eu46y, Eu46z, Eu930, Eu931, Eu932, M240E, Eu45., Eu450, Eu451, Eu455, Eu45y, Eu45z, Eu46., ZN114, ZS7C7	d2a6. , d2a7. , d2az. , do41. , d2b.. , d2b1. , d2b2. , d2by. , d2bz. , d2c.. , d2c1. , d2c2. , d2c3. , d2c4. , d2c5. , d2c6. , d2d.. , d2d1. , d2d2. , d2d3. , d2d4. , d2d5. , d2d6. , d2d7. , d27.. , d271. , d272. , d27y. , d27z. , d2e.. , d2e1. , d2ez.
Irritable Bowel Syndrome	14CF., J521., J5210, J529., J52y., J52yz, J52z., Jyu53	

Cancer	1O0.., 7G03K, A7886, A788W, A7898, B0..., B00.., B000., B0000, B0001, B000z, B001., B0010, B0011, B001z, B002., B0020, B0021, B0022, B0023, B002z, B003., B0030, B0031, B0032, B0033, B003z, B004., B0040, B0041, B0042, B0043, B004z, B005., B006., B007., B00y., B00z., B00z0, B00z1, B00zz, B01.., B010., B0100, B010z, B011., B0110, B0111, B011z, B012., B013., B0130, B0131, B013z, B014., B015., B016., B017., B01y., B01z., B02.., B020., B021., B022., B023., B02y., B02z., B03.., B030., B031., B03y., B03z., B04.., B040., B041., B042., B04y., B04z., B05.., B050., B051., B0510, B0511, B0512, B0513, B051z, B052., B053., B054., B055., B0550, B0551, B055z, B056., B05y., B05z., B06.., B060., B0600, B0601, B0602, B060z, B061., B062., B0620, B0621, B0622, B0623, B062z, B063., B064., B0640, B0641, B064z, B065., B066., B067., B06y., B06y0, B06yz, B06z., B07.., B070., B071., B0710, B0711, B071z, B072., B0720, B0721, B072z, B073., B0730, B0731, B0732, B073z, B074., B07y., B07z., B08.., B080., B081., B082., B083., B084., B08y., B08z., B0z.., B0z0., B0z1., B0z2., B0zy., B0zz., B1..., B10.., B100., B101., B102., B103., B104., B105., B106., B107., B10y., B10z., B11.., B110., B1100, B1101,	

	B110z, B111., B1110, B1111, B111z, B112., B113., B114., B115., B116., B117., B118., B119., B11y., B11y0, B11y1, B11yz, B11z., B12.., B120., B121., B122., B123., B124., B12y., B12z., B13.., B130., B131., B132., B133., B134., B135., B136., B137., B138., B139., B13y., B13z., B14.., B140., B141., B142., B1420, B143., B14y., B14z., B15.., B150., B1500, B1501, B1502, B1503, B150z, B151., B1510, B1511, B1512, B1513, B1514, B151z, B152., B153., B15z., B16.., B160., B161., B1610, B1611, B1612, B1613, B161z, B162., B163., B16y., B16z., B17.., B170., B171., B172., B173., B174., B175., B176., B17y., B17y0, B17yz, B17z., B18.., B180., B1800, B1801, B1802, B180z, B181., B182., B18y., B18y0, B18y1, B18y2, B18y3, B18y4, B18y5, B18y6, B18y7, B18yz, B18z., B1z.., B1z0., B1z1., B1z10, B1z11, B1z1z, B1z2., B1zy., B1zz., B2..., B20.., B200., B2000, B2001, B2002, B2003, B200z, B201., B2010, B2011, B2012, B2013, B201z, B202., B203., B204., B205., B206., B20y., B20z., B21.., B210., B211., B212., B213., B2130, B2131, B2132, B2133, B213z, B214., B215., B21y., B21z., B22.., B220., B2200, B2201, B220z, B221., B2210, B2211, B221z, B222., B2220, B2221, B222z, B223., B2230, B2231, B223z, B224.,	

	B2240, B2241, B224z, B225., B226., B22y., B22z., B23.., B230., B231., B232., B23y., B23z., B24.., B240., B241., B2410, B2411, B2412, B2413, B2414, B241z, B242., B243., B24X., B24y., B24z., B25.., B26.., B2z.., B2z0., B2zy., B2zz., B3..., B30.., B300., B3000, B3001, B3002, B3003, B3004, B3005, B3006, B3007, B3008, B3009, B300A, B300B, B300C, B300z, B301., B302., B3020, B3021, B3022, B302z, B303., B3030, B3031, B3032, B3033, B3034, B3035, B303z, B304., B3040, B3041, B3042, B3043, B3044, B304z, B305., B3050, B3051, B3052, B3053, B3054, B3055, B3056, B3057, B3058, B3059, B305A, B305B, B305C, B305D, B305z, B306., B3060, B3061, B3062, B3063, B3064, B3065, B306z, B307., B3070, B3071, B3072, B307z, B308., B3080, B3081, B3082, B3083, B3084, B3085, B3086, B3087, B3088, B3089, B308A, B308B, B308C, B308D, B308z, B309., B30W., B30X., B30z., B30z0, B31.., B310., B3100, B3101, B3102, B3103, B3104, B3105, B310z, B311., B3110, B3111, B3112, B3113, B3114, B3115, B311z, B312., B3120, B3121, B3122, B3123, B3124, B3125, B3126, B312z, B313., B3130, B3131, B3132, B3133, B313z, B314., B3140, B3141, B314z, B315., B3150, B3151, B3152, B3153, B315z, B316.,	

	B317., B31y., B31z., B31z0, B32.., B320., B321., B322., B3220, B3221, B322z, B323., B3230, B3231, B3232, B3233, B3234, B3235, B323z, B324., B3240, B3241, B324z, B325., B3250, B3251, B3252, B3253, B3254, B3255, B3256, B3257, B3258, B325z, B326., B3260, B3261, B3262, B3263, B3264, B3265, B326z, B327., B3270, B3271, B3272, B3273, B3274, B3275, B3276, B3277, B3278, B3279, B327z, B32y., B32y0, B32z., B33.., B330., B331., B3310, B3311, B3312, B332., B3320, B3321, B3322, B332z, B333., B3330, B3331, B3332, B3333, B3334, B3335, B333z, B334., B3340, B3341, B334z, B335., B3350, B3351, B3352, B3353, B3354, B3355, B3356, B3357, B3358, B3359, B335A, B335z, B336., B3360, B3361, B3362, B3363, B3364, B3365, B336z, B337., B3370, B3371, B3372, B3373, B3374, B3375, B3376, B3377, B3378, B3379, B337z, B338., B339., B33X., B33y., B33z., B33z0, B33z1, B34.., B340., B3400, B3401, B340z, B341., B342., B343., B344., B345., B346., B347., B34y., B34y0, B34yz, B34z., B35.., B350., B3500, B3501, B350z, B35z., B35z0, B35zz, B3y.., B3z.., B4..., B40.., B41.., B410., B4100, B4101, B410z, B411., B412., B41y., B41y0, B41y1, B41yz, B41z., B42.., B420., B43.., B430., B4300,	

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	B5244, B5245, B5246, B524W, B524X, B525., B52W., B52X., B52y., B52z., B53.., B54.., B540., B5400, B5401, B540z, B541., B542., B5420, B5421, B542z, B543., B544., B545., B5450, B5451, B5452, B545z, B546., B54X., B54y., B54z., B55.., B550., B5500, B5501, B5502, B5503, B5504, B5505, B550z, B551., B5510, B5511, B5512, B551z, B552., B553., B5530, B5531, B5532, B553z, B554., B555., B55y., B55y0, B55y1, B55y2, B55yz, B55z., B56.., B560., B5600, B5601, B5602, B5603, B5604, B5605, B5606, B5607, B5608, B5609, B560z, B561., B5610, B5611, B5612, B5613, B5614, B5615, B5616, B5617, B5618, B5619, B561z, B562., B5620, B5621, B5622, B5623, B5624, B562z, B563., B5630, B5631, B5632, B5633, B563z, B564., B5640, B5641, B5642, B564z, B565., B5650, B5651, B5652, B5653, B5654, B565z, B56y., B56z., B57.., B570., B571., B572., B573., B574., B5740, B5741, B5742, B574z, B575., B5750, B5751, B575z, B576., B5760, B5761, B5762, B576z, B577., B57y., B57z., B58.., B580., B581., B5810, B5811, B5812, B581z, B582., B5820, B5821, B5822, B5823, B5824, B5825, B5826, B582z, B583., B5830, B5831, B5832, B583z, B584., B585., B5850, B586., B587., B58y., B58y0,	

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	B67y0, B67yz, B67z., B68.., B680., B681., B682., B68y., B68z., B69.., B690., B691., B692., B6y.., B6y0., B6y1., B6z.., B6z0., B831., B8310, B8311, ByuFA, BB2K., BBG4., BBG5., BBGN., BBGP., BBm1., BBm4., BBM6., BBM7., BBM8., BBmA., BBmB., BBmC., BBmE., BBmF., BBmG., BBmK., BBmz., BBN0., BBN1., BBN2., BBN3., BBNz., BBrA6, BBrA7, BBrA8, BBs.., BBs0., BBS1., BBS2., BBs4., BBs5., BBsz., ByuD., ByuD4, ByuDA, ByuDB, BBR.., BBr0., BBr00, BBr01, BBr02, BBr03, BBr04, BBr0z, BBR1., BBr10, BBr1z, BBr2., BBr20, BBr21, BBr22, BBr23, BBr24, BBr25, BBr26, BBr27, BBr2z, BBr3., BBr30, BBr3z, BBR4., BBr40, BBr41, BBr42, BBr4z, BBR5., BBr50, BBr5z, BBR6., BBr60, BBr61, BBr62, BBr63, BBr64, BBr65, BBr66, BBr67, BBr68, BBr6z, BBR7., BBr70, BBr7z, BBr8., BBr80, BBr8z, BBr9., BBr90, BBr91, BBr92, BBr93, BBr94, BBr9z, BBrA., BBrA0, BBrA1, BBrA2, BBrA4, BBrA5, BBrAz, BBRz., ByuD5, ByuD6, ByuD7, ByuD8, ByuD9, BBg1., BBg10, BBg2., BBg3., BBg7., BBg8., BBg9., BBgA., BBgB., BBgC., BBgD., BBgE., BBgF., BBgG., BBgH., BBgJ., BBgK., BBgL., BBgM., BBgR., BBgS., BBgT., BBgV., BBgz., BBK.., BBk0., BBk1., BBK2., BBK3., BBk4., BBk5., BBk6., BBk7., BBk8., BBKz.,	

	BBM5., BBM9., BBmD., BBmH., BBQ.., BBQ0., BBQz., BBV0., BBV2., ByuD1, ByuD2, ByuD3, ByuDC, ByuDD, ByuDE, ByuDF, BBJ.., BBJ0., BBJ1., BBj10, BBj11, BBj2., BBJ3., BBj4., BBJ5., BBJ6., BBj60, BBj61, BBj62, BBJ7., BBJ8., BBJ9., BBJA., BBJz., ByuD0, BB..., BB0.., BB02., BB03., BB07., BB08., BB09., BB0A., BB0z., BB1.., BB12., BB13., BB14., BB16., BB17., BB18., BB19., BB1A., BB1B., BB1C., BB1D., BB1E., BB1F., BB1G., BB1H., BB1J., BB1K., BB1L., BB1M., BB1N., BB2.., BB20., BB22., BB24., BB26., BB2A., BB2B., BB2C., BB2D., BB2E., BB2F., BB2G., BB2H., BB2J., BB2M., BB2N., BB2z., BB3.., BB30., BB31., BB32., BB33., BB34., BB35., BB36., BB3z., BB4.., BB41., BB43., BB46., BB47., BB48., BB49., BB4A., BB50., BB500, BB52., BB520, BB53., BB54., BB55., BB56., BB57., BB58., BB5a1, BB5B., BB5B4, BB5C., BB5c0, BB5C0, BB5c2, BB5d1, BB5f., BB5f1, BB5f2, BB5f3, BB5f6, BB5f7, BB5h., BB5hz, BB5J., BB5j3, BB5j4, BB5K., BB5L1, BB5L2, BB5L3, BB5M1, BB5P., BB5Q., BB5R., BB5R0, BB5R1, BB5R2, BB5R3, BB5R4, BB5R5, BB5R6, BB5R8, BB5R9, BB5RA, BB5Rz, BB5S., BB5Sz, BB5T1, BB5U1, BB5U2, BB5V1, BB5V3, BB5V5, BB5V7, BB5W1, BB5X1, BB5y., BB5y0, BB5y1,	

	BB5y3, BB5y5, BB5y6, BB6.., BB60z, BB611, BB621, BB63., BB64., BB65., BB66., BB67., BB68., BB6A1, BB7.., BB70., BB71., BB7z., BB8.., BB80., BB801, BB81., BB812, BB815, BB818, BB819, BB81A, BB81B, BB81E, BB81H, BB81J, BB81K, BB81L, BB81M, BB81z, BB821, BB83., BB84., BB85., BB850, BB851, BB85z, BB8z., BB9.., BB90., BB91., BB910, BB911, BB92., BB93., BB94., BB96., BB98., BB9B., BB9C., BB9D., BB9E0, BB9F., BB9G., BB9H., BB9J., BB9L., BB9M., BB9z., BBa.., BBA.., BBA1., BBA2., BBa3., BBa4., BBAz., BBB.., BBB0., BBB1., BBB2., BBB3., BBb4., BBB4., BBb5., BBB5., BBb7., BBB7., BBb8., BBb9., BBbA., BBbD., BBbE., BBbz., BBBz., BBc.., BBC.., BBc0., BBC0., BBc00, BBc1., BBC11, BBC12, BBC1z, BBc2., BBC2., BBc3., BBC3., BBC30, BBc4., BBC4., BBc5., BBC5., BBC6., BBC61, BBC6z, BBc8., BBc9., BBCA., BBCB., BBCC., BBcD., BBCD., BBCG., BBcz., BBCz., BBd.., BBd0., BBd1., BBd5., BBd7., BBd8., BBD8., BBd9., BBDA., BBdB., BBDB., BBDC., BBDD., BBDE., BBDF., BBdz., BBDz., BBe.., BBE.., BBe0., BBE0., BBe1., BBE2., BBe3., BBe4., BBe5., BBe6., BBe7., BBE7., BBe8., BBE8., BBe9., BBeA., BBEa., BBEF., BBez., BBf.., BBF.., BBf0., BBF0., BBf1., BBF1.,	

	BBf2., BBF2., BBF3., BBF4., BBF5., BBF6., BBfz., BBFz., BBg.., BBG.., BBG1., BBG2., BBG3., BBg6., BBG8., BBG9., BBGA., BBGB., BBGC., BBGD., BBGE., BBGF., BBGG., BBGH., BBGJ., BBGK., BBGL., BBGM., BBgN., BBgP., BBgQ., BBGz., BBh.., BBH.., BBh0., BBH0., BBh1., BBH1., BBh2., BBhz., BBHz., BBHZ., BBj.., BBj1., BBJ2., BBj3., BBJ4., BBj5., BBj6., BBj7., BBj8., BBJB., BBJB0, BBJB1, BBJB2, BBJB3, BBJBz, BBJC., BBJD., BBJE., BBJF., BBJH., BBjz., BBk.., BBK0., BBK00, BBK01, BBK02, BBK03, BBK04, BBK05, BBK06, BBK07, BBK0z, BBK1., BBK10, BBK11, BBK1z, BBk2., BBK20, BBK21, BBK2z, BBk3., BBK30, BBK34, BBK35, BBK38, BBK3z, BBkz., BBL.., BBl1., BBL1., BBL2., BBL3., BBL4., BBL5., BBL6., BBL70, BBL71, BBL72, BBL73, BBL9., BBLA., BBLB., BBLC., BBLC0, BBLC1, BBLCz, BBLD., BBLE., BBLG., BBLH., BBLJ., BBLz., BBm.., BBM.., BBm0., BBM01, BBM1., BBm2., BBM2., BBm3., BBM3., BBM4., BBm5., BBm6., BBm7., BBm8., BBm9., BBMA., BBMB., BBmJ., BBMz., BBn.., BBN.., BBn0., BBN4., BBN5., BBnz., BBp.., BBP.., BBP0., BBP1., BBp2., BBP8., BBP9., BBPX., BBpz., BBPz., BBq.., BBq0., BBQ2., BBQ3., BBQ4., BBQ5., BBQ6., BBQ7., BBQ71, BBQ72, BBQ73, BBQ74,	

	BBQ75, BBQ7z, BBQA., BBQA0, BBQA2, BBQAz, BBQB., BBqz., BBrA3, BBS.., BBS0., BBs1., BBs2., BBs3., BBS3., BBSz., BBT0., BBT1., BBT2., BBT3., BBT4., BBT5., BBT7., BBT70, BBT71, BBT7z, BBT8., BBT9., BBTA., BBTB., BBTC., BBTD., BBTD0, BBTD1, BBTD2, BBTDz, BBTE., BBTF., BBTG., BBTH., BBTJ., BBTK., BBTL., BBTz., BBU.., BBU0., BBU1., BBU2., BBU3., BBU4., BBU5., BBU6., BBU7., BBUz., BBV.., BBV1., BBVz., BBW.., BBW0., BBW1., BBW2., BBW3., BBW4., BBW5., BBW6., BBW7., BBWA., BBWz., BBX.., BBX0., BBX2., BBX3., BBXz., BBY0., BBy1., BBY1., BBY2., BByz., BBYz., BBz.., BBZ.., BBZ1., BBZ2., BBZ3., BBZ4., BBZ6., BBZ7., BBZ8., BBZ9., BBZA., BBZC., BBZD., BBZE., BBZF., BBZJ., BBZK., BBZL., BBZM., BBZN., BBZP., BBZz., By..., Byu.., ByuC., ByuC0, ByuC1, ByuC2, ByuC3, ByuC4, ByuC5, ByuC6, ByuC7, ByuC8, ByuE., ByuE0, BBb.., BBb0., BBb1., BBb2., BBb3., BBbC., BBbR., BBbT., BBbU., BBbV., BBbW., BBbX., BBbZ., BBD2., ByuA0, ByuA1, ByuA2, ByuA3, BBcA., BBCC1, BBQ1., BBQ10, BBQ11, BBQ1z, Byu8., Byu80, Byu81, Byu82, BBQA1, Byu7., Byu70, Byu71, Byu72, Byu73, BB5j2, BB5j5, BBL0., BBR2., BBR3., BBcB., BBG7., BBK31, BBK32, BBK33, BBK36,	

	BBK37, Byu5., Byu50, Byu51, Byu52, Byu53, Byu54, Byu55, Byu56, Byu57, Byu58, Byu59, Byu5B, BB601, BB612, BB691, BB6z., BBEV., BBl.., BBl0., BBlz., BBQ9., Byu4., Byu42, Byu43, Byu5A, BBE1., BBE10, BBE11, BBe2., BBE4., BBEA., BBEC., BBEE., BBEG., BBEG0, BBEH., BBEM., BBEP., BBEQ., BBER., BBES., BBET., BBEX., Byu40, Byu41, BBg5., BBn1., BBn2., BBn3., BBv1., BBv2., BBV3., BBV4., BBV5., BBV6., BBV8., BBV9., BBVA., BBW8., BBW9., BBX1., Byu3., Byu30, Byu31, Byu32, Byu33, BBp1., BBP3., BBP5., BBP7., Byu2., Byu21, Byu22, Byu23, Byu24, Byu25, BB5S2, BB5S4, Byu20, Byu1., Byu12, Byu13, BB5B1, BB5B2, BB5B3, BB5B5, BB5B6, BB5D., BB5D0, BB5D1, BB5D3, BB5D5, BB5D7, BB5D8, BB5Dz, Byu10, Byu11, BB5N., BB5N1, BB5C1, BB5Cz, BBZG., BBZH., Byu0.	
Alcohol Problems[m]	13Y8., 1462, 1B1c., 66e.., 66e0., 8BA8., 8H35., 8H7p., 8HkG., 8HkJ., 9NN2., C1505, E01.., E010., E011., E0110, E0111, E011z, E012., E0120, E013., E014., E015., E01y., E01y0, E01yz, E01z., E23.., E230., E2300, E2301, E2302, E2303, E230z, E231., E2310, E2311, E2312, E2313, E231z, E23z., Eu101, Eu102, Eu103, Eu104, Eu105, Eu106, Eu107, Eu108, F11x0, F1440, F25B., F375., F3941, G555., J153., J610., J611.,	

	J612., J6120, J613., J6130, J617., J6170, J6710, Z1911, Z4B1.	
Psychoactive Substance Misuse[m]	13c.., 13c0., 13c1., 13c2., 13c3., 13c4., 13c5., 13c6., 13c7., 13c8., 13c9., 13cA., 13cB., 13cC., 13cD., 13cE., 13cH., 13cK., 13cM., 13cN., 13cQ., 13cR., 13cS., 13cT., 1B1c., 1P30., 1P31., 1P6.., 1P60., 1P62., 1P63., 1P64., 1TE.., 1TF.., 68U.., 68U0., 8AA.., 8B23., 8B2N., 8B2P., 8B2Q., 8B2R., 8B2S., 8B2T., 8BA9., 8BAd., 8BE0., 8BE1., 8FB.., 8FB0., 9HC.., 9HC0., 9HC1., E02.., E020., E021., E0210, E0211, E021z, E022., E02y., E02y0, E02y1, E02y2, E02y3, E02y4, E02yz, E02z., E24.., E240., E2400, E2401, E2402, E2403, E240z, E241., E2410, E2411, E2412, E2413, E241z, E242., E2420, E2421, E2422, E2423, E242z, E243., E2430, E2431, E2432, E2433, E243z, E244., E2440, E2441, E2442, E2443, E244z, E245., E2450, E2451, E2452, E2453, E245z, E246., E2460, E2461, E2462, E2463, E246z, E247., E2470, E2471, E2472, E2473, E247z, E248., E2480, E2481, E2482, E2483, E248z, E249., E2490, E2491, E2492, E2493, E249z, E24A., E24z., E25.., E252., E2520, E2521, E2522, E2523, E252z, E253., E2530, E2531, E2532, E2533, E253z, E254., E2540, E2541, E2542, E2543, E254z, E255., E2550, E2551,	

	E2552, E2553, E255z, E256., E2560, E2561, E2562, E2563, E256z, E257., E2570, E2571, E2572, E2573, E257z, E258., E2580, E2581, E2582, E2583, E258z, E259., E2590, E2591, E2592, E2593, E2594, E259z, E25y., E25y0, E25y1, E25y2, E25y3, E25yz, E25z., E24.., E240., E2400, E2401, E2402, E2403, E240z, E241., E2410, E2411, E2412, E2413, E241z, E242., E2420, E2421, E2422, E2423, E242z, E243., E2430, E2431, E2432, E2433, E243z, E244., E2440, E2441, E2442, E2443, E244z, E245., E2450, E2451, E2452, E2453, E245z, E246., E2460, E2461, E2462, E2463, E246z, E247., E2470, E2471, E2472, E2473, E247z, E248., E2480, E2481, E2482, E2483, E248z, E249., E2490, E2491, E2492, E2493, E249z, E24A., E24z., E25.., E252., E2520, E2521, E2522, E2523, E252z, E253., E2530, E2531, E2532, E2533, E253z, E254., E2540, E2541, E2542, E2543, E254z, E255., E2550, E2551, E2552, E2553, E255z, E256., E2560, E2561, E2562, E2563, E256z, E257., E2570, E2571, E2572, E2573, E257z, E258., E2580, E2581, E2582, E2583, E258z, E259., E2590, E2591, E2592, E2593, E2594, E259z, E25y., E25y0, E25y1, E25y2, E25y3, E25yz, E25z., Eu1.., Eu11., Eu110, Eu111, Eu112, Eu113,	

	Eu114, Eu115, Eu116, Eu117, Eu11y, Eu11z, Eu12., Eu120, Eu121, Eu122, Eu123, Eu124, Eu125, Eu126, Eu127, Eu12y, Eu12z, Eu13., Eu130, Eu131, Eu132, Eu133, Eu134, Eu135, Eu136, Eu137, Eu13y, Eu13z, Eu14., Eu140, Eu141, Eu142, Eu143, Eu144, Eu145, Eu146, Eu147, Eu14y, Eu14z, Eu16., Eu160, Eu161, Eu162, Eu163, Eu164, Eu165, Eu166, Eu167, Eu16y, Eu16z, Eu18., Eu180, Eu181, Eu182, Eu183, Eu184, Eu185, Eu186, Eu187, Eu18y, Eu18z, Eu19., Eu190, Eu191, Eu192, Eu193, Eu194, Eu195, Eu196, Eu197, Eu19y, Eu19z, Eu1A., Eu1A0, Eu1A1, Eu1A2, Eu1A3, Eu1A4, Eu1A5, Eu1A6, Eu1A7, Eu1Ay, Eu1Az, ZV114	
Stroke or Transient Ischaemic Attack	14AB., 14AK., 14A7., 1M4.., 662e., 662M., 662o., 7P242, 8HBJ., G61.., G610., G611., G612., G613., G614., G615., G616., G617., G618., G61X., G61X0, G61X1, G61z., G62.., G620., G621., G622., G623., G62z., G63y0, G63y1, G64.., G6400, G6410, G64z., G64z0, G64z2, G64z3, G64z4, G65.., G650., G651., G6510, G652., G653., G654., G656., G65y., G65z., G65z0, G65z1, G65zz, G66.., G663., G664., G667., G668., G669., G6760, G6W.., G6X.., Gyu62, Gyu63, Gyu64, Gyu65, Gyu66, Gyu6F, Gyu6G, ZV12D, Fyu55	

Atrial Fibrillation	14AN., 3272, 662S., 6A9.., G573., G5730, G5732, G5733, G5734, G5735, G573z	
Peripheral Vascular Disease	14NB., G73.., G730., G7300, G7301, G730z, G731., G7310, G7311, G731z, G732., G7320, G7321, G7322, G7323, G7324, G733., G73y., G73y0, G73y1, G73y2, G73y4, G73y5, G73y6, G73y7, G73y8, G73yz, G73z., G73z0, G73zz, Gyu74, P76.., G830., G831., G832., G833., G835., G836., G837., G8y1., G8y3., G8yy0, G702., G702z	
Heart Failure	14A6., 14AM., 1O1.., 662p., 662T., 662W., 8B29., 8H2S., 9N0k., G1yz1, G58.., G580., G5800, G5801, G5802, G5803, G5804, G581., G5810, G582., G583., G58z., G5y4z, L09y2, Q48y1	
Prostate Disorders	8L51., A1650, A9812, A9832, AD103, B46.., B58y5, B7C2., B834., B8340, B915., K20.., K200., K201., K202., K20z., K21.., K210., K211., K212., K213., K214., K2140, K2141, K2142, K2143, K2144, K2145, K2146, K214z, K21y., K21z., K22.., K220., K221., K2210, K2211, K221z, K222., K22y., K22y0, K22y1, K22y2, K22y3, K22yz, K22z., Kyu60, Kyu61, Kyu68, PCy01, PCyx., Pyu69	
Glaucoma	66T1., 7275, F4421, F45.., F450., F4501, F4502, F4503, F450z, F451., F4510, F4511, F4512, F4513, F4514,	

	F4515, F451z, F452., F4520, F4521, F4522, F4523, F4524, F452z, F453., F4530, F4531, F453z, F454., F4540, F4541, F4542, F4543, F4544, F454z, F455., F4550, F4551, F455z, F456., F4560, F4561, F4562, F4563, F4564, F4565, F4566, F456z, F45y., F45y0, F45y1, F45y2, F45yz, F45z., F4631, F4H14, FyuG., FyuG0, FyuG1, FyuG2, P3200, Q20y7	
Epilepsy	1473, 1B1W., 1O30., 667.., 6671, 6672, 6673, 6674, 6675, 6676, 6677, 6678, 6679, 667D., 667E., 667G., 667H., 667J., 667K., 667L., 667M., 667N., 667Q., 667R., 667S., 667T., 667V., 667W., 667X., 667Z., 8B66., 8BIF., Eu803, F1321, F25.., F250., F2500, F2501, F2502, F2503, F2504, F2505, F250y, F250z, F251., F2510, F2511, F2512, F2513, F2514, F2515, F2516, F251y, F251z, F252., F253., F254., F2540, F2541, F2542, F2543, F2544, F2545, F254z, F255., F2550, F2551, F2552, F2553, F2554, F2555, F2556, F255y, F255z, F256., F2560, F2561, F256z, F257., F258., F259., F25A., F25B., F25C., F25D., F25E., F25F., F25X., F25y., F25y0, F25y1, F25y2, F25y3, F25y4, F25y5, F25yz, F25z., Fyu50, Fyu51, Fyu52, Fyu59, SC200	AND Four or more prescriptions for antiepilpetics issued per year. Medication read codes: dnc.. , dnc1. , do... , do1.. , do11. , do12. , do14. , do15. , do16. , do18. , do19. , do1A. , do1B. , do1t. , do1u. , do1v. , do1w. , do1x. , do1y. , dn2.. , dn21. , dn2z. , dnx.. , dnx2. , dnx4. , dnx6. , dnx8. , dnxA. , dnxC. , dnxE. , dn3.. , dn31. , dn32. , dn33. , dn34. , dn35. , dn36. , dn37. , dn38. , dn39. , dn3a. , dn3A. , dn3b. , dn3B. , dn3c. , dn3C. , dn3d. , dn3D. , dn3e. , dn3E. , dn3f. , dn3F. , dn3G. , dn3H. , dn3I. , dn3J. , dn3K. , dn3v. , dn3w. , dn3x. , dn3y. , dn3z. , dn4.. , dn41. , dn42. , dn4w. , dn4x. , dn4y. , dn4z. , do2.. , do21. , do2z. , dnu.. , dnu1. , dnu2. , dn5.. , dn53. , dn54. , dn55. , dn56. , dn5x. , dn5y. , dn5z. , dni.. , dni1. , dni2. , dnj.. , dnj1. , dnj2. , dnj3. , dnj4. , dnj5. , dnj6. , dnj7. , dnj8. , dnj9. , dnjA. , dnjx. , dnjy. , dnjz. , dnt.. , dnt1. , dnt2. , dnt3. , dnt4. , dnt5. , dnt6. , dnt7. , dnt8. , dnt9. , dntA. , dntB. , dntC. , dntD. , dntE. ,

		dnf.. , dnf1. , dnf2. , dnf3. , dnf4. , dnf5. , dnf6. , dnf7. , dnf8. , dnf9. , dnfA. , dnfB. , dnfC. , dnfD. , dnfE. , dnfF. , dnfG. , dnfH. , dnfJ. , dnfz. , dno.. , dno1. , dno2. , dno3. , dno4. , dno5. , dno6. , dno7. , dno8. , dno9. , dnor. , dnos. , dnot. , dnou. , dnov. , dnow. , dnox. , dnoy. , dnoz. , dn6.. , dn61. , dn62. , dn63. , dn6x. , dn6y. , dn6z. , dnm.. , dnm1. , dnm2. , dnm3. , dnm4. , dnmw. , dnmx. , dnmy. , dnmz. , dnw.. , dnw1. , dnw2. , dnw3. , dnw4. , dnw5. , dnw6. , dnwu. , dnwv. , dnww. , dnwx. , dnwy. , dnwz. , dn7.. , dn71. , dn72. , dn73. , dn74. , dn75. , dn76. , dn77. , dn78. , dn79. , dn7a. , dn7b. , dn7c. , dn7d. , bc6.. , bc61. , bc62. , dn8.. , dn81. , dn82. , dn83. , dn8y. , dn8z. , dn9.. , dn91. , dn92. , dn93. , dn94. , dn95. , dn96. , dn97. , dn98. , dn9w. , dn9x. , dn9y. , dn9z. , do6.. , do61. , do6z. , dnp.. , dnp1. , dnp2. , dnp3. , dnp4. , dnp5. , dnp6. , dnp7. , dnp8. , dnp9. , dnpr. , dnps. , dnpt. , dnpu. , dnpv. , dnpw. , dnpx. , dnpy. , dnpz. , dna.. , dna1. , dna2. , dna3. , dnax. , dnay. , dnaz. , dnv.. , dnv1. , dnv2. , dnv3. , dnv4. , dnv5. , dnv6. , dnv7. , dnv8. , dnv9. , dnvA. , dnvB. , dnvC. , dnr.. , dnr1. , dnr2. , dnr3. , dnr4. , dnrw. , dnrx. , dnry. , dnrz. , dns.. , dns1. , dns2. , dns3. , dns4. , dnsw. , dnsx. , dnsy. , dnsz. , dnl.. , dnl1. , dnl2. , dnl3. , dnl4. , dnl5. , dnl6. , dnk.. , dnk1. , dnk2. , dnk3. , dnk4. , dnk5. , dnk6. , dnk7. , dnk8. , dnk9. , dnkA. , dnkB. ,

		dnkC. , dnkD. , dnkE. , dnb.. , dnb1. , dnb2. , dnb3. , dnb4. , dnb5. , dnb6. , dnb7. , dnb8. , dnb9. , dnba. , dnbA. , dnbb. , dnbB. , dnbc. , dnbC. , dnbd. , dnbD. , dnbe. , dnbE. , dnbF. , dnbG. , dnbH. , dnbI. , dnbJ. , dnbK. , dnbL. , dnbM. , dnbn. , dnbN. , dnbo. , dnbO. , dnbp. , dnbP. , dnbq. , dnbQ. , dnbr. , dnbR. , dnbs. , dnbS. , dnbt. , dnbT. , dnbu. , dnbU. , dnbv. , dnbw. , dnbx. , dnby. , dnbz. , dnh.. , dnh1. , dnh2. , dnh3. , dnh4. , dnh5. , dnh6. , dnh7. , dnh8. , dnhy. , dnhz. , dne.. , dne1. , dne2. , dne3. , dne4. , dnq.. , dnq1. , dnq2. , dnq3. , dnq4. , dnq5. , dnq6.
Dementia[m]	66h.., 6AB.., E000., E001., E0010, E0011, E0012, E0013, E001z, E002., E0020, E0021, E002z, E003., E004., E0040, E0041, E0042, E0043, E004z, E012., E02y1, E041., Eu00., Eu000, Eu001, Eu002, Eu00z, Eu01., Eu010, Eu011, Eu012, Eu013, Eu01y, Eu01z, Eu02., Eu020, Eu021, Eu022, Eu023, Eu024, Eu025, Eu02y, Eu02z, Eu041, F110., F1100, F1101, F111., F112., F116., Fyu30	
Schizophrenia and Bipolar Affective Disorder[m]	1464, E10.., E100., E1000, E1001, E1002, E1003, E1004, E1005, E100z, E101., E1010, E1011, E1012, E1013, E1014, E1015, E101z, E102., E1020, E1021, E1022, E1023, E1024, E1025, E102z, E103., E1030, E1031, E1032, E1033, E1034, E1035, E103z, E104.,	OR Four or more prescriptions for antipsychotics issued per year. Medication read codes: d6... , d61.. , d611. , d612. , d613. , d614. , d615. , d616. , d617. , d618. , d619. , d61s. , d61v. , d61w. , d61x. , d61y. ,

	E105., E1050, E1051, E1052, E1053, E1054, E1055, E105z, E106., E107., E1070, E1071, E1072, E1073, E1074, E1075, E107z, E10y., E10y0, E10y1, E10yz, E10z., E11.., E110., E1100, E1101, E1102, E1103, E1104, E1105, E1106, E110z, E111., E1110, E1111, E1112, E1113, E1114, E1115, E1116, E111z, Eu2.., Eu20., Eu200, Eu201, Eu202, Eu203, Eu204, Eu205, Eu206, Eu20y, Eu20z, Eu21., Eu22., Eu220, Eu221, Eu222, Eu223, Eu22y, Eu22z, Eu23., Eu230, Eu231, Eu232, Eu233, Eu23y, Eu23z, Eu24., Eu25., Eu250, Eu251, Eu252, Eu25y, Eu25z, Eu26., Eu2y., Eu2z., ZV110, E114., E1140, E1141, E1142, E1143, E1144, E1145, E1146, E114z, E115., E1150, E1151, E1152, E1153, E1154, E1155, E1156, E115z, E116., E1160, E1161, E1162, E1163, E1164, E1165, E1166, E116z, E117., E1170, E1171, E1172, E1173, E1174, E1175, E1176, E117z, E11y., E11y0, E11y1, E11y2, E11y3, E11yz, Eu31., Eu310, Eu311, Eu312, Eu313, Eu314, Eu315, Eu316, Eu317, Eu31y, Eu31z	d61z. , d62.. , d621. , d622. , d623. , d624. , d625. , d62w. , d62x. , d62y. , d62z.
Psoriasis and Eczema	14F2., M160., M1600, M1601, M160z, M161., M1610, M1611, M1612, M1613, M1614, M1615, M1616, M1617, M1618, M1619, M161A, M161B, M161C, M161D, M161E, M161F, M161G, M161H, M161z, M16y., M16y0,	AND Four or more prescriptions for creams issued per year. Medication read codes: m4... , m4b5. , m51.. , m513. , m514. , m518. , m519. , m51A. , m51c. , m51C. , m51d. , m51F. , m51G. , m51h. ,

	M16z., Myu30, N0452, Nyu13, 14F1., 26C4., F4D30, F5024, M102., M111., M112., M113., M114., M119., M11A., M12z1, M12z2, M12z3, M12z4, M1y2., Myu2., Myu22	m51H. , m51I. , m51l. , m51L. , m51m. , m51R. , m51T. , m51u. , m51v. , m5D.. , m5D1. , m5G.. , m5G1. , m5G2. , m5G3. , m5G4. , m5G5. , m5G6. , m5G7. , m5G8. , mb51. , m5A.. , m5A1. , m5A2. , m5A3. , m5A4. , mh1k. , mh1l. , m46.. , m461. , m462. , m463. , m464. , m46y. , m46z. , m47.. , m479. , m47a. , m47y. , m47z. , m48.. , m482. , m483. , m485. , m486. , m487. , m489. , m48a. , m48A. , m48b. , m48B. , m48c. , m48C. , m48d. , m48D. , m48e. , m48E. , m48f. , m48g. , m48h. , m48i. , m48j. , m48k. , m48l. , m48m. , m48n. , m48o. , m48p. , m48q. , m48r. , m48s. , m48t. , m48z. , m49.. , m496. , m497. , m499. , m49a. , m49c. , m49d. , m49e. , m49f. , m49r. , m49s. , m49t. , m49u. , m49v. , m49w. , m49x. , m49y. , m49z. , me46. , me4D. , me4x. , m492. , m494. , m4o.. , m4o1. , m4o2. , m4o3. , m4o4. , m4o5. , m4o6. , m4o7. , m4o8. , m59.. , m591. , m592. , m593. , m594. , m595. , m596. , m597. , m598. , m599. , m59A. , m59B. , m59C. , m59D. , m59E. , m59F. , m59G. , m59H. , m59I. , m59J. , m59K. , m59L. , m59M. , ip29. , ip2A. , ip2B. , m4a.. , m4a1. , m4a2. , m4a3. , m4a4. , m4a5. , m4a6. , m4a9. , m4aa. , m4ab. , m4ac. , m4ad. , m4ae. , m4af. , m4ag. , m4ah. , m4ai. , m4aj. , m4ak. , m4al. , m4aw. , m4ax. , m4ay. , m4az. , m4a7. , m4a8. , m4b.. , m4b1. , m4b2. , m4b3. , m4b4. ,

		m4b7. , m4by. , m4bz. , m4c.. , m4c1. , m4c2. , m4c3. , m4cy. , m4cz. , m4d.. , m4d1. , m4d2. , m4d4. , m4d5. , m4dy. , m4dz. , m4e.. , m4e1. , m4e2. , m4e3. , m4e4. , m4e5. , m4e6. , m4e7. , m4e8. , m4eu. , m4ev. , m4ew. , m4ex. , m4ey. , m4ez. , m53.. , m531. , m532. , m533. , m534. , m535. , m536. , m537. , m53a. , m53b. , m53c. , m53d. , m53n. , m53o. , m53p. , m53q. , m53r. , m53s. , m53t. , m54.. , m5z.. , m5z1. , m5z2. , m5z3. , m5z4. , m5z5. , m5z6. , m5z7. , m5z8. , m5z9. , m5zm. , m5zn. , m5zo. , m5zp. , m5zq. , m5zr. , m5zs. , m5zt. , m5zu. , m5zv. , m5zw. , m5zx. , m5zy. , m5zz. , m53A. , m53B. , m53C. , m53e. , m53f. , m53F. , m53g. , m53h. , m53i. , m53k. , m53l. , m53m. , m55.. , m551. , m552. , m55y. , m55z. , m4f.. , m4f1. , m4f2. , m4f3. , m4f4. , m4fy. , m4fz. , m4j.. , m4j1. , m4j2. , m4j7. , m4j8. , m4ju. , m4jv. , m4jw. , m4jx. , m4jy. , m4jz. , m4j5. , m4j6. , m4g.. , m4g1. , m4g2. , m4g3. , m4g4. , m4g5. , m4g6. , m4g7. , m4g8. , m4g9. , m4gi. , m4gj. , m4gs. , m4gt. , m4gu. , m4gv. , m4gw. , m4gz. , m4ge. , m4gf. , m4gg. , m4gh. , m4go. , m4gp. , m4gq. , m4gr. , m4gc. , m4gd. , m4h.. , m4h1. , m4h2. , m4h3. , m4h4. , m4h5. , m4hx. , m4hy. , m4hz. , m4i.. , m4i1. , m4i3. , m4i6. , m4i8. , m4i9. , m4ia. , m4ib. , m4ic. , m4id. , m4ie. , m4if. , m4ig. , m4r.. , m4r1. , m4r2. , m4r3. ,

		m4r4. , m4r5. , m4r6. , m4r7. , m4r8. , m4r9. , m4rA. , m4k.. , m4k1. , m4kz. , m41.. , m411. , m412. , m413. , m414. , m415. , m416. , m417. , m418. , m419. , m41a. , m41A. , m41b. , m41B. , m41c. , m41C. , m41d. , m41D. , m41e. , m41f. , m41k. , m41l. , m41m. , m41n. , m41o. , m41p. , m41q. , m41t. , m41u. , m41v. , m41w. , m42.. , m421. , m422. , m423. , m424. , m429. , m42a. , m42A. , m42b. , m42B. , m42c. , m42C. , m42d. , m42D. , m42e. , m44.. , m441. , m442. , m443. , m444. , m446. , m447. , m448. , m44c. , m44d. , m44e. , m44f. , m4p1. , m44a. , m44b. , m45.. , m451. , m452. , m453. , m454. , m455. , m457. , m458. , m459. , m45a. , m45A. , m45b. , m45B. , m45c. , m45C. , m45d. , m45e. , m45g. , m45k. , m45l. , m45m. , m45n. , m45o. , m45p. , m45q. , m45r. , m45s. , m45t. , m45T. , m45u. , m45v. , m45V. , m45w. , m45W. , m45x. , m45X. , m45y. , m45Y. , m45Z. , m44z. , m4l.. , m4l1. , m4l2. , m4l3. , m4l4. , m4l5. , m4l6. , m4l7. , m4la. , m4lb. , m4lt. , m4lw. , m4lx. , m4ly. , m4lz. , m4l8. , m4l9. , m4m.. , m4m1. , m4my. , m4mz. , m4q.. , m4q1. , m4q2. , m4q3. , m4q4. , m4q5. , m4q6. , m4q7. , m4q8. , m4q9. , m4qA. , m4qB. , m5B.. , m5B1. , m5B2. , m5B3. , m5B4. , m5B5. , m5B6. , m5C.. , m5C1. , m5C2. , m5C3. , m5C4. , m5C5. , m5C6. , m4n.. , m4n1. , m4n2. , m4n3. , m4n4. , m4n5. ,

		m4n6. , m4ny. , m4nz. , m4n7. , m4n9. , m4na. , m4nb. , m4ne. , m4ng. , m4nv.
Inflammatory Bowel Disease	14C4., J08z9, J40.., J400., J4000, J4001, J4002, J4003, J4004, J4005, J400z, J401., J4010, J4011, J4012, J401z, J402., J40z., J41.., J410., J4100, J4101, J4102, J4103, J4104, J410z, J411., J412., J41y., J4212, J4213, J42z0, J4302, J4303, J4312, J4313, J4322, J4323, J4332, J4333, J436., J4360, J4361, J437., J4z3., J4z5., J4z6., Jyu4., Jyu40, Jyu41, N0310, N0454, J08z9, J40.., J4002, J4003, J4004, J4005, J400z, J4012, J401z, Jyu40, N0311, N0453	
Hearing Loss	1493, 1C12., 1C13., 1C131, 1C132, 1C133, 1C16., 1C18., 1C19., 1C1Z., 2BL2., 2BL3., 2BL4., 2BL5., 2BM2., 2BM3., 2BM4., 2DG.., 2DH0., 31343, 31344, 31345, 31346, F5801, F5812, F582., F59.., F590., F5900, F5901, F5902, F5903, F5904, F5905, F5906, F590y, F590z, F591., F5910, F5911, F5912, F5913, F5914, F5915, F5916, F5917, F5918, F591y, F591z, F592., F5920, F5921, F593., F594., F595., F596., F597., F598., F599., F59A., F59y., F59z., F5A.., FyuU0, FyuU1, P40.., P400., P402., P402z, P40z., P40zz, ZE63., ZE7.., ZE812, ZE813, ZE822, ZE823, ZE832, ZE833, ZE842, ZE843, ZE86., ZE87., ZV412	

Chronic Sinusitis	H13.., H130., H131., H132., H133., H134., H135., H13y., H13y0, H13y1, H13yz, H13z., Hyu22, J0835	
Anorexia Nervosa and Bulimia[m]	1467, E271., E2751, Eu500, Eu501, Eu502, Eu503	
Bronchiectasis	A115., H34.., H340., H341., H34z., P861.	
Parkinson's Disease	147F., 297[a]., 2987, 2994, A94y1, Eu023, F11x9, F12.., F120., F121., F123., F124., F12W., F12X., F12z., F1303, Fyu20, Fyu21, Fyu22, Fyu29, Fyu2B	
Multiple Sclerosis	666[a]., 666B., 8CS1., F20.., F200., F201., F202., F203., F204., F205., F206., F207., F208., F20z.	
Viral Hepatitis	141E., 65Q7., A702., A7020, A703., A7030, A7040, A7050, A7051, A7054, A707., A7070, A7071, A7072, A707X, A70z0, AE23., AyuB1, AyuB2, AyuJ9, Q409., Q4091, Q409y, Q409z, ZV026, ZV02B, ZV02C	
Chronic Liver Disease	G8522, J601., J6010, J6011, J6012, J601z, J60z., J61.., J614., J6140, J6141, J6142, J6143, J6144, J614y, J614z, J615., J6150, J6151, J6152, J6153, J6154, J6155, J6156, J6157, J6158, J6159, J615A, J615B, J615C, J615D, J615E, J615F, J615G, J615H, J615y, J615z, J616., J6160, J6161, J6162, J616z, J617., J6170, J61y., J61y0, J61y1, J61y2, J61y3, J61y4, J61y5, J61y6, J61y7, J61y8, J61yz, J61z., J623., J624., J62y., J62z., J630., Jyu71, PB62., PB620	

Diverticular Disease	77180, J23z3, J5126, J5111, J51z., J5115, J512y, J5127, J511., J5113, J511z, J5116, J5125, J5102, J510z, J5108, J5117, J5124, J510., J5112, J51.., J513., J5103, J512., J5128, J5100, J5123, J5104, J5122, J512z, J5120, J511y, J5107, J5114, J5109, J5101, J5121, J5105, J510y, J5106, J5110	
Osteoporosis	585O., 584E., 58E8., 58EA., 58EE., 58EG., 58EK., 58ES., 58EM., 58EV., 7230ª, 7230B, 7230D, 7230PM, 7230PT, N330., N330000, N330100, N330200, N330400, N330500, N330600, N330700, N330800, N330900, N330A00, N330B00, N330C00, N330C00, N330D00, N330z00, N331200, N331300, N331400, N331500, N331600, N331800, N331900, N331A00, N331B00, N331M00, N331N00, NyuB100, NyuB200, NyuB800	
Pernicious Anaemia	D010., F381500	
Endometriosis	7E0D800, BL1., K50.., K500., K500000, K500100, K500111, K500200, K500z00, K501., K502., K503., K503000, K503100, K503200, K503300, K503z00, K504., K504., K504000, K504100, K504z00, K505., K505000, K505100, K505200, K505z00, K506.00,	

	K50y.00, K50y000, K50y100, K50y200, K50y300, K50yz00, K50., Kyu9000	
Chronic Fatigue Syndrome	8Q1.., F286., F286000, F286100, F286200	
Polycystic Ovarian Syndrome	C164., C165.	
Meniere's Disease	1491, F560000, F560100, F560200, F560300, F560400, F560., F560z00	
Constipation		Four or more prescriptions for laxatives issued per year. Medication read codes: ab... , ab1.. , ab13. , ab14. , ac... , ac6.. , ac61. , ad... , ae... , ae4.. , ae41. , ae42. , ae43. , ae44. , ae45. , ae46. , ae4a. , ae4h. , af... , af1.. , af1f. , af1k. , af1o. , af1q. , af1v. , ag... , ag1.. , l41b. , ac1.. , ac1.. , ac11. , ac11. , ac12. , ac13. , ac14. , ac15. , ac16. , af11. , af11. , af12. , af12. , af1a. , af1b. , af1c. , ac2.. , ac21. , ac3.. , ac31. , af1C. , ac4.. , ac42. , ac43. , ac44. , ac45. , ac46. , ac47. , ac48. , ac49. , ac4A. , ac4B. , ac4C. , ac4D. , ac4E. , ac4F. , ac4G. , ac5.. , ac51. , ac52. , ac53. , ac54. , ac55. , ac56. , ac57. , ac58. , ac59. , ac5A. , ac5B. , af1e. , af1p. , af1t. , af13. , af14. , af15. , ab2.. , ab21. , ab22. , ab23. , ab24. , ab25. , ab26. , ab28. , ab29. , ab2A. , ab2B. , ab2C. , ab2D. , ab2E. , ab2F. , ab2G. , ab2H. , ab2J. , ab2K. , ab2L. , ab2M. , ab2n. , ab2N. ,

		ab2o. , ab2O. , ab2p. , ab2P. , ab2q. , ab2Q. , ab2r. , ab2R. , ab2t. , ab2u. , ab2v. , ab2w. , ab2x. , ab2y. , ae6.. , ae61. , ae6z. , ae1.. , ae11. , ae12. , ae13. , ae14. , ae15. , ae16. , ae17. , ae18. , ae19. , ae1A. , ae1B. , af1l. , af1m. , a4i.. , a4i1. , a4i2. , ad1.. , ad11. , ad12. , ad13. , ae21. , ag11. , ag15. , ag19. , ag1A. , ag1H. , ae47. , ae48. , ae49. , ae4g. , ae4b. , ae4c. , ae4d. , ae4e. , ae4f. , ae4i. , ae4j. , ae5.. , ae51. , ae3.. , ae31. , ae32. , ae33. , ag17. , ab3.. , ab32. , ab33. , ab35. , ab36. , ab37. , ax1.. , iz1D. , ax2.. , ax23. , ax24. , af1d. , af1s. , af1n. , ag12. , ag16. , ag1C. , ag1E. , ac7.. , ac71. , ac74. , ac75. , ac76. , ac77. , ac78. , ac79. , ac7A. , ac7v. , ac7w. , ac7x. , ac7y. , ac7z. , ae7.. , ae71. , af16. , af1A. , af1B. , af1g. , af1h. , af1w. , af1x. , af1y. , ac8.. , ac81. , ac82. , ac84. , ac85. , ac8w. , ac8x. , ac8y. , ac83. , ac86. , ac8z. , ab4.. , ab41. , ab42. , ab4y. , ab4z. , ab43. , ab44. , ab45. , ab46. , ab4x.
Dyspepsia		Four or more prescriptions for dyspepsia medication issued per year. Medication read codes: a22w. , a22x. , a22y. , a22z. , a23K. , a23L. , a23M. , a23P. , a23Q. , a6... , a67.. , a671. , a6g.. , a6g1. , a6g2. , a6g3. , a6g4. , a22u. , a22v. , a23A. , a23b. , a23B. , a23c. , a23C. , a23D. , a23e. , a23E. , a23f. , a23F. , a23G. , a23H. , a23i. , a23I. , a23j. , a23J. , a23k. , a23l. , a23m. , a23n. , a23N. ,

		a23o. , a23O. , a23p. , a23q. , a23s. , a23t. , a23v. , a23w. , a23x. , a23y. , a23z. , a24z. , a642. , a643. , a64y. , a64z. , a66.. , a661. , a662. , a66z. , a663. , a664. , a61.. , a611. , a612. , a613. , a614. , a615. , a616. , a617. , a618. , a619. , a61A. , a61B. , a61C. , a61d. , a61D. , a61e. , a61E. , a61f. , a61F. , a61g. , a61G. , a61H. , a61I. , a61J. , a61K. , a61L. , a61M. , a61N. , a61O. , a61P. , a61Q. , a61R. , a61S. , a61u. , a61v. , a61w. , a61x. , a61y. , a61z. , a61a. , a61b. , a61s. , a61t. , a61T. , a61U. , a6h.. , a6h1. , a6h2. , a6h3. , a6h4. , a6h5. , a6h6. , a6hu. , a6hv. , a6hw. , a6hx. , a6hy. , a6hz. , a24x. , a68.. , a681. , a682. , a683. , a684. , a6c.. , a6c1. , a6c2. , a6c3. , a6c4. , a6c5. , a6c6. , a6c7. , a6c8. , a6c9. , a6cA. , a6a.. , a6a1. , a6a2. , a69.. , a691. , a692. , a693. , a694. , a695. , a696. , a697. , a698. , a6b.. , a6b1. , a6b2. , a6b3. , a6b4. , a6b5. , a6b6. , a6b7. , a6b8. , a6b9. , a6bA. , a6bB. , a6bC. , a6bD. , a6bE. , a6bF. , a6bG. , a6bH. , a6bI. , a6bJ. , a6bK. , a6bL. , a6bM. , a6bN. , a6bO. , a6bP. , a6bQ. , a6bR. , a6bS. , a6bu. , a6bv. , a6bw. , a6bx. , a6by. , a6bz. , a6e.. , a6e1. , a6e2. , a6e3. , a6e4. , a6e5. , a6e6. , a6e7. , a63.. , a631. , a63z. , a6f.. , a6f1. , a6f2. , a6f3. , a6f4. , a62.. , a621. , a622. , a623. , a624. , a625. , a626. , a627. , a628. , a629. , a62A. , a62B. , a62C. , a62D. , a62E. , a62F. , a62G. , a62H. , a62I. , a62J. , a62K. , a62L. ,

		a62M. , a62N. , a62O. , a62P. , a62Q. , a62u. , a62v. , a62w. , a62x. , a62y. , a62z. , a6d.. , a6d1. , a6d2. , a65.. , a651. , a652. , a65y. , a65z. EXCEPT if also administered non-steroidal anti-inflammatory drugs and/or antiplatelets. Medication read codes:, bu... , bu9.. , bu91. , bu92. , bu93. , bu94. , j28H. , j28z. , bu3.. , bu31. , bu32. , bu2.. , bu21. , bu22. , bu23. , bu24. , bu25. , bu26. , bu27. , bu28. , bu29. , bu2a. , bu2A. , bu2b. , bu2B. , bu2c. , bu2C. , bu2d. , bu2D. , bu2E. , bu2F. , bu2G. , bu2H. , bu2I. , bu2J. , bu2K. , bu9.. , bu91. , bu93. , bu5.. , bu51. , bu52. , bu53. , bu54. , bu55. , bu4.. , bu41. , bu42. , j2t.. , j2t1. , j2t2. , j2ty. , j2tz. , j2q.. , j2q1. , j2qz. , bu1.. , bu11. , bu12. , bu13. , bu14. , bu15. , bu16. , bu17. , bu18. , bu19. , bu1A. , bu1B. , bu1C. , bu1D. , bu1E. , bu1z. , br5.. , br51. , br52. , br53. , br54. , bu7.. , bu71. , bu72. , bu7y. , bu7z. , j25.. , j252. , j253. , j254. , j255. , j256. , j257. , j258. , j259. , j25A. , j25B. , j25y. , j25z. , di5.. , di51. , di5z. , j26.. , j261. , j262. , j263. , j264. , j27.. , j271. , j272. , j273. , j274. , j275. , j27x. , j27y. , j27z. , lf32. , di6.. , diaW. , j28.. , j281. , j282. , j283. , j284. , j285. , j286. , j287. , j288. , j289. , j28a. , j28A. , j28b. , j28B. , j28c. , j28C. , j28d. , j28D. , j28e. , j28E. , j28f. , j28F. , j28g. , j28G. , j28h. , j28i. , j28j. , j28J. , j28k. , j28K. , j28l. , j28m. , j28M. , j28n. , j28N. , j28o. , j28p. , j28P. , j28q. , j28r. , j28R. , j28s. , j28S. ,

		j28t. , j28T. , j28u. , j28v. , j28w. , j28W. , j28x. , j28X. , j28y. , j28Y. , j28Z. , j2p.. , j2p1. , j2p2. , j2p3. , j2p4. , j2p5. , j2p6. , j2p7. , j2p8. , j2p9. , j2pa. , j2pA. , j2pb. , j2pB. , j2pc. , j2pC. , j2pD. , j2pE. , j2pF. , j2pG. , j2pH. , j2pI. , j2pJ. , j2pK. , j2pL. , j2pN. , j2pO. , j2pP. , j2pQ. , j2pR. , j2pS. , j2pU. , j2pV. , j2pW. , j2pX. , j2pY. , j2pZ. , dicw. , dicZ. , j28I. , j28O. , j28U. , j28V. , j2pM. , j2pT. , bn7.. , bn71. , bn72. , bn73. , bn74. , bn75. , j2a.. , j2a1. , j2a2. , j2a3. , j2a4. , j2a5. , j2a6. , j2a7. , j2a8. , j2a9. , j2aa. , j2aA. , j2ab. , j2aB. , j2aC. , j2aD. , j2aE. , j2aF. , j2aG. , j2aH. , j2aI. , j2aJ. , j2aK. , j2aL. , j2aM. , j2aO. , j2aP. , j2aQ. , j2aR. , j2aS. , j2aw. , j2ax. , j2ay. , j2az. , j2ac. , j2ad. , j2au. , j2av. , di8.. , di81. , di8z. , j2c.. , j2c1. , j2c2. , j2c3. , j2c4. , j2c5. , j2c6. , j2c7. , j2c8. , j2c9. , j2ca. , j2cA. , j2cb. , j2cB. , j2cc. , j2cC. , j2cd. , j2cD. , j2ce. , j2cE. , j2cf. , j2cF. , j2cg. , j2cG. , j2ch. , j2cH. , j2ci. , j2cI. , j2cj. , j2cJ. , j2ck. , j2cK. , j2cl. , j2cL. , j2cm. , j2cM. , j2cn. , j2cN. , j2co. , j2cO. , j2cp. , j2cq. , j2cr. , j2cs. , j2ct. , j2cu. , j2cv. , j2cw. , j2cx. , j2cy. , j2cz. , j2cP. , j2cZ. , buA.. , buA2. , buA4. , j2g.. , j2g1. , j2g2. , j2g3. , j2g4. , j2g5. , j2gx. , j2gy. , j2gz. , buB.. , buB1. , buBz. , bu6.. , bu61. , bu62. , bu8.. , bu81. , bu82. , bu8y. , bu8z.
Migraine		Four or more prescriptions for migraine medication issued per year. Medication read codes:

		dl... , dl1.. , dl11. , dl12. , dl13. , dl14. , dl15. , dl16. , dl17. , dl18. , dl19. , dl1a. , dl1A. , dl1b. , dl1B. , dl1C. , dlE.. , dlE1. , dlE2. , dm... , dlC.. , dlC1. , dlCz. , dm1.. , dm11. , dm1z. , dl3.. , dl31. , dl32. , dl33. , dl3x. , dl3y. , dl3z. , dlB.. , dlB1. , dlB2. , dlD.. , dlD1. , dlD2. , dl2.. , dl23. , dl24. , dl2y. , dl2z. , dl21. , dl22. , dl25. , dl26. , dl27. , dlE.. , dlE1. , dq7.. , dq71. , dm2.. , dm21. , dm2z. , dl9.. , dl91. , dl92. , dm3.. , dm31. , dm32. , dm33. , dm3x. , dm3y. , dm3z. , dlA.. , dlA1. , dlA2. , dlA3. , dlA4. , dlA5. , dlA6. , dl5.. , dl51. , dl52. , dl53. , dl54. , dl55. , dl56. , dl57. , dl58. , dl59. , dl5A. , dl5B. , dl5C. , dl5D. , dl5E. , dl7.. , dl71. , dl72. , dl73. , dl74. , dl8.. , dl81. , dl82. , dl83. , dl84. , dl85. , dl86. , dl87. , dl88.
Painful Condition		Four or more prescriptions for painkillers issued per year. Medication read codes: di... , diaN. , dibC. , dj... , dj23. , dj24. , dj26. , dl... , dl1.. , dl11. , dl12. , dl13. , dl14. , dl15. , dl16. , dl17. , dl18. , dl19. , dl1a. , dl1A. , dl1b. , dl1B. , dl1C. , dlE.. , dlE1. , dlE2. , dm... , j1... , di1.. , di11. , di12. , di15. , di16. , di17. , di18. , di1a. , di1c. , di1d. , di1f. , di1g. , di1h. , di1i. , di1k. , di1m. , di1n. , di1o. , di1r. , j11.. , j111. , j112. , dia4. , dia5. , dia8. , diab. , diaB. , diaE. , diaG. , diai. , diaO. , diaP. , diay. , diaz. , dicH. , diaf. , dlC.. , dlC1. , dlCz. , di1e. , di3.. , j12.. , j121. , j122. , j124. , j12x. , j12y. , j12z. , dj3.. , dj31. , dj32. , dj33. , dj34. ,

		dj35. , dj3A. , dj3B. , dj3C. , dj3f. , dj3g. , dj3o. , dj3p. , dj3q. , dj3x. , dj3y. , dj3z. , j13.. , j131. , j13z. , dm1.. , dm11. , dm1z. , dj5.. , dj51. , dj52. , dj53. , dj54. , dj55. , dj56. , dj57. , dj58. , dj59. , dj5a. , dj6.. , dj61. , dj62. , dia7. , diad. , diae. , diaw. , dibh. , di4.. , j23.. , j231. , j232. , j233. , j234. , dj8.. , dj81. , dj82. , dj83. , dj84. , dj85. , dj86. , dj87. , dj88. , dj89. , dj8a. , dj8b. , dj8c. , dj8d. , dj8e. , dibE. , dibF. , dibH. , dibI. , dibJ. , dibK. , dibv. , dibw. , dibx. , dicb. , dicc. , dl3.. , dl31. , dl32. , dl33. , dl3x. , dl3y. , dl3z. , dlB.. , dlB1. , dlB2. , dlD.. , dlD1. , dlD2. , dl2.. , dl23. , dl24. , dl2y. , dl2z. , dl21. , dl22. , dl25. , dl26. , dl27. , o424. , o425. , o426. , o427. , o428. , o429. , o42a. , o42A. , o42b. , o42B. , o42c. , o42C. , o42d. , o42D. , o42e. , o42E. , o42f. , o42F. , o42g. , o42G. , o42h. , o42H. , o42i. , o42I. , o42j. , o42J. , o42k. , o42K. , o42l. , o42L. , o42m. , o42M. , o42n. , o42N. , o42o. , o42O. , o42p. , o42P. , o42q. , o42Q. , o42r. , o42R. , o42s. , o42S. , o42t. , o42T. , o42u. , o42U. , o42v. , o42V. , o42W. , o42X. , o42Y. , o42Z. , o4d.. , o4d1. , o4d2. , o4d3. , o4d4. , o4d5. , o4d6. , o4d7. , o4d8. , o4d9. , o4da. , o4dA. , o4db. , o4dB. , o4dc. , o4dC. , o4dd. , o4dD. , o4de. , o4dE. , o4df. , o4dF. , o4dg. , o4dh. , o4di. , o4dj. , o4dk. , o4dl. , o4dm. , o4dn. , o4do. , o4dp. , o4dq. , o4dr. , o4ds. , o4dt. , o4du. , o4dv. , o4dw. , o4dx. , o4dy. , o4dz. , dlE.. , dlE1. , djj.. , djj1. , djj2. ,

		djj3. , djj4. , djj5. , djj6. , djj7. , djj8. , djj9. , djjA. , djjB. , djjC. , djjD. , djjE. , dq7.. , dq71. , djb.. , djb3. , djb4. , o44.. , o443. , o44z. , dm2.. , dm21. , dm2z. , dj1.. , dj11. , dj12. , dj13. , dj14. , dj15. , dj16. , dj17. , dj18. , dj19. , dj1a. , dj1A. , dj1B. , dj1C. , dj1D. , dj1e. , dj1E. , dj1f. , dj1F. , dj1g. , dj1G. , dj1h. , dj1H. , dj1i. , dj1I. , dj1j. , dj1J. , dj1k. , dj1K. , dj1l. , dj1L. , dj1m. , dj1M. , dj1n. , dj1N. , dj1o. , dj1O. , dj1p. , dj1P. , dj1q. , dj1Q. , dj1r. , dj1R. , dj1s. , dj1S. , dj1t. , dj1T. , dj1u. , dj1U. , dj1v. , dj1V. , dj1w. , dj1W. , dj1x. , dj1X. , dj1y. , dj1Y. , dj1z. , dj1Z. , dj2.. , dj21. , djy.. , djy1. , djy2. , djy3. , djy4. , djy5. , djy6. , djy7. , djy8. , djy9. , djyA. , djyB. , djyC. , djyD. , djyE. , djyF. , djyG. , djyH. , djyI. , djz.. , djz1. , djz2. , djz3. , djz4. , djz5. , djz6. , djz7. , djz8. , djz9. , djza. , djzA. , djzb. , djzB. , djzc. , djzC. , djzd. , djzD. , djze. , djzE. , djzf. , djzF. , djzg. , djzG. , djzh. , djzH. , djzi. , djzI. , djzj. , djzJ. , djzk. , djzK. , djzl. , djzL. , djzm. , djzM. , djzn. , djzo. , djzO. , djzp. , djzP. , djzq. , djzQ. , djzr. , djzR. , djzs. , djzS. , djzt. , djzT. , djzu. , djzU. , djzv. , djzV. , djzw. , djzW. , djzx. , djzX. , djzy. , djzY. , djzz. , djzZ. , o45.. , o451. , o452. , o453. , o454. , o455. , o456. , o457. , dia9. , dj1c. , dj1d. , dj25. , o458. , o473. , o47B. , di1j. , dj22. , dj7.. , dj71. , dj72. , dj73. , dj74. , dj75. , dj76. , dj77. , dj78. , dj79. , dj7A. , dj7B. , dj7C. , dj7D. , dj7E. , dj7F. , dj7G. , dA2.. , dA21. , dA22. , djd.. ,

		djd1. , djd2. , djd3. , djdz. , o46.. , o461. , o462. , o46z. , dl9.. , dl91. , dl92. , di9.. , di91. , di92. , di9y. , di9z. , dj1b. , djk.. , djk1. , djk2. , djk3. , djk4. , djk5. , djk6. , djk7. , djk8. , djk9. , djkA. , djkB. , djke. , djkE. , djkf. , djkg. , djkh. , djkH. , djkI. , djkJ. , djkk. , djkK. , djkL. , djkM. , djkn. , djkN. , djko. , djkO. , djkp. , djkP. , djkq. , djkQ. , djkr. , djkR. , djks. , djkS. , djkt. , djkT. , djku. , djkU. , djkv. , djkV. , djkw. , djkW. , djkx. , djkX. , djky. , djkz. , djkC. , djkD. , djkF. , djkG. , djki. , djkj. , djkl. , djkm. , dje.. , o47.. , o471. , o472. , o474. , o475. , o476. , o477. , o478. , o479. , o47A. , o47y. , o47z. , o4b.. , o4b1. , o4b2. , di2.. , di21. , di22. , di23. , di24. , di25. , di26. , di27. , di28. , di29. , di2a. , di2A. , di2b. , di2B. , di2c. , di2C. , di2d. , di2e. , di2E. , di2F. , di2g. , di2h. , di2i. , di2I. , di2j. , di2J. , di2K. , di2l. , di2L. , di2m. , di2M. , di2n. , di2N. , di2o. , di2O. , di2p. , di2P. , di2q. , di2Q. , di2r. , di2R. , di2s. , di2S. , di2t. , di2T. , di2u. , di2U. , di2V. , di2w. , di2W. , di2x. , di2X. , di2y. , di2Y. , di2Z. , diaA. , diaC. , did.. , did1. , did2. , did3. , did4. , did5. , did7. , did8. , did9. , didA. , didB. , didC. , didD. , didE. , didF. , didG. , didH. , didu. , didv. , didw. , didx. , didy. , didz. , di2f. , di2G. , di2H. , di2v. , dia1. , dia2. , dia3. , dia6. , diaa. , diaD. , diaF. , diah. , diaH. , diaI. , diaJ. , diaK. , dial. , diaL. , diam. , diaM. , dian. , diao. , diap. , diaq. , diaQ. , diar. , diaR. , diaS. , diaT. , diau. , diaU. , diaV. ,

		diaX. , diaY. , diaZ. , dib3. , dib5. , dib8. , diba. , dibb. , dibB. , dibD. , dibe. , dibf. , dibG. , dibj. , dibL. , dibM. , dibn. , dibN. , dibO. , dibp. , dibP. , dibQ. , dibR. , dibs. , dibS. , dibt. , dibT. , dibu. , dibU. , dibV. , dibW. , dibX. , dibY. , dibz. , dibZ. , dic1. , dic2. , dic3. , dic4. , dic5. , dic9. , dica. , dicA. , dicD. , dicE. , dicF. , dicG. , dicI. , dicJ. , dicK. , dicL. , dicM. , dicN. , dicQ. , dicR. , dicS. , dicT. , dicU. , dicv. , dicV. , dicW. , dicX. , dicy. , did6. , diaj. , dib2. , diby. , djf.. , djf1. , djf2. , djf3. , djf4. , djf5. , djf6. , djf7. , djf8. , djf9. , djfa. , djg.. , djg2. , djg3. , djg4. , djg6. , o48.. , o481. , o482. , o483. , o484. , djg5. , o485. , djh.. , djh1. , djhz. , dm3.. , dm31. , dm32. , dm33. , dm3x. , dm3y. , dm3z. , dlA.. , dlA1. , dlA2. , dlA3. , dlA4. , dlA5. , dlA6. , j14.. , j141. , j14z. , j15.. , j151. , j152. , dl5.. , dl51. , dl52. , dl53. , dl54. , dl55. , dl56. , dl57. , dl58. , dl59. , dl5A. , dl5B. , dl5C. , dl5D. , dl5E. , dl7.. , dl71. , dl72. , dl73. , dl74. , djB.. , djB1. , djB2. , djB3. , djB4. , djB5. , djB6. , djB7. , djBT. , djBU. , djBV. , djBW. , djBX. , djBY. , djBZ. , djA.. , djA1. , djA2. , djA3. , djA4. , djA5. , djA6. , djA7. , djA8. , djA9. , djAa. , djAb. , djAc. , djAd. , djAe. , djAf. , djAg. , djAh. , djAi. , djAj. , djAk. , djAl. , djAm. , djAn. , djAo. , dji.. , dji1. , dji2. , dji3. , dji4. , dji5. , dji6. , dji7. , dji8. , dji9. , djia. , djiA. , djib. , djiB. , djic. , djiC. , djid. , djiD. , djie. , djiE. , djif. , djiF. , djig. , djiG. , djih. , djiH. , djii. , djiI. , djij. , djiJ. ,

		djik. , djiK. , djil. , djiL. , djim. , djiM. , djin. , djiN. , djio. , djiO. , djip. , djiP. , djiq. , djiQ. , djir. , djiR. , djis. , djiS. , djit. , djiT. , djiU. , djiv. , djiV. , djiw. , djiW. , djix. , djiX. , djiy. , djiY. , djiz. , djiZ. , dicO. , dicx. , dicY. , dicz. , die.. , dieA. , dieB. , diey. , diez. , dl8.. , dl81. , dl82. , dl83. , dl84. , dl85. , dl86. , dl87. , dl88. The following medication read codes were aso included, unless the participant also had epilepsy: dn3.. , dn31. , dn32. , dn33. , dn34. , dn35. , dn36. , dn37. , dn38. , dn39. , dn3a. , dn3A. , dn3b. , dn3B. , dn3c. , dn3C. , dn3d. , dn3D. , dn3e. , dn3E. , dn3f. , dn3F. , dn3G. , dn3H. , dn3I. , dn3J. , dn3K. , dn3v. , dn3w. , dn3x. , dn3y. , dn3z. , dnj.. , dnj1. , dnj2. , dnj3. , dnj4. , dnj5. , dnj6. , dnj7. , dnj8. , dnj9. , dnjA. , dnjx. , dnjy. , dnjz. , dnp.. , dnp1. , dnp2. , dnp3. , dnp4. , dnp5. , dnp6. , dnp7. , dnp8. , dnp9. , dnpr. , dnps. , dnpt. , dnpu. , dnpv. , dnpw. , dnpx. , dnpy. , dnpz.

Appendix Table 4. Method of admission codes to identify emergency admissions**.** HES, Hospital Episode Statistics, SMR, Scottish Morbidity Record, PEDW, Patient Episode Database for Wales, A&E Accident & Emergency, GP, General Practitioner, NHS National Health Service.

Method of Admission Code	Source	Method of Admission Description
2A	HES	Emergency: via A&E of another hospital provider
2B	HES	Emergency: Transfer from another hospital provider
2D	HES	Emergency: Other
4	SMR	Emergency: Deliberate Self injury or poisoning
5	SMR	Emergency: Road Traffic Accident
6	SMR	Emergency: Home Accident
7	SMR	Emergency: Other injury
8	SMR	Emergency: Other
20	SMR	Urgent Admission, no additional detail added
21	PEDW	Emergency: via A&E or dental casualty department
22	PEDW	Emergency: after GP request for immediate admission
23	PEDW	Emergency: Bed bureau
24	PEDW	Emergency: Consultant clinic of this or other provider
25	PEDW	Emergency: Domiciliary visit by Consultant
27	PEDW	Emergency: Via NHS Direct Services
28	PEDW	Emergency: Other means, incl. other A&E department
29	PEDW	Emergency: Other
30	SMR	Emergency Admission, no additional detail added
31	SMR	Patient Injury: Self Inflicted (Injury or Poisoning)
32	SMR	Patient Injury: Road Traffic Accident (RTA)
33	SMR	Patient Injury: Home Accident
34	SMR	Patient Injury: Accident at Work
35	SMR	Patient Injury: Other Injury, not elsewhere classified
36	SMR	Patient Non-Injury
38	SMR	Other Emergency Admission (including emergency transfers)
39	SMR	Emergency Admission, type not known