Associations between chronic kidney disease and mental health disorders and psychoactive drugs in the UK general population

Masao Iwagami

Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy of the University of London

September 2018

Department of Non-Communicable Disease Epidemiology
Faculty of Epidemiology and Population Health
LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Funded by the Honjo International Scholarship Foundation
Research group affiliation: Electronic Health Records Research Group

Declaration

I, Masao Iwagami, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed [redacted]

Date 13/sep/2018

Abstract

This thesis examined the association between chronic kidney disease (CKD) and both mental health disorders and psychoactive drugs, using a large contemporary UK database of routine medical record data (Clinical Practice Research Datalink [CPRD]). To fill the gap between what is known and what is unknown in this field, I focused on two main topics: (i) severe mental illness (SMI), with and without a history of lithium use, and CKD, and (ii) CKD and antidepressants (mainly prescribed for common mental health disorders such as depression and anxiety) and associated serious adverse outcomes.

I first conducted a population-level validation study comparing prevalence estimates of decreased kidney function (defined as estimated glomerular filtration rate of <60 ml/min/1.73 m^2) and renal replacement therapy (RRT) in the CPRD population with nationally representative statistics (Health Survey for England and UK Renal Registry). Findings suggested that most patients with decreased kidney function and RRT are probably captured in the CPRD.

Secondly, I conducted a cross-sectional study on the association between SMI, including schizophrenia and bipolar disorder, and CKD (defined as two measurements of estimated glomerular filtration rate of <60 ml/min/1.73 m^2 over ≥3 months in the past five years). Patients with SMI, especially lithium users, had a significantly higher prevalence of both CKD and RRT than the general population.

Thirdly, I conducted a matched cohort study comparing the prevalence and incidence of antidepressant prescription between patients with and without CKD (matched for age, sex, general practice, and calendar time). Patients with CKD were approximately one and a half times more likely to receive antidepressants for mental health conditions such as depression and anxiety.

Finally, I examined the gastrointestinal (GI) bleeding risk of selective serotonin reuptake inhibitors (SSRIs) by level of kidney function. While the relative risk for GI bleeding associated with SSRIs (i.e. the fully-adjusted rate ratio between periods with and without SSRI prescription) was constant regardless of baseline kidney function, the excess risk for GI bleeding associated with SSRIs (i.e. the fully-adjusted rate difference between periods with and without SSRI exposure) increased markedly as baseline kidney function deteriorated.

In conclusion, a close association between CKD and mental health disorders was suggested in the UK general population. It is evident that patients with CKD are more likely to be prescribed antidepressants, and this may cause serious adverse outcomes such as GI bleeding associated with SSRIs. The risk-benefit balance of antidepressants for patients with CKD may need to be reconsidered in light of this new evidence.

Acknowledgements

I am very grateful to my supervisors, Dorothea Nitsch and Laurie A Tomlinson, for their advice, encouragement, and support throughout my Master's and research degrees at London School of Hygiene and Tropical Medicine.

I am also grateful to my advisory committee members, Liam Smeeth, Kathryn E Mansfield, Ian Douglas and Stephen Evans, and my upgrading examiners, Krishnan Bhaskaran and Ben Caplin.

I would like to thank my other coauthors in published papers, Helen I McDonald, Anna Casula, Fergus J Caskey, Grant Aitken, Simon DS Fraser, Paul J Roderick, Joseph F Hayes, Kate Walters, and David PJ Osborn, for their suggestions and contributions.

I would also like to thank all members of the Electronic Health Research Group at London School of Hygiene and Tropical Medicine for sharing their expertise.

I am grateful to the Honjo International Scholarship Foundation in Japan for supporting me to stay in London and undertake the research degree at London School of Hygiene and Tropical Medicine.

Finally, I would like to express my gratitude to my family, Ren, Junko, Sanae, and Etsuo Iwagami for their supports and encouragement.

Funding

Masao Iwagami was supported by the Japanese Honjo International Scholarship Foundation to undertake the research degree at London School of Hygiene and Tropical Medicine. The funder had no role in the execution of this thesis or interpretation of study results.

Table of Contents

List of tables

List of figures

Abbreviations

ACEI/ARBs = Angiotensin converting enzyme inhibitors and angiotensin-receptor blockers

AKI = acute kidney injury

BMI = body mass index

CKD = chronic kidney disease

CKD-EPI equation = Chronic Kidney Disease Epidemiology Collaboration equation

CPRD = Clinical Practice Research Datalink

CI = confidence interval

DPC = Diagnosis Procedure Combination

ESRD = end-stage renal disease

eGFR = estimated glomerular filtration rate

GI = gastrointestinal

GP = general practitioner

GFR = glomerular filtration rate

HES = Hospital Episodes Statistics

ICD-10 = International Classification of Diseases version 10

IDMS = isotope dilution mass spectrometry

IMD = Index of Multiple Deprivation

IQR = interquartile range

ISAC = Independent Scientific Advisory Committee

KDIGO = Kidney Disease Improving Global Outcomes

MDRD equation = Modification of Diet in Renal Disease equation

NHS = National Health Service

NICE = National Institute for Health and Care Excellence

NKF K/DOQI = National Kidney Foundation, Kidney Disease Outcomes Quality Initiative

NSAIDs = non-steroidal anti-inflammatory drugs

QOF = Quality and Outcomes Framework

RCT = randomised controlled trial

RRT = renal replacement therapy

SMI = severe mental illness

SSRI = selective serotonin reuptake inhibitor

VAMP = Value Added Medical Products

Chapter 1: Introduction

In this introductory chapter, I present a brief overview of chronic kidney disease (CKD), mental health disorders and psychoactive drugs. I will then summarise the aims and objectives of the thesis and provide an outline of the thesis.

1.1. General background

1.1.1. Chronic kidney disease (CKD)

Kidneys are important organs, the main role of which is to remove metabolic waste products in the body by producing urine. CKD is broadly defined as the presence of kidney damage or decreased kidney function that persists for three months [1, 2]. A more technical definition of decreased kidney function and CKD will be provided in **chapter 3**. Briefly, this thesis focuses on CKD stages 3 to 5, defined as two or more consecutive measurements of decreased kidney function (i.e. estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) for over three months.

CKD is common in patients with a variety of conditions, including ageing, diabetes, hypertension, cardiovascular diseases, smoking, and obesity [1]. The worldwide prevalence of CKD, based on evidence of kidney damage or decreased kidney function, is estimated to be 8-16% [3]. According to the Health Survey for England 2009/2010 (a population representative survey), the prevalence of eGFR <60 mL/min/1.73 m^2 (as proxy for CKD stages 3 to 5) was approximately 6% in men and 7% in women [4]. A study comparing the results of Health Surveys for England 2003 and 2009/2010 suggested that the prevalence of eGFR <60 mL/min/1.73 m^2 within each age and gender group decreased slightly over this seven-year period [5]. However, because age is a strong determinant of CKD (e.g. the Health Survey for England 2009/2010 showed that the prevalence of eGFR <60 mL/min/1.73 m^2 was less than 5% in people aged <55, but it increased up to over 30% in people aged >75 [4]), the overall prevalence of CKD is expected to be increasing in most developed countries as the population ages [6].

One serious consequence of CKD is end-stage renal disease (ESRD) requiring renal replacement therapy (RRT); this involves haemodialysis, peritoneal dialysis, and kidney transplantation. However, only a very small minority of patients with CKD end up undergoing

RRT [7]. According to the UK Renal Registry 2014, the incidence and prevalence of RRT was 115 (per year) and 913 per million population, respectively [8, 9].

CKD is a silent disease, meaning that patients with CKD do not have any symptoms until the kidney function is severely decreased (e.g. GFR 20–30 mL/min/1.73 m^2). However, even moderate CKD (e.g. eGFR 45–59 mL/min/1.73 m^2) was found to be associated with an increased risk of death, cardiovascular events, and hospitalisation [10]. Moreover, accumulating evidence suggests that moderate CKD is also associated with non-cardiovascular outcomes, including infection [11, 12], bleeding [13, 14], and fracture [15, 16].

The mainstream of care related to CKD consists of early detection and prevention of CKD progression by intervening in modifiable risk factors (e.g. better control of diabetes, smoking cessation), and treatment of comorbidities such as high blood pressure and dyslipidemia [1]. In addition, when caring for patients with decreased kidney function in daily practice, drug choice and dosage need to be carefully considered, as some drugs and their metabolites are cleared by the kidneys.

1.1.2. Mental health disorders and psychoactive drugs

As represented by the Diagnostic and Statistical Manual of Mental Disorders [17], mental health disorders have been sophisticatedly categorised through decades of effort by hundreds of international experts (i.e. psychiatrists) across all aspects of mental health. However, the focus of this thesis is the association between CKD and mental health problems in the primary care setting. Therefore, with reference to the Quality and Outcomes Framework (QOF), a system governing the performance management and payment of general practitioners (GPs) [18], and National Institute for Health and Care Excellence (NICE) guidance [19], I will focus on two broad categories of mental health disorders: (i) severe mental illness (SMI), including schizophrenia, bipolar disorder, and other psychoses, and (ii) common mental health disorders, including depression and anxiety disorders.

Psychoactive drug generally suggests a chemical substance that affects mood, perception or consciousness as a result of changes in the functioning of the nervous system (brain and spinal cord) [20]. In medicine, psychoactive drugs include anaesthetics, analgesics, anticonvulsants, antiparkinsonian drugs, antidepressants, anxiolytics, antipsychotics, and stimulant medications.

Among a range of psychoactive drugs, I will focus on lithium (mainly prescribed for SMI) and antidepressants (mainly prescribed for common mental health disorders).

(i) Severe mental illness (schizophrenia, bipolar disorder, and other psychoses)

The QOF included SMI as one of its important clinical areas in 2004 [18] and defined SMI as comprising schizophrenia, bipolar disorder, and other non-organic psychotic illnesses.

In brief, schizophrenia is the most common form of the psychotic disorders and is characterised by hallucinations (i.e. perception in the absence of any stimulus) and delusions (i.e. fixed or falsely held beliefs). Schizophrenia affects approximately seven in 1000 adults, and its onset is mostly between the ages of 15 and 35 [21]. The mainstay of the treatment for schizophrenia is oral antipsychotic medication under the supervision of psychiatrists, in conjunction with psychological interventions (e.g. family intervention and individual cognitive behavioural therapy) [22].

Bipolar disorder is characterised by episodes of mania (i.e. abnormally elevated mood or irritability and related symptoms, with severe functional impairment or psychotic symptoms for seven days or more) or hypomania (i.e. abnormally elevated mood or irritability and related symptoms, with decreased or increased function for four days or more) and episodes of depressed mood [23]. The lifetime prevalence of bipolar disorder is estimated at around 1.4% of the adult population, and the peak age of onset is 15-19 years. Treatment drugs include lithium (as the first-line monotherapy), valproate, and antipsychotics such as olanzapine and quetiapine, which may be initiated in secondary care (i.e. by psychiatrists) but continued in primary care [24].

(ii) Common mental health disorders (depression and anxiety disorders)

The relevant NICE guidance (‘Common mental health problems: identification and pathways to care’) regards depression and anxiety disorders (i.e. generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and social anxiety disorder) as “common mental health problems” [25]. These conditions may affect up to 15% of the population at any one time, with a lifelong course of relapse and remission. According to the guidance, the vast majority of diagnosed depressive and anxiety disorders are treated in primary care.

For subthreshold symptoms and mild to moderate common mental health disorders, low intensity interventions (e.g. cognitive behavioural therapy, interpersonal therapy, structured group physical activity programme, group-based peer support programme) are initially recommended. However, if these treatments are ineffective, the next step includes antidepressant medication. For people with an initial presentation of moderate or severe depression, a psychological intervention in combination with an antidepressant may be the first choice. For people with anxiety disorders who have not responded to low-intensity interventions, treatment options include cognitive behavioural therapy and antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs). Use of benzodiazepine is currently discouraged except as a short-term measure during crises [26].

1.1.3. Known and unknown associations between CKD and mental health disorders and psychoactive drugs

(i) SMI and CKD

People with SMI are known to have shorter life expectancy than the general population, by around 10-20 years [27-32]. Their premature deaths are attributable not only to suicide and accident, but also to physical illnesses, especially cardiovascular diseases such as coronary heart disease and stroke [31-35]. The high rate of cardiovascular deaths in patients with SMI has been attributed to a high prevalence of lifestyle-related conditions (e.g. smoking and obesity) [36-39], sub-optimal screening/assessment of cardiovascular risks [40, 41] and sub-optimal management of underlying diseases (e.g. hypertension, diabetes, and dyslipidaemia) [42-44]. For these reasons, the QOF has focused on the management of physical health conditions in people with SMI by including indicators related to annual monitoring of blood pressure, total cholesterol:high-density lipoprotein ratio, blood glucose or haemoglobin A1c, and body mass index (BMI) [18].

People with SMI have an increased prevalence of several risk factors for CKD, including smoking and diabetes [39, 42, 45]. Moreover, patients with SMI may be treated with lithium, which is a known risk factor for kidney function decline [46, 47]. According to a systematic review and meta-analysis published in 2012 (which included nine case-control studies) [48], the GFR of patients taking lithium was significantly lower than that of matched controls. Although only a small number of studies have looked at ESRD as a research outcome, a large Swedish study showed that the prevalence of ESRD requiring RRT was 0.5% (18 out of 3369)

among ever lithium users, while the prevalence of RRT in the Swedish general population is around 0.08% [49].

Therefore, it can be hypothesised that people with SMI are more likely to develop CKD than those without SMI in the general population. However, there has been limited research investigating the prevalence of CKD in people with SMI, especially in non-lithium users [39, 50, 51]. According to a cross-sectional study in London, UK, the prevalence of recorded diagnosis of CKD was 4.9% (212/4,346) and 1.8% (5,487/304,297), in those with and without SMI, respectively [39]. A Taiwanese cohort study showed that people with schizophrenia were more likely to receive a diagnosis of CKD [50]. A cross-sectional analysis of Scottish primary care demonstrated that people with bipolar disorder had a higher prevalence of recorded diagnosis of CKD than people without (7.3% vs. 2.4%) [44]. The major limitation of these studies was that CKD was defined based on recorded diagnosis of CKD. The validity of this measure is generally unsatisfactory compared to biochemical definitions of CKD in electronic health records [52]. In addition, the studies did not sufficiently consider differences in known CKD risk factors between those with and without SMI. Moreover, the sample sizes employed in these studies were insufficient to examine the association between SMI and ESRD requiring RRT.

(ii) CKD and antidepressants for common mental health disorders

Antidepressant prescription in patients with CKD

The high prevalence of depression and anxiety among patients with ESRD requiring RRT is established [53, 54]. In addition, the association between pre-dialysis CKD and depression and anxiety has been well-studied to date. A systematic review and meta-analysis published in 2013 [55], which included 228 studies, found that (interview-defined) depression affected almost one quarter of adults with pre-dialysis CKD. Some of the studies included in the meta-analysis also assessed anxiety via the Hospital Anxiety and Depression Scale. For example, Lee et al. reported that the prevalence of anxiety based on Hospital Anxiety and Depression Scale was 27.6% among patients with pre-dialysis CKD [56]. The potential explanations for the association between CKD and common mental health disorders include (i) patients' concerns about CKD progression towards dependence on maintenance dialysis [57, 58], (ii) co-existing chronic diseases, such as diabetes and heart failure, which are also known to be associated with depressive symptoms [59, 60], and (iii) uremic toxins in the advanced stage of CKD [61].

However, a relatively small number of studies have been conducted regarding how antidepressants (i.e. the first-line treatment drug for depression and anxiety) are prescribed for CKD patients in real-world clinical practice. To the best of my knowledge, there has been no such study in the UK, although two large US studies have investigated antidepressant prescription among patients with pre-dialysis CKD [62, 63]. In a study based on the US Veterans Affairs database, antidepressants were prescribed for nearly 30% of 598,153 veterans with non-dialysis-dependent CKD stages 1 to 5 [62]. However, these findings may not be generalisable, as veterans are more likely to have common mental health problems than the general population [64]. In the baseline cross-sectional survey of the Chronic Renal Insufficiency Cohort study, 18.2% of nearly 4,000 patients with pre-dialysis CKD were using antidepressants [63]. However, the study population consisted of volunteer participants recruited from nephrology clinics, causing selection bias. Moreover, neither study utilised a comparison group of people without CKD. Therefore, the extent to which prescription frequency differs between patients with and without CKD remains unknown.

Efficacy and risk of antidepressants in patients with CKD

In addition to the unknown antidepressant prescription pattern, a recent systematic review published in 2012 concluded that the efficacy and safety of antidepressants in patients with pre-dialysis CKD have not been studied [65]. Of the 19 relevant articles published between 1950 and 2011, 17 targeted patients on maintenance dialysis. The remaining two articles, which focused on patients with pre-dialysis CKD, were merely case reports [66, 67]. Because antidepressants are removed by dialysis, pharmacokinetics and pharmacodynamics are quite different in CKD patients with and without dialysis. Therefore, findings obtained from the dialysis population cannot be applied to the pre-dialysis CKD population. The lack of safety information pertaining to this patient group matters a lot, as patients with pre-dialysis CKD account for the vast majority (>95%) of the CKD population [68].

Regarding the efficacy of antidepressants among patients with CKD, the results of a randomised controlled trial (RCT) from the US have been recently reported [69]. This randomised, double-blind, placebo-controlled trial involving 201 patients with non-dialysis-dependent CKD stages 3 to 5 found that treatment with normal (50 mg/day) to higher dose (up to 200 mg/day) of sertraline (an SSRI) for 12 weeks did not significantly improve depressive symptoms: the 16-item Quick Inventory of Depression Symptomatology-Clinician Rated

(QIDS-SR16) score changed by -4.1 in the sertraline group and by -4.2 in the placebo group (between-group difference 0.1 [95% CI, -1.1 to 1.3]; P = 0.82). There was no significant difference in the incidence of prespecified serious adverse events (death, dialysis initiation, hospitalisation, and bleeding episode) between the groups. However, because the sample size was determined based on the drug's expected efficacy (i.e. difference of improved QIDS-SR16 score between the groups), the study did not have adequate power to identify the serious adverse outcomes associated with this antidepressant.

In the general population, several studies have suggested an association between antidepressant use and increased risk of serious adverse outcomes, including stroke [70], hip fracture [71], and gastrointestinal (GI) bleeding [72]. However, these studies did not differentiate between patients with and without CKD. Many antidepressants are excreted by the kidneys, with or without metabolism in the liver. Therefore, serum antidepressant levels or their metabolites may tend to be higher in patients with CKD. In addition, baseline risks of these adverse outcomes are higher in patients with CKD, who have a larger number of comorbidities and medications, than those without CKD. Therefore, it is of concern that antidepressants may be more strongly associated with serious adverse outcomes in patients with CKD than those without.

1.2. Aims and objectives of thesis

The overall aim of the thesis is to better understand the associations between CKD and both mental health disorders and psychoactive drugs in the UK general population, by filling the gap between what is known and what is unknown in this research field. To this end, I use a large, contemporary UK database of routine medical record data (Clinical Practice Research Datalink [CPRD]).

The main reasons why I use this data source are as follows:

- The CPRD is broadly representative of the UK general population in terms of age and sex [73], enabling me to examine the association between CKD and mental health disorders in the general population.
- A large sample size is required for studies examining serious (but uncommon) adverse outcomes of antidepressants, such as GI bleeding associated with SSRIs, in patients with

CKD.

- From a practical perspective, the data were available to me as a member of the Electronic Health Records Research Team at the London School of Hygiene and Tropical Medicine.

Considering what remains unknown in the associations between CKD and both mental health disorders and psychoactive drugs (as already discussed in **section 1.1.3**), I established the following four research questions:

1.2.1. Research question 1: What is the prevalence of CKD and RRT in the CPRD, and is it similar to the nationally representative statistics?

This is important groundwork for the following research questions, which examine the associations between CKD and both mental health disorders and psychoactive drugs. CKD is generally a silent disease until the end-stage, and therefore the diagnosis of pre-dialysis CKD is almost entirely driven by laboratory testing. In this thesis, patients with CKD (stages 3 to 5) will be identified using the laboratory test results recorded in the CPRD. However, creatinine testing is not universal in UK primary care. Therefore, it is vital to understand what proportion of patients with CKD can be identified in the current CPRD, and whether these patients are representative or only a subset of CKD patients in the community. It is expected that GPs are selectively (instead of randomly) testing patients with known CKD risk factors (e.g. diabetes). A study comparing the prevalence of CKD between the CPRD and nationally representative statistics (Health Survey for England 2009/2010) will reveal whether people without serum creatinine testing in the CPRD are likely or unlikely to have CKD. In addition, the prevalence of RRT, which can be defined as recorded diagnoses suggesting RRT in the CPRD, will be compared with UK Renal Registry, which registers all patients on RRT in the UK.

1.2.2. Research question 2: Is CKD more common in patients with SMI than those without SMI in the general population?

People with SMI have an increased prevalence of several risk factors for CKD, such as smoking and diabetes. Moreover, lithium is also a strong risk factor for decreased kidney function. Therefore, it can be hypothesised that patients with SMI are more likely to develop CKD. Accordingly, it is expected that patients with SMI show a higher prevalence of CKD and ESRD requiring RRT than those without SMI in the general population. However, the prevalence of biochemically-defined CKD in the SMI population has not been well-studied to date. Moreover,

sample sizes in previous studies were insufficient to examine the association between SMI and RRT. Thus, new research using a large population-based database is warranted to address this question.

1.2.3. Research question 3: Are patients with CKD more likely to be prescribed antidepressants than those without CKD in the general population?

Although the association between CKD and common mental health problems is well established, a relatively small number of studies have been conducted regarding how antidepressants (i.e. the first line of drug treatment for depression and anxiety) are prescribed for CKD patients in real-world clinical practice. To my knowledge, there has been no study examining this in the UK general population. Frequency and patterns of antidepressant prescription need to be compared between patients with and without CKD, as different (class of) antidepressants may be used for different purposes (e.g. depression, anxiety, pain and insomnia as an off-label use) between the groups.

1.2.4. Research question 4: Is the risk of serious adverse outcomes associated with antidepressants (e.g. GI bleeding risk of SSRIs) increased in patients with lower kidney function?

There has been no study examining the association between antidepressants and serious adverse outcomes in the CKD population. Because (i) CKD patients may have limited ability to excrete antidepressants into urine, and (ii) CKD patients tend to have a higher baseline risk of adverse outcomes due to multi-morbidity and polypharmacy, it can be hypothesised that the risk of serious adverse outcomes associated with antidepressants is larger in patients with CKD compared to patients without CKD. A large study is warranted to examine the association between antidepressants and serious adverse outcomes among patients with CKD, as well as to test whether the risks differ between patients with and without CKD.

GI bleeding is one of the serious adverse outcomes associated with SSRIs, which block serotonin reuptake in platelets and inhibit platelet aggregation [74, 75]. A number of studies have shown an association between the use of SSRIs and GI bleeding [72, 76-85]. However, none of these studies focused on the GI bleeding risk of SSRIs among patients with CKD. Therefore, I here take GI bleeding risk of SSRIs as an appropriate example through which to

examine the association between antidepressants and serious adverse outcomes by CKD status and level of kidney function.

1.3. Outline of thesis

The thesis is comprised of ten chapters. Owing to the research paper-style format, five research papers (including three published papers and two accepted papers in peer-reviewed journals) are incorporated into some chapters. A concise summary of these research papers is presented in **Table 1** below. Each chapter containing a research paper consists of: a brief introduction, the published or accepted paper, additional analyses and discussions, and chapter summary. Other chapters have their own structures. The outline of the thesis is as follows:

Chapter 1 introduced the general background, aims, objectives, and research questions.

Chapter 2 describes the details of the data sources used in the thesis.

Chapter 3 explains how to estimate kidney function and how to define decreased kidney function and CKD (stages 3 to 5) using the CPRD.

Chapter 4 describes the rationale and method used to create a dataset for cross-sectional studies in the first and second research papers.

Chapter 5 includes the first research paper, which concerns the validity of CKD and RRT prevalence estimates in the CPRD.

Chapter 6 incorporates the second research paper on the association between SMI and CKD.

Chapter 7 introduces the process used to establish a matched cohort of patients with and without CKD (stages 3 to 5) in the third and fourth research papers.

Chapter 8 includes the third research paper, comparing frequency and patterns of antidepressant prescription between matched patients with and without CKD.

Chapter 9 incorporates the fourth research paper regarding the GI bleeding risk of SSRIs by level of kidney function.

Chapter 10 summarises the main results of each study, explores the implications of the findings for clinical practice and future research, discusses the overall strengths and limitations, and concludes the thesis.

Table 1. Concise summary of published and accepted papers

	Chapter	Short title	Study design	Study population	Exposure	Outcome	CKD is regarded as
Paper 1[a]	5	Prevalence of CKD and RRT in CPRD	Cross-sectional	People aged ≥25 registered in CPRD at 31/3/2014 (N = 2,761,755)	n/a	Decreased kidney function, CKD and RRT	Outcome
Paper 2[b]	6	SMI and CKD		People aged 25-74 registered in CPRD at 31/3/2014 (N = 2,418,730)	SMI (vs. no SMI)	CKD and RRT	Outcome
Paper 3[c]	8	CKD and antidepressant prescription	Cohort	Matched patients with and without CKD (stages 3 to 5) in HES-linked CPRD between 2004 and 2014 (N = 484,698)	CKD (vs. no CKD)	Antidepressant prescription	Exposure
Paper 4[d]	9	GI bleeding risk of SSRIs by kidney function		Same cohort as in Paper 3	SSRIs (vs. no SSRIs)	Hospitalisation for GI bleeding	Effect modifier
Additional paper[e]	Appendix A (related to chapter 7)	CKD and cause-specific hospitalisation		Same cohort as in Paper 3	CKD (vs. no CKD)	Cause-specific hospitalisation	Exposure

Abbreviations: CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; GI = gastrointestinal; HES = Hospital Episode Statistics; RRT = renal replacement therapy; SSRIs = selective serotonin reuptake inhibitors; SMI = severe mental illness.

[a]Iwagami M, et al. Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom. *Nephrol Dial Transplant.* 2017;32(suppl_2):ii142-ii150.

[b]Iwagami M, et al. Severe mental illness and chronic kidney disease: a cross-sectional study in the United Kingdom. *Clin Epidemiol*. 2018;10:421-429.

[c]Iwagami M, et al. Prevalence, incidence, indication, and choice of antidepressants in patients with and without chronic kidney disease: a matched cohort study in UK Clinical Practice Research Datalink. *Pharmacoepidemiol Drug Saf.* 2017;26:792-801.

[d]Iwagami M, et al. Gastrointestinal bleeding risk of selective serotonin reuptake inhibitors by level of kidney function: a population-based cohort study. *Br J Clin Pharmacol* (in press)

[e]Iwagami M, et al. CKD and cause-specific hospitalisation: a matched cohort study using Clinical Practice Research Datalink. *Br J Gen Pract.* (in press)

1.4. Chapter summary

Introduction

- CKD is common and associated with a variety of outcomes, including cardiovascular and non-cardiovascular conditions.
- In this thesis, I focus on two broad categories of mental health disorders, namely SMI (i.e. schizophrenia, bipolar disorder, and other psychoses) and common mental health disorders (i.e. depression and anxiety disorders).
- There have been a limited number of population-based studies on the burden of CKD among patients with SMI, with or without lithium use.
- Although a number of studies have suggested an association between CKD and common mental health disorders (depression and anxiety), the frequency and patterns of antidepressant prescription in patients with CKD are unknown in real-world clinical practice.
- There has been almost no epidemiological research investigating the serious adverse outcomes associated with antidepressants in patients with CKD.
- This thesis aims to better understand the associations between CKD and both mental health disorders and psychoactive drugs in the general population, using the CPRD.

Chapter 2: Data sources

This chapter describes the details of the data sources employed for this thesis, namely the CPRD with or without linkages to Hospital Episodes Statistics (HES) and Index of Multiple Deprivation (IMD).

2.1. Healthcare system in the UK

In the UK, a primary care system acts as a gatekeeper to health care; patients need to be registered with a primary care GP to access National Health Service (NHS) nonemergency care [86]. Patients are then referred to secondary care (i.e. specialists) as necessary. The NHS is free at the point of access for all UK residents, and over 98% of the UK population are registered with a GP [87].

Primary care practices have used computerised electronic health records since around 1990. There is only a limited number of suppliers of electronic health record software including EMIS, SystmOne, Vision, and Evolution [88]. GPs or healthcare practitioners in primary care electronically record patient information or events in primary care through coded diagnosis and free text. Prescriptions and most test results are automatically recorded in the system, while reports from secondary care (e.g. key diagnoses by specialists, and discharge data from hospitals) are also entered into the system retrospectively by practice staff.

2.2. Clinical Practice Research Datalink (CPRD)

The CPRD was originally launched in 1987 as the Value Added Medical Products (VAMP) dataset. The VAMP grew into the General Practice Research Database in 1993, and expanded to become the CPRD in 2012 [73, 89]. The CPRD collates routinely collected anonymised data from general practices using the Vision software system (at the time of this thesis), which agreed to provide data on a monthly basis. All people registered in participating practices are included in the dataset, except for those who have requested to their GPs to opt out of data sharing.

To ensure data quality, the CPRD checks quality indicators of each general practice and individual patients. At the practice level, the CPRD suggests an ‘up to standard’ date, based on

assurance of continuity in data recording and appropriate death recording. The data recorded after the 'up to standard' date in each practice are considered to have sufficiently high quality for use in research. At the individual level, the CPRD flags patients with records of 'acceptable' quality, based on over ten quality indicators related to registration date, year of birth, date and reason for being transferred out, gender, and the timing of recorded episodes. Data on patients where the recorded information is of acceptable quality are recommended for use in research. As of July 2013, the CPRD held information on 11.3 million patients whose information was of acceptable quality in 674 'up to standard' general practices, 4.4 million of whom were active (i.e. alive and registered at July 2013) and represented 6.9% of the total UK population [73].

The data in the CPRD are split into several files (see **Table 2** below). Each file includes a unique patient identifier, by which the patient-level files can be linked. Notably, Read codes (used in clinical, referral, immunisation, and test files) were developed in the UK in the early 1980s by Dr James Read as a hierarchical clinical classification system. At the time of this thesis, the CPRD used Read version 2, containing over 96,000 Read codes. In the CPRD, Medical codes ('Medcode') and Product codes ('Prodcode') are used in practice, which correspond to Read codes and the British National Formulary codes [90], respectively.

Table 2. Data files supplied by the CPRD

File type	What it holds	Example of contents
Patient	Demographic and registration status of patients	Patient identifier, month and year of birth, registration status, death date, transfer out date
Practice	Practice administrative data	Practice identifier, geographical region, date practice became 'Up to standard', last data collection date
Staff	Information about the staff members entering data	Staff identifier, gender, role
Consultation	Administrative information about the consultation	Date of clinical event, date of data entry, type of consultation, staff identifier and duration of consultation
Clinical	Clinical data regarding medical history	Date of clinical event, date of data entry, the CPRD medical code for the chosen Read code, additional details identifier, entity type
Additional Clinical Details	Specific data about a clinical event	Type of information held, called an 'entity', specific clinical details relating to that entity
Referral	Details on referrals to secondary care or specialists	The CPRD medical code for the chosen Read code, method of referral, referral specialty, urgency of referral
Immunisation	Data associated with immunisations	Reason for immunisation, type, stage, status and the compound used
Test	Test results	Type of test, result, normal range of result, unit of measure
Therapy	Information about therapies including medications and appliances	The CPRD product code for the medication, British National Formulary code, quantity of product, dose, pack size, number of days prescribed

Note: this table was entirely copied from the paper introducing the CPRD [73].

There is a linkage scheme in the CPRD. A subset of English practices in the CPRD (around 75% of all English CPRD practices, and nearly 60% of all UK CPRD practices) have consented to link their data with other data sources, including HES and IMD data for deprivation indices. The linkages are conducted via a trusted third party, mainly by using patients' NHS numbers for HES and the postcode of patients' residences for IMD data.

2.3. Hospital Episodes Statistics (HES)

HES is a database containing details of all admissions, outpatient appointments, attendances, and emergency admissions at NHS hospitals or independent-sector providers (private or charitable hospitals) in England [91, 92]. National data collection started in 1987, but the linkage with the CPRD became available in 1997 when patients' NHS numbers became a mandated return from hospitals. Among the entire HES data, I here explain the HES Admitted Patient Care only, which was used for part of this thesis.

HES was originally set up to manage and plan hospital services, and is now also used to reimburse hospital activity. In the HES Admitted Patient Care, a hospital admission is referred to as a 'spell' defined as an uninterrupted inpatient stay at one hospital. A 'spell' includes one or more 'episodes' (Finished Consultant Episode); an 'episode' represents a continuous period of care under one consultant team. The data recorded in HES Admitted Patient Care include age, sex, ethnicity, dates of admission, operations and discharge, admission method (emergency or planned), clinical diagnoses, and procedures. For each 'episode', up to 20 International Classification of Diseases version 10 (ICD-10) codes [93] are entered, based on a discharge summary completed by the treating clinician(s). The first (primary) diagnosis for the first 'episode' is expected to relate to the main reason for admission, although misclassification of code position is possible, if a patient had several medical conditions at the time of admission. For example, for patients admitted with myocardial infarction and heart failure, either diagnosis could be considered as the primary diagnosis.

2.4. Index of Multiple Deprivation (IMD)

The IMD is a deprivation index that is updated by the Department for Communities and Local Government every few years [94]. Although it has seen a number of small changes, the IMD mainly uses seven indicators: income, employment, health and disability, education, barriers to housing and services, living environment, and crime. Deprivation is categorised into quintiles, from one (representing the least deprived) to five (representing the most deprived). Patient-level IMD is assigned based on the postcode of residence of individual patients, while practice level IMD is also available, based on the postcode of general practices. It should be

noted that deprivation indices in different UK countries (i.e. England, Northern Ireland, Scotland, and Wales) are not comparable.

2.5. Data used for this thesis

For this thesis, I used the July 2014 version of CPRD. I used the CPRD without linkage in Papers 1 (Prevalence of CKD and RRT in CPRD) and 2 (SMI and CKD), while I used the CPRD linked to HES version 10 (covering the period from April 1997 to March 2014) in Papers 3 (CKD and antidepressant prescription) and 4 (GI bleeding risk of SSRIs by kidney function). The July 2014 version of the CPRD included data from 685 general practices in the UK. Of these practices, 398 (58%) of practices in England had links with HES version 10. The IMD evaluated in 2010 was used for this thesis, assuming that the deprivation status did not change over time. Practice-level IMD was used as a covariate for Paper 2, while individual-level IMD was used for Papers 3 and 4, supplemented by practice-level IMD (for less than 1% of patients with missing data from individual-level IMD).

Details on the cross-sectional datasets and cohorts created for each research question are given in the respective chapters.

2.6. Ethical approval

The CPRD has broad National Research Ethics Service Committee ethical approval for purely observational research using the primary care data and established data linkages. Ethical approval for this thesis was obtained from the London School of Hygiene and Tropical Medicine ethics committee (reference: 9196), as well as the Independent Scientific Advisory Committee, which oversees research involving CPRD data (protocol No. 16_055 for Papers 1 and 2, and protocol No. 15_219R for Papers 3 and 4).

2.7. Chapter summary

Data sources

- The CPRD is a database of anonymised primary care electronic health record data in the UK and includes the information on patient demographics, diagnoses (based on Read codes), prescriptions, laboratory test results, and referrals made by GPs.
- The CPRD can be linked to HES, which contains details of all admissions in English NHS trusts and consists of primary and subsidiary diagnoses, based on ICD-10 codes. Nearly 60% of general practices in the CPRD (75% of English general practices in the CPRD) have consented to linkages with HES data for research purposes.
- The IMD is a composite area-level marker of deprivation and is categorised into quintiles to suggest the socio-economic status of individual patients.
- The current thesis used the July 2014 version of the CPRD, with or without linkages to HES version 10 (covering the period from April 1997 to March 2014) and IMD (evaluated in 2010).

Chapter 3: Definition of decreased kidney function and CKD (stages 3 to 5) and estimation of glomerular filtration rate in this thesis

This chapter explains how to define decreased kidney function and CKD (stages 3 to 5) and how to estimate GFR of individual patients in this thesis, using the CPRD.

3.1. Existing guidelines to define decreased kidney function and CKD

CKD was formally defined in 2002 by the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) as follows [95]: 'The presence of chronic kidney disease should be established, based on presence of kidney damage and level of kidney function (glomerular filtration rate [GFR]), irrespective of diagnosis'. Either the marker(s) of kidney damage or decreased GFR, present for over three months, is required for the definition of CKD (see **Table 3** below). This definition of CKD has been consistent within the subsequent guidelines, including the NICE guidance for CKD (published in 2008) [1] and Kidney Disease Improving Global Outcomes (KDIGO) guideline for CKD (published in 2012) [96].

Table 3. Definition of chronic kidney disease in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guideline

1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either: - Pathological abnormalities; or - Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR <60 ml/min/1.73 m^2 for ≥3 months, with or without kidney damage

Abbreviation: GFR = glomerular filtration rate.
Note: this table was entirely copied from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guideline [95].

Notably, within these criteria, a GFR of <60 ml/min/1.73 m^2 was considered to be 'decreased kidney function' [1, 95, 96]. This cut-off was justified by a subsequent meta-analysis led by

the CKD Prognosis Consortium, demonstrating that all-cause mortality starts to increase from eGFR <60 ml/min/1.73 m^2, independent of age [97]. In the classification of CKD, GFR <60 ml/min/1.73 m^2 corresponds to CKD stages 3 to 5 in the NKF K/DOQI guideline [95], CKD stages 3a to 5 in the NICE guidance [1], and GFR categories G3a to G5 in the KDIGO guideline [96].

Therefore, throughout this thesis, decreased kidney function is defined as a single GFR <60 ml/min/1.73 m^2, whereas CKD (stages 3 to 5) is defined as two or more consecutive measurements of decreased kidney function (i.e. GFR <60 ml/min/1.73 m^2) for ≥3 months. Notably, decreased kidney function is not equal to CKD (stages 3 to 5), because a single low eGFR observed in real-world clinical practice may reflect temporarily decreased kidney function due to acute kidney injury (AKI) or increased serum creatinine level due to exercise or protein intake [96]. The benefits and limitations by use of the chronicity criterion to define CKD in the CPRD will be examined and discussed in detail in the following chapters.

3.2. How to estimate glomerular filtration rate (GFR) in this thesis

GFR represents the rate at which waste products in the blood are cleared through the kidney glomerular capillaries to make urine. The gold standard of GFR measurement is when exogenous markers (e.g. inulin, iothalamate) are given to patients and the rate of renal clearance of these substances is measured over time [98]. However, using this method, patients need to receive a bolus injection and close monitoring of these substances in their blood and urine. Alternatively, a single time point measurement of endogenous markers (e.g. serum creatinine, serum cystatin C) has been practically carried out to estimate GFR in routine clinical practice. The assumption underlying the use of such markers is that these substances are produced in the body and cleared by the kidney at a relatively constant rate (i.e. 'steady state assumption'). Creatinine is a waste product of muscle metabolism and is generated in the body at a relatively constant rate unless patients are in a catabolic condition.

In addition to the 'steady state assumption', there are further assumptions required to use serum creatinine to compare kidney function between different individuals. At a population level, creatinine production is influenced by a variety of factors including patients' demographics (age, sex, and ethnicity) and behaviours (exercise and dietary protein). Thus, taking patients'

demographics into account, several GFR estimation equations have been developed and validated (by comparing estimated GFRs based on these equations with GFRs estimated by exogenous markers) since the 1970s, including the Cockcroft-Gault equation [99], Modification of Diet in Renal Disease (MDRD) Study equation [100], and the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation [101]. Notably, the MDRD Study equation was proposed in 1999 and has been used in the automatic reporting system of eGFR in UK laboratories [102]. As of 2016, many UK laboratories are still reporting eGFR based on the MDRD Study equation [103]. However, the CKD-EPI creatinine equation (published in 2009) is more accurate, with smaller extent of measurement error, than the MDRD Study equation, especially among older patients and those with mildly decreased kidney function [98, 104]. Therefore, in this thesis, GFR is estimated from serum creatinine based on the CKD-EPI creatinine equation [101]:

$eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black ethnicity]

(where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of (Scr/κ) or 1, and max indicates the maximum of (Scr/κ) or 1)

More recently, the CKD-EPI cystatin C equation and CKD-EPI creatinine-cystatin C equation were proposed in 2012, which may be even more accurate than the CKD-EPI creatinine equation, because cystatin C production in the body is not affected by exercise and diet [98]. The measurement of cystatin C is recommended for people with a creatinine-based eGFR of 45–59 ml/min/1.73 m^2 and no proteinuria (to confirm or rule out CKD), according to the NICE guidance [1]. However, the cystatin C measurement is expensive (at the time of this thesis), and the testing rate of cystatin C among these eligible patients is seemingly very low within current UK primary care [105]. Thus, an additional use of cystatin C records does not seem to be helpful in improved classification of the CKD status in the current thesis.

3.3. Creatinine calibration

In laboratories, serum creatinine level can be measured by several types of assay methods, including CX3 and enzymatic creatinine assays. The CKD-EPI creatinine equation was

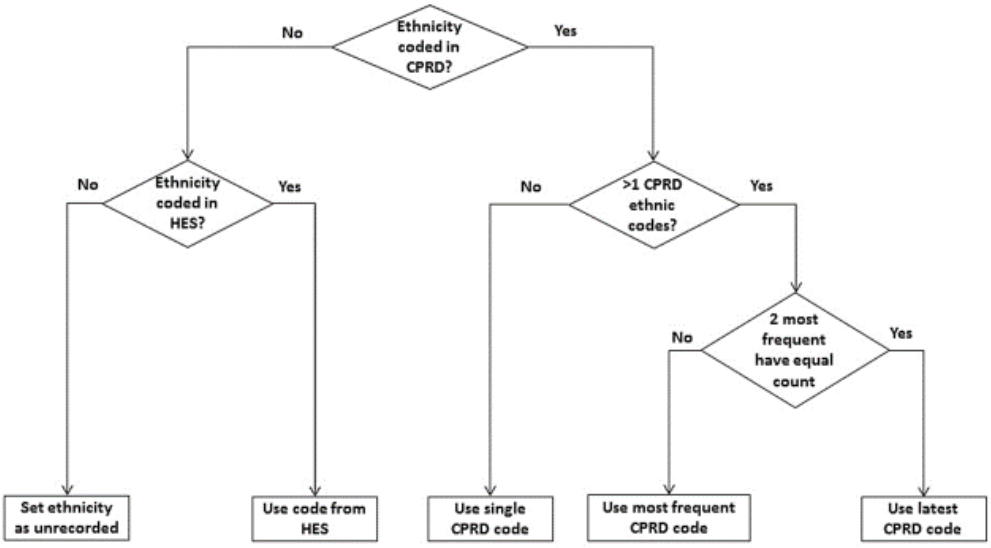
developed for serum creatinine measured by an internationally standardized enzymatic method, which is traceable to isotope dilution mass spectrometry (IDMS) [101]. In the past, the UK laboratories used the CX3 assay method and reported non-IDMS-traceable creatinine values. However, a phased introduction of laboratory-specific standardisation was proposed in the UK in 2006 [102]. It is thus expected that the proportion of laboratories reporting IDMS creatinine has increased since then, although the exact timing of standardisation in each laboratory is unknown. There is a systematic difference between non-IDMS-traceable and IDMS-traceable creatinine values, and it was suggested to multiply non-IDMS-traceable creatinine values by 0.95 to use the GFR estimation equations established for IDMS-traceable creatinine values [106].

Considering this temporal change in the assay method in the UK laboratories, in cross-sectional studies at 31 March 2014 in Papers 1 (Prevalence of CKD and RRT in CPRD) and 2 (CKD and SMI), I assumed that all the UK laboratories reported IDMS-traceable creatinine values in the main analysis, and conducted a sensitivity analysis by assuming that all the UK laboratories reported non-IDMS-traceable creatinine values. Meanwhile, in cohort studies during the period between April 2004 and March 2014 in Papers 3 (CKD and antidepressant prescription) and 4 (GI bleeding risk of SSRIs by kidney function), the majority (>80%) of patients were included into the cohort during the first half of the study period, i.e. before 2010 (see **chapter 7** for details). Therefore, in the cohort studies, I assumed that all the UK laboratories reported non-IDMS-traceable creatinine values, and multiplied the recorded creatinine values in the CPRD by 0.95 to use the CKD-EPI creatinine equation.

3.4. Determining ethnicity in the CPRD

Ethnicity information, black or non-black, is required in the use of the CKD-EPI creatinine equation [101]. It is known that ethnicity recording is not complete in the CPRD, although the QOF improved it greatly by incentivising ethnicity recording between 2006/07 and 2011/12 [107]. An algorithm was used to determine ethnicity in the CPRD with or without linkage to HES, that was established by Rohini Mathur and colleagues in the Electronic Health Record Research group at the London School of Hygiene and Tropical Medicine (see **Figure 1** below).

Figure 1. **Algorithm to determine ethnicity in the CPRD**



Abbreviations: CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics.
Note: this figure was copied from the reference [108].

Patients with missing ethnicity information were assumed to be non-black. This strategy is reasonable because the proportion of black patients (Black, African, Caribbean, or Black British) was low, at 3.5%, according to the 2011 UK census [109]. In particular, among those aged 65 or older, who account for the majority of patients with CKD [110], the proportion of black patients was 1.5% [109]. Moreover, GPs seem to be more likely to record ethnicity for non-white patients [107].

3.5. Proteinuria and other information related to kidney damage in the CPRD

Patients with no decreased kidney function but persistent proteinuria are classified as CKD stage 1 or 2 in the NKF K/DOQI guideline [95]. Moreover, the 2012 KDIGO guideline recommends the classification of patients according to GFR categories (G1 to G5) and persistent albuminuria categories (A1 to A3) [96]. However, in UK primary care, proteinuria is infrequently tested in the general population [111]: even among patients with CKD stages 3

to 5, for whom proteinuria testing was incentivised in the QOF [18], the testing rate of urinary albumin to creatinine ratio was 35.7% between 2007 and 2013 [112]. In the matched cohort of patients with and without CKD (stages 3 to 5) that were established as part of this thesis (see **chapter 7**), even by including dipstick tests, the testing rate of proteinuria in the year prior to cohort entry was low at 23.2% in the CKD group and 12.6% in the matched comparison group of no-known CKD during the study period between 2004 and 2014 [113]. In the diabetic population, in which the rate of urine testing is high [114], it may be accepted to assume that those without abnormal records did not have proteinuria [115, 116]. In the general population, however, it seems inappropriate to assume that people without urinalysis results did not have proteinuria.

Other information suggesting kidney damage, such as pathology specimens and results of imaging tests, are usually unavailable in the CPRD. This information may be recorded by GPs in the free text part of the CPRD. A strategy of automatic (computerised) free text searches may be useful in the future, but this was unavailable at the time of this thesis. Also, there is a limited access to the free texts in the CPRD for ethical reasons [89].

Therefore, throughout this thesis, I did not focus on CKD stages 1 and 2 based on proteinuria or other information related to kidney damage. Also, I was not able to stratify patients by the level of albuminuria or the presence or absence of kidney damage among patients with CKD stages 3 to 5.

3.6. Chapter summary

Definition of decreased kidney function and CKD and estimation of GFR in this thesis

- In this thesis, decreased kidney function is defined as a single GFR <60 ml/min/1.73 m^2.
- CKD (stages 3 to 5) is defined as two or more consecutive measurements of GFR <60 ml/min/1.73 m^2 over three months.
- GFR is estimated from serum creatinine records in the CPRD by using the CKD-EPI creatinine equation.
- Ethnicity (black or non-black) is determined using a previously established algorithm based on the CPRD with or without linkage to HES, and people with missing ethnicity information are assumed to be non-black.
- Proteinuria information is not used in this thesis, because proteinuria is infrequently tested in the general population within UK primary care.

Chapter 4: Establishing a dataset for cross-sectional studies and identifying patients with decreased kidney function and CKD

This chapter presents the rationale and method for establishing a dataset for the cross-sectional studies in Papers 1 (Prevalence of CKD and RRT in CPRD) and 2 (SMI and CKD). I also explain how to identify patients with decreased kidney function and CKD (stages 3 to 5) in the established cross-sectional dataset.

4.1. Introduction (rational for the cross-sectional design)

(i) Paper 1 (Prevalence of CKD and RRT in CPRD)

The purpose of the first study is to estimate the prevalence of decreased kidney function (in the main analysis) and CKD (in a sensitivity analysis) and RRT in the CPRD, and compare it with the nationally representative statistics (Health Survey for England 2009/2010 and UK Renal Registry 2014). For estimating a disease prevalence, the simplest way is to include all people registered in the CPRD on one day as the denominator. I chose 31 March 2014 for the study date, which is the most recent end date of a financial or QOF year (i.e. from 1 April to 31 March) among the available data (i.e. the July 2014 version of CPRD).

(ii) Paper 2 (SMI and CKD)

This second study used the same cross-sectional dataset as Paper 1. The general weakness of cross-sectional design is that the temporal relationship between SMI and CKD remains unknown. A cohort study comparing the incidence of CKD between patients with and without SMI would be better than a cross-sectional study in confirming the temporal relationship between SMI and CKD. However, an accurate identification of incident CKD is extremely difficult in routinely collected general practice data, in which kidney function is not constantly monitored for everyone. Moreover, the frequency of serum creatinine measurement changed considerably in UK primary care after the introduction of QOF in 2004 [117], causing a large detection bias of incident CKD in a cohort study using the CPRD. Therefore, with the currently available data, a cohort design does not seem to be more beneficial than a cross-sectional design to examine the association between SMI and CKD.

4.2. Methods

For Paper 1 (Prevalence of CKD and RRT in CPRD), using the July 2014 version of CPRD, I identified all people ≥25 years of age who were alive and registered in 'up to standard' general practices in the CPRD for at least one year on 31 March 2014. The choice of age 25 years as a lower limit was made for the best comparability between the CPRD and Health Survey for England and UK Renal Registry: the Health Survey for England and UK Renal Registry collected data of people <25 years of age differently (the Health Survey for England grouped people 16–24 years of age [4], while the UK Renal Registry grouped people 18–24 years of age [7]). In addition, the number of patients aged <25 with decreased kidney function and RRT was very small in the Health Survey for England and UK Renal Registry, limiting power for the comparison with the CPRD. One-year registration was considered necessary for GPs to record a history of morbidity (including RRT) for newly registered patients [118] and to test their kidney function if they had CKD risk factors such as diabetes.

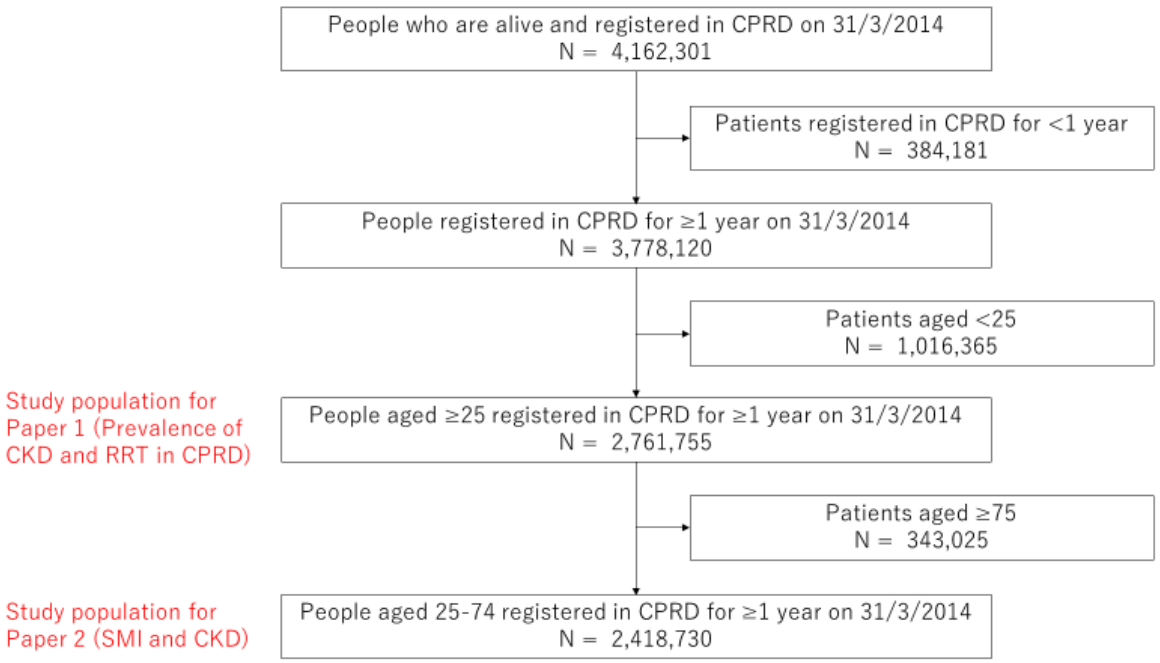
For Paper 2 (SMI and CKD), I restricted the study participants to patients aged 74 or younger. This was because SMI is rare among those aged 75 years or older (as people with SMI are known to die earlier, by around 10-20 years, than the general population [27-32]), limiting power for the comparison of the CKD prevalence between those with and without SMI.

After establishing the cross-sectional dataset in the CPRD, the age-sex distribution of these study participants was compared with that of the UK Census 2013, to confirm that they are broadly representative of the UK general population in terms of age and sex.

4.3. Results (details of the dataset)

As shown in **Figure 2** below, on the study date (i.e. 31 March 2014), I identified 2,761,755 people aged ≥25 who were alive and registered for at least one year in the CPRD. Of these patients, 2,418,730 people were aged 25–74 years and, therefore, were included in Paper 2 (SMI and CKD). The age-sex distribution of these study participants was broadly similar to that of the UK Census 2013 (see **Table 4** below).

Figure 2. Flow chart for the identification of study participants in cross-sectional studies



Abbreviation: CKD = chronic kidney disease; RRT = renal replacement therapy; SMI = severe mental illness; CPRD = Clinical Practice Research Datalink.

Table 4. Age-sex distribution of the study participants for the cross-sectional studies in the CPRD and UK census 2013

Age (years)	Study participants for cross-sectional studies in the CPRD (on 31 March 2014)		UK census 2013	
	No. of people	Proportion (%)	No. of people	Proportion (%)
Total:	2,761,755	100	44,600,143	100
Men:				
25-29	117,261	4.2	2,171,395	4.9
30-34	120,023	4.3	2,148,903	4.8
35-39	120,256	4.4	1,975,110	4.4
40-44	136,483	4.9	2,221,431	5.0
45-49	148,763	5.4	2,310,722	5.2
50-54	144,341	5.2	2,149,309	4.8
55-59	123,154	4.5	1,854,877	4.2
60-64	108,541	3.9	1,734,599	3.9
65-69	109,100	4.0	1,697,784	3.8
70-74	81,192	2.9	1,201,622	2.7
75-79	62,543	2.3	954,347	2.1
80-84	44,307	1.6	650,871	1.5
>=85	36,294	1.3	491,300	1.1
Women:				
25-29	114,601	4.1	2,178,575	4.9
30-34	120,740	4.4	2,177,964	4.9
35-39	118,908	4.3	1,991,769	4.5
40-44	134,237	4.9	2,274,838	5.1
45-49	145,120	5.3	2,375,928	5.3
50-54	141,266	5.1	2,194,934	4.9
55-59	121,259	4.4	1,901,770	4.3
60-64	110,258	4.0	1,806,214	4.0
65-69	114,370	4.1	1,793,663	4.0
70-74	88,857	3.2	1,337,533	3.0
75-79	73,334	2.7	1,137,778	2.6
80-84	58,348	2.1	899,031	2.0
>=85	68,199	2.5	967,876	2.2

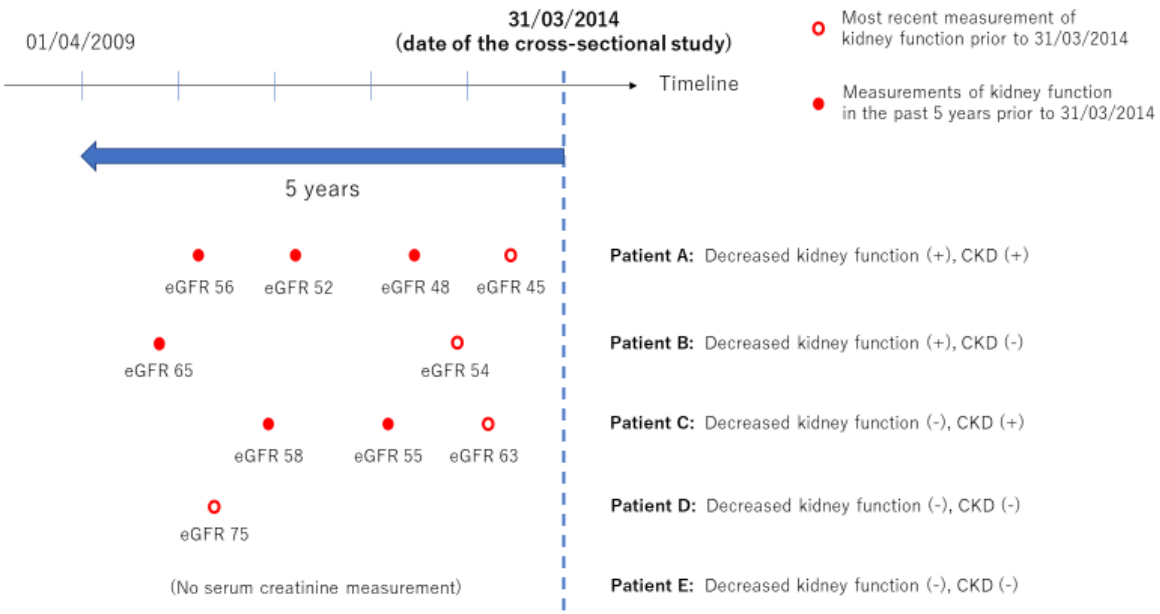
Abbreviation: CPRD = Clinical Practice Research Datalink.

4.4. Strategy to identify patients with decreased kidney function and CKD in the cross-sectional studies

In the established datasets, patients with decreased kidney function will be identified, based on the most recent serum creatinine record in the past five years prior to the study date (i.e. 31 March 2014). Patients with CKD (stages 3 to 5) will be also identified, based on whether their serum creatinine records during the past five years (i.e. from 1 April 2009 to 31 March 2014) satisfy the definition of CKD (i.e. two or more consecutive measurements of GFR <60 ml/min/1.73 m^2 for ≥3 months). The five-year period was chosen to identify as many patients with decreased kidney function or CKD as possible, since the recent National CKD Audit survey (in England and Wales) suggested that people with hypertension (i.e. the most common risk factor for CKD) were mostly tested during a period of five years, whereas people with diabetes were tested annually [103].

By these definitions, it is possible that patients with decreased kidney function do not satisfy the definition of CKD, and vice versa (see examples in **Figure 3** below). The distribution of patients satisfying the definition of decreased kidney function and those satisfying the definition of CKD will be shown and discussed in the next **chapter 5**. People without serum creatinine measurement in the past five years are assumed to have neither decreased kidney function nor CKD. The validity of this assumption will be substantially tested in Paper 1 (Prevalence of CKD and RRT in CPRD) in the next **chapter 5**.

Figure 3. Graphical representation of the strategy to identify patients with decreased kidney function and CKD in the cross-sectional studies in the CPRD



Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate. Note: Unit of eGFR (i.e. mL/min/1.73m^2) was omitted because of limited space. Patient A satisfies the definitions of decreased kidney function (i.e. most recent eGFR <60 ml/min/1.73 m^2) and CKD (i.e. two or more consecutive measurements of GFR <60 ml/min/1.73 m^2 for ≥3 months in the past five years). Patient B is identified as having decreased kidney function, but not regarded as having CKD. Patient C satisfies the definition of CKD, but is not regarded as having decreased kidney function (because the most recent eGFR is over 60 ml/min/1.73 m^2). Patients D and E are regarded as having neither decreased kidney function nor CKD.

4.5. Chapter summary

Establishment of datasets for cross-sectional studies and identification of patients with decreased kidney function and CKD

- Cross-sectional datasets were established for Papers 1 (Prevalence of CKD and RRT in CPRD) and 2 (SMI and CKD).
- On 31 March 2014, there were 2,761,755 people aged ≥25 who were alive and registered for at least one year in the CPRD. The age-sex distribution in the dataset was broadly similar to the UK Census 2013.
- Of these patients, 2,418,730 people were aged 25–74 years and, therefore, were included in Paper 2. People aged 75 or younger were excluded because SMI is rare among this age group due to the shorter life expectancy.
- In the established cross-sectional datasets, patients with decreased kidney function will be identified based on the most recent serum creatinine record prior to the study date (i.e. 31 March 2014). Patients with CKD (stages 3 to 5) will be identified based on whether their serum creatinine records during the past five years (i.e. from 1 April 2009 to 31 March 2014) satisfy the definition of CKD (i.e. two or more consecutive measurements of GFR <60 ml/min/1.73 m^2 for ≥3 months).

Chapter 5: Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom (Paper 1)

5.1. Introduction

This chapter presents the population-level validation study of decreased kidney function, CKD, and RRT in the CPRD, published in *Nephrology Dialysis Transplantation* [119]. This study is important ground work for the following studies: CKD is the study outcome in Paper 2 (SMI and CKD), exposure of interest in Paper 3 (CKD and antidepressant prescription) and a potential effect modifier in Paper 4 (GI bleeding risk of SSRIs by kidney function), whereas RRT is used as part of the exclusion criteria. Therefore, it is important to ensure that most patients with CKD and RRT are captured in the current CPRD.

The main research question is: What is the prevalence of CKD and RRT in the CPRD, and is it similar to the nationally-representative statistics?

Briefly, in the dataset established in the previous **chapter 4**, which includes 2,761,755 people aged ≥25 who were alive and registered for at least one year in the CPRD on 31 March 2014, I identified patients with decreased kidney function (in the main analysis), CKD (in a sensitivity analysis), and RRT. Then, I compared the prevalence estimates of decreased kidney function and CKD (stages 3 to 5) with that of Health Survey for England 2009/2010, and compared the prevalence estimates of RRT with that of UK Renal Registry 2014.

By definition, patients with decreased kidney function (based on the most recent single eGFR <60 ml/min/1.73 m^2 prior to 31 March 2014) and those with CKD (based on two or more consecutive measurements of eGFR <60 ml/min/1.73 m^2 for ≥3 months in the past five years) may be slightly different populations, as illustrated in **Figure 3** in the previous **chapter 4**. The distribution of these patients will be shown and discussed later in this chapter.

5.2. Published paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Masao Iwagami
Principal Supervisor	Dorothea Nitsch
Thesis Title	Association between chronic kidney disease and mental health disorders and psychoactive drugs in the UK general po

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Nephrol Dial Transplant.32(suppl_2):ii142-ii150		
When was the work published?	1 Apirl 2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I planned the study, carried out the data extraction, cleaning, analysis, and drafted the manuscript.

Student Signature: [redacted] **Date:** 30/May/2018

Supervisor Signature: [redacted] **Date:** 30/5/18

Nephrol Dial Transplant (2017) 32: ii142–ii150
doi: 10.1093/ndt/gfw318
Advance Access publication 11 February 2017

ndt
Nephrology Dialysis Transplantation

Original Article

Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom

Masao Iwagami[1], Laurie A. Tomlinson[1], Kathryn E. Mansfield[1], Anna Casula[2], Fergus J. Caskey[2], Grant Aitken[3], Simon D.S. Fraser[4], Paul J. Roderick[4] and Dorothea Nitsch[1]

[1]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK, [2]UK Renal Registry Bristol, UK, [3]Geography & Environment, Faculty of Social and Human Sciences, University of Southampton, Southampton, UK and [4]Academic Unit of Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

Correspondence and offprint requests to: Masao Iwagami; E-mail: masao.iwagami@lshtm.ac.uk

ABSTRACT

Background. Anonymous primary care records are an important resource for observational studies. However, their external validity is unknown in identifying the prevalence of decreased kidney function and renal replacement therapy (RRT). We thus compared the prevalence of decreased kidney function and RRT in the Clinical Practice Research Datalink (CPRD) with a nationally representative survey and national registry.

Methods. Among all people ≥25 years of age registered in the CPRD for ≥1 year on 31 March 2014, we identified patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, according to their most recent serum creatinine in the past 5 years using the Chronic Kidney Disease Epidemiology Collaboration equation and patients with recorded diagnoses of RRT. Denominators were the entire population in each age–sex band irrespective of creatinine measurement. The prevalence of eGFR <60 mL/min/1.73 m^2 was compared with that in the Health Survey for England (HSE) 2009/2010 and the prevalence of RRT was compared with that in the UK Renal Registry (UKRR) 2014.

Results. We analysed 2 761 755 people in CPRD [mean age 53 (SD 17) years, men 49%], of whom 189 581 (6.86%) had an eGFR <60 mL/min/1.73 m^2 and 3293 (0.12%) were on RRT. The prevalence of eGFR <60 mL/min/1.73 m^2 in CPRD was similar to that in the HSE and the prevalence of RRT was close to that in the UKRR across all age groups in men and women, although the small number of younger patients with an eGFR <60 mL/min/1.73 m^2 in the HSE might have hampered precise comparison.

Conclusions. UK primary care data have good external validity for the prevalence of decreased kidney function and RRT.

Keywords: chronic kidney disease, epidemiology, primary care, renal replacement therapy, validity

BACKGROUND

Chronic kidney disease (CKD) is a major public health problem that increases in prevalence with age and is associated with increased morbidity and mortality [1–3]. The number of people with end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) has been increasing worldwide and is predicted to double by 2030 [4]. Appropriate identification of CKD is thus important for early intervention, including prevention of both CKD progression and cardiovascular diseases [5]. At the population level, accurate estimation of CKD prevalence is essential to assess the burden of CKD in the community and to evaluate the effectiveness of population approaches for CKD [6]. However, potential methodological difficulties may make

it problematic to determine the community prevalence of CKD [7, 8]. For example, people who have kidney function measured routinely by serum creatinine may not represent the general population and serum creatinine assays may not be uniformly standardized.

Data derived from routine patient care, such as the anonymous primary care records held in the UK Clinical Practice Research Datalink (CPRD) [9], are an important resource for observational studies [10]. Because CRPD broadly represents the UK population in terms of demographics [11], it can be a useful source to estimate a disease prevalence in the UK. However, using routine electronic records to investigate renal disease is only possible if the general practitioners (GPs) appropriately test, identify and record everyone in the population who has kidney disease. Reliable measures of renal disease in electronic health records would allow a more robust use of primary care data to investigate renal disease epidemiology; for example, researchers would be able to investigate the association between kidney diseases and other comorbidities or medications recorded in primary care data. To date, a number of definitions for diseases or specific conditions have been validated in the CPRD at the individual or population level [12, 13]. However, to our knowledge, there has been no external validation study for the prevalence of decreased kidney function and RRT in the CPRD. The best available methods to identify CKD and RRT in CPRD are to use serum creatinine records measured by GPs and recorded diagnoses of RRT in the CPRD, respectively, yet the validity or appropriateness of these methods are unknown.

The Health Survey for England (HSE), a nationally representative survey of health condition, included measurement of kidney function in 2009 and 2010 [14]. Every consenting participant had kidney function measured, giving representative statistics for the prevalence of decreased kidney function in the general population. Meanwhile, the UK Renal Registry (UKRR), which records information regarding all people on RRT in the UK, provides annual reports of the prevalence of RRT [15]. Referring to these two nationally representative sources of data, we aimed to evaluate the external validity of the prevalence of decreased kidney function and RRT in the CPRD.

MATERIALS AND METHODS

Details of the CPRD and study population

In the UK, the primary care system acts as a gatekeeper to health care—patients need to be registered with a primary care doctor to access National Health Service (NHS) non-emergency care. Health care is free at the point of access. Primary care practices have used computerized electronic health records since the early 1990s. There are only a limited number of suppliers of GP electronic health record software. The CPRD uses data from VISION software system (In Practice Systems, London, UK) and has evolved as an observational data and interventional research service provided by the NHS. Currently >650 GP practices contribute data meeting quality control standards to the CPRD, covering and representing nearly 7% of the UK population [11]. Previous studies have suggested that the distribution of age, sex, ethnicity, practice location deprivation, and other health indicators such as smoking and morbidities are similar to that of external UK-based sources [11, 16–19]. The database includes patient demographics, coded diagnoses and outpatient laboratory test results. The Secretary of State waived informed consent for CPRD data because data are anonymized and there is an overall benefit for research. Ethical approval for this study was obtained from the Independent Scientific Advisory Committee, which oversees research on CPRD data (protocol no. 16_055), as well as the London School of Hygiene and Tropical Medicine Ethics Committee (reference: 9196).

The study population was all people ≥25 years of age who were alive and registered in the CPRD for at least 1 year on 31 March 2014. The choice of age 25 years as a lower limit was made for the best comparability between the CPRD and HSE or UKRR: the HSE and UKRR collected data of people <25 years of age differently (the HSE grouped people 16–24 years of age, while the UKRR grouped people 18–24 years of age). One-year registration was considered necessary for GPs to record a history of RRT for newly registered patients or to test their kidney function if they had a key CKD risk factor such as diabetes [5].

Details of external data

For the prevalence of decreased kidney function, we compared the data from the CPRD with those from the HSE 2009 and 2010 (combined) [14]. Briefly, the HSE 2009/2010 included a cross-sectional study of kidney disease among people selected using a multistage stratified random probability sampling method. Blood samples were taken from nearly 6000 consenting participants, accounting for 77% for men and 73% for women among all the HSE participants. Data were weighted for non-response to reduce response bias. Creatinine was measured by an internationally standardized enzymatic method, which is traceable to isotope dilution mass spectrometry (IDMS) [20]. Estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine value using the Modification of Diet in Renal Disease Study equation in the original HSE report [14], whereas a *post hoc* analysis was conducted using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21]. The prevalence of people with a single eGFR <60 mL/min/1.73 m^2 was reported according to age (every 10 years) and sex.

For RRT prevalence, we referred to the data from the UKRR 2014 [15]. The UKRR 2014 collected data from all 71 renal centres in the UK. The prevalence of RRT in 2013 was estimated by dividing the number of patients on RRT by the 2013 UK population, according to age (every 10 years), sex and RRT modality: haemodialysis, peritoneal dialysis or kidney transplantation.

Definition of decreased kidney function and RRT in the CPRD

We identified patients with an eGFR <60 mL/min/1.73 m^2 according to their most recent single serum creatinine measured by a GP in the past 5 years (i.e. the period between 1 April 2009 and 31 March 2014) using the CKD-EPI equation [22]. We used a single eGFR to define decreased kidney

ORIGINAL ARTICLE

Table 1. Prevalence of eGFR <60 mL/min/1.73 m^2 in the CPRD and HSE

	Age group (years)					
	25–34	35–44	45–54	55–64	65–74	≥75
Men						
Prevalence of eGFR <60 mL/min/1.73 m^2 in CPRD, % (95% CI)	0.11 (0.10–0.12)	0.27 (0.25–0.29)	0.76 (0.73–0.79)	2.59 (2.53–2.66)	10.16 (10.02–10.29)	35.32 (35.07–35.57)
Prevalence of eGFR <60 mL/min/1.73 m^2 in HSE, % (95% CI)	0	0.19 (0–1.06)	1.22 (0.45–2.63)	1.94 (0.84–3.78)	14.04 (10.27–18.56)	31.39 (25.36–37.92)
Difference (prevalence in CPRD−HSE), % (95% CI)	0.11 (0.09–0.12)	0.08 (−0.30–0.45)	−0.46 (−1.43–0.51)	0.65 (−0.68–1.99)	−3.88 (−7.87–0.10)	3.93 (−2.17–10.03)
Proportion of patients with serum creatinine measurement in past 5 years in CPRD, % (numerator/denominator)	25.85 (61 339/237 284)	38.47 (98 759/256 739)	55.61 (163 001/293 104)	72.44 (167 841/231 695)	86.15 (163 933/190 292)	92.29 (132 103/143 144)
Women						
Prevalence of eGFR <60 mL/min/1.73 m^2 in CPRD, % (95% CI)	0.10 (0.09–0.12)	0.27 (0.25–0.29)	0.90 (0.87–0.94)	3.22 (3.15–3.29)	11.13 (10.99–11.27)	38.50 (38.29–38.72)
Prevalence of eGFR <60 mL/min/1.73 m^2 in HSE, % (95% CI)	0.65 (0.13–1.89)	0.78 (0.21–1.97)	2.00 (0.96–3.64)	4.70 (2.93–7.09)	9.48 (6.53–13.19)	35.41 (30.04–41.06)
Difference (prevalence in CPRD−HSE), % (95% CI)	−0.55 (−1.29–0.19)	−0.51 (−1.27–0.25)	−1.10 (−2.32–0.13)	−1.48 (−3.44–0.48)	1.65 (−1.53–4.83)	3.09 (−2.28–8.47)
Proportion of patients with serum creatinine measurement in past 5 years in CPRD, % (numerator/denominator)	46.22 (108 767/235 341)	55.30 (139 977/253 145)	67.35 (192 872/286 386)	75.27 (174 268/231 517)	84.45 (171 620/203 227)	91.88 (183 655/199 881)

function in the main analysis because the HSE (reference data in this study), as well as previous large epidemiological studies [23, 24], have used this definition. For the main analysis, we made the following assumptions: (i) all the UK laboratories reported IDMS-traceable creatinine; (ii) people with a missing record of ethnicity in the CPRD had non-black ethnicity and (iii) people without any creatinine measurement for the past 5 years did not have decreased kidney function.

We identified patients on RRT based on the diagnoses recorded in the CPRD anytime from the date of their registration to 31 March 2014. The list of diagnosis codes (Read codes) indicative of RRT was determined by using a recommended strategy [25] and agreed upon among the authors (Supplementary data, Table S1). In addition, in order to examine the validity of diagnoses of different RRT modality in CPRD, we classified patients with RRT into those with haemodialysis, peritoneal dialysis or kidney transplantation. We used the most recent recorded diagnosis, as this is the best available approach to estimate the prevalence of the current RRT modality in CPRD.

Data analysis

We calculated the prevalence [95% confidence interval (CI)] of eGFR <60 mL/min/1.73 m^2 according to age (every 10 years) and sex in the CPRD and HSE, respectively, using the CKD-EPI equation. Denominators in the CPRD were the entire population in each age–sex band irrespective of creatinine measurement in the past 5 years. Patients ≥75 years of age were grouped in the CPRD to be consistent with the HSE. We calculated the difference (95% CI) in the prevalence of eGFR <60 mL/min/1.73 m^2 between the CPRD and HSE. We also reported the proportion of patients with at least one creatinine measurement for the past 5 years in the CPRD.

Similarly, we calculated the prevalence of RRT in the CPRD and UKRR, respectively, and then the difference between the CPRD and UKRR, in 10-year age bands by sex. We also reported results by RRT modality.

All statistical analyses were conducted using Stata 14 software (StataCorp, College Station, TX, USA).

Sensitivity analyses

We repeated our analyses using a number of alternative eGFR definitions and restricted study populations in order to determine the impact of the definition for decreased kidney function that we used. We defined decreased kidney function as follows: (i) we assumed that all the UK laboratories reported non-IDMS-traceable creatinine, and therefore multiplied the recorded creatinine value by 0.95 to use the CKD-EPI equation for IDMS-traceable creatinine [26]; (ii) we conducted a complete case analysis for ethnicity (restricting the analysis to people with recorded ethnicity in the CPRD); (iii) we used the participants' most recent creatinine in the past 2 years, instead of 5 years; (iv) we restricted the region to England, by excluding data from Scotland, Wales and Northern Ireland; (v) we additionally required a measure of chronicity to define decreased kidney function [27]: two or more eGFR results <60 mL/min/1.73 m^2 needed to be recorded consecutively ≥3 months apart in the past 5 years; and (vi) we conducted a complete case

analysis for creatinine by restricting the analysis to people with at least one creatinine measurement in the past 5 years.

We also compared the prevalence of eGFR <45 mL/min/1.73 m^2 (calculated from the most recent creatinine in the past 5 years) between the CPRD and HSE, which may be a more robust indicator of decreased kidney function with prognostic implications [28, 29].

RESULTS

From 685 GP practices, we identified 2 761 755 people [mean age 53 (SD 17) years, men 49%] who were alive and registered in the CPRD for ≥1 year on 31 March 2014. Their age–sex distribution was broadly similar to that of the UK Census 2013 (Supplementary data, Table S2). Of those identified, 189 581 patients (6.86%) had an eGFR <60 mL/min/1.73 m^2 and 3293 patients (0.12%) were on RRT.

The prevalence of eGFR <60 mL/min/1.73 m^2 increased steeply with age (Table 1 and Figure 1). There was no evidence that the prevalence of eGFR <60 mL/min/1.73 m^2 in the CPRD was different from that in the HSE across age groups, both in men and women, except for the group of men 25–34 years of age, in which no one had an eGFR <60 mL/min/1.73 m^2 in the HSE. The proportion of people who had a recorded measurement of creatinine increased with age, with 26% of men and 46% of women 25–34 years of age with tests in the past 5 years, up to 92% (both men and women) among people 75 years of age.

The prevalence of RRT gradually increased according to age (Table 2 and Figure 2). The difference between the CRPD and the UKRR was small across all age groups, both in men and women. Table 3 shows the subgroup analysis by RRT modality. The prevalence of patients with haemodialysis in the CPRD was slightly lower than that in the UKRR across all age groups, while the prevalence of those with peritoneal dialysis and kidney transplantation in the CPRD were similar to or slightly higher than those in the UKRR.

Table 4 shows the results of sensitivity analyses. By assuming all creatinine results were non-IDMS traceable, the prevalence of eGFR <60 mL/min/1.73 m^2 in the CPRD decreased predominantly among older people, and overall prevalence decreased from 6.86 to 5.35%. Restricting to people with recorded ethnicity in the CPRD, using a serum creatinine value in the past 2 years and restricting to English data produced similar results to the main analysis. By defining decreased kidney function including a measure of chronicity, the prevalence decreased slightly in each age group, and overall prevalence decreased from 6.86 to 6.27%. Finally, in a complete case analysis (using as the denominator only those with serum creatinine tests) the prevalence of eGFR <60 mL/min/1.73 m^2 increased substantially compared to that in the main analysis.

The overall prevalence of eGFR <45 mL/min/1.73 m^2 was 2.33% (64 425/2 761 755) in the CPRD. The number of people with an eGFR <45 mL/min/1.73 m^2 was small and CIs of the prevalence estimates were large in the HSE (Table 5). The proportion of people with an eGFR <45 mL/min/1.73 m^2 in the age group ≥75 years in the CPRD was significantly higher than that of the HSE, both in men and women.

DISCUSSION

In this study, we examined the external validity of the prevalence of decreased kidney function (based on serum creatinine measured by GPs) and RRT (based on recorded diagnoses) in the CPRD by comparing them with results from two nationally representative sources (the HSE and UKRR). Across all ages for men and women the prevalence of eGFR <60 mL/min/1.73 m^2 in the CPRD was similar to that in the HSE, although the small number of younger patients with an eGFR <60 mL/min/1.73

ORIGINAL ARTICLE

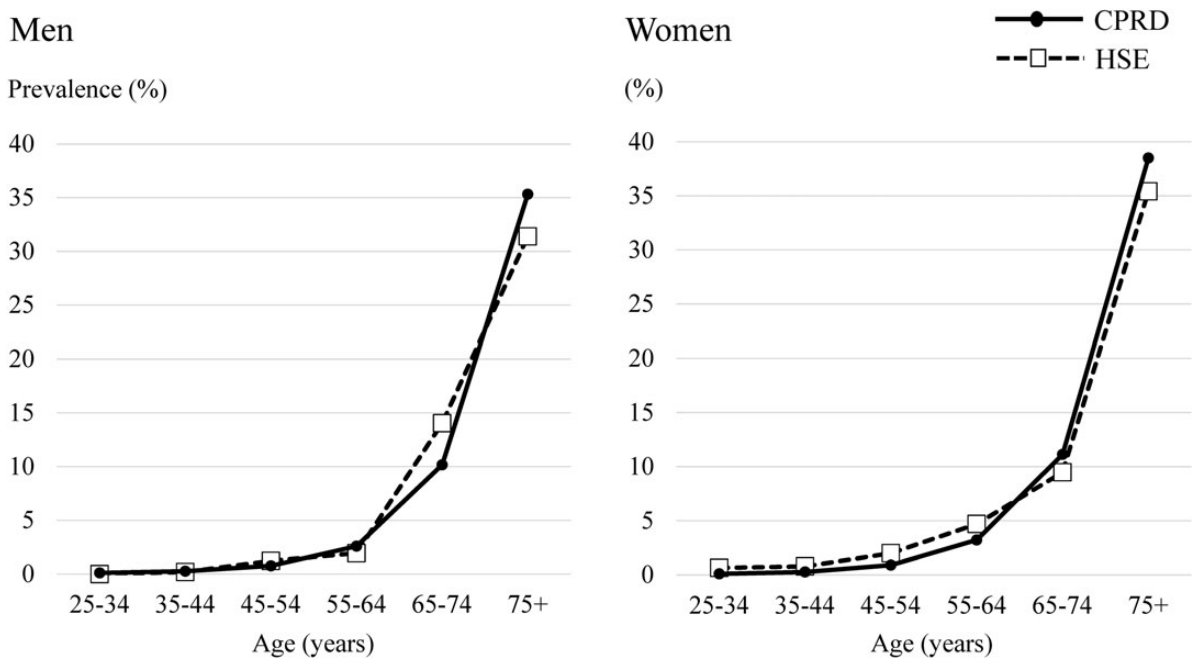


FIGURE 1: Prevalence of eGFR <60 mL/min/1.73 m^2 in the CPRD and HSE.

Table 2. Prevalence of RRT in the CPRD and UKRR

	Age group (years)					
	25–34	35–44	45–54	55–64	65–74	≥75
Men						
Prevalence of RRT in CPRD, % (95% CI)	0.05 (0.04–0.06)	0.09 (0.08–0.10)	0.14 (0.12–0.15)	0.17 (0.16–0.19)	0.22 (0.20–0.24)	0.25 (0.23–0.28)
Prevalence of RRT in UKRR, % (95% CI)	0.05 (0.05–0.06)	0.10 (0.10–0.10)	0.17 (0.16–0.17)	0.22 (0.21–0.22)	0.25 (0.25–0.26)	0.29 (0.28–0.29)
Difference (prevalence in CPRD−UKRR), % (95% CI)	0 (−0.01–0.01)	−0.01 (−0.02–0)	−0.03 (−0.05–−0.02)	−0.05 (−0.06–−0.03)	−0.03 (−0.05–−0.01)	−0.03 (−0.06–0)
Women						
Prevalence of RRT in CPRD, % (95% CI)	0.04 (0.03–0.05)	0.07 (0.06–0.08)	0.09 (0.08–0.11)	0.13 (0.11–0.14)	0.15 (0.13–0.17)	0.12 (0.10–0.13)
Prevalence of RRT in UKRR, % (95% CI)	0.04 (0.03–0.04)	0.07 (0.06–0.07)	0.11 (0.10–0.11)	0.13 (0.13–0.14)	0.15 (0.15–0.16)	0.11 (0.11–0.12)
Difference (prevalence in CPRD−UKRR), % (95% CI)	0 (−0.01–0.01)	0 (−0.01–0.01)	−0.01 (−0.03–0)	−0.01 (−0.02–0.01)	0 (−0.02–0.02)	0 (−0.01–0.02)

m^2 in the HSE might have hampered precise comparison. The prevalence of RRT in the CPRD was broadly similar to that obtained from the UKRR, although there were differences in the RRT modality-specific prevalence between the CPRD and UKRR.

Routinely collected primary care data can be a useful resource for epidemiological studies, particularly in the UK, where >98% of citizens are registered with NHS GPs [11]. Although the prevalence or incidence of various diseases in the CPRD have good comparability with other UK-based data sources [12, 13], the external validity of the prevalence of decreased kidney function and RRT has not been studied. Concerns specific to kidney diseases include that GPs do not test every registered patient's kidney function, which could lead to underestimation of the true prevalence of decreased kidney function. In our study, the proportion of people with creatinine measurement was small among young and middle-aged people, especially men. However, using the entire practice population as a denominator, the prevalence of eGFR <60 mL/min/1.73 m^2 in the CPRD was close to that in the HSE across all age groups, both in men and women. A possible explanation would be that, in line with the current National Institute for Health and Care Excellence (NICE) guidance for CKD [5], GPs are efficiently testing kidney function for people with CKD risk factors, including hypertension, diabetes, cardiovascular diseases and hereditary kidney disease (e.g. autosomal dominant polycystic kidney disease). In addition, the Quality and Outcome Framework (QOF) incentivizes GPs to register and manage patients with CKD [30]. Since the launch of the QOF for CKD in 2006/7, the identification and management of patients with CKD have been improving in the UK [31], although there are delays in coding patients with CKD in the system [32]. In older age groups, very high proportions had undergone testing of kidney function, and it is likely that those not tested are healthier, with a lower risk of CKD.

In sensitivity analyses, we examined to what extent the prevalence estimates for decreased kidney function changed under different assumptions related to uncertainties in the CPRD. First, the estimation changed considerably with the assumption of whether the UK laboratories reported creatinines traceable to IDMS or not. We expect that most of the UK laboratories reported IDMS-traceable creatinines during the study period, yet if a few laboratories reported non-IDMS-traceable creatinines, the true prevalence of eGFR <60 mL/min/1.73 m^2 in the CPRD would become lower than our estimation in the main analysis. Standardization of serum creatinine assays is thus important in studies regarding CKD epidemiology. Second, the assumption of non-black ethnicity for people with missing ethnicity data in the CPRD affected the prevalence estimates only slightly. This is probably because the proportion of people with black ethnicity is small in the UK, at ∼3% [18]. Third, using creatinine records for the past 2 instead of 5 years made little change to prevalence estimates for decreased kidney function. This may relate to recommendations for regular testing in line with the QOF and the current NICE guidance for CKD [5]. Fourth, in the CPRD the prevalence of eGFR <60 mL/min/1.73 m^2 in England was similar to that in the whole UK, ensuring comparability between the

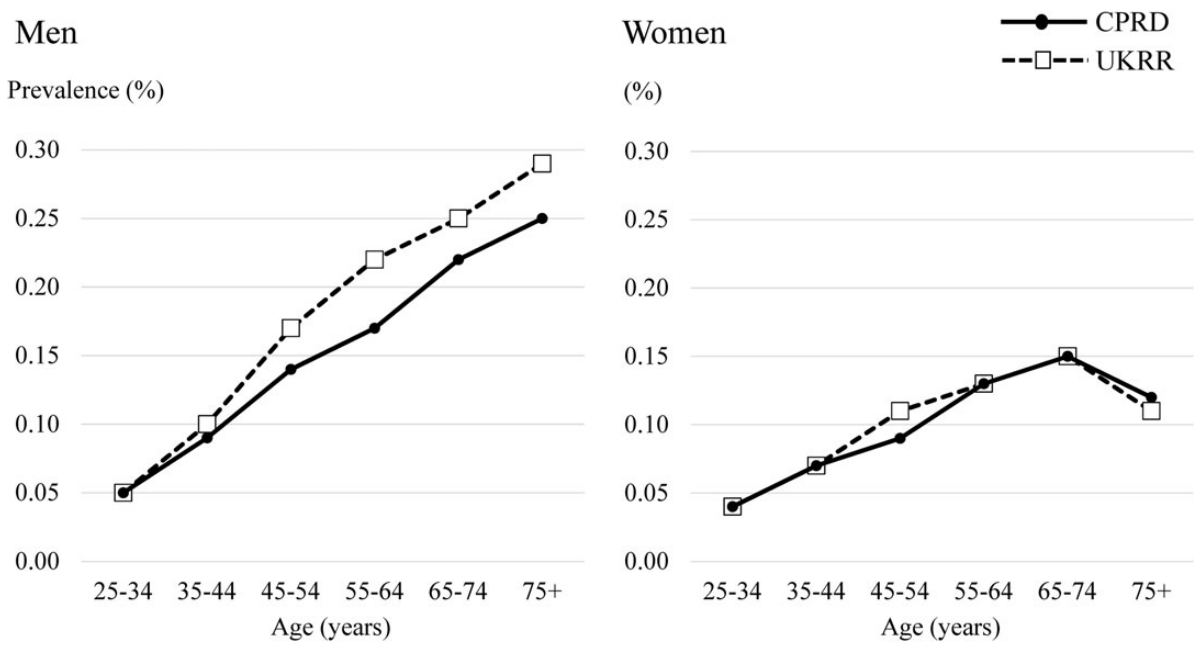


FIGURE 2: Prevalence of RRT in the CPRD and the UKRR

HSE and CPRD in our study. Fifth, the prevalence estimates slightly decreased by using the CKD criteria including chronicity. This may suggest that some patients with a single eGFR <60 mL/min/1.73 m^2 had transient kidney dysfunction, probably because serum creatinine was measured at the time of acute illness when they may have developed acute kidney injury. Finally, the prevalence of decreased kidney function was likely to be overestimated by restricting the denominator to only people with creatinine measurement. This suggests that GPs selectively test people at high risk of CKD, especially among younger people.

The prevalence of RRT was also similar between the CPRD and UKRR across all age groups in men and women. Patients receiving RRT are in frequent contact with kidney units, so GPs do not provide comprehensive routine care for these individuals. However, patients on RRT remain registered with their GPs and therefore we would anticipate that GPs update patient records to reflect commencement of RRT. Our results suggest that the estimated prevalence of RRT based on recorded diagnoses in the CPRD was broadly valid when compared against comprehensive UKRR. However, using the most recent diagnosis indicating RRT modality, the prevalence of haemodialysis was underestimated in the CPRD, while those of peritoneal dialysis and kidney transplantation were similar, or somewhat overestimated, especially among older people. This may be because patients with peritoneal dialysis and kidney transplantation are often healthier and have more regular contact with their GPs compared with those on haemodialysis. In addition, for patients with a change in their RRT modality (e.g. from peritoneal dialysis to haemodialysis) there may be a delay in updating the modality in the GP record. Therefore, some patients currently on haemodialysis might be misclassified into the group of peritoneal dialysis or kidney transplantation because their previous diagnoses (i.e. peritoneal dialysis or kidney transplantation) are not yet updated. Another possibility is that patients commencing haemodialysis died before this was recorded in the CPRD, given the high early mortality rates of these patients [33].

There are several limitations to our study. First, this is a cross-sectional study examining the validity of prevalence of decreased kidney function and RRT. Our results do not ensure that UK primary care data are reliable for identifying the incidence of CKD and RRT. Second, our comparison of data between the CPRD and HSE or UKRR was only at the population rather than the individual level. Our analyses did not allow us to calculate the sensitivity or specificity of RRT diagnoses. In the absence of linked data, it is possible that there was a similar extent of misclassification between cases and non-cases, resulting in an overall agreement of the prevalence estimates in the CPRD with those in the HSE and UKRR. Third, the prevalence of decreased kidney function in the HSE was the best available estimate, but not a perfect reference standard. The survey did not include people who were temporarily hospitalized for acute illness or were in residential care [14]. In addition, people with poor health might be reluctant to give a blood sample, and the existing adjustment for non-response in the HSE may not have fully dealt with this bias. This may explain the finding in our sensitivity analysis that the proportion of people with an eGFR <45 mL/min/1.73 m^2 in the oldest age group in the CPRD was significantly higher than that of the HSE. Blood sampling was conducted on only one occasion in the HSE. Accordingly, we defined decreased kidney function in the CPRD using one serum creatinine measurement in our main analysis. However, some patients might have had their kidney function checked as a result of acute illness, and therefore their decreased kidney function might have been transient. Previous research has shown that creatinine fluctuation can affect the CKD prevalence estimates in routinely collected data [34], although the influence was not large in our study. At ~6000, the sample size in the HSE was not small, yet

Table 3. Prevalence of RRT by modality in the CPRD and UKRR

	Age group (years)					
	25–34	35–44	45–54	55–64	65–74	≥75
Clinical Practice Research Datalink						
Denominator, *N*	472 625	509 884	579 490	463 212	393 519	343 025
Number of patients with haemodialysis, *n* (%)	39 (0.08)	84 (0.16)	144 (0.25)	202 (0.44)	257 (0.65)	378 (1.10)
Number of patients with peritoneal dialysis, *n* (%)	27 (0.06)	15 (0.03)	48 (0.08)	37 (0.08)	67 (0.17)	67 (0.20)
Number of patients with kidney transplantation, *n* (%)	141 (0.30)	299 (0.59)	480 (0.83)	455 (0.98)	399 (1.01)	154 (0.45)
UK Renal Registry						
Denominator, *N*	8 676 837	8 463 148	9 030 893	7 297 460	6 030 602	5 101 203
Number of patients with haemodialysis, *n* (%)	887 (0.10)	1677 (0.20)	3513 (0.39)	4560 (0.62)	5939 (0.98)	7324 (1.44)
Number of patients with peritoneal dialysis, *n* (%)	180 (0.02)	321 (0.04)	585 (0.06)	740 (0.10)	918 (0.15)	830 (0.16)
Number of patients with kidney transplantation, *n* (%)	2836 (0.33)	5047 (0.60)	8361 (0.93)	7538 (1.03)	5224 (0.87)	1269 (0.25)

Table 4. Prevalence of eGFR <60 mL/min/1.73 m^2 in the CPRD: results of main analysis and sensitivity analyses

	Age group (years)						Total
	25–34	35–44	45–54	55–64	65–74	≥75	
Main analysis, % (numerator/denominator)	0.11 (497/472 625)	0.27 (1360/509 884)	0.83 (4800/579 490)	2.90 (13 455/463 212)	10.66 (41 949/393 519)	37.18 (127 520/343 025)	6.86 (189 581/2 761 755)
Sensitivity analyses, % (numerator/denominator)							
(i) Assuming all creatinine results non-IDMS traceable	0.09 (429/472 625)	0.21 (1066/509 884)	0.56 (3246/579 490)	1.86 (8612/463 212)	7.45 (29 304/393 519)	30.66 (105 171/343 025)	5.35 (147 828/2 761 755)
(ii) Complete case analysis for ethnicity	0.11 (332/295 942)	0.27 (815/299 641)	0.93 (2710/292 837)	3.24 (7313/225 881)	11.26 (22 496/199 805)	38.25 (64 923/169 738)	6.64 (98 589/1 483 844)
(iii) Using creatinine records in past 2 years	0.09 (439/472 625)	0.24 (1202/509 884)	0.73 (4202/579 490)	2.59 (11 993/463 212)	9.93 (39 081/393 519)	35.08 (120 323/343 025)	6.42 (177 240/2 761 755)
(iv) Restricting region to England	0.11 (368/346 641)	0.26 (999/377 675)	0.85 (3596/423 030)	3.00 (9935/331 404)	10.71 (30 302/282 983)	37.22 (93 887/252 246)	6.91 (139 087/2 013 979)
(v) Using CKD criteria including chronicity[a]	0.07 (353/472 625)	0.19 (977/509 884)	0.56 (3234/579 490)	2.19 (10 156/463 212)	9.34 (36 770/393 519)	35.44 (121 564/343 025)	6.27 (173 054/2 761 755)
(vi) Complete case analysis for creatinine	0.29 (497/170 148)	0.57 (1360/238 786)	1.35 (4800/355 929)	3.93 (13 455/342 151)	12.50 (41 949/335 581)	40.38 (127 520/315 777)	10.78 (189 581/1 758 372)

[a]eGFR rate <60 mL/min/1.73 m^2 twice consecutively for ≥3 months in the past 5 years.

Table 5. Prevalence of eGFR <45 mL/min/1.73 m^2 in the CPRD and HSE

	Age group (years)					
	25–34	35–44	45–54	55–64	65–74	≥75
Men						
Prevalence of eGFR <45 mL/min/1.73 m^2 in CPRD, % (95% CI)	0.08 (0.07–0.09)	0.16 (0.14–0.17)	0.30 (0.28–0.32)	0.66 (0.63–0.70)	2.36 (2.30–2.43)	13.49 (13.32–13.67)
Prevalence of eGFR <45 mL/min/1.73 m^2 in HSE, % (95% CI)	0	0	0.41 (0.05–1.46)	0	4.11 (2.14–7.07)	8.97 (5.56–13.51)
Difference (prevalence in CPRD−HSE), % (95% CI)	0.08 (0.07–0.09)	0.16 (0.14–0.17)	−0.11 (−0.67–0.45)	0.66 (0.63–0.70)	−1.75 (−4.02–0.53)	4.53 (0.77–8.28)
Women						
Prevalence of eGFR <45 mL/min/1.73 m^2 in CPRD, % (95% CI)	0.06 (0.05–0.07)	0.12 (0.11–0.14)	0.24 (0.23–0.26)	0.60 (0.57–0.63)	2.36 (2.29–2.43)	15.14 (14.99–15.30)
Prevalence of eGFR <45 mL/min/1.73 m^2 in HSE, % (95% CI)	0	0	0.40 (0.05–1.43)	0.89 (0.24–2.28)	2.75 (1.27–5.16)	10.82 (7.57–14.86)
Difference (prevalence in CPRD−HSE), % (95% CI)	0.06 (0.05–0.07)	0.12 (0.11–0.14)	−0.16 (−0.71–0.40)	−0.29 (−1.17–0.58)	−0.39 (−2.17–1.38)	4.32 (0.83–7.81)

the relatively wide 95% CIs for the prevalence estimates in each age–sex group hampered more precise comparisons. In particular, the number of patients with an eGFR <60 mL/min/1.73 m^2 was small among younger age groups. We could not compare the prevalence of more severe kidney dysfunction, because patients with an eGFR <30 mL/min/1.73 m^2 were rare, even among older people in the HSE [14]. Meanwhile, testing of albuminuria is known to be incomplete in UK primary care electronic health records [32], which prevented us from comparing the prevalence of albuminuria, or CKD stages 1 and 2, between the CPRD and HSE. Because albuminuria is an important prognostic factor in people with and without low eGFR [35], the unknown validity of albuminuria in UK primary care remains an obstacle to the study of CKD using the CPRD. Finally, our findings may not be generalizable to other GP practices in the UK if GP practices contributing to the CPRD were more likely to measure kidney function and record the diagnoses of RRT. Generalizability to primary care electronic health records in other European countries is also uncertain, because the frequency of practices such as blood testing, chronic disease monitoring, recording of diagnoses, incentives and access to public primary care clinics differ.

In the era of a rising global prevalence of ESRD [4], high-quality epidemiological research on kidney diseases is becoming more important. Routinely collected electronic health record data would play an important role for kidney research, because most patients with CKD are diagnosed and managed in primary care. Accurate identification of CKD and RRT in the CPRD would allow investigation of the association between kidney diseases and other comorbidities or medications. It is also possible to investigate equity of care (e.g. referral to nephrologists), given that the database is less biased for ascertaining advanced CKD than population surveys and disease registries. In this study, we demonstrated that identifying the prevalence of CKD and RRT is valid at the population level in the CPRD. Although further validation of individual-level data is needed, our findings support the use of UK primary care data for research into kidney disease.

CONCLUSIONS

We examined the external validity of the prevalence of decreased kidney function and RRT in the CPRD. The prevalence of eGFR <60 mL/min/1.73 m^2 in the CPRD was similar to that in a national sampling survey (HSE 2009/2010), and the prevalence of RRT in the CPRD was close to that obtained from a national disease registry (UKRR 2014) across all age groups, in both men and women. These findings suggest that UK primary care data can be used to identify the prevalence of decreased kidney function and RRT in future studies.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

AUTHORS' CONTRIBUTIONS

M.I., L.T. and D.N. planned the study. M.I. carried out the data extraction from the Clinical Practice Research Datalink, cleaning and analysis, and drafted the manuscript. K.M. supported the data analysis and drafted the manuscript. A.C. and F.C. managed the data from the UK Renal Registry 2014. G.A., S. F. and P.R. managed the data from the Health Survey for England 2009 and 2010. All authors contributed substantially to interpretation of the results and the writing of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

M.I. is funded by the Honjo International Scholarship Foundation. L.T. is funded by a Wellcome Trust Intermediate Clinical Fellowship (WT101143MA). The funders had no role in the execution of this study or interpretation of results.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no any competing interests (both financial and non-financial) related to this manuscript.

ORIGINAL ARTICLE

REFERENCES

1. Jha V, Garcia-Garcia G, Iseki K *et al.* Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; 382: 260–272
2. Castro AF, Coresh J. CKD surveillance using laboratory data from the population-based National Health and Nutrition Examination Survey (NHANES). *Am J Kidney Dis* 2009; 53: S46–S55
3. Levey AS, Atkins R, Coresh J *et al.* Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007; 72: 247–259
4. Liyanage T, Ninomiya T, Jha V *et al.* Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015; 385: 1975–1982
5. National Institute for Health and Care Excellence. *Chronic kidney disease in adults: assessment and management*. CG182. https://www.nice.org.uk/guidance/cg182 (1 March 2016, date last accessed)
6. Ackland P. Prevalence, detection, evaluation and management of chronic kidney disease. *BMJ* 2014; 348: f7688
7. Brück K, Jager KJ, Dounousi E *et al.* Methodology used in studies reporting chronic kidney disease prevalence: a systematic literature review. *Nephrol Dial Transplant* 2015; 30: 6–16
8. McCullough K, Sharma P, Ali T *et al.* Measuring the population burden of chronic kidney disease: a systematic literature review of the estimated prevalence of impaired kidney function. *Nephrol Dial Transplant* 2012; 27: 1812–1821
9. Clinical Practice Research Datalink. http://www.cprd.com/intro.asp (1 March 2016, date last accessed)
10. de Lusignan S, van Weel C. The use of routinely collected computer data for research in primary care: opportunities and challenges. *Fam Pract* 2006; 23: 253–263
11. Herrett E, Gallagher AM, Bhaskaran K *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; 44: 827–836
12. Herrett E, Thomas SL, Schoonen WM *et al.* Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010; 69: 4–14
13. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010; 60: e128–e136
14. Health Survey for England – 2010. Respiratory health: Chapter 8, Kidney disease and renal function. http://www.hscic.gov.uk/pubs/hse10report(1 March 2016, date last accessed)
15. Rao A, Casula A, Castledine C. UK Renal Registry 17th Annual Report: Chapter 2 UK renal replacement therapy prevalence in 2013: national and centre-specific analyses. *Nephron* 2015; 129(Suppl 1): 31–56
16. Hollowell J. The General Practice Research Database: quality of morbidity data. *Popul Trends* 1997; 87: 36–40
17. Booth HP, Prevost AT, Gulliford MC. Validity of smoking prevalence estimates from primary care electronic health records compared with national population survey data for England, 2007 to 2011. *Pharmacoepidemiol Drug Saf* 2013; 22: 1357–1361
18. Mathur R, Bhaskaran K, Chaturvedi N *et al.* Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf)* 2014; 36: 684–692
19. Kontopantelis E, Springate D, Reeves D *et al.* Withdrawing performance indicators: retrospective analysis of general practice performance under UK Quality and Outcomes Framework. *BMJ* 2014; 348: g330
20. Health Survey for England – 2010. Respiratory health: Volume 2, Methods and documentation. http://www.hscic.gov.uk/pubs/hse10report(1 March 2016, date last accessed)
21. Fraser SD, Aitken G, Taal MW *et al.* Exploration of chronic kidney disease prevalence estimates using new measures of kidney function in the health survey for England. *PLoS One* 2015; 10: e0118676
22. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
23. Tonelli M, Wiebe N, Culleton B *et al.* Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006; 17: 2034–2047
24. Anderson J, Glynn LG. Definition of chronic kidney disease and measurement of kidney function in original research papers: a review of the literature. *Nephrol Dial Transplant* 2011; 26: 2793–2798
25. Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiol Drug Saf* 2009; 18: 704–707
26. Levey AS, Coresh J, Greene T *et al.* Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; 53: 766–772
27. KDIGO 2012 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150
28. Roderick PJ, Atkins RJ, Smeeth L *et al.* Detecting chronic kidney disease in older people; what are the implications? *Age Ageing* 2008; 37: 179–186
29. Roderick PJ, Atkins RJ, Smeeth L *et al.* CKD and mortality risk in older people: a community-based population study in the United Kingdom. *Am J Kidney Dis* 2009; 53: 950–960
30. Quality and Outcomes Framework. http://www.hscic.gov.uk/qof (1 March 2016, date last accessed)
31. Stevens PE, de Lusignan S, Farmer CK *et al.* Engaging primary care in CKD initiatives: the UK experience. *Nephrol Dial Transplant* 2012; 27(Suppl 3): iii5–iii11
32. Fraser SD, Parkes J, Culliford D *et al.* Timeliness in chronic kidney disease and albuminuria identification: a retrospective cohort study. *BMC Fam Pract* 2015; 16: 18
33. Goodkin DA, Young EW, Kurokawa K *et al.* Mortality among hemodialysis patients in Europe, Japan, and the United States: case-mix effects. *Am J Kidney Dis* 2004; 44(5 Suppl 2): 16–21
34. de Lusignan S, Tomson C, Harris K *et al.* Creatinine fluctuation has a greater effect than the formula to estimate glomerular filtration rate on the prevalence of chronic kidney disease. *Nephron Clin Pract* 2011; 117: c213–c224
35. Matsushita K, van der Velde M, Astor BC *et al.* Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; 375: 2073–2081

Received for publication: 16.4.2016; Accepted in revised form: 24.7.2016

Supplementary data Table 1. List of diagnosis codes indicative of renal replacement therapy in Clinical Practice Research Datalink

Medcode	Read code	Read term
Haemodialysis:		
2996	7L1A200	Haemodialysis NEC
11773	7L1A.11	Dialysis for renal failure
20073	7L1A000	Renal dialysis
20196	14V2.00	H/O: renal dialysis
22252	ZV45100	[V]Renal dialysis status
28158	TB11.00	Kidney dialysis with complication without blame
31549	7L1A.00	Compensation for renal failure
35921	TA22.00	Failure of sterile precautions during perfusion
44422	14V2.11	H/O: kidney dialysis
46145	ZV56011	[V]Aftercare involving renal dialysis NOS
48022	7L1Ay00	Other specified compensation for renal failure
54844	U612200	[X]Failure sterile precautions dur kidney dialys/other perf
60302	7A60600	Creation of graft fistula for dialysis
60743	ZV56.00	[V]Aftercare involving intermittent dialysis
64636	7L1Az00	Compensation for renal failure NOS
65089	7L1Cz00	Placement other apparatus- compensate for renal failure NOS
66714	TB11.11	Renal dialysis with complication without blame
69266	TA22000	Failure of sterile precautions during kidney dialysis
69427	TA02z00	Accid cut puncture perf h'ge - perfusion NOS
69760	ZVu3G00	[X]Other dialysis
71124	7L1A300	Haemofiltration
83513	7L1C.00	Placement other apparatus for compensation for renal failure
96184	TA02000	Accid cut puncture perf h'ge - kidney dialysis
101756	7L1A011	Thomas intravascular shunt for dialysis
Peritoneal dialysis:		
2994	7L1A100	Peritoneal dialysis
8037	7L1B000	Insertion of ambulatory peritoneal dialysis catheter
23773	7L1B100	Removal of ambulatory peritoneal dialysis catheter
30709	7L1C000	Insertion of temporary peritoneal dialysis catheter
30756	7L1A500	Continuous ambulatory peritoneal dialysis
36442	7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
56760	7L1B.00	Placement ambulatory apparatus compensation renal failure
59194	7L1By00	Placement ambulatory apparatus- compensate renal failure OS
64828	7L1A600	Peritoneal dialysis NEC

88597	7L1A400	Automated peritoneal dialysis
Kidney transplantation:		
2997	7B00.00	Transplantation of kidney
5504	7B00z00	Transplantation of kidney NOS
5911	ZV42000	[V]Kidney transplanted
11553	SP08300	Kidney transplant failure and rejection
11745	7B00100	Transplantation of kidney from live donor
17253	8L50.00	Renal transplant planned
18774	TB00111	Renal transplant with complication without blame
24361	7B00200	Transplantation of kidney from cadaver
26862	7B06300	Exploration of renal transplant
48057	K0B5.00	Renal tubulo-interstitial disordrs in transplant rejectn
49028	14S2.00	H/O: kidney recipient
54990	TB00100	Kidney transplant with complication without blame
66705	7B00111	Allotransplantation of kidney from live donor
70712	SP08011	Det.ren.func.after ren.transpl
70874	7B00y00	Other specified transplantation of kidney
72004	7B01511	Excision of rejected transplanted kidney
89924	7B00300	Allotransplantation of kidney from cadaver heart-beating
90952	7B0F100	Pre-transplantation of kidney work-up recipient
93366	7B0F.00	Interventions associated with transplantation of kidney
94964	7B0F400	Post-transplantation of kidney examination live donor
96095	7B0F200	Pre-transplantation of kidney work-up live donor
96133	7B00400	Allotransplantation kidney from cadaver heart non-beating
98364	7B00211	Allotransplantation of kidney from cadaver
100693	Kyu1C00	[X]Renal tubulo-interstitial disorders/transplant rejection

Supplementary data Table 2. Age-sex distribution in Clinical Practice Research Datalink and UK census 2013

Age	Clinical Practice Research Datalink		UK census 2013	
(years)	No. of people	Proportion (%)	No. of people	Proportion (%)
Men:				
25-29	117,261	4.2	2,171,395	4.9
30-34	120,023	4.3	2,148,903	4.8
35-39	120,256	4.4	1,975,110	4.4
40-44	136,483	4.9	2,221,431	5.0
45-49	148,763	5.4	2,310,722	5.2
50-54	144,341	5.2	2,149,309	4.8
55-59	123,154	4.5	1,854,877	4.2
60-64	108,541	3.9	1,734,599	3.9
65-69	109,100	4.0	1,697,784	3.8
70-74	81,192	2.9	1,201,622	2.7
75-79	62,543	2.3	954,347	2.1
80-84	44,307	1.6	650,871	1.5
>=85	36,294	1.3	491,300	1.1
Women:				
25-29	114,601	4.1	2,178,575	4.9
30-34	120,740	4.4	2,177,964	4.9
35-39	118,908	4.3	1,991,769	4.5
40-44	134,237	4.9	2,274,838	5.1
45-49	145,120	5.3	2,375,928	5.3
50-54	141,266	5.1	2,194,934	4.9
55-59	121,259	4.4	1,901,770	4.3
60-64	110,258	4.0	1,806,214	4.0
65-69	114,370	4.1	1,793,663	4.0
70-74	88,857	3.2	1,337,533	3.0
75-79	73,334	2.7	1,137,778	2.6
80-84	58,348	2.1	899,031	2.0
>=85	68,199	2.5	967,876	2.2
Total:	2,761,755	100	44,600,143	100

5.3. Additional data and discussions

Further to the results and discussions presented in the published paper, here I show the additional data and related discussions regarding the serum creatinine testing rate by known CKD risk factors, as well as the distribution of patients satisfying the definition of decreased kidney function and those satisfying the definition of CKD (stages 3 to 5).

5.3.1. Serum creatinine testing rate by known CKD risk factors

(i) Backgrounds and methods

In the published paper, the serum creatinine testing rate (i.e. the proportion of people receiving at least one serum creatinine measurement during the five years between 1 April 2009 and 31 March 2014) was shown only by age category and sex. Here I present the serum creatinine testing rate by known CKD risk factors, in order to confirm that GPs are selectively (instead of randomly) testing patients at risk of CKD. The known CKD risk factors here include diabetes, hypertension, cardiovascular disease (myocardial infarction, chronic heart failure, peripheral arterial disease, or stroke), urological disease (vesicoureteral reflux, renal tract stone, or prostatic hypertrophy), systematic lupus erythematosus, and polycystic kidney disease [1, 18]. I also show the testing rate of people without any known CKD risk factors.

(ii) Results and discussions

Patients with known CKD risk factors had a very high serum creatinine testing rate (over 90% except for those with polycystic kidney disease) in the testing period (see **Table 5** below). In particular, those with diabetes, hypertension, and cardiovascular disease showed testing rates of approximately 97%. On the contrary, people with no known CKD risk factors showed a low serum creatinine testing rate, with approximately 50%. This data indeed suggests that GPs are selectively testing patients at risk of CKD. In addition, with or without CKD risk factors, the proportion of serum creatinine testing increased with age, probably because of increased opportunities to receive blood tests. As CKD mostly occurs in patients with known CKD risk factors or older people, the current serum creatinine testing strategy in UK primary care (i.e. selective testing of patients at risk of CKD and frequent testing of older patients) is expected to identify most patients with decreased kidney function.

Table 5. Serum creatinine testing rate by known CKD risk factors in CPRD during the five years between April 2009 and March 2014

Gender	Men						Women						Overall
Age category	25-34	35-44	45-54	55-64	65-74	≥75	25-34	35-44	45-54	55-64	65-74	≥75	
Overall (N = 2,761,755), %	25.9	38.5	55.6	72.4	86.2	92.3	46.2	55.3	67.4	75.3	84.5	91.9	63.7
Patients with diabetes (N = 232,824), %	89.4	94.1	96.7	98.3	99.1	99.4	88.0	92.6	96.2	98.0	98.9	99.2	98.0
Patients with hypertension (N = 569,922), %	83.8	90.4	93.9	96.4	97.9	98.5	83.7	89.5	94.7	96.2	97.6	97.9	96.8
Patients with cardiovascular disease (N = 152,310), %	65.0	85.1	93.9	96.9	98.3	98.6	78.5	85.5	93.1	96.6	98.0	98.0	97.5
Patients with urological disease (N = 116,884), %	44.6	61.5	77.5	89.6	94.9	97.0	64.9	72.4	82.2	87.9	92.7	96.1	91.0
Patients with systematic lupus erythematosus (N = 4,100), %	65.2	74.6	77.7	89.3	92.9	98.1	84.6	82.7	89.7	91.6	95.1	97.2	90.3
Patients with polycystic kidney disease (N = 2,229), %	58.2	79.5	81.3	93.7	94.1	99.0	68.5	79.4	87.0	90.1	96.8	99.1	85.4
People with no known CKD risk factor (N = 1,984,217), %	24.6	34.7	47.0	57.4	68.6	73.0	45.2	53.0	62.7	66.7	72.7	78.2	51.2

Abbreviation: CKD = chronic kidney disease.

5.3.2. Distribution of patients satisfying the definition of decreased kidney function and those satisfying the definition of CKD

(i) Backgrounds and methods

In the published paper, the prevalence of patients with decreased kidney function (i.e. most recent eGFR <60 ml/min/1.73 m^2 prior to 31 March 2014) was estimated in the main analysis, and that of patients with CKD (i.e. satisfying two or more consecutive measurements of eGFR <60 ml/min/1.73 m^2 for ≥3 months in the past five years) was estimated in a sensitivity analysis. However, some patients may satisfy the definition of decreased kidney function but not the definition of CKD, and vice versa (as illustrated in **Figure 3** in the previous **chapter 4**). To further explore this, I created a two by two table showing the distribution of these patients and interpreted the results.

(ii) Results and discussions

Some discrepancy was observed between patients satisfying the definition of decreased kidney function and those satisfying the CKD definition (see **Table 6** below).

Table 6. Distribution of patients satisfying the definition of decreased kidney function and those satisfying the definition of CKD

		CKD (i.e. two or more consecutive measurements of eGFR <60 ml/min/1.73 m^2 for ≥3 months in 5 years between 1 April 2009 to 31 March 2014)		Total
		Yes	No	
Decreased kidney function (i.e. most recent single eGFR <60 ml/min/1.73 m^2 prior to 31 March 2014)	Yes	144,913 (83.7%) (*76.4%*)	44,668 (*23.6%*)	189,581 (*100%*)
	No	28,141 (16.3%)	2,544,033	2,572,174
Total		173,054 (100%)	2,588,701	2,761,755

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

On the one hand, among 189,581 patients with decreased kidney function, 144,913 (76.4%) satisfied the CKD criteria in the past five years, while 44,668 (23.6%) did not. These 44,668 people are probably a mixture of (i) patients with temporarily low eGFR, and (ii) patients who had continuously decreased kidney function but received only one serum creatinine measurement in the past five years. On the other hand, among 173,054 patients satisfying the CKD criteria in the past five years, 144,913 (83.7%) patients showed their most recent eGFR <60 ml/min/1.73 m^2, whereas 28,141 (16.3%) showed their most recent eGFR ≥60 ml/min/1.73 m^2. Probably these 28,141 patients do not have continuously decreased kidney function, but by chance satisfied the CKD criteria when they received two or more blood samplings at the time of AKI or post-exercise/protein intake.

These data highlight the difficulty in identifying patients with "true CKD" in routinely collected data. There is a risk that patients with a single measurement of eGFR <60 ml/min/1.73 m^2 includes patients with temporarily decreased kidney function (i.e. AKI) or increased serum creatinine level due to exercise or protein intake. Meanwhile, there is a risk that the CKD chronicity criterion (i.e. two or more consecutive measurements of decreased kidney function over ≥3 months) may inadvertently exclude patients with "true CKD" who received only one serum creatinine measurement during a study period.

Another difficulty found is that even patients satisfying the chronicity criterion of CKD may not show continuously decreased kidney function thereafter. This was already suggested in previous studies using routinely collected data. For example, in a UK study recruiting people who previously satisfied the definition of CKD (i.e. at least two measurements of eGFR <60 ml/min/1.73 m^2 for ≥3 months) in primary care records, 24% had an eGFR of ≥60 ml/min/1.73 m^2 at the first study visit for baseline assessment of the study [120], and five years later 19.3% still showed eGFR >60 ml/min/1.73 m^2 and no albuminuria [121]. In a Norwegian study based on routinely collected primary and secondary care data, among patients satisfying the definition of CKD, 4.8% showed a subsequent improvement of GFR [122]. Even when they extended the chronicity criterion of three months to six months, nine months, and one year, the subsequent improvement of GFR was observed in 3.7%, 2.8%, and 2.3% of the study participants, respectively.

In summary, the strategies (i) to use a single measurement of decreased kidney function, and (ii) to apply the internationally accepted criteria of CKD (including the chronicity criterion) to routinely collected data, have their own limitations. However, proposing alternative criteria to identify "true CKD" in routinely collected data seems to be beyond the scope of this thesis focusing on kidney disease and mental health disorders. Therefore, in the next cross-sectional study in Paper 2 (SMI and CKD), I will simply compare the proportion of patients satisfying the definition of CKD (i.e. two or more consecutive measurements of decreased kidney function over ≥3 months in the past five years) between people with and without SMI, and will conduct a sensitivity analysis to examine the proportion of patients satisfying the definition of decreased kidney function (i.e. most recent eGFR <60 ml/min/1.73 m^2 prior to 31 March 2014).

It should be noted that the strategy to identify patients with decreased kidney function and CKD and associated limitations in cross-sectional studies (which used the serum creatinine records retrospectively among people who are currently alive) may not be directly applicable to cohort studies (which use the serum creatinine records prospectively). Therefore, for the cohort studies in Papers 3 (CKD and antidepressant prescription) and 4 (GI bleeding risk of SSRIs by kidney function), the strategy to identify patients with CKD and associated limitations will be differently discussed in **chapter 7**.

5.4. Chapter summary

Prevalence of CKD and RRT in CPRD

- Among patients aged ≥25 registered in the CPRD on 31 March 2014, the prevalence of patients with decreased kidney function (i.e. most recent single eGFR <60 mL/min/1.73m^2), CKD (two or more consecutive measurements of eGFR <60 ml/min/1.73 m^2 for ≥3 months in the past five years), and RRT (based on recorded diagnoses) was 6.86% (189,581/2,761,755), 6.27% (173,054/2,761,755), and 0.12% (3,293/2,761,755), respectively.

- The prevalence of decreased kidney function (in the main analysis) and CKD (in a sensitivity analysis) in the CPRD was broadly similar to that in the Health Survey for England 2009/2010, and the prevalence of RRT in the CPRD was similar to that estimated from the UK Renal Registry 2014, across all age groups in men and women.

- Serum creatinine testing rate was very high (over 90%) among patients with known CKD risk factors such as diabetes, hypertension, and cardiovascular disease, and among people aged 75 or older.

- These results indicate that most patients with decreased kidney function or CKD and RRT are probably captured with the current serum creatinine testing strategy and recording practice in the CPRD.

- The findings of discrepancy between patients satisfying the definition of decreased kidney function and those satisfying the definition of CKD criteria highlight the difficulty in identifying patients with “true CKD” in routinely collected data such as the CPRD.

Chapter 6: Severe mental illness and chronic kidney disease: a cross-sectional study in the United Kingdom (Paper 2)

6.1. Introduction

This chapter presents a cross-sectional study on the association between SMI, including schizophrenia and bipolar disorder, and CKD in the CPRD, which is published in *Clinical Epidemiology* [123].

The main research question is: Is CKD more common in patient with SMI than those without in the UK general population?

Briefly, in the dataset established in **chapter 4**, which includes 2,418,730 people aged 25–74 who were alive and registered for at least one year in the CPRD on 31 March 2014, I compared the prevalence of patients satisfying the definition of CKD in the past five years and RRT between people with a recorded diagnosis of SMI (with and without a history of lithium prescription in the CPRD) and those without SMI in the general population. I also compared the prevalence of several conditions associated with CKD (e.g. diabetes and smoking) between the groups, and conducted adjusted logistic regression analyses to examine to what extent these factors explain the association between SMI and CKD. Diagnosis codes (Read codes) suggesting SMI are shown in **Appendix B**.

Although the assumption that people without serum creatinine measurement in the past five years do not have CKD was suggested to be valid in Paper 1 (Prevalence of CKD and RRT in CPRD), this will be further explored later in the context of this study.

6.2. Published paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Masao Iwagami
Principal Supervisor	Dorothea Nitsch
Thesis Title	Association between chronic kidney disease and mental health disorders and psychoactive drugs in the UK general po

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Clin Epidemiol.10:421-429		
When was the work published?	16 Apirl 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I planned the study, carried out the data extraction, cleaning, analysis, and drafted the manuscript.

Student Signature: [redacted] **Date:** 30/May/2018

Supervisor Signature: [redacted] **Date:** 30.5.18

Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Severe mental illness and chronic kidney disease: a cross-sectional study in the United Kingdom

This article was published in the following Dove Press journal:
Clinical Epidemiology

Masao Iwagami[1]
Kathryn E Mansfield[1]
Joseph F Hayes[2]
Kate Walters[3]
David PJ Osborn[2,4]
Liam Smeeth[1]
Dorothea Nitsch[1]
Laurie A Tomlinson[1]

[1]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK; [2]Division of Psychiatry, University College London, London, UK; [3]Department of Primary Care and Population Health, University College London, London, UK; [4]Camden and Islington NHS Foundation Trust, London, UK

Objective: We investigated the burden of chronic kidney disease (CKD) among patients with severe mental illness (SMI).

Methods: We identified patients with SMI among all those aged 25–74 registered in the UK Clinical Practice Research Datalink as on March 31, 2014. We compared the prevalence of CKD (two measurements of estimated glomerular filtration rate <60 mL/min/1.73 m^2 for ≥3 months) and renal replacement therapy between patients with and without SMI. For patients with and without a history of lithium prescription separately, we used logistic regression to examine the association between SMI and CKD, adjusting for demographics, lifestyle characteristics, and known CKD risk factors.

Results: The CKD prevalence was 14.6% among patients with SMI and a history of lithium prescription (n = 4,295), 3.3% among patients with SMI and no history of lithium prescription (n = 24,101), and 2.1% among patients without SMI (n = 2,387,988; $P < 0.001$). The prevalence of renal replacement therapy was 0.23%, 0.15%, and 0.11%, respectively ($P = 0.012$). Compared to patients without SMI, the fully adjusted odds ratio for CKD was 6.49 (95% CI 5.84–7.21) for patients with SMI and a history of lithium prescription and 1.45 (95% CI 1.34–1.58) for patients with SMI and no history of lithium prescription. The higher prevalence of CKD in patients with SMI may, in part, be explained by more frequent blood testing as compared to the general population.

Conclusion: CKD is identified more commonly among patients with SMI than in the general population.

Keywords: severe mental illness, schizophrenia, bipolar disorder, chronic kidney disease, lithium

Introduction

People with severe mental illness (SMI), including schizophrenia, bipolar disorder, and other nonorganic psychotic illnesses, are known to have shorter life expectancy, by ~10–20 years, than the general population.[1–6] Their premature death is attributed not only to suicide and accident but also to physical illnesses – especially cardiovascular diseases such as coronary heart disease and stroke.[5–9] The high rate of cardiovascular deaths in patients with SMI has been attributed to the high prevalence of lifestyle-related conditions (eg, smoking and obesity),[10–13] suboptimal screening/assessment of cardiovascular risks,[14,15] and suboptimal management of underlying diseases (eg, hypertension, diabetes, dyslipidemia).[16–18]

Chronic kidney disease (CKD) – the continuous presence of kidney damage and/or decreased level of kidney function[19] – is independently associated with increased risk of death, cardiovascular events, and all-cause hospitalization.[20] CKD

Correspondence: Masao Iwagami
Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
Email masao.iwagami@lshtm.ac.uk

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/CLEP.S154841

can progress to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT), a substantial burden for both – quality of life of patients and health budgets. The UK National Institute for Health and Care Excellence guidance for CKD recommends early identification and appropriate management of CKD.[21]

People with SMI have an increased prevalence of several risk factors for CKD, including smoking and diabetes.[13,16,22] Moreover, patients with SMI may be treated with lithium, which is associated with the development of CKD.[23,24] However, there has been limited research investigating the prevalence of, and risk factors for, CKD in people with SMI.[13,25,26] In the UK, primary care plays an important role in the management of physical health conditions in people with SMI. As part of the Quality and Outcomes Framework (QOF), there have been recent financial incentives for general practitioners (GPs) to undertake physical health checks in people with SMI.[27] However, it is unclear whether CKD in patients with SMI is appropriately recognized and managed by GPs.

Therefore, we used a UK primary care database to: 1) compare the prevalence of CKD and RRT among patients with SMI (with and without a history of lithium use) and those without SMI; 2) investigate whether there is an independent association between SMI and CKD after adjusting for known CKD risk factors; and 3) compare the recognition and management of CKD between CKD patients with and without SMI.

Materials and methods

Data source

The Clinical Practice Research Datalink (CPRD) is an observational data and interventional research service provided by the National Health Service. Around 98% of the UK population are registered with a primary care practice. Currently, >650 general practices contribute data conforming to quality control standards to the CPRD, including ~ 7% of the UK population. The included practices are representative of the UK general population in terms of age and sex.[28] The database includes the following data: patient demographics, diagnoses based on Read codes (a hierarchical coding system), prescriptions based on British National Formulary codes, laboratory test results, and referrals made by GPs. Ethical approval for this study was obtained from the Independent Scientific Advisory Committee of CPRD (protocol no. 16_055). Informed consent was waived because data are anonymized for research purposes.

Study population

Our study population included all people, aged 25–74 years, registered in the CPRD for at least 1 year as on March 31, 2014 (ie, the end of a financial or QOF year). We selected the 25–74 age range because our preliminary analysis suggested that CKD and/or SMI were rare in people outside these parameters, thereby limiting the power for comparative prevalence analyses. To ensure that we had reliable measures of morbidity (to allow time for the recording of past medical history in newly registered patients), we required that all participants had at least 1 year of continuous registration in the CPRD.

Disease definition

We identified SMI using Read morbidity codes that have been validated in UK primary care data, with high sensitivity (91%), specificity (99.9%), and positive predictive value (91%).[29] Patients with SMI were further classified as those with and without any record of lithium prescription in the period between the CPRD registration and March 31, 2014. We excluded patients who had been prescribed lithium without recorded SMI from the general population comparison group because the indication for treatment was not known.

Our definition of CKD was based on two measurements of estimated glomerular filtration rate <60 mL/min/1.73 m^2 separated by 3 months or longer,[19] calculated from serum creatinine records in the CPRD in the past 5 years, using the Chronic Kidney Disease Epidemiology Collaboration equation.[30] RRT was characterized on the basis of diagnosis codes suggesting hemodialysis, peritoneal dialysis, or kidney transplantation. Previous research has shown that the prevalence of estimated glomerular filtration rate <60 mL/min/1.73 m^2 and RRT in the CPRD is similar to that estimated in a nationally representative population survey (Health Survey for England) and disease registry (UK Renal Registry), suggesting that most cases of CKD and RRT are captured in the CPRD.[31]

Covariate definition

We defined baseline characteristics of patients with and without SMI: age, sex, ethnicity, socioeconomic status (SES), country of the UK (ie, England, Northern Ireland, Scotland, and Wales) body mass index (BMI), smoking status, chronic diseases that are associated with CKD[21] – diabetes, hypertension, cardiovascular disease (ie, myocardial infarction, chronic heart failure, peripheral arterial disease, and stroke), urological disease (ie, vesicoureteral reflux, renal tract stone, and prostatic hypertrophy), systematic lupus erythematosus, and polycystic kidney disease – based on relevant diagnosis

codes. Based on previous studies using UK primary care data,[32,33] we grouped patients with no record of ethnicity into those of white ethnicity. SES was assigned at the general practice level using quintiles of the Index of Multiple Deprivation in each country of the UK.[34] BMI and smoking status were based on the most recent records prior to the date of study inclusion (ie, March 31, 2014). For chronic diseases, if a diagnosis code was recorded for a patient during the period between CPRD registration and the study date, then that disease was regarded as being present.

Data analysis

We compared baseline characteristics and overall prevalence of CKD (including patients on RRT) among the three groups: patients with SMI with and without a history of lithium prescription as well as those without SMI, using chi-squared tests. We stratified CKD prevalence by age (using 10-year age bands) and sex. We estimated the prevalence of RRT among the three groups and compared it overall by chi-squared tests. Moreover, we compared the distribution of the most recent category of RRT modality (hemodialysis, peritoneal dialysis, or kidney transplantation) between patients with and without SMI using chi-squared tests.

Next, we carried out logistic regression analyses to examine the association between SMI (with and without a history of lithium use) and CKD. To understand which factors are more likely to explain the association between SMI and CKD, we adjusted step-by-step for age and sex, ethnicity, SES, BMI, smoking status, and chronic diseases associated with decline in kidney function (ie, diabetes, hypertension, cardiovascular disease, urological disease, systemic lupus erythematosus, and polycystic kidney disease).[21] Patients with missing data of BMI and smoking status were excluded from the analysis. We took into account variations in coding and testing practices by different general practices through clustering by general practice in the logistic regression models.

Finally, we restricted analysis to patients with CKD who were not on RRT and compared the recognition and management of CKD between patients with and without SMI. We used the QOF CKD indicators (QOF version 2013/14) as markers of the recognition and management of CKD in the UK primary care.[27] We determined the proportion of CKD patients with and without SMI who had: 1) a record of a diagnostic code for CKD, using CKD codes listed in the QOF version 2013/14;[35] 2) the most recent blood pressure measure ≤140/90 mmHg (recorded in the year before the date of the study); 3) urine test for proteinuria/albuminuria (including dipstick test) in the year before the date of the study; and 4) for those with hypertension and proteinuria (recorded any time between CPRD registration and study date), at least one prescription for a renin–angiotensin system antagonist in the past 3 months. In addition, because the National Institute for Health and Care Excellence guidance for cardiovascular disease recommends statins as primary prevention for all CKD patients regardless of serum cholesterol levels,[36] we compared the proportion of CKD patients with and without SMI who had at least one prescription for a statin in the past 3 months.

All statistical analyses were conducted using Stata 14 (Stata Corp, College Junction, TX, USA).

Results

Of the 2,418,730 people aged 25–74 years who were registered in the CPRD for >1 year on March 31, 2014, we identified 28,396 (1.17%) patients with SMI, including 4,295 patients with a history of lithium prescription in the CPRD and 24,101 without (Figure 1). In patients with SMI (both with and without

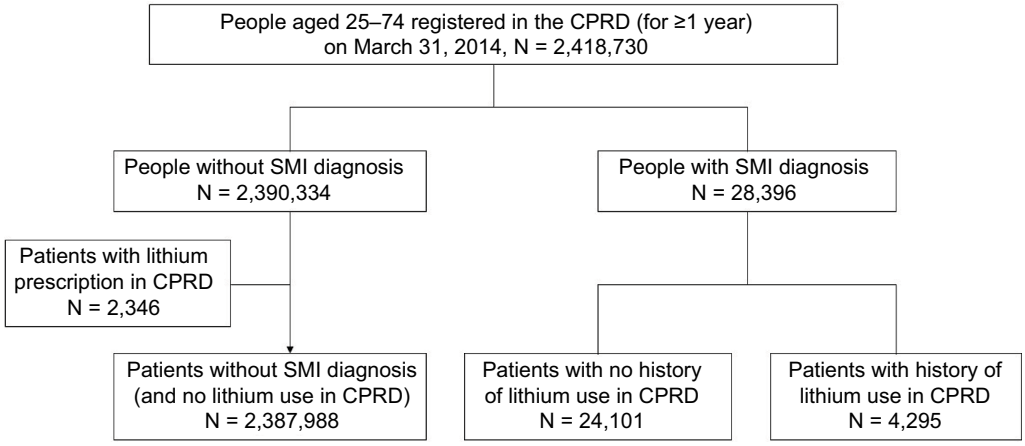


Figure 1 Flow chart showing identification of study participants.
Abbreviations: CPRD, Clinical Practice Research Datalink; SMI, severe mental illness.

a previous lithium prescription) compared to those without, the SES was generally lower and the proportions of black ethnicity, obesity (BMI ≥30 kg/m^2), and current smokers were higher. Diabetes, hypertension, and cardiovascular diseases were more common in patients with SMI, whereas the prevalence of other diseases (urological disease, systematic lupus erythematosus, and polycystic kidney disease) was similar between patients with and without SMI (Table 1).

Overall, the prevalence of CKD was 14.64% (629/4,295) in patients with SMI and history of lithium prescription, 3.34% (805/24,101) in patients with SMI and no history of lithium prescription, and 2.09% (49,870/2,387,988) in patients without SMI ($P < 0.001$). The absolute difference in CKD prevalence among the three groups increased with age in both men and women (Figure 2). Moreover, there was evidence ($P = 0.012$) that the overall prevalence of RRT was higher in patients with SMI (0.23% [10/4, 295] and 0.15% [36/24, 101] in those with and without a history of lithium prescription, respectively) than those without SMI (0.11% [2,645/2,387,988]). There was strong evidence that the distribution of RRT modalities was different between patients with and without SMI ($P = 0.001$). In patients with SMI, 50% (23/46) were receiving hemodialysis and 2% (1/46) peritoneal dialysis, and 48% (22/46) underwent kidney transplantation. However, in patients without SMI, the corresponding figures were 26% (700/2,645), 7% (194/2,645), and 66% (1,751/2,645).

The age–sex-adjusted odds ratio (OR) for CKD was 7.13 (95% confidence interval [CI] 6.47–7.85) for patients with SMI and history of lithium use, and 1.69 (1.56–1.83) for those with SMI and no history of lithium use, compared to those without SMI. After adjusting for SES, BMI, smoking, and chronic diseases associated with CKD, the adjusted ORs decreased to 6.49 (5.84–7.21) and 1.45 (1.34–1.58) but were still significant in patients with SMI with and without previous lithium prescription, respectively (Table 2).

Among patients with biochemically defined CKD (not on RRT), a higher proportion of people with SMI had a recorded diagnosis of CKD (SMI 70.3%, without SMI 65.5%) and a recorded blood pressure ≤140/90 mmHg (SMI 80.1%, without SMI 75.6%; Table 3). However, a lower proportion of patients with SMI had recently been prescribed statins (SMI 50.5%, without SMI 59.0%).

Discussion

Main findings

We found that, in UK primary care, patients with SMI had a greater prevalence of CKD compared to the general population. This was pronounced (6.5-fold increase) in patients with a history of lithium prescription, but there was a 1.5-fold increase in odds of CKD even among patients never known to be prescribed lithium and after adjustment for differences in known risk factors for CKD. In addition, patients with SMI had an increased prevalence of RRT and were more likely to be receiving hemodialysis as their modality than patients without SMI on RRT.

Strengths and limitations

There are several strengths of our study. There is likely to be a good recording of the diagnoses examined because GPs manage patients with SMI for their physical and mental health – with or without the support of psychiatrists in secondary care. In addition, the QOF – the reward and incentive program for GPs – included both SMI and CKD during this time period.[27] Moreover, the diagnosis of SMI has been validated at the individual level,[29] and the prevalence estimates of CKD and RRT have been validated at the population level.[31]

However, we need to acknowledge several limitations. First, this is a cross-sectional study, in which temporal relationships cannot always be clarified. The majority of patients with SMI have developed symptoms by early adulthood,[37] whereas the prevalence of CKD starts to increase after age 55.[31] Therefore, it is unlikely that CKD precedes the onset of SMI. However, the interpretation of potential risk factors in the association between SMI and CKD requires caution. For example, cessation of smoking and lithium may be as a result of the development of CKD. Therefore, we did not differentiate previous and current users in the regression models. Second, a greater prevalence of CKD among patients with SMI may, in part, be influenced by surveillance or ascertainment bias. Patients with SMI take medications, such as lithium and other psychotropic drugs, which need regular monitoring. In addition, in 2013–2014, GPs were incentivized to monitor blood glucose and cholesterol levels for people with SMI; therefore, many patients would have had concurrent testing of renal function.[38] In contrast, in the general population, creatinine testing in primary care is not universal: in 2013–2014, this was recommended and incentivized only for people with known CKD risk factors.[21,27] However, we have previously demonstrated that the prevalence of CKD identified in the CPRD was very similar to that seen in the Health Survey for England, a nationally representative survey of the general population.[31] This suggests that most patients with CKD are captured by the current testing strategy in primary care, and the proportion of patients with unmeasured CKD in CPRD is small. Therefore, underascertainment of CKD in people

Table 1 Characteristics of patients by SMI diagnosis and history of lithium use

Characteristic	Patients without SMI diagnosis N = 2,387,988	Patients with SMI diagnosis (N = 28,396)	
		Patients with no history of lithium use N = 24,101	Patients with history of lithium use N = 4,295
	n (%)	n (%)	n (%)
Type of SMI diagnosis			
Schizophrenia	–	9,134 (37.9)	448 (10.4)
Bipolar disorder	–	5,881 (24.4)	3,374 (78.6)
Other nonorganic psychosis	–	9,086 (37.7)	473 (11.0)
Age category (years)			
25–34	468,602 (19.6)	3,654 (15.2)	242 (5.6)
35–44	503,405 (21.1)	5,475 (22.7)	688 (16.0)
45–54	571,325 (23.9)	6,361 (26.4)	1,187 (27.6)
55–64	456,457 (19.1)	4,844 (20.1)	1,209 (28.2)
65–74	388,199 (16.3)	3,767 (15.6)	969 (22.6)
Sex (male)	1,193,218 (50.0)	13,183 (54.7)	1,761 (41.0)
Ethnicity			
White/unrecorded*	2,232,403 (93.5)	22,051 (91.5)	4,184 (97.4)
Black	42,339 (1.8)	836 (3.5)	35 (0.8)
South Asian	72,190 (3.0)	734 (3.1)	42 (1.0)
Other	41,056 (1.7)	480 (2.0)	34 (0.8)
Country			
England	1,739,874 (72.9)	17,507 (72.6)	2,815 (65.5)
North Ireland	92,714 (3.9)	931 (3.9)	234 (5.5)
Scotland	307,936 (12.9)	3,084 (12.8)	765 (17.8)
Wales	247,464 (10.4)	2,579 (10.7)	481 (11.2)
Socioeconomic status			
1 (least deprived)	468,867 (19.6)	3,463 (14.4)	856 (19.9)
2	496,229 (20.8)	4,295 (17.8)	864 (20.1)
3	483,617 (20.3)	4,706 (19.5)	833 (19.4)
4	508,424 (21.3)	6,084 (25.2)	948 (22.1)
5 (most deprived)	430,851 (18.0)	5,553 (23.0)	794 (18.5)
Body mass index (kg/m^2)			
<18.5	37,526 (1.6)	497 (2.1)	56 (1.3)
18.5 to <25	772,208 (32.3)	6,868 (28.5)	988 (23.0)
≥25 to <30	716,303 (30.0)	7,480 (31.0)	1,482 (34.5)
≥30	530,065 (22.2)	8,281 (34.4)	1,724 (40.1)
Missing data	331,886 (13.9)	975 (4.1)	45 (1.1)
Smoking status			
Nonsmoker	962,061 (40.3)	5,578 (23.1)	1,123 (26.2)
Current smoker	516,109 (21.6)	10,677 (44.3)	1,485 (34.6)
Ex-smoker	861,414 (36.1)	7,773 (32.3)	1,685 (39.2)
Missing data	48,404 (2.0)	73 (0.3)	<5 (<0.1)
Chronic diseases associated with CKD			
Diabetes mellitus	166,917 (7.0)	3,421 (14.2)	718 (16.7)
Hypertension	682,868 (28.6)	8,826 (36.6)	2,138 (49.8)
Cardiovascular disease			
Myocardial infarction	31,659 (1.3)	390 (1.6)	81 (1.9)
Chronic heart failure	10,997 (0.5)	192 (0.8)	38 (0.9)
Peripheral arterial disease	15,383 (0.6)	232 (1.0)	47 (1.1)
Stroke	24,097 (1.0)	419 (1.7)	96 (2.2)
Urological disease			
Vesicoureteral reflux	1,676 (0.1)	16 (0.1)	5 (0.1)
Renal tract stone	30,665 (1.3)	266 (1.1)	41 (1.0)
Prostatic hypertrophy	40,855 (1.7)	379 (1.6)	105 (2.4)
Other			
Systemic lupus erythematosus	3,423 (0.1)	47 (0.2)	5 (0.1)
Polycystic kidney disease	1,980 (0.1)	22 (0.1)	<5 (<0.1)

Note: *Number of patients without recorded ethnicity was 1,141,478 (47.8%), 9,687 (40.2%), and 2,045 (47.6%), respectively.
Abbreviations: CKD, chronic kidney disease; SMI, severe mental illness.

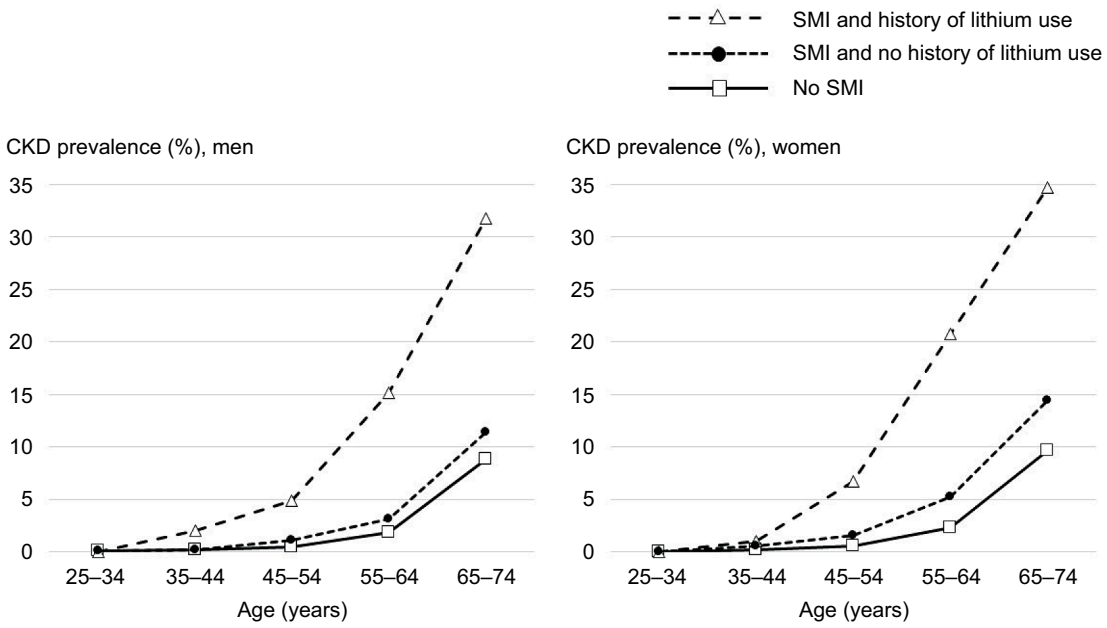


Figure 2 Prevalence of CKD in patients with and without SMI by age in men and women.
Abbreviations: CKD, chronic kidney disease; SMI, severe mental illness.

Table 2 Adjusted logistic regression analyses of the association between SMI and chronic kidney disease

Model	Adjusted odds ratio (95% CI) for chronic kidney disease		
	Patients without SMI	Patients with SMI and no history of lithium use	Patients with SMI and history of lithium use
Model 1: adjusted by age and sex	1 (ref)	1.69 (1.56–1.83)	7.13 (6.47–7.85)
Model 2: Model 1 + adjusted by ethnicity, country, and socioeconomic status	1 (ref)	1.65 (1.52–1.79)	7.13 (6.48–7.86)
Model 3: Model 2 + adjusted by smoking status	1 (ref)	1.60 (1.48–1.74)	6.91 (6.27–7.61)
Model 4: Model 3 + adjusted by body mass index	1 (ref)	1.53 (1.42–1.66)	6.44 (5.84–7.09)
Model 5: Model 4 + adjusted by diabetes	1 (ref)	1.42 (1.31–1.54)	6.23 (5.64–6.88)
Model 6: Model 5 + adjusted by other chronic diseases*	1 (ref)	1.45 (1.34–1.58)	6.49 (5.84–7.21)

Note: *Hypertension, cardiovascular disease (myocardial infarction, chronic heart failure, peripheral arterial disease, and stroke), urological disease (vesicoureteral reflux, renal tract stone, and prostatic hypertrophy), systematic lupus erythematosus, and polycystic kidney disease.
Abbreviations: CI, confidence interval; ref, reference; SMI, severe mental illness.

Table 3 Recognition and management of CKD in CKD patients with and without SMI

Indicator of CKD recognition/management	Patients with biochemically defined CKD (not on RRT)	
	With SMI N = 1,388, n (%)	Without SMI N = 47,225, n (%)
1) Recorded diagnosis of CKD	976 (70.3)	30,922 (65.5)
2) Most recent blood pressure ≤140/90 mmHg	1,112 (80.1)	35,705 (75.6)
3) Prescription of renin–angiotensin system antagonists (among patients with hypertension and proteinuria diagnoses), numerator/denominator (%)	52/66 (78.8)	2,905/3,428 (84.7)
4) Proteinuria/albuminuria testing in the past year	421 (30.3)	15,263 (32.3)
5) Prescription of statins	701 (50.5)	27,853 (59.0)

Abbreviations: CKD, chronic kidney disease; RRT, renal replacement therapy; SMI, severe mental illness.

without SMI is unlikely to be a substantial contributor to our results. Third, RRT is a rare outcome: the incidence of RRT in the UK is ~100 per million population.[39] Combined with the cross-sectional design, this meant that, despite the large sample size, the number of patients with SMI and RRT was limited (n = 46). Although there was a statistically significant difference in the prevalence of RRT between patients with and without SMI, more detailed comparison (eg, stratification

by age and sex) or analysis of risk factors for RRT was not possible with these numbers. Finally, our adjusted analyses suggested that differences in the prevalence of risk factors between patients with and without SMI did not completely explain the association between SMI and CKD. This finding may be due to additional unconsidered risk factors, differences in patient management, or residual confounding. For example, antipsychotics used for SMI have been suggested to cause acute kidney injury,[40,41] which is a known risk factor for subsequent CKD.[21] Furthermore, insufficient control – or later initiation – of treatment for the CKD risk factors (eg, high blood pressure, diabetes, and obesity) may lead to higher incidence of CKD in the SMI population; however, this information could not be adequately captured in this cross-sectional study. Using recorded CPRD diagnoses, moreover, means that the misclassification or underidentification of disease status (eg, diabetes and heart failure) is possible. We did not have any information on the use of lithium before the CPRD registration and, therefore, some patients may have been wrongly classified as not having used lithium. This also meant that we were unable to examine the association between the length or cumulative dose of lithium prescription and CKD.

Comparison with other studies

Few studies have examined the prevalence of CKD in the population with SMI. A small cross-sectional study in London, UK, found a similar relative difference in CKD prevalence between those with and without SMI despite a less accurate CKD definition than in the present study.[13] A Taiwanese cohort study showed that people with schizophrenia are more likely to develop CKD,[25] whereas a cross-sectional analysis of Scottish primary care demonstrated that people with bipolar disorder had a higher prevalence of CKD than people without the condition.[18] Several studies have focused on the prevalence or incidence of CKD in patients using lithium. A Swedish cohort study showed that the prevalence of CKD (defined as serum creatinine level >150 μmol/L) and ESRD requiring RRT was higher in people ever exposed to lithium than in the general population,[42] whereas a Danish cohort study also showed that lithium prescription was associated with an increased rate of CKD diagnosis.[26]

The relative risk of lithium use for the prevalence of CKD in our study (the fully adjusted OR of 6.5) was larger than those estimated in previous studies: the adjusted hazard ratio by lithium for CKD was nearly 2 in a cohort study in Oxford, UK,[43] and around 3 in the Danish cohort study.[26] These differences can be explained by the different nature of the study population in each study. We compared people with lithium prescription for SMI and those without SMI in the general population, whereas the UK cohort study compared those with and without lithium use among people with at least two blood samplings in hospitals in Oxford,[43] and the Danish study estimated the risk of lithium prescription in the population with a single manic episode or bipolar disorder.[26] Therefore, our comparison group is healthier than in the other studies, although again, ascertainment bias may play a role to some extent in our study.

The management of CKD includes prevention of cardiovascular events. Several previous studies have focused on inequalities in medication use for cardiovascular risk between patients with and without SMI. Studies from the UK showed that statin prescribing is lower in patients with schizophrenia and bipolar disorder than in the general population, although their cardiovascular risks are higher.[16,18] A US study suggests that prescribing of renin–angiotensin system antagonists and statins is suboptimal in patients with SMI and type 2 diabetes.[17] Our finding of lower prescribing of statins among patients with SMI and CKD, compared to the general population, are consistent with these earlier studies.

Explanation of findings and clinical relevance

CKD is strongly and independently associated with mortality and cardiovascular risk.[20] Therefore, the higher prevalence of CKD we have established may contribute to the known shorter life expectancy in people with SMI. Moreover, we have shown that the difference in CKD prevalence between patients with and without SMI increased with age. It is possible that progressive accumulation and biological effect of CKD risk factors in patients with SMI (eg, obesity, smoking, and diabetes) leads to an increased incidence of CKD at an older age.

We have confirmed a higher burden of CKD risk factors among patients with SMI, and adjustment for these partially explained the association between SMI and CKD. However, many questions about the cause of the higher prevalence of CKD remain unanswered. Our snapshot of GP's management of patients with SMI suggests that CKD is more commonly coded as a diagnosis than in the general population. The extent to which this is driven by incentivized management schemes and regular testing of renal function for patients with SMI – particularly those prescribed lithium and other psychotropic medications – is unknown. Whereas blood pressure appeared better controlled among SMI patients, this may reflect different underlying renal pathologies associated with

lower rates of hypertension (eg, interstitial nephritis related to lithium). Other aspects of management – proteinuria testing as well as prescription of statins and renin–angiotensin system antagonists – were lower among patients with SMI.

Of greatest concern is our finding of the substantial increase in the prevalence of RRT among patients with SMI. The development of ESRD results in markedly reduced quality of life and psychological stress. Renal transplantation is associated with better quality of life and, possibly, longer survival.[44] However, our results showed that the proportion of patients receiving kidney transplantation was substantially lower in patients with SMI than those without. It is important to understand why this difference arises and ensure that there are no inappropriate barriers to the consideration for renal transplantation for people with SMI.

Conclusion

We found that the prevalence of CKD and RRT was substantially higher in patients with SMI as compared to the general population. There was a greater burden of risk factors among patients with SMI, but these did not fully explain the increased prevalence of CKD. Further information about the management of CKD in SMI patients such as referral to specialist care and management of comorbidities is needed to identify opportunities for prevention of CKD and its progression.

Acknowledgments

Masao Iwagami is supported by the Honjo International Scholarship Foundation. Laurie A Tomlinson is funded by a Wellcome Intermediate Clinical Fellowship (WT101143MA). Liam Smeeth is supported by a Wellcome Senior Research Fellowship in Clinical Science (grant number 098504/Z/12/Z). David PJ Osborn is supported by the UCLH NIHR Biomedical Research Centre and he was also in part supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames at Bart's Health NHS Trust. The funders had no role in the execution of this study or in the interpretation of results.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Chang CK, Hayes RD, Perera G, et al. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. *PLoS One*. 2011;6(5):e19590.
2. Dembling BP, Chen DT, Vachon L. Life expectancy and causes of death in a population treated for serious mental illness. *Psychiatr Serv*. 1999;50(8):1036–1042.
3. Hannerz H, Borgå P, Borritz M. Life expectancies for individuals with psychiatric diagnoses. *Public Health*. 2001;115(5):328–337.
4. Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. *Psychiatr Serv*. 2009;60(2):147–156.
5. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. *Am J Psychiatry*. 2013;170(3):324–333.
6. Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry*. 2010;196(2):116–121.
7. Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Rsearch Database. *Arch Gen Psychiatry*. 2007;64(2):242–249.
8. Osby U, Correia N, Brandt L, Ekbom A, Sparén P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res.* 2000;45(1–2):21–28.
9. Osby U, Brandt L, Correia N, Ekbom A, Sparén P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry*. 2001;58(9):844–850.
10. Osborn DP, Nazareth I, King MB. Risk for coronary heart disease in people with severe mental illness: cross-sectional comparative study in primary care. *Br J Psychiatry.* 2006;188:271–277.
11. Daumit GL, Clark JM, Steinwachs DM, Graham CM, Lehman A, Ford DE. Prevalence and correlates of obesity in a community sample of individuals with severe and persistent mental illness. *J Nerv Ment Dis*. 2003;191(12):799–805.
12. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res.* 2005;80(1):19–32.
13. Woodhead C, Ashworth M, Schofield P, Henderson M. Patterns of physical co-/multi-morbidity among patients with serious mental illness: a London borough-based cross-sectional study. *BMC Fam Pract*. 2014;15:117.
14. Osborn DP, Baio G, Walters K, et al. Inequalities in the provision of cardiovascular screening to people with severe mental illnesses in primary care: cohort study in the United Kingdom THIN Primary Care Database 2000–2007. *Schizophr Res*. 2011;129(2–3):104–110.
15. Smith DJ, Langan J, McLean G, Guthrie B, Mercer SW. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. *BMJ Open*. 2013;3(4):e002808.
16. Hippisley-Cox J, Parker C, Coupland C, Vinogradova Y. Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study. *Heart*. 2007;93(10):1256–1262.
17. Kreyenbuhl J, Medoff DR, Seliger SL, Dixon LB. Use of medications to reduce cardiovascular risk among individuals with psychotic disorders and Type 2 diabetes. *Schizophr Res*. 2008;101(1–3):256–265.
18. Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. *BMC Med*. 2013;11:263.
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2 Suppl 1):S1–S266.
20. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296–1305.
21. National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. Available from: https://www.nice.org.uk/guidance/cg182. Accessed October 22, 2017.

22. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull*. 2000;26(4):903–912.
23. Markowitz GS, Radhakrishnan J, Kambham N, Valeri AM, Hines WH, D'Agati VD. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. *J Am Soc Nephrol*. 2000;11(8):1439–1448.
24. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DP. Adverse renal, endocrine, hepatic, and metabolic events during maintenance mood stabilizer treatment for bipolar disorder: a population-based cohort study. *PLoS Med*. 2016;13(8):e1002058.
25. Tzeng NS, Hsu YH, Ho SY, et al. Is schizophrenia associated with an increased risk of chronic kidney disease? A nationwide matched-cohort study. *BMJ Open*. 2015;5(1):e006777.
26. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of lithium and anticonvulsants and the rate of chronic kidney disease: a nationwide population-based study. *JAMA Psychiatry*. 2015;72(12):1182–1191.
27. Health and Social Care Information Centre. Quality and outcomes framework. Available from: www.Hscic.Gov.Uk/qof. Accessed October 22, 2017.
28. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol.* 2015;44(3):827–836.
29. Nazareth I, King M, Haines A, Rangel L, Myers S. Accuracy of diagnosis of psychosis on general practice computer system. *BMJ*. 1993;307(6895):32–34.
30. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612.
31. Iwagami M, Tomlinson LA, Mansfield KE, et al. Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom. *Nephrol Dial Transplant*. 2017;32(Suppl 2):ii142–ii150.
32. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. *BMJ*. 2012;344:e3427.
33. Hippisley-Cox J, Coupland C. Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores. *BMJ.* 2014;349:g4606.
34. Department for Communities and Local Government. English indices of deprivation. Available from: www.Gov.Uk/government/collections/english-indices-of-deprivation. Accessed October 22, 2017.
35. NHS Staffordshire Commissioning Support Unit. Recommended read codes for quality & outcomes framework. Available from: https://www.pcc-cic.org.uk/article/qof-read-codes-v28. Accessed October 22, 2017.
36. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. Available from: https://www.nice.org.uk/guidance/cg181. Accessed October 22, 2017.
37. Ochoa S, Usall J, Cobo J, Labad X, Kulkarni J. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. *Schizophr Res Treatment*. 2012;2012:916198.
38. Quality and Outcomes Framework guidance for GMS contract 2013/14. Available from: https://www.bma.org.uk/-/media/files/pdfs/practical%20advice%20at%20work/contracts/gpqofguidance20132014.pdf. Accessed October 22, 2017.
39. Rao A, Casula A, Castledine C. UK Renal Registry 17th Annual Report: Chapter 2 UK Renal Replacement Therapy Prevalence in 2013: National and Centre-specific Analyses. *Nephron*. 2015;129(Suppl 1):31–56.
40. Jiang Y, McCombs JS, Park SH. A retrospective cohort study of acute kidney injury risk associated with antipsychotics. *CNS Drugs*. 2017;31(4):319–326.
41. Hwang YJ, Dixon SN, Reiss JP, et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. *Ann Intern Med*. 2014;161(4):242–248.
42. Bendz H, Schön S, Attman PO, Aurell M. Renal failure occurs in chronic lithium treatment but is uncommon. *Kidney Int*. 2010;77(3):219–224.
43. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet*. 2015;386(9992):461–468.
44. Thiruchelvam PT, Willicombe M, Hakim N, Taube D, Papalois V. Renal transplantation. *BMJ*. 2011;343:d7300.

6.3. Additional data and discussions

Further to the results and discussions presented in the published paper, here I show the additional data on the prevalence of decreased kidney function (i.e. most recent single eGFR <60 mL/min/1.73m^2 prior to 31 March 2014), instead of CKD (i.e. two or more consecutive measurements of eGFR<60 mL/min/1.73m^2 for ≥3 months in the past five years), and that of severely decreased kidney function (i.e. most recent eGFR <30 mL/min/1.73m^2). I also show the serum creatinine testing rate by SMI status and known CKD risk factors to discuss potential ascertainment/surveillance bias in more detail.

6.3.1. Prevalence of decreased kidney function and severely decreased kidney function by SMI status and history of lithium use

(i) Backgrounds and methods

The published paper estimated the prevalence of CKD, defined as two or more consecutive measurements of eGFR <60 mL/min/1.73m^2 for ≥3 months during the five years between 1 April 2009 and 31 March 2014, by SMI status and history of lithium use. However, according to Paper 1 (Prevalence of CKD and RRT in CPRD), there may be some discrepancy between patients satisfying the definition of decreased kidney function and those satisfying the internationally-accepted CKD criteria in the past five years. Therefore, as a sensitivity analysis, I here show the prevalence of decreased kidney function by SMI status and history of lithium use, to confirm that my conclusion regarding the association between SMI and kidney diseases does not change by different definitions of kidney function. Moreover, I examine whether the prevalence of severely decreased kidney function, defined as the most recent single eGFR <30 mL/min/1.73m^2, is also higher in patients with SMI.

(ii) Results and discussions

The prevalence of decreased kidney function was broadly similar to that of CKD in each subgroup (see **Table 7** below). People with severely decreased kidney function accounted for a very small minority among people with decreased kidney function. However, the association between SMI and severely decreased kidney function was similarly observed. These additional findings support the robustness of the main finding in the association between SMI and kidney function.

Table 7. Prevalence of CKD, decreased kidney function, and severely decreased kidney function by SMI status and lithium use

Outcome	Gender	Men					Women					Overall
	Age category	25–34	35–44	45–54	55–64	65–74	25–34	35–44	45–54	55–64	65–74	
Prevalence of CKD[a], % (main analysis)	No SMI	0.1	0.2	0.5	1.9	8.8	0.1	0.2	0.6	2.3	9.6	2.1
	SMI and no lithium use	0.1	0.2	1.1	3.1	11.4	0.1	0.6	1.6	5.3	14.4	3.3
	SMI and lithium use	0	2.0	4.9	15.1	31.7	0	1.0	6.8	20.8	34.7	14.6
Prevalence of decreased kidney function[b], %	No SMI	0.1	0.2	0.7	2.6	10.1	0.1	0.3	0.9	3.1	11.0	2.5
	SMI and no lithium use	0.2	0.4	1.3	3.1	11.3	0.2	0.6	2.2	6.0	14.8	3.6
	SMI and lithium use	0	1.4	4.9	15.3	29.8	0	1.3	7.2	17.0	33.5	13.8
Prevalence of severely decreased kidney function[c], %	No SMI	0.1	0.1	0.2	0.3	0.7	0.1	0.1	0.2	0.3	0.5	0.2
	SMI and no lithium use	0.1	0.2	0.3	0.4	1.3	0	0.3	0.2	0.7	0.9	0.4
	SMI and lithium use	0	0.3	0.4	1.6	4.3	0	0	0.6	1.6	3.5	1.5

Abbreviations: CKD = chronic kidney disease; SMI = severe mental illness.

[a] CKD is defined as two measurements of eGFR for ≥3 months during the five years between 1 April 2009 and 31 March 2014.

[b] Decreased kidney function is defined as the most recent eGFR <60 mL/min/1.73m^2 in the past five years prior to 31 March 2014.

[c] Severely decreased kidney function is defined as the most recent eGFR <30 mL/min/1.73m^2 in the past five years prior to 31 March 2014.

6.3.2. Serum creatinine testing rate by SMI status and known CKD risk factors to explore potential ascertainment/surveillance bias

(i) Backgrounds and methods

Generally, ascertainment or surveillance bias could happen when there is more intense surveillance for the outcome among exposed than among unexposed, or vice versa [124]. In the context of this study, if patients with SMI were more likely to have serum creatinine testing than those without SMI (or if patients without SMI in the general population were less likely to have serum creatinine testing than those with SMI), this may explain part of the higher prevalence of CKD in patients with SMI. To estimate the size of ascertainment/surveillance bias accurately, all people without serum creatinine testing in the CPRD need to be tested, but this is unrealistic. Meanwhile, Paper 1 (Prevalence of CKD and RRT in CPRD) suggested that most cases with decreased kidney function or CKD are probably captured in the current CPRD [119], as GPs are selectively testing patients at risk of CKD, and those without serum creatinine testing are unlikely to have CKD. This implies that under-ascertainment of CKD is limited in the current CPRD, and therefore ascertainment/surveillance bias is expected to be small.

To better explain this in the context of the study, here I show the serum creatinine testing rate (i.e. the proportion of people with at least one serum creatinine measurement in the past five years prior to 31 March 2014), according to the presence or absence of known CKD risk factors (diabetes, hypertension, cardiovascular disease, renal tract disease, systemic lupus erythematosus, and polycystic kidney disease), by SMI status and lithium use. Then, I calculate the prevalence of CKD among people with and without serum creatinine testing in each subgroup, to discuss whether the influence of ascertainment/surveillance bias is small or large in the current study.

(ii) Results and discussions

The serum creatinine testing rate was substantially different among people with no known CKD risk factors: 45.7% in the no SMI group, 73.8% in the SMI and no lithium group, and 95.2% in the SMI and lithium group (see **Table 8** below). This suggests that people with SMI indeed had more testing opportunities than people without SMI. However, there was less difference in

the testing rate among people with ≥1 known CKD risk factors, at 87.7%, 92.8%, and 99.0% respectively.

Then, looking at the prevalence of CKD among people tested, most cases with CKD came from the subgroups with ≥1 known CKD risk factors. Among people with no known CKD risk factors, even if they were tested, the prevalence of CKD was very low in people without SMI (0.66%) and people with SMI and no lithium use (1.19%). The lithium users showed high prevalence of CKD, even without other known CKD risk factors (7.82%). These results suggest that GPs are selectively testing people at risk of CKD (i.e. people with ≥1 known CKD risk factors or lithium users), and that CKD is unlikely to be identified among people with no known CKD risk factors. Therefore, the large difference in the serum creatinine testing rate (between people with and without SMI) among those with no known CKD risk factor is unlikely to be causing substantial ascertainment/surveillance bias.

Table 8. Serum creatinine testing rate (in the past five years prior to 31 March 2014) and prevalence of CKD among people with serum creatinine testing by SMI status (with and without a history of lithium use) and known CKD risk factors

	People without SMI (N = 2,387,988)		Patients with SMI and no lithium use (N = 24,101)		Patients with SMI and lithium use (N = 4,295)	
	No known CKD risk factors[a] (N = 1,615,097)	≥1 known CKD risk factors[a] (N = 772,891)	No known CKD risk factors[a] (N = 13,649)	≥1 known CKD risk factors[a] (N = 10,452)	No known CKD risk factors[a] (N = 1,881)	≥1 known CKD risk factors[a] (N = 2,414)
Serum creatinine testing rate, %	45.7	87.7	73.8	92.8	95.2	99.0
Prevalence of CKD among people with creatinine testing, % (numerator/denominator)	0.66 (4,891/738,614)	6.61 (44,761/677,679)	1.19 (120/10,072)	7.06 (685/9,700)	7.82 (140/1,790)	20.46 (489/2,390)

Abbreviations: CKD = chronic kidney disease; SMI = severe mental illness.

[a] Known CKD risk factors include diabetes mellitus, hypertension, cardiovascular diseases (myocardial infarction, chronic heart failure, peripheral arterial disease, and stroke), renal tract diseases (vesicoureteral reflux, renal tract stone, prostatic hypertrophy), systemic lupus erythematosus, and polycystic kidney disease.

6.4. Chapter summary

SMI and CKD

- The association between SMI, including schizophrenia and bipolar disorder, and CKD was examined in a cross-sectional study on 31 March 2014 among people aged 25–75 years in the CPRD.

- The prevalence of CKD (i.e. two or more consecutive measurements of eGFR <60 mL/min/1.73m^2 for ≥3 months in the past five years) was 14.6% among patients with SMI and history of lithium prescription, 3.3% among patients with SMI and no history of lithium prescription, and 2.1% among people without SMI.

- The prevalence of RRT, as well as that of severely decreased kidney function (i.e. eGFR <30 mL/min/1.73m^2), was also highest among patients with SMI and history of lithium prescription, followed by patients with SMI and no history of lithium prescription, and people without SMI.

- Adjustment for known CKD risk factors, including obesity, smoking, and diabetes, attenuated the odds ratios between SMI and CKD in the logistic regression analysis, suggesting that these factors are confounding or mediating the association between SMI and CKD.

- Among patients with biochemically-defined CKD, although blood pressure control and proteinuria testing rate were not very different between those with and without SMI, the proportion of patients receiving potentially beneficial drugs for CKD (ACEI/ARBs for patients with proteinuria, and statins) was lower in those with SMI than those without.

Chapter 7: Establishing a matched cohort of patients with and without CKD (stages 3 to 5)

This chapter presents the rationale and method for establishing a matched cohort of patients with and without CKD (stages 3 to 5) in the CPRD linked to HES, which will be used in the following studies in Papers 3 (CKD and antidepressant prescription) and 4 (GI bleeding risk of SSRIs by kidney function). I also demonstrate cohort details and discuss the limitations of the cohort.

7.1. Rationale for establishing a matched cohort of patients with and without CKD

The study hypothesis in Paper 3 (CKD and antidepressant prescription) is that patients with CKD are more likely to receive antidepressants for mental health problems (e.g. depression, anxiety, pain) than those without CKD. A cohort study comparing the incidence of antidepressant prescription between patients with and without CKD would better suggest the temporal relationship, compared with a cross-sectional study. A cross-sectional analysis only cannot deny the possibility that mental health conditions such as depression and anxiety resulted in CKD.

To better understand the characteristics of patients with CKD, a comparison group of patients without CKD is required. Therefore, after identifying patients with CKD, I decided to make a comparison group of patients without known CKD, matched for age, sex, general practice, and calendar time. Matching on age and sex is important to fairly and efficiently compare patients with and without CKD, because the CKD prevalence is largely influenced by age and sex [119]. Matching on general practice and calendar time is also effective to remove the confounding effect of these factors between patients with and without CKD. This is because identification, recording, and management of CKD and comorbidities appear to depend on general practice [103] and calendar time [117] in UK primary care. Therefore, patients with and without CKD in different general practices, or with different cohort entry timing, may not have good comparability. Moreover, adjusting for these factors in a statistical analysis may be difficult, due to too many fixed parameters (i.e. nearly 400 general practices in the HES-linked CPRD).

7.2. A preliminary analysis to decide whether I should include patients based on one or two measurements of decreased kidney function

(i) Backgrounds

In the cross-sectional dataset established in **chapter 4**, patients satisfying the definition of decreased kidney function (i.e. the most recent eGFR<60 ml/min/1.73 m^2 prior to 31 March 2014) and those satisfying the definition of CKD (i.e. two or more consecutive measurements of eGFR <60 ml/min/1.73 m^2 for ≥3 months in the past five year) were slightly different populations. Patients with a single measurement of eGFR <60 ml/min/1.73 m^2 probably include patients with temporarily decreased kidney function (i.e. AKI) or increased serum creatinine level due to exercise or protein intake. Meanwhile, the chronicity criterion requiring ≥2 measurements of kidney function may inadvertently exclude patients with "true CKD" who received only one serum creatinine measurement during a study period.

In a cohort study, I also need to decide whether I should include patients into the cohort suggesting kidney disease (i.e. "decreased kidney function cohort" or "CKD cohort"), based on one or two measurements of eGFR <60 ml/min/1.73 m^2. To examine the benefits and limitations of each strategy, I conducted a preliminary analysis looking at the association between the first record of eGFR <60 ml/min/1.73 m^2 and the next measurement of kidney function in a cohort using the CPRD.

(ii) Methods

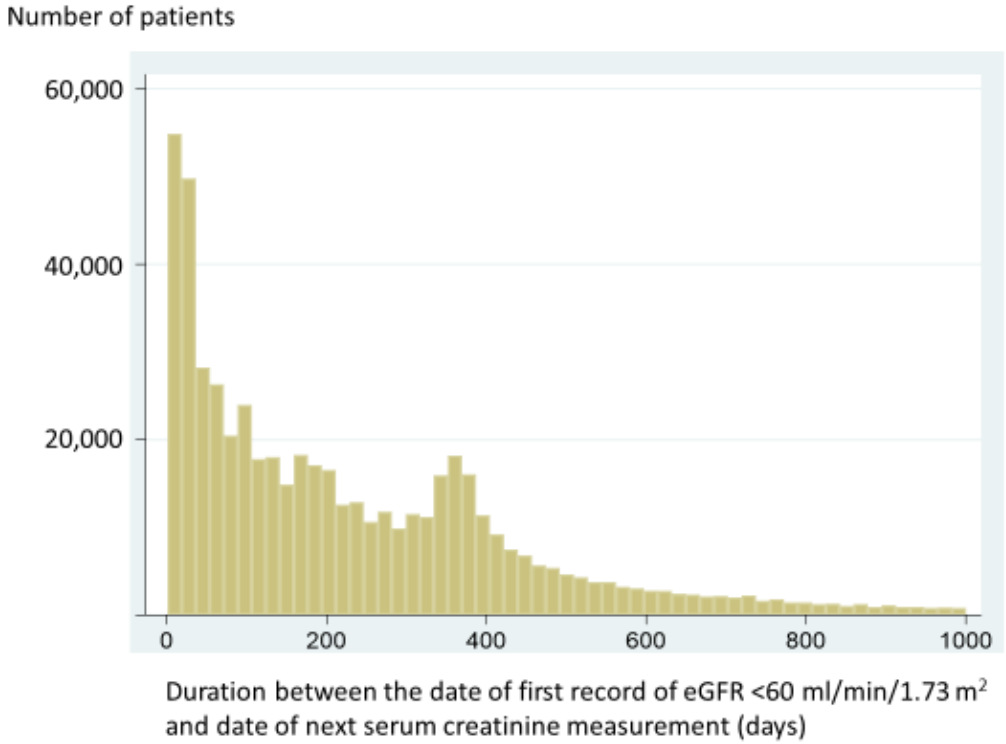
Using the July 2014 version of CPRD, I identified adult patients (not on RRT) with the first record of eGFR <60 ml/min/1.73 m^2 during the period between April 2004 and March 2014 (with or without existing records of eGFR <60 ml/min/1.73 m^2 before April 2004). Among these patients, I looked at the timing of the next serum creatinine measurement in primary care, and whether the next eGFR was consistently less than 60 ml/min/1.73 m^2.

(iii) Results

Among nearly seven million adults registered in the CPRD during the period between April 2004 and March 2014, I identified 635,523 adult patients (mean age 73.9±11.2 years old, 39.4% male) with the first record of eGFR <60 ml/min/1.73 m^2. Of these patients, 74,481

(11.7%) patients did not receive a subsequent measurement of serum creatinine until March 2014 in the CPRD, whereas 561,042 (88.3%) received the next serum creatinine measurement at median 184 days (IQR 58–370 days) later (see **Figure 4** below). Among these 561,042 patients with the first record eGFR <60 ml/min/1.73 m^2, 361,595 (64.5%) patients consistently showed eGFR less than 60 ml/min/1.73 m^2, whereas 199,447 (35.6%) patients showed eGFR over 60 ml/min/1.73 m^2 in their next creatinine measurement.

Figure 4. Distribution of the duration between the date of first record of eGFR <60 ml/min/1.73 m^2 and date of next serum creatinine measurement



Abbreviation: eGFR = estimated glomerular filtration rate.

(iv) Discussions

According to this preliminary analysis, it seems inappropriate to include patients into "decreased kidney function cohort" based on a single eGFR <60 ml/min/1.73 m^2, because around one third of patients with the first record of eGFR <60 ml/min/1.73 m^2 no longer showed decreased kidney function in the next measurement. In these patients, the first observed

eGFR <60 ml/min/1.73 m^2 was probably due to AKI or temporarily increased serum creatinine level due to exercise or protein diet. This (i.e. the fact that many patients included into the "decreased kidney function cohort" subsequently show no decreased kidney function) would matter when creating a matched cohort of patients with and without decreased kidney function. As shown later in **section 7.3**, a matched cohort needs a prerequisite that patients selected as a case (i.e. those with decreased kidney function) continue to be a case, whereas patients selected as a control (i.e. those without decreased kidney function) may become a case later (but this is only one time).

The vast majority of patients with the first record of eGFR <60 ml/min/1.73 m^2 received the second measurement of kidney function during their observation in the CPRD. Around 10% of patients with the first record of eGFR <60 ml/min/1.73 m^2 did not receive the next serum creatinine measurement. They are probably a mixture of unhealthy patients (who were hospitalised, sent to a nephrologist, or died) and healthy patients (who no longer came to GPs or received blood testing). Around half of patients with the first record of eGFR <60 ml/min/1.73 m^2 were re-measured within six months, and around three quarters were re-measured in one year. Therefore, even by using the chronicity criterion of CKD, the risk that patients with "true CKD" are not included into the CKD cohort for a long time (until the second serum creatinine measurement is done in primary care) is seemingly small.

In conclusion, I decided to include patients into the "CKD cohort" based on the internationally-accepted criteria of CKD (i.e. two or more consecutive measurements of eGFR <60 ml/min/1.73 m^2 for ≥3 months). This strategy appears to be better than the other strategy to include patients into the "decreased kidney function cohort" based on single measurement of eGFR <60 ml/min/1.73 m^2, in which around one third of patients returned to eGFR >60 ml/min/1.73 m^2 in the next measurement.

However, as suggested in the cross-sectional dataset in **chapter 4** and previous studies using routinely collected data [120-122], even if satisfying the chronicity criterion of CKD, some patients still may not show consistently decreased kidney function thereafter. One possible solution may be to extend the chronicity criterion of three months to longer (e.g. six, nine, and one year), as suggested in a Norwegian study [122]. However, the Norwegian study also reported that, by using the longer chronicity criterion, unhealthier patients with higher mortality tended to be excluded, causing selection bias. Therefore, I here decide not to modify the

chronicity criterion of three months, and simply follow the internationally-accepted criteria of CKD.

7.3. Method for establishing a matched cohort of patients with and without CKD

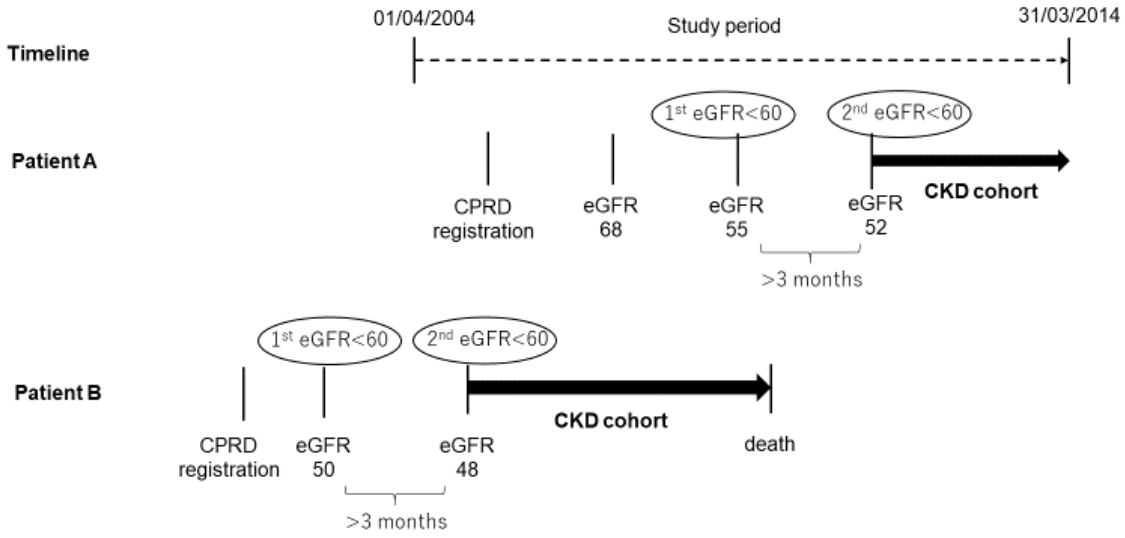
7.3.1. Study population

All individuals aged 18 and older in the HES-linked CPRD from 1 April 2004 to 31 March 2014 were potentially eligible for inclusion. The choice of start date was related to the launch of QOF on 1 April 2004, which improved the identification, recording, and management of CKD and comorbidities in UK primary care [73, 117]. Patients were eligible for inclusion at the latest of: one year after practice registration (for GPs to record previous medical history [118]); the 'up-to-standard' date that the general practice achieved the CPRD quality standards [73]; or 1 April 2004. Patients with a recorded diagnosis of RRT (haemodialysis, peritoneal dialysis, and kidney transplantation) at the time of study eligibility were excluded, as most patients with RRT are not primarily managed by GPs. Patients were no longer eligible for follow-up at the earliest of: death, initiation of RRT (defined as the first date of recorded diagnosis suggesting RRT), change of practice, final data collection from the practice, or 31 March 2014.

7.3.2. Identification of patients with CKD

Among the eligible patients, I first identified patients with CKD, which was defined as two or more consecutive measurements of eGFR <60 ml/min/1.73m^2 for ≥3 months. As explained in **chapter 3**, eGFR was calculated from serum creatinine records in the CPRD, after multiplication of 0.95 to allow for a lack of creatinine calibration [106], using the CKD-EPI creatinine equation [101]. Patients, including those who had CKD prior to April 2004, were included in the cohort on the date when they satisfied the CKD definition (i.e. second eGFR <60 ml/min/1.73m^2) following their eligibility (see **Figure 5** below). Once a patient was identified as having CKD, they were considered to have CKD for the rest of the follow-up.

Figure 5. Graphical representation of the identification of patients with CKD



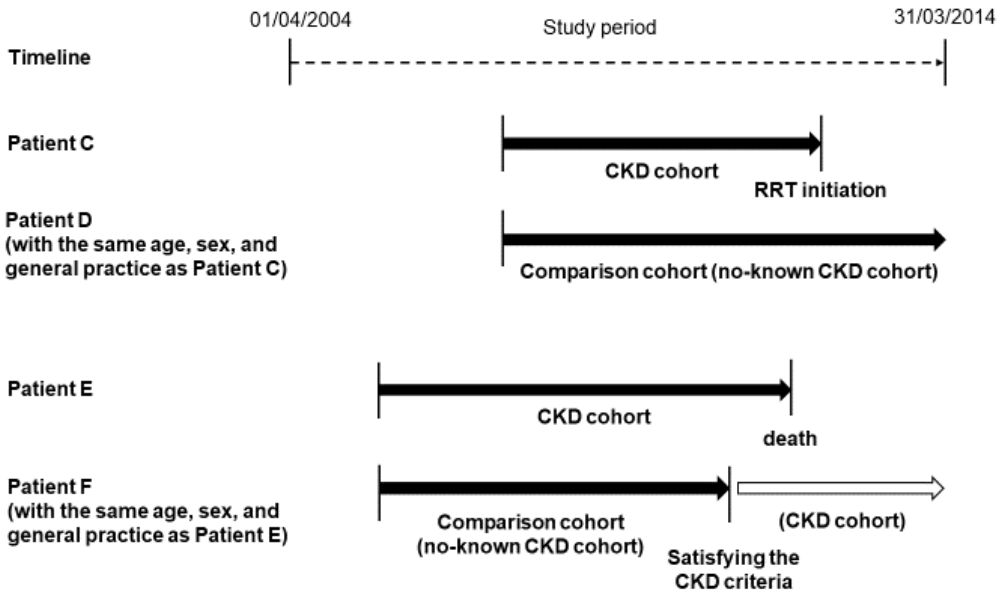
Abbreviations: CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; eGFR = estimated glomerular filtration rate.

Note: Unit of eGFR (mL/min/1.73m^2) was omitted because of limited space. Patient A was registered to the CPRD after 1 April 2004 and included into the CKD cohort at the time of second eGFR <60 ml/min/1.73m^2. Patient B was registered to the CPRD before 1st April 2004 and included into the CKD cohort when the second eGFR <60 ml/min/1.73m^2 was observed after 1 April 2004.

7.3.3. Identification of a comparison group of patients without known CKD

Next, as a comparison group, I selected patients without known CKD (with or without serum creatinine measurement) randomly from the rest of the HES-linked CPRD population at a 1:1 ratio, matched for age, sex, general practice, and calendar time (i.e. same date of cohort entry) (see **Figure 6** below). The matching was done, using the STATA commands of Dr Krishnan Bhaskaran of the Electronic Health Records Research group at the London School of Hygiene and Tropical Medicine, which had been created for a previous matched cohort study [125]. Individuals selected to a comparison group (i.e. patients without known CKD) could be found to have CKD later; in this situation they were censored at the time of satisfying CKD definition, because they were already included in the CKD group from that point forward (with their own matched control).

Figure 6. Graphical representation of matching patients with and without CKD for age, sex, general practice, and calendar time



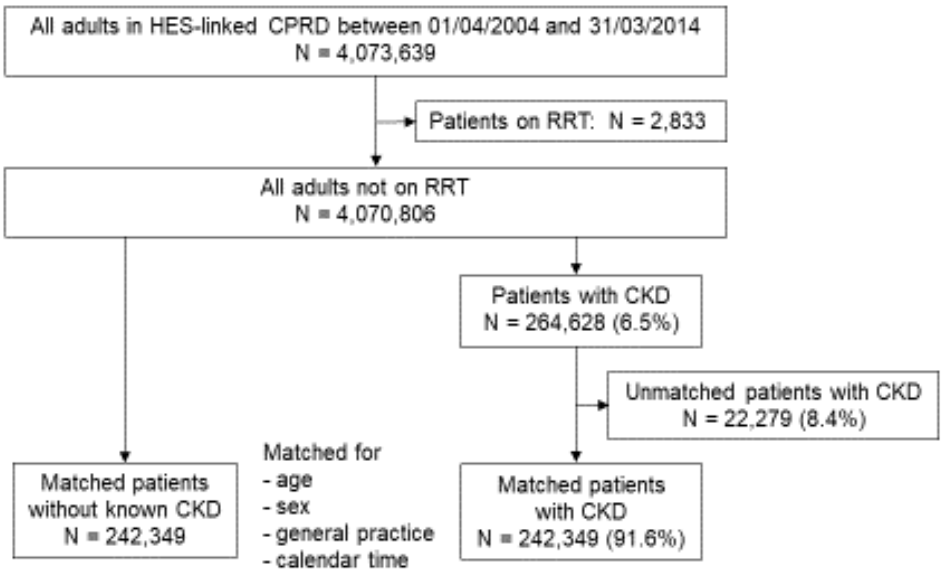
Abbreviations: CKD = chronic kidney disease; RRT = renal replacement therapy.

Note: Patients C and D were matched, whereas Patients E and F were matched. Because Patient F subsequently satisfied the CKD criteria, he/she was censored from the comparison cohort at that time and included in the CKD cohort from that point forward (with their own matched control).

7.4. Results (details of the cohort)

Figure 7 shows the flow chart for the selection of matched patients with and without CKD. There were 4,073,639 eligible people in the HES-linked CPRD between 1 April 2004 and 31 March 2013. Among them, 2,833 patients already receiving RRT were excluded. Among the remaining 4,070,806 eligible people not receiving RRT (median age 39 [IQR 27–56] at the time of satisfying the eligibility; male, 48.8%), there were 264,628 (6.5%) patients with CKD (median age 77 [IQR 71–83] at the time of cohort entry; male, 38.7%). Of those with CKD, 242,349 (91.6%) (median age 76 [IQR 70–82]; male, 39.3%) were matched with patients without CKD. Unmatched 22,279 (8.4%) patients with CKD were older and more likely to be female (mean age 88 [IQR 84–92]; male, 31.5%).

Figure 7. **Flow chart for the selection of matched patients with and without CKD**



Abbreviations: CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; HES = hospital episode statistics; RRT = renal replacement therapy.

The age-sex distribution was largely different between eligible people not receiving RRT in the HES-linked CPRD (see **Figure 8** below) and patients with CKD (see **Figure 9** below). After matching, the age-sex distribution of patients with and without CKD became comparable (see **Figure 10** below).

Figure 8. Age-sex distribution of eligible patients without RRT in the HES-linked CPRD

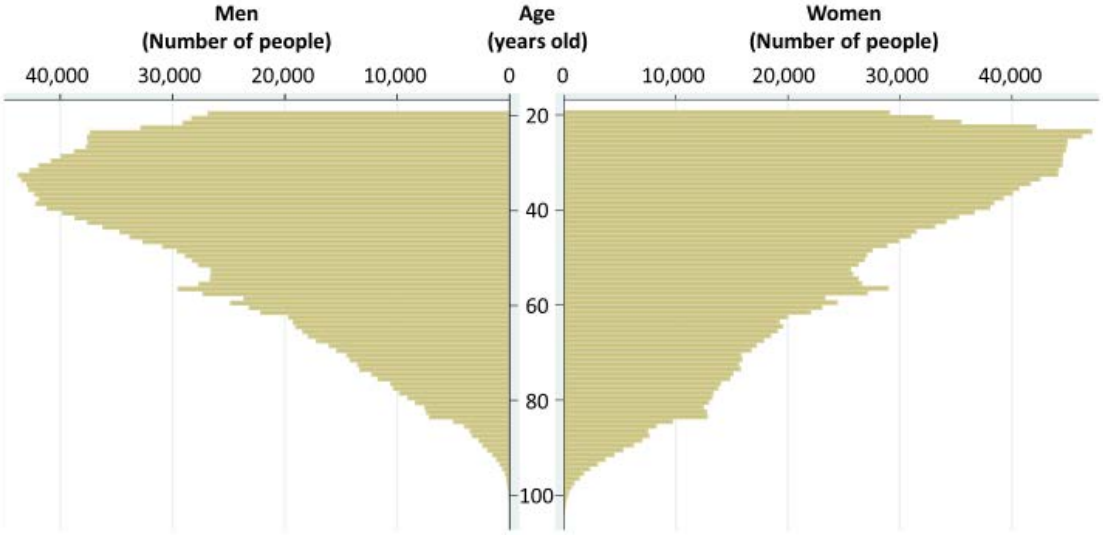


Figure 9. Age-sex distribution of unmatched patients with CKD

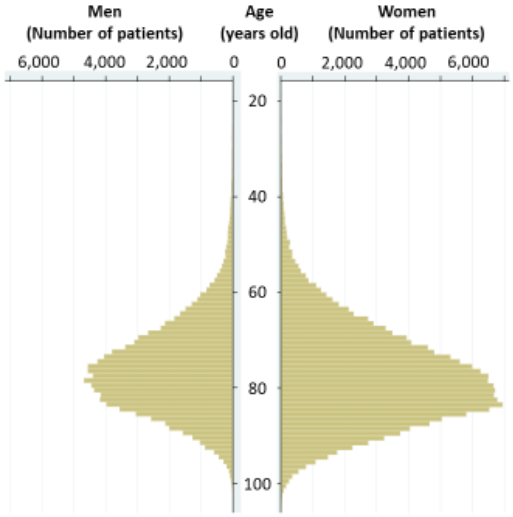


Figure 10. Age-sex distribution of matched patients with and without CKD

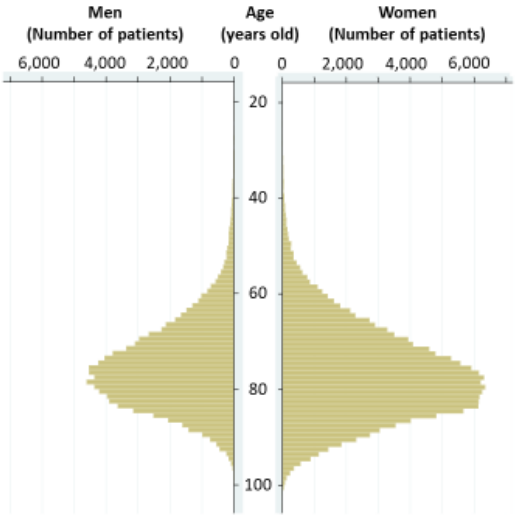


Table 9 shows the baseline characteristics of matched patients with and without CKD. The majority of matched patients with and without CKD were included into the cohort in the early years of the 10-year study period, probably because patients with prevalent CKD (i.e. those who had CKD prior to April 2004) were confirmed soon after the start of the study period.

Table 9. Baseline characteristics of matched patients with and without CKD

	Patients without known CKD (N = 242,349)	Patients with CKD (N = 242,349)	P value (by χ^2 test)
Age (years):			-
<55	6,845 (2.8)	6,845 (2.8)	
55-64	23,556 (9.7)	23,556 (9.7)	
65-74	71,112 (29.3)	71,112 (29.3)	
75-84	102,594 (42.3)	102,594 (42.3)	
≥85	38,242 (15.8)	38,242 (15.8)	
Sex:			-
Men	95,318 (39.3)	95,318 (39.3)	
Women	147,031 (60.7)	147,031 (60.7)	
Financial year of cohort entry:			-
2004	80,947 (33.4)	80,947 (33.4)	
2005	35,413 (14.6)	35,413 (14.6)	
2006	27,577 (11.4)	27,577 (11.4)	
2007	23,136 (9.6)	23,136 (9.6)	
2008	18,560 (7.7)	18,560 (7.7)	
2009	15,142 (6.3)	15,142 (6.3)	
2010	11,706 (4.8)	11,706 (4.8)	
2011	10,552 (4.4)	10,552 (4.4)	
2012	10,063 (4.2)	10,063 (4.2)	
2013	9,253 (3.8)	9,253 (3.8)	
Ethnicity:			<0.001
White	97,749 (40.3)	102,019 (42.1)	
South Asian	1,796 (0.7)	2,317 (1.0)	
Black	1,156 (0.5)	1,060 (0.4)	
Other ethnicity	864 (0.4)	834 (0.3)	
Not recorded	140,784 (58.1)	136,119 (56.2)	

Abbreviation: CKD = chronic kidney disease.

The total follow-up lengths were 960,686 person-years (median 3.4 years [IQR 1.4–6.2 years]) and 108,654 person-years (median 4.2 years [IQR 1.8–6.9 years]) in matched patients with and without CKD, respectively. **Table 10** shows the reasons for stopping the follow-up of matched patients with and without CKD. The mortality was nearly double in patients with CKD than

those without known CKD during follow-up (30.2% vs. 16.9%). There were 1,672 patients starting RRT among those with CKD, and a further 23 patients commenced RRT without fulfilling a prior definition of CKD. The proportion of patients finishing follow-up for other reasons (i.e. change of practice, last data collection from the practice, and end of the study period) was similar between matched patients with and without CKD. Finally, 17% of patients without known CKD were identified as having CKD during follow-up.

Table 10. **Reasons for stopping the follow-up of matched patients with and without CKD**

	Patients without known CKD (N = 242,349) n (%)	Patients with CKD (N = 242,349) n (%)
Death	40,952 (16.9)	73,121 (30.2)
Initiation of RRT	23 (<0.1)	1,672 (0.7)
Change of practice	43,035 (17.8)	35,100 (14.5)
Last data collection from the practice	35,694 (14.7)	41,356 (17.1)
End of the study period (31 March 2014)	81,494 (33.6)	91,100 (37.6)
Identification of CKD	41,151 (17.0)	0 (0)
Total	242,349 (100)	242,349 (100)

Abbreviations: CKD = chronic kidney disease; RRT = renal replacement therapy.

7.5. Discussion

In this chapter, I established a matched cohort of patients with and without CKD for the subsequent studies on antidepressant prescription and associated adverse outcomes. An ideal cohort study comparing patients with and without CKD may be achieved by measuring the serum creatinine of all eligible patients at a particular time point (e.g., 1 July 2007) or during a short recruitment period (e.g. from 1 January to 31 December, 2007), classifying them into patients with and without CKD, and following up on them in the same manner. However, in routinely collected data, the timing of serum creatinine measurement varies widely, and therefore, patients with CKD can be identified at any time point during a long study period. Therefore, recruiting patients over a short period does not seem to be a good idea. In this matched cohort, patients with CKD could enter the cohort at any time during the 10-year study period between 1 April 2004 and 31 March 2014.

A strength of this cohort is that it includes an appropriate comparison group, i.e. patients without known CKD, sampled from the general population, of the same age, sex, general practice, and the same cohort entry timing as patients with CKD. As shown in **Figures 8** and **9**, the age-sex distribution was largely different between the general population (median age 39, male 48.8%) and patients with CKD (median age 77, male 38.7%). Therefore, matching according to age and sex is important for making the two groups (i.e. patients with and without CKD) more comparable.

I kept patients who had never had a kidney function tested in the denominator when creating the comparison group. This strategy is supported by the validation study in Paper 1 (Prevalence of CKD and RRT in CPRD) [119], which suggests that most patients with CKD are captured in the CPRD at some point prior to 31 March 2014, and people without creatinine tests are unlikely to have CKD. If I excluded healthy people without serum creatinine testing from the denominator, the comparison group would not represent the general population with the same age and sex as patients with CKD.

However, a limitation of this cohort is that the comparison group may include some patients with unmeasured CKD. Moreover, there may be a time lag between the actual incidence of CKD and its identification in the CPRD. This misclassification of CKD status will dilute the true association between CKD and observed outcomes in following studies.

Another limitation may arise from the fact that patients with CKD were quite an old population (median age 77 [IQR 71–83]; male, 38.7%). As kidney function declines with age, matching according to age may have resulted in limited differences in renal function between patients with and without CKD among older people. Misclassification of CKD status is also possible among older patients with the boundary level of eGFR (i.e. 60 mL/min/1.73m^2) even if the chronicity criterion of CKD was used.

Despite these limitations, I consider the established cohort to be useful for comparing the outcomes in subsequent studies (i.e. antidepressant prescription and associated serious adverse outcomes) between patients with and without CKD, and for examining the contribution of CKD to study outcomes.

7.6. Use of the established cohort for research on CKD

I conducted a study outside the scope of my PhD thesis by using the established cohort, and published a paper entitled 'Chronic kidney disease and cause-specific hospitalisation: a matched cohort study using Clinical Practice Research Datalink' in *British Journal of General Practice* [113]. Briefly, I compared the matched patients with and without CKD in terms of the incidence of hospitalisations for ten common conditions as the primary admission diagnosis: myocardial infarction; heart failure; cerebral infarction; pneumonia; urinary tract infection; gastrointestinal bleeding; intracranial bleeding; venous thromboembolism; hip fracture; and AKI. The main finding was that, among the range of cause-specific hospitalisations, those for heart failure, infection, and AKI showed strong associations with CKD in absolute and/or relative terms. My conclusion is that, aside from prevention of ESRD, there are high-priority outcomes that warrant detection of CKD in primary care and improvement of preventive care for patients with CKD in the community. More details are given in the accepted paper included in **Appendix A**.

7.7. Chapter summary

Establishment of a matched cohort with and without CKD

- A matched cohort of patients with and without CKD was established in the HES-linked CPRD for the following studies in Papers 3 (CKD and antidepressant prescription) and 4 (GI bleeding risk of SSRIs by kidney function).
- Patients with CKD (stages 3 to 5) were identified based on two or more consecutive measurements of eGFR <60 ml/min/1.73m^2 for ≥3 months.
- To establish a balanced comparison group in terms of important patient characteristics, I randomly selected a patient without known CKD of the same age, sex, general practice, and calendar time (i.e. same date of cohort entry) as a patient with CKD.
- Among approximately four million adults not requiring RRT in the HES-linked CPRD between 31 March 2004 and 1 April 2014, I identified 264,628 patients with CKD, of which 242,349 were matched with 242,349 patients without known CKD.
- A potential limitation of this cohort is a possible misclassification of CKD status, which may dilute the true association between CKD and observed outcomes in further studies.

Chapter 8: Prevalence, incidence, indication, and choice of antidepressants in patients with and without chronic kidney disease: a matched cohort study in the UK Clinical Practice Research Datalink (Paper 3)

8.1. Introduction

This chapter presents a matched cohort study comparing the prevalence, incidence, indication, and choice of antidepressants between patients with and without CKD, published in *Pharmacoepidemiology and Drug Safety* [126].

The main research question is: Are patients with CKD more likely to be prescribed antidepressants than those without CKD in the general population?

Briefly, using the matched cohort of 242,349 pairs with and without CKD established in **chapter 7**, I compared the frequency (prevalence and incidence) and patterns (indication and choice) of antidepressant prescription between patients with and without CKD. The prevalence of antidepressant prescription was defined as the proportion of patients receiving antidepressants in the past six months prior to cohort entry (i.e. the date of satisfying CKD definition for CKD patients, and the same date for matched controls without CKD), whereas the incidence of antidepressant was defined as the initiation of antidepressants among non-prevalent users.

Later in this chapter, I am showing additional data on the characteristics of 22,279 unmatched patients with CKD when establishing the matched cohort, as well as temporal trend in the prevalence of antidepressant prescribing by CKD status.

8.2. Published paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Masao Iwagami
Principal Supervisor	Dorothea Nitsch
Thesis Title	Association between chronic kidney disease and mental health disorders and psychoactive drugs in the UK general po

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Pharmacoepidemiol Drug Saf.26(7):792-801		
When was the work published?	July 2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I planned the study, carried out the data extraction, cleaning, analysis, and drafted the manuscript.

Student Signature: [redacted] **Date:** 30/May/2018

Supervisor Signature: [redacted] **Date:** 30.5.18

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; **26**: 792–801
Published online 11 April 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4212

ORIGINAL REPORT

Prevalence, incidence, indication, and choice of antidepressants in patients with and without chronic kidney disease: a matched cohort study in UK Clinical Practice Research Datalink

Masao Iwagami*, Laurie A. Tomlinson, Kathryn E. Mansfield, Helen I. McDonald, Liam Smeeth and Dorothea Nitsch

Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

ABSTRACT

Purpose People with chronic kidney disease (CKD) have an increased prevalence of depression, anxiety, and neuropathic pain. We examined prevalence, incidence, indication for, and choice of antidepressants among patients with and without CKD.

Methods Using the UK Clinical Practice Research Datalink, we identified patients with CKD (two measurements of estimated glomerular filtration rate < 60 mL/min/1.73m^2 for ≥3 months) between April 2004 and March 2014. We compared those with CKD to a general population cohort without CKD (matched on age, sex, general practice, and calendar time [index date]). We identified any antidepressant prescribing in the six months prior to index date (prevalence), the first prescription after index date among non-prevalent users (incidence), and recorded diagnoses (indication). We compared antidepressant choice between patients with and without CKD among patients with a diagnosis of depression.

Results There were 242 349 matched patients (median age 76 [interquartile range 70–82], male 39.3%) with and without CKD. Prevalence of antidepressant prescribing was 16.3 and 11.9%, and incidence was 57.2 and 42.4/1000 person-years, in patients with and without CKD, respectively. After adjusting for confounders, CKD remained associated with higher prevalence and incidence of antidepressant prescription. Regardless of CKD status, selective serotonin reuptake inhibitors were predominantly prescribed for depression or anxiety, while tricyclic antidepressants were prescribed for neuropathic pain or other reasons. Antidepressant choice was similar in depressed patients with and without CKD.

Conclusions The rate of antidepressant prescribing was nearly one and a half times higher among people with CKD than in the general population. © 2017 The Authors. Pharmacoepidemiology & Drug Safety Published by John Wiley & Sons Ltd

KEY WORDS—antidepressants; chronic kidney disease; prevalence; incidence; depression

Received 28 September 2016; Revised 3 March 2017; Accepted 19 March 2017

INTRODUCTION

Antidepressants are among the most commonly prescribed classes of medication in industrialized countries, including the USA[1] and UK.[2] The recent increase in the prescription of antidepressants is dramatic, with an average 10% increase per year from 1998 to 2010.[3] Antidepressants can be prescribed not only for depressive symptoms but also for other conditions such as anxiety and neuropathic pain.[4] In addition, off-label use of antidepressants is common for chronic pain, including non-neuropathic pain, and conditions where non-specific sedation is required.[5–7]

Chronic kidney disease (CKD), an impairment of kidney structure or function, is now recognized as a major public health problem.[8] Chronic kidney disease is associated with a range of comorbidities including obesity, hypertension, diabetes, and cardiovascular disease.[9,10] Level of kidney function, expressed as estimated glomerular filtration rate (eGFR), is closely associated with increased risk of death, cardiovascular events, and hospitalization.[11]

Chronic kidney disease is also associated with a range of mental health problems including anxiety[12] and depression;[13] almost one quarter of adults with pre-dialysis CKD are depressed. These conditions

*Correspondence to: M. Iwagami, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. E-mail: masao.iwagami@lshtm.ac.uk

may be due to co-existing chronic diseases such as diabetes and heart failure, which are also associated with depression and anxiety symptoms,[14,15] or directly related to CKD. In addition, other indications for antidepressants such as chronic pain and insomnia are more common among patients with CKD.[16,17]

Patients with CKD are frequently excluded from clinical trials,[18,19] and concerns have been recently raised about the lack of knowledge regarding how kidney function is related to adverse effects of antidepressants.[20,21] Despite this, there has been no systematic research investigating frequency and patterns of antidepressant prescribing among patients with CKD. Understanding how antidepressants are actually prescribed in patients with CKD, compared to those without CKD, is important groundwork for the planning of future studies on the safety of antidepressants in this population. Therefore, we aimed to compare the frequency (prevalence and incidence), indications for, and choice of antidepressant prescription between patients with and without CKD, in the UK general population.

METHODS

Data sources

The Clinical Practice Research Datalink (CPRD) is a database of routinely recorded primary care electronic health record data from 7% of the UK population.[22] The database includes the following data: patient demographics; diagnoses; prescriptions; laboratory test results; and referrals made by general practitioners (GPs). Diseases can be identified using diagnostic codes (Read codes) recorded in routine data. We used CPRD linked to additional data sources: the inpatient Hospital Episodes Statistics (HES) database to provide data on ethnicity (to improve data completeness);[23] Office for National Statistics (ONS) data for mortality; and Index of Multiple Deprivation (IMD) data for deprivation indices. We obtained study approval from the institutional review board of the London School of Hygiene and Tropical Medicine (reference: 9196), as well as the Independent Scientific Advisory Committee, which oversees research involving CPRD data (Protocol 15_219R). Informed consent from individual patients was waived because the data are anonymous.

Study population and matched cohort

All adults (age 18 or older) alive and contributing to HES-linked CPRD anytime from 1 April 2004 to 31 March 2014 were potentially eligible for inclusion. Patients were eligible for inclusion at the latest of: one year after practice registration,[24] the date that the practice reached CPRD quality control standards, or 1 April 2004. Patients were no longer eligible for follow-up at the first of renal replacement therapy (RRT) initiation, death, change of practice, last data collection from the practice, or 31 March 2014. We excluded patients already receiving RRT (hemodialysis, peritoneal dialysis, and kidney transplantation) prior to cohort entry.

First, we identified patients with CKD based on two consecutive measurements of eGFR <60 mL/min/1.73 m^2 more than three months apart.[25] Estimated GFR was calculated from serum creatinine values recorded in CPRD, using the Chronic Kidney Disease Epidemiology Collaboration equation.[26] Patients, including those who had CKD before April 2004, were included in the cohort on the date when they first satisfied the CKD definition (i.e. second eGFR <60 mL/min/1.73 m^2) during eligible follow-up (index date).

Next, as a control group, we selected at random patients without CKD from the general population. Because (i) CKD status largely depends on age and sex, and (ii) pattern of antidepressant prescription is expected to depend on general practice and calendar time, we matched controls to patients with CKD by age (same year of birth), sex, general practice, and calendar time. Each control entered the cohort on the same index date as their CKD counterpart. Individuals selected as controls (i.e. non-CKD patients) may be found to have CKD later; in this situation, they were censored as a control at the time of satisfying CKD definition and contributed separately as an incident patient with CKD from that time point forward (with their own matched control).

Prevalence and incidence of antidepressant prescription

We estimated the prevalence of existing users of antidepressants, defined as receiving an antidepressant prescription within six months prior to the index date. Incidence of antidepressant prescription was based on the first antidepressant prescription after index date, after exclusion of existing users.[27]

Covariates

In order to examine the independent association between CKD status and antidepressant prescription, we considered baseline characteristics of patients: age and sex; ethnicity; socio-economic status (SES); smoking status; body mass index (BMI); and common chronic physical illnesses that are considered to be associated with mental health conditions (diabetes

mellitus, congestive heart failure, myocardial infarction, stroke, chronic obstructive pulmonary disease, rheumatoid arthritis, cancer, Parkinson's disease, and epilepsy).[28,29] Based on previous studies using UK primary care data,[30,31] we classified patients with no record of ethnicity as white. Socio-economic status was assigned by quintile at an individual level, using 2010 ONS estimates of the IMD (a composite area-level marker of deprivation).[32] For patients with missing individual-level SES, we used the SES for the patient's general practice. Smoking status and BMI were assigned using the data recorded closest to the index date. We defined each chronic physical illness as present if a relevant diagnosis code of that illness was recorded at least once before a patient's index date.

Indication

We identified morbidity codes for three common diagnoses suggesting indications for antidepressant prescription:[4] depression, anxiety, and neuropathic pain (included in Appendix 1). We included symptom codes as well as diagnostic codes because GPs in the UK commonly use symptom codes (e.g. "depressive symptoms", "anxiousness") rather than definitive diagnostic codes (e.g. "major depression", "general anxiety disorder").[33–35] We included codes recorded by GPs any time prior to the first antidepressant prescription until three months later, to account for possible time lag in recording diagnosis codes in electronic health records.[36,37] We categorized type of antidepressant, according to British National Formulary headings, into the following categories:[4] selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), or other antidepressants. Monoamine oxidase inhibitors were grouped into other antidepressants because of a small number of prescriptions. For each type of antidepressant, we identified the proportion of patients with each indication as well as those with none of the three indications.

Choice of antidepressants and initial prescription dose

There are 26 antidepressants currently available in the UK, only a few are indicated for anxiety and neuropathic pain, whilst all 26 are indicated for depressive conditions.[4] Therefore, we restricted this analysis to patients with a recorded diagnosis of depression. We compared the pattern of antidepressant choice (the proportion of patients prescribed each antidepressant as their first incident prescription) between depressed patients with and without CKD. We also compared the initial dose prescribed in those with and without CKD to examine whether antidepressants were started at a lower dose in patients with CKD than those without.

Statistical analyses

We compared the baseline characteristics of patients with and without CKD using χ^2 tests. We calculated crude prevalence and incidence rates for antidepressant prescribing. We then conducted a conditional logistic regression analysis (to account for matching) to investigate the association between CKD status and *prevalence* of antidepressant prescription. After excluding existing users of antidepressants (meaning matching was no longer maintained), we conducted an unconditional Poisson regression analysis to investigate the association between CKD status and *incidence* of new antidepressant prescription, adjusting for age, sex, and financial year, and taking account of clustering by general practice using robust standard errors. We adjusted for financial year (by including financial year as a categorical variable, i.e. from 1 April to 31 March for each year) because the frequency of antidepressant prescribing has been increasing year by year.[3] We further adjusted for ethnicity, SES, smoking status, and BMI, and, then, in a fully adjusted model, also included chronic physical illnesses. In models including smoking status and BMI, we included an additional absent category for those with no recorded smoking status or BMI. In a subsequent sensitivity analysis, we dropped all those with missing smoking or BMI status. All the data management and statistical analyses were conducted using STATA version 14 (Stata Corp, Texas).

Renal function subgroup analyses

To examine the association between severity of kidney function and antidepressant prescribing, we classified patients with CKD according to the level of kidney function on the index date into two categories: eGFR 30–59 (CKD stage 3), and <30 mL/min/1.73 m^2 (CKD stage 4 and 5).[25] In patients without CKD, we differentiated patients with and without serum creatinine results recorded in CPRD prior to index date, because these subgroups are expected to be systematically different due to testing incentives for those at risk of CKD in the UK Quality and Outcomes Framework.[38] To compare the prevalence of existing users of antidepressants between subgroups of renal function, we used an unconditional logistic regression analysis, adjusting for age, sex, and financial year, and taking account of clustering by general practice using robust

standard errors. We also repeated all other principal analyses (described under 'Statistical analyses' subheading) using renal function subgroups.

Additional analyses

Any difference in the duration of follow-up lengths between patients with and without CKD may affect the likelihood of starting antidepressants. Therefore, as a post hoc analysis, we compared the proportion of patients starting antidepressants within the first six months of follow-up in those with and without CKD.

We undertook a further analysis to investigate whether patients with CKD were more likely to start antidepressants for the first episode of depression in their life, or for a recurrent episode of depression. In CPRD, GPs routinely record a patient's past medical history shortly after registration with a new practice, and, therefore, a previous episode of depression would be recorded between CPRD registration and index date of the study (as index dates need to be at least one year after CPRD registration by our definition). Therefore, in patients starting antidepressants with a recorded diagnosis of depression, we compared the proportion of those with and without CKD who had: (i) their first depression diagnosis in CPRD recorded between CPRD registration and index date (more likely to suggest a recurrence); and (ii) their first depression diagnosis recorded in CPRD after index date (more likely to suggest the first ever depression diagnosis).

RESULTS

Among 4 070 806 eligible patients (median age 39 [IQR 27–56], male 48.8%), we identified 264 628 patients with CKD (median age 77 [IQR 71–83], male 38.7%) (Figure 1). Of those with CKD, 242 349 (91.6%) (median age 76 [IQR 70–82], male 39.3%) were matched with a control patient without CKD who had the same age, sex, and general practice on the index date of their CKD counterpart. Unmatched patients with CKD (n = 22 279) were older and more likely to be female (median age 88 [IQR 84–92], male 31.5%). Of the 242 349 matched control patients without CKD, 41 151 (17.0%) were subsequently found to have CKD.

Compared to patients without CKD, patients with CKD were more likely to be deprived, ex-smokers, and overweight (BMI ≥25 kg/m^2) (Table 1). Chronic physical illnesses, except for Parkinson's disease and epilepsy, were more common among patients with CKD.

Prevalence of existing use of antidepressants at index date was 16.3 and 11.9% in patients with and without CKD, respectively (Table 2). The incidence rate of new antidepressant prescription was 57.2 and 42.4/1000 person-years in patients with and without CKD, respectively (Table 3). After adjusting for confounding, CKD remained positively associated with increased prevalence and incidence of antidepressant prescribing (Tables 2 and 3). Our results were similar to those in the main analysis after excluding patients with missing smoking status and BMI (data not shown).

The pattern of recorded diagnoses was broadly similar between patients with and without CKD (Table 4). Regardless of CKD status, the majority of patients prescribed SSRIs had recorded diagnoses of depression

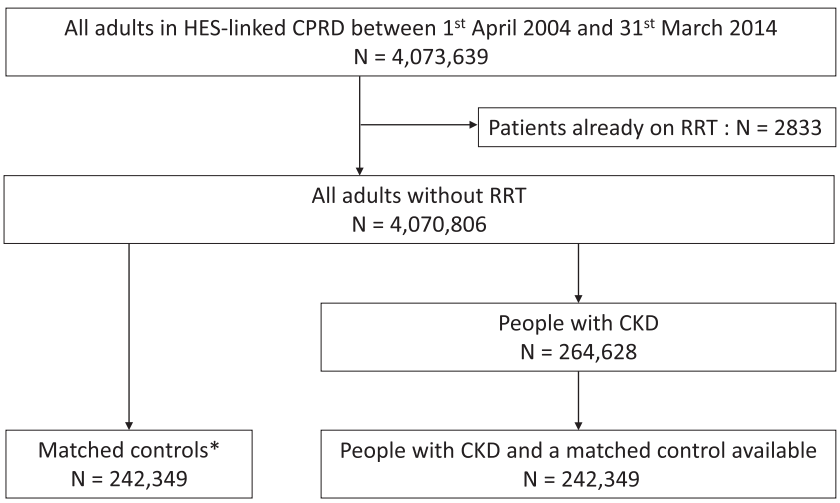


Figure 1. Flow chart for the selection of matched patients with and without chronic kidney disease. CKD = chronic kidney disease, CPRD = clinical practice research datalink, HES = hospital episode statistics, RRT = renal replacement therapy. *Matched cohort: randomly selected individuals without chronic kidney disease matched for age, sex, general practice, and calendar time

Table 1. Baseline characteristics of matched patients with and without chronic kidney disease

	Patients without CKD *N* = 242 349	Patients with CKD *N* = 242 349	
	n (%)	*n* (%)	*p* Value
Age (years):			1.000
<55	6845 (2.8)	6845 (2.8)	
55–64	23 556 (9.7)	23 556 (9.7)	
65–74	71 112 (29.3)	71 112 (29.3)	
75–84	102 594 (42.3)	102 594 (42.3)	
≥85	38 242 (15.8)	38 242 (15.8)	
Sex (male):	95 318 (39.3)	95 318 (39.3)	1.000
Ethnicity:			
White/not-recorded*	238 533 (98.4)	238 138 (98.3)	<0.001
South Asian	1796 (0.7)	2317 (1.0)	
Black	1156 (0.5)	1060 (0.4)	
Other ethnicity	864 (0.4)	834 (0.3)	
Socio-economic status**:			
1 (least deprived)	56 800 (23.4)	53 034 (21.9)	<0.001
2	61 647 (25.4)	60 501 (25.0)	
3	50 466 (20.8)	50 709 (20.9)	
4	42 221 (17.4)	44 692 (18.4)	
5 (most deprived)	31 215 (12.9)	33 413 (13.8)	
Smoking status:			<0.001
Non-smoker	92 363 (38.1)	80 721 (33.3)	
Ex-smoker	107 737 (44.5)	131 510 (54.3)	
Current-smoker	36 338 (15.0)	29 243 (12.1)	
Missing	5911 (2.4)	875 (0.4)	
Body mass index (kg/m^2):			<0.001
<18.5	6638 (2.7)	4562 (1.9)	
18.5–25	85 473 (35.3)	70 102 (28.9)	
≥25	80 458 (33.2)	88 083 (36.4)	
≥30	40 326 (16.6)	63 183 (26.1)	
Missing	29 454 (12.2)	16 419 (6.8)	
Chronic physical illnesses:			
Diabetes mellitus	24 292 (10.0)	52 802 (21.8)	<0.001
Congestive heart failure	7581 (3.1)	23 774 (9.8)	<0.001
Myocardial infarction	11 459 (4.7)	25 746 (10.6)	<0.001
Stroke	12 243 (5.1)	19 982 (8.3)	<0.001
Chronic obstructive pulmonary disease	14 996 (6.2)	18 229 (7.5)	<0.001
Rheumatoid arthritis	4270 (1.8)	6031 (2.5)	<0.001
Cancer	47 431 (19.6)	54 450 (22.5)	<0.001
Parkinson's disease	2691 (1.1)	2293 (1.0)	<0.001
Epilepsy	3972 (1.6)	3682 (1.5)	0.001

CKD = chronic kidney disease.
*White/not-recorded: 136 119 (56.2%) and 140 784 (58.1%) patients with and without CKD, respectively, had no recorded ethnicity.
**Socio-economic status: 259 (0.1%) and 272 (0.1%) patients with and without CKD, respectively, did not have individual-level data; we therefore used the socio-economic status of their general practice.

Table 2. Prevalence of antidepressant prescription by chronic kidney disease status

	No. of patients receiving antidepressants in the past 6 months	Prevalence % (95%CI)	Adjusted odds ratio (95%CI)		
			Model 1*	Model 2**	Model 3***
Patients without CKD (*N* = 242 349)	28 738	11.9 (11.7–12.0)	1 (Reference)	1 (Reference)	1 (Reference)
Patients with CKD (*N* = 242 349)	39 428	16.3 (16.1–16.4)	1.46 (1.43–1.48)	1.43 (1.41–1.46)	1.35 (1.32–1.37)

CI = confidence interval, CKD = chronic kidney disease.
*Model 1: Accounted for the matched nature of the groups (age, sex, general practice, and calendar time) in conditional logistic regression analysis.
**Model 2: Model 1 + adjusted by ethnicity, socio-economic status, smoking status, and body mass index.
***Model 3: Model 2 + adjusted by chronic physical illnesses.

or anxiety, while TCAs were prescribed for neuropathic pain or other reasons. Among patients with a recorded diagnosis of depression, the choice of antidepressant was similar between patients with and without CKD (Table 5). Irrespective of CKD status, the most commonly prescribed antidepressant was citalopram,

Table 3. Incidence of new antidepressant prescription by chronic kidney disease status

	Total follow-up length (person-years)	No. of patients starting antidepressants	Incidence rate (/1000 person-years) (95%CI)	Adjusted rate ratio (95%CI)		
				Model 1*	Model 2**	Model 3***
Patients without CKD (N = 213 611)	774 660	32 846	42.4 (41.9–42.9)	1 (Reference)	1 (Reference)	1 (Reference)
Patients with CKD (N = 202 921)	794 150	45 394	57.2 (56.6–57.7)	1.35 (1.33–1.37)	1.30 (1.28–1.32)	1.25 (1.23–1.26)

CI = confidence interval, CKD = chronic kidney disease, IQR = interquartile range.
*Model 1: Adjusted by age, sex, and financial year, and taking account of clustering by general practice with robust standard errors using unconditional Poisson regression analysis.
**Model 2: Model 1 + adjusted by ethnicity, socio-economic status, smoking status, and body mass index.
***Model 3: Model 2 + adjusted by chronic physical illnesses.

Table 4. Recorded diagnoses for patients prescribed antidepressants stratified by chronic kidney disease status and type of antidepressant

	Patients without CKD (N = 32 846)			Patients with CKD (N = 45 394)		
	SSRI N = 12 924	TCA N = 17 672	Others N = 2250	SSRI N = 17 992	TCA N = 24 262	Others N = 3140
Depression, n (%)*	8123 (62.9)	4430 (25.1)	1035 (46.0)	11 363 (63.2)	6257 (25.8)	1456 (46.4)
Anxiety, n (%)*	4843 (37.5)	3902 (22.1)	708 (31.5)	6131 (34.1)	5055 (20.8)	935 (29.8)
Neuropathic pain, n (%)*	625 (4.8)	2536 (14.4)	152 (6.8)	997 (5.5)	3491 (14.4)	209 (6.7)
None of the above, n (%)	3188 (24.7)	9699 (54.9)	894 (39.7)	4683 (26.0)	13 259 (54.7)	1256 (40.0)

CKD = chronic kidney disease, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressants.
*Percentages are column percentages. Each patient may have one or more recorded diagnosis.

Table 5. Choice of antidepressants and initial prescription dose for patients with diagnosed depression by chronic kidney disease status

	Patients without CKD N = 13 588		Patients with CKD N = 19 076	
	n (%)*	Median initial dose (mg/day) [IQR]	n (%)*	Median initial dose (mg/day) [IQR]
Selective serotonin reuptake inhibitors				
Citalopram	4934 (36.3)	10 [10–20]	7070 (37.1)	10 [10–20]
Escitalopram	353 (2.6)	5 [5–10]	429 (2.3)	5 [5–10]
Fluoxetine	1651 (12.2)	20 [20–20]	2270 (11.9)	20 [20–20]
Fluvoxamine	<5 (<0.1)	n/a	<5 (<0.1)	n/a
Paroxetine	132 (1.0)	20 [20–20]	144 (0.8)	20 [20–20]
Sertraline	1053 (7.8)	50 [50–50]	1449 (7.6)	50 [50–50]
Tricyclic and related antidepressants				
Amitriptyline	3506 (25.8)	10 [10–20]	5024 (26.3)	10 [10–15]
Clomipramine	26 (0.2)	25 [10–37.5]	27 (0.1)	20 [10–37.5]
Dosulepin	407 (3.0)	37.5 [25–75]	512 (2.7)	37.5 [25–75]
Doxepin	19 (0.1)	25 [25–37.5]	24 (0.1)	25 [20–30]
Imipramine	30 (0.2)	25 [10–30]	45 (0.2)	25 [10–30]
Lofepramine	113 (0.8)	70 [70–140]	186 (1.0)	70 [70–140]
Nortriptyline	94 (0.7)	15 [10–15]	158 (0.8)	10 [10–15]
Trimipramine	15 (0.1)	25 [10–37.5]	26 (0.1)	25 [20–50]
Mianserin	7 (0.1)	30 [30–30]	5 (<0.1)	30 [30–30]
Trazodone	213 (1.6)	50 [50–100]	250 (1.3)	50 [50–75]
Monoamine oxidase inhibitors**	<5 (<0.1)	n/a	<5 (<0.1)	n/a
Other antidepressants:				
Agomelatine	<5 (<0.1)	n/a	<5 (<0.1)	n/a
Duloxetine	98 (0.7)	40 [30–60]	169 (0.9)	40 [30–60]
Flupentixol	63 (0.5)	1 [0.5–1]	88 (0.5)	1 [0.5–1]
Mirtazapine	758 (5.6)	15 [15–15]	1045 (5.5)	15 [15–15]
Reboxetine	<5 (<0.1)	n/a	<5 (<0.1)	n/a
Venlafaxine	85 (0.6)	75 [75–75]	97 (0.5)	75 [75–75]
Two or more different antidepressants	27 (0.2)	n/a	53 (0.3)	n/a

CKD = chronic kidney disease, IQR = interquartile range.
*Cell counts less than five have been suppressed to preserve patient privacy.
**Phenelzine, isocarboxazid, tranylcypromine, and moclobemide are combined due to small sample sizes.

followed by amitriptyline, fluoxetine, sertraline, and mirtazapine. There was no clear evidence that antidepressants were started at a reduced dose in patients with CKD, compared to those without CKD.

When we repeated our analyses in subgroups of renal function (Appendix 2 Tables 1–5), as the level of kidney function decreased, patients tended to be older and sicker. Among patients without CKD, those with serum creatinine results recorded in CPRD were sicker than those without. Prevalence and incidence of antidepressant prescribing increased among people with more severe kidney function: prevalence was 16.1 and 18.3%, and incidence was 56.9 and 62.3/1000 person-years in patients with eGFR 30–59 and <30 mL/min/1.73 m^2, respectively. This trend remained after adjusting for confounders. Patterns of indication for and choice of antidepressant, as well as initial prescription dose, were broadly similar for patients with different levels of kidney function.

In additional analyses with follow-up restricted to the first six months, the percentage of patients starting antidepressants was higher amongst patients with CKD (3.5%; 7155/202 921) than amongst those without it (2.5%; 5233/213 611) ($p < 0.001$).

The proportion of patients starting antidepressants with their first depression diagnosis recorded between CPRD registration and index date was larger among patients with CKD (5.8%; 11 781/202 921) than those without CKD (4.0%; 8476/213 611) ($p < 0.001$). Similarly, the proportion of patients starting antidepressants with their first depression diagnosis recorded in CPRD after index date was larger among patients with CKD (3.6%; 7295/202 921) than those without CKD (2.4%; 5112/213 611) ($p < 0.001$). These results suggest that patients with CKD are more likely than those without CKD to start antidepressants both for recurrent episodes of depression, and for their first ever episode of depression.

DISCUSSION

Main findings

In this large study, we found that patients with CKD were more likely than patients without CKD to be receiving an antidepressant, or among non-users, to start one during follow-up. The increase in prevalence and incidence was graded according to severity of kidney function, and the association remained after adjusting for baseline characteristics including chronic physical illnesses. The pattern of indication for and choice of antidepressants, as well as initial prescription dose, were broadly similar between patients with and without CKD.

Strengths and limitations

We used a detailed source of routinely collected data that is representative of UK population demographics.[22] In the UK, GPs manage the vast majority of non-refractory cases of mental health disorders,[39,40] and even when patients see psychiatrists in secondary care, prescriptions are usually administered by primary care.[41] Therefore, we expect that most antidepressant prescriptions are captured in CPRD. To better understand the characteristics of patients with CKD, we used a comparison group of patients without CKD matched on age, sex, general practice, and calendar time. Although previous studies suggested that the proportion of patients with CKD receiving antidepressants may be high as an absolute value,[42,43] we are not aware of any study that has directly compared frequency and patterns of antidepressant prescribing between patients with and without CKD. We defined CKD using eGFR calculated from serum creatinine measurement. This method is more accurate than using recorded diagnosis of CKD, which has low sensitivity for detecting people with CKD in UK primary care databases.[44]

We must acknowledge several limitations of our study. First, serum creatinine testing in primary care is not universal—currently, it is only recommended and incentivized for people who are considered to be at risk for CKD.[9,38] We may have misclassified patients with unmeasured CKD to the matched control cohort, which could dilute the true association between CKD and antidepressant prescription. However, a recent study showed that the prevalence of CKD identified in CPRD is similar to that estimated in a nationally representative survey (Health Survey for England), suggesting that most CKD patients are captured in CPRD.[45] Second, although we adjusted for important confounders that may be associated with mental health conditions,[28,29] the observed association between CKD status and the prevalence/incidence of antidepressant prescribing could be influenced by residual confounding due to un-coded poor health status or access to talking therapies. Third, we examined three common diagnoses associated with antidepressant use (depression, anxiety, and neuropathic pain). However, for patients with two or more different diagnoses (e.g. depression and neuropathic pain), it was not possible to determine the most likely indication for antidepressant prescription because diagnosis and prescription records are separate in CPRD. Also, patients may have received antidepressants for other reasons, such as non-neuropathic pain and insomnia, but reliable

identification of these conditions has not been established in CPRD. Finally, we demonstrated that the initial dose of antidepressant prescribed was similar in depressed patients with and without CKD. However, this does not ensure that the subsequent dose was also similar between those with and without CKD (as doctors may increase or decrease antidepressant dose after initial prescription, according to perceived effectiveness or side effects).

Comparison with other studies

Two studies conducted in the USA have examined antidepressant use in patients with CKD.[42,43] The Chronic Renal Insufficiency Cohort study investigated the proportion of patients with CKD receiving an antidepressant at recruitment.[43] Of 3853 participants, 700 (18.2%) were taking antidepressants. This number is close to the prevalence of existing users of antidepressants in patients with CKD (16.3%) found in our study. Another US cohort study showed that around 30% of patients with CKD (with or without diagnosis of depression) were receiving antidepressants at any time during a 2-year period between 2004 and 2006.[42] These antidepressant users appeared to include both existing and new users of antidepressants. Our study demonstrated the incident rate of antidepressant prescription at 57.2/1000 person-years in patient with CKD. Together with the prevalence of existing users (16.3%), the cumulative effect of this was consistent with over 30% of CKD patients exposed to antidepressants during follow-up. Neither US study included a comparison group of patients without CKD in order to compare prescribing in CKD patients to that in the general population. Indication and choice of antidepressants were also not examined.

Explanation of findings and implication for future studies

Patients with mild CKD generally do not have related physical symptoms. However, a previous study has suggested that negative perception of CKD is associated with depression and lower quality of life, even in the early stages of CKD.[46] Patients with more advanced CKD (eGFR <30 mL/min/1.73m^2) tend to have symptoms including fatigue, nausea, sleep disturbances, itching, and peripheral neuropathy, any of which could influence quality of life and mental health. This is in line with our finding that patients with advanced CKD were more likely to be prescribed antidepressants, even without a specifically coded diagnosis of depression and anxiety.

While most SSRIs were associated with a coded diagnosis of depression or anxiety, more than half of patients starting TCAs (mostly amitriptyline) did not have any recorded diagnoses of depression, anxiety, or neuropathic pain. Amitriptyline may have been predominantly prescribed as an off-label indication for non-psychiatric conditions such as chronic pain and insomnia.[5–7] When restricted to patients with a coded diagnosis of depression, SSRIs accounted for the majority of antidepressant prescribing, which is in keeping with current guidelines for management of depression.[39] Patterns of antidepressant choice did not differ substantially according to CKD status or level of kidney function. This is probably because to date there is no evidence of greater efficacy or safety concerns for specific antidepressants among patients with CKD.[20,21]

Increased adverse events as renal function declines are an important concern. For example, amitriptyline clearance is reduced in patients with decreased kidney function.[47] As a result, amitriptyline may accumulate, causing serious adverse outcomes through neurotoxicity[48] and cardiotoxicity.[49] Another example is the potential amplification of bleeding risk both with use of SSRIs and with decreased kidney function itself.[50] Finally, the results of our analyses stratified by severity of renal function demonstrate that many patients are prescribed antidepressants at levels of renal function below those where cessation is recommended by manufacturers (e.g. eGFR <30 mL/min/1.73 m^2). According to the British National Formulary,[4] escitalopram, paroxetine, sertraline, imipramine, lofepramine, trazodone, duloxetine, mirtazapine, and venlafaxine should be used with caution or avoided in those with reduced renal function, but our real-world data suggest that these drugs are prescribed similarly in patients with moderately or severely decreased kidney function, compared to those with normal kidney function. Better evidence regarding the potential adverse effects of these drugs for patients with decreased kidney function is needed.

CONCLUSIONS

This study using a large UK database suggests that patients with CKD are more likely to be prescribed antidepressants than the general population, whilst prescribing patterns did not appear to be influenced by kidney function. These real-world data emphasize the need for research investigating the potential

adverse effects of antidepressant therapy in people with decreased kidney function.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- This study examined details of antidepressant prescribing in patients with chronic kidney disease using a large, contemporary UK database of routine medical record data. We defined chronic kidney disease using serum creatinine measurements and compared people with and without chronic kidney disease matched for age, sex, general practice, and calendar time.
- Patients with chronic kidney disease were exposed to antidepressants more frequently; with higher prevalence and incidence of antidepressant prescribing than the general population. The positive association between chronic kidney disease and increased frequency of antidepressant prescribing remained after adjusting for measured confounders such as diabetes and cardiovascular disease.
- Among patients starting antidepressants, indication for antidepressant prescription (recorded diagnoses of depression, anxiety, or neuropathic pain) was similar between patients with and without chronic kidney disease. Antidepressant choice was also similar between depressed patients with and without chronic kidney disease.

ACKNOWLEDGMENTS

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. At an individual level, Dr Masao Iwagami is funded by Honjo International Scholarship Foundation, Dr Laurie Tomlinson is funded by a Wellcome Trust Intermediate Clinical Fellowship [WT101143MA], and Dr Helen McDonald was funded by a Kidney Research UK studentship [ST2/2011]. The funders had no role in the execution of this study or interpretation of results.

AUTHOR CONTRIBUTIONS

M.I. planned the study, carried out the data extraction, processing and analysis, and drafted the manuscript. D.N. and L.T. contributed substantially to the study design, interpretation of the results, and writing of the manuscript. K.M. and H.M. supported the data processing and writing of the manuscript. L.S. was involved in discussions of the analytical approach to this study and made comments on the results. All authors read and approved the final manuscript.

REFERENCES

1. Hsiao CJ, Cherry DK, Beatty PC, Rechtsteiner EA. National Ambulatory Medical Care Survey: 2007 summary. *Natl Health Stat Rep* 2010; **27**: 1–32.
2. Health & Social Care Information Centre. Health Survey for England—2013. Available at: http://www.hscic.gov.uk/catalogue/PUB16076 [1 August 2016].
3. Ilyas S, Moncrieff J. Trends in prescriptions and costs of drugs for mental disorders in England, 1998–2010. *Br J Psychiatry* 2012; **200**: 393–398 https://doi.org/10.1192/bjp.bp.111.104257.
4. British Medical Association, Royal Pharmaceutical Society of Great Britain. British national formulary. Available at: https://www.medicinescomplete.com/mc/bnf/current/ [1 August 2016].
5. Chouinard G. The search for new off-label indications for antidepressant, antianxiety, antipsychotic and anticonvulsant drugs. *J Psychiatry Neurosci* 2006; **31**: 168–176.
6. Mercier A, Auger-Aubin I, Lebeau JP, *et al.* Evidence of prescription of antidepressants for non-psychiatric conditions in primary care: an analysis of guidelines and systematic reviews. *BMC Fam Pract* 2013; **14**: 55 https://doi.org/10.1186/1471-2296-14-55.
7. Lai LL, Tan MH, Lai YC. Prevalence and factors associated with off-label antidepressant prescriptions for insomnia. *Drug Healthc Patient Saf* 2011; **3**: 27–36 https://doi.org/10.2147/DHPS.S21079.
8. Jha V, Garcia-Garcia G, Iseki K, *et al.* Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; **382**: 260–272 https://doi.org/10.1016/S0140-6736(13)60687-X.
9. National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. Available at: https://www.nice.org.uk/guidance/cg182 [1 August 2016].
10. MacLaughlin HL, Hall WL, Sanders TA, Macdougall IC. Risk for chronic kidney disease increases with obesity: Health Survey for England 2010. *Public Health Nutr* 2015; **18**: 3349–3354 https://doi.org/10.1017/s1368980015000488.
11. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296–1305 https://doi.org/10.1056/NEJMoa041031.
12. Lee YJ, Kim MS, Cho S, Kim SR. Association of depression and anxiety with reduced quality of life in patients with predialysis chronic kidney disease. *Int J Clin Pract* 2013; **67**: 363–368 https://doi.org/10.1111/ijcp.12020.
13. Palmer S, Vecchio M, Craig JC, *et al.* Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. *Kidney Int* 2013; **84**: 179–191 https://doi.org/10.1038/ki.2013.77.
14. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001; **24**: 1069–1078.
15. Nair N, Farmer C, Gongora E, Dehmer GJ. Commonality between depression and heart failure. *Am J Cardiol* 2012; **109**: 768–772 https://doi.org/10.1016/j.amjcard.2011.10.039.
16. Cohen SD, Patel SS, Khetpal P, Peterson RA, Kimmel PL. Pain, sleep disturbance, and quality of life in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2007; **2**: 919–925 https://doi.org/10.2215/cjn.00820207.
17. Wu J, Ginsberg JS, Zhan M, *et al.* Chronic pain and analgesic use in CKD: implications for patient safety. *Clin J Am Soc Nephrol* 2015; **10**: 435–442 https://doi.org/10.2215/cjn.06520714.
18. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int* 2006; **70**: 2021–2030 https://doi.org/10.1038/sj.ki.5001934.
19. Glassman AH, O'Connor CM, Califf RM, *et al.* Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002; **288**: 701–709.
20. Nagler EV, Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3–5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). *Nephrol Dial Transplant* 2012; **27**: 3736–3745 https://doi.org/10.1093/ndt/gfs295.
21. Hedayati SS, Yalamanchili V, Finkelstein FO. A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. *Kidney Int* 2012; **81**: 247–255 https://doi.org/10.1038/ki.2011.358.

22. Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44**: 827–836 https://doi.org/10.1093/ije/dyv098.
23. Hospital Episode Statistics. Available at: http://www.hscic.gov.uk/hes [1 August 2016].
24. Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2005; **14**: 443–451 https://doi.org/10.1002/pds.1115.
25. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1–266.
26. Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612.
27. van Eijk ME, Bahri P, Dekker G, *et al.* Use of prevalence and incidence measures to describe age-related prescribing of antidepressants with and without anticholinergic effects. *J Clin Epidemiol* 2000; **53**: 645–651.
28. Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M. Antidepressants for depression in physically ill people. *Cochrane Database Syst Rev* 2010; **3**: CD007503 https://doi.org/10.1002/14651858.CD007503.pub2.
29. National Institute for Health and Care Excellence. Depression in adults with chronic physical health problem: recognition and management. Available at: https://www.nice.org.uk/guidance/cg91 [1 August 2016].
30. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. *BMJ* 2012; **344**: e3427 https://doi.org/10.1136/bmj.e3427.
31. Hippisley-Cox J, Coupland C. Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores. *BMJ* 2014; **349**: g4606 https://doi.org/10.1136/bmj.g4606.
32. Department for Communities and Local Government. English indices of deprivation 2010. Available at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010 [1 August 2016].
33. Rait G, Walters K, Griffin M, Buszewicz M, Petersen I, Nazareth I. Recent trends in the incidence of recorded depression in primary care. *Br J Psychiatry* 2009; **195**: 520–524 https://doi.org/10.1192/bjp.bp.108.058636.
34. Walters K, Rait G, Griffin M, Buszewicz M, Nazareth I. Recent trends in the incidence of anxiety diagnoses and symptoms in primary care. *PLoS One* 2012; **7**: e41670 https://doi.org/10.1371/journal.pone.0041670.
35. Kendrick T, Stuart B, Newell C, Geraghty AW, Moore M. Changes in rates of recorded depression in English primary care 2003–2013: time trend analyses of effects of the economic recession, and the GP contract quality outcomes framework (QOF). *J Affect Disord* 2015; **180**: 68–78 https://doi.org/10.1016/j.jad.2015.03.040.
36. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts AC. Indications for antidepressant drug prescribing in general practice in the Netherlands. *J Affect Disord* 2007; **98**: 109–115 https://doi.org/10.1016/j.jad.2006.07.003.
37. Abbing-Karahagopian V, Huerta C, Souverein PC, *et al.* Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. *Eur J Clin Pharmacol* 2014; **70**: 849–857 https://doi.org/10.1007/s00228-014-1676-z.
38. Health & Social Care Information Centre. Quality and outcomes framework. Available at: http://www.hscic.gov.uk/qof [1 August 2016].
39. National Institute for Health and Care Excellence. Depression in adults: recognition and management. Available at: https://www.nice.org.uk/guidance/cg90 [1 August 2016].
40. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder in adults: management. Available at: https://www.nice.org.uk/guidance/cg113 [1 August 2016].
41. Crump BJ, Panton R, Drummond MF, Marchment M, Hawkes RA. Transferring the costs of expensive treatments from secondary to primary care. *BMJ* 1995; **310**: 509–512.
42. Balogun RA, Abdel-Rahman EM, Balogun SA, *et al.* Association of depression and antidepressant use with mortality in a large cohort of patients with nondialysis-dependent CKD. *Clin J Am Soc Nephrol* 2012; **7**: 1793–1800 https://doi.org/10.2215/cjn.02650312.
43. Fischer MJ, Xie D, Jordan N, *et al.* Factors associated with depressive symptoms and use of antidepressant medications among participants in the Chronic Renal Insufficiency Cohort (CRIC) and Hispanic-CRIC Studies. *Am J Kidney Dis* 2012; **60**: 27–38 https://doi.org/10.1053/j.ajkd.2011.12.033.
44. Fraser SD, Parkes J, Culliford D, Santer M, Roderick PJ. Timeliness in chronic kidney disease and albuminuria identification: a retrospective cohort study. *BMC Fam Pract* 2015; **16**: 18 https://doi.org/10.1186/s12875-015-0235-8.
45. Iwagami M, Tomlinson LA, Mansfield KE, *et al.* Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared to national survey and registry data in the UK. *Nephrol Dial Transplant* 2017; **32**: ii142–ii150 https://doi.org/10.1093/ndt/gfw318.
46. Shidler NR, Peterson RA, Kimmel PL. Quality of life and psychosocial relationships in patients with chronic renal insufficiency. *Am J Kidney Dis* 1998; **32**: 557–566.
47. Tasset JJ, Singh S, Pesce AJ. Evaluation of amitriptyline pharmacokinetics during peritoneal dialysis. *Ther Drug Monit* 1985; **7**: 255–257.
48. Livingston RL, Zucker DK, Isenberg K, Wetzel RD. Tricyclic antidepressants and delirium. *J Clin Psychiatry* 1983; **44**: 173–176.
49. Scollins MJ, Robinson DS, Nies A. Cardiotoxicity of amitriptyline. *Lancet* 1972; **2**: 1202.
50. Olesen JB, Lip GY, Kamper AL, *et al.* Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012; **367**: 625–635 https://doi.org/10.1056/NEJMoa1105594.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Appendix 1. List of diagnosis codes indicative of depression, anxiety, and neuropathic pain in Clinical Practice Research Datalink.

Read code	Medcode*	Read term
Depression:		
E2B..00	324	Depressive disorder NEC
Eu32z11	543	[X]Depression NOS
E112.14	595	Endogenous depression
E200300	655	Anxiety with depression
E135.00	1055	Agitated depression
E204.00	1131	Neurotic depression reactive type
Eu31.11	1531	[X]Manic-depressive illness
E290.00	1533	Brief depressive reaction
2257.00	1908	O/E - depressed
1B17.00	1996	Depressed
1B1N.00	2147	Poor self esteem
E11..12	2560	Depressive psychoses
E204.11	2639	Postnatal depression
1465.00	2716	H/O: depression
62T1.00	2923	Puerperal depression
1B17.12	2930	C/O - feeling unhappy
Eu32z00	2970	[X]Depressive episode, unspecified
E2B0.00	2972	Postviral depression
Eu32z12	3291	[X]Depressive disorder NOS
Eu33.00	3292	[X]Recurrent depressive disorder
E2B1.00	4323	Chronic depression
Eu32.00	4639	[X]Depressive episode
E115.00	4677	Bipolar affective disorder, currently depressed
Eu31500	4732	[X]Bipolar affect dis cur epi severe depres with psyc symp
1B17.11	4824	C/O - feeling depressed
Eu53012	4979	[X]Postpartum depression NOS
E112.11	5879	Agitated depression
Eu32z14	5987	[X] Reactive depression NOS
E113700	6482	Recurrent depression
E112.12	6546	Endogenous depression first episode
Eu32y00	6854	[X]Other depressive episodes
E113.11	6932	Endogenous depression - recurrent
E112.13	6950	Endogenous depression first episode
E112z00	7011	Single major depressive episode NOS

1BJ..00	7412	Loss of confidence
Eu32.13	7604	[X]Single episode of reactive depression
Eu34113	7737	[X]Neurotic depression
Eu41211	7749	[X]Mild anxiety depression
Eu34100	7953	[X]Dysthymia
E130.00	8478	Reactive depressive psychosis
Eu34111	8584	[X]Depressive neurosis
Eu33.15	8826	[X]SAD - Seasonal affective disorder
Eu33.11	8851	[X]Recurrent episodes of depressive reaction
Eu33.13	8902	[X]Recurrent episodes of reactive depression
1BT..11	8928	Low mood
Eu32.11	9055	[X]Single episode of depressive reaction
E11z200	9183	Masked depression
Eu32100	9211	[X]Moderate depressive episode
Eu32200	9667	[X]Severe depressive episode without psychotic symptoms
1B1U.00	9796	Symptoms of depression
1BT..00	10015	Depressed mood
Eu34112	10290	[X]Depressive personality disorder
1B1U.11	10438	Depressive symptoms
E211200	10455	Depressive personality disorder
E112.00	10610	Single major depressive episode
Eu32400	10667	[X]Mild depression
Eu32y11	10720	[X]Atypical depression
E118.00	10825	Seasonal affective disorder
Eu33212	11252	[X]Major depression, recurrent without psychotic symptoms
Eu33211	11329	[X]Endogenous depression without psychotic symptoms
E11y000	11596	Unspecified manic-depressive psychoses
Eu32000	11717	[X]Mild depressive episode
Eu41200	11913	[X]Mixed anxiety and depressive disorder
Eu32300	12099	[X]Severe depressive episode with psychotic symptoms
E115.11	12831	Manic-depressive - now depressed
Eu53011	13307	[X]Postnatal depression NOS
E113200	14709	Recurrent major depressive episodes, moderate
E113.00	15099	Recurrent major depressive episode
E112200	15155	Single major depressive episode, moderate
E112300	15219	Single major depressive episode, severe, without psychosis
Eu34114	15220	[X]Persistant anxiety depression
E115000	15923	Bipolar affective disorder, currently depressed, unspecified

E112100	16506	Single major depressive episode, mild
Eu31300	16562	[X]Bipolar affect disorder cur epi mild or moderate depressn
E291.00	16632	Prolonged depressive reaction
Eu33315	16861	[X]Recurrent severe episodes of psychotic depression
E130.11	17770	Psychotic reactive depression
Eu32.12	18510	[X]Single episode of psychogenic depression
Eu3y111	19054	[X]Recurrent brief depressive episodes
Eu33.12	19696	[X]Recurrent episodes of psychogenic depression
Eu20400	20785	[X]Post-schizophrenic depression
E002100	21887	Senile dementia with depression
ZV11112	22080	[V]Personal history of manic-depressive psychosis
Eu33400	22116	[X]Recurrent depressive disorder, currently in remission
Eu32212	22806	[X]Single episode major depression w'out psychotic symptoms
Eu31400	23713	[X]Bipol aff disord, curr epis sev depress, no psychot symp
Eu33311	23731	[X]Endogenous depression with psychotic symptoms
ZV11111	23963	[V]Personal history of manic-depressive psychosis
Eu32313	24112	[X]Single episode of psychotic depression
Eu32311	24117	[X]Single episode of major depression and psychotic symptoms
E113400	24171	Recurrent major depressive episodes, severe, with psychosis
1BQ..00	25435	Loss of capacity for enjoyment
E113z00	25563	Recurrent major depressive episode NOS
E113300	25697	Recurrent major depressive episodes, severe, no psychosis
1BT..12	26028	Sad mood
E11y200	27491	Atypical depressive disorder
E001300	27677	Presenile dementia with depression
Eu02z16	27759	[X] Senile dementia, depressed or paranoid type
E115200	27890	Bipolar affective disorder, currently depressed, moderate
Eu32z13	28248	[X]Prolonged single episode of reactive depression
Eu33312	28677	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33.14	28756	[X]Seasonal depressive disorder
Eu32314	28863	[X]Single episode of reactive depressive psychosis
E113100	29342	Recurrent major depressive episodes, mild
Eu33213	29451	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33100	29520	[X]Recurrent depressive disorder, current episode moderate
R007z13	29527	[D]Postoperative depression
Eu33000	29784	[X]Recurrent depressive disorder, current episode mild
Eu3y011	30688	[X]Mixed affective episode
1BP..00	30740	Loss of interest

Eu33314	31757	[X]Recurr severe episodes/psychogenic depressive psychosis
E112400	32159	Single major depressive episode, severe, with psychosis
Eu33313	32941	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33200	33469	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu31z00	33751	[X]Bipolar affective disorder, unspecified
E112000	34390	Single major depressive episode, unspecified
E115300	35607	Bipolar affect disord, now depressed, severe, no psychosis
E113000	35671	Recurrent major depressive episodes, unspecified
E115100	35734	Bipolar affective disorder, currently depressed, mild
E290z00	36246	Brief depressive reaction NOS
Eu33z11	36616	[X]Monopolar depression NOS
E115z00	37296	Bipolar affective disorder, currently depressed, NOS
Eu33316	37764	[X]Recurrent severe episodes/reactive depressive psychosis
E002z00	41089	Senile dementia with depressive or paranoid features NOS
Eu32211	41989	[X]Single episode agitated depressn w'out psychotic symptoms
E004300	43292	Arteriosclerotic dementia with depression
E112500	43324	Single major depressive episode, partial or unspec remission
Eu33z00	44300	[X]Recurrent depressive disorder, unspecified
E002.00	44674	Senile dementia with depressive or paranoid features
Eu31600	44693	[X]Bipolar affective disorder, current episode mixed
Eu33300	47009	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33y00	47731	[X]Other recurrent depressive disorders
Eu32312	52678	[X]Single episode of psychogenic depressive psychosis
1BU..00	53148	Loss of hope for the future
Eu31y00	53840	[X]Other bipolar affective disorders
E113600	55384	Recurrent major depressive episodes, in full remission
E113500	56273	Recurrent major depressive episodes,partial/unspec remission
Eu32y12	56609	[X]Single episode of masked depression NOS
E115600	57465	Bipolar affective disorder, now depressed, in full remission
Eu32213	59386	[X]Single episode vital depression w'out psychotic symptoms
1BP0.00	59869	Loss of interest in previously enjoyable activity
E11y.00	60178	Other and unspecified manic-depressive psychoses
E115400	63701	Bipolar affect disord, now depressed, severe with psychosis
E115500	72026	Bipolar affect disord, now depressed, part/unspec remission
Eu31y11	73924	[X]Bipolar II disorder
Eu33214	73991	[X]Vital depression, recurrent without psychotic symptoms
Eu32600	98252	[X]Major depression, moderately severe
Eu32500	98346	[X]Major depression, mild

Eu32700	98414	[X]Major depression, severe without psychotic symptoms
Eu32800	98417	[X]Major depression, severe with psychotic symptoms
Anxiety:		
1B13.00	131	Anxiousness
E200111	462	Panic attack
1B12.12	514	Tension - nervous
E200.00	636	Anxiety states
E200300	655	Anxiety with depression
E20z.11	791	Nervous breakdown
Eu41111	962	[X]Anxiety neurosis
E205.11	1582	Nervous exhaustion
E200400	1758	Chronic anxiety
R2y2.00	2509	[D]Nervousness
1BK..00	2524	Worried
E202100	3076	Agoraphobia with panic attacks
1B1..00	3328	General nervous symptoms
E200100	4069	Panic disorder
Eu41012	4081	[X]Panic state
E200z00	4534	Anxiety state NOS
E200500	4634	Recurrent anxiety
E200200	4659	Generalised anxiety disorder
Eu41.00	5385	[X]Other anxiety disorders
1B13.11	5902	Anxiousness - symptom
E292000	6221	Separation anxiety disorder
Eu41011	6408	[X]Panic attack
E200000	6939	Anxiety state unspecified
Eu41211	7749	[X]Mild anxiety depression
Z4L1.00	7999	Anxiety counselling
Eu41000	8205	[X]Panic disorder [episodic paroxysmal anxiety]
Eu60600	8424	[X]Anxious [avoidant] personality disorder
2259.00	8725	O/E - nervous
Eu41100	10344	[X]Generalized anxiety disorder
E202D00	10390	Fear of death
R2y2.12	10723	[D]Nervous tension
1B1V.00	11890	C/O - panic attack
Eu41200	11913	[X]Mixed anxiety and depressive disorder
E280.00	11940	Acute panic state due to acute stress reaction
E202200	12838	Agoraphobia without mention of panic attacks

2258.00	13124	O/E - anxious
Eu40012	14890	[X]Panic disorder with agoraphobia
Eu40011	16729	[X]Agoraphobia without history of panic disorder
Eu51511	17687	[X]Dream anxiety disorder
225J.00	19000	O/E - panic attack
1B1Z.00	20089	General nervous symptom NOS
1B1H.12	20163	Apprehension
Eu41z00	23838	[X]Anxiety disorder, unspecified
Eu41y00	24066	[X]Other specified anxiety disorders
Eu41z11	25638	[X]Anxiety NOS
225K.00	26331	O/E - fearful mood
Eu41y11	28167	[X]Anxiety hysteria
Z4I7200	28381	Alleviating anxiety
8HHp.00	28925	Referral for guided self-help for anxiety
1B12.00	29608	'Nerves' - nervousness
Eu40z00	34064	[X]Phobic anxiety disorder, unspecified
Eu41112	35825	[X]Anxiety reaction
2255.00	38155	O/E - afraid
1B1P000	40431	Cries easily
Eu41300	44321	[X]Other mixed anxiety disorders
Eu41113	50191	[X]Anxiety state
E292400	56924	Adjustment reaction with anxious mood
1B13.12	93401	Anxious
16ZB100	101422	Feeling low or worried

Neuropathic pain:

F262500	321	Periodic migrainous neuralgia
F301.00	1541	Other specified trigeminal neuralgia
A531.11	1598	Post-herpetic neuralgia
N242000	2284	Neuralgia unspecified
F301z00	6581	Trigeminal neuralgia NOS
F356100	6884	Morton's neuralgia
F300.00	7584	Post-herpetic trigeminal neuralgia
A531511	10223	Postherpetic neuralgia
A531200	11498	Postherpetic trigeminal neuralgia
N242300	11544	Neuropathic pain
1475.00	16481	H/O: trigeminal neuralgia
F321.00	16932	Glossopharyngeal neuralgia
A531500	17180	Postzoster neuralgia

N242z00	23839	Neuralgia, neuritis or radiculitis NOS
F262100	33362	Horton's (histamine) neuralgia
F372100	35785	Chronic painful diabetic neuropathy
F372000	48078	Acute painful diabetic neuropathy
N242.00	54992	Neuralgia, neuritis and radiculitis unspecified

*There is a one-to-one correspondence between Medcode and Read code in Clinical Practice Research Datalink.

Appendix 2. Subgroup analyses according to level of kidney function (among patients with CKD) and creatinine measurement (among patients without CKD).

Table 1. Baseline characteristics.

	Patients without CKD (N = 242,349)		Patients with CKD (N = 242,349)		
	without creatinine measurement in CPRD N = 62,971 n (%)	with creatinine measurement in CPRD N = 179,378 n (%)	with eGFR 30-59 mL/min/1.73m^2 at baseline N = 228,055 n (%)	with eGFR <30 mL/min/1.73m^2 at baseline N = 14,294 n (%)	P value
Age (years):					<0.001
<55	3,279 (5.2)	3,566 (2.0)	6,022 (2.6)	823 (5.8)	
55-64	7,693 (12.2)	15,863 (8.8)	22,531 (9.9)	1,025 (7.2)	
65-74	17,450 (27.7)	53,662 (29.9)	68,494 (30.0)	2,618 (18.3)	
75-84	23,536 (37.4)	79,058 (44.1)	96,868 (42.5)	5,726 (40.1)	
≥85	11,013 (17.5)	27,229 (15.2)	34,140 (15.0)	4,102 (28.7)	
Sex (male):	23,015 (36.6)	72,303 (40.3)	89,289 (39.2)	6,029 (42.2)	<0.001
Ethnicity:					<0.001
White/not-recorded	62,319 (99.0)	176,214 (98.2)	224,211 (98.3)	13,927 (97.3)	
South Asian	302 (0.5)	1,494 (0.8)	2,141 (0.9)	176 (1.2)	
Black	146 (0.2)	1,010 (0.6)	932 (0.4)	128 (0.9)	
Other ethnicity	204 (0.3)	660 (0.4)	771 (0.3)	63 (0.4)	
Socio-economic status:					<0.001
1 (least deprived)	14,724 (23.4)	42,076 (23.5)	50,295 (22.1)	2,739 (19.2)	
2	15,603 (24.8)	46,044 (25.7)	57,190 (25.1)	3,311 (23.2)	
3	12,950 (20.6)	37,516 (20.9)	47,616 (20.9)	3,093 (21.6)	
4	11,222 (17.8)	30,999 (17.3)	41,829 (18.3)	2,863 (20.0)	

5 (most deprived)	8,472 (13.5)	22,743 (12.7)	31,125 (13.7)	2,288 (16.0)	
Smoking status:					<0.001
Non-smoker	27,736 (44.1)	64,627 (36.0)	75,701 (33.2)	5,020 (35.1)	
Ex-smoker	18,549 (29.5)	89,188 (49.7)	124,290 (54.5)	7,220 (50.5)	
Current-smoker	11,791 (18.7)	24,547 (13.7)	27,374 (12.0)	1,869 (13.1)	
Missing	4,895 (7.8)	1,016 (0.6)	690 (0.3)	185 (1.3)	
Body mass index:					<0.001
<18.5	1,628 (2.6)	5,010 (2.8)	4,189 (1.8)	373 (2.6)	
18.5 - 25	21,981 (34.9)	63,492 (35.4)	65,841 (28.9)	4,261 (29.8)	
≥25	17,526 (27.8)	62,932 (35.1)	83,733 (36.7)	4,350 (30.4)	
≥30	6,829 (10.8)	33,497 (18.7)	59,910 (26.3)	3,273 (22.9)	
Missing	15,007 (23.8)	14,447 (8.1)	14,382 (6.3)	2,037 (14.3)	
Chronic physical illnesses:					
Diabetes mellitus	669 (1.1)	23,623 (13.2)	49,017 (21.5)	3,785 (26.5)	<0.001
Congestive heart failure	824 (1.3)	6,757 (3.8)	20,723 (9.1)	3,051 (21.3)	<0.001
Myocardial infarction	783 (1.2)	10,676 (6.0)	23,664 (10.4)	2,082 (14.6)	<0.001
Stroke	1,507 (2.4)	10,736 (6.0)	18,330 (8.0)	1,652 (11.6)	<0.001
Chronic obstructive pulmonary disease	2,312 (3.7)	12,684 (7.1)	17,006 (7.5)	1,223 (8.6)	<0.001
Rheumatoid arthritis	527 (0.8)	3,743 (2.1)	5,674 (2.5)	357 (2.5)	<0.001
Cancer	8,593 (13.7)	38,838 (21.7)	50,799 (22.3)	3,651 (25.5)	<0.001
Parkinson’s disease	500 (0.8)	2,191 (1.2)	2,143 (0.9)	150 (1.1)	<0.001
Epilepsy	670 (1.1)	3,302 (1.8)	3,450 (1.5)	232 (1.6)	<0.001

CKD = chronic kidney function, eGFR = estimated glomerular filtration rate.

Table 2. Prevalence of antidepressant prescription.

	No. of patients receiving antidepressants in the past 6 months	Prevalence, % (95% CI)	Adjusted odds ratio (95% CI)		
			Model 1*	Model 2**	Model 3***
Non-CKD patients without creatinine measurement in CPRD (N = 62,971)	4,515	7.2 (7.0 – 7.4)	0.49 (0.47 – 0.51)	0.48 (0.46 – 0.50)	0.52 (0.49 – 0.54)
Non-CKD patients with creatinine measurement in CPRD (N = 179,378)	24,223	13.5 (13.3 – 13.7)	1 (Reference)	1 (Reference)	1 (Reference)
CKD patients with eGFR 30-59 mL/min/1.73m^2 at baseline (N = 228,055)	36,815	16.1 (16.0 – 16.3)	1.24 (1.22 – 1.27)	1.23 (1.21 – 1.26)	1.19 (1.16 – 1.21)
CKD patients with eGFR <30 mL/min/1.73m^2 at baseline (N = 14,294)	2,613	18.3 (17.6 – 18.9)	1.35 (1.26 – 1.44)	1.31 (1.23 – 1.41)	1.20 (1.12 – 1.29)

CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate.

*Model 1: Adjusted by age, sex and financial year, and taking account of clustering by general practices with robust standard errors using unconditional logistic regression analysis.

**Model 2: Model 1 + adjusted by ethnicity, socio-economic status, smoking status and body mass index.

***Model 3: Model 2 + adjusted by chronic physical illnesses.

Table 3. Incidence of new antidepressant prescription.

	Total follow-up length (person-years)	No. of patients starting antidepressants	Incidence rate (/1000 person-years) (95%CI)	Adjusted rate ratio (95%CI)		
				Model 1**	Model 2***	Model 3***
Non-CKD patients without creatinine measurement in CPRD (N = 58,456)	258,474	7,076	27.4 (26.7 – 28.0)	0.55 (0.53 – 0.56)	0.58 (0.56 – 0.59)	0.60 (0.59 – 0.62)
Non-CKD patients with creatinine measurement in CPRD (N = 155,155)	516,186	25,770	49.9 (49.3 – 50.5)	1 (Reference)	1 (Reference)	1 (Reference)
CKD patients with eGFR 30-59 mL/min/1.73m^2 (N = 191,240)	762,310	43,410	56.9 (56.4 – 57.5)	1.14 (1.12 – 1.16)	1.13 (1.11 – 1.15)	1.10 (1.09 – 1.12)
CKD patients with eGFR <30 mL/min/1.73m^2 (N = 11,681)	31,839	1,984	62.3 (59.6 – 65.1)	1.24 (1.18 – 1.30)	1.23 (1.17 – 1.28)	1.16 (1.11 – 1.22)

CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, IQR = interquartile range.

*Model 1: Adjusted by age, sex and financial year, and taking account of clustering by general practices with robust standard errors using unconditional Poisson regression analysis.

**Model 2: Model 1 + adjusted by ethnicity, socio-economic status, smoking status and body mass index.

***Model 3: Model 2 + adjusted by chronic physical illnesses.

Table 4. Recorded diagnoses for patients prescribed antidepressants stratified by type of antidepressant.

	Patients without CKD (N = 32,846)					
	without creatinine measurement in CPRD (N = 7,076)			with creatinine measurement in CPRD (N = 25,770)		
	SSRI	TCA	Others	SSRI	TCA	Others
	N = 2,984	N = 3,591	N = 501	N = 9,940	N = 14,081	N = 1,749
Depression, n (%)*	1,741 (58.3)	759 (21.1)	197 (39.3)	6,382 (64.2)	3,671 (26.1)	838 (47.9)
Anxiety, n (%)*	1,030 (34.5)	646 (18.0)	133 (26.6)	3,813 (38.4)	3,256 (23.1)	575 (32.9)
Neuropathic pain, n (%)*	76 (2.6)	478 (13.3)	19 (3.8)	549 (5.5)	2,058 (14.6)	133 (7.6)
None of the above, n (%)	850 (28.5)	2,149 (59.8)	244 (48.7)	2,338 (23.5)	7,550 (53.6)	650 (37.2)

	Patients with CKD (N = 45,394)					
	eGFR 30-59 mL/min/1.73m^2 (N = 43,410)			eGFR <30 mL/min/1.73m^2 (N = 1,984)		
	SSRI	TCA	Others	SSRI	TCA	Others
	N = 17,124	N = 23,286	N = 3,000	N = 868	N = 976	N = 140
Depression, n (%)*	10,871 (63.5)	6,017 (25.8)	1,390 (46.3)	492 (56.7)	240 (24.6)	66 (47.1)
Anxiety, n (%)*	5,904 (34.5)	4,874 (20.9)	897 (29.9)	227 (26.2)	181 (18.6)	38 (27.1)
Neuropathic pain, n (%)*	942 (5.5)	3,348 (14.4)	201 (6.7)	55 (6.3)	143 (14.7)	8 (5.7)
None of the above, n (%)	4,395 (25.7)	12,715 (54.6)	1,195 (39.8)	288 (33.2)	544 (55.7)	61 (43.6)

CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressants.

*Percentages are column percentages. Each patient may have one or more recorded diagnosis.

Table 5. Choice of antidepressants and initial prescription dose for patients with diagnosed depression.

	Patients without CKD (N = 13,588)				Patients with CKD (N = 19,076)			
	without creatinine measurement in CPRD N = 2,697		with creatinine measurement in CPRD N = 10,891		with eGFR 30-59 mL/min/1.73m^2 at baseline N = 18,278		with eGFR <30 mL/min/1.73m^2 at baseline N = 798	
	n (%)*	Median initial dose (mg/day) [IQR]	n (%)*	Median initial dose (mg/day) [IQR]	n (%)*	Median initial dose (mg/day) [IQR]	n (%)*	Median initial dose (mg/day) [IQR]
Selective serotonin reuptake inhibitors								
Citalopram	1,051 (39.0)	10 [10 – 20]	3,883 (35.7)	10 [10 – 20]	6,760 (37.0)	10 [10 – 20]	310 (38.9)	10 [10 – 20]
Escitalopram	80 (3.0)	10 [5 – 10]	273 (2.5)	5 [5 – 10]	407 (2.2)	5 [5 – 10]	22 (2.8)	5 [5 – 10]
Fluoxetine	381 (14.3)	20 [20 – 20]	1,270 (11.7)	20 [20 – 20]	2,171 (11.9)	20 [20 – 20]	99 (12.4)	20 [20 – 20]
Fluvoxamine	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Paroxetine	35 (1.3)	20 [20 – 20]	97 (0.9)	20 [20 – 20]	133 (0.7)	20 [20 – 20]	11 (1.4)	20 [20 – 20]
Sertraline	194 (7.2)	50 [50 – 50]	859 (7.9)	50 [50 – 50]	1,399 (7.7)	50 [50 – 50]	50 (6.3)	50 [50 – 50]
Tricyclic and related antidepressants								
Amitriptyline	548 (20.3)	10 [10 – 15]	2,958 (27.2)	10 [10 – 20]	4,847 (26.5)	10 [10 – 15]	177 (22.2)	10 [10 – 15]
Clomipramine	<5 (<0.2)	n/a	22 (0.2)	20 [10 – 37.5]	27 (0.2)	20 [10 – 37.5]	<5 (<0.6)	n/a
Dosulepin	105 (3.9)	50 [25 – 75]	302 (2.8)	37.5 [25 – 75]	481 (2.6)	37.5 [25 – 50]	31 (3.9)	37.5 [25 – 75]
Doxepin	<5 (<0.2)	n/a	17 (0.2)	25 [25 – 37.5]	23 (0.1)	25 [20 – 25]	<5 (<0.6)	n/a
Imipramine	<5 (<0.2)	n/a	27 (0.3)	15 [10 – 25]	44 (0.2)	25 [10 – 30]	<5 (<0.6)	n/a
Lofepramine	26 (1.0)	70 [70 – 140]	87 (0.8)	70 [70 – 140]	179 (1.0)	70 [70 – 140]	7 (0.9)	70 [70 – 140]
Nortriptyline	10 (0.4)	15 [10 – 25]	84 (0.8)	15 [10 – 15]	155 (0.9)	10 [10 – 15]	<5 (<0.6)	n/a

Trimipramine	<5 (<0.2)	n/a	12 (0.1)	25 [15 – 37.5]	24 (0.1)	30 [15 – 50]	<5 (<0.6)	n/a
Mianserin	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Trazodone	55 (2.0)	50 [50 – 100]	158 (1.5)	50 [50 – 100]	233 (1.3)	50 [50 – 75]	17 (2.1)	50 [50 – 75]
Monoamine oxidase inhibitors**	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Other antidepressants:								
Agomelatine	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Duloxetine	15 (0.6)	60 [40 – 60]	83 (0.8)	40 [30 – 60]	164 (0.9)	40 [30 – 60]	5 (0.6)	60 [60 – 60]
Flupentixol	17 (0.6)	1 [0.5 – 1]	46 (0.4)	0.5 [0.5 – 1]	82 (0.5)	1 [0.5 – 1]	6 (0.8)	0.5 [0.5 – 0.5]
Mirtazapine	139 (5.2)	15 [15 – 15]	619 (5.7)	15 [15 – 15]	998 (5.5)	15 [15 – 15]	47 (5.9)	15 [15 – 15]
Reboxetine	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Venlafaxine	19 (0.7)	75 [75 – 75]	66 (0.6)	75 [75 – 75]	94 (0.5)	75 [75 – 75]	<5 (<0.6)	n/a
Two or more different antidepressants	7 (0.3)	n/a	20 (0.2)	n/a	48 (0.3)	n/a	5 (0.6)	n/a

CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, IQR = interquartile range.

*Cell counts less than five have been suppressed to preserve patient privacy.

**Phenelzine, isocarboxazid, tranylcypromine and moclobemide are combined due to small sample sizes.

8.3. Additional data and discussions

Further to the results and discussions presented in the published paper, here I show the additional data of unmatched patients with CKD and discuss the influence of excluding them from the main analysis. I also show the prevalence of antidepressant prescribing by year of cohort entry (i.e. the date of satisfying CKD definition for CKD patients, and the same date for matched controls without CKD) to discuss the temporal trend of antidepressant prescription in patients with and without CKD.

8.3.1. Characteristics of unmatched patients with CKD

(i) Backgrounds and methods

When establishing a matched cohort of 242,349 pairs with and without CKD (median age 76 years [IQR 70–82]; male, 39.3%) in **chapter 7**, I excluded 22,279 unmatched patients with CKD (mean age 88 years [IQR 84–92]; male, 31.5%) because of a lack of comparable patients without CKD. It is important to check their characteristics in detail. Here, I compared the baseline characteristics, including the distribution of CKD stage at the time of cohort entry, between unmatched and matched patients with CKD by chi-squared test. I also estimated the prevalence and incidence of antidepressant prescribing in unmatched patients with CKD, and combined the results of unmatched and matched patients with CKD to see how much the inclusion of unmatched patients with CKD could change the overall results.

(ii) Results and discussions

In addition to the older age and higher proportion of females, unmatched patients were more likely to be deprived and had more comorbidities except for diabetes, myocardial infarction, and rheumatoid arthritis, than matched patients with CKD (see **Table 11** below). The distribution of CKD stage at cohort entry was worse in unmatched patients with CKD.

Table 11. Baseline characteristics of unmatched and matched patients with CKD

	Unmatched patients with CKD N = 22,279	Matched patients with CKD N = 242,349	P value
	n (%)	n (%)	
Age (years):			-
<55	<5 (<0.1)	6,845 (2.8)	
55-64	<5 (<0.1)	23,556 (9.7)	
65-74	129 (0.6)	71,112 (29.3)	
75-84	5,848 (26.3)	102,594 (42.3)	
≥85	16,300 (73.2)	38,242 (15.8)	
Sex (male):	7,015 (31.5)	95,318 (39.3)	<0.001
Ethnicity:			<0.001
White/not-recorded	22,084 (99.1)	238,138 (98.3)	
South Asian	97 (0.4)	2,317 (1.0)	
Black	52 (0.2)	1,060 (0.4)	
Other ethnicity	46 (0.2)	834 (0.3)	
Socio-economic status:			<0.001
1 (least deprived)	4,633 (20.8)	53,034 (21.9)	
2	5,510 (24.7)	60,501 (25.0)	
3	4,546 (20.4)	50,709 (20.9)	
4	4,166 (18.7)	44,692 (18.4)	
5 (most deprived)	3,424 (15.4)	33,413 (13.8)	
Smoking status:			<0.001
Non-smoker	9,465 (42.5)	80,721 (33.3)	
Ex-smoker	10,881 (48.8)	131,510 (54.3)	
Current-smoker	1,752 (7.9)	29,243 (12.1)	
Body mass index (kg/m^2):			<0.001
<18.5	961 (4.3)	4,562 (1.9)	
18.5 – 25	8,536 (38.3)	70,102 (28.9)	
≥25	6,339 (28.5)	88,083 (36.4)	
≥30	2,638 (11.8)	63,183 (26.1)	
Chronic physical illnesses:			
Diabetes mellitus	3,182 (14.3)	52,802 (21.8)	<0.001
Congestive heart failure	2,974 (13.4)	23,774 (9.8)	<0.001
Myocardial infarction	2,109 (9.5)	25,746 (10.6)	<0.001
Stroke	2,424 (10.9)	19,982 (8.3)	<0.001
COPD	1,681 (7.6)	18,229 (7.5)	0.899
Rheumatoid arthritis	466 (2.1)	6,031 (2.5)	<0.001
Cancer	6,402 (28.7)	54,450 (22.5)	<0.001
Parkinson's disease	190 (1.3)	2,293 (1.0)	<0.001
Epilepsy	327 (1.5)	3,682 (1.5)	0.547
CKD stage at cohort entry:			<0.001
3a (eGFR 45-59 mL/min/1.73m^2)	13,398 (60.1)	172,555 (71.2)	
3b (eGFR 30-44 mL/min/1.73m^2)	6,959 (31.2)	55,500 (22.9)	
4/5 (eGFR <30 mL/min/1.73m^2)	1,922 (8.6)	14,294 (5.9)	

Abbreviations: CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate.

The prevalence and incidence of antidepressant prescription were slightly higher in unmatched patients with CKD than matched patients with CKD (see **Tables 12** and **13** below). However, by adding the results of unmatched patients with CKD, the total prevalence and incidence of antidepressant prescription in all patients with CKD were very similar to those in matched patients with CKD.

Unmatched patients with CKD had quite different characteristics from matched patients with CKD. The reason for failure to match was probably because almost all patients had CKD in the oldest age group (i.e. those aged >85 years), especially females. Accordingly, most of the differences in characteristics between unmatched and matched patients with CKD were probably ascribed to the large age-sex difference between the groups. The prevalence and incidence of antidepressant prescription were slightly higher in unmatched patients with CKD than matched patients with CKD. However, because of the small proportion of unmatched group (8.4% [22,279/264,628]), the exclusion of unmatched patients with CKD rarely affected the study results. Therefore, the exclusion of these patients from the main analysis, prioritising a fairer comparison between patients with and without CKD, is justified.

Table 12. Prevalence of antidepressant prescription in unmatched and matched patients with CKD

	No. of prevalent users (i.e. patients receiving antidepressants in the past six months	Prevalence, % (95% confidence interval)
Unmatched patients with CKD (N = 22,279)	4,005	18.0 (17.5 – 18.5)
Matched patients with CKD (N = 242,349)	39,428	16.3 (16.1 – 16.4)
Total (N = 264,628)	43,433	16.4 (16.3 – 16.6)

Abbreviation: CKD = chronic kidney disease.

Table 13. Incidence of antidepressant prescription in unmatched and matched patients with CKD

	Total follow-up length (person-years)	No. of new users (i.e. patients starting antidepressants among non-prevalent users)	Incidence rate (/1000 person-years) (95% confidence interval)
Unmatched patients with CKD (N = 18,274)	47,894	3,015	63.0 (60.7 – 65.2)
Matched patients with CKD (N = 202,921)	794,150	45,394	57.2 (56.6 – 57.7)
Total (N = 221,195)	842,044	48,409	57.5 (57.0 – 58.0)

Abbreviation: CKD = chronic kidney disease.

8.3.2. Temporal trend in the prevalence of antidepressant prescribing by CKD status

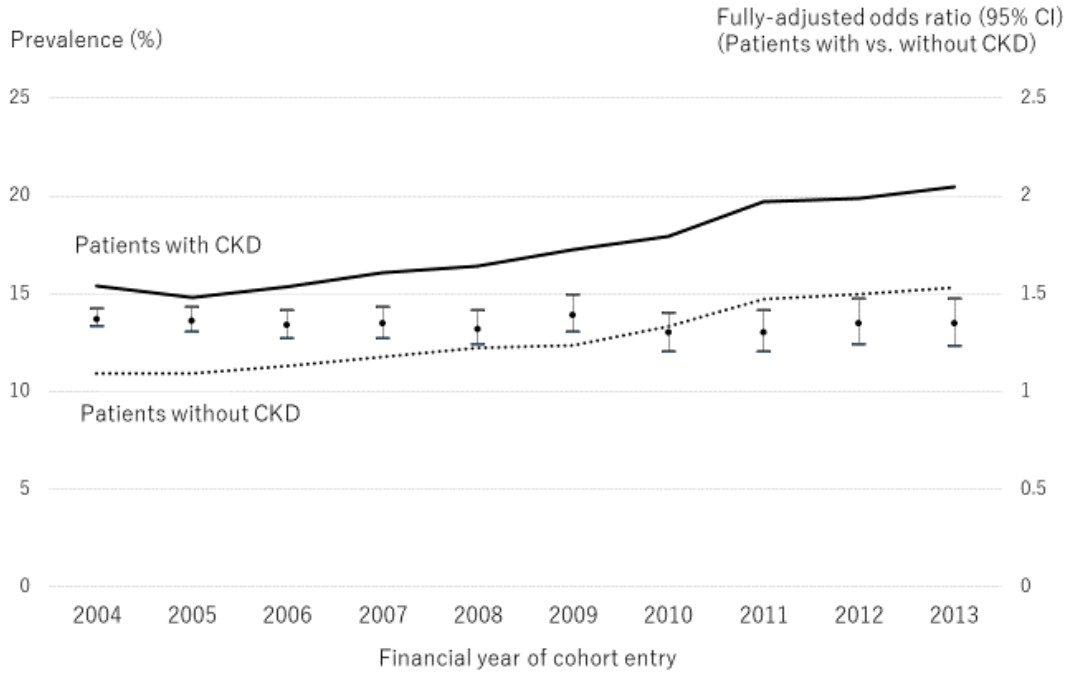
(i) Backgrounds and methods

In the published paper, I showed the overall prevalence of antidepressant users by CKD status at the time of cohort entry and estimated an adjusted odds ratio by assuming that the association between CKD and prevalence of antidepressant prescription was constant throughout the study period. Here, to examine the temporal trend, I show the prevalence of antidepressant prescription by financial year (i.e. from 1 April to 31 March) of cohort entry (i.e. the date of satisfying CKD definition for CKD patients, and the same date for matched controls without CKD) and test whether the adjusted odds ratio changed significantly over the study period. P value for trend was estimated by including an interaction term between CKD status and financial year (as a continuous variable) in the multivariable logistic regression model.

(ii) Results and discussions

The crude prevalence of patients with antidepressant prescribing gradually increased from 15.4% in 2004 to 20.5% in 2013 among patients with CKD, while it also increased from 10.9% in 2004 to 15.3% in 2013 among patients without known CKD (see the left axis and lines in **Figure 11** below). The fully-adjusted odds ratio (patients with versus without CKD) for the prevalence of antidepressant prescription was almost constant at around 1.35 (see the right axis and point estimates with CIs in **Figure 11**), with no statistically significant change over the ten years (P for trend = 0.318).

Figure 11. Prevalence of antidepressant prescription in patients with and without CKD and adjusted odds ratio by financial year of cohort entry



Abbreviations: CKD = chronic kidney disease; CI = confidence interval.
Note: The solid and dotted lines suggest the prevalence of antidepressant users at the time of cohort entry (i.e. the date of satisfying CKD definition for CKD patients, and the same date for matched controls without CKD) in patients with and without CKD, respectively, with the scales on the left axis. The point estimates and confidence intervals imply the fully-adjusted odds ratio comparing patients with and without CKD each year, with the scales on the right axis.

The upward trend in the prevalence of antidepressant prescription, regardless of CKD status, is in line with an English study showing that the number of antidepressant prescription constantly increased from 1998 to 2010 [127]. The strength of the association between CKD and prevalence of antidepressant prescription was almost constant over the ten years. However, because of its continuous increase in absolute number and proportion of antidepressant users, examining the safety of antidepressant use in patients with CKD seems to be becoming more and more important.

8.4. Chapter summary

CKD and antidepressant prescription

- This study examined the prevalence, incidence, indication, and choice of antidepressants in patients with CKD, as compared with those without known CKD in the general population matched for age, sex, general practice, and calendar time.

- The crude prevalence and incidence of antidepressant prescribing in patients with CKD were around one and half times as high as those without CKD.

- After adjusting for potential confounding factors (e.g. diabetes and heart failure), there was an independent association between CKD status and prevalence/incidence of antidepressant prescription.

- Indication and choice of antidepressant prescribing were similar between patients with and without CKD.

- There was an upward trend in the prevalence of antidepressant prescription over the ten-year study period, both in patients with and without CKD.

Chapter 9: Gastrointestinal bleeding risk of selective serotonin reuptake inhibitors by level of kidney function: a population-based cohort study (Paper 4)

9.1. Introduction

This chapter presents a cohort study estimating the GI bleeding risk of SSRIs by level of kidney function, accepted by *British Journal of Clinical Pharmacology* [128].

The main research question is: Is the risk of GI bleeding associated with SSRIs increased in patients with lower kidney function?

Briefly, I used the cohort established in **chapter 7**, including 242,349 patients with CKD (consisting of 172,555 patients with CKD stage 3a, 55,500 patients with CKD stage 3b, and 14,294 patients with CKD stage 4/5 at the time of cohort inclusion) and 242,349 patients without known CKD.

Exposure was time-dependent SSRI prescription, because SSRIs are frequently started and stopped in clinical care: a previous study in UK primary care suggested that, among older people with a diagnosis of depression, duration of antidepressant treatment per treatment episode was median 179 (IQR 56–528) days (including 90-day washout periods), and more than half of the study participants had two or more treatment episodes during follow-up [129]. Outcome was first hospitalisation for GI bleeding. I estimated the relative risk of GI bleeding associated with SSRIs (i.e. the fully-adjusted rate ratio between periods with and without SSRI prescription) and the excess risk of GI bleeding associated with SSRIs (i.e. the fully-adjusted rate difference between periods with and without SSRI exposure) by level of kidney function. Then, I tested whether the relative risk and excess risk increased as kidney function deteriorated.

Later in this chapter, I am showing an additional sensitivity analysis by including diagnoses of GI bleeding recorded in the CPRD (in addition to HES Admitted Patient Care).

9.2. Published paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Masao Iwagami
Principal Supervisor	Dorothea Nitsch
Thesis Title	Association between chronic kidney disease and mental health disorders and psychoactive drugs in the UK general po

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	British Journal of Clinical Pharmacology
Please list the paper's authors in the intended authorship order:	Masao Iwagami, Laurie A Tomlinson, Kathryn E Mansfield, Ian J Douglas, Liam Smeeth, Dorothea Nitsch
Stage of publication	**In press**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I planned the study, carried out the data extraction, cleaning, analysis, and drafted the manuscript.

Student Signature: [redacted] **Date:** 30/May/2018

Supervisor Signature: [redacted] **Date:** 30.5.18

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 2142–2151 2142

ORIGINAL ARTICLE

Gastrointestinal bleeding risk of selective serotonin reuptake inhibitors by level of kidney function: A population-based cohort study

Correspondence Masao Iwagami, MD, MPH, MSc, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. Keppel Street, London, WC1E 7HT, UK. Tel.: +44 (0)20 7636 8636; Fax: +44 (0)20 7436 5389; E-mail: masao.iwagami@lshtm.ac.uk

Received 27 November 2017; **Revised** 9 May 2018; **Accepted** 30 May 2018

Masao Iwagami, Laurie A. Tomlinson, Kathryn E. Mansfield, Ian J. Douglas, Liam Smeeth and Dorothea Nitsch

Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

Keywords additive interaction, gastrointestinal bleeding, kidney function, multiplicative interaction, selective serotonin reuptake inhibitor

AIM

To estimate the risk of gastrointestinal (GI) bleeding associated with serotonin reuptake inhibitors (SSRIs) by level of kidney function.

METHODS

We conducted a cohort study using the Clinical Practice Research Datalink linked to Hospital Episode Statistics. We identified patients with chronic kidney disease (CKD; estimated glomerular filtration rate $<$60 ml min^{-1} 1.73 m^{-2} for $\geq$3 months), and a comparison group of patients without it. Patients with CKD were further classified as stage 3a (eGFR 45–59 ml min^{-1} 1.73 m^{-2}), 3b (30–44 ml min^{-1} 1.73 m^{-2}) and 4/5 ($<$30 ml min^{-1} 1.73 m^{-2}). We excluded prevalent SSRI users at cohort entry. Exposure was time-dependent SSRI prescription and outcome was first hospitalization for GI bleeding. We estimated adjusted rate ratio (aRR) and rate difference (aRD) of GI bleeding comparing periods with and without SSRI prescription at each level of kidney function.

RESULTS

The aRRs and aRDs were: (i) no CKD (n = 202 121) aRR: 1.66 (95%CI 1.37–2.01), aRD: 2.0/1000 person–years (5.5 *vs.* 3.5/1000 person–years in period with and without SSRIs); (ii) CKD stage 3a (n = 153 316) aRR: 1.86 (1.62–2.15), aRD: 4.2/1000 person–years (8.3 *vs.* 4.1/1000 person–years); (iii) CKD stage 3b (n = 46 482) aRR: 1.61 (1.27–2.04), aRD: 4.8/1000 person–years (9.9 *vs.* 5.1/1000 person–years); and (iv) CKD stage 4/5 (n = 11 197) aRR: 1.84 (1.14–2.96), aRD: 7.9/1000 person–years (15.3 *vs.* 7.4/1000 person–years). While there was no evidence of increase in the aRR (P = 0.922), there was strong evidence that the aRD increased as kidney function deteriorated (P = 0.001).

CONCLUSIONS

While the relative risk was constant, the excess risk of GI bleeding associated with SSRIs markedly increased among patients with decreased kidney function.

DOI:10.1111/bcp.13660

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Previous studies have suggested that use of selective serotonin reuptake inhibitors (SSRIs) is associated with increased risk of gastrointestinal (GI) bleeding.
- Patients with decreased kidney function are known to have an increased risk of bleeding.
- However, no study has investigated the risk of GI bleeding associated with SSRIs at different levels of kidney function.

WHAT THIS STUDY ADDS

- We estimated the relative and absolute risks of GI bleeding associated with SSRI prescription at different levels of kidney function.
- While the relative risk of GI bleeding associated with SSRIs was similar at different levels of kidney function, the excess risk of GI bleeding associated with SSRIs increased as kidney function deteriorated.
- Therefore, we recommend careful use of SSRIs in patients with decreased kidney function.

Introduction

Chronic kidney disease (CKD) is a common condition in the community [1], and is independently associated with increased risk of bleeding in operative and nonoperative settings [2–4]. Gastrointestinal (GI) bleeding is the most common manifestation of bleeding [5].

Patients with CKD are known to have increased prevalence of mental-health problems such as depression and anxiety [6, 7]. Accordingly, our recent study suggested that patients with CKD (not on dialysis) have antidepressants prescribed more frequently than patients without it [8]. Selective serotonin reuptake inhibitors (SSRIs) are currently recommended as the first choice of drug therapy for depressed patients [9]. The number of SSRI prescriptions has been steadily increasing in the UK and US [10, 11].

There is concern regarding the bleeding risk associated with SSRIs, because SSRIs block serotonin reuptake in platelets and inhibit platelet aggregation [12, 13]. A number of studies have shown an association between the use of SSRIs and GI bleeding [14–24]. However, none of these studies focused on the risk of GI bleeding associated with SSRIs among patients with CKD. SSRI-associated GI bleeding is of particular concern among patients with CKD [25, 26], because: (i) CKD is itself a risk factor for GI bleeding [3]; and (ii) SSRIs may accumulate in patients with CKD due to reduced renal clearance and altered pharmacokinetics [27].

Despite these concerns, the absolute and relative risks of GI bleeding associated with SSRI use amongst patients with reduced kidney function have not been quantified. We therefore undertook a population-based study addressing this question in a large UK primary care database.

Methods

Data sources

The Clinical Practice Research Datalink (CPRD) is a database of routinely recorded primary care electronic health record data from 7% of the UK population [28]. The CPRD includes the following information: patient demographics, coded diagnoses (Read codes), prescriptions, laboratory test results, and referrals recorded by general practitioners (GPs). The CPRD is linked with other resources, including Hospital Episode Statistics (HES), Office for National Statistics mortality data and Index of Multiple Deprivation data. HES contains details of all hospital admissions to the National Health Service hospitals in England, and consists of primary and subsidiary diagnoses recorded during admission using the 10th revision of International Classification of Disease (ICD-10) codes [29]. Currently, around 400 general practices in CPRD (accounting for 75% of general practices in CPRD in England) have agreed to linkage with HES data for research purposes. Study approval was obtained from the ethics committee of the London School of Hygiene and Tropical Medicine (reference: 9196) and the Independent Scientific Advisory Committee, which oversees research involving CPRD data (Protocol 15_219R).

Study cohort

We used a matched cohort including 242 349 patients with CKD and 242 349 patients without it, which was established in our previous study for the prevalence and incidence of antidepressant prescribing by CKD status [8]. Using HES-linked CPRD between 1 April 2004 and 31 March 2014, we first identified adult patients with CKD (not on renal replacement therapy) based on two consecutive measurements of eGFR <60 ml min^{-1} 1.73 m^{-2} for $\geq$3 months [30] (Figure 1). Estimated GFR was calculated from serum creatinine values recorded in CPRD, using the Chronic Kidney Disease Epidemiology Collaboration equation [31]. Patients were eligible for cohort entry from the latest of: 1 April 2004, 1 year after practice registration (to allow GPs to record the past medical history of newly registered patients) or the date the patient's general practice reached CPRD's data quality standards [28]. Patients entered the cohort on the date when they first satisfied the CKD definition (i.e. second eGFR <60 ml min^{-1} 1.73 m^{-2}) after meeting the eligibility criteria. We then identified a comparison group of patients without known CKD from the remaining HES-linked CPRD population. To establish a balanced comparison group in terms of basic patient characteristics, we randomly selected a patient without known CKD with the same age, sex, general practice and calendar time (i.e. same date of cohort entry) as a patient with CKD.

Patients with CKD were further classified according to eGFR on the date of cohort entry: CKD stage 3a (eGFR 45–59 ml min^{-1} 1.73 m^{-2}), stage 3b (30–44 ml min^{-1} 1.73 m^{-2}), and stage 4 or 5 (<30 ml min^{-1} 1.73 m^{-2}) [30]. CKD stage

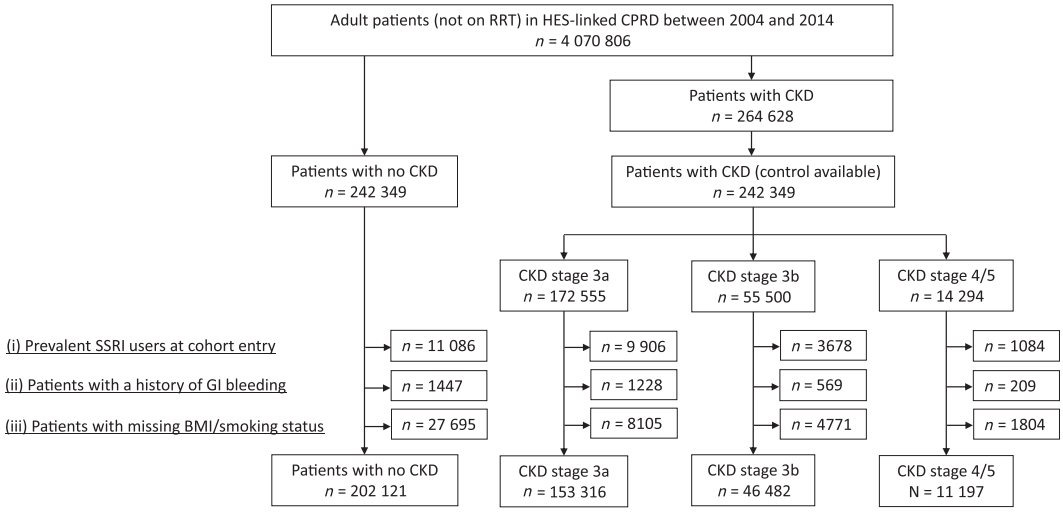


Figure 1

Flow chart for selecting the study participants. BMI = body mass index, CKD = chronic kidney disease, CPRD = Clinical Practice Research Datalink, GI = gastrointestinal, HES = Hospital Episode Statistics, RRT = renal replacement therapy, SSRI = selective serotonin reuptake inhibitor

was regarded as constant (i.e. non-time updated) during follow-up. We then excluded the following patients: (i) prevalent SSRI users (GI bleeding could occur shortly after SSRI initiation [17], therefore inclusion of prevalent SSRI users with drug tolerance may cause bias [32]); (ii) those with a history of GI bleeding (to capture new-onset GI bleeding more likely to be related to drug exposure); and (iii) those with missing values of smoking status and body mass index (BMI).

Exposure and outcome

SSRIs are frequently started and stopped in clinical care [33]. Our exposure of interest was therefore *time-dependent* prescription of SSRIs. The duration of each prescription was estimated by dividing the total number of tablets prescribed by the number of tablets to be taken each day (daily dose). When the daily dose or total number of tablets was missing (9.6% of the records), we imputed the median prescription duration (28 days). We assumed that patients were continuously exposed to SSRIs if there were no gaps of more than 30 days between the end of one prescription and the start of the next (to allow potential medication stockpiling or prescribing in secondary care) [14]. If there was no subsequent prescription of SSRIs, we considered patients could be influenced by the effect of SSRIs until 30 days after the end of the prescription. Thus, each episode of SSRI treatment started at the first SSRI prescription (as a new treatment episode) and continued until 30 days after a break in continuous prescribing of 30 days (or more). A patient could contribute multiple episodes of SSRI treatment during follow-up. In sensitivity analyses, we changed our assumption of a 30-day duration of periods between prescriptions and washout periods to 60 days and 90 days.

The outcome was the first hospitalization with a primary diagnosis of GI bleeding, based on a list of ICD-10 codes (Appendix S1). Patients were followed up until the earliest of: the outcome of interest, initiation of renal replacement therapy, death, change of general practice, last data collection from the practice or 31 March 2014.

Covariates

We considered the following potential confounders in the association between SSRI prescription and GI bleeding [14–24]: age and sex; ethnicity; socio-economic status; BMI; smoking status; comorbidities (diabetes mellitus, chronic liver disease, congestive heart failure, cancer, and rheumatoid arthritis); and prescribed drugs including anticoagulants, antiplatelet drugs (including aspirin), nonsteroidal anti-inflammatory drugs (excluding aspirin), oral corticosteroids, and acid-suppressing agents. We classified patients with no record of ethnicity as white, consistent with previous UK studies [34]. Socioeconomic status was assigned at an individual level, using quintiles of 2010 Office for National Statistics estimates of the Index of Multiple Deprivation (a composite area-level marker of deprivation) [35]. Smoking status and BMI were assigned using the data recorded closest to cohort entry and assumed to be constant during follow-up. We defined each comorbidity as present or absent based on recording of a relevant diagnostic code in CPRD on the day of, or prior to, cohort entry. For prescribed drugs, we used the same strategy as SSRIs by regarding them as *time-dependent* confounding factors.

Statistical analysis

We described baseline patient characteristics by level of kidney function. We showed the length of time people received an SSRI prescription and the time without, at each level of kidney function (i.e. no CKD, CKD stage 3a, stage 3b, and stage 4 or 5). We also showed the number of first hospitalizations due to GI bleeding, providing the crude incidence rate of the outcome by SSRI prescription status at each level of kidney function.

We conducted prespecified analyses using two common measures of effect to understand the GI bleeding risk

associated with SSRIs: risk ratio and risk difference [36]. First, we estimated an adjusted rate ratio for GI bleeding when prescribed an SSRI, compared to time not prescribed an SSRI, using *multiplicative* Poisson regression analyses. Multiplicative models assume that the risk of the outcome is multiplied by different risk factors. We established multiplicative Poisson models for hospitalization due to GI bleeding comparing periods with and without SSRI prescription at each level of kidney function, first adjusting for age and sex; and then further adjusting for ethnicity, socioeconomic status, BMI, smoking status, comorbidities, and prescribed drugs. We then conducted a test for multiplicative interaction (effect modification) between SSRI prescription and kidney function in the fully-adjusted model. A significant multiplicative interaction would suggest that the risk ratio (period with *vs*. without SSRI prescription) is different at different levels of kidney function. We estimated a multiplicative interaction *P*-value for trend, using the log-likelihood ratio test comparing the Poisson models with and without an interaction term between SSRI prescription status and kidney function.

Next, we estimated an adjusted rate difference (between period with and without SSRI prescription) for GI bleeding at each level of kidney function and tested whether the adjusted rate difference increased as kidney function deteriorated, using *additive* Poisson regression analyses. Additive models assume that risk differences from different risk factors are added together to estimate the risk of outcome [37] and, therefore, can directly test an additive interaction [38]. We established a fully-adjusted additive Poisson model for GI bleeding (Appendix S2 for more detail). We then calculated an adjusted incidence rate with or without SSRI prescription at each level of kidney function, by applying the average effect of each covariate on the risk of GI bleeding in the study population in the fully-adjusted additive Poisson model (Appendix S3 for more detail). Thus, the adjusted incidence rate in each group stratified by SSRI prescription status and level of kidney function represents a hypothetical incidence rate if the confounders (e.g. diabetes) are equally distributed between the groups. We then estimated an adjusted rate difference between the period with and without SSRI prescription at each level of kidney function. Finally, we conducted a test for additive interaction between SSRI prescription status and kidney function. A significant additive interaction would suggest that the risk difference (between period with and without SSRI prescription) is different at different levels of kidney function. We calculated an additive interaction *P*-value for trend, using the log-likelihood ratio test comparing the models with and without an interaction term between SSRI prescription and kidney function.

All the data management and statistical analyses were conducted using STATA version 14 (Stata Corp, Texas). A *P*-value of < 0.05 was inferred as statistically significant.

Subgroup analysis

We conducted *posthoc* subgroup analyses (separately) by SSRI dose and receptor affinity in the fully-adjusted multiplicative Poisson regression models. Based on the defined daily dose (DDD) of each SSRI (20 mg day^{-1} for citalopram, 10 mg day^{-1} for escitalopram, 20 mg day^{-1} for fluoxetine, 100 mg day^{-1} for fluvoxamine, 20 mg day^{-1} for paroxetine and 50 mg day^{-1} for sertraline) [39], we dichotomized the periods of SSRI prescription into two categories: periods of low dose (i.e. smaller daily dose than DDD), and periods of normal or high dose (i.e. same as or higher dose than DDD). Low and normal/high dose periods were compared to periods without SSRI prescription. For the serotonin receptor affinity subgroup analysis, we divided the periods of SSRI prescription into two categories [17]: SSRIs with intermediate affinity to the serotonin receptor (including citalopram, fluvoxamine and escitalopram), and those with high affinity (including fluoxetine, paroxetine and sertraline).

Results

Among 4 070 806 adult patients without renal replacement therapy [median age 39 years (interquartile range, IQR 27–56), male 48.8%] registered in HES-linked CPRD between 2004 and 2014, we identified 264 628 patients with CKD [median age 77 years (IQR 71–83), male 38.7%]. Of those with CKD, 242349 [92%; median age 76 years (IQR 70–82), male 39.3%] were matched with a patient without known CKD who had the same age, sex, general practice, and same date of cohort entry (Figure 1). After excluding (i) prevalent SSRI users at cohort entry, (ii) those with a history of GI bleeding and (iii) those with missing values of BMI and smoking status, there were 413 116 study participants including 202 121 patients without known CKD, 153316 patients with CKD stage 3a, 46 482 patients with CKD stage 3b, and 11 197 patients with CKD stage 4 or 5. The number of patients exposed to SSRIs during the study period was 16 911 (4.1% of patients without known CKD), 18 545 (12.1% of patients with CKD stage 3a), 5803 (12.5% of patients with CKD stage 3b) and 1063 (9.5% of patients with CKD stage 4 or 5), respectively. The patterns of prescribed SSRI and dose were similar at different levels of kidney function (Appendix S4). Patients with CKD were more likely to have a lower socioeconomic status, had a higher prevalence of many comorbidities and were more likely to be prescribed medications at baseline (Table 1).

In the total cohort, there were 7249 first hospitalizations due to GI bleeding during total follow up of 1 801 316 person–years [median follow-up length 4.0 years (IQR 1.7–6.8 years)]. Crude incidence rate for GI bleeding was generally higher among patients with more advanced CKD stages, and was higher during the period with SSRI prescription than the period without SSRI prescription at each level of kidney function (Table 2).

In the fully-adjusted multiplicative Poisson regression model, the adjusted rate ratio (period with *vs*. without SSRI prescription) was 1.66 [95% confidence interval (CI), 1.37–2.01] among patients with no CKD, 1.86 (1.62–2.15) among patients with CKD stage 3a, 1.61 (1.27–2.04) among patients with CKD stage 3b, and 1.84 (1.14–2.96) among patients with CKD stage 4 or 5 (Table 2). A test for multiplicative interaction in the fully-adjusted multiplicative Poisson model gave a *P*-value for trend of 0.922, suggesting that there is no evidence of increased relative risk of GI bleeding related to SSRI prescription among patients with more advanced CKD stages.

Table 1

Baseline characteristics of patients by level of kidney function

	Patients with no CKD (*N* = 202 121) *n* (%)	Patients with CKD stage 3a (*N* = 153 316) *n* (%)	Patients with CKD stage 3b (*N* = 46 482) *n* (%)	Patients with CKD s tage 4/5 (*N* = 11 197) *n* (%)
Age (years):				
<65	26 464 (13.1)	21 437 (14.0)	3835 (8.3)	1565 (14.0)
65–74	63 882 (31.6)	52 388 (34.2)	10 676 (23.0)	2292 (20.5)
75–84	86 433 (42.8)	63 509 (41.4)	22 241 (47.9)	4653 (41.6)
≥85	25 342 (12.5)	15 982 (10.4)	9730 (20.9)	2687 (24.0)
Sex (male)	81 861 (40.5)	62 828 (41.0)	17 928 (38.6)	5044 (45.1)
Ethnicity:				
White/not recorded	198 618 (98.3)	150 538 (98.2)	45 673 (98.3)	10 855 (97.0)
South Asian	1657 (0.8)	1552 (1.0)	444 (1.0)	164 (1.5)
Black	1089 (0.5)	687 (0.5)	194 (0.4)	121 (1.1)
Other ethnicity	757 (0.4)	539 (0.4)	171 (0.4)	57 (0.5)
Socioeconomic status:				
1 (least deprived)	47 706 (23.6)	34 538 (22.5)	9552 (20.6)	2083 (18.6)
2	51 542 (25.5)	38 806 (25.3)	11 362 (24.4)	2567 (22.9)
3	41 977 (20.8)	31 792 (20.7)	9749 (21.0)	2394 (21.4)
4	35 234 (17.4)	27 911 (18.2)	8860 (19.1)	2318 (20.7)
5 (most deprived)	25 662 (12.7)	20 269 (13.2)	6959 (15.0)	1835 (16.4)
Body mass index (kg m^{-2}):				
<18.5	6105 (3.0)	2590 (1.7)	1193 (2.6)	338 (3.0)
18.5–25	81 294 (40.2)	46 340 (30.2)	15 342 (33.0)	3898 (34.8)
≥25	76 780 (38.0)	61 231 (39.9)	17 618 (37.9)	3997 (35.7)
≥30	37 942 (18.8)	43 155 (28.2)	12 329 (26.5)	2964 (26.5)
Smoking status:				
Non-smoker	74 991 (37.1)	48 878 (31.9)	15 173 (32.6)	3636 (32.5)
Ex-smoker	96 231 (47.6)	86 433 (56.4)	25 597 (55.1)	6056 (54.1)
Current-smoker	30 899 (15.3)	18 005 (11.7)	5712 (12.3)	1505 (13.4)
Comorbidities:				
Diabetes mellitus	21 908 (10.8)	33 463 (21.8)	11 082 (23.8)	3205 (28.6)
Chronic liver disease	963 (0.5)	1068 (0.7)	348 (0.8)	95 (0.9)
Congestive heart failure	5873 (2.9)	10 700 (7.0)	6607 (14.2)	2344 (20.9)
Cancer	40 291 (19.9)	32 872 (21.4)	11 240 (24.2)	2864 (25.6)
Rheumatoid arthritis	3571 (1.8)	3667 (2.4)	1156 (2.5)	276 (2.5)
Prescribed drugs (at cohort entry)[a]:				
Antiplatelet drugs	46 531 (23.0)	55 929 (36.5)	19 082 (41.1)	4655 (41.6)
Anticoagulants	6672 (3.3)	10 120 (6.6)	3882 (8.4)	904 (8.1)
Non-steroidal anti-inflammatory drugs	14 084 (7.0)	14 245 (9.3)	4810 (10.4)	933 (8.3)
Oral corticosteroids	5343 (2.6)	6319 (4.1)	2432 (5.2)	673 (6.0)
Acid-suppressing agents	32 476 (16.1)	37 370 (24.4)	12 803 (27.5)	3472 (31.0)

CKD, chronic kidney disease.

[a]prescribed drugs were time-updated during the follow-up.

Table 2

Crude incidence rate by selective serotonin reuptake inhibitor prescription status and adjusted rate ratio for the first hospitalization due to gastrointestinal bleeding among patients with different levels of kidney function

	Length of follow-up (person–years)	Number of outcomes	Crude incidence rate (95%CI) (/1000 person–years)	Age- and sex-adjusted rate ratio (95% CI)	Fully-adjusted[a] rate ratio (95% CI)
Total in the cohort (*N* = 413 116)	1 801 316	7249	4.0 (3.9–4.1)	-	-
Among patients with no CKD (*N* = 202 121):					
Period without SSRI prescription	808 125	2413	3.0 (2.9–3.1)	1 (Ref.)	1 (Ref.)
Period with SSRI prescription	19 152	110	5.7 (4.8–6.9)	1.98 (1.64–2.40)	1.66 (1.37–2.01)
Among patients with CKD stage 3a (*N* = 153 316):					
Period without SSRI prescription	709 140	2962	4.2 (4.0–4.3)	1 (Ref.)	1 (Ref.)
Period with SSRI prescription	23 311	204	8.8 (7.6–10.0)	2.16 (1.88–2.49)	1.86 (1.62–2.15)
Among patients with CKD stage 3b (*N* = 46 482):					
Period without SSRI prescription	198 735	1174	5.9 (5.6–6.3)	1 (Ref.)	1 (Ref.)
Period with SSRI prescription	6904	73	10.6 (8.4–13.3)	1.85 (1.46–2.34)	1.61 (1.27–2.04)
Among patients with CKD stage 4/5 (*N* = 11 197):					
Period without SSRI prescription	34 894	295	8.5 (7.5–9.5)	1 (Ref.)	1 (Ref.)
Period with SSRI prescription	1055	18	17.1 (10.8–27.1)	2.10 (1.30–3.38)	1.84 (1.14–2.96)

CI = confidence interval, CKD = chronic kidney disease, SSRI = selective serotonin reuptake inhibitor.
[a]adjusted for age, sex, ethnicity, socio-economic status, body mass index, smoking status, comorbidities (diabetes mellitus, chronic liver disease, congestive heart failure, cancer, and rheumatoid arthritis), and prescribed drugs (antiplatelet drugs, anticoagulants, non-steroidal anti-inflammatory drugs, oral corticosteroids, and acid-suppressing agents).

In the fully-adjusted additive Poisson model (Appendix S2), we applied the average effect of each covariate on the risk of GI bleeding in the study population (Appendix S3) to estimate adjusted rates for GI bleeding by SSRI prescription status at each level of kidney function (Figure 2). The adjusted rate difference increased from 2.0/1000 person–years among patients with no CKD (due to the adjusted rate of 5.5 *vs*. 3.5/1000 person–years in period with and without SSRI prescription, respectively), to 4.2/1000 person–years among patients with CKD stage 3a (8.3 *vs*. 4.1/1000 person–years), to 4.8/1000 person–years among patients with CKD stage 3b (9.9 *vs*. 5.1/1000 person–years), and to 7.9/1000 person–years among patients with CKD stage 4/5 (15.3 *vs*. 7.4/1000 person–years). A test for additive interaction gave a *P*-value for trend of 0.001, suggesting that there is strong evidence of increased risk difference of GI bleeding related to SSRI prescription as kidney function deteriorates.

In sensitivity analyses, the results were similar after changing our assumption about the length of periods between prescriptions and washout periods of SSRI prescription from 30 days to 60 and 90 days (Appendix S5).

In subgroup analyses, at each level of kidney function, the 95% CIs of adjusted rate ratios for periods with low and normal/higher dose of SSRIs largely overlapped, as did the CIs for periods exposed to SSRIs with intermediate affinity and those for SSRIs with high affinity (Appendices S6 and S7).

Discussion

In this large population-based study, we demonstrated that the relative risk of GI bleeding associated with SSRI exposure (i.e. the fully-adjusted rate ratio between periods with and without SSRI prescription) was around 1.7 regardless of kidney function. However, we showed strong evidence that the excess risk of GI bleeding (i.e. the fully-adjusted rate difference between periods with and without SSRI exposure) increased substantially as renal function declined; ranging from 2.0/1000 person–years among patients with no CKD to 7.9/1000 person–years among patients with CKD stage 4/5.

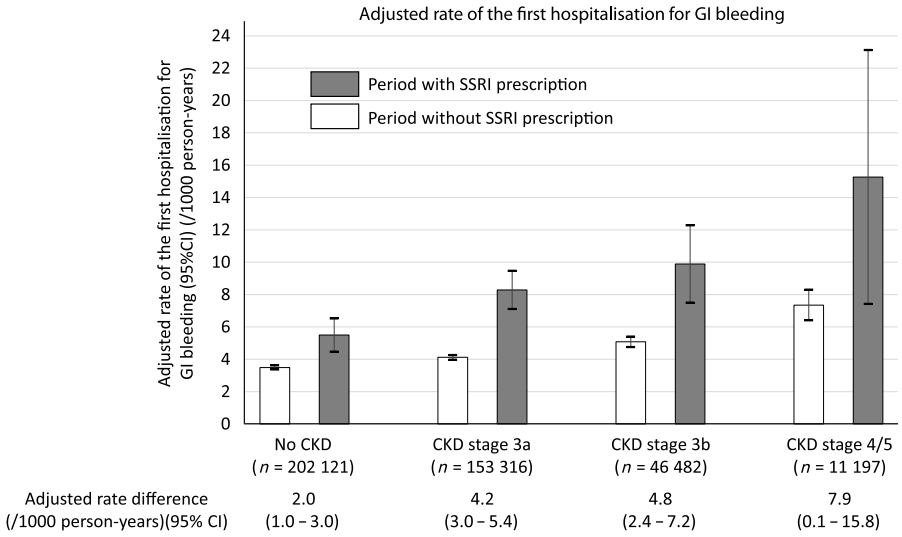


Figure 2

Adjusted rates and rate difference (between period with and without selective serotonin reuptake inhibitor prescription) for the first hospitalization due to gastrointestinal bleeding among patients with different levels of kidney function. CKD = chronic kidney disease, CI = confidence interval, GI = gastrointestinal, SSRI = selective serotonin reuptake inhibitor

To our knowledge, this is the first study examining the risk of GI bleeding associated with SSRIs at different levels of kidney function, and testing multiplicative and additive interactions between SSRI prescription and kidney function. The relative risk of GI bleeding due to SSRI prescription found in our study (around 1.7 regardless of kidney function) was consistent with that of a recent meta-analysis [13], which found a pooled relative risk of GI bleeding associated with SSRI use of 1.55 (95% CI, 1.35–1.78) across 22 studies. However, none of the studies included in the meta-analysis estimated an adjusted rate difference between patients (or periods of time) with and without SSRI prescription. This additional information is extremely useful. Because there are likely to be many confounders between patients (or periods of time) with and without SSRI prescriptions, a crude rate difference of the outcome between the groups may be substantially different from that attributable to the medication.

There are several reasons for being concerned about a potential amplification of the relative risk of GI bleeding associated with SSRIs among patients with decreased kidney function. Firstly, there is some evidence that renal clearance of SSRIs is decreased and their elimination half-life is prolonged in patients with decreased kidney function [27]. Other aspects of pharmacokinetics, such as liver metabolism and plasma protein binding, may also be altered among patients with CKD [40]. Furthermore, polypharmacy is common among patients with CKD [41], and, therefore, a potential drug–drug interaction between SSRIs and other drugs could increase the bleeding risk of SSRIs in the CKD population. However, in our real-world data, the relative risk of SSRIs was found to be similar irrespective of baseline kidney function, with no evidence of multiplicative interaction.

However, there was strong evidence that the excess risk of GI bleeding associated with SSRI exposure increased substantially as kidney function declined. This represents a *public-health interaction* [42]; a larger absolute risk increase means a larger number of patients experiencing the outcome, suggesting a larger public-health burden in the population. Even when the relative risk of a drug is constant across subgroups, the absolute number of patients who experience an adverse effect of the drug will be larger in a group with a high risk of the outcome. We formally tested if this was the case in our study by adjusting for comorbidities and medications, the distribution of which was different between the groups at each level of kidney function. Therefore, the observed graded increase in the excess risk of GI bleeding (i.e. adjusted rate difference between periods with and without SSRIs) can be ascribed to CKD itself, rather than conditions associated with CKD (e.g. diabetes, antiplatelet use). The pathophysiology of bleeding tendency in patients with CKD is multifactorial, including platelet dysfunction and vessel wall damage [43]. In addition, patients with CKD are more likely to have antecedents of GI bleeding, such as peptic ulcer disease [44].

We need to acknowledge several limitations of the study. Firstly, we defined CKD using strict criteria based on two serum creatinine results in CPRD, and identified a comparison group sampled from the rest of the general population. However, creatinine testing in primary care is not universal (currently, this is recommended and incentivized for people at risk of CKD [45, 46]), and therefore we may have misclassified some patients with unmeasured CKD into the comparison group. Nevertheless, because the prevalence of CKD (eGFR <60 ml min^{-1} 1.73 m^{-2}) identified in CPRD is known to be similar to that in a nationally-representative survey (Health Survey for England) [47], we expect that the proportion of unmeasured CKD is small in CPRD and people

without creatinine tests are unlikely to have CKD. It would have been inappropriate for us to use a comparison group sampled from people with creatinine testing in CPRD, because those with creatinine testing are a less healthy group of individuals who were not representative of the general population [48]. Secondly, consistent with a recent US study [3], our outcome definition was based on hospitalization recorded in linked hospital inpatient data, because the timing of GI bleeding recorded in HES is likely to be more accurate than that recorded in CPRD [49]. Moreover, we expect that hospitalization recorded with a primary diagnosis of GI bleeding will capture most severe cases. However, we lack greater detail such as endoscopy findings and requirement for blood transfusion. Nevertheless, we would not anticipate that these characteristics are substantially different between patients (or periods of time) with and without SSRI prescription. Thirdly, we adjusted for a variety of potential confounders of the relationship between SSRI prescription and GI bleeding, including demographics, socioeconomic and smoking status, BMI, comorbidities, and prescribed drugs [14–24]. However, confounding cannot be fully removed in observational studies. Unmeasured confounders could include over-the-counter aspirin and nonsteroidal anti-inflammatory drugs, as well as severity of depression or anxiety; although to our knowledge there is no clear evidence that mental-health conditions directly increase the risk of GI bleeding. Fourth, we excluded patients with missing records for BMI and smoking status, prioritizing the statistical adjustment for these important confounding factors over maximizing the sample size. Although the proportion of patients with missing data was not large [with 8.7% of study participants (42 375/484698)], the exclusion of these patients could affect the generalizability of our study results. This would imply that our study findings may be limited to people who are well monitored in primary care and thus have had these characteristics recorded. Finally, although the current study is one of the largest studies of the association between SSRIs and GI bleeding to date [13], the statistical power may still be insufficient in the group with the most severely reduced kidney function (as indicated by the wide confidence intervals). Study power also made it difficult to draw robust conclusions from our *posthoc* subgroup analyses by SSRI dose and receptor affinity.

It is recommended that any increase in the absolute risk of adverse outcomes should be taken into account in clinical decision-making [42]. In our study, we found that at more advanced stages of CKD, a larger number of patients suffered from GI bleeding potentially related to SSRIs. Therefore, the balance between risks and benefits of SSRI prescription may need to be considered differently in patients with decreased kidney function. Careful consideration of the potential risks of GI bleeding after SSRI prescription for patients with CKD is recommended.

Contributors

M.I. planned the study, carried out the data extraction, processing and analysis, and drafted the manuscript. D.N. and L.A.T. contributed substantially to the study design, interpretation of the results, and writing of the manuscript. K.M. supported the data processing and writing of the manuscript. I.J.D. and L.S. was involved in discussions of the analytical approach to this study and made comments on the results. All authors read and approved the final manuscript.

Competing Interests

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. At an individual level, M.I. is funded by Honjo International Scholarship Foundation, L.A.T. is funded by a Wellcome Intermediate Clinical Fellowship [WT101143MA] and L.S. was supported by a Wellcome Senior Research Fellowship in Clinical Science (grant number 098504/Z/12/Z). I.J.D. is funded by an unrestricted grant from, and holds stock in GlaxoSmithKline. The funders had no role in the execution of this study or interpretation of results. Other authors have no competing interests to declare.

References

1 McCullough K, Sharma P, Ali T, Khan I, Smith WC, MacLeod A, *et al*. Measuring the population burden of chronic kidney disease: a systematic literature review of the estimated prevalence of impaired kidney function. Nephrol Dial Transplant 2012; 27: 1812–21.

2 Acedillo RR, Shah M, Devereaux PJ, Li L, Iansavichus AV, Walsh M, *et al*. The risk of perioperative bleeding in patients with chronic kidney disease: a systematic review and meta-analysis. Ann Surg 2013; 258: 901–13.

3 Ishigami J, Grams ME, Naik RP, Coresh J, Matsushita K. Chronic kidney disease and risk for gastrointestinal bleeding in the community: the atherosclerosis risk in communities (ARIC) study. Clin J Am Soc Nephrol 2016; 11: 1735–43.

4 Molnar AO, Bota SE, Garg AX, Harel Z, Lam N, McArthur E, *et al*. The risk of major hemorrhage with CKD. J Am Soc Nephrol 2016; 27: 2825–32.

5 Jun M, James MT, Manns BJ, Quinn RR, Ravani P, Tonelli M, *et al*. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. BMJ 2015; 350: h246.

6 Lee YJ, Kim MS, Cho S, Kim SR. Association of depression and anxiety with reduced quality of life in patients with predialysis chronic kidney disease. Int J Clin Pract 2013; 67: 363–8.

7 Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, *et al*. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int 2013; 84: 179–91.

8 Iwagami M, Tomlinson LA, Mansfield KE, McDonald HI, Smeeth L, Nitsch D. Prevalence, incidence, indication, and choice of antidepressants in patients with and without chronic kidney disease: a matched cohort study in UK clinical practice research datalink. Pharmacoepidemiol Drug Saf 2017; 26: 792–801.

9 National Institute for Health and Care Excellence. Depression in adults: recognition and management. Available at https://www.nice.org.uk/guidance/cg90 (Accessed September 1, 2017).

10 Ilyas S, Moncrieff J. Trends in prescriptions and costs of drugs for mental disorders in England, 1998-2010. Br J Psychiatry 2012; 200: 393–8.

11 Hsiao CJ, Cherry DK, Beatty PC, Rechtsteiner EA. National Ambulatory Medical Care Survey: 2007 summary. Natl Health Stat Report 2010; 27: 1–32.

12 Serebruany VL. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? Am J Med 2006; 119: 113–6.

13 Jiang HY, Chen HZ, Hu XJ, Yu ZH, Yang W, Deng M, *et al*. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2015; 13: 42–50.

14 van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. BMJ 2001; 323: 655–8.

15 Meijer WE, Heerdink ER, Nolen WA, Herings RM, Leufkens HG, Egberts AC. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Arch Intern Med 2004; 164: 2367–70.

16 Lewis JD, Strom BL, Localio AR, Metz DC, Farrar JT, Weinrieb RM, *et al*. Moderate and high affinity serotonin reuptake inhibitors increase the risk of upper gastrointestinal toxicity. Pharmacoepidemiol Drug Saf 2008; 17: 328–35.

17 Wang YP, Chen YT, Tsai CF, Li SY, Luo JC, Wang SJ, *et al*. Short-term use of serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding. Am J Psychiatry 2014; 171: 54–61.

18 Dalton SO, Johansen C, Mellemkjaer L, Nørgård B, Sørensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Arch Intern Med 2003; 163: 59–64.

19 Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 2011; 343: d4551.

20 de Abajo FJ, Rodríguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. BMJ 1999; 319: 1106–9.

21 de Abajo FJ, García-Rodríguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. Arch Gen Psychiatry 2008; 65: 795–803.

22 Opatrny L, Delaney JA, Suissa S. Gastro-intestinal haemorrhage risks of selective serotonin receptor antagonist therapy: a new look. Br J Clin Pharmacol 2008; 66: 76–81.

23 Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. Clin Gastroenterol Hepatol 2009; 7: 1314–21.

24 Quinn GR, Singer DE, Chang Y, Go AS, Borowsky LH, Udaltsova N, *et al*. Effect of selective serotonin reuptake inhibitors on bleeding risk in patients with atrial fibrillation taking warfarin. Am J Cardiol 2014; 114: 583–6.

25 Hedayati SS, Yalamanchili V, Finkelstein FO. A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. Kidney Int 2012; 81: 247–55.

26 Jain N, Trivedi MH, Rush AJ, Carmody T, Kurian B, Toto RD, *et al*. Rationale and design of the chronic kidney disease antidepressant sertraline trial (CAST). Contemp Clin Trials 2013; 34: 136–44.

27 Baghdady NT, Banik S, Swartz SA, McIntyre RS. Psychotropic drugs and renal failure: translating the evidence for clinical practice. Adv Ther 2009; 26: 404–24.

28 Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, *et al*. Data resource profile: clinical practice research datalink (CPRD). Int J Epidemiol 2015; 44: 827–36.

29 Hospital episode statistics. Available at http://www.hscic.gov.uk/hes (Accessed September 1, 2017).

30 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013; 3: 1–150.

31 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al*. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–12.

32 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003; 158: 915–20.

33 Coupland CA, Dhiman P, Barton G, Morriss R, Arthur A, Sach T, *et al*. A study of the safety and harms of antidepressant drugs for older people: a cohort study using a large primary care database. Health Technol Assess 2011; 15: 1–202.

34 Hippisley-Cox J, Coupland C. Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores. BMJ 2014; 349: g4606.

35 Department for Communities and Local Government. English indices of deprivation 2010. Available at https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010 (Accessed September 1, 2017).

36 Rothman KJ, Greenland S, Lash T. Modern Epidemiology, 3rd edn. Philadelphia, US: Lippincott Williams & Wilkins, 2008.

37 Boshuizen HC, Feskens EJ. Fitting additive Poisson models. Epidemiol Perspect Innov 2010; 7: 4.

38 Greenland S. Additive risk versus additive relative risk models. Epidemiology 1993; 4: 32–6.

39 World Health Organization's Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2018. Available at https://www.whocc.no/atc_ddd_index/ (Accessed May 1, 2018).

40 Skorecki K, Chertow G, Marsden P, Taal M, Yu A. Brenner and Rector's The Kidney, 10th edn. Amsterdam, Netherlands: Elsevier, 2015.

41 Fraser SD, Roderick PJ, May CR, McIntyre N, McIntyre C, Fluck RJ, *et al*. The burden of comorbidity in people with chronic kidney disease stage 3: a cohort study. BMC Nephrol 2015; 16: 193.

42 Rothman KJ, Greenland S, Walker AM. Concepts of interaction. Am J Epidemiol 1980; 112: 467–70.

43 Kalman RS, Pedrosa MC. Evidence-based review of gastrointestinal bleeding in the chronic kidney disease patient. Semin Dial 2015; 28: 68–74.

44 Liang CC, Muo CH, Wang IK, Chang CT, Chou CY, Liu JH, *et al*. Peptic ulcer disease risk in chronic kidney disease: ten-year incidence, ulcer location, and ulcerogenic effect of medications. PLoS One 2014; 9: e87952.

45 National Institute for Health and Care Excellence. Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. Available at http://guidance. nice.org.uk/CG73/NICEGuidance/pdf/English (Accessed September 1, 2017).

46 Quality and outcomes framework. Available at http://www.hscic.gov.uk/qof (Accessed September 1, 2017).

47 Iwagami M, Tomlinson LA, Mansfield KE, Casula A, Caskey FJ, Aitken G, *et al*. Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared to national survey and registry data in the UK. Nephrol Dial Transplant 2017; 32 (suppl_2): ii142–50.

48 McDonald HI, Shaw C, Thomas SL, Mansfield KE, Tomlinson LA, Nitsch D. Methodological challenges when carrying out research on CKD and AKI using routine electronic health records. Kidney Int 2016; 90: 943–9.

49 Crooks CJ, Card TR, West J. Defining upper gastrointestinal bleeding from linked primary and secondary care data and the effect on occurrence and 28 day mortality. BMC Health Serv Res 2012; 12: 392.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13660/suppinfo

Appendix S1 List of International Classification of Diseases 10th Revision codes used to identify hospitalization due to gastrointestinal bleeding
Appendix S2 Equation to estimate the adjusted incidence rate for the first hospitalization due to gastrointestinal bleeding based on a fully-adjusted additive Poisson model
Appendix S3 Average effect of each covariate on the risk of gastrointestinal bleeding in the study population applied in the fully-adjusted additive Poisson model
Appendix S4 Patterns in the choice of selective serotonin reuptake inhibitors and daily dose among patients with different levels of kidney function
Appendix S5 Sensitivity analysis changing our assumption on the length of grace and washout periods of selective serotonin reuptake inhibitor prescription
Appendix S6 Subgroup analysis by dose of selective serotonin reuptake inhibitors
Appendix S7 Subgroup analysis by affinity of selective serotonin reuptake inhibitors to the serotonin receptor

Appendix 1. List of International Classification of Diseases 10th Revision codes used to identify hospitalisation due to gastrointestinal bleeding.

I850 Oesophageal varices with bleeding	K271 Peptic ulcer, site unspecified - Acute with perforation
K226 Gastro-oesophageal laceration-bleed syndrome	K272 Peptic ulcer, site unspecified - Acute with both bleed and perforation
K250 Gastric ulcer - Acute with bleed	K274 Peptic ulcer, site unspecified - Chronic or unspecified with bleed
K251 Gastric ulcer - Acute with perforation	K275 Peptic ulcer, site unspecified - Chronic or unspecified with perforation
K252 Gastric ulcer - Acute with both bleed and perforation	K276 Peptic ulcer, site unspecified - Chronic or unspecified with both bleed and perforation
K254 Gastric ulcer - Chronic or unspecified with bleed	K280 Gastrojejunal ulcer - Acute with bleed
K255 Gastric ulcer - Chronic or unspecified with perforation	K281 Gastrojejunal ulcer - Acute with perforation
K256 Gastric ulcer - Chronic or unspecified with both bleed and perforation	K282 Gastrojejunal ulcer - Acute with both bleed and perforation
K260 Duodenal ulcer - Acute with bleed	K284 Gastrojejunal ulcer - Chronic or unspecified with bleed
K261 Duodenal ulcer - Acute with perforation	K285 Gastrojejunal ulcer - Chronic or unspecified with perforation
K262 Duodenal ulcer - Acute with both bleed and perforation	K286 Gastrojejunal ulcer - Chronic or unspecified with both bleed and perforation
K264 Duodenal ulcer - Chronic or unspecified with bleed	K290 Acute haemorrhagic gastritis
K265 Duodenal ulcer - Chronic or unspecified with perforation	K920 Haematemesis
K266 Duodenal ulcer - Chronic or unspecified with both bleed and perforation	K921 Melaena
K270 Peptic ulcer, site unspecified - Acute with bleed	K922 Gastrointestinal bleed, unspecified

Appendix 2. Equation to estimate the adjusted incidence rate for the first hospitalisation due to gastrointestinal bleeding based on a fully-adjusted additive Poisson model.

For the fitting of the additive Poisson model, we used the following commands in STATA version 14 (Stata Corp, Texas):

(i) First, we generated a variable suggesting the observed rates of outcome in individual patients:

gen rate = outcome/y

(where **outcome** is a binary valuable for the first hospitalisation due to GI bleeding, and **y** suggests person-time-at-risk)

(ii) Second, we used the **glm** command with the options **f(p)** and **l(i)** to fit a linear Poisson model, by taking the observed rates (**rate**) as the dependent variable and declaring the person-time-at-risk (**y**) as an "**iweight**":

glm rate i.age i.sex i.ethnicity i.SES i.BMI i.smoker i.diabetes i.CLD i.CHF, i.cancer i.RA i.antiplatelet i.anticoagulant i.NSAIDs i.corticosteroid i.acidsuppressing i.SSRI#i.CKDstage [iweight=y], f(p) l(i)

(where **i.age** ~ **i.acidsuppressing** suggest confounding factors (categorical or binary variables), and **i.SSRI#i.CKDstage** suggests SSRI prescription status (i.e. period with or without SSRI) at each level of kidney function (i.e. no CKD, CKD stage 3a, CKD stage 3b, and CKD stage 4 or 5))

Based on the STATA output showing the coefficient (95% confidence interval [CI]) of each variable, the following equation was finally established:

Adjusted incidence rate for the first hospitalisation due to gastrointestinal bleeding (/1000 person-years)

= 0 × [if age <65] + 0.43 (95%CI, 0.24 – 0.62) × [if age 65-74] + 1.77 (95%CI, 1.55 – 1.99) × [if age 75-84] + 3.28 (95%CI, 2.86 – 3.70) × [if age ≥85]

+ 0.80 (95%CI, 0.62 – 0.97) × [if male]

+ 0 (reference) × [if ethnicity White/not-recorded] + 0.06 (95%CI, -0.75 – 0.88) × [if ethnicity South Asian] + 0.09 (95%CI, -1.16 – 1.34) × [if ethnicity Black] + 0.43 (95%CI, -0.98 – 1.83) × [if ethnicity others]

+ 0 (reference) × [if socio-economic status (SES) 1st group] + 0.19 (95%CI, -0.02 – 0.39) × [if SES 2nd group] + 0.19 (95%CI, -0.02 – 0.41) × [if SES 3rd group] + 0.66 (95%CI, 0.40 – 0.92) × [if SES 4th group] + 0.86 (95%CI, 0.56 – 1.15) × [if SES 5th group]

+ 0.95 (95%CI, 0.24 – 1.65) × [if body mass index (BMI) <18.5] + 0.13 (95%CI, -0.05 – 0.31) × [if BMI 18.5-25] + 0 × [if BMI ≥25] + 0.14 (95%CI, -0.06 – 0.34) × [if body mass index (BMI) ≥30]

+ 0.39 (95%CI, 0.16 – 0.63) × [if smoker]

+ 0.27 (95%CI, 0.01 – 0.53) × [if diabetes mellitus]

+ 6.27 (95%CI, 4.18 – 8.35) × [if chronic liver disease]

+ 1.78 (95%CI, 1.20 – 2.37) × [if congestive heart failure]
+ 0.98 (95%CI, 0.73 – 1.22) × [if cancer]
+ 0.59 (95%CI, -0.10 – 1.29) × [if rheumatoid arthritis]
+ 0.90 (95%CI, 0.68 – 1.12) × [if antiplatelet prescription]
+ 2.72 (95%CI, 2.12 – 3.31) × [if anticoagulant prescription]
+ 0.59 (95%CI, 0.27 – 0.92) × [if non-steroidal anti-inflammatory drug prescription]
+ 0.99 (95%CI, 0.37 – 1.62) × [if oral corticosteroid prescription]
+ 1.26 (95%CI, 1.00 – 1.52) × [if acid-suppressing agent prescription]
+ 0 × [if no chronic kidney disease (CKD) without selective serotonin reuptake inhibitor (SSRI) prescription] + 2.01 (95%CI, 0.98 – 3.04) × [if no CKD with SSRI prescription] + 0.62 (95%CI, 0.45 – 0.80) × [if CKD stage 3a without SSRI prescription] + 4.80 (95%CI, 3.61 – 5.99) × [if CKD stage 3a with SSRI prescription] + 1.59 (95%CI, 1.23 – 1.94) × [if CKD stage 3b without SSRI prescription] + 6.40 (95%CI, 4.00 – 8.79) × [if CKD stage 3b with SSRI prescription] + 3.86 (95%CI, 2.91 – 4.82) × [if CKD stage 4/5 without SSRI prescription] + 11.78 (95%CI, 3.92 – 19.63) × [if CKD stage 4/5 with SSRI prescription]
+ 0.54 (95%CI, 0.33 – 0.75) (i.e. constant)

Appendix 3. Average effect of each covariate on the risk of gastrointestinal bleeding in the study population applied in the fully-adjusted additive Poisson model.

	(A) Coefficient (95% CI) (estimated in Appendix 2)	Length of follow-up (person-years)	(B) Length of follow-up/ total observational period in the study population	Average effect in the study population = (A) × (B) (95% CIs are omitted)
Total observational period in the study population (N = 413,116)	-	1,801,316	-	-
Age <65	0	265,427	0.147	0 × 0.147 (=0)
Age 65-74	0.43 (0.24 – 0.62)	637,583	0.354	0.43 × 0.354
Age 75-84	1.77 (1.55 – 1.99)	738,822	0.410	1.77 × 0.410
Age ≥85	3.28 (2.86 – 3.70)	159,484	0.089	3.28 × 0.089
Sex (male)	0.80 (0.62 – 0.97)	705,263	0.392	0.80 × 0.392
Ethnicity White/not-recorded	0	1,770,994	0.983	0 × 0.983 (=0)
Ethnicity South Asian	0.06 (-0.75 – 0.88)	15,635	0.009	0.06 × 0.009
Ethnicity Black	0.09 (-1.16 – 1.34)	8,282	0.005	0.09 × 0.005
Ethnicity others	0.43 (-0.98 – 1.83)	6,406	0.004	0.43 × 0.004
Socio-economic status 1st group (least deprived)	0	424,096	0.235	0 × 0.235 (=0)
Socio-economic status 2nd group	0.19 (-0.02 – 0.39)	458,223	0.254	0.19 × 0.254
Socio-economic status 3rd group	0.19 (-0.02 – 0.41)	368,558	0.205	0.19 × 0.205
Socio-economic status 4th group	0.66 (0.40 – 0.92)	317,915	0.176	0.66 × 0.176
Socio-economic status 5th group (most deprived)	0.86 (0.56 – 1.15)	232,524	0.129	0.86 × 0.129
Body mass index <18.5	0.95 (0.24 – 1.65)	33,908	0.019	0.95 × 0.019
Body mass index 18.5-25	0.13 (-0.05 – 0.31)	621,647	0.345	0.13 × 0.345
Body mass index ≥25	0	716,744	0.398	0 × 0.398 (=0)
Body mass index ≥30	0.14 (-0.06 – 0.34)	429,017	0.238	0.14 × 0.238
Smoker	0.39 (0.16 – 0.63)	245,946	0.137	0.39 × 0.137
Diabetes mellitus	0.27 (0.01 – 0.53)	285,945	0.159	0.27 × 0.159

Chronic liver disease	6.27 (4.18 – 8.35)	8,929	0.005	6.27 × 0.005
Congestive heart failure	1.78 (1.20 – 2.37)	85,889	0.048	1.78 × 0.048
Cancer	0.98 (0.73 – 1.22)	335,372	0.186	0.98 × 0.186
Rheumatoid arthritis	0.59 (-0.10 – 1.29)	35,606	0.020	0.59 × 0.020
Antiplatelet drug prescription	0.90 (0.68 – 1.12)	530,433	0.294	0.90 × 0.294
Anticoagulant prescription	2.72 (2.12 – 3.31)	80,897	0.045	2.72 × 0.045
Non-steroidal anti-inflammatory drug prescription	0.59 (0.27 – 0.92)	159,598	0.089	0.59 × 0.089
Oral corticosteroid prescription	0.99 (0.37 – 1.62)	54,151	0.030	0.99 × 0.030
Acid-suppressing agent prescription	1.26 (1.00 – 1.52)	446,974	0.248	1.26 × 0.248

We applied these values in the equation in the Appendix 2 to calculate the adjusted incidence rate by SSRI prescription status at each level of kidney function.
For example, the adjusted incidence rate for the first hospitalisation due to gastrointestinal bleeding during SSRI prescription in the no CKD group (/1000 person-years)

= 0 × 0.147 + 0.43 (95%CI, 0.24 – 0.62) × 0.354 +1.77 (95%CI, 1.55 – 1.99) × 0.410 + 3.28 (95%CI, 2.86 – 3.70) × 0.089 + 0.80 (95%CI, 0.62 – 0.97) × 0.392 + 0 × 0.983 + 0.06 (95%CI, -0.75 – 0.88) × 0.009 + 0.09 (95%CI, -1.16 – 1.34) × 0.005 + 0.43 (95%CI, -0.98 – 1.83) × 0.004 + 0 × 0.235 + 0.19 (95%CI, -0.02 – 0.39) × 0.254 + 0.19 (95%CI, -0.02 – 0.41) × 0.205 + 0.66 (95%CI, 0.40 – 0.92) × 0.176 + 0.86 (95%CI, 0.56 – 1.15) × 0.129 + 0.95 (95%CI, 0.24 – 1.65) × 0.019 + 0.13 (95%CI, -0.05 – 0.31) × 0.345 + 0 × 0.398 + 0.14 (95%CI, -0.06 – 0.34)× 0.238 + 0.39 (95%CI, 0.16 – 0.63) × 0.137 + 0.27 (95%CI, 0.01 – 0.53)× 0.159 + 6.27 (95%CI, 4.18 – 8.35) × 0.005 + 1.78 (95%CI, 1.20 – 2.37) × 0.048 + 0.98 (95%CI, 0.73 – 1.22)× 0.186 + 0.59 (95%CI, -0.10 – 1.29) × 0.020 + 0.90 (95%CI, 0.68 – 1.12) × 0.294 + 2.72 (95%CI, 2.12 – 3.31) × 0.045 + 0.59 (95%CI, 0.27 – 0.92)× 0.089 + 0.99 (95%CI, 0.37 – 1.62) × 0.030 + 1.26 (95%CI, 1.00 – 1.52) × 0.248
+ 2.01 (95%CI, 0.98 – 3.04) × 1 (in the group of “no CKD with SSRI prescription”)
+ 0.54 (95%CI, 0.33 – 0.75) (i.e. constant)
= 5.50 (95%CI, 4.47 - 6.52)

Appendix 4. Patterns in the choice of selective serotonin reuptake inhibitors and daily dose among patients with different levels of kidney function.

	No CKD (N = 16,911)		CKD stage 3a (N = 18,545)		CKD stage 3b (N = 5,803)		CKD stage 4/5 (N = 1,063)	
	Total number of prescription in the group†, n (%)	Dose direction, median [IQR] (mg/day)	Total number of prescription in the group†, n (%)	Dose direction, median [IQR] (mg/day)	Total number of prescription in the group†, n (%)	Dose direction, median [IQR] (mg/day)	Total number of prescription in the group†, n (%)	Dose direction, median [IQR] (mg/day)
Citalopram	157,474 (63.7)	20 [10 – 20]	213,068 (65.9)	20 [10 – 20]	69,293 (65.8)	20 [10 – 20]	11,829 (72.4)	20 [10 – 20]
Escitalopram	14,174 (5.7)	10 [5 – 10]	13,833 (4.3)	10 [5 – 10]	4,826 (4.6)	10 [5 – 10]	588 (3.6)	10 [5 – 10]
Fluoxetine	33,234 (13.5)	20 [20 – 20]	44,475 (13.8)	20 [20 – 20]	15,778 (15.0)	20 [20 – 20]	1,898 (11.6)	20 [20 – 20]
Fluvoxamine	51 (<0.1)	50 [50 – 50]	90 (<0.1)	100 [50 – 100]	<5 (<0.1)	n/a	<5 (<0.1)	n/a
Paroxetine	7,565 (3.1)	20 [20 – 20]	6,711 (2.1)	20 [20 – 20]	2,173 (2.1)	20 [20 – 20]	233 (1.4)	20 [20 – 20]
Sertraline	34,600 (14.0)	50 [50 – 100]	45,207 (14.0)	50 [50 – 100]	13,311 (12.6)	50 [50 – 100]	1,784 (10.9)	50 [50 – 100]
Total	247,098 (100)		323,384 (100)		105,384 (100)		16,332 (100)	

Abbreviations: CKD = chronic kidney disease; IQR = interquartile range.

†counted as one per doctor visit.

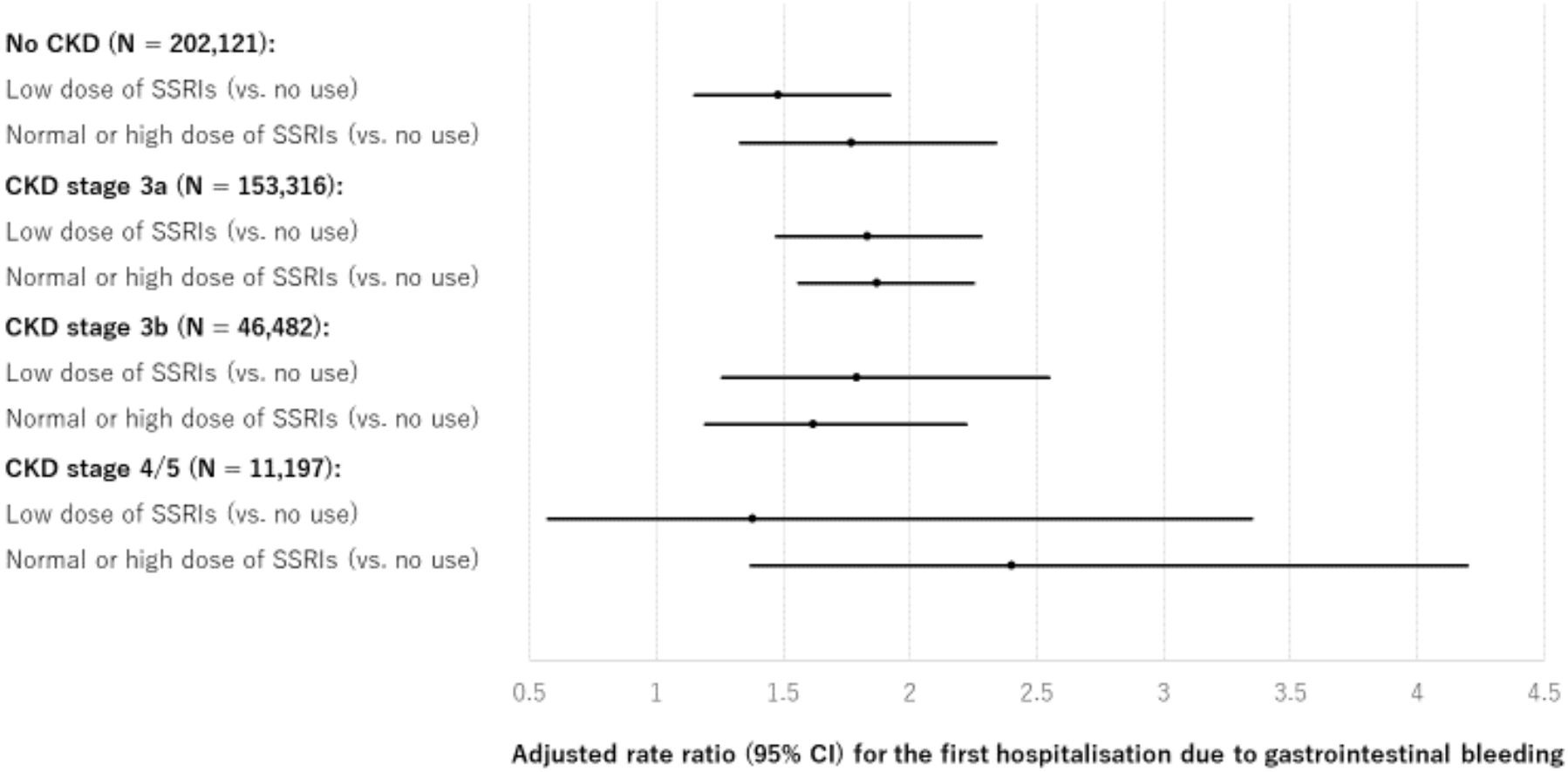
Appendix 5. Sensitivity analysis changing our assumption on the length of grace and washout periods of selective serotonin reuptake inhibitor prescription.

	Adjusted rate ratio (95% CI) (period with versus without SSRI prescription)					Adjusted rate difference (95% CI) (between period with and without SSRI prescription)				
Length of grace and washout periods of SSRI prescription	No CKD	CKD stage 3a	CKD stage 3b	CKD stage 4/5	p-trend	No CKD	CKD stage 3a	CKD stage 3b	CKD stage 4/5	p-trend
30 days (main analysis)†	1.66 (1.37-2.01)	1.86 (1.62-2.15)	1.61 (1.27-2.04)	1.84 (1.14-2.96)	0.922	2.0 (1.0-3.0)	4.2 (3.0-5.4)	4.8 (2.4-7.2)	7.9 (0.1-15.8)	0.001
60 days	1.67 (1.39-2.02)	1.80 (1.56-2.07)	1.68 (1.33-2.10)	1.88 (1.18-2.99)	0.801	2.0 (1.0-3.1)	3.9 (2.8-5.0)	5.1 (2.6-7.5)	8.1 (0.3-15.9)	<0.001
90 days	1.68 (1.40-2.02)	1.78 (1.54-2.04)	1.67 (1.33-2.09)	2.03 (1.30-3.16)	0.228	2.2 (1.2-3.2)	4.0 (2.9-5.1)	5.1 (2.7-7.5)	9.8 (1.8-17.8)	<0.001

Abbreviations: CKD = chronic kidney disease; CI = confidence interval; SSRI = selective serotonin reuptake inhibitor.

†We assumed that patients were continuously exposed to SSRIs if there were no gaps of more than 30 days between the end of one prescription and the start of the next (to allow potential medication stockpiling or prescribing in secondary care). If there was no subsequent prescription of SSRIs, we considered patients could be influenced by the effect of SSRIs until 30 days after the end of the prescription.

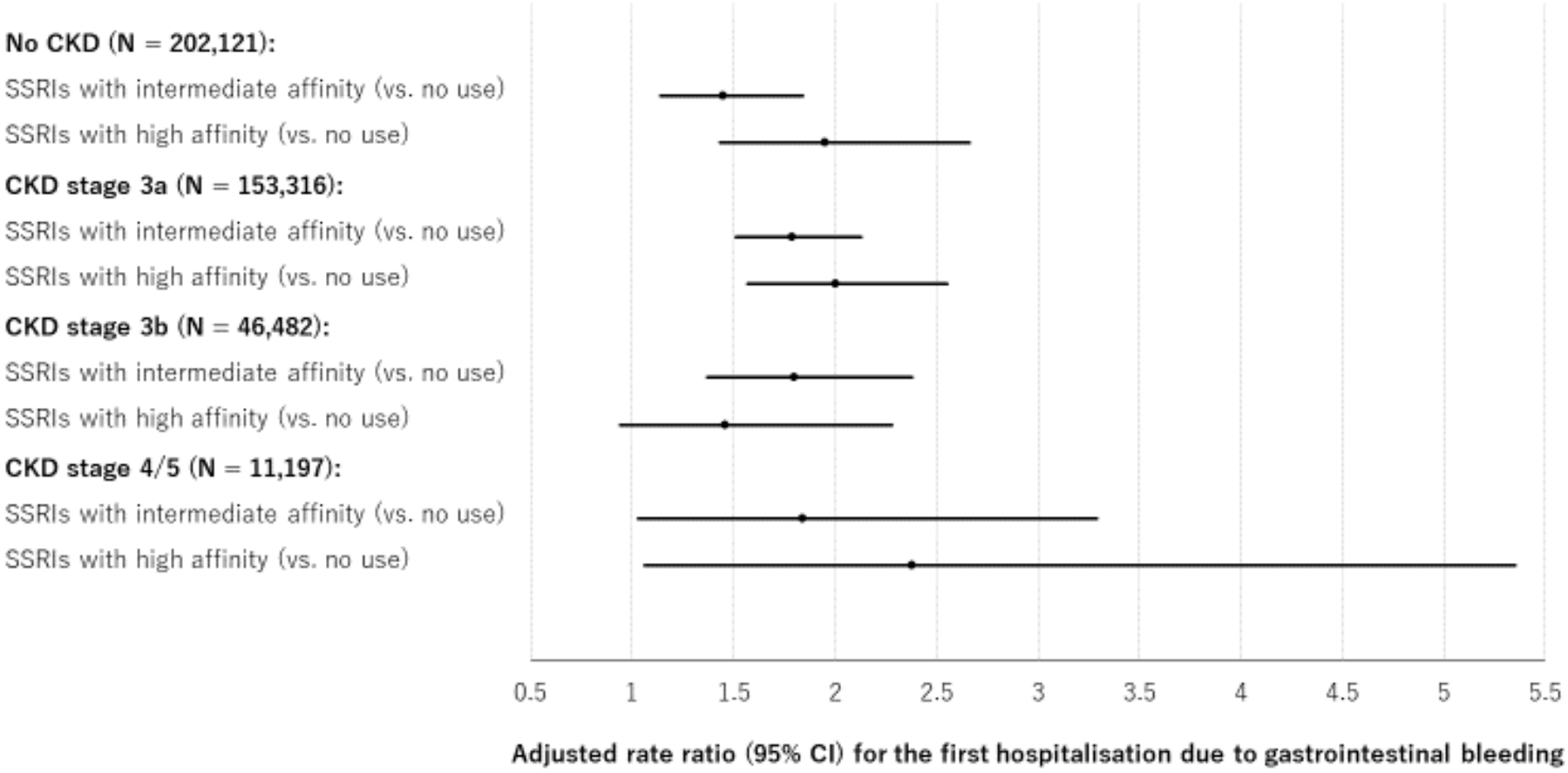
Appendix 6. Subgroup analysis by dose of selective serotonin reuptake inhibitors.



Abbreviations: CKD = chronic kidney disease; CI = confidence interval; SSRI = selective serotonin reuptake inhibitor.

Note: Based on the defined daily dose (DDD) of each SSRI (20 mg/day for citalopram, 10 mg/day for escitalopram, 20mg/day for fluoxetine, 100 mg/day for fluvoxamine, 20mg/day for paroxetine, and 50mg/day for sertraline), we dichotomised the periods of SSRI prescription into two groups: low dose period (i.e. smaller daily dose than DDD) and normal or high dose period (i.e. same as or higher dose than DDD).

Appendix 7. Subgroup analysis by affinity of selective serotonin reuptake inhibitors to the serotonin receptor.



Abbreviations: CKD = chronic kidney disease; CI = confidence interval; SSRI = selective serotonin reuptake inhibitor.
Note: SSRIs with intermediate affinity include citalopram, escitalopram, and fluvoxamine, whereas SSRIs with high affinity include fluoxetine, paroxetine, and sertraline.

9.3. Additional data and discussions

Further to the results and discussions presented in the published paper, here I show an additional sensitivity analysis to treat potential uncertainties of the data in the CPRD and HES.

9.3.1. Sensitivity analysis including GI bleeding diagnoses recorded in the CPRD

(i) Backgrounds and methods

In the main analysis, I focused on GI bleeding episodes requiring hospitalisation recorded in HES Admitted Patient Care. Episodes of hospitalisation are also supposed to be recorded in the CPRD, but may be less accurate than HES, because practice staff retrospectively enter the admission episode into the system based on a letter from the hospital.

Indeed, a previous validation study on myocardial infarction suggested that some hospitalisation episodes in HES were not recorded in the CPRD [130]. In addition, there was a time lag between the date of event retrospectively recorded in the CPRD and the date of admission in HES in many cases with myocardial infarction. Provided that most patients with myocardial infarction are smoothly sent to the hospital, the retrospectively recorded event date was probably inaccurate in the CPRD. Furthermore, there were some cases which were recorded in neither of HES nor the disease registry (Myocardial Ischaemia National Audit Project). Although a possibility remains that HES and the registry were incomplete, it is likely that the CPRD included suspected cases or a previous history of myocardial infarction.

I anticipated that misreporting of GI bleeding episodes is also possible in the CPRD. A previous study defined the GI bleeding outcome as hospitalisations recorded in HES only [126]. Therefore, I took the same approach to define the GI bleeding outcome in the main analysis.

However, different from myocardial infarction, some GI bleeding cases may be just mild and do not require hospitalisation [131]. It is also possible that there is a true time lag between the onset of GI bleeding and hospital admission. Therefore, in a sensitivity analysis, I defined the GI bleeding outcome as the diagnoses of GI bleeding recorded either in HES Admitted Patient Care or CPRD (whichever occurred first). Diagnosis codes (Read codes) suggesting GI bleeding are shown in **Appendix C**.

(ii) Results and discussions

Overall, by including the diagnoses suggestive of GI bleeding recorded in the CPRD, the number of outcomes slightly increased from 7,249 to 8,432 among 413,116 study participants. Accordingly, the adjusted rate ratio and adjusted rate difference changed to some extent in each kidney function group (see **Table 14** below). However, the overall conclusion (i.e. the relative risk of GI bleeding associated with SSRIs was constant, while the excess risk of GI bleeding associated with SSRIs was significantly increased among patients with lower kidney function) did not change.

The inclusion of GI bleeding diagnoses in the CPRD (in addition to the hospitalisation episodes in HES Admitted Patient Care) to define the study outcome may have both merits and demerits. Although more comprehensive assessment of the associating between SSRIs and GI bleeding (including mild GI bleeding cases not requiring hospitalisation) may be achieved, some of these diagnoses in the CPRD may be given to suspected cases or for justifying the endoscopic examination. Therefore, misclassification of the outcome status is more likely by the use of records in the CPRD. However, importantly, the extent of increase in the number of outcomes was found to be small, and the overall conclusion did not change with and without the inclusion of GI bleeding diagnoses in the CPRD.

Table 14. Sensitivity analysis including GI bleeding diagnoses recorded in the CPRD

	Main analysis (in which the study outcome was defined as hospitalisation with GI bleeding recorded in HES)					Sensitivity analysis (in which the study outcome was defined as hospitalisation with GI bleeding in HES or GI bleeding diagnosis recorded in the CPRD, whichever occurred first)				
	No CKD	CKD stage 3a	CKD stage 3b	CKD stage 4/5	p-trend	No CKD	CKD stage 3a	CKD stage 3b	CKD stage 4/5	p-trend
Number of patients	202,121	153,316	46,482	11,197		202,121	153,316	46,482	11,197	
Number of outcomes	2,523	3,166	1,247	313		2,885	3,664	1,504	379	
Adjusted rate ratio (95% CI)	1.66 (1.37–2.01)	1.86 (1.62–2.15)	1.61 (1.27–2.04)	1.84 (1.14–2.96)	0.922	1.87 (1.58–2.21)	1.98 (1.75–2.25)	1.92 (1.57–2.33)	1.92 (1.26–2.92)	0.873
Adjusted rate difference (95% CI)	2.0 (1.0–3.0)	4.2 (3.0–5.4)	4.8 (2.4–7.2)	7.9 (0.1–15.8)	0.001	2.4 (1.3–3.4)	4.5 (3.4–5.7)	6.8 (4.2–9.4)	8.4 (0.5–16.4)	<0.001

Abbreviations: CKD = chronic kidney disease; CI = confidence interval; CPRD = Clinical Practice Research Datalink; GI = gastrointestinal; HES = Hospital Episode Statistics.

9.4. Chapter summary

GI bleeding risk of SSRIs by kidney function

- This study estimated the relative and excess risks of GI bleeding associated with SSRI prescription at different levels of kidney function, and tested whether there was an interaction (effect modification) between baseline kidney function and the GI bleeding risk of SSRIs in multiplicative and additive scales.

- The relative risk of GI bleeding associated with SSRIs (i.e. the fully-adjusted rate ratio between periods with and without SSRI prescription) was around 1.7 regardless of kidney function, with no evidence of multiplicative interaction.

- The excess risk of GI bleeding associated with SSRIs (i.e. the fully-adjusted rate difference between periods with and without SSRI prescription) increased substantially as renal function declined, with strong evidence of additive interaction.

- Due to the increase in the excess risk of GI bleeding associated with SSRIs among patients with lower kidney function, careful use of SSRIs may be recommended for patients with decreased kidney function.

Chapter 10. Overall discussions and conclusions

10.1. Summary of main findings

In this thesis, I examined the associations between CKD and both mental health disorders and psychoactive drugs in the UK general population, using a large linked primary care database. To fill the gap between what is known and what is unknown in this field, I focused on two main topics: (i) the association between SMI (with and without a history of lithium use) and CKD, and (ii) the association between CKD and antidepressants (mainly prescribed for common mental health disorders such as depression and anxiety) and associated adverse outcomes (for which I chose the GI bleeding risk of SSRIs as an example).

I first conducted a cross-sectional population-level validation study comparing prevalence estimates of decreased kidney function (defined as the most recent eGFR prior to 31 March 2014 of <60 ml/min/1.73 m^2), CKD (defined as two or more consecutive measurements of <60 ml/min/1.73 m^2 for ≥3 months in the past five years) and RRT in the CPRD population with the nationally representative statistics (Health Survey for England 2009/2010 and UK Renal Registry 2014). Findings suggested that most patients with CKD and RRT are probably captured in the current CPRD, although a concern remained that patients with a single time-point decreased kidney function and those satisfying the CKD criteria in the CPRD may be slightly different populations.

Secondly, I conducted a cross-sectional study on the association between SMI and CKD. Patients with SMI, with or without a history of lithium prescription, had a higher prevalence of both CKD and RRT than the general population, and the association remained after adjusting for patients' characteristics and known CKD risk factors. Subsequent analyses suggested that the proportion of patients receiving potentially beneficial drugs for CKD (ACEI/ARBs for patients with proteinuria, and statins) might be lower in CKD patients with SMI than those without SMI.

Thirdly, I conducted a matched cohort study comparing the prevalence and incidence of antidepressant prescription between patients with and without CKD (matched for age, sex, general practice, and calendar time). Patients with CKD were approximately one and a half times more likely to receive antidepressants than matched patients without known CKD.

Regardless of CKD status, SSRIs were predominantly prescribed for depression or anxiety, while tricyclic antidepressants were prescribed for neuropathic pain or other reasons.

Finally, I estimated the GI bleeding risk of SSRIs by level of kidney function (i.e. no CKD, CKD stage 3a, stage 3b, and stage 4/5 at baseline) and tested whether the relative risk (i.e. the fully-adjusted rate ratio between periods with and without SSRI prescription) and excess risk associated with SSRIs (i.e. the fully-adjusted rate difference between periods with and without SSRI exposure) increase as baseline kidney function declines. The relative risk for GI bleeding associated with SSRIs was constant at around 1.7, regardless of baseline kidney function, and with no evidence of multiplicative interaction. Meanwhile, the excess risk for GI bleeding risk associated with SSRIs increased markedly as baseline kidney function deteriorated, with strong evidence of additive interaction.

10.2. Implications for clinical practice

10.2.1. Greater awareness is needed for the burden of CKD in patients with SMI

Paper 2 (SMI and CKD) identified the burden of CKD among patients with SMI. This may in part explain the fact that people with SMI tend to have a shorter life expectancy than the general population by around 10–20 years [27-32]. The mainstream of CKD-related care consists of early detection and prevention of CKD progression by intervening in modifiable risk factors (e.g. better control of diabetes, smoking cessation), and treatment of comorbidities such as high blood pressure and dyslipidemia. Subsequent analysis determined that, although the recognition of CKD (defined as receiving records of diagnostic Read codes suggesting CKD) and management of blood pressure in CKD patients with SMI were as good as for CKD patients in the general population, the proportion of people receiving potentially beneficial drugs for patients with CKD (i.e. ACEI/ARBs for patients with proteinuria, and statins) was lower in CKD patients with SMI than in those without SMI. Thus, greater awareness of the burden of CKD in patients with SMI (by GPs, clinical staff, patients, and patients' family) may be important to improve the intervention associated with CKD in patients with SMI.

10.2.2. Risk-benefit balance of antidepressants in patients with CKD may be different from the general population

Paper 3 (CKD and antidepressant prescription) demonstrated that patients with CKD are around one and a half times more likely to receive antidepressants than those without CKD, whereas Paper 4 (GI bleeding risk of SSRIs by kidney function) suggested that the GI bleeding risk of SSRIs (a good example of serious adverse outcomes associated with antidepressants) is increased in absolute terms among patients with lower kidney function.

The present PhD was not able to assess the benefit of antidepressants in patients with CKD, because there was no valid way of ascertaining the temporal change in the degree of anxiety and depressive symptoms via the CPRD. Therefore, the risk-benefit balance or cost-effectiveness of antidepressants could not be assessed in this PhD only. Ultimately, the decision of whether or not to use antidepressants for CKD patients with depression and anxiety should be based on the risk-benefit balance or cost-effectiveness of antidepressants in this population.

Meanwhile, a recent RCT examined the efficacy of antidepressants among patients with CKD (stages 3 to 5) for the first time [69]. This randomised, double-blind, placebo-controlled trial, which involved 201 patients with non-dialysis-dependent CKD (stages 3 to 5), found that 12 weeks of treatment with normal (50 mg/day) to higher dose (up to 200 mg/day) of sertraline (an SSRI with the most favourable balance between benefits, acceptability, and acquisition cost, according to a meta-analysis of RCTs assessing 12 antidepressants in the general population [132]) did not significantly improve depressive symptoms; the QIDS-SR16 score changed by -4.1 in the sertraline group and by -4.2 in the placebo group (between-group difference 0.1 [95% CI, -1.1 to 1.3]; $P = 0.82$). The authors noted that one of the reasons for this lack of efficacy could be that depression comorbid with CKD is a different clinical entity than major depressive disorder among those without comorbidity. It should be noted that, although the study was conducted based on a reasonable sample size calculation to identify a clinically meaningful difference between the sertraline and placebo groups [69], the study might be still underpowered and not long enough.

Although careful interpretation of this RCT and further research (e.g. a larger RCT assessing a different SSRI) is needed, the current best available evidence indicates that the risk-benefit balance of SSRIs for depression may be leaning toward the risk side in patients with CKD, compared to the general population. Therefore, careful use of SSRIs may be generally recommended in patients with decreased kidney function.

10.3. Implications for research

10.3.1. The association between SMI and CKD should be further explored

Paper 2 (SMI and CKD) was only a snapshot of the association between SMI and CKD in a cross-sectional study. To better indicate a causal link between SMI and CKD, a cohort study may be warranted. For example, a matched cohort study comparing the rate of kidney function decline in patients with and without SMI would better indicate causality. Furthermore, subgroup analyses in the SMI population would enable identification of a particularly high-risk group for kidney function decline. However, in order to conduct such a study, a method to appropriately estimate the rate of kidney function decline needs to be established in the CPRD.

Another important question concerns the impact of stopping lithium on subsequent kidney function decline and the incidence of ESRD. Currently, there is marked variation in practice, with some nephrologists recommending continued treatment, while others choose to prioritise mental health. A cohort study, including patients stopping lithium and those continuing it, may be warranted to examine the impact of lithium cessation on the subsequent trajectory of kidney function, stratified by the level of kidney function at the time of lithium cessation.

10.3.2. Further research is needed for the appropriate use of antidepressant in patients with CKD

Many questions remain regarding the appropriate use of antidepressants in patients with CKD. Apart from depression and anxiety, Paper 3 (CKD and antidepressant prescription) suggested that many antidepressants may be prescribed as off-label in real-world clinical practice (e.g. amitriptyline for chronic pain), regardless of CKD status. This is in line with findings of a recent Canadian descriptive study of antidepressant prescriptions from an indication-based electronic prescribing system [133]. The authors of the Canadian study suggested that these indications were usually not supported by strong scientific evidence [133]. As such, the risk-benefit balance of off-label use of antidepressant remains unknown in general, let alone among patients with CKD.

In addition, the recently updated NICE guidance 2017 newly added mirtazapine (a noradrenergic and specific serotonergic antidepressant) as the first-line pharmacological

treatment for depression [134], although the previous NICE guidance 2009 included only SSRIs as the first-line [135]. Therefore, while mirtazapine prescription was uncommon in Paper 3 (CKD and antidepressant prescription) covering from 2004 to 2014 (5.6% and 5.5% of the choice to initiate antidepressants in patients with and without CKD, respectively), it is possible that mirtazapine prescription starts to increase in UK primary care. However, according to the British National Formulary, renal clearance of mirtazapine is reduced by 30% if eGFR less than 40 mL/min/1.73 m^2, and therefore should be used with caution in patients with CKD [90]. Although the current PhD was not able to compare the risk of serious adverse outcomes between individual SSRIs and mirtazapine among patients with CKD due to a lack of statistical power, a future study may need to assess the comparative risk of mirtazapine use in patients with CKD.

10.4. Strengths

There are several strengths of the present PhD, which are mainly associated with the use of the CPRD. Here, I briefly summarise what I have discussed in each paper.

10.4.1. Population representativeness

This PhD has placed a high level of importance on describing the burden of a disease or drug in a certain population (i.e. the burden of CKD in the SMI population, the burden of antidepressants in the CKD population) rather than proving causality. The population representativeness of the CPRD was particularly useful when I prepared for a comparison group in each study. In Paper 2 (SMI and CKD), the comparison group consisted of all people registered to the CPRD except for those with SMI. In Paper 3 (CKD and antidepressant prescription), people without known CKD (matched for age, sex, general practice, and calendar year) were randomly sampled from the general population. If the CRPD was not representative of the UK general population, the crude prevalence of CKD in patients without SMI (in Paper 2) and the crude prevalence/incidence of antidepressant prescription in patients without known CKD (in Paper 3) would not be very informative as a comparison group.

10.4.2. Breadth of data

The CPRD includes not only disease diagnoses and prescriptions, but also information on lifestyle-related factors including smoking status and BMI. Following the crude analyses, I conducted adjusted analyses in each paper. Smoking status and BMI are known to be associated with CKD, SMI, common mental health disorders, and GI bleeding. Therefore, the inclusion of these important confounding factors in the adjusted analyses was vital for each study.

In addition, the CPRD can be linked to other data sources including HES and IMD. Linkage with HES enabled me to obtain additional information about ethnicity. In a study examining the completeness of ethnicity information, the linkage with HES largely reduced the proportion of patients with missing ethnicity information [107]. The linkage with IMD was also effective for obtaining information about individual area-level socio-economic status, enabling this to be adjusted for as an important confounding factor. Furthermore, in Paper 4 (GI bleeding risk of SSRIs by kidney function), the study outcome was defined as hospitalisations for GI bleeding recorded in HES, which are expected to be more accurate than the GI bleeding episodes recorded in the CPRD.

10.4.3. Sample size

The CPRD is one of the largest electronic health records databases in the world, with coverage of over 11 million patients, 4.4 million of which are active (i.e. alive and currently registered) [73]. Generally, a large sample size improves the precision of estimates, although the accuracy of these estimates is another issue and associated with bias. A large sample size is generally required for pharmacoepidemiological studies examining serious but uncommon adverse outcomes of drugs, such as the GI bleeding risk of SSRIs. Indeed, the crude incidence rate of GI bleeding hospitalisation was only 4.0 (95% CI 3.9–4.1)/1000 person-years in the study population in Paper 4 (GI bleeding risk of SSRIs by kidney function). Notably, the present PhD has focused on patients with CKD (stages 3 to 5), the prevalence of which was around 6–7% in the general population. If the database was smaller, the number of GI bleeding outcomes among SSRI users with CKD would be extremely small, preventing any meaningful statistical analyses from being conducted.

10.5. Limitations

Despite the many strengths of the present PhD, there may also be several limitations, which may be ascribed to the nature of CPRD as well as the strategy employed to define the study population, exposure of interest and outcomes. I here summarise what I have discussed in each paper.

10.5.1. Misclassification

Misclassification is itself subclassified into non-differential and differential misclassification. Generally, non-differential misclassification of the study outcome, exposure, and confounding factors will prejudice the study results towards the null association between exposure and outcome, whereas the direction of the bias due to differential misclassification varies according to each study.

(i) Misclassification of CKD status and stage

In Paper 1 (prevalence of CKD and RRT in CPRD), misclassification of CKD status could occur due to (i) measurement error of serum creatinine level in laboratories, and (ii) use of the GFR estimating equation (i.e. CKD-EPI creatinine equation). However, the apparent prevalence of CKD in the CPRD would not be changed by these misclassification, because it is expected that patients with and without CKD would be misclassified into the other group to similar extents. Therefore, caution is needed to interpret the study results; an overall agreement of the prevalence estimates of CKD in the CPRD with those in the Health Survey for England does not ensure an individual-level validity. In addition, in routine clinical practice, serum creatinine level may be temporarily increased because of AKI, recent exercise, and/or protein intake. This misclassification could result in the overestimation of the prevalence of CKD in the CPRD. On the other hand, among older and frail patients with decreased muscle mass, GFR calculated from serum creatinine records may be underestimated, meaning that the prevalence of CKD could be underestimated.

In Paper 2 (SMI and CKD), in addition to the non-differential misclassification (due to measurement error of serum creatinine and use of the GFR estimating equation), differential misclassification of CKD status could occur due to differences in the frequency of blood testing between patients with and without SMI. If the probability of misclassification (i.e. that patients

with CKD were regarded as non-CKD because of non-testing) was larger in people without SMI than people with SMI, this would cause an overestimation of the association between SMI and CKD. However, the additional analysis suggested that the influence of this bias was small, mainly because GPs were selectively testing people at risk for CKD (meaning that those without serum creatinine testing were unlikely to have CKD) regardless of SMI status (see **section 6.3.2**).

In Paper 3 (CKD and antidepressant prescription), some patients satisfying the CKD criteria in the CPRD may not have "true CKD" due to measurement error of serum creatinine, use of the GFR estimating equation, and temporarily increased serum creatinine (due to AKI, recent exercise, and/or protein intake). On the other hand, some patients in the matched comparison group (i.e. those without known CKD) may have CKD because of measurement error of serum creatinine, use of the GFR estimating equation, decreased muscle mass, and lack of measurement of serum creatinine in primary care. This misclassification of CKD status could dilute the association between CKD and antidepressant prescription.

In Paper 4 (GI bleeding risk of SSRIs by kidney function), patients with CKD were further classified into subgroups according to eGFR on the date of cohort entry: CKD stage 3a (eGFR 45–59 ml/min/1.73m^2), stage 3b (30–44 ml/min/1.73m^2), and stage 4 or 5 (<30 ml/min/1.73m^2). Therefore, in addition to the potential misclassification of CKD status, misclassification of CKD stage is also possible. Misclassification of CKD stage is likely to be random, and could therefore dilute the adjusted rate ratios and rate differences (between periods with and without SSRIs) across groups with different levels of kidney function.

(ii) Misclassification of SMI status

According to a validation study of UK primary care, diagnosis codes (Read codes) suggesting SMI have high sensitivity (91%), specificity (99.9%), and positive predictive value (91%) [136]. Therefore, extensive misclassification of SMI status is unlikely. Due to the slightly decreased sensitivity, it is possible that a small number of people with SMI might have been misclassified into the group of those without SMI. However, the influence of this misclassification appears to be subtle, because the denominator (i.e. the number of people in the group without SMI) was huge (N = 2,387,988).

(iii) Misclassification of antidepressant prescription and adherence

Prescription of drugs is automatically recorded in the current CPRD, meaning that misclassification of prescription records is very unlikely. In Paper 3 (CKD and antidepressant prescription), prescription by GPs itself was of interest, and adherence did not matter. However, in Paper 4 (GI bleeding risk of SSRIs by kidney function), adherence could influence the association between SSRIs and GI bleeding at each level of kidney function. If the adherence of SSRIs was poor, the observed association would be influenced towards the null association between SSRIs and GI bleeding. Furthermore, the possibility remains that the adherence was poorer among patients with lower kidney function, and the observed constant relative risk is thus ascribed to the different degree of adherence according to the level of kidney function.

(iv) Misclassification of GI bleeding outcome

Although the primary diagnosis in hospital discharge records generally has high specificity [137], there has been no study assessing the validity of ICD-10 codes suggesting GI bleeding in HES. However, this misclassification is unlikely to be related to SSRI prescription status in primary care, and therefore would not affect the relative risk between periods with and without SSRIs. However, if sensitivity of the GI bleeding ICD-10 codes was low, the absolute risks and risk differences between periods with and without SSRIs would have been underestimated.

(v) Misclassification of comorbidities

In the CPRD, it has been a common strategy to assume that people without recorded diagnoses of a comorbidity (e.g. diabetes) do not have the condition. According to previous validation studies, many diseases showed a high positive predictive value in the CPRD [138, 139], whereas sensitivity is unknown. If identification and recording of comorbidities were positively associated with the exposure of interest as well as the study outcome, statistical adjustment for comorbidities would result in underestimation of the (true) adjusted relative risk between the exposure and outcome. For example, for the association between CKD and antidepressant prescription, the identification and recording of comorbidities are expected to be positively associated with CKD as well as antidepressant prescription. Therefore, the fully-adjusted odds ratio of 1.35 (95% 1.32–1.37) and the fully-adjusted rate ratio of 1.25 (1.23–1.26) in the association between CKD and prevalence and incidence of antidepressant prescription, respectively, are probably underestimated due to misclassification of comorbidities.

10.5.2. Confounding

Generally, confounding in observational studies includes unmeasured confounding factors (which are truly unknown, or which are known but unmeasured or unrecorded in the database) and residual confounding when dichotomising or categorising measured factors (e.g. diabetes) for statistical adjustment. Minimising the influence of confounding by adjusted analyses is particularly important when discussing a potential causal link between exposure and outcome of the study.

(i) Paper 2 (SMI and CKD)

After describing the burden of CKD among patients with SMI in a crude analysis, I conducted multivariable logistic regression analyses of the association between SMI and CKD. The purpose of this analysis was to examine (i) to what extent the association between SMI and CKD can be explained by each of the patients' characteristics (e.g. socio-economic status) and known CKD risk factors (e.g. diabetes), and (ii) what remains after adjusting for all the selected covariates.

Firstly, it should be noted that I was not able to differentiate potential confounding and mediating factors in the association between SMI and CKD in this cross-sectional study. For example, diabetes may be mediating the association between SMI and CKD (i.e. SMI has led to diabetes, and diabetes resulted in CKD), but diabetes also could be a confounding factor in the association between SMI and CKD (i.e. diabetes has resulted in both SMI and CKD). I only tried to remove the effect of diabetes regardless of the nature of this factor. I found that the odds ratio changed from 1.53 (95% CI 1.42–1.66) to 1.42 (95% CI 1.31–1.54) in the association between SMI (non-lithium users) and CKD after adjusting for diabetes status. However, this decrease in odds ratio does not reveal whether diabetes mediated or confounded the association between SMI and CKD.

Secondly, after adjusting for all selected covariates, the fully-adjusted odds ratio was 1.45 (1.34–1.58) for patients with SMI and no history of lithium use and 6.49 (5.84–7.21) for patients with SMI and history of lithium use. Apparently, the remaining association is a mixture of true causality, unmeasured confounding factors, and residual confounding. Causality between lithium and CKD has been widely suggested in basic research and previous observational studies [49, 51, 140]; indeed, I could argue that such a strong association (i.e. fully-adjusted odds ratio of 6.49) between the lithium group and CKD cannot be fully explained by unmeasured confounding factors and residual confounding. However, it is difficult to

discuss whether the weaker association between the non-lithium group and CKD (i.e. fully-adjusted odds ratio of 1.45) can be fully explained by unmeasured confounding factors (e.g. low birth weight) and residual confounding due to dichotomisation of disease status (e.g. diabetes, heart failure). Given the limitations of cross-sectional design such as unknown temporality, the current study results provide limited information regarding the direction of causality between SMI and CKD.

(ii) Paper 3 (CKD and antidepressant prescription)

Similar to Paper 2, after describing the tendencies in antidepressant prescription for patients with and without CKD, adjusted analyses were subsequently conducted on the association between CKD and the prevalence/incidence of antidepressant prescription. The odds ratio of prevalent antidepressant prescription (CKD vs. non-CKD) decreased from 1.46 (1.43–1.48) to 1.35 (1.32–1.37), whereas the incidence rate ratio of antidepressant prescription decreased from 1.35 (1.33–1.37) to 1.25 (1.23–1.26) after adjusting for the potential confounding factors. These results suggest that the selected confounding factors explained some of the association between CKD and the high incidence/prevalence of antidepressant prescription, but CKD remained "independently" associated with more frequent antidepressant prescription by GPs. Nevertheless, caution is needed when interpreting this "independent" association as a causal link between CKD and antidepressant prescription by GPs, because unmeasured confounding factors (e.g. un-coded poor health status) and residual confounding due to dichotomisation of disease status (e.g. diabetes, heart failure) could explain the remaining association.

(iii) Paper 4 (GI bleeding risk of SSRIs by kidney function)

In this study, the primary comparison was between periods with and without SSRI prescription for the incidence of hospitalisation due to GI bleeding, at each level of kidney function. It is anticipated that periods with and without SSRI prescription are systematically different in two aspects: (i) periods without SSRI prescription include observational periods of people who have never received SSRIs, and there may be systematic differences between people with and without SSRI prescription (e.g. smoking history and disease status such as diabetes), and (ii) even among people receiving at least one SSRI prescription during follow-up, periods with and without SSRIs may be systematically different in terms of the prescription of other drugs and severity of depression/anxiety.

Therefore, when estimating the adjusted rate ratios and rate differences between periods with and without SSRI prescription, I adjusted for (i) basic patient characteristics (i.e. age, sex, ethnicity, socio-economic status, BMI, smoking status) and comorbidities known to be associated with GI bleeding (i.e. diabetes mellitus, chronic liver disease, congestive heart failure, cancer, and rheumatoid arthritis), in order to minimise between-person confounding, and (ii) time-dependent prescription of other drugs associated with GI bleeding (i.e. anticoagulants, antiplatelet drugs, non-steroidal anti-inflammatory drugs [NSAIDs], oral corticosteroids, and acid-suppressing agents), in order to minimise within-person confounding.

I did not adjust for status or severity of depression and anxiety in the analysis. However, I consider that the lack of statistical adjustment for mental health conditions is not critical to examining the association between SSRIs and GI bleeding, because there is no strong evidence that mental health conditions directly increase GI bleeding. In other words, mental health conditions do not seem to satisfy the criteria for confounding factors, as a confounding factor needs to be independently associated with outcome (i.e. GI bleeding).

However, the possibility remains that the fully-adjusted rate ratios of 1.66 (95% CI, 1.37–2.01) among patients with no CKD, 1.86 (1.62–2.15) among patients with CKD stage 3a, 1.61 (1.27–2.04) among patients with CKD stage 3b, and 1.84 (1.14–2.96) among patients with CKD stage 4 or 5 were still influenced by unmeasured confounding factors (e.g. over-the-counter aspirin and NSAIDs, and alcohol), and that there is residual confounding due to the dichotomisation of comorbidities and medication status.

Generally, the influence of unmeasured confounding factors (named “confounding by indication” in the context of pharmacoepidemiology) could be minimised if a good comparator drug (class) exists in real-world clinical practice. For example, Crellin et al. compared several different antibiotic classes prescribed for urinary tract infection on the incidence of AKI, hyperkalaemia, and sudden death [141]. This is a reasonable comparison, as GPs may wonder which antibiotic class they should choose for their patients in daily practice. However, in the present study, is there a good comparator drug (group) for SSRIs? The answer may have been ‘yes’ twenty years ago when GPs had a choice between SSRIs and tricyclic antidepressants for their patients with depression or anxiety. However, the current NICE guidance clearly suggests that SSRIs should be the first choice for common mental health disorders [25], which was confirmed in Paper 3 (CKD and antidepressant prescription). Therefore, patients receiving

SSRIs (mainly for depression and anxiety) and those receiving tricyclic antidepressants (mainly for neuropathic pain and other reasons) seem to be systematically different. This means that there is little to no benefit to regarding tricyclic antidepressant users as a comparator group for SSRIs to minimise "confounding by indication".

10.5.3. Generalisability

Generalisability of the findings in this thesis (to the whole UK population) is expected to be good because of the population representativeness of the CPRD. However, the exclusion of patients not registered (e.g. migrants) and those who declined the data transfer from the CPRD could harm the generalisability of the findings to some extent.

In Papers 3 (CKD and antidepressant prescription) and 4 (GI bleeding risk of SSRIs by kidney function), I restricted the study population to patients registered in general practices that agreed to HES linkage. The possibility remains that patient characteristics and prescribing habits of antidepressants by GPs are systematically different between general practices in the CPRD that do and do not contribute to the HES linkage.

In Paper 4, I further excluded (i) prevalent SSRI users (because the inclusion of prevalent SSRI users with drug tolerance may have caused bias [142]); (ii) those with a history of GI bleeding (in order to capture new-onset GI bleeding); and (iii) those with missing values of smoking status and BMI (i.e. important confounding factors). I believe that these exclusion criteria were important to ensure the internal validity of the study, in return for limiting the external validity (i.e. generalisability). Consequently, the study results may be applicable only to non-prevalent users of SSRIs without a history of GI bleeding, who are highly monitored in primary care with records of smoking status and BMI.

10.5.4. Sample size

Although the large sample size of the CPRD was earlier listed as a strength, the statistical power of the study in Paper 4 (GI bleeding risk of SSRIs by kidney function) to examine the risk of SSRIs in the group with the most severely reduced kidney function (i.e. eGFR <30 ml/min/1.73m^2) may be still limited, as indicated by the wide CI (the fully-adjusted rate ratio of 1.84 [95% CI, 1.14–2.96]). Accordingly, the lack of statistical significance in the multiplicative interaction across different kidney function subgroups may be partly ascribed to

the limited statistical power. This issue of study power also made it difficult to draw robust conclusions from the post hoc subgroup analyses by SSRI dose and receptor affinity. Further subgroup analysis, for example by individual SSRIs, would not be informative.

10.6. Personal learning

Throughout this PhD, I have gained new knowledge and skills to deal with large electronic health records, especially in outpatient settings. Before coming to the UK, I had experience with a large Japanese inpatient database, named the Diagnosis Procedure Combination (DPC) database [143-147]. The DPC database is similar to HES in the UK, but includes more detailed inpatient information such as intravenous and oral drugs prescribed on a daily basis. I learned that the CPRD and DPC database have many differences in their characteristics (see **Table 15** below).

Table 15. Comparison of main characteristics between the CPRD and DPC database

	CPRD	DPC database
Country	UK	Japan
Setting	Outpatient	Inpatient
Nature of database	Electronic medical records	Administrative claims data
Size of the data	More than 11.3 million patients' data, collected from nearly 700 general practices (representative of the UK population in terms of age and sex) since around 1990	Around 0.5 million hospitalisation episodes per month, collected from around 1000 hospitals (not representative of the Japanese hospitals) since 2002
Data collection	Diagnoses are recorded by GPs and practice staff in primary care, prospectively or retrospectively. Prescriptions and laboratory results are automatically recorded on time.	Diagnoses are recorded by attending physicians at the time of discharge. Prescribed intravenous and oral drugs are automatically recorded on time.
Diagnosis coding	Read code	ICD-10 code
Timing of the start of data recording	When a patient is registered to the general practice participating in the CPRD (but, data may not be valid until the general practice reaches the 'up to standard')	Admission
Timing of the end of data recording	Death, change of general practice, last data collection from the general practice	Discharge (with or without death)
Laboratory results	Available	Not available
Linkage	Available (e.g. HES)	Not available

Abbreviations: GPs = general practitioners; HES = Hospital Episode Statistics.

Due to these differences, my previous knowledge and skills gained through the use of the DPC database were not very helpful in some situations during my research using the CPRD. I encountered the following difficulties:

Firstly, in most studies using inpatient databases (e.g. DPC database), the timing of cohort entry is simply the day of hospital admission for all study participants. However, this varies widely in the CPRD, because of differences in (i) the timing of the start of data collection (although this may be random, and therefore, unbiased), and (ii) the timing of cohort entry depending on the research questions. For example, in Paper 3 (CKD and antidepressant prescription), patients entered the CKD cohort on the day they first satisfied the CKD definition (i.e. second eGFR <60 ml/min/1.73m^2) after their eligibility criteria have been met (one year after practice registration, the date that the general practice reached CPRD quality standards, or 1st April

2004). I learned that, in this type of outpatient databases such as the CPRD, it is sometimes difficult to decide when to start follow-up for individual study participants.

Secondly, in all of my five studies using the DPC database [143-147], the primary outcome was all-cause in-hospital death. This was mainly because (i) in-hospital death is almost always clinically important and relevant in acute inpatient settings, (ii) other outcomes (e.g. post-admission events such as delirium and sepsis) may not be well recorded and have not been sufficiently validated in the DPC database, and (iii) post-discharge outcomes are not available due to the end of data collection upon discharge. Meanwhile, all-cause death, if accurately recorded, seems to be the easiest outcome to deal with, because (i) death is unlikely to be affected by ascertainment bias, (ii) death occurs only once, and (iii) there is no competing risk against death.

Meanwhile, in the CPRD (with or without linkage with HES), a variety of conditions can be candidates for study outcomes. However, unlike death, some outcome definitions in the database may have low validity (e.g. low sensitivity). Therefore, researchers need to fully consider whether their outcome definitions are appropriate and whether there is no differential misclassification of outcome between those with and without exposure. Moreover, I had to learn competing risk analysis skills to account for death as a competing risk for my additional paper examining the association between CKD and cause-specific hospitalisation (see **Appendix A** for more detail) [113].

Thirdly, disease status and medications may change over time in outpatient databases with a long follow-up period. I learned that research on adverse outcomes associated with intermittently prescribed drugs (e.g. antidepressants) is difficult, especially when using a cohort design to estimate incident rates (instead of case-control design to estimate only relative risks). Previous studies suggested that one consecutive period of treatment was only 2–3 months for most patients receiving antidepressants, but they could have several treatment episodes over a longer follow-up in the CPRD [129]. Thus, in Paper 4 (GI bleeding risk of SSRIs by kidney function), I needed to consider the prescription of antidepressants as a time-dependent exposure. This knowledge would also be useful in my future studies dealing with time-dependent confounding factors.

Research using routinely collected electronic health records has not been popular in Japan, especially in outpatient settings. However, the Japanese public and private organisations are

currently trying their best to establish a good database for clinical research. With the new skills and knowledge acquired during this PhD, I hope to lead clinical and epidemiological research in Japan using electronic health records.

10.7. Conclusions

In conclusion, a close association between CKD and mental health disorders (SMI and common mental health disorders such as depression and anxiety) in the UK general population was suggested. It is evident that patients with CKD are more likely to be prescribed antidepressants, and that this may increase the risk of serious drug-related adverse outcomes such as GI bleeding associated with SSRIs. The risk-benefit balance of antidepressants for patients with CKD should be reconsidered in light of this new evidence.

References

1. National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. https://www.nice.org.uk/guidance/cg182 (accessed 1 May 2018).
2. Wetzels JF, Kiemeney LA, Swinkels DW, Willems HL, den Heijer M. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. Kidney international. 2007;72(5):632-7.
3. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260-72.
4. Health Survey for England - 2010, Respiratory health: Chapter 8, Kidney disease and renal function. http://www.hscic.gov.uk/pubs/hse10report (accessed 1 May 2018).
5. Aitken GR, Roderick PJ, Fraser S, Mindell JS, O'Donoghue D, Day J, et al. Change in prevalence of chronic kidney disease in England over time: comparison of nationally representative cross-sectional surveys from 2003 to 2010. BMJ open. 2014;4(9):e005480.
6. Tonelli M, Riella M. Chronic kidney disease and the ageing population. Nephron Clinical practice. 2014;128(3-4):319-22.
7. Rao A, Casula A, Castledine C. UK Renal Registry 17th Annual Report: Chapter 2 UK Renal Replacement Therapy Prevalence in 2013: National and Centre-specific Analyses. Nephron. 2015;129 Suppl 1:31-56.
8. MacNeill SJ, Casula A, Shaw C, Castledine C. UK Renal Registry 18th Annual Report: Chapter 2 UK Renal Replacement Therapy Prevalence in 2014: National and Centre-specific Analyses. Nephron. 2016;132 Suppl 1:41-68.
9. Gilg J, Caskey F, Fogarty D. UK Renal Registry 18th Annual Report: Chapter 1 UK Renal Replacement Therapy Incidence in 2014: National and Centre-specific Analyses. Nephron. 2016;132 Suppl 1:9-40.
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. The New England journal of medicine. 2004;351(13):1296-305.
11. Dalrymple LS, Katz R, Kestenbaum B, de Boer IH, Fried L, Sarnak MJ, et al. The risk of infection-related hospitalization with decreased kidney function. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;59(3):356-63.
12. Ishigami J, Grams ME, Chang AR, Carrero JJ, Coresh J, Matsushita K. CKD and Risk for Hospitalization With Infection: The Atherosclerosis Risk in Communities (ARIC) Study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2016.
13. Molnar AO, Bota SE, Garg AX, Harel Z, Lam N, McArthur E, et al. The Risk of Major Hemorrhage with CKD. Journal of the American Society of Nephrology : JASN. 2016;27(9):2825-32.
14. Ishigami J, Grams ME, Naik RP, Coresh J, Matsushita K. Chronic Kidney Disease and Risk for Gastrointestinal Bleeding in the Community: The Atherosclerosis Risk in

Communities (ARIC) Study. Clinical journal of the American Society of Nephrology : CJASN. 2016.
15. Naylor KL, McArthur E, Leslie WD, Fraser LA, Jamal SA, Cadarette SM, et al. The three-year incidence of fracture in chronic kidney disease. Kidney international. 2014;86(4):810-8.
16. Daya NR, Voskertchian A, Schneider AL, Ballew S, McAdams DeMarco M, Coresh J, et al. Kidney Function and Fracture Risk: The Atherosclerosis Risk in Communities (ARIC) Study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2016;67(2):218-26.
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Books Wagon; 2014.
18. Health and Social Care Information Centre. Quality and Outcomes Framework. www.Hscic.Gov.Uk/qof (accessed 1 May 2018).
19. National Institute for Health and Care Excellence. Common mental health problems: identification and pathways to care. https://www.nice.org.uk/guidance/cg123 (accessed 1 May 2018).
20. Department of Health. Bushbook. CHAPTER 1 Alcohol and Other Drugs. https://web.archive.org/web/20150328060739/http://www.nt.gov.au/health/healthdev/health_promotion/bushbook/volume2/chap1/sect1.htm (accessed 1 May 2018).
21. Kuipers E, Yesufu-Udechuku A, Taylor C, Kendall T. Management of psychosis and schizophrenia in adults: summary of updated NICE guidance. BMJ. 2014;348:g1173.
22. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. https://www.nice.org.uk/guidance/cg178 (accessed 1 May 2018).
23. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. https://www.nice.org.uk/guidance/cg185 (accessed 1 May 2018).
24. Hayes J, Prah P, Nazareth I, King M, Walters K, Petersen I, et al. Prescribing trends in bipolar disorder: cohort study in the United Kingdom THIN primary care database 1995-2009. PloS one. 2011;6(12):e28725.
25. National Institute for Health and Care Excellence. Common mental health problems: identification and pathways to care. https://www.nice.org.uk/guidance/cg123 (accessed 1 May 2018).
26. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder in adults: management. https://www.nice.org.uk/guidance/cg113 (accessed 1 May 2018).
27. Chang CK, Hayes RD, Perera G, Broadbent MT, Fernandes AC, Lee WE, et al. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. PloS one. 2011;6(5):e19590.
28. Dembling BP, Chen DT, Vachon L. Life expectancy and causes of death in a population treated for serious mental illness. Psychiatric services. 1999;50(8):1036-42.
29. Hannerz H, Borga P, Borritz M. Life expectancies for individuals with psychiatric diagnoses. Public health. 2001;115(5):328-37.

30. Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. Psychiatric services. 2009;60(2):147-56.
31. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. The American journal of psychiatry. 2013;170(3):324-33.
32. Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. The British journal of psychiatry : the journal of mental science. 2010;196(2):116-21.
33. Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Rsearch Database. Archives of general psychiatry. 2007;64(2):242-9.
34. Osby U, Correia N, Brandt L, Ekbom A, Sparen P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophrenia research. 2000;45(1-2):21-8.
35. Osby U, Brandt L, Correia N, Ekbom A, Sparen P. Excess mortality in bipolar and unipolar disorder in Sweden. Archives of general psychiatry. 2001;58(9):844-50.
36. Osborn DP, Nazareth I, King MB. Risk for coronary heart disease in people with severe mental illness: cross-sectional comparative study in primary care. The British journal of psychiatry : the journal of mental science. 2006;188:271-7.
37. Daumit GL, Clark JM, Steinwachs DM, Graham CM, Lehman A, Ford DE. Prevalence and correlates of obesity in a community sample of individuals with severe and persistent mental illness. The Journal of nervous and mental disease. 2003;191(12):799-805.
38. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophrenia research. 2005;80(1):19-32.
39. Woodhead C, Ashworth M, Schofield P, Henderson M. Patterns of physical co-/multi-morbidity among patients with serious mental illness: a London borough-based cross-sectional study. BMC family practice. 2014;15:117.
40. Osborn DP, Baio G, Walters K, Petersen I, Limburg H, Raine R, et al. Inequalities in the provision of cardiovascular screening to people with severe mental illnesses in primary care: cohort study in the United Kingdom THIN Primary Care Database 2000-2007. Schizophrenia research. 2011;129(2-3):104-10.
41. Smith DJ, Langan J, McLean G, Guthrie B, Mercer SW. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. BMJ open. 2013;3(4).
42. Hippisley-Cox J, Parker C, Coupland C, Vinogradova Y. Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study. Heart. 2007;93(10):1256-62.

43. Kreyenbuhl J, Medoff DR, Seliger SL, Dixon LB. Use of medications to reduce cardiovascular risk among individuals with psychotic disorders and Type 2 diabetes. Schizophrenia research. 2008;101(1-3):256-65.
44. Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. BMC medicine. 2013;11:263.
45. Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophrenia bulletin. 2000;26(4):903-12.
46. Markowitz GS, Radhakrishnan J, Kambham N, Valeri AM, Hines WH, D'Agati VD. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. Journal of the American Society of Nephrology : JASN. 2000;11(8):1439-48.
47. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DP. Adverse Renal, Endocrine, Hepatic, and Metabolic Events during Maintenance Mood Stabilizer Treatment for Bipolar Disorder: A Population-Based Cohort Study. PLoS medicine. 2016;13(8):e1002058.
48. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379(9817):721-8.
49. Bendz H, Schon S, Attman PO, Aurell M. Renal failure occurs in chronic lithium treatment but is uncommon. Kidney international. 2010;77(3):219-24.
50. Tzeng NS, Hsu YH, Ho SY, Kuo YC, Lee HC, Yin YJ, et al. Is schizophrenia associated with an increased risk of chronic kidney disease? A nationwide matched-cohort study. BMJ open. 2015;5(1):e006777.
51. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of Lithium and Anticonvulsants and the Rate of Chronic Kidney Disease: A Nationwide Population-Based Study. JAMA psychiatry. 2015;72(12):1182-91.
52. Vlasschaert ME, Bejaimal SA, Hackam DG, Quinn R, Cuerden MS, Oliver MJ, et al. Validity of administrative database coding for kidney disease: a systematic review. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2011;57(1):29-43.
53. Cohen SD, Cukor D, Kimmel PL. Anxiety in Patients Treated with Hemodialysis. Clinical journal of the American Society of Nephrology : CJASN. 2016;11(12):2250-5.
54. King-Wing Ma T, Kam-Tao Li P. Depression in dialysis patients. Nephrology. 2016;21(8):639-46.
55. Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, et al. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney international. 2013;84(1):179-91.
56. Lee YJ, Kim MS, Cho S, Kim SR. Association of depression and anxiety with reduced quality of life in patients with predialysis chronic kidney disease. International journal of clinical practice. 2013;67(4):363-8.

57. Moynihan R, Glassock R, Doust J. Chronic kidney disease controversy: how expanding definitions are unnecessarily labelling many people as diseased. BMJ. 2013;347:f4298.
58. Blakeman T, Protheroe J, Chew-Graham C, Rogers A, Kennedy A. Understanding the management of early-stage chronic kidney disease in primary care: a qualitative study. The British journal of general practice : the journal of the Royal College of General Practitioners. 2012;62(597):e233-42.
59. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes care. 2001;24(6):1069-78.
60. Nair N, Farmer C, Gongora E, Dehmer GJ. Commonality between depression and heart failure. The American journal of cardiology. 2012;109(5):768-72.
61. Meyer TW, Hostetter TH. Uremia. The New England journal of medicine. 2007;357(13):1316-25.
62. Balogun RA, Abdel-Rahman EM, Balogun SA, Lott EH, Lu JL, Malakauskas SM, et al. Association of depression and antidepressant use with mortality in a large cohort of patients with nondialysis-dependent CKD. Clinical journal of the American Society of Nephrology : CJASN. 2012;7(11):1793-800.
63. Fischer MJ, Xie D, Jordan N, Kop WJ, Krousel-Wood M, Kurella Tamura M, et al. Factors associated with depressive symptoms and use of antidepressant medications among participants in the Chronic Renal Insufficiency Cohort (CRIC) and Hispanic-CRIC Studies. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;60(1):27-38.
64. Kuehn BM. Military probes epidemic of suicide: mental health issues remain prevalent. Jama. 2010;304(13):1427, 9-30.
65. Nagler EV, Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3-5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2012;27(10):3736-45.
66. Momen MN, Sebastian CS, Buckley PF. Paradoxical reaction to fluoxetine. Psychosomatics. 2003;44(3):259-60.
67. Iraqi AH. A case report of paranoid delusion with venlafaxine use. Journal of the American Geriatrics Society. 2003;51(7):1045-6.
68. Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney international. 2007;72(1):92-9.
69. Hedayati SS, Gregg LP, Carmody T, Jain N, Toups M, Rush AJ, et al. Effect of Sertraline on Depressive Symptoms in Patients With Chronic Kidney Disease Without Dialysis Dependence: The CAST Randomized Clinical Trial. Jama. 2017;318(19):1876-90.
70. Douglas I, Smeeth L, Irvine D. The use of antidepressants and the risk of haemorrhagic stroke: a nested case control study. British journal of clinical pharmacology. 2011;71(1):116-20.

71. Hubbard R, Farrington P, Smith C, Smeeth L, Tattersfield A. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. American journal of epidemiology. 2003;158(1):77-84.
72. de Abajo FJ, Rodriguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. BMJ. 1999;319(7217):1106-9.
73. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology. 2015;44(3):827-36.
74. Serebruany VL. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? The American journal of medicine. 2006;119(2):113-6.
75. Jiang HY, Chen HZ, Hu XJ, Yu ZH, Yang W, Deng M, et al. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: a systematic review and meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2015;13(1):42-50.e3.
76. van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. BMJ. 2001;323(7314):655-8.
77. Meijer WE, Heerdink ER, Nolen WA, Herings RM, Leufkens HG, Egberts AC. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Archives of internal medicine. 2004;164(21):2367-70.
78. Lewis JD, Strom BL, Localio AR, Metz DC, Farrar JT, Weinrieb RM, et al. Moderate and high affinity serotonin reuptake inhibitors increase the risk of upper gastrointestinal toxicity. Pharmacoepidemiology and drug safety. 2008;17(4):328-35.
79. Wang YP, Chen YT, Tsai CF, Li SY, Luo JC, Wang SJ, et al. Short-term use of serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding. The American journal of psychiatry. 2014;171(1):54-61.
80. Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Archives of internal medicine. 2003;163(1):59-64.
81. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551.
82. de Abajo FJ, Garcia-Rodriguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. Archives of general psychiatry. 2008;65(7):795-803.
83. Opatrny L, Delaney JA, Suissa S. Gastro-intestinal haemorrhage risks of selective serotonin receptor antagonist therapy: a new look. British journal of clinical pharmacology. 2008;66(1):76-81.
84. Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J. An association between selective serotonin reuptake inhibitor use and serious upper

gastrointestinal bleeding. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2009;7(12):1314-21.
85. Quinn GR, Singer DE, Chang Y, Go AS, Borowsky LH, Udaltsova N, et al. Effect of selective serotonin reuptake inhibitors on bleeding risk in patients with atrial fibrillation taking warfarin. The American journal of cardiology. 2014;114(4):583-6.
86. The National Health Service in England. About the National Health Service (NHS). https://www.nhs.uk/NHSEngland/thenhs/about/Pages/overview.aspx (accessed 1 May 2018).
87. Health and Social Care Information Centre. Attribution Data Set GP-Registered Populations Scaled to ONS Population Estimates - 2011. http://www.hscic.gov.uk/catalogue/PUB05054 (accessed 1 May 2018).
88. Kontopantelis E, Stevens RJ, Helms PJ, Edwards D, Doran T, Ashcroft DM. Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: a cross-sectional population study. BMJ open. 2018;8(2):e020738.
89. Clinical Practice Research Datalink http://www.cprd.com/intro.asp (accessed 1 May 2018).
90. British Medical Association, Royal Pharmaceutical Society of Great Britain. British national formulary. https://www.medicinescomplete.com/mc/bnf/current/ (accessed 1 May 2018).
91. Hospital Episode Statistics. http://www.hscic.gov.uk/hes (accessed 1 May 2018).
92. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). International journal of epidemiology. 2017;46(4):1093-i.
93. World Health Organization. International Classification of Diseases (ICD)-10. http://apps.who.int/classifications/apps/icd/icd10online2003/fr-icd.htm (accessed 1 May 2018).
94. Department for Communities and Local Government. English Indices of Deprivation. www.Gov.Uk/government/collections/english-indices-of-deprivation (accessed 1 May 2018).
95. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2002;39(2 Suppl 1):S1-266.
96. The Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012 2:1-138.
97. Hallan SI, Matsushita K, Sang Y, Mahmoodi BK, Black C, Ishani A, et al. Age and association of kidney measures with mortality and end-stage renal disease. Jama. 2012;308(22):2349-60.
98. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2014;63(5):820-34.

99. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
100. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Annals of internal medicine. 1999;130(6):461-70.
101. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604-12.
102. Department of Health. Estimating glomerular filtration rate: information for laboratories. 2007. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4133025.pdf (accessed 1 May 2018).
103. Healthcare Quality Improvement Partnership. National Chronic Kidney Disease Audit: National Report (Part 1). 2017. http://www.hqip.org.uk/resources/national-chronic-kidney-disease-audit-national-report-part-1/ (accessed 1 May 2018).
104. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Annals of internal medicine. 2012;156(11):785-95.
105. Lasserson DS, Shine B, O'Callaghan CA, James T. Requirement for cystatin C testing in chronic kidney disease: a retrospective population-based study. The British journal of general practice : the journal of the Royal College of General Practitioners. 2017;67(663):e732-e5.
106. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clinical chemistry. 2007;53(4):766-72.
107. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. Journal of public health. 2014;36(4):684-92.
108. George J, Mathur R, Shah AD, Pujades-Rodriguez M, Denaxas S, Smeeth L, et al. Ethnicity and the first diagnosis of a wide range of cardiovascular diseases: Associations in a linked electronic health record cohort of 1 million patients. PloS one. 2017;12(6):e0178945
109. Office for National Statistics. Ethnic group by sex by age. https://www.nomisweb.co.uk/census/2011/DC2101EW/view/2092957699?rows=c_ethpuk11&cols=c_age (accessed 1 May 2018).
110. Health Survey for England - 2014, Chapter 5; Use of prescribed medicines. http://content.digital.nhs.uk/catalogue/PUB16076/HSE2013-Ch5-pres-meds.pdf (accessed 1 May 2018).
111. Fraser SD, Roderick PJ, Taal MW. Where now for proteinuria testing in chronic kidney disease?: Good evidence can clarify a potentially confusing message. The British

journal of general practice : the journal of the Royal College of General Practitioners. 2016;66(645):215-7.
112. Fraser SD, Parkes J, Culliford D, Santer M, Roderick PJ.Timeliness in chronic kidney disease and albuminuria identification: a retrospective cohort study. BMC Fam Pract. 2015 Feb 13;16:18.
113. Iwagami M, Caplin B, Smeeth L, Tomlinson LA, Nitsch D. Chronic kidney disease and cause-specific hospitalisation: a matched cohort study using Clinical Practice Research Datalink. Br J Gen Pract (in press).
114. Healthcare Quality Improvement Partnership. National Diabetes Audit: National Diabetes Audit Report 1- Findings and Recommendations 2016-17. https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/national-diabetes-audit-report-1-findings-and-recommendations-2016-17 (accessed 1 May 2018).
115. McDonald HI, Thomas SL, Millett ER, Nitsch D. CKD and the risk of acute, community-acquired infections among older people with diabetes mellitus: a retrospective cohort study using electronic health records. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2015;66(1):60-8.
116. McDonald HI, Nitsch D, Millett ER, Sinclair A, Thomas SL. Are pre-existing markers of chronic kidney disease associated with short-term mortality following acute community-acquired pneumonia and sepsis? A cohort study among older people with diabetes using electronic health records. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2015;30(6):1002-9.
117. McDonald HI, Shaw C, Thomas SL, Mansfield KE, Tomlinson LA, Nitsch D. Methodological challenges when carrying out research on CKD and AKI using routine electronic health records. Kidney international. 2016;90(5):943-9.
118. Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. Pharmacoepidemiology and drug safety. 2005;14(7):443-51.
119. Iwagami M, Tomlinson LA, Mansfield KE, Casula A, Caskey FJ, Aitken G, et al. Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2017;32(suppl_2):ii142-ii50.
120. McIntyre NJ, Fluck RJ, McIntyre CW, Taal MW. Risk profile in chronic kidney disease stage 3: older versus younger patients. Nephron Clinical practice. 2011;119(4):c269-76.
121. Shardlow A, McIntyre NJ, Fluck RJ, McIntyre CW, Taal MW. Chronic Kidney Disease in Primary Care: Outcomes after Five Years in a Prospective Cohort Study. PLoS medicine. 2016;13(9):e1002128.

122. Eriksen BO, Ingebretsen OC. In chronic kidney disease staging the use of the chronicity criterion affects prognosis and the rate of progression. Kidney international. 2007;72(10):1242-8.
123. Iwagami M, Mansfield KE, Hayes JF, Walters K, Osborn DP, Smeeth L, et al. Severe mental illness and chronic kidney disease: a cross-sectional study in the United Kingdom. Clin Epidemiol. 2018;10:421-429.
124. Rothman KJ, Greenland S, Lash T. Modern Epidemiology 3rd Edition. Philadelphia, US: Lippincott Williams & Wilkins; 2008.
125. Matthews A, Langan SM, Douglas IJ, Smeeth L, Bhaskaran K. Phosphodiesterase Type 5 Inhibitors and Risk of Malignant Melanoma: Matched Cohort Study Using Primary Care Data from the UK Clinical Practice Research Datalink. PLoS medicine. 2016;13(6):e1002037.
126. Iwagami M, Tomlinson LA, Mansfield KE, McDonald HI, Smeeth L, Nitsch D. Prevalence, incidence, indication, and choice of antidepressants in patients with and without chronic kidney disease: a matched cohort study in UK Clinical Practice Research Datalink. Pharmacoepidemiology and drug safety. 2017;26(7):792-801.
127. Ilyas S, Moncrieff J. Trends in prescriptions and costs of drugs for mental disorders in England, 1998-2010. The British journal of psychiatry : the journal of mental science. 2012;200(5):393-8.
128. Iwagami M, Tomlinson LA, Mansfield KE, Douglas IJ, Smeeth L, Nitsch D. Gastrointestinal bleeding risk of selective serotonin reuptake inhibitors by level of kidney function: A UK population-based cohort study. Br J Clin Pharmacol (in press).
129. Coupland CA, Dhiman P, Barton G, Morriss R, Arthur A, Sach T, et al. A study of the safety and harms of antidepressant drugs for older people: a cohort study using a large primary care database. Health technology assessment (Winchester, England). 2011;15(28):1-202.
130. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ. 2013;346:f2350.
131. Crooks CJ, Card TR, West J. Defining upper gastrointestinal bleeding from linked primary and secondary care data and the effect on occurrence and 28 day mortality. BMC health services research. 2012;12:392.
132. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373(9665):746-58.
133. Wong J, Motulsky A, Abrahamowicz M, Eguale T, Buckeridge DL, Tamblyn R. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system. BMJ. 2017;356:j603.
134. National Institute for Health and Care Excellence. Depression in adults: recognition and management. Draft for consultation, July 2017. https://www.nice.org.uk/guidance/gid-cgwave0725/documents/short-version-of-draft-guideline-2 (accessed 1 May 2018).

135. National Institute for Health and Care Excellence. Depression in adults: recognition and management. https://www.nice.org.uk/guidance/cg90 (accessed 1 May 2018).
136. Nazareth I, King M, Haines A, Rangel L, Myers S. Accuracy of diagnosis of psychosis on general practice computer system. BMJ. 1993;307(6895):32-4.
137. Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, et al. Systematic review of discharge coding accuracy. Journal of public health. 2012;34(1):138-48.
138. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. British journal of clinical pharmacology. 2010;69(1):4-14.
139. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. The British journal of general practice : the journal of the Royal College of General Practitioners. 2010;60(572):e128-36.
140. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. Lancet. 2015;386(9992):461-8.
141. Crellin E, Mansfield KE, Leyrat C, Nitsch D, Douglas IJ, Root A, et al. Trimethoprim use for urinary tract infection and risk of adverse outcomes in older patients: cohort study. BMJ. 2018;360:k341.
142. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. American journal of epidemiology. 2003;158(9):915-20.
143. Iwagami M, Yasunaga H, Doi K, Horiguchi H, Fushimi K, Matsubara T, et al. Postoperative polymyxin B hemoperfusion and mortality in patients with abdominal septic shock: a propensity-matched analysis. Critical care medicine. 2014;42(5):1187-93.
144. Iwagami M, Yasunaga H, Noiri E, Horiguchi H, Fushimi K, Matsubara T, et al. Choice of renal replacement therapy modality in intensive care units: data from a Japanese Nationwide Administrative Claim Database. Journal of critical care. 2015;30(2):381-5.
145. Iwagami M, Yasunaga H, Noiri E, Horiguchi H, Fushimi K, Matsubara T, et al. Current state of continuous renal replacement therapy for acute kidney injury in Japanese intensive care units in 2011: analysis of a national administrative database. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2015;30(6):988-95.
146. Iwagami M, Yasunaga H, Matsui H, Horiguchi H, Fushimi K, Noiri E, et al. Impact of end-stage renal disease on hospital outcomes among patients admitted to intensive care units: A retrospective matched-pair cohort study. Nephrology. 2017;22(8):617-23.
147. Iwagami M, Yasunaga H, Noiri E, Horiguchi H, Fushimi K, Matsubara T, et al. Potential Survival Benefit of Polymyxin B Hemoperfusion in Septic Shock Patients on Continuous Renal Replacement Therapy: A Propensity-Matched Analysis. Blood purification. 2016;42(1):9-17.

Appendix A: Chronic kidney disease and cause-specific hospitalisation: a matched cohort study using Clinical Practice Research Datalink

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Masao Iwagami
Principal Supervisor	Dorothea Nitsch
Thesis Title	Association between chronic kidney disease and mental health disorders and psychoactive drugs in the UK general po

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	British Journal of General Practice
Please list the paper's authors in the intended authorship order:	Masao Iwagami, Ben Caplin, Liam Smeeth, Laurie A Tomlinson, Dorothea Nitsch
Stage of publication	**In press**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I planned the study, carried out the data extraction, cleaning, analysis, and drafted the manuscript.

Student Signature: [redacted] **Date:** 30/May/2018

Supervisor Signature: [redacted] **Date:** 30.5.18

Masao Iwagami, Ben Caplin, Liam Smeeth, Laurie A Tomlinson and Dorothea Nitsch

Chronic kidney disease and cause-specific hospitalisation:

a matched cohort study using primary and secondary care patient data

Abstract

Background
Although chronic kidney disease (CKD) is associated with various outcomes, the burden of each condition for hospital admission is unknown.

Aim
To quantify the association between CKD and cause-specific hospitalisation.

Design and setting
A matched cohort study in primary care using Clinical Practice Research Datalink linked to Hospital Episode Statistics in England.

Method
Patients with CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2 for ≥3 months) and a comparison group of patients without known CKD (matched for age, sex, GP, and calendar time) were identified, 2004–2014. Outcomes were hospitalisations with 10 common conditions as the primary admission diagnosis: heart failure; urinary tract infection; pneumonia; acute kidney injury (AKI); myocardial infarction; cerebral infarction; gastrointestinal bleeding; hip fracture; venous thromboembolism; and intracranial bleeding. A difference in the incidence rate of first hospitalisation for each condition was estimated between matched patients with and without CKD. Multivariable Cox regression was used to estimate a relative risk for each outcome.

Results
In a cohort of 242 349 pairs of patients, with and without CKD, the rate difference was largest for heart failure at 6.6/1000 person-years (9.7/1000 versus 3.1/1000 person-years in patients with and without CKD, respectively), followed by urinary tract infection at 5.2, pneumonia at 4.4, and AKI at 4.1/1000 person-years. The relative risk was highest for AKI with a fully adjusted hazard ratio of 4.90, 95% confidence interval (CI) = 4.47 to 5.38, followed by heart failure with 1.66, 95% CI = 1.59 to 1.75.

Conclusion
Hospitalisations for heart failure, infection, and AKI showed strong associations with CKD in absolute and(or) relative terms, suggesting targets for improved preventive care.

Keywords
acute kidney injury; chronic kidney diseases; general practice; heart failure; hospitalisation; infection.

INTRODUCTION

Chronic kidney disease (CKD) is a common condition in the community.[1,2] In the UK, according to the Quality and Outcomes Framework,[3] GPs have been incentivised to register patients with CKD stages 3–5 (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 for ≥3 months) since 2006. The majority of these patients are in CKD stage 3 (eGFR of 30–59 mL/min/1.73 m^2) and managed by GPs without referral to nephrology services.[4]

There have been concerns, particularly among GPs, regarding potential overdiagnosis of CKD in older patients with mildly reduced kidney function.[5,6] Some have argued that labelling people as having CKD may unnecessarily create anxiety, while only a minority of patients with CKD progress to end-stage kidney disease requiring renal replacement therapy.[7,8] However, patients with CKD are at higher risk of cardiovascular events, death, and all-cause hospitalisation,[9] an important outcome for both patients and the national healthcare system.[10] Awareness of the causes of admission among patients with CKD could offer opportunities for prevention. However, previous studies suggesting a positive association between CKD and hospitalisations have not investigated the specific causes in detail.[11–13]

Accumulating evidence suggests that CKD is causally associated with a wide range of adverse outcomes, including acute kidney injury (AKI),[14] cardiovascular (myocardial infarction,[15,16] heart failure,[17,18] and stroke[19,20]) and non-cardiovascular conditions (infection,[21,22] bleeding,[23,24] venous thromboembolism,[25,26] and fracture[27,28]). However, to the researchers' knowledge, there has been no study examining the extent to which these conditions explain the increased risk of all-cause hospitalisation in patients with CKD. Identification of more common and specific causes of admission among patients with CKD is warranted to reaffirm the importance of identifying CKD in primary care and guide areas of focus for outpatient management of these patients.

Therefore, this study aimed to quantify the association between CKD and cause-specific hospitalisation, using a primary care database linked to hospital admission data. The main purpose of the study was to estimate and rank the size of absolute risk difference and relative risk between patients with and without CKD (matched for age, sex, GP, and calendar time) across 10 common causes of hospital admission.

METHOD

Data sources

The Clinical Practice Research Datalink (CPRD) is a database of routinely recorded

M Iwagami, MSc, MD, MPH, research degree student; **L Smeeth**, PhD, FRCGP, professor of clinical epidemiology; **LA Tomlinson**, MSc, MBBS, PhD, associate professor; **D Nitsch**, MSc, MD, professor of clinical epidemiology and honorary consultant nephrologist, Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London. **B Caplin**, PhD, FRCP, senior clinical lecturer, Centre for Nephrology, University College London, London.

Address for correspondence
Masao Iwagami, Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.

Email: masao.iwagami@lshtm.ac.uk

Submitted: 11 January 2018; **Editor's response:** 5 February 2018; **final acceptance:** 28 March 2018.

How this fits in

Although chronic kidney disease (CKD) is associated with a wide range of adverse outcomes, more strongly associated conditions with hospital admission among patients with CKD are unknown. This study is the first to examine the association between CKD and common reasons for hospital admission in a systematic way and highlights the high burden of hospitalisation due to heart failure, infection, and acute kidney injury among patients with CKD compared with the general population. These findings suggest that, aside from prevention of end-stage kidney disease, there are important high-priority outcomes that warrant identification of CKD in primary care and improved preventive care of patients with CKD in the community.

primary care electronic health record data.[29] The database represents around 7% of the UK population and includes the following information: patient demographics; coded diagnoses (Read Codes); prescriptions; laboratory test results; and referrals made by GPs. The CPRD can be linked with Hospital Episode Statistics (HES), which contains details of all hospital admissions at NHS hospitals in England and consists of main and subsidiary diagnoses, using the 10th revision of International Classification of Disease (ICD-10) codes.[30] Currently around 400 GPs in CPRD have consented to linkage with HES, representing 75% of English practices in CPRD.[29]

Study population and matched cohort

All adults in HES-linked CPRD from 1 April 2004 to 31 March 2014 were potentially eligible for inclusion. Patients were eligible for inclusion at the latest of: 1 year after practice registration,[31] the date that the GP reached CPRD quality standards,[29] and 1 April 2004. Patients already on renal replacement therapy (haemodialysis, peritoneal dialysis, or kidney transplantation) at cohort entry were excluded.

First, patients with CKD (stages 3–5) were identified, defined as two consecutive measurements of eGFR <60 ml/min/1.73 m^2 for ≥3 months.[32] Estimated GFR was calculated from serum creatinine records in CPRD (after multiplication of 0.95 to allow for lack of creatinine calibration[33]) using the Chronic Kidney Disease Epidemiology Collaboration equation.[34] Patients, including those who had CKD before April 2004, were included in the cohort on the date when they first satisfied the CKD definition (second eGFR <60 mL/min/1.73 m^2) after their eligibility.

Second, for a comparison group, patients without known CKD were randomly selected from the rest of the study population in a 1:1 ratio, matched for age, sex, GP, and calendar time.

Outcomes and follow-up

The primary diagnosis in the first episode (a single period of care under one consultant team) within a spell (a patient's entire stay in hospital) in the HES was examined; this was considered to be the main reason why a patient required hospital admission.[30] Outcomes of this study were hospitalisations for 10 common conditions as the primary admission diagnosis: heart failure; urinary tract infection; pneumonia; AKI; myocardial infarction; cerebral infarction; gastrointestinal bleeding; hip fracture; venous thromboembolism; and intracranial bleeding, defined using ICD-10 codes (Appendix 1). In this study, the researchers focused on the first hospitalisation for each condition after cohort entry.

For each outcome, a patient was followed up until the first hospitalisation for that outcome or the end of eligibility (initiation of renal replacement therapy, death, change of GP, last data collection from the GP, or 31 March 2014), meaning that every patient could develop more than one of the outcomes. In addition, individuals selected in the comparison group (patients without known CKD) could be found to have CKD later; in this situation they were censored at the time of satisfying the CKD definition because they were already included in the CKD group from that point forward.

Covariates

In addition to the matched factors, the researchers accounted for potential confounders in the association between CKD and cause-specific hospitalisation: ethnicity; socioeconomic status; smoking status; body mass index (BMI); and 17 comorbidities (asthma, atrial fibrillation, cancer, chronic obstructive pulmonary disease [COPD], coronary heart disease, dementia, depression, diabetes mellitus, epilepsy, heart failure, hypertension, hypothyroidism, severe mental illness, osteoporosis, peripheral arterial disease, rheumatoid arthritis, and stroke and transient ischaemic attack [TIA]).

Patients with no record of ethnicity were classed as white, based on previous studies in UK primary care.[35,36] Socioeconomic status was assigned by quintile at an individual level using the Index of Multiple

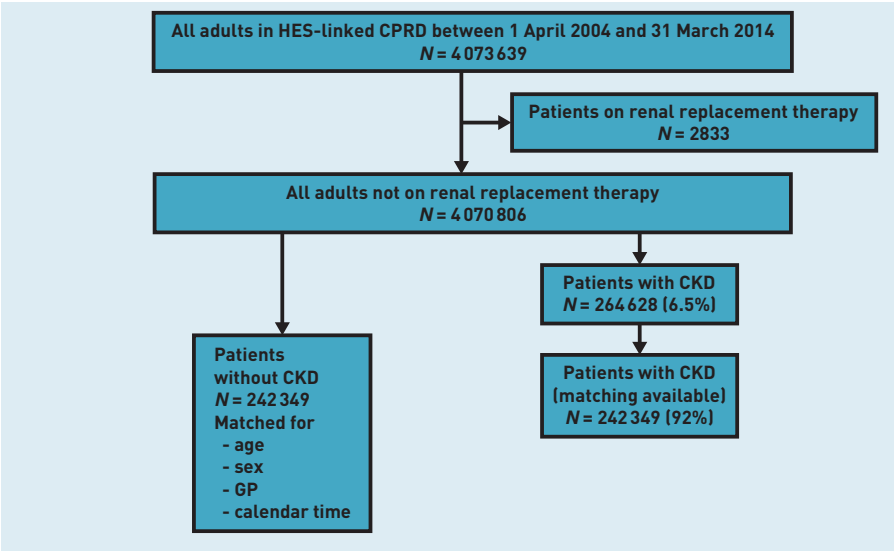


Figure 1. Selection method of matched patients with and without CKD from the general population. CKD = chronic kidney disease. CPRD = Clinical Practice Research Datalink. HES = Hospital Episode Statistics.

Deprivation as a composite area-level marker of deprivation.[37] Smoking status and BMI were assigned using the data recorded closest to the cohort entry. The definitions of hypertension and diabetes were based on relevant diagnosis codes recorded before the cohort entry or prescription (antihypertensive and antidiabetic drugs, respectively) in the past 1 year prior to the cohort entry. Other comorbidities were based on relevant diagnosis codes recorded before the cohort entry.

Statistical analysis

The baseline characteristics of matched patients with and without CKD were compared using χ^2 tests. Incidence rates of each outcome in matched patients with and without CKD, respectively, were estimated and a difference of incidence rates between the groups was calculated. Multivariate Cox regression analyses for each outcome were then conducted, stratified by matched set to account for the matching on age, sex, GP, and calendar time (Model 1). Further adjustments were made for ethnicity, socioeconomic and smoking status, BMI, and diabetes mellitus (Model 2). Instead of excluding patients with a missing status of smoking or BMI from the analysis, an additional absent category was included for these patients to maintain the matched set between patients with and without CKD. Subsequently, adjustments for comorbidities not directly related to CKD (asthma, cancer, COPD, dementia, depression, epilepsy, hypothyroidism, severe mental illness, osteoporosis, and rheumatoid arthritis)[38] (Model 3) were made, and also for comorbidities, which may occur concordantly with CKD (atrial fibrillation, coronary heart disease, heart failure, hypertension, peripheral arterial disease, stroke and TIA)[38] (Model 4). A fully adjusted sub-hazard ratio for each outcome using the Fine and Gray model was estimated to account for potential competing risk (initiation of renal replacement therapy and death) between patients with and without CKD. Because of the computational burden related to size of the dataset, this competing risk analysis was conducted using a 20% random sample of the whole dataset. All the statistical analyses were carried out using STATA (version 14).

Subgroup analyses

Several subgroup analyses were conducted. First, as previous studies suggested that the impact of CKD on outcomes may change with age,[39,40] all the analyses were repeated by classifying the study population into two age groups; ≥75 and <75 years. Second, to examine the extent of graded association between CKD stage and cause-specific hospitalisation, the researchers conducted Cox regression analyses by dividing patients with CKD according to baseline CKD stage: 3a (eGFR 45–59 mL/min/1.73 m^2), 3b (eGFR 30–44 mL/min/1.73 m^2), and 4 or 5 (eGFR <30 mL/min/1.73 m^2).[32] Third, to see the impact of CKD on cause-specific hospitalisation among patients with no history of cardiovascular disease, patients with either diagnosis of atrial fibrillation, coronary heart disease, heart failure, peripheral arterial disease, and stroke and TIA at the cohort entry were excluded, and Cox regression analyses were performed by CKD stage. In the second and third subgroup analyses where the matched nature between patients with and without CKD was no longer maintained, adjustments for age, sex, and financial year were made, and robust standard errors to allow for clustering by GP were used, instead of stratification by matched set in the Cox regression models.

RESULTS

Among 4 070 806 eligible patients not requiring renal replacement therapy (mean age 42.7 [SD 18.8] years, male 48.8%), the researchers identified 264 628 (6.5%) patients with CKD (mean age 76.4 [SD 10.0] years, male 38.7%) (Figure 1). Of those with CKD, 242 349 (92%) were matched with patients without CKD (mean age 75.4 [SD 9.7] years, male 39.3%). Unmatched 22 279 patients with CKD (8% of those with CKD) were older and more likely to be female (mean age 87.9 [SD 5.4] years, male 31.5%). Patients with CKD were more likely to have a deprived

socioeconomic status, be ex-smokers, and overweight, with a larger number of comorbidities (Table 1). Total length of follow-up, if not censored for each cause-specific hospitalisation, was 2.0 million person-years (mean 4.2 [SD 2.9] years/person).

Table 1. Baseline characteristics of matched patients with and without chronic kidney disease

Characteristic	Patients without CKD *N* = 242 349 *n* (%)	Patients with CKD *N* = 242 349 *n* (%)	*P*-value
Age, years			1.000
<55	6845 (2.8)	6845 (2.8)	
55–64	23 556 (9.7)	23 556 (9.7)	
65–74	71 112 (29.3)	71 112 (29.3)	
75–84	102 594 (42.3)	102 594 (42.3)	
≥85	38 242 (15.8)	38 242 (15.8)	
Sex (male)	95 318 (39.3)	95 318 (39.3)	1.000
Ethnicity			<0.001
White/not recorded	238 533 (98.4)	238 138 (98.3)	
South Asian	1796 (0.7)	2317 (1.0)	
Black	1156 (0.5)	1060 (0.4)	
Other	864 (0.4)	834 (0.3)	
Socioeconomic status			<0.001
1 (least deprived)	56 800 (23.4)	53 034 (21.9)	
2	61 647 (25.4)	60 501 (25.0)	
3	50 466 (20.8)	50 709 (20.9)	
4	42 221 (17.4)	44 692 (18.4)	
5 (most deprived)	31 215 (12.9)	33 413 (13.8)	
Smoking status			<0.001
Non-smoker	92 363 (38.1)	80 721 (33.3)	
Ex-smoker	107 737 (44.5)	131 510 (54.3)	
Current smoker	36 338 (15.0)	29 243 (12.1)	
Missing	5911 (2.4)	875 (0.4)	
Body mass index, kg/m²			<0.001
<18.5	6638 (2.7)	4562 (1.9)	
18.5–25	85 473 (35.3)	70 102 (28.9)	
≥25	80 458 (33.2)	88 083 (36.4)	
≥30	40 326 (16.6)	63 183 (26.1)	
Missing	29 454 (12.2)	16 419 (6.8)	
Comorbidities			
Asthma	28 002 (11.6)	31 271 (12.9)	<0.001
Atrial fibrillation	15 448 (6.4)	29 515 (12.2)	<0.001
Cancer	47 431 (19.6)	54 450 (22.5)	<0.001
Chronic obstructive pulmonary disease	14 996 (6.2)	18 229 (7.5)	<0.001
Coronary heart disease	27 961 (11.5)	54 049 (22.3)	<0.001
Dementia	8954 (3.7)	7345 (3.0)	<0.001
Depression	38 490 (15.9)	46 233 (19.1)	<0.001
Diabetes mellitus	24 372 (10.1)	52 927 (21.8)	<0.001
Epilepsy	3972 (1.6)	3682 (1.5)	0.001
Heart failure	7581 (3.1)	23 774 (9.8)	<0.001
Hypertension	128 828 (53.2)	203 963 (84.2)	<0.001
Hypothyroidism	17 443 (7.2)	29 318 (12.1)	<0.001
Severe mental illness	3522 (1.5)	4890 (2.0)	<0.001
Osteoporosis	16 469 (6.8)	16 610 (6.9)	0.422
Peripheral arterial disease	7481 (3.1)	14 815 (6.1)	<0.001
Rheumatoid arthritis	4270 (1.8)	6031 (2.5)	<0.001
Stroke and transient ischaemic attack	12 243 (5.1)	19 982 (8.3)	<0.001

CKD = chronic kidney disease

Among the 10 cause-specific hospitalisations, the largest incidence rate difference was seen for heart failure at 6.6/1000 person-years (9.7/1000 versus 3.1/1000 person-years in matched patients with and without CKD, respectively), followed by urinary tract infection at 5.2/1000 person-years, pneumonia at 4.4/1000 person-years, and AKI at 4.1/1000 person-years (Table 2). Hip fracture, venous thromboembolism, and intracranial bleeding marked relatively small differences of incidence rates between matched patients with and without CKD.

The relative risk was consistently highest for AKI, followed by heart failure in all the models, though the rank order of other outcomes varied depending on the extent of adjustment for confounding factors (Table 3). The age- and sex-adjusted hazard ratio for AKI in Model 1 was 6.49, 95% CI = 5.99 to 7.03, followed by heart failure with 3.28, 95% CI = 3.15 to 3.41. The fully adjusted hazard ratio for AKI in Model 4 was 4.90, 95% CI = 4.47 to 5.38, followed by heart failure with 1.66, 95% CI = 1.59 to 1.75. Intracranial bleeding and hip fracture marked relatively small fully adjusted hazard ratios. Results of competing risk analyses were generally similar to or slightly higher than those estimated in the main analysis. Likewise, AKI and heart failure exhibited higher sub-hazard ratios than others.

In subgroup analysis by age, the incidence rate difference between matched patients with and without CKD tended to be larger and the relative risk tended to be smaller in the older subgroup (≥75 years of age) than the younger subgroup (<75 years of age) for almost all the cause-specific hospitalisations (Table 4). However, the rank order in the size of absolute rate difference and relative risk was almost the same as the main results in each age group.

Of 242 349 matched patients with CKD, 71.2% (*n* = 172 555) , 22.9% (*n* = 55 500), and 5.9%, (*n* = 14 294) patients were in stage 3a, 3b, and 4 or 5, respectively. Patients tended to be older and sicker as kidney function declined. Details of baseline characteristics of patients with different stages of CKD are available from the authors. There were graded associations between CKD stage and all the cause-specific hospitalisations, but the strength of the association was larger for AKI and heart failure (Figure 2 and Appendix 2).

Among patients with no history of cardiovascular disease, the strength of the association was similar to that in the main analysis for all the studied cause-specific hospitalisations (Appendix 3).

Table 2. Difference in the incidence rate of cause-specific hospitalisation between matched patients with and without chronic kidney disease by rank order of rate difference

	Number of outcome, *n*		Incidence rate per 1000 person-years (95%CI)		
Cause of hospitalisation	Patients with CKD (*N* = 242 349)	Patients without CKD (*N* = 242 349)	Patients with CKD	Patients without CKD	Rate difference
Heart failure	10 394	2955	9.7 (9.5 to 9.9)	3.1 (3.0 to 3.2)	6.6 (6.4 to 6.8)
Urinary tract infection	14 266	7654	13.1 (12.9 to 13.3)	7.9 (7.7 to 8.1)	5.2 (4.9 to 5.5)
Pneumonia	13 483	7803	12.6 (12.4 to 12.8)	8.2 (8.0 to 8.4)	4.4 (4.1 to 4.7)
Acute kidney injury	5257	787	4.9 (4.7 to 5.0)	0.8 (0.8 to 0.9)	4.1 (3.9 to 4.2)
Myocardial infarction	7418	3590	6.9 (6.8 to 7.1)	3.8 (3.6 to 3.9)	3.2 (3.0 to 3.4)
Cerebral infarction	6142	3335	5.7 (5.6 to 5.8)	3.5 (3.4 to 3.6)	2.2 (2.0 to 2.4)
Gastrointestinal bleeding	5492	3048	5.1 (5.0 to 5.2)	3.2 (3.1 to 3.3)	1.9 (1.7 to 2.1)
Hip fracture	9336	6751	8.7 (8.6 to 8.9)	7.1 (7.0 to 7.3)	1.6 (1.4 to 1.9)
Venous thromboembolism	3299	1882	3.1 (3.0 to 3.2)	2.0 (1.9 to 2.1)	1.1 (1.0 to 1.2)
Intracranial bleeding	2144	1427	2.0 (1.9 to 2.1)	1.5 (1.4 to 1.6)	0.5 (0.4 to 0.6)

CKD = chronic kidney disease.

DISCUSSION

Summary

In this population-based cohort study, among people with CKD (stages 3–5) large absolute increases in rates of hospitalisations due to heart failure, infection (urinary tract infection and pneumonia), and AKI were found, compared with age- and sex-matched controls without known CKD from the same GP. Before and after adjustment for confounding factors, the relative risk of hospitalisation was highest for AKI, followed by heart failure. Results were similar in subgroup analyses by age and CKD stage, and among patients with no history of cardiovascular disease. The vast majority of patients in the cohort had CKD stage 3a or 3b so would be primarily diagnosed and managed in primary care, making these findings useful and relevant

Table 3. Relative risk for cause-specific hospitalisation between matched patients with and without chronic kidney disease by rank order of fully adjusted hazard ratio

	Adjusted hazard ratio (95% CI)[a]				Fully adjusted sub-hazard ratio (95% CI)[b]
Cause of hospitalisation	Model 1	Model 2	Model 3	Model 4 (fully adjusted model)	
Acute kidney injury	6.49 (5.99 to 7.03)	5.95 (5.46 to 6.47)	5.82 (5.34 to 6.35)	4.90 (4.47 to 5.38)	4.98 (4.23 to 5.87)
Heart failure	3.28 (3.15 to 3.41)	2.84 (2.73 to 2.96)	2.79 (2.67 to 2.90)	1.66 (1.59 to 1.75)	2.07 (1.88 to 2.28)
Venous thromboembolism	1.60 (1.53 to 1.68)	1.57 (1.49 to 1.65)	1.54 (1.46 to 1.62)	1.55 (1.46 to 1.64)	1.57 (1.37 to 1.80)
Myocardial infarction	1.84 (1.78 to 1.91)	1.70 (1.64 to 1.76)	1.67 (1.61 to 1.73)	1.40 (1.34 to 1.46)	1.53 (1.38 to 1.69)
Urinary tract infection	1.62 (1.58 to 1.67)	1.53 (1.49 to 1.57)	1.50 (1.46 to 1.54)	1.39 (1.35 to 1.43)	1.59 (1.50 to 1.69)
Gastrointestinal bleeding	1.59 (1.53 to 1.66)	1.55 (1.49 to 1.62)	1.52 (1.46 to 1.58)	1.34 (1.28 to 1.40)	1.55 (1.41 to 1.72)
Cerebral infarction	1.55 (1.49 to 1.61)	1.51 (1.46 to 1.58)	1.51 (1.45 to 1.58)	1.27 (1.22 to 1.33)	1.45 (1.30 to 1.60)
Pneumonia	1.47 (1.43 to 1.51)	1.46 (1.42 to 1.50)	1.44 (1.40 to 1.49)	1.24 (1.20 to 1.29)	1.49 (1.39 to 1.59)
Hip fracture	1.11 (1.08 to 1.14)	1.18 (1.14 to 1.21)	1.17 (1.13 to 1.21)	1.11 (1.07 to 1.15)	1.37 (1.27 to 1.48)
Intracranial bleeding	1.28 (1.21 to 1.36)	1.30 (1.22 to 1.38)	1.29 (1.21 to 1.38)	1.10 (1.02 to 1.19)	1.30 (1.11 to 1.52)

[a]Adjusted hazard ratio (patients with chronic kidney disease versus those without) was estimated in the following Cox regression models: Model 1: Stratified by matched set to account for the matching on age, sex, general practice, and calendar time. Model 2: Model 1 + adjusted by ethnicity, socioeconomic and smoking status, body mass index, and diabetes mellitus. Model 3: Model 2 + adjusted by comorbidities not directly related to chronic kidney disease (asthma, cancer, chronic obstructive pulmonary disease, dementia, depression, epilepsy, hypothyroidism, severe mental illness, osteoporosis, and rheumatoid arthritis). Model 4: Model 3 + adjusted by all the other comorbidities that may occur concordantly with chronic kidney disease (atrial fibrillation, coronary heart disease, heart failure, hypertension, peripheral arterial disease, and stroke and transient ischaemic attack). [b]Fully adjusted sub-hazard ratio was estimated by the model of Fine and Gray to account for competing risk (initiation of renal replacement therapy and death) between patients with and without chronic kidney disease, using a 20% random sample of the whole dataset.

Table 4. Difference in the incidence rate of cause-specific hospitalisation and relative risk between matched patients with and without chronic kidney disease by age

Causes hospitalisation	Patients aged ≥75 years (*N* = 140 836 matched pairs)				Patients aged <75 years (*N* = 101 513 matched pairs)			
	Incidence rate per 1000 person years				Incidence rate per 1000 person-years (95% CI)			
	Patients with CKD	Patients without CKD	Rate difference	Fully adjusted HR[a] (95% CI)	Patients with CKD	Patients without CKD	Rate difference	Fully adjusted HR[a] (95% CI)
Heart failure	13.0 (12.7 to 13.3)	4.8 (4.6 to 5.0)	8.2 (7.9 to 8.6)	1.61 (1.52 to 1.70)	6.0 (5.8 to 6.2)	1.4 (1.3 to 1.5)	4.6 (4.4 to 4.8)	1.78 (1.61 to 1.98)
Urinary tract infection	18.5 (18.2 to 18.9)	12.8 (12.5 to 13.1)	5.7 (5.2 to 6.2)	1.27 (1.23 to 1.32)	7.8 (7.6 to 8.0)	3.5 (3.3 to 3.6)	4.3 (4.0 to 4.6)	1.71 (1.61 to 1.81)
Pneumonia	17.4 (17.1 to 17.8)	12.6 (12.2 to 12.9)	4.9 (4.4 to 5.3)	1.17 (1.13 to 1.22)	7.2 (7.0 to 7.4)	3.9 (3.8 to 4.1)	3.3 (3.0 to 3.6)	1.46 (1.36 to 1.57)
Acute kidney injury	5.5 (5.3 to 5.7)	1.2 (1.1 to 1.3)	4.3 (4.1 to 4.5)	4.27 (3.80 to 4.80)	4.2 (4.0 to 4.4)	0.5 (0.4 to 0.5)	3.7 (3.5 to 3.9)	6.64 (5.62 to 7.84)
Myocardial infarction	8.8 (8.6 to 9.1)	5.0 (4.8 to 5.2)	3.9 (3.6 to 4.2)	1.43 (1.35 to 1.50)	4.8 (4.6 to 5.0)	2.6 (2.4 to 2.7)	2.2 (1.9 to 2.4)	1.34 (1.24 to 1.44)
Cerebral infarction	7.8 (7.6 to 8.1)	5.3 (5.1 to 5.5)	2.6 (2.3 to 2.9)	1.22 (1.16 to 1.29)	3.3 (3.2 to 3.5)	1.8 (1.6 to 1.9)	1.6 (1.4 to 1.8)	1.42 (1.29 to 1.56)
Gastrointestinal bleeding	6.3 (6.1 to 6.5)	4.2 (4.0 to 4.4)	2.1 (1.9 to 2.4)	1.34 (1.27 to 1.42)	3.7 (3.6 to 3.9)	2.2 (2.1 to 2.3)	1.5 (1.3 to 1.7)	1.31 (1.21 to 1.42)
Hip fracture	13.8 (13.5 to 14.1)	12.3 (12.0 to 12.6)	1.6 (1.1 to 2.0)	1.07 (1.03 to 1.11)	3.1 (2.9 to 3.2)	2.1 (2.0 to 2.3)	0.9 (0.7 to 1.1)	1.31 (1.19 to 1.43)
Venous thromboembolism	3.4 (3.2 to 3.5)	2.4 (2.3 to 2.6)	1.0 (0.8 to 1.2)	1.48 (1.37 to 1.60)	2.7 (2.6 to 2.8)	1.5 (1.4 to 1.6)	1.2 (1.0 to 1.4)	1.65 (1.50 to 1.81)
Intracranial bleeding	2.7 (2.5 to 2.8)	2.2 (2.1 to 2.3)	0.5 (0.3 to 0.7)	1.06 (0.97 to 1.16)	1.2 (1.1 to 1.3)	0.8 (0.7 to 0.9)	0.4 (0.3 to 0.5)	1.19 (1.03 to 1.37)

[a] *Fully adjusted hazard ratio (patients with versus without CKD) was estimated using Cox regression models, stratified by matched set to account for the matching on age, sex, general practice, and calendar time, and adjusted by ethnicity, socioeconomic and smoking status, body mass index, and comorbidities (asthma, atrial fibrillation, cancer, chronic obstructive pulmonary disease, coronary heart disease, dementia, depression, diabetes mellitus, epilepsy, heart failure, hypertension, hypothyroidism, severe mental illness, osteoporosis, peripheral arterial disease, rheumatoid arthritis, and stroke and transient ischaemic attack). CKD = chronic kidney disease. HR = hazard ratio.*

for routine clinical care.

Strengths and limitations

A major strength of this study was that it compared those with CKD to those without, sampled from the general population. A comparison was possible because over 98% of the UK population are registered with a primary care practice. The study results obtained from HES-linked CPRD are likely to be generalisable to the entire English population.[29]

Limitations of the study include, first, that patients who had never had kidney function tested were kept in the denominator in order for the comparison group to be representative of the general population. Currently in the UK, serum creatinine testing is recommended and incentivised for people with known CKD risk factors.[3,41] If some patients had been misclassified with unmeasured CKD to the matched comparison group, the true association between CKD and each cause-specific hospitalisation may have been underestimated. However, the researchers have recently shown that the prevalence of patients with an eGFR <60 mL/min/1.73 m^2 identified in CPRD was similar to that in a population-representative survey (Health Survey for England),[42] suggesting that most of these patients are captured with the current testing strategy in UK primary care, and people without creatinine tests are unlikely to have CKD stages 3–5.[43] If healthy people without creatinine measurement were excluded from the denominator, severe selection bias would arise and estimated absolute risk differences between patients with and without CKD would not be informative.[44]

Second, relative risks between CKD status (stage) and cause-specific hospitalisation depend partly on the extent of adjustment for potential confounders. Previous studies on the association between CKD and outcomes adjusted for disease diagnoses (based on patient charts, administrative claim data, or questionnaire answered by patients), physiological measurements, blood test results, or prescriptions to various degrees conclude that CKD is 'independently' associated with their studied outcomes.[15–28] However, the possibility of residual confounding inevitably remains. In this study, adjustments were made for important patient characteristics as well as diagnoses of 17 comorbidities. Recording of these conditions has been incentivised since the introduction of the UK Quality and Outcomes Framework in 2004,[3] resulting in marked improvements in data quality.[29] Further, differences of disease diagnosis

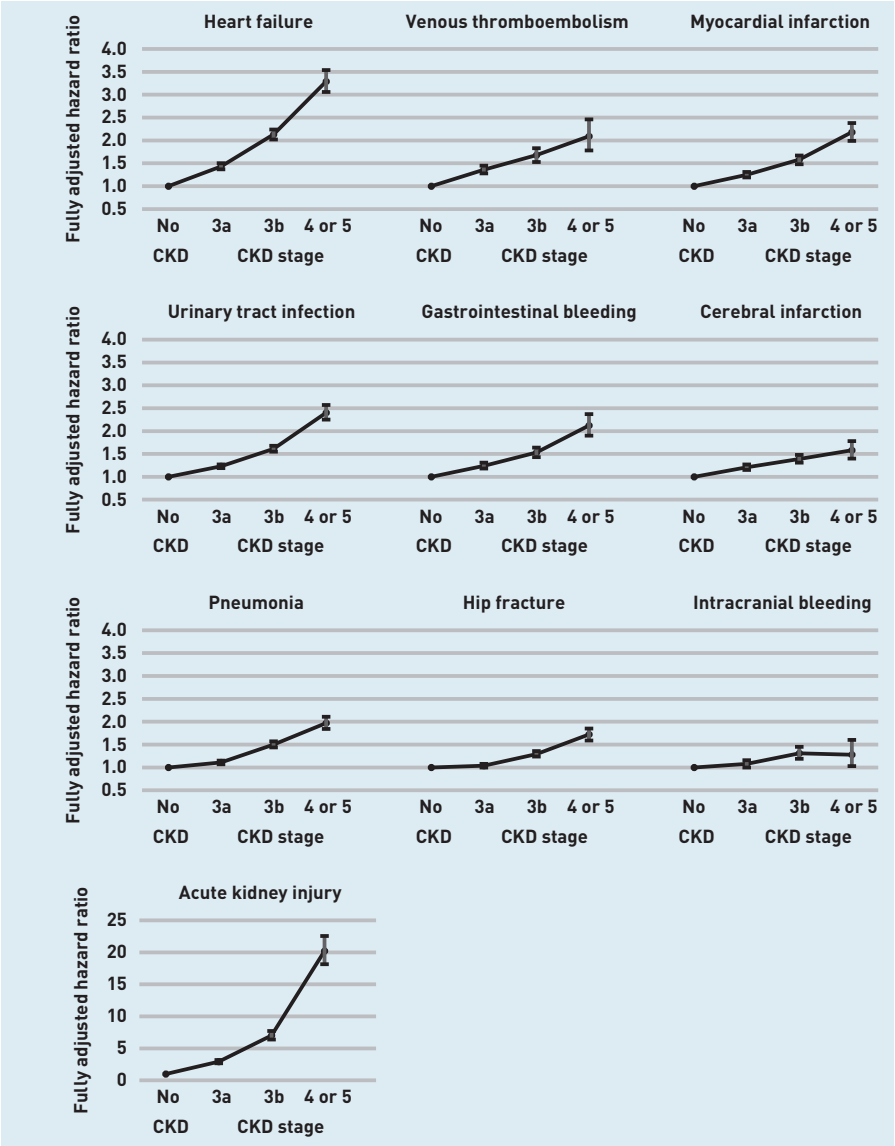


Figure 2. Fully adjusted hazard ratio for cause-specific hospitalisation by chronic kidney disease stage estimated using Cox regression models, adjusted by age, sex, financial year, ethnicity, socioeconomic and smoking status, body mass index, and comorbidities (asthma, atrial fibrillation, cancer, chronic obstructive pulmonary disease, coronary heart disease, dementia, depression, diabetes mellitus, epilepsy, heart failure, hypertension, hypothyroidism, severe mental illness, osteoporosis, peripheral arterial disease, rheumatoid arthritis, and stroke and transient ischaemic attack) and clustered by general practice using robust standard errors (corresponding to Appendix 2). CKD = chronic kidney disease.

and coding among different GPs and over time was minimised by matching on GP and calendar time between patients with and without CKD. Therefore, the authors believe that the best available approach of adjustment for confounding was used to compare the relative risks between CKD and different types of cause-specific hospitalisations.

Finally, although the researchers acknowledge that proteinuria is an important outcome prediction marker,[32] the authors of this study were not able to stratify patients by the level of proteinuria or quantify the association between proteinuria and cause-specific hospitalisation. This is because proteinuria was infrequently checked in CPRD: testing rate of proteinuria (including dipstick testing) in the year prior to cohort entry was 23.2% (56 431 out of 242 349 patients) in the CKD group and 12.6% (30 616 out of 242 349 patients) in the comparison group. It would not be appropriate to assume that people without urine testing did not have proteinuria.

Comparison with existing literature

There have been several studies demonstrating an association between CKD and increased risk of all-cause hospitalisations.[9,11–13] However, these studies did not clearly differentiate causes of hospitalisation, and therefore it remained unclear why this is the case. Meanwhile, a previous study recruiting patients with elevated serum creatinine suggested that cardiovascular disease and hypertension were the most common reason for hospitalisation, followed by infection.[45] However, in the absence of a comparison group without CKD, it remained unclear whether these hospitalisations were specific to CKD or common in the community regardless of CKD status.

As well as a known association between CKD and AKI,[46] a number of studies have reported positive associations between CKD and incidence of non-renal conditions.[15–28] Many of these studies used hospital admission for their outcome definitions. However, these individual studies did not allow a comparison of the impact of CKD across different outcomes, because absolute and relative risk related to CKD were estimated in different study populations and with various degrees of statistical adjustment for confounders. To the authors' knowledge, the current study is the first to quantify the association between CKD status (stage) and cause-specific hospitalisation.

Implications for research and practice

After the classification of CKD, and the implementation of testing and registering of patients with CKD through the Quality and Outcomes Framework for CKD in 2006,[3] some have questioned the benefits of this approach.[47] Patients with mild CKD may be perceived to have normal kidney ageing, or with multiple morbidities putting them at increased risk for many adverse outcomes. This study was planned to clarify the adverse outcomes (that were likely to be causally related to kidney function) that were more common and specific among patients with CKD in primary care, enabling the possibility of better-targeted care.

The adjusted hazard ratios were small for most of the outcomes in patients with CKD stage 3a (Figure 2), except for AKI with a threefold increase in the adjusted

hazard ratio for hospitalisations; and nearly one and a half-fold increase for heart failure. These results highlight the marked increase in risk of AKI and heart failure for patients with only mild reductions in kidney function, with implications for targeted prevention and medication management; for example, minimisation of non-steroidal antiinflammatory drug use.

Both absolute and relative risk provide important information about the impact of CKD on cause-specific hospitalisation.[40,48] The relative risk (adjusted hazard ratio) is a measure of the strength of the association between CKD and each cause-specific hospitalisation, after taking into account a range of comorbidities. Meanwhile, the absolute risk difference reflects the relative risk and the baseline frequency of each outcome in the community, indicating the actual burden of each condition among patients with CKD as compared with the general population. For example, infections, such as urinary tract infection and pneumonia, showed intermediate relative risks among the studied outcomes, but their absolute risk differences between patients with and without CKD were large because hospitalisations for infection were common in the general population. The absolute risk difference is also useful for understanding the potential benefits of preventive strategies. For example, Table 2 shows that 9.7 and 3.1 patients per 1000 patients with and without CKD (stages 3–5), respectively, were hospitalised for heart failure in a year, meaning that, of 1000 people with CKD, up to 6.6 could benefit from targeted heart failure admission prevention. This would translate to three people per year in a GP practice of 7400 patients (average number of patients per practice)[49] where 6.5% have CKD. Further estimates for all outcomes are available from the authors. However, these numbers are likely to be underestimates of the overall benefits because follow-up of patients at the time of first hospitalisation after cohort entry was stopped and, therefore, did not account for repeated admissions.

Patients with CKD, even without renal replacement therapy, are known to incur substantive healthcare costs through frequent hospitalisations.[10] Based on results from this study, a focus on strategies to reduce hospitalisations for heart failure, such as education on dietary salt restriction[50] and improved medication adherence,[51] could help to minimise the difference in the overall hospitalisation rate between patients with and without CKD. Similarly, a proportion of hospitalisations due to infections may be preventable through prompt antibiotic treatment and improvement of vaccination coverage among patients with CKD.[52] Pneumococcal vaccination has been underutilised in patients with CKD (stages 4 and 5) to date.[53]

Funding

Ben Caplin and Dorothea Nitsch were part-funded through a grant for the National CKD Audit commissioned by Healthcare Quality Improvement Partnership, which is funded by NHS England, the Welsh Government, and, with some individual audits, also funded by the Health Department of the Scottish Government, DHSSPS Northern Ireland, and the Channel Islands. Laurie A Tomlinson is funded by a Wellcome Intermediate Clinical Fellowship (reference: WT101143MA). Liam Smeeth is funded by a Wellcome Senior Research Fellowship in Clinical Science (grant number: 098504/Z/12/Z). Masao Iwagami is supported by Honjo International Scholarship Foundation. None of these funding sources had a role in the design, conduct, analysis, or reporting of the study.

Ethical approval

The study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency (reference number: 17_055R).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

Discuss this article

Contribute and read comments about this article: **bjgp.org/letters**

REFERENCES

1. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health* 2008; **8:** 117.
2. McCullough K, Sharma P, Ali T, *et al.* Measuring the population burden of chronic kidney disease: a systematic literature review of the estimated prevalence of impaired kidney function. *Nephrol Dial Transplant* 2012; **27(5):** 1812–1821.
3. Health and Social Care Information Centre. *Quality and Outcomes Framework.* http://www.nhsemployers.org/your-workforce/primary-care-contacts/general-medical-services/quality-and-outcomes-framework (accessed 26 Jun 2018).
4. McIntyre NJ, Fluck R, McIntyre C, *et al.* Treatment needs and diagnosis awareness in primary care patients with chronic kidney disease. *Br J Gen Pract* 2012; DOI: https://doi.org/10.3399/bjgp12X636047.
5. Winearls CG, Glassock RJ. Classification of chronic kidney disease in the elderly: pitfalls and errors. *Nephron Clin Pract* 2011; **119(Suppl 1):** c2–c4.
6. Ellam T, Twohig H, Khwaja A. Chronic kidney disease in elderly people: disease or disease label? *BMJ* 2016; **352:** h6559.
7. Moynihan R, Glassock R, Doust J. Chronic kidney disease controversy: how expanding definitions are unnecessarily labelling many people as diseased. *BMJ* 2013; **347:** f4298.
8. Blakeman T, Protheroe J, Chew-Graham C, *et al.* Understanding the management of early-stage chronic kidney disease in primary care: a qualitative study. *Br J Gen Pract* 2012; DOI: https://doi.org/10.3399/bjgp12X636056.
9. Go AS, Chertow GM, Fan D, *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351(13):** 1296–1305.
10. Kent S, Schlackow I, Lozano-Kuhne J, *et al.* What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? *BMC Nephrol* 2015; **16:** 65.
11. Nitsch D, Nonyane BA, Smeeth L, *et al.* CKD and hospitalization in the elderly: a community-based cohort study in the United Kingdom. *Am J Kidney Dis* 2011; **57(5):** 664–672.
12. Chan TC, Yap DY, Shea YF, *et al.* Chronic kidney disease and its association with mortality and hospitalization in Chinese nursing home older residents: a 3-year prospective cohort study. *J Am Med Dir Assoc* 2012; **13(9):** 782–787.
13. Nishikawa K, Takahashi K, Yamada R, *et al.* Influence of chronic kidney disease on hospitalization, chronic dialysis, and mortality in Japanese men: a longitudinal analysis. *Clin Exp Nephrol* 2017; **21(2):** 316–323.
14. Hsu CY, Ordonez JD, Chertow GM, *et al.* The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int* 2008; **74(1):** 101–107.
15. Meisinger C, Doring A, Lowel H. Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. *Eur Heart J* 2006; **27(10):** 1245–1250.
16. Hemmelgarn BR, Manns BJ, Lloyd A, *et al.* Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 2010; **303(5):** 423–429.
17. Kottgen A, Russell SD, Loehr LR, *et al.* Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol* 2007; **18(4):** 1307–1315.
18. Dhingra R, Gaziano JM, Djousse L. Chronic kidney disease and the risk of heart failure in men. *Circ Heart Fail* 2011; **4(2):** 138–144.
19. Mahmoodi BK, Yatsuya H, Matsushita K, *et al.* Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. *Stroke* 2014; **45(7):** 1925–1931.
20. Koren-Morag N, Goldbourt U, Tanne D. Renal dysfunction and risk of ischemic stroke or TIA in patients with cardiovascular disease. *Neurology* 2006; **67(2):** 224–228.
21. Dalrymple LS, Katz R, Kestenbaum B, *et al.* The risk of infection-related hospitalization with decreased kidney function. *Am J Kidney Dis* 2012; **59(3):** 356–363.
22. Ishigami J, Grams ME, Chang AR, *et al.* CKD and risk for hospitalization with infection: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2017; **69:** 752–761.
23. Molnar AO, Bota SE, Garg AX, *et al.* The risk of major hemorrhage with CKD. *J Am Soc Nephrol* 2016; **27(9):** 2825–2832.
24. Ishigami J, Grams ME, Naik RP, *et al.* Chronic kidney disease and risk for gastrointestinal bleeding in the community: the Atherosclerosis Risk in Communities (ARIC) Study. *Clin J Am Soc Nephrol* 2016; **11(10):** 1735–1743.
25. Wattanakit K, Cushman M, Stehman-Bree C, *et al.* Chronic kidney disease increases risk for venous thromboembolism. *J Am Soc Nephrol* 2008; **19(1):** 135–140.
26. Mahmoodi BK, Gansevoort RT, Naess IA, *et al.* Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. *Circulation* 2012; **126(16):** 1964–1971.
27. Naylor KL, McArthur E, Leslie WD, *et al.* The three-year incidence of fracture in chronic kidney disease. *Kidney Int* 2014; **86(4):** 810–818.
28. Daya NR, Voskertchian A, Schneider AL, *et al.* Kidney function and fracture risk: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2016; **67(2):** 218–226.
29. Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44(3):** 827–836.
30. Herbert A, Wijlaars L, Zylbersztejn A, *et al.* Data resource profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017; **46(4):** 1093–1093i.
31. Lewis JD, Bilker WB, Weinstein RB, *et al.* The relationship between time since registration and measured incidence rates in the General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2005; **14(7):** 443–451.
32. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; **3:** 1–150.
33. Levey AS, Coresh J, Greene T, *et al.* Expressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53(4):** 766–772.
34. Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150(9):** 604–612.
35. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. *BMJ* 2012; **344:** e3427.
36. Hippisley-Cox J, Coupland C. Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores. *BMJ* 2014; **349:** g4606.
37. Ministry of Housing, Communities and Local Government. *English indices of deprivation.* https://www.gov.uk/government/collections/english-indices-of-deprivation (accessed 29 Jun 2018).
38. Tonelli M, Wiebe N, Guthrie B, *et al.* Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. *Kidney Int* 2015; **88(4):** 859–866.
39. James MT, Quan H, Tonelli M, *et al.* CKD and risk of hospitalization and death with pneumonia. *Am J Kidney Dis* 2009; **54(1):** 24–32.
40. Hallan SI, Matsushita K, Sang Y, *et al.* Age and association of kidney measures with mortality and end-stage renal disease. *JAMA* 2012; **308(22):** 2349–2360.
41. National Institute for Health and Care Excellence. *Chronic kidney disease: early identification and management of chronic disease in adults in primary and secondary care.* CG73. London: NICE, 2008.
42. Roth M, Roderick P, Mindell J. Kidney disease and renal function. In: Craig R, and Mindell J, eds. *Health survey for England 2010: volume 1 respiratory health.* 2011. https://files.digital.nhs.uk/publicationimport/pub03xxx/pub03023/heal-surv-eng-2010-resp-heal-ch8-kidn.pdf (accessed 26 Jun 2018).
43. Iwagami M, Tomlinson M, Mansfield KE, *et al.* Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom. *Nephrol Dial Transplant* 2017; **32(Suppl 2):** ii142–ii150.
44. McDonald HI, Shaw C, Thomas, SL, *et al.* Methodological challenges when carrying out research on CKD and AKI using routine electronic health records. *Kidney Int* 2016; **90(5):** 943–949.
45. Khan SS, Kazmi WH, Abichandani R, *et al.* Health care utilization among patients with chronic kidney disease. *Kidney Int* 2002; **62(1):** 229–236.
46. Chawla LS, Eggers PW, Star RA, *et al.* Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014; **371(1):** 58–66.
47. Spence D. Bad medicine: chronic kidney disease. *BMJ* 2010; **340:** c3188.
48. Foley RN, Murray AM, Li S, *et al.* Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005; **16(2):** 489–495.
49. Health and Social Care Information Centre. *General practice trends in the UK to 2015.* http://content.digital.nhs.uk/media/21726/General-Practice-Trends-in-the-UK-to-2015/pdf/General_Practice_Trends_in_the_UK_to_2015.pdf. (accessed 29 Jun 2018).
50. Mills KT, Chen J, Yang W, *et al.* Sodium excretion and the risk of cardiovascular

disease in patients with chronic kidney disease. *JAMA* 2016; **315(20):** 2200–2210.

51. Herzog CA, Asinger RW, Berger AK, *et al*. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011; **80(6):** 572–586.

52. McDonald HI, Thomas SL, Millett ERC, *et al*. Do influenza and pneumococcal vaccines prevent community-acquired respiratory infections among older people with diabetes and does this vary by chronic kidney disease? A cohort study using electronic health records: *BMJ Open Diabetes Res Care* 2017; **5(1):** e000332.

53. Health Quality Improvement Partnership. *National Chronic Kidney Disease Audit: national report (Part 1)*. 2017. https://www.hqip.org.uk/resources/national-chronic-kidney-disease-audit-national-report-part-1/ (accessed 30 Apr 2018).

Appendix 1. List of International Classification of Diseases 10th Revision codes used to identify cause-specific hospitalisations

Outcome	International Classification of Diseases 10th Revision codes
Myocardial infarction	I21, I22, I23
Heart failure	I50
Cerebral infarction	I63
Pneumonia	B01.2, B05.2, B20.6, B25.0, J10.0, J11.0, J12, J13, J14, J15, J16, J17, J18, J85.1, U04
Urinary tract infection	N10, N12, N13.6, N15.1, N15.9, N30.0, N30.8, N30.9, N39.0
Gastrointestinal bleeding	I85.0, K22.6, K25.0, K25.1, K25.2, K25.4, K25.5, K25.6, K26.0, K26.1, K26.2, K26.4, K26.5, K26.6, K27.0, K27.1, K27.2, K27.4, K27.5, K27.6, K28.0, K28.1, K28.2, K28.4, K28.5, K28.6, K29.0, K92.0, K92.1, K92.2
Intracranial bleeding	I60, I61, I62, S06.5, S06.6
Venous thromboembolism	I80.1, I80.2, I80.3, I81, I82.2, I82.3, I82.8, I82.9, I26
Hip fracture	S72
Acute kidney injury	N17

Appendix 2. Fully adjusted hazard ratio for cause-specific hospitalisation by chronic kidney disease stage

	Fully adjusted hazard ratio (95% CI)[a] by CKD stage			
		Patients with CKD (*N* = 242 349)		
Cause of hospitalisation	Patients without CKD (*N* = 242 349)	CKD stage 3a (*N* = 172 555)	CKD stage 3b (*N* = 55 500)	CKD stage 4 or 5 (*N* = 14 294)
Acute kidney injury	1[b]	2.94 (2.69 to 3.20)	7.03 (6.39 to 7.73)	20.22 (18.14 to 22.54)
Heart failure	1[b]	1.43 (1.37 to 1.50)	2.13 (2.02 to 2.24)	3.29 (3.06 to 3.54)
Venous thromboembolism	1[b]	1.36 (1.28 to 1.45)	1.68 (1.53 to 1.83)	2.09 (1.78 to 2.46)
Myocardial infarction	1[b]	1.25 (1.19 to 1.31)	1.58 (1.48 to 1.67)	2.18 (1.99 to 2.38)
Urinary tract infection	1[b]	1.23 (1.19 to 1.27)	1.61 (1.55 to 1.68)	2.40 (2.25 to 2.57)
Gastrointestinal bleeding	1[b]	1.24 (1.18 to 1.31)	1.53 (1.43 to 1.64)	2.12 (1.90 to 2.37)
Cerebral infarction	1[b]	1.21 (1.15 to 1.27)	1.39 (1.31 to 1.48)	1.58 (1.40 to 1.78)
Pneumonia	1[b]	1.11 (1.07 to 1.15)	1.50 (1.44 to 1.57)	1.97 (1.84 to 2.11)
Hip fracture	1[b]	1.04 (1.00 to 1.08)	1.29 (1.24 to 1.36)	1.72 (1.59 to 1.85)
Intracranial bleeding	1[b]	1.08 (1.00 to 1.16)	1.31 (1.19 to 1.45)	1.28 (1.03 to 1.60)

[a]Fully adjusted hazard ratio was estimated using Cox regression models, adjusted by age, sex, financial year, ethnicity, socioeconomic and smoking status, body mass index, and comorbidities (asthma, atrial fibrillation, cancer, chronic obstructive pulmonary disease, coronary heart disease, dementia, depression, diabetes mellitus, epilepsy, heart failure, hypertension, hypothyroidism, severe mental illness, osteoporosis, peripheral arterial disease, rheumatoid arthritis, and stroke and transient ischaemic attack) and clustered by general practice using robust standard errors. [b]Reference. CKD = chronic kidney disease.

Appendix 3. Fully adjusted hazard ratio for cause-specific hospitalisation by chronic kidney disease stage among patients with no history of cardiovascular disease

	Fully adjusted hazard ratio (95% CI)[a] by CKD stage			
		Patients with CKD (*N* = 143 715)		
Cause of hospitalisation	**Patients without CKD (*N* = 187 322)**	**CKD stage 3a (*N* = 107 803)**	**CKD stage 3b (*N* = 29 085)**	**CKD stage 4 or 5 (*N* = 6827)**
Acute kidney injury	1[b]	2.65 (2.39 to 2.93)	7.09 (6.29 to 8.00)	24.20 (21.22 to 27.61)
Heart failure	1[b]	1.25 (1.17 to 1.35)	1.95 (1.78 to 2.14)	3.41 (2.96 to 3.94)
Venous thromboembolism	1[b]	1.43 (1.33 to 1.54)	1.66 (1.48 to 1.85)	2.23 (1.80 to 2.76)
Myocardial infarction	1[b]	1.25 (1.16 to 1.34)	1.61 (1.47 to 1.76)	2.24 (1.92 to 2.60)
Urinary tract infection	1[b]	1.27 (1.21 to 1.33)	1.75 (1.66 to 1.85)	3.15 (2.87 to 3.46)
Gastrointestinal bleeding	1[b]	1.29 (1.20 to 1.38)	1.56 (1.41 to 1.72)	2.13 (1.79 to 2.54)
Cerebral infarction	1[b]	1.19 (1.11 to 1.28)	1.45 (1.33 to 1.58)	1.56 (1.31 to 1.86)
Pneumonia	1[b]	1.14 (1.09 to 1.19)	1.56 (1.47 to 1.65)	2.33 (2.11 to 2.58)
Hip fracture	1[b]	1.03 (0.98 to 1.08)	1.27 (1.19 to 1.35)	1.69 (1.50 to 1.91)
Intracranial bleeding	1[b]	1.10 (0.99 to 1.21)	1.42 (1.24 to 1.63)	1.35 (0.98 to 1.85)

[a]After excluding patients with a history of cardiovascular disease (atrial fibrillation, coronary heart disease, heart failure, peripheral arterial disease, or stroke and transient ischaemic attack) from the matched patients with and without CKD, fully adjusted hazard ratios were estimated using Cox regression models, adjusted by age, sex, financial year, ethnicity, socioeconomic and smoking status, body mass index, and comorbidities (asthma, cancer, chronic obstructive pulmonary disease, dementia, depression, diabetes mellitus, epilepsy, hypertension, hypothyroidism, severe mental illness, osteoporosis, and rheumatoid arthritis) and clustered by general practice using robust standard errors. [b]Reference. CKD = chronic kidney disease.

Appendix B: List of diagnosis codes indicative of severe mental illness in the Clinical Practice Research Datalink

Read code	Medcode	Read term
Schizophrenia:		
E104.00	576	Acute schizophrenic episode
E10..00	854	Schizophrenic disorders
E103.00	1494	Paranoid schizophrenia
E100200	3984	Chronic schizophrenic
1464.00	6325	H/O: schizophrenia
E10z.00	8407	Schizophrenia NOS
E103z00	9281	Paranoid schizophrenia NOS
E100000	15733	Unspecified schizophrenia
Eu20000	16764	[X]Paranoid schizophrenia
Eu2..00	17281	[X]Schizophrenia, schizotypal and delusional disorders
Eu20y13	18053	[X]Schizophrenifrm psychos NOS
Eu20211	20572	[X]Catatonic stupor
Eu20400	20785	[X]Post-schizophrenic depression
ZV11000	22104	[V]Personal history of schizophrenia
E100100	23616	Subchronic schizophrenia
Eu20511	24107	[X]Chronic undifferentiated schizophrenia
E102.00	25546	Catatonic schizophrenia
Eu23112	26143	[X]Cycloid psychosis with symptoms of schizophrenia
E101.00	30619	Hebephrenic schizophrenia
E103200	31362	Chronic paranoid schizophrenia
Eu20214	31493	[X]Schizophrenic flexibilatis cerea
E100.00	32222	Simple schizophrenia
E10y000	33338	Atypical schizophrenia
E103000	33383	Unspecified paranoid schizophrenia
Eu20.00	34236	[X]Schizophrenia
Eu20z00	34966	[X]Schizophrenia, unspecified
Eu20600	35848	[X]Simple schizophrenia
Eu20213	35877	[X]Schizophrenic catatonia
E103500	36172	Paranoid schizophrenia in remission
E106.00	38063	Residual schizophrenia
E10y.00	39062	Other schizophrenia
Eu21.15	40386	[X]Prodromal schizophrenia
Eu20100	43405	[X]Hebephrenic schizophrenia
E100400	44498	Acute exacerbation of chronic schizophrenia
E101z00	48054	Hebephrenic schizophrenia NOS
Eu20y00	49420	[X]Other schizophrenia
E10yz00	49761	Other schizophrenia NOS
Eu21.16	49852	[X]Pseudoneurotic schizophrenia
Eu20011	50060	[X]Paraphrenic schizophrenia
E103300	51322	Acute exacerbation of subchronic paranoid schizophrenia
E103400	53032	Acute exacerbation of chronic paranoid schizophrenia
E100z00	53625	Simple schizophrenia NOS
Eu20111	53985	[X]Disorganised schizophrenia
Eu21.12	54387	[X]Borderline schizophrenia
ZS7C611	57376	Schizophrenic language

E100300	57666	Acute exacerbation of subchronic schizophrenia
E100500	58687	Schizophrenia in remission
E102000	58716	Unspecified catatonic schizophrenia
Eu20300	60013	[X]Undifferentiated schizophrenia
Eu20200	61501	[X]Catatonic schizophrenia
Eu21.14	62449	[X]Prepsychotic schizophrenia
E102z00	63867	Catatonic schizophrenia NOS
Eu20500	64264	[X]Residual schizophrenia
Eu20212	64533	[X]Schizophrenic catalepsy
Eu21.13	64993	[X]Latent schizophrenia
E105.00	66410	Latent schizophrenia
E101000	66506	Unspecified hebephrenic schizophrenia
E101500	67768	Hebephrenic schizophrenia in remission
Eu21.17	71250	[X]Pseudopsychopathic schizophrenia
E100.11	73295	Schizophrenia simplex
Eu21.11	91511	[X]Latent schizophrenic reaction
Eu20311	91547	[X]Atypical schizophrenia
E10y.11	92994	Cenesthopathic schizophrenia
Eu20y12	94001	[X]Schizophreniform disord NOS
E105200	94299	Chronic latent schizophrenia
Eu23214	94604	[X]Schizophrenic reaction
E105500	96883	Latent schizophrenia in remission
E101400	97919	Acute exacerbation of chronic hebephrenic schizophrenia
E107.11	99000	Cyclic schizophrenia
E10y100	99070	Coenesthopathic schizophrenia
E102100	99199	Subchronic catatonic schizophrenia
E105000	102311	Unspecified latent schizophrenia
E102500	102427	Catatonic schizophrenia in remission
E105z00	102446	Latent schizophrenia NOS
E103100	104760	Subchronic paranoid schizophrenia
Eu25211	104763	[X]Cyclic schizophrenia
E102400	107222	Acute exacerbation of chronic catatonic schizophrenia
Bipolar disorder:		
Eu31.11	1531	[X]Manic-depressive illness
Eu30000	2741	[X]Hypomania
E114.00	3702	Bipolar affective disorder, currently manic
E115.00	4677	Bipolar affective disorder, currently depressed
Eu30z11	4678	[X]Mania NOS
Eu31500	4732	[X]Bipolar affect dis cur epi severe depres with psyc symp
Eu31.12	6710	[X]Manic-depressive psychosis
Eu31.00	6874	[X]Bipolar affective disorder
E11..11	8567	Bipolar psychoses
Eu30.11	9521	[X]Bipolar disorder, single manic episode
146D.00	11548	H/O: manic depressive disorder
E11y000	11596	Unspecified manic-depressive psychoses
Eu30.00	12173	[X]Manic episode
E115.11	12831	Manic-depressive - now depressed
Eu30100	13024	[X]Mania without psychotic symptoms
E110100	14728	Single manic episode, mild
E117.00	14784	Unspecified bipolar affective disorder

E115000	15923	Bipolar affective disorder, currently depressed, unspecified
E114300	16347	Bipolar affect disord, currently manic, severe, no psychosis
Eu31300	16562	[X]Bipolar affect disorder cur epi mild or moderate depressn
Eu31000	16808	[X]Bipolar affective disorder, current episode hypomanic
E114.11	17385	Manic-depressive - now manic
E110.11	18909	Hypomanic psychoses
E111000	19967	Recurrent manic episodes, unspecified
E110000	20110	Single manic episode, unspecified
Eu30200	21065	[X]Mania with psychotic symptoms
ZV11112	22080	[V]Personal history of manic-depressive psy
Eu31400	23713	[X]Bipol aff disord, curr epis sev depress, no psychot symp
ZV11111	23963	[V]Personal history of manic-depressive psy
E117600	24230	Unspecified bipolar affective disorder, in full remission
E110200	24640	Single manic episode, moderate
E116100	24689	Mixed bipolar affective disorder, mild
E11..13	26161	Manic psychoses
E111.00	26227	Recurrent manic episodes
Eu31100	26299	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Eu31700	27584	[X]Bipolar affective disorder, currently in remission
E111200	27739	Recurrent manic episodes, moderate
E115200	27890	Bipolar affective disorder, currently depressed, moderate
E117z00	27986	Unspecified bipolar affective disorder, NOS
Eu31200	28277	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu33312	28677	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33213	29451	[X]Manic-depress psychosis,depressd,no psychotic symptoms
ZRby100	30282	Profile of mood states, bipolar
E116.00	31316	Mixed bipolar affective disorder
E116000	31535	Mixed bipolar affective disorder, unspecified
Eu30y00	32088	[X]Other manic episodes
E111400	32295	Recurrent manic episodes, severe, with psychosis
E11yz00	33426	Other and unspecified manic-depressive psychoses NOS
Eu31z00	33751	[X]Bipolar affective disorder, unspecified
E115300	35607	Bipolar affect disord, now depressed, severe, no psychosis
E115100	35734	Bipolar affective disorder, currently depressed, mild
E114000	35738	Bipolar affective disorder, currently manic, unspecified
E114100	36126	Bipolar affective disorder, currently manic, mild
E110z00	36611	Manic disorder, single episode NOS
E110.00	37070	Manic disorder, single episode
Eu30211	37102	[X]Mania with mood-congruent psychotic symptoms
E111600	37178	Recurrent manic episodes, in full remission
E115z00	37296	Bipolar affective disorder, currently depressed, NOS
E110300	43093	Single manic episode, severe without mention of psychosis
Eu30z00	44513	[X]Manic episode, unspecified
Eu31600	44693	[X]Bipolar affective disorder, current episode mixed
E111z00	46415	Recurrent manic episode NOS
E111100	46425	Recurrent manic episodes, mild
E114200	46434	Bipolar affective disorder, currently manic, moderate
Eu30212	48632	[X]Mania with mood-incongruent psychotic symptoms
E117000	49763	Unspecified bipolar affective disorder, unspecified
E110400	50218	Single manic episode, severe, with psychosis

Eu31y12	51032	[X]Recurrent manic episodes
Eu31y00	53840	[X]Other bipolar affective disorders
E116400	54195	Mixed bipolar affective disorder, severe, with psychosis
E116600	55064	Mixed bipolar affective disorder, in full remission
E114400	55829	Bipolar affect disord, currently manic,severe with psychosis
E115600	57465	Bipolar affective disorder, now depressed, in full remission
E114z00	57605	Bipolar affective disorder, currently manic, NOS
E111500	58863	Recurrent manic episodes, partial or unspecified remission
E114500	59011	Bipolar affect disord,currently manic, part/unspec remission
E11y.00	60178	Other and unspecified manic-depressive psychoses
E116200	63150	Mixed bipolar affective disorder, moderate
E116300	63284	Mixed bipolar affective disorder, severe, without psychosis
E116z00	63583	Mixed bipolar affective disorder, NOS
E116500	63651	Mixed bipolar affective disorder, partial/unspec remission
E117100	63698	Unspecified bipolar affective disorder, mild
E115400	63701	Bipolar affect disord, now depressed, severe with psychosis
E114600	63784	Bipolar affective disorder, currently manic, full remission
E111300	65811	Recurrent manic episodes, severe without mention psychosis
Eu31.13	66153	[X]Mainc-depressive reaction
E117400	68326	Unspecified bipolar affective disorder,severe with psychosis
E117200	68647	Unspecified bipolar affective disorder, moderate
E110600	70000	Single manic episode in full remission
E11y300	70399	Other mixed manic-depressive psychoses
E117500	70721	Unspecified bipolar affect disord, partial/unspec remission
E11y100	70925	Atypical manic disorder
E115500	72026	Bipolar affect disord, now depressed, part/unspec remission
E117300	73423	Unspecified bipolar affective disorder, severe, no psychosis
Eu31y11	73924	[X]Bipolar II disorder
Other nonorganic psychotic illnesses:		
Eu2z.11	694	[X]Psychosis NOS
Eu22011	2113	[X]Paranoid psychosis
E107.00	2117	Schizo-affective schizophrenia
E11..12	2560	Depressive psychoses
E13z.11	3636	Psychotic episode NOS
E121.00	3890	Chronic paranoid psychosis
E12..00	4261	Paranoid states
Eu22015	4843	[X]Paranoia
E130.00	8478	Reactive depressive psychosis
Eu25.00	9422	[X]Schizoaffective disorders
E107z00	10575	Schizo-affective schizophrenia NOS
Eu25100	11055	[X]Schizoaffective disorder, depressive type
Eu22012	11172	[X]Paranoid state
Eu2z.00	11244	[X]Unspecified nonorganic psychosis
Eu23200	11778	[X]Acute schizophrenia-like psychotic disorder
Eu24.13	11973	[X]Induced psychotic disorder
Eu32300	12099	[X]Severe depressive episode with psychotic symptoms
E12z.00	12771	Paranoid psychosis NOS
146H.00	12777	H/O: psychosis
E11..00	14656	Affective psychoses
E120.00	14743	Simple paranoid state

E13z.00	14965	Nonorganic psychosis NOS
E122.00	14971	Paraphrenia
E133.00	15053	Acute paranoid reaction
E1...00	15958	Non-organic psychoses
E13y.00	16333	Other reactive psychoses
E1y..00	16537	Other specified non-organic psychoses
Eu33315	16861	[X]Recurrent severe episodes of psychotic depression
Eu25011	16905	[X]Schizoaffective psychosis, manic type
E130.11	17770	Psychotic reactive depression
E13..11	20228	Reactive psychoses
Eu23012	21455	[X]Cycloid psychosis
Eu23100	21595	[X]Acute polymorphic psychot disord with symp of schizophren
E13y000	22117	Psychogenic stupor
E1z..00	22188	Non-organic psychosis NOS
E13y100	23538	Brief reactive psychosis
Eu33311	23731	[X]Endogenous depression with psychotic symptoms
Eu32313	24112	[X]Single episode of psychotic depression
Eu32311	24117	[X]Single episode of major depression and psychotic symptoms
E113400	24171	Recurrent major depressive episodes, severe, with psychosis
E134.00	24345	Psychogenic paranoid psychosis
Eu23.00	25019	[X]Acute and transient psychotic disorders
E13yz00	26119	Other reactive psychoses NOS
Eu21.18	26859	[X]Schizotypal personality disorder
Eu23312	27770	[X]Psychogenic paranoid psychosis
Eu44.14	28168	[X]Hysterical psychosis
Eu22.00	28562	[X]Persistent delusional disorders
Eu32314	28863	[X]Single episode of reactive depressive psychosis
Eu23z12	29651	[X]Reactive psychosis
E131.00	29937	Acute hysterical psychosis
Eu2y.00	30985	[X]Other nonorganic psychotic disorders
E12yz00	31455	Other paranoid states NOS
E12y.00	31589	Other paranoid states
Eu3z.11	31633	[X]Affective psychosis NOS
Eu23z11	31707	[X]Brief reactive psychosis NOS
Eu2y.11	31738	[X]Chronic hallucinatory psychosis
Eu33314	31757	[X]Recurr severe episodes/psychogenic depressive psychosis
E13..00	31984	Other nonorganic psychoses
E112400	32159	Single major depressive episode, severe, with psychosis
Eu33313	32941	[X]Recurr severe episodes/major depression+psychotic symptom
Eu25z11	33410	[X]Schizoaffective psychosis NOS
E11zz00	33425	Other affective psychosis NOS
Eu25200	33693	[X]Schizoaffective disorder, mixed type
Eu25000	33847	[X]Schizoaffective disorder, manic type
Eu23z00	34168	[X]Acute and transient psychotic disorder, unspecified
Eu22000	34389	[X]Delusional disorder
Eu25111	35274	[X]Schizoaffective psychosis, depressive type
Eu23000	36720	[X]Acute polymorphic psychot disord without symp of schizoph
Eu25212	37580	[X]Mixed schizophrenic and affective psychosis
Eu25z00	37681	[X]Schizoaffective disorder, unspecified
Eu33316	37764	[X]Recurrent severe episodes/reactive depressive psychosis

Eu21.00	39316	[X]Schizotypal disorder
Eu22y11	40981	[X]Delusional dysmorphophobia
Eu25112	41022	[X]Schizophreniform psychosis, depressive type
E11z.00	41992	Other and unspecified affective psychoses
E107200	43800	Chronic schizo-affective schizophrenia
Eu23300	44307	[X]Other acute predominantly delusional psychotic disorders
Eu23y00	44503	[X]Other acute and transient psychotic disorders
Eu33300	47009	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu24.12	47230	[X]Induced paranoid disorder
Eu22013	47947	[X]Paraphrenia - late
Eu22z00	49223	[X]Persistent delusional disorder, unspecified
Eu23011	50023	[X]Bouffee delirante
Eu22y12	50248	[X]Involutional paranoid state
E123.11	50868	Folie a deux
Eu24.00	51302	[X]Induced delusional disorder
Eu25012	51903	[X]Schizophreniform psychosis, manic type
Eu32312	52678	[X]Single episode of psychogenic depressive psychosis
Eu84314	53848	[X]Symbiotic psychosis
E11z000	54607	Unspecified affective psychoses NOS
Eu22111	55221	[X]Capgras syndrome
Eu22y13	55236	[X]Paranoia querulans
E107500	56438	Schizo-affective schizophrenia in remission
Eu25y00	58532	[X]Other schizoaffective disorders
E107000	58862	Unspecified schizo-affective schizophrenia
E107300	58866	Acute exacerbation subchronic schizo-affective schizophrenia
Eu23211	59096	[X]Brief schizophreniform disorder
E107100	61098	Subchronic schizo-affective schizophrenia
E212200	61969	Schizotypal personality
Eu22100	62405	[X]Delusional misidentification syndrome
E123.00	62680	Shared paranoid disorder
E107400	63478	Acute exacerbation of chronic schizo-affective schizophrenia
Eu22014	65127	[X]Sensitiver Beziehungswahn
Eu22y00	66077	[X]Other persistent delusional disorders
E12y000	66766	Paranoia querulans
E133.11	68058	Bouffee delirante
Eu23212	70884	[X]Brief schizophrenifrm psych
E104.11	93167	Oneirophrenia
Eu32800	98417	[X]Major depression, severe with psychotic symptoms
Eu22200	98821	[X]Cotard syndrome
Eu24.11	105606	[X]Folie a deux

Appendix C: List of diagnosis codes suggesting gastrointestinal bleeding in the Clinical Practice Research Datalink

Read code	Medcode	Read term
J68z.11	1642	GIB - Gastrointestinal bleeding
J12y100	2814	Unspecified duodenal ulcer with haemorrhage
J68..00	3097	Gastrointestinal haemorrhage
J68z200	4354	Upper gastrointestinal haemorrhage
J68zz00	4636	Gastrointestinal tract haemorrhage NOS
14CA.00	10534	H/O: GIT haemorrhage NOS
J110111	11124	Bleeding acute gastric ulcer
J68z.00	12471	Gastrointestinal haemorrhage unspecified
J68z000	15517	Gastric haemorrhage NOS
J10y000	16114	Haemorrhage of oesophagus
J120100	18001	Acute duodenal ulcer with haemorrhage
J121111	18625	Bleeding chronic duodenal ulcer
7619100	23813	Gastrotomy and ligation of bleeding point of stomach
J12yy00	28366	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J110100	30054	Acute gastric ulcer with haemorrhage
14CD.00	34466	H/O: upper GIT haemorrhage
J111111	36583	Bleeding chronic gastric ulcer
J130100	44637	Acute peptic ulcer with haemorrhage
J130300	45304	Acute peptic ulcer with haemorrhage and perforation
J120300	48730	Acute duodenal ulcer with haemorrhage and perforation
J121100	48951	Chronic duodenal ulcer with haemorrhage
J131100	53126	Chronic peptic ulcer with haemorrhage
J11y100	57958	Unspecified gastric ulcer with haemorrhage
J111100	63582	Chronic gastric ulcer with haemorrhage
J13y100	70456	Unspecified peptic ulcer with haemorrhage
J110300	71403	Acute gastric ulcer with haemorrhage and perforation
J121300	71881	Chronic duodenal ulcer with haemorrhage and perforation
J111300	71897	Chronic gastric ulcer with haemorrhage and perforation
J12y300	93436	Unspecified duodenal ulcer with haemorrhage and perforation
J11yy00	94397	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J13y300	96622	Unspecified peptic ulcer with haemorrhage and perforation
J140100	96628	Acute gastrojejunal ulcer with haemorrhage
G852000	96756	Oesophageal varices with bleeding in diseases EC

Appendix D: List of diagnosis codes used to define covariates in the Clinical Practice Research Datalink

Read code	Medcode	Read term
Diabetes mellitus:		
C100112	506	Non-insulin dependent diabetes mellitus
C10..00	711	Diabetes mellitus
C10F.00	758	Type 2 diabetes mellitus
C100011	1038	Insulin dependent diabetes mellitus
F420.00	1323	Diabetic retinopathy
C10FJ00	1407	Insulin treated Type 2 diabetes mellitus
C10E.00	1549	Type 1 diabetes mellitus
C108.00	1647	Insulin dependent diabetes mellitus
C101.00	1682	Diabetes mellitus with ketoacidosis
66A4.00	1684	Diabetic on oral treatment
F381311	2340	Diabetic amyotrophy
F372.12	2342	Diabetic neuropathy
66AJ.00	2378	Diabetic - poor control
K01x100	2471	Nephrotic syndrome in diabetes mellitus
C104.11	2475	Diabetic nephropathy
66AJ100	2478	Brittle diabetes
F420200	2986	Preproliferative diabetic retinopathy
F420100	3286	Proliferative diabetic retinopathy
F420400	3837	Diabetic maculopathy
C109.00	4513	Non-insulin dependent diabetes mellitus
F372.11	5002	Diabetic polyneuropathy
C109.11	5884	NIDDM - Non-insulin dependent diabetes mellitus
66AS.00	6125	Diabetic annual review
9NM0.00	6430	Attending diabetes clinic
C108700	6509	Insulin dependent diabetes mellitus with retinopathy
C108800	6791	Insulin dependent diabetes mellitus - poor control
14F4.00	7045	H/O: Admission in last year for diabetes foot problem
8H2J.00	7059	Admit diabetic emergency
F420000	7069	Background diabetic retinopathy
M037200	7328	Cellulitis in diabetic foot
66A3.00	7563	Diabetic on diet only
C106.12	7795	Diabetes mellitus with neuropathy
C109700	8403	Non-insulin dependent diabetes mellitus - poor control
66AR.00	8836	Diabetes management plan given
66A5.00	8842	Diabetic on insulin
66AJ.11	9013	Unstable diabetes
2BBL.00	9835	O/E - diabetic maculopathy present both eyes
M271200	9881	Mixed diabetic ulcer - foot
42W..00	9958	Hb. A1C - diabetic control
9N1v.00	9974	Seen in diabetic eye clinic
C10yy00	10098	Other specified diabetes mellitus with other spec comps
F420300	10099	Advanced diabetic maculopathy
C10ED00	10418	Type 1 diabetes mellitus with nephropathy
ZC2C800	10642	Dietary advice for diabetes mellitus
F464000	10659	Diabetic cataract

C10EM00	10692	Type 1 diabetes mellitus with ketoacidosis
F420600	10755	Non proliferative diabetic retinopathy
9N1i.00	10824	Seen in diabetic foot clinic
66Ac.00	10977	Diabetic peripheral neuropathy screening
8HBG.00	11018	Diabetic retinopathy 12 month review
66AH000	11047	Conversion to insulin
9NND.00	11094	Under care of diabetic foot screener
2BBQ.00	11129	O/E - left eye background diabetic retinopathy
2BBP.00	11433	O/E - right eye background diabetic retinopathy
8B3l.00	11471	Diabetes medication review
7276.00	11599	Pan retinal photocoagulation for diabetes
F420z00	11626	Diabetic retinopathy NOS
M271100	11663	Neuropathic diabetic ulcer - foot
8H7r.00	11677	Refer to diabetic foot screener
8BL2.00	12213	Patient on maximal tolerated therapy for diabetes
8I6G.00	12247	Diabetic foot examination not indicated
8I3X.00	12262	Diabetic retinopathy screening refused
66AU.00	12307	Diabetes care by hospital only
C10E.11	12455	Type I diabetes mellitus
66AP.00	12506	Diabetes: practice programme
C10FC00	12640	Type 2 diabetes mellitus with nephropathy
66AQ.00	12675	Diabetes: shared care programme
66AI.00	13071	Diabetic - good control
13AC.00	13078	Diabetic weight reducing diet
2BBT.00	13097	O/E - right eye proliferative diabetic retinopathy
2BBR.00	13099	O/E - right eye preproliferative diabetic retinopathy
2BBV.00	13101	O/E - left eye proliferative diabetic retinopathy
2BBW.00	13102	O/E - right eye diabetic maculopathy
2BBS.00	13103	O/E - left eye preproliferative diabetic retinopathy
2BBX.00	13108	O/E - left eye diabetic maculopathy
C104y00	13279	Other specified diabetes mellitus with renal complications
42WZ.00	14049	Hb. A1C - diabetic control NOS
42c..00	14050	HbA1 - diabetic control
C100100	14803	Diabetes mellitus, adult onset, no mention of complication
C100111	14889	Maturity onset diabetes
C103.00	15690	Diabetes mellitus with ketoacidotic coma
C106.00	16230	Diabetes mellitus with neurological manifestation
66AH.00	16490	Diabetic treatment changed
C106.13	16491	Diabetes mellitus with polyneuropathy
C104.00	16502	Diabetes mellitus with renal manifestation
ZV65312	16881	[V]Dietary counselling in diabetes mellitus
F171100	17067	Autonomic neuropathy due to diabetes
2G5A.00	17095	O/E - Right diabetic foot at risk
14P3.00	17236	H/O: insulin therapy
F35z000	17247	Diabetic mononeuritis NOS
C109600	17262	Non-insulin-dependent diabetes mellitus with retinopathy
F440700	17313	Diabetic iritis
C108F11	17545	Type I diabetes mellitus with diabetic cataract
7L19800	17817	Subcutaneous injection of insulin
C108.12	17858	Type 1 diabetes mellitus

C109.12	17859	Type 2 diabetes mellitus
66AL.00	17869	Diabetic-uncooperative patient
66AM.00	17886	Diabetic - follow-up default
2G5C.00	18056	Foot abnormality - diabetes related
N030000	18142	Diabetic cheiroarthropathy
C109G11	18143	Type II diabetes mellitus with arthropathy
66AT.00	18167	Annual diabetic blood test
C109012	18209	Type 2 diabetes mellitus with renal complications
C109.13	18219	Type II diabetes mellitus
C108J12	18230	Type 1 diabetes mellitus with neuropathic arthropathy
C109J12	18264	Insulin treated Type II diabetes mellitus
C109J00	18278	Insulin treated Type 2 diabetes mellitus
68A7.00	18311	Diabetic retinopathy screening
C10E700	18387	Type 1 diabetes mellitus with retinopathy
C10FM00	18390	Type 2 diabetes mellitus with persistent microalbuminuria
C10FB00	18425	Type 2 diabetes mellitus with polyneuropathy
C10F600	18496	Type 2 diabetes mellitus with retinopathy
C108.11	18505	IDDM-Insulin dependent diabetes mellitus
C10EH00	18642	Type 1 diabetes mellitus with arthropathy
8HBH.00	18662	Diabetic retinopathy 6 month review
C10E500	18683	Type 1 diabetes mellitus with ulcer
8I6F.00	18747	Diabetic retinopathy screening not indicated
C10F000	18777	Type 2 diabetes mellitus with renal complications
8I3W.00	18824	Diabetic foot examination declined
8HTk.00	19381	Referral to diabetic eye clinic
68A9.00	19739	Diabetic retinopathy screening offered
66AA.11	20696	Injection sites - diabetic
C102.00	21482	Diabetes mellitus with hyperosmolar coma
C108012	21983	Type 1 diabetes mellitus with renal complications
66AJz00	22023	Diabetic - poor control NOS
C106z00	22573	Diabetes mellitus NOS with neurological manifestation
66Ab.00	22823	Diabetic foot examination
C10EP00	22871	Type 1 diabetes mellitus with exudative maculopathy
C10F.11	22884	Type II diabetes mellitus
2BBF.00	22967	Retinal abnormality - diabetes related
C350011	23479	Bronzed diabetes
8A13.00	24363	Diabetic stabilisation
C108.13	24423	Type I diabetes mellitus
C109711	24458	Type II diabetes mellitus - poor control
C100000	24490	Diabetes mellitus, juvenile type, no mention of complication
F372200	24571	Asymptomatic diabetic neuropathy
C109G00	24693	Non-insulin dependent diabetes mellitus with arthropathy
C108B00	24694	Insulin dependent diabetes mellitus with mononeuropathy
C109C12	24836	Type 2 diabetes mellitus with nephropathy
ZC2CA00	25041	Dietary advice for type II diabetes
C10FQ00	25591	Type 2 diabetes mellitus with exudative maculopathy
C10F700	25627	Type 2 diabetes mellitus - poor control
C10FL00	26054	Type 2 diabetes mellitus with persistent proteinuria
2G5B.00	26664	O/E - Left diabetic foot at risk
2G5E.00	26666	O/E - Right diabetic foot at low risk

2G5I.00	26667	O/E - Left diabetic foot at low risk
C108400	26855	Unstable insulin dependent diabetes mellitus
N030100	27891	Diabetic Charcot arthropathy
2G51000	27921	Foot abnormality - diabetes related
66AV.00	28769	Diabetic on insulin and oral treatment
8CP2.00	28856	Transition of diabetes care options discussed
66Ai.00	28873	Diabetic 6 month review
66AN.00	29041	Date diabetic treatment start
C109900	29979	Non-insulin-dependent diabetes mellitus without complication
TJ23000	30247	Adverse reaction to insulins
C10EL00	30294	Type 1 diabetes mellitus with persistent microalbuminuria
C10EK00	30323	Type 1 diabetes mellitus with persistent proteinuria
F420700	30477	High risk proliferative diabetic retinopathy
9N4p.00	30648	Did not attend diabetic retinopathy clinic
2G5J.00	31156	O/E - Left diabetic foot at moderate risk
2G5F.00	31157	O/E - Right diabetic foot at moderate risk
2G5G.00	31171	O/E - Right diabetic foot at high risk
2G5K.00	31172	O/E - Left diabetic foot at high risk
C108900	31310	Insulin dependent diabetes maturity onset
F372.00	31790	Polyneuropathy in diabetes
ZRbH.00	32359	Perceived control of insulin-dependent diabetes
C10FN00	32627	Type 2 diabetes mellitus with ketoacidosis
C105.00	33254	Diabetes mellitus with ophthalmic manifestation
C10y.00	33343	Diabetes mellitus with other specified manifestation
C10F200	34268	Type 2 diabetes mellitus with neurological complications
C105z00	34283	Diabetes mellitus NOS with ophthalmic manifestation
C10FK00	34450	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
3882.00	34528	Diabetes well being questionnaire
C109400	34912	Non-insulin dependent diabetes mellitus with ulcer
C104100	35105	Diabetes mellitus, adult onset, with renal manifestation
C104z00	35107	Diabetes mellitus with nephropathy NOS
2G5L.00	35116	O/E - Left diabetic foot - ulcerated
C10E800	35288	Type 1 diabetes mellitus - poor control
2G5H.00	35316	O/E - Right diabetic foot - ulcerated
8H3O.00	35321	Non-urgent diabetic admission
9OLD.00	35383	Diabetic patient unsuitable for digital retinal photography
C10FH00	35385	Type 2 diabetes mellitus with neuropathic arthropathy
F372100	35785	Chronic painful diabetic neuropathy
C109K00	36633	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10D.00	36695	Diabetes mellitus autosomal dominant type 2
7L10000	36798	Continuous subcutaneous infusion of insulin
F3y0.00	37315	Diabetic mononeuropathy
C109J11	37648	Insulin treated non-insulin dependent diabetes mellitus
M21yC00	38076	Insulin lipohypertrophy
ZRB6.00	38130	Diabetes wellbeing questionnaire
C108711	38161	Type I diabetes mellitus with retinopathy
C101y00	38617	Other specified diabetes mellitus with ketoacidosis
C100.00	38986	Diabetes mellitus with no mention of complication
C10EE00	39070	Type 1 diabetes mellitus with hypoglycaemic coma
C106100	39317	Diabetes mellitus, adult onset, + neurological manifestation

F381300	39420	Myasthenic syndrome due to diabetic amyotrophy
C108J00	39809	Insulin dependent diab mell with neuropathic arthropathy
C102000	40023	Diabetes mellitus, juvenile type, with hyperosmolar coma
C10E900	40682	Type 1 diabetes mellitus maturity onset
C10EN00	40837	Type 1 diabetes mellitus with ketoacidotic coma
C109H00	40962	Non-insulin dependent d m with neuropathic arthropathy
C108712	41049	Type 1 diabetes mellitus with retinopathy
C105100	41389	Diabetes mellitus, adult onset, + ophthalmic manifestation
Cyu2000	41686	[X]Other specified diabetes mellitus
C108C00	41716	Insulin dependent diabetes mellitus with polyneuropathy
C101z00	42505	Diabetes mellitus NOS with ketoacidosis
C103000	42567	Diabetes mellitus, juvenile type, with ketoacidotic coma
C108E11	42729	Type I diabetes mellitus with hypoglycaemic coma
C109612	42762	Type 2 diabetes mellitus with retinopathy
C10E200	42831	Type 1 diabetes mellitus with neurological complications
C102100	43139	Diabetes mellitus, adult onset, with hyperosmolar coma
C10F311	43227	Type II diabetes mellitus with multiple complications
C10C.00	43453	Diabetes mellitus autosomal dominant
M21yC11	43493	Insulin site lipohypertrophy
C109D00	43785	Non-insulin dependent diabetes mellitus with hypoglyca coma
C10M.00	43857	Lipoatrophic diabetes mellitus
C10E400	43921	Unstable type 1 diabetes mellitus
66AK.00	43951	Diabetic - cooperative patient
F345000	44033	Diabetic mononeuritis multiplex
C108F00	44260	Insulin dependent diabetes mellitus with diabetic cataract
9M10.00	44312	Informed dissent for diabetes national audit
C108E00	44440	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108500	44443	Insulin dependent diabetes mellitus with ulcer
C109E12	44779	Type 2 diabetes mellitus with diabetic cataract
C10FE00	44982	Type 2 diabetes mellitus with diabetic cataract
C10E312	45276	Insulin dependent diabetes mellitus with multiple complicat
C109B00	45467	Non-insulin dependent diabetes mellitus with polyneuropathy
C10z.00	45491	Diabetes mellitus with unspecified complication
C109712	45913	Type 2 diabetes mellitus - poor control
C108812	45914	Type 1 diabetes mellitus - poor control
C109212	45919	Type 2 diabetes mellitus with neurological complications
C108y00	46290	Other specified diabetes mellitus with multiple comps
C10EC00	46301	Type 1 diabetes mellitus with polyneuropathy
C10C.11	46624	Maturity onset diabetes in youth
C108811	46850	Type I diabetes mellitus - poor control
C10FD00	46917	Type 2 diabetes mellitus with hypoglycaemic coma
C108000	46963	Insulin-dependent diabetes mellitus with renal complications
8CS0.00	47032	Diabetes care plan agreed
8Hg4.00	47058	Discharged from care of diabetes specialist nurse
C10F711	47315	Type II diabetes mellitus - poor control
C10F100	47321	Type 2 diabetes mellitus with ophthalmic complications
2BBk.00	47328	O/E - right eye stable treated prolif diabetic retinopathy
8A12.00	47341	Diabetic crisis monitoring
8HLE.00	47370	Diabetology D.V. done
C105y00	47377	Other specified diabetes mellitus with ophthalmic complicatn

C109B11	47409	Type II diabetes mellitus with polyneuropathy
C10E000	47582	Type 1 diabetes mellitus with renal complications
F420500	47584	Advanced diabetic retinal disease
C10E100	47649	Type 1 diabetes mellitus with ophthalmic complications
C10E300	47650	Type 1 diabetes mellitus with multiple complications
C109H11	47816	Type II diabetes mellitus with neuropathic arthropathy
C10F900	47954	Type 2 diabetes mellitus without complication
F372000	48078	Acute painful diabetic neuropathy
C109E11	48192	Type II diabetes mellitus with diabetic cataract
ZV6DA00	48310	[V]Admitted for commencement of insulin
C10F400	49074	Type 2 diabetes mellitus with ulcer
C108211	49146	Type I diabetes mellitus with neurological complications
C108100	49276	Insulin-dependent diabetes mellitus with ophthalmic comps
C10EF00	49554	Type 1 diabetes mellitus with diabetic cataract
2G5W.00	49640	O/E - left chronic diabetic foot ulcer
C10F611	49655	Type II diabetes mellitus with retinopathy
C109G12	49869	Type 2 diabetes mellitus with arthropathy
6761.00	49884	Diabetic pre-pregnancy counselling
C10E411	49949	Unstable type I diabetes mellitus
66AW.00	50175	Diabetic foot risk assessment
C109011	50225	Type II diabetes mellitus with renal complications
C109100	50429	Non-insulin-dependent diabetes mellitus with ophthalm comps
C10FB11	50527	Type II diabetes mellitus with polyneuropathy
L180600	50609	Pre-existing diabetes mellitus, non-insulin-dependent
C109A11	50813	Type II diabetes mellitus with mononeuropathy
L180500	50960	Pre-existing diabetes mellitus, insulin-dependent
C100z00	50972	Diabetes mellitus NOS with no mention of complication
C10E.12	51261	Insulin dependent diabetes mellitus
C10G.00	51697	Secondary pancreatic diabetes mellitus
C10FP00	51756	Type 2 diabetes mellitus with ketoacidotic coma
ZV6DB00	51939	[V]Admitted for conversion to insulin
C108511	51957	Type I diabetes mellitus with ulcer
2BBl.00	52041	O/E - left eye stable treated prolif diabetic retinopathy
C108300	52104	Insulin dependent diabetes mellitus with multiple complicatn
Cyu2.00	52212	[X]Diabetes mellitus
9360.00	52237	Patient held diabetic record issued
C108200	52283	Insulin-dependent diabetes mellitus with neurological comps
C109000	52303	Non-insulin-dependent diabetes mellitus with renal comps
2BBo.00	52630	O/E - sight threatening diabetic retinopathy
C101000	53200	Diabetes mellitus, juvenile type, with ketoacidosis
66AG.00	53238	Diabetic drug side effects
C10F911	53392	Type II diabetes mellitus without complication
C110.11	53630	Insulin coma
R054200	53634	[D]Gangrene of toe in diabetic
C10EJ00	54008	Type 1 diabetes mellitus with neuropathic arthropathy
C10E412	54600	Unstable insulin dependent diabetes mellitus
9NN8.00	54601	Under care of diabetologist
C101100	54856	Diabetes mellitus, adult onset, with ketoacidosis
C109411	55075	Type II diabetes mellitus with ulcer
C10EQ00	55239	Type 1 diabetes mellitus with gastroparesis

L180X00	55431	Pre-existing diabetes mellitus, unspecified
C109200	55842	Non-insulin-dependent diabetes mellitus with neuro comps
C109D11	56268	Type II diabetes mellitus with hypoglycaemic coma
C108A00	56448	Insulin-dependent diabetes without complication
C10F011	57278	Type II diabetes mellitus with renal complications
N030011	57333	Diabetic cheiropathy
93C4.00	57389	Patient consent given for addition to diabetic register
C108D00	57621	Insulin dependent diabetes mellitus with nephropathy
8HHy.00	57723	Referral to diabetic register
ZLD7500	58133	Discharge by diabetic liaison nurse
8I3k.00	58159	Insulin therapy declined
C109611	58604	Type II diabetes mellitus with retinopathy
C10FG00	59253	Type 2 diabetes mellitus with arthropathy
C103y00	59288	Other specified diabetes mellitus with coma
C109C00	59365	Non-insulin dependent diabetes mellitus with nephropathy
C109111	59725	Type II diabetes mellitus with ophthalmic complications
C106.11	59903	Diabetic amyotrophy
C10D.11	59991	Maturity onset diabetes in youth type 2
C108411	60107	Unstable type I diabetes mellitus
C108J11	60208	Type I diabetes mellitus with neuropathic arthropathy
C10FL11	60796	Type II diabetes mellitus with persistent proteinuria
68AB.00	61021	Diabetic digital retinopathy screening offered
C109D12	61071	Type 2 diabetes mellitus with hypoglycaemic coma
TJ23z00	61210	Adverse reaction to insulins and antidiabetic agents NOS
C108011	61344	Type I diabetes mellitus with renal complications
9M00.00	61461	Informed consent for diabetes national audit
C110000	61520	Iatrogenic hyperinsulinism
C106y00	61523	Other specified diabetes mellitus with neurological comps
8HKE.00	61557	Diabetology D.V. requested
C108212	61829	Type 1 diabetes mellitus with neurological complications
C109300	62146	Non-insulin-dependent diabetes mellitus with multiple comps
C10EM11	62209	Type I diabetes mellitus with ketoacidosis
C108H11	62352	Type I diabetes mellitus with arthropathy
2G5V.00	62384	O/E - right chronic diabetic foot ulcer
C10EA11	62613	Type I diabetes mellitus without complication
C10FA00	62674	Type 2 diabetes mellitus with mononeuropathy
C108911	63017	Type I diabetes mellitus maturity onset
U602312	63364	[X] Adverse reaction to insulins
C10y100	63371	Diabetes mellitus, adult, + other specified manifestation
8CR2.00	63412	Diabetes clinical management plan
C10FR00	63690	Type 2 diabetes mellitus with gastroparesis
C10z100	63762	Diabetes mellitus, adult onset, + unspecified complication
8Hl1.00	64142	Referral for diabetic retinopathy screening
C10zy00	64283	Other specified diabetes mellitus with unspecified comps
C10zz00	64357	Diabetes mellitus NOS with unspecified complication
C108z00	64449	Unspecified diabetes mellitus with multiple complications
C109C11	64571	Type II diabetes mellitus with nephropathy
C10FJ11	64668	Insulin treated Type II diabetes mellitus
C103z00	65062	Diabetes mellitus NOS with ketoacidotic coma
C10F300	65267	Type 2 diabetes mellitus with multiple complications

F420800	65463	High risk non proliferative diabetic retinopathy
C108H00	65616	Insulin dependent diabetes mellitus with arthropathy
U602311	65684	[X] Adverse reaction to insulins and antidiabetic agents
C109412	65704	Type 2 diabetes mellitus with ulcer
C10EN11	66145	Type I diabetes mellitus with ketoacidotic coma
66Ah.00	66274	Insulin needles changed for each injection
C108D11	66872	Type I diabetes mellitus with nephropathy
C109H12	66965	Type 2 diabetes mellitus with neuropathic arthropathy
C106000	67853	Diabetes mellitus, juvenile, + neurological manifestation
C109211	67905	Type II diabetes mellitus with neurological complications
C10EB00	68105	Type 1 diabetes mellitus with mononeuropathy
C108512	68390	Type 1 diabetes mellitus with ulcer
ZRB4.00	68546	Diabetes clinic satisfaction questionnaire
C10z000	68792	Diabetes mellitus, juvenile type, + unspecified complication
ZRB5.11	68818	DTSQ - Diabetes treatment satisfaction questionnaire
C103100	68843	Diabetes mellitus, adult onset, with ketoacidotic coma
TJ23.00	68928	Adverse reaction to insulins and antidiabetic agents
ZC2C900	69043	Dietary advice for type I diabetes
66Aj.00	69152	Insulin needles changed less than once a day
C109E00	69278	Non-insulin depend diabetes mellitus with diabetic cataract
C10EA00	69676	Type 1 diabetes mellitus without complication
C105000	69748	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C109112	70316	Type 2 diabetes mellitus with ophthalmic complications
C108E12	70766	Type 1 diabetes mellitus with hypoglycaemic coma
C10yz00	70821	Diabetes mellitus NOS with other specified manifestation
C109A00	72320	Non-insulin dependent diabetes mellitus with mononeuropathy
8HME.00	72333	Listed for Diabetology admissn
C102z00	72345	Diabetes mellitus NOS with hyperosmolar coma
C10E812	72702	Insulin dependent diabetes mellitus - poor control
66Am.00	83485	Insulin dose changed
66Ao.00	83532	Diabetes type 2 review
66An.00	85660	Diabetes type 1 review
C10FM11	85991	Type II diabetes mellitus with persistent microalbuminuria
66Ag.00	90301	Insulin needles changed daily
ZRB4.11	91164	CSQ - Diabetes clinic satisfaction questionnaire
C10F411	91646	Type II diabetes mellitus with ulcer
C10E311	91942	Type I diabetes mellitus with multiple complications
C10EC11	91943	Type I diabetes mellitus with polyneuropathy
C10N100	93380	Cystic fibrosis related diabetes mellitus
9OLH.00	93390	Attended DAFNE diabetes structured education programme
9OLJ.00	93491	DAFNE diabetes structured education programme completed
9OLL.00	93631	XPERT diabetes structured education programme completed
8Hj3.00	93704	Referral to DAFNE diabetes structured education programme
C10FE11	93727	Type II diabetes mellitus with diabetic cataract
8Hj5.00	93870	Referral to XPERT diabetes structured education programme
C10E712	93875	Insulin dependent diabetes mellitus with retinopathy
C10E511	93878	Type I diabetes mellitus with ulcer
C104000	93922	Diabetes mellitus, juvenile type, with renal manifestation
9OLG.00	94011	Attended XPERT diabetes structured education programme
ZRB5.00	94699	Diabetes treatment satisfaction questionnaire

9NiE.00	94955	Did not attend XPERT diabetes structured education programme
8I84.00	94956	Did not complete XPERT diabetes structured education program
C10E711	95343	Type I diabetes mellitus with retinopathy
C10FA11	95351	Type II diabetes mellitus with mononeuropathy
C10ER00	95636	Latent autoimmune diabetes mellitus in adult
C108A11	95992	Type I diabetes mellitus without complication
66Aq.00	95994	Diabetic foot screen
66Ap.00	96010	Insulin treatment initiated
9kL..00	96143	Insulin initiation - enhanced services administration
C10E911	96235	Type I diabetes mellitus maturity onset
C10G000	96506	Secondary pancreatic diabetes mellitus without complication
C108912	97446	Type 1 diabetes mellitus maturity onset
C108412	97474	Unstable type 1 diabetes mellitus
8I82.00	97809	Did not complete DAFNE diabetes structured education program
ZRB6.11	97824	DWBQ - Diabetes wellbeing questionnaire
C10E912	97849	Insulin dependent diabetes maturity onset
C10EP11	97894	Type I diabetes mellitus with exudative maculopathy
C10E112	98071	Insulin-dependent diabetes mellitus with ophthalmic comps
C10C.12	98392	Maturity onset diabetes in youth type 1
C10F211	98616	Type II diabetes mellitus with neurological complications
C10E512	98704	Insulin dependent diabetes mellitus with ulcer
C10FD11	98723	Type II diabetes mellitus with hypoglycaemic coma
3883.00	98954	Diabetes treatment satisfaction questionnaire
C108B11	99231	Type I diabetes mellitus with mononeuropathy
9NiC.00	99277	Did not attend DAFNE diabetes structured education programme
C10E111	99311	Type I diabetes mellitus with ophthalmic complications
Kyu0300	99628	[X]Glomerular disorders in diabetes mellitus
C10EE12	99716	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EA12	99719	Insulin-dependent diabetes without complication
U60231E	100033	[X] Adverse reaction to insulins and antidiabetic agents NOS
Cyu2300	100292	[X]Unspecified diabetes mellitus with renal complications
C10EF12	100770	Insulin dependent diabetes mellitus with diabetic cataract
C10F111	100964	Type II diabetes mellitus with ophthalmic complications
C10EC12	101311	Insulin dependent diabetes mellitus with polyneuropathy
C10E212	101735	Insulin-dependent diabetes mellitus with neurological comps
2BBr.00	101881	Impaired vision due to diabetic retinopathy
C10ED12	102163	Insulin dependent diabetes mellitus with nephropathy
C10FC11	102201	Type II diabetes mellitus with nephropathy
Hypertension:		
G2...00	204	Hypertensive disease
G20..11	351	High blood pressure
G20..00	799	Essential hypertension
G201.00	1894	Benign essential hypertension
14A2.00	2666	H/O: hypertension
662O.00	3425	On treatment for hypertension
G20z.11	3712	Hypertension NOS
G202.00	4372	Systolic hypertension
G22..00	4668	Hypertensive renal disease
8HT5.00	5513	Referral to hypertension clinic
G2z..00	7057	Hypertensive disease NOS

G24..00	7329	Secondary hypertension
G2...11	8732	BP - hypertensive disease
G21z011	8857	Cardiomegaly - hypertensive
G20z.00	10818	Essential hypertension NOS
662H.00	12948	Hypertension treatm.stopped
662G.00	13188	Hypertensive treatm.changed
G22z.00	15106	Hypertensive renal disease NOS
G200.00	15377	Malignant essential hypertension
G24z.00	16059	Secondary hypertension NOS
G21zz00	16173	Hypertensive heart disease NOS
G21..00	16292	Hypertensive heart disease
6627.00	16565	Good hypertension control
G22..11	17434	Nephrosclerosis
662c.00	18482	Hypertension six month review
662b.00	18590	Moderate hypertension control
G2y..00	18765	Other specified hypertensive disease
662d.00	19070	Hypertension annual review
662F.00	21826	Hypertension treatm. started
G232.00	21837	Hypertensive heart&renal dis wth (congestive) heart failure
8I3N.00	22333	Hypertension treatment refused
G241000	25371	Secondary benign renovascular hypertension
6628.00	27511	Poor hypertension control
9N1y200	27634	Seen in hypertension clinic
G233.00	28684	Hypertensive heart and renal disease with renal failure
G22z.11	29310	Renal hypertension
6629.00	30776	Hypertension:follow-up default
G24z100	31341	Hypertension secondary to drug
G24z000	31387	Secondary renovascular hypertension NOS
G21z.00	31464	Hypertensive heart disease NOS
G240.00	31755	Secondary malignant hypertension
G222.00	32423	Hypertensive renal disease with renal failure
6146200	32976	Hypertension induced by oral contraceptive pill
G244.00	34744	Hypertension secondary to endocrine disorders
G220.00	39649	Malignant hypertensive renal disease
G24zz00	42229	Secondary hypertension NOS
G221.00	43935	Benign hypertensive renal disease
G210.00	50157	Malignant hypertensive heart disease
G241z00	51635	Secondary benign hypertension NOS
G211100	52127	Benign hypertensive heart disease with CCF
G211.00	52427	Benign hypertensive heart disease
G241.00	57288	Secondary benign hypertension
G234.00	57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
G240000	59383	Secondary malignant renovascular hypertension
G21z000	61166	Hypertensive heart disease NOS without CCF
G211000	61660	Benign hypertensive heart disease without CCF
G21z100	62718	Hypertensive heart disease NOS with CCF
G231.00	63000	Benign hypertensive heart and renal disease
G23..00	63466	Hypertensive heart and renal disease
G230.00	67232	Malignant hypertensive heart and renal disease
G23z.00	68659	Hypertensive heart and renal disease NOS

Gyu2.00	69753	[X]Hypertensive diseases
G210100	72668	Malignant hypertensive heart disease with CCF
G240z00	73293	Secondary malignant hypertension NOS
G203.00	83473	Diastolic hypertension
G210000	95334	Malignant hypertensive heart disease without CCF
662r.00	95359	Trial withdrawal of antihypertensive therapy
Gyu2100	97533	[X]Hypertension secondary to other renal disorders
662q.00	99259	Trial reduction of antihypertensive therapy
662P000	102406	Hypertension 9 month review
Gyu2000	102458	[X]Other secondary hypertension
Myocardial infarction:		
G30..00	241	Acute myocardial infarction
G30..14	1204	Heart attack
G30..15	1677	MI - acute myocardial infarction
G308.00	1678	Inferior myocardial infarction NOS
G30..12	2491	Coronary thrombosis
G307.00	3704	Acute subendocardial infarction
G32..00	4017	Old myocardial infarction
44H3.00	5221	Cardiac enzymes abnormal
G301.00	5387	Other specified anterior myocardial infarction
323..00	7783	ECG: myocardial infarction
G302.00	8935	Acute inferolateral infarction
G307000	9507	Acute non-Q wave infarction
G307100	10562	Acute non-ST segment elevation myocardial infarction
G300.00	12139	Acute anterolateral infarction
G30X000	12229	Acute ST segment elevation myocardial infarction
G30..11	13566	Attack - heart
G30..16	13571	Thrombosis - coronary
G30z.00	14658	Acute myocardial infarction NOS
G301z00	14897	Anterior myocardial infarction NOS
G305.00	14898	Lateral myocardial infarction NOS
G310.11	15661	Dressler's syndrome
G32..11	16408	Healed myocardial infarction
G32..12	17464	Personal history of myocardial infarction
G30..17	17689	Silent myocardial infarction
G301100	17872	Acute anteroseptal infarction
G35..00	18842	Subsequent myocardial infarction
G310.00	23579	Postmyocardial infarction syndrome
G361.00	23708	Atrial septal defect/curr comp folow acut myocardal infarct
G304.00	23892	Posterior myocardial infarction NOS
G360.00	24126	Haemopericardium/current comp folow acut myocard infarct
32E3.00	26966	ECG: S-T elevation
3234.00	26972	ECG:posterior/inferior infarct
3233.00	26975	ECG: antero-septal infarct.
G30y000	28736	Acute atrial infarction
G366.00	29553	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G303.00	29643	Acute inferoposterior infarction
G30X.00	29758	Acute transmural myocardial infarction of unspecif site
G309.00	30330	Acute Q-wave infarct
G30..13	30421	Cardiac rupture following myocardial infarction (MI)

G38..00	32272	Postoperative myocardial infarction
G30B.00	32854	Acute posterolateral myocardial infarction
7929100	33650	Percut transluminal coronary thrombolysis with streptokinase
G30y.00	34803	Other acute myocardial infarction
32B..00	34952	ECG: Q wave
14A3.00	35674	H/O: myocardial infarct <60
G36..00	36423	Certain current complication follow acute myocardial infarct
G362.00	37657	Ventric septal defect/curr comp fol acut myocardal infarctn
G351.00	38609	Subsequent myocardial infarction of inferior wall
3232.00	39904	ECG: old myocardial infarction
14A4.00	40399	H/O: myocardial infarct >60
G301000	40429	Acute anteroapical infarction
7929111	40996	Percut translum coronary thrombolytic therapy- streptokinase
G30y200	41221	Acute septal infarction
G384.00	41835	Postoperative subendocardial myocardial infarction
G350.00	45809	Subsequent myocardial infarction of anterior wall
G30yz00	46017	Other acute myocardial infarction NOS
G380.00	46112	Postoperative transmural myocardial infarction anterior wall
G35X.00	46166	Subsequent myocardial infarction of unspecified site
32B2.00	46227	ECG: Q wave abnormal
G381.00	46276	Postoperative transmural myocardial infarction inferior wall
14AH.00	50372	H/O: Myocardial infarction in last year
3236.00	52705	ECG: lateral infarction
3235.00	55401	ECG: subendocardial infarct
323Z.00	59032	ECG: myocardial infarct NOS
G363.00	59189	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	59940	Ruptur chordae tendinae/curr comp fol acute myocard infarct
44H3000	60664	Cardiac enzymes abnormal - first set
889A.00	61670	Diab mellit insulin-glucose infus acute myocardial infarct
32B3.00	62270	ECG: Q wave pathological
G30y100	62626	Acute papillary muscle infarction
G306.00	63467	True posterior myocardial infarction
32BZ.00	66285	ECG: Q wave NOS
G31y100	68357	Microinfarction of heart
G38z.00	68748	Postoperative myocardial infarction, unspecified
G365.00	69474	Rupture papillary muscle/curr comp fol acute myocard infarct
G353.00	72562	Subsequent myocardial infarction of other sites
Gyu3400	96838	[X]Acute transmural myocardial infarction of unspecif site
44p2.00	97001	Cardiac troponin positive
Gyu3600	99991	[X]Subsequent myocardial infarction of unspecified site
14AT.00	100139	History of myocardial infarction
Chronic heart failure:		
G580.00	398	Congestive heart failure
G581.00	884	Left ventricular failure
G58..11	1223	Cardiac failure
G58..00	2062	Heart failure
G580.11	2906	Congestive cardiac failure
G58z.00	4024	Heart failure NOS
G581000	5255	Acute left ventricular failure
G581.13	5942	Impaired left ventricular function

G580.14	9524	Biventricular failure
1O1..00	9913	Heart failure confirmed
G580.12	10079	Right heart failure
G580.13	10154	Right ventricular failure
G580300	11424	Compensated cardiac failure
662T.00	12366	Congestive heart failure monitoring
G58z.11	12590	Weak heart
9N0k.00	12627	Seen in heart failure clinic
662g.00	13189	New York Heart Association classification - class II
14A6.00	15058	H/O: heart failure
G58z.12	17278	Cardiac failure NOS
8HBE.00	17851	Heart failure follow-up
662f.00	18853	New York Heart Association classification - class I
662h.00	19066	New York Heart Association classification - class III
R2y1000	20324	[D]Cardiorespiratory failure
G232.00	21837	Hypertensive heart&renal dis wth (congestive) heart failure
G1yz100	22262	Rheumatic left ventricular failure
G581.11	23481	Asthma - cardiac
G580000	23707	Acute congestive heart failure
8B29.00	24503	Cardiac failure therapy
ZRad.00	26242	New York Heart Assoc classification heart failure symptoms
G580200	27884	Decompensated cardiac failure
G582.00	27964	Acute heart failure
662W.00	30779	Heart failure annual review
G580100	32671	Chronic congestive heart failure
8H2S.00	32898	Admit heart failure emergency
G581.12	43618	Pulmonary oedema - acute
14AM.00	46912	H/O: Heart failure in last year
G557100	49844	Beriberi heart disease
662i.00	51214	New York Heart Association classification - class IV
G211100	52127	Benign hypertensive heart disease with CCF
G234.00	57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
G21z100	62718	Hypertensive heart disease NOS with CCF
SP11111	66306	Heart failure as a complication of care
G210100	72668	Malignant hypertensive heart disease with CCF
G580400	94870	Congestive heart failure due to valvular disease
G5y4z00	96799	Post cardiac operation heart failure NOS
G583.11	101137	HFNEF - heart failure with normal ejection fraction
G583.00	101138	Heart failure with normal ejection fraction
Peripheral arterial disease:		
G700.00	1318	Aortic atherosclerosis
G73z000	1517	Intermittent claudication
G73..12	1826	Ischaemia of legs
G73zz00	2760	Peripheral vascular disease NOS
G73z.00	3530	Peripheral vascular disease NOS
G73yz00	4325	Other specified peripheral vascular disease NOS
R054.00	4970	[D]Gangrene
G73..11	5702	Peripheral ischaemic vascular disease
G73..00	5943	Other peripheral vascular disease
M271.12	6308	Ischaemic leg ulcer
G73..13	6827	Peripheral ischaemia
G73z011	6853	Claudication

G732.00	9204	Peripheral gangrene
G732100	12735	Gangrene of foot
C10F500	12736	Type 2 diabetes mellitus with gangrene
G702.00	14797	Extremity artery atheroma
G742z00	15302	Peripheral arterial embolism and thrombosis NOS
G702z00	16260	Extremity artery atheroma NOS
G731000	23497	Buerger's disease
G73y100	23871	Peripheral angiopathic disease EC NOS
M271000	24327	Ischaemic ulcer diabetic foot
R054300	31053	[D]Widespread diabetic foot gangrene
C107.11	32403	Diabetes mellitus with gangrene
C107.12	32556	Diabetes with gangrene
C107200	33807	Diabetes mellitus, adult with gangrene
G73y000	34152	Diabetic peripheral angiopathy
G731.00	34638	Thromboangiitis obliterans
C107.00	35399	Diabetes mellitus with peripheral circulatory disorder
R054z00	37750	[D]Gangrene NOS
C10FF00	37806	Type 2 diabetes mellitus with peripheral angiopathy
G73y.00	38907	Other specified peripheral vascular disease
G731100	40068	Presenile gangrene
C109500	40401	Non-insulin dependent diabetes mellitus with gangrene
C109512	46150	Type 2 diabetes mellitus with gangrene
C109F00	54212	Non-insulin-dependent d m with peripheral angiopath
C109F11	54899	Type II diabetes mellitus with peripheral angiopathy
C107400	56803	NIDDM with peripheral circulatory disorder
C108600	60499	Insulin dependent diabetes mellitus with gangrene
C109F12	60699	Type 2 diabetes mellitus with peripheral angiopathy
C109511	62107	Type II diabetes mellitus with gangrene
C107100	63357	Diabetes mellitus, adult, + peripheral circulatory disorder
C108G00	64446	Insulin dependent diab mell with peripheral angiopathy
C107z00	65025	Diabetes mellitus NOS with peripheral circulatory disorder
G731z00	67401	Thromboangiitis obliterans NOS
C107300	69124	IDDM with peripheral circulatory disorder
C10E600	69993	Type 1 diabetes mellitus with gangrene
C107000	70448	Diabetes mellitus, juvenile +peripheral circulatory disorder
Gyu7400	73961	[X]Other specified peripheral vascular diseases
C10EG00	93468	Type 1 diabetes mellitus with peripheral angiopathy
G733.00	98174	Ischaemic foot
8HlP.00	100475	Referred for peripheral artery disease assessment
G73z012	101866	Vascular claudication
C10E611	102112	Type I diabetes mellitus with gangrene
Stroke:		
G64..12	569	Infarction - cerebral
G66..11	1298	CVA unspecified
G66..00	1469	Stroke and cerebrovascular accident unspecified
G64z.00	3149	Cerebral infarction NOS
G61z.00	3535	Intracerebral haemorrhage NOS
F051200	3585	Thrombosis lateral sinus
G631.12	4152	Thrombosis, carotid artery
G631.00	4240	Carotid artery occlusion

G61..00	5051	Intracerebral haemorrhage
G64z111	5185	Lateral medullary syndrome
G650.11	5268	Insufficiency - basilar artery
G64..11	5363	CVA - cerebral artery occlusion
G64z.12	5602	Cerebellar infarction
14A7.12	5871	H/O: stroke
G66..13	6116	CVA - Cerebrovascular accident unspecified
G64..13	6155	Stroke due to cerebral arterial occlusion
G68X.00	6228	Sequelae of stroke,not specfd as h'morrhage or infarction
G66..12	6253	Stroke unspecified
14A7.11	6305	H/O: CVA
G61..11	6960	CVA - cerebrovascular accid due to intracerebral haemorrhage
ZV12512	7138	[V]Personal history of cerebrovascular accident (CVA)
G667.00	7780	Left sided CVA
G614.00	7912	Pontine haemorrhage
G663.00	8443	Brain stem stroke syndrome
G64..00	8837	Cerebral arterial occlusion
G678.00	9943	Cereb autosom dominant arteriop subcort infarcts leukoenceph
G64z200	9985	Left sided cerebral infarction
G64z300	10504	Right sided cerebral infarction
G668.00	12833	Right sided CVA
G613.00	13564	Cerebellar haemorrhage
14AB.00	13567	H/O: TIA
G641.00	15019	Cerebral embolism
G64z.11	15252	Brainstem infarction NOS
G640.00	16517	Cerebral thrombosis
G664.00	17322	Cerebellar stroke syndrome
G61..12	18604	Stroke due to intracerebral haemorrhage
662e.00	18686	Stroke/CVA annual review
G660.00	18689	Middle cerebral artery syndrome
G61X100	19201	Right sided intracerebral haemorrhage, unspecified
G662.00	19260	Posterior cerebral artery syndrome
G661.00	19280	Anterior cerebral artery syndrome
ZV12511	19348	[V]Personal history of stroke
F051100	20161	Thrombosis of superior longitudinal sinus
G62z.00	20284	Intracranial haemorrhage NOS
G651000	21118	Vertebro-basilar artery syndrome
F051000	22006	Thrombosis cavernous sinus
G63y000	23671	Cerebral infarct due to thrombosis of precerebral arteries
G650.00	23942	Basilar artery syndrome
G671100	24385	Chronic cerebral ischaemia
G63y100	24446	Cerebral infarction due to embolism of precerebral arteries
G64z000	25615	Brainstem infarction
G64z400	26424	Infarction of basal ganglia
G641000	27975	Cerebral infarction due to embolism of cerebral arteries
S62..14	28077	Traumatic cerebral haemorrhage
F051300	28309	Thrombosis transverse sinus
G61X000	28314	Left sided intracerebral haemorrhage, unspecified
G616.00	30045	External capsule haemorrhage
G617.00	30202	Intracerebral haemorrhage, intraventricular

G61X.00	31060	Intracerebral haemorrhage in hemisphere, unspecified
F051.00	31390	Thrombosis of central nervous system venous sinuses
G610.00	31595	Cortical haemorrhage
G62..00	31805	Other and unspecified intracranial haemorrhage
G630.00	32447	Basilar artery occlusion
G651.00	33377	Vertebral artery syndrome
G665.00	33499	Pure motor lacunar syndrome
G6X..00	33543	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
14A7.00	34135	H/O: CVA/stroke
G641.11	34758	Cerebral embolus
G640000	36717	Cerebral infarction due to thrombosis of cerebral arteries
G676.00	37947	Nonpyogenic venous sinus thrombosis
G676000	39344	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G683.00	39403	Sequelae of cerebral infarction
G611.00	40338	Internal capsule haemorrhage
G6W..00	40758	Cereb infarct due unsp occlus/stenos precerebr arteries
G632.00	40847	Vertebral artery occlusion
G605.00	41910	Subarachnoid haemorrhage from basilar artery
ZLEP.00	42248	Discharge from stroke serv
G682.00	43451	Sequelae of other nontraumatic intracranial haemorrhage
G653.00	44765	Carotid artery syndrome hemispheric
G63..00	45781	Precerebral arterial occlusion
L440.11	47607	CVA - cerebrovascular accident in the puerperium
G64z100	47642	Wallenberg syndrome
G681.00	48149	Sequelae of intracerebral haemorrhage
G654.00	50594	Multiple and bilateral precerebral artery syndromes
G63y.00	51326	Other precerebral artery occlusion
G677000	51759	Occlusion and stenosis of middle cerebral artery
G666.00	51767	Pure sensory lacunar syndrome
L417.00	52679	Obstetric cerebral venous thrombosis
Gyu6400	53745	[X]Other cerebral infarction
Gyu6200	53810	[X]Other intracerebral haemorrhage
7P24200	55351	Delivery of rehabilitation for stroke
G677300	55602	Occlusion and stenosis of cerebellar arteries
L417100	55974	Cerebral venous thrombosis in the puerperium
L440.12	56279	Stroke in the puerperium
8HHM.00	56458	Ref to multidisciplinary stroke function improvement service
G618.00	57315	Intracerebral haemorrhage, multiple localized
G63..11	57495	Infarction - precerebral
G677100	57527	Occlusion and stenosis of anterior cerebral artery
F051z00	61366	Thrombosis of central nervous system venous sinus NOS
G677200	65770	Occlusion and stenosis of posterior cerebral artery
14AK.00	66873	H/O: Stroke in last year
L417000	69686	Cerebral venous thrombosis in pregnancy
G671000	70536	Acute cerebrovascular insufficiency NOS
G677400	71274	Occlusion+stenosis of multiple and bilat cerebral arteries
G63z.00	71585	Precerebral artery occlusion NOS
Gyu6500	90572	[X]Occlusion and stenosis of other precerebral arteries
Gyu6300	91627	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6600	92036	[X]Occlusion and stenosis of other cerebral arteries

Gyu6G00	94482	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
Gyu6F00	96630	[X]Intracerebral haemorrhage in hemisphere, unspecified
G633.00	98642	Multiple and bilateral precerebral arterial occlusion
1M4..00	100639	Central post-stroke pain
G67A.00	101733	Cerebral vein thrombosis
C154211	101824	Adrenocortical haemorrhage
Vesicoureteral reflux:		
K137.00	2421	Vesicoureteric reflux
K137.11	4443	Ureteric reflux
K19C.00	10880	Other obstructive and reflux uropathy
K19X.00	12123	Obstructive and reflux uropathy, unspecified
Kyu1300	105941	[X]Obstructive and reflux uropathy, unspecified
Kyu1200	107866	[X]Other obstructive and reflux uropathy
Renal stone:		
K12z.00	1256	Urinary calculus NOS
K120.12	1858	Renal calculus
K140.11	1912	Bladder stone
K141.00	2105	Calculus in urethra
K120.13	2258	Renal stone
7B07.12	2315	Percutaneous lithotripsy of renal calculus
K121.11	2410	Ureteric calculus
K121.00	3308	Calculus of ureter
7B1C.00	3449	Extracorporeal shockwave lithotripsy of ureteric calculus
K12..12	3669	Urinary calculus
K120z00	3906	Renal calculus NOS
7B05000	4139	Unspecified open removal of calculus from kidney
7B19.00	4216	Cystoscopic removal of ureteric calculus
K120.00	4928	Calculus of kidney
7B18.00	5366	Ureteroscopic operations for ureteric calculus
K140.00	5729	Bladder calculus
K121.12	6048	Ureteric stone
4G8..00	6978	O/E - bladder calculus
4G4..11	6979	O/E: kidney stone
7B07z00	7119	Percutaneous renal stone surgery NOS
7B0B.00	7682	Extracorporeal shockwave lithotripsy for renal calculus
7B07.00	8190	Percutaneous renal stone surgery
4G4..00	8399	O/E: renal calculus
7B07211	8677	Endoscopic laser fragmentation of renal calculus
K12..11	8777	Kidney calculus
C341111	9162	Renal stone - uric acid
7B29400	9323	Electrokinetic lithotripsy of bladder calculus
K12..00	9950	Calculus of kidney and ureter
K120000	10282	Staghorn calculus
7B19211	10587	Basket extraction of ureteric calculus
4G6..00	14276	O/E - ureteric calculus
7B18100	16025	Other ureteroscopic fragmentation of ureteric calculus
7B0B000	17685	ESWL for renal calculus of unspecified size
7B19000	18190	Cystoscopic laser lithotripsy of ureteric calculus
4G...00	18846	Calculus examination
7B17111	20813	Other nephroscopic lithotripsy of ureteric calculus

7B0B.11	21401	Extracorporeal fragmentation of renal calculus
7B25000	23381	Open removal of bladder calculus
7B17100	23897	Other nephroscopic fragmentation of ureteric calculus
Kyu3100	23917	[X]Calculus of urinary tract in other diseases CE
7B19212	24933	Dormia basket extraction of ureteric calculus
14D3.00	24994	H/O: urinary stone
4G43.00	27786	O/E: uric acid renal calculus
7B0Bz00	28514	Extracorporeal shockwave lithotripsy for renal calculus NOS
7B29100	28595	Other endoscopic extraction of bladder calculus
7B18011	28790	Ureteroscopic laser fragmentation of ureteric calculus
7B43900	28953	Endoscopic removal of urethral calculus
4G82.11	29242	Uric acid bladder stone
7B1Cz00	29464	Extracorporeal shockwave lithotripsy ureteric calculus NOS
7B1Cy00	29477	Extracorporeal shockwave lithotripsy of ureteric calculus OS
4G81.11	31773	Oxalate bladder stone
4G42.11	32858	Phosphate kidney stone
K122.00	33746	Calculus of kidney with calculus of ureter
7B42300	34097	Open urethrotomy and removal of calculus
7B07400	34139	Endoscopic extraction of calculus of kidney nec
7B19300	35743	Cystoscopic catheter drainage for ureteric calculus
7B07011	36157	Endoscopic ultrasound fragmentation of renal calculus
7B18000	36792	Ureteroscopic laser lithotripsy of ureteric calculus
7B19200	37073	Cystoscopic extraction of ureteric calculus
4G4Z.00	38461	O/E: renal stone NOS
7B18200	38804	Ureteroscopic extraction of ureteric calculus
7B19400	39048	Cystoscopic dilation of ureter for drainage of calculus
7B17000	39511	Nephroscopic laser lithotripsy of ureteric calculus
7B2B400	40272	Removal of bladder calculus by urethral catheter suction
7B07000	41619	Nephroscopy and ultrasound lithotripsy of renal calculus
7B19100	41871	Other cystoscopic fragmentation of ureteric calculus
7B07200	43350	Nephroscopy and laser lithotripsy of renal calculus
K14z.00	44648	Lower urinary tract calculus NOS
4G7..00	45245	O/E - urethral calculus
7B17200	45673	Nephroscopic extraction of ureteric calculus
K14y.00	46291	Other lower urinary tract calculus
K14..00	47869	Lower urinary tract calculus
4G44.00	49783	O/E: cystine renal calculus
7B1C000	51305	Extracorp shockwave lithotripsy of unspec ureteric calculus
K1A..00	52569	Urinary calculus in schistosomiasis
7B0B100	52721	ESWL for renal calculus less than 2 cm in diameter
7B07.11	56462	Nephroscopic percutaneous lithotripsy of renal calculus
PD31.00	56531	Congenital calculus of kidney
7B17011	58004	Nephroscopic laser fragmentation of ureteric calculus
7B19z00	58149	Cystoscopic removal of ureteric calculus NOS
K140z00	59834	Bladder calculus NOS
7B07100	60234	Nephroscopy & electrohydraulic lithotripsy of renal calculus
7B1C100	61904	Extracorporeal shockwave therapy for stone in upper ureter
4G8Z.00	64699	O/E - bladder calculus NOS
4G83.11	65920	Phosphate bladder stone
7B0By00	66113	Extracorporeal shockwave lithotripsy for renal calculus OS

7B07y00	66743	Other specified percutaneous renal stone surgery
7B1C300	71131	Extracorporeal shockwave lithotripsy stone in lower ureter
7B19y00	72447	Other specified cystoscopic removal of ureteric calculus
7B42400	90777	Open extraction of calculus from urethra
7B0B200	94219	ESWL for renal calculus 2 cm or more in diameter
4G9E.00	96314	Calculus ammonium urate content
7B1C200	101583	Extracorporeal shockwave lithotripsy for stone in mid-ureter
7B1F000	102036	Endoscopic extraction of calculus of urinary diversion
Kyu3000	106912	[X]Other lower urinary tract calculus
Prostatic hypertrophy:		
K200.00	929	Prostatic hyperplasia unspecified
K20..16	2627	Prostatism
K20..00	3045	Benign prostatic hypertrophy
1AA..00	5906	Prostatism
K20..15	7555	BPH - benign prostatic hypertrophy
K20..14	7702	Enlarged prostate - benign
K20z.00	16035	Prostatic hyperplasia NOS
K202.00	35676	Prostatic hyperplasia of the medial lobe
K201.00	64296	Prostatic hyperplasia of the lateral lobe
Systematic lupus erythematosus:		
M154.00	4125	Lupus erythematosus
M154z00	7522	Lupus erythematosus NOS
N000.00	7871	Systemic lupus erythematosus
N000400	11920	Systemic lupus erythematosus with pericarditis
N000000	20007	Disseminated lupus erythematosus
K01x411	22205	Lupus nephritis
M154700	25390	Subacute cutaneous lupus erythematosus
N000300	29519	Systemic lupus erythematosus with organ or sys involv
H57y400	31564	Lung disease with systemic lupus erythematosus
M154000	33449	Lupus erythematosus chronicus
N000200	36942	Drug-induced systemic lupus erythematosus
M154200	40797	Lupus erythematosus migrans
N000z00	42719	Systemic lupus erythematosus NOS
F371000	44095	Polyneuropathy in disseminated lupus erythematosus
M154500	44984	Lupus erythematosus tumidus
ZRq9.00	45726	Systemic lupus erythematosus disease activity index
M154400	46148	Lupus erythematosus profundus
K01x400	47672	Nephrotic syndrome in systemic lupus erythematosus
ZRq8.00	51798	Systemic lupus activity measure
Nyu4300	58706	[X]Other forms of systemic lupus erythematosus
M154600	63955	Lupus erythematosus unguium mutilans
M154300	65391	Lupus erythematosus nodularis
N000500	99435	Neonatal lupus erythematosus
N000600	101433	Cerebral lupus
Polycystic kidney disease:		
PD11.00	4503	Polycystic kidney disease
PD1..13	4504	Polycystic kidney
PD11100	4505	Polycystic kidneys, adult type
12F1.00	11406	FH: Polycystic kidney
PD11000	21381	Polycystic kidneys, infantile type

7B03300	45880	Rovsing's operation for polycystic kidney
Z4B4.00	55233	Polycystic kidney disease counselling
PD11z00	56852	Polycystic kidney disease NOS
PD11111	105143	Autosomal dominant polycystic kidney disease
PD11011	105919	Autosomal recessive polycystic kidney disease
Chronic obstructivepulmonarydisease:		
H32..00	794	Emphysema
H3...11	998	Chronic obstructive airways disease
H3...00	1001	Chronic obstructive pulmonary disease
H312200	1446	Acute exacerbation of chronic obstructive airways disease
H31..00	3243	Chronic bronchitis
H3z..00	5710	Chronic obstructive airways disease NOS
H3y1.00	7884	Chron obstruct pulmonary dis wth acute exacerbation, unspec
66YB.00	9520	Chronic obstructive pulmonary disease monitoring
H38..00	9876	Severe chronic obstructive pulmonary disease
H37..00	10802	Moderate chronic obstructive pulmonary disease
H36..00	10863	Mild chronic obstructive pulmonary disease
H322.00	10980	Centrilobular emphysema
8H2R.00	11019	Admit COPD emergency
H311.00	11150	Mucopurulent chronic bronchitis
66YM.00	11287	Chronic obstructive pulmonary disease annual review
H3y..00	12166	Other specified chronic obstructive airways disease
H312100	14798	Emphysematous bronchitis
H31z.00	15157	Chronic bronchitis NOS
H310000	15626	Chronic catarrhal bronchitis
66YL.11	18476	COPD follow-up
66YI.00	18501	COPD self-management plan given
66YL.00	18621	Chronic obstructive pulmonary disease follow-up
9Oi..00	18792	Chronic obstructive pulmonary disease monitoring admin
66Ye.00	19003	Emergency COPD admission since last appointment
66Yd.00	19106	COPD accident and emergency attendance since last visit
H3y0.00	21061	Chronic obstruct pulmonary dis with acute lower resp infectn
H320z00	23492	Chronic bullous emphysema NOS
H313.00	24248	Mixed simple and mucopurulent chronic bronchitis
H310.00	25603	Simple chronic bronchitis
66YS.00	26018	Chronic obstructive pulmonary disease monitoring by nurse
H320.00	26306	Chronic bullous emphysema
H312.00	27819	Obstructive chronic bronchitis
9Oi0.00	28755	Chronic obstructive pulmonary disease monitoring 1st letter
H32z.00	33450	Emphysema NOS
9Oi1.00	34202	Chronic obstructive pulmonary disease monitoring 2nd letter
9Oi2.00	34215	Chronic obstructive pulmonary disease monitoring 3rd letter
H3z..11	37247	Chronic obstructive pulmonary disease NOS
66YD.00	37371	Chronic obstructive pulmonary disease monitoring due
H311100	37959	Fetid chronic bronchitis
9Oi4.00	38074	Chronic obstructive pulmonary disease monitor phone invite
H311000	40159	Purulent chronic bronchitis
9Oi3.00	42258	Chronic obstructive pulmonary disease monitoring verb invite
66YL.12	42624	COAD follow-up
H312z00	44525	Obstructive chronic bronchitis NOS

66Yg.00	45770	Chronic obstructive pulmonary disease disturbs sleep
66Yh.00	45771	Chronic obstructive pulmonary disease does not disturb sleep
8CR1.00	45777	Chronic obstructive pulmonary disease clini management plan
66YT.00	45998	Chronic obstructive pulmonary disease monitoring by doctor
66Yi.00	46036	Multiple COPD emergency hospital admissions
H321.00	46578	Panlobular emphysema
H320000	56860	Segmental bullous emphysema
H320200	60188	Giant bullous emphysema
H310z00	61118	Simple chronic bronchitis NOS
H311z00	61513	Mucopurulent chronic bronchitis NOS
H464000	64721	Chronic emphysema due to chemical fumes
Hyu3100	65733	[X]Other specified chronic obstructive pulmonary disease
H31y.00	66043	Other chronic bronchitis
H3y..11	67040	Other specified chronic obstructive pulmonary disease
H31yz00	68066	Other chronic bronchitis NOS
H39..00	93568	Very severe chronic obstructive pulmonary disease
14OX.00	96931	At risk of chronic obstructive pulmonary diseas exacerbation
9kf2.00	98283	COPD structured smoking assessment declined - enh serv admin
9kf1.00	98284	Refer COPD structured smoking assessment - enhanc serv admin
H320300	99536	Bullous emphysema with collapse
9kf0.00	99948	COPD patient unsuitable for pulmonary rehab - enh serv admin
8BMW.00	101042	Issue of chronic obstructive pulmonary disease rescue pack
66YB000	102685	Chronic obstructive pulmonary disease 3 monthly review
66YB100	103007	Chronic obstructive pulmonary disease 6 monthly review
9kf1.11	103400	Referred for COPD structured smoking assessment
Rheumatoid arthritis:		
N040.00	844	Rheumatoid arthritis
N043.00	4186	Juvenile rheumatoid arthritis - Still's disease
N042200	5723	Rheumatoid nodule
N040P00	6916	Seronegative rheumatoid arthritis
N040T00	8350	Flare of rheumatoid arthritis
N047.00	9707	Seropositive errosive rheumatoid arthritis
H570.00	9954	Rheumatoid lung
N04X.00	12019	Seropositive rheumatoid arthritis, unspecified
N040Q00	18155	Rheumatoid bursitis
N040200	21358	Rheumatoid arthritis of shoulder
N043200	21533	Pauciarticular juvenile rheumatoid arthritis
N041.00	23552	Felty's syndrome
N005.00	23834	Adult Still's Disease
N043z00	27557	Juvenile rheumatoid arthritis NOS
N04..00	27603	Rheumatoid arthritis and other inflammatory polyarthropathy
N04y012	28853	Fibrosing alveolitis associated with rheumatoid arthritis
N040N00	30548	Rheumatoid vasculitis
N040S00	31054	Rheumatoid arthritis - multiple joint
F396400	31209	Myopathy due to rheumatoid arthritis
N045500	31360	Juvenile rheumatoid arthritis
N04y000	31724	Rheumatoid lung
N04y200	32001	Adult-onset Still's disease
2G27.00	33264	O/E-hands-rheumatoid spindling
N043300	36276	Monarticular juvenile rheumatoid arthritis

N042z00	37431	Rheumatoid arthropathy + visceral/systemic involvement NOS
N040900	41941	Rheumatoid arthritis of PIP joint of finger
N040800	42299	Rheumatoid arthritis of MCP joint
G5yA.00	43816	Rheumatoid carditis
N040100	44203	Other rheumatoid arthritis of spine
N040000	44743	Rheumatoid arthritis of cervical spine
N042100	46436	Rheumatoid lung disease
N043100	47831	Acute polyarticular juvenile rheumatoid arthritis
N040700	48832	Rheumatoid arthritis of wrist
N040B00	49067	Rheumatoid arthritis of hip
N042.00	49227	Other rheumatoid arthropathy + visceral/systemic involvement
G5y8.00	49787	Rheumatoid myocarditis
N043000	50644	Juvenile rheumatoid arthropathy unspecified
N040D00	50863	Rheumatoid arthritis of knee
N040K00	51238	Rheumatoid arthritis of 1st MTP joint
N040F00	51239	Rheumatoid arthritis of ankle
N040R00	53621	Rheumatoid nodule
Nyu1G00	56202	[X]Seropositive rheumatoid arthritis, unspecified
N04y011	56838	Caplan's syndrome
N040500	59738	Rheumatoid arthritis of elbow
F371200	62401	Polyneuropathy in rheumatoid arthritis
N040A00	63198	Rheumatoid arthritis of DIP joint of finger
N040600	63365	Rheumatoid arthritis of distal radio-ulnar joint
Nyu1200	70221	[X]Other specified rheumatoid arthritis
N040H00	70658	Rheumatoid arthritis of talonavicular joint
N040J00	71784	Rheumatoid arthritis of other tarsal joint
N040G00	73619	Rheumatoid arthritis of subtalar joint
Nyu1100	93715	[X]Other seropositive rheumatoid arthritis
N040L00	99414	Rheumatoid arthritis of lesser MTP joint
N040C00	100776	Rheumatoid arthritis of sacro-iliac joint
N040400	100914	Rheumatoid arthritis of acromioclavicular joint
7P20300	102088	Delivery of rehabilitation for rheumatoid arthritis
Parkinson's disease:		
F12..00	4321	Parkinson's disease
Eu02300	9509	[X]Dementia in Parkinson's disease
F12z.00	14912	Parkinson's disease NOS
F11x900	96860	Cerebral degeneration in Parkinson's disease
147F.00	101090	History of Parkinson's disease
Epilepsy:		
F25..00	573	Epilepsy
F251000	988	Grand mal (major) epilepsy
F250011	1715	Epileptic absences
F250000	2907	Petit mal (minor) epilepsy
F254000	3175	Temporal lobe epilepsy
F25z.11	3607	Fit (in known epileptic) NOS
8B66.00	3784	Anticonvulsant therapy
F253.11	4093	Status epilepticus
SC20000	4109	Traumatic epilepsy
667B.00	4602	Nocturnal epilepsy
F251300	4801	Epileptic seizures - myoclonic

F253.00	5117	Grand mal status
F251400	5152	Epileptic seizures - tonic
F255011	5525	Focal epilepsy
F251600	5668	Grand mal seizure
F25X.00	6271	Status epilepticus, unspecified
Eu05y11	6709	[X]Epileptic psychosis NOS
2823.00	7809	O/E - petit mal fit
2822.00	7811	O/E - grand mal fit
2828.00	8097	Absence seizure
F251500	8187	Tonic-clonic epilepsy
F132z12	8487	Myoclonic seizure
8BIF.00	9326	Epilepsy medication review
F255000	9569	Jacksonian, focal or motor epilepsy
F25z.00	9747	Epilepsy NOS
F252.00	9886	Petit mal status
F25y200	9887	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset
F25yz00	9979	Other forms of epilepsy NOS
667F.00	11015	Seizure free >12 months
F250.00	11186	Generalised nonconvulsive epilepsy
F254500	11394	Complex partial epileptic seizure
1B26.00	11454	Trigger factor for seizure
1B27.00	11505	Seizures in response to acute event
8BL3.00	11752	Patient on maximal tolerated anticonvulsant therapy
6677.00	13073	Epilepsy drug side effects
667P.00	13219	No seizures on treatment
667D.00	13220	Epilepsy control poor
667R.00	13221	2 to 4 seizures a month
F250400	17399	Juvenile absence epilepsy
F251200	18471	Epileptic seizures - clonic
667T.00	18899	Daily seizures
F25y400	19170	Benign Rolandic epilepsy
F25A.00	19363	Juvenile myoclonic epilepsy
667S.00	19549	1 to 7 seizures a week
667C.00	19550	Epilepsy control good
667E.00	19551	Epilepsy care arrangement
667L.00	19552	Epilepsy does not limit activities
667A.00	20566	Epilepsy treatment stopped
1O30.00	22341	Epilepsy confirmed
F251011	22804	Tonic-clonic epilepsy
667N.00	22991	Epilepsy severity
F254100	23634	Psychomotor epilepsy
F250200	24309	Epileptic seizures - atonic
F25y300	25330	Complex partial status epilepticus
F255.00	26015	Partial epilepsy without impairment of consciousness
F251.00	26144	Generalised convulsive epilepsy
6672.00	26511	Follow-up epilepsy assessment
6678.00	26512	Epilepsy treatment changed
667Q.00	26618	1 to 12 seizures a year
667K.00	26619	Epilepsy limits activities
667G.00	26620	Epilepsy restricts employment

F255y00	26733	Partial epilepsy without impairment of consciousness OS
44WF000	26961	Anticonvulsant level therapeutic
F255z00	27526	Partial epilepsy without impairment of consciousness NOS
F25B.00	30604	Alcohol-induced epilepsy
F25F.00	30635	Photosensitive epilepsy
F25C.00	30816	Drug-induced epilepsy
F250300	31830	Epileptic seizures - akinetic
Eu05212	31877	[X]Schizophrenia-like psychosis in epilepsy
F254z00	31920	Partial epilepsy with impairment of consciousness NOS
F254.00	32288	Partial epilepsy with impairment of consciousness
F254400	34079	Epileptic automatism
6679.00	34473	Epilepsy treatment started
F254200	36203	Psychosensory epilepsy
F255200	37592	Somatosensory epilepsy
F132100	37644	Progressive myoclonic epilepsy
F251100	37782	Neonatal myoclonic epilepsy
F25y.00	38307	Other forms of epilepsy
1B1W.00	38919	Transient epileptic amnesia
667V.00	39160	Many seizures a day
F255600	40105	Simple partial epileptic seizure
F251z00	40806	Generalised convulsive epilepsy NOS
667J.00	40863	Epilepsy impairs education
Eu80300	43679	[X]Acquired aphasia with epilepsy [Landau - Kleffner]
F250z00	44252	Generalised nonconvulsive epilepsy NOS
6671.00	45746	Initial epilepsy assessment
F251y00	45927	Other specified generalised convulsive epilepsy
667W.00	46603	Emergency epilepsy treatment since last appointment
F255100	48134	Sensory induced epilepsy
Eu06013	48462	[X]Limbic epilepsy personality
ZS82.00	49889	Acquired epileptic aphasia
6674.00	50012	Epilepsy associated problems
667H.00	50702	Epilepsy prevents employment
U606614	52273	[X] Adverse reaction to anticonvulsants NOS
667X.00	52632	No epilepsy drug side effects
F25y100	53483	Gelastic epilepsy
F25y000	55260	Cursive (running) epilepsy
F254300	55665	Limbic system epilepsy
667M.00	55706	Epilepsy management plan given
F255400	55739	Visual reflex epilepsy
F25D.00	56359	Menstrual epilepsy
Fyu5200	59120	[X]Other status epilepticus
F250y00	59185	Other specified generalised nonconvulsive epilepsy
TJ63z00	60306	Adverse reaction to anticonvulsants NOS
TJ63.00	63234	Adverse reaction to other anticonvulsants
F25E.00	65673	Stress-induced epilepsy
F255012	65699	Motor epilepsy
F255500	68946	Unilateral epilepsy
Fyu5100	69831	[X]Other epilepsy
F257.00	71719	Kojevnikov's epilepsy
Fyu5900	71801	[X]Status epilepticus, unspecified

F255300	73542	Visceral reflex epilepsy
U606600	73879	[X]Oth unspec antiepileptics caus adverse eff in therap use
U606611	95658	[X] Adverse reaction to other anticonvulsant
F255311	98870	Partial epilepsy with autonomic symptoms
F250100	99548	Pykno-epilepsy
Fyu5000	99731	[X]Other generalized epilepsy and epileptic syndromes
R003400	99834	[D]Nocturnal seizure
6110.00	100652	Contraceptive advice for patients with epilepsy
67IJ000	100920	Pre-conception advice for patients with epilepsy
8IB2.00	101143	Contraceptiv advice for patients with epilepsy not indicated
8IAg.00	102190	Contraceptive advice for patients with epilepsy declined
8IAi.00	102191	Pregnancy advice for patients with epilepsy declined
8IB3.00	102264	Pre-conception advic fr patients with epilepsy not indicated
8IAh.00	102265	Pre-conception advice for patients with epilepsy declined
67AF.00	102359	Pregnancy advice for patients with epilepsy
8IB4.00	102375	Pregnancy advice for patients with epilepsy not indicated
Chronic liver disease:		
J615z13	1638	Cirrhosis of liver NOS
J614.00	1754	Chronic hepatitis
J614200	1755	Chronic aggressive hepatitis
J61y200	1780	Hepatosplenomegaly
J611.00	3216	Acute alcoholic hepatitis
J615300	3450	Diffuse nodular cirrhosis
J612.00	4743	Alcoholic cirrhosis of liver
J616000	5638	Primary biliary cirrhosis
J61..00	6863	Cirrhosis and chronic liver disease
J617000	7602	Chronic alcoholic hepatitis
J613.00	7885	Alcoholic liver damage unspecified
J617.00	7943	Alcoholic hepatitis
J614111	7957	Autoimmune chronic active hepatitis
J614100	9029	Chronic active hepatitis
J616.00	9494	Biliary cirrhosis
J61y100	10234	Non-alcoholic fatty liver
J61z.00	10539	Chronic liver disease NOS
J61y700	10572	Steatosis of liver
J610.00	10691	Alcoholic fatty liver
J616100	15424	Secondary biliary cirrhosis
J614z00	15489	Chronic hepatitis NOS
J615z00	16455	Non-alcoholic cirrhosis NOS
J615.00	16725	Cirrhosis - non alcoholic
J613000	17330	Alcoholic hepatic failure
J615z12	18739	Cryptogenic cirrhosis of liver
J612000	21713	Alcoholic fibrosis and sclerosis of liver
J615z11	22841	Macronodular cirrhosis of liver
J614000	23578	Chronic persistent hepatitis
J61y400	25383	Hepatic fibrosis
J615700	27438	Cardiac portal cirrhosis
J61yz00	33597	Other non-alcoholic chronic liver disease NOS
J615600	40567	Capsular portal cirrhosis
J61y300	40963	Portal fibrosis without cirrhosis

J61y.00	42843	Other non-alcoholic chronic liver disease
J615400	44676	Fatty portal cirrhosis
J615.11	47257	Portal cirrhosis
J615H00	48928	Infectious cirrhosis NOS
J614300	53480	Recurrent hepatitis
J614y00	53877	Chronic hepatitis unspecified
J615y00	55454	Portal cirrhosis unspecified
J615812	58184	Indian childhood cirrhosis
J616z00	58630	Biliary cirrhosis NOS
J61y500	60104	Hepatic sclerosis
J614400	66534	Chronic lobular hepatitis
J612.11	68376	Florid cirrhosis
J615100	69204	Multilobular portal cirrhosis
J615z15	71453	Hepatic fibrosis
J615D00	73482	Bacterial portal cirrhosis
J616200	91591	Biliary cirrhosis of children
J615500	92909	Hypertrophic portal cirrhosis
J615800	96664	Juvenile portal cirrhosis
J61y800	98148	Nonalcoholic steatohepatitis
J615C00	100253	Xanthomatous portal cirrhosis
J612.12	100474	Laennec's cirrhosis
J61y600	100592	Hepatic fibrosis with hepatic sclerosis
J61y900	103466	Fatty change of liver
J61y911	103706	Fatty liver