Evaluating the current state of nephrotoxic medication use and prescriptions in adults and children with chronic kidney disease using two approaches: a systematic review and a matched cohort-study

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ACE-I	Angiotensin Converting Enzyme Inhibitor
ACR	Albumin-to-Creatinine Ratio
AER	Albumin Excretion Rate
AINS	Anti-Inflammatoires Non-Stéroïdiens
AKI	Acute Kidney Injury
ARB	Angiotensin Receptor Blockers
BNF	British National Formulary
CI	Confidence Interval
C-G	Cockgroft-Gault
CKD	Chronic Kidney Disease
CKiD	Chronic Kidney Disease in Children
CPRD	Clinical Practice Research Datalink
DM	Diabetes Mellitus
EMR	Electronic Medical Record
ESRD	End-Stage Renal Disease
eGFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
GP	General Practitioner
HES	Hospital Episode Statistics
HTN	Hypertension
KDIGO	Kidney Disease: Improving Global Outcomes
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IQR	Interquartile Range
IRC	Insuffisance Rénale Chronique
MDRD	Modification of Diet in Renal Disease Study
MG	Médecin Généraliste
MORE	Methodological Evaluation of Observational Research
MNT	Médicament Néphrotoxique
NICU	Neonatal Intensive Care Unit
NR	Not Reported
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NTM	Nephrotoxic Medication
ONS	Office of National Statistics
OTC	Over the Counter
PPI	Proton Pump Inhibitor
PY	Person Year
RR	Rate Ratio
SD	Standard Deviation
THIN	The Health Improvement Network
UK	United Kingdom

ABSTRACT

Introduction: Pediatric chronic kidney disease (CKD) management focuses on limiting further kidney injury, including avoiding nephrotoxic medications (NTMs). NTM prescription practices are poorly characterized in adults and unknown in children with CKD. My objectives were 1) to determine the prevalence of primary care Non-steroidal anti-inflammatory (NSAID) prescriptions (a widely recognized NTM) to patients with CKD as described in the current literature and 2) to compare the prevalence and rate of primary care prescriptions of NTMs between children with and without CKD.

Methods: I conducted a systematic review evaluating the prevalence of NSAID prescriptions to the primary care CKD population and a retrospective, population-based, matched cohort study comparing NTM prescriptions between children with and without CKD. *Systematic review:* I systematically searched MEDLINE and EMBASE from inception to October 2017 without an age restriction to allow capture of pediatric data. Methodological quality of included studies was assessed using a modified version of the Agency for Healthcare Research and Quality's Methodological Evaluation of Observational Research checklist. Cross-sectional and period prevalence measures were summarized across studies. *Matched cohort study*: I included patients aged <18 years at the time of cohort entry, registered with a general practitioner practice participating in the UK Clinical Practice Research Datalink (CPRD) from 1997 to 2017, with linkage to Hospital Episode Statistics data. Patients with incident CKD were matched 4:1 to non-CKD patients on CKD diagnosis date, sex, age, CPRD practice, and number of pre-cohort entry general practitioner visits. The prevalence of NTM prescriptions was compared between CKD and non-CKD patients, with adjusted prescription rate ratios calculated using multivariable binomial regression.

Results: *Systematic review:* Of 8,055 potentially relevant publications, 304 were retrieved for full-text review. Fourteen studies, representing 49,209 adult CKD patients, met inclusion criteria. No pediatric studies met inclusion criteria. Cross-sectional prevalence of NSAID use in CKD patients was 8-21%. Annual prevalence was 3-33%. *Matched cohort study:* 1,018 incident CKD patients were matched to 4,072 non-CKD patients. Mean age was 9.8 years [range: 1.1-17.9]. A total of 32% of CKD patients and 14.6% of non-CKD patients were prescribed ≥1 NTM during follow-up. From cohort entry to end of follow-up, the proportion of CKD patients receiving ≥1 NTM remained similar (17.6%-19.5%/year). NTM prescription rates in CKD *vs.* non-CKD patients were 133.5 (95% CI 110.8-160.8) *vs.* 7.8 (95% CI 7.0-8.7) prescriptions per 100 person years. The rate ratio of NTM prescriptions in CKD vs non-CKD patients, when adjusting for additional confounders was 10.1 (95% CI 7.6-13.6).

Conclusions: Despite important heterogeneity within the existing literature, NSAIDs are prescribed at variable and relatively elevated rates to adults with CKD in primary care. When evaluating NTM as a group and looking specifically at the pediatric age group, prescription rates are elevated and significantly higher in children with CKD compared to those without. There may be a need for awareness/education interventions aimed at primary care practitioners on potential harm from NTMs on CKD progression in both adults and children.

RÉSUMÉ

Introduction : Le traitement de l'insuffisance rénale chronique (IRC) chez l'enfant est axé sur l'empêchement de la progression de la maladie, ce qui inclus l'évitement des médicaments néphrotoxiques (MNT). Le taux de prescriptions de MNT chez les adultes avec IRC n'est pas bien caractérisé et la littérature pédiatrique à ce sujet l'est encore moins. Les objectifs principaux de cette thèse sont de 1) déterminer la prévalence des prescriptions d'anti-inflammatoires non-stéroïdiens (AINS) par les médecins généralistes (MG) chez les patients avec IRC et 2) de comparer le taux de prescriptions de MNT par les MG entre les enfants avec et sans IRC.

Méthodes : J'ai réalisé une revue systématique évaluant la prévalence des prescriptions d'AINS chez les patients avec IRC ainsi qu'une étude de cohorte appariée rétrospective comparant le taux de prescriptions de MNT chez les enfants avec et sans IRC. *Revue systématique :* J'ai réalisé une recherche systématique de MEDLINE et EMBASE (date de création jusqu'en Octobre 2017) sans imposer de restriction d'âge pour permettre l'inclusion d'études pédiatriques. La qualité des études a été évaluée avec l'outil « Methodological Evaluation of Observational Research checklist » du *Agency for Healthcare Research and Quality*. Les prévalences transversales et annuelles ont été synthétisées. *Étude de cohorte :* Enfants âgés de moins de 18 ans inscrits à une pratique de MG participante au UK Clinical Practice Research Datalink (CPRD) de 1997 à 2007 et liée au Hospital Episode Statistics database. Les enfants avec un premier diagnostic d'IRC étaient appariés 4 à 1 avec des enfants sans IRC sur la date du diagnostic de l'IRC, le sexe, l'âge, la pratique CPRD et le nombre de visites médicales dans l'année précédant la date d'inclusion dans la cohorte. J'ai comparé la prévalence de prescriptions pour un MNT chez les enfants avec et sans IRC et j'ai calculé le rapport de taux de prescriptions utilisant une régression binomiale à variables multiples.

Résultats : *Revue systématique :* Des 8,055 publications potentielles, 304 ont été sélectionnées pour une revue du texte intégral. Au final, quatorze études ont été incluses, représentant un total de 49 209 adultes avec IRC. Aucune étude pédiatrique n'a satisfait les critères d'inclusion. La prévalence transversale des prescriptions d'AINS chez les adultes avec IRC était de 8-21%. La prévalence annuelle était de 3-33%. *Étude de cohorte :* Parmi les patients inscrits au CPRD, j'ai identifié 1018 enfants avec un premier diagnostic d'IRC appariés à 4072 enfants sans IRC. L'âge moyen était de 9.8 ans [1.1 à 17.9 ans]. Un total de 32% des patients avec IRC et 14.6% des patients sans IRC ont reçu ≥1 prescriptions pour un MNT pendant leur suivi. Pendant la durée de l'étude, la proportion d'enfants avec IRC prescrits ≥1 MNT est restée stable (17.6%-19.5%/année). Les taux de prescription chez les enfants avec *vs.* sans IRC étaient de 133.5 (95% CI 110.8-160.8) *vs.* 7.8 (95% CI 7.0-8.7) prescriptions par 100 années-personnes respectivement. Le ratio des taux de prescription de MNT chez les enfants avec *vs.* sans IRC après ajustement des variables confusionnelles était de 10.1 (95% CI 7.6-13.6).

Conclusion : Malgré une hétérogénéité importante dans la littérature, il semble que les AINS sont prescrit à de taux variables et relativement élevés par les MG chez leurs patients adultes avec IRC. Les taux de prescriptions des MNT par les MG chez les enfants sont très élevés surtout en comparaison avec les enfants sans IRC. Il serait important d'offrir des interventions visées à augmenter la sensibilisation des MG aux effets néfastes de ces médicaments sur la progression de l'IRC chez l'adulte et chez l'enfant.

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PREFACE & CONTRIBUTION OF AUTHORS

This thesis is an original work by the author, Claire Lefebvre. It consists of 7 chapters, two of which are original research manuscripts. Chapters 1, 2, 5, 6 & 7 were written by Dr. Lefebvre and revised by Drs Platt, Zappitelli and Filion

The systematic review included in this thesis (Chapter 3) was conceptualized and designed by Drs. Claire Lefebvre, Kristian Filion, Michael Zappitelli and Robert Platt. Dr. Lefebvre designed the search strategy, ran the search, selected articles for inclusion, designed the data-extraction form, extracted data, contacted study authors, carried out the analyses and drafted the original manuscript. Dr. Jade Hindié helped to design the data-extraction form, independently selected articles for inclusion, extracted data and contributed to data interpretation and manuscript revision.

Dr. Filion was the principal supervisor of this project and provided expert advice for search strategy design and analysis. He reviewed and revised the manuscript and approved the final version as submitted. Dr. Zappitelli offered expert advice for study design and data presentation; he reviewed and revised the manuscript and approved the final version as submitted. Dr. Platt offered expert advice for study design and data presentation, reviewed and revised the manuscript and approved the final version as submitted.

The matched cohort study of this thesis (Chapter 4) was conceptualized and designed by Drs. Lefebvre, Filion, Zappitelli and Platt and Pauline Reynier. Dr. Lefebvre drafted the study protocol with original analysis plan. With expert advice and support from Dr. Zappitelli, Dr. Lefebvre created definitions for the exposure, outcomes and confounders of the study including coding these for the study database. Dr. Lefebvre performed the main study analyses and drafted the manuscript. Pauline Reynier contributed her expertise to the design of the matched cohort. She created the matched cohort and did the major data management to allow Dr. Lefebvre to perform study analyses.

Dr. Platt offered expert advice and guidance for the matched cohort design and analysis plan. He reviewed and revised the manuscript and approved the final version as submitted. Dr. Zappitelli offered expert clinical advice for exposure and outcome definitions, and clinically-relevant analysis design. He reviewed and revised the manuscript and approved the final version as submitted. Dr. Filion offered expert advice and guidance for the matched cohort design and

analysis plan. He was instrumental in coordinating the data downloading process. He reviewed and revised the manuscript and approved the final version as submitted.

CHAPTER 1: OVERALL INTRODUCTION AND AIMS

1.1 Overview

With improved survival of patients, pediatric chronic kidney disease (CKD) is increasing in prevalence despite stable incidence rates[1]. Current CKD management is focused on limiting disease progression to avoid kidney failure and to limit the development of associated comorbidities such as cardiovascular disease which have important impacts on morbidity and mortality[2]. A multi-faceted approach is necessary to slow CKD progression as there are many mechanisms that contribute to ongoing kidney injury in CKD patients[1]. One important strategy is the avoidance of medications that have the potential to damage the kidney (known as nephrotoxic medications or NTMs)[3].

The extent to which children are prescribed NTMs is not well known. The study of this problem is hindered by variable definitions of what constitutes a NTM as well as the various clinical settings in which it can be evaluated – ranging from the neonatal intensive care unit to outpatient clinics. Current evidence suggests that NTM prescriptions to children are quite variable ranging from 3.3% when definitions are restricted to high-dose NTM exposure to over 80% in studies considering various mechanisms of nephrotoxicity[4-6]. Importantly, to our knowledge, no study to date has evaluated the prescribing practices of NTMs in children with CKD in whom these medications pose a risk for disease progression.

Though a large proportion of children with CKD are closely followed by nephrologists, primary care providers can play an important role in the outpatient care of these patients and may be the children's first point of contact with the healthcare system. Using population databases of primary care prescriptions to understand NTM prescription practices in children with CKD will provide information needed to understand the extent of this problem and may help to identify opportunities for knowledge translation interventions at the primary care level.

1.2 Thesis Hypothesis and Objectives

The overall hypotheses of my thesis are:

1. Pediatric patients are prescribed nephrotoxic medications in the primary care setting
2. The prevalence of primary care NTM prescriptions does not differ significantly between children with CKD and children without CKD

The objectives of my thesis are:

- To determine the prevalence of primary care Non-steroidal anti-inflammatory (NSAID) prescriptions to patients with CKD as described in the current literature by conducting a systematic review
- To determine the prevalence of primary-care nephrotoxic medication prescriptions in children with a diagnosis of CKD and to determine whether it differs from children without CKD
    - Using the UK Clinical Practice Research Datalink (CPRD) and the Hospital Episode Statistics (HES) databases
- To determine whether primary-care nephrotoxic medication prescription rates differ in children with and without a diagnosis of CKD
    - Using the UK Clinical Practice Research Datalink (CPRD) and the Hospital Episode Statistics (HES) databases
- To determine whether time from CKD diagnosis has an impact on NTM prescription prevalence in CKD patients

1.3 Outline of Thesis

In chapter 2 of my thesis, I will present an overview of CKD in children, including currently accepted guidelines for its diagnosis. I will then highlight some key differences in the definition of CKD between adults and children. The chapter will then focus on one aspect of CKD management in children – the avoidance of NTMs. I will highlight the various mechanisms of nephrotoxicity as well as the major classes of medications associated with each. Chapter 3 is a systematic review manuscript evaluating primary care NSAID prescription prevalence in CKD patients. It focuses on NSAIDs as these are the most ubiquitously prescribed NTMs worldwide[7]. Chapter 4 is a manuscript of a matched cohort study of children with and without CKD in the UK CPRD and the HES databases. It describes prescription prevalence and prescription rates of NTMs to children with and without CKD within primary care. Chapter 5 explains in further detail the methodology of the study in Chapter 4 and is meant to be complimentary to the manuscript's methods section. Chapter 6 provides a detailed discussion of the findings contained in both manuscripts. It summarizes the major findings of this thesis and highlights the specific strengths and limitations of the studies presented. Finally, Chapter 7 presents the conclusions of this thesis and offers some proposed directions for future research.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

2.1 Overview of Pediatric Chronic Kidney Disease

Current international guidelines (KDIGO: Kidney Disease: Improving Global Outcomes) define chronic kidney disease (CKD) as an "abnormality of kidney structure or function present for >3 months with implications for the health of an individual." [8] This definition relies on a constellation of imaging, laboratory and pathological evidence of disease, as outlined in Table 1.

Table 2.1. 1: KDIGO Criteria for CKD (either of the following present for >3 months)

Markers of Kidney Damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2

Abbreviations: AER, Albumin excretion rate; CKD, chronic kidney disease; GFR, glomerular filtration rate.

The definition is arguably more easily applied to adults than to children in whom ongoing kidney development poses specific diagnostic challenges. Estimated glomerular filtration rate (eGFR) is accepted as one of the best indicators of kidney function with adult cutoffs defined for decreased eGFR (<60 ml/min/ 1.73 m^2) and for kidney failure (<15 ml/min/ 1.73m^2)[8]. In children, these cutoffs cannot always be directly applied[8]. For example, in newborns, normal eGFR is often less than 60 ml/min/1.73 m^2 and increases progressively as the glomerulus grows, mean arterial pressure increases and renal vascular resistance decreases[9]. Furthermore, below the age of 2 years, children's eGFR values must be adjusted for their body surface area to allow meaningful interpretations and even these adjusted values are not comparable to adult cutoffs so definitions must reflect this variation[8]. Lastly, it has been argued that many congenital renal abnormalities should be recognized as indicative of CKD even if they are detected before 3 months of life[10]. While there is continued debate around the applicability of the KDIGO guidelines to the pediatric population, they have served to provide a better consensus for defining CKD among pediatric nephrology researchers which was lacking prior to their first publication in 2002. Due to this lack of consensus, the study of pediatric CKD epidemiology has been quite

challenging as large population-based registries have used varying thresholds of creatinine or eGFR for their definitions [11]. Taking into consideration these limitations, evidence suggests that while the incidence of pediatric CKD has remained relatively stable over the last few decades, survival has remarkably improved leading to increasing prevalence. In Europe, where most population-based registry studies have been conducted, age-adjusted yearly incidence rates are estimated to be approximately 11-12 cases per million and prevalence is currently estimated at approximately 55 to 60 per million[1].

CKD in children is unique from adult CKD due to its implications for children's growth and development. In children, the degree of kidney insufficiency has been correlated with the extent of growth restriction and pubertal delay [2]. This is likely due to a combination of factors including malnutrition, metabolic acidosis, bone mineralization disorders, anemia and growth-hormone (GH) abnormalities[1]. While advances in the management of pediatric CKD have improved these outcomes considerably over the last decades, they continue to have lasting impacts on children's functioning and quality of life[12,13]. There is also evidence that pediatric CKD increases the risk of cardiovascular morbidity. Children with CKD have been found to share many of the pathophysiological changes present in adult cardiovascular disease including endothelial dysfunction and arterial stiffening[1]. Recent evidence from the North American Chronic Kidney Disease in Children (CKiD) trial, a prospective cohort of children aged 1 to 16 years with eGFR between 30-75, suggests children with CKD are at higher risk of hypertension and secondary left ventricular hypertrophy – known risk factors for future cardiovascular disease and stroke.[2] Importantly, these factors may develop even in the early stages of CKD and progress with worsening kidney function[1].

As children with CKD age, the comorbidities associated with their underlying disease have the potential to increase existing morbidity and mortality rates in this population. Furthermore, increased survival of premature and low-birth-weight infants as well as the ongoing obesity epidemic (recognized risk factors for CKD) will likely exacerbate this problem further[1]. Prevention is therefore an important strategy in mitigating the potential health impacts of pediatric CKD. Targeted strategies such as hypertension control for the prevention of cardiovascular disease and nutritional support for growth failure are crucial; but a key factor in managing CKD-associated comorbidities is to prevent the progression of the underlying kidney disease. Though CKD may progress rapidly to kidney failure, most often there is a progressive

deterioration of kidney function over many years during which strategies to delay progression can be instituted. If initiated early, such strategies can not only decrease complications but can prevent disease progression to the stage of kidney failure[8]. Slowing CKD progression requires a multi-faceted approach as multiple contributing factors have been and continue to be defined in the pediatric population. This thesis will focus on studying the current state of one such preventative strategy – the avoidance of medications that are recognized as toxic to the kidney (known as nephrotoxic medications or NTMs)[8].

2.3 Nephrotoxic Kidney Injury

2.3.1 Kidney Susceptibility to Nephrotoxins

The kidney is an organ that is particularly susceptible to damage by medication. Among its functions are the metabolism and clearance of drugs, exposing its tissues to high concentrations of these agents[14]. Susceptibility to medication toxicity is also affected by kidney function and factors influencing kidney perfusion such as hydration status and blood pressure. In CKD where both renal function and perfusion are likely to be impaired due to underlying disease and accompanying comorbidities, there may be a significant alteration of drug pharmacokinetics, exposing patients to a higher risk of medication injury and drug interactions[8]. Specific recommendations with regards to nephrotoxic medications in CKD include complete avoidance, adjusting doses for renal function and discontinuation during periods of illness where decreased renal perfusion increases the risk of acute kidney injury (AKI)[8].

2.3.2 Challenges in Diagnosing Nephrotoxic Kidney Injury

There are many challenges to diagnosing nephrotoxic kidney injury. First, the kidney has a significant functional reserve. Currently existing biomarkers of kidney dysfunction such as creatinine, which reflect the kidney's ability to clear nitrogenous waste products, are not affected until a reduction in GFR of approximately two-thirds normal[14]. This complicates the detection of nephrotoxicity especially in cases of low-level chronic damage. Secondly, children do not often have health conditions that require regular bloodwork and repeated creatinine measures are therefore rarely requested. This makes recognizing and documenting nephrotoxic injury particularly difficult in the outpatient context[15]. This is especially true for nephrotoxin-associated AKI where the diagnosis requires a documented change in creatinine from a previously-known

reference value [15]. One study conducted in over 500 children hospitalized in non-intensive care unit settings found that fewer than 50% had a serum creatinine drawn at least every four days despite being on a prolonged course of a known nephrotoxic medication[16]. In the ambulatory setting, these rates are likely to be much lower. Thirdly, in contrast to other forms of AKI, nephrotoxin-associated AKI is often clinically subtle with urine output seldom affected and as a result, may easily go unnoticed in its early stages[17]. Lastly, even when nephrotoxic kidney injury is suspected, it may be difficult to determine which drug is the cause in patients on multiple concurrent medication therapies.

2.4 Standardizing the Approach to Nephrotoxic Kidney Injury

A proposed step toward improving the recognition of nephrotoxic kidney injury in the face of these diagnostic challenges has been to create a standardized definition. A recent effort by the International Serious Adverse Event Consortium (through a panel of adult and pediatric nephrologists and pharmacists) has proposed a classification of nephrotoxic kidney injury into four specific phenotypes[15]. These are nephtotoxin-associated AKI, glomerular injury, tubular injury and nephrolithiasis. However, this is not an exhaustive list of the potential mechanisms by which medications can cause kidney injury. For example, it does not address hemodynamic injury as this is diagnostically challenging to establish and the consortium was focused on developing guidelines that could be practically applied. Nevertheless, this classification provides a good basis for thinking about nephrotoxic kidney injury in terms of the interaction of medications with the various subunits of the kidney.

The kidney is composed grossly of its vasculature, its interstitium and its functional unit, the nephron. The two major components of the nephron are the glomerulus (where the blood is filtered by capillaries) and the renal tubules (where filtrate is carried and modified to produce the final urine) [14]. Medication toxicity may be predictable and dose-dependent or arise from idiosyncratic drug reactions, that are seemingly unrelated to the pharmacology of the drugs themselves.[15] Examples of predictable drug reactions are medication-induced hemodynamic injury, acute tubular necrosis and nephrolithiasis. Idiosyncratic drug reactions are more likely to produce glomerular injury and interstitial nephritis. Some medications have the potential to cause injury through various mechanisms and yet others require the presence of a second insult for their nephrotoxic potential to be manifest. Furthermore, as previously discussed, compounding factors such as inadequate kidney perfusion, age-related kidney susceptibility, and underlying

kidney function may all influence a medication's nephrotoxic potential. In the following sections, I will review the principal mechanisms of nephrotoxic-associated kidney injury (based on those proposed by the International Serious Adverse Event panel) and discuss the most common drug associated with each.

2.4.1 Hemodynamic Injury

Medications that influence the hemodynamics to or blood flow to the kidney have the potential to cause perfusion injuries. Drugs commonly associated with this type of injury include angiotensin-coverting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and non-steroidal anti-inflammatory drugs (NSAIDs)[15]. The kidney tightly regulates its perfusion by maintaining a pressure gradient across the glomerular capillaries which, in turn, regulates glomerular filtration and urine output. It does so through a host of inter-related mechanisms that control the vascular tone of the afferent and efferent arterioles which bring blood to and from the glomerulus, respectively[18]. Vasodilation of the afferent arteriole and concomitant vasoconstriction of the efferent arteriole are essential in maintaining this pressure gradient across the glomerulus. The principle hormone involved in this vasoconstriction is angiotensin II which is produced following the conversion of Angiotensin I by ACE in response to reduced blood flow to the kidney. Medications that interfere with this process include ACE-inhibitors and ARBs[18]. Their effects are particularly detrimental in the context of reduced kidney blood flow, where glomerular pressures depend heavily on efferent arteriolar tone/constriction.

NSAIDs pose a risk for hemodynamic-mediated kidney injury through their inhibition of prostaglandin synthesis. While states of reduced renal flow result in increased angiotensin II production to maintain efferent arteriolar tone, prostaglandins ensure a balance to this process and preserve renal perfusion through afferent arteriolar dilatation[19]. Administration of NSAIDs in the context of increased angiotensin II activity (e.g. in states of hypoperfusion) may therefore cause kidney injury. Cyclosporin A is another agent that can adversely affect kidney perfusion through direct stimulation of angiotensin production and by increasing the sensitivity of the kidney's vasculature to other vasoconstrictors[20]. Calcineurin inhibitors, immunosuppressive agents often used in the context of solid organ transplants or in patients with immune-mediated kidney diseases, also result in potentially detrimental afferent arteriolar vasoconstriction thought to be mediated by increased production of the hormones endothelin and thomboxin A_2[21]. Though

some of these agents such as ACE-inhibitors, ARBs and calcineurin inhibitors may sometimes be indicated in patients with CKD, their use requires careful consideration of their nephrotoxic potential especially in the context of combination therapies that can significantly impact renal hemodynamics.

2.4.2 Tubular Disorders

Renal tubules are lined with tubular epithelial cells which are exquisitely sensitive to different types of cell injury. Injury to the renal tubules often involves damage to these epithelial cells, either from direct drug toxicity or secondarily from drug-induced ischemia[18]. Cell damage often causes the sloughing of epithelial cells into the tubular lumen resulting in obstruction and secondary acute tubular necrosis (or acute renal tubular cell death) [22]. The tubules are particularly susceptible to several nephrotoxins due to their role in transporting (reabsorbing or excreting) these medications via cell membrane transporters, resulting in high intra-cellular concentrations. As a result, acute tubular necrosis is among the most common manifestations of drug-induced kidney injury. A class of nephrotoxic medications frequently associated with acute tubular necrosis in children is aminoglycoside antibiotics that exert damage through excessive intra-cellular accumulation[23]. Their nephrotoxic potential increases with prolonged, cumulative exposure and an important strategy in mitigating this effect is allowing greater intervals between doses to lower trough serum levels[21]. Amphotericin B is an antifungal agent widely recognized as a potent nephrotoxin that triggers tubular kidney injury through two synergistic mechanisms. It causes direct renal epithelial cellular toxicity, resulting in a state of increased cellular oxygen demand, and simultaneously causes renal vascular vasoconstriction, compounding its toxicity via ischemia, and resulting in clinical nephrotoxicity in a high proportion of patients[21].

2.4.3 Interstitial Nephritis

Interstitial nephritis is a form of nephrotoxicity that is often unpredictable and unrelated to drug dosage. Findings on kidney biopsy reveal infiltration of the interstitium by inflammatory immune cells[24]. The cause is thought to be the triggering of antibody production against endogenous renal antigens[24]. It has been proposed that this might be secondary to mimicry of drug components to renal antigens or drug modification of renal antigens triggering the immune system to recognize them as foreign[24]. Particular to this form of nephrotoxicity is its delayed

presentation which can occur up to two weeks after the offending drug has been discontinued[21]. This form of nephrotoxicity was first described with the antibiotic methicillin but emerging evidence has found it to be a feature of all beta-lactam antibiotics including penicillins and cephalosporins as well as sulfonamides, fluoroquinolones and vancomycin[21,22,24]. More recently, proton-pump inhibitors have emerged as a recognized culprit of acute interstitial nephritis which can present months into treatment, complicating its diagnosis[21]. A chronic form of interstitial nephritis has been described with prolonged use of NSAIDs, lithium and calcineurin-inhibitors. [21,24]. Though acute interstitial nephritis accounts for a relatively small proportion of acute kidney injury in adults, it has the potential to cause chronic damage[24]. Unfortunately, there are no consistent clinical or histopathological features that currently allow for the prediction of which affected patients will go on to develop chronic disease[24].

2.4.4 Glomerular Injury

Injury to the glomerulus is a relatively rare manifestation of nephrotoxicity. It is principally characterized by the presence of proteinuria. There are four major recognized forms of drug-induced glomerular injury, each thought to be mediated by an immune response: nephrotic syndrome, focal segmental glomerulosclerosis, membranous nephropathy and membranoproliferative glomerulonephritis [21]. Nephrotic syndrome is thought to be a cell-mediated immune response due to the identification of T-lymphocytic infiltrates on kidney biopsy. It has been described with NSAIDs, ampicillin, rifampin and lithium[18,21]. Focal segmental glomerulosclerosis shares many features with nephrotic syndrome including interstitial involvement but is characterized by sclerosing lesions of the glomeruli and has been associated with the use of lithium and pamidronate. The most common form of drug-induced glomerulonephritis is membranous nephropathy. The immune response responsible for this injury type is thought to be the attachment of drug-related antigens to the glomerular basement membrane, triggering antibody-production against this glomerular structure, resulting in increased permeability and proteinuria. The final type of injury, membranoproliferative glomerulonephritis causes a lupus-like syndrome and kidney injury, most notably associated with hydralazine and procainamide[25].

2.4.5 Nephrolithiasis

Certain nephrotoxic medications may exert damage through their precipitation within the kidney. This may lead to a picture of acute interstitial nephritis or result in obstructive stones as seen with acyclovir, ciprofloxacin, sulfonamides and methotrexate [18]. Susceptibility to this so-called crystal nephropathy is increased markedly in states of decreased kidney perfusion such as dehydration and in the context of reduced kidney function as fewer nephrons filter a relatively higher concentration of medication crystals[19]. Urine acidity can also affect individual medication's solubility as is the case with methotrexate and indinavir[21].

2.4.6 Interruption of Nephrogenesis

Another important mechanism of nephrotoxicity unique to the neonatal population is the effect of certain drugs on nephrogenesis. In a normal gestation, kidney development and the production of nephrons continues until 36 weeks. While autopsy models suggest this process continues ex-utero, there is evidence it may not continue past forty days of life, resulting in a lower nephron mass potential for extremely premature infants who do not benefit from the full 36 weeks of nephrogenesis [26]. Exposure to nephrotoxic agents in this context can have an especially detrimental impact. Medications such as NSAIDs and aminoglycoside antibiotics, frequently used in the neontatal intensive care environment, have been shown in experimental models to disrupt nephrogenesis[6]. For example, animal models have shown that NSAID and gentamycin exposure in rodents results in smaller and fewer glomeruli respectively[26]. In humans, there is also evidence that nephrotoxic medication exposure results in abnormally formed glomeruli[27].

2.5 Nephrotoxic Medication Use in Adults

Studies of outpatient NTM prescriptions to individuals with CKD are limited to adults and report very variable results. An underlying difficulty in understanding the burden of NTM prescriptions to patients with CKD is the variability of the definition of a NTM. Many studies evaluate renally-excreted medications in general, focusing on the proportion that are appropriately adjusted for individual patients' renal function[28-31]. A cohort study conducted across three French cities of community-dwelling elderly (>65 years) patients with a documented eGFR combined pharmacist expertise with a national drug reference to determine adjustment thresholds for renally-excreted drugs[28]. The proportion of patients with moderate (eGFR 30-59

mL/min/1.73 m^2) and severe (eGFR <30 mL/min/1.73 m^2) CKD prescribed inappropriate medications was 52.5% and 96% respectively. A single-center Turkish study employed the same definition of an inappropriate medication but in addition to using eGFR thresholds for patient inclusion, broadened their CKD definition to include patients with evidence of persistent (>3 months) structural or functional kidney damage as per recent international guidelines. Medication prescriptions were also based on patient report, validated by national database records and were prescribed at similarly high rates (80% of the study population)[31]. A Dutch study limited to adult patients with more severe renal dysfunction (eGFR <40 ml/min/1.73 m^2) determined that 15% of their cohort received a medication requiring renal adjustment over the one year study period based on general practitioner (GP) and community pharmacy records[29]. Importantly, this prospective study was conducted after a campaign to inform GPs and patients about its implementation. Furthermore, alerts were issued to GPs on a rolling basis throughout the study when a medication was determined to be inappropriate, possibly informing subsequent prescribing. This may explain the much lower rate of inappropriate prescriptions and offers some support for the role medication alert systems in decreasing inappropriate prescribing.

Studies focusing on medications recognized as nephrotoxic also employ varying definitions of nephrotoxicity. Medication lists are drawn up based on data from the existing literature or using various local or national prescribing guidelines. Some studies restrict to a single class of drug while others limit inclusion to one mechanism of nephrotoxicity[32]. Despite this important source of heterogeneity, taken together, these studies also seem to suggest elevated rates of NTM prescriptions to CKD patients. An American study using the Medical Expenditure Panel Survey focused on outpatient NTM exposures to pre-dialysis CKD patients and defined a NTM as any medication reported to be associated with acute tubular nephritis or tubular toxicity[32]. Patients with CKD were identified based on International Classification of Diseases (ICD)-9 clinical codes and medication use was self-reported. Despite this narrower NTM definition, authors reported that over 70% of the study's patients had received at least one NTM and more than 50% had received two or more[32]. Another population-based study in Southern Italy conducted over a 6-year study period found that 45.2% of their adult CKD cohort received at least one NTM within a year following their CKD diagnosis and 33.9% received a NTM within one year of starting dialysis[33]. Data were collected from a primary care database grouping almost 300 general practices. CKD patients were identified by the presence of clinical

and procedure codes for CKD and NTM were defined based on literature review and pharmacist expertise. Studies specifically evaluating NSAID prescriptions to CKD patients in primary care report annual prescription prevalence rate between 3-33% as discussed in detail in Chapter 3 of this thesis.

When considered collectively, these studies reveal that the current literature around inappropriate medication prescribing to patients with CKD is extremely variable. Not only are the definitions of an inappropriate medication wide-ranging but even the definitions of CKD differ from one study to another. Therefore, even when considering studies with fairly homogenous definitions of NTMs such as those focusing on a single class of NTM (e.g. NSAIDs), generalizing results remains difficult. A recent systematic review of 49 studies evaluating inappropriate medication prescribing to adult patients with CKD in both the hospital and outpatient setting highlights some of these difficulties in synthesizing the existing literature[34]. Included studies utilized over 13 different drug references to inform medication inclusion. Furthermore, eGFR cutoffs for inclusion ranged from <20 to <90 mL/min/1.73 m^2 with various estimation methods employed. Overall prevalence of inappropriate prescribing was understandably quite variable, ranging from 13%-81% in the ambulatory setting.

2.6 Nephrotoxic Medication Use in Pediatrics

Even less data exist describing the extent to which nephrotoxic medications are prescribed to the pediatric population and all are limited to the hospital setting. Furthermore, none focus specifically on children with known CKD. A case-control study conducted in children admitted to non-intensive care units at Texas Children's hospital in 2008 revealed that 86% of 714 patients were exposed to one or more medications listed as nephrotoxic in the hospital formulary[5]. The study was limited to children who had two serum creatinine measurements available less than 4 days apart and likely represented a higher risk sample in which this screening was judged necessary. However, results remain striking and showed that children received up to eight separate NTMs and a median of two NTMs simultaneously. Duration of nephrotoxin exposure was also prolonged with a median duration of 9 days and a maximum duration of up to 271 days. A neonatal intensive care unit (NICU) study conducted between 2011 and 2012 in very low birthweight infants revealed surprisingly similar rates[6]. Exposure to one or more nephrotoxic medications was noted in 86.7% of the study population

with a median of 2 nephrotoxic medications per infant. Again, mean exposure duration was quite prolonged at 13.6 days. When adjusted for length of stay, this amounted to one nephrotoxic medication exposure for every 6 days spent in the NICU. This study excluded infants who died before their hospital discharge likely resulting in an underrepresentation of the true nephrotoxic medication exposure in this population.

A prospective quality improvement project conducted at Cincinnati Children's hospital screened all children admitted to non-intensive care units for presence of ≥3 days of aminoglycoside exposure or prescription of ≥3 simultaneous nephrotoxic medications – considered high-dose nephrotoxicity exposure[4]. The authors used the same NTM list as the Texas Children's hospital study[5]. There were 726 children exposed to high-dose nephrotoxicity, representing 3.3% of the study cohort. Interestingly, a follow up study published in 2017 seeking to evaluate the success of the widespread implementation of this screening program revealed a 38% decrease in nephrotoxic medication exposure. However, exposure rates remained elevated with just under 10% of the 1,749 children studied received two or more nephrotoxic medications[4].

A prospective cohort study designed to create a screening tool for AKI in children also reports on nephrotoxic medication rates in their pediatric patients[35]. Patients between the ages of 28 days and 21 years were admissible if they had two recorded serum creatinine measurements and were hospitalized to Vanderbilt University School of Medicine between 2011 and 2012. Authors categorized nephrotoxic medications into high and moderate risk depending on the consistency of their association with kidney injury. Among 1332 children admitted to the ICU, 231 (17.3%) received one or more NTM. Among non-ICU admitted children, this rate was as high as 21.7% (508/2,337).

The existing literature on pediatric NTM exposure has so far focused on hospitalized children. The most likely reason for this is that inpatient data are readily available, even if by chart review, and this patient population is easy to capture with certainty. Moreover, there has been a great surge in research on AKI in hospitalized children in the last 10 years, which has been a motivating factor for studying inpatient use of NTMs. Existing studies have helped to expose worrying trends in prescribing practices and have correlated these findings to concrete outcomes such as medication-induced AKI. Ongoing research evaluating the impact of interventional strategies to mitigate these harmful prescribing practices and their consequences is

promising. The only pediatric interventional study regarding nephrotoxic medications studied the effects of implementing an institution-wide creatinine surveillance program and resulted in a dramatic drop in inappropriate prescriptions and in documented cases of AKI (38% and 64% respectively)[4]. These findings attest to the importance of studying medication-induced kidney injury because of its potential to create beneficial changes to clinical practice. Unfortunately, hospital based studies overlook an important aspect of the clinical care pathway of most pediatric CKD patients – the outpatient setting. This is often the first and most frequent point of contact these children have with the health care system and merits special attention. Furthermore, inherent differences between the outpatient and hospital settings make extrapolations from inpatients studies limited. For example, regular creatinine surveillance may be feasible in hospital and unlikely to result in an increased burden of care in children who are often already undergoing regular blood tests, but such interventions may be impractical and unrealistic in the outpatient setting. In this context, educational campaigns focused on increasing awareness of the importance of NTM avoidance may be of greater value. A better understanding of the current state of NTM prescribing to children with CKD in primary care could also help to inform where such knowledge translation interventions would best be focused as the pathway to inappropriate prescribing involves multiple providers from GPs, to pharmacists and even to parents and patients themselves. However, a first step toward considering strategies for decreasing NTM exposure and ultimately, improving outcomes in children with CKD must be to determine the extent of the problem as no literature currently exists on the subject. This is therefore the focus of this thesis.

CHAPTER 3: NSAID PRESCRIPTIONS IN CHRONIC KIDNEY DISEASE

As a first step in determining the extent to which NTMs are being prescribed to patients with CKD in primary care, I conducted a systematic review to explore the existing literature in detail. Because there is no universally recognized definition of what constitutes a NTM, studies of NTM prescriptions range from evaluating specific drug classes to determining the appropriateness of dosing adjustments for individual patient renal function. I therefore determined that a systematic review on NTM prescriptions as a group would be excessively difficult to conduct in terms of building the search strategy and more importantly, would likely result in such a high degree of study heterogeneity as to make meaningful result interpretation difficult. I therefore chose to focus on studying NSAIDs – a class of medications that is prescribed ubiquitously worldwide and is universally recognized as being nephrotoxic. The following Chapter therefore presents my systematic review manuscript evaluating the prevalence of NSAID prescriptions to the primary care CKD population. No age restriction was imposed for study inclusion in the hopes of capturing pediatric prescription trends which was the main interest of this thesis. Unfortunately, my search did not reveal any studies evaluating primary care NSAID prescriptions for children with CKD and my results are therefore limited to the adult population.

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3.1 Manuscript Cover Page

Non-Steroidal Anti-Inflammatory Drugs in Chronic Kidney Disease: A Systematic Review of Prescription Practices and Use in Primary Care

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3.2 Abstract

Objective: Chronic kidney disease (CKD) management focuses on limiting further renal injury including avoiding nephrotoxic medications such as non-steroidal anti-inflammatory drugs (NSAIDs). We performed a systematic review to evaluate the prevalence of primary care NSAID prescribing in this population.

Study Design and Setting: We systematically searched MEDLINE and EMBASE from inception to October 2017 for observational studies examining primary care NSAID prescriptions/use in CKD patients. Two authors independently assessed methodological quality of included studies using a modified version of the Agency for Healthcare Research and Quality's Methodological Evaluation of Observational Research checklist.

Results: Our search generated 8,055 potentially relevant publications; 304 were retrieved for full-text review. Fourteen studies from thirteen publications met inclusion criteria. There were eight cohort studies, three cross-sectional studies, two quality improvement studies, and one prospective survey, representing 49 209 CKD patients in total. All studies were found to have at least a moderate risk of bias. Cross-sectional prevalence of NSAID use in CKD patients was 8-21%. Annual prevalence was 3-33%. Meta-analysis was not performed due to important clinical heterogeneity across studies.

Conclusion: Evidence suggests that NSAID prescriptions/use in primary care CKD patients is variable and relatively high. Future research should explore reasons for this to better focus knowledge translation interventions aimed at reducing NSAID use in this patient population.

KEYWORDS: Chronic Kidney Disease; Non-steroidal anti-inflammatory drugs; Primary Care; Inappropriate Prescribing; Nephrotoxicity; Systematic Review
RUNNING TITLE: Systematic Review of Primary Care NSAID prescriptions in CKD
ABSTRACT WORD COUNT: 200 words

3.3 What is New

Our study represents the first systematic review of non-steroidal anti-inflammatory drug (NSAID) primary care prescription practices and usage among patients with chronic kidney disease (CKD). Despite the existence of international practice guidelines recommending complete NSAID avoidance in patients with advanced CKD (corresponding to a glomerular filtration rate (GFR) <30 ml/min/1.73m^2) and avoidance of prolonged use in patients with a GFR <60 ml/min/1.73m^2, there is evidence that many prescribers are unaware of the importance of NSAID avoidance in patients with impaired kidney function. We found that the use of NSAIDs, a class of drugs with known nephrotoxic effects, among patients with CKD is variable and relatively high. Given the widespread use of NSAIDS in the general population and the high prevalence of CKD, these findings have important clinical and policy implications. They suggest a need to better understand reasons behind persistent NSAID use in patients with CKD to tailor knowledge translation interventions that target reduced NSAID use in this patient population.

3.4 Manuscript

3.4.1 Introduction

Chronic kidney disease (CKD) is a global health burden to patients and healthcare systems with an estimated population prevalence of approximately 10%[1,2]. Treatment is supportive and aimed at preventing CKD progression. Key to achieving this goal is limiting further kidney injury [3,4] by avoiding the use of nephrotoxic medications when alternative, safer therapies exist. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most ubiquitously prescribed medications and alternatives exist for many of their clinical applications[5,6]. NSAIDs lead to decreased kidney perfusion via inhibition of prostaglandin synthesis[7]. Their use in the general population is known to be strongly associated with the development of acute kidney injury (AKI), which in turn is a risk factor for CKD[8,9]. International practice guidelines recommend complete NSAID avoidance in patients with a glomerular filtration rate (GFR) <30 ml/min/1.73m^2 and avoidance of prolonged use in patients with a GFR <60 ml/min/1.73m^2 [4]. Despite these recommendations, there is evidence that many prescribers are unaware of the importance of NSAID avoidance in patients with impaired kidney function[10-12]. As the primary care setting is the most frequent point of healthcare provider contact for many patients with CKD, it is important to better understand prescribing practices to patients

with CKD in this setting. We therefore performed a systematic review to evaluate prescribing practices and use of NSAIDs in adults with CKD. Our objective was to quantify and describe primary care NSAID prescribing practices and use among patients with CKD to elucidate the need for knowledge translation interventions aimed at reducing NSAID exposure in this vulnerable population.

3.4.2 Materials and Methods

The protocol for this systematic review has been published on PROSPERO (registration number CRD42018081292). The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

3.4.2.1 Search Strategy

We systematically searched MEDLINE and EMBASE (via Ovid) from inception to October 17th, 2017 to identify observational studies examining NSAID prescribing practices or usage in CKD patients in a primary care setting. The full search strategy is reported in the Appendix (Items A1-2, Tables A1-2). We applied keywords for the concepts of "kidney disease", "non-steroidal anti-inflammatory" and "prescription" and relevant database-specific Medical Subject Heading (MEDLINE) and EMTREE (EMBASE) terms. An exhaustive list of generic NSAID names was also included. Trade names were not included as they were deemed unlikely to substantially increase the search sensitivity[13]. To limit our search to the primary care setting, we combined two validated primary care/family practice search filters with a Boolean "OR" operator to maximize sensitivity [14,15]. We restricted our search to non-animal studies and conducted it without language restriction. We queried authors of relevant studies regarding knowledge of ongoing or unpublished research in the area. We also manually searched the reference lists of relevant reviews and articles to identify additional studies.

3.4.2.2 Study selection

Two reviewers (C.L. and J.H.) independently screened titles and abstracts of identified studies. Studies deemed potentially relevant by either reviewer were read in full. Decisions to include or exclude full-text articles were made independently, and disagreements were resolved through consensus. We included studies reporting NSAID use and/or prescription prevalence in

CKD patients in primary care. For studies within multiple health care settings, >50% of patients had to be included from the primary care setting, and extraction of primary care data had to be feasible. We excluded studies describing only hospitalized patients. We restricted inclusion to studies whose objectives included describing or quantifying medication use and to those in which CKD diagnosis was objectively determined using diagnostic codes or laboratory testing (defined as per international guidelines)[4]. Only full-texts available in French and English were included for review. We restricted inclusion to cohort, case control, and cross-sectional designs (excluding commentaries, editorials, letters to the editor, reviews, case reports, and case series). Clinical trials were excluded with the rationale that prescribing practices and factors influencing them would significantly differ from routine primary care practices.[16,17] In studies where multiple prevalences were reported from the same population, we included the first measure taken after CKD diagnosis. A single study could contribute more than one prevalence value if it described distinct CKD populations. Full details of the application of exclusion criteria are listed in Figure 3.7.1.

We excluded studies in which the timing of NSAID use/prescription in relation to CKD diagnosis could not be established and those in which NSAID use/prescription clearly preceded CKD diagnosis or was established at the same time as CKD diagnosis; prevalence measures from these studies do not likely reflect prescribing to patients with known CKD. Seven study authors were contacted to clarify the timing of NSAID use/prescription in relation to CKD diagnosis, five of whom confirmed that the timing did not meet our inclusion criteria [18-22] and two of whom provided information allowing us to include their study.

3.4.2.3 Data Extraction

Data extraction was performed independently by two authors (C.L. and J.H.) using a standardized, pilot-tested form. Disagreements were resolved through consensus. Extracted data included study design, country, study period, number of CKD patients, method of CKD diagnosis, NSAID definition, and prevalence of NSAID use and/or prescription.

3.4.2.4 Quality Assessment

Study quality was assessed using a modified version of the Agency for Healthcare Research and Quality's Methodological Evaluation of Observational Research (MORE)

checklist[23]. This checklist is specifically designed for observational studies examining incidence and prevalence of chronic diseases.[24] MORE provides a descriptive quality assessment of studies and assigns "no flaw", "minor flaw", "major flaw", or "poor reporting" descriptors to each criterion which we adapted to signify a low, moderate, high, or unclear risk of bias (due to poor reporting). All studies were included in the systematic review, regardless of their quality.

The checklist was adapted to our specific research question. In assessing external validity, MORE assigns a major flaw when the sampling frame is health-care based as it may not capture prevalence rates in the general population[23]. As the purpose of our study was to evaluate prescriptions by healthcare practitioners, we did not assign a major flaw to studies using such sampling methods. However, we did assign a minor flaw to studies that used claims data that restricted to insured patients . MORE also assigns flaws to studies based on absolute cutoffs for participant response rates and exclusions from analysis whereas we also considered whether studies assessed differences between responders and non-responders and between included and excluded patients. For the assessment of internal validity, we specifically evaluated whether NSAID prevalence was assessed objectively, whether it relied on patient recall for less than 6 months, or patient recall for more than 6 months, assigning no flaw, a minor flaw, or a major flaw, respectively.

3.4.2.5 Statistical Analysis

Prevalences of use/prescription are presented along with 95% confidence intervals (CIs). Period prevalences over varying follow-up times were converted to yearly prevalence to allow comparability of results, assuming that the NSAID prescription rate remained stable throughout each individual study's follow-up period. Data from included studies were synthesized qualitatively via systematic review rather than quantitatively via meta-analysis due to important clinical heterogeneity across studies. As there were only two studies comparing NSAID use in CKD patients to that in non-CKD patients, we did not present relative effect measures[25,26].

3.4.3 Results

Our search generated 8,055 potentially relevant publications (Figure 1). After removal of duplicates and title/abstract screening, 304 articles were retrieved for full-text review. Of these, 12 met our inclusion criteria, two of which were derived from a single publication[27]. Two

additional studies were identified through reference screening of included articles. A total of 14 studies from 13 separate publications were thus included in our review.

3.4.3.1 Study and Patient Characteristics

The fourteen studies included 49,209 CKD patients (Tables 1 & 2). Study size varied from 8 [26] to 27,668 CKD patients [28]. There were eight cohort studies [27-33], three cross-sectional studies[25,26,34], two studies of quality improvement interventions[35,36], and one prospective survey[37]. One publication described two separate CKD populations, which were considered independently in our analysis [27]. Two studies were performed within a single primary practice centre[27]. The remaining studies were conducted across two or more practices, four of which grouped data from over 100 practices using centralized electronic medical records databases[21,28,29,38].

Study populations varied widely (Tables 1 & 2). Mean age ranged from 47 to 83 years, with all patients aged >18 years. Four studies selected their patient population based on a comorbidity other than CKD (e.g., diabetes, hypertension, musculoskeletal complaints, gout)[29,35-37]. Two studies were not specifically based in a primary care practice. One was conducted using claims data from a major New York State insurer and was eligible for inclusion because authors specifically provided prescription data for patients who had not been seen by a nephrologist and were therefore considered primary care patients[32]. The other study was conducted in a nursing home and was included because >96% of the patients were regularly followed by a primary care physician and a very small proportion were followed by medical specialists[25].

3.4.3.2 CKD and NSAID Definitions

The definition of CKD differed substantially across studies. Seven studies required a single low eGFR value. [25,26,29,33,35-37] Three studies required two separate eGFR values separated by at least three months[31,32,34]. Of studies using eGFR, severity of CKD among included patients varied widely (Tables 1 & 2). [33,37] [26,29]. Only one study considered microalbuminuria, allowing for the identification of CKD stages 1 and 2 [33]. Three studies relied on recorded CKD diagnostic and procedure codes without specific staging information[27,28,38].

Nine studies assessed NSAID prescriptions using patients' medical records[27-29,31,33,35,36,39], of which five specifically excluded low-dose aspirin from reported

estimates[27,33,35,36]. Two studies reported on prescriptions reimbursed by either a national health provider[38] or by private insurance. [32] Two studies used patient-administered questionnaires [26,34] and one used physician-filled study forms[37] to assess NSAID use. Only one study provided a list of included NSAIDs [38].

3.4.3.3 Quality Assessment

All studies had at least a moderate risk of bias (Tables A3-4). Eleven studies were considered to have moderate risk of sampling bias, and all but one failed to provide age-adjusted prevalences. Two studies were deemed to be at a high risk of bias[29,37]. The first had a sample size of 8 CKD patients and relied on questionnaire data to assess NSAID use, with a 26% response rate[26]. Furthermore, patients could be excluded based on their treating physicians' preference, and relevant clinical characteristics differed significantly between included and excluded patients. The second study used a random sampling method to identify multiple primary care practitioners but had <50% participation rate and provided no comparisons between patients from participating and non-participating practices.

3.4.3.4 Prevalence of NSAID Use/Prescriptions

Eleven studies reported exclusively on NSAID prescriptions by primary care physicians, one study evaluated over-the-counter NSAID use [26], and two others evaluated a combination of both[25,34]. The seven studies reporting cross-sectional point prevalence of NSAID use in CKD patients found prevalences between 8 and 21% (Figure 2).[25,27,29,34,35,37] The remaining seven studies reported period prevalences over follow-up times ranging from 4 weeks[26] to 7 years[32]. Assuming stable prescription rates, the annual prevalence of NSAID use in CKD patients ranged from 3 to 33% (Figure 3)[28,30,31,33]. One study was excluded from this analysis due to very small study size (8 CKD patients, 2 of which had been prescribed NSAIDs) making the prevalence too unstable for meaningful extrapolation to an annual prevalence value[26]. Due to the small number of studies, we were not able to perform a meta-regression analysis to examine the impact of follow-up duration on the overall NSAID prevalence.

3.4.4 Discussion

To our knowledge, this is the first systematic review to evaluate physician prescribing or patient use of NSAIDs among CKD patients. We identified 14 studies (13 publications) addressing this question specifically in a primary care setting. Cross sectional (point) prevalence of NSAID use/prescriptions ranged from 8 to 21%; annual period prevalence ranged from 3 to 33%. These results suggest that despite guidelines recommending against their use, a substantial proportion of CKD patients continue to receive NSAIDs.

Several factors may explain these findings, including lack of awareness of CKD diagnosis by patients and physicians as well as a lack of appreciation of the importance of NSAID avoidance in CKD. Two studies in our review assessing physicians' recognition of CKD status found it to be only 21-24%.[31,35]. While strategies such as automated GFR reporting may be helpful in increasing physicians' identification of CKD patients [40,41], this may not be the only challenge. In our review, one study assessed change in NSAID prescription prevalence before and after a physician-documented CKD diagnosis and found only a very small decrease in NSAID prescribing (from 47 to 42%).[30] A much more significant drop in prescribing prevalence was seen in the year following patient entry into dialysis (30%). Furthermore, another study [31] reported only a small decrease from 24 to 20% of inappropriate medication prescriptions between CKD patients whose physicians had recognized their diagnosis versus those whose physicians had not, although data for NSAIDs alone were not available.

Only one study evaluated the indication for NSAID prescription and found that the overwhelming majority were prescribed for osteoarticular disease.[30] Though alternative therapies exist, NSAIDs may offer superior pain relief in conditions such as arthritis, and our findings may reflect instances where alternatives to NSAIDs have been attempted but were unsuccessful[42]. Thus, despite recommendations to avoid NSAIDs in CKD patients, it may be difficult to do so given the potential beneficial effects of NSAIDs on quality of life and pain relief in such patients. Indications of use and the presence of therapeutic alternatives remain important considerations to be assessed in future studies in this area.

Our study has several potential limitations. There was heterogeneity of the primary care settings of individual studies (e.g., variations in health care organization and practice characteristics). Heterogeneity was also present in the quality of NSAID reporting. Due to the

absence of NSAID dose and duration data in most studies, we were unable to present data for chronic NSAID use as we had originally intended. [43] The only study to explicitly evaluate chronic NSAID use reported elevated rates, with 36% of CKD patients treated with NSAIDs for periods >90 days and 17% for >6 months. [30] Lastly, several studies used a single eGFR value for the diagnosis of CKD which has been shown to overestimate true CKD prevalence and may have resulted in misclassification of CKD status or stage.

3.4.5 Conclusion

Overall, there are few studies specifically evaluating NSAID prescriptions to CKD patients in the primary care setting despite the widespread use of NSAIDS in the general population and the relatively high prevalence of CKD. More research designed to understand and reduce NSAID prescribing in CKD is warranted. Future studies should use standardized and accepted CKD definitions and should explore the reasons behind persistent NSAID use in patients with CKD to tailor knowledge translation interventions with a goal of reducing NSAID use in this patient population.

3.4.6 Disclosures

None

3.4.7 Acknowledgements

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3.6 Tables

Table 3.6. 1: Characteristics of Studies Assessing Point Prevalence of NSAID Use Among Patients with Chronic Kidney Disease

First Author (Location, year)	Source population	Number of CKD patients (% female)	Mean age (SD)	CKD definition (Stages included)	NSAID definition	Study period	Prevalence of NSAIDs (95% CI)
Dorks (Germany, 2016)	21 nursing homes (>96% followed by primary care physician)	601 (75%*)	83 (11)*	Single eGFR ≤60 (C-G) Stage 2: 28% Stage 3: 55% Stage 4-5: 18%	NSAID prescription or OTC use in nursing home chart	2014-2015	21% (18-24)
Fox (USA, 2008)	Patients from a private primary care practice & DM and/or HTN patients from an urban primary care practice	181 (NR)	NR (>18 yrs)	Single eGFR Stages 3-5: 100%	NSAID use in EMR or paper chart review	NR	13% (8-18)
Koffeman (2) (Netherlands, 2014)	Patients presenting a musculoskeletal complaint at practices participating in the Integrated Primary Care Information database	285 (54%*)	47 (17)*	Single eGFR Stages 4-5: 100%	NSAID prescription issued during musculoskeletal complaint episode from EMR	2000-2010	19% (14-24)
Lioté (France, 2012)	Patients with gout or gouty arthritis in a random sample of primary care and rheumatology practices (primary care data presented)	112 (13%*)	63 (11)*	Single eGFR (C-G) Stages 1-3: 100%	NSAID prescription recorded on a case-report form during baseline visit	2008-2009	10% (4-15)
McIntyre (UK, 2012)	32 primary care practices participating in the Renal Risk in Derby study	1741 (60%)	73 (10)	Two eGFRs separated by at least 3 months Stage 3A: 77% Stage 3B: 23%	NSAID prescription or OTC use by questionnaire (validated with latest prescription)	2008-2010	8% (7-10)
Weddle (1) (USA, 2017)	Resident-based primary care clinic	29 (NR)	72 (6)	CKD diagnosis present in patient's EMR	NSAID prescription in EMR	2014-2015	21% (6-35)
Weddle (2) (USA, 2017)	Resident-based primary care clinic	32 (NR)	74 (7)	CKD diagnosis present in patient's EMR	NSAID prescription in EMR	2014	13% (10-24)

CKD: Chronic kidney disease, SD: standard deviation, NSAID: non-steroidal anti-inflammatory drug, CI: confidence interval, eGFR: estimated glomerular filtration rate, C-G: Cockcroft–Gault formula, OTC: over the counter, DM: diabetes mellitus, HTN: hypertension, NR: not reported, EMR: electronic medical records

*Values given for whole study population

Table 3.6. 2: Characteristics of Studies Assessing Period Prevalence of NSAID Use Among Patients with Chronic Kidney Disease

First Author (Location, year)	Source population	Number of patients with CKD (% female)	Mean age (SD)	CKD definition (Stages included)	NSAID definition	Study period	Prevalence of NSAIDs (95% CI)
Allen (USA, 2010)	Multi-specialty group practice of 15 ambulatory health centers in Massachusetts (only 10% followed by a nephrologist)	11774 (60%)	73 (12)	Two eGFRs separated by at least 3 months (MDRD) Stage 3 (97%) Stage 4 (3%)	NSAID prescription in the EMR	2008-2009	10% (9-10)
Arora (USA, 2015)	Claims data from major insurer (analysis restricted to patients not referred to a nephrologist)	15177 (61%)	72 (NR)	Two eGFRs separated by at least three months (MDRD) Stage 3 (97%) Stage 4 (3%) Stage 5 (<1%)	Insurance claim for NSAID prescription	2007-2013	24% (23-25)
Guthrie (Scotland, 2011)	315 primary care practices contributing to the Scottish program for improving clinical effectiveness in primary care	27668 (52%*)	NR (≥65 years)	CKD diagnosis codes	NSAID prescription in the EMR	2007	8% (8-9)
Ingrasciotta (Italy, 2014)	123 Primary care physicians meeting standard quality criteria within Ariana database	1989 (51%)	72 (NR)	CKD diagnosis codes	NSAID prescription reimbursed by National Health System	2006-2011	56% (54-58)
Keohane (Ireland, 2017)	At risk patients** from primary care "training practice" (currently 18 practices)	158 (56%*)	76 (10)	Single eGFR Stages 3 (92%) Stage 4 (6%) Stage 5 (1%)	NSAID prescription in EMR	NR	3% (1-5)

Koffeman (1) (Netherlands, 2014)	4 primary care practices in the Rotterdam region	8 (49%*)	69 (10)*	Single eGFR Stages 4-5: 100%	Any OTC NSAID use reported via questionnaire	2012	25% (0-50)
Martinez-Ramirez (Mexico, 2006)	Patients without a nephrology referral from two primary care units	53 (38%)	62.8 (9.9)	eGFR and/or micro/macroalbuminuria (MDRD) Stage 1 (39%) Stage 2 (34%) Stage 3 (27%)	NSAID use in medical chart	NR	32% (20-45)

CKD: Chronic kidney disease, SD: standard deviation, NSAID: non-steroidal anti-inflammatory drug, CI: confidence interval
eGFR: estimated glomerular filtration rate, MDRD: Modification of Diet in Renal Disease Study equation, EMR: electronic medical record
NR: Not reported, OTC: over the counter
*Values given for whole study population
**Patients with a known renal disorder or impairment, type 1 and 2 DM, HTN, cardiovascular disease, peripheral vascular disease, hyperlipidemia and structural urological disorders

3.7 Figure Legend

Figure 1: Flow Diagram of Included Observational Studies of NSAID Prescription Prevalence in Primary Care CKD Patients

Figure 2: Forest Plot of Studies Assessing Point Prevalence of NSAID Prescription/Use Among CKD Patients in Primary Care

Figure 3: Forest Plot of Studies Assessing Period Prevalence of NSAID Prescription/Use Among CKD Patients in Primary Care, Expressed as Annual Prevalence

Figure 3.7. 1: Flow Diagram of Included Observational Studies of NSAID Prescription Prevalence in Primary Care CKD Patients

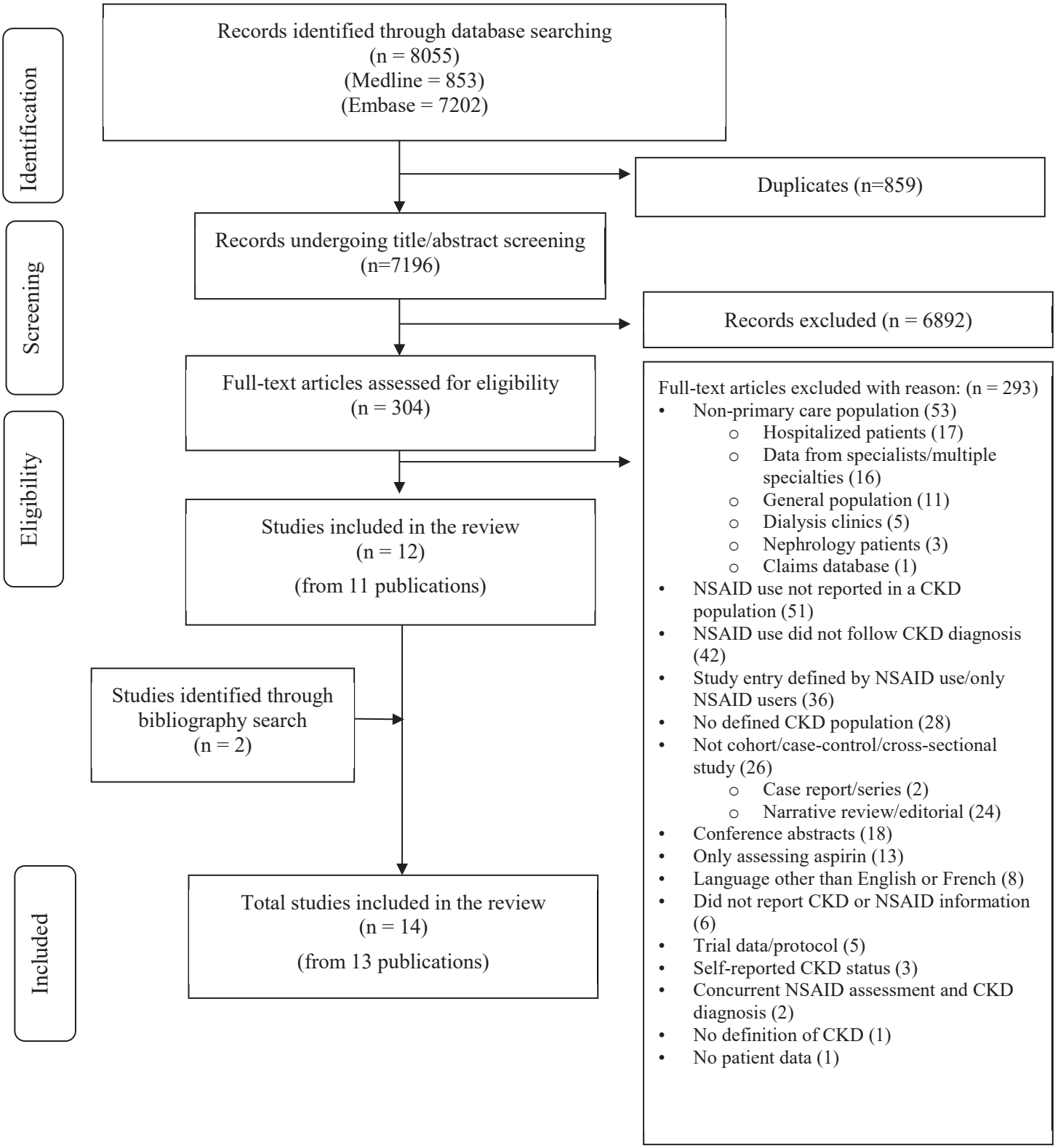
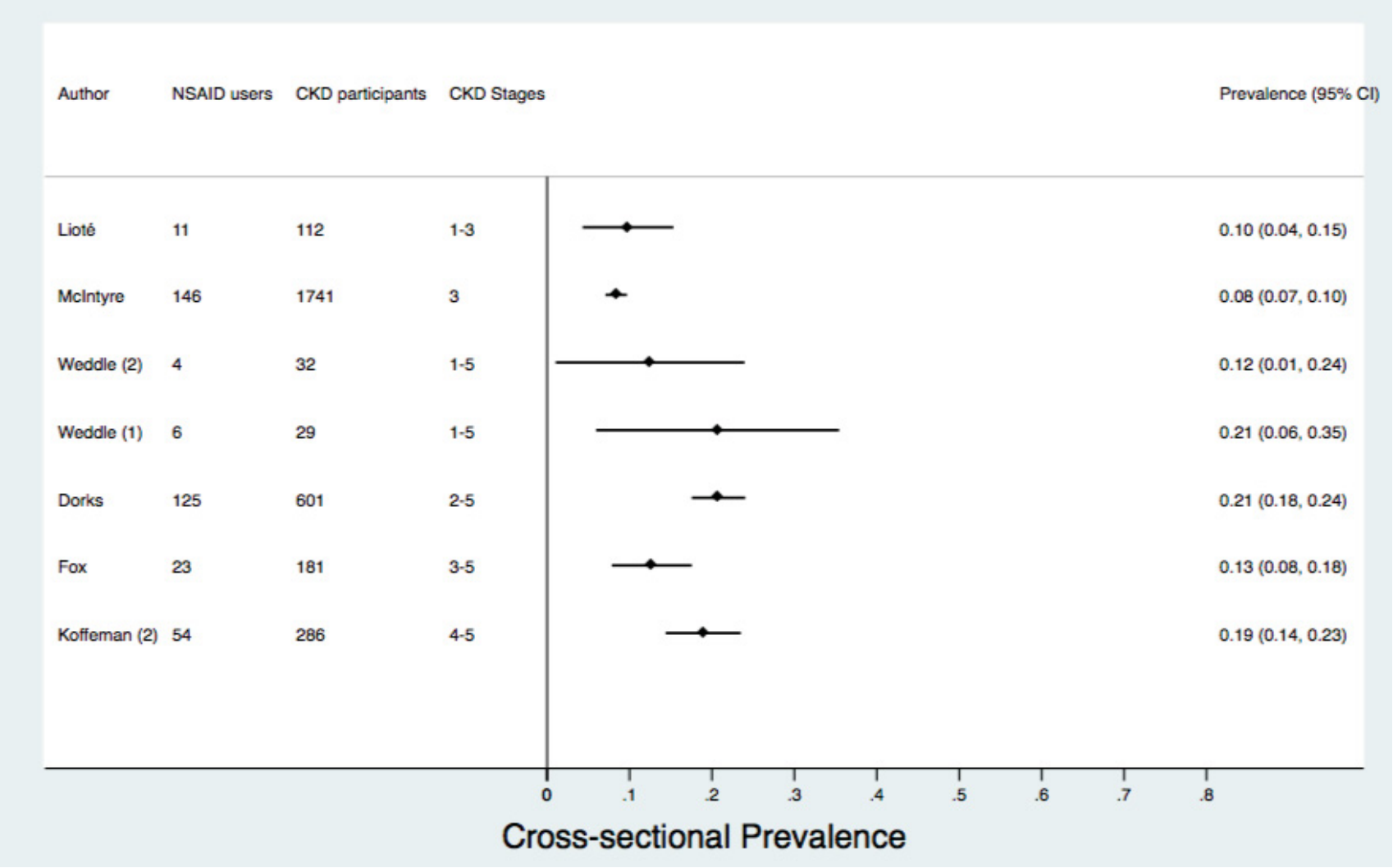
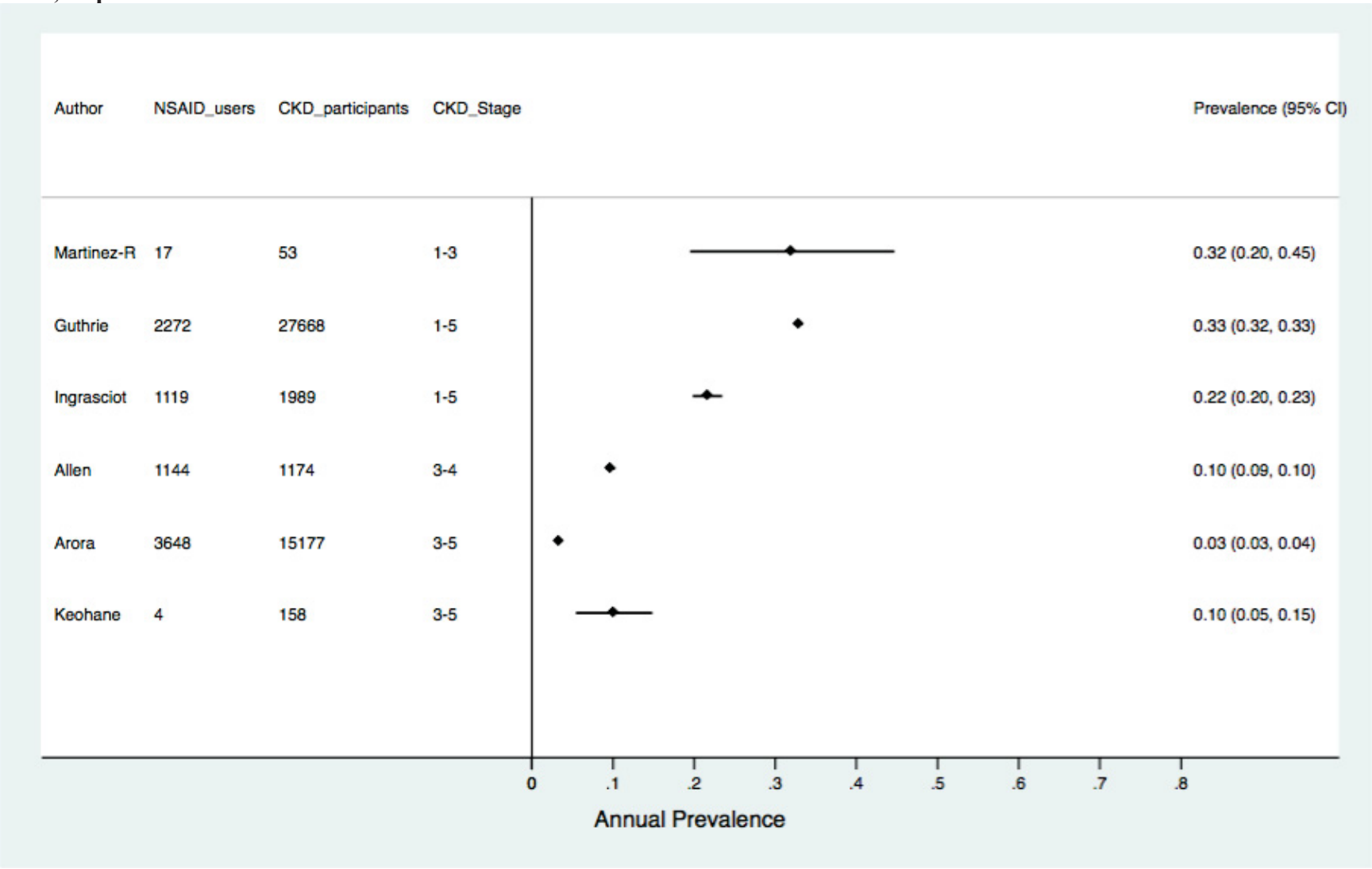


Figure 3.7. 2: Forest Plot of Studies Assessing Point Prevalence of NSAID Prescription/Use Among CKD Patients in Primary Care



NSAID: Non-steroidal anti-inflammatory drug
CKD: Chronic kidney disease

Figure 3.7. 3: **Forest Plot of Studies Assessing Period Prevalence of NSAID Prescription/Use Among CKD Patients in Primary Care, Expressed as Annual Prevalence**



NSAID: Non-steroidal anti-inflammatory drug
CKD: Chronic kidney disease

CHAPTER 4: PRIMARY CARE PRESCRIPTIONS OF NEPHROTOXIC MEDICATIONS IN CHILDREN WITH CHRONIC KIDNEY DISEASE

This next chapter presents a matched cohort study comparing primary care NTM prescriptions for children with and without CKD using the Clinical Practice Research Datalink (CPRD). As previously discussed in Chapters 2 and 3, there are few pediatric studies on NTM use and none addressing the issue within the context of primary care. Furthermore, studies in children with CKD have not previously been conducted. This study's matched design allowed us to overcome an important challenge in comparing medication prescriptions between CKD and non-CKD patients by effectively controlling for differences between these patient groups that would otherwise have made meaningful comparisons difficult. The methodology used to conduct this study was more extensive than what is presented within the manuscript. I have therefore included, as a separate chapter, a detailed description of the methodologies. This additional chapter is meant to be complementary to the methods chapter of the manuscript.

The manuscript in Chapter 3 is currently being prepared for submission to JAMA Pediatrics.

4.1 Title Page

Primary Care Prescriptions of Nephrotoxic Medications in Children with Chronic Kidney Disease

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4.2 Key Points

Question: Are nephrotoxic medications being prescribed to children with CKD in primary care at a similar rate to age and sex-matched healthy controls?

Findings: In this retrospective, population-based, primary care matched cohort study with up to 5 years of follow-up, the proportion of children with CKD receiving at least 1 nephrotoxic medication was 32% compared to 14.6% without CKD. Adjusted prescription rate ratio for primary care NTMs between CKD and non-CKD patients was 10.1 (95% CI 7.6-13.6).

Meaning: NTMs are prescribed at elevated rates to children with CKD and there may be a need for educational interventions aimed at general practitioners on potential harm from NTMs on pediatric CKD progression.

4.3 Abstract

Importance: Pediatric chronic kidney disease (CKD) management focuses on limiting kidney injury, including avoiding nephrotoxic medications. However, nephrotoxic medication prescription practices for children with CKD are unknown.

Objective: To determine the prevalences and rates of primary care nephrotoxic medication prescriptions in children with CKD compared to children without CKD.

Design: A retrospective, matched cohort study of patients <18 years at cohort entry, registered with a general practice participating in the Clinical Practice Research Datalink (CPRD) from 1997 to 2017, with linkage to Hospital Episode Statistics data. Follow-up was up to 5 years.

Setting: UK population-based, primary care database of general practices participating in CPRD.

Participants: All eligible patients with incident CKD were matched 4:1 to non-CKD patients on CKD diagnosis date, sex, age, CPRD practice, and number of general practitioner visits in the year prior to cohort entry.

Exposure(s): CKD was defined by first occurrence of either an outpatient or inpatient diagnostic or procedure code for renal disease. Exposure began at cohort entry and was continuous until end of follow-up

Main Outcome(s) and Measure(s): Nephrotoxic medication prescription prevalences were compared between CKD and non-CKD patients. Adjusted prescription rates were calculated using multivariable binomial regression to account for differential follow-up time.

Results: From our base cohort of 1,535,816 patients, we identified 1,018 with incident CKD and 4,072 non-CKD matches; mean age: 9.8 years [range: 1.1-17.9]; 52% male; mean follow-up time 3.2 vs. 3.3 years in CKD vs. non- CKD patients. CKD patients had higher prevalences of diabetes, hypertension, heart failure/surgery, and past hospitalizations. Overall, 32% CKD patients and 14.6% non-CKD patients were prescribed ≥1 nephrotoxic medication during follow-up. The overall rate of nephrotoxic medication prescriptions was 133.5 (95% CI 110.8-160.8) prescriptions per 100 person-years in CKD patients and 7.8 (95% CI 7.0-8.7) prescriptions per 100 person-years in non-CKD patients (adjusted RR 10.1; 95% CI 7.6-13.6).

Conclusion: Nephrotoxic medications are prescribed at elevated rates to children with CKD. Additional research should focus on indications for these prescriptions to determine appropriateness. There may be a need for educational interventions aimed at general practitioners on potential harm from nephrotoxic medications on pediatric CKD progression.

4.3 Manuscript

4.3.1 Introduction

Chronic kidney disease (CKD) in adults is a strong, established risk factor for cardiovascular disease and for the development of hypertension[1,2]. Though pediatric data are limited, longitudinal studies suggest an elevated prevalence of hypertension and left ventricular hypertrophy in children with CKD[3]. Furthermore, cardiovascular disease remains a leading cause of death in this population[4,5]. Considering that children with CKD are at the beginning of their lifespan; reducing CKD progression could have an important impact on altering their long-term risk for cardiovascular disease. One strategy for preventing CKD progression is to limit the use of nephrotoxic medications (NTMs)[6]. Studies of outpatient NTM prescriptions in patients with kidney disease are currently limited to the adult CKD population and report prescription prevalences between 13% and 70% [7-10]. A significant limitation of these studies is the inconsistent definition of a NTM as well as the paucity of population-based data. Nonetheless, these data raise concerns about whether children with CKD may also be at risk for inappropriate prescribing of NTMs.

Though many children with CKD are closely followed by nephrologists, primary care providers can play an important role in their outpatient care and are often the children's first point of contact with the healthcare system[11]. Using population databases of primary care prescriptions to understand NTM prescription practices in children with CKD will provide information needed to understand the burden of this problem and may reveal opportunities for interventions at the primary care level.

Our primary objective is to describe and compare the prevalence and rate of primary care prescriptions of NTMs to children with an incident diagnosis of CKD *vs* in children without an incident diagnosis of CKD. We hypothesize that due to the under-recognition of the importance of kidney protection in children with kidney disease, children with a diagnosis of CKD would be prescribed NTM at a rate similar to matched controls without CKD.

4.3.2 Methods

4.3.2.1 Data Source

This is a retrospective, matched cohort study of children <18 years of age at the time of cohort entry, registered to the United Kingdom (UK) Clinical Practice Research Datalink

(CPRD), with linkage to the Hospital Episode Statistics (HES) database. The CPRD is a database of anonymized primary care medical records providing information on patient demographics, medical diagnoses and general practitioner (GP) prescriptions. It captures approximately 7% of the UK population and has been shown to be broadly representative with regards to age and sex distribution of patients as well as geographic distribution of practices[12]. Healthcare information is recorded in the CPRD using Read Codes. These codes represent, among others, medical diagnoses, signs and symptoms of disease and summaries of test results[13]. Drug data is obtained by automatic recording of prescriptions issued by GPs and coded according to the British National Formulary (BNF), the prescription reference for UK physicians[12]. Data quality and consistency with medical files are subject to regular checks and their validity has been demonstrated in adult populations[14-16]. HES is a database of hospital admissions that is linked to 75% of England-based CPRD practices (58% of all CPRD practices)[12,14].

We included patients registered in the CPRD database between April 1997 and December 2017 to a practice that was linkable to the HES. At least 1 year of observation time prior to cohort entry date was required for inclusion. Linkage with the HES allowed us to increase the sensitivity of our CKD diagnosis by including in-hospital diagnoses which are coded within the HES according to the ICD-10 classification system. Mortality data was obtained through linkage with the Office of National Statistics (ONS) database – the UK's national statistics institute[12]. Approval for this study was granted by the CPRD Independent Scientific Advisory Committee (reference 17_190RA) and the Research Ethics Board of the Jewish General Hospital.

4.3.2.2 Study Population

CKD was defined by the first occurrence of either an outpatient or inpatient diagnostic code for renal disease (including but not limited to CKD, cystic kidney disease, nephropathy, renal dysplasia and others). Inpatient nephrectomy procedure codes were also included in the CKD definition. Outpatient dialysis codes were included if they appeared at least 3 months following a hospitalization where both an acute kidney injury and dialysis code had been recorded (to minimize exposure misclassification of children with resolving acute kidney injury but no future evidence of CKD codes). We excluded kidney transplant patients as they are unlikely to be generalizable to the wider CKD population in terms of medication prescriptions. Patients were classified as having CKD from the date of first recorded code unless this code

occurred during a hospitalization, in which case the date of hospital discharge was used. Patients meeting CKD exposure criteria before having at least 1 year of up-to-standard CPRD history were excluded to restrict inclusion to incident CKD patients.

The list of codes included in our operationalized definition of CKD was generated iteratively; first by identifying any code potentially related to kidney conditions, followed by initial detailed review/screening and removal of inappropriate codes by one investigator (CL); detailed review by a second investigator with high expertise in pediatric kidney disease (MZ), revision of codes (CL) and a second review (MZ); discussion between the two investigators to arrive at consensus, and the generation of the final list of codes (Supplement eTables 1.1-1.3).

Cohort entry for CKD patients was the date of their incident CKD diagnosis (defined above). Incident CKD patients were matched 4:1 with non-CKD patients on date of CKD diagnosis, sex, age (caliper: ± 2 years), CPRD practice, and exact number of GP visits in the 12-month period prior to cohort entry (as a surrogate measure of health care exposure). Where exposed patients had fewer than 4 eligible matches, the GP visits matching criterion was broadened. Matching was then based on a categorization of 0, 1-3, or >3 GP visits in the 12 months prior to cohort entry and in cases persisting with fewer than 4 matches, on 0-1 and >1 GP visits. Cohort entry date for the non-CKD patients was inherited from their CKD match. To create a comparison group free from kidney disease, we excluded patients from our unexposed group if they had any kidney-related diagnoses, including those that were not included in our CKD definition (Supplement eTables 2.1-2.3).

Follow-up began at cohort entry date and continued until an event (prescription of an NTM medication; defined below) or censoring due to end of follow-up (maximum 5 years), end of the study period (December 2017), death from any cause (recorded in CPRD, HES, or ONS), date of last data collection from the CPRD practice, or departure from the CPRD practice, whichever occurred first. We limited follow-up to five years to control for temporal trends of overall prescription patterns over calendar time.

4.3.2.3 Outcome definition

In the absence of a universally recognized NTM list, our definition of a NTM was derived, in part, from three recent studies using robust and complementary methodologies to draw up separate lists of medications recognized as being nephrotoxic in either adult or pediatric

populations[17-19]. In addition to considering data from these studies, we assessed face validity of the included medications. We reached consensus about the inclusion of additional drugs that did not appear on these lists but that were deemed to have sufficient evidence supporting their nephrotoxicity.

We developed two lists: one of established NTMs and another of potential NTMs (Supplement eTables 3.1 and 3.2). Our definition of an established NTM included medications that were considered definitively nephrotoxic in at least two of the three reference studies. To this list, we added medications in the BNF for Children belonging to medication classes widely recognized as nephrotoxic (e.g. Non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycoside antibiotics, Angiotensin-converting-enzyme (ACE) inhibitors, salicylates). Following a literature review of the association of proton pump inhibitors with kidney disease, these drugs were also included on our list of established NTMs[20-24]. Our second list was broadened to include medications considered to be "potentially" nephrotoxic (providing as wide a capture of potential NTMs as possible). This list included our previously defined established NTMs as well as medications considered to have nephrotoxic "potential" in any of the three reference studies or medications which only one of the three studies considered definitively nephrotoxic.

4.3.2.4 Confounders

Confounders were established a priori based on the literature and on discussion and consensus among investigators. These were selected because of their association with CKD and their role as risk factors for receiving a NTM prescription. Confounders included number of hospitalizations in the year prior to cohort entry and each of the following, measured at any time prior to cohort entry: premature birth, diagnosis of diabetes mellitus, hypertension, cancer, and either heart failure or heart surgery. Cancer diagnoses were limited to the most common pediatric cancer types: leukemia, lymphoma, central nervous system tumors, soft tissue sarcoma and neuroblastoma[25]. Socio-economic status was also included as a confounder and estimated using Index of Multiple Deprivation quintile using patient's postal code[26].

4.3.3 Statistical Analyses

Baseline patient characteristics were reported using mean with standard deviation for

continuous variables and frequencies with percentages for categorical variables. Continuous variables with skewed distributions were presented using median and interquartile range.

Ever-exposure to a NTM was evaluated by comparing the proportion of CKD and non-CKD patients who received ≥1 NTM prescriptions during the follow-up period. Proportions of children receiving ≥1 NTM prescriptions are also presented by major NTM class. We repeated analyses for both our established NTM and potential NTM definitions. These first analyses did not explicitly account for differential follow-up time between exposure groups.

Prescription rates for established and potential NTM prescriptions were calculated for CKD and non-CKD patients, accounting for the differential follow up between exposure groups. These analyses were performed using binomial regression analysis to account for over-dispersion in the data that could not be adequately handled with Poisson regression[27]. Rate ratios (RRs) are presented for the baseline matched analysis. RR are also presented for multivariable analyses adjusted for additional confounders not included as matching variables (described above). These adjusted analyses also include matching variables as covariates in the model for increased robustness[28]. Ninety-five percent confidence intervals for RRs were calculated using robust standard errors. All RRs are reported for the overall follow up period.

Secondary analyses were performed to evaluate whether the proportion of patients receiving a NTM varied by year since cohort entry (corresponding to year since CKD diagnosis for exposed patients). Secondary analyses were also performed to evaluate "NTM load", defined as the proportion of patients receiving 1, 2, 3, >3, and >5 NTMs over the entire follow-up period and by year since cohort entry. Sensitivity analyses were performed with the exclusion of salicylates and ACE-inhibitors as these may be indicated in several conditions associated with CKD. Data management and cohort matching was performed using SAS version 9.4 while primary and secondary analyses were performed using the COUNT package in R (version 1.1.423).

4.3.4 Results

4.3.4.1 Matching, CKD diagnosis and study population characteristics

There were 15,160,693 patients registered to the CPRD between April 1997 and December 2017 of which 1,537,589 met our inclusion criteria (Figure 1). A total of 1,773 patients were subsequently excluded because they met our CKD exposure definition before

having at least 1 year of observation in the CPRD at the time of diagnosis. The final cohort included 1,535,816 patients, of which 1,019 were identified as having CKD (0.07% of total population). There were 231 CKD patients (23%) with fewer than 4 eligible matches when matching on the exact number of GP visits in the year preceding cohort entry. We therefore chose to match on a category of 0, 1-3, or >3 GP visits in the year preceding cohort entry. For the 18 CKD patients who did not have a minimum of four eligible matches using this criterion, we broadened the matching categories to 0-1 and >1 GP visits in the year prior to cohort entry. This left only one CKD patient without any eligible matches, who was excluded from the study. The remaining 1,018 CKD patients were matched to 4,072 unexposed children to create our final cohort of 5,090 children.

Study population characteristics are described in Table 1. Mean age was 9.75 years (13 months –17 years 11 months). Fifty two percent of the cohort was male. Mean duration of follow up was 3.2 and 3.3 years for CKD and non-CKD patients, respectively. The CKD group had a significantly higher proportion of patients with diabetes mellitus, hypertension, cancer, heart failure/surgery, and previous hospitalizations.

4.3.4.2 CKD diagnosis ascertainment

Of the 1,018 CKD participants, 351 were diagnosed based on outpatient diagnostic codes and 551 were identified based on inpatient diagnostic codes. One hundred and six patients were included after having undergone a nephrectomy. Eleven patients (1%) had an outpatient dialysis code recorded during follow-up. Further details regarding breakdown of specific CKD inclusion codes in our cohort are summarized in Supplement eTables 4.1-4.4.

4.3.4.3 Prescription of at least one NTM during the study period

Overall, 32% of CKD participants and 14.6% of non-CKD participants were prescribed at least one established NTM during follow-up (Figure 2). NSAIDs accounted for the majority of established NTM prescriptions and were prescribed at least once to 17.2% of CKD patients and to 13.3% of non-CKD patients. No non-CKD patient received an ACE-inhibitor compared to 10.3% of CKD patients. After excluding ACE-inhibitors and salicylates, 25.8% of CKD patients were prescribed an established NTM.

When including potential NTMs (in addition to established NTMs), 70.7% of CKD patients and 50% of non-CKD patients received at least one NTM medication during follow-up (Figure 3). When excluding ACE-inhibitors and salicylates, these proportions were 68.3% and 50%, respectively. The two most commonly prescribed drug classes were penicillins and cephalosporins, prescribed to 56.9% and 18.3% of CKD patients, respectively, compared to 44.1% and 3.9% of non-CKD patients.

4.3.4.4 CKD vs. non-CKD NTM prescription rate

The rate of NTM prescriptions for established NTM during follow-up was 133.5 (95% CI 110.8-160.8) prescriptions per 100 person-years in CKD patients and 7.8 (95% CI 7.0-8.7) prescriptions per 100 person-years in non-CKD patients (adjusted RR 10.1; 95% CI 7.6-13.6) (Table 2). When considering potential NTMs, the rate of prescriptions was 262.6 (95% CI 230.2-299.7) prescriptions per 100 person-years in CKD patients and 44.5 (95% CI 41.7-47.5) prescriptions per 100 person-years in non-CKD patients (adjusted RR 3.7; 95% CI 2.9-4.5). When we excluded salicylates and ACE-inhibitors from our NTM definition, the adjusted RR for CKD versus non-CKD patients was 4.0 (95% CI 2.7-6.0) and 2.6 (95% CI 2.1-3.2) for prescription of established and for potential NTMs, respectively (Table 2).

4.3.4.5 Secondary analyses

When considering time since cohort entry, the proportion of CKD patients receiving at least one established NTM remained relatively stable, ranging from 17.6%-19.5% per year (Supplement eFigure5.1). This remained true for the most commonly prescribed classes such as NSAIDs, ACE-inhibitors and proton pump inhibitors. When considering number of NTMs prescribed, the proportion of CKD patients receiving 1, 2, 3 or more than 3 individual NTM prescriptions did not vary with time since cohort entry (or time since diagnosis for CKD patients) (Supplemental eFigure 5.2).

4.3.5 Discussion

Our study was designed to describe and compare the prevalence and rate of primary care prescriptions of NTMs to children with *vs* without an incident diagnosis of CKD. We found that in an outpatient UK population-based data source, children with CKD were prescribed NTMs by

GPs at almost 10 times the rate of matched non-CKD children. During the first 5-years from CKD diagnosis, over 30% of children with CKD were prescribed at least one established NTM and 71% were prescribed a medication with potential nephrotoxicity. Our results have potentially important implications because NTMs may contribute to kidney disease progression which in turn, is associated with higher rates of mortality, end-stage-renal disease and morbidity from cardiovascular disease.

Children with CKD generally have more comorbidities than their healthy counterparts, occasionally justifying the use of NTMs. Though our models were adjusted for major comorbidities associated with CKD, residual confounding might explain part of the identified difference in prescription rates. However, it is important to note that the most commonly prescribed NTMs were NSAIDs for which safer alternatives exist in CKD and whose indication may therefore be more difficult to justify[29,30]. Furthermore, the RR of NTM prescriptions remained significantly elevated at 4.0 after the removal of medications such as ACE-inhibitors and salicylates which may be indicated for comorbidities associated with CKD.

If GPs were aware of the contraindication of the medications included in our study, we might expect the prescription rates to decrease in the period immediately following CKD diagnosis. Though we did not compare prescription rates before and after CKD diagnosis, we did assess the prescription rate and proportion of patients receiving NTM prescriptions by year following CKD diagnosis (Supplemental eTable 5.1 & eFigure 5.1). That yearly prescription rates did not significantly differ with time since CKD suggests the diagnosis may not have been considered by prescribing GPs. Under-recognition of CKD by GPs may also be an issue as only 35% of our CKD cohort was identified using outpatient codes, with the remaining identified using inpatient codes. Of note, many of our inclusion codes represented diseases strongly associated with CKD, though not explicitly coded as such. These include cystic kidney disease (13%), small kidneys (13%), obstructive and reflux nephropathy (11%), recurrent and persistent hematuria with morphological changes (9%) and renal dysplasia (8%). These diagnoses may not be recognized by GPs as indicative of CKD but have been associated with a significantly increased risk of adult end-stage kidney disease making NTM avoidance in these cases equally important[31].

Previous studies on NTM prescriptions in CKD patients have focused on the adult population. The most comprehensive population-based study revealed that 45.2% of CKD

patients received a NTM within one year of their CKD diagnosis and 56.3% received a prescription for a NSAID over their entire follow-up[32]. Considering that pediatric patients have a lower medication burden overall, our corresponding proportions of 19.5% and 17.2% respectively are similarly worrisome. Other studies reporting wide-ranging proportions of CKD patients receiving NTM prescriptions suffer from variable definitions of CKD and NTM, making comparisons difficult[7-10].

Our study has several strengths. It is the first population-based pediatric study to evaluate NTM prescriptions in children with CKD. Our use of CPRD allowed us to follow a relatively large pediatric population of CKD patients. Inclusion of both outpatient and inpatient procedure and diagnostic codes allowed for a greater sensitivity for our CKD definition and our matched design allowed for strong control of potentially confounding variables such as age, sex and prior health care contact. Matching on previous number of GP visits helped us to control for the frequency of healthcare contact and the opportunity to receive a primary care NTM prescription which might otherwise be inherently different between CKD and non-CKD patients. Furthermore, our ability to match on GP practice allowed us to control for prescriber variability which can account for important differences in comparison analyses of CKD and non-CKD patients.

Our study also has some potential limitations. As discussed earlier, we did not evaluate indications for NTM prescriptions and cannot therefore comment on the justification of their use. Due to absence of specific eGFR measurements and medication dosage information, we were unable to evaluate whether appropriate medication dose adjustments had been made for individual patients' renal function. Furthermore, CPRD does not include information on in-hospital drug prescriptions or prescriptions prescribed by specialists, which likely led to underestimation of true NTM prescriptions in our study population (e.g. intravenous aminoglycoside antibiotics or antiviral agents). However, the purpose of this study was to evaluate prescriptions by GPs, and CPRD provides excellent capture of this outcome. Some underestimation of NSAID use is also likely as these medications are available over the counter in the UK. Though interesting to consider, the main interest of this paper was to evaluate GP prescribing behaviours which are not necessarily reflected in over-the-counter medication use. In the absence of objective laboratory measure of estimated glomerular filtration rate (eGFR), our CKD definition relied on diagnostic and procedural codes, which may have limited sensitivity[33].

Validation studies of overall CPRD data suggest that they have high validity, though data are not available specifically for CKD. Furthermore, absence of staging information for most of our CKD patients as well as the limited number of children in our study did not allow us to compare prescription rates by CKD stage.

4.3.6 Conclusion

NTMs appear to be prescribed at elevated rates to pediatric CKD patients. Although their use may be justified depending on the clinical context, it is apparent that there is a need for increased awareness of their harmful potential in this high-risk patient group. Further research regarding NTM prescription practices in pediatric kidney disease patients could focus on determining the appropriateness of these prescriptions as well as identifying specific factors contributing to elevated prescription rates. This could eventually help direct clinical decision support systems and physician education programs aimed at reducing inappropriate medication prescribing in pediatric CKD patients.

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4.3.8 Disclosures

None

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4.5 Tables

Table 4.5. 1: Characteristics of Pediatric Patients with CKD and Matched Controls

	CKD	No CKD (Matched Controls[a])
No.	1018	4072
Male (No., %)	532 (52.3)	2128 (52.3)
Age in years (mean (SD))	9.75 (4.96)	9.75 (4.96)
Follow-up time		
Median [IQR]	3.3 [1.5, 5.0]	3.7 [1.8, 5.0]
Mean (SD)	3.2 (1.8)	3.3 (1.7)
Categorization: No. (%)		
<1 year of follow up	170 (16.7)	552 (13.6)
1-2 years of follow up	149 (14.6)	563 (13.8)
2-3 years of follow up	152 (14.9)	590 (14.5)
3-4 years of follow up	104 (10.2)	455 (11.2)
4-5 years of follow up	76 (7.5)	371 (9.1)
Full 5 years of follow up	367 (36.1)	1541 (37.8)
GP visits in year prior to cohort entry: No. (%)		
0	731 (71.8)	2952 (72.5)
1	137 (13.5)	654 (16.1)
>1	150 (14.7)	466 (11.4)
Hospitalization in year prior to cohort entry: No. (%)	573 (56.3)	146 (3.6)
Premature birth: No. (%)	45 (4.4)	115 (2.8)
DM prior to cohort entry: No. (%)	33 (3.2)	<5[b] (<0.01)
HTN prior to cohort entry: No. (%)	33 (3.2)	<5 (<0.01)
Cancer diagnosis prior to cohort entry: No.(%)	12 (1.2)	<5 (<0.01)
Heart failure or heart surgery prior to cohort entry: No. (%)	20 (2.0)	9 (0.2)

a. Matched on date of CKD diagnosis, sex, age ±2 years, GP practice and number of GP visits in 12 months prior to cohort entry

b. Table values under 5 are suppressed in accordance with CPRD policy

Abbreviations: No.: Absolute number, CKD: Chronic kidney disease, SD: Standard deviation, IQR: Interquartile range, GP: General practitioner, DM: Diabetes mellitus, HTN: Hypertension

Table 4.5. 2: Rate of Prescription of Nephrotoxic Medications over the Entire Study Period

	Matched[a]			Matched and adjusted[b]
	Prescription Rate (per 100 PYs)		Rate Ratio (95% CI)	Rate Ratio (95% CI)
Established NTM	**CKD (n=326)**	**Non-CKD (n=593)**	17.20 (13.9-21.3)	10.1 (7.6-13.6)
	133.5 (110.8-160.8)	7.8 (7.0-8.7)		
Established NTM excl. ACE-I & salicylates	**CKD (n=263)**	**Non-CKD (n=592)**	9.0 (6.8-12.0)	4.0 (2.7-6.0)
	70.1 (53.7-91.4)	7.8 (7.1-8.6)		
Potential NTM	**CKD (n=720)**	**Non-CKD (n=2037)**	5.90 (5.1-6.8)	3.7 (2.9-4.5)
	262.6 (230.2-299.7)	44.5 (41.7-47.5)		
Potential NTM excl. ACE-I and salicylates	**CKD (n=695)**	**Non-CKD (n=2037)**	4.5 (3.8-5.3)	2.6 (2.1-3.2)
	199.1 (171.9-230.6)	44.5 (41.7-47.5)		

a. Matched on date of CKD diagnosis, sex, age ±2 years, GP practice and number of GP visits in 12 months prior to cohort entry

b. Adjusted further for sex, age, Index of Multiple Deprivation quintile, GP practice region, number of hospitalizations in 12 months prior to cohort entry, prematurity, diabetes, hypertension, cancer, history of heart surgery or heart failure

Abbreviations: PY: Person year, CI: Confidence interval, NTM: Nephrotoxic medication, CKD: Chronic kidney disease, ACE-I: Angiotensin converting enzyme-inhibitor

4.6 Figure Legend

1. Figure 1: Flow Diagram of Patient inclusion from CPRD Database

2. Figure 2: Proportion of CKD vs. Non-CKD Patients Who Received an Established NTM, by NTM Class
    a. CKD: Chronic Kidney Disease
    b. NTM: Nephrotoxic Medication

3. Figure 3: Proportion of CKD vs. Non-CKD Patients Who Received an Established or Potential NTM, by NTM Class
    a. CKD: Chronic Kidney Disease
    b. NTM: Nephrotoxic Medication

Figure 4.6. 1: Flow Diagram of Patient inclusion from CPRD Database

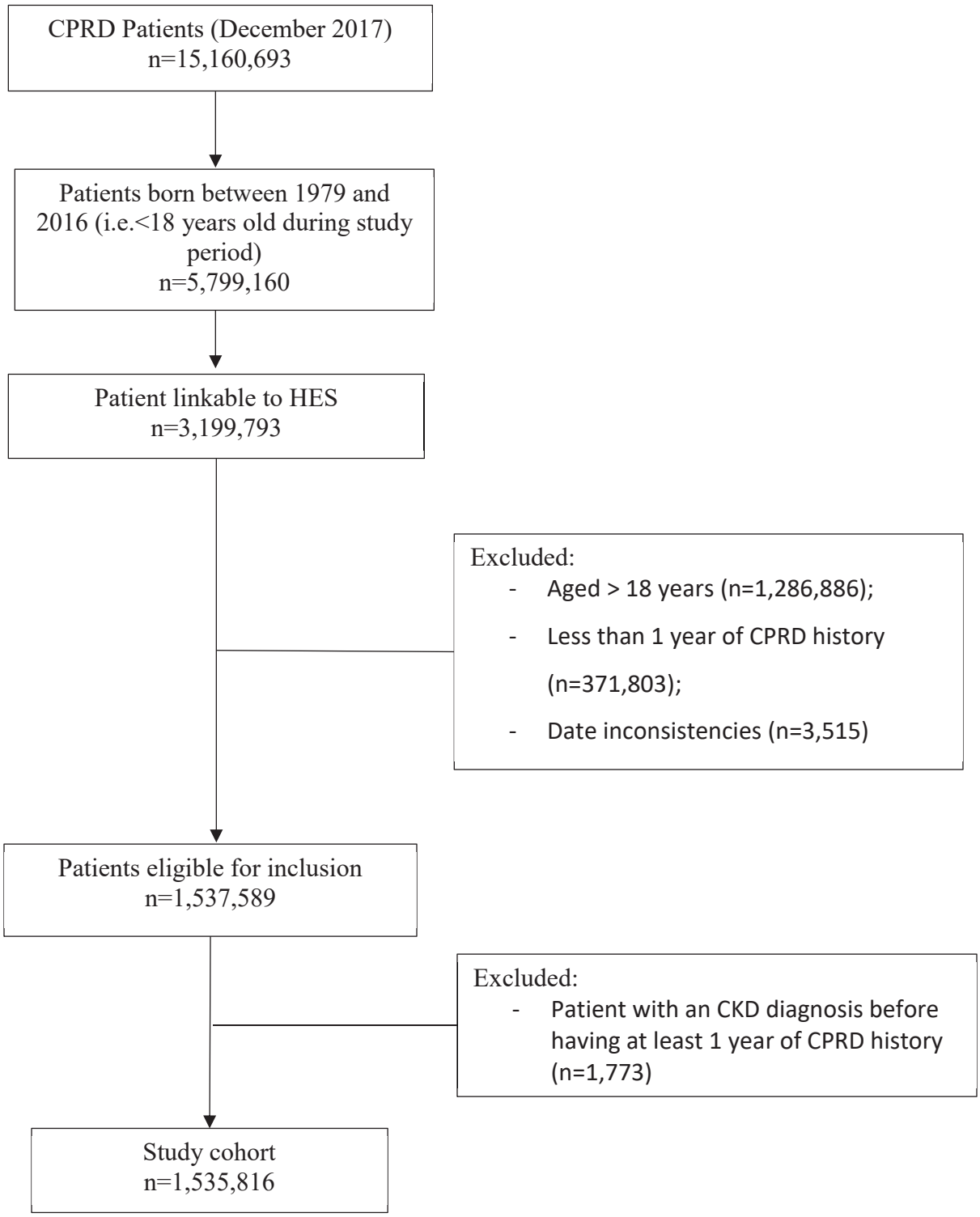


Figure 4.6. 2: Proportion of CKD vs. Non-CKD Patients Who Received an Established NTM, by NTM Class

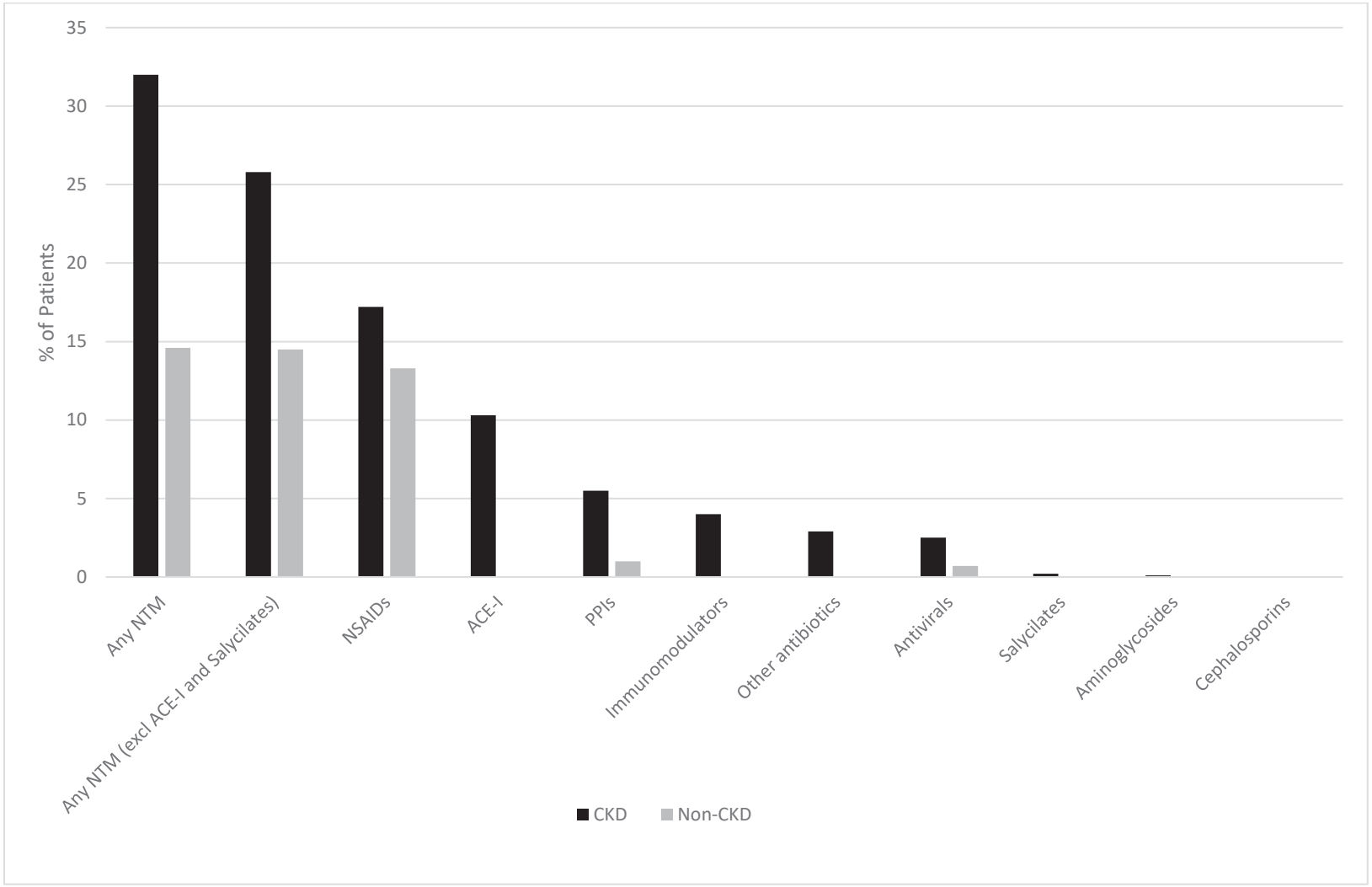
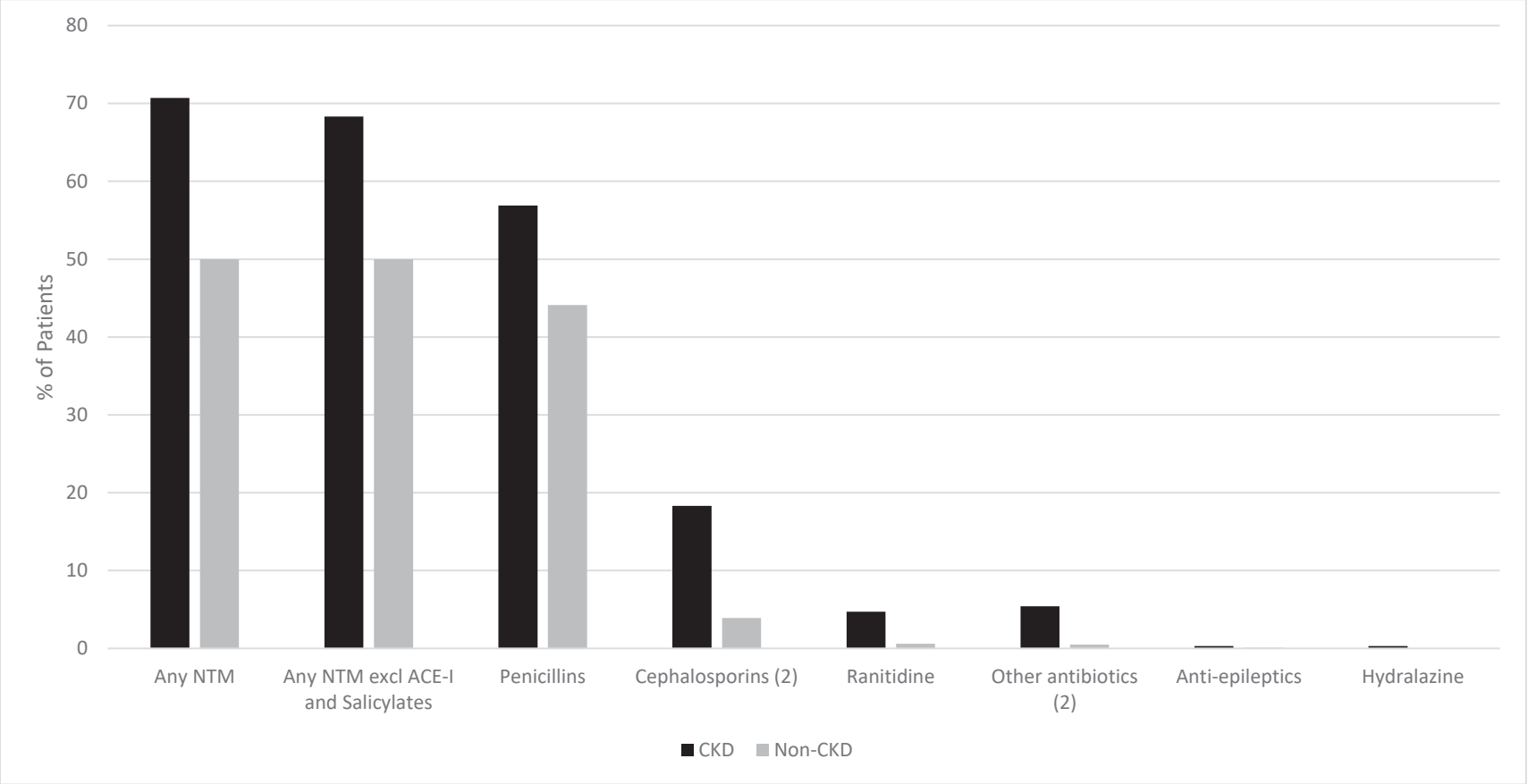


Figure 4.6. 3: Proportion of CKD vs. Non-CKD Patients Who Received an Established or Potential NTM, by NTM Class



CHAPTER 5: METHODS

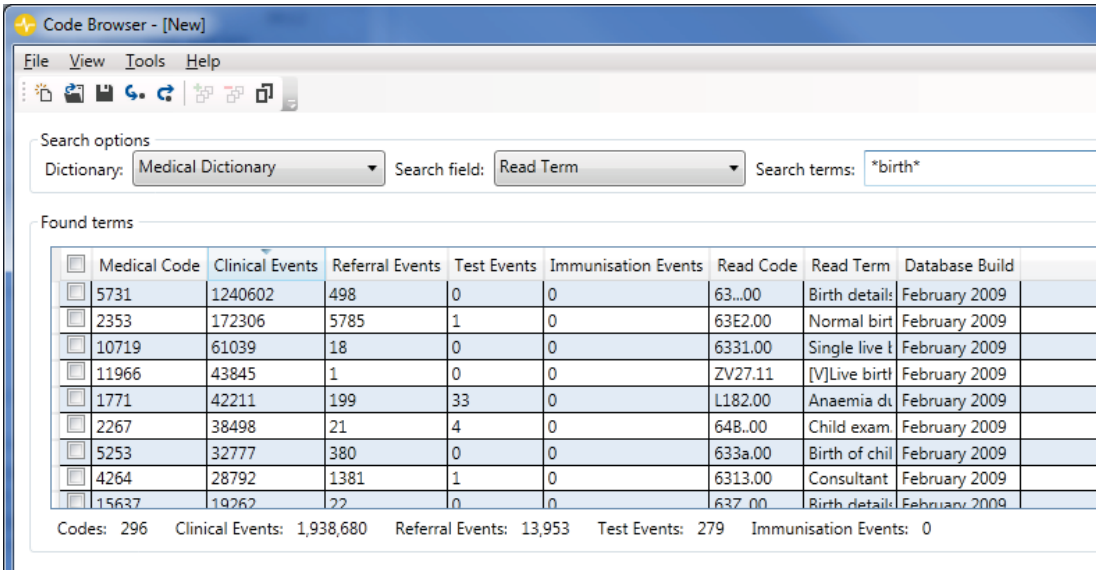
5.1 CPRD Coding and Search Structure

The CPRD offers a wealth of primary care level data due to almost universal patient registration to GP practices within the UK as well the widespread use of computerized systems within these practices[36,37]. Furthermore, the UK health system is organized such that GPs are the gatekeepers to secondary care[38]. When patients access secondary care services, information regarding investigations and therapies are almost universally fed back to the GP who is expected to provide ongoing follow-up. As such, the CPRD has the potential to capture the full scope of a patient's health care experience. Healthcare information is coded within the CPRD using Read Codes. These codes are very versatile, allowing the documentation of specific diagnoses but also of signs or symptoms of disease and summaries of test results, among others[38]. They are used by GPs to record active and previous patient healthcare experiences and are the principal source of outpatient data recording. The Read code system is the national standard for primary care coding in the UK[39]. The hospital-based HES database records all NHS hospital attendances in England. It has been linked to participating England-based CPRD practices since 1997. Currently, 58% of UK CPRD practices are linkable to HES including 75% of CPRD practices based in England[40]. HES uses the ICD-10 international coding classification for in-hospital clinical and diagnostic codes and the OPCS coding scheme for in-hospital procedural and surgical codes.

The Code Browser tool of CPRD allows searching of a Read code dictionary for clinical codes and a medication product code dictionary for drug searches. Using the Code Browser, I performed a text-based search with wildcard characters (*) to identify a list of Read terms referring to kidney disease (Figure 1). The search terms are shown in Table 1. For the identification of NTMs, I did a text-based search of all medications identified from my literature search as nephrotoxic (described in detail below). I used generic and trade names as well as medication classes to maximize the sensitivity of the text search. I then used the "British National Formulary (BNF) Header" feature of the Code Browser to broadly search relevant NTM classes. Any drugs newly identified by this method were then once again text-searched to identify any derivatives thereof. Results from both searches were then combined to create the final list of included medications. ICD-10 codes were searched using an online coding dictionary[41]. I performed a text-based search using the following terms: kidney, renal, dialysis,

glomerulonephritis, anuria, uremia, proteinuria, albuminuria, nephritis, nephropathy, cortical necrosis and hydronephrosis. All ICD-10 codes retrieved in these individual searches were assessed for inclusion. Using the ICD-10 coding hierarchy, all identified codes were then expanded to identify their subject heading. I then browsed all the codes within each subject heading to assess their eligibility for inclusion. The OPCS4 codes for dialysis and nephrectomy were identified by searching the OPCS-4.8 Metadata file[42]. All codes falling under the category of "arteries and veins" (for dialysis fistulas) and "urinary" were assessed individually for inclusion.

Figure 5.1. 1: CPRD Code Browser Tool Interface



All diagnosis and procedure codes were initially identified (C.L.) and classified as representing either CKD, AKI or kidney disease not otherwise classified as CKD – the two latter of which were the basis of an exclusion from my unexposed cohort. This initial classification was revised with M.Z. who is a senior clinical nephrologist. Following these discussions, codes were reclassified and further searches were executed by C.L. This second set of codes was once again revised and consensus was reached about the final inclusion codes. A similar process was applied for the finalization of the NTM code lists.

5.2 Nephrotoxic Medication Definition

In the absence of a universally recognized list of medications considered to be NTM, I sought to create a list based on existing evidence within the medical literature. An extensive search was conducted of publications relating to nephrotoxicity and kidney injury. A total of 18 studies were identified that provided a comprehensive list of NTMs. These studies are listed in Table 2. Each study was appraised for the rigor and transparency of its methodology for selecting its list of NTMs. Following discussion with a senior nephrologist (M.Z.), three of these studies were selected to form the basis from which my own NTM definition was derived[15,43,44]. These studies were considered to have used robust and complementary methodologies to draw up separate lists of medications recognized as being nephrotoxic in either adult or pediatric populations. From these studies' NTM lists, I developed two NTM lists: one of established NTMs and another of potential NTMs. My definition of established NTMs included medications that were considered definitely nephrotoxic in at least two of the three reference studies. My list of potential NTMs included established NTMs as well as medications considered to have nephrotoxic "potential" in any of the three reference studies. To this list, I also added medications which only one of the three studies considered definitively nephrotoxic.

The first study from which my NTM list was derived was by Mehta et al.[15] In conjunction with the International Serious Adverse Event Consortium, the authors developed consensus definitions for "drug induced kidney disease" using Delphi criteria involving an international committee of adult and pediatric nephrologists and pharmacists. They defined two types of drug reactions: 1) Type A reactions, considered dose-dependent toxicities and predictable based on the known pharmacology of the drug; and 2) type B reaction which are non-dose dependent and unpredictable based on the known pharmacology of the drug. For the purposes of my study, drugs listed as causing Type A reactions were considered definitely nephrotoxic and drugs causing Type B reactions were considered potentially nephrotoxic. The study by Mehta et al. was the only identified study to derive a list based on an international consensus of experts and explicitly describe justifications for medication inclusion based on recognized pathophysiological mechanisms of drug interactions with the kidneys.

The second study by Ingrasciotta et al. [33] derived its NTM list from a literature review that yielded a list of 127 potentially NTMs, which were then validated by a team of nephrologists and clinical pharmacologists using the Summary of Product Characteristics. Authors then

classified these medications as either "contraindicated" in CKD or "to be used with caution" in CKD. For the purposes of my study, drugs appearing on the former list were considered definitely nephrotoxic and those on the latter list were considered potentially nephrotoxic. My decision to include this study was based on the authors' rigor in conducting their literature search as well as their decision to involve both nephrology and pharmacy-specific expertise in the validation of their search results. This was felt to offer a good balance of sensitivity and specificity of their final NTM list.

Lastly, I included a pediatric study by Goldstein et al.[43], where authors based their NTM list on reported toxicities listed in the Drug Information Handbook (Hudson, OH, Lexi-Comp, 2009). All drugs listed in this study were considered definitely nephrotoxic. My justification for using this study is that the team involved in its development consists of recognized leaders in pediatric kidney disease research and the list features in many of the few existing pediatric nephrotoxicity studies[4,45].

In addition to considering data from these three studies, my established NTM list also included medications from the BNF for Children belonging to medication classes widely recognized as nephrotoxic (e.g. NSAIDs, aminoglycoside antibiotics, ACE inhibitors and salicylates). The BNF for Children was first published in 2005 and has been updated annually since[46]. This resource was used because it is the prescription reference book for UK physicians and is the basis for the CPRD's medical coding classification system. A 2010 market research study revealed universal use of the BNF by medical practitioners and pharmacists in the UK making it an excellent resource from which to derive a list of medications which should be recognized as nephrotoxic by primary care physicians[46].

Proton pump inhibitors (PPIs) are a class of medications whose nephrotoxic potential has more recently been described. I performed a literature review to assess the evidence for including this class of medications in my NTM definition. My literature review revealed 5 studies reporting a statistically significant association between use of PPIs as a class and subsequent kidney injury. Three of these studies, published in the last 3 years, are large-scale cohort studies and the two others are case-control designs. A cohort study involving over 10,000 adult patients recruited to the Atherosclerosis Risk in Communities (ARIC) study demonstrated a 20-50% increase in incident CKD in PPI users versus non-users. Similar results were found when comparisons were made between histamine H_2-receptor antagonist users and non-users[47].

Another cohort study of new PPI users and new histamine H_2-receptor antagonist users from the Department of Veterans Affairs (VA) national databases used propensity score weighted analyses and reported a HR of 1.22 (95% CI 1.18 to 1.26) for the development of incident CKD and a HR of 1.96 (95% CI, 1.21 to 3.18) for the development of end-stage renal disease (ESRD) among medication users as compared to non-users. Authors also demonstrated an increased risk of kidney disease with increased duration of PPI use[48]. An Ontario-based cohort study of over 290,000 PPI users, propensity matched to non-PPI users evaluated interstitial nephritis rates as well as hospital admissions for AKI within 120 days of PPI initiation. Risk of AKI hospitalization was more than doubled in PPI users (HR 2.52; 95% CI 2.27 to 2.79) and the risk of acute interstitial nephritis was tripled (95% CI 1.47 to 6.14)[49]. A recent case-control study of almost 100,000 patients registered with primary care clinics in the VA Health Care Upstate New York database revealed an OR for the development of CKD of 1.10 (95 % CI 1.05–1.16) in PPI ever-users versus never-users[50]. A second case-control study including 854 privately insured patients with a coded diagnosis of kidney disease and their matched controls showed an OR of 1.72 (95% CI 1.27-2.32) for PPI use after adjustment for confounders[51]. Following this literature review and the solid body of evidence to suggest an association between PPI use and kidney disease risk, I decided to include PPIs on my list of established NTMs.

5.3 Confounding

Confounders of the association between CKD and NTM prescriptions were established *a priori* based on literature and discussion and consensus amongst investigators prior to performing any analyses. These were selected because of their association with CKD and their role as risk factors for receiving a NTM prescription. Matching was established as the surest way to control for confounders such as age, sex, primary healthcare contact, CPRD practice and date of cohort entry; it was deemed to be feasible given the availability of a large patient database. CPRD patient files were searched for year of birth, gender and CPRD practice. Age calculations were performed using January 1st as an arbitrary birth date as information on birth month was missing in 99% of cases. Matching on CPRD practice allowed us to control for physician variability in medication prescribing and was considered much more efficient than adjusting given the large number of CPRD practices. Matching on calendar date of cohort entry allowed me to control for temporal trends in prescribing given the long study period.

With an outcome of nephrotoxic medication prescriptions by general practitioners, I chose to match on the number of visits with the GP in the year prior to cohort entry as a proxy for contact with the healthcare system. This was done to balance the likelihood of receiving the outcome (a NTM prescription) between exposed and unexposed patients which would otherwise likely be inherently different. I therefore considered only visit types that were likely to have been performed by a GP (these are presented in Table 3). This list was finalized following discussion with an author familiar with CPRD coding practices (K.B.F.). Hospital admissions recorded in the CPRD were not considered GP visits for matching purposes. In cases where more than one GP visit was recorded on a given day, it was counted as a single visit as duplications were considered the likely result of administrative errors in coding rather than separate visit types.

Other *a priori* confounders were controlled for by including them as covariates in my multivariable regression models. These included socio-economic status and medical comorbidities associated with CKD and NTM prescriptions. Socio-economic status was estimated using the patient-level index of multiple deprivation (IMD) using the patient's postal code[52]. The IMD is based on seven aspects of socio-economic deprivation including income, education and health. As my study period extended between 1997 and 2017, the 2007 IMD was used as it represented the midpoint of my study. This covariate was expressed as a quintile and categorized as such in the multivariable regression models. Six patients had missing IMD. Given that so few data were missing, I used a complete case approach for the regression analysis.

Medical co-morbidities were identified by the presence of diagnostic or procedure codes recorded at any time prior to cohort entry. They were modelled as time-fixed binary variables and were considered to exist continuously throughout the study period. These included heart failure, prematurity and major pediatric cancer diagnoses, including blood, brain and soft tissue cancers as well as neuroblastoma. These were coded using both inpatient ICD-10 codes recorded in HES and Read codes recorded in the CPRD to optimize their sensitivity. Heart surgery for congenital cardiac anomalies codes were captured using OPCS4 within the HES. Hyperglycemia/diabetes and hypertension codes were restricted to the CPRD as elevated blood pressure and blood sugar recordings are common in pediatric inpatients due to pain and medication use and are often transient. Presence of a hospitalization in the year prior to cohort entry was used as a proxy for health status and included as a binary variable in my regression models. Hospitalizations were identified in the HES database. I excluded hospital visits with a

same-day admission and discharge if patients presented from and were discharged to their home as these are likely to represent outpatient visits or emergency room presentations which, in children, may reflect mild episodes not thought to reflect underlying health status (e.g. benign viral infections or non-severe injuries).

5.4 Additional Details on Cohort Construction

Data management and cohort matching was performed by P.R. using SAS version 9.4. For children who entered the cohort based on inpatient HES codes, the discharge date of the hospitalization containing the diagnostic or procedure code served as the cohort entry date. This was done because my study outcome, primary care prescriptions, can only occur after hospital discharge and patients should only contribute person-time to the analysis if they are at risk of the event. Any time between an in-hospital CKD diagnosis and discharge would therefore be immortal time and would not be appropriate to include in the analyses. Furthermore, due to the nature of HES coding, CKD diagnoses recorded during a hospitalization are not assigned an exact date within the hospitalization period. Three patients (<0.01%) with a recorded CKD diagnosis occurring during a hospitalization did not have a recorded discharge date. To avoid making any assumptions about the appropriate cohort entry date for these patients, they were excluded from the study. Of note, three patients entered the cohort as unexposed and developed a diagnosis of CKD during their follow-up. These unexposed patients were censored at the date of CKD diagnosis and their subsequent follow-up time was classified as exposed, contributing to the CKD branch of the cohort.

I allowed for matching with replacement so that unexposed patients could serve as matches for more than one exposed patient. Consequently, seven of my unexposed patients were selected twice as matches. Considering this very small number, it was deemed unnecessary to adjust the variances in my final analyses. When matching on exact number of GP visits in the 12 months prior to cohort entry, there were 231 CKD patients (23% of the entire CKD cohort) with fewer than 4 matches. Following evaluation of the distribution of number of GP visits for my cohort, I chose to categorize GP visits (0, 1-3 or >3) in the year preceding cohort entry for matching. Eighteen CKD patients failed to meet the requirement of four matches using this criterion so a second matching iteration was performed for those patients, broadening the categorizations to 0-1 and >1 GP visits in the year prior to cohort entry. This process left one

CKD patient without any eligible matches; this patient was excluded from the study. The remaining 1018 CKD patients were matched to 4,072 unexposed children to create my final cohort of 5,090 children.

5.5 Statistical Analyses

To calculate baseline rates and prescription rate comparisons between CKD and non-CKD patients, I used a Binomial regression model. The Binomial model was chosen over the Poisson model due to over-dispersion present in my data which violated the assumptions of a Poisson model. I evaluated over-dispersion through several modes. I first calculated the variance of the response variable in my data and found it to be significantly greater than the mean. I also calculated the Pearson Dispersion statistic of the adjusted models. This statistic represents the difference between observed and predicted model counts, adjusted for the size and variance of the model[53]. This statistic has an expected value of 1 if the variance of the model is entirely explained by the variance function. Values above 1 indicate over-dispersion of the data and values below 1 indicate under-dispersion[53]. The dispersion statistic for my adjusted Poisson model was 39.9 suggesting important over-dispersion. The adjusted negative binomial model gave me a dispersion statistic of 1.11, suggesting a better fit for my data. Furthermore, the Akaike Information Criteria of the adjusted models were 33,190 *vs.* 7,755 for the Poisson and Negative Binomial models respectively suggesting the latter was a better fit.

Because my outcome was NTM prescriptions over time, each child had the possibility of receiving more than one prescription over the follow-up period. As such, prescription counts occurring within a same child were likely to be more highly correlated than prescription counts between individual children[53]. I accounted for this non-independence of observations with the use of modified sandwich variance estimators or robust variance estimators for the calculation of my confidence intervals.

Matching variables were included as covariates in my regression models. This was done following a literature review of the methodologies of matched cohort studies which demonstrated that ignoring matching variables in analyses while valid in most cases, may be inappropriate if adjustment for further confounders is subsequently implemented[54]. This is because while matching variables are balanced across exposure groups overall, they may not be balanced across exposure groups conditional on the subsequently included covariates. Consequently, matching

variables such as age and sex were included as covariates in my multivariable regression model. Due to the high number of CPRD practices, model adjustment was made for the region of CPRD practice as a proxy for individual CPRD practice.

5.7 Tables

Table 5.7. 1CPRD Visit Types Considered GP Visits for Matching Purposes

GP VISITS			
Code	**Description**	**Code**	**Description**
1	Clinic	34	Walk-in Centre
3	Follow-up/routine visit	40	Community Clinic
4	Night visit, Local rota	50	Night Visit
6	Night visit , practice	2	Night visit, Deputising service
11	Acute visit	30	Nursing Home Visit
18	Emergency Consultation	31	Residential Home Visit
20	Casualty Attendance	24	Children's Home Visit
27	Home Visit		

Table 5.7. 2: CPRD Visit Types Not Considered GP Visits for Matching Purposes

NON-GP VISITS			
Code	**Description**	**Code**	**Description**
0	Data Not Entered	37	Co-op Home Visit
5	Mail from patient	38	Minor Injury Service
7	Out of hours, Practice	39	Medicine Management
8	Out of hours, Non Practice	41	Community Nursing Note
9	Surgery consultation	42	Community Nursing Report
10	Telephone call from a patient	43	Data Transferred from other system
12	Discharge details	44	Health Authority Entry
13	Letter from Outpatients	45	Health Visitor Note
14	Repeat Issue	46	Health Visitor Report
15	Other	47	Hospital Inpatient Report
16	Results recording	48	Initial Post Discharge Review
17	Mail to patient	49	Laboratory Request
19	Administration	51	Radiology Request
21	Telephone call to a patient	52	Radiology Result
25	Day Case Report	53	Referral Letter
26	GOS18 Report	54	Social Services Report
28	Hotel Visit	55	Telephone Consultation
29	NHS Direct Report	56	Template Entry
32	Twilight Visit	57	GP to GP communication transaction
33	Triage	58	Non-consultation medication data
35	Co-op Telephone advice	59	Non-consultation data
36	Co-op Surgery Consultation		

Table 5.7. 3: Results of Literature Review of Nephrotoxic Medication Definitions

Reference	Nephrotoxic definition

Mehta[15]
Kidney International
2016
	• In conjunction with the International Serious Adverse Event Consortium, we have developed consensus definitions for DIKD (drug induced kidney disease) using Delphi criteria with International, adult and pediatric, nephrologists and pharmacists
	• Mechanisms of nephrotoxicity
	  • Type A reactions are dose-dependent toxicities that are predictable based on the known pharmacology of the drug and alleviated by reducing drug exposure or withdrawal
	  • Type B reactions are unpredictable based on the known pharmacology of the drug. Toxicity is not dose-dependent and usually requires drug withdrawal for resolution

McGregor[55]
AJKD
2016
	• Nephrotoxic medications categorized using a modified Delphi method
	  o Group 1 (high risk): nephrotoxin as single agent;
	  o Group 2 (moderate risk): nephrotoxin in at-risk clinical situation (not defined further) or in conjunction with additional agent by their relative contribution to the development of AKI

Vassalotti[56] Am J Med 2016	• Provides Guidelines for prescribing in CKD by medication class o Includes contraindications according to level of kidney function
Meuweseen[57] Int J Clin Pharm 2016	• Study of NSAID use in patients with CKD (based in South Africa) • NSAID identified by NAPPI (National Pharmaceutical Product Index) codes – specific to South Africa • NSAIDS classified using Monthly Index of Medical Specialities (MIMS) system o Pharmaceutical prescribing reference guide published in the United Kingdom since 1959 by Haymarket Media Group • Defined a prescribed daily dosage (dose and quantity prescribed / # days prescribed for) and compared it to recommended daily dose (using MIMS and South African Medicines Formulary)
Davis-Ajami[32] J Manag Care Spec Pharm 2016	• Limited NTX to 1 underlying mechanism: acute tubular nephritis and/or tubular toxicity o To classify medications as nephrotoxic, the medication had to be referred to in the literature as potentially associated with inducing acute tubular nephritis and/or tubular toxicity • Used MEPS (Medical Expenditure Panel Survey) prescribed medication files (using MEPS variable MULTUM – to identify drugs with potential for causing acute tubular nephritis or tubular toxicity)**
Bartoli[58] Eur J Intern Med 2016	• List of drugs potentially responsible for various clinical kidney syndromes (e.g. acute tubular necrosis, chronic interstitial nephritis, analgesic nephropathy, etc.)

Wu[59]
Clin J Am Soc Nephrol
2015
	• Used nomenclature from Strand et al (1990) to define "Drug related problem"
	  o Dose exceeding upper threshold for given eGFR
	• Renal dosing information for analgesics was obtained primarily from Micromedex
	  o Supplemented with data from Drug Facts and Comparisons, American Hospital Formulary Service, Lexicomp online, the Directory of Drug Dosage in Kidney Disease, and the Directory of Drug Dosage in Renal Failure: Dosing Guide- lines for Adults

Doody[60] Curr Med Res Opin 2015	• Drugs with potential nephrotoxicity and/or elimination through the kidney were assessed for appropriateness at admission and discharge using the Australian Medicines Handbook (AMH) and/or the drug product information
Ingrasciotta[44] PLOS one	• A literature review was conducted by using specific MeSH terms 'nephrotoxic drug' and 'drug-induced renal failure',

2014	○ Yielded a list of 127 potentially nephrotoxic drugs which was validated by two nephrologists (DS, VC) and two clinical pharmacologists (GT, VA) • Based on the Summary of Product Characteristic (SPC), we classified all these drugs as "contraindicated drugs" or "drugs to be used with caution (i.e., precaution of use)" in renal diseases • For each contraindicated nephrotoxic drug we identified the specific contraindication as reported in the SPC
Goldstein[43] Pediatrics 2013	• Used Moffet et al.[45] definition for NTX and added iodinated contrast agents • Included all members of a nephrotoxin class (e.g. ACE inhibs) available in their hospital's formulary
Cox[61] CJASN 2013	• Committee of nephrologists, internists, and pharmacists reviewed medication package inserts, textbooks and primary literature • Include all medications that could contribute to AKI or have the potential for adverse effects with accumulation in AKI • Limited to medications on VUH's formulary • Some medications triggered inclusion in the study only if administered during increasing SCr, whereas antibiotics with a wide therapeutic window triggered inclusion only when exceeding a prespecified dose threshold
Bilge[31] Renal Failure 2013	• Drugs were categorized in view of each patient's GFR which Breton et al.[28] used to check contraindication of drugs • Drugs that may be contraindicated and that require dose adjustment were identified based on glomerular filtration rate (GFR) calculated in their first visit
Jones[62] Postgrad Med J 2013	• Study specific to the elderly (use BEERS criteria) • Use latest British National Formulary (BNF) guidance for prescribing in patients with renal impairment.
Moffett[45] Clin J Am Soc Nephrol 2011	• The initial list of nephrotoxic medications included was based upon the formulary of approved medications at our institution and included any medication with reported nephrotoxicity, defined as functional kidney impairment, from: Drug Information Handbook, Hudson, OH, Lexi-Comp, 2009
Breton[28] Nephrol Dialy Transplant 2011	• Substances were coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification system • Pharmacist (GB) searched for any dosing recommendation or contraindication according to eGFR level through the principal French drug dictionaries (Vidal and Dorosz), as well as from Information Conseil Adaptation Renale (ICAR) website a database updating renal dose adjustment guidelines based on international pharmacokinetic studies • With the help of senior ICAR pharmacists, an eGFR threshold was assigned to each substance that was either contraindicated or required dose adjustment
Nolin[18] Adverse drug reactions 2010	• Review of major mechanisms of Drug-Induced Nephrotoxicity and associated medications
Choudhury[63] Nat Clin Pract Nephrol 2006	• Review of acute kidney injury pathophysiology and associated medications
Chertow[64] JAMA 2001	• After reviewing the relevant literature, expert panel including a nephrologist, a pharmacist and a general internist convened to review all medications in the hospital's drug formulary and selected those medications that were renally cleared and/or nephrotoxic • The expert panel then determined optimal adjustments in dose list, default dose amount, and default frequency for each medication in the application in each of the renal insufficiency categories

Table 5.7. 4: CPRD Code Browser Search Terms for Kidney Disease

Search term
CKD
CKD
chronic kidney
chronic renal
Kidney disease
*kidney*disease*
*Renal*disease*
*Kidney*disorder*
*renal*disorder*
Kidney function/failure
*kidney*insufficien*
*renal*insuffic*
*kidney*funct*
*renal*funct*
*renal*impair*
*kidney*fail*
renal fail
end stage
Other
*polycyst*kidney*
*kidney*dysplas*
*renal*dysplas*
*kidney*scar*
*renal*scar*
*renal*fibrosis*
*cortical*necrosis*
*renal*injur*
*small*kidney*
hydronephrosis
nephritis
nephropath
uraemia
proteinuria
albuminuria
glomerulonephritis
Dialysis
dialys
Transplant
*renal*transplant*
*kidney*transplant*

CHAPTER 6: DISCUSSION

6.1 Overall Summary of Findings

In this thesis, I conducted a systematic review and cohort study to determine if children with chronic kidney disease (CKD) are being prescribed nephrotoxic medications (NTMs) in a primary care setting and whether this is occurring at a similar rate as children without CKD. My systematic review focused on a specific NTM (NSAIDs) as well as a single clinical setting (primary care) to minimize heterogeneity between studies and facilitate a comprehensive interpretation of summarized findings. This restriction was especially important in the context of a systematic review evaluating the concept of nephrotoxicity, which remains inconsistently defined throughout the literature. To my knowledge, there were no pediatric data available on NSAID prescribing in the primary care setting. Previous studies conducted in adults with CKD revealed a variable prescription prevalence ranging from 8-21% for studies evaluating point prevalence and from 3-33% per year for those evaluating period prevalence. These results suggest that despite guidelines recommending against their use, a substantial proportion of CKD patients continue to receive NSAIDs in the primary care setting.

To more specifically evaluate the question of NTM prescriptions for children with CKD, I designed a cohort study of pediatric patients within a national primary care database with extensive prescription data from a population where almost all children are registered with a GP. In the absence of a standardized list of NTMs, I derived a definition using existing studies considered to be methodologically rigorous in combination with a nephrologist. My results showed that compared to children without CKD who were matched on age, sex, previous number of GP visits, and GP practice, children with CKD were prescribed NTMs almost 10 times more frequently. This relative rate of prescriptions remained elevated (RR 4.0, 95% CI 2.7-6,0) after the exclusion of ACE-inhibitors and salicylates, classes that are sometimes indicated in patients with CKD. Overall, I found that over a follow-up period of up to 5 years, more than 30% of pediatric CKD patients had received at least one medication considered to be nephrotoxic and a staggering 70.7% received a medication with potential nephrotoxicity. These prevalences remained elevated at 25.8% and 68.3%, respectively, when excluding ACE inhibitors and salicylate medications.

6.2 Novelty and significance of the findings (What was known, what was added)

My cohort study is, to our knowledge, the first to evaluate NTM prescribing for children within the primary care setting. Existing studies quantifying pediatric NTM prescriptions are limited to hospitalized patients and focus on evaluating the risk of acute kidney injury (AKI) in children without previously known kidney disease[5,6,35]. These studies revealed alarmingly elevated NTM prescription rates but only provided a glimpse into the extent of the problem. Besides their focus on children without previously known CKD, inpatient studies can only capture a limited period in the life of children with CKD whose contact with the health care system occurs more frequently through outpatient encounters such as primary care, and pediatric and nephrology clinics. Since the cornerstone of CKD management is the prevention of kidney disease progression, including NTM avoidance, prescribing practices in these outpatient contexts are particularly important to understand because they provide important opportunities for intervention. My study findings suggest that physician awareness or acceptance of the importance of NTM avoidance in children with CKD is lacking. Interventions aimed at informing physicians of the importance of NTM avoidance or at pediatric nephrology specialists to systematically educate primary care providers in medical communications, may lead to substantial impacts in the care and CKD outcomes of these patients.

6.3 Strengths

6.3.1 CPRD: Extensive and Inclusive Data

My use of the CPRD allowed capture of inclusive population-level data about outpatient NTM prescriptions. Databases of outpatient drug prescriptions are often linked to insurance coverage and are therefore limited in their generalizability[65]. A major advantage of the CPRD is its extensive representation of UK primary care which is funded by the National Health Service and provides free care to all UK residents[66]. Furthermore, the UK medical system is organized such that primary care physicians are often the primary medication prescriber to their patients and even when medications are initiated by a specialist, ongoing prescription is typically provided by the GP[38,67]. For pediatric CKD patients who may be jointly followed by other specialists, this database offers a unique opportunity to understand the true extent of their outpatient NTM exposure. Lastly, a major strength of the CPRD is that it represents a population where >95% of children are registered with a GP, also ensuring excellent capture of prescription

data in the pediatric population[68].

6.3.2 External Data Linkage

Linkages to external databases is an exciting feature of the CPRD that allowed me to capitalize on the added advantages of each of these resources. Use of the HES increased the sensitivity of my exposure definition (CKD) through the use of inpatient diagnoses to supplement outpatient GP diagnoses. It also helped me avoid misclassification of person time by exposure status in patients who were diagnosed with CKD in hospital but whose GP may not have updated their diagnosis into the CPRD. Linkage also allowed me to avoid misclassifying certain AKI cases as CKD. I was able to identify patients whose only potential inclusion code was a dialysis code recorded within 3 months of a hospitalization where they had AKI and received dialysis. Because the definition of CKD relies on evidence of persistent renal dysfunction beyond the 3-month mark, these patients with AKI were excluded from my CKD cohort. Furthermore, use of a primary care database alone may have led to misclassification of comorbidities for remote diagnoses such as prematurity or corrected congenital heart disease no longer having a clinical impact which might not have been recorded if patient follow-up began later in life. However, my use of hospital-based data likely greatly improved capture (sensitivity) of these diagnoses.

6.3.3 Matched Cohort Design

My matched cohort design allowed for matching on previous number of GP visits which created exposure groups that were comparable in terms of prior health care utilization. This would otherwise be inherently different between children with and without CKD and was especially important to control for as the opportunity to receive a NTM prescription (my outcome of interest) is strongly associated with the frequency of health care system contact. Matching also provided an effective means of controlling for important confounders such as age and sex as well as CPRD practice. The latter would at least partially account for physician variability in prescribing practices. Matching on age allowed me to effectively account for variations in prescription trends by age, which have previously been shown to be significant[69,70]. Lastly, given the long period over which my study was conducted, matching on cohort entry date had the added advantage of accounting for any secular trends in NTM prescribing over the study

period. An interesting sensitivity analysis to consider would be to apply less restrictive matching criteria and compare estimates with primary analyses. This could also provide information on the actual impact of certain of our a priori matching variables on estimates.

6.4 Limitations

6.4.1 Validity of CKD coding within CPRD

As with any study using routinely collected healthcare data, my study was limited by the quality of these data, including coding accuracy and completeness. There are many published studies suggesting that CKD diagnostic codes, while being specific, have modest sensitivity. A systematic review of 19 studies assessing CKD clinical code validity with respect to CKD diagnoses based on chart review and laboratory measures revealed a median specificity of 98% but very variable sensitivity (range 3-88%, median 41%) [71]. Similar results were found in another systematic review of 30 studies, in which 16 validation studies compared recorded CKD diagnoses to a documented eGFR <60 mL/min/1.73 m^2[72]. Extrapolation of these findings to my study is limited to inpatient codes identified in HES. Pediatric studies on kidney disease code sensitivities are also restricted to the hospital setting and describe the pediatric AKI population. A study by Schaffzin et al. compared discharge coding of an AKI diagnosis with laboratory values of AKI by modified Risk, Injury, Failure, Loss, and End-Stage Renal Disease (pRIFLE) criteria[73]. Again, though specificity was high, sensitivity was low at 23.2% (95% CI 14.0–32.3).

Validation studies of overall CPRD data suggest that they have high validity, though data are not available specifically for CKD[74]. Validation studies specific to CKD have been conducted using other primary care UK databases such as the Health Improvement Network (THIN) database. These studies suggest primary care CKD coding may be more sensitive compared to inpatient coding studies. One THIN study assessed Read code validity for identifying Stage 3-5 CKD (based on two eGFR values <60 ml/min/1.73 m^2 recorded at least seven days apart). Sensitivity was found to be 72.1% (95% CI 71.8–72.3)[75]. Another THIN study compared a composite of 45 Read codes for CKD to the current laboratory standard (two eGFR values <60 mL/ minute/1.73m^2 separated by 90 days or more)[67]. Interestingly, this study included a large population of children 2-18 years old (n= 64,440). It is worth noting that sensitivity was higher in children compared to the overall population (76.4% versus 48.8%, respectively). The higher sensitivity may be due to the relatively selective screening for CKD in

pediatric patients compared to adults. Physicians who order a serum creatinine in their pediatric patients are likely responding to the presence of specific risk factors for CKD and may be more likely to document an abnormal result compared to their adult patients in whom serum creatinine may be ordered as part of routine bloodwork.

Overall, there are a few validation studies of outpatient CKD codes, but only one that included pediatric patients. As discussed, generalizability of many of these studies' results to my population may not be appropriate due to possible differences in coding validity in children. Furthermore, existing validation studies mostly rely on eGFR calculations as the benchmark for CKD diagnosis. This measure may be less appropriate in children where other findings such as structural abnormalities may account for up to 50% of pediatric CKD cases, even in the absence of abnormal eGFR[9]. To address the limitation of poor CKD coding sensitivity, I incorporated broader kidney disease codes into my CKD definition and included codes from both the inpatient and outpatient settings. This was reasonable because, by definition, if a child has an underlying kidney disorder, but has a normal eGFR, they are classified as having CKD stage 1, and thus should be considered at "kidney risk"[8]. Suggestions that this may have been effective are evidenced by the relatively higher prevalence of CKD within my study as compared to that in the previously mentioned THIN study (0.07% versus 0.003%, respectively)[67]. Poor CKD code sensitivity remains an issue to consider when interpreting the results of my study, particularly if it was non-differential. For example, if children with co-morbidities associated with CKD and with NTM prescriptions (e.g., diabetes) were more likely to have their CKD coded in response to an abnormal eGFR because of heightened physician awareness of their kidney disease risk, we might expect an over-estimation of the association between CKD and NTM use.

6.4.2 Clinical Diagnostic Codes versus Laboratory Measures

Although the CPRD does record laboratory measures such as creatinine, I chose not to use these data as part of my CKD definition due to problems with missing data. Blood tests are rarely performed in the routine follow-up of children and restricting my CKD definition to children who meet laboratory criteria for diagnosis would have severely restricted my cohort, and the proportion of individuals with missing eGFR values would have exceeded that that could be imputed via multiple imputation. Furthermore, it would have possibly led to the over-representation of children with other comorbidities, the presence of which would have prompted

GPs to perform the creatinine measurements. Furthermore, GFR estimation (required to determine the presence of CKD) in children requires a height measurement which is often lacking in primary care records. Moreover, height measures would have to be available within a reasonable time frame relative to serum creatinine measurement, to be reliable for GFR estimation because height changes throughout childhood. The previously cited THIN study revealed that fewer than 50% of pediatric patients had a height recorded within 18 months of a serum creatinine measurement[67]. The study did demonstrate similarities in the distributions of eGFR values calculated in patients with an available height compared to patients in whom height values were imputed based on the 50th percentile for age. However, authors recognized potential flaws with this approach. For example, in a cohort of pediatric CKD patients where growth impairment is prevalent due to the underlying CKD, imputations based on the 50th percentile may not be appropriate. My approach of using recorded clinical diagnoses and procedures for my exposure definition might therefore provide an advantage over this method though it is not without limitations as previously discussed. Alternatively, I could have used laboratory data to supplement my CKD cohort (i.e., as another method of identifying patients with CKD) and performed subsequent sensitivity analyses to assess NTM prescription prevalence in CKD patients identified though diagnostic coding versus those identified by laboratory data to verify the consistency of my results . Future work should determine the extent to which CPRD CKD diagnosis and procedure codes relate to serum creatinine measures (i.e., estimated GFR) available in CPRD databases, to learn how to most appropriately utilize them for child kidney research.

6.4.3 Prescription Data

Another limitation of this study is that I did not have data on the indication for drug prescriptions. There may be instances when prescribing a NTM to a child with CKD is justified and no safer alternative exists. In the absence of data on NTM indication in my study, future analyses could include evaluating NSAID prescribing rates specifically. As they are frequently prescribed and because alternatives often exist for their use, these analyses could highlight an important and potentially modifiable harmful prescribing practice. At a minimum, patients with CKD who require prescriptions of NTMs should have serum creatinine measured prior to initiating the NTM and then periodic measurements to ensure stability of their renal function.

Future studies should determine the appropriateness of kidney function monitoring in children with CKD, during NTM prescriptions periods, as a way to better understand physician awareness.

Furthermore, drug dosages were not considered for this study, and it is possible that dosage adjustments were made by GPs for certain medications, mitigating their nephrotoxic potential. Importantly, our study did not evaluate adherence to prescribed medications. There are several steps between a GP issued prescription and actual drug use such as parental willingness to fill the prescription, pharmacist dispensing and physical consumption. It is possible that checks and balances along the healthcare delivery process may have led to prescriptions not being filled which would not have been captured by our study. However, the main interest of this study was to evaluate GP prescribing behaviors which should not have been affected by these factors.

Finally, we only considered outpatient prescription as we wanted to capture GP prescribing. However, over 50% of our CKD patients had a recorded hospitalization in the year prior to cohort entry which suggests they may also have been hospitalized over the course of the follow-up period. Though this was not evaluated explicitly, hospitalization rates throughout follow-up likely differed between our CKD and non-CKD cohort which could affect GP NTM prescription rates in several ways. For example, during their hospitalization, patients do not have the opportunity to receive a NTM from their GP even though I considered them to be at continuous risk of this exposure throughout the follow-up. Furthermore, contact with specialized healthcare teams during hospitalization might affect NTM risk awareness on the part of patients and for GPs who may receive a summary report of the hospitalization. It would be interesting to evaluate the impact of hospitalization on GP NTM prescribing by performing a sensitivity analysis restricted to CKD patients who were not hospitalized during their follow up to see whether this impacts my estimates.

6.4.4 Confounding

Residual confounding always remains a possibility in observational studies. Although I applied a conceptual framework to select potential confounders for statistical adjustment, my list is likely not exhaustive, and omission of certain confounders could lead to residual confounding. If I omitted confounders that affect both the risk of CKD and of NTM prescriptions, I might

expect this to cause either an over- or under-estimation of the association between CKD and NTM prescriptions in my study. Misclassification is also a possibility if confounders are not recorded in medical records. Again, this could lead to an over-estimation in the association between CKD and NTM prescriptions if these confounders are more likely to be recorded in children with CKD because they are more closely followed by their GP (i.e., recording is differential). However, I tried to mitigate this by matching unexposed (non-CKD) children on the number of GP visits in the year prior to cohort entry. Furthermore, linkages with HES likely improved my capture of relevant comorbidities and would have mitigated non-differential misclassification through increased sensitivity.

CHAPTER 7: CONCLUSIONS

My thesis has evaluated the extent to which children with CKD are prescribed NTMs in primary care. It serves as a first step in exposing an important area in need of improvement in the management of children with CKD. I hope to build on this research by focusing on understanding the reasons underlying these harmful prescribing practices so that future intervention strategies may be directed appropriately. Future research could also explore the potential consequences of NTM prescribing to pediatric CKD patients and whether it translates into harmful outcomes such as accelerated disease progression. This work will complement existing research on NTMs which is currently focused on the hospital setting. One of the few interventional studies in pediatric kidney disease has focused on decreasing NTM burden to hospitalized children[4,43]. This prospective AKI monitoring program implemented institution-wide creatinine surveillance to patients with exposure to ≥3 NTMs or to a prolonged course (>3 days) of aminoglycoside antibiotics. As a result of this surveillance, there was a 38% decrease in NTM exposure and a 64% decrease in incidence of AKI. These results suggest that improved awareness of NTM burden and risk can lead to substantial clinical improvements in kidney disease outcomes in children. An extrapolation of this concept to the outpatient CKD context could be to recommend yearly creatinine measurements to any child receiving recurrent NTM prescriptions, which is the standard of care in adult CKD[76]. Other strategies could capitalize on the expanding use of electronic health records. Synchronization of laboratory systems with electronic prescribing software could allow for the creation of alerts when documented eGFR levels decrease below a threshold requiring medication dose adjustment or discontinuation and have been implemented with some success in adults[64]. More simply, reminders to physicians to be aware of recent creatinine measurements when renewing NTM or renally-excreted medications have shown some success in prompting medication dose adjustments or discontinuation altogether[77].

The most recent KDIGO guidelines for the Evaluation and Management of CKD advise referral to nephrology specialists for children with CKD who demonstrate rapid progression of their disease or who develop symptoms of more advanced renal disease such as uncontrolled hypertension and disturbances in electrolyte balance[3]. However, in the early stages of their disease, children with CKD may be co-managed by primary care providers. Though there are no clinical trials to confirm this in children, early in CKD severity is likely an optimal time to

prevent CKD progression with conservative approaches, like avoiding NTMs, with a goal to reduce secondary consequences of CKD. Importantly, primary care prescriptions reflect practices and knowledge gaps at multiple stages of the healthcare delivery process. For example, patients' and parents' own awareness of contraindications of certain medications may be lacking and educational interventions aimed at empowering them in this respect may result in fewer NTM prescriptions. Furthermore, pharmacists are the gatekeepers to medication dispensing in most countries and offer another opportunity for knowledge translation interventions. Another potential target for education are pediatricians who often provide second-line care to children with chronic diseases. Pediatricians' prescribing practices to children with CKD is beyond the scope of this thesis but would be an interesting question to explore. If awareness is indeed higher among pediatricians, greater communication between these specialists and other primary care physicians as to recommendations regarding medication prescriptions should be encouraged.

Changing pediatric demographics including increased survival of premature and low-birth-weight infants as well as rising obesity rates may contribute to an increased incidence of CKD over the next generation[78,79]. Due to limited medical resources and specialist availabilities, the burden to absorb this increase may fall to primary care providers [80]. Consequently, better awareness of CKD management with regards to NTM prescribing among primary care physicians could potentially help a significant number of children. Another increasingly important contributor to pediatric CKD is previous AKI, with recent studies suggesting up to 10% of AKI survivors go on to develop CKD[81-84]. However, evidence suggests that even though these children have had a significant renal insult, only a small proportion of them are followed up by pediatric nephrologists[85]. A pediatric study followed up 29 children with a previous diagnosis of AKI and found that fewer than one-third of them had seen a pediatric nephrologist 3-5 years following their AKI. Interestingly, a subsequent study revealed that despite low rates of nephrology referrals for children with previous AKI, over 90% were referred for follow-up in a non-nephrology clinic. This evidence reinforces that the primary care setting offers an important opportunity for implementing measures aimed at improving care to these children. It should therefore continue to be an area of focus for high-quality research that aims to understand factors underlying current practices and to identify areas where interventions aimed at improving these practices should be focused.

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87. Gill PJ, Roberts NW, Wang KY, Heneghan C. Development of a search filter for identifying studies completed in primary care. *Fam Pract.* 2014;31(6):739-745.

APPENDICES

Appendix to Manuscript 1

Table of Contents

Item A1: Primary Care Search Filters

McGill Sensitive Family medicine filter[86]

(1) Pols DH, Bramer WM, Bindels PJ, van de Laar FA, Bohnen AM. Development and Validation of Search Filters to Identify Articles on Family Medicine in Online Medical Databases. Ann Fam Med. 2015;13(4):364-6.

(family.af. or physician$.af. or practice$.mp. or primary care.af. or exp Primary Health Care/ or primary.mp. or general pract$.af. or gp.tw. or gps.tw.)

Medline Senstive Family medicine filter[87]

(2) Gill PJ, Roberts NW, Wang KY, Heneghan C. Development of a search filter for identifying studies completed in primary care. Fam Pract. 2014;31(6):739-45.

(clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center? or office).ti,ab.

Item A2: List of Included NSAIDs

aceclofenac
acemetacin
alclofenac
aminophenazone
ampyrone
antipyrine
apazone
azapropazone
carbasalate calcium
carprofen
celecoxib
clonixin
colestyramine
dexibuprofen
dexketoprofen
diclofenac
diflunisal
droxicam
epirizole
etodolac
etoricoxib
fenbufen
fenoprofen
feprazone
floctafenine
flufenamic acid
flunixin
flurbiprofen
ibuprofen
indomethacin
indoprofen
isoxicam
ketoprofen
ketorolac
lornoxicam
lumiracoxib
meclofenamic acid
mefenamic acid
meloxicam
mesalamine
mesalazine
methyl salicylate
nabumetone
naproxen
niflumic acid
nimesulide
nimesulide
oxaprozin
oxyphenbutazone
parecoxib
phenazone
phenylbutazone
pirizole
piroxicam
propyphenazone
rofecoxib
salazosulfapyridine
salicylic acid
sulfasalazine
sulfinpyrazone
sulindac
suprofen
tenoxicam
tiaprofenic acid
tolfenamic acid
tolmetin
tromethamine
valdecoxib
zomepir

Table A 1: Ovid MEDLINE Search Strategy for Studies of Prevalence of NSAID Prescriptions/Use in Primary Care CKD Patients*

Search Number	Description	Number of Publications
1	*Kidney/ab, ae, de, gd, in, pa, pd, pp, to [Abnormalities, Adverse Effects, Drug Effects, Growth & Development, Injuries, Pathology, Pharmacology, Physiopathology, Toxicity] or exp Renal Insufficiency/ or (renal insufficien* or kidney insufficien*).ab,kf,ti. or (renal impair* or kidney impair*).ab,kf,ti. or (renal injur* or kidney injur*).ab,kf,ti.) or exp Kidney Diseases/ or (kidney disease* or renal disease*).ab,kf,ti. or (kidney fail* or renal fail*).ab,kf,ti. or exp Renal Insufficiency, Chronic/ or (chronic renal disease* or chronic kidney disease*).ab,kf,ti. or (chronic renal insufficien* or chronic kidney insufficien*).ab,kf,ti. or (chronic renal impair* or chronic kidney impair*).ab,kf,ti. or (CKF or CKD or CRF or CRD).ab,kf,ti. or (end stage renal or end stage kidney or endstage renal or endstage kidney).ab,kf,ti. or (ESRF or ESKF or ESRD or ESKD).ab,kf,ti. or exp Diabetic Nephropathies/ or diabetic nephropath*.ab,kf,ti. or exp Kidney Transplantation/ or (renal transplant* or kidney transplant*).ab,kf,ti.	690,191
2	(family or physician$).af. or practice$.mp. or primary care.af. or exp Primary Health Care/ or primary.mp. or general pract$.af. or gp.tw. or gps.tw. or (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center? or office).ti,ab,kf.	7,864,787
3	exp Anti-Inflammatory Agents, Non-Steroidal/ or ((nonsteroid* or non steroid*) and (antiinflammator* or anti inflammator*)).mp. or NSAID*.mp. or exp cyclooxygenase inhibitors/ or cyclooxygenase 2 inhibitors/ or ((cyclooxygenase or cyclo oxygenase) adj3 inhibitor*).mp. or (cox 2 adj3 inhibitor*).mp. or Ampyrone/ or Antipyrine/ or Apazone/ or Celecoxib/ or Clonixin/ or Diclofenac/ or Diflunisal/ or Epirizole/ or Etodolac/ or Fenoprofen/ or Flufenamic Acid/ or Flurbiprofen/ or Ibuprofen/ or exp Indomethacin/ or Indoprofen/ or Ketoprofen/ or Ketorolac/ or Ketorolac Tromethamine/ or Meclofenamic Acid/ or Mefenamic Acid/ or Mesalamine/ or Naproxen/ or Niflumic Acid/ or exp Phenylbutazone/ or Piroxicam/ or Sulfasalazine/ or Sulindac/ or Suprofen/ or Tolmetin/ or (ampyrone or antipyrine or apazone or celecoxib or clonixin or diclofenac or diflunisal or epirizole or etodolac or fenoprofen or flufenamic acid or flurbiprofen or ibuprofen or indomethacin or indoprofen or ketoprofen or ketorolac tromethamine or ketorolac or meclofenamic acid or mefenamic acid or mesalamine or naproxen or niflumic acid or phenylbutazone or piroxicam or sulfasalazine or sulindac or suprofen or tolmetin or methyl salicylate or methylsalicylate or aceclofenac or acemetacin or alclofenac or azapropazone or carbasalate calcium or dexibuprofen or dexketoprofen or etoricoxib or fenbufen or droxicam or feprazone or floctafenine or isoxicam or lornoxicam or lumiracoxib$ or meloxicam or mesalazine or nabumetone or nimesulide or oxaprozin or oxyphenbutazone or parecoxib or phenazone or propyphenazone or rofecoxib or sulfinpyrazone or tenoxicam or tiaprofenic acid or tolfenamic acid or valdecoxib or carprofen or flunixin or ketoprofen or salazosulfapyridine or sulindac or zomepirac).mp.	240,281
4	nephrotoxi*.ab,ti,kf. or ((renal or kidney) and toxi*).ab,ti,kf. Or exp Drug Utilization/ or ((drug or medic* or prescri*) and utili*).ab,ti,kf. or ((drug or medic* or prescri*) and indicat*).ab,ti,kf. or ((drug or medic* or prescri*) and expos*).ab,ti,kf. or ((drug or medic* or prescri*) and contraindicat*).ab,ti,kf. or Practice Patterns, Physicians'/ or exp inappropriate prescribing/ or (inappropriate and (prescri* or medic*)).ab,ti,kf. or exp Prescriptions/ or ((drug* or medic*) adj3 (prescript* or prescrib*)).mp. or ((prescrib* or prescrip*) adj3 (pattern* or practice*)).mp. or (prescript* or prescrib*).mp.	809,860
5	exp animals/ not humans.sh.	4,675,984
6	**1** and **2** and **3** and **4** not **5**	853

*Date of search: October 17, 2017

Table A 2: Ovid EMBASE Search Strategy for Studies of Prevalence of NSAID Prescriptions/Use in Primary Care CKD Patients*

Search Number	Description	Number of Publications
1	kidney failure/ or anuria/ or cardiorenal syndrome/ or chronic kidney failure/ or contrast induced nephropathy/ or end stage renal disease/ or experimental renal failure/ or frasier syndrome/ or kidney cortex necrosis/ or kidney tubule necrosis/ or mild renal impairment/ or moderate renal impairment/ or oliguria/ or renal replacement therapy-dependent renal disease/ or severe renal impairment/ or subclinical renal impairment/ or uremia/ or exp kidney disease/ or (kidney disease* or renal disease*).ab,kw,ti. or exp end stage renal disease/ or (ESRF or ESKF or ESRD or ESKD).ab,kw,ti. or (chronic renal disease* or chronic kidney disease*).ab,kw,ti. or exp chronic kidney failure/ or (kidney fail* or renal fail*).ab,kw,ti. or exp diabetic nephropathy/ or diabetic nephropath*.ab,kw,ti. or exp severe renal impairment/ or (renal impair* or kidney impair*).ab,kw,ti. or (chronic renal impair* or chronic kidney impair*).ab,kw,ti. or (CKF or CKD or CRF or CRD).ab,kw,ti. or (renal insufficien* or kidney insufficien*).ab,kw,ti. or (chronic renal insufficien* or chronic kidney insufficien*).ab,kw,ti. or (renal injur* or kidney injur*).ab,kw,ti. or exp kidney transplantation/	1,027,564
2	(family or physician$).af. or practice$.mp. or primary care.af. or exp Primary Health Care/ or primary.mp. or general pract$.af. or gp.tw. or gps.tw. or (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center? or office).ti,ab,kw.	10,170,078
3	exp nonsteroid antiinflammatory agent/ or ((nonsteroid* or non steroid*) and (antiinflammator* or anti inflammator*)).mp. or NSAID*.mp. or exp prostaglandin synthase inhibitor/ or exp cyclooxygenase 2 inhibitor/ or ((cyclooxygenase or cyclo oxygenase) adj3 inhibitor*).mp. or (cox 2 adj3 inhibitor*).mp. or exp 4 aminophenazone/ or exp phenazone/ or exp azapropazone/ or exp celecoxib/ or exp clonixin lysine/ or exp clonixin/ or exp diclofenac colestyramine/ or exp diclofenac plus thiocolchicoside/ or exp diclofenac potassium/ or exp diclofenac/ or exp codeine plus diclofenac/ or exp diclofenac plus misoprostol/ or exp diflunisal/ or exp epirizole/ or exp etodolac/ or exp fenoprofen calcium/ or exp fenoprofen/ or exp flufenamic acid/ or exp flurbiprofen 4 nitroxybutyl ester/ or exp flurbiprofen/ or exp flurbiprofen axetil/ or exp ibuprofen lysine/ or exp chlorpheniramine maleate plus ibuprofen plus pseudoephedrine/ or exp famotidine plus ibuprofen/ or exp ibuprofen plus oxycodone/ or exp hydrocodone bitartrate plus ibuprofen/ or exp diphenhydramine plus ibuprofen/ or exp ibuprofen plus pseudoephedrine/ or exp codeine phosphate plus ibuprofen/ or exp ibuprofen arginine/ or exp ibuprofen/ or exp ibuprofen plus phenylephrine/ or exp ibuprofen derivative/ or exp indometacin/ or exp indoprofen/ or exp ketoprofen/ or exp ketoprofen lysine/ or exp ketorolac trometamol/ or exp ketorolac/ or exp ketorolac trometamol plus phenylephrine/ or exp meclofenamic acid/ or exp mefenamic acid/ or exp mesalazine/ or exp naproxen etemesil/ or exp naproxen plus sumatriptan succinate/ or exp diphenhydramine plus naproxen/ or exp naproxen/ or exp lansoprazole plus naproxen/ or exp naproxen plus pseudoephedrine/ or exp esomeprazole plus naproxen/ or exp naproxen plus sumatriptan/ or exp niflumic acid/ or exp oxyphenbutazone/ or exp flunixin/ or exp phenylbutazone megallate/ or exp flunixin meglumine/ or exp phenylbutazone/ or exp carprofen/ or exp clonixin/ or exp aminophenazone plus phenylbutazone/ or exp piroxicam beta cyclodextrin/ or exp piroxicam/ or exp salazosulfapyridine/ or exp sulindac sulfide/ or exp sulindac/ or exp sulindac sulfone/ or exp suprofen/ or exp tolmetin glycinamide/ or exp tolmetin/ or exp zomepirac/ or exp salicylic acid methyl ester/ or exp aceclofenac/ or exp acemetacin/ or exp alclofenac/ or exp azapropazone/ or exp carbasalate calcium/ or exp dexibuprofen/ or exp dexketoprofen/ or exp etoricoxib/ or exp fenbufen/ or exp	602,829

	droxicam/ or exp feprazone/ or exp floctafenine/ or exp isoxicam/ or exp lornoxicam/ or exp lumiracoxib/ or exp meloxicam/ or exp nabumetone/ or exp nimesulide/ or exp oxaprozin/ or exp parecoxib/ or exp propyphenazone/ or exp caffeine plus paracetamol plus propyphenazone/ or exp rofecoxib/ or exp sulfinpyrazone/ or exp tenoxicam/ or exp tiaprofenic acid/ or exp tolfenamic acid/ or exp valdecoxib/ or (ampyrone or antipyrine or apazone or celecoxib or clonixin or diclofenac or diflunisal or epirizole or etodolac or fenoprofen or flufenamic acid or flurbiprofen or ibuprofen or indomethacin or indoprofen or ketoprofen or ketorolac tromethamine or ketorolac or meclofenamic acid or mefenamic acid or mesalamine or naproxen or niflumic acid or phenylbutazone or piroxicam or sulfasalazine or sulindac or suprofen or tolmetin or methyl salicylate or methylsalicylate or aceclofenac or acemetacin or alclofenac or azapropazone or carbasalate calcium or dexibuprofen or dexketoprofen or etoricoxib or fenbufen or droxicam or feprazone or floctafenine or isoxicam or lornoxicam or lumiracoxib$ or meloxicam or mesalazine or nabumetone or nimesulide or oxaprozin or oxyphenbutazone or parecoxib or phenazone or propyphenazone or rofecoxib or sulfinpyrazone or tenoxicam or tiaprofenic acid or tolfenamic acid or valdecoxib or carprofen or flunixin or ketoprofen or salazosulfapyridine or sulindac or zomepirac).mp.	
4	exp nephrotoxicity/ or nephrotoxi*.ab,ti,kw. Or ((renal or kidney) and toxi*).ab,ti,kw. Or exp drug indication/ or ((drug or medic* or prescri*) and indicat*).ab,ti,kw. Or exp drug utilization/ or ((drug or medic* or prescri*) and utili*).ab,ti,kw. Or exp drug exposure/ or ((drug or medic* or prescri*) and expos*).ab,ti,kw. or exp drug contraindication/ or ((drug or medic* or prescri*) and contraindicat*).ab,ti,kw. or exp inappropriate prescribing/ or (inappropriate and (prescri* or medic*)).ab,ti,kw. or exp prescription/ or ((drug* or medic*) adj3 (prescript* or prescrib*)).ab,ti,kw. or ((prescrib* or prescrip*) adj3 (pattern* or practice*)).ab,ti,kw. or (prescript* or prescrib*).ab,ti,kw.	1,291,569
5	(exp animal/ or nonhuman/) not exp human/	6,577,118
6	**1** and **2** and **3** and **4** not **5**	7202

*Date of search: October 17, 2017

Table A 3: Quality Assessment of Included Studies Evaluating Point Prevalence Using a Modified Methodological Evaluation of Observational Research (MORE) Checklist

	Descriptive			External validity (Selection bias)			Internal validity			Overall
Criterion	**Conflict of interest**	**Ethical approval**	**Funding**	**Sampling**	**Response**	**Exclusion**	**Source of exposure measure (CKD)**	**Source of outcome measure (NSAID)**	**Prevalence assessment (relied on recall, crude)**	
Dorks	◯	◯	◯	∅	◯	◯	◯	◯	∅	∅
Fox	◯	◯	?	∅	◯	?	◯	?	∅	∅
Koffeman (2)	◯	◯	◯	◯	◯	◯	◯	◯	∅	∅
Lioté	◯	◯	◯	∅	●	∅	◯	◯	∅	●
McIntyre	◯	◯	◯	∅	●	?	◯	∅	∅	●
Weddle (1)	◯	◯	◯	∅	◯	?	◯	◯	∅	∅
Weddle (2)	◯	◯	◯	∅	◯	∅	◯	∅	∅	∅

◯ Low risk of bias ∅ Moderate risk of bias (Minor flaw present)

● High risk of bias (Major flaw present) "?" Not reported

Table A 4: Quality Assessment of Included Studies Evaluating Period Prevalence Using a Modified Methodological Evaluation of Observational Research (MORE) Checklist

	Descriptive			External validity (Selection bias)			Internal validity			Over all
Criterion	**Conflict of interest**	**Ethical approval**	**Funding**	**Sampling**	**Response**	**Exclusion**	**Source of exposure measure (CKD)**	**Source of outcome measure (NSAID)**	**Prevalence assessment (relied on recall, crude)**	
Allen	◯	◯	?	∅	◯	?	◯	◯	∅	∅
Arora	◯	◯	◯	∅	◯	◯	◯	◯	∅	∅
Guthrie	◯	◯	◯	◯	◯	?	◯	◯	∅	∅
Ingrasciotta	◯	?	◯	∅	◯	◯	◯	◯	◯	∅
Keohane	?	?	?	∅	◯	∅	◯	◯	∅	∅
Koffeman (1)	◯	◯	◯	∅	●	●	◯	∅	∅	●
Martinez-Ramirez	◯	◯	?	◯	◯	◯	◯	?	∅	∅

◯ Low risk of bias ∅ Moderate risk of bias (Minor flaw present)

● High risk of bias (Major flaw present) "?" Not reported

Appendix to Manuscript 2
Table of Contents

Supplement 1: Codes Defining CKD for Study Inclusion

eTable 1. 1: CPRD Read Codes Defining CKD for Study Inclusion

Medcode	Read term (Code description)
16929	Anaemia secondary to renal failure
22205	Lupus nephritis
12465	Membranoproliferative nephritis unspecified
5291	Membranous nephritis unspecified
57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
28684	Hypertensive heart and renal disease with renal failure
4668	Hypertensive renal disease
15106	Hypertensive renal disease NOS
32423	Hypertensive renal disease with renal failure
41148	Renal tubulo-interstitial disorder in SLE
107216	[X]Hereditary nephropathy, unspecif morphological changes
53940	[X]Other chronic renal failure
101453	[X]Other chronic tubulo-interstitial nephritis
72877	[X]Other cystic kidney diseases
104079	Acquired renal cystic disease
100205	Acute-on-chronic renal failure
25394	Anaemia secondary to chronic renal failure
8607	Analgesic nephropathy
105143	Autosomal dominant polycystic kidney disease
105919	Autosomal recessive polycystic kidney disease
99139	Balkan nephropathy
21423	Berger's IgA or IgG nephropathy
9500	Bilateral renal dysplasia
38774	Bilateral small kidneys
56893	Chron neph syn difus mesangial prolifrtiv glomerulonephritis
57168	Chron nephritic syndrom difuse membranous glomerulonephritis
65400	Chronic diffuse glomerulonephritis
4669	Chronic focal glomerulonephritis
7804	Chronic glomerulonephritis
97758	Chronic glomerulonephritis + diseases EC
15097	Chronic glomerulonephritis NOS
106060	Chronic infective interstitial nephritis
104981	Chronic kidney disease
30735	Chronic kidney disease annual review
19473	Chronic kidney disease monitoring

71271	Chronic kidney disease monitoring administration
30739	Chronic kidney disease monitoring first letter
72962	Chronic kidney disease monitoring second letter
69679	Chronic kidney disease monitoring telephone invite
72964	Chronic kidney disease monitoring third letter
88494	Chronic kidney disease monitoring verbal invite
108766	Chronic kidney disease self-management plan agreed
105392	Chronic kidney disease stage 1
29013	Chronic kidney disease stage 1
94789	Chronic kidney disease stage 1 with proteinuria
95572	Chronic kidney disease stage 1 without proteinuria
12586	Chronic kidney disease stage 2
105383	Chronic kidney disease stage 2
95146	Chronic kidney disease stage 2 with proteinuria
95121	Chronic kidney disease stage 2 without proteinuria
12566	Chronic kidney disease stage 3
104619	Chronic kidney disease stage 3
94793	Chronic kidney disease stage 3 with proteinuria
95123	Chronic kidney disease stage 3 without proteinuria
94965	Chronic kidney disease stage 3A
95408	Chronic kidney disease stage 3A with proteinuria
95175	Chronic kidney disease stage 3A without proteinuria
95179	Chronic kidney disease stage 3B
95178	Chronic kidney disease stage 3B with proteinuria
95177	Chronic kidney disease stage 3B without proteinuria
12479	Chronic kidney disease stage 4
104963	Chronic kidney disease stage 4
95122	Chronic kidney disease stage 4 with proteinuria
95406	Chronic kidney disease stage 4 without proteinuria
105151	Chronic kidney disease stage 5
12585	Chronic kidney disease stage 5
95508	Chronic kidney disease stage 5 with proteinuria
95405	Chronic kidney disease stage 5 without proteinuria
61494	Chronic membranoproliferative glomerulonephritis
10809	Chronic membranous glomerulonephritis
73026	Chronic neph syn difus mesangiocapillary glomerulonephritis
60857	Chronic nephritic syn diffuse crescentic glomerulonephritis
48855	Chronic obstructive pyelonephritis
34998	Chronic proliferative glomerulonephritis

4654	Chronic pyelonephritis
48111	Chronic pyelonephritis NOS
57568	Chronic pyelonephritis with medullary necrosis
99631	Chronic pyelonephritis without medullary necrosis
65064	Chronic rapidly progressive glomerulonephritis
512	Chronic renal failure
12720	Chronic renal impairment
10081	Chronic uraemia
97980	CKD stage 1 with proteinuria
111022	CKD stage 1 without proteinuria
97979	CKD stage 2 with proteinuria
97978	CKD stage 2 without proteinuria
95145	CKD stage 3 with proteinuria
95188	CKD stage 3 without proteinuria
95571	CKD stage 3A with proteinuria
95176	CKD stage 3A without proteinuria
95180	CKD stage 3B with proteinuria
100633	CKD stage 3B without proteinuria
99312	CKD stage 4 with proteinuria
97587	CKD stage 4 without proteinuria
99160	CKD stage 5 with proteinuria
97683	CKD stage 5 without proteinuria
110033	CKD with GFR category G1 & albuminuria category A1
110003	CKD with GFR category G1 & albuminuria category A2
110484	CKD with GFR category G1 & albuminuria category A3
110269	CKD with GFR category G2 & albuminuria category A1
110108	CKD with GFR category G2 & albuminuria category A2
110251	CKD with GFR category G2 & albuminuria category A3
109804	CKD with GFR category G3a & albuminuria category A1
109805	CKD with GFR category G3a & albuminuria category A2
109905	CKD with GFR category G3a & albuminuria category A3
109963	CKD with GFR category G3b & albuminuria category A1
109657	CKD with GFR category G3b & albuminuria category A2
109990	CKD with GFR category G3b & albuminuria category A3
109980	CKD with GFR category G4 & albuminuria category A1
109904	CKD with GFR category G4 & albuminuria category A2
110626	CKD with GFR category G4 & albuminuria category A3
110133	CKD with GFR category G5 & albuminuria category A1
109981	CKD with GFR category G5 & albuminuria category A2

110467	CKD with GFR category G5 & albuminuria category A3
107881	Clinical diabetic nephropathy
15917	Congenital cystic kidney disease
50331	Congenital cystic kidney disease NOS
20629	Congenital cystic renal disease
47342	Congenital renal failure
9240	Cystic kidney disease NEC
35107	Diabetes mellitus with nephropathy NOS
2475	Diabetic nephropathy
95422	Did not attend chronic kidney disease monitoring clinic
10063	Dysplasia of kidney
54798	Dysplasia of kidney NOS
6712	End stage renal failure
53852	End stage renal failure
8330	End-stage renal disease
40100	Exc chronic kidney disease quality indicators: Inform dissen
12860	Except chronic kidney disease qual indic: Patient unsuitable
46626	Exception reporting: chronic kidney disease quality indicato
24384	Familial glomerulonephritis in Alport's syndrome
67486	Fibrocystic kidney disease
21687	Gout due to impairment of renal function
51113	Hereditary nephropathy NEC, minor glomerular abnormality
41239	Hereditary nephropathy NEC,focal+segmnt glomerular lesion
36205	Hereditary nephropathy not elsewhere classified
91738	Hereditary nephropathy, NEC, dense deposit disease
62980	Hereditary nephropathy, unspecif morphological changes
44270	Hereditry nephropathy NEC,difus membran glomerulnephritis
50305	Hypocomplementaemic persistent glomerulonephritis NEC
56939	Hypokalaemic nephropathy
85659	IgA nephropathy
102163	Insulin dependent diabetes mellitus with nephropathy
57621	Insulin dependent diabetes mellitus with nephropathy
111077	Juvenile nephropathic cystinosis
18331	Multicystic renal dysplasia
68112	Nephropathic amyloidosis
11875	Nephropathy - chronic
59365	Non-insulin dependent diabetes mellitus with nephropathy
35360	Nonobstructive reflux-associated chronic pyelonephritis
60960	Other chronic glomerulonephritis

63615	Other chronic glomerulonephritis NOS
59031	Other congenital cystic kidney disease NOS
59018	Other specified congenital cystic kidney disease
4504	Polycystic kidney
4503	Polycystic kidney disease
56852	Polycystic kidney disease NOS
4505	Polycystic kidneys, adult type
21381	Polycystic kidneys, infantile type
19454	Polyneuropathy in uraemia
89332	Predicted stage chronic kidney disease
105302	Proteinuric diabetic nephropathy
60856	Recur+persist haematuria difus crescentic glomerulonephritis
61317	Recur+persist haematuria difus membranous glomerulonephritis
49642	Recur+persist haemuria df mesangial prolif glomerulnephritis
60484	Recur+persist hmuria df mesangiocapilary glomerulonephritis
105657	Renal dysplasia and retinal aplasia
22876	Renal fibrosis
41013	Renal function impairment with growth failure
45880	Rovsing's operation for polycystic kidney
107027	Sickle cell nephropathy
7154	Small kidney of unknown cause
38768	Small kidneys unspecified
10418	Type 1 diabetes mellitus with nephropathy
24836	Type 2 diabetes mellitus with nephropathy
12640	Type 2 diabetes mellitus with nephropathy
66872	Type I diabetes mellitus with nephropathy
64571	Type II diabetes mellitus with nephropathy
102201	Type II diabetes mellitus with nephropathy
24120	Unilateral renal dysplasia
43919	Unilateral small kidney
105369	Unilateral small kidney with contralateral hypertrophy
105742	Aneurysm of anastomotic site of dialysis AV fistula
107188	Aneurysm of dialysis arteriovenous fistula
107220	Aneurysm of needle site of dialysis arteriovenous fistula
110095	Aneurysm of superficialised artery of dialysis AV fistula
60302	Creation of graft fistula for dialysis
106975	Haemorrhage of dialysis arteriovenous fistula
107260	Infection of dialysis arteriovenous fistula
108213	Infection of dialysis arteriovenous graft

96347	Ligation of arteriovenous dialysis fistula
107719	Ligation of arteriovenous dialysis graft
107082	Occlusion of dialysis arteriovenous fistula
109135	Occlusion of dialysis arteriovenous graft
108116	Occlusion of dialysis vascular access
108423	Rupture of dialysis arteriovenous graft
59315	Stenosis of arteriovenous dialysis fistula
108699	Stenosis of dialysis arteriovenous graft
106720	Thrombosis of dialysis arteriovenous fistula

eTable 1. 2: ICD-10 Diagnostic Codes Defining CKD for Study Inclusion

ICD-10 Code	Code Description
N05.1	Unspecified nephritic syndrome with focal and segmental glomerular lesions
N05.2	Unspecified nephritic syndrome with diffuse membranous glomerulonephritis
N05.5	Unspecified nephritic syndrome with diffuse mesangiocapillary glomerulonephritis
N05.6	Unspecified nephritic syndrome with dense deposit disease
N13.8	Other obstructive and reflux nephropathy
N13.9	Obsturctive and reflux nephropathy unspecified
N13.73	VUR with reflux nephropathy with hydroureter
M32.14	Glomerular disease in systemic lupus erythematosus
N06.1	Isolated proteinuria with focal and segmental glomerular lesions
N06.2	Isolated proteinuria with diffuse membranous glomerulonephritis
N06.5	Isolated proteinuria with diffuse mesangiocapillary glomerulonephritis
N06.6	Isolated proteinuria with dense deposit disease
N04.1	Nephrotic syndrome with focal and segmental glomerular lesions
N04.2	Nephrotic syndrome with diffuse membranous GN
N04.5	Nephrotic syndrome with diffuse mesangiocapillary glomerulonephritis
N04.6	Nephrotic syndrome with dense deposit disease
N27.0	Small kidney, unilateral
N27.9	Small kidney, unspecified
Q60.1	Renal agenesis bilateral
Q60.3	Renal hypoplasia, unilateral
Q60.5	Renal hypoplasia, unspecified (congential hypoplasia, oligomeganephronia)
D63.1	Anemia in chronic kidney disease
M32.15	Tubulo-interstitial nephropathy in SLE
I12.0	Hypertensive CKD with stage 5 CKD or end stage renal disease
I12.9	Hypertensive CKD with stage 1-4 or unspecified CKD
I13	Hypertesnive heart and CKD
I13.0	Hypertensive heart and chronic kidney diease with heart failure and stage 1-4 CKD or unspecified
I13.1	Hypertensive heart and chronic kidney diease without heart failure
I13.2	Hypertensive heart and chronic kidney diease with heart failure and stage 5 or end stage CKD
M10.3	Gout due to renal impairment
M1A.3	Chronic gout due to renal impairment
N02	Recurrent and persistent hematuria
N02.1	Recurrent and persistent hematuria with focal and segmental glomerular lesions
N02.2	Recurrent and persistent hematuria with diffuse membranous glomerulonephritis
N02.3	Recurrent and persistent hematuria with diffuse mesangial proliferative glomerulonephritis
N02.4	Recurrent and persistent hematuria with diffuse endocapillary proliferative glomerulonephritis
N02.5	Recurrent and persistent hematuria with diffuse mesangiocapillary glomerulonephritis
N02.6	Recurrent and persistent hematuria with dense deposit disease
N02.7	Recurrent and persistent hematuria with diffuse crescentic glomerulonephritis
N02.8	Recurrent and persistent hematuria with other morphologic changes
N02.9	Recurrent and persistent hematuria with unspecificed morphologic changes
N03	Chronic nephritic syndrome
N03.0	Chronic nephritic syndrome with minor glomerular abnormality
N03.1	Chronic nephritic syndrome with focal and segmental glomerular lesions
N03.2	Chronic nephritic syndrome with diffuse membranous glomerulonephritis
N03.3	Chronic nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
N03.4	Chronic nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis
N03.5	Chronic nephritic syndrome with diffuse mesangiocapillary glomerulonephritis
N03.6	Chronic nephritic syndrome with dense deposit disease
N03.7	Chronic nephritic syndrome with diffuse crescentic glomerulonephritis

N03.8	Chronic nephritic syndrome with other morphologic changes
N03.9	Chronic nephritic syndrome with unspecified morphologic changes
N07	Hereditary nephropathy, not elsewhere classified
N07.0	Hereditary nephropathy, not elsewhere classified with minor glomerular abnormality
N07.1	Hereditary nephropathy, not elsewhere classified with focal and segmental glomerular lesions
N07.2	Hereditary nephropathy, not elsewhere classified with diffuse membranous glomerulonephritis
N07.3	Hereditary nephropathy, not elsewhere classified with diffuse mesangial proliferative glomerulonephritis
N07.4	Hereditary nephropathy, not elsewhere classified with diffuse endocapillary proliferative glomerulonephritis
N07.5	Hereditary nephropathy, not elsewhere classified with diffuse mesangiocapillary glomerulonephritis
N07.6	Hereditary nephropathy, not elsewhere classified with dense deposit disease
N07.7	Hereditary nephropathy, not elsewhere classified with diffuse crescentic glomerulonephritis
N07.8	Hereditary nephropathy, not elsewhere classified with other morphologic lesions
N07.9	Hereditary nephropathy, not elsewhere classified with unspecified morphologic lesions
N11	Chronic tubule-interstitial nephritis
N11.0	Nonobstructive reflux-associated chronic pyelonephritis
N11.1	Chronic obstructive pyelonephritis
N11.8	Other chronic tubulo-interstitial nephritis
N11.9	Chronic tubulo-interstitial nephritis, unspecified
N14.0	Analgesic nephropathy
N15.0	Balkan nephropathy
N18	Chronic kidney disease
N18.1	Chronic kidney disease, stage 1 (Kidney damage with normal or increased GFR (≥ 90 mL/min))
N18.2	Chronic kidney disease, stage 2 (Kidney damage with mild decreased GFR (60-89 mL/min))
N18.3	Chronic kidney disease, stage 3 (Kidney damage with moderately decreased GFR (30-59 mL/min))
N18.4	Chronic kidney disease, stage 4 (Kidney damage with severely decreased GFR (15-29 mL/min))
N18.5	Chronic kidney disease, stage 5
N18.6	End stage renal disease
N18.9	Chronic kidney disease, unspecified
N25.0	Renal osteodystrophy
N25.81	Secondary hyperparathyroidism of renal origin
N27.1	Small kidney bilateral
O10.2	Pre-existing hypertensive chronic kidney disease complicating pregnancy, childbirth and the puerperium
O10.3	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, childbirth and the puerperium
P96.0	Congenital renal failure
Q60.4	Renal hypoplasia, bilateral
Q60.6	Potter's syndrome
Q61.02	Congenital multiple renal cysts
Q61.1	Polycystic kidney, infantile type
Q61.19	Other polycystic kidney, infantile type
Q61.2	Polycystic kidney, adult type
Q61.3	Polycystic kidney, unspecified
Q61.4	Renal dyaplsia (multicystic dysplastic, multycystic)
Q61.5	Medullary cystic kidney (UTD: end-stage renal disease (ESRD) onset that is highly variable, usually between the ages of 20 and 70 years)
Q61.8	Other cystic kidney diseases (applicable to fibrocystic kidney, fibrocystic renal degeneration or disease)
Q61.9	Cystic kidney diease, unspecified (includes Meckel gruber syndrome)
Q87.81	Alport syndrome

eTable 1. 3: OPCS-4 Procedure Codes Defining CKD for Study Inclusion

OPCS4 Code	Code Description
L74.6	Creation of graft fistula for dialysis
M02.1	Nephrectomy and excision of perirenal tissue
M02.2	Nephroureterectomy NEC
M02.3	Bilateral nephrectomy
M02.5	Nephrectomy NEC
M02.7	Other specified total excision of kidney
M02.9	Unspecified total excision of kidney

Supplement 2: Nonspecific Renal Codes Defining Exclusion From the Unexposed Cohort

eTable 2. 1: Nonspecific CPRD Read Codes Defining Exclusion From the Unexposed Cohort

Medcode	Read term (Code Description)
5451	[D]Albuminuria
22327	[D]Kidney function test abnormal
10924	[D]Microalbuminuria
11248	[D]Proteinuria
38284	[D]Proteinuria NOS
10768	[D]Renal function test abnormal
34320	[D]Renal scarring
98067	[X]Hydronephrosis with ureteral stricture NEC
72478	[X]Nephropathy induced by other drugs+biological substances
72621	[X]Other and unspecified hydronephrosis
70157	[X]Other disorders of kidney and ureter
96819	[X]Other disorders resulting/impaired renal tubular function
56896	[X]Other specified disorders of kidney and ureter
64030	[X]Persistent proteinuria, unspecified
61930	[X]Renal failure
94842	[X]Renal tubulo-interstitial diseases
103757	[X]Tubulo-interstit nephritis, not specif as acute or chron
63000	Benign hypertensive heart and renal disease
43935	Benign hypertensive renal disease
105634	Candida pyelonephritis
62045	Closed injury of kidney
31549	Compensation for renal failure
5379	Congenital hydronephrosis
26001	Deteriorating renal function
110092	Emphysematous pyelonephritis
52969	Gouty nephropathy
61145	Gouty nephropathy NOS
6774	H/O: kidney disease
8828	H/O: nephritis
9959	H/O: renal disease
3277	Hydronephrosis
27302	Hydronephrosis NOS
8522	Hydronephrosis with pelviureteric junction obstruction
27592	Hydronephrosis with renal and ureteral calculous obstruction
28159	Hydronephrosis with ureteral stricture NEC

10410	Hydronephrosis with ureteropelvic junction obstruction
6842	Impaired renal function
8919	Impaired renal function disorder
25980	Impaired renal function disorder NOS
105967	Inherited renal tubule insuffic with cholestatic jaundice
16496	Injury to kidney
52339	Injury to kidney NOS
102947	Ischaemic nephropathy
43611	Isolated proteinuria with specified morphological lesion
101572	Isolated proteinuria, with oth specif morpholog changes
59992	Isolated proteinuria, with unspecified morpholog changes
2991	Kidney and ureter disease NOS
39598	Kidney failure as a complication of care
107771	Kidney failure unspecified
66213	Kidney injury due to birth trauma
110554	Kidney injury with open wound into cavity, unspecified
71500	Kidney injury without mention of open wound into cavity NOS
62728	Kidney injury without open wound into cavity, unspecified
67232	Malignant hypertensive heart and renal disease
39649	Malignant hypertensive renal disease
33580	Nephritis and nephropathy unspecified
4850	Nephritis and nephropathy unspecified
2773	Nephritis, nephrosis and nephrotic syndrome
15780	Nephritis, nephrosis and nephrotic syndrome NOS
41159	Nephropathy induced by other drugs meds and biologl substncs
57784	Nephropathy induced by unspec drug medicament or biol subs
38312	Nephropathy NOS in pregnancy without hypertension
11873	Nephropathy, unspecified
11436	Non-functioning kidney
39840	Other impaired renal function disorder
50804	Other impaired renal function disorder NOS
34669	Other interstitial nephritis
36273	Other kidney and ureter disorders
44657	Other kidney and ureteric disorders
34675	Other kidney and ureteric disorders NOS
8098	Other kidney disorders
27335	Other nephritis and nephrosis in diseases EC
44055	Other nephritis and nephrosis NOS
35065	Other nephritis and nephrosis unspecified

48022	Other specified compensation for renal failure
49150	Other specified nephritis, nephrosis or nephrotic syndrome
16465	Persistent proteinuria, unspecified
16008	Proliferative nephritis unspecified
1802	Proteinuria
58164	Rapidly progressive nephritis unspecified
107765	Renal disorders in systemic disease
11554	Renal failure as a complication of care
350	Renal failure unspecified
106860	Renal failure-associated hyperphosphataemia
3980	Renal function tests abnormal
25763	Renal function tests borderline
11787	Renal impairment
18770	Renal injury due to birth trauma
64622	Renal tubulo-interstitial disorder/ neoplastic diseases
45523	Renal tubulo-interstitial disorders in diseases EC
106045	Renal vascular disease
10460	Renal vascular disorders
15340	Renal vascular disorders NOS
20516	Salt-losing nephritis
50893	Toxic nephropathy, not elsewhere classified
52272	Tuberculous nephropathy
49235	Tuberculous pyelonephritis
23990	Tubulo-interstit nephritis, not specif as acute or chron
30294	Type 1 diabetes mellitus with persistent microalbuminuria
30323	Type 1 diabetes mellitus with persistent proteinuria
18390	Type 2 diabetes mellitus with persistent microalbuminuria
26054	Type 2 diabetes mellitus with persistent proteinuria
102620	Type I diabetes mellitus with persistent microalbuminuria
85991	Type II diabetes mellitus with persistent microalbuminuria
60796	Type II diabetes mellitus with persistent proteinuria
47080	Unspecified renal disease in pregnancy
96724	Unspecified renal disease in pregnancy - delivered
54938	Unspecified renal disease in pregnancy unspecified
4809	Uraemia NOS
106058	Urate nephropathy
106213	Uric acid nephropathy
11992	Vascular disorders of kidney
38572	Xanthogranulomatous pyelonephritis

eTable 2. 2: Nonspecific HES ICD-10 Codes Defining Exclusion From the Unexposed Cohort

ICD-10 Code	Code Description
E08.2	Diabetes mellitus due to underlying condition with kidney complications
E09.2	Drug or chemical induced DM with kidney complications
E10.2	Type 1 DM with diabetic kidney complications
E11.2	Type 2 DM with diabetic kidney complications
E13.2	Other specified DM with kidney complication
R80.1	Persistent proteinuria, unspecified
N04.0	Nephrotic syndrome with minor glomerular abnormality
N04.3	Nephrotic syndrome with diffuse mesangial proliferative glomerulonephritis
N04.4	Nephrotic syndrome with diffuse endocapillary proliferative glomerulonephritis
N04.7	Nephrotic syndrome with diffuse crescentif GN
N04.8	Nephrotic syndrome with other morphologic changes
N04.9	Nephrotic syndrome with unspecified morphologic changes
D86.84	Sarcoid pyelonephritis
I15.1	Hypertension secondary to other renal disorders
I70.1	Atherosclerosis of renal artery
I72.2	Aneurysm of renal artery
I75.81	Atheroembolism of kidney (excluded because code asks to specify AKI or CKD with separate code if applicable)
I77.73	Dissection of renal artery
M31.31	Wegner's granulomatosis with renal involvement
M35.04	Sicca syndrome with tubulo-interstitial nephropathy
N05.0	Unspecified nephritic syndrome with minor glomerular abnormality
N05.3	Unspecified nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
N05.4	Unspecified nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis
N05.7	Unspecified nephritic syndrome with diffuse crescentic glomerulonephritis
N05.8	Unspecified nephritic syndrome with other morphologic changes
N05.9	Unspecified nephritic syndrome with unspecified morphologic changes
N06.0	Isolated proteinuria with minor glomerular abnormality
N06.3	Isolated proteinuria with diffuse mesangial proliferative glomerulonephritis
N06.4	Isolated proteinuria with diffuse endocapillary proliferative glomerulonephritis
N06.7	Isolated proteinuria with diffuse crescentic glomerulonephritis
N06.8	Isolated proteinuria with other morphologic lesion
N06.9	Isolated proteinuria with unspecified morphologic lesion
N08	Glomerular disorders in diseases classified elsewhere
N12	Tubulointerstitial nephritis not specified as acute or chronic
N13.0	HN with UP junction obstruction
N13.1	HN with ureteral stricture, NEC
N13.2	HN with renal and ureteral calculous obstruction
N13.4	Hydroureter
N13.7	Vesicoureteral reflux
N14.1	Nephropathy induced by other drugs, medicaments and biological substances
N14.2	Nephropathy induced by unspecified drug, medicament or biologic substance
N14.3	Nephropathy induced by heavy metals
N14.4	Toxic nephropathy not elsewhere classified
N15.8	Other specified renal tubule-interstitial disease
N15.9	Renal tubule-interstitial disease, unspecified
N16	Renal tubule-interstitial disorders in diseases classified elsewhere
N19	Unspecified kidney failure
N25.8	Other disorders resulting from impaired renal tubular function
N25.9	Disorder resulting form impaired renal tubular function, unspecified
N26.1	Atrophy of kidney (terminal) – includes renal atrophy;unilateral renal atrophy

N28.8	Other specified disorders of kidney and ureter
N28.9	Disorder of kidney and ureter, unspecified
N29	Other disorders of kidney and ureter in diseases classified elsewhere
N39.8	Other specified disorders of urinary system
N39.9	Disorder of urinary system, unspecified
N99.0	Postprocedural (acute) (chronic) kidney failure
O26.83	Pregnancy related renal disease
O26.839	Pregnancy-related renal disease
Q27.1	Congenital renal artery stenosis
Q27.2	Other congenital malformations of renal artery
Q27.34	Arteriovenous malformation of renal vessel
Q60.0	Renal agenesis, unilateral
Q60.2	Renal agenesis unspecified
Q62.1	Congenital occlusion of ureter
Q62.2	Congenital megaureter
Q62.31	Congenital ureterocele, orthotopic
R94.4	Abnormal results of kidney function studies
S35.40	Unspecified injury of renal blood vessel
S35.41	Laceration of renal blood vessel (artery/vein)
S35.49	Other specified injury of renal blood vessel
S37.0	Injury of kidney (excludes acute nontraumatic kidney injury)
T81.711	Complication of a renal artery following a procedure, NEC
Z52.4	Kidney donor
Z87.448	Personal history of other diseases of urinary system
Z90.5	Acquired absence of kidney (applies to total and partial nephrectomy)

eTable 2. 3: Nonspecific OPCS-4 Procedure Codes Defining Exclusion From the Unexposed Cohort

OPCS-4 Code	Code Description
M02.4	Excision of half of horseshoe kidney
M03.1	Heminephrectomy of duplex kidney
M03.8	Other specified partial excision of kidney
M03.9	Unspecified partial excision of kidney

Supplement 3: List of Established and of Potential Nephrotoxic Medications Included in the Study

eTable 3. 1: List of Established Nephrotoxic Medications Included in the Study

Medications included in our definition	Medications included in the study
Aminoglycosides	
Amikacin sulfate	
Framycetin Sulphate	
Gentamicin	Gentamicin
Kanamycin	
Neomycin	
Netilmicin sulfate	
Streptomycin	
Tobramycin	
Paromomycin	
NSAIDS	
Aceclofenac	
Acemetacin	
Celecoxib	Celecoxib
Codeine Phosphate/Ibuprofen	
Dexibuprofen	
Dexketoprofen trometamol	
Diclofenac	Diclofenac
Diflunisal	
Etodolac	
Etoricoxib	
Fenbufen	
Fenoprofen calcium	
Flurbiprofen	
Ibuprofen	Ibuprofen
Indometacin	Indometacin
Ketoprofen	Ketoprofen
Lornoxicam	
Magnesium Trisilicate	
Mefenamic acid	Mefenamic acid
Meloxicam	
Nabumetone	
Naproxen	Naproxen
Phenylbutazone	
Piroxicam	Piroxicam
Salsalate	
Sulindac	
Tenoxicam	
Tiaprofenic acid	
Tolfenamic Acid	
Tolmetin Sodium	
ACE-Inhibitors	
Captopril	Captopril
Cilazapril	
Enalapril	Enalapril
Imidapril	

Lisinopril	Lisinopril
Moexipril hydrochloride	
Perindopril	Perindopril
Quinapril	
Ramipril	Ramipril
Trandolapril	
Antivirals	
Aciclovir	Aciclovir
Valaciclovir	Valaciclovir
Ganciclovir	
Cidofovir	
Foscarnet sodium	
Valganciclovir hydrochloride	Valganciclovir hydrochloride
Indinavir sulfate	
Salicylates	
Balsalazide disodium	
Mesalazine	Mesalazine
Olsalazine sodium	
Sulfapyridine	
Sulfasalazine	Sulfasalazine
Aspirin	
Para-aminosalicylic Acid	
Bismuth subsalicylate	
Sodium salicylate	
Acetylsalicylic acid	
Cephalosporins	
Cefotaxime sodium	
Ceftazidime pentahydrate	
Cefuroxime axetil	Cefuroxime axetil
PPIs	
Esomeprazole	Esomeprazole
Lansoprazole	Lansoprazole
Omeprazole	Omeprazole
Pantoprazole	
Rabeprazole sodium	
Other antimicrobials	
Amphotericin	
Amphotericin B	
Colistimethate sodium	Colistimethate sodium
Colistin sulfate	
Sulfamethoxazole/Trimethoprim	Sulfamethoxazole/Trimethoprim
Vancomycin hydrochloride	Vancomycin hydrochloride
Piperacillin Sodium	
Immunomodulators/suppressors	
Ciclosporin	Ciclosporin
Cisplatin	
Ifosfamide	
Methotrexate	Methotrexate
Tacrolimus	Tacrolimus
Lithium	
Pamidronate	

eTable 3. 2: List of Potentially Nephrotoxic Medications Included in the Study

Medications included in our definition	Medications included in the study
Cephalosporins	
Cefaclor	Cefaclor
Cefadroxil monohydrate	Cefadroxil monohydrate
Cefalexin	Cefalexin
Cefamandole	
Cefazolin sodium	
Cefixime	Cefixime
Cefodizime	
Cefoxitin sodium	
Cefpodoxime proxetil	
Cefprozil	
Cefradine	Cefradine
Ceftibuten	
Ceftizoxime	
Ceftriaxone sodium	Ceftriaxone sodium
Other antibiotics	
Cinoxacin	
Ciprofloxacin	Ciprofloxacin
Dapsone	Dapsone
Enoxacin	
Levofloxacin	Levofloxacin
Moxifloxacin hydrochloride	
Nalidixic acid	
Norfloxacin	Norfloxacin
Ofloxacin	Ofloxacin
Pentamidine isetionate	
Rifampicin	Rifampicin
Penicillins	
Amoxicillin	Amoxicillin
Amoxicillin sodium/Potassium clavulanate	Amoxicillin sodium/Potassium clavulanate
Ampicillin	Ampicillin
Bacampicillin	
Benzylpenicillin	Benzylpenicillin
Flucloxacillin	Flucloxacillin
Phenoxymethylpenicillin potassium	Phenoxymethylpenicillin potassium
Pivampicillin	
Talampicillin	
Ticarcillin Sodium	
Immunomodulators/suppressors	
Bevacizumab	
Carboplatin	
Interferon Alfa-2b	
Peginterferon Alfa-2b	
Sirolimus	
Temsirolimus	
Anti-epileptic	
Topiramate	Topiramate
Zonisamide	Zonisamide

HIV meds and other antivirals	
Abacavir sulfate	
Adefovir dipivoxil	
Atazanavir sulfate	
Didanosine	
Lamivudine	
Ritonavir	
Tenofovir	
Contrast agents	
Iodixanol	
Iohexol	
Iopamidol	
Ioversol	
Meglumine gadopentetate	
Other	
Auranofin	
Propylthiouracil	
Zoledronic Acid	
Quinine	
Clopidogrel	
Ranitidine	Ranitidine
Allopurinol	
Hydralazine	Hydralazine

Supplement 4: CKD Diagnosis and Procedure codes of Included Study Patients

eTable 4. 1: CPRD Read Codes for Renal Disease of Included Study Patients

Code description	Number of Patients
Cystic kidney disease	**100**
Polycystic kidney disease	70
Congenital cystic kidney disease	14
Cystic kidney disease	9
Multicystic renal dysplasia	5
Polycystic kidneys infantile type	2
Chronic kidney disease	**99**
Chronic kidney disease/CKD	29
Chronic renal failure	31
Except chronic kidney disease qual indic: Patient unsuitable	17
Chronic renal impairment	11
Chronic kidney disease monitoring	7
End-stage renal disease	4
Nephropathy/nephritis	**72**
Chronic pyelonephritis	16
IgA nephropathy	14
Berger's nephropathy	9
Chronic glomerulonephritis	9
Chronic nephropathy	8
Lupus nephritis	8
Familal GN in Alport's	3
Diabetic nephropathy	3
Chronic membranoproliferative glomerulonephritis	1
Membranoproliferative nephritis unspecified	1
Renal dysplasia/hypoplasia	**70**
Small kidney(s)	50
Kidney dysplasia	16
Unilateral renal dysplasia	3
Bilateral renal dysplasia	1
Other	**10**
Hypertensive renal disease	5
Renal fibrosis	4
Juvenile nephropathic cystinosis	1
Total	**351**

eTable 4. 2: HES ICD-10 Codes for Renal Disease of Included Study Patients

Code description	Number of Patients
Nephropathy/nephritis	**295**
Obstructive and reflux nephropathy	115
Recurrent and persistent hematuria with morphological changes	91
Chronic tubulo-interstitial nephritis	24
Chronic nephritic syndrome with morphological changes	17
Nonobstructive reflux-associated chronic pyelonephritis	15
Nephrotic syndrome with focal and segmental glomerular lesions	14
Unspecified nephritic syndrome with diffuse mesangiocapillary GN	6
Unspecified nephritic syndrome focal and segmental glomerular lesions	4
Nephrotic syndrome with diffuse mesangiocapillary glomerulonephritis	3
Hereditary nephropathy with morphological changes	2
Chronic obstructive pyelonephritis	2
Unspecified nephritic syndrome with diffuse membranous GN	1
Isolated proteinuria with diffuse mesangiocapillary glomerulonephritis	1
Renal dysplasia/hypoplasia	**144**
Small kidney(s)	79
Renal dysplasia	51
Renal hypoplasia	14
Chronic kidney disease	**79**
Chronic kidney disease	58
Hypertensive chronic kidney disease stage 5 or end stage	11
Hypertensive chronic kidney disease stage 1-4 or unspecified	10
Cystic kidney disease	**28**
Polycystic kidney, unspecified	15
Cystic kidney disease	8
Polycystic kidney, infantile type	5
Other	**5**
Potter’s syndrome	2
Congenital renal failure	2
Renal osteodystrophy	1
Total	**551**

eTable 4. 3: HES OPCS-4 Procedure codes for Renal Disease of Included Study Patients

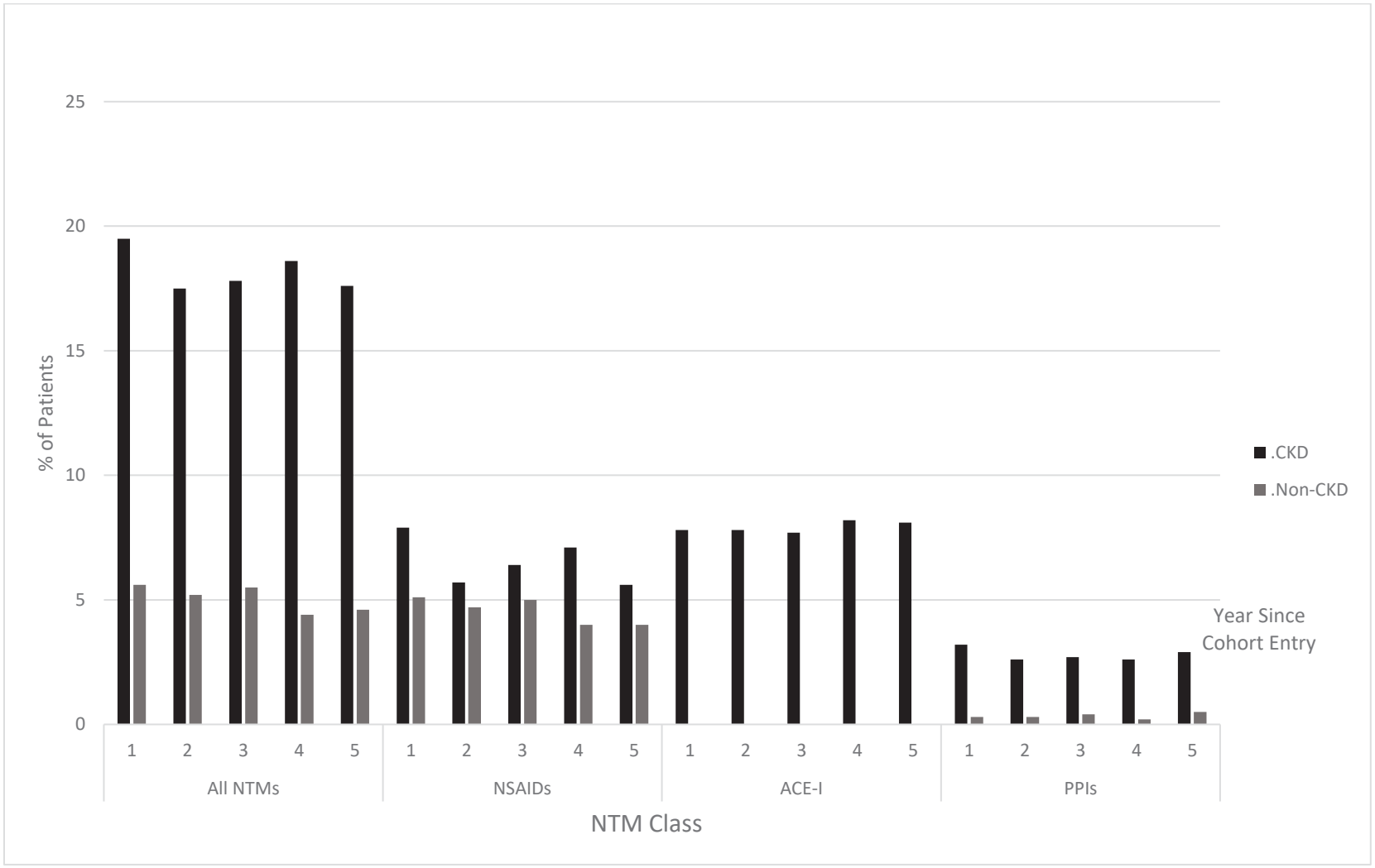
Code description	Number of Patients
Nephrectomy	**106**
Nephrectomy	81
Nephrectoureterectomy	22
Unspecified total excision of kidney	2
Bilateral nephrectomy	1

eTable 4. 4: CPRD Read codes for Dialysis of Included Study Patients

Code description	Number of Patients
Dialysis	**10**
Peritoneal dialysis	5
Dialysis for renal failure	3
Haemodialysis	1
Removal of ambulatory peritoneal dialysis catheter	1

Supplement 5: Trends in Established Nephrotoxic Medication Prescribing by Year Since Cohort Entry

eFigure 5. 1: Percentage of Patients Receiving at Least One Established NTM by Year Since Cohort Entry



eFigure 5. 2: Number of Established NTMs Prescribed Per Patient Throughout Entire Follow-Up and by Year Since Cohort Entry