Influence of non-steroidal anti-inflammatory drugs on chronic kidney disease progression: an epidemiological study in general practice populations

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Paul Nderitu

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Institute of Science and Technology in Medicine

Keele University

Abstract

Chronic kidney disease (CKD) is a major cause of morbidity and mortality worldwide. Identifying and avoiding disease progression risk factors is important in the management of CKD. Non-Steroidal Anti-inflammatory Drugs (NSAIDs), which are commonly prescribed analgesia, are widely regarded as one risk factor which influences CKD progression. However, the published literature is conflicting and the association between NSAID use and CKD is unclear.

This thesis encompasses a systematic review and a two phase observational study. The systematic review found that high dose NSAID use significantly increased the risk of accelerated CKD progression but normal dose NSAID use did not. However, NSAID doses were unstandardised, the effects of co-morbidity or co-drug therapy were unknown and outcome measures were varied.

The observational phases were performed using linked consultation and prescription general practice data. Subjects aged 40 years and over with at least one estimated Glomerular Filtration Rate (eGFR) measurement (N=7,657) between the 1st/Jan/2009 and 31st/Dec/2010 were included. Cumulative drug prescription (NSAID, aspirin or paracetamol) was standardised using the defined daily dose (DDD) and use categorised into non-user (0 DDD), normal (DDD's <85th percentile) and high dose (DDD's ≥85th percentile) groups. Phase 1 (cross-sectional study) characterised the CKD population and explored associations between drug prescription and moderate to severe CKD. Phase 2 (cohort design study) investigated the effects of drug prescribing on the development of

moderate to severe CKD and significant CKD progression. Multiple logistic regression analyses, adjusting for socio-demographic, co-morbidity and co-drug therapy factors, were used to estimate risk.

Phase 1 findings were that drug prescribing was not significantly associated with moderate to severe CKD. Phase 2 findings were that NSAID or paracetamol prescription did not affect the risk of significant CKD progression. However, high dose aspirin prescribing significantly decreased the risk of significant CKD progression but normal dose aspirin did not.

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Publications

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List of Common Abbreviations

AA	Arachidonic Acid
ACE-i	Angiotensin Converting Enzyme Inhibitors
AKI	Acute Kidney Injury
APKD	Adult Polycystic Kidney Disease
ARBs	Angiotensin Receptor Blockers
ATC	Anatomical Therapeutic Chemical (Classification)
BNF	British National Formulary
BP	Blood Pressure
BSA	Body Surface Area
Ccr	Creatinine Clearance
CG	Cockcroft-Gault
CI	Confidence Interval
CKD	Chronic Kidney Disease
COX	Cyclo-oxygenase
CVD	Cardiovascular Disease
DDD	Defined Daily Dose
DM	Diabetes Mellitus
ECM	Extracellular Matrix
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
GH	Glomerular Hypertension
GI	Gastrointestinal
GN	Glomerulonephritis
GP	General Practitioner
GS	Glomerulosclerosis
HR	Hazard Ratio
HTN	Hypertension
IDMS	Isotope Dilution Mass Spectrometry
IMD	Index of Multiple Deprivation
IQR	Inter Quartile Range
MDRD	Modification of Diet in Renal Disease

mGFR	Measured Glomerular Filtration Rate
NHANES	National Health and Nutrition Examination Surveys
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
NKF-KDOQI	National Kidney Foundation – Kidney Disease Outcomes Quality Initiative
NSAID(s)	Non-Steroidal Anti-Inflammatory Drug(s)
OR	Odds Ratio
OTC	Over-the-counter
PDGF	Platelet-Derived Growth Factor
PG	Prostaglandins
RAAS	Renin Angiotensin Aldosterone System
Renin-i	Renin Inhibitors
RRT	Renal Replacement Therapy
SD	Standard Deviation
TGF-β	Transforming Growth Factor-β
TIF	Tubulointersitial Fibrosis
TIN	Tubulointerstitial Nephritis
VS	Vascular Sclerosis
WHO	World Health Organisation
WHO-CCDSM	World Health Organisation - Collaborating Centre for Drug Statistics and Methodology

Introduction

Chronic kidney disease (CKD) is an umbrella term that encompasses a myriad of disorders that affect the kidneys structure and function.[1,2] CKD is often an irreversibly progressive condition requiring treatments focus on slowing the rate of disease progression.[1] Progressive renal dysfunction can lead to End Stage Renal Disease (ESRD) requiring renal replacement therapy (RRT).[1] Although patients with ESRD only comprise 0.05% of the total UK population, they consume 2% of the total National Health Service (NHS) budget.[3]

CKD is now a global public health problem.[4] In the UK, it is estimated that 8.5% (5.8% in males, 10.6% in females) of the adult population have moderate to severe CKD.[5] US figures show that CKD prevalence rose from approximately 10% to 13% between the years 1988-1994 and 1999-2004 respectively.[4,6,7] The prevalence of CKD rises exponentially with age[5], therefore, given the UKs ageing population[8], the prevalence of the disease as well as the numerous associated complications and co-morbidities will no doubt rise.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used to control pain in patients with chronic inflammatory musculoskeletal conditions.[9-11] However, there is a generally held belief that regular NSAID use is a preventable cause of CKD progression.[4] This lead to the 2008 National Institute for Health and Clinical Excellence (NICE) CKD guidelines, published by the National Collaborating Centre for Chronic Conditions[6], recommending that patients taking these drugs should be screened annually. Their argument for including patients on regular NSAIDs in the 'at risk' group for screening for CKD was based on 4 published studies (1 small RCT[12] and 3 case-control studies[13-15]).

Given the increasing prevalence of CKD and the significant overlap between renal disease and NSAID use, the potential for harm is evident. As equally important is the risk of preventing patients from taking pain medication based on limited evidence which could affect their quality of life. Therefore, it is essential that the relationship between NSAID use and CKD progression is thoroughly investigated given the implications for prescribing healthcare professionals, NHS budgets and most importantly CKD patients.

Thesis Plan

Chapter one focuses on introducing CKD and measures of renal function. In chapter two, the causes of chronic renal disease are explored including the pathological mechanisms and complications of renal dysfunction. In chapter three, CKD progression is defined and associated risk factors for progression are laid out.

Chapter four details the pharmacology of NSAIDs. Thereafter, the actions of prostaglandins in the kidney are laid out followed by the adverse renal effects of NSAID use. In the final part of this chapter, issues of measuring drug dose are discussed.

The fifth chapter lays out common epidemiological and statistical methodologies used in health-care related research. Methodologies for performing systematic reviews and meta-analysis are also presented. Then, the systematic review on NSAIDs and CKD progression, which forms the basis for the main study, is presented in chapter six.

The study objectives and methods are laid out in the seventh chapter. The study is presented in two phases. Phase 1 is a cross-sectional study based on all patient records and mainly describes the CKD population (chapter eight). Phase 2 is a cohort design study including patients with two or more eGFR measurements; it mainly explores the association between drug use and CKD progression (chapter nine).

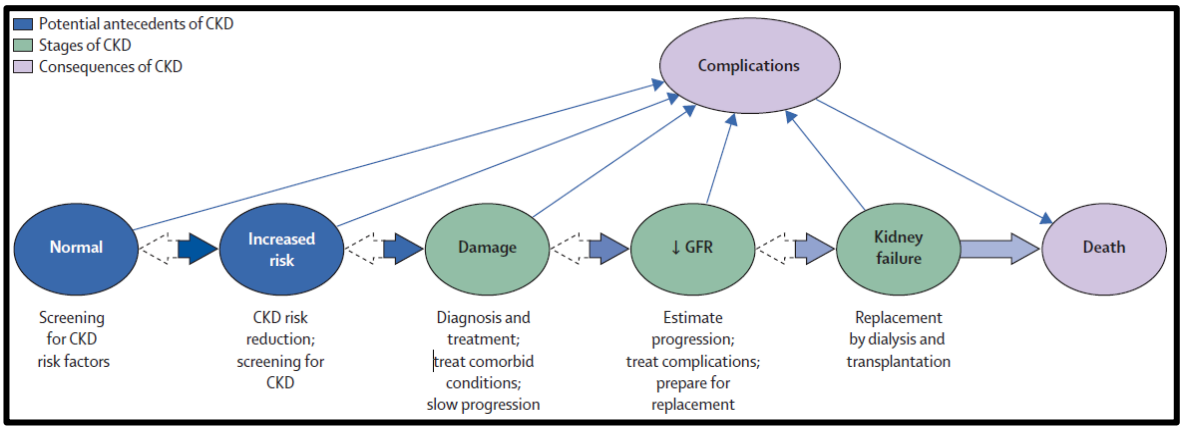
The discussion and conclusions are set out in chapter ten with the aim of answering five main study objectives. Finally, my reflections on the research experience and how it will inform my future career as a clinician are given in chapter eleven.

Chapter 1. An Introduction to Chronic Kidney Disease

1.1. Defining Chronic Kidney Disease

Given the asymptomatic nature of CKD, a key challenge in developing treatment strategies for renal disease was to try and measure the degree of kidney damage in order to diagnose the disease in its early stages.[1,16] A new conceptual model of renal disease and novel measurement techniques were developed over a decade ago with the aim of identifying such patients.[17,18] The conceptual model (**Figure 1.1**) shows the theoretical progression through different stages of CKD, as well as detailing the areas for intervention.[18]

Figure 1.1 Conceptual model of Chronic Kidney Disease



Taken from Levey *et al*., (2005)[18], originally made by the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative[4,7].

US National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines set out a new staging system for CKD based both on evidence of kidney damage (e.g. structural abnormality, haematuria or proteinuria) and on the level of residual kidney function (as measured by the glomerular filtration rate (GFR)).[4] NKF-KDOQI guidelines recommend that a CKD diagnosis be made where evidence of renal dysfunction is present on at least 2 occasions for >3 months.[4,18] Given the pivotal role that the GFR plays in the staging of the disease, it is important to understand how it is

measured or calculated and the unique advantages and disadvantages of each of the measurement techniques.

1.2. Measuring the Glomerular Filtration Rate

The GFR is a measure of the average amount of fluid filtered by all of the kidney's nephrons.[1] The GFR can be approximated by measuring the renal clearance of any substance not metabolised by the kidney.[1] The renal clearance is equal to the volume of plasma needed to deliver the amount of excreted substance in the urine per unit time.[1] Where the substance in question is freely filtered by the kidney and not absorbed or actively secreted by the renal tubules, then its renal clearance will be equal to the GFR.[1] The equation for renal clearance is as follows:

$$Cy = \frac{[Uy * V]}{Py}$$

Cy, renal clearance of substance y; Uy, urinary concentration of substance y; V, urine flow rate; Py, plasma concentration of substance y.[1]

The standardised GFR is expressed as a volume (mL) per unit time (minutes) per average body surface area ($1.73m^2$).[19,20] The normal GFR varies greatly with age, but is typically around $120mL/min/1.73m^2$ in healthy young adults.[1,4,19] A GFR of $\geq 90mL/min/1.73m^2$ without evidence of kidney damage is considered normal.[1,4,19] As detailed previously, the GFR can be used to stratify patients according to their renal function. **Table 1.1** shows the five stages of CKD according to the GFR and markers of renal injury.

Table 1.1 NKF-KDQOI stages of Chronic Kidney Disease

CKD Stage	Description	GFR (mL/min/1.73m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild reduction in GFR	60-89
3	Moderate reduction in GFR	30-59
4	Severe reduction in GFR	15-29
5	End-Stage Kidney Disease (ESRD)	<15 (or Dialysis)

From the NKF-KDOQI guidelines[4].

A variety of techniques have been developed that can directly measure the GFR with great accuracy or estimate the GFR according to pre-defined equations.[4,19-21] These measurement techniques try and use substances that best fit the criteria for a good GFR marker.

1.2.1. Exogenous filtration markers

Many exogenous substances have been identified that fit the criteria for an excellent marker of the GFR.[1,21] The non-radioactive substances, Inulin, Iohexol and Iothalamate can all been used to accurately measure the GFR.[1,4,19,21] Inulin is widely considered a gold standard measurement of the GFR.[4,22] The radioactive substances I^{125}-iothalamate, ^{51}Cr-Ethylenediaminetetraacetic acid (^{51}Cr-EDTA) and ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) have also been used as markers; they have the advantage over non-radioactive substances as they do not need lengthy urinary collections.[1,4,20,21] Although these substances are ideal filtration markers, using them is complex, time consuming and therefore they are impractical for clinical use.[19] Moreover, there are issues of safety with the handling of radioactive substances and the measured Glomerular Filtration Rate (mGFR) is not always concordant between exogenous markers.[19,20] The use of endogenous markers begins to overcome some of these problems.

1.2.2. Endogenous filtration markers

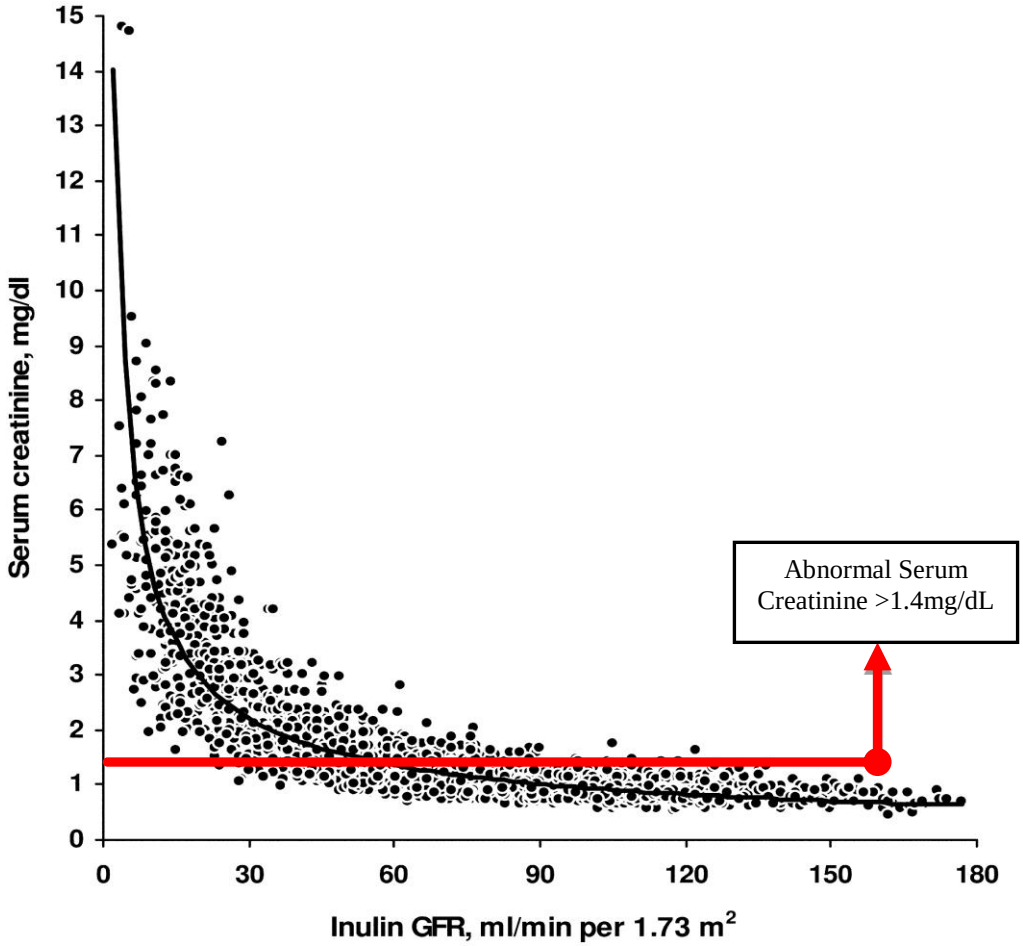
1.2.2.1. Urea

Elevated plasma urea was used initially as an indicator for renal impairment, but it is a poor marker of the level of renal function.[1,21] Plasma urea concentration can be affected by protein catabolism, protein intake, tissue breakdown, gastrointestinal haemorrhage and corticosteroid therapy; 40-50% of the filtered urea is also reabsorbed by the tubules.[1,21]

1.2.2.2. Creatinine

Serum creatinine is the marker most commonly used to measure renal function.[20] It is produced by muscle metabolism of phosphocreatine.[1,20,21] The production of creatinine is fairly constant but reflects overall muscle mass, therefore measurements underestimate the renal impairment in patients with low muscle mass.[1,4,20,21] The relationship between serum creatinine and the GFR is non-linear (**Figure 1.2**) with large changes in the GFR corresponding to small changes in the serum creatinine.[1,4,20] Therefore, the plasma creatinine may not rise until the GFR is <40mL/min/1.73m2.[1,4,20]

Figure 1.2 Relationship between serum creatinine and the GFR



From Botev *et al*., (2009)[22].

Serum measurements are therefore not ideal as measurements of renal function.[4] Creatinine clearance is a closer approximation of the GFR.[1] It relies upon the time consuming and often inaccurate 24-hour urine collection to calculate the urinary creatinine concentration.[1,21] Although this method improves upon the accuracy of measurement compared to serum creatinine measurements alone, it does have other major limitations.[1] Creatinine is not an ideal marker as 15% is actively secreted by the tubules leading to an overestimation of the GFR by 10-40% in normal individuals.[1,4,19-21] Other factors that affect creatinine excretion are dietary intake of creatinine, daily variations in creatinine generation, certain drugs (such Cimetidine and Trimethoprim) and different creatinine assay methods (Jaffé reaction and enzymatic methods).[1,4,19-21]

1.2.2.3. Cystatin C

Cystatin C, although not an ideal maker due to the fact it can be vary in patients with thyroid disease and malignancy, has shown promise as a potentially more accurate marker of renal impairment than serum creatinine especially in patients with GFRs between 40 and 70mL/min/1.73m^2.[19-21] Cystatin C has also shown promise as a possible risk marker for incident CKD.[23]

1.2.3. Estimation equations

Given the many limitations of the endogenous filtration markers, several equations have been formulated that utilise patient parameters to improve upon the estimation of the GFR.[4,20,21] These have been shown to be more accurate than serum creatinine alone.[4] Over a dozen such equations have been developed[4] but the Cockroft-Gault (CG) and the Modification of Diet in Renal Disease (MDRD) equations are the most widely used in clinical practice to calculate the estimated GFR (eGFR).[1,4,19-22]

1.2.3.1. The Cockcroft-Gault Equation

Developed in 1973, the CG equation was the first to be widely used in practice.[19,21,24] The equation was developed and calibrated by measuring the creatinine clearance (Ccr) of 249 men; a correction coefficient was developed later to estimate the Ccr in women.[19,22] The classic formula estimates the Ccr in (mL/min) rather than the GFR as it is not standardised per body-surface-area (BSA).[19,20,22,24] The CG formulae can however be adjusted for the BSA with the use of equations such as the Dubois and Dubois formulae allowing the CG equation to estimate the GFR.[25] The CG formula estimates the Ccr using the parameters of serum creatinine, age, weight and sex.[19-22,24] The CG equation does not adjust for the active

tubular secretion of creatinine hence it consistently overestimates the GFR (**Figure 1.3**).[19-21] Due to the inclusion of weight in the equation, the GFR is overestimated in obese patients or those with low protein diets.[1]

1.2.3.2. The Modification of Diet in Renal Disease Equation

The MDRD equation came later (1999) and is currently the recommended equation of choice in the UK.[6] The MDRD equation was created by analysis of the mGFR in 1628 participants with CKD using I^{125}-Iothalamate as a marker.[17] The formula estimates the GFR directly as is adjusted for the BSA.[17] The original equation used the serum creatinine, urea, albumin, age, sex and ethnicity as the input parameters.[17] The equation was then simplified to include just the serum creatinine, age, sex and ethnicity; this new equation was the simplified 4-variable MDRD.[4] Given the participants used to formulate the equation had pre-existing CKD, the equation should ideally only be used in patients with stage 3 CKD or worse ($\leq$60mL/min/1.73m^2).[4,21] As mentioned previously, the level of measured serum creatinine can be affected by the assay method used resulting in inter-laboratory variation.[21] Therefore, a modified 4-variable MDRD equation was formulated using a correction factor for standardised creatinine assays which are calibrated using 'gold standard' isotope dilution mass spectrometry (IDMS).[26] With this new equation, 91% of the estimated GFRs are within 30% of the mGFRs.[19] The MDRD equation tends to slightly underestimate the mGFR and this effect is worse for GFRs >60mL/min/1.73m^2 (**Figure 1.3**).[26] The formulae for both equations are presented below.

Cockroft-Gault equation[24]

$$Ccr = \left[\frac{(140 - age) \times weight}{72 \times Serum\ Creatinine}\right] \times 0.85\ (if\ female)$$

6-variable MDRD equation[4,17]

$$GFR = 170 \times (Serum\ Createnine^{-0.999}) \times (age^{-0.176}) \times (Serum\ Urea^{-0.170}) \times (Serum\ Albumin^{+0.318}) \times 0.762\ (if\ female)\ or \times 1.180\ (if\ black)$$

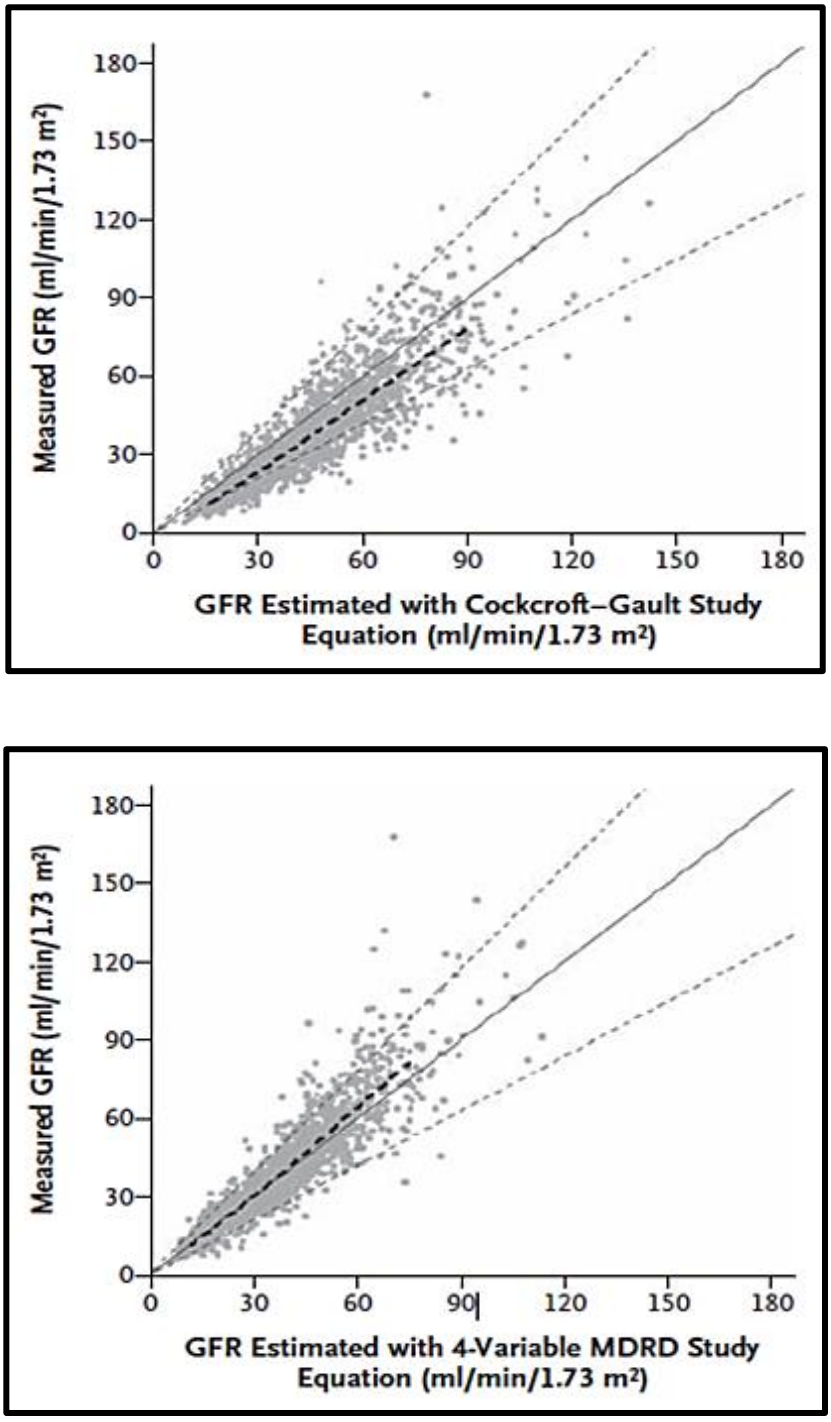
Simplified 4-variable MDRD equation[4,17]

$$GFR = 186 \times (Serum\ Createnine^{-1.154}) \times (age^{-0.203}) \times 0.742\ (if\ female)\ or \times 1.210\ (if\ black)$$

Modified 4-variable MDRD equation (IDMS-traceable)[26]

$$GFR = 175 \times (Serum\ Createnine^{-1.154}) \times (age^{-0.203}) \times 0.742\ (if\ female)\ or \times 1.210\ (if\ black)$$

Figure 1.3 Relationship between measured and estimated GFR for the MDRD and CG equations

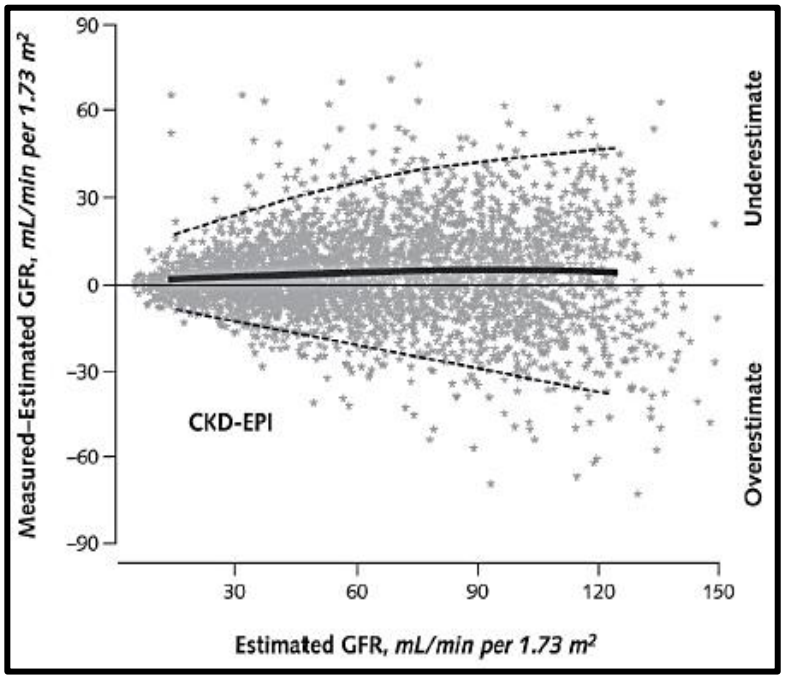


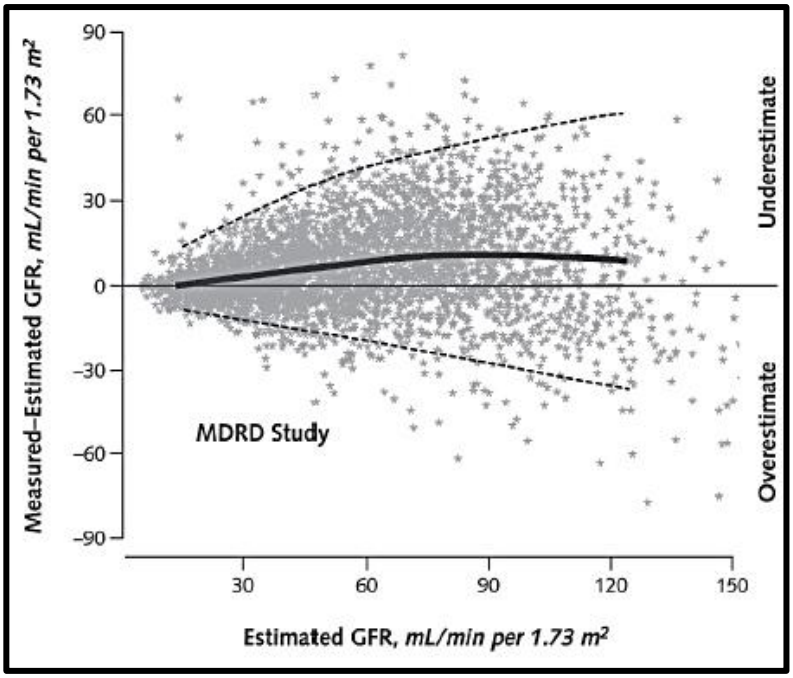
The GFR was measured in 1628 patients as the urinary clearance of [^{125}I] iothalamate and adjusted for body-surface area. The estimated GFR is expressed with the use of the MDRD study equation (R2=0.88) (bottom) and the Cockcroft–Gault equation (R2=0.83) (top). Each point represents the baseline measurement. The solid diagonal line represents the line of identity. The bold dashed line represents the fitted line with smoothing-splines function plotted from the 2.5 to the 97.5 percentile of estimated GFR. Thin dashed lines represent the difference of ±30 percent between estimated and measured GFR. Taken from Stevens *et al.*, (2006)[19].

1.2.3.3. Future estimation equations

Cystatin C has been gaining interest as a potential new marker for the measurement of the GFR.[19] Equations that estimate the GFR using serum cystatin C have been developed for both children and adults.[27,28] Moreover, the Chronic Kidney Disease - Epidemiology (CKD-EPI) collaboration formulated a new equation to estimate the GFR from the serum creatinine.[29] In recent studies, the CKD-EPI equation has been shown to perform better than the MDRD equation (especially when the GFR is >60ml/min/1.73m^2, **Figure 1.4**) and it is hoped that it will eventually replace the MDRD formula given this higher levels of accuracy in patients with well-reserved renal function.[29]

Figure 1.4 Relationship between the measured and estimated GFR for the CKD-EPI and MDRD equations





Taken from Levey *et al.*, (2009)[29].

1.3. Epidemiology of Chronic Kidney Disease

CKD is now a global public health problem[4] and the number of patients with CKD is also increasing rapidly.[4,6,30] CKD is strongly associated with age and with a number of other co-morbid conditions.[4,5,31] Moreover, CKD is now regarded an independent risk factor for cardiovascular disease (CVD).[3,5] Equally, CVD contributes to 50% of the mortality seen in CKD.[5,6] Patients with progressive CKD eventually have ESRD requiring they undergo renal replacement therapy (RRT).[4] Not only does this have significant implications for a patient's quality of life, it also carries an annual mortality of 20%.[3] RRT also exerts a heavy financial cost on the NHS budget.[3] Finally, patients on RRT have a life expectancy from 2.7-3.9 years shorter if aged 60 to 64 years increasing to 7.1-11.5 years shorter if aged 40 to 44 years than their healthy age-matched counterparts.[4] Given the increase in the prevalence CKD, the number of patients with ESRD has also increased, doubling in the past decade to 100 patients per million.[4,31,32]

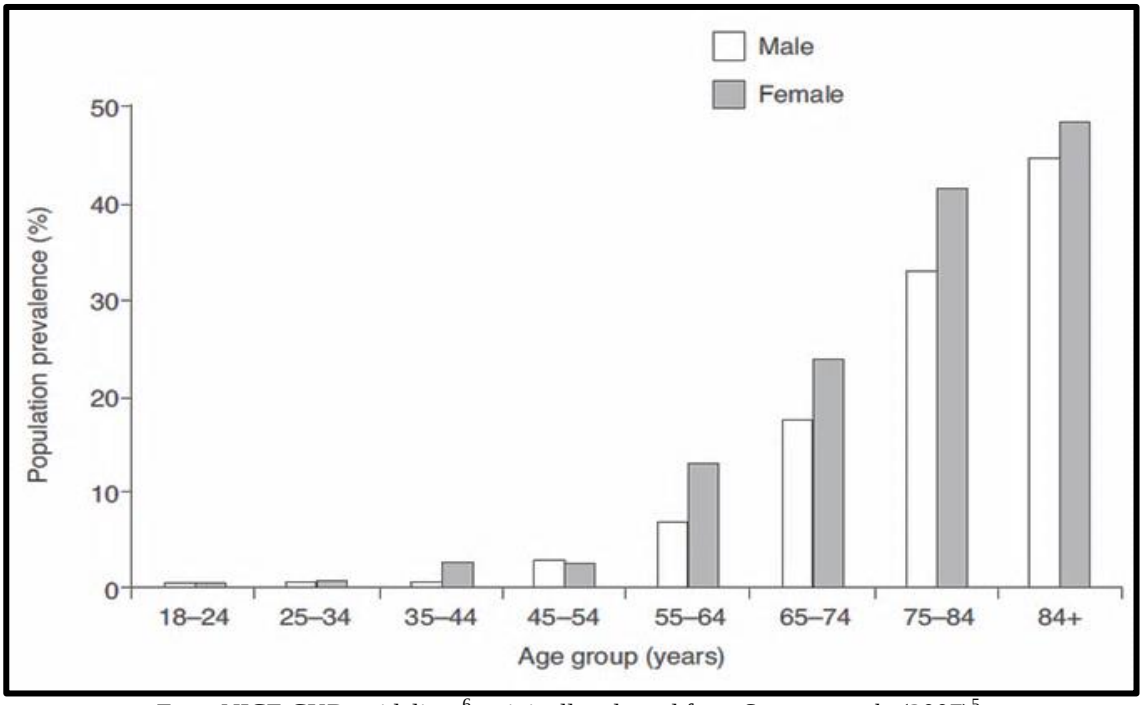
1.3.1. Prevalence and associations

The NEw Opportunities for EaRly Intervention by Computerised Assessment (NEOERICA) study found the age-standardised prevalence of stage 3 to 5 CKD to be 8.5% (5.8% in males and 10.6% in females) in the UK.[5] In addition, the prevalence of CKD is expected to rise at a rate of 5-8% per year.[32] Similarly, the prevalence of overall CKD in the US, using estimates from the National Health and Nutrition Examination Surveys (NHANES), increased from 10% to 13% between 1988-1994 and 1999-2004 respectively.[4,6,7] Comparable CKD prevalence figures have been reported in other developed countries (such as Australia, Netherlands, Korea, China and Mexico) with the prevalence being as high as 20% (in Japan).[3,31,33-37]

1.3.1.1. Age, gender and the prevalence of CKD

Typically, women have a higher prevalence of CKD compared to men; this effect stays true even between different ethnic groups.[31] The prevalence of CKD rises remarkably with age, increasing exponentially as shown in **Figure 1.5**.[5] The prevalence of stage 3 to 5 CKD in patients aged 65 years and has been reported to be approximately 23% to 36%.[31] The increase in CKD prevalence with age is evident regardless of the population in question or the estimation equation used.[3-5,31,33-37] Given that the prevalence of CKD rises exponentially with age, the increase in the proportion of elderly people within the UK population[8] will no doubt contribute significantly to the rising number of CKD patients.

Figure 1.5 Age-standardised stage 3 to 5 CKD prevalence in the UK



From NICE CKD guidelines[6], originally adapted from Stevens *et al*., (2007)[5].

1.3.1.2. Co-morbidity and the prevalence of CKD

There has been an increase in the prevalence of co-morbidities known to cause CKD such as type II diabetes.[5,6] Diabetes mellitus (DM) is known to cause 40% of all new cases of CKD.[2] Equally, the prevalence of the DM increases as the GFR decreases; a similar picture is seen with hypertension (HTN).[4,5] CKD prevalence is known to be higher in countries with high levels of type II DM and HTN.[32] The burden of co-morbidity in CKD is most evident in relation to CVD as almost 75% of patients with stage 3 to 5 CKD have some evidence of CVD.[38] This is likely due to the fact that CKD and CVD share many common risk factors (such as HTN, DM, smoking and dyslipidaemia).[39] Other factors known to affect CKD prevalence are; ethnicity, genetic inheritance, socio-economic factors, levels of nephrotoxic drug use and infections.[3]

1.3.1.3. CKD awareness

Given the asymptomatic nature of the disease, CKD patients are often under-diagnosed or unaware of their condition.[6,40] In fact, over 90% of CKD patients may be unknown to renal or primary care services.[6,38]

Chapter 2. Causes and Consequences of Chronic Kidney Disease

2.1. Common Causes of Chronic Kidney Disease

The term CKD describes chronic kidney damage that can be initiated by a myriad of diverse conditions.[16] Renal disease causes damage to various structures within the kidney, which over time lead to decreasing renal function and eventually to ESRD.[16] They can be broadly classified into the following groups; glomerular, tubulointerstitial, vascular, inherited and obstructive diseases.[16] There are differences however as to the prevalence of the various pathologies with DM and HTN being prominent causes of renal dysfunction.[3] Equally, the prevalence of the various pathologies also varies between different populations as shown in **Table 2.1**.[3]

Table 2.1 The incidence of different causes of CKD in patients undergoing renal replacement therapy

Diagnosis	UK		Netherlands		Norway		USA		Australia
	%	*pmp*	%	*pmp*	%	*pmp*	%	*pmp*	%
GN	**11.7**	12.6	**7.1**	8.6	**19.5**	21.8	**6.7**	24	**22**
PN	**6.7**	7.2	**3.2**	3.9	**6.8**	7.6	N/A	N/A	N/A
Diabetes	**20.6**	22.2	**18.1**	28.1	**18.2**	20.3	**44**	153	**34**
RVD	**4.4**	4.7	**13.6**	16.4	**2.6**	2.9	N/A	N/A	N/A
HTN	**5.2**	5.6	**11.3**	13.6	**22.7**	25.4	**27.9**	99	**15**
APKD	**6.0**	6.5	**4.5**	5.5	**6.6**	7.3	**2.4**	9	**6**
Urologic	N/A	N/A	N/A	N/A	N/A	N/A	**1.4**	5	N/A
Other	**15.3**	16.5	**17.6**	21.2	**20.1**	22.4	**12.7**	45	**10**
Unknown	**21.2**	22.7	**11.8**	14.2	**3.6**	4	**3.9**	14	**8**
Missing data	**8.8**	9.4	**12.9**	15.6	**0**	0	**1.1**	2	**0**

All data from 2008; %, percentage of incident renal replacement population; pmp, rates per million population; HTN, hypertension; APKD, adult polycystic kidney disease; GN, glomerulonephritis; PN, chronic pyelonephritis; RVD, renovascular disease; N/A, not applicable. Modified from Evans & Taal., (2011)[3].

2.1.1. Diabetic nephropathy

Diabetes mellitus is now the most common cause of ESRD.[2,30] There are four types DM, of which type 1 and type 2 are the most prevalent.[16] Type 1 DM is caused by an autoimmune reaction to the pancreatic β-islet cells leading to a lack of insulin production and usually presents in childhood.[16] Type 1 DM leads to nephropathy in 15% of patients with the condition.[41] Type 2 DM is a metabolic disorder caused by a gradual resistance to insulin leading to glucose dysregulation.[16] Type 2 DM typically affects patients over the age of 40 and leads to nephropathy in a 20-40% of patients.[41,42] Overall, about 31% of the CKD cases are due to type 2 and 6% are due to type 1 DM.[41] As well as being a risk factor for CKD[43], DM is a major risk factor for CVD as it markedly accelerates atherosclerosis.[16]

Regardless of the type of DM, the underlying mechanism of diabetic nephropathy is hyperglycaemia.[1,44,45] Glucose reacts with proteins in blood to from protein complexes known as advanced glycosylated end-products (AGEs).[45] The AGEs are able to cause cross linking between matrix proteins consequently inhibiting proteolysis, encouraging vessel wall stiffness and impeding protein function.[45] The formation of AGEs often occurs in a setting of HTN and dyslipidaemia, both of which often coexist in diabetic patients.[41,45] These factors accelerate endothelial dysfunction.[41,45] Kidney function is reliant upon the intricate glomerular micro-vasculature[1,41] so alterations to this micro-vascular environment by hyperglycaemic damage results in the loss of the normal glomerular function.[41,45] The glomerulus loses its ability to selectively filter plasma and initially, micro-protein leak occurs followed later on by macro-protein leak if treatment is not initiated.[41] The presence of persistent microalbuminuria, which acts as an important marker of the disease, is a powerful indicator of CKD progression.[46-48]

2.1.2. Hypertensive nephropathy

The term hypertensive nephropathy is used to describe kidney damage secondary to HTN.[49,50] A systolic blood pressure (BP) of >140/90mmHg is considered hypertensive.[4,16] HTN is graded in accordance to severity and cause.[16] Primary HTN is diagnosed when no cause is found for the elevated BP.[16] Given the kidneys role in the regulation of BP, it is difficult to ascertain exactly to what extent HTN directly contributes to kidney damage.[1,49] HTN is more prevalent in males, Asians/African-Americans and in older patients.[1] Psychological stress, low physical activity, obesity, a high salt diet and excessive alcohol consumption are all risk factors for HTN.[1] Like DM, HTN is also strongly associated with CVD.[1]

Hypertensive nephrosclerosis describes a characteristic set of histological changes in the pre-glomerular vessels and is therefore usually a diagnosis of exclusion.[1,49] Primarily, there is myointimal hyperplasia of the interlobular and afferent arterioles.[50] This is accompanied by the hyalinization of the afferent arteriole leading to the eventual collapse of the glomerular tuft with resultant global glomerulosclerosis.[50] The underlying pathophysiological mechanism is one of glomerular ischaemia as a result of arteriolar narrowing, myogenic reflexes and the tubuloglomerular feedback mechanism in response to the increased glomerular BP.[1,50] As the entire nephron derives its blood supply from the efferent glomerular vessels, tubulointersitial ischaemia becomes inevitable.[1] The eventual outcome is one of tubular atrophy and interstitial fibrosis; nephron over time with eventually leads to ESRD.[1] HTN is the second most common cause of ESRD after DM.[1,49,50]

2.1.3. Chronic glomerulonephritis

Glomerulonephritis (GN) is a term used to describe a number of inflammatory and non-inflammatory conditions that affect the glomerulus.[1] Primary GN has effects restricted to the kidney whilst secondary GN has renal and systemic effects.[1] GN is classified according to the histological appearance of the renal pathology.[1] The histological descriptions detail the disease manifestation at the individual glomerular and global level.[1] There are numerous causes of GN but the differing conditions share a common autoimmune aetiology.[1]

Immune dysregulation, through inappropriate interaction with self or foreign antigens, initiates an inflammatory response within the glomerular structure resulting in renal damage.[1] The severity of glomerular injury is dependent upon the degree to which the initial autoimmune event recruits inflammatory mediators.[1] Inflammatory cells, complement components, cytokines and other soluble factors of inflammation all play a role in the pathogenesis of the disease.[1] Damage to the glomerular structure, especially the basement membrane, leads to proteinuria.[1,51] Where inflammation leads to the proliferation of endothelial or mesangial cells, microscopic haematuria develops.[51] Thus GN may present with proteinuria, haematuria or both and when severe frank nephrotic and/or nephritic syndrome develops.[1,51] The result of the continued damage by inflammation is one of progressive renal failure due to glomerulosclerosis and associated interstitial fibrosis.[1] GN is the third most common cause of ESRD accounting for 10-15% of cases.[16]

2.1.4. Chronic tubulointerstitial nephritis

Chronic tubulointerstitial nephritis (TIN), more commonly referred to as simply chronic interstitial nephritis is a histological diagnosis characterised by progressive fibrosis of the

tubules and the interstitium.[1] There are numerous primary and secondary causes of TIN.[1] Some of the secondary causes of TIN such as GN, DM and HTN are detailed above. The common causes of primary TIN are analgesic drugs (e.g. NSAIDs), vesicouretic reflux, chronic urinary obstruction, sickle cell nephropathy, urate nephropathy and heavy metal intoxication.[1,16]

The damage caused by these primary pathologies all act to initiate an inflammatory response within the renal interstitium.[1] Injury to the tubule or peritubular capillaries results in the production of chemotactic and adhesive factors leads to the accumulation of macrophages and T-cells.[1] The macrophages and tubular cells release a variety of growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) stimulating fibroblast activation and proliferation.[1] Activated fibroblasts will increase collagen production resulting in interstitial fibrosis.[1] Nephron loss is thought to be a result of disruption to the tubular segment and periglomerular fibrosis with obstruction of filtrate from Bowman's space.[1] Loss of the tubular function and damage to the glomerulus usually leads non-nephrotic proteinuria with poly/nocturia.[1] Primary chronic TIN causes relatively few cases of ESRD with secondary TIN accounting for most cases.[1]

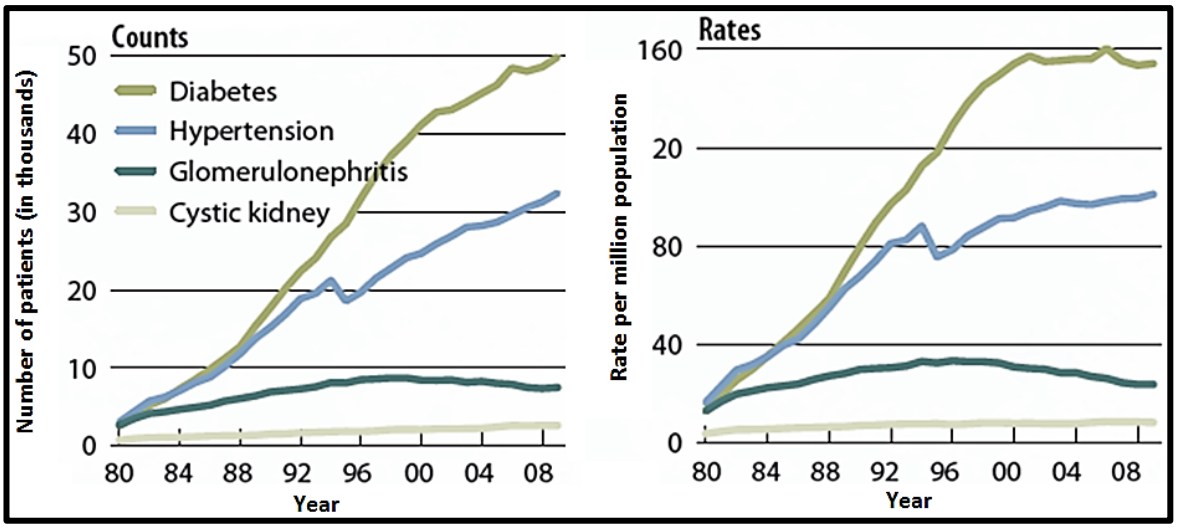
2.1.5. Inherited kidney disease

Adult polycystic kidney disease (APDK) is the most common monogenetic cause of CKD affecting 1 in 400 to 1 in 1000 individuals.[1,3] It is a multisystem disorder typically affecting both kidneys.[1] It is characterised by the formation of multiple cysts mainly in the kidney but they can occur in other organs.[1] APKD is autosomal dominant with 100% penetration and usually presents in the third or fourth decade.[1,3]

Polycystic kidney disease gene-1 (PKD-1) is responsible for 80-90% of APKD with PKD-2 accounting for the majority of the remaining cases.[1,51] Haematuria and HTN, sometimes accompanied by loin pain, are the hallmarks of the disease.[16] Kidney damage in APKD is due to preglomerular vascular sclerosis accompanied by epithelial hyperplasia and interstitial fibrosis.[1] Preglomerular vascular sclerosis is thought to result from HTN which if left untreated leads to ESRD.[1] The outcome for APKD can be variable but 50% of patients reach ESRD by the age of 57-73 years.[1]

Figure 2.1 shows results from the US Renal Data System (USRDS) annual data report (2011) showing the relative incidence of the aforementioned pathologies as present in patients with ESRD.

Figure 2.1 Incidence counts and adjusted rates of ESRD by primary prognosis



Modified from volume two, chapter one of the USRDS 2011 Atlas of CKD and ESRD.[30]

2.2. Pathological Mechanisms of Renal Disease

Regardless of the underlying pathology, progressive nephropathies share a common disease progression mechanism that leads eventually to ESRD.[52] Nephron loss, initially caused by the various pathologies, leads to the initiation of renal adaptation mechanisms in an attempt to increase the filtration capacity of the remaining nephrons.[42,48,52,53] Where nephron loss is significant, the afferent and efferent arteriolar tone in the remaining nephrons decreases but the decrease in tone is more marked in the afferent arteriole.[42,48] This has the effect of increasing the glomerular capillary hydrostatic pressure which in turn increases the single-nephron GFR (SNGFR) as demonstrated by the formula below.[1,42,48,52,53]

$$SNGFR = Kf\left[\left(Pgs - Pbs\right) - \left(\Pi gc - \Pi bs\right)\right]^{1}$$

K_f = Ultrafiltration co-efficient; P_{gs}= Glomerular capillary hydrostatic pressure (Normal = 45mmHg); P_{bs} = Bowman's space hydrostatic pressure (Normal = 10mmHg); π_{gc} = Glomerular oncotic pressure (Normal = 25 mmHg);π_{bs}= Bowman's space oncotic pressure (Normal = 0 mmHg).

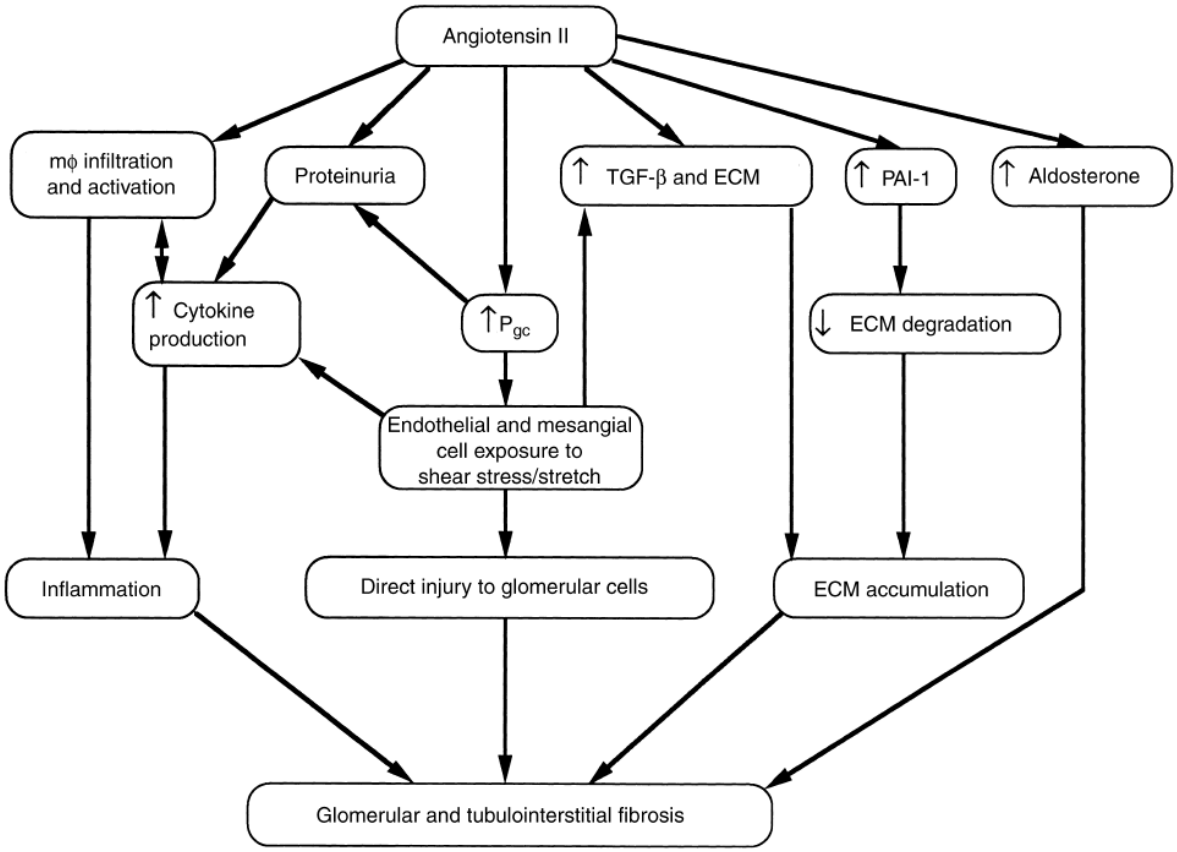
The increase in SNGFR is often referred to as glomerular hyperfiltration whilst the subsequent increase in the glomerular capillary hydrostatic pressure is called glomerular hypertension (GH).[52] When the GFR falls below 50% of normal, the decline in GFR can be inevitable due to the adaptive changes set in motion by the remaining nephrons.[53] Studies show that attenuating these adaptation mechanisms leads do a decrease or cessation of further renal damage.[42,48,52,54]

2.2.1. Glomerular hypertension

Glomerular hypertension lies at the centre of the pathophysiological mechanism of renal disease progression.[52-54] GH is distinct from systemic HTN.[53] Drugs that decrease systemic

HTN have relatively little effect on GH and do not slow renal disease progression.[53] GH is maintained by the Renin-Angiotensin-Aldosterone-System (RAAS), the effector of which is the angiotensin-II peptide.[52,53] Angiotensin-II is the central mediator of the glomerular haemodynamic changes (**Figure 2.2**), but has also been found to cause numerous detrimental non-haemodynamic changes.[52,53,55-57] Glomerular haemodynamic changes also affect the permeability of the glomerular wall and can lead to proteinuria.[56]

Figure 2.2 Effects of Angiotensin-II in renal injury



ECM, extracellular matrix; mϕ, macrophage; PAI-1, plasminogen activator inhibitor-1; Pgc, glomerular capillary hydraulic pressure; TGF-β, transforming growth factor-β. Taken from Taal and Brenner (2000)[57].

2.2.2. Proteinuria

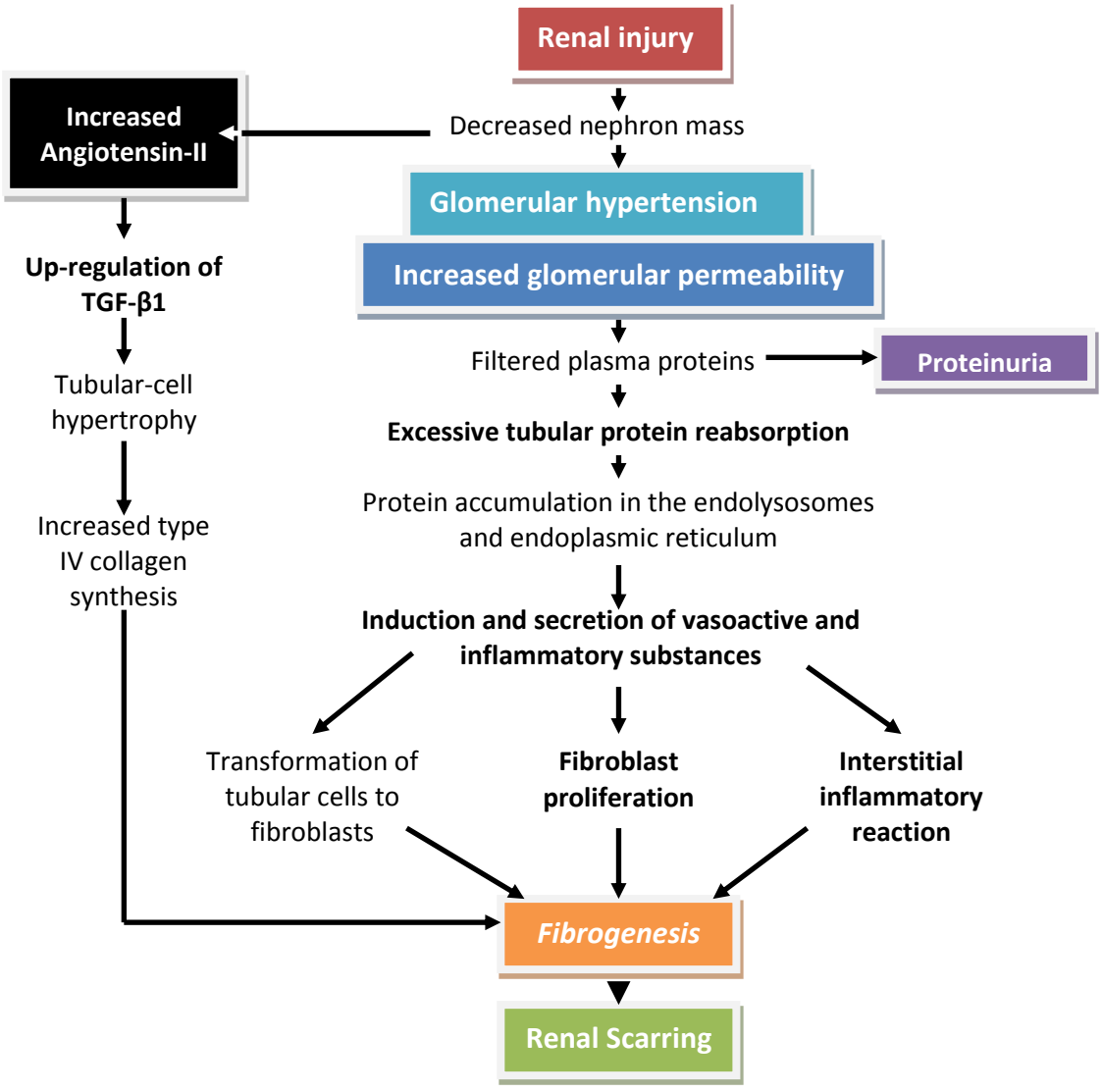
In the normal kidney, complex filtration mechanisms are employed to ensure that proteins do not leak into Bowmans space.[1] The process begins at the endothelial lined, fenestrated capillaries (50-100nm) which work in conjunction with the glomerular basement membrane and the visceral epithelial cells (podocytes) with their slit like foot-processes (30-40nm) to minimise protein leak.[1] Podocyte foot-processes have interconnected proteins which form the slit-diaphragm.[1,55] This series of ever narrowing filtration slits effectively exclude substances with a radius >4nm.[1,52,56] A negative charge at the glomerular membrane means that that anionic substances with an effective radius >3nm are largely removed from the filtrate (e.g. Albumin = 3.6nm).[1,52,56] Proteins with an effective radius of <3nm are not effectively excluded from the filtrate but are reabsorbed almost completely by the tubular epithelium.[56] Proteinuria therefore can result by two different mechanisms, either by the increased permeability to proteins at the glomerulus due changes to the membrane structure/charge or at the tubular epithelium due to impairment of protein reabsorption.[56]

Initially, selective proteinuria, consisting of low molecular (<3nm) and intermediate (mainly albumin) weight proteins, occurs as the glomerular membrane becomes leaky and reabsorption mechanisms are overwhelmed.[56] However, worsening membrane permeability, accumulating tubular toxic damage and the saturation of reabsorption mechanisms leads to non-selective proteinuria with the leakage of high molecular weight proteins.[56]

Proteinuria is a powerful marker for disease progression.[4,6,42,48,53,58,59] However, it is more than just a marker for disease progression; proteinuria directly damages the renal

system.[1,53] Filtered plasma proteins initiate an inflammatory process within the glomerulus and the tubularinterstitium (**Figure 2.3**).[48,53] Reducing proteinuria therefore slows the decline of renal function.[60,61]

Figure 2.3 Effects of filtered proteins on the progression of renal injury



Adapted from Remuzzi and Bertani (1998)[48].

2.2.3. Glomerulosclerosis

Glomerulosclerosis (GS) is the progressive destruction of the delicate glomerular structure and is the endpoint of many nephropathies.[1] Insult to the glomerular endothelium by various mechanisms (haemodynamic, immune and metabolic) initiates an inflammatory response.[1,32] Proinflammatory compounds lead to the activation and proliferation of the mesangial cells.[32] It is thought that abnormal permeability to plasma proteins can initiate pathological interactions with mesangial cells.[62] These cells secrete excessive amounts of extracellular matrix (ECM) under the influence of profibrotic factors such as TGF-β1.[1,32] Angiotensin-II has numerous direct actions on the mesangial cells and is closely linked with the TGF-β1 pathway.[63] Excessive ECM production under the influence of TGF-β1 and PDGF leads to irreversible GS.[1]

Podocyte injury also plays a key role in the pathogenesis of the disease[55] with a reduction in the number of podocytes resulting in the exposure of "bare" glomerular basement membrane.[55,64] The denuded capillaries form adhesions to Bowmans capsule, known as tuft-to-capsule lesions, which have a tendency to spread and destroy any capillary loops caught within[64]. Where this occurs, the lack of blood supply to the tubules leads to tubular atrophy and interstitial fibrosis.[1]

2.2.4. Tubulointerstitial fibrosis

Tubulointerstitial fibrosis (TIF) like GS begins due to cell injury and is a common occurrence in many renal diseases.[1,32,65] Like GS, the initiators of injury can be of immune, haemodynamic or metabolic origin but exogenous substances (e.g. NSAIDs) can also lead to tubular injury.[1] Cell injury induces an inflammatory response which in turn leads to the production of proinflammatory mediators.[1] Inflammation also leads to tubular cell atrophy

and apoptosis.[1,32] There is recruitment and activation of monocytes which, in conjunction with tubular cells, secrete profibrotic factors of which TGF-β and PDGF are the most important.[1,32,65] Autacoids such as endothelin and the peptide hormone angiotensin-II (**Figure 2.2**) have also been implicated in renal scarring.[32] Fibroblasts become stimulated and secrete excessive amounts of ECM (mainly of type I and III collagen) which accumulates leading to interstitial fibrosis.[1,32,65] If the ECM is not degraded by proteolytic pathways, the fibrotic process becomes irreversible with resultant renal scarring and loss of function.[1]

2.2.5. Vascular sclerosis

Vascular sclerosis (VS) describes an atherosclerotic process that occurs within the delicate renal arterioles.[1,66] Changes in the arterioles of VS are akin to those seen in atherosclerosis of large vessels.[1] Therefore, VS can be seen as a marker of wider pathology within the vascular tree. Moreover, risk factors for VS (e.g. HTN and DM) are similar to those for atherosclerosis.[1] Progressive hyalinosis, especially of the afferent arteriole, is implicated in the changes seen in diabetic GS.[1]

In VS, narrowing of the afferent arteriole reduces the blood flow to the glomerulus hence the rest of the nephron.[1,66] This leads to ischaemic changes within the renal tubules which, as a result of the ensuing hypoxia, undergo atrophy, induce an inflammatory response and initiate fibrogenic responses.[1,66] The distal part of the proximal convoluted tubule and the thick ascending limp of the loop of Henle are especially vulnerable due to their normally borderline hypoxic environment.[66] This process in exacerbated by damage that can also occurs at the efferent glomerular arteriole and at the peritubular capillaries.[1,66]

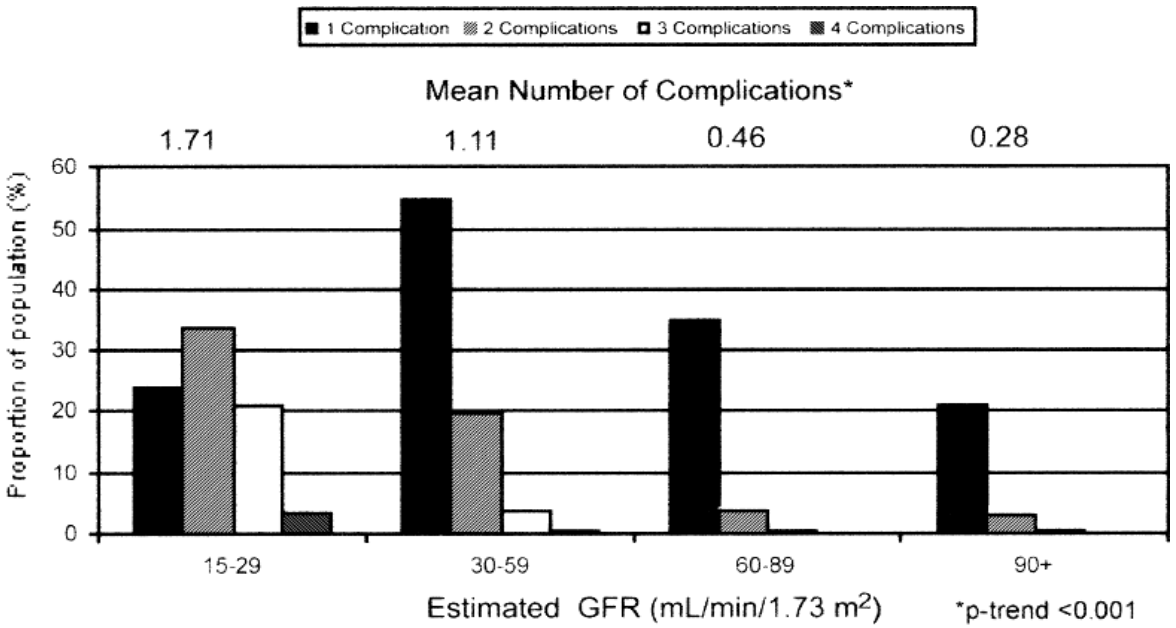
Angiotensin-II and endothelin cause intrarenal vasoconstriction and are attributed to the establishment of the ischaemic milieu.[66]

2.3. Complications of Chronic Kidney Disease

In addition to their vital function as filtration organs, the kidneys are also involved in blood pressure control, erythropoiesis, calcium metabolism and acid base balance.[16] Their involvement in disease therefore has wide ranging detrimental effects upon nearly all other body systems.[1]

The early stages of CKD are usually completely asymptomatic.[1,2,16] Symptoms are not usually apparent until stage 3 CKD.[1,2,4] However, as renal function declines, other symptoms and signs become evident with severe manifestations being the result of ESRD.[1,16] The number complications associated with CKD increase with worsening CKD (**Figure 2.4**).[4]

Figure 2.4 Number of complications associated with stage 1-4 CKD



Estimated distribution of the number of complications, by category of estimated GFR among participants age ≥20 years in NHANES III, 1988 to 1994. These estimates are not adjusted for age, the mean of which is 33 years higher at an estimated GFR of 15 to 29 mL/min/1.73 m^2 than at an estimated GFR of ≥90 mL/min/1.73 m^2. Taken from the NKF - KDOQI: Clinical practice guidelines for Chronic Kidney Disease: Evaluation, classification and stratification (2002).[4]

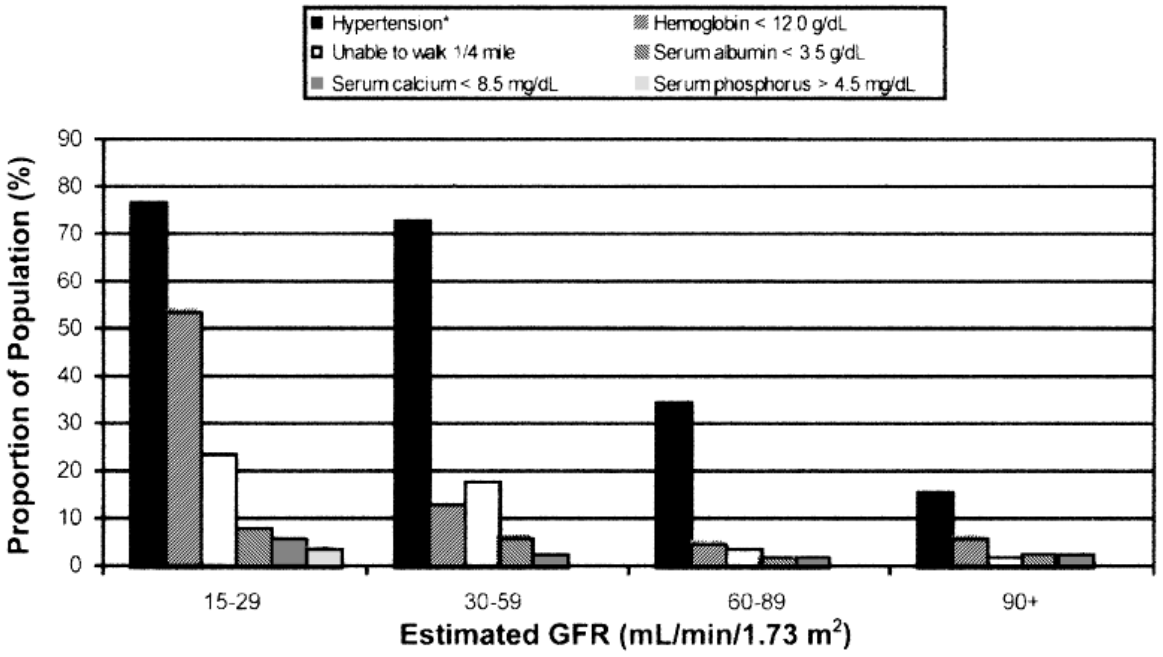
2.3.1. Hypertension

Hypertension is a common, early sign of CKD (**Figure 2.5**).[4] The prevalence of HTN can be as high as 75% in patients within stage 4 CKD.[4] HTN is both a cause and a complication of CKD.[4] HTN is a risk factor for both CKD and CVD.[4,52] A vicious spiral can develop where worsening CKD leads to an increase in BP which in turn leads to worsening CKD.[52] Several neurohormonal changes occur in worsening CKD that maintain and ensure worsening HTN.[52]

The RAAS is the most important system in the control of BP.[52] As CKD worsens, the net sum of renin production across the kidney increases hence there is an increase in the effector peptide angiotensin-II which can lead to further renal injury (*see section 2.2.*1).[52]

HTN may also be the result of increased activity in the sympathetic nervous system.[52] Treating HTN reduces the rate of renal function decline.[59,60,67]

Figure 2.5 Estimated prevalence of select complications in stage 1-4 CKD



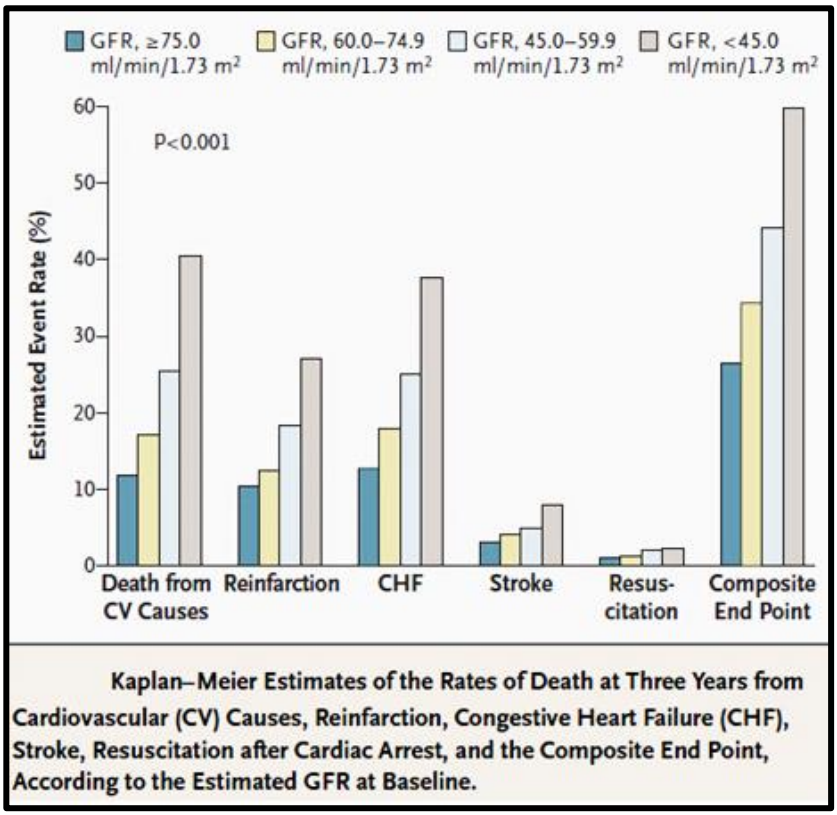
Estimated prevalence of selected complications, by category of estimated GFR, among participants age ≥20 years in NHANES III, 1988 to 1994. These estimates are not adjusted for age, the mean of which is 33 years higher at an estimated GFR of 15 to 29 mL/min/1.73 m^2 than at an estimated GFR of ≥90 mL/min/1.73 m^2. Taken from the Taken from the NKF - KDOQI: Clinical practice guidelines for Chronic Kidney Disease: Evaluation, classification and stratification (2002).[4]

2.3.2. Cardiovascular disease

Cardiovascular disease is the principal cause of death in patients with CKD.[52] Patients are much more likely to die of CVD than they are of CKD.[4,68] Up to 50% of all deaths in ESRD patients are due to CVD, a prevalence of mortality 15 times higher than in the general population.[4,52,68] A relatively small decline in the GFR (30%) results in a significant increase in risk of CVD.[52] The relative risk for CVD increases greatly for each

successfully worse stage of CKD.[68,69] The risk is more evident in patients with pre-existing CVD, even mild renal disease in such patients should be considered a major risk factor for future heart disease (**Figure 2.6**).[70]

Figure 2.6 Cardiovascular pathology with worsening eGFR in patients with a previous acute Myocardial Infarction (MI)



Taken from Anavekar *et al*., (2004)[70].

CKD risk factors such as DM, HTN, obesity, dyslipidaemia and smoking are also risk factors for CVD.[52,68] Furthermore, where CKD and CVD coexist, the prevalence of associated risk factors are also higher.[4] A number of factors, such as calcium, phosphate and parathyroid hormone, which have been implicated as risk factors for CVD all become raised with worsening CKD.[4,68] Moreover, traditional CKD risk factors, such as albuminuria, have been shown to be associated with poorer cardiovascular outcomes.[4,52,68]

Finally, other consequences of CKD such as uraemia, hypercoagulation, increased extracellular volume and anaemia also have a negative impact upon cardiovascular health.[52,71] The most common clinical consequences of CVD in CKD patients are due to cardiomyopathy or ischaemic heart disease,[52] which can lead to cardiac failure with poor outcomes for the patient.[68]

2.3.3. Anaemia

Anaemia is defined by the World Health Organisation (WHO) as a haemoglobin (Hb) value of <13.0g/dL in males and <12.0 g/dL in females but these values are based on physiologically normal individuals.[72] The kidneys are responsible for inducing the production of red blood cells by the bone marrow[16,73] through the secretion of erythropoietin (EPO).[52] Anaemia occurs in CKD because worsening renal damage decreases the production of EPO in turn decreasing erythropoiesis.[1,52] There is no absolute level of renal disease at which anaemia develops but in general, anaemia is evident at GFRs <35ml/min/1.73m^2 (**Figure 2.5**).[1] Other factors, such as increased red blood cell haemolysis and decreased red blood cell survival, may contribute to the anaemic processes present in CKD patients.[52]

2.3.4. Platelet dysfunction and coagulation defects

CKD patients display a number of abnormalities in platelet adhesion, aggregation, coagulation and fibrinolysis.[1,52] CKD patients can therefore be precariously balanced at a saddle point between an increased risk of haemorrhage and/or thrombosis.[52]

The most frequent manifestation of platelet and coagulation defects is hypercoagulability leading to vascular access thrombosis.[1] Bleeding occurs in uraemic patients and is

normally minor presenting as petechia, ecchymosis and epistaxis.[1] However, major gastrointestinal (GI) bleeding occurs with greater frequency and severity in uraemic patients and is the second leading cause of death in acute renal failure.[52]

2.3.5. Chronic Kidney Disease – Mineral bone disorder

CKD mineral bone disorder (CKD-MBD, previously renal osteodystrophy) is an overarching term that covers a variety of skeletal abnormalities which are the result of high or low bone turnover.[1,52] In addition, disturbances of mineral metabolism ensue almost universally during the course of CKD (**Figure 2.5**).[1] This is because the kidneys play a critical role in calcium and phosphate homeostasis.[1]

CKD-MBD is often a silent condition presenting symptomatically only when severe.[1] Common symptoms include joint pain, bone pain, pruritus and muscle weakness.[1,52] Extra-skeletal manifestations of renal osteodystrophy are the result of high levels of calcium and phosphate which accumulate within various body tissues.[1,52] Calcification of the vascular system, joints, skin, lungs and even the ocular tissues can occur.[52] Calcific uraemic arteriolopathy (calciphylaxis) is a severe manifestation of metastatic calcification.[1,52]

2.3.6. Uraemia

Uraemia is caused by the kidneys inability to excrete waste but not all renal failure patients are uraemic.[52] This stems from the fact the uremic toxins originate from dietary proteins.[52] Therefore, uraemia can develop in patients with moderate CKD but have high protein intake or not at all if they have low protein intake.[52] Uraemic complications, which occur due to the retention of unfiltered waste products, affect nearly every system in the body (**Table 2.2**).[52]

Table 2.2 Systemic complications of uraemia

Central Nervous System	Daytime somnolence & inattention Imprecise memory & slurred speech Asterixis & myclonus Seizures Disorientation and confusion
Peripheral Nervous System	Sensorimotor peripheral neuropathy Restless leg syndrome Muscle fatigue & cramping Hiccough
Cardiovascular	Accelerated atherosclerosis Cardiomyopathy Pericarditis
Pulmonary	Atypical pulmonary oedema Pneumonitis Fibrinous pleuritis
Gastrointestinal	Anorexia, nausea & vomiting Stomatitis, gingivitis & parotitis Gastritis, duodenitis & enterocolitis Pancreatitis Ascites
Dermatological	Pruritus Dystrophic calcification Brown pigmentation
Haematological	Anaemia Haemorrhagic diathesis (e.g. peptic ulcer) Impaired immunity
Endocrine	Secondary hyperparathyroidism Insulin resistance Type IV hyperlipidaemia Testicular atrophy & ovarian dysfunction Altered peripheral thyroxin metabolism
Ophthalmic	Conjunctival and corneal calcifications

Modified from Brenner & Rector's The Kidney 7th ed. Vol 2 (2004).[52]

2.3.7. Nervous system dysfunction

Numerous abnormalities of the nervous system, especially the peripheral nervous system, occur in CKD patients; most usually manifest in ESRD and are related to uraemia (**Table 2.2**).[1,52] Uraemic patients often have a sensorimotor peripheral polyneuropathy with a predilection for the lower extremities.[52] Restless leg syndrome can be present in up to 40% of CKD patients.[52] Often dysesthesia, loss of deep tendon reflexes and impaired vibration sense occur early in CKD.[52]

2.3.8. Endocrine effects

In addition to the effects on the parathyroid gland and changes to erythropoietin production, numerous other endocrine changes occur in CKD. The dysfunction seen in the endocrine systems are attributable to uraemia and changes in renal clearance (**Table 2.2**).[52] Uraemic toxins may act by inhibiting or promoting the release of an inhibitor (e.g. dopamine or binders of insulin like growth factor 1 (IGF-1)), promoting hormone release (e.g. testosterone), affect enzymes metabolism (e.g. cytochrome P-450) or induce end-organ resistance (e.g. insulin).[52]

2.3.9. Dermatological and muscle effects

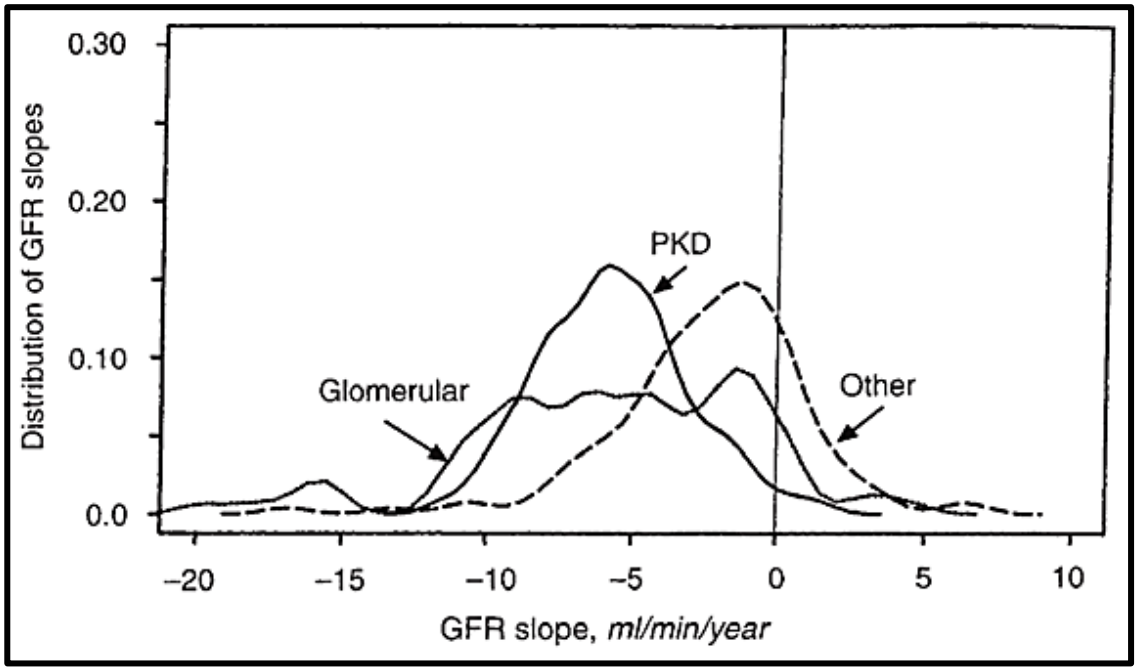
Several dermatological complications occur commonly in uraemia (**Table 2.2**) and are a source of discomfort for ESRD patients.[1] Diffuse brown pigmentation, xerosis with marked pruritus and, rarely, bullous eruptions are possible cutaneous manifestations of renal disease.[1] Uraemic myopathy is a common cause of muscle weakness in ESRD patients with uraemic toxins being implicated in the pathogenesis.[74] Uraemic myopathy normally presents when the GFR is <25ml/min/1.73m^2.[74]

Chapter 3. Factors Affecting Chronic Kidney Disease Progression

3.1. Defining Chronic Kidney Disease Progression

The decline of renal function, as measured by the GFR, is commonly described as a linear process.[1,4] The MDRD study found that 85% of patients experienced a decline in the GFR at an average rate of 4ml/min/1.73m^2 per year.[75] Damage to the renal parenchyma by a plethora of initiating pathologies results in the gradual decline in renal function (*see section 2.1 and 2.2*).[4,71] The rate of GFR decline varies according to the underlying pathology[4,75] (**Figure 3.1**), but both modifiable and non-modifiable risk factors augment this rate of decline.[1] Moreover, modifiable risk factors of CKD progression are often a consequence of pathologies that initiate renal injury (e.g. hyperglycaemia and DM).[1]

Figure 3.1 GFR slopes as a function of renal pathology in normal BP patients



PKD, Polycystic Kidney Disease. Taken from the MDRD study group (1997)[75].

3.1.1. What is significant CKD progression?

NICE define clinically significant CKD progression as a GFR decline rate >5ml/min/1.73m^2 per year or >10ml/min/1.73m^2 over 5 years.[6] NICE guidelines also define a GFR decline rate >2ml/min/1.73m^2 per year as being due to more than just the effects of ageing.[6]

3.2. Non-Modifiable Risk Factors of CKD Progression

3.2.1. Age and gender

The prevalence of CKD increases exponentially with age being higher in females (*see Figure 1.5*).[5] Although females have a higher prevalence of disease, it is in fact males who tend to have a faster rate of CKD progression (although one Japanese study found faster GFR decline rates in females).[4,75] The incidence rate of renal failure and death is also more pronounced in men.[76] However, both men and women are at greater risk of death than they are of progressing to renal failure, especially those aged 70 years and over.[76] Age is considered an independent risk factor for developing CKD.[43] Generally, older patients tend to have higher rates of renal function decline.[4,76] In patients with DM however, this is reversed with younger patients having more rapid rates of GFR decline.[4]

3.2.2. Ethnicity and genetics

Studies have demonstrated that the prevalence of conditions such as DM and HTN are higher within the black population that in caucasians.[1] In the UK population, patients from the Indian subcontinent have also been found to have a higher prevalence of hypertensive disease.[1] Studies found that patients of African descent had faster rates of CKD

progression and, given that both DM and HTN are risk factors for disease progression, this finding is concordant with current knowledge.[75,77] Black patients also have a higher burden of ESRD than white patients but strangely, the prevalence of CKD is nearly the same.[77] Although we know the decline rate is different between different ethnic groups, the question remains as to why these differences exist. The answer probably lies in environmental, socio-demographic and genetic factors.[1,77]

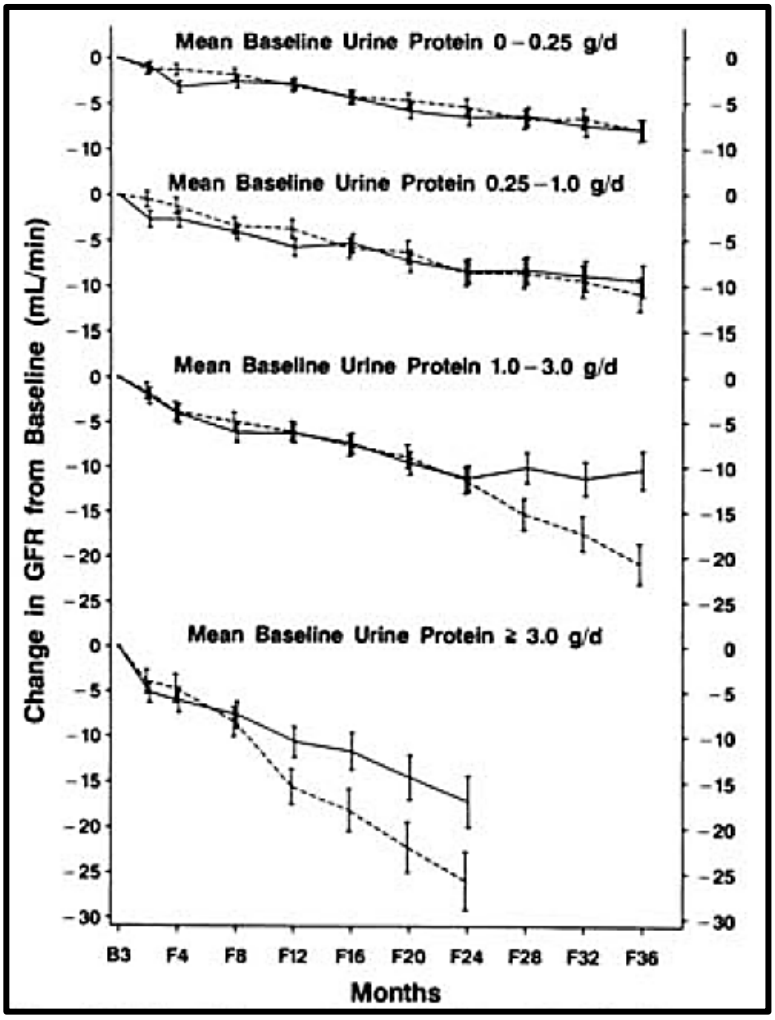
The underlying genetics mechanisms that drive renal pathology are poorly understood. Some changes in gene expression associated with aging, such as telomere shortening leading to cell senescence, have been observed.[78] Efforts are underway to identify CKD biomarkers and to further study numerous age-associated gene expression candidates.[78]

3.3. Modifiable Risk Factors of CKD Progression

3.3.1. Proteinuria

Normally, the glomerulus is not permeable to plasma proteins.[1,52] Proteinuria is caused by the loss of glomerular permselectivity leading to the leakage of protein into the urine.[1,52] Proteinuria is widely considered a powerful prognostic marker of renal disease progression.[4] Patients with higher urinary protein have been shown to have a poorer renal prognosis than those without and the effect is compunded in those with higher BPs (**Figure 3.2**).[58,59] It is thought that proteinuria directly contributes to CKD progression by initiating inflammatory responses within the kidney leading to fibrosis *(see section 2.2.2 and Fig 2.3).*[1] Angiotensin converting enzyme inhibitors (ACE-i) have anti-proteinuric effects hence are beneficial to patients with proteinuria as they renoprotective.[57,61]

Figure 3.2 Change in the GFR as a consequence of proteinuria



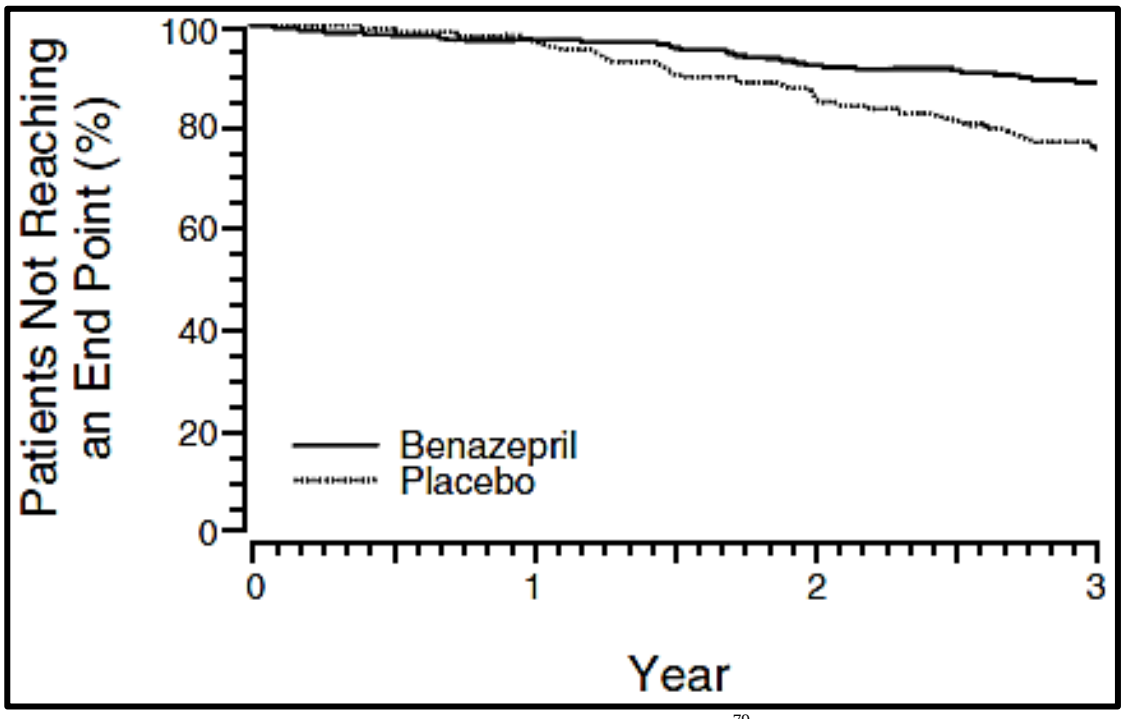
Dashed line - Usual blood pressure group; Solid line - Low blood pressure group. Taken from Peterson *et al.*, (1995)[59].

3.3.2. Hypertension

Many studies have linked high BP with an increasing rate of GFR decline.[4,43] Locatelli *et al.,* (1996) showed that patients with a mean arterial pressure (MAP) of <107mmHg had better renal survival than those with higher MAPs.[58] It is thought that the transmission of high systemic pressure to the delicate glomerular network contributes to glomerulosclerosis *(see section 2.2.3).*[1] HTN is especially problematic as a viscous spiral can occur where increasing BP leads to nephron loss which in turn sets in motion adaptive mechanisms that further raise the BP.[52]

The RAAS is central to the control of BP[52,57], consequently patients given ACE-i have a better prognosis (**Figure 3.3**).[79] The RAAS also has proteinuric effects *(see section 2.2.1 and Fig 2.2)* and as a result, hypertensive patients with proteinuria require even stricter BP control to achieve the same level of renoprotection.[59]

Figure 3.3 Effects of Benazepril on the progression to chronic renal disease



Taken from Maschio *et al*,. (1996)[79].

3.3.3. Hyperglycemia

Poor glycaemic control is associated with the initiation of CKD with DM being the most common cause of ESRD (*section 2.1.1*).[2] However, the link between hyperglycaemia and an increased rate of disease progression remains controversial.[4] As many studies have found a link between hyperglycaemia and increased disease progression as those that have not.[4] Of the 13 studies performed investigating the effects of hyperglycaemia control on

CKD progression, 6 showed an association and the rest did not.[4] However, it is known that diabetic patients with better glucose control will have better renal prognosis.[4]

3.3.4. Dyslipidaemia

Although there is experimental evidence linking hyperlipidaemia to the progression of CKD[80], the association is not clear-cut. Of the 14 studies conducted in this area, half have found an association between dyslipidaemia and increased CKD progression whilst the remaining studies have not.[4] A postulated mechanism for the association is one of proteinuria leading to dyslipidaemia and the trapping of lipid within the renal ECM with lipid oxidation subsequently causing renal dysfunction.[81]

3.3.5. Anaemia

Anaemia is an important complication of renal disease (*section 2.3.3*). Patients with lower haematocrit levels tend to have worse renal function compared to those with higher haematocrit.[4] However, studies looking at the treatment of anaemia have failed to show a convincing slowing effect on disease progression.[4]

3.3.6. Hyperuricaemia

Hyperuricaemia has long been associated with renal disease often accompanied by systemic HTN and CVD.[82] Although few studies have investigated the effects of hyperuricaemia on CKD progression, Kang *et al.*, (2002) found an association between uric acid levels and the progression of renal disease in rats.[82]

3.3.7. Obesity

Obesity is associated with an increased risk of HTN, dyslipidaemia, proteinuria and abnormal RAAS activation.[83] A systematic review by Navaneethan *et al*., (2009) found that a reduction in weight not only reduced the level of proteinuria but patients also had a better renal prognosis suggesting a clinically relevant link between obesity and worsening renal function.[84]

3.3.8. Smoking

Smoking is an important risk factor of CVD.[1] CVD is also a risk for CKD (*section 2.3.2*). Although studies report conflicting results, larger studies with better methodological designs have found significant associations between smoking, poor renal function[43,85] and CKD progression.[4]

3.3.9. Alcohol

Light to moderate alcohol intake is not linked to renal function decline.[1,43,86] In fact, some studies suggest light-moderate alcohol may have a protective role similar to that in CVD.[87] However, heavy alcohol consumption has been associated with a significantly increased risk of renal dysfunction.[85,88]

3.3.10. Socioeconomic factors

In general, studies have shown that patients with lower annual incomes and those with a lower social economic score (parameters are income, wealth, education, and occupation) were more likely to have incident ESRD.[89,90] Studies in the UK and Europe have found a higher prevalence of deprivation to be associated with poor renal function.[91-93] Merkin *et*

al., (2005) found that the individual-level socioeconomic status was significantly inversely related to the progression of CKD in white men with up to a 60% increase in risk between patients in the highest and lowest socioeconomic status quartiles.[94]

Black patients are more likely to have a lower socioeconomic status and consequently they are more likely to have progressive CKD and hence ESRD.[94] However, this effect does not fully explain the disparity between CKD and ethnicity[89] (*see section 3.2.2*).

3.3.11. Caffeine

High caffeine has been shown to increase the BP in APKD rats.[95] Studies in obese, diabetic rats have also found significant interactions between caffeine, proteinuria and reduced creatinine clearance.[96] Caffeine is generally not considered a risk factor for CKD progression in humans.[4]

3.3.12. Disease risk factors

A number of non-classical diseases have recently being found to be associated with CKD. Although not established CKD progression risk factors, evidence is accumulating relating to the important role they play in CKD prognosis and the potential benefits of treating these exacerbating pathologies. Presented below are examples of diseases that have recently been linked to the prognosis of CKD.

3.3.12.1. Chronic Obstructive Pulmonary Disease

The prevalence of Chronic Obstructive Pulmonary Disease (COPD) is inversely related to the level of kidney function.[97] CKD patients with moderate to severe COPD are also at an

increased risk of long term mortality.[97] COPD is significantly associated with CVD, itself a common risk factor in CKD. All three pathologies share smoking as a common risk factor.

3.3.12.2. Obstructive sleep apnoea

A relatively new risk factor, Obstructive Sleep Apnoea (OSA) has been shown to be associated with CKD.[98,99] Chou *et al*., (2011) found that the severity of OSA correlated significantly with worsening renal function.[99] OSA is independently associated with GH (*section 2.2.1*), HTN and proteinuria; all factors which lead to CKD progression.[98] The postulated pathological mechanism is one of hypoxemia leading to oxidative stress and excessive arousal prompting systemic nervous system and RAAS up regulation, the outcome being systemic and glomerular HTN and fibrosis.[98] With 50% of ESRD patients suffering from OSA, further study is needed to quantify this new and important risk factor.[98]

3.3.13. Drugs and Toxins

There are numerous recognised drugs and toxins which are associated with renal dysfunction from cyclosporine to aristolochic acid and iodinated radiographic contrast.[1,2] However, although the acute detrimental renal effects of NSAIDs are known[100,101], the role of NSAIDs as a risk factor for CKD progression is unresolved (*see chapter 6 for the systematic review*).

Chapter 4. Non-Steroidal Anti-Inflammatory Drugs and the Kidney

4.1. The Pharmacology of Non-Steroidal Anti-Inflammatory Drugs

In 1971, JR Vane proposed that NSAIDs acted by preventing the formation of prostaglandins by inhibiting the cyclo-oxygenase (COX) enzymes (1 and 2).[102] Most NSAIDs inhibit the COX enzymes by preventing the initial dioxygenation of arachidonic acid (AA) and are competitive inhibitors.[103] NSAIDs block the enzymes by entering the hydrophobic active site and preventing AA from entering the active site.[103] Most NSAIDs bind reversibly with the COX enzymes but Aspirin forms an irreversible bond with the enzymes permanently inactivating them.[103,104] NSAIDs also differ in their selectivity for either the COX-1 or COX-2 enzymes which have a 60% homogeneity in the amino acid structure.[103-105] Selectivity largely determines both the therapeutic and side effect profile of the NSAID.[105] NSAIDs have a number of therapeutic actions; most notably they are analgesic, anti-inflammatory, anti-pyretic and anti-thrombotic.[103] In general, the inhibition of the COX-1 enzyme is responsible for many of the side effects of NSAIDs.[103,105] The most common side effect of NSAIDs use is GI disturbance which, if severe, can lead to GI bleeding.[9,103] A review of epidemiological studies (2000) found that the risk of upper GI bleeding was nearly four times higher amongst NSAID users compared to non-users.[106] Other NSAID side effects are skin reactions, acute kidney injury, cardiovascular events and aspirin sensitive-asthma.[103] Side effects are more common in the elderly population.[9] As well as side effects, NSAIDs, like many drugs, have a number of pharmacokinetic/dynamic interactions that can be detrimental to patients taking multiple drugs (such as combined NSAID and ACE-i use leading to a reduced anti-hypertensive effect).[9]

4.1.1. COXIBS

It was hypothesised that selective COX-2 inhibitors (COXIBS) would decrease the prevalence of GI side effects by minimally inhibiting the constitutive enzyme COX-1.[107] COXIBS were shown to provide symptomatic relief to patients with arthritic conditions.[107] In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, the incidence if severe GI disturbances (symptomatic ulcer, perforation or haemorrhage) was 54% lower in the rofecoxib group compared to the naproxen group.[107] However, COX-2 is now though to have important roles in the healing of gastric ulcers and is induced in settings of gastric damage.[107] Furthermore, evidence emerged of the detrimental cardiovascular effects of COXIBS leading to several drugs being withdrawn.[103,107] Currently, three COXIBS are available in the UK and their use is restricted to treating patients who cannot take convectional NSAIDs.[103]

4.1.2. Aspirin

Aspirin (acetylsalicylic acid) was previously a common analgesic as its method of action relates closely to that of NSIADs. However, it is now mainly used in patients at risk of thrombotic events.[103] This is due to its ability to irreversibly inhibit the COX enzymes within platelets leading to a prolonged antithrombotic effect.[103] Recent evidence has also shown aspirin to be beneficial in the prevention of certain types of bowel cancer.[108] Aspirin shares many of the general side effects of NSAIDs but also has some specific side effects (salicylism and Reye's syndrome).[103] Because of the thromboprophylactic effect of aspirin, it is perhaps no surprise that it increases the risk of major bleeding (by up to 70%) but the absolute risk is modest (0.13%).[109]

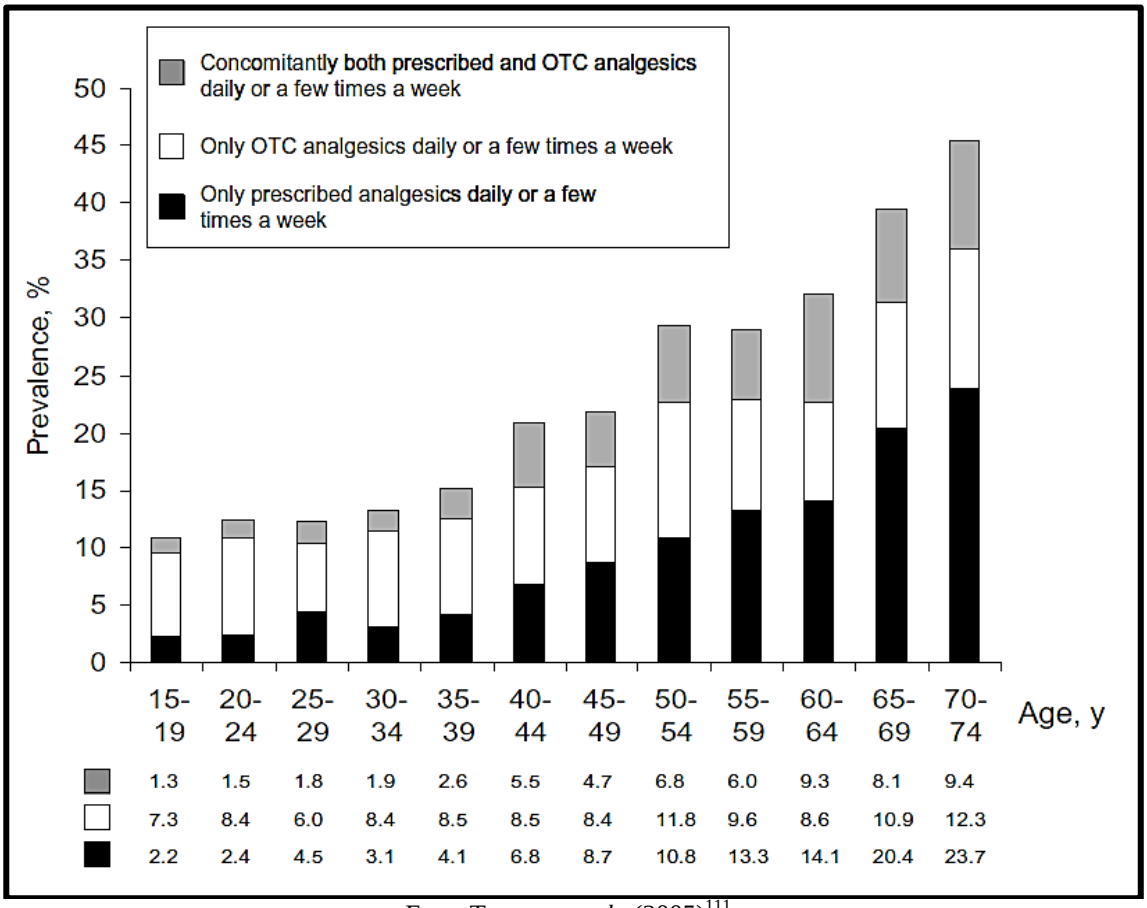
4.1.3. Paracetamol

Paracetamol is not classed as a NSAID as it has a different method of action.[103] Paracetamol, is a metabolite of the nephrotoxic and carcinogenic drug Phenacetin but is much less toxic.[103,110] It is thought to exert its main therapeutic effect (analgesia) through the inhibition of a third COX enzyme (COX-3, a COX-1 splice variant) within the central nervous system.[103] Paracetamol is also a potent antipyretic.[103] Paracetamol is a well-tolerated drug with few side effects, however, in toxic doses (10-15g), the drug saturates normal enzyme metabolism pathways and undergoes oxidative metabolism forming a hepatotoxic compound N-acetyl-p-benzoquinoneimine.[103]

4.2. Common Indications for NSAID use

NSAIDs are used for a wide variety of indications but the most common indications for use in adults are for analgesia, thromoboprophylaxis and as anti-inflammatories. NSAIDs can be obtained over-the-counter (OTC) or can be prescribed. Analgesia use is more common in older patients but the rise in the prevalence of use is largely due to an increase in the prescription of drugs rather than over the OTC use which remains fairly stable between different age groups (6.0% in 25–29 years old and 12.3% in 70–74 years old) (**Figure 4.1**).[111] Elderly patients (≥65 years old) are commonly prescribed NSAIDs. In evidence of this are the findings by Sun *et al*., (2004) who reported that 27% of the study participants had at least 1 NSAID prescription of which 68% had a prescription for a COX-2 selective NSAID over a 1-year period.[112] Women are also more likely to use non-opioid analgesics[113] and NSAIDs[112] than men. In patients prescribed analgesics, the vast majority (91%) will have the prescription issued by a primary health care provider.[11]

Figure 4.1 Prevalence of OTC and prescription analgesic use patterns stratified by age



From Turunen *et al*., (2005)[111].

The British National Formulary (BNF) (2011)[114], used in the UK as the premier medico-pharmaceutical reference book for adults, lists the licensed indications for NSAIDs.[114] NSAIDs can be administered by a variety of routes but are usually given orally.[114] The dose of NSAIDs prescribed can vary depending on the drug given, the indication and the tolerance to side effects.[114] Moreover, although NSAIDs share common detrimental side effects, each drug has its own particular side effect profile and this can also vary between patients.[114]

4.2.1. Analgesia

NSAIDs, along with paracetamol, are especially useful as analgesics in patients with mild to moderate pain.[103,114] Chronic pain is strongly associated with NSAID use. Clarke *et al.*, (2002) found that 75% of patients with chronic pain of non-malignant origin were prescribed at least one analgesic (67% NSAIDs, 29% paracetamol).[11] Equally, Maxwell *et al*., (2008) reported that of the patients aged 65 years and over with current daily pain, 56% were prescribed NSAIDs and 39% were prescribed paracetamol.[10] The most common indication of NSAID use, particularly for long term use, is for controlling chronic inflammatory musculoskeletal pain.[9-11] In the Maxwell study, patients with current daily pain receiving a non-opioid analgesic were 2.5 (95%Cl: 2.85-3.38) times more likely to have arthritis compared to patients using no analgesics.[10] NSAIDs also provide symptomatic relief in patients with headaches, dysmenorrhoea, post-op pain, dental/orofacial pain and those with secondary bone metastasis or mild sickle cell crises.[114] Paracetamol is mainly used for symptomatic pain relief where NSAIDs are contraindicated and is the preferred simple analgesic in the elderly; however it possesses little anti-inflammatory activity.[9,103,114] Paracetamol is commonly given alongside codeine as a compound analgesic for more severe pain.[114] Although indicated as an analgesic, aspirin is largely prescribed for its anti-platelet effects and is seldom used as an analgesic in the UK.[114]

4.2.2. Anti-inflammatory

NSAIDs are used commonly in patients with inflammatory arthritidies (e.g. rheumatoid arthritis) and are also indicated in advanced osteoarthritis.[114] NSAIDs can also be used for their anti-inflammatory action in patients with back pain or soft tissue disorders.[114]

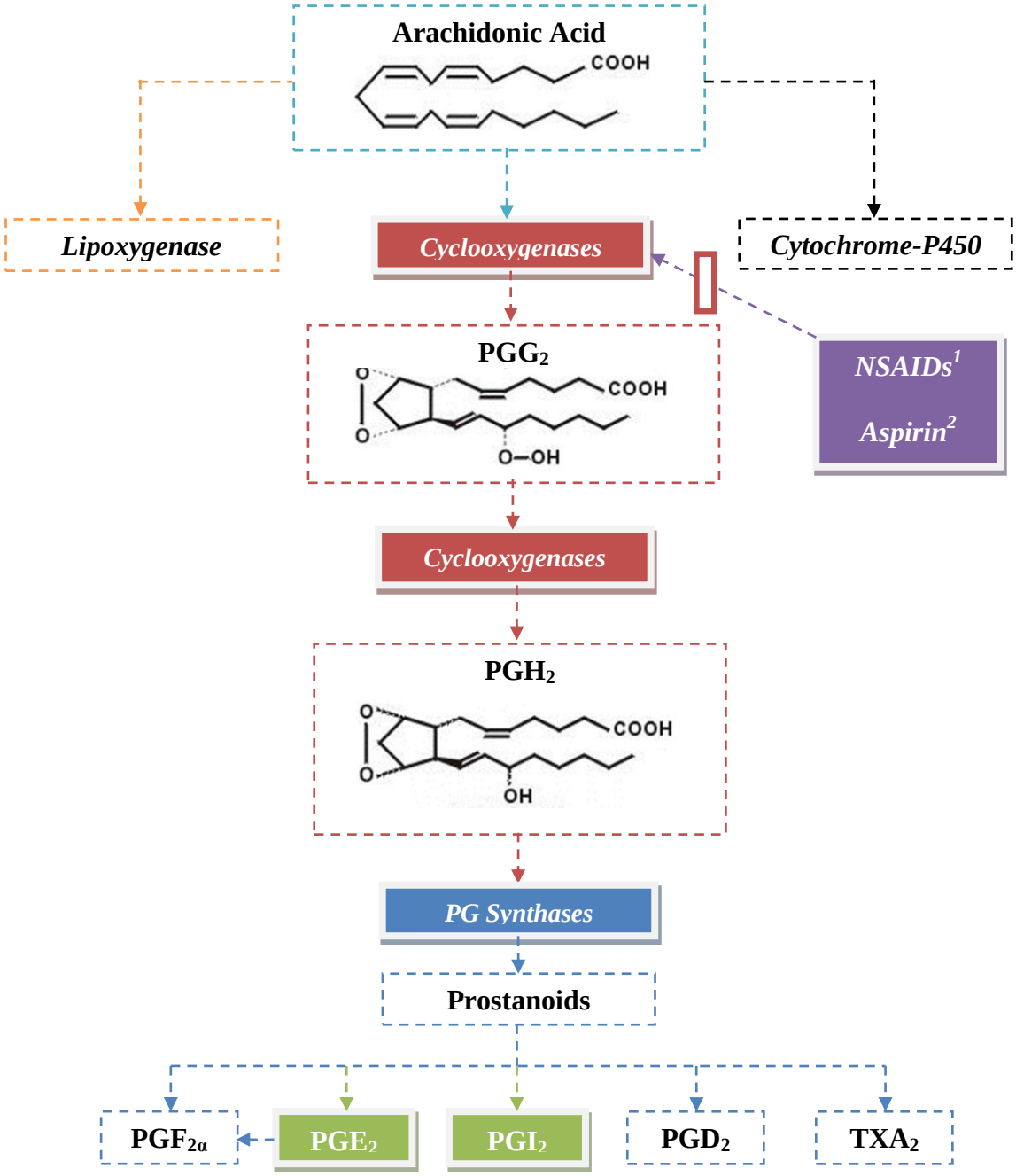
4.2.3. Thromboprophylaxis

The prescription of aspirin (along with other antiplatelet drugs) is indicated for use as an antiplatelet drug and in the management of acute coronary syndromes.[114] Of increasing importance is the use of aspirin in CKD patients at risk of CVD where use has been shown to be beneficial in patients with an eGFR <45ml/min/1.73m^2.[115,116] The maintenance dose of aspirin when used for thromboprophylaxis is 75mg daily.[114]

4.3. Prostaglandins and the Kidney

Prostaglandins (PG) are a subgroup of a family of active AA metabolites known as the eicosanoids.[1,52] AA is itself formed from linoleic acid (which we derived from dietary sources) and is released from its membrane-bound state when the activation of cellular phospholipases (mainly phospholipase A_2) occurs. The eicosanoids are a product of three enzymatic reactions catalysed by lipoxygenase, cyclooxygenase and cytochrome-P450 enzymes.[1,52] The production of PG is catalysed by the COX enzymes (of which there are two isoforms, COX-1 and COX-2, in the kidney) and the PG synthases.[1,52] The COX-1 enzyme is considered a constitutive enzyme whilst the COX-2 enzyme is inducible.[1,52] A variety of processes can lead to the induction of COX-2 in the kidney from cellular stresses (hypoxia, shear stress and cell volume changes) to cytokines and growth factors.[52] The product of COX metabolism is PGG_2 and subsequently PGH_2 which is then acted upon by various PG synthases to produce a variety of protanoids (most importantly PGE_2 and PGI_2).[52] The enzymatic pathways are shown in **Figure 4.2**.

Figure 4.2 The Cyclo-oxygenase pathway



TXA_2, Thromboxane. Modified from Brenner & Rector's The Kidney 7th ed. Vol 1 (2004)[52]. [1]NSAIDs bind reversibly to the COX-1 and 2 enzymes. [2]Aspirin binds to the COX-1 and 2 enzymes irreversibly. Paracetamol is thought to inhibit COX-3 in the central nervous system and does not affect renal haemodynamics.

4.3.1. Cyclo-oxygenase-1

The COX-enzymes are expressed differently within the kidney and have differing physiological roles.[1,52] The COX-1 enzyme is expressed within the afferent arteriole, the glomerular parietal cells and most notably within the collecting system.[52] The exact role of COX-1 expression is not well understood but it is thought that they influence the normal renal haemodynamics.[117]

4.3.2. Cyclo-oxygenase-2

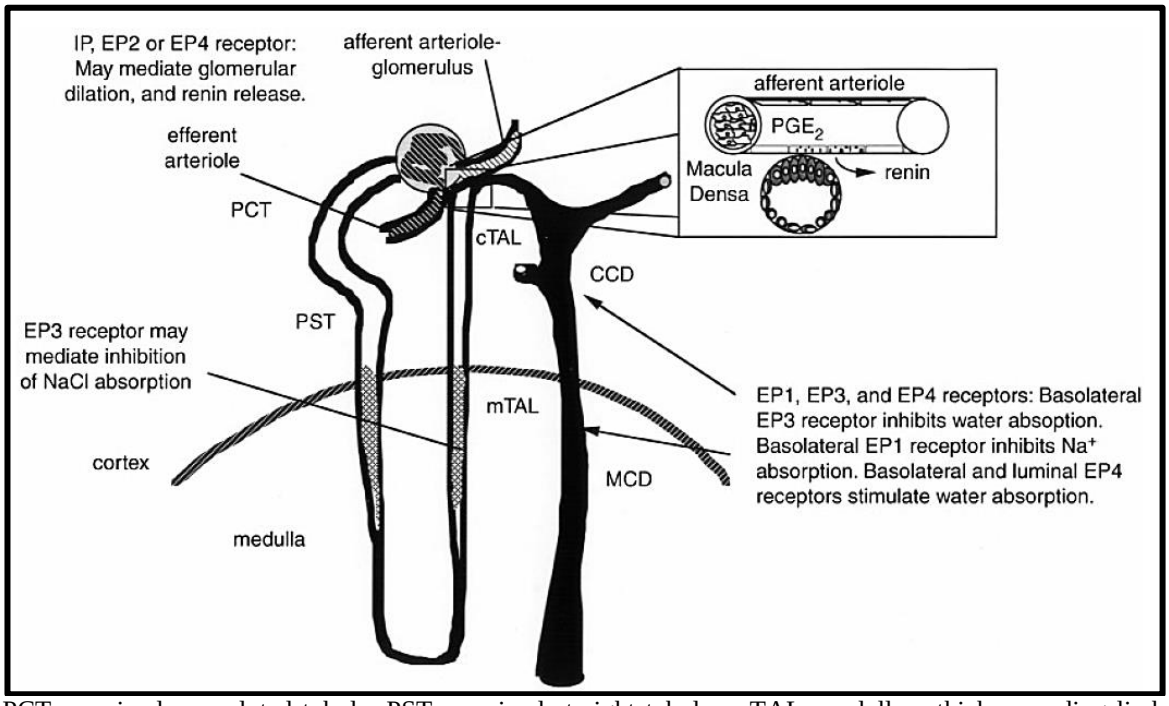
The COX-2 expression is restricted to the macula densa, the medullary interstitial cells and to a few cells within the thick ascending limp of Henle's loop.[52,117] The macula densa acts as a detector of low-salt and volume deletion (by way of $Na^+/K^+/2CL^-$ co-transporter).[1,52] Given the expression of COX-2 within the macula densa, it is thought that COX-2 plays a vital role in regulating the GFR by releasing vasodilatory prostaglandins (PGE_2 and PGI_2), influencing tubulo-glomerular feedback and promoting renin release.[1,52,117,118] The promotion of renin release is of particular importance as renin activates the RAAS which leads to an increase in blood pressure, as well as causes electrolyte changes (increases sodium and decreases potassium).[52] The inhibition of COX-2 enzymes by NSAIDs has been shown to reduce renin secretion mediated by the macula densa.[1,52] Equally, a sodium depleted state leads to the induction of COX-2 within the macula densa cell.[1] The expression of COX-2 has also been shown to be important in medullary adaption to physiological stresses such as water deprivation and endotoxin exposure.[52]

4.3.3. Renal effects of prostaglandins

PGE_2 and PGI_2 are the most important prostanoids in the kidney and have important roles in maintaining physiological homeostasis.[52] All prostanoids have distinct receptors which

like the COX enzymes have variable expression throughout the renal parenchyma (**Figure 4.3**).[52] PGE_2 has no less than four receptors (receptors 1 & 3 are antagonistic whilst 2 & 4 are agonistic) whilst PGI_2 has one.[52] Both PGE_2 and PGI_2 have distinct but additive vasodilatory actions upon the glomerular microvasculature.[52] PGE_2 has also been linked to a number of other renal effects from the vasodilation of the medullary vasa recta to the modulation of salt and water transport at the thick ascending loop, the distal tubule and the collecting duct (mostly prevents sodium and water reabsorption).[52,119] Most importantly however, PGE_2 has been linked to renin secretion.[1,52,119] Therefore, depending on the setting (volume depletion vs. HTN), PGE_2 can act either as a vasodilator or a vasoconstrictor and can increase (through the actions of angiotensin-II) or decrease sodium reabsorption.[52,119]

Figure 4.3 Localisation and action of the PGE_2 receptors



PCT, proximal convoluted tubule; PST, proximal straight tubule; mTAL, medullary thick ascending limb; cTAL, cortical thick ascending limb; CCD, cortical collecting duct; MCD, medullary collecting duct; PGE_2, prostaglandin E_2; EP1-4, prostaglandin E_2 receptors. Taken from Breyer *et al*., (1998)[119].

4.4. Adverse Renal Effects of Cyclooxygenase Inhibitors

Although there are numerous physiological roles for the COX enzymes, inhibition by NSAIDs in normal individuals does not tend to lead adverse renal effects.[117] However, in certain settings of PG dependence (such as established renal dysfunction, sodium intake, volume depletion, renal artery stenosis, lupus nephritis, partial renal ablation, therapy with RAAS inhibitors, cirrhosis and heart failure), the enzymes and their products become vital to maintaining renal haemodynamics.[117,118,120]

4.4.1. Hypertension

The use of selective and non-selective NSAIDs exacerbates HTN in patients with pre-existing treated HTN.[52,117,119,121] The BP may be raised either through the attenuation of the effects of medication (such as ACE-i, β-blockers or diuretics) or by the promotion of sodium retention.[117,118,122] Overall, the increase in blood pressure is modest but clinically significant if sustained.[122] A meta-analysis by Johnson *et al*., (1994) found that NSAID use increased supine systemic blood pressure by 5mmHg.[122]

4.4.2. Fluid and electrolyte effects

It is known that prostaglandins prevent sodium reabsorption and can activate the RAAS by promoting renin release.[52,119] The administration of both selective and non-selective NSAIDs reduces urinary sodium excretion leading to sodium retention and subsequently oedema.[52,117-120] Oedema is most prominent amongst COX-2 selective NSAID users and usually affects the lower extremities.[117,118,120] An uncommon but important complication of fluid retention is congestive heart failure.[117] Hyperkalaemia also occurs with NSAID use

due to inhibition of the RAAS system and due to a decrease in the GFR.[52,117,118] As with other adverse renal effects of NSAIDs, hyperkalaemia tends to occur in at risk patients.[52]

4.4.3. Haemodynamic acute kidney injury

Acute kidney injury (AKI) is a well-recognised complication of NSAID use in at risk patients (volume depletion, renal insufficiency, congestive heart failure, DM and old age).[52,100,101,121] NSAID-associated AKI is rare[100] but occurs in a significant proportion of at risk patients; NSAID use increases the risk of AKI by 58%.[100] AKI is more likely to occur where there is the concomitant use of diuretics and calcium channel blockers.[101] In patients with PG-dependant vasodilation, inhibition of COX enzymes leads to a critical decrease in the GFR leading to acute renal insufficiency.[52] Stopping NSAID administration leads to an improvement in renal function.[101]

4.4.4. Immunological acute kidney injury

NSAIDs may cause AKI injury as a consequence of an allergic hypersensitivity reaction known as drug-induced acute interstitial nephritis (AIN).[1,52,118] It is thought that the drug may act as a hapten thus provoking an autoimmune reaction.[1,123] AIN is a relatively uncommon condition[123] and the disease rapidly regresses once the offending agent has been withdrawn.[52]

4.4.5. Analgesic nephropathy

In 1953, Spühler and Zollinger[124] reported a link between chronic Phenacetin use and kidney injury. Such patients had specific renal abnormalities, namely chronic interstitial nephritis (CIN) and renal papillary necrosis (RPN).[124] In CIN, subacute inflammatory

infiltration of the renal interstitium occurs with chronic analgesia use resulting in fibrosis and tubular atrophy if sustained (*see sections 2.2.4*).[1,52] RPN is an indication of ischaemic damage caused by the loss of PG-related vasodilation which may be critical in the oxygen poor milieu of the renal medulla in at risk chronic NSAID users.[1,52]

A new condition, analgesic nephropathy (AN), a slow, progressive renal disease occurring in patients with chronic combined use of at least two analgesics (one of which was Phenacetin) usually in combination with caffeine and/or codeine characterised by CIN and RPN was recognised.[125] Numerous cases of AN have been reported since, however, most were attributed to Phenacetin use.[125] Since the connection between Phenacetin and kidney damage was made, numerous countries began to stop its use and the drug was finally banned in 1983.[125] Although AN was once a common cause of ESRD, estimates in Australia (2001) place the incidence of AN in ESRD patients at 5%.[1] A review by the 'INTERNATIONAL STUDY GROUP ON ANALGESICS AND NEPHROPATHY' (2000) were unable to find any convincing evidence linking non-phenacetin containing analgesics with nephropathy largely due to sparse information and substantial methodological problems in the reviewed literature.[126]

4.4.6. Modern NSAIDs and chronic kidney disease

The evidence linking NSAID use to CKD is inconsistent.[125] However, because some studies have reported significant detrimental renal effects with NSAID use and because Paracetamol is a major metabolite of Phenacetin[110], this has fuelled the notion that all non-narcotic analgesics lead to renal dysfunction.[125] However, studies performed since the late 60's have given conflicting evidence as to whether a true association between NSAID use and CKD exists.[12-14,127-146] A major limitation has been the flawed study designs and

numerous methodological issues that have hampered research in this area.[125,147] Recent epidemiological data has tried to address some of the methodological faults that have affected previous work in this area and the connection between NSAID use and CKD is becoming clearer (*see chapter 6 for the systematic review*).

4.5. Non-Steroidal Anti-Inflammatory Drug use among Chronic Kidney Disease patients

4.5.1. Defining NSAID use

Studies investigating the effects of NSAID use (either prescribed or OTC) on CKD progression have often employed various methods of defining the level of drug use. The problem facing studies is trying to define patients considered as "users" to compare against "non-users". A common approach taken by most studies to solve this problem was to set a threshold of "use". If a patient had a level of "use" greater than that set by the study authors, they would be classified as users. Studies employing this approach defined the threshold of use either by a subjective frequency of drug intake per day/week/month[13-15,130,133,136,138,140,141,144,145,148,149] or by a given number of prescriptions over the study period[135,150-153].

There are several disadvantages to this strategy; firstly, patients may not be classified as users if they do not reach the set threshold discounting any NSAID use they might have. Equally, those with extremely high NSAID use are just described as users and are likely to skew the study results in favour of a positive effect. Finally, this approach does not take into account the duration of "use" which could significantly alter the results of a study.

Several more in depth approaches used by studies included dividing patients according to the cumulative NSAID dose used in grams[12,12,14,15,128,134,138,139,142,146,149], number of number of tablets taken[132,137,138,142] or the duration of use (in years) above a study defined threshold[12-14,140,143,148].

There are major disadvantages to these approaches also. The comparison of different NSAIDs gram for gram (or by the number of tablets) is not accurate because the recommended NSAID dose and frequency of use varies depending on the given drug, the indication of use and the patients' tolerance to side effects. For example, two patients being treated for rheumatoid arthritis with ibuprofen (1.2 grams daily) or diclofenac sodium (100 milligrams daily) would, if they consumed the drug for a year, have a cumulative dose intake of 438 grams and 36.5 grams respectively; a 12 fold difference in NSAID dose. This is of importance as it may be the case that both drugs could affect renal function at the given doses. Therefore, the outcome of a study could be significantly altered by the chosen ranges of cumulative use. Classifying drug use by duration is also problematic because, as mentioned previously, a threshold must be set for "use" discounting patients falling below this threshold. Moreover, although one can crudely estimate the amount of drug use using this approach, the measure cannot accurately track changes in drug dose or patterns of use in those patients above the set threshold.

The best approach would be to measure the level of cumulative NSAID use using a standardised measure of drug dose that would allow for equivalent comparisons between NSAIDs. The Defined Daily Dose (DDD) is a system capable of standardising exposure across drug classes and has been employed by more recent studies in this area.[13,131,150]

4.5.2. The anatomical therapeutic chemical classification and the defined daily dose

The Anatomical Therapeutic Chemical (ATC) classification and the DDD system were developed in the early 1970's.[154] Given its increasing international appeal, the WHO Collaborating Centre for Drug Statistics and Methodology (WHO-CCDSM) adopted the system and has updated it ever since.[154] Officially, "*the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults."*[155] A substance is firstly given an ATC classification and then it is assigned a DDD (in grams/day) for a given indication.[155] Therefore, using ATC classified drugs and the DDD system, it is possible to compare different types of NSAIDs equally. Applying the system to the previous example, a patient consuming 438 grams of ibuprofen per year for rheumatoid arthritis would have an intake of 365 DDDs/year (1 DDD of ibuprofen = 1.2 grams) whilst another patient consuming 36.5 grams per year of dicofenac sodium (1 DDD of diclofenac = 0.1 grams) for rheumatoid arthritis would also have an intake of 365 DDDs/year.[155]

The DDD system is dynamic and can change over time meaning studies must detail which DDD index they use and should ideally only be compared with those using the same index.[154] Advantages of the ATC/DDD system however are; the ability to make international comparisons, the ability to compare multiple drug classes and the ability to study long-term drug use.[154] The DDD is not the same as the average recommend drug dose as set out by clinical guidelines, this is known as the recommended daily dose (RDD).[155,156] In addition, because various clinical and patients factors influence what dose of drug is actually prescribed and dispensed, the average prescribed daily dose (PDD) may also differ from DDD and RDD.[155,156] There are numerous examples where the PDD and

DDD differ in patients taking anti-epileptics[157], antibacterials[158,159], ACE-i as well as anti-diabetic drugs[160]. A final factor to consider is patient compliance. Patients may be prescribed a drug but might not take it. The most accurate measure of exposure would therefore be the average consumed daily dose (CDD) but this is rarely measured as it requires constant patient monitoring.

4.5.3. Prevalence of NSAID use amongst CKD patients

NSAID use among CKD patients is prevalent[161,162] despite current guidelines suggesting the avoidance of such drugs in patients with renal dysfunction. Bhopal *et al*., (2010) reported that of the stage 3 to 5 CKD patients included in their UK study, 55.5% (range 48.9–76.9%) were prescribed at least 1 NSAID (81% of these were low-dose aspirin).[161] NSAID users also tend to have prolonged drug use. Paulose-Ram *et al*., (2005) conducted a study in the US and found that 20% of adults had used aspirin, NSAIDs or paracetamol frequently at some point in their lives.[163] Almost 50% of NSAIDs users in their study took the drug frequently for at least a year.[163] The findings are echoed by a later study by Plantinga *et al*., (2011) who found that 66% of CKD patients reporting current NSAID use, had used the drug for 1 year of longer.[164]

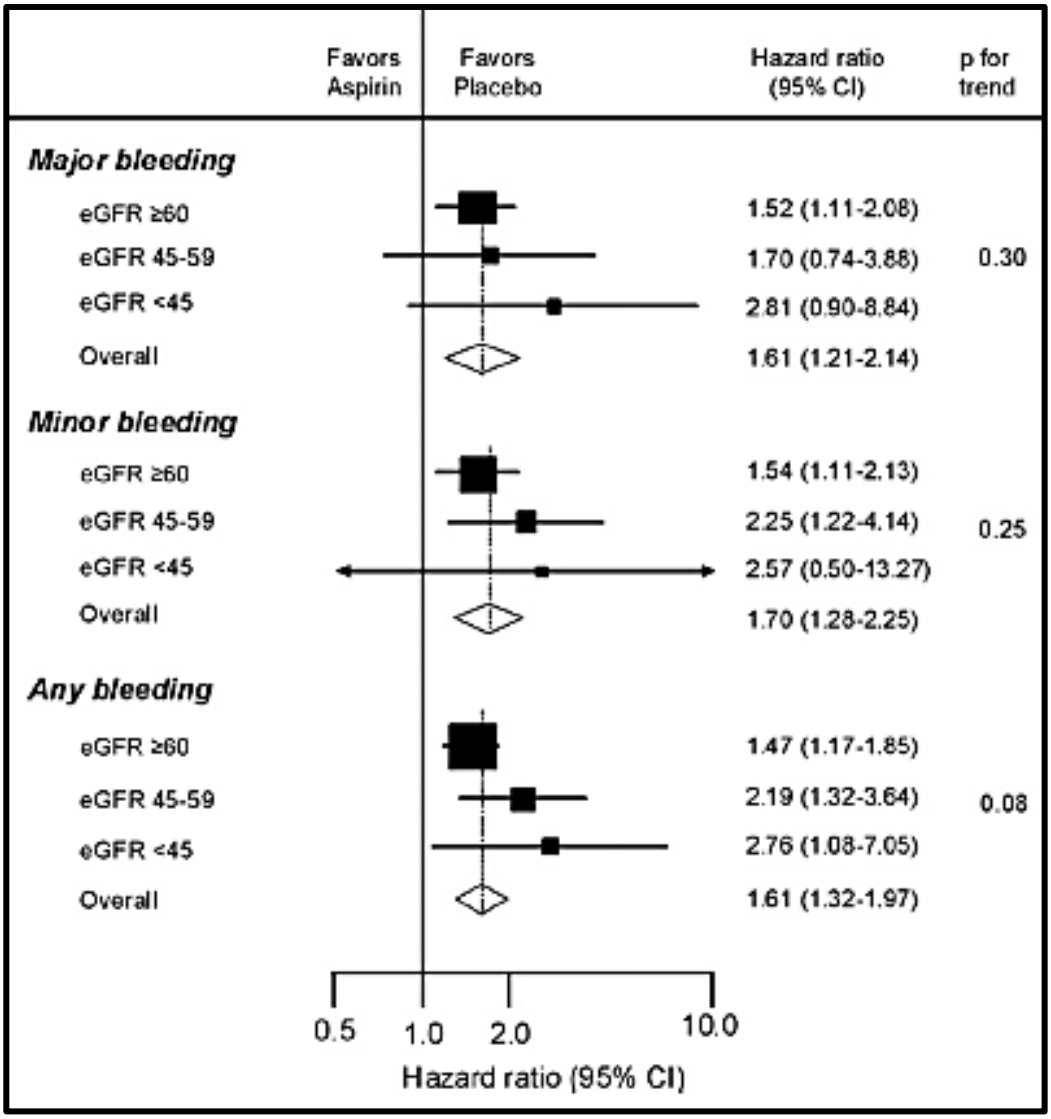
Although it is clear that NSAID use in prevalent among CKD patients, what is unclear is the NSAID dose used. Moreover, the definitions of "use" vary widely between studies and few use the DDD measure. Another potential problem in many studies is the use of self-reported data which can be prone to recall bias. Studies looking at the effects of NSAID use on CKD progression reporting on the prevalence of NSAID use are reviewed in detail in chapter 6.

4.5.4. Harmful extra-renal effects of NSAID use in CKD patients

The harmful effects of NSAIDs in the general population are well documented (*see section 4.1*). However, the complications of CKD such as platelet dysfunction (*see section 2.3.4*) have the potential to augment the tradition NSAID side effects. Moreover, CKD patients may be at an increased risk of adverse effects because of enhanced drug sensitivity, comorbid conditions, and concurrent medication use. Jankovic *et al*., (2009) found that among patients undergoing haemodialysis, NSAID users were at a significantly increased risk of gastrointestinal bleeding compared to non-users; adjusted odds ratio (OR) = 5.84 (95%CI: 1.27-26.86).[165]

Given the wide range of renal disease severity, the risk of harmful due to NSAIDs use may also vary according to the stage of CKD. In evidence of this is a post-hoc subgroup analysis of the Hypertensive Optimal Trial (HOT) data by Jardine *et al*., (2010).[115] They investigated the cardioprotective effects of low-dose aspirin in hypertensive CKD patients and found that that the risk of bleeding increased with worsening eGFR although not significantly (p = 0.08) (**Figure 4.4**).[115]

Figure 4.4 Effect of Aspirin on bleeding rates according to the eGFR



Taken from Jardine *et al*., (2010)[115].

Chapter 5. Epidemiological and Statistical Methodology

5.1. What is Epidemiology?

The term epidemiology comes from the Greek words meaning study upon population (epi = upon, demos = people, logos = the study of).[166] But epidemiology is more than just the study of people, the WHO defines epidemiology as "*the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems*".[167] Therefore, questions relevant to epidemiologists include those of definition, occurrence, causation, outcome, management and prevention of health-related events.[167,168] A primary step in conducting epidemiological research is deciding upon an exposure variable for study.[166] In principle, the chosen variable should impact on individual and population health, be accurately measurable, differentiate populations by health characteristics and generate testable aetiological hypothesis.[166] Once an exposure of interest is established, a focused question is formulated; this largely determines the appropriate study design. In our study, our exposure of interest was NSAID use. We wanted to investigate how NSAID use affected the occurrence and progression of CKD in patients aged 40 years and older.

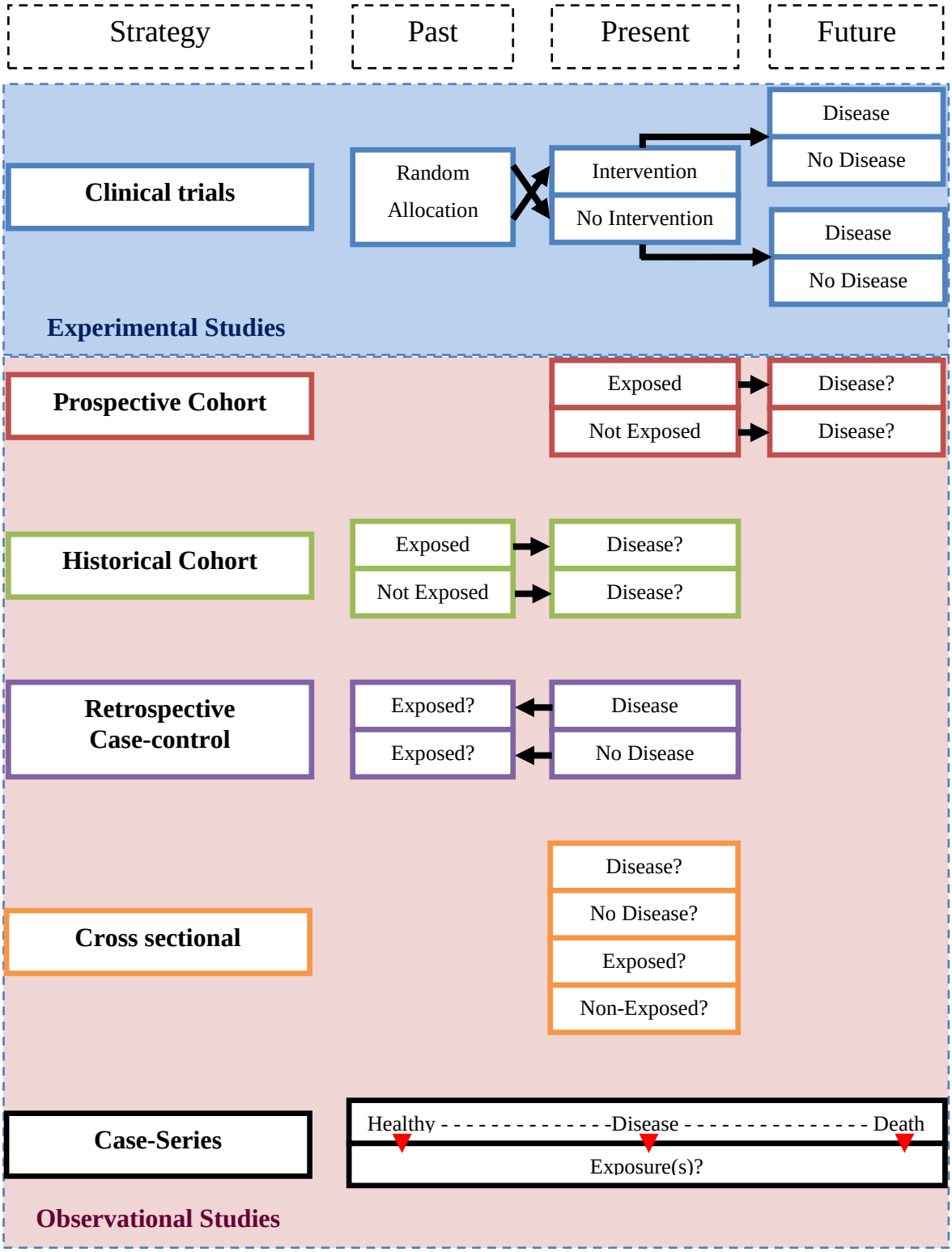
5.2. Epidemiological Study Designs

There are numerous study designs employed in epidemiology. The five basic epidemiological studies are; trials, cohort, case-control, cross-sectional, and case-series.[166] They are broadly classified into experimental (trials) and observational studies (case-series, cross-sectional, case-control and cohort) (**Figure 5.1**).[166] Another useful classification divides studies into those describing disease patterns (descriptive = case-series and cross-

sectional) and those exploring hypothesis through inference (analytical = case-control, cohort and trials.).[166] Essentially, studies can analyse the association between exposure and disease at a current time point (cross-sectional), prospectively or retrospectively (longitudinal).[168]

Numerous facts influence the choice of study design but ultimately it is a balanced between maximising scientific validity and maintaining practicality.[168] In the hierarchy of evidence, experimental designs (specifically randomised controlled trials) are considered superior to observational studies.[169] However, Concato *et al*., (2000) found that when the results from randomised controlled trials or well-designed observational studies (cohort or case-control) in five different subject areas were summarised, the outcomes were remarkably similar.[169]

Figure 5.1 Epidemiological study designs



Modified from Silman AJ. *Epidemiological studies: a practical guide*. Cambridge: Cambridge University Press; 1995.[168]

5.2.1. Trials

Trials, specifically clinical trials, are studies where an intervention is given to one group of individuals and not to another in order to determine the relative influence that the intervention has on the natural history of disease.[166] Because the influence on disease can be quantified, an estimation of cost and benefit can also be made.[166] Clinical trials are performed on live individuals. Therefore, any intervention given to them must be designed to improve health if the trial is to be deemed ethical.[166] A further approach, known as a preventative trial, is to neglect one group of participants a substance thought to be harmful (e.g. salt) and not another.[166] As with clinical trials, ethical considerations make it difficult to perform preventative trial studies.[166] Trails are often designed with a target population in mind and ideally in patients at the same stage of disease.[166] Therefore, interventions shown to work in a target population do not necessarily produce the same results in the general population or at all stages of disease.[166] As numerous factors affect disease, trials randomly allocate individuals into either the intervention or control group to safeguard against selection bias.[166] The control group is sometimes given a "placebo" when there is no known beneficial alternative.[166] To reduce the risk of bias, the subject, health professional (double blind) and even the researcher (triple blind) are left unaware of which group each individual is allocated to.[166] The major difference between an experimental and an observational study is that the intervention ('*exposure*') is determined and manipulated by the researcher and is not merely measured.[166] Apart from the ethical considerations, trials are technically and financially more taxing than observational studies normally requiring a committed multidisciplinary effort to complete successfully.[166]

5.2.2. Cohort studies

A cohort study is one in which a group of individuals who share a common feature (usually an exposure) are tracked over a period of time to determine the development of disease in relation to the proposed risk factor.[166,168] The exposure can either be measured from the start of the study (prospective cohort) or can be determined from historical data (historical cohort), depending on the quality of data available.[168] Ideally, associations should be made between the individuals of a defined cohort but multiple cohorts can be set up to if there are inadequate numbers of exposed or non-exposed individuals.[166,168] In a cohort study, health data is collected over a period of time to track part of the natural history of disease against a measured baseline.[166] Cohort studies are analytical allowing for the exploration and generation of hypothesis.[166] The main disadvantage of cohort studies is that they require a prolonged period of follow-up, possibly with large sample sizes increasing cost and complexity.[166,168] However, the current availability of regularly collected computerised data on risk factors and disease outcomes (e.g. in CKD patients[38]) offers the opportunity to perform relatively cheap and quick historical cohort studies.

5.2.3. Case-control studies

Theoretically, a case-control study compares and contrasts individuals with a disease of interest to those without and are especially useful in rare diseases.[166,168] The aim of a case-control study is to measure the potential risk factor associated with disease.[168] Cases can be identified in a variety of ways (e.g. surveys) and from numerous sources (e.g. case-series registers).[168] The method of selecting cases will also determine the method for selecting controls (e.g. random case selection from a register).[168] Controls should be representative of the population from which the cases were selected and so should have an equal chance of being selected as a case if they were to develop the disease.[166] The difficulty in selecting

controls is that ideally they should only differ from cases by the exposure variable of interest but this is rarely the case.[166] To try and limit this, researchers can "match" certain characteristics between cases and controls but this might in fact introduce a selection bias if multiple matching criteria are interlinked with the disease.[166]

5.2.4. Cross-sectional studies

Cross-sectional studies look at patients with disease and exposure at the same time over a narrow time-period.[166] Classically, cross-sectional studies are used to measure prevalence but can be used to explore the associations between multiple exposures and disease.[166] The use of multiple cross-sectional studies at different time periods can be used to measure changes in the study population.[166] A common problem in cross-sectional studies is that they often rely on survey data thus selection bias due to non-response is almost unavoidable.[166]

5.2.5. Case-series

A case-series is effectively a register of cases gathered at a clinical (unrestricted catchment area) or population (specified catchment area) level.[166] The case series are advantageous in aiding clinical management and exploring common characteristics in a group of individuals sharing a disease of interest.[166] Often, case-series form the basis from which more analytical epidemiological studies are derived.[166] The disadvantage of the case series is that it includes patients in a variety of stages of the disease in question making the establishment of causality difficult.[166]

5.3. Data

5.3.1. Major sources of health data

Health-related data is routinely collected from a variety of sources. The type and detail of data varies between sources. The source of data to use is determined by the study question. Increasingly, data from multiple sources can be linked to gain an ever greater detail of patient health.[170]

5.3.1.1. National records

Most countries have a record of vital statistics.[170] These are usually records of births, deaths and marriages nationwide.[170] This data is useful in calculating a demographic profile for the population and can be used to determine the rates of birth, death and the life expectancy.[170] Although useful for describing demographics, national records lack the fidelity needed to study disease.[170]

5.3.1.2. Survey data

A survey is a data collection tool that is used to gather information about characteristics of interest from a population.[170] They are generally carried out in order to ascertain disease prevalence.[171] Some surveys are carried out on a regular basis at a national level.[170] The census, an obligatory national survey carried out every ten years, collects information on demographic and health-care related data.[170] The data from such surveys is accurate but they are lengthy and expensive to conduction and analyse.[170] Other large surveys that collect health-related data are the General Lifestyle Survey (previously the General Household Survey) and the Health Survey for England.[170] Although useful for a general

sense of morbidity, national statistics lack the depth of information needed to investigate conditions in detail.

It would be complex, expensive and inefficient to conduct a detailed survey of the whole population in order to gather detailed information on one disease of interest. Therefore, a common approach is to ask a representative sample of members from a population questions related to a health characteristic of interest.[168] Surveys must be carefully designed to ensure that the answers given by participants are accurate, "truthful" and consistent.[168] A further challenge in using surveys is ensuring maximal participation.[168] Non-response introduces bias, hence every effort must be made to identify and reduce any barriers to participation.[168] Although survey data is commonly used in epidemiology, there are other sources of easily accessible clinical data.[168]

5.3.1.3. Primary and secondary care data

Data is continually collected by primary and secondary health care providers on a wide variety of health-related events.[170] In secondary care, this can be in the form of national databases (Hospital Episode Statistics) or can be abstracted from patient records.[170] In the UK, the majority of the population are registered with a general practitioner (GP).[170] Being the first port of call for ill patients, GP data is rich with a great diversity of clinical content.[170] Similar to secondary care, national statistics are produced from GP practices (e.g. General Practice Research Database - GPRD).[170] An added benefit of GP data is that the collection of prescribing data is a statutory requirement in the UK making it highly accurate.[170] The use of computerised databases in primary and secondary makes it easy to quickly retrieve and link data from multiple sources. As with survey data, it is important to

ensure that computerised databases have accurate, representative information that faithfully represents the population being studied.

5.3.1.4. Disease registries

A further source of data are disease registers.[170] Registers contain specific information on individuals with a health-characteristic of interest (usually a disease).[170] Numerous registers exist for different diseases (e.g. cancer, congenital abnormalities).[170] They are an excellent source of data on rare diseases.[170]

5.3.2. Diagnostic tests

Regardless of the source of data, an important requirement in determining the presence or absence of disease is being able to diagnose patients. In healthcare, a common approach is to use a diagnostic test to identify diseased individuals. A diagnostic test should test positive in diseased patients (sensitivity) and test negative if the patient does not have disease (specificity).[171] Also, a positive test must accurately distinguish diseased patients from healthy ones (positive predictive value (PPV)) and a negative test must differentiate healthy patients from those with disease (negative predictive value (NPV)).[171] The equations for sensitivity, specificity, PPV and NPV are shown in **Table 5.1**.

Table 5.1 A contingency table for diagnostic tests and disease

	Disease	**No disease**	*Total*
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

$$Sensitivity = \frac{a}{a+c} \qquad Specificity = \frac{d}{b+d}$$

$$PPV = \frac{a}{a+b} \qquad NPV = \frac{d}{c+d}$$

5.3.3. Sampling

In order to study an association, data on exposure and disease are required.[168] Data is gathered from an identified target population.[171] If the target population is too large to study as a whole, a sample population is studied instead.[171] Using a sample population allows us to make inferences about the target population but the inferences may not hold true in other populations.[171] The essential feature of the sample population is to be representative of the target population.[171] Fundamentally, the methods of sampling can either be random or non-random.[171] There is inevitably always some random fluctuation if multiple samples were drawn (sample variation) which is important to consider when making population estimates.[171] An important consideration to make when selecting a sample is to ensure the sample size is large enough to detect the clinically relevant effect which can be established through power analysis.[171] Computerised general practice databases offer the opportunity to study large general populations and form representative

and comparable sample populations. This is demonstrated by studies by de Lusignan *et al*., (2005)[38] and Stevens *et al*., (2007)[5] who were able to use computerised patient data from GPs in Kent, Manchester, and Surrey to identify patients with stage 3 to 5 CKD that may benefit from early intervention.

5.3.4. Types of data

There are different types of data which can be divided into two groups, categorical and numerical data.[171] Categorical data, also known as qualitative data, can be divided into two types, nominal data which is unordered (e.g. skin colour) and ordinal data which is ordered (e.g. likert scale).[171] Where there are only two options (e.g. yes or no), the categorical data is dichotomous.[171] Numerical data, also known as quantitative data, can also be divide into two groups.[171] In discrete data, numerical values can only take certain values (e.g. number of co-morbidities).[171] Continuous data on the other hand can take any value.[171] If numerical values are equally spaced, the data is described as interval data (e.g. weight) and where there is a true zero, the data is describes as a ratio (e.g. Kelvin scale).[171] Statistically therefore, ratio data carries the most information with nominal data carrying the least.[171] Every attempt should be made to record the highest level of data available as this greatly influences the statistical analyses available.[171]

5.3.5. Presenting data

Epidemiological studies usually gather large amounts of data. Therefore, it would be impractical and confusing to present it verbatim. Data therefore can be summarised in a number of ways to allow the reader to quickly grasp important characteristics.[171] Data can be presented in a tabulated form or diagrammatically.[171] Tabulated data is often presented in frequencies, percentages, proportions or rates.[171] Representing data diagrammatically

has the advantage of visual representation allowing for the quick comparison of differing variables.[171] Although powerful, diagrams must be chosen wisely if they are to faithfully represent the data and must not be perplexing. The choice of diagram is dictated both by the type of data and the variable(s) in question.[171] The purpose of displaying summarised data is more than informing the reader, it also serves as a quick method of spotting outliers or errors in the data before statistical analysis is performed.[171]

5.4. Statistical Analysis in Epidemiology

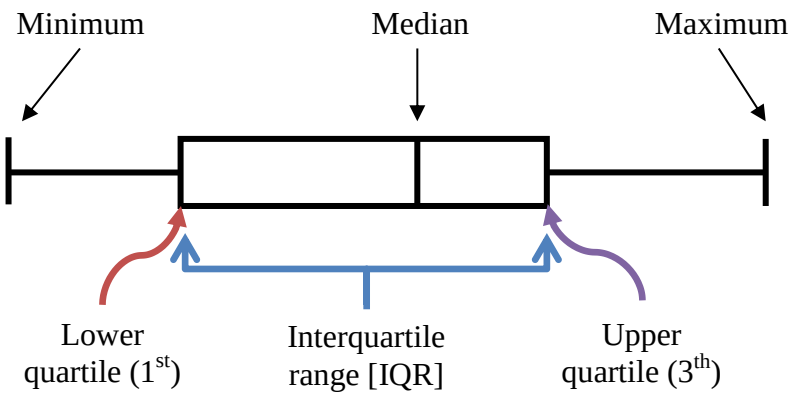
Statistics has been defined as "*the science of assembling and interpreting numerical data*".[171] Before data is interpreted however, it must be correctly prepared to ensure its completeness and accuracy.[168] A statistic is a quantity calculated from a sample population which tries to estimate the population parameter.[171] Statistics can be descriptive or inferential.[171]

5.4.1. Measures of central tendency and dispersion

In order to gain a quick impression of the overall data, a useful strategy is to find the "average" value for a sample and also give a measure of the level of variation from the typical value.[171] There are three main strategies of describing central tendency depending on the level of data and the distribution of values.[171] The arithmetic mean is the average value for a sample group calculated by summing all the values in a given variable and dividing by the number of participants.[171] The mean is used with numerical data only.[171] The arithmetic mean can be misleading if there are extreme values in a dataset or if the distribution of the values is skewed.[171] In such a scenario, the median is a better measure of

central tendency as it represents the middle value of the ordered data.[171] The median can be used to describe ordinal and numerical data.[171] The mode is a representation of the value that occurs most frequently in a data set.[171] Although it can be used to describe all levels of data, it is the only measure of central tendency for nominal data.[171] A measure of central tendency is only useful if accompanied by a measure of dispersion. Although the range is a useful measure of maximum and minimum values, it also includes extreme values.[171] Therefore, other measures of dispersion are normally given.[171] The standard deviation is an indication of the difference between values and the mean.[171] Given the sample is normally distributed (Gaussian distribution), approximately 68% of the study participants will lie at ±1 standard deviations; 95% and 99% lie at ±2 and ±3 standard deviations respectively.[171] Where the assumption of normal distribution is not met or there are extreme values, centiles can be used instead.[171] Centiles allow us to describe the central range of values with the 50th centile (2nd quartile) being equivalent to the median.[171] Therefore, 50% of the values lie between the 25th and 75th centiles (between the 1st to 3rd quartiles); this is known as the interquartile range.[171] The data can then be diagrammatically displayed with the addition of maximum and minimum values creating a whisker and box plot (**Figure 5.2**).[171]

Figure 5.2 Whisker and box plot



5.4.2. Confidence intervals

For numerical data, the calculated mean from our sample population is used as an estimate of the true population mean.[171] There is a level of error involved in the calculation because sample variation introduces differences between our calculated mean and the true population mean.[171] Therefore, we can give a range of values in which we would expect the true population mean to lie.[171] This is known as a confidence interval (CI) and it is an example of an inferential statistic because it uses sample data to make conclusions about the general population.[171] Normally, the 95% CI is given to indicate the degree of mathematical certainty to which we believe the population mean to lie.[171] The CI is calculated using the mean ± (standard error * 1.96 (or $t_{0.05}$ for samples of 30 or less)).[171] Where the CI(s) for two means do not overlap, it provides statistical evidence to indicate that the two means are "truly" different.[171]

5.4.3. Hypothesis testing

A hypothesis is an unproven theory that is formulated at the beginning of a study (a priori).[171] In epidemiology, the hypothesis is usually a statement that relates to a difference between two interventions or exposures (two-sided); the hypothesis may also propose the direction of difference (one-sided).[171] For every hypothesis, there is a null equivalent.[171] Known as the null hypothesis (H_0), it is a statement of no difference.[171] The inverse of the null hypothesis is the alternative hypothesis (H_1).[171] Thus a hypothesis test is aimed at either rejecting or accepting the null hypothesis (but not the alternative hypothesis).[171] To test a hypothesis, we must first place a threshold at which we can reject the null hypothesis.[171] Known as the *p*-value, it relates to the probability that the observed effect (or more extreme) could have occurred by chance (e.g. due to sample variation) and that is does not actually exist in the population (meaning the null hypothesis is still true).[171]

Normally, the *p*-value is set at 0.05.[171] To test the hypothesis, we calculate an appropriate test statistic and then use this to look up the *p*-value.[171] If the *p*-value is ≤0.05, we reject the null hypothesis and this increases the evidence towards the alternative hypothesis.[171] With a *p*-value of 0.05, it means that there is still a 5% chance of rejecting a "true" null hypothesis; this is known as a type 1 error (α).[171] Failing to reject a "false" null hypothesis is known as a type 2 error (β).[171] The ability to reject an incorrect null hypothesis and therefore to detect a clinically relevant effect is determined by a number of factors such as the size of effect being measured, the sample size, the level of significance (*p*-value) and the variability in the observations.[171] This is known as the power, it is the inverse of the probability of making a type 2 error (1-β).[171]

5.4.4. Parametric and non-parametric tests

In order to produce a test statistic, we need to employ the correct test for the hypothesis in question. Conceptually, a test statistic is the ratio of systematic variance (e.g. due to exposure) to unsystematic variance (e.g. random variation).[172] There are numerous parametric and non-parametric test that produce test statistics for different scenarios.[172] Parametric tests require that a number of assumptions be fulfilled whilst non-parametric tests do not.[171]

Student's *t*-test (after W.S. Gossett who used the pseudonym student) is used to compare differences in means either between a single group and a proposed population mean or between two related (paired) or unrelated (unpaired) groups.[171] The *t*-test requires that the sample data be normally distributed with equal variance (otherwise Welch's *t*-test can be used if there is unequal variance).[171] It may be possible to transform data to fit a normal distribution but where this not possible, there are non-parametric equivalents.[171] The

Wilcoxon signed ranks test and the Wilcoxon rank sum/Mann-Whitney *U* test are the non-parametric equivalents of the paired *t*-test and the independent *t*-test respectively.[171] When comparing numerous means of a variable of interest (e.g eGFR) between one categorical group (e.g. different ethnicities), it would be inappropriate to use multiple *t*-tests as the probability of making type error I increases with every test.[171] In such a scenario, the one-way Analysis of Variance (ANOVA) test is necessary.[171] Where two or more categorical groups are used, (e.g. sex and ethnicity) the two-way ANOVA is appropriate.[171] As with all parametric tests, the one-way ANOVA test requires that assumptions be fulfilled which can be checked using Levene's test.[171] Welch's F and the Brown-Forsythe F can be a useful alternatives where variances not homogenous.[172] The Kruskal-Wallis test is the non-parametric equivalent of the ANOVA test.[171]

The tests so far have been for numerical data but parametric and non-parametric tests also exist for categorical data.[171] The Chi-squared (χ^2) test is used to assess whether associations exists between two different groups and two characteristics of interest.[171] The data must be in the form of frequencies and is usually displayed in a 2×2 table (contingency table).[171] The χ^2 statistic works by looking at the difference between the observed and expected counts.[171] Where there are small frequencies, Yate's correction formulae should be used as it gives more conservative estimates.[171] Where the expected frequency is <5 in any one cell, Fishers exact test is required.[171] The χ^2 test can also be used for trend between ordinal data (e.g. age groups) and a dichotomous variable (e.g. presence or absence of pain).[171] The χ^2 test is only relevant if the groups are unrelated; if the groups are related, the appropriate statistic is calculated using McNemar's test.[171]

5.4.5. Correlation

Correlation is used to test for the strength of association between two continuous variables.[171] If there is a linear relationship between two continuous variables, the correlation can be absolutely positive (+1), absolutely negative (-1) or anything in between.[171] The parametric test of correlation is Pearson's product moment correlation coefficient, known simply as the correlation coefficient (r).[171] We use the correlation coefficient when there is a linear association, there is no data clustering or outliers and the data is unpaired.[171] It should be noted that the correlation coefficient is not accurate at small sample sizes.[171] The square of the correlation coefficient (r^2) represents the proportion of variability of the y variable that can be attributed to its linear relationship to the x variable.[171] Spearman's rank correlation coefficient (r_s), the non-parametric equivalent, is useful when the sample size is small, one of the data are ordinal or the relationship between them is non-linear.[171] Kendall's Tau is an alternative to Spearman's rank correlation co-efficient.[171]

5.4.6. Linear regression

Where we know two continuous variables have a linear relationship, we can work out the linear regression line which describes, as a mathematical formulae, the straight line relationship between the two variables.[171] The equation is in the form;

$$Y_i = (b_0 + b_1 X_i) + \varepsilon_i$$

Y_i, predicted value for each individual; b_0, intercept; b_1, slope; X_i, explanatory variable value for each individual; ε_i, residual error (difference between predicted and observed value for each individual)

Mathematically, linear regression involves choosing a line of best fit to the data points so that the sum of the squared residuals (vertical difference between the "fitted" Y and the

measured Y) is at a minimum.[171] Linear regression therefore allows us to predict the probable value of Y for a given value of X.[171] There are a number of assumptions that must be fulfilled, these are; the association between variables is linear, the observations are independent, for any value of X, the values of Y are normally distributed and the variability of Y values is constant.[171] The assumptions can be checked by studying the distribution of the residuals.[172] The variable X may only partially explain the changes in Y and in fact, multiple variables may be involved in determining the value of Y.[171] Where this is the case, we can calculate partial regression coefficients (b_n) for each variable using multiple linear regression.[171] Each individual slope will represent the degree of change that occurs in Y when the individual X variable is altered by 1 unit whilst controlling for the effects of the other X variables.[171] The equation therefore becomes;

$$Y_i = (b_0 + b_n X_{ni}) + \varepsilon_i$$

Y_i, predicted value for each individual; b_0, intercept; *b*n, slope for the *n*th explanatory variable; Xn_i, the value for the *n*th explanatory variable per individual; ε_i, residual error (difference between predicted and observed value for each individual)

The assumptions for multiple linear regression are the same as those for simple regression except that the explanatory variables should not be highly correlated with each other (collinearity).[171] Multiple linear regression can be performed using categorical explanatory variables (X) which can be binary or nominal.[171] Other types of regression analysis exist for use with binary dependant variables (logistic regression) and for analysing factors affecting the rate of event occurrence (Poisson regression).[171] In multiple logistic regression, the exponential of a partial coefficient (*b*) for a variable (X) is the estimated "adjusted" OR.[172]

5.5. Common Epidemiological Measures of Disease Occurrence

In epidemiology, the measurement of the level of disease in a population is an important descriptive tool.[170] The two most important measures are the incidence and the prevalence.[170]

5.5.1. Incidence

The incidence is a measure of new cases of disease occurring over a specific time period in the population (e.g. 5 new cases per year) .[170] The cumulative incidence (also known as the attack rate) is similar to the incidence but related to the number of new cases divided by the at risk population at the beginning of the study (e.g. 5/1000 per year).[170] The incidence density rate is calculated by dividing the number of new cases in a given time period by the person years at risk (e.g. 5/1000 person years).[170] As it only counts new cases, the incidence is not inflated by the duration of disease.[170] However, it requires a period of follow-up (technically for the whole population).[170] The incidence is the preferred measure for assessing risk.[170]

5.5.2. Prevalence

The prevalence is the number of cases in a given population.[170] The prevalence can be for a fixed time point (point prevalence), a defined time period (period prevalence) or over the entire lifespan of every individual in a population (cumulative prevalence).[170] Although the prevalence can be given as a number, it is typically given as a proportion with the at risk population being the denominator (e.g. 39/1000).[170] The prevalence counts both new and old cases and does not require follow-up.[170] However, the prevalence is inflated by

diseases with long durations as old cases are continually recounted.[170] The prevalence is the preferred measure of disease burden.[170]

5.6. Common Epidemiological Measures of Association

There are numerous methods of measuring association in epidemiology. The measure of association gives an indication of the degree of risk associated with a given risk factor.[168] This is required because most diseases are multifactorial and the presence of exposure does not guarantee disease, it simply augments the risk of disease.[168] However, an association does not necessarily infer causality.[171] Austin Bradford Hill (1965) set out criteria to determine the strength of evidence for suspected causality.[171,173] The evidence for causality increases if; there is a clear dose response, there is a strong association, the exposure specificity for disease is high, the exposure to disease time relationship is maintained, the interaction if biologically plausible, the effect is consistent and there is supportive experimental evidence.[171,173]

5.6.1. Absolute risk

The absolute risk is the probability of having a disease due to exposure as a proportion of all exposed individuals.[171]

$$\frac{number\ of\ cases\ of\ disease\ in\ exposed\ individuals}{number\ of\ exposed\ individuals}$$

The absolute risk ratio is not useful as an association measure on its own as it discounts unexposed individuals.[171] However, it is useful in giving a sense of the scale of effect that exposure has on developing disease and is usually given as a percentage.[171]

5.6.2. Relative risk

As the name suggests, the relative risk (also known as the risk ratio) is a measure of the risk of developing disease if exposed relative to the risk of developing disease if unexposed.[171]

$$\frac{Disease\ incidence\ in\ exposed\ individuals}{Disease\ incidence\ in\ unexposed\ individuals}$$

A relative risk of 1 actually indicates no association between exposure and disease.[171] A relative risk of >1 or < 1 indicates an increase or decrease in the risk of developing disease if exposed.[171] The relative risk can be used as measure of effect (effect size) (*see section 5.9.3*).[172]

5.6.3. Odds ratio

The odds ratio is a measure of association that assesses the probability of disease occurrence with exposure compared to the probability of disease occurrence in unexposed patients.[171]

$$\frac{Odds\ of\ disease\ \boldsymbol{with}\ exposure}{Odds\ of\ disease\ \boldsymbol{without}\ exposure}$$

It is normally used in retrospective case-control studies and approximates the relative risk where the risk of developing disease is rare.[171] Moreover, like the relative risk, an OR of 1 indicates no association between exposure and disease.[171] The OR is also a common measure of effect (*see section 5.9.3*).[172]

5.6.4. Attributable risk

The attributable risk (also known as the risk difference) is the probability of developing disease if exposed minus the pre-existing risk if not exposed.[171]

$$Disease\ incidence\ if\ exposed - Disease\ incidence\ if\ unexposed$$

An attributable risk of 0 indicates no extra risk of developing disease if exposed.[171] The attributable risk is often given as the excess number of cases per 1000.[171]

The population attributable risk is similar but it assesses how much of the disease in the population is attributed to the exposure.[171]

$$Total\ disease\ incidence - Disease\ incidence\ if\ unexposed$$

The attributable risk and the population attributable risk should not be calculated in case-control studies.[171]

5.6.5. Number needed to treat and number needed to harm

Both the number needed to treat (NNT) and the number needed to harm (NNH) measures the difference in effect either between intervention and control groups or exposure and

non-exposure groups.[171] Both the NNT/NNH show the number of patients needed to be exposed or given an intervention for 1 patient to come to harm or be treated.[171] They are the inverse of the absolute risk reduction/increase (risk difference).[171] In NNT, the equation is;

$$\frac{1}{Chance\ of\ survival\ in\ new\ drug\ users - Chance\ of\ survival\ in\ old\ drug\ users}$$

For NNH, the equation is;

$$\frac{1}{Probability\ of\ disease(exposed) - Probability\ of\ disease(unexposed)}$$

5.6.6. Summary

The calculation of association measures can be visualised using a 2x2 table (**Table 5.2**).[171]

Table 5.2 A contingency table for exposure and disease

	Disease	**No disease**	*Total*
Exposed	a	b	a+b
Unexposed	c	d	c+d
Total	a+c	b+d	a+b+c+d

- Absolute Risk

$$\frac{a}{(a+b)}$$

- Relative risk

$$\left[\frac{a}{a+b}\right] \Big/ \left[\frac{c}{c+d}\right]$$

- Odds ratio

$$\left[\frac{a}{b}\right] \Big/ \left[\frac{c}{d}\right]$$

- Attributable risk (risk difference)

$$\left[\frac{a}{a+b}\right] - \left[\frac{c}{c+d}\right]$$

- Number needed to harm

$$\frac{1}{\left[\frac{a}{a+b}\right] - \left[\frac{c}{c+d}\right]}$$

5.7. Bias, Confounding and Chance

Errors in a study can be random or systematic.[171] Bias occurs when there is unequal error between two comparison groups resulting in a false understanding in either directional.[166,168] However, even errors occurring equally amongst different groups (non-directional) may lead to false conclusions.[166] Generally, bias is introduced by systematic errors in the study methods either in the sampling of individuals (selection bias) or in the gathering of data (information bias).[171]

5.7.1. Selection bias

Selection bias comes from the methods used to form the study sample.[166,168,171] Commonly, it occurs when there is a systematic difference in the recruitment or allocation of the study groups.[166,168,171] Studies collecting data from surveys or questionnaires are especially prone if participants do not respond.[166,168,171] Selection bias is of importance in CKD because the disease is largely asymptomatic. It may be the case that patients who have their eGFR measured are more likely to seek medical attention. Consequently, they may have different characteristics to the general, but yet unidentified, CKD population.

5.7.2. Information bias

Information bias occurs when measurements in the exposure or outcome are incorrect or unrepresentative of the target population.[171] Because epidemiological data is derived from free living individuals, it is inevitable that there is some inaccuracy in the measurement of disease or exposure.[166] This is especially important to consider in scenarios where the data has been input by an independent observer (e.g. the GP in computerised databases). In such a study, an added risk is that patients were not completely followed up (follow-up bias).[171] Furthermore, there is always an element of error in biochemical measurements due to variability in the quality of the specimen, differences in laboratory techniques/equipment and the overall sensitivity/specificity of the test.[166] For example, serum creatinine assays are subject to inter and intra-laboratory variation if not correctly calibrated (*see section 1.2.3*). In the above example, measurement bias could lead to misclassification of patients into inappropriate stages of CKD (misclassification bias).

5.7.3. Confounding

Confounding occurs when a separate factor(s) can interact with the disease and/or exposure in such a way as to augment the risk but is not in the causal pathway between the exposure and disease of interest.[171] Because the other factor may not be known or have been measured, it can exert a significant effect in the overall estimates generated.[166] Where significant, confounding can lead to spurious associations between exposure and disease.[166] This is of importance in studies looking at drug effects (such as NSAIDs). A common confounder in such a study may be the indication for the drug (e.g. gout) which may influence the natural history of the disease in question (e.g. CKD). Several strategies exist to minimise confounding either at the design (randomisation, matching) or analysis (stratification, statistical adjustment) phase.[171]

5.7.4. Chance

A near unavoidable source of error in studies is random error.[171] It stems from the fact that most studies must obtain a sample from the population because it would not be practical to study the entire population.[171] Although samples are meant to be representative of the target population, there is always some variation between the characteristics of individuals in each sample.[171] Therefore, the measured outcomes from multiple samples would give a slightly different answer to the true effect in the population.[171] Random error can be minimised by ensuring the sampling methods are adequate and the sample size is large enough to capture the majority of the characteristics of the individuals in the target population.[171]

5.8. Systematic Reviews

5.8.1. What is a systematic review?

Traditionally, reviews were written by experts in the field but often, the methods used were unclear or were not published.[174] There was also a lot of disagreement between experts leading to opposing conclusions about the literature.[174] Oxman and Guyatt (1993) showed the disparity between "authoritative" reviews and advocated a more systematic approach be taken.[174]

A systematic review is "*an attempt to collate and summarise evidence using predefined criteria*".[175] Systematic reviews must use methods that maximise reliability but minimise bias.[174,175] To achieve this, systematic reviewers must use rigorous, reproducible methods and must ensure that their results are valid.[174,175] Systematic reviews are a vital part of evidence-based medicine and are considered the top level of evidence.[175] Such is the importance of systematic reviews that an international collaboration (the Cochrane Collaboration) was set up to "*prepare, maintain and promote systematic reviews to inform healthcare decisions*".[175]

5.8.2. Systematic review methodology

Systematic reviews ensure reproducibility and rigour by abiding to a series of well-defined processes.[176] Firstly, a systematic review starts with a focused enquiry.[175,176] The topic will largely determine the criteria the author choses for the inclusion of relevant studies.[176] Just as important as the inclusion criteria, some evidence must be excluded to ensure that accuracy and focus is maintained.[175,176] All efforts must be made to search all relevant

sources, both published and unpublished.[175] The search strategy used should therefore be stated as it allows other readers to gauge whether relevant studies were likely to be included.[175] In selecting studies, two (or more) reviewers should be involved in the process to minimise the effects of reviewer bias and human error.[175] Once studies are identified, a vital step is to check the "validity" of the included studies.[175,176] Systematic bias poses the greatest threat to skewing the conclusion of a review hence each included study must be critically appraised to ensure that the design and conduction of the study protected against bias where possible.[176] Once the included studies are deemed valid, the relevant data is extracted and analysed.[175,176] This is an important step in determining the "precision" of the study results.[176] To increase the overall precision and to provide a quantitative summary of the available evidence, statistical analysis can be used in the form of a meta-analysis.[175,176] The final part of a systematic review is to discuss the review findings in the context of the current evidence.[175,176] Conclusions and recommendations should be appropriate and must be based on the strength of the presented evidence.[175,176] Authors should always be open and critical and therefore should highlight the limitations of their review.[175,176]

5.9. Meta-analysis

5.9.1. What is a meta-analysis?

A meta-analysis is a form of statistical analysis that combines the information from all relevant studies to provide more precise estimates of the effect of interest.[175,177] The meta-analysis will provide an indication of the direction, size and consistency of the effect.[175] However, meta-analysis do not provide an overall measure of the strength of evidence.[175] It

can provide a measure of statistical uncertainty but ultimately judgements on the strength of the evidence base must be made in the context of the entire review.[175]

5.9.2. When is it appropriate to perform a meta-analysis?

Performing a meta-analysis is not an absolute requirement of a systematic review.[175,176] A qualitative synthesis of evidence is able to answer the same questions that a quantitative synthesis can.[175] However, with a qualitative review, there is a risk of bias if, for example, one study is preferred by the reviewer.[175]

Classically, meta-analyses are used to combine the results from clinical trials.[175] However, increasingly, epidemiological studies are using meta-analysis to summarise observational study data.[178] A meta-analysis should not be used if studies report on a clinically diverse group of patients.[175] The comparisons made will not be valid as there is not enough commonality between studies.[175] Similarly, including studies at risk of bias simply distorts the results further.[175] A final consideration is to ensure that the review safeguards against reporting bias if the conclusions are to be valid.[175]

In performing a meta-analysis, the following five considerations[175] should be made;

1. Which comparisons should be made?
2. Which study results should be used in each comparison?
3. What is the best summary of effect for each comparison?
4. Are the results of studies similar within each comparison?
5. How reliable are those summaries?

It should be clear which comparisons will be made and this should be related to the focused review question.[175] Once the comparisons to be made are decided upon, a suitable effect measure (effect size) is then needed.[175]

5.9.3. Common effect sizes

Borenstein *et al*., (2009) defines the effect size as "*the value which reflects the magnitude of the treatment effect or (more generally) the strength of relationship between two variables*".[178] The effect size is usually accompanied by a measure of the degree of precision (e.g. CI) and significance (*p*-value) (*see section 5.4*).[178] The degree of precision is used to provide weight to the study size in the inverse of variance method.[178] Because precision is driven by sample size, bigger studies are given more weight in a meta-analysis.[178] The type of study design also affects the precision of the effect measure.[178]

A number of considerations should be met when choosing an effect size. Firstly, the effect size should measure the same outcome equally between studies.[178] Secondly, the effect size should be computable from published data and should not need re-computation of raw data.[178] Thirdly, the effect size should have good statistical properties so that variances and CIs can be computed (e.g. OR).[178] Finally, the effect size is easy to interpret.[178] The reported effect sizes are determined by the study design and gathered data.[178] We can roughly classify the common effect sizes into those based on continuous (raw/standardised mean difference), binary (relative risk, OR, risk difference) and correlation data (r).[178] Some studies may also report effect sizes based on rates/counts (e.g. rate ratio/difference) and time-to-event (hazard ratio) data.[175] It is possible to convert between different effect measures but this does not guarantee that studies do not differ in other ways.[178] Normally, the effect size used in the meta-analysis is the same as the summary effect estimate.[179]

However, it is possible, for example, to input data as one effect size (OR) and report the outcome of the meta-analysis in a different format (relative risk).[179] The absolute risk in the unexposed group would need to be known in such an approach.[179]

5.9.4. Statistical models in meta-analysis

Most meta-analysis are based on two statistical models, the fixed and random effects models.[178] In a fixed effects model, we assume that there is one true effect size in the population which all included studies are trying to estimate, hence the meta-analysis produces a pooled estimate for this true effect.[178] The differences between studies are assumed to be due to random error.[178] The weighting of effects sizes is, therefore, geared toward minimising the within-study error (inverse variance method).[178]

However, in a random effects model, we assume that the true effect size in the population is distributed over a range of values; hence the meta-analysis aims to estimate the mean of the distribution of the possible effect sizes.[178] Therefore, differences between studies are due to both random error and the true variation between effect sizes.[178] Similar to the fixed effects model, studies in a random effects model can also be weighted according to the inverse study variance.[178] However, the total variance is a sum of both the within-study variance and between-study variance.[178] In general, a random effects model tends to give more balanced weighting between studies with varying sample sizes.[178] Therefore, in a random effects model, larger studies receive proportionally less weight than would be the case if a fixed effects model was used.[178] Moreover, due to the inclusion of two sources of error, the random effects model produces wider CIs.[178] The choice on which model is most appropriate is dependent on the measured characteristics between studies.[178] For example, if studies used participants with different stages of disease, age or co-morbidity, it is likely

that the effect size would be different between studies.[178] Therefore, a random effects model would be the most appropriate choice.[178] The choice of which model to choose should not be based on the level of heterogeneity.[178]

With both models, it is possible to compute the effect size for more than one group of studies as well as combining the effect estimates between groups; this is known as subgroup analysis.[178] The assumption of subgroup analysis is that the studies compare variants of the same intervention (or exposure).[178]

5.9.5. Heterogeneity

Statistical heterogeneity is a measure of the variation that exists between "true" (population) effect sizes.[178] Where there is only one "true" effect in the population, heterogeneity would be zero.[178] Any variation in the sample effect estimate would be purely due to random variation.[178] If there are a range of "true" effect sizes, there would be variation both due to actual differences between effects size (heterogeneity) and random variation (sampling error).[178] Therefore, heterogeneity is the amount of excess variation than would be expected to be due to random error.[178] Statistical heterogeneity can be due to differences in the participants/exposures/outcomes studied (clinical heterogeneity) and/or methodological diversity (methodological heterogeneity).[175]

The I^2 statistic, first proposed by Higgins *et al*., (2003) is a popular measure of heterogeneity.[179] The advantage of the I^2 statistic over other methods of representing heterogeneity is that it is not affected by the number of included studies.[179] The I^2 statistic is used to give an indication of the excess variation as a ratio of overall variation.[178] Conceptually, it gives a sense of the degree of inconsistency between studies.[178]

$$I^2 = \frac{Between\ study\ variation}{(Between\ study\ variation + Within\ study\ variation)} \times 100$$

The I^2 statistic is measured on a scale of 0-100% and allows for the calculation of CIs.[179] Higgins *et al*., (2003) suggested the values of 25%, 50% and 75% be regarded as evidence for low, moderate and high heterogeneity.[179]

Sources of heterogeneity should always be explored.[179] Subgroup analysis is a useful strategy for exploring sources of heterogeneity.[175] An extension of subgroup analysis, meta-regression, can be implemented to investigate the correlation between the outcome effect estimate (e.g. risk of developing CKD) and one or more explanatory variables (e.g. subgroups of increasing doses of NSAIDs use).[179] Meta-regression should not be performed if there are less than 10 studies.[179]

5.9.6. Reporting bias

Meta-analysis uses data from studies to estimate the effects of exposure on disease.[178] Since published studies are more readily available, they are more likely to be incorporated in a meta-analysis.[178] This source of bias, known as publication bias, can influence the results of a meta-analysis and the systematic review in general.[178] Of concern is if the published studies are systematically different from unpublished studies.[178] The trend in the literature is that studies reporting positive effects are more likely to be published.[178] Other sources of bias that influence the reporting of study findings and therefore reduce the likelihood of inclusion include; language, availability, cost, familiarity, citation and duplication.[178]

To address reporting bias, every effort must be made to obtain both published and unpublished material through various sources.[178,179] Once all sources of data are sought, one can evaluate the possible effects of publication bias on a meta-analysis using a funnel plot.[178] The basic assumption is that large studies (with more precise estimates) are more likely to be published regardless of the result (as they involved a large investment in resources) whilst smaller studies (with less precise estimates) are less like to be published unless they have significant results.[178] Therefore, if the standard error (the measure of precision) is plotted against the effect size, it will be skewed towards a significant effect in smaller studies where publication bias is present.[178,179] However, a funnel plot needs careful interpretation as asymmetry can be due to more than just publication bias.[179] Several statistical tests exist for providing a more objective analysis of publication bias.[179]

5.9.7. Advantages and disadvantages of performing a meta-analysis

Meta-analyses are extremely useful as they have the ability to increase the power and precision of effect estimates.[179] Therefore, they can detect effects missed by individual studies.[179] Using subgroup analysis, it is possible to answer questions not posed by individual studies.[179] The meta-analysis also gives an objective "review" of the evidence whilst a traditional narrative review may be biased by the authors.[178]

However, one must be careful when performing and interpreting a meta-analysis as they can be misleading if performed incorrectly.[179] A meta-analysis should only be used when it is appropriate and it should always be interpreted in context of the evidence.[179] Like all statistical tests, there needs to be an evaluation of the methods used to safeguard against bias and minimise the probability of coming to spurious conclusions.[179]

Chapter 6. Non-Steroidal Anti-Inflammatory Drugs and Chronic Kidney Disease Progression: A Systematic Review and Meta-Analysis

Review Summary

NSAIDs are widely regarded as one risk factor which influences the progression of CKD. Previously published studies have reported conflicting results on this relationship. They have also been criticised for employing flawed study designs. However, recently published studies have begun to shed new light on the true nature of the relationship between NSAID use and CKD progression. Given the common use of NSAIDs by patients in general practice and the potential clinical significance of any negative renal effects, the need for a systematic review has never been greater.

We carried out MEDLINE, EMBASE, COCHRANE, AMED, BNI and CINAHL databases searches with no language or date of publication restrictions. Other sought sources were; hand/electronic reference checking of the obtained articles, unpublished literature (openSIGLE), the Lancet Journal, CKD experts and the British Library.

Studies evaluating NSAID use in patients aged 45 years and over with stages 3 to 5 CKD reporting on the GFR were sought. The minimum study period and sample size were 6 months and 50 respectively. Studies using ESRD as the primary outcome or including Phenacetin users were excluded.

The study type, period, population, NSAID data, definition of use and outcomes were extracted. A meta-analysis was performed assessing the Odds Ratio (OR) for a rapid CKD progression (estimated GFR decline of $\geq$15ml/min/1.73m^2) and the OR for developing stage 3 to 5 CKD.

We identified 7 studies (1,640,194 total participants) performed up to September 2011. We concluded that regular NSAID use did not significantly affect CKD progression; pooled OR= 0.96 (95% CI: 0.86-1.07). However, high-dose NSAID use was associated with a significantly increased risk of rapid CKD progression; pooled OR= 1.26 (95% CI: 1.06-1.50).

6.1. Introduction

6.1.1. Chronic Kidney Disease, the challenge

CKD is now a major cause of morbidity and mortality worldwide,[4] with recent prevalence estimates of stages 3 to 5 CKD of 8.5% in the adult UK population.[5] Similar figures have been reported in other developed countries (such as USA, Australia, Netherlands, Korea, China and Mexico) with the prevalence being as high as 20% (in Japan).[3,31,33-37] The number of patients with CKD is increasing rapidly.[4,6] There has also been an increase in the prevalence of co-morbidities known to cause CKD such as type II DM and HTN.[5,6]

Given that the prevalence of CKD rises exponentially with age, the increase in the proportion of elderly people within the population[8] will no doubt lead to an increase in the disease prevalence.[6,31] Furthermore, there is a lack of awareness of the condition partly due to the asymptomatic nature of CKD and the lack of a physician diagnosis.[6,40] In fact, over 90% of patients with CKD may be unknown to renal or primary care services.[38,163]

CKD stages 3 to 5 are seen as the perfect opportunity to augment any risk factors (such as NSAIDs) that may result in the progression of CKD.[2,180] However, NSAIDs such as aspirin

are also used to treat co-morbidities like CVD which are independently associated with worsening CKD.[116,181] NICE CKD guidelines clearly state that the biggest impact that can be made in reducing the prevalence of CKD is by delaying disease progression.[6] NSAIDs, identified by NICE as nephrotoxic drugs, are targeted as amendable factors.[6] NICE guidelines recommend that patients on long-term systemic NSAIDs have their GFR checked at least annually.[6] The GFR is widely estimated using the simplified 4-variable MDRD equation which is a quick, easy and fairly accurate measure of renal function.[17,19] Studies have shown that at risk patients can be readily identified using currently available computerised records.[5,38]

6.1.2. Stages of Chronic Kidney Disease

CKD is universally classified into five stages as set out by the US NKF-KDOQI guidelines.[4] The stages are divided according to the level of renal function as measured by the GFR (**Table 6.1**).[4] Stage 1 and 2 also require there to be evidence of kidney pathology either through the presence of proteinuria, haematuria, albuminuria or a structural abnormality.[4] The UK NICE guidelines also divide CKD stage 3 into two parts, CKD 3A and CKD 3B.[6] The definition requires that the renal dysfunction be present for at least 3 months.[4]

Table 6.1 Modified NKF-KDQOI stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild reduction in GFR	60-89
3A*	Moderate reduction in GFR	45-59
3B*	Moderate reduction in GFR	30-44
4	Severe reduction in GFR	15-29
5	End-Stage Renal Disease (ESRD)	<15 (or Dialysis)

*As categorised by NICE[6]

6.1.3. Non-Steroidal Anti-Inflammatory Drugs and the Kidney

Since the early 1950's, the excessive use of analgesics has been linked to renal disease.[124,182] An early analgesic, Phenacetin, was shown to cause analgesic nephropathy with chronic use leading to worsening kidney function.[124,182] Paracetamol (acetaminophen) is a derivative of Phenacetin[110], this led to the suspicion that it might affect kidney function[183] but soon the investigation widened to include all NSAIDs.

Cyclo-oxygenase enzymes are involved in the formation of prostaglandins which are especially important in promoting vasodilation in the renal arterioles of patients with renal impairment.[118,184] The inhibition of the COX enzymes by NSAIDs in patients with moderate to severe renal dysfunction might therefore be associated with adverse renal outcomes.[117,118,120] It is known that NSAIDs can cause acute renal failure.[100,101] However, studies performed since the late 1960's have uncovered conflicting evidence as to whether NSAIDs are associated with chronic renal failure.[12-14,127-146]

NSAIDs are some of the most commonly used classes of drugs worldwide.[104,163] NSAIDs are commonly used to control pain in patients with chronic inflammatory musculoskeletal conditions.[9-11] There is a significant overlap between NSAID use and CKD and studies have reported that over 50% of elderly patients with CKD are prescribed NSAIDs with low-dose aspirin accounting for the majority of prescriptions.[161,162,164,185] Patients with stage 3 to 5 CKD often have a multitude of other co-morbidities which in turn are inevitably linked to polypharmacy.[162,185,186] Therefore, it is of paramount importance that any risk NSAIDs pose on CKD patients be quantified.

6.1.4. Chronic Kidney Disease and co-morbidity

CKD is now considered as an independent risk factor for CVD.[39,187,188] Equally, CVD contributes to 50% of the mortality seen in CKD.[5,6] As the severity of CKD increases, the risk to cardiovascular health and mortality increases[4,6,69] whilst the quality of life decreases[189]. Worsening renal function is associated with an increasing prevalence of other co-morbidities including DM, HTN and even COPD.[190] CKD patients with worsening renal function are still 16-40 times more likely to die of complications of the disease than they are to progress to ESRD (stage 5 CKD).[6,191] However, patients with ESRD will require renal replacement therapy (RRT).[6] The quality of life for patients on RRT can be poor with high morbidity and mortality.[3,4,192] Moreover, 2% of the NHS budget is used on RRT.[3] This makes the identification of factors that lead to the progression of renal pathology to ESRD a matter of great clinical and economic importance.[3,6] There has been a significant shift in the treatment approach for CKD from that of simply treating ESRD to an emphasis on primary and secondary prevention[6,32,193-195] *(see section 2.1 and 2.3 for details on CKD and co-morbidity).*

6.1.5. Previous literature reviews

Two previous in depth epidemiological literature reviews by McLaughlin *et al*., (1998) and Delzell *et al*., (1998) assessing the association between chronic NSAID use and CKD have been inconclusive.[125,147] The major limiting factor given by the reviewers was the relatively poor quality of evidence and flawed study designs.[125,147] In the review by McLaughlin *et al*., (1998), a number of improvements to future studies designs were suggested.[125] The 'Ad Hoc Committee of the International Study Group on Analgesics and Nephrology' (2000), a peer reviewed committee of scientists, selected jointly by the regulatory authorities of Germany, Switzerland, Austria and the pharmaceutical industry

also found ‘sparse information and substantial methodological problems’ in the reviewed evidence.[126]

6.1.6. A gap in the evidence

It is clear that the prevalence of CKD is rising, the use of NSAIDs widespread and the outcome of ESRD detrimental. There is now an emphasis on identifying and modifying risk factors for CKD progression at a primary care level. The literature on chronic NSAID use and renal function is unclear. Previous studies recruited patients with ESRD and so were unable to study the effects of NSAID use at earlier stages of renal disease. However, since the establishment of NKF-KDOQI CKD staging using the GFR and the increasing availability of routinely collected clinical data, studies have been able to use large population-based samples of patients with less severe renal disease. There is no systematic review in the literature that assesses the use of NSAIDs and the progression of CKD in the general population. Therefore, we hope to provide the current evidence-base in which health professionals can make informed decisions on the prescription of NSAIDs. We hope the reader will be better placed to balance the risks and benefits of NSAID use in patients with moderate to severe CKD.

6.2. Objectives

The three objectives are:

1. To establish whether NSAID use increases the risk of CKD progression.
2. To establish whether NSAID use is associated with the development of stage 3 to 5 CKD.
3. To quantify the degree of NSAID use amongst patients with stage 3 to 5 CKD.

6.3. Methods

The approach taken in this systematic review was to focus on studies capturing large, population-based epidemiological studies investigating the effects of chronic NSAID use in patients aged 45 years and over with stage 3 to 5 CKD. In order to allow for generalisation from our research, we decided to use the GFR as a standardised measure of renal function. Studies were included in our systematic review if they meet the criteria set out in **Table 6.2**.

Table 6.2 Selection criteria used to identify studies in the systematic review

	Inclusion Criteria	Exclusion Criteria
Types of studies	• Population-based epidemiological studies with a focus on those performed in a primary care setting. • A study period of 6 months or longer. • A minimum of 50 participants. • No language or date of publication restrictions.	• A study period of less than 6 months. • A sample size of less than 50 patients.
Types of participants	• Male and female participants with CKD stages 3 to 5. • **Some** inclusion of participants aged 45 years and over.	• **Only** male or female participants. • **No** participants with CKD stage 3, 4 or 5 (*only* CKD stage 1-2). • **No** participants aged 45 years or over.
Types of interventions and comparison	• All orally administered selective and non-selective NSAIDs including Aspirin. • Study defined regular and non-regular NSAID user groups.	• Studies using Phenacetin as one of the NSAIDs either as a single agent or in combination with other NSAIDs.
Types of outcome measures	• The GFR calculated from gold standard methods (e.g. Inulin clearance) or using the 4-variable MDRD or Body-Surface-Area standardised CG estimation equations. • Studies reporting on the OR for a GFR or eGFR decrease. • Studies reporting on the OR/hazard ratio (HR) for developing CKD (stage 3 to 5).	• Studies **not** reporting on the GFR or eGFR. • Estimation equations other than the 4-variable MDRD or the BSA standardised CG equation. • ESRD as the primary outcome measure.

6.3.1. Search strategy

Three search interfaces were used for the electronic database search; (i) the NHS interface, (ii) the EBSCO interface and (iii) the COCHRANE interface. Any duplicates between the conducted searches were removed. All relevant studies conducted up to the 30th of September 2011 were considered. All databases were limited to human studies only. There was no language or date of publication restriction. On the MEDLINE database, papers were filtered to only include studies where the participants were ≥45 years to fit with the selection criteria. This was not possible on the other databases thus the relevant papers were filtered manually.

Relevant articles were obtained from the following electronic databases:

- MEDLINE – United States National Library of Medicine's. (NHS and EBSCO interfaces)
- EMBASE – The Excerpta Medica Database. (NHS interface)
- AMED – Allied and Complementary Medicine Database. (EBSCO interface)
- BNI – British Nursing Index. (EBSCO interface)
- CINAHL – Cumulative Index to Nursing and Allied Health Literature. (EBSCO interface)
- CDSR – Cochrane Database of Systematic Reviews. (COCHRANE interface)
- DARE – Database of Abstracts of Reviews of Effects. (COCHRANE interface)
- CENTRAL – Cochrane Central Register of Controlled Trials. (COCHRANE interface)
- CMR – Cochrane Methodology Register. (COCHRANE interface)
- HTA – Health Technology Assessment. (COCHRANE interface)
- NHS EED – NHS Economic Evaluation Database. (COCHRANE interface)

Other searched resources:

- Hand-searching of reference lists in the relevant full-text articles.
- Electronic citation checking via the WEB of KNOWLEDGE on all full-text articles.
- Unpublished 'grey' literature searching via OpenSIGLE.
- Hand searching of the Lancet Journal to obtain CKD review papers.
- Online searching on the NICE website for CKD guidelines.
- Online search of the British Library main catalogue.
- Consulted with Professor SJ Davies, an expert in CKD and co-morbidity.

The following exploded (ex) MeSH and free-text terms were used in all the database searching:

AND
- NSAID*
- non-steroidal AND anti-inflammatory AND drugs
- nonsteroidal AND antiinflammatory AND drugs
- exMeSH – Analgesics (or Analgesic Agent)
- exMeSH - Anti-Inflammatory Agents
- exMeSH - Anti-Inflammatory Agents, Non-Steroidal

AND
- Chronic Kidney Disease
- CKD
- exMeSH - Kidney Failure, Chronic (or Renal Insufficiency, Chronic)

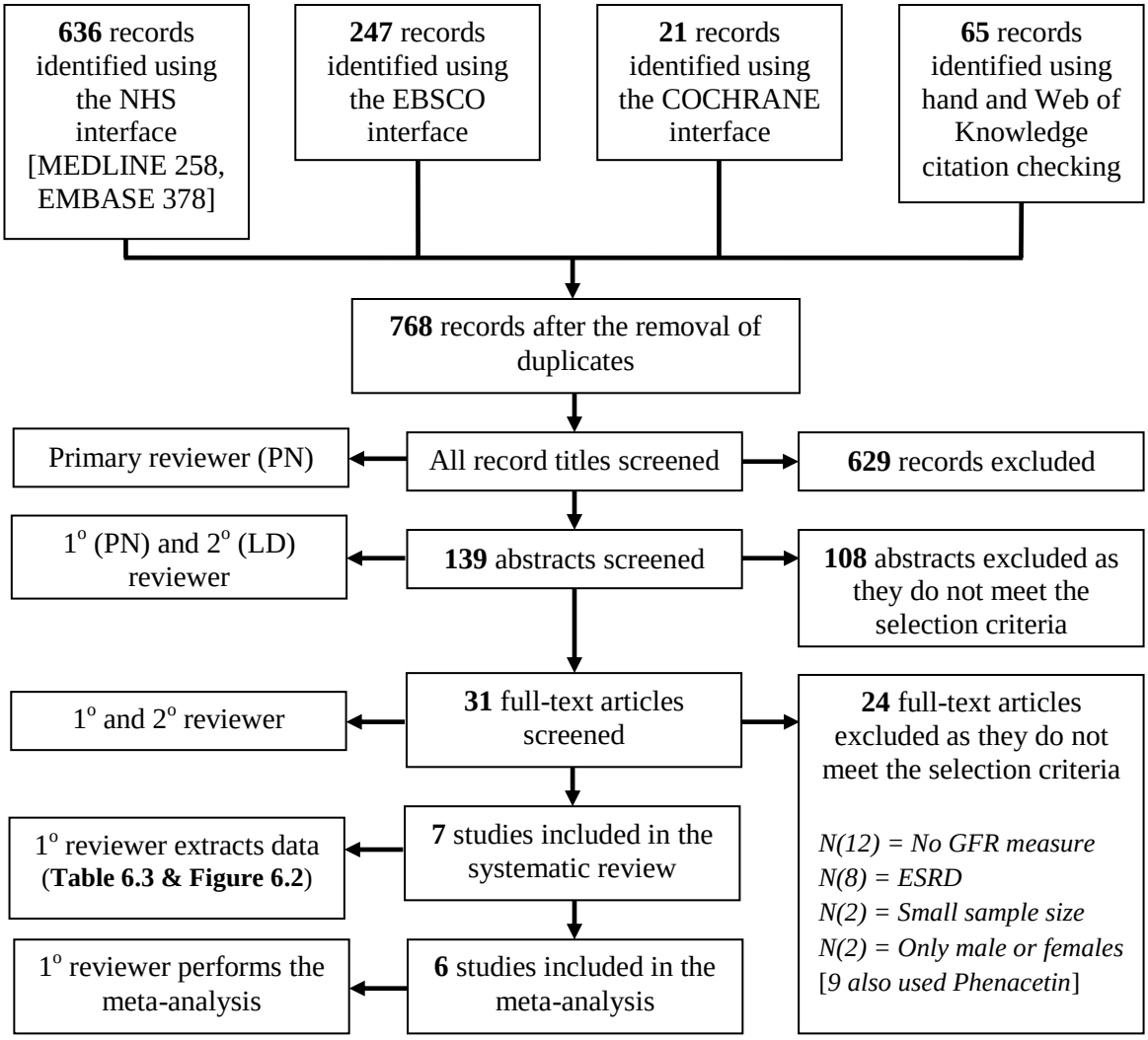
AND
- eGFR
- GFR
- Glomerular Filtration
- exMeSH - Glomerular Filtration Rate

6.4. Data Collection and Analysis

All citations from the various sources were pooled into the REFWORKS referencing software (version 2.0).[196] After the removal of duplicates, the titles of all remaining papers were screened to obtain a list of relevant abstracts. The abstracts and full text-articles were then selected for against the inclusion and exclusion criteria. The selection of the studies from the pool of identified abstracts was performed independently by two reviewers (Paul Nderitu (PN) and Lucy Doos (LD)) and any discrepancies were discussed and resolved.

Full-text articles included in the review underwent a methodological quality and risk of bias assessment examining the selection process, exposure/outcome measures and data analysis. This was performed by the primary author (PN) using the Critical Appraisal Skill Program (CASP) checklists for observational studies.[197] Data on the study period, type, location, participant population, NSAID data collection methods, exposure definition and outcomes were extracted by the primary author (PN). The primary outcome measures reported were; the adjusted OR for rapid eGFR decline, the difference in the eGFR decline rate per year between users and non-users and the adjusted OR/HR for CKD stage 3 to 5. **Figure 6.1** demonstrates how the included full text-articles were sourced. The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (2000) were used to improve the quality of this systematic review.[198]

Figure 6.1 Study selection flow diagram



6.4.1. Description of studies

Due to the nature of the research question and the selection criteria, the full-text articles obtained after the screening of abstracts contained mainly observational studies. Of the 31 studies identified, 11 were case-control studies, 16 were cohort studies, 3 were cross-sectional studies and 1 was a randomised cross-over study; all were available in English. Of these, 24 studies did not meet the selection criteria leaving 7 studies to be included in the review. A summary of the characteristics of included studies are given in **Table 6.3** with a more detailed description of all the included/excluded studies and specific reasons for exclusion reported in **Appendix 1** and **2**.

Table 6.3 Characteristics of included studies

Study	Study type	Location	Population	Sample size	NSAID data	Definition of NSAID use	Outcome
Fored *et al*., 2001[15]	Case-control	Sweden	18-74 year olds ± chronic renal failure (CRF)	926 CRF patients vs. 998 controls	Questionnaire. Standardised interview	Regular use, twice a week for 2 months; non-users <20 tablet lifetime use	OR for CKD 4-5 Aspirin, **2.50** (95% CI, 1.90-3.30); Paracetamol, **2.50** (95% CI, 1.70-3.60)
Gooch *et al*., 2007[150]	Cohort	Canada	Patients aged ≥66 years and older	10,184 patients	Prescription data	Use, ≥1 prescription (Rx) 1 year before 1st creatinine measurement. High-dose use ≥90th percentile.	OR for eGFR decline (≥15ml/min/1.73m^2) Any NSAID use (CKD 3), **0.82** (95% CI 0.59-1.15); High dose (CKD 1-5), **1.26** (95% CI, 1.04-1.53)
Hemmelgarn *et al*., 2007[151]	Cohort	Canada	Patients aged ≥66 years and older	10,184 patients	Prescription data	Use, ≥1 Rx in 6 months before 1st creatinine measurement.	OR for 25% eGFR decline (≥15ml/min/1.73m^2) Any NSAID use (CKD 1-5), **1.00** (95%CI 0.90–1.20)
Agodoa *et al*., 2008[148]	Cross-sectional	USA	All non-institutionalised residents ≥20 years old	8,057 healthy residents	Standardised survey	Habitual use, ever intake of an analgesic every day for at least 1 month.	OR for CKD 3 or worse (<60ml/min/1.73m^2) Ibuprofen, **1.21** (95% CI, 0.70-2.10); Aspirin, **0.95** (95% CI, 0.70-1.20)
Evans *et al*., 2009[149]	Cohort	Sweden	18-74 year olds ± CRF	801 patients	Questionnaire. Standardised interview	Regular use, twice a week for 2 months; non-users <20 tablet lifetime use	Difference in the mean eGFR decline coefficient Aspirin, **+0.80**ml/min/1.73m^2 (95% CI, 0.10-1.50)
Hippisley-Cox & Coupland., 2010[152]	Cohort	England and Wales	All patients aged 35-74 without pre-existing CKD	1,574,749 patients	Prescription data	Use, ≥2 Rx 6 months before study inclusion	HR for CKD stage 3B (<45ml/min/1.73m^2) **1.30** (95% CI, 1.27-1.34) for men; **1.29** (95% CI, 1.25-1.33) for women
Yarger *et al*., 2011[153]	Cohort	USA	All patients aged ≥67 years treated at a military health facility	34,295 patients	Prescription data	No use, low-medium and high NSAID use. (*Dose and criteria not defined)*	OR for eGFR decline (≥15ml/min/1.73m^2) Low-medium dose (CKD 3), **0.94** (95% CI, 0.78-1.12); High dose (CKD 3), **1.28** (95% CI, 0.84-1.93)

Shaded = CKD progression studies.

6.4.1.1. Geographical and Population

All included studies were performed in the last 10 years (2001-2011) and, with the exception of the Yarger *et al*., study[153], were available in a full-text format.[15,148-152] Three were European studies (two Swedish, one UK)[15,149,152] and four American studies.[148,150,151,153] There were five cohort[149-153], one cross-sectional[148] and one case-control[15] studies.

The sample size varied from 801 to 1,574,749 adult participants with a minimum inclusion age of 18 years.[15,148-153] The mean age of the study participants ranged between 45[148] and 76[150,151] years respectively.

Two studies used data from the same study population. Fored *et al.,*[15] and Evans *et al.,*[149] used data from the Swedish population register whilst Hemmelgarn *et al.,*[151] and Gooch *et al.,*[150] used data from the Calgary Laboratory Services database (Alberta, Canada).

6.4.1.2. Exposure (NSAID) and Outcome (CKD) measurement

There are substantial variations in the source of gathering information on the exposure measure across the studies included in our review. Three studies used self-reported lifetime consumption questionnaires to collect data on analgesics[15,148,149] while the other four studies used prescription databases.[150-153]

The GFR, as our core outcome measure, was mainly calculated using the 4-variable MDRD equation.[148-152] Only Fored *et al*., estimated the GFR using the BSA-standardised CG equation.[15] However, it was unclear which method was used by Yarger *et al*.[153]

Gooch *et al.*,[150], Yarger *et al.*,[153] and Hemmelgarn *et al.*,[151] reported on the OR for rapid CKD progression (eGFR decline of ≥15ml/min/1.73m^2). Evans *et al.*, reported on the difference in the mean eGFR decline rate per year between aspirin users and non-users.[149] The remaining studies reported on the OR for stage 3 (or worse)[148], the HR for stage 3B[152] and the OR for stage 4-5[15] CKD. All studies either directly reported on the prevalence of NSAID use or the level of use could be calculated from the published data.[15,148-153]

The majority of studies were primarily designed to investigate the association between chronic analgesia use and renal dysfunction.[15,148-150,153] The studies by Hemmelgarn *et al.*,[151] and Hippisley-Cox and Coupland[152] were primarily concerned with identifying numerous factors that could help predict the probability of CKD progression in at risk patients.

6.5. Results

This section presents the results of the seven studies included in our review. These will include; firstly, the effects of NSAID use on CKD progression, secondly, the risk of developing stage 3 to 5 CKD given a degree of NSAID use and finally, the prevalence NSAID use among CKD patients. Results are summarised in **Table 6.4** and **Figure 6.2**.

6.5.1. Non-Steroidal Anti-Inflammatory Drug use and the rapid progression of Chronic Kidney Disease

Gooch *et al.*, recruited subjects aged 66 years and over with all stages of CKD and recorded the change in the mean eGFR over a 2-year period.[150] In this study, 13.3% of the participants experienced rapid CKD progression.[150] They found that high cumulative

NSAID exposure was significantly associated with an overall increased risk of rapid CKD progression; OR= 1.26 (95% CI: 1.04-1.53).[150] Each 100-unit increase in the defined daily dose (DDD) of NSAIDs was associated with a 0.08ml/min/1.73m^2 decrease in the eGFR over a 2-year period.[150] Users of COX-2 selective or non-selective NSAIDs with stage 1-2 disease were at a greater risk of rapid CKD progression but users of both selective and non-selective NSAIDs did not have a significantly increased risk in this group.[150] In patients with stage 3 to 5 disease, neither COX-2 selective or non-selective NSAIDs as single or combined agents, were associated with a rapid CKD progression; OR= 0.82 (95% CI: 0.59-1.15).[150] The authors concluded that selective and non-selective agents were equally associated with kidney function decline, hence chronic exposure should be avoided.[150]

Hemmelgarn *et al.,* recruited subjects aged 66 years and over with all stages of CKD and recorded the change in the mean eGFR over a 2-year period.[151] Patients prescribed either selective or non-selective NSAIDs six months prior to the first serum creatinine measurement did not have an increased risk of rapid decline compared to those without a prescription; OR= 1.0 (95% CI: 0.9-1.2).[151] The study concluded that NSAID use is not a marker for the rapid progression of kidney dysfunction.[151]

Yarger *et al*., recruited subjects aged 67 years and over with stage 2-3 CKD and recorded the change in the mean eGFR over a 2-year time-period.[153] 10.9% of all the participants experienced rapid CKD progression. This was comprised of 10.5% (2,063 of 19,720) non-users, 11.2% (1,465 of 13,125) low-medium dose NSAID users and 13.4% (195 of 1,450) high dose NSAID users.[153] Low-medium NSAID use was not associated with an increased risk of rapid CKD progression in patients with stage 3 disease; OR= 0.936 (95% CI: 0.782

to 1.122).[153] High dose NSAID users with CKD stage 3 were at a higher risk of rapid CKD progression but the result was not statistically significant; OR= 1.276 (95% CI: 0.844 to 1.927).[153] The study conclusion was that NSAID exposure in patients with CKD stage 2 or 3 was not associated with an increased risk of rapid CKD progression in the elderly cohort.[153]

Evans *et al.,* recorded the rate of eGFR decline over a maximum follow-up period of 7 years (mean follow-up = 2.1 years).[149] Patients with regular aspirin use at inclusion progressed at a rate of 0.80ml/min/1.73m^{2}per year ***slower*** than non-users (95% CI: 0.1 to 1.5).[149] Similar results were seen with regular paracetamol use.[149] Differing levels of aspirin or paracetamol use did not significantly affect the progression rate.[149] Aspirin users without CVD risk factors had a slower rate of progression compared to those with CVD risk factors.[149] A similar picture was seen when stratification was performed by sex, with male regular aspirin users progressing slower than female regular aspirin users.[149] The protective effects of aspirin were evident amongst all primary renal diseases but appeared most pronounced in glomerulonephritis.[149] The authors concluded that single aspirin or paracetamol use may be safe in patients with advanced renal disease.[149]

6.5.2. Non-Steroidal Anti-Inflammatory Drugs use and the risk of developing Chronic Kidney Disease

Fored *et al*., performed a study in which adults aged 18-74 years with advanced CKD were enrolled along with matched controls (1 to 1 ratio).[15] Compared to those in the control group, patients with stage 4-5 CKD were significantly more likely to have had regular aspirin use; OR= 2.5 (95% CI: 1.9 to 3.3).[15] The association increased significantly with increasing cumulative use (defined in grams as 1-99g, 100-499g and >500g).[15] This

association was also evident in regular paracetamol users but was more pronounced when compared to equivalent doses of aspirin.[15] Subgroup analysis revealed that regular aspirin and paracetamol use was associated with advanced CKD compared to exclusive aspirin use; OR= 2.2 (95% CI: 1.4 to 3.5).[15] The authors conclusions were that paracetamol and aspirin use has exacerbating effects on chronic renal failure but cautioned that the results may have been skewed due to indication bias.[15]

Agodoa *et al*., used NHANES data (1999-2002) which included healthy, non-institutionalised residents aged ≥20 years.[148] The age-standardised prevalence for reduced eGFR (stage 3 to 5 CKD) was 8.3%.[148] The prevalence of stage 3 to 5 CKD was higher amongst habitual (*defined in* **Table 6.3**) single analgesic users.[148] Habitual users of aspirin, ibuprofen and paracetamol were not at a significantly increased risk of CKD stage 3 or worse compared to non-habitual users; OR= 0.95 (95% CI: 0.7 to 1.2), 1.21 (95% CI: 0.7 to 2.1) and 1.03 (95% CI: 0.6 to 1.7) respectively.[148] Except in ibuprofen users, multiple analgesia use was not significantly associated with an increased risk of renal dysfunction (aspirin and paracetamol use; OR= 1.25 (95% CI: 0.7 to 2.1).[148] There was a gradual trend of increasing risk with prolonged habitual analgesic use but statistical significance was not reached in any individual group.[148] The authors concluded that habitual use of single or multiple products was not associated with an increased prevalence CKD (stage 3 or worse).[148]

Hippisley-Cox and Coupland used the data from patients aged 35-74 years without pre-existing CKD.[152] The overall incidence rate of stage 3B CKD was 58.46 and 42.02 per 10,000 person years for women and men respectively.[152] The HR for CKD stage 3B was 1.30 (95% CI: 1.27 to 1.34) in men and 1.29 (95% CI: 1.25 to 1.33) in women.[152] NSAIDs

were not found to be significantly associated with ESRD.[152] The authors decided that NSAID use is a significant risk factor for development of stage 3B CKD.[152]

Table 6.4 Study outcome measures of Chronic Kidney Disease progression

Measure of change	Study	Outcome
OR for rapid CKD progression (≥15ml/min/1.73m^2)	Gooch *et al*., 2007[150]	All NSAID use (CKD 3); **0.82** (95% CI 0.59-1.15) High dose NSAID use (CKD 1-5); **1.26** (95% CI 1.04-1.53)
	Hemmelgarn *et al*., 2007[151]	≥1 NSAID prescription (CKD 1-5); **1.0** (95% CI 0.9-1.2)
	Yarger *et al*., 2011[153]	Regular dose NSAID use (CKD 3); **0.936** (95% CI, 0.782-1.122) High dose NSAID use (CKD 3); **1.276** (95% CI, 0.844-1.927)
Difference in the rate of eGFR decline	Evans *et al*., 2009[149]	Regular Aspirin use; **+0.80** ml/min/1.73m^2
OR/HR of CKD stage 3, 3B or 4-5	Fored *et al*., 2001[15]	Regular aspirin use (CKD 4-5); **2.5** (95% CI 1.9-3.3) Combined Aspirin & Paracetamol (CKD 4-5); **2.2** (95% CI 1.4-3.5)
	Agodoa *et al*., 2008[148]	Habitual Ibuprofen use (CKD 3 to 5); **1.21** (95% CI 0.7-2.1). Habitual Aspirin use (CKD 3 to 5); **0.95** (95% CI 0.7-1.2) Combined Aspirin & Paracetamol (CKD 3 to 5); **1.25** (95% CI 0.7 to 2.1)
	Hippisley-Cox and Coupland., 2010[152]	≥2 NSAID prescriptions (CKD 3B) **[HR]**; **1.30** (95% CI 1.27-1.34) in men **1.29** (95% CI 1.25 to 1.33) in women

Green = CKD progression studies, Blue = Development of stage 3 to 5 CKD.

6.5.3. The prevalence of Non-Steroidal Anti-Inflammatory Drug use among Chronic Kidney Disease patients

Studies using prescription data found that 26.9% to 48% of the participants had at least one NSAID prescription over a six month to one year period respectively.[150,151,153] In these studies, the majority of patients had CKD stage 2-3 with a mean age of between 74 and 76

years.[150,151,153] The results of study reported prevalence of NSAID use in CKD patients are presented in **Figure 6.2**.

The studies by Fored *et al.,* and Evans *et al*., used self-reported NSAID data[15,149] These studies had a younger cohort (mean age, 57 years) of patients with more severe disease (CKD stage 4-5).[15,149] As such, 33% to 37% of participants had regular aspirin use and 16% to 25% of the study participants were regular paracetamol users respectively.[15,149] Only Fored *et al*., study had a control group, they reported on the prevalence of aspirin and paracetamol use to be 19% and 12% respectively.[15]

The studies by Hippisley-Cox and Coupland and Agodoa *et al*., had patients without pre-existing CKD and so were not included in figure 6.2.[148,152] NSAID use was still prevalent with rates of 27% and 24% respectively.[148,152]

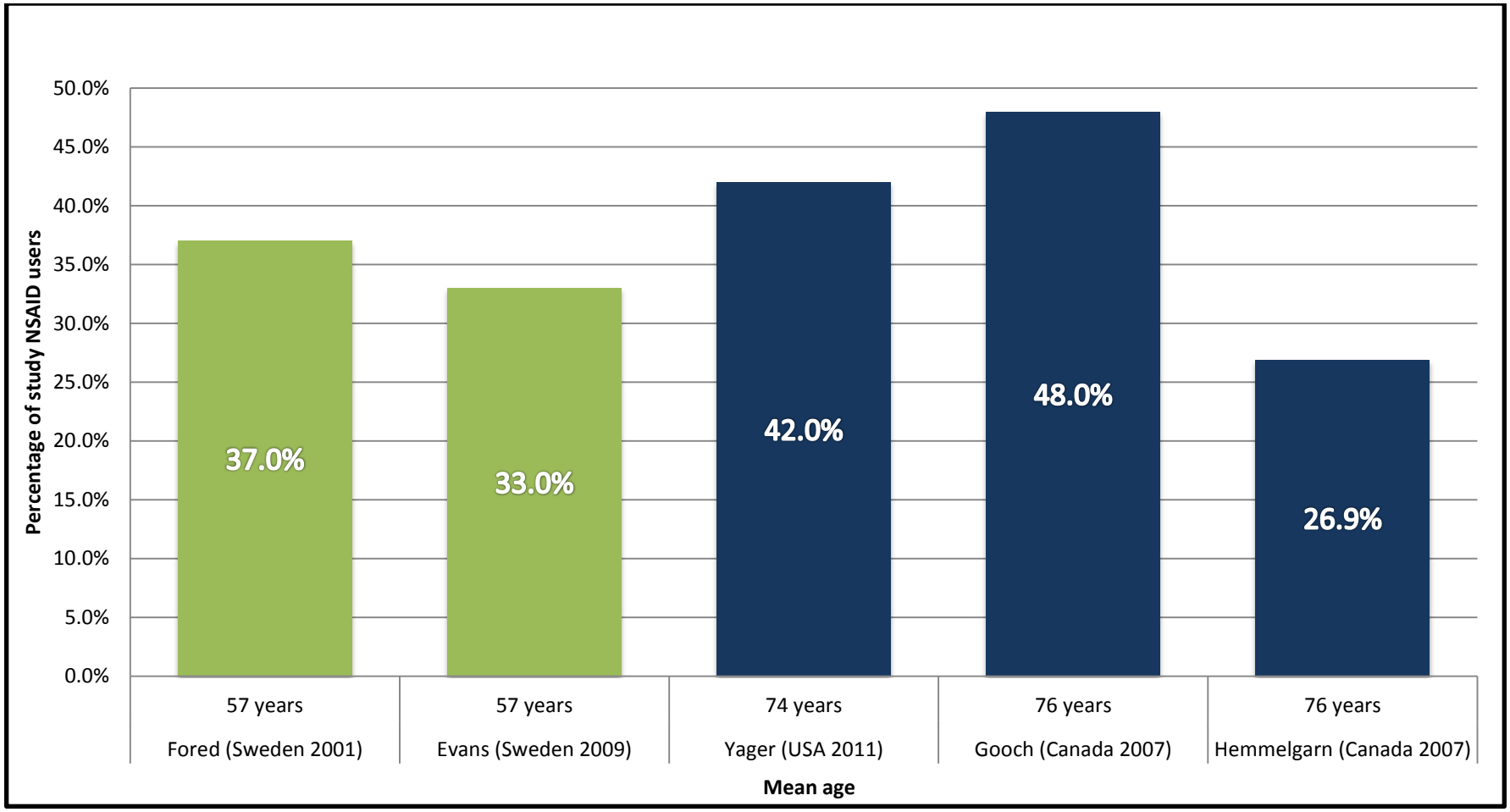
The studies used different measures of cumulative NSAID use[15,148-150,153] whilst some did not measure it at all.[151,152] Studies measuring cumulative use defined it as either a duration of use[148], a calculated cumulative lifetime consumption (in grams)[15,149], in categorical groups[153] or in terms of a standardised DDD measure.[150]

6.5.3.1. The length and quantity of NSAID use

Of the 24% of users in the Agodoa *et al*., study, 40% had used the drugs habitually for 1-5 years whilst 25% and 35% had used analgesics habitually for <1 and >5 years respectively.[148]

Overall, few participants had high dose NSAID use. In the Yarger *et al*., study, of the participants defined as NSAID users, less than 10% took high doses of the drugs.[153] Equally, only 20% of users in the Evans *et al*., study reported more than 500g of lifetime aspirin consumption.[149] These figures are further echoed by those in the Gooch *et al*., study who reported that the vast majority of the patients classified as users had limited exposure and only a few patients had >500 DDDs of use (equivalent to 600g of ibuprofen).[150]

Figure 6.2 Study prevalence of Non-Steroidal Anti-Inflammatory Drug use among Chronic Kidney Disease patients



Blue = Any NSAID use, Green = Aspirin use.

6.5.4. Meta-analysis

Six out of the seven studies were included in the meta-analysis. The included studies provided a dichotomous outcome measure[15,148,150-153] whilst the excluded study by Evans *et al.*,[149] reported on an incompatible continuous outcome measure (β coefficient). RevMan[199] software (version 5.1) was used for the statistical analysis. The HR was treated as equivalent to the OR as the incident rate of CKD was rare.[200] The ORs are weighted according to the inverse variance method and a random effects model was used. The I^2 statistic was used to assess the degree of heterogeneity. I^2 statistics of 25-50%, 50-75% and >75% were considered evidence of mild, moderate and marked heterogeneity respectively.[179]

The outcomes of the meta-analysis were:

1. The OR for rapid CKD progression with regular and high dose NSAID use.
2. The OR for developing moderate to severe CKD (stage 3 to 5) with regular single NSAID (*defined as exclusive use of one type of NSAID*) or combined aspirin and paracetamol use.

6.5.5. The odds ratio for rapid Chronic Kidney Disease progression

The meta-analysis (**Figure 6.3)** revealed that there is no association between overall NSAID use and the risk of rapid CKD progression; pooled OR= 1.04 (95% CI: 0.90-1.2). The result is not significant (p=0.63) but there is evidence of moderate heterogeneity (I^2=52%). On subgroup analysis, it is clear that regular NSAID use is not significantly associated with an increased risk of CKD progression; pooled OR= 0.96 (95% CI: 0.86-1.07); p=0.43; I^2=0%. However, the risk of rapid CKD progression was significantly

higher in patients with high dose NSAID use; pooled OR= 1.26 (95% CI: 1.06-1.50); p=0.009; I^2=0%, (p-value for subgroup difference = 0.008).

6.5.6. The odds ratio for developing stage 3 to 5 Chronic Kidney Disease

The meta-analysis (**Figure 6.4**) suggest that regular NSAID use can significantly increase the risk of developing stage 3 to 5 CKD; pooled OR= 1.48 (95% CI: 1.11-1.98) p=0.008; I^2=84% (marked heterogeneity) but this risk was not significantly raised in patients who regularly used a single type of NSAID; pooled OR= 1.41 (95% CI: 0.98-2.02); p=0.06; I^2=88%. Patients with combined aspirin and paracetamol use tended to have a higher risk of developing stage 3 to 5 CKD compared to non-users or exclusive aspirin users; pooled OR= 1.69 (95% CI: 0.97-2.94); I^2=58% (moderate heterogeneity), but this did not reach statistical significance (p=0.06).

Figure 6.3 Meta-analysis: Non-Steroidal Anti-Inflammatory Drugs and the OR for Rapid Chronic Kidney Disease Progression

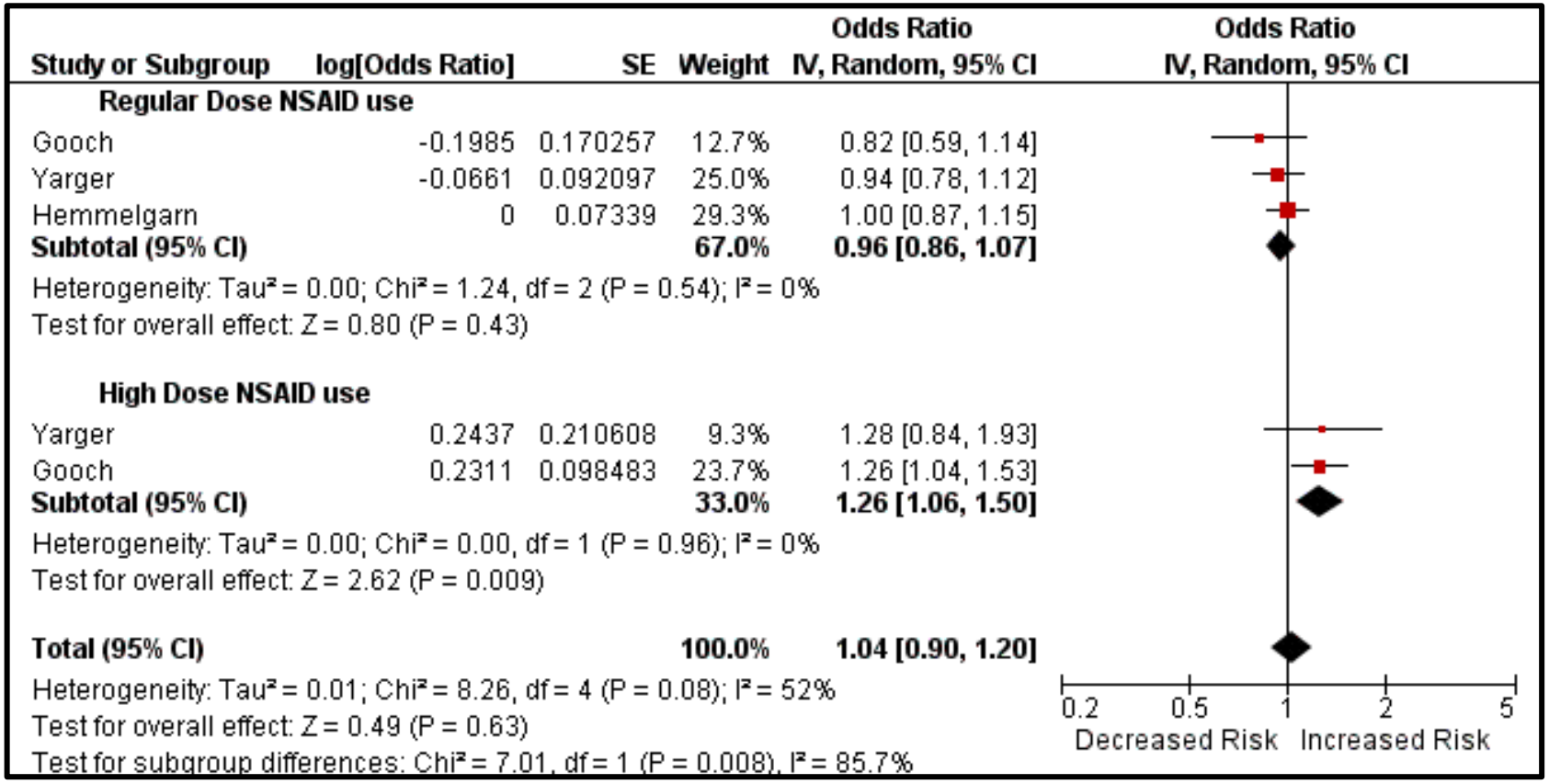
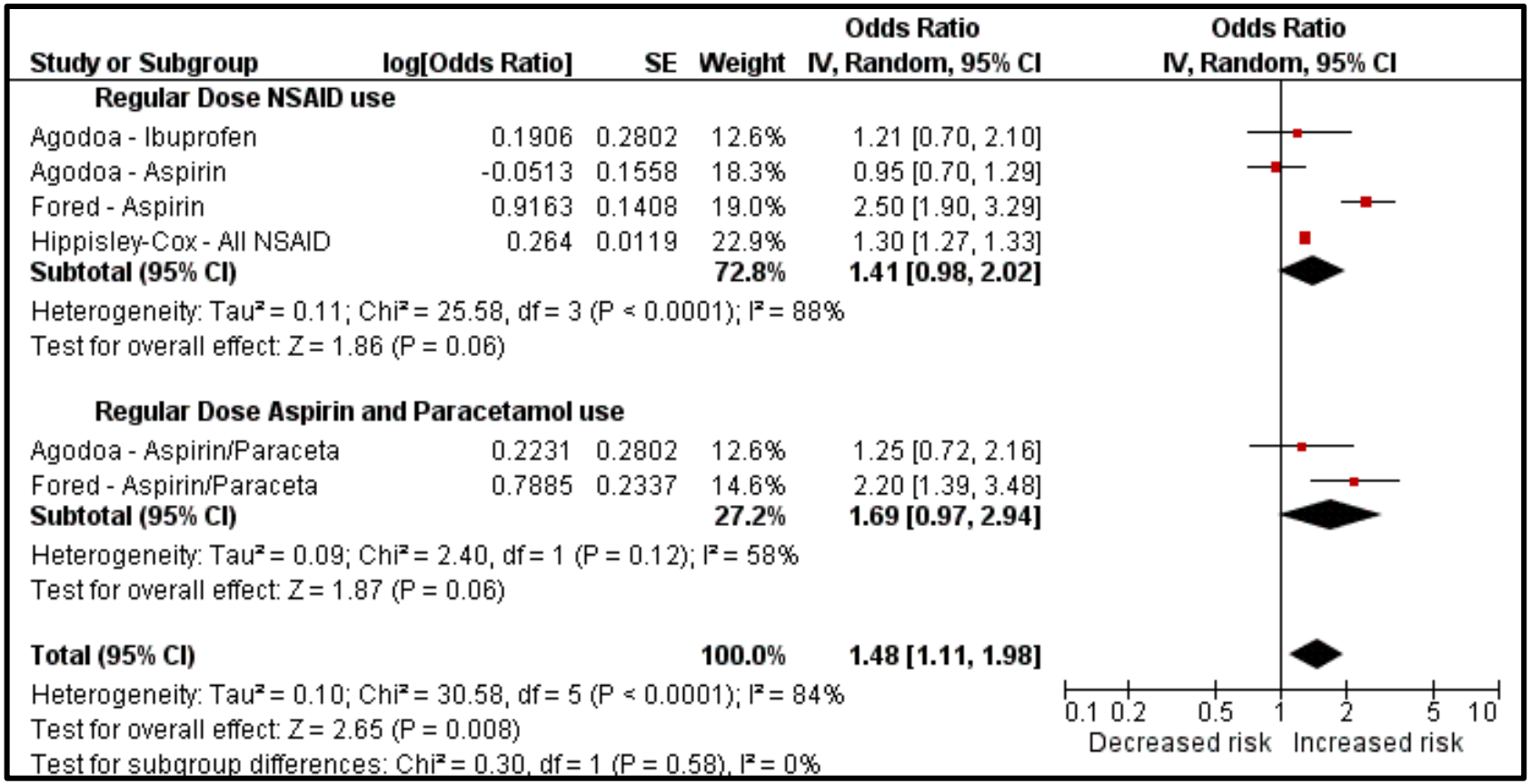


Figure 6.4 Meta-analysis: Non-Steroidal Anti-Inflammatory Drugs and the OR for Developing Chronic Kidney Disease



6.6. Discussion

This section discusses the key findings which have emerged from our systematic review with emphasis on methodological quality of the reviewed studies and the findings related to NSAID use and rapid progression of CKD, NSAID use and the development of CKD and the prevalence of NSAID use among CKD patients.

6.6.1. Methodological quality and bias

All the included studies underwent an assessment of the methodological quality and the risk of bias in the selection process, exposure, outcome and data analysis. This was achieved with the use of the CASP assessment checklists.[197] Presented below are the key strengths and weaknesses in the four areas mentioned above. A subjective assessment of bias is also given for each area.

6.6.1.1. The selection process

The recruitment process in the included studies was appropriate for our objectives and population of interest. Studies using computerised database data recruited participants with at least 1[150,151,153] or 2[152] serum creatinine measurements. Recruitment in the Yarger *et al*., study also required that participants had stage 2 or 3 CKD, were continually eligible for TRICARE and had sought medical treatment form a military facility.[153] There is a risk that some patients may have been missed if they had not sought medical attention or were not eligible for care. The elderly military cohort in the Yarger *et al*., study may not necessarily reflect the general population if they have had different lifetime exposures given their background.[153]

Fored *et al*.,[15] and Evans *et al*.,[149] both used data from the Swedish population register. They recruited patients with a serum creatinine >300µmol/l for men or >250µmol/l for women for the first time. In the case of Evans *et al*.,[149] the measurement had to remain above this level for the entirety of the study. The Fored *et al*., case-control study included an age (±10y) and sex matched control group.[15] These recruitment strategies will effectively capture adult patients with advanced renal failure and the use of a national register allows for an accurate sample to be drawn. However, the use of serum creatinine as the inclusion measure, given its variable nature, may lead to patients with advanced renal failure and relatively low serum creatinine measurements being excluded from these studies.

Agodoa *et al*., used data from NHANES 1999-2002 which included non-institutionalised US residents aged 20 years and over.[148] Pregnant women, those in menses, dialysis patients as well as 1628 participants with missing serum creatinine or analgesia use data were excluded.[148] Overall, the population sample groups will be representative of the general population but the exclusion of a significant proportion of patients due to missing data may bias the results if the excluded patients had high or low NSAID use.[148]

All the studies had a large sample sizes (801-1,574,749 participants).[15,148-153] For the studies by Evans, Fored, Agodoa, Hemmelgarn, Gooch and Hippisley-Cox, after the application of the relevant exclusion criteria, 67%, 77%, 78%, 80%, 81% and 99% of the initially eligible patients were included in the final data analysis respectively.[15,148-152] The Fored *et al*., study included a control group in which 74% of the eligible participants were enrolled.[15] Yarger *et al*., did not report on the percentage of eligible patients included.[153]

Overall, although some patients may have been missed if incorrectly diagnosed, the use of the eGFR to estimate renal function minimised the risk of misclassification.[19]

6.6.1.2. Exposure measure

Four out of the seven studies used prescription data to define NSAID use.[150-153] With all of these studies, NSAID prescriptions are likely to be captured accurately but the OTC use will not be captured. The length of exposure measured is also of some concern if the effects of NSAID use only become apparent over a longer period of time than is recorded in the included studies.

The remaining three studies[15,148,149] relied on self-reported lifetime analgesia using standardised questionnaires and interviews with the use of memory aids to facilitate more accurate recall. These studies should therefore capture OTC and prescription use. Given that the cumulative lifetime drug use is recorded, any long term effects of use are more likely to be demonstrated. However, the reliability of self-reported analgesia use behaviour was not assessed in any of the above studies. Therefore, there is a concern that recall bias could significantly affect the results of these studies.

With all the above studies, the definition of regular NSAID use varies widely. Studies using self-reported analgesia use define regular NSAID users according to a frequency of intake per month.[15,148,149] Those reporting on prescription data define it according to the number of prescriptions in a given time period.[150-153] Cumulative lifetime NSAID use was also defined differently between studies. With the exception of Gooch *et al.*, study which used the DDD[150], other studies did not report on a standardised NSAID dose measure.[15,148,149,151-153] With such variation in the definition of regular NSAID use, it is

likely that the different patterns of behaviour/prescribing will likely have an effect on the outcome. This makes it more difficult to compare the results of these studies equally.

Symptoms that predispose patients to use NSAIDs may be initiated by pathologies that can lead to CKD (e.g. gout) and hence may be the real cause of any associations found. As the studies do not stratify NSAIDs use by indication nor do they adjust for all the possible cofounders, indication[201] bias cannot be fully ruled out and may significantly affect the results.

6.6.1.3. Outcome measures

The outcomes reported were the risk of rapid progression of CKD[150,151,153], the risk of developing CKD stage 3 to 5.[15,148,152] and the difference in the mean rate of eGFR decline per year.[149] All studies used at least one serum creatinine measurement to estimate the GFR.[15,148,150-153] Five of the seven studies used the 4-variable MDRD equation[148-152]; Fored *et al*., used the CG equation[15]. Yarger *et al*., do not list which equation is used in their study.[153] The MDRD equation is widely adopted and used within acceptable limits in the included studies. However, none of the studies used isotope dilution mass spectrometry (IDMS) traceable serum creatinine measurements and therefore there could be intra and inter-laboratory variation. In addition, there is a risk with all the studies that patients with more symptomatic pathologies which can contribute to the development of CKD are more likely to seek medical attention which required laboratory investigation and would therefore be more likely to be recruited into the studies. However, the large population samples in the studies could minimise this effect. Overall, the risk of misclassification is relatively small and the use of accepted and widely adopted estimation equations makes the results applicable to general practice.

6.6.1.4. Data analysis

In all the studies, the ORs were adjusted for age and sex but there was a great deal of variation in the covariates adjusted for. Six studies adjusted for at least one co-morbidity (usually DM, HTN or CVD). The outcome by Hemmelgarn *et al*.,[151] is univariate and so was not adjusted for confounders. There was also some variability in how covariates were recorded with some studies using database data[150-153] whilst others relied on self-reported information.[15,148,149] The differences in the covariates measured means that there will be differences in how the final ORs are adjusted for cofounders. Patients with worsening CKD may also have prodromal symptoms of disease which may lead to increased NSAID use. Only Fored *et al*.,[15] analysed data in such a way as to limit this. Even so, the risk of protopathic bias remains present. Given the array of possible confounding factors in patients with CKD, especially those on NSAIDs who often have multiple co-morbidities, the risk of bias to significantly affect the result is ever present. However, the recruitment of patients with less severe disease in the presented studies mitigates some of the risk.

6.6.2. Non-Steroidal Anti-Inflammatory Drug use and the rapid progression of Chronic Kidney Disease

Our systematic review revealed that NSAID use is not associated with the rapid progression of CKD. Although not included in the meta-analysis, the study by Evans *et al*., supports this finding as the authors found a slower rate of eGFR decline in regular aspirin users compared to non-users.[149] The findings are also in agreement with the Nurses' Health Study by Curhan *et al*., (2004)[128], and the Physicians Health Study by Kurth *et al*., (2003)[132] who found no association between NSAIDs use and renal function decline.

However, 'high dose' NSAID use may exacerbate renal function decline. This finding differs to that in both the Curhan *et al*., and Kurth *et al.,* studies.[128,132] Neither found any association between high dose NSAID use and renal function decline.[128,132] The contradictions in the findings can be explained by the differences in the age and genders of the study participants as both can affect the levels of NSAID use[111,112] and CKD prognosis[76] (*see section 3.2.1*). The mean age in the Gooch *et al*.,[150] and Yarger *et al.,*[153] studies were 74 and 76 years compared to 57 and 49 in the Nurses'[128], and the Physicians[132] health studies respectively. The latter studies also included only female or male participants.[128,132] Although our review shows that the use of high doses of NSAIDs is associated with an increased risk of CKD progression, the absolute risk attributable to high dose NSAID use is likely to be minor. In the Yarger *et al*.,[153] study, the prevalence of high dose NSAIDs use was low (4.2% of the total sample population) and only 13.4% of high dose NSAID users had rapid CKD progression.[153] Therefore, high dose NSAID users who had rapid CKD progression made up just 0.6% of the total sample population.[153]

NICE guidelines define significant renal decline as a drop in the GFR of >5.0ml/min/1.73m^2 per year or a decline of >10.0ml/min/1.73m^2 over 5 years.[6] Therefore, the definition of rapid CKD progression (≥15ml/min/1.73m^2 over 2-3 years) used in the studies presented above indicated a clinically significant change in renal function.

A limitation of the studies investigating CKD progression is that they do not measure the rate of eGFR decline. For example, two patients may have a decline in the GFR of 6ml/min/1.73m^2 but if the decline occurs over 1 year compared to over 2 years, the overall rate of decline (6 vs 3ml/min/1.73m^2 per year) will determine the clinical significance. Measuring the rate of change in the GFR is seen as the best representation of the true

change in renal function as it takes into account the time period over which such decline takes place.[202] In our review, only Evans *et al*.,[149] used this outcome measurement. Overall, given the homogeneity in the study designs, populations and outcome measures, the findings of the meta-analysis (**Figure 6.3**), although based on a relatively small number of studies, are fairly accurate.

6.6.3. Non-Steroidal Anti-Inflammatory Drug use and the risk of developing Chronic Kidney Disease

The meta-analysis (**Figure 6.4**) results suggest a significant association between NSAID use and the risk of developing stage 3 to 5 CKD. This association is not statistically significant for patients who used one type of NSAID exclusively. Other studies have given conflicting evidence as to whether NSAID use is associated with impaired renal function. Studies by Murray *et al*.,[135] Rexrode *et al*.,[139] and Stürmer *et al*.,[144] found no significant association between NSAID use and renal dysfunction. Conversely, other studies by Sandler *et al*.,[140,141] and Segasothy *et al*.,[142] have found the contrary. In fact, Sandler *et al*., reported up to a twofold increase in risk of developing chronic renal failure in patients with a history of NSAID use.[140] The discrepancy in the findings could be explained that studies which find no association tended to have larger population samples with younger participants and used better measures of renal function.[135,139,144] On the other hand, studies which found a positive association tended to have smaller cohorts with older patients and higher levels of NSAID use.[140-142] There are also conflicting results as to whether NSAID use is associated with ESRD. Whilst most studies have found no association between NSAID use and ESRD[13,136-138,146,152], two studies by Kuo *et al*., (Taiwan)[131] and Morlans *et al*., (USA)[14] have reported statistically significant results. Poor study design, flawed

methodology and susceptibility to bias given the late stage of CKD of recruited patients could be seen as reasons to explain the inconsistency in the results.[125,147]

Overall, the current evidence base suggests that long term regular NSAID use is not strongly associated with the development of stage 3 to 5 CKD as supported by CKD progression studies included in our review.[149-151,153] In some studies, CKD could have erroneously been linked to NSAID use due to the influence of bias. It may be the case that users of NSAIDs have underlying pathology with prompts drug use but which in itself is linked to the development of CKD.[201] Moreover, since these studies do not use multiple measurements over time nor do they relate the decline in renal function directly to the period of NSAID use, this may have allowed confounding factors to skew the results. In evidence of this is the paradox posed by the Evans *et al.*,[149] and Fored *et al.*,[15] studies which both used data from the Swedish Population Register. Evans *et al.*,[149] showed a decreased rate of renal decline in aspirin users whilst Fored *et al.*,[15] found an increased risk of developing CKD in aspirin users. Therefore it may be the case that in the Fored *et al.*,[15] study, unknown confounders erroneously showed aspirin increased the risk of renal dysfunction but when aspirin use was directly compared against the rate of CKD progression, those effects are eliminated. In examining the meta-analysis findings, we see that the results of the Fored *et al.,* study[15] contribute most greatly to the positive association between NSAID use and the risk of developing stage 3 to 5 CKD. There is a high likelihood that bias significantly skewed their results as they conclude that "*we cannot rule out the possibility of bias due to the triggering of analgesic consumption by predisposing conditions*".[15] Therefore, given the possibility of bias influencing this study, it may be the case that the reported association does not occur in the general population. Further care must also be taken in interpreting this part of the meta-analysis. Although the

studies use a similar outcome measure, they have different study designs (a matched case-control[15], cross-sectional[148] and cohort study[152]). Moreover, the populations are heterogeneous with varying age, definitions of NSAID use and stages of CKD.[15,148,152] Therefore, although the meta-analysis seems to indicate an association between NSAID use and CKD status, the significant heterogeneity indicates inconsistency between studies. Consequently, this estimate is unlikely to represent the true effect of single NSAID use on the risk of developing CKD in the population. Further study is needed to address the inconsistency in the current evidence base.

6.6.4. Combined aspirin and paracetamol use and the risk of developing Chronic Kidney Disease

The meta-analysis also seems to indicate an increased risk of developing stage 3 to 5 CKD in aspirin and paracetamol users; however, the result is not statistically significant. Few studies investigate the effects of combined aspirin and paracetamol use on renal dysfunction. Although not included in the meta-analysis, Evans *et al*.,[149] found no association between the combined use of aspirin and paracetamol and renal function decline. Moreover, Murray *et al*., (1983) found no association between combined aspirin and paracetamol use and ESRD.[136]

Most studies in the literature do not find any association between aspirin use and renal dysfunction.[128,132,136,137,139,141,146] Only three identified studies have reported poor renal function with aspirin use.[13,14,131] However, regular single paracetamol use has been linked to renal pathology in some studies[15,128,137,141] but not in others[13,136,139,148,149]. In almost all cases, the association was only evident at high cumulative doses.[15,128,137,141] Given mixed findings in the literature, and the challenges to the meta-analysis mentioned previously,

there is insufficient evidence to conclude on whether combined paracetamol and aspirin use is detrimental to renal function but single aspirin use does not appear to have a negative effect.

6.6.5. The prevalence of Non-Steroidal Anti-Inflammatory Drug use among Chronic Kidney Disease patients

The definition of NSAID use varied greatly between studies as did the data collection methods. Some studies used prescription databases whilst others used questionnaires/surveys of self-reported NSAID use (see **Table 6.3**). There was also variation between the ages and CKD status of the study participants at inclusion. As such, it is difficult to compare the prevalence of NSAID use between studies given the lack of a standardised definition of 'regular' use.

However, this review has shown that NSAID use amongst patients with CKD is prevalent. Almost 50% of the elderly patients (≥66 years) in the Gooch *et al*., study were prescribed at least one NSAID over a one-year period.[150] In the Hemmelgarn *et al*., study, 27% of the sample population (≥66 years) received a prescription within 6 months.[151] These figures are in keeping with studies by Bhopal *et al*.,[161],who found similar levels of NSAID prescription in CKD patients.

Aspirin use was widespread in patients with advanced CKD and a third or more had used the drug on a regular basis at some point in their lifetime.[15,149] These results echo those found by Bailie *et al*., who found that 37% of the patients in their study were prescribed aspirin.[162] In addition, in the Bhopal *et al*., study, low-dose aspirin was prescribed to 47% of the general practice patients.[161]

Although it is clear that NSAID use is prevalent in CKD patients, what was less clear was the reasons for intake, the doses and duration of use. Apart from the study by Gooch *et al*.,[150], most studies used non-descript or arbitrary measurements of cumulative NSAID use.[15,148,149,153]. Neither the studies by Hippisley-Cox and Coupland nor Hemmelgarn *et al*., assessed cumulative NSAID use.[151,152] Without a standardised comparative measure of NSAID use, it is difficult to interpret what the exact clinical significance of the data is. What is encouraging is the relatively low prevalence of study defined high dose NSAID use.

6.7. Conclusions

In conclusion, the primary findings of this review are that regular dose NSAID use does not increase the risk of CKD progression but high dose use may be detrimental to kidney function in patients with stage 3 to 5 disease aged 45 years and over. The result of the meta-analysis suggests that single type NSAID and combined aspirin and paracetamol use are associated with an increased risk of developing stage 3 to 5 CKD. However, the results are not statistically significant in either subgroup and there are limitations on the accuracy of the meta-analysis. The majority of published evidence does not find an association between NSAID or aspirin use and CKD but high dose paracetamol use has been linked to renal dysfunction in a number of studies. Finally, NSAIDs use is prevalent in patients with established CKD with aspirin being the most commonly used drug but the common dose and duration of use remain unclear.

Compared to earlier reviews by McLaughlin *et al*.,[125] and Delzell *et al*.,[147], our findings include recently performed studies without many of the methodological problems that have

prevented reviews from quantifying the risk of NSAID use of CKD progression. To the best of our knowledge, this review samples the largest number of papers investigating the effects of chronic NSAID use and kidney function. The selection criteria were designed to allow the findings of this review to be generalisable to clinical practice. The results are divided to answer two distinct questions; whether the decline of kidney function accelerates with NSAID use and whether NSAID use is associated with an increased risk of developing stage 3 to 5 disease. The meta-analysis combines the data from the two study types and is able to quantify, for the first time, the risk of both high and regular dose NSAID use. Finally, the findings of this review echo those in the literature showing the frequent use of NSAIDs in CKD patients.

6.7.1. Systematic review limitations

A major limitation to our systematic review is the inability to give a standardised measure of 'high dose' NSAID use and the safe length of non-high dose use. There is a notable amount of heterogeneity in some of the meta-analysis due to variability in some aspects of the study designs leading to a degree of uncertainty in some of the results. The findings assume that NSAID use affects patients of different ages, genders, ethnicities and CKD stages equally. Moreover, the effects of co-drug therapy have not been explored by this review. Given the prevalent use of NSAIDs, any possible nephrotoxic interactions with other drugs would be of clinical importance. Although the populations of Europe and America share many similarities with the UK population, there are notable differences in the co-morbidities that affect these patient groups which might in turn influence how the results apply to the UK.

As to the quality of the evidence, one must always be cautious about interpreting findings from observational studies as they are liable to effects of bias and confounding. The meta-analysis is also based on a relatively small number of studies. Further studies are needed to strengthen the evidence base and to address the common study design problems highlighted in this review.

Publication bias is an ever present threat in systematic reviewing. To ensure that the effects of bias were minimised, no language or date of publication restrictions used in the selection criteria. A thorough search for unpublished 'grey' literature was performed to ensure that all available articles were sampled by the review. The reported findings support the conclusion that this review is not affected by bias given that papers found positive, negative and null effects. An objective assessment of publication bias can also be performed through use of funnel plots[175] where by the study size (estimated by the standard error) is plotted against the effect size and a skewed plot indicates the possible presence of publication bias.[175] However, due to the limited number of studies, funnel plots would not be reliable in assessing for publication bias in our review.[175]

6.7.2. Implications for practice

This review shows that the blanket avoidance of NSAIDs is not justified. As we are unable to give a measure of high dose NSAID use, we recommend that patients should be given the lowest effective dose of NSAIDs for the specific indication. Annual screening should be performed in CKD patients with continued NSAID use. NSAIDs have a number of other detrimental effects on kidney function and so should always be used with caution in patients with established renal dysfunction balancing the benefits and risks of their prescription.

6.7.3. Future research

Further research is required in this area which should:

i. Use a standardised drug dose measure,

ii. Establish a safe dose of NSAID use and define the level of high dose use,

iii. Assess the effects of combined NSAID/aspirin and paracetamol use on renal function,

iv. Look at the effects of co-morbidity, and finally

v. Assess the effects of co-drug therapy.

Chapter 7. A General Practice Study - Introduction and Methods

Study Summary

Introduction

In the literature, there is conflicting evidence on whether NSAIDs, including aspirin, are associated with CKD. Paracetamol has also been linked to renal disease in some studies and is a major metabolite of the nephrotoxic compound Phenacetin. However, previous studies have used flawed methodologies when defining the dose of NSAIDs, aspirin and paracetamol use and the primary outcomes used to measure renal function decline have not been ideal. Given the prevalent use of NSAIDs, aspirin and paracetamol amongst patients with established CKD, there is a need to understand the relationship between renal function and drug prescription.

Methods

To study the effects of NSAID, aspirin and paracetamol use on CKD, a two phase study was carried out using prescription and consultation data from two general practices in Stoke-on-Trent Primary Care Trust, England.

Phase 1 was a cross-sectional study including general practice patients aged 40 years and over with at least one eGFR measurement (calculated using the simplified 4-variable MDRD equation) between the 1st of January 2009 and the 31st of December 2010.

Phase 2 of the study was a cohort design study analysing the dataset of a subgroup of patients with at least two eGFR measurements spaced at least 90 days apart.

Descriptive statistics on the baseline socio-demographic characteristics (age, gender and quartile of deprivation), levels of co-morbidity (CVD and DM), drug prescribing (NSAIDs, aspirin and paracetamol) and the prevalence of co-drug therapy (ACE-i/ angiotensin receptor blockers (ARBs)/ Renin inhibitors (Renin-i)) were given for both phases.

Drug use was defined in our study by general practice prescribing using two approaches. The first approach categorised study subjects into users and non-users based on the presence or absence of one or more drug prescriptions during the whole study period and prescribing preceding the last eGFR measure (used for hypothesis testing). In the second approach, the DDD measure, based on the WHO classification, was used to standardise drug dose. Subjects were then categorised into normal (DDDs $<85^{th}$ percentile) and high dose (DDDs $\geq 85^{th}$ percentile) drug user groups based on prescribing given during the whole study period and prescribing preceding the last eGFR. Co-drug therapy was measured by the presence of absence of one or more prescriptions during the whole study period.

Three primary outcomes were used in our study:

(i) The outcome in phase 1 was the presence of stage 3 to 5 CKD based on the subjects last recorded eGFR measure.

(ii) The first outcome in phase 2 was the development of stage 3 to 5 CKD on the last recorded eGFR in subjects without stage 3 to 5 CKD on the first recorded eGFR during the study period.

(iii) The second outcome in phase 2 was the presence of significant CKD progression (defined as an eGFR decline rate >5ml/min/1.73m^2 per year). The eGFR decline rate was calculated using the difference between the first and last recorded eGFR measurements standardised as a yearly eGFR decline rate.

Three major hypotheses were tested:

(i) In phase 1, is there an association between drug use and stage 3 to 5 CKD at the last eGFR?

(ii) In phase 2, does drug use increase the risk of developing stage 3 to 5 CKD?

(iii) In phase 2, does drug use increase the risk of significant CKD progression?

To test the hypothesis, multiple logistic regression models were performed adjusting for socio-demographic factors, co-morbidity, co-drug therapy, other drug use (either aspirin or paracetamol in the case of NSAID users) and baseline CKD status (phase 2 only). Estimates were given as an Odds Ratio (OR) for normal and high dose drug use. The analysis was repeated on a subgroup of subjects who used multiple combinations of two or three of the listed analgesics comparing against subjects who used NSAIDs only.

Results

In the phase 1 cross-sectional study, 7,657 (33.2% of the practice patients) were aged 40 years or over and had a valid eGFR over the two year study period. The prevalence of stage 3 to 5 CKD was 13.3% amongst phase 1 subjects. In this group, the prevalence of CVD was 53%, DM was 17% and co-drug therapy was 40%. The prevalence of drug use over the study period was 22% for NSAIDs, 30% for aspirin and 21% for paracetamol.

Normal or high dose drug use was not significantly associated with stage 3 to 5 CKD. Multiple drug combinations were not associated with stage 3 to 5 CKD.

In the phase 2 cohort study, 4,145 (18% of the practice patients) were included. The prevalence of stage 3 to 5 CKD in these subjects was 16.1%. The prevalence of CVD was 69%, DM was 26% and co-drug-therapy was 54%. Amongst phase 2 subjects, the prevalence of drug use before the last eGFR measurement was 17% for NSAIDs, 39% for aspirin and 22% for paracetamol. Normal or high dose drug use was not significantly associated with an increased risk of developing stage 3 to 5 CKD. Multiple drug combinations were not significantly associated with an increased risk of developing stage 3 to 5 CKD. However, the estimate for NSAID and paracetamol use was greater than for other drug combinations; OR= 2.309 (95%CI: 0.878-6.072). Normal or high dose NSAID or paracetamol use and normal dose aspirin use were not significantly associated with an increased risk of significant CKD progression. However, high dose aspirin use was associated with a significantly decreased risk of significant CKD progression in subjects with a normal or mildly impaired eGFR at baseline; OR= 0.516 (95%CI: 0.346-0.771). Multiple drug use combinations were not significantly associated with an increased risk of significant CKD progression.

Conclusions

NSAID or paracetamol use were not significantly associated with the presence or development of stage 3 to 5 CKD and neither did they affect the risk of significant CKD progression over a 2-year period. Aspirin use was not significantly associated with the presence or development of stage 3 to 5 CKD. However, over a two year period, high dose

aspirin use significantly decreased the risk of significant CKD progression in subjects with a normal or mildly impaired eGFR.

7.1. Introduction

7.1.1. Identifying CKD from computerised general practice data

Considerable effort is being made to identify and where possible delay the progression of CKD[6], with the emphasis being placed on primary prevention.[6,203] Numerous modifiable risk factors for the progression of renal dysfunction such as DM, HTN, smoking, dyslipidaemia and obesity are well documented.[204,205] The NEw Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) cohort study demonstrated the availability of UK general practice clinical data amongst CKD patients.[5] In the NEOERICA cohort, approximately 30% of the patients had a valid serum creatinine measurement as well as records on numerous clinically relevant CKD risk factors such as HTN, DM and haemoglobin levels.[5] Moreover, UK (Hippilsey-Cox and Coupland)[151,152] and US (Hemmelgarn *et al*.,)[151] studies have been able to use rich computerised clinical databases to formulate and validate accurate CKD risk scores. As well as using clinical data, prescription databases are increasingly being used to assess the prescription of NSAIDs in CKD patients[161] and in the elderly[112].

7.1.2. Aetiology of NSAID induced renal dysfunction

Cyclo-oxygenase enzymes are involved in the formation of prostaglandins which are important in promoting vasodilation in the renal arterioles of patients with renal impairment (*see chapter 4*).[52,118,184] Therefore, the inhibition of the COX enzymes by

NSAIDs in patients with moderate to severe renal dysfunction might be associated with renal function decline.[52,117,118,120] Although the acute effects of NSAIDs are well known[100,101], doubt remains on the association between chronic NSAID use and renal dysfunction, especially in studies which recruited patients with ESRD.[125,126,147] Recent studies have focused on the association between NSAIDs use and the progression of CKD in patients with less severe renal disease.[128,132,149-151,153] By correlating the use of NSAIDs directly to a decline in the eGFR over time, the exact causality of the relationship is becoming clearer.

7.1.3. Common reasons for NSAID use

NSAIDs, especially aspirin, are used widely in the general adult population.[10,163] Prescriptions make up a significant proportion of the NSAIDs used in European countries.[111,206] NSAIDs are prescribed for a myriad of reasons but most commonly for pain[111] brought on by chronic inflammatory musculoskeletal pathologies[207] which is especially evident in the elderly[10]. Therefore, automatically stopping NSAIDs in CKD patients could impact severely on quality of life.[10]

7.1.4. CKD, co-morbidity and polypharmacy

Patients with established CKD, often have co-morbidities such as CVD[39,208] which are associated with an increased risk of disease progression confounding the true attributable effects of individual risk factors (e.g. aspirin[116]). Equally, CKD patients are often taking a multitude of drugs[162,185,186] which may also be linked with renal dysfunction or may be renoprotective[57,209]. Therefore, there is a need to understand the true impact of NSAID use on CKD progression in the context of co-morbidity and co-drug therapy.

7.1.5. The role of paracetamol

In settings where NSAID use is contraindicated, paracetamol (acetaminophen) is often the preferred simple analgesic.[210] Given that paracetamol is a major metabolite of the banned nephrotoxic analgesic phenacetin[110], and its use has been associated in some studies with renal dysfunction[15,128,137,141] but not in others[13,136,137,139,148,149], further study into its effects on renal function is warranted.

7.1.6. The need for the current study

It is clear that CKD is now a major health problem[4] with NICE guidelines (2008) advocating the identification and avoidance of risk factors.[6] For some time, NSAIDs have been considered as risk factors for CKD progression but the published studies portray contradictory evidence.[125,126,147] Moreover, several questions were raised by our systematic review. Firstly, the methods of defining NSAID use have not been ideal as most studies did not use a standardised drug dose measure. Few studies have described in detail the use of NSAID, aspirin and paracetamol amongst CKD patients. Furthermore, multiple drug interactions and the effects of use at different stages of CKD have not been fully explored. The current study aims to address the identified issues, expand upon previously published methodologies and explore in greater detail the interaction between NSAID, aspirin and paracetamol prescription and CKD progression in the general practice setting.

7.2. Main Study Objectives

1. To describe the characteristics, co-morbidity and co-drug therapy status of the CKD population in Stoke-on-Trent based on a sample of patients aged 40 years and over from two local general practices.

2. To estimate the prevalence, dose and patterns of NSAIDs, aspirin or paracetamol prescribing over a 2-year period in CKD patients aged 40 years and over.

3. To investigate whether NSAIDs, aspirin or paracetamol prescribing is associated with stage 3 to 5 CKD in patients aged 40 years and over.

4. To investigate whether NSAIDs, aspirin or paracetamol prescribing increases the risk of developing stage 3 to 5 CKD in patients aged 40 years and over.

5. To investigate whether NSAIDs, aspirin or paracetamol prescribing increases the risk of significant CKD progression in patients aged 40 years and over.

7.3. Methods

This section describes in detail how the study data were acquired, the setting and sample selection, drug use ('exposure definition'), renal function ('outcome definition'), covariates measured and the statistical analysis used. The study was carried out in two phases:

(i) Phase 1, a cross-sectional study of the population testing the hypothesis that drug use is related to stage 3 to 5 CKD at the last eGFR measurement.

(ii) Phase 2, a cohort design study testing whether drug use is related to an increased risk of developing stage 3 to 5 CKD or significant CKD progression.

7.3.1. Study design and setting

Clinical data from two large general practices from a large local database were used. Data were downloaded from the Consultations in Primary Care Archive (CiPCA) and the Prescriptions in Primary Care Archive (PiPCA) databases. These databases contain data from 10 general practices in the Stoke-on-Trent area (UK) with data recorded from 2001 to date with a catchment population of up to 40,000. The databases collect blood tests, including renal function tests (after 2009). Therefore, the study period was a 2-year period between the 1st of January 2009 and the 31st of December 2010. Consultation variables were downloaded from the CiPCA database and prescription data for the PiPCA database using an anonymised patient ID to link the data for each individual patient from the two databases. Access to the anonymised datasets was under current governance processes and ethics permission for the use of these data archives.

In this database consultation-prescription linkage study, the designs employed were:

(i) Cross-sectional study – Phase 1

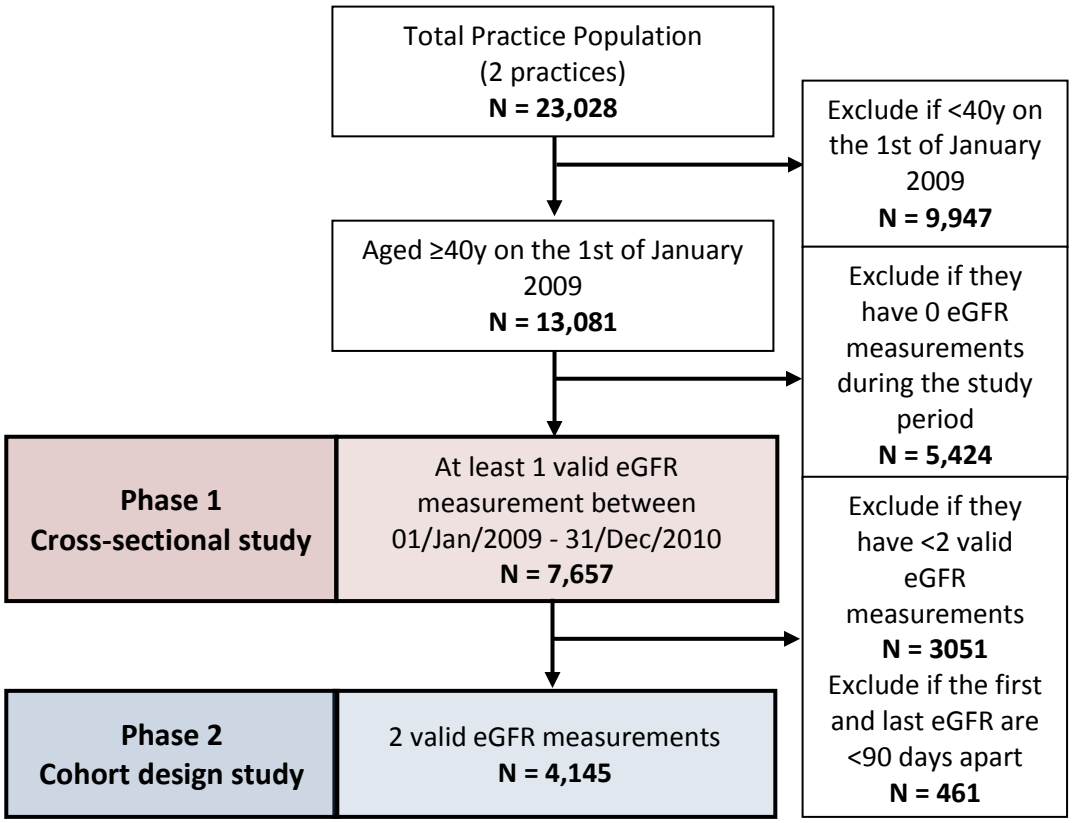
(ii) Cohort design study – Phase 2

7.3.2. Study sample

Patients were eligible for inclusion if they were aged 40 years or over on the 1st of January 2009 and had **at least one** eGFR measurement during the 2-year study period. The ≥40 age group was chosen because the proportion of patients with established CKD decreases rapidly with age and very few patients under the age of 35 years (<1%) will have moderate to severe CKD.[5] **Figure 7.1** shows how subjects were selected from the database.

A subgroup analysis was performed on a cohort of patients with a minimum of two eGFR measurements spaced at least 90 days apart between the **first** and **last** measurement (phase 2). In this cohort design study, we analysed the effects of drug use on the risk of developing stage 3 to 5 CKD as well as the risk of significant CKD progression. Those with <90 days between eGFR measurements were excluded as they are more likely to have acute renal decline and, according to the NICE guidelines, the diagnosis of stage 3 to 5 CKD requires at least 90 days apart between GFR measurements.[6]

Figure 7.1 Flow chart of the patient selection process



7.4. Measure of 'exposure': NSAIDs, aspirin or paracetamol

The primary drug 'exposure' of interest was NSAIDs including aspirin which has a smiliar method of action; paracetamol was chosen as a secondary 'exposure' due to the contradictory evidence in the literature linking its use to CKD and the increasing importance of paracetamol in replacing NSAIDs amongst at risk NSAID users. The PiPCA database contains all prescriptions given to general practice patients during the 2-year study period. Data on the BNF 2009[211] chapter, drug dose, frequency, and number of tablets are recorded for each drug prescription. Therefore, prescription data on NSAIDs (BNF section 10.1.1[211]), aspirin/paracetamol (BNF section 2.9 and 4.7.1[211]) and ACE-

i/ARBs/Renin-i (BNF section 2.5.5 and all subsections[211]) were obtained for all eligible patients. Prescription entries for clopidogrel, dipyridamole and nefopam were excluded from the study database.

7.4.1. Defining drug equivalence for exposure

A major challenge for the study was to formulate a standardised drug dose measure that would allow the comparison of numerous NSAIDs, aspirin and paracetamol types which are all given at different gram/milligram doses and at different daily frequencies.

Initially, the study aim was to calculate the daily dose of each drug based on the frequency and dose. However, many of the NSAIDs had a range of daily usage frequencies (e.g. 1-2 per day) and did not have a fixed frequency of daily use. Moreover, some drugs were given as fluids or injections making it difficult to accurately gauge the amount used per day. In addition, many NSAIDs and aspirin come in a number of dose strengths. Therefore, it was felt that cumulative exposure, based on the number of tablets/mls prescribed and the dose per tablet/ml would be more reliable. The equation below shows how exposure was calculated.

$$Cumulative\ Exposure\ =\ Total\ tablets\ or\ mls\ *\ strength\ per\ tablet\ or\ ml\ (g)$$

For example, a patient taking 1000 tablets of ibuprofen (600mg) over the study period would have an overall cumulative exposure (in grams) of 1000*0.6 = 600 grams.

Two exposure measures were calculated (**Figure 7.2a and b**):

(i) Overall cumulative exposure was defined as the total amount of drug used within the 2-year study period.

(ii) Preceding cumulative exposure was defined as the total amount of drug used between the study inclusion date and a patient's last eGFR measurement date.

The same patient may therefore have only taken 500 tablets of ibuprofen (600mg) before the last eGFR measurement. This would result in a preceding cumulative exposure of 500 * 0.6 = 300 grams.

Figure 7.2a Phase 1 study design diagram

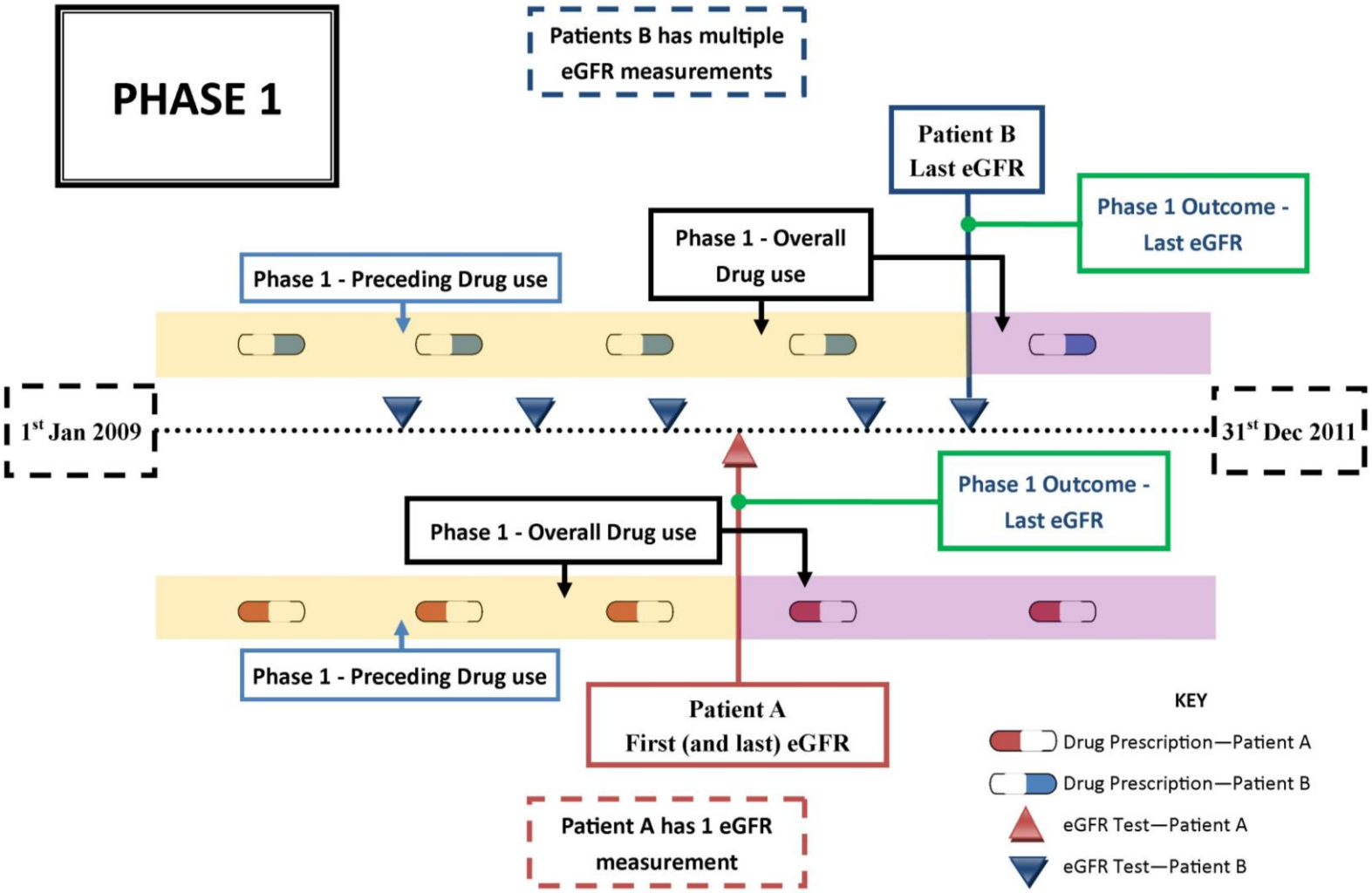
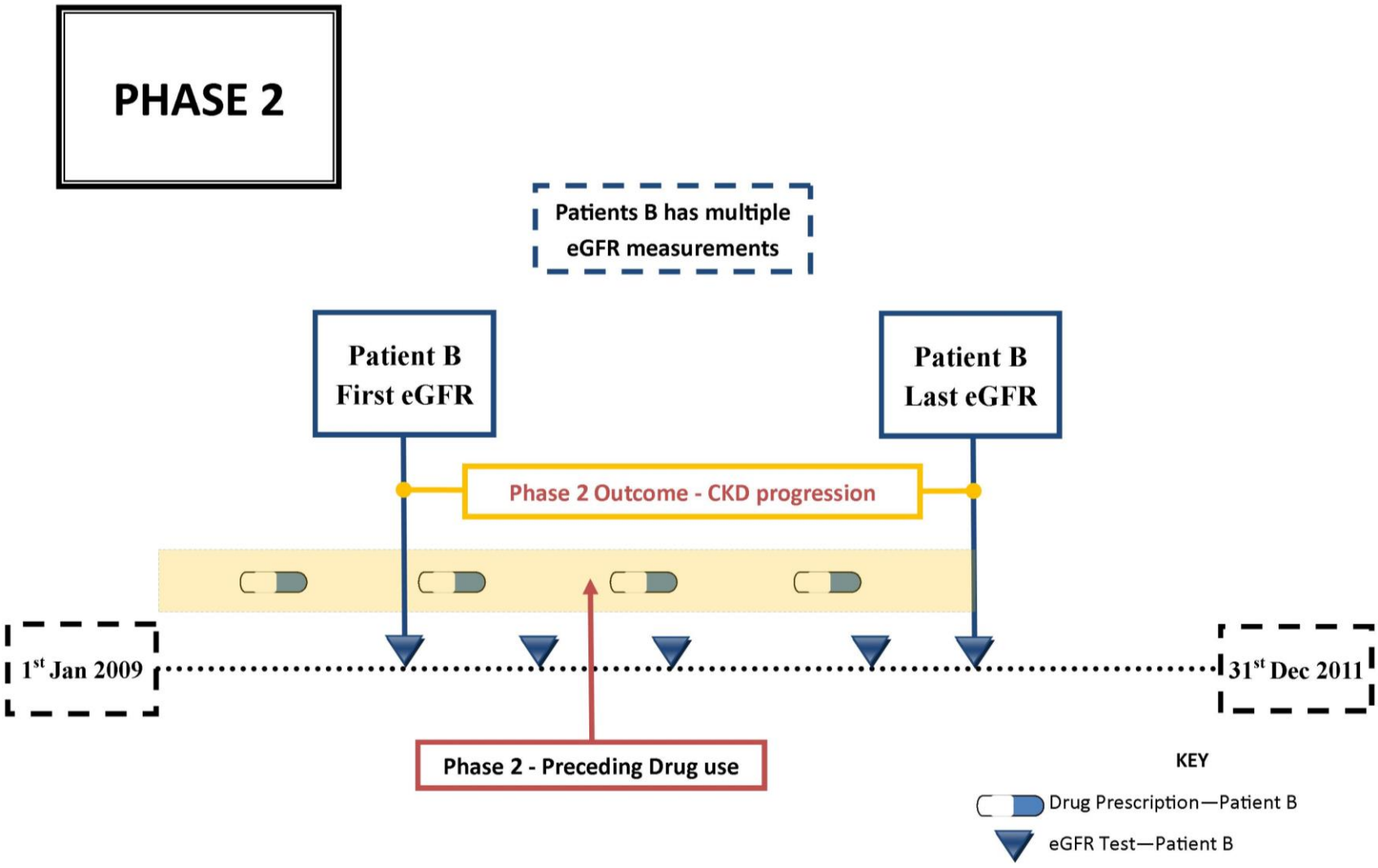


Figure 7.2b Phase 2 study design diagram



7.4.2. International standardisation of drug exposure

To standardise the measure of drug dose, the ATC and DDD system was used (*see section 4.5.2 for details*).[212] To calculate the cumulative DDDs prescribed, the cumulative exposure for each drug had to be divided by its DDD (in grams).[155] The individual DDD for each drug is set out by the WHO-CCDSM and is dependent on the main indication of use.[155] Since the most common indication for NSAIDs is pain relief in musculoskeletal conditions, this was assumed to be the case for patients prescribed NSAIDs.[10,11,211] The indication for use in patients given aspirin was assumed to be for thromboprophylaxis.[211] All paracetamol prescriptions were assumed to be for simple analgesia.[211] The ATC codes, drugs used by the patients and the WHO-CCDSM DDD for each drug included in our study are shown in **Appendix 3**. The equation for the cumulative DDDs is shown below.

$$Cumulative\ DDDs\ per\ drug = \frac{Cumulative\ Exposure\ per\ drug}{WHO\_CCDSM\ DDD\ per\ drug}$$

Therefore, for the patient in our example, the overall cumulative DDD would be 600/1.2 = 500 DDDs of ibuprofen. The preceding cumulative DDDs of ibuprofen use (the use up to the last eGFR) would be 300/1.2 = 250 DDDs. If the patient also took another NSAID, the cumulative DDDs for both drugs would be summed together. Therefore, each patient had a calculated DDD for NSAIDs, aspirin and paracetamol both for the overall study period and the period between the study start date and the last eGFR date.

7.4.3. Drug 'exposure' study group definitions

NSAID, aspirin and paracetamol exposure was then categorised using two approaches. The first approach was based on the presence or absence of drug use ('exposure'). Patients

were divided into non-users (no use of NSAIDs **or** aspirin **or** paracetamol) and users (defined as subjects with a **prescription** of NSAIDs **or** aspirin **or** paracetamol). They were categorised twice, once for overall use and once for drug use from the study inclusion date up to the last eGFR (preceding use). A subgroup of exclusive combined users of NSAIDs and aspirin, NSAIDs and paracetamol, aspirin and paracetamol and users of all three drugs were used to explore the effects of multiple drug prescriptions. This group of exclusive users were defined as having ≥1 prescription of each of the defined drugs before their last eGFR measure. Patients with preceding exclusive NSAID use (patients receiving prescriptions for NSAIDs only before the last eGFR measurement date) acted as a reference group in order to study the possible added risks of multiple drug use.

The second approach, which takes account of the dose prescribed, divided patients into three groups; non-users, normal dose users and high dose users of the respective drugs (NSAID, aspirin or paracetamol) according to the cumulative DDDs prescribed. The chosen cut-offs for normal and high dose NSAID use are similar to those used in the Gooch *et al*., 2007 study but are adjusted for differences in the duration of study periods[150]; this was done in the following manner. In the Gooch *et al.,* study[150], a patient taking 3540 tablets of ibuprofen (200mg) over the study period (assumed to be 2.75 years) would be categorised as a high dose user (≥90th percentile in their study). This would result in (3540 * 0.2)/1.2 = 590 cumulative DDDs of use over the study period of 2.75 years.[150] However, since cumulative use is dependent on the study duration, the same patient would actually have 590 * (2/2.75) = 429 cumulative DDDs of use in a two year period (equivalent to our study period). Therefore, the percentile of cumulative DDDs in our study closest to this value (to the nearest 5th percentile) amongst NSAID users was searched; this corresponded to the 85th percentile. Each subject was categorised as either a non-user (0 DDDs), a

normal-dose user (>0 DDDs and <85th percentile) or a high-dose user (≥85th percentile). The same percentile cut-off values were then used to define normal and high dose aspirin and paracetamol use. Patients were categorised twice using this approach, both for overall cumulative DDDs (DDDs during the study) and preceding cumulative DDDs (DDDs up to the last eGFR).

7.5. Measure of Outcomes

7.5.1. Determining CKD status

The CKD status was determined using the eGFR as the measure of renal function. The eGFR was calculated using the simplified 4-variable MDRD equation which, in addition to serum creatinine, includes the variables for age, gender and ethnicity (*see section 1.2.3*).[17] General practice patients with a serum creatinine recording automatically have their eGFR calculated. To identify patients who had an eGFR during the study period, the CiPCA database was searched for entries under the READ-5 code (version 2) **451E.**.[213] READ-5 codes are unique, standardised clinical identifiers and relate to computerised consultation and clinical data routinely recorded by GPs.

In the descriptive analysis, patients were stratified according to the baseline (first) eGFR measurement. GFR values are used to classify CKD into five stages as defined by the NKF-KDOQI guidelines (*see Table 1.1*).[4] Stages 3 to 5 CKD can be categorised from the eGFR alone.[4] However, stage 1 and 2 CKD require further evidence of renal pathology[4] which is not available in our study. Therefore, we used an approach used by de Lusignan *et*

al., (2006)[38] whereby patients with an eGFR between 60 and 89 were categorised as "mildly impaired" and those with an eGFR ≥90 were categorised as "normal".

In the hypothesis testing (phase 1), the last eGFR was used to determine the CKD status to test for the association between drug use and stage 3 to 5 CKD (**Figure 7.2a**).

7.5.2. Measuring CKD progression

Phase 2, patients had two eGFR measurements, hence it was possible to measure the change in the eGFR over time. Several approaches were considered including fitting a regression line to each individual patient and calculating the rate of decline or finding the mean difference between eGFR measurements in two 6-month periods placed at the beginning and the end of the study.

A simpler and more practical measure of change was settled upon using the patients' first and last eGFR and standardising the change over a one year period to calculate the eGFR decline rate per year. This was calculated by searching the data for a patients' first and last eGFR measurement. Then, the value of the last eGFR measurement was subtracted from the value of the first eGFR measurement to work out the change in the eGFR (**Figure 7.2b**). Finally, to standardise the eGFR change over a one year period, the change in eGFR was multiplied by 365/eGFR interval (the time difference between the last and first eGFR measurements in days) as shown by the equation below.

$$eGFR\ decline\ rate/year\ =\ (last\ eGFR - first\ eGFR) * \left(\frac{365}{eGFR\ interval\ (days)}\right)$$

7.5.3. Interval measurement

For patients with multiple eGFR measurements, the mean difference (in days) between two eGFR measurements (if it were assumed that all eGFR measurements were equally spaced apart over time) could also be calculated as follows.

$$Mean\ difference\ between\ eGFR\ measurements = \frac{eGFR\ interval(days)}{(number\ of\ eGFR\ measurements - 1)}$$

This was used to give an indication of the testing interval and could therefore give an insight into whether the interval varied between drug users and non-users or between practices. Finally, to give an indication of the time patients could have been used drug for, the maximum exposure period was calculated by finding the interval between the start of the study and the last eGFR date. This was necessary because prescriptions were censored at the date of the last eGFR and an indication of the time period between the study start and the last eGFR date was needed.

$$Exposure\ period\ (days) = Date\ of\ last\ eGFR - 1st/Jan/2009$$

7.6. Covariates

7.6.1. Socio-demographics

The socio-demographic data downloaded from the CiPCA database included the age, sex and index of multiple deprivation (IMD) score (2007)[214] of the study subjects at inclusion. The IMD score combines seven weighted indicators which cover economic, health, social and housing domains into a single deprivation score. It is widely used to access patterns of

deprivation in the UK population.[214] In our study, patients were divided into quartiles based on their relative IMD scores. 171 of the 7,657 patients did not have an IMD score thus could not be placed into quartiles. The groups were therefore representative of relative deprivation between the included subjects. Given the significantly higher levels of deprivation in Stoke-on-Trent compared to the UK population, included subjects are likely to be more deprived that the average patient in the UK.[215]

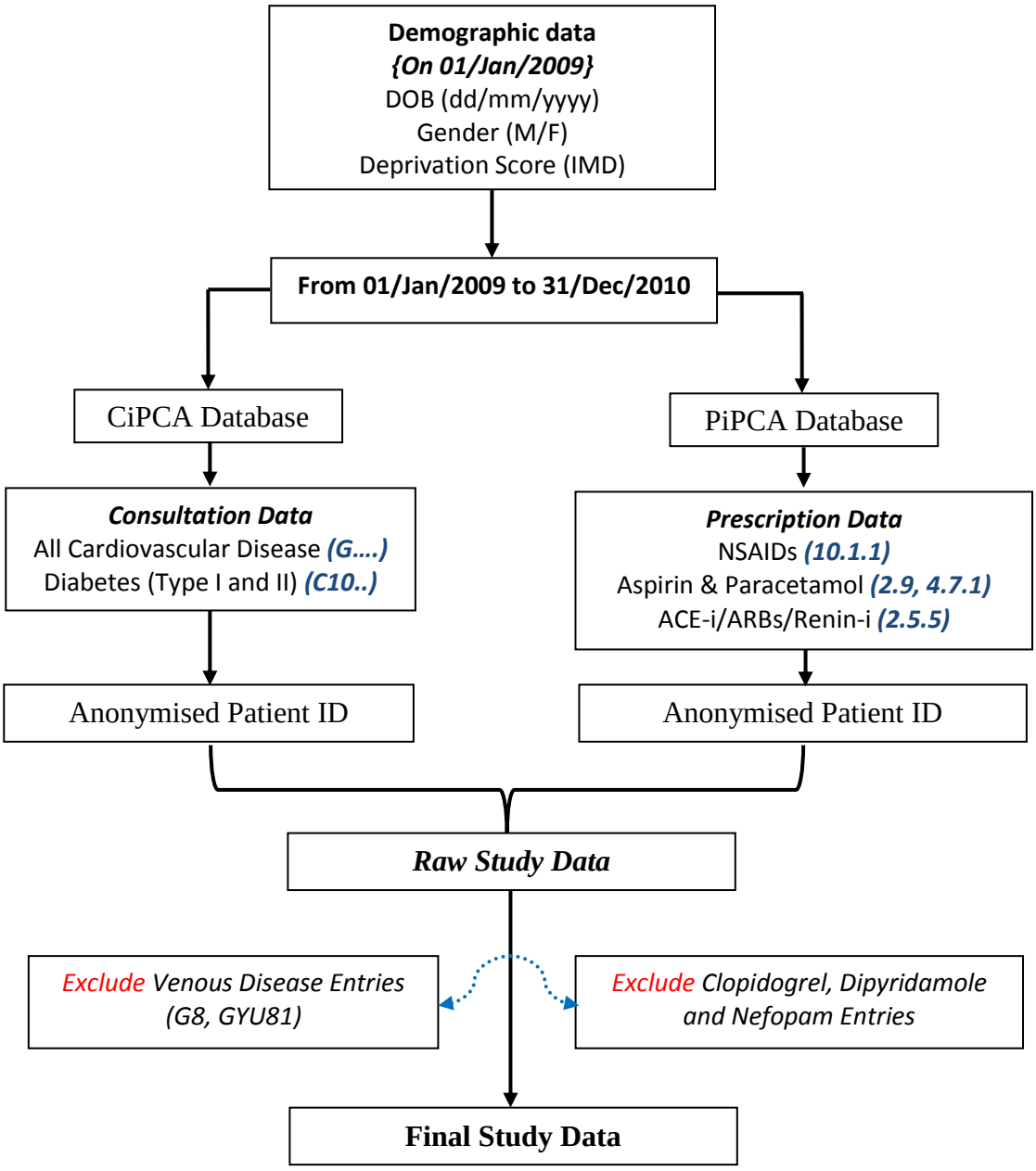
7.6.2. Co-morbidity

DM and CVD status were identified from the CiPCA database according to 5-byte READ codes similar to the eGFR. Subjects with READ 5 codes [C10..] & all daughter codes over the study period were identified as having DM. Those with READ 5 codes [G....] & all daughter codes were selected as these codes capture all CVD. Patients were then grouped into six cardiovascular disease groups (hypertensive disease, ischaemic heart disease, heart failure, dysrhythmia, cerebrovascular disease and peripheral arterial disease). Entries for venous disease were excluded from this classification as they did not accurately represent cardiovascular disorders (e.g. varicose eczema). The classification of DM and CVD are shown in **Appendix 4** and **5**.

7.6.3. Co-drug therapy

Co-drug therapy was defined as one or more ACE-i/ARBs/Renin-i prescriptions (BNF section 2.5.5 and all subsections[211]) over the study period. ACE-i/ARBs/Renin-i are used as renoprotective drugs in patients with HTN and proteinuria.[6] They were chosen both as they would act as a proxy indictor of proteinuria and because there is a possible interaction between NSAIDs and ACE-i/ARBs/Renin-i as both drug types can disrupt renal haemodynamics. **Figure 7.3** shows how the final study data was formed.

Figure 7.3 Flow chart of the formation of study data



7.7. Statistical Analysis

7.7.1. Descriptive Statistics – Phase 1 and Phase 2

Data is presented as means and standard deviations (SD) for normally distributed continuous data whilst skewed continuous data is presented as medians with interquartile ranges [IQR]. Dichotomous data are presented as counts and/or percentages. Data tables were stratified according the practice, the *baseline* eGFR measure and the level of drug use. Parametric tests for significant differences between groups were determined by the *t*-test, ANOVA test, Welch's F test and the Chi-squared (χ^2) test where appropriate. Non-parametric tests for significant differences between groups were determined by the Mann-Whitney *U* test and the Kruskal-Wallis analysis where appropriate. The *p*-value is significant if ≤ 0.05.

7.7.2. Hypothesis Testing – Phase 1

7.7.2.1. Drug use and stage 3 to 5 CKD

The adjusted OR for stage 3 to 5 CKD at the ***last*** eGFR measurement compared to patients with an eGFR $\geq$60ml/min/1.73m^2 with preceding (prescribing up to the ***last*** eGFR) normal and high dose drug use (**Figure 7.2a**) compared to non-users was calculated using multiple logistic regression adjusting for socio-demographics, co-morbidity, co-drug therapy and other drug use (either aspirin or paracetamol in the case of NSAID users). The analysis was repeated for preceding exclusive multiple drug users with preceding exclusive NSAID users acting as the reference group. NSAID users were chosen as the reference group because they were the primary focus of this study and in a clinical setting, a clinician

would want to know the added risk of prescribing a second drug (aspirin or paracetamol) on top of the NSAIDs already being given.

7.7.3. Hypothesis Testing – Phase 2

7.7.3.1. Drug use and the development of stage 3 to 5 CKD

In phase 2, records with at least two eGFR measurements spaced ≥90 days apart were searched to find patients with a baseline (*first*) eGFR ≥60ml/min/1.73m^2. Those patients were then categorised into two groups, patients progressing to stage 3 to 5 CKD at the ***last*** measurement (eGFR <60ml/min/1.73m^2) and those that did not (**Figure 7.2b**). Multiple logistic regression was run to calculate the OR for developing stage 3 to 5 CKD with preceding normal and high dose drug use adjusting for socio-demographics, co-morbidity, co-drug therapy, other drug use (either aspirin or paracetamol in the case of NSAID users) and the baseline CKD status as this has been shown to influence progression in the Gooch *et al*., 2007 study.[150] The analyses were repeated in exclusive multiple drug users.

7.7.3.2. Drug use and significant CKD progression

To further explore the relationship between drug use and CKD progression, **all** phase 2 patients were categorised into two groups, those with significant CKD progression (defined as eGFR decline of >5ml/min/1.73m^2 per year) and those without (defined as an eGFR decline of ≤5ml/min/1.73m^2 per year) calculated using the values of the first and last eGFR (**Figure 7.2b**). Multiple logistic regression analysis was repeated accessing for the risk of significant CKD progression. The analyses were repeated in exclusive multiple drug users. Finally, because the MDRD equation can be inaccurate in eGFR ranges above 60 hence a subgroup analysis was carried out in these patients by stratifying them into two groups

(eGFR ≥60 and <60ml/min/1.73m^2). The multiple logistic regression analysis was then rerun adjusting for the previously detailed covariates to see if this had an effect on the ORs.

The adjusted covariates were chosen as they are clinically important[6,216], are associated with renal function decline[4,43] and feature prominently in the literature[15,128,139,144,149,150,153]. All the assumptions of logistic regression were met; the statistical analyses were carried out on SPSS (Version 20.0, SPSS, IBM, USA).

7.8. Chapter Summary

- **Setting –** Two general practices in Stoke-on-Trent over a two year study period between the 1st Jan 2009 and the 31st Dec 2010.

- **Design –** Two phase clinical linkage study using consultation and prescription data.
    - Phase 1 = cross-sectional study.
    - Phase 2 = cohort design study.

- **Population**
    - Phase 1 = patients aged 40 years and over with at least one eGFR measurement over the two year period.
    - Phase 2 = a subgroup of patients with two or more eGFR measurements spaced at least 90 days apart.

- **Exposure –** Drug (NSAIDs, aspirin and paracetamol) 'exposure' defined using the cumulative dose of general practice prescribing. Drug 'exposure' standardised using the international DDD system. Subjects categorised into non-user (0 DDDs), normal dose (<85th percentile) and high dose (≥85th percentile) user groups. Prescriptions given after the last eGFR are censored in the hypothesis testing (preceding drug use).

- **Covariates –** Socio-demographics (age, gender and IMD quartiles), co-morbidity (CVD and DM) and co-drug therapy (ACE-i/ARBs/Renin-i).

- **Analysis** – Multiple logistic regression analyses adjusting for socio-demographics, co-morbidity, co-drug therapy, other drug use and baseline CKD status (in phase 2 only).

- **Outcomes**
    - Phase 1 = the association between drug use and stage 3 to 5 CKD at the last eGFR measurement.
    - Phase 2 = the association between drug use and the development of stage 3 to 5 CKD between the baseline and last eGFR measurement.
    - Phase 2 = the association between drug use and significant CKD progression (eGFR decline rate of >5ml/min/1.73m^2).

Chapter 8. Phase 1 - The Influence of Non-Steroidal Anti-Inflammatory Drugs on Chronic Kidney Disease: A Cross-sectional Study

This chapter presents the results of subjects with at least one eGFR measurement aged 40 years and over. Much of this chapter aims to describe the CKD population but it also begins to explore not only cross-sectional associations between drug prescription and CKD status but also socio-demographics, co-morbidity, co-drug therapy and other drug use.

Chapter Plan

- **Study sample: baseline characteristics**
    - Study inter-practice differences.
    - Socio-demographics, co-morbidity and co-drug therapy in the CKD population.

- **Drug exposure**
    - Prevalence of drug prescription.
    - Drug prescription dose.
    - Age and drug prescribing.

- **Characteristics of drug users**
    - Drug use and baseline CKD status.
    - Factors associated with drug use.

- **Drug use and stage 3 to 5 CKD**
    - Single drug use and stage 3 to 5 CKD at the last eGFR.
    - Multiple drug use and stage 3 to 5 CKD at the last eGFR.

8.1. Study Sample: Baseline Characteristics

8.1.1. Study subjects - Demographics

There were 23,068 patients registered to the two selected practices. Of these, 7,657 (33.2% of the practice population) patients were aged over 40 years and had one or more eGFR measurements during the defined study period

The mean age of the study subjects was 64 years (SD=13). The female to male ratio was 1.2:1 which differs from the population in England and Wales (F:M = 1.10:1 as of June 2009) [217].

The age-sex distribution of the study subjects tended to over represent older people and under represent younger people (especially the 40-59y age group) in both males and females when compared to the distribution in England and Wales (aged 40 years and over, June 2009) (**Figure 8.1a & b**).[217]

Figure 8.1a Age distribution of male subjects vs England and Wales (≥40y, June-2009)

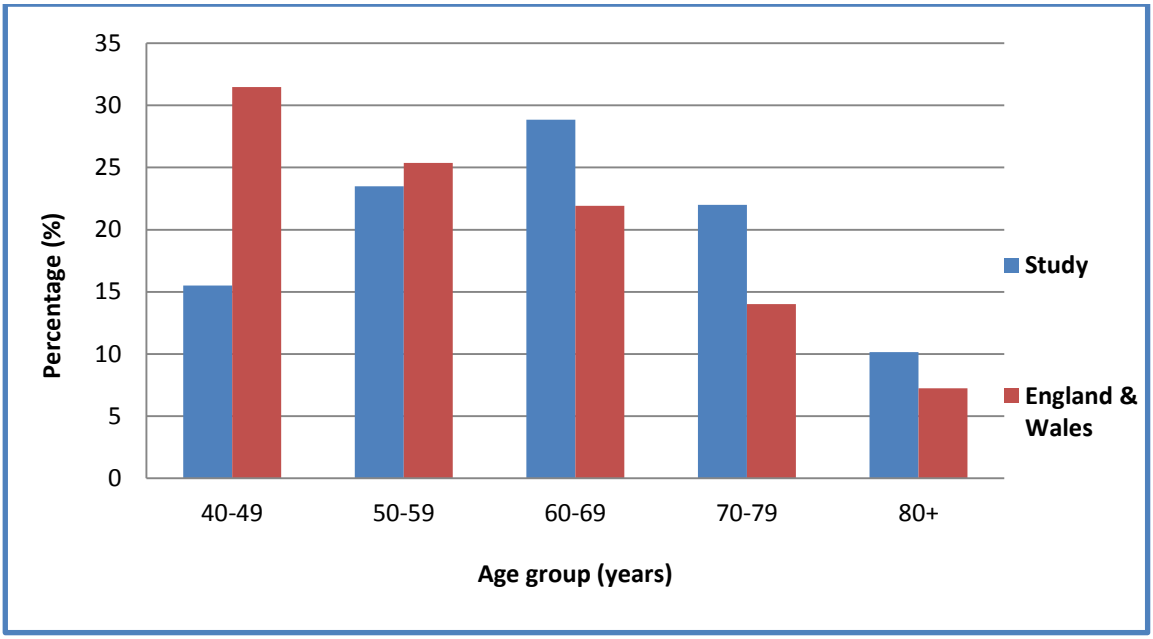
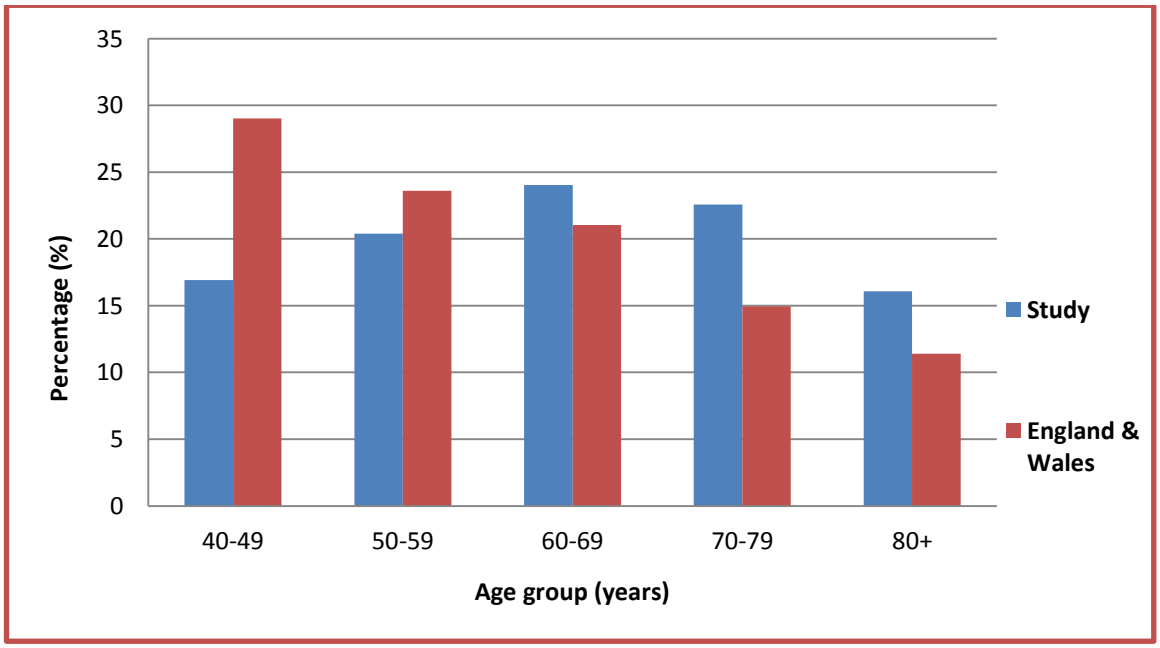


Figure 8.1b Age distribution of female subjects vs England and Wales (≥40y, June-2009)



8.1.2. Study sample by practice

Of the 7,657 subjects, 3,486 were from practice H and 4,171 were from practice I. In general, the basic demographics of mean age and gender did not significantly differ between the two practices. However, there were significant differences in the deprivation of the practice subjects with practice I having a greater degree of deprived patients compared to practice H ($p<0.001$). The practice characteristics are shown in **Table 8.1**.

There were significant differences in the prescription of NSAIDs, aspirin and paracetamol. Compared to practice H, practice I had a higher proportion of NSAID and aspirin users but a lower proportion of paracetamol users both throughout the study period and up to the date of the last eGFR measurement.

The proportions of patients with CVD or DM did not significantly differ between the two practices. However, co-drug therapy was significantly higher in practice I than in practice H.

The median baseline eGFR and median number of eGFR measurements were the same in both practices (although practice I had a significantly different distribution of eGFR measurements).

Table 8.1 Practice characteristics of patients with at least one eGFR test aged 40 years and over

Variable		Practice H N=3486	Practice I N=4171	*p*-value
Mean Age (SD)		64 (13)	64 (13)	0.350
Gender (%)	Male	45.7	44.0	0.148
	Female	54.3	56.0	
Deprivation (%)	Least Deprived Quartile	25.8	25.9	**<0.001***
	IMD 2	34.5	16.6	
	IMD 3	35.8	17.6	
	Most Deprived Quartile	4.0	39.9	
NSAID use (%) *(n=1676)*	Non-user	79.1	77.2	**0.046***
	User	20.9	22.8	
Aspirin use (%) *(n=2256)*	Non-user	71.7	69.6	**0.049***
	User	28.3	30.4	
Paracetamol use (%) *(n=1626)*	Non-user	76.1	81.0	**<0.001***
	User	23.9	19.0	
[1]Preceding NSAID use (%) *(n=1321)*	Non-user	83.7	81.9	**0.037***
	User	16.3	18.1	
[1]Preceding Aspirin use (%) *(n=2128)*	Non-user	73.5	71.2	**0.025***
	User	26.5	28.8	
[1]Preceding Paracetamol use (%) *(n=1311)*	Non-user	80.8	84.7	**<0.001***
	User	19.2	15.3	
All CVD (%) *(n=4038)*	No	47.6	47.0	0.601
	Yes	52.4	53.0	
All Diabetes (%) *(n=1323)*	No	82.0	83.3	0.151
	Yes	18.0	16.7	
ACE-i/ARB/Renin-i (%) *(n=3077)*	Non-user	61.2	58.7	**0.028***
	User	38.8	41.3	
Median [IQR] number of eGFR measurements		2 [1-3]	2 [1-3]	**0.001***
Median [IQR] baseline eGFR		85 [71-91]	84 [70-91]	0.226

[1]Drugs given before the last eGFR measurement i.e. censored, *Statistically significant at $p \leq 0.05$.

8.1.3. Socio-demographic characteristics of the study sample

There were 19,108 eGFR measurements during the 2-year period. Of the 7,657 subjects, 40.6% had a normal eGFR, 46.1% had a mildly impaired eGFR, 12.3% had stage 3 CKD, 0.8% had stage 4 CKD and 0.2% had stage 5 CKD.

The study prevalence of stage 3 to 5 CKD based on the baseline (*first*) eGFR was 13.3% (females, 15.6%; males, 10.5%). The age-adjusted prevalence for stage 3 to 5 CKD in patients aged 40 years and over (England and Wales, June 2009 figures[217]) was 9.9% (females, 11.9%; males, 7.8%). In our study, the percentage of patients with stage 3 to 5 CKD increased exponentially with age as shown in **Figure 8.2**.

The severity of renal dysfunction correlated with increasing age in both males and females. Older patients were significantly more likely to have poor renal function, whilst younger patients were more likely to have normal or mildly impaired eGFR values in both males and females ($p<0.001$) (**Table 8.2**). The mean age in both males and females increased with worsening CKD status from 59 in males and females with a normal eGFR to 74 in males and 80 in females with stage 4 CKD. Patients with stage 5 CKD had a lower mean age (males 72, females 77) than stage 4 CKD patients. With poorer CKD status, females tended to have a higher maximum mean age (80) than males (74).

The results show that deprivation correlated significantly with worsening renal function ($p<0.001$). Patients with a lower eGFR were more likely to be in the most deprived quartile compared to patients with a normal eGFR. The proportion of patients with a normal eGFR in the least deprived quartile was 25.4% and fell to just 11.8% in stage 5 CKD. Equally, 22.8% of patients with a normal eGFR were in the most derived quartile increasing to 41.2% at stage 5 CKD (**Table 8.2**).

Figure 8.2 Study sample distribution of stage 3 to 5 CKD at baseline stratified by age and gender

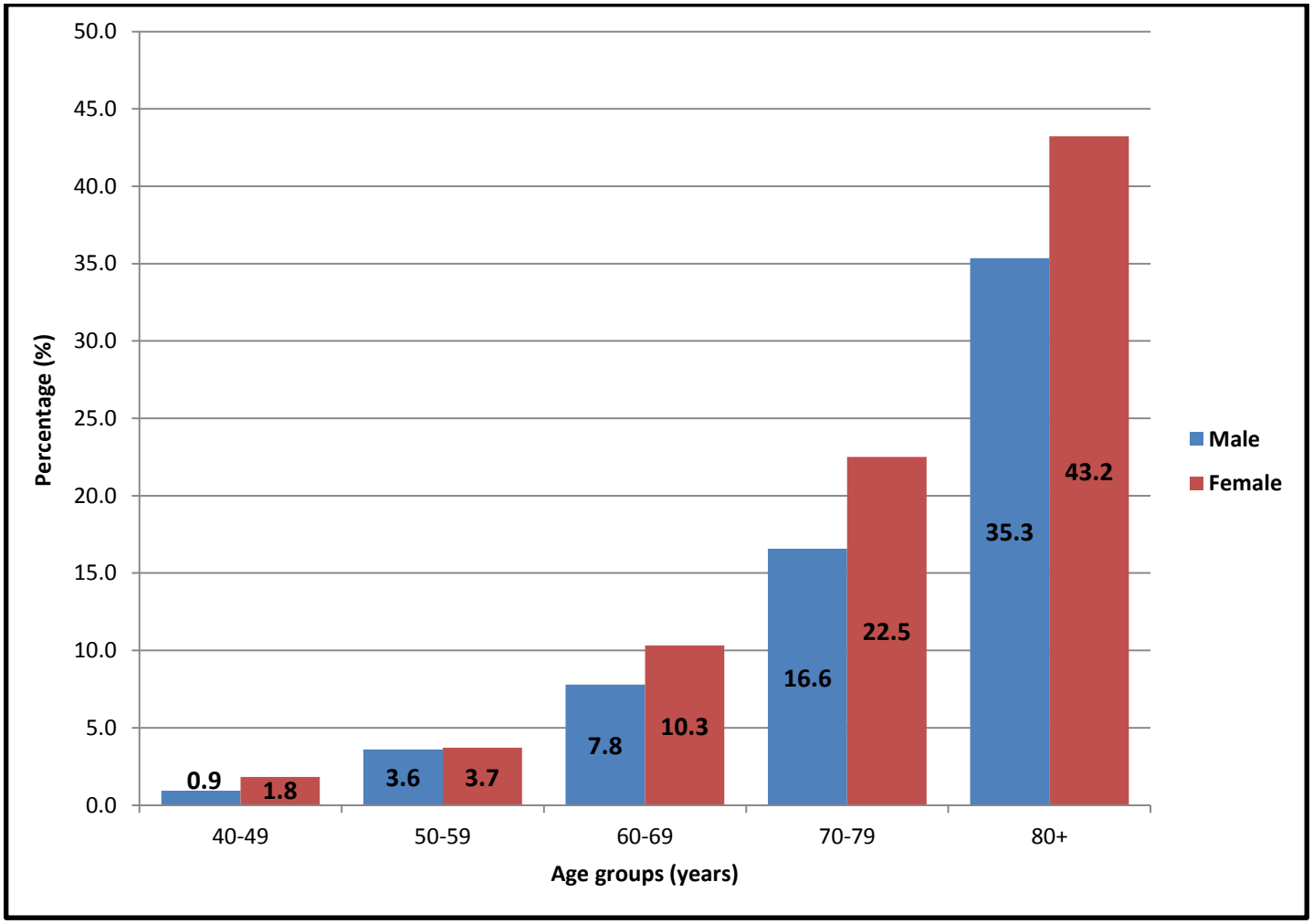


Table 8.2 Socio-demographic characteristics and baseline CKD status

Demographic	Gender	Normal N=3110		Mildly impaired N=3529		Stage 3 CKD N=941		Stage 4 CKD N=60		Stage 5 CKD N=17		*p*-value
		n	%	n	%	n	%	n	%	n	%	
40-49	Male	360	**24.0**	167	**10.6**	5	**1.5**	0	**0.0**	0	**0.0**	**<0.001[a]***
(n=1247)	Female	469	**29.1**	233	**11.9**	13	**2.1**	0	**0.0**	0	**0.0**	
50-59	Male	459	**30.6**	317	**20.2**	25	**7.7**	3	**12.5**	1	**11.1**	
(n=1667)	Female	419	**26.0**	411	**21.0**	29	**4.7**	2	**5.6**	1	**12.5**	
60-69	Male	409	**27.3**	503	**32.1**	72	**22.1**	4	**16.7**	1	**11.1**	
(n=2006)	Female	384	**23.9**	528	**26.9**	101	**16.4**	3	**8.3**	1	**12.5**	
70-79	Male	207	**13.8**	422	**26.9**	112	**34.4**	6	**25.0**	7	**77.8**	
(n=1709)	Female	245	**15.2**	495	**25.3**	207	**33.7**	7	**19.4**	1	**12.5**	
80+	Male	65	**4.3**	160	**10.2**	112	**34.4**	11	**45.8**	0	**0.0**	
(n=1028)	Female	93	**5.8**	293	**14.9**	265	**43.1**	24	**66.7**	5	**62.5**	
Total	Male	1500	**100**	1569	**100**	326	**100**	24	**100**	9	**100**	*N/A*
(n=7657)	Female	1610	**100**	1960	**100**	615	**100**	36	**100**	8	**100.0**	
Least Deprived *(n=1932)*		775	**25.4**	955	**27.7**	189	**20.7**	11	**19.3**	2	**11.8**	**<0.001***
IMD 2 *(n=1850)*		746	**24.5**	860	**24.9**	228	**25.0**	13	**22.8**	3	**17.6**	
IMD 3 *(n=1937)*		833	**27.3**	843	**24.4**	241	**26.4**	15	**26.3**	5	**29.4**	
Most deprived *(n=1767)*		694	**22.8**	793	**23.0**	255	**27.9**	18	**31.6**	7	**41.2**	

[a]Significant differences between ages and CKD status for both males and females, *Statistically significant at $p \leq 0.05$.

8.1.4. Co-morbidity and co-drug therapy of the study sample

There were 5,153 consultation entries relating to DM during the 2-year period. The prevalence of DM was 17.3% (n=1,323) among the study sample. The proportion of diabetic patients varied significantly with worsening CKD status. The percentage of DM among patients with a normal eGFR at baseline was 18.8% increasing to 29.4% among those with stage 5 CKD (**Table 8.3**). In addition, 20.8% of patients with an eGFR <60ml/min/1.73m^2 at baseline had DM which was significantly higher than the 16.7% in those with an eGFR ≥60ml/min/1.73m^2 (see **Appendix 6**).

There were 17,030 consultation entries relating to CVD excluding 611 entries for venous disease. The prevalence of any CVD was 52.7% (n=4,038) among the study subjects. The proportion of patients with CVD did not increase in the same linear fashion as with DM, reaching a peak at stage 3 CKD (66.1%) (**Table 8.3**). Overall, the proportion of patients with CVD was significantly higher in patients with an eGFR <60ml/min/1.73m^2 (65.6%) compared to those with an eGFR ≥60ml/min/1.73m^2 (50.8%) (**Appendix 6**). The CVD group was divided further into its individual diagnosis as detailed in **Appendix 5**. The study prevalence of the CVD conditions was as follows; HTN (42.2%), ischaemic heart disease (9.9%), heart failure (2.2%), peripheral vascular disease (1.3%), cerebrovascular disease (4.9%) and dysrhythmia (2.5%). The CVD disease components were all significantly associated with worsening renal function (p<0.001) with the exception of peripheral vascular disease (p=0.068) (**Table 8.3**). The prevalence of CVD disease components was significantly higher in patients with stage 3 to 5 CKD compared to those with a normal or mildly impaired eGFR (**Appendix 6**).

There were 59,505 prescriptions for ACE-i/ARBs/Renin-i during the study period and 40.2% (n=3,077) of patients had at least one prescription for the drugs over 2-years (**Table 8.3**). In those with at least one prescription, the median number of prescriptions was 21 [IQR=12-26]; the maximum was 101. The proportion of co-drug therapy users increased significantly with worsening eGFR; 37.7% of patients with an eGFR ≥60 had a prescription for the drug compared to 54.7% in those with an eGFR <60 (**Appendix 6**).

Table 8.3 Co-morbidity and co-drug therapy and baseline CKD status

Cofactor		eGFR ≥60				eGFR <60						*p*-value
		Normal N=3110		Mildly impaired N=3529		Stage 3 CKD N=941		Stage 4 CKD N=60		Stage 5 CKD N=17		
		n	%	n	%	n	%	n	%	n	%	
[1]**Diabetes** *(n=1323)*	No	2525	**81.2**	3003	**85.1**	748	**79.5**	46	**76.7**	12	**70.6**	**<0.001***
	Yes	585	**18.8**	526	**14.9**	193	**20.5**	14	**23.3**	5	**29.4**	
All CVD *(n=4038)*	No	1654	**53.2**	1615	**45.8**	319	**33.9**	24	**40.0**	7	**41.2**	**<0.001***
	Yes	1456	**46.8**	1914	**54.2**	622	**66.1**	36	**60.0**	10	**58.8**	
[2]Hypertension *(n=3234)*	No	1923	**61.8**	1998	**56.6**	461	**49.0**	32	**53.3**	9	**52.9**	**<0.001***
	Yes	1187	**38.2**	1531	**43.4**	480	**51.0**	28	**46.7**	8	**47.1**	
[3]Ischaemic Heart Disease *(n=758)*	No	2865	**92.1**	3148	**89.2**	815	**86.6**	55	**91.7**	16	**94.1**	**<0.001***
	Yes	245	**7.9**	381	**10.8**	126	**13.4**	5	**8.3**	1	**5.9**	
[4]Heart failure *(n=167)*	No	3068	**98.6**	3457	**98.0**	892	**94.8**	57	**95.0**	16	**94.1**	**<0.001***
	Yes	42	**1.4**	72	**2.0**	49	**5.2**	3	**5.0**	1	**5.9**	
[5]Peripheral Vascular Disease *(n=101)*	No	3076	**98.9**	3484	**98.7**	921	**97.9**	59	**98.3**	16	**94.1**	0.068
	Yes	34	**1.1**	45	**1.3**	20	**2.1**	1	**1.7**	1	**5.9**	
[6]Cerebrovascular disease *(n=379)*	No	2991	**96.2**	3358	**95.2**	856	**91.0**	57	**95.0**	16	**94.1**	**<0.001***
	Yes	119	**3.8**	171	**4.8**	85	**9.0**	3	**5.0**	1	**5.9**	
[7]Dysrhythmia *(n=193)*	No	3052	**98.1**	3445	**97.6**	898	**95.4**	52	**86.7**	17	**100.0**	**<0.001***
	Yes	58	**1.9**	84	**2.4**	43	**4.6**	8	**13.3**	0	**0.0**	
[8]**ACE-i/ARBs/Renin-i** *(n=3077)*	Non-user	2026	**65.1**	2113	**59.9**	410	**43.6**	25	**41.7**	6	**35.3**	**<0.001***
	User	1084	**34.9**	1416	**40.1**	531	**56.4**	35	**58.3**	11	**64.7**	

READCODES = [1]C10, [2]G2, [3]G3, [4](G1, G4, G50, G51, G54, G55, G58, G5Y, G5UYT), [5]G6, [6](G7, GY), [7](G56, G57). All CVD = 2-7. [8]BNF chapter 2.5.5 and all subsections. See **Appendix 4** and **5.** *Statistical significance at $p \leq 0.05$.

8.2. Drug Exposure

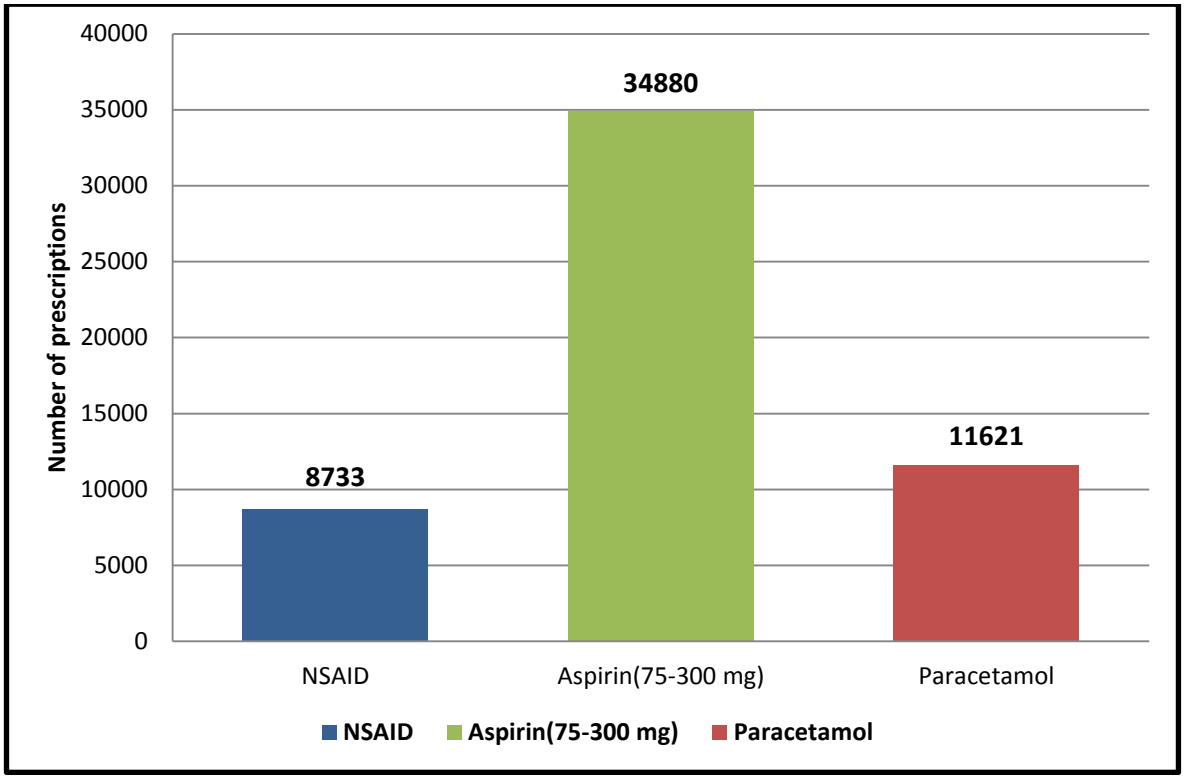
8.2.1. The prevalence of study drug prescriptions

During the study period, there were 8,733 prescriptions for NSAIDs, 34,880 prescriptions for low-medium dose tables (*75-300mg*) of aspirin, and 11,621 prescriptions for paracetamol (**Figure 8.3**). During the 2-year period there were n=1,676 (21.9%) NSAID, n=2,256 (29.5%) aspirin and n=1,626 (21.2%) paracetamol users.

Amongst NSAID users, the median number of NSAID prescriptions was 2 [IQR=1-6]; the maximum number of NSAID prescriptions was 67. Amongst patients with at least one aspirin prescription, the median number of aspirin prescriptions was 14 [IQR=7-24], maximum = 103. Equally, amongst users of paracetamol, the median number of paracetamol prescriptions was 4 [IQR=1-10], maximum = 101.

It can be accurately assumed that each prescription was given over a monthly basis because less than 2% of all patients were given >28 prescriptions for NSAIDs, aspirin or paracetamol which is in agreement with the theoretical maximum number of prescriptions which can be given over 2-year period if given on a monthly basis (12 months * 2 = 24). Therefore, the typical number of monthly prescriptions was 2 for NSAIDs, 14 for aspirin and 4 for paracetamol. Those receiving more than the theoretical maximum number of prescriptions (maximum aspirin prescriptions was 103) were probably given the drugs over a weekly basis as the theoretical maximum number of prescriptions then would be 104 (52 weeks * 2 = 104).

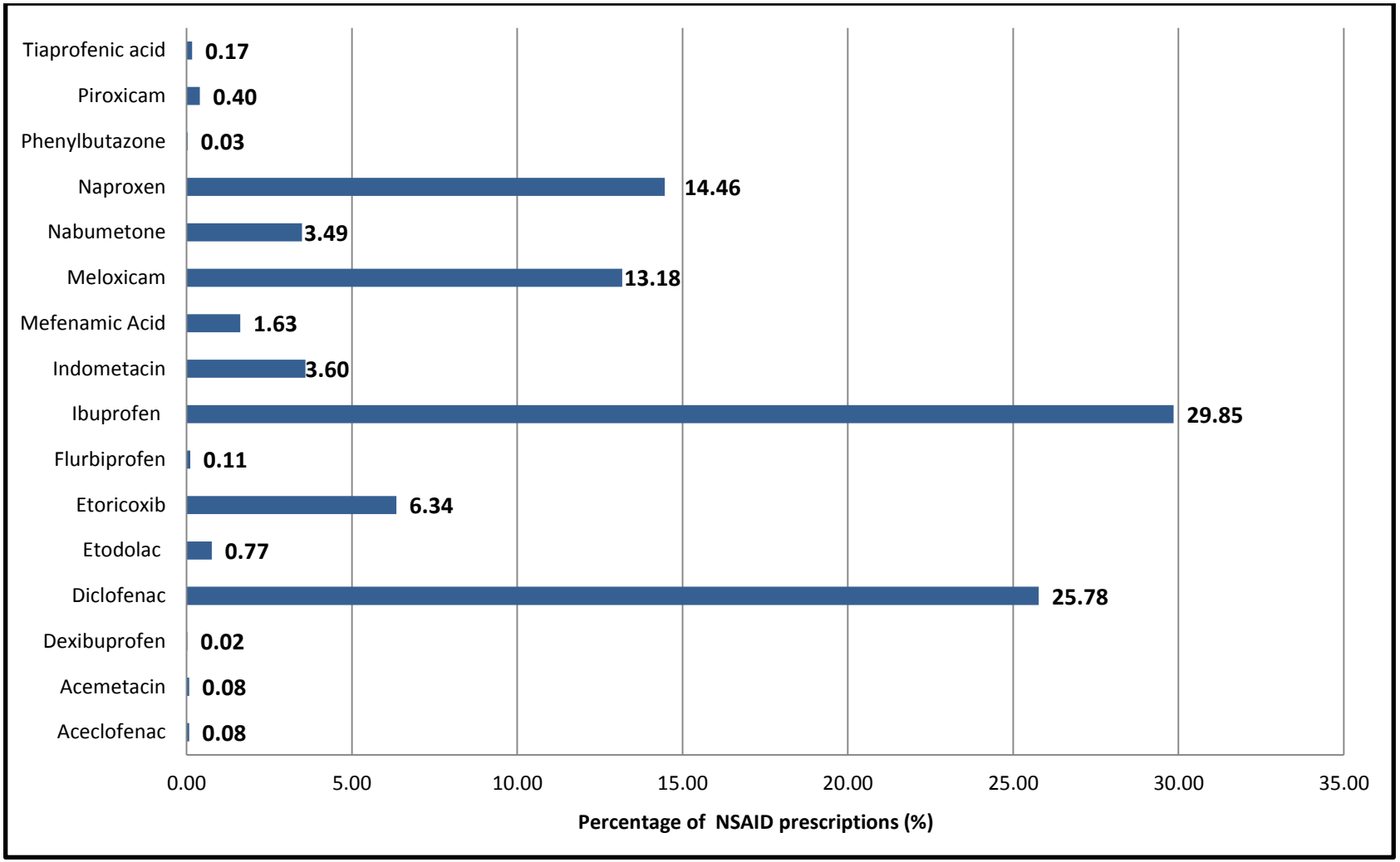
Figure 8.3 Number of drug prescriptions over the 2-year period for the two practices



8.2.2. Proportion of prescribed NSAIDs by type

Although there are over twenty NSAIDs listed in the BNF (2009) chapter 10.1.1[211], eight NSAIDs made up over 98% of all prescriptions given with just four NSAIDs accounting for over 83% of all NSAID prescriptions (**Figure 8.4**). The most commonly prescribed NSAID was Ibuprofen at 29.85% of NSAIDs prescriptions, closely followed by Diclofenac (25.78%). Naproxen and Meloxicam made up a near equal share of 27.64% of NSAID prescriptions. Etoricoxib, Indometacin, Nabumetone and Mefenamic acid made up just over 15% of the NSAID prescriptions. The remaining seven NSAIDs made up less than 2% of all NSAID prescriptions.

Figure 8.4 NSAID prescriptions by drug type

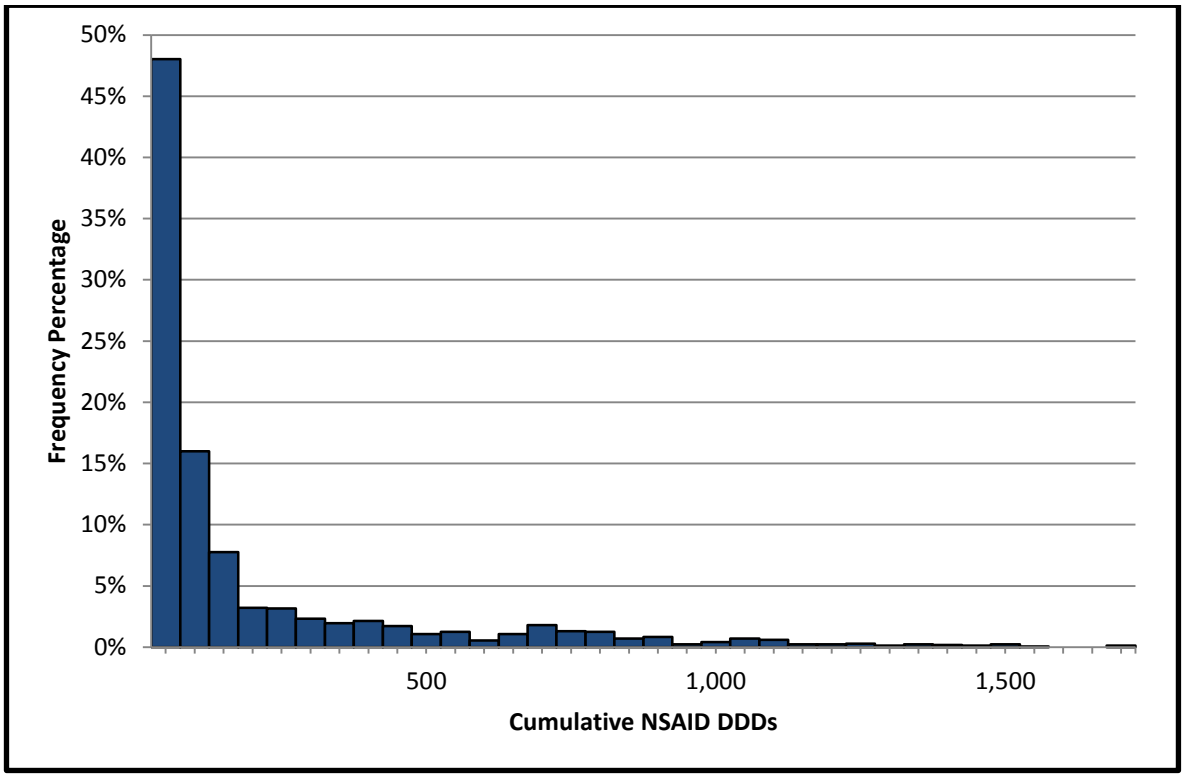


8.2.3. NSAID prescription dose

Amongst the 21.9% of study patients who received at least one NSAID prescription, nearly half had up to 56 DDDs of NSAID during the study period, a relatively small amount of NSAID (**Figure 8.5**). This would be the equivalent of 56 * 1.2 = 67 grams of ibuprofen during the 2-year study period. The percentage of users decreased rapidly with increasing cumulative NSAID dose; in fact, 75% of patients had <201 DDDs of cumulative NSAID use. However, even though the proportion of high dose NSAID users was small, some patients had excessive NSAID use (max = 1,680 DDDs). Amongst patients categorised as high dose users (top 15% of cumulative DDDs), the median DDD was 720. Given our study period was 730 days, this level of use would be equivalent to taking nearly one DDD of NSAID every day. To convert this in terms of ibuprofen, the level of use would be 1.2 grams * 720 = 864 grams of use.

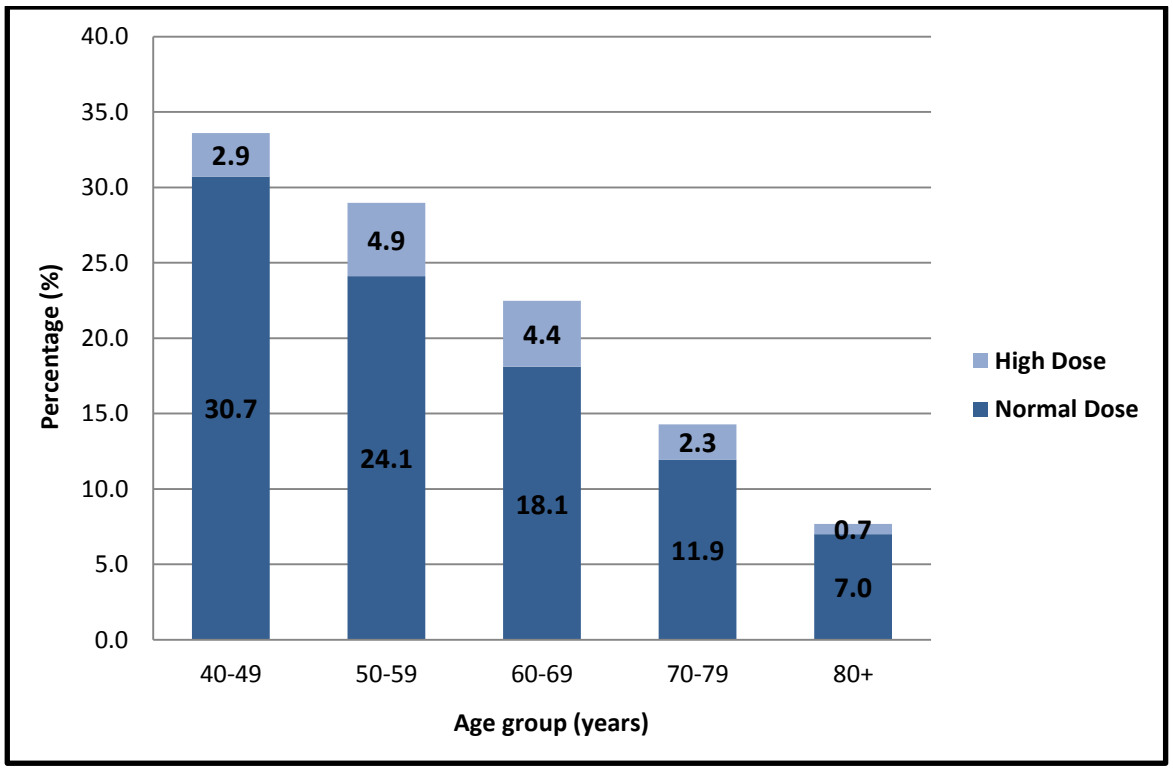
When NSAID use was stratified by age, there was a dramatic decrease in the proportion of normal and high dose NSAID users with increasing age. The overall proportion of NSAID users of any dose went from 33.6% in patients aged 40-49 years old to 7.7% in those aged 80 years and over respectively (**Figure 8.6**).

Figure 8.5 Distribution of overall cumulative DDD amongst NSAID users



50 DDDs per interval

Figure 8.6 Percentage of normal and high dose NSAID users per age group

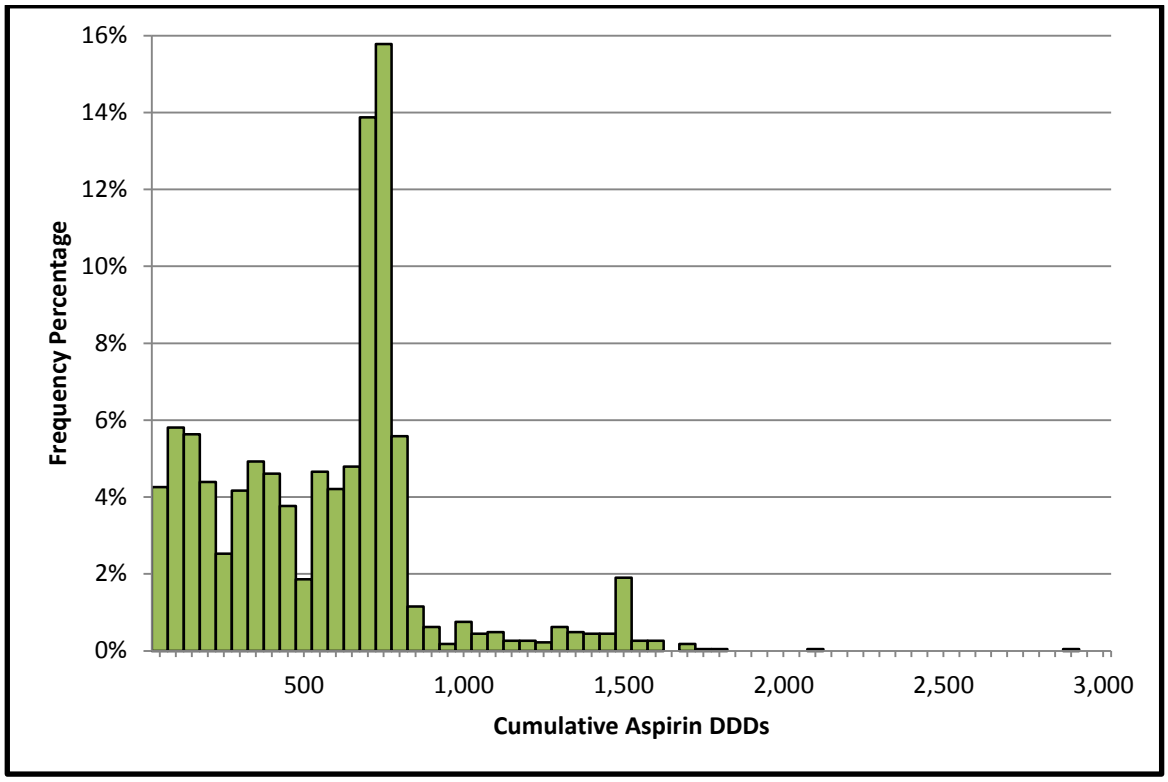


8.2.4. Aspirin prescription dose

Nearly 30% of patients in our study were prescribed low-medium dose aspirin. The median cumulative DDD of aspirin was 588 and 75% of patients had <728 cumulative DDDs (**Figure 8.7**). The typical aspirin user would take 588 tablets of low-medium dose aspirin over the study period. In terms of low-dose aspirin (*75mg*), this would be a cumulative dose of 588 * 0.075g = 44.1 grams during the study. Although the cumulative DDD was higher than in NSAID users, the amount consumed in grams for a typical patient on low-dose aspirin was markedly less than in a typical NSAID user. As reported earlier, aspirin was also given more consistently throughout the study period (median number of prescriptions = 14). The typical "high-dose" aspirin user had 898 DDDs of use (or 1.23 DDDs per day over 2 years), equivalent to 898 tablets (or 67.35 grams) of low-dose aspirin. The maximum cumulative DDD of aspirin given was 2,888 DDDs.

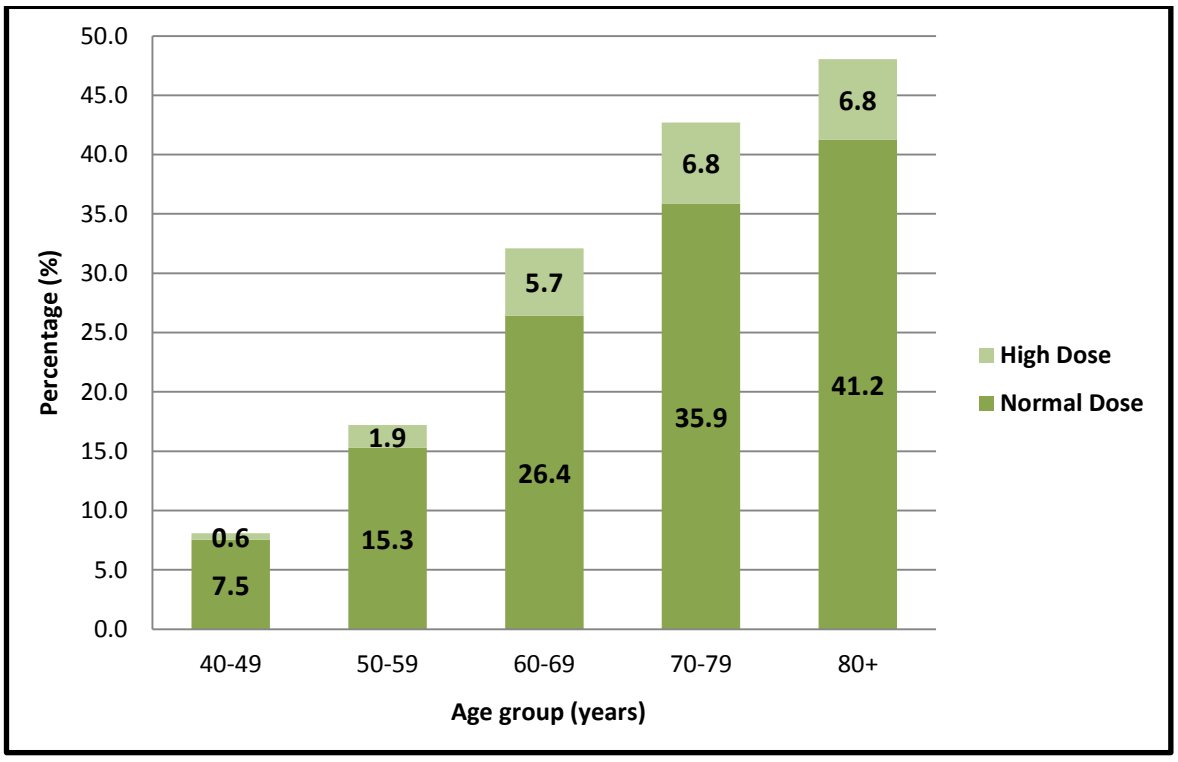
The proportion of normal dose aspirin users increased dramatically with age from 7.5% in patients aged 40-49 years old to 41.2% in those age 80 years and over (**Figure 8.8**). A similar picture was seen amongst high dose users with an increase of 6.2% between the 40-49y and ≥80y age groups.

Figure 8.7 Distribution of overall cumulative DDD amongst Aspirin users



50 DDDs per interval

Figure 8.8 Percentage of normal and high dose Aspirin users per age group

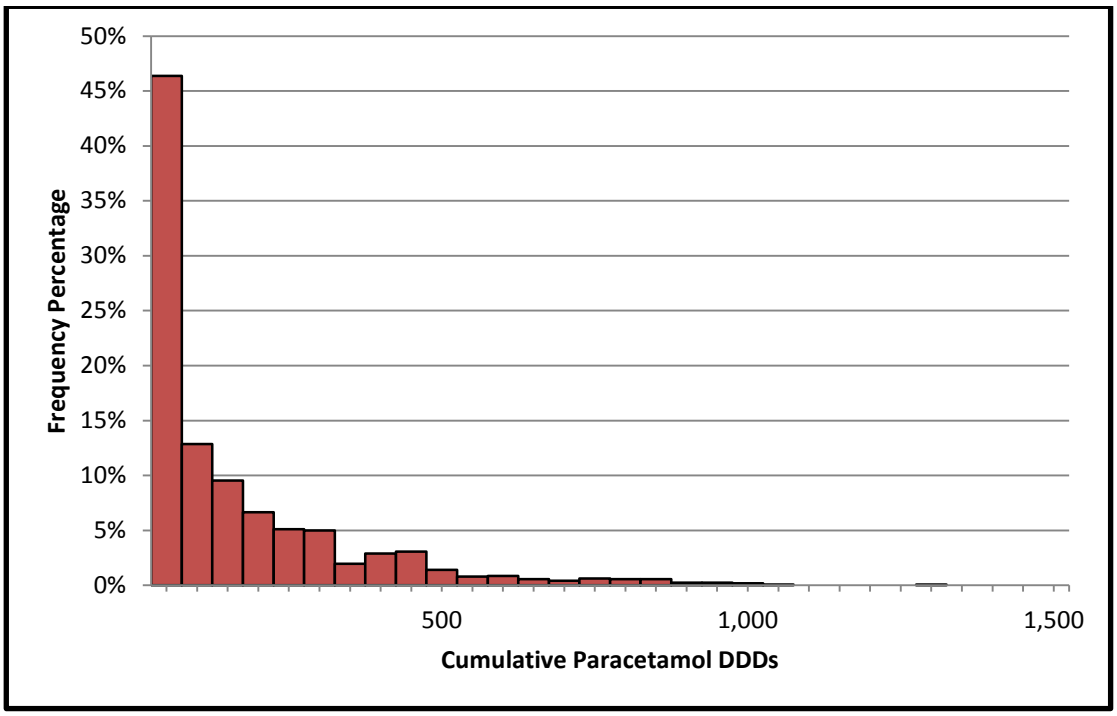


8.2.5. Paracetamol prescription dose

Paracetamol users had relatively low cumulative DDD of use. Half of all paracetamol users had up to 67 DDDs of use during the 2-year period (**Figure 8.9**). Since 1 DDD of paracetamol is 3 grams, this would be equivalent to up to 201 grams of paracetamol in two years. The percentage of patients with higher doses of use also fell rapidly with 75% having <200 DDDs of cumulative paracetamol use, nearly identical to NSAID users. Among high dose paracetamol users, the median DDD was 433 (or 0.59 DDDs per day over 2 years); equivalent to 1299 grams of use. The maximum DDD of paracetamol prescribed was 1,272 DDD.

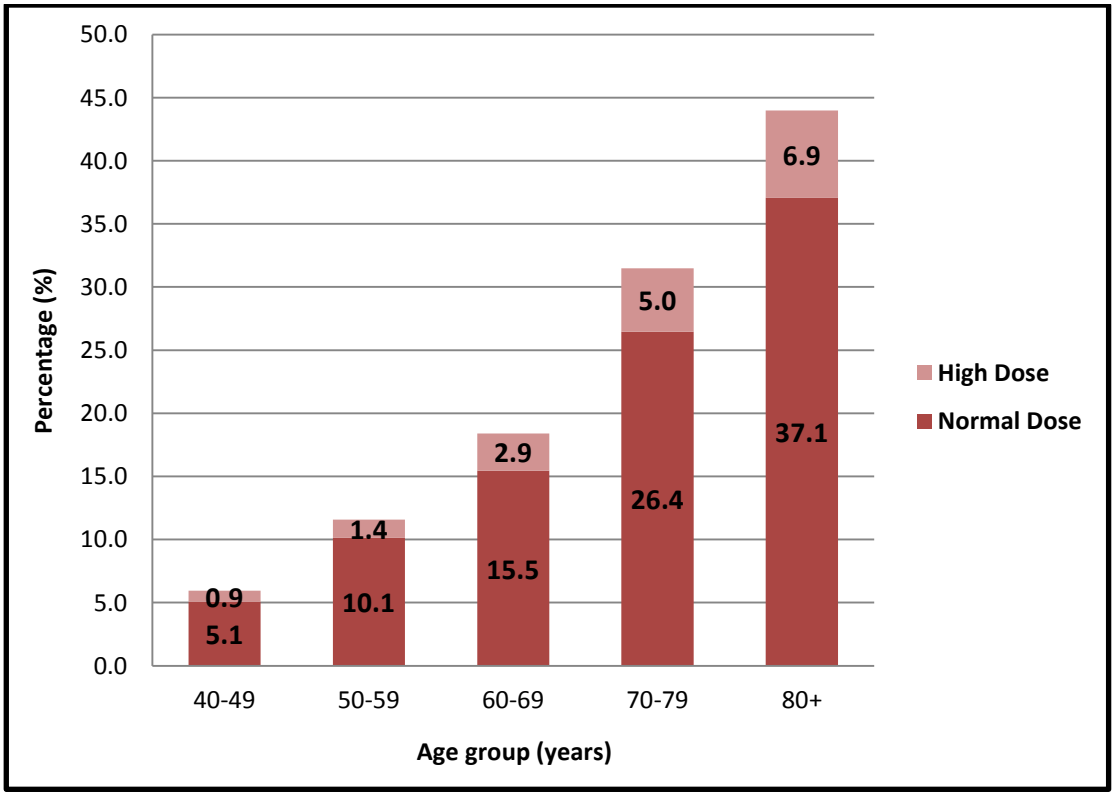
When paracetamol use was stratified by age, the graph shows a near mirror reflection of the NSAID user graph (**Figure 8.10**). There was a gradual increase in the proportion of normal and high dose paracetamol users with increasing age. The proportion of normal and high dose users increased from 5.1% and 0.9% in patients aged 40-49 years old to 37.1% and 6.9% in those aged 80 years and over respectively.

Figure 8.9 Distribution of overall cumulative DDD amongst Paracetamol users



50 DDDs per interval

Figure 8.10 Percentage of normal and high dose Paracetamol users per age group



8.3. Characteristics of Drug Users

8.3.1. Drug use and baseline CKD status

The percentage of non-users of any drug (NSAIDs, aspirin or paracetamol) decreased as renal function worsened (**Table 8.4**). The differences in the percentage of non-users varied significantly between the five eGFR groups ($p<0.001$) with those having stage 5 CKD at baseline having the lowest percentage of no analgesia users (23.5%).

The proportion of NSAID users decreased significantly with worsening renal function falling from 26.5% in patients with a normal eGFR to just 5.9% in stage 5 CKD patients with the proportions of both normal and high dose users falling significantly. In fact, no stage 4 or 5 CKD patients used high doses of NSAIDs. There were twice as many NSAID users within patients with a baseline eGFR ≥60 compared to the <60 group (**Appendix 7**).

The percentage of both normal and high dose aspirin users was higher among patients with stage 3 to 5 CKD than in those with a normal or mildly impaired eGFR at baseline (**Table 8.4**).

The proportion of paracetamol users increased dramatically with worsening renal function, rising from 17.6% to over 50% between patients with a normal eGFR and stage 5 CKD patients. The differences between the 5 eGFR groups were statistically significant. The majority of paracetamol users had normal dose use but there was an increase in the proportion of high dose users with worsening eGFR. Nearly twice as patients used paracetamol in the eGFR <60 group compared to the eGFR ≥60 group **(Appendix 7)**.

Table 8.4 Drug use and baseline CKD status

Analgesia use	eGFR ≥60				eGFR <60						*p*-value
	Normal N=3110		Mildly impaired N=3529		Stage 3 CKD N=941		Stage 4 CKD N=60		Stage 5 CKD N=17		
	n	%	n	%	n	%	n	%	n	%	
[1]**Non users of any of the three drugs** *(n=3360)*	1460	**46.9**	1575	**44.6**	301	**32.0**	20	**33.3**	4	**23.5**	**<0.001***
Non-NSAID users *(n=5981)*	2287	**73.5**	2802	**79.4**	818	**86.9**	58	**96.7**	16	**94.1**	
Normal Dose NSAID users *>0 - <420 DDD (n=1424)*	711	**22.9**	613	**17.4**	97	**10.3**	2	**3.3**	1	**5.9**	**<0.001***
High Dose NSAID users *≥420 DDD (n=252)*	112	**3.6**	114	**3.2**	26	**2.8**	0	**0.0**	0	**0.0**	
Non-Aspirin users *(n=5401)*	2367	**76.1**	2464	**69.8**	530	**56.3**	31	**51.7**	9	**52.9**	
Normal Dose Aspirin users *>0 - <736 DDD (n=1916)*	634	**20.4**	909	**25.8**	339	**36.0**	28	**46.7**	6	**35.3**	**<0.001***
High Dose Aspirin users *≥736 DDD (n=340)*	109	**3.5**	156	**4.4**	72	**7.7**	1	**1.7**	2	**11.8**	
Non-Paracetamol users *(n=6031)*	2565	**82.5**	2805	**79.5**	617	**65.6**	36	**60.0**	8	**47.1**	
Normal Dose Paracetamol users *>0 - <300 DDD (n=1375)*	453	**14.6**	628	**17.8**	264	**28.1**	22	**36.7**	8	**47.1**	**<0.001***
High Dose Paracetamol users *≥300 DDD (n=251)*	92	**3.0**	96	**2.7**	60	**6.4**	2	**3.3**	1	**5.9**	

[1]Non-users of NSAIDs, Aspirin and Paracetamol. *Statistical significance at $p \leq 0.05$.

8.3.2. Factors associated with drug use

8.3.2.1. Socio-demographic factors

NSAID users were significantly younger (mean age= 59 years, SD= 12) than non-users (mean age= 63 years, SD= 13, $p<0.001$) and this was true at any dose of NSAID use. Females were more significantly more likely to use NSAIDs than males ($p=0.001$) and the percentage of females increased with higher doses of NSAIDs. Deprivation did not significantly differ between users and non-users of NSAIDs at any dose (**Table 8.5**).

On the other hand, aspirin users were significantly older (mean age 70 years, SD= 11) than non-users (mean age 61 years, SD= 13, $p<0.001$) but the mean age did not vary much between normal and high dose users (**Table 8.6**). Males were significantly more likely to use aspirin than females ($p=0.001$) but the proportion of males did not increase with the higher aspirin doses. Deprivation was significantly associated with aspirin use ($p<0.001$). The percentage of patients in the most deprived quartile increased with an equivalent decrease in those in the least deprived category between users and non-users of aspirin and between normal and high dose aspirin users.

Paracetamol users were significantly older (mean age 72 years, SD= 12) than non-users (mean age 62 years, SD= 13, $p<0.001$) but the mean age was equivalent in normal and high dose users (**Table 8.7**). Females were significantly more likely to use paracetamol than males ($p=0.001$) with higher proportions of females using high dose paracetamol compared to those in the normal dose group. Deprivation was significantly associated with paracetamol use ($p<0.001$) especially among high dose paracetamol users.

8.3.2.2. Other drug use

Approximately 20% of NSAID users also had at least one prescription for aspirin or paracetamol. The proportion of non-users of NSAIDs prescribed aspirin was significantly higher (32.2%) than in the NSAID user group (19.8%) but paracetamol prescriptions remained the same. In relation to the dose of NSAID use, the proportion of concomitant paracetamol use was 9.5% higher in high dose NSAID users in comparison to normal dose users; this difference was not as evident amongst co-users of aspirin (**Table 8.5**).

Around 15% of Aspirin users also had some NSAID use. This percentage was nearly double in co-users of paracetamol at 30%. Compared to non-users, aspirin users were significantly less likely to have a prescription of NSAIDs but were significantly more likely to have a prescription for paracetamol. Similar trends were also seen between normal dose and high dose aspirin users (**Table 8.6**).

Just over 20% of paracetamol users had a prescription for NSAIDs, similar to non-users. However, over 40% of paracetamol users also used aspirin which was significantly higher than the proportion in non-users of paracetamol. The percentage of aspirin users was higher in patients with high dose paracetamol use in comparison to normal dose users but this was not the case for NSAIDs (**Table 8.7**).

8.3.2.3. Co-morbidity and co-drug therapy

The prevalence of co-morbidity and co-drug therapy was significantly lower in users of NSAIDs than in non-users, $p<0.001$. However, co-morbidity and co-drug therapy was more prevalent amongst patients with high dose NSAID use than in normal dose NSAID users (**Table 8.5**).

Aspirin users were 1.8, 2.6 and 1.8 times more likely to have CVD, DM or co-drug therapy use than non-users respectively, p<0.001 (**Table 8.6**). The proportion of aspirin users with CVD and co-drug therapy were both higher between normal and high dose users but this was not the case for DM.

Paracetamol users had significantly higher levels of co-morbidity and co-drug therapy than non-users (**Table 8.7**). Stratification by dose revealed that the percentage of CVD and co-drug therapy rose greatly between normal dose and high dose paracetamol users but the change was modest for DM.

8.3.2.4. CKD status

The proportion of patients with stages 3 to 5 CKD at the last eGFR measurement was significantly lower amongst NSAID users compared to non-users but the proportion of patients with stage 3 to 5 CKD was higher in patients with high dose users when compared to those with normal dose use (**Table 8.5**).

Amongst aspirin users, the prevalence of stage 3 to 5 CKD was significantly higher among users than non-users. This trend was also seen between normal and high dose aspirin user groups (**Table 8.6**).

Stages 3 to 5 CKD was twice as high in paracetamol users (24%) compared to non-users (12%) and tended to increase with high dose paracetamol (**Table 8.7**).

Table 8.5 Characteristics of NSAID users and non-users stratified by dose

Variable		Non-users[a] (n=5981)	Normal-dose users (n=1424)	High-dose users (n=252)	*p*-value	Non-users[a] (n=5981)	NSAID users (n=1676)	*p*-value
Mean Age (SD)		65 (13)	58 (12)	60 (10)	**<0.001***	63 (13)	59 (12)	**<0.001***
Gender (%)	M	45.8	41.9	37.7	**0.002***	45.8	41.2	**0.001***
	F	54.2	58.1	62.3		54.2	58.8	
[1]**Deprivation (%)**	Least Deprived Quartile	25.8	26.3	22.2	0.445	25.8	25.7	0.553
	IMD 2	24.7	24.2	27.4		24.7	24.7	
	IMD 3	25.5	27.4	25.0		25.5	27.1	
	Most Deprived Quartile	23.9	22.1	25.4		23.9	22.6	
[2]**Cumulative NSAID DDDs**		0	42 [28-100]	720 [557-924]	N/A	0	56 [28-201]	N/A
Aspirin use (%)	users	32.2	19.6	21.0	**<0.001***	32.2	19.8	**<0.001***
Paracetamol use (%)	users	21.1	20.3	29.8	**0.003***	21.1	21.7	0.584
All CVD (%)	Yes	56.0	39.9	46.8	**<0.001***	56.0	40.9	**<0.001***
Diabetes (%)	Yes	18.2	13.8	15.5	**<0.001***	18.2	14.1	**<0.001***
ACE-i/ARB/Renin-i use (%)	users	43.2	28.9	32.5	**<0.001***	43.2	29.5	**<0.001***
[3]**Stage 3 to 5 CKD (%)** *(n=1114)*	Yes	16.4	7.2	11.9	**<0.001***	16.4	7.9	**<0.001***

[1]171 subjects did not have a deprivation score, [2]Given as a Median [IQR], [3]At last eGFR measurement, [a]Non-users of NSAIDs only, *Statistical significance at $p \leq 0.05$.

Table 8.6 Characteristics of Aspirin users and non-users stratified by dose

Variable		Non-users[a] (n=5401)	Normal-dose users (n=1916)	High-dose users (n=340)	*p*-value	Non-users[a] (n=5401)	Aspirin users (n=2256)	*p*-value
Mean Age (SD)		61 (13)	70 (11)	71 (10)	**<0.001***	61 (13)	70 (11)	**<0.001***
Gender (%)	M	41.3	53.0	53.2	**<0.001***	41.3	53.1	**0.001***
	F	58.7	47.0	46.8		58.7	46.9	
[1]Deprivation (%)	Least Deprived Quartile	27.5	22.2	18.3	**<0.001***	27.5	21.6	**<0.001***
	IMD 2	24.7	24.4	26.5		24.7	24.7	
	IMD 3	25.9	25.8	26.0		25.9	25.8	
	Most Deprived Quartile	21.9	27.6	29.2		21.9	27.8	
[2]Cumulative Aspirin DDDs		0	504 [224-700]	898 [782-1344]	N/A	0	588 [280-728]	N/A
NSAID use (%)	users	24.9	15.0	12.9	**<0.001***	24.9	14.7	**<0.001***
Paracetamol use (%)	users	17.7	29.3	31.5	**<0.001***	17.7	29.6	**<0.001***
All CVD (%)	Yes	43.2	74.9	78.8	**<0.001***	43.2	75.5	**<0.001***
Diabetes (%)	Yes	11.8	31.0	27.4	**<0.001***	11.8	30.5	**<0.001***
ACE-i/ARB/Renin-i use (%)	users	32.3	58.7	60.3	**<0.001***	32.3	59.0	**<0.001***
[3]Stage 3 to 5 CKD (%) *(n=1114)*	Yes	11.4	21.8	23.2	**<0.001***	11.4	22.0	**<0.001***

[1]171 subjects did not have a deprivation score, [2]Given as a Median [IQR], [3]At last eGFR measurement, [a]Non-users of Aspirin only, *Statistical significance at $p \leq 0.05$.

Table 8.7 Characteristics of Paracetamol users and non-users stratified by dose

Variable		Non-users[a] (n=6031)	Normal-dose users (n=1375)	High-dose users (n=251)	*p*-value	Non-users[a] (n=6031)	Paracetamol users (n=1626)	*p*-value
Mean Age (SD)		63 (13)	72 (12)	72 (12)	**<0.001***	62 (13)	72 (12)	**<0.001***
Gender (%)	M	46.4	39.5	34.3	**<0.001***	46.4	38.7	**0.001***
	F	53.6	60.5	65.7		53.6	61.3	
[1]Deprivation (%)	Least Deprived Quartile	27.7	19.9	13.0	**<0.001***	27.7	18.8	**<0.001***
	IMD 2	24.5	25.7	24.3		24.5	25.5	
	IMD 3	25.1	28.2	32.0		25.1	28.8	
	Most Deprived Quartile	22.7	26.2	30.8		22.7	26.9	
[2]Cumulative Paracetamol DDDs		0	50 [17-125]	433 [367-567]	N/A	0	67 [17-200]	N/A
NSAID use (%)	users	21.8	22.4	22.3	0.861	21.8	22.4	0.584
Aspirin use (%)	users	26.3	39.9	47.4	**<0.001***	26.3	41.1	**<0.001***
All CVD (%)	Yes	51.2	56.3	69.3	**<0.001***	51.2	58.3	**<0.001***
Diabetes (%)	Yes	16.1	21.0	23.9	**<0.001***	16.1	21.5	**<0.001***
ACE-i/ARB/Renin-i use (%)	users	38.9	43.1	56.2	**<0.001***	38.9	45.1	**<0.001***
[3]Stage 3 to 5 CKD (%) *(n=1114)*	Yes	12.0	23.3	27.5	**<0.001***	12.0	24.0	**<0.001***

[1]171 subjects did not have a deprivation score, [2]Given as a Median [IQR], [3]At last eGFR measurement, [a]Non-users of Paracetamol only, *Statistical significance at $p \leq 0.05$.

8.4. Drug Use and Stage 3 to 5 CKD

8.4.1. Single drug use and stage 3 to 5 CKD at the last eGFR

In order to test whether there was an association between stage 3 to 5 CKD (at the last eGFR measurement) and normal or high dose drug (NSAID, aspirin or paracetamol) use, prescriptions given after a patient's last eGFR were disregarded to maintain the exposure to disease time relationship; a vital component of the Bradford Hill causality criteria (*see section 5.6*).[173] Patients were then re-categorised into their respective users groups. The proportion of subjects prescribed drugs before the last eGFR was 17.5% for NSAIDs, 27.8% for aspirin and 16.9% for paracetamol. 171 patients were not included in the multiple logistic regression analysis as they lacked an IMD score leaving 7,486 patients in the analysis. Non-users (no prescriptions up to the date of the last eGFR) of each of the respective drugs acted as the reference group.

Adjusted multiple logistic regression analysis found that neither normal or high dose NSAID, aspirin or paracetamol use were significantly associated with stage 3 to 5 CKD at the last eGFR. However, there was a trend for the estimate to increase between the normal and high dose groups for NSAIDs and paracetamol and a slight decrease in the aspirin group. **Table 8.8** illustrates the crude and adjusted OR for having stage 3 to 5 CKD with normal and high dose NSAID, aspirin or paracetamol use up to the last eGFR.

Table 8.8 Association between drug use and stage 3 to 5 CKD at the last eGFR

Category of Drug use	Normal dose use		High dose use	
	Crude OR (95% CI)	***Adjusted OR (95% CI)***[a]	*Crude OR (95% CI)*	***Adjusted OR (95% CI)***[a]
Non-NSAID users	*1*	***1***	*1*	***1***
[1]Preceding NSAID users (n=1306)	0.503 (0.403-0.628)	**0.898 (0.704-1.145)**	0.810 (0.533-1.229)	**1.421 (0.903-2.235)**
Non-Aspirin users	*1*	***1***	*1*	***1***
[1]Preceding Aspirin users (n=2078)	2.240 (1.948-2.575)	**1.119 (0.953-1.313)**	2.139 (1.614-2.833)	**1.074 (0.789-1.463)**
Non-Paracetamol users	*1*	***1***	*1*	***1***
[1]Preceding Paracetamol users (n=1264)	2.381 (2.033-2.788)	**1.160 (0.971-1.385)**	2.968 (2.160-4.079)	**1.345 (0.945-1.913)**

[1]171 patients did not have a deprivation score thus were not included in this analysis. [a]Adjusted for age (continuous), gender, deprivation quartile, all cardiovascular disease, diabetes, ACE-i/ARB/Renin-i use and other drug use (either aspirin or paracetamol in the case of NSAID users).

8.4.2. Multiple drug use and stage 3 to 5 CKD at the last eGFR

To further explore the relationship between multiple drug use and stage 3 to 5 CKD, a subgroup analysis was carried on patients who used combinations of two or three of the drugs exclusively before the last eGFR measurement.

In phase 1, the most common drug combination was aspirin and paracetamol at 6.0% whilst the least commonly used combination was all three drugs together at 1%.

None of the drug combinations were significantly associated with stage 3 to 5 CKD when compared to exclusive NSAID use. However, the estimates for NSAID and paracetamol use and aspirin and paracetamol use were higher than in the other groups (**Table 8.9**).

Table 8.9 Association between multiple drug use and stage 3 to 5 CKD at the last eGFR

Category of Drug use	**Overall use**	
	Crude OR (95% CI)	***Adjusted OR (95% CI)*[a]**
[1]*Ref*	*1*	***1***
Preceding exclusive NSAID & Aspirin users (n=186)	2.996 (1.823-4.826)	**1.334 (0.787-2.261)**
[1]*Ref*	*1*	***1***
Preceding exclusive NSAID & Paracetamol users (n=170)	3.032 (1.841-4.995)	**1.653 (0.969-2.820)**
[1]*Ref*	*1*	***1***
Preceding exclusive Aspirin & Paracetamol users (n=460)	6.811 (4.817-9.630)	**1.442 (0.970-2.143)**
[1]*Ref*	*1*	***1***
Preceding NSAID & Aspirin & Paracetamol users (n=80)	3.116 (1.614-6.016)	**0.970 (0.479-1.964)**

[1]Preceding exclusive NSAID users (N=870), [a]Adjusted for age (continuous), gender, deprivation quartile, all cardiovascular disease, diabetes and ACE-i/ARB/Renin-i use.

8.5. Chapter Summary

- **Study sample: baseline characteristics**
    - The CKD population is readily identifiable, over 30% of patients had an eGFR measure in our study over two years.
    - Our study identified differences in the characteristics of CKD subjects in two practices. Deprivation, drug prescribing, co-drug therapy and renal function testing differed between the included practices but the age, gender, level of co-morbidity and CKD status of the included subjects did not.
    - Socio-demographics, co-morbidity and co-drug therapy all varied with the CKD status. Stage 3 to 5 CKD increased exponentially with age and showed a female preponderance. Equally, higher levels of deprivation correlated with worsening CKD status. Moreover, the prevalence of co-morbidity and co-drug therapy was higher in patients with poor renal function at baseline compared to patients with better renal function.

- **Drug exposure**
    - The prescription of drugs was common. One in five patients had a prescription for NSAIDs or paracetamol and almost one in three were prescribed aspirin over the two year period.
    - Although drug prescribing was common, the patterns of prescribing varied between the three drugs. NSAIDs (most commonly ibuprofen and diclofenac) were prescribed to younger patients but at relatively low doses. Paracetamol on the other hand was prescribed to older patients but it too was given at relatively low doses. However, there was a small group of

extreme users in both the NSAID and paracetamol user groups. Aspirin prescribing was more prevalent in older patients and it was given more regularly than NSAIDs or paracetamol.

- **Characteristics of drug users**
    - The prevalence of both normal and high dose NSAID use decreased significantly as the CKD status deteriorated. The inverse picture was seen with paracetamol and aspirin use which significantly increased with worsening CKD status.
    - As well as age and CKD status, the characteristics of gender, deprivation, other drug use, co-morbidity and co-drug therapy differed between the three drugs. NSAID users tended to be female with significantly lower levels of aspirin use, co-morbidity and co-drug therapy compared to non-NSAID users. Paracetamol users were also more likely to be female but had significantly higher levels of deprivation, aspirin use, co-morbidity and co-drug therapy compared to non-users of paracetamol. In contrast, when compared to non-users, aspirin users tended to be males with significantly higher paracetamol use, co-morbidity and co-drug therapy.

- **Drug use and stage 3 to 5 CKD**
    - Single drug use was not significantly associated with stage 3 to 5 CKD at the last eGFR.
    - Multiple drug use was not significantly associated with stage 3 to 5 CKD at the last eGFR but some drug combinations neared statistical significance.

Chapter 9. Phase 2 - The Influence of Non-Steroidal Anti-Inflammatory Drugs on Chronic Kidney Disease Progression: A Cohort Design Study

This chapter concentrates on the results related to patients with two eGFR measurements spaced at least 90 days apart. This chapter primarily explores the associations between drug use before the last eGFR and CKD progression. It also describes the characteristics of patients with multiple eGFR measurements and compares them to the phase 1 study group.

Chapter Plan

- **Phase 2 sample: baseline characteristics**
    - Comparison of phase 1 and phase 2 subject characteristics.
    - Phase 2 sample inter-practice differences.

- **Drug exposure**
    - Prevalence of drug prescription before the last eGFR.
    - Drug prescription dose before the last eGFR.
    - Age and drug prescribing before the last eGFR.

- **Characteristics of drug users**
    - Drug use and baseline CKD status.
    - Factors associated with drug use.

- **Drug use and the development of stage 3 to 5 CKD**
    - Single drug use and the development of stage 3 to 5 CKD.
    - Multiple drug use and the development of stage 3 to 5 CKD.

- **Factors associated with CKD progression**
    - Characteristics of subjects with significant CKD progression.

- **Drug use and significant CKD progression**
    - Single drug use and significant CKD progression.
    - Multiple drug use and significant CKD progression.

9.1. Phase 2 Sample: Baseline Characteristics

9.1.1. Phase 2 patients - Demographics

A cohort of 4,145 patients (18% of the practice population) had at least two eGFR measurements spaced 90 days apart.

The mean age of the phase 2 of patients was 66 years (SD= 12). In this cohort, the female to male ratio was 1.2:1 which differed from ratio in England and Wales (F:M = 1.10:1)[217].

Older age groups (≥60y) were dramatically over-represented whilst the younger age groups (40-59y) were under-represented when compared to the normal age-sex distribution in England and Wales[217] as shown in **Figure 9.1a & b**.

Among this cohort, the prevalence of stage 3 to 5 CKD at baseline was 16.1% (females = 19.1%, males = 12.5%). The estimated age-adjusted prevalence for stage 3 to 5 CKD was 11.2% (13.4% in females and 8.7% in males) in the ≥40 population in England and Wales.[217]

With increasing age, the proportion of stage 3 to 5 CKD patients increased exponentially in both males and females from 2.2% and 3.8% in 40-49 year olds to over 35.2% and 47% in the 80+ year olds respectively (**Figure 9.2**).

Figure 9.1a Age distribution of male subjects vs England and Wales (≥40y, June-2009)

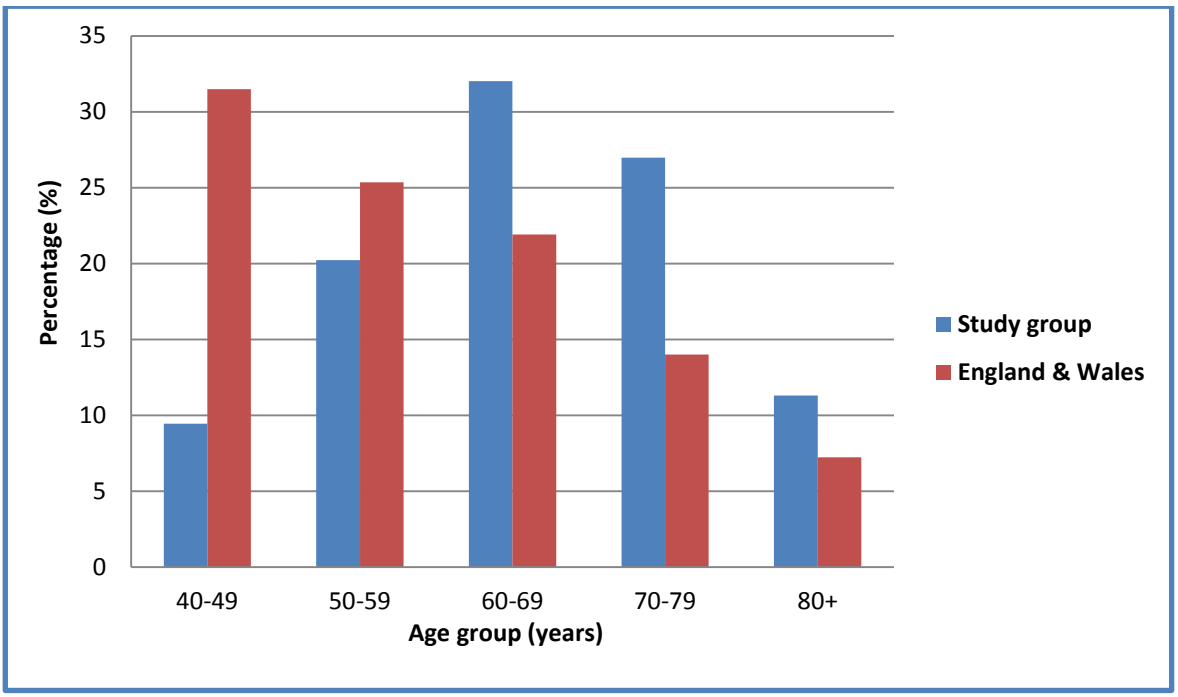


Figure 9.1b Age distribution of female subjects vs England and Wales (≥40y, June-2009)

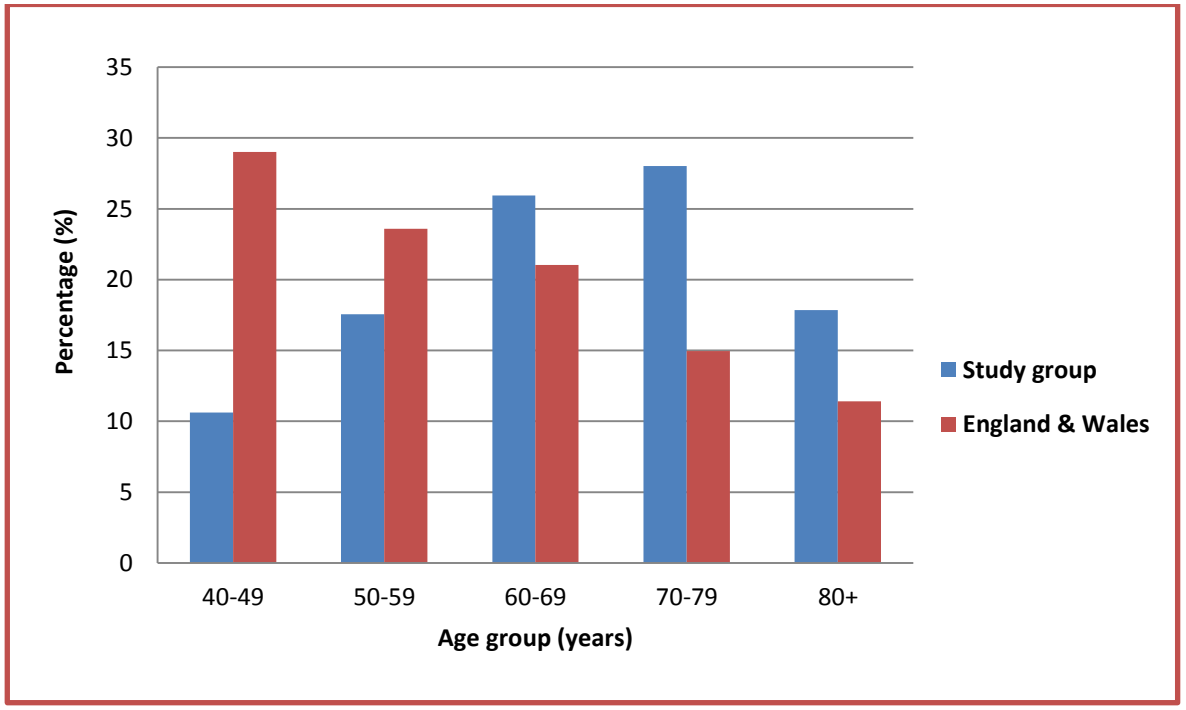
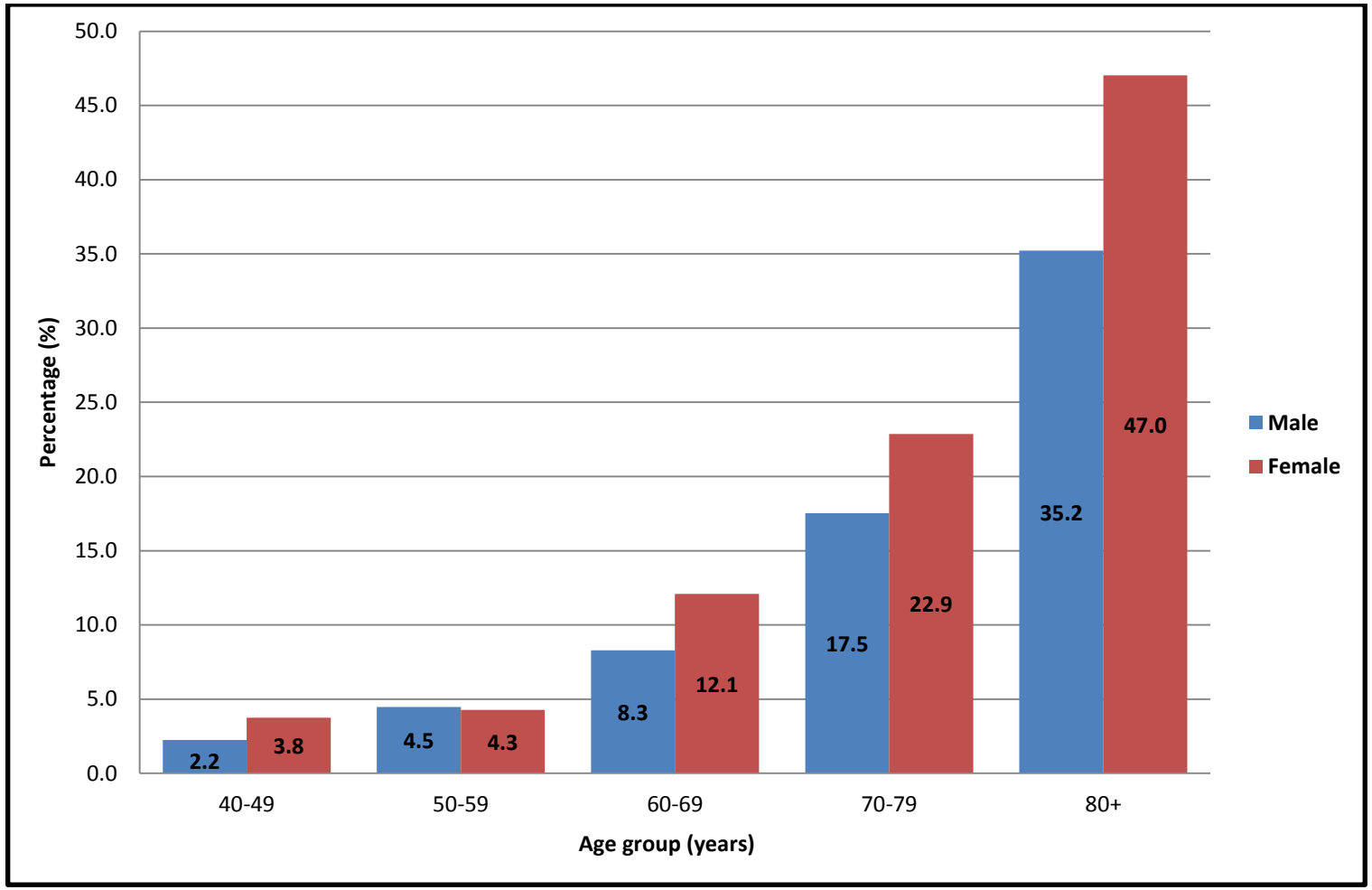


Figure 9.2 Phase 2 distribution of stage 3 to 5 CKD at baseline stratified by age and gender



9.1.2. Comparison of phase 1 and phase 2 subject characteristics

To evaluate if there are intrinsic differences between the study sample and the subgroup of patients with multiple eGFR measurements, phase 1 and 2 subject characteristics were tabulated (**Table 9.1a)**.

Comparing phase 1 and 2 subjects, the socio-demographic characteristics remained similar between the two groups. Although the number of subjects prescribed drugs fell between phase 1 and 2 (due to the smaller sample size in phase 2), the prevalence of aspirin and paracetamol use before the last eGFR was higher in phase 2 patients than in phase 1. Moreover, the prevalence of co-morbidity and co-drug therapy increased between phase 1 and phase 2. The median baseline eGFR was similar between phases 1 and 2.

Table 9.1a Comparison of phase 1 and phase 2 subject characteristics

Variable		Phase 1 subjects N=7657		Phase 2 subjects N=4145	
Mean Age (SD)		64 (13)		66 (12)	
Gender [n %]	Male	3428	**44.8**	1883	**45.4**
	Female	4229	**55.2**	2262	**54.6**
Deprivation [n %]	Least Deprived Quartile	1932	**25.8**	986	**24.0**
	IMD 2	1850	**24.7**	1037	**25.2**
	IMD 3	1937	**25.9**	1099	**26.7**
	Most Deprived Quartile	1767	**23.6**	991	**24.1**
[1]Preceding NSAID use [n %]	Non-user	6336	**82.7**	3434	**82.8**
	User	1321	**17.3**	711	**17.2**
[1]Preceding Aspirin use [n %]	Non-user	5529	**72.2**	2536	**61.2**
	User	2128	**27.8**	1609	**38.8**
[1]Preceding Paracetamol use [n %]	Non-user	6346	**82.9**	3237	**78.1**
	User	1311	**17.1**	908	**21.9**
All CVD [n %]	No	3619	**47.3**	1286	**31.0**
	Yes	4038	**52.7**	2859	**69.0**
Diabetes [n %]	No	6334	**82.7**	3051	**73.6**
	Yes	1323	**17.3**	1094	**26.4**
ACE-i/ARB/Renin-i [n %]	Non-user	4580	**59.8**	1909	**46.1**
	User	3077	**40.2**	2236	**53.9**
Median baseline eGFR [IQR]		84 [70-91]		83 [68-91]	

[1]Drugs given before the last eGFR measurement i.e. censored.

9.1.3. Phase 2 sample by practice

Practice H and I contributed 47% and 53% of the patients respectively. There were no significant differences between the mean age or gender of the subjects in practice I and H. However, the distribution of deprivation differed significantly between the two practices ($p<0.001$) with 41.9% of practice I patients being in the most deprived quartile compared to just 4.1% of practice H patients. The practice characteristics are shown in **Table 9.1b**.

Practice I had a significantly higher proportion of aspirin users compared to practice H (41.1% vs. 36.2%) but a significantly lower proportion of paracetamol users than in practice H (19.9% vs. 24.2%). The proportion of NSAID users was equivalent between the two practices ($p=0.152$).

In phase 2, the prevalence of CVD was 69.0%, DM was 26.4% and co-drug therapy was 53.9%. The level of CVD and co-drug therapy was significantly higher in practice I than in practice H but the level of DM was similar between the two practices.

Although both practices had the same median number of eGFR measurements, there was a significant difference in the distribution of multiple eGFR tests ($p=0.022$). Moreover, practice I also had a significantly longer time period (mean= 273 days, SD= 126) between eGFR tests when compared to practice H (mean= 262 days, SD= 123), $p=0.008$. The median baseline eGFR and median rate of eGFR decline per year did not differ significantly between the two practices. Overall the significant inter-practice differences amongst phase 2 patients were similar to those seen amongst phase 1 patients (compared to **Table 8.1**) with the exception of the prevalence of CVD and preceding NSAID use.

Table 9.1b Practice characteristics of patients with at least two eGFR measurements spaced 90 days apart aged 40 years and over

Variable		Practice H N=1951	Practice I N=2194	*p*-value
Mean Age (SD)		66 (13)	67 (12)	0.493
Gender (%)	Male	46.1	44.8	0.428
	Female	53.9	55.2	
Deprivation (%)	Least Deprived Quartile	24.6	23.5	**<0.001***
	IMD 2	35.2	16.3	
	IMD 3	36.1	18.4	
	Most Deprived Quartile	4.1	41.9	
[1]Preceding NSAID use (%) *(n=711)*	Non-user	82.0	83.6	0.152
	User	18.0	16.4	
[1]Preceding Aspirin (%) *(n=1609)*	Non-user	63.8	58.9	**0.001***
	User	36.2	41.1	
[1]Preceding Paracetamol use (%) *(n=908)*	Non-user	75.8	80.1	**0.001***
	User	24.2	19.9	
All CVD (%) *(n=2859)*	No	33.7	28.6	**<0.001***
	Yes	66.3	71.4	
All Diabetes (%) *(n=1094)*	No	72.9	74.2	0.321
	Yes	27.1	25.8	
ACE-i/ARB/Renin-i (%) *(n=2236)*	Non-user	49.2	43.3	**<0.001***
	User	50.8	56.7	
Median number of eGFR measurements [IQR]		3 [2-4]	3 [2-4]	**0.022***
Mean (SD) difference in days between eGFR measurements		262 (123)	273 (126)	**0.008***
Median baseline eGFR [IQR]		84 [68-91]	82 [67-91]	0.062
Median rate of eGFR decline per year [IQR]		0 [-5.42, +0.67]	0 [-5.44, +0.91]	0.818

[1]Drugs given before the last eGFR measurement i.e. censored, *Statistically significant at $p \leq 0.05$.

9.2. Drug Exposure

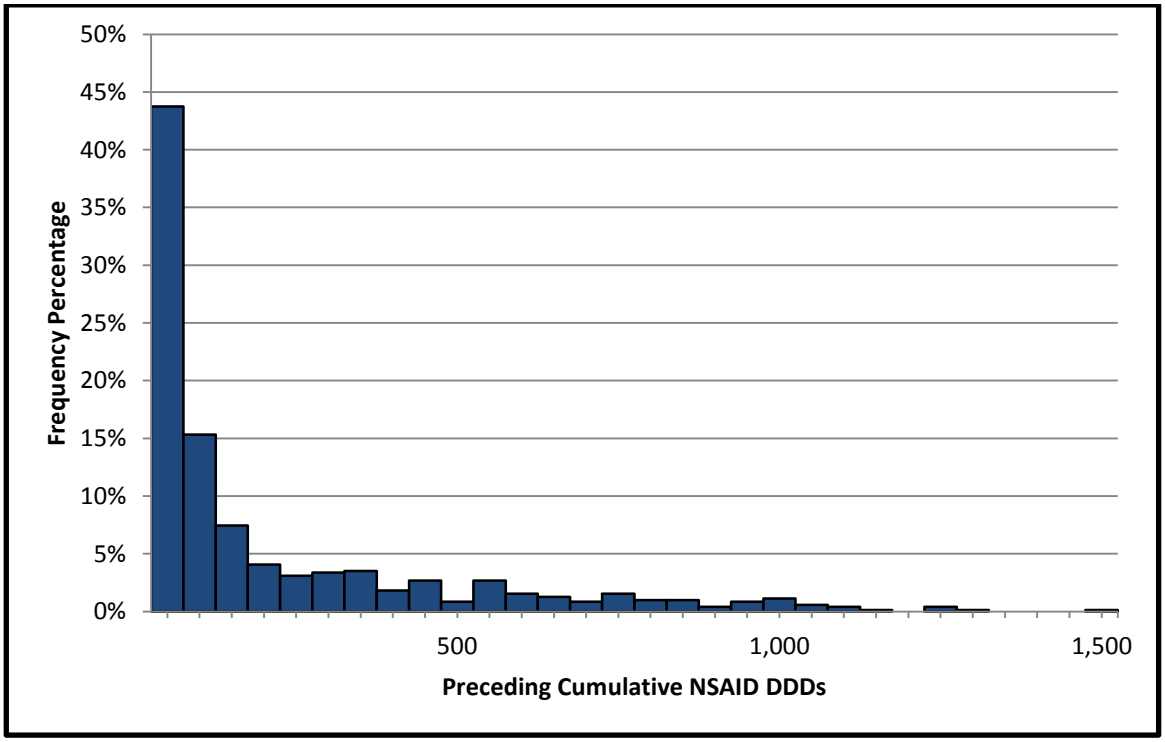
In phase 2, drug use was defined by general practice prescribing between the study start date and the date of the last eGFR measurement for each patient (see **Figure 7.2b**). This was done firstly to ensure that the trends seen with overall drug use were maintained when this approach was applied and also to maintain an exposure-disease time relationship which is a vital component of the Bradford Hill causality criteria.[173]

9.2.1. NSAID prescription dose before the last eGFR

Of all 4,145 phase 2 patients, 17.2% (n= 711) were prescribed at least one NSAIDs before the date of the last eGFR test. Most NSAID users had low cumulative DDDs (preceding the last eGFR) with 50% having up to 70 DDDs of NSAID use and 75% of patients were prescribed <280 DDDs of NSAIDs (max = 1,493 DDDs). High dose users were given a median 717 DDDs (**Figure 9.3**).

The median exposure period (time in days between the beginning of the study and the last eGFR) was 592 days [IQR=498-666] amongst NSAID users. Therefore, a typical high dose NSAID user would consume 717/592 = 1.21 DDDs of NSAIDs per day, equivalent to 1.2 * 1.21 = 1.45 grams of ibuprofen per day. Therefore, a typical high dose NSAID user within this cohort was given 1.45 * 592 = 858 grams of ibuprofen.

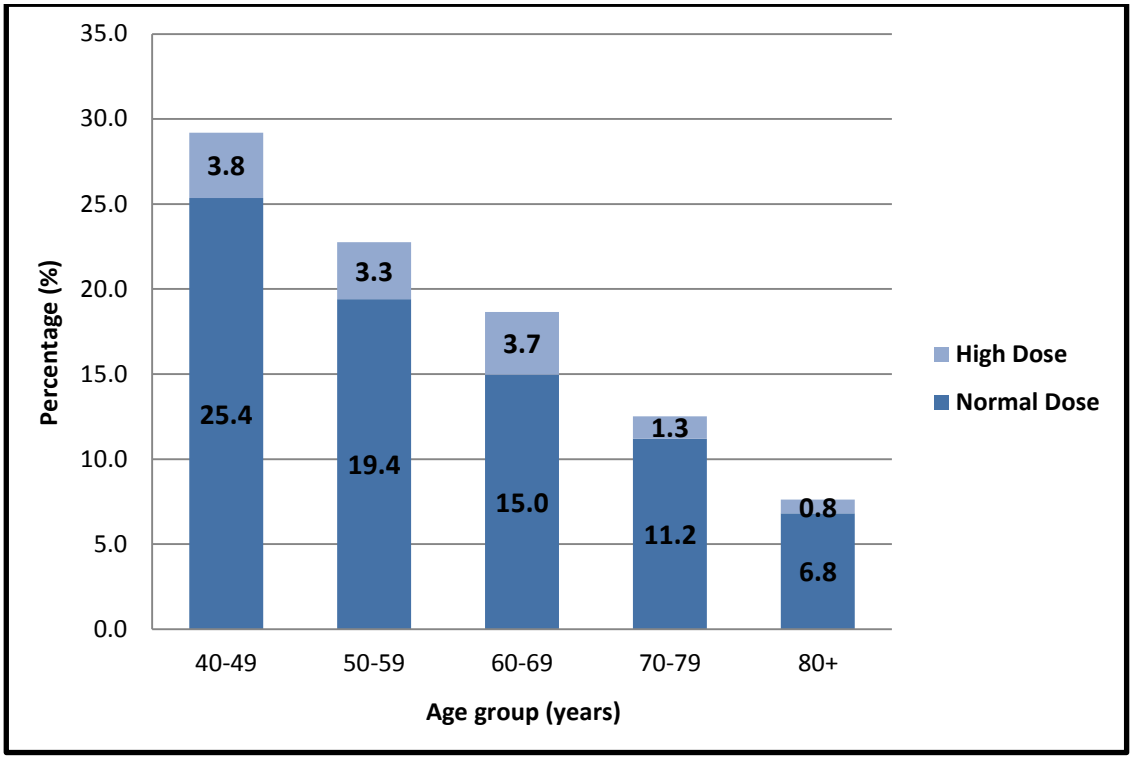
Figure 9.3 Distribution of phase 2 preceding cumulative NSAID DDDs



50 DDDs per interval

Stratifying NSAID use by age and dose, there was a steady decline in the normal and high dose users with increasing age and this was especially evident in the normal dose user group. The overall proportion of NSAID users of any dose declined from 29.2% in patients aged 40-49 years old to 7.6% in those aged 80 years and over respectively (**Figure 9.4**). The dose distribution and the age-prevalence trends seen in phase 2 NSAID users were similar to those seen in phase 1 patients (see **Figure 8.5** and **Figure 8.6**).

Figure 9.4 Percentage of normal and high dose preceding NSAID users per age group

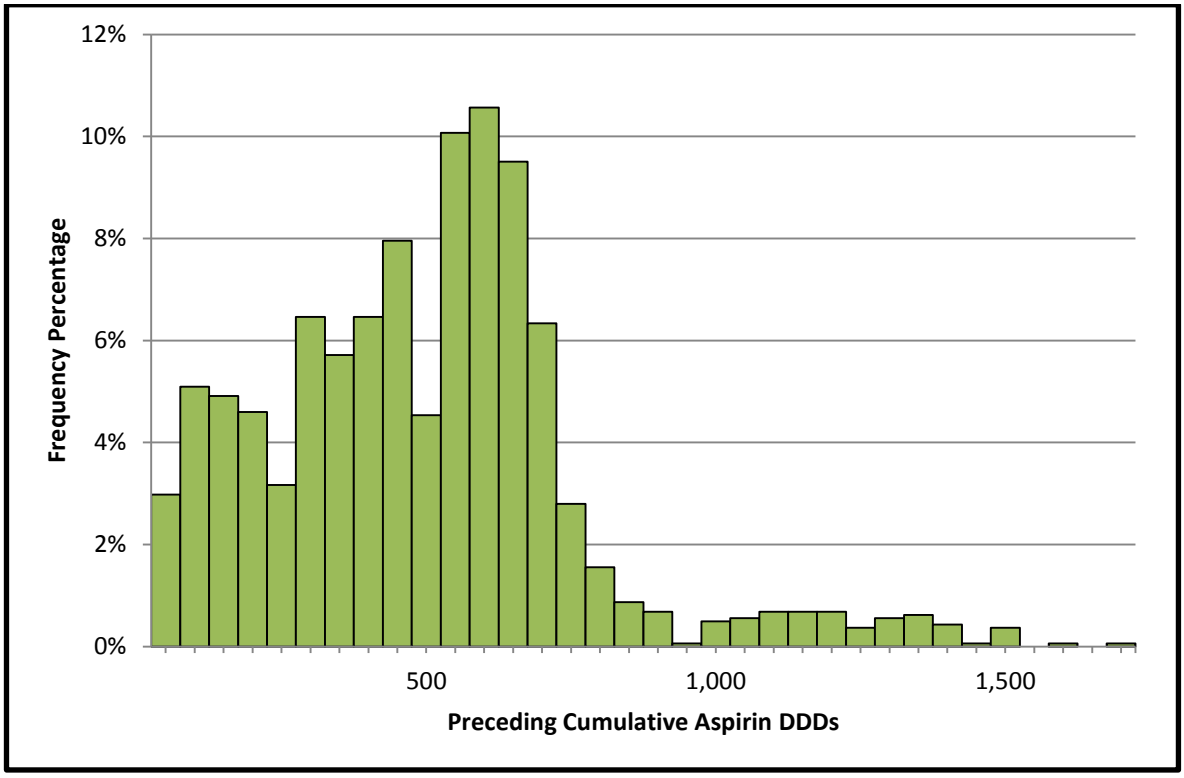


9.2.2. Aspirin prescription dose before the last eGFR

Aspirin was prescribed to 38.8% (n=1,609) of the phase 2 patients. 50% of aspirin users had up to 476 DDDs of use (**Figure 9.5**). 75% of aspirin users were prescribed <616 DDDs (max = 1,700 DDDs) of aspirin but high dose users were given a median 840 DDDs of aspirin.

Patients given at least one aspirin prescription in phase 2 had a median exposure period of 582 days [IQR=505-662] days. Hence, a typical high dose aspirin user would consume 840/582 = 1.44 DDDs of low-medium dose aspirin per day. This is equivalent to 0.075 * 1.44 = 0.11 grams of low-dose aspirin (*75mg*) per day or 0.11 * 585 = 64 grams during the exposure period.

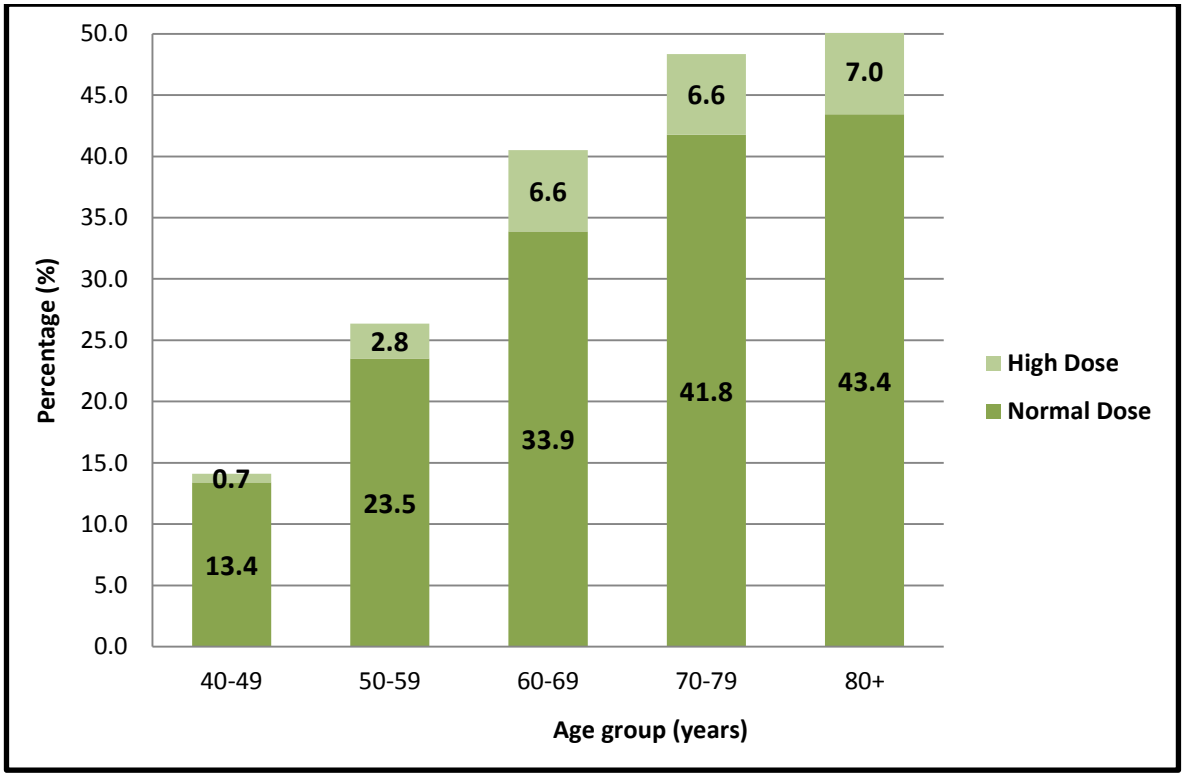
Figure 9.5 Distribution of phase 2 preceding cumulative Aspirin DDDs



50 DDDs per interval

When aspirin use was stratified by age and dose, it was clear that the percentage of users increased with advancing age in both the normal and high dose groups. The proportion of any aspirin users increased markedly from 14.1% in patients aged 40-49 years old to 50.4% in those aged 80 years and over respectively (**Figure 9.6**). The dose distribution and the age-prevalence trends seen in phase 2 aspirin users were similar to those seen in phase 1 patients (see **Figure 8.7** and **Figure 8.8**).

Figure 9.6 Percentage of normal and high dose preceding Aspirin users per age group

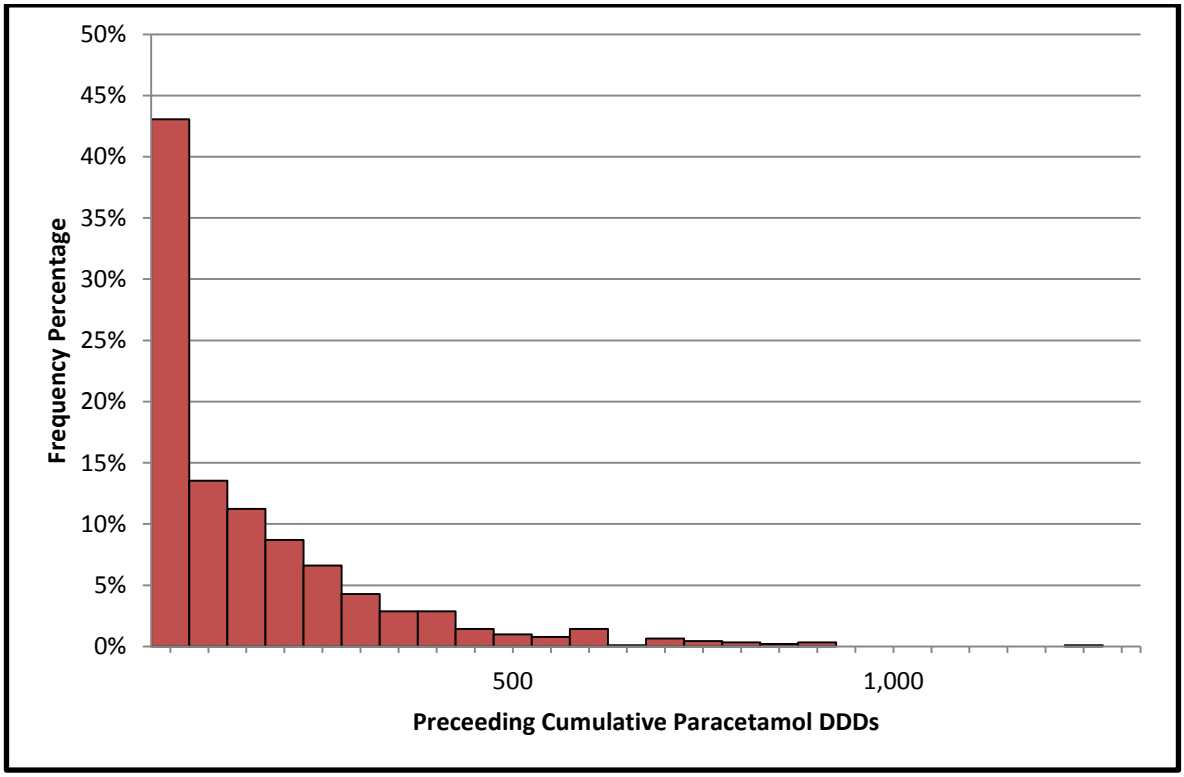


9.2.3. Paracetamol prescription dose before the last eGFR

Paracetamol was prescribed to 21.9% (n=908) of the phase 2 patients of which 50% had up to 83 DDDs of use (**Figure 9.7**). Three out of four of paracetamol users were prescribed <200 DDDs (max = 1,234 DDDs) but high dose users were given a median 383 DDDs.

Patients prescribed paracetamol had a median exposure period of 586 days [IQR=504-659]. As such, a typical high dose paracetamol user would consume 383/586 = 0.65 DDDs per day. This is equivalent to 3 * 0.65 = 1.95 grams of paracetamol per day or 1.95 * 586 = 1,143 grams during the exposure period.

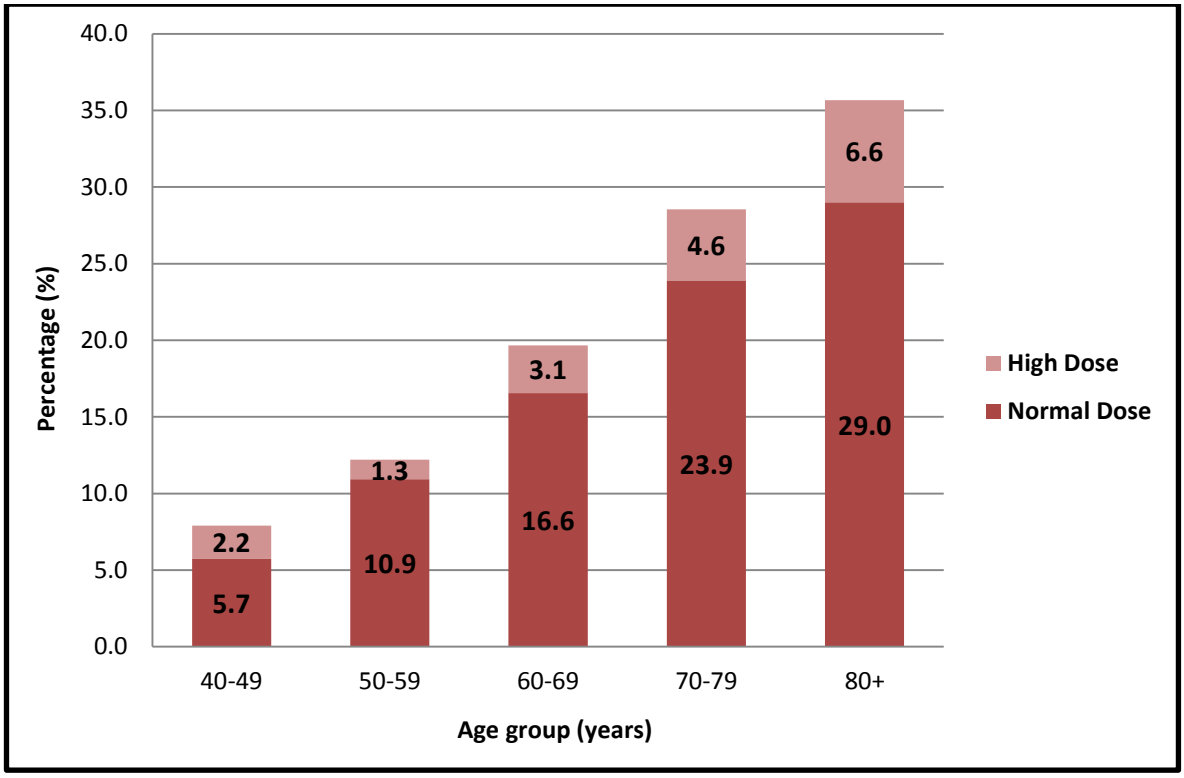
Figure 9.7 Distribution of phase 2 preceding cumulative Paracetamol DDDs



50 DDDs per interval

When paracetamol users were stratified by age and dose, it was evident that there was an increase in the proportion of patients with normal and high dose use with the advance of age. The proportion of paracetamol users increased decidedly from 7.9% in patients aged 40-49 years old to 35.6% in those aged 80 years and over respectively (**Figure 9.8**). The dose distribution and the age-prevalence trends seen in phase 2 paracetamol users were similar to those seen in phase 1 patients (see **Figure 8.9** and **Figure 8.10**).

Figure 9.8 Percentage of normal and high dose preceding Paracetamol users per age group



9.3. Characteristics of Drug Users

9.3.1. Drug use and baseline CKD status

Among phase 2 patients, the proportion of non-users of any drug (NSAIDs, aspirin or paracetamol) decreased significantly from 42.7% in patients with a normal eGFR at baseline to 14.3% in stage 5 CKD patients (**Table 9.2**).

The percentage of NSAID users decreased significantly with increasing renal dysfunction. Over 20% of patients with a normal eGFR used any NSAIDs falling to just 5.1% in stage 4 CKD. No stage 4 or 5 CKD patients were prescribed high doses of NSAIDs and no stage 5

CKD patients were prescribed any NSAIDs at all. There was a 6.2% decrease in the proportion of NSAID users between patients with an eGFR ≥60 at baseline compared to those with an eGFR <60 at baseline (**Appendix 8**).

Aspirin use increased substantially with worsening eGFR. A third of all patients with a normal eGFR had some aspirin use rising to over 70% in those with stage 5 disease. Most of the increase was in the normal dose user group with the high dose user group summiting at stage 3 CKD. There were significant increases in the proportion of aspirin users between patients with an eGFR ≥60 compared to those with an eGFR <60 at baseline (**Appendix 8**).

Generally, the proportion of paracetamol users was higher amongst those with poor renal function with a maximum of 35.9% at stage 4 CKD. The majority of the change could be attributed to an increase in the proportion of normal dose users with no high dose paracetamol users in stage 5 CKD. Paracetamol use was 11.4% higher in the <60 eGFR group (31.5%) compared to the ≥60 eGFR group (20.1%) (Data shown in **Appendix 8**)

Table 9.2 Level of preceding drug use and baseline CKD status

Analgesia use	eGFR ≥60				eGFR <60						*p*-value
	Normal N=1589		Mildly impaired N=1889		Stage 3 CKD N=621		Stage 4 CKD N=39		Stage 5 CKD N=7		
	n	%	n	%	n	%	n	%	n	%	
[1]**Non users of any the three drugs** *(n=1661)*	679	**42.7**	761	**40.3**	209	**33.7**	11	**28.2**	1	**14.3**	**0.001***
Non-NSAID users *(n=3434)*	1252	**78.8**	1595	**84.4**	543	**87.4**	37	**94.9**	7	**100.0**	
Normal Dose NSAID users *>0 - <452 DDD (n=605)*	285	**17.9**	251	**13.3**	67	**10.8**	2	**5.1**	0	**0.0**	**<0.001***
High Dose NSAID users *≥452 DDD (n=106)*	52	**3.3**	43	**2.3**	11	**1.8**	0	**0.0**	0	**0.0**	
Non-Aspirin users *(n=2536)*	1053	**66.3**	1132	**59.9**	33	**53.6**	16	**41.0**	2	**28.6**	
Normal Dose Aspirin users *>0 - <672 DDD (n=1387)*	471	**29.6**	648	**34.3**	241	**38.8**	22	**56.4**	5	**71.4**	**<0.001***
High Dose Aspirin users *≥672 DDD (n=222)*	65	**4.1**	109	**5.8**	47	**7.6**	1	**2.6**	0	**0.0**	
Non-Paracetamol users *(n=3237)*	1288	**81.1**	1492	**79.0**	427	**68.8**	25	**64.1**	5	**71.4**	
Normal Dose Paracetamol users *>0 - <267 DDD (n=758)*	247	**15.5**	341	**18.1**	155	**25.0**	13	**33.3**	2	**28.6**	**<0.001***
High Dose Paracetamol users *≥267 DDD (n=150)*	54	**3.4**	56	**3.0**	39	**6.3**	1	**2.6**	0	**0.0**	

[1]Non-users of NSAIDs, Aspirin and Paracetamol, *Statistically significant at $p \leq 0.05$.

9.3.2. Factors associated with drug use

9.3.2.1. Socio-demographic factors

The mean age amongst preceding NSAID users (62 years, SD= 12) was significantly lower than the mean age in non-users (67 years, SD= 12, $p<0.001$). Within this cohort, there were no statistically significant differences in the gender or status of deprivation between users and non-users of NSAIDs (**Table 9.3**).

Preceding aspirin users had a mean age of 70 years (SD= 11) which was significantly older than the mean age in non-users (64 years, SD= 12, $p<0.001$). Aspirin users were significantly more likely to be males (53.3%) compared to non-users (40.5%), $p<0.001$. Aspirin use also interacted significantly with deprivation ($p=0.002$) with a higher proportion of users in the most deprived quartile (**Table 9.4**).

Preceding paracetamol users had a mean age of 71 years (SD= 11) which was significantly older than the mean age in non-users (65years, SD= 12, $p<0.001$). There was a significantly higher proportion of females (and a lower proportion of males) in the paracetamol user group compared to the non-user group, $p=0.012$. Paracetamol users were more likely to be in the most deprived quartile than non-users ($p<0.001$) and this trend was more pronounced in the high dose user group (**Table 9.5**).

9.3.2.2. Other drug use

Around one in three of all NSAID users also had at least one prescription for aspirin with 25% of high dose NSAID users also receiving aspirin (**Table 9.3**). However, non-users of NSAIDs were significantly more likely to be prescribed aspirin than NSAID users,

$p<0.001$. A quarter of all NSAID users had a prescription for paracetamol and this proportion was higher in high dose users (28.3%) than in normal dose users (24.8%). NSAID users were significantly more likely to be prescribed paracetamol than non-users, $p=0.016$.

Aspirin users at any dose were significantly less likely to be prescribed NSAIDs than non-users, $p<0.001$ (**Table 9.4**). However, aspirin users were significantly more likely to be prescribed paracetamol than non-users ($p<0.001$) with one in four of aspirin users also receiving paracetamol.

Paracetamol users at any dose were significantly more likely to be prescribed aspirin ($p<0.001$) or NSAIDs ($p=0.016$) than non-users (**Table 9.5**). Paracetamol users co-prescribed aspirin or NSAIDs approached 50% and 20% respectively. The proportion of paracetamol users prescribed NSAIDs decreased in the high dose group compared to the normal dose group but those prescribed aspirin increased.

9.3.2.3. Co-morbidity and co-drug therapy

The prevalence of CVD and co-drug therapy was significantly lower in users of NSAIDs than in non-users, and in either case, the proportion decreased in patients taking higher doses of NSAIDs (**Table 9.3**). The prevalence of DM did not differ significantly between users and non-users of NSAIDs.

The prevalence of co-morbidity and co-drug therapy was significantly higher in aspirin users than in non-users and the prevalence also increased with increasing aspirin dose (**Table 9.4**).

The prevalence of CVD and co-drug therapy was approximately equivalent between users and non-users of paracetamol. However, high dose paracetamol users had a higher proportion of co-drug therapy use than in the normal or non-user groups. The proportion of patients with DM was significantly higher amongst paracetamol users compared to non-users (29.4% vs. 25.5%) (**Table 9.5**).

9.3.2.4. Renal function testing interval, CKD status and CKD progression

There were no significant differences in the rate of eGFR decline per year or in the mean difference between eGFR measurements between NSAID users and non-users. The proportion of patients with stages 3 to 5 CKD at the last eGFR measurement was significantly lower amongst preceding NSAID users compared to non-users. Moreover, the proportion of stage 3 to 5 CKD patients decreased between the normal and high dose user groups (**Table 9.3**).

The mean difference between eGFR measurements was not significantly different between aspirin users and non-users. Aspirin users were significantly more likely to have stages 3 to 5 CKD at the last eGFR measurement compared to non-users but the proportion was equivalent between the normal and high dose aspirin user groups (**Table 9.4**). Although aspirin users and non-users had similar overall rates of eGFR decline per year, the distribution of eGFR decline rates differed significantly amongst high dose users compared to non-users and normal dose users, p=0.028. High dose users were less likely to have renal function decline with some having renal function improvement (median eGFR decline rate per year 0 [IQR = -4.01, +2.56]) which differed significantly from normal dose aspirin users, p=0.013.

The mean difference between eGFR measurements varied significantly between paracetamol users (246 days, SD= 122) and non-users (274, SD= 124) with paracetamol users tested on average 4 weeks earlier than non-users of paracetamol. Paracetamol users were significantly more likely to have stages 3 to 5 CKD at the last eGFR measurement compared to non-users. In addition, the proportion of stage 3 to 5 CKD patients was higher in the high dose paracetamol user group compared to the normal dose group (**Table 9.5**). However, there were no noticeable differences between paracetamol users at any dose and non-users in relation to the eGFR decline rate per year.

Table 9.3 Characteristics of preceding NSAID users and non-users stratified by dose

Variable		Non-users[a] (n=3434)	Normal-dose user (n=605)	High-dose users (n=106)	*p*-value	Non-users[a] (n=3434)	NSAID users (n=711)	*p*-value
Mean Age (SD)		67 (12)	62 (12)	61 (10)	**<0.001***	67 (12)	62 (12)	**<0.001***
Gender (%)	M	46.0	43.3	39.6	0.227	46.0	42.8	0.116
	F	54.0	56.7	60.4		54.0	57.2	
[1]Deprivation (%)	Least Deprived Quartile	24.2	24.0	17.9	0.289	24.2	22.6	0.462
	IMD 2	24.8	27.1	27.4		24.8	27.0	
	IMD 3	26.6	27.8	24.5		26.6	26.0	
	Most Deprived Quartile	24.4	21.2	30.2		24.4	24.3	
[2]Preceding Cumulative NSAID DDDs		0	49 [28-126]	717 [560-908]	N/A	0	70 [28-280]	N/A
Aspirin use (%)	users	40.6	31.1	26.4	**<0.001***	40.6	30.4	**<0.001***
Paracetamol use (%)	users	21.2	24.8	28.3	**0.039***	21.2	25.3	**0.016***
All CVD (%)	Yes	71.3	58.3	54.7	**<0.001***	71.3	57.8	**<0.001***
Diabetes (%)	Yes	26.9	23.6	25.5	0.237	26.9	23.9	0.099
ACE-i/ARB/Renin-i use (%)	users	55.9	45.6	37.7	**<0.001***	55.9	44.4	**<0.001***
Mean difference in days between eGFR measurements (SD)		269 (125)	261 (123)	261 (122)	0.089	269 (125)	261 (123)	0.104
[3]Stage 3 to 5 CKD (%) *(n=778)*	Yes	20.0	12.7	12.3	**<0.001***	20.0	12.7	**<0.001***
[2]Rate of eGFR decline		0 [-5.59, +0.84]	0 [-4.93, 0]	0 [-4.18, +1.24]	0.571	0 [-5.59, +0.84]	0 [-4.87, 0]	0.340

[1]32 subjects did not have a deprivation score, [2]Given as a Median [IQR], [3]At the last eGFR measurement, [a]Non-users of NSAIDs only, *Statistically significant at $p \leq 0.05$.

Table 9.4 Characteristics of preceding Aspirin users and non-users stratified by dose

Variable		Non-users[a] (n=2536)	Normal-dose users (n=1387)	High-dose users (n=222)	*p*-value	Non-users[a] (n=2536)	Aspirin users (n=1609)	*p*-value
Mean Age (SD)		64 (12)	70 (11)	71 (10)	**<0.001***	64 (12)	70 (11)	**<0.001***
Gender (%)	M	40.5	53.5	51.8	**<0.001***	40.5	53.3	**<0.001***
	F	59.5	46.5	48.2		59.5	46.7	
[1]Deprivation (%)	Least Deprived Quartile	25.1	22.0	23.1	**0.013***	25.1	22.1	**0.002***
	IMD 2	25.8	24.1	25.8		25.8	24.3	
	IMD 3	26.9	26.9	23.1		26.9	26.4	
	Most Deprived Quartile	22.2	27.0	28.1		22.2	27.1	
[2]Preceding Cumulative Aspirin DDDs		0	448 [252-560]	840 [728-1120]	N/A	0	476 [280-616]	N/A
NSAID use (%)	users	19.5	13.2	14.9	**<0.001***	19.5	13.4	**<0.001***
Paracetamol use (%)	users	19.4	25.0	30.6	**<0.001***	19.4	25.8	**<0.001***
All CVD (%)	Yes	60.7	81.8	82.9	**<0.001***	60.7	82.0	**<0.001***
Diabetes (%)	Yes	20.3	36.5	32.4	**<0.001***	20.3	35.9	**<0.001***
ACE-i/ARB/Renin-i use (%)	users	47.0	64.7	65.8	**<0.001***	47.0	64.9	**<0.001***
Mean difference in days between eGFR measurements (SD)		265 (128)	271 (120)	276 (119)	0.146	265 (128)	272 (119)	0.111
[3]Stage 3 to 5 CKD (%) *(n=778)*	Yes	16.4	22.6	22.1	**<0.001***	16.4	22.5	**<0.001***
[2]Rate of eGFR decline		0 [-5.43, +0.27]	0 [-5.62, +0.84]	0 [-4.01, +2.56]	**0.028***	0 [-5.43, +0.27]	0 [-5.43, +0.95]	0.416

[1]32 subjects did not have a deprivation score, [2]Given as a Median [IQR], [3]At the last eGFR measurement, [a]Non-users of Aspirin only, *Statistically significant at $p \leq 0.05$.

Table 9.5 Characteristics of preceding Paracetamol users and non-users stratified by dose

Variable		Non-users[a] (n=3237)	Normal-dose users (n=758)	High-dose users (n=150)	*p*-value	Non-users[a] (n=3237)	Paracetamol users (n=908)	*p*-value
Mean Age (SD)		65 (12)	71 (11)	72 (12)	**<0.001***	65 (12)	71 (11)	**<0.001***
Gender (%)	M	46.5	42.5	38.0	**0.025***	46.5	41.7	**0.012***
	F	53.5	57.5	62.0		53.5	58.3	
[1]Deprivation (%)	Least Deprived Quartile	25.5	19.9	12.7	**<0.001***	25.5	18.7	**<0.001***
	IMD 2	25.3	24.3	28.0		25.3	24.9	
	IMD 3	26.2	28.8	26.7		26.2	28.5	
	Most Deprived Quartile	23.0	27.0	32.7		23.0	27.9	
[2]Preceding Cumulative Paracetamol DDDs		0	50 [17-133]	383 [315-517]	N/A	0	83 [25-200]	N/A
NSAID use (%)	users	16.4	20.2	18.0	**0.044***	16.4	19.8	**0.016***
Aspirin use (%)	users	37.9	45.0	52.0	**<0.001***	37.9	46.1	**<0.001***
All CVD (%)	Yes	68.6	69.5	74.0	0.354	68.6	70.3	0.342
Diabetes (%)	Yes	25.5	29.4	29.3	0.066	25.5	29.4	**0.020***
ACE-i/ARB/Renin-i use (%)	users	53.9	52.0	64.0	**0.026***	53.9	54.0	0.989
Mean difference in days between eGFR measurements (SD)		274 (125)	244 (123)	258 (118)	**<0.001***	274 (125)	246 (122)	**<0.001***
[3]Stage 3 to 5 CKD (%) *(n=778)*	Yes	16.3	26.8	30.7	**<0.001***	16.3	27.4	**<0.001***
[2]Rate of eGFR decline		0 [-5.43, +0.65]	0 [-5.29, +1.69]	-0.96 [-5.49, 0]	0.148	0 [-5.43, +0.65]	0 [-5.36, +1.49]	0.237

[1]32 subjects did not have a deprivation score, [2]Given as a Median [IQR], [3]At the last eGFR measurement, [a]Non-users of Paracetamol only, *Statistically significant at $p \leq 0.05$.

9.4. Drug Use and the Development of Stage 3 to 5 CKD

An important clinical outcome is the progression of CKD to stage 3 (or worse). This is associated with a poor prognosis for patients with a higher association with multi-morbidity and increasing renal complications (see *section 2.3*). Therefore, there is a need to quantify the risk of developing stage 3 to 5 CKD with normal or high dose NSAID, aspirin or paracetamol use.

9.4.1. Single drug use and the development of stage 3 to 5 CKD

To test this association, 3,478 patients (out of 4,145 phase 2 patients) with a baseline (*first*) eGFR measurement ≥60ml/min/1.73m^2 were selected (representing patients with a normal or mildly impaired eGFR). Amongst the selected patients, the last recorded eGFR was searched and if the eGFR value was <60ml/min/1.73m^2 (equivalent to stage 3 to 5 CKD), the patient was coded as having **developed** stage 3 to 5 CKD; 6.4% (223/3,478) of the selected patients reached this outcome during the two year study period. Multiple logistic regression analysis was then used to calculate the adjusted OR for developing stage 3 to 5 disease with normal or high dose NSAID, aspirin or paracetamol use compared to the respective non-users of each drug.

As shown in **Table 9.6**, normal and high dose NSAID, aspirin or paracetamol use was not significantly associated with an increased risk of developing stage 3 to 5 CKD. However, there was a fall in the risk estimate amongst high dose aspirin users compared to the estimate in the normal dose user group.

Table 9.6 Association between preceding drug use and the development of stage 3 to 5 CKD

Category of Drug use	Normal dose use		High dose use	
	Crude OR (95% CI)	***Adjusted OR (95% CI)*[a]**	*Crude OR (95% CI)*	***Adjusted OR (95% CI)*[a]**
Non-NSAID users	*1*	*1*	*1*	*1*
[1]Preceding NSAID users (n=631)	0.666 (0.435-1.021)	**1.036 (0.659-1.628)**	0.756 (0.304-1.884)	**1.351 (0.518-3.524)**
Non-Aspirin users	*1*	*1*	*1*	*1*
[1]Preceding Aspirin users (n=1283)	1.189 (0.892-1.585)	**0.801 (0.588-1.092)**	0.939 (0.484-1.821)	**0.583 (0.294-1.157)**
Non-Paracetamol users	*1*	*1*	*1*	*1*
[1]Preceding Paracetamol users (n=694)	1.699 (1.233-2.342)	**1.245 (0.882-1.755)**	1.457 (0.723-2.934)	**1.095 (0.521-2.303)**

[1]26 patients did not have a deprivation score thus were not included in this analysis. [a]Adjusted for age (continuous), gender, deprivation quartile, all cardiovascular disease, diabetes, ACE-i/ARB/Renin-i use, other drug use (either aspirin or paracetamol in the case of NSAID users) and baseline CKD status.

9.4.2. Multiple drug use and the development of stage 3 to 5 CKD

To explore the relationship between multiple drug use and the development of stage 3 to 5 CKD, patients prescribed combinations of two or three of the drugs exclusively before the last eGFR measurement were selected.

Amongst patients with a baseline eGFR ≥60ml/min/1.73m^2, the most commonly prescribed drug combination was aspirin and paracetamol (7.2%); the least common was all three drugs (1.6%) given together (**Table 9.7**).

None of the drug use combinations were significantly associated with an increased risk of developing stage 3 to 5 CKD when compared to exclusive users of NSAIDs but the estimate for NSAIDs and paracetamol use was greater than the other drug combinations.

Table 9.7 Association between multiple drug use and the risk of developing stage 3 to 5 CKD

Category of Drug use	Overall use	
	Crude OR (95% CI)	***Adjusted OR (95% CI)***[a]
[1]*Ref*	*1*	***1***
Preceding exclusive NSAID & Aspirin users (n=126)	1.834 (0.695-4.840)	**0.985 (0.353-2.752)**
[1]*Ref*	*1*	***1***
Preceding exclusive NSAID & Paracetamol users (n=96)	3.226 (1.296-8.028)	**2.309 (0.878-6.072)**
[1]*Ref*	*1*	***1***
Preceding exclusive Aspirin & Paracetamol users (n=250)	3.159 (1.511-6.607)	**0.983 (0.433-2.228)**
[1]*Ref*	*1*	***1***
Preceding NSAID & Aspirin & Paracetamol users (n=55)	1.799 (0.486-6.664)	**0.757 (0.190-3.015)**

[1]Preceding exclusive NSAID users (N=354). [a]Adjusted for age (continuous), gender, deprivation quartile, all cardiovascular disease, diabetes, ACE-i/ARB/Renin-i use and baseline CKD status. *Significant result.

9.5. Factors Associated with Significant CKD Progression

The final hypothesis we wished to test was whether NSAID, aspirin or paracetamol use is associated with significant CKD progression (defined by NICE as an eGFR decline rate of >5min/min/1.73m^2 per year[6]). All phase 2 patients (n=4,145) were included of whom 26.5% (n=1,099) had significant CKD progression over 2-years. Firstly, the characteristics of patients with significant CKD progression were explored. Alongside the dichotomous outcome measure of significant CKD progression used in this study, a continuous measure of CKD progression (median rate of eGFR decline per year) was used to explore in greater detail the factors that drive renal function decline.

9.5.1. Characteristics of subjects with significant CKD progression

9.5.1.1. Socio-demographics and significant CKD progression

On average, patients with significant CKD progression were two years older than those without significant CKD progression (**Table 9.8**). Significant CKD progression was not significantly associated with gender or deprivation.

However, by plotting the median rate of eGFR decline by age and stratifying by gender, it was evident that eGFR decline was faster among older patients and was more pronounced in males aged over 60 years than in females (**Figure 9.9**). Therefore, using a continuous measure of CKD progression gave a more detailed picture of disease progression than when using the dichotomous measure alone.

9.5.1.2. Prevalence of drug use and significant CKD progression

The prevalence of drug use was equivalent between the significant and non-significant CKD progression groups (**Table 9.8**).

9.5.1.3. Co-morbidity, co-drug therapy and significant CKD progression

Co-morbidity and co-drug therapy were not significantly associated with CKD progression. However, the prevalence of ischaemic heart disease, heart failure and dysrhythmia were significantly higher in the significant CKD progression group compared to the non-significant CKD progression group (**Table 9.8**).

9.5.1.4. Baseline CKD status, renal function testing interval and significant CKD progression

The mean interval between the first and last eGFR measurements was around 400 days in both patients with and without significant disease progression indicating a similar overall follow-up period between the two CKD progression groups. Patients with significant CKD progression were significantly less likely to have stage 3 to 5 CKD at baseline (13.6%) compared to non-significant CKD patients who had higher rates of stage 3 to 5 CKD at baseline (17%) (**Table 9.8**) indicating that it is in fact the normal or mildly impaired eGFR groups who had the faster rate of decline.

This is demonstrated in **Figure 9.10** where patients with a mildly impaired eGFR at baseline had the fastest rate of eGFR decline in both males and females. Moreover, stage 4 or 5 CKD patients (especially females) actually had improvements in renal function.

Table 9.8 Characteristics of patients with significant and non-significant CKD progression

Variable		Non-significant progression (n=3046)	Significant progression (n=1099)	*p*-value
[1]**Age**		66 (12)	68 (12)	**<0.001**
Gender (%)	M	44.9	47.0	0.237
	F	55.1	53.0	
[2]**Deprivation (%)**	Least Deprived Quartile	24.2	23.5	0.939
	IMD 2	25.0	25.8	
	IMD 3	26.6	26.9	
	Most Deprived Quartile	24.2	23.8	
Preceding NSAID use (%)	user	17.7	15.6	0.367
Preceding Aspirin use (%)	user	38.5	39.6	0.545
Preceding Paracetamol use (%)	user	22.0	21.6	0.869
[3]**Diabetes (%)** *(n=1094)*	Yes	26.5	26.2	0.237
All CVD (%) *(n=2859)*	Yes	68.2	71.2	0.058
[4]Hypertension (%) *(n=2259)*	Yes	54.3	55.1	0.669
[5]Ischaemic Heart Disease (%) *(n=642)*	Yes	14.7	17.7	**0.021***
[6]Heart failure (%) *(n=128)*	Yes	2.4	5.0	**<0.001***
[7]Peripheral Vascular Disease (%) *(n=63)*	Yes	1.3	2.1	0.070
[8]Cerebrovascular Disease (%) *(n=297)*	Yes	7.0	7.7	0.394
[9]Dysrhythmia (%) *(n=141)*	Yes	3.0	4.5	**0.014***
ACE-i/ARB/Renin-i use (%) *(n=2236)*	user	53.3	55.9	0.135
[1]**Interval between last and first eGFR measurements in days**		399 (143)	391 (153)	0.131
[10]**Baseline stage 3 to 5 CKD (%)** *(n=667)*	Yes	17.0	13.6	**0.01***

[1]Given as a Mean (SD),[2]32 subjects did not have a deprivation score, READCODES = [3]C10, [4]G2, [5]G3, [6](G1, G4, G50, G51, G54, G55, G58, G5Y, G5UYT), [7]G6, [8](G7, GY), [9](G56, G57). All CVD = 4-9, [10]At the first eGFR measurement, *Statistically significant at $p \leq 0.05$.

Figure 9.9 Median rate of eGFR decline per year stratified by age group and gender

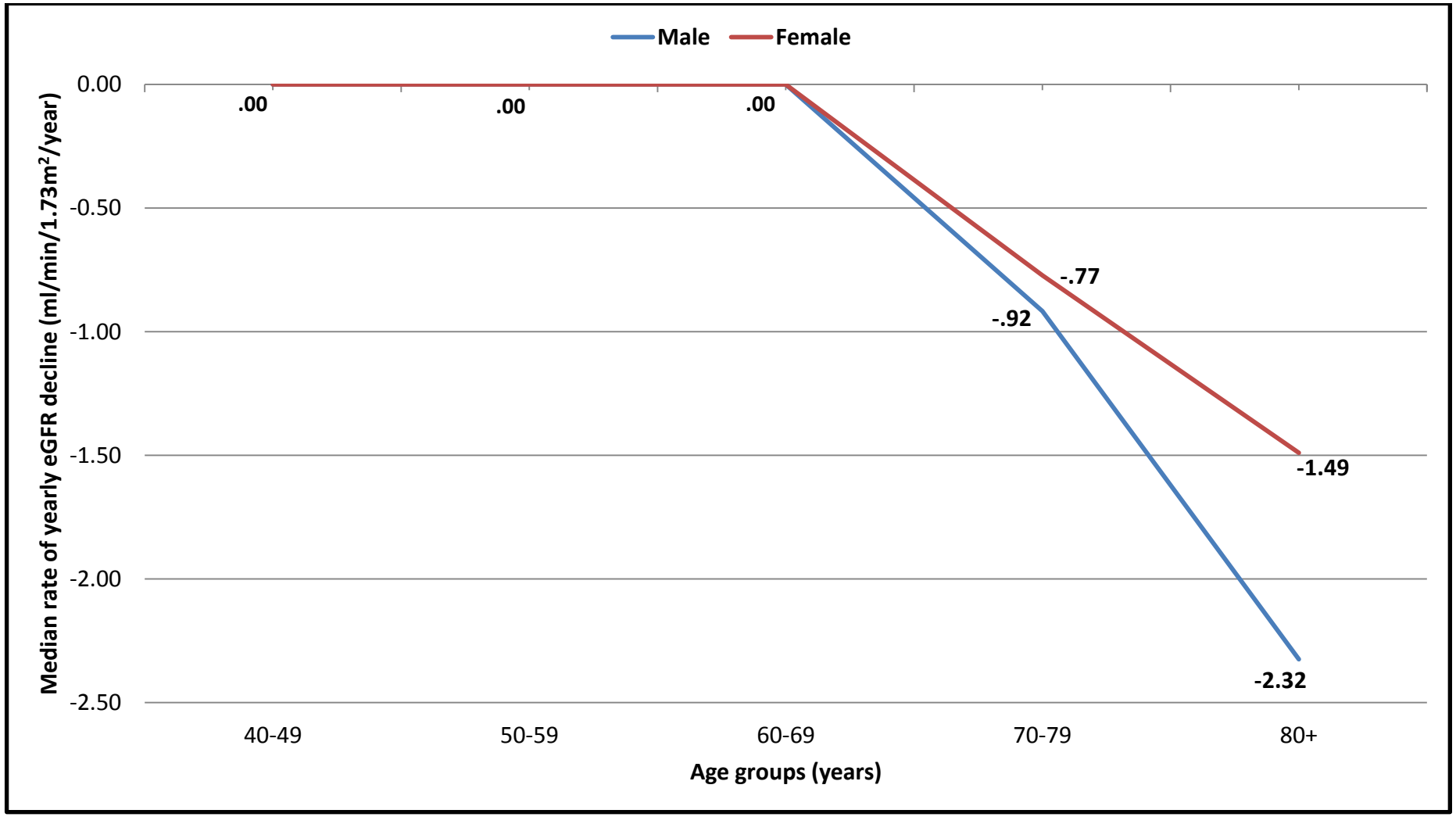
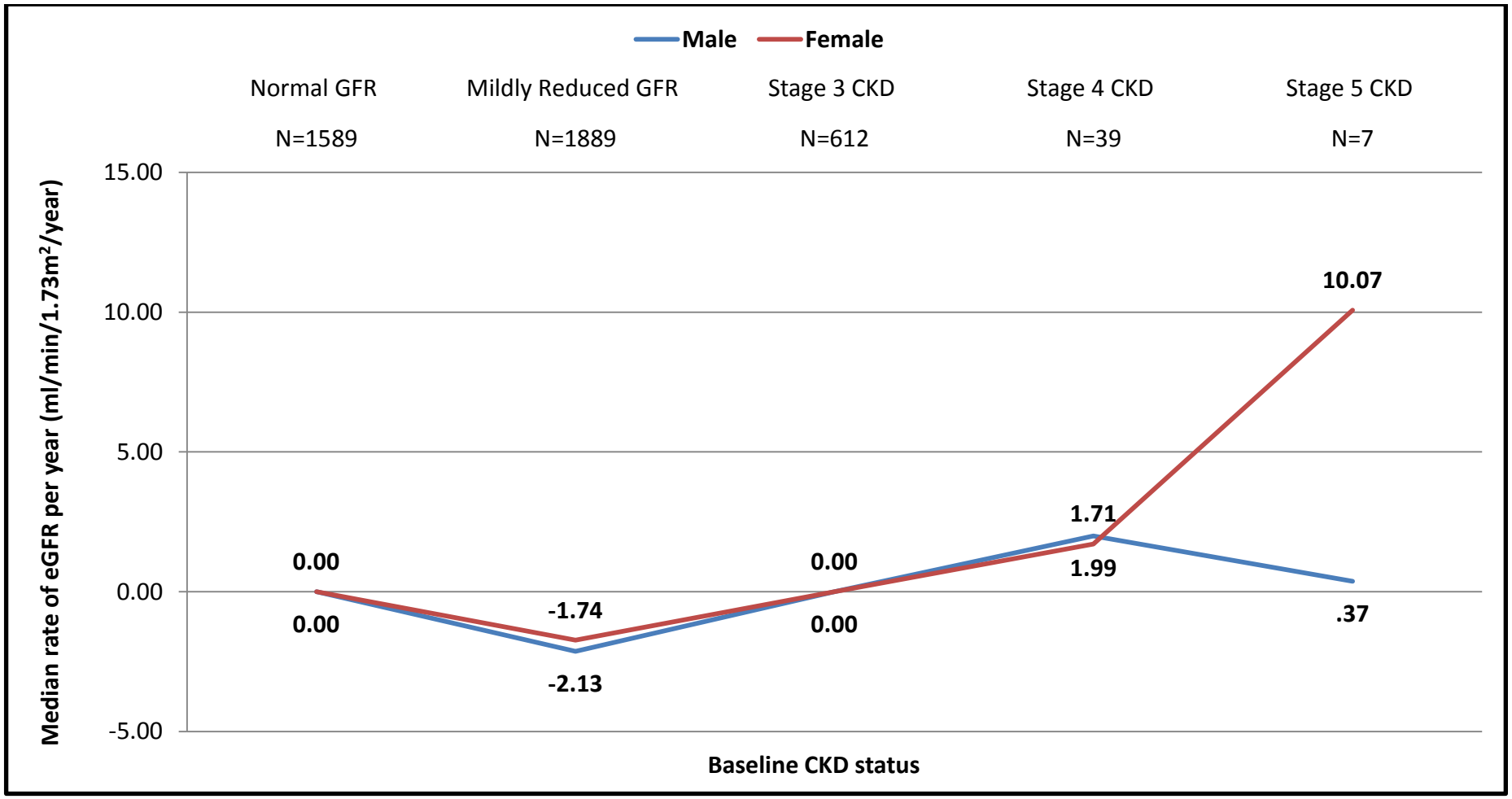


Figure 9.10 Median rate of eGFR decline per year stratified by gender and baseline CKD status



9.6. Drug Use and significant CKD progression

It was evident that several factors were associated with significant CKD progression. Therefore, multiple logistic regression analysis was performed to estimate the risk of preceding drug use on significant CKD progression adjusting for socio-demographics, co-morbidity, co-drug therapy, other drug use and baseline CKD status.

9.6.1. Single drug use and significant CKD progression

Normal dose drug use was not significantly associated with an increased risk of significant CKD progression. High dose NSAID or paracetamol use was not significantly associated with an increased risk of significant CKD progression. However, high dose aspirin use significantly decreased the risk of significant CKD progression (**Table 9.9**).

Table 9.9 Association between preceding drug use and significant CKD progression

Category of Drug use	**Normal dose use**		**High dose use**	
	Crude OR (95% CI)	***Adjusted OR (95% CI)*[a]**	*Crude OR (95% CI)*	***Adjusted OR (95% CI)*[a]**
Non-NSAID users	*1*	***1***	*1*	***1***
[1]Preceding NSAID users (n=711)	0.882 (0.722-1.077)	**1.019 (0.828-1.254)**	0.707 (0.439-1.137)	**0.832 (0.512-1.351)**
Non-Aspirin users	*1*	***1***	*1*	***1***
[1]Preceding Aspirin users (n=1595)	1.086 (0.937-1.258)	**0.942 (0.804-1.105)**	0.759 (0.543-1.060)	**0.629* (0.447-0.887)**
Non-Paracetamol users	*1*	***1***	*1*	***1***
[1]Preceding Paracetamol users (n=903)	0.961 (0.802-1.152)	**0.868 (0.718-1.048)**	1.000 (0.691-1.448)	**0.935 (0.639-1.369)**

[1]32 patients did not have a deprivation score thus were not included in this analysis. [a]Adjusted for age (continuous), gender, deprivation quartile, all cardiovascular disease, diabetes, ACE-i/ARB/Renin-i use, other drug use (either aspirin or paracetamol in the case of NSAID users) and baseline CKD status. *Significant result.

9.6.2. Subgroup analysis: single drug use and significant CKD progression

To explore if the baseline eGFR affected the estimates and to ascertain the stage of CKD that aspirin seemed to be renoprotective, patients were stratified into two groups; those with an eGFR ≥60 (equivalent to a normal or mildly impaired eGFR) and those with an eGFR <60ml/min/1.73m^2 (equivalent to stage 3 to 5 CKD) at baseline. Multiple logistic regression was then repeated to calculate the risk of significant CKD progression with normal and high dose NSAID, aspirin or paracetamol use (**Table 9.10**).

Normal and high dose NSAID or paracetamol use was not significantly associated with an increased risk of CKD progression either in patients with a baseline eGFR ≥60 or <60ml/min/1.73m^2. Normal dose aspirin use was not significantly associated with CKD progression in either stratum. However, high dose aspirin use significantly decreased the risk of significant CKD progression compared to non-aspirin use in patients with a baseline eGFR ≥60ml/min/1.73m^2 but not in those with a baseline eGFR <60ml/min/1.73m^2.

Table 9.10 Association between preceding drug use and significant CKD progression stratified by the eGFR

Category of Drug use	eGFR ≥60[a] (n=3452)		Category of Drug use	eGFR <60[b] (n=661)	
	Normal Dose	**High Dose**		**Normal Dose**	**High Dose**
	***Adjusted OR (95% CI)*[1]**	***Adjusted OR (95% CI)*[1]**		***Adjusted OR (95% CI)*[1]**	***Adjusted OR (95% CI)*[1]**
Non-NSAID users	***1***	***1***	Non-NSAID users	***1***	***1***
Preceding NSAID users (n=631)	**1.022 (0.819-1.274)**	**0.881 (0.533-1.455)**	**Preceding NSAID users (n=80)**	**1.008 (0.544-1.868)**	**0.436 (0.054-3.547)**
Non-Aspirin users	***1***	***1***	Non-Aspirin users	***1***	***1***
Preceding Aspirin users (n=1283)	**0.961 (0.808-1.143)**	**0.516* (0.346-0.771)**	**Preceding Aspirin users (n=312)**	**0.864 (0.572-1.304)**	**1.223 (0.606-2.465)**
Non-Paracetamol users	***1***	***1***	Non-Paracetamol users	***1***	***1***
Preceding Paracetamol users (n=694)	**0.854 (0.692-1.054)**	**0.979 (0.635-1.509)**	**Preceding Paracetamol users (n=209)**	**0.921 (0.597-1.423)**	**0.812 (0.357-1.850)**

[a]26 patients with an eGFR≥60 did not have a deprivation score and are not included in this analysis. [b]6 patients with an eGFR<60 did not have a deprivation score and are not included in this analysis. [1]Adjusted for age (continuous), gender, deprivation quartile, all cardiovascular disease, diabetes, ACE-i/ARB/Renin-i use, baseline CKD status and other drug use (either aspirin or paracetamol in the case of NSAID users). *Significant result.

9.6.3. Multiple drug use and significant CKD progression

To explore the relationship between multiple drug use and significant CKD progression, all phase 2 subjects prescribed combinations of two or three of the drugs exclusively before the last eGFR measurement were selected.

Amongst the phase 2 subjects, the most commonly prescribed drug combination was aspirin and paracetamol at 8.3% and the least common was all there drugs (1.6%).

None of the drug use combinations were significantly associated with an increased risk of significant CKD progression when compared to NSAID use alone (**Table 9.11**).

Table 9.11 Association between multiple drug use and significant CKD progression

Category of Drug use	Overall use	
	Crude OR (95% CI)	***Adjusted OR (95% CI)***[a]
[1]*Ref*	***1***	***1***
[1]Preceding exclusive NSAID & Aspirin users (n=149)	1.104 (0.710-1.716)	**0.952 (0.599-1.514)**
[1]*Ref*	***1***	***1***
[1]Preceding exclusive NSAID & Paracetamol users (n=113)	1.101 (0.675-1.795)	**1.010 (0.612-1.668)**
[1]*Ref*	***1***	***1***
[1]Preceding exclusive Aspirin & Paracetamol users (n=345)	1.092 (0.776-1.537)	**0.855 (0.581-1.259)**
[1]*Ref*	***1***	***1***
[1]Preceding NSAID & Aspirin & Paracetamol users (n=67)	1.227 (0.680-2.215)	**1.015 (0.547-1.884)**

[1]Preceding exclusive NSAID users (N=382). [a]Adjusted for age (continuous), gender, deprivation quartile, all cardiovascular disease, diabetes, ACE-i/ARB/Renin-i use and baseline CKD status.

9.7. Chapter Summary

Figure 9.11 Full study flow diagram for the phase 1 cross-sectional study

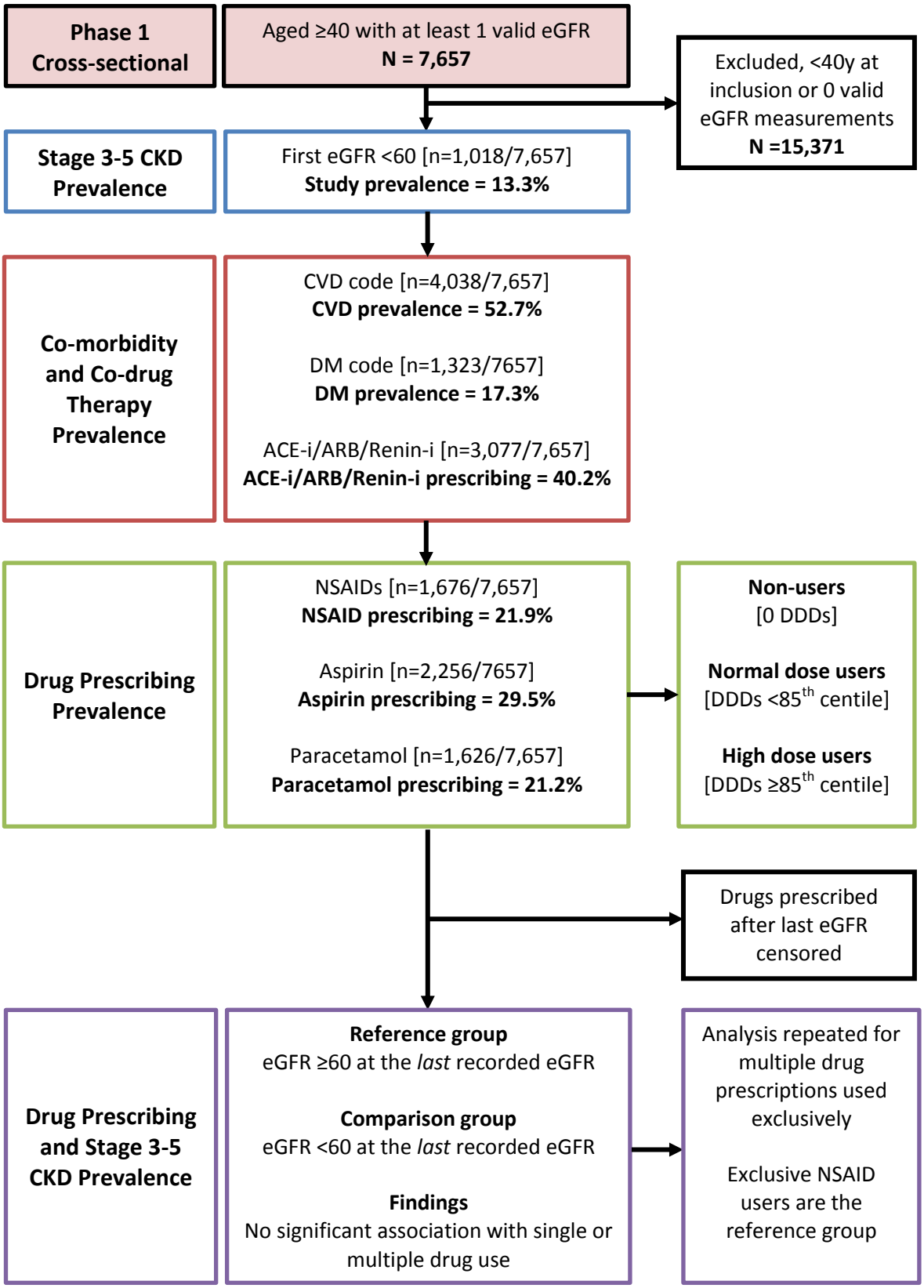
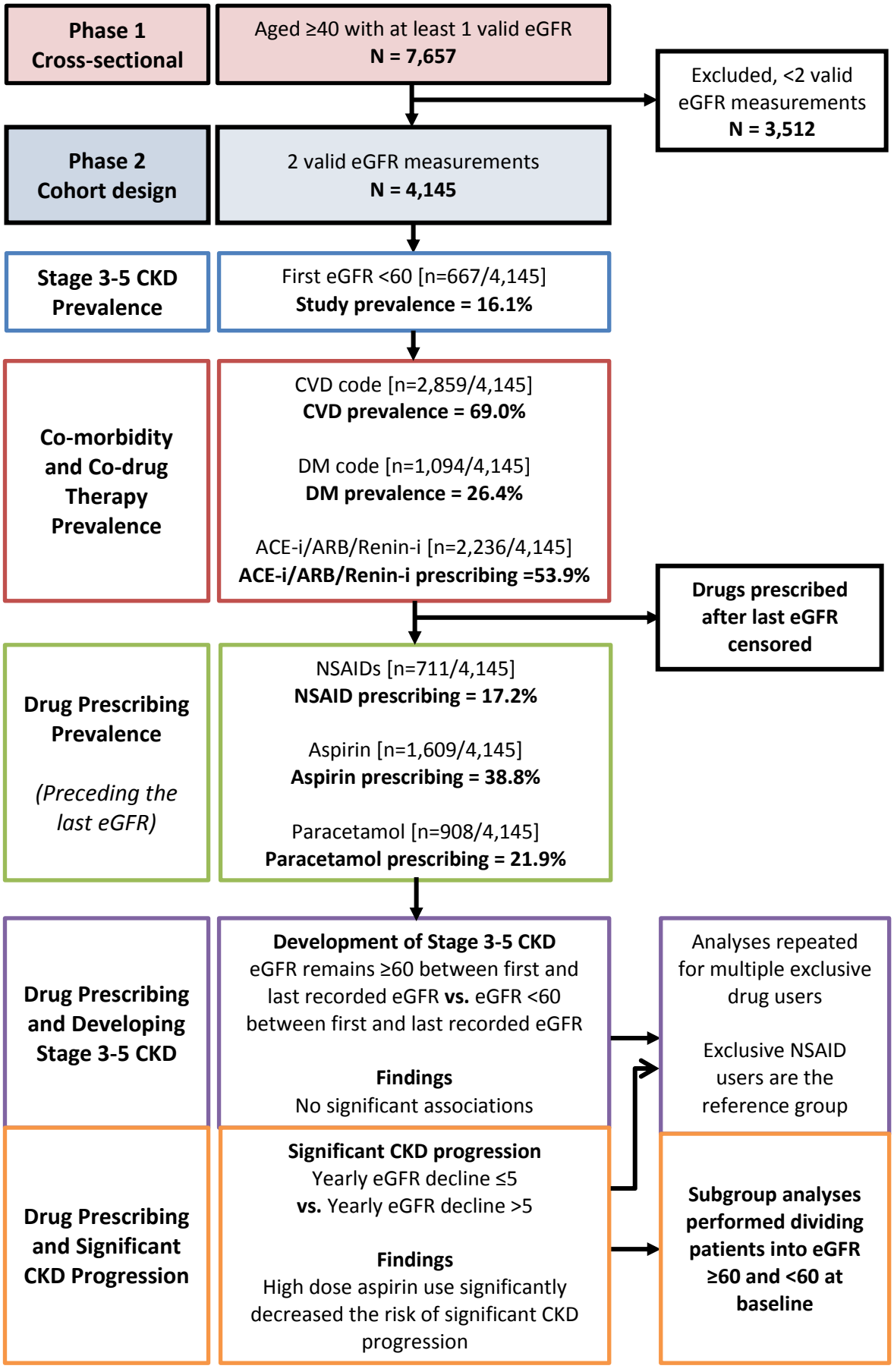


Figure 9.12 Full study flow diagram for the phase 2 cohort design study



- **Phase 2 sample: baseline characteristics**
    - Major baseline characteristic and findings are summarised in the flow diagrams above (**Figure 9.11** - Phase 1 study and **Figure 9.12** - Phase 2 study).
    - Nearly one in five patients in our study had at least two eGFR measurements spaced at least 90 days apart.
    - Phase 2 subjects had similar socio-demographic and baseline renal function characteristics to phase 1. The prevalence of baseline stage 3 to 5 CKD increased exponentially in this cohort as it did in phase 1. However, phase 2 subjects had a higher prevalence of co-morbidity, co-drug therapy, aspirin use and paracetamol use than phase 1 subjects.
    - Similar inter-practice differences were seen in phase 2 with higher deprivation, co-drug therapy and aspirin use in practice I than in practice H. Furthermore, as in phase 1, practice I had a more eGFR tests per individual then practice H. However, the mean testing interval between eGFR measurements was significantly longer in practice I than in H.

- **Drug exposure**
    - Even after censoring prescriptions given after the last eGFR, the prevalence of drug use was high. 17% of phase 2 patients were prescribed NSAIDs, 39% were prescribed aspirin and 22% were prescribed paracetamol before the last eGFR measurement.
    - Although prescriptions were censored at the date of the last eGFR, the doses used were comparable between phase 1 and 2 drug users. Like phase 1, phase 2 subjects were prescribed relatively low doses of NSAIDs or

paracetamol. NSAID users tended to be younger whilst paracetamol users were older. Aspirin use was more evident in the elderly but prescibed doses were equivalent to those seen in phase1.

- **Characteristics of drug users**
    - In this group of patients, NSAID use before the last eGFR decreased with worsening CKD status whilst paracetamol and aspirin use increased. This was identical to the pattern seen in the study group as a whole (phase 1) using all prescriptions given during the study period.
    - Similarly, socio-demographic, other drug use, co-morbidity, co-drug therapy and CKD status characteristics between drug users and non-users remained largely similar between phase 1 and 2 subjects. In phase 2, NSAID users were likely to be younger, female with lower co-morbidity and co-drug therapy compared to non-users. On the other hand, paracetamol users were older, female with higher deprivation, co-morbidity and co-drug therapy. Aspirin users like paracetamol users tended to be older with higher deprivation, co-morbidity and co-drug therapy but were more likely to be male. Although NSAID and paracetamol users had similar eGFR decline rates to non-users, high dose aspirin users were more likely to have renal function improvement than normal dose aspirin users or non-users of aspirin.

- **Drug use and the development of stage 3 to 5 CKD**
    - Single drug use did not significantly increase the risk of developing stage 3 to 5 CKD.

- Multiple drug use was not significantly associated with an increased risk of developing stage 3 to 5 CKD.

- **Factors associated with CKD progression**
  - Older patients (especially males age 60 years and over) had a higher rate of renal function decline than younger patients. The prevalence of drug use was equivalent between significant and non-significant CKD progression groups. Although DM prevalence was not associated with significant CKD progression, the prevalence of several CVD conditions (namely ischaemic heart disease, heart failure and dysrhythmia) were. The prevalence of stage 3 to 5 CKD at baseline was lower in the significant CKD progression group than the non-significant CKD progression group. Moreover, patients with a mildly impaired eGFR at baseline had the highest rate of renal function decline with stage 3 to 5 patients having stable or improving renal function. This suggests that in our study, patients with well-preserved renal function were actually more likely to have faster renal function decline.

- **Drug use and significant CKD progression**
  - Single any NSAID or paracetamol use and normal dose aspirin use were not significantly associated with significant CKD progression. However, high dose aspirin use significantly decreased the risk of significant CKD progression in patients with a normal or mildly impaired eGFR at baseline.
  - Multiple drug use was not significantly associated with an increased risk of significant CKD progression.

Chapter 10. Discussion and Conclusions

This chapter aims to answer the five objectives set out in the beginning of the study. In each section, the results from the cross-sectional study will be contrasted to those from the cohort design study. Both sets of results will then be put into the context of current literature. The strengths, limitations and conclusions including recommendations are presented in each section and relate to each of the study objectives shown below.

1. Describe the characteristics of the CKD population.

2. Estimate the prevalence, dose and patterns of drug prescribing in the CKD population.

3. The association between drug use and stage 3 to 5 CKD.

4. The association between drug use and the development of stage 3 to 5 CKD.

5. The association between drug use and significant CKD progression.

Chapter Plan

- **Characteristics of the CKD population**
    - Socio-demographics.
    - Co-morbidity and co-drug therapy.
    - Strengths and limitations.
    - Conclusions.
    - Recommendations.

- **Drug use among the CKD population**
    - The prevalence and patterns of NSAID use.
    - Factors associated with NSAID use.
    - The prevalence and patterns of aspirin use.
    - Factors associated with aspirin use.
    - The prevalence and patterns of paracetamol use.
    - Factors associated with paracetamol use.
    - Strengths and limitations.
    - Conclusions.
    - Recommendations.

- **Drug use and stage 3 to 5 CKD**
    - Drug use and stage 3 to 5 CKD.
    - Drug use and the development of stage 3 to 5 CKD.
    - Strengths and limitations.
    - Conclusions.
    - Recommendations.

- **Drug use and significant CKD progression**
    - Factors associated with CKD progression
    - Drug use and significant CKD progression
    - Strengths and limitations.
    - Conclusions.
    - Recommendations.

10.1. Characteristics of the CKD Population

10.1.1. Socio-demographic characteristics of the CKD population

10.1.1.1. Renal function testing

This study confirms the availability of CKD staging data within computerised general practice databases. Almost a third of the practice had a recorded eGFR measurement over a two year period and nearly one in five had at least two eGFR measurements spaced at least 90 days apart. The levels of eGFR recording in our study are higher than those reported by de Lusignan *et al*., (2005) who found the rate of single valid serum creatinine measurement to be 25.7%.[38]

10.1.1.2. Practice demographics

This study demonstrated differences occur between CKD patients at the practice level. Phase 1 and 2 results show that practice I had a significantly higher prevalence of deprivation and co-drug therapy compared to practice H. The prevalence of drug prescribing also differed significantly between the two practices in both phase 1 and 2. Moreover, practice I performed more multiple eGFR measurements than practice H but it also had a delayed eGFR testing interval. The differences seen in the deprivation status of practice patients could mean that practice I has more demanding patients. For example, CVD disease has been shown to be higher in more deprived patients.[218] Therefore, it may be the case that practice I patients exert a greater pressure on resources and hence influence both prescribing behaviour and eGFR testing intervals.

10.1.1.3. Gender and CKD status

The female to male ratio in this study matches that reported by other studies[5,31,38] showing a greater preponderance of CKD in females.

10.1.1.4. Study prevalence of stage 3 to 5 CKD

At baseline, the majority of patients had a normal or mildly impaired eGFR, only 13.3% and 16.1% of phase 1 and 2 subjects had stage 3 to 5 CKD respectively. The figures are higher than reported 8.5% population prevalence of stage 3 to 5 CKD by Stevens *et al*.[5] However, the Stoke-on-Trent population has a higher burden of CVD[215] than the rest of the UK and our figures are not age adjusted which explains the difference in CKD prevalence.

10.1.1.5. Age and stage 3 to 5 CKD

It was evident that with increasing age, there was an exponential increase in the proportion of stage 3 to 5 CKD patients both in males and females as shown in the phase 1 and 2 results. The relationship between age and stage 3 to 5 CKD has been reported both in the UK by Stevens *et al*., (2007)[5] who found a similar exponential trend and elsewhere in Europe and the US as presented in the comprehensive systematic review by Zhang *et al*., (2008)[31]. However, previous studies have used single eGFR measurements but our study shows that the relationship between stage 3 to 5 CKD with increasing age is present in patients with multiple eGFR measurements.

10.1.1.6. Deprivation and CKD status

Deprivation was significantly associated with worsening CKD status. The proportion of patients in the least deprived quartile fell by around 13% between the normal eGFR group

and the stage 5 CKD group with an 18% increase in the proportion of patients in the most deprived quartile. Studies in the UK by Bello *et al*., (2006)[91] and Bello *et al*., (2008)[92] and similarly in Sweden by Fored *et al*., (2003)[93] found an increased risk of poor CKD status in patients with a lower socio-economic status. In a review by Shoham *et al*., (2005)[218], several causative mechanisms were suggested for an association between deprivation and disease. Various factors including demographic (age, gender and ethnicity), clinical (HTN, DM and obesity), behavioural (poor diet, smoking and alcohol) and healthcare (access and disease-management) may interact during the patient's life-course to significantly influence renal and co-morbidity outcomes.

10.1.2. Co-morbidity and co-drug therapy amongst Chronic Kidney Disease patients

10.1.2.1. Diabetes and CKD

The burden of co-morbidity was evident within the CKD population. Over 15% of all patients in our study had a diagnosis of DM during the study period. Similar figures have been reported by de Lusignan *et al*., (15.4%)[38], and Stevens *et al*., (10.6%)[5]. In the phase 2 analysis, the prevalence of DM was higher at around 25%. The prevalence of DM increased by over 10% between the normal and stage 5 CKD groups. Likewise, UK studies recruiting both younger and older general practice patients have shown equivalent increases in the prevalence of DM with worsening renal function.[5,38,219]

10.1.2.2. Cardiovascular disease and CKD

Over 50% of all the patients in this study had a diagnosis of CVD over two years increasing to over 66% in phase 2. The proportion of CVD inversely correlated with renal

function being 66% in those with stage 3 to 5 CKD falling to 51% in patients with a normal of mildly reduced eGFR in phase 2. The findings match those reported by studies using general practice data which found comparable prevalence trends between CVD and CKD.[5,38]

Interestingly, the peak prevalence of CVD was in stage 3 CKD patients and declined slightly in stage 4 to 5 patients. This is likely to be a representation of the high risk of mortality in these patients because they are much more likely to die of CVD than they are to progress to stage 5 CKD.[6,191] Moreover, worsening CKD is associated with poorer CVD outcomes[70] and both diseases share many common risk factors[39].

Of the six diseases coded as CVD, HTN was the most prevalent but five out of the six conditions (except peripheral vascular disease) were significantly associated with worsening renal function; a finding reflected in the study by de Lusignan *et al*.[5,38,219]

10.1.2.3. Co-drug therapy and CKD

In line with findings on co-morbidity, it is unsurprising to find that the prevalence of co-drug therapy increased as renal function worsened. Furthermore, NICE guidelines recommend the use of the renoprotective agents in HTN, CKD and DM (with microalbuminuria).[6]

Two out of five patients had at least one prescription for an ACE-i/ARBs/Renin-i during the study period with a higher prevalence of use in the phase 2 subjects (over 50%). Roderick *et al*., (2008) reported comparable levels of anti-hypertensive drug use with worsening renal function in the elderly general practice population.[219]

10.1.3. Strengths and limitations

Our study has shown the availability of rich clinical data that is routinely collected by general practitioners. Given the fact that less than 1% of patients with stage 3 to 5 CKD are aged <35 years old[5], it can be reasonably assumed that the inclusion criteria used allowed the study to capture the majority of the CKD population who had an eGFR measurement during the study period. The study reported on two important co-morbidities and an important renoprotective prescription used in the prevention and attenuation of CKD progression. In addition, CVD was divided into its individual components showing, with greater fidelity, the associations between heart disease and renal disease. Furthermore, the use of the IMD score as a measure of deprivation not only makes the results applicable to the general population but this important finding also highlights the association between socio-demographic factors and renal disease. The use of two unique study designs also showed that patients with multiple eGFR measurements have higher levels of co-morbidity and co-drug therapy compared to the study population as a whole.

It is likely that the true prevalence of stage 3 to 5 disease is even higher due to missed cases with more severe disease who may has been censored given the high mortality[216] in the CKD population (Neyman Bias). Furthermore, patients may be lost to follow-up because of lack of presentation due to the asymptomatic nature of CKD, none attendance to the practice or because they moved to another area and registered at a different practice (Follow-up bias). The use of the MDRD equation, which is used widely in general practice, makes the classification used in our study reflective of real world practice. However, the equation is somewhat inaccurate in eGFRs above 60[22] which could lead to some error in classification in these groups (misclassification bias). There are some limitations to the way deprivation, co-morbidity and co-drug therapy were measured. 171

patients did not have an IMD score but since this makes up just 2.2% of the study sample, it is unlikely to lead to bias. Moreover, ethnicity was not included in the MDRD equation. For a diagnosis of CVD or DM to be recorded in our study, an entry needed to be made during the two year study period by the GP. Therefore, patients may have had CVD or DM but if they were not followed-up, did not attend clinic, died or moved away from the practice, an entry would not be made during the study and thus would be missed. Furthermore, the severity of the CVD or DM was not known. Therefore, associations found in our study do not tell us whether they exist for both mild and severe forms of the diseases. In terms of CVD conditions, some, such as heart failure, may be under-represented possibly due to their late presentation. Finally, the information recorded within the prescription databases is very accurate but it is based on issued and not necessarily collected or consumed drug prescriptions. However, the importance of ACE-i/ARBs/Renin-i in improving renal disease prognosis makes this effect limited.

10.1.4. Conclusions

This study (amongst others) has shown that the CKD population is readily identifiable from general practice records. The study confirms the recognised problem of CKD in the general population and highlights the need for effective disease identification and management strategies.

Age and gender are known to be significant risk factors for CKD. However, an interesting result found by this study is the association between deprivation and CKD. It is know that deprivation can increase the risk of associated risk factors such as obesity, DM and HTN but this study demonstrates that the effects of deprivation may translate to worse renal outcomes. It indicates that deprivation may be a modifiable factor not previously targeted

as a means of improving renal outcomes. Given the results of this and other studies, targeting deprivation may be an effective way of simultaneously reducing a multitude of risk factors to CKD patients.

This study has also shown that the burden of co-morbidity, especially CVD, in marked among patients with renal dysfunction, especially in patients with multiple eGFR tests. It is also clearly demonstrated that the levels of CVD and DM increase as the eGFR declines. This study has shown the important role that co-morbidity plays in the prognosis of CKD patients. The high prevalence of both co-morbid conditions poses a significant risk to CKD progression, multi-morbidity and mortality. However, it is encouraging to see the high prevalence of renoprotective ACE-i/ARBs/Renin-i prescription in such patients which will no doubt reduce the risk. The increasing level of co-drug therapy with decreasing CKD status illustrates the importance of good preventative management if prognosis is to be improved in CKD patients.

10.1.5. Recommendations

Targeting patients from more deprived backgrounds could be an effective way of reducing the risk of developing CKD and decreasing the burden of renal disease in general practice. However, further study is needed in this area to ensure that deprivation is a significant contributor to CKD progression and that is can be effectively targeted to improve renal outcomes.

Given the prevalence and importance of CVD and DM, future studies on CKD progression should include at least the one of the two diseases (if not both) as covariates. Future studies should try and sub-classify the severity of co-morbidity to probe deeper into the

associations between CKD and co-morbidity. The prevalence of co-drug therapy shows that confounders can not only negatively affect the outcome of CKD progression studies but can do so positively as well requiring future studies take this into account.

10.2. Drug Use among the CKD Population

10.2.1. NSAID prescription among Chronic Kidney Disease patients

10.2.1.1. The prevalence and dose of NSAID prescription

NSAIDs were prescribed to a fifth of patients included in our study. In phase 2, the proportion of patients prescribed NSAIDs was lower (17%) because prescriptions in this group were censored at the date of the last eGFR. The majority of NSAID prescriptions were for ibuprofen and diclofenac followed by naproxen and meloxicam. A study by Hawkey *et al*., (2000)[220] found a parallel pattern of NSAID prescription in Nottingham general practices with ibuprofen and diclofenac making up nearly 64% of NSAID prescriptions. Studies have reported estimates ranging from 27% to 48% for the prevalence of NSAID prescription in the CKD population.[112,150-153] Estimates vary because the duration of the studies ranged from six months to two years and the recruited patients were older (mean age ~76 years) than in our study[112,150-153].

Although the prevalence of NSAID prescription was high, the typical patient was prescribed a relatively small dose of NSAID typically over two monthly prescriptions during the two year study period. Equally, the vast majority of patients in the study by Gooch *et al*., (2007)[150] also had very limited NSAID exposure. Furthermore, the distribution of NSAID use was remarkably similar between our study and the study by

Gooch *et al*[150]. However, as in the Gooch *et al.*,[150] study, there was a minority of high dose NSAID users. Similarly, the top 15% of NSAID users in our study sample were prescribed substantial amounts of the drug. On average, the typical high dose NSAID users were given 720 DDDs, equivalent to around 1 DDDs per day, during the 2 year period. High dose users in phase 2 were prescribed even higher doses and on average they were given 1.21 DDDs per day.

10.2.1.2. Patterns of NSAID prescribing

Age was inversely related to NSAID use in both normal and high dose users. In the study sample, the percentage of NSAID users was 26% lower in the oldest age group (≥80 years) compared to the youngest age group (40-49 years). NSAID use also decreased dramatically as the eGFR decreased in both phase 1 and phase 2 patients. The proportion of NSAID users was especially low amongst stage 4 and 5 CKD patients with only 3.3% and 5.9% of normal dose users respectively and no high dose users in phase 1. Promisingly, these findings suggest that physician prescribing patterns changed according to both the renal function and age of patients minimising the risk not only of possible renal complications but of gastrointestinal complications as well. This is in contrast to a US study by Plantinga *et al*., (2011) who report that the prevalence of regular NSAID use increased with worsening CKD status. [164] Our findings also differ to those by Quartarolo *et al*., (2007) who found that eGFR reporting did not lead to a significant decrease in the proportion of patients prescribed NSAIDs.[221]

10.2.2. Significant factors related to the use of NSAIDs

10.2.2.1. Socio-demographic factors

NSAID users were younger and were significantly more likely to be female (not significant in phase 2) than NSAID non-users but deprivation did not differ between these two groups. Sun *et al*., (2004) also reported that females are more likely to be prescribed NSAIDs than males.[112]

10.2.2.2. Other drug use

One in five NSAID users also had a prescription for paracetamol (25% in phase 2); a similar proportion of non-users of NSAIDs were prescribed paracetamol. However, there were significantly more paracetamol users in the high dose NSAID user group than in the normal dose NSAID or non-NSAID user groups. This may represent a group of patients with poor pain control necessitating aggressive multiple, high dose analgesic therapy to manage their symptoms. Aspirin use was lower in NSAID users than in non-users of NSAIDs. This is probably related to the lower prevalence of CVD in the NSAID user group.

10.2.2.3. Co-morbidity and co-drug therapy

In general, NSAID users had significantly lower levels of co-morbidity and co-drug therapy than non-users. This is likely to be related to the fact that NSAID users were younger and more likely to be female hence had lower levels of co-morbidity (especially CVD) and co-drug therapy.

10.2.2.4. Renal function testing interval

In phase 2, to test whether NSAID users were more or less frequently followed up, the average time interval between eGFR tests was calculated. This testing interval was roughly equivalent (just under 300 days) in both NSAID users and non-users with two or more eGFR tests. This time interval is promising as it was below the recommended annual screening time for NSAID users advocated by NICE.[6]

10.2.2.5. CKD status and CKD progression

The prevalence of stage 3 to 5 CKD at the last eGFR measurement was actually lower amongst NSAID users than non-users. However, this finding is related to the fact that fewer patients with stage 3 to 5 CKD were prescribed NSAIDs.

The rate of eGFR decline per year did not differ significantly between NSAID users and non-users in phase 2. As CKD progression was not be as affected by NSAID prescribing, it suggests that NSAIDs may not be associated with renal function decline but other confounding factors may be at play.

10.2.3. Aspirin prescription among Chronic Kidney Disease patients

10.2.3.1. The prevalence and dose of Aspirin prescription

Nearly a third of all included patients were prescribed aspirin during the study period. Aspirin was prescribed on a regular basis with the typical patient having 14 prescriptions over two years. In phase 2, the proportion of aspirin users was higher (39%) despite prescriptions given after the last eGFR being disregarded. This may reflect the higher levels of CVD in these patients. Although the definitions of "use" vary widely in the

literature and few studies report on the prescription of aspirin in general practice, our study findings reflect those reporting on regular aspirin use (both self-reported and prescribed)[15,141,149,161]. The proportion of regular aspirin users in these studies ranged from around 30% and approached 50% amongst stage 3 to 5 CKD patients.[15,141,149,161]

Typically, an aspirin user would be given 588 DDDs during a two year period. In phase 2 the DDDs given (476) was lower as would be expected given the shorter exposure period. The typical "high dose" aspirin user had around 1.23 DDDs per day (1.44 DDDs per day in phase 2). Therefore, although labelled as high dose users, in reality, the dose taken by these patients per day would be around 1.23 * 0.075 = 92*mg* (108*mg* in phase 2) which actually falls within the low-medium dose category in the clinical setting.

10.2.3.2. Patterns of Aspirin prescribing

The level of aspirin use increased dramatically both with increasing age and worsening CKD status. Between the youngest and oldest age groups, the proportion of aspirin users increased by 40%, a pattern echoed in phase 2. Equally, the number of aspirin users was 15% higher in stage 3 to 5 CKD patients compared to patients with a normal or mildly reduced eGFR with equivalent differences seen in phase 2. The increase in aspirin use is likely due to an increase in the level of CVD in these patients. The increase in CVD is due to the increasing age and worsening renal function which are both associated with CVD. Since aspirin use is beneficial in reducing the risk of major CVD events, it is likely that this reason for the observed patterns. Interestingly, studies have suggested that the effectiveness of aspirin may increase as renal function decreases meaning the patterns observed in this study could hold added benefits.[116]

10.2.4. Significant factors related to the use of Aspirin

10.2.4.1. Socio-demographic factors

Aspirin users were older than non-users and unlike NSAIDs, were more likely to be male. Moreover, aspirin users were more likely to be in a more deprived quartile, a trend that was also seen with increasing aspirin dose. It may be the case that risk factors for diseases such as CVD are more common in deprived patients[218], therefore, stratifying by the treatment for such diseases (e.g. aspirin) will also result in a picture of greater deprivation in drug users.

10.2.4.2. Other drug use

Aspirin users were significantly less likely to also be prescribed NSAID than non-users. The inverse was true in relation to paracetamol with a higher proportion of paracetamol users in the aspirin user group than in the non-user group. Aspirin users were older than their non-user counterparts. Consequently, they were more likely to be prescribed paracetamol and were less likely to be prescribed NSAIDs as shown earlier (see **Figure 8.6 and 8.8**).

10.2.4.3. Co-morbidity and co-drug therapy

Patients prescribed aspirin had significantly higher levels of co-morbidity than non-users of aspirin. Aspirin is given in CVD for thromboprophylaxis thus it is unsurprising to find that CVD is higher amongst the aspirin user group. DM shares common risk factors with CVD (e.g. obesity) and can also accelerate atherosclerosis worsening CVD. This may explain the higher proportion of diabetics in the aspirin user group. The prescription of ACE-i/ARBs/Renin-i was also higher in the aspirin user group. This is unsurprising given

the use of these drugs in the treatment of both HTN and microalbuminuria which are associated with CVD and DM respectively.

10.2.4.4. Renal function testing interval

The mean eGFR interval did not differ between users and non-users of aspirin. However, the mean testing interval was slightly earlier amongst aspirin users than in NSAID users. This may be due to the older age and higher level of co-morbidity in aspirin users compared to NSAID users requiring that they have closer follow-up.

10.2.4.5. CKD status and CKD progression

The prevalence of stage 3 to 5 CKD at the last eGFR measurement was higher in the aspirin user group than in non-users. This is probably due to the increased age and burden of co-morbidity in these patients.

Although the rate of eGFR decline did not differ significantly between any aspirin users and non-users, stratifying use by dose showed that high dose aspirin users had a significantly different distribution of eGFR decline rates. High dose aspirin users were less likely to have CKD progression than normal dose aspirin users or non-aspirin users. Given the equivalent characteristics between the normal and high dose user groups, it is less likely that this a confounding effect thereby suggesting a renoprotective action of ‘high’ aspirin.

10.2.5. Paracetamol prescription among Chronic Kidney Disease patients

10.2.5.1. The prevalence and dose of Paracetamol prescription

Like NSAIDs, paracetamol was prescribed to around one in five patients in our study. Few studies have reported on the prescription of paracetamol in CKD patients. However, Evans *et al*., (2008) reported that 25% of patients with stage 4 to 5 CKD had a history of regular self-reported paracetamol use during their lifetime.[149] Equally, Fored *et al*., (2001) found that 16% of the study participants had reported having regular paracetamol during their lifetime.[15]

Similar to NSAIDs, patients prescribed paracetamol had relatively few DDDs of use. Moreover, as in the NSAID group, there was a minority of patients who were prescribed high doses of paracetamol. High dose paracetamol users consumed around 433 DDDs, equal to 1,300 grams (1,143 grams in phase 2) over the two year period. This would be comparable to approximately 2g of paracetamol use per day over a two year period.

10.2.5.2. Patterns of Paracetamol prescribing

The relationship between age and the proportion of paracetamol users was the inverse of that seen in NSAID users. With increasing age, the proportion of paracetamol use increased significantly (by nearly 40%) between the youngest and oldest age groups with a similar pattern in phase 2 patients. In addition, the proportion of paracetamol users also increased with worsening CKD status, increasing by 16% between the normal or mildly impaired eGFR group and stage 3 to 5 CKD patients; a comparable increased (11%) was evident amongst the phase 2 patients. There are several possible explanations for the observed patterns of paracetamol prescribing. CKD patients are often less likely to be

prescribed analgesia compared to other patients[222], with 35% of patients on haemodialysis not being given any analgesia[222]. The altered pharmacokinetics, possible adverse side effects (especially NSAIDs) and co-morbidity are some of the reasons for decreased prescribing.[222] However, paracetamol is considered the analgesic of choice for mild to moderate pain in CKD patients.[222] Therefore, it is likely that these factors (alongside the risk of gastrointestinal side effects with advancing age with regard to NSAID use) are the driving force behind the decreasing prescription of NSAIDs with age and worsening CKD and the concurrent increase in paracetamol prescription. This illustrates the need for a better understanding of the effects of paracetamol on the CKD population given its increasingly important role as an alternative simple analgesic.

10.2.6. Significant factors related to the use of Paracetamol

10.2.6.1. Socio-demographic factors

Paracetamol users were significantly older than non-users and were more likely to be female. Paracetamol users were also more likely to be more deprived than non-users. There is a possible link between deprivation and paracetamol use. Studies have reported that pain is reported more frequently in people with higher deprivation and that the experience of pain is also greater.[223,224] Therefore, since paracetamol is used as a simple analgesic for many painful disorders, it may be the case that deprived patients have a stronger experience of pain hence they take more medication to help them cope with the symptoms.

10.2.6.2. Other drug use

In phase 1 patients, concomitant NSAID use was similar between paracetamol users and non-users (not in phase 2 where they were significantly higher proportions of NSAID

users). However, there were more patients with aspirin use in the paracetamol user group than in the non-user group in both phase 1 and 2 patients, possibly related to the level of CVD and the increased age of paracetamol users compared to non-users.

10.2.6.3. Co-morbidity and co-drug therapy

Similar to the picture in aspirin users, paracetamol users had higher levels of DM and co-drug therapy possibly related to the fact that paracetamol users were significantly older than non-users. The levels of CVD were however comparable between paracetamol users and non-users.

10.2.6.4. Renal function testing interval

Surprisingly, the interval between eGFR tests was significantly shorter in paracetamol users than in non-users. Moreover, the testing interval was shorter than the NSAID or aspirin user groups despite the disease profile of paracetamol users being less severe than in the aspirin user group.

10.2.6.5. CKD status and CKD progression

The prevalence of stage 3 to 5 CKD at the last eGFR was higher in paracetamol users than non-users. This is probably related to the age and co-morbidity status of these patients and not necessarily to the use of paracetamol.

The rate of eGFR decline did not vary significantly between paracetamol users at any dose and non-users re-enforcing the notion that paracetamol use may not be associated with renal dysfunction.

10.2.7. Strengths and limitations

A major strength in this study is the use of an internationally recognised, externally validated, standardised drug dose measure to describe the prescription patterns of NSAIDs, aspirin and paracetamol amongst general practice patients. The DDD allowed for comparable comparisons between different classes of drugs but also allowed the doses of drugs to be added together. For example, a patient given ibuprofen at 1.2 grams and diclofenac at 0.1 grams would have a cumulative NSAID use of just 1.3 grams but with the DDD system, the two doses are equal to 1 DDD resulting in a cumulative DDD of 2 which is more representative of what the patient actually took. Furthermore, the use of the DDD not only allowed equivalent drug comparisons but it was also possible to convert the measure back into grams for the drug in question. This study has also helped validate the effectiveness of the cut-off values set out by Gooch *et al.*, (2007) as a means of accurately categorising normal and high dose NSAID users.[150] Moreover, their study only included users of NSAIDs, but in this study, we have been able to apply the methodology to paracetamol and aspirin users and show the efficacy of the approach in categorising users of these drugs as well. Finally, we have explored in detail the dose and patterns of drug prescribing as well as characteristics of drug users amongst the CKD population. To the best of my knowledge, our study is the first to show the contrasting patterns of NSAID and paracetamol prescribing in general practice.

The limitation of using prescription data is that OTC drug use is not captured in our study. However, the study aims were to investigate the effects of prescribed drugs on renal function and any positive findings would not doubt have implications for OTC use. Although the prescription data used in this study is accurate, it is based on issued prescriptions but there is no guarantee that they were collected or the drugs were

consumed. On the other hand, because the included drugs are given for chronic, painful musculoskeletal conditions (in the case of NSAIDs and paracetamol) or prophylactically to prevent potentially life threatening cardiovascular events (in the case of aspirin), the problem of non-compliance is likely to be limited.

10.2.8. Conclusions

This study has found that NSAIDs, aspirin and paracetamol are prescribed frequently to CKD patients. However, the dose and patterns of drug prescription are very different. This study shows that generally, NSAIDs (mainly diclofenac and ibuprofen) are given to younger patients with well-preserved renal function but as the age increases and the CKD status worsens, these patients are increasingly prescribed paracetamol instead. Aspirin prescription on the other hand is linked to the level of CVD which increases with age, deteriorating CKD status and co-morbidity.

By dividing patients into different dose groups, this study has also found that NSAIDs and paracetamol are prescribed at relatively low doses but a small group of patients are prescribed significantly higher dose of the drugs.

The characteristics of patients in each of the three drugs groups are vastly different. The results demonstrate that factors commonly linked with drug prescribing (such as CVD and aspirin) are also present in the CKD population. However, the results also show that other factors, such as deprivation (in the case of aspirin and paracetamol), may also be associated with drug prescription by a range of possible mechanisms (for example co-morbidity or pain perception). Finally, issues of multiple drug use are raised because it clear that many CKD patients take more than one drug that may be detrimental to renal function.

10.2.9. Recommendations

Given the strengths of the DDD measure in comparing the effects and doses of NSAIDs, aspirin and paracetamol, future studies in this area should employ similar methodologies to improve inter-study comparisons and formulate a consistent evidence base. Future studies should also investigate what, if any, patient factors influence the prescription of drugs in the CKD population. Finally, an evaluation of OTC and prescription use is required to evaluate the relative proportions of drug intake from the two sources.

10.3. Drug Use and Chronic Kidney Disease

10.3.1. Drug use and stage 3 to 5 Chronic Kidney Disease at the last eGFR

10.3.1.1. Single drug use and stage 3 to 5 CKD

In this study, single drug use at any dose was not significantly associated with stage 3 to 5 CKD at the last eGFR measurement. These findings are in agreement with those by Rexrode *et al*., (2001) who found that NSAIDs, aspirin or paracetamol use were not significantly associated with a reduced creatinine clearance (<55ml/min).[139] Likewise, Agodoa *et al*., (2008) found no association between NSAID or aspirin use and a reduced eGFR (<60ml/min/1.73m^2).[148] Furthermore, Stümer *et al*., (2001) found no significant association between NSAID use and a reduced creatinine clearance of <60ml/min.[144] However, Fored *et al*., (2001) found that patients with advanced renal disease (stages 4-5) had significantly higher levels of aspirin and paracetamol use.[15] Sandler *et al*., (1989) also reported a significant association between paracetamol use and chronic renal disease (defined as a serum creatinine ≥130μmol/l).[141] In addition, a similar study by Sandler *et al*., (1991) found a significant association between NSAID use and chronic renal disease

(defined as a serum creatinine ≥130μmol/l) in males aged ≥65 but not in younger males or females.[140] There are several reasons for the differences in findings. The Fored *et al*., case-control study had patients with more advanced renal failure and had different definitions of drug use than our own study.[15] Equally, Sandler *et al.*, (1989) a case-control study, used serum creatinine as the measure of renal function, had different measures of drug use and adjusted for different variables in their analysis compared to this study.[141] Similarly, the study by Sandler *et al*., (1991) another case-control study, not only used serum creatinine as the measure of renal function but it also had very low numbers of patients or controls who actually used NSAIDs on a regular basis.[140] Only 28 patients and 13 controls actually used NSAIDs in the whole study and only 14 patients and 1 control in the ≥65 years males group where a significant association was reported actually had regular NSAID use resulting in an inaccurate estimate of association; OR= 16.6 (95%CI; 2.1 to 129).[140] On the whole, more recent evidence using better measures of renal function have begun to consistently show that single NSAID, aspirin or paracetamol use is not associated with stage 3 to 5 CKD, in concordance with the results of this study.

10.3.1.2. Multiple drug use and stage 3 to 5 CKD

In our study, multiple drug use was not significantly associated with stage 3 to 5 CKD at the last eGFR when compared to single NSAID use. However, the estimates for combined NSAID and paracetamol use as well as aspirin and paracetamol use came close to reaching statistical significance. There are few published studies reporting on the effects of multiple drug use on renal function. In addition, the published evidence in this area is conflicting with varying exposure and outcome measures. Fored *et al*., (2001) reported a significantly increased risk of advanced renal failure (stage 4-5 CKD) with aspirin and paracetamol use when compared to aspirin use alone but not when compared to exclusive paracetamol

use.[15] In contrast, van der Woude *et al*., (2007) found no significant association between any combinations of phenacetin-free analgesics (NSAIDs, aspirin and paracetamol) and ESRD in young patients.[146] The variability in the study methodologies and definitions of exposure and outcome make it difficult to make any meaningful comparisons between our studies and those by Fored *et al*.,[15] and van der Woude *et al*[146].

10.3.2. Drug use and the development of stage 3 to 5 CKD

10.3.2.1. Single drug use and the development of stage 3 to 5 CKD

In this study, single drug use at any dose was not significantly associated with the development of stage 3 to 5 CKD. The findings are mirrored by studies by Curhan *et al*., (2004) and Kurth *et al*., (2003) who reported on the risk of a GFR decline of 30 ml/min/1.73m^2 over 11 years in women and 29 ml/min/1.73m^2 over 14 years in men respectively.[128,132] Both studies found no significantly increased risk of eGFR decline with drug use. However, very high paracetamol use (>3000g) was associated with an increased risk of developing stage 3 to 5 CKD in the Curhan *et al*., study[128] but not in the Kurth *et al*., study (at ≥2500g)[132]. On the other hand, Hippisley-Cox and Coupland (2010) found that patients without pre-existing CKD prescribed two or more NSAIDs were significantly more likely to develop stage 3B CKD than non-users.[152] However, this study was not primarily designed to investigate the association between NSAID use and CKD[152] and as such did not adjust for the same confounders as our study or the studies by Kurth *et al*., and Curhan *et al*.[128,132] Overall, studies designed to investigate the association between drug use and the development of stage 3 to 5 CKD have found no significant association, in agreement with our own findings.

10.3.2.2. Multiple drug use and the development of stage 3 to 5 CKD

Multiple drug use was not associated with a significantly increased risk of developing stage 3 to 5 CKD. However, the estimate for NSAID and paracetamol use suggested a possibility that this combination may affect renal function decline. No other studies have reported on the effects of multiple drug use and the decline of renal function levels equivalent to stage 3 to 5 CKD. However, given the possibility of an association, and the concordance of results between the phase 1 and 2 findings, further study into the effects of multiple drug use on renal function decline is warranted.

10.3.3. Strengths and limitations

The study findings support a growing body of recently published evidence showing that NSAID, aspirin or paracetamol use is not significantly associated with stage 3 to 5 CKD either as a cross-sectional association or in the development of the disease. The effects of multiple drug use are not well researched but our study begins to probe into the effects of multiple drug use and renal function revealing potentially detrimental effects. The use of computerised database data enabled the use of both a cross-sectional and cohort design to be employed in one study. This allowed two distinct outcomes related to stage 3 to 5 CKD to be formulated; (i) comparing patients with and without stage 3 to 5 CKD at the last eGFR measurement and relating this back to drug use and (ii) comparing patients who previously had a normal or mildly impaired eGFR who then developed stage 3 to 5 CKD during the study period with those who did not and linking this back to drug use. Therefore, although the two hypotheses test different associations, the level of concordance between the results shows the effectiveness of the methods used. Finally, the outcome of

stage 3 to 5 CKD is an important clinical outcome associated with increasing co-morbidity and mortality making our results relevant and meaningful to clinical practice.

As mentioned previously, our study did not measure the degree of OTC use. Therefore, although drug prescriptions were not associated with an increased risk of renal disease, our study may underestimate the effect of drug use as only some of the drug doses are captured. In addition, CKD patients are more likely to die than to progress to stage 5 CKD in which case they would lack an eGFR measure and therefore would either be completely censored from our study or would not have a second eGFR measurement and in either case, this would lead to an under-representation of stage 3 to 5 CKD patients. There is a small risk that symptoms associated with worsening renal function (especially at the advanced stages) may lead to an increase in the amount of drug use. However, the majority of patients in this study had mild disease limiting this effect. Although the overall sample size of patients included in our study is large, given the definition of high dose use ($\geq 85^{th}$ percentile), the number of high dose users may be insufficient to clearly demonstrate a statistically significant result. Moreover, only 223 patients actually developed stage 3 to 5 CKD during the study period and most patients had fairly stable renal function. Furthermore, the study period of two years may not be long enough to detect changes in renal function with long term drug use. Although the MDRD is widely used to estimate the GFR, it can be less accurate when the GFR is >60ml/min/1.73m^2.[22] Computerised general practice data is reliant on accurate data entry and sufficient patient follow-up by the GP in order to be valid. However, the CiPCA and PiPCA databases have been shown to be of a high quality minimising the risks of incomplete data and errors.[225] Finally, cross-sectional associations are liable to the effects of bias but using a cohort design study to look at

disease progression minimised this source of bias and allowed effect estimates on a similar outcome from two study designs to be compared.

10.3.4. Conclusions

Normal or high dose drug use (NSAIDs, aspirin or paracetamol) over a two year period was not associated with a significantly increased risk of having or developing stage 3 to 5 CKD. Compared to single NSAID use, multiple drug use was not significantly associated with an increased risk of having or developing stage 3 to 5 CKD.

10.3.5. Recommendations

Overall, the study has used robust epidemiological methods and critical statistical analysis to demonstrate that over a two year period, normal or high dose drug use is not associated with stage 3 to 5 CKD. Therefore, where indicated, the prescription of single NSAIDs, aspirin or paracetamol at the lowest effective dose may be given over a two year period in patients with well-preserved renal function without a significantly increased risk of developing stage 3 to 5 CKD.

Future studies should recruit more patients and study the effects of drug use over a 5 to 10 year period to evaluate the long term safety of drug use. The limited number of studies on the association between multiple drug use and renal dysfunction requires that further study is performed to form a more consistent evidence base.

10.4. Drug Use and Significant CKD Progression

10.4.1. Factors associated with significant CKD progression

10.4.1.1. Prevalence of significant CKD progression

A clinically important outcome was whether patients had an eGFR decline rate of >5ml/min/1.73m^2 per year, defined by NICE as significant renal decline that would be of concern to clinicians.[6] A noteworthy proportion of patients (26.5%) had significant CKD progression over a two year period. However 29.1% of patients did not experience any eGFR decline and 25.9% had at least some improvement in renal function. The mean eGFR decline rate in our study (2ml/min/1.73m^2 per year) was lower than that reported in the MDRD study (1997) (mean decline rate 4ml/min/1.73m^2 per year)[75] but matched closely with estimate by Eriksen and Ingebretsen (2006) (eGFR decline of 1ml/min/1.73m^2 per year).[76]

10.4.1.2. Socio-demographic factors and significant CKD progression

There were important differences between patients with significant CKD progression and those without. Demographically, patients with significant CKD progression were significantly older but the gender and deprivation status did not vary significantly. On the other hand, the median rate of eGFR decline per year was faster with increasing age, especially in males aged over 60 (**Figure 9.9**). This coincides with findings by Eriksen and Ingebretsen (2006) who found that older stage 3 CKD patients had a faster mean eGFR decline rate than younger patients and that males also had a faster rate of eGFR decline than females.[76]

10.4.1.3. Prevalence of drug use and significant CKD progression

There were no significant differences in the prevalence of drug use before the last eGFR between patients with significant and non-significant CKD progression. This supports the previous findings showing a lack of association between drug use and renal function decline.

10.4.1.4. Co-morbidity, co-drug therapy and significant CKD progression

The levels of overall co-morbidity and co-drug therapy did not vary significantly between the two CKD progression groups. However, dividing CVD into individual conditions, it was clear that the prevalence of ischaemic heart disease, heart failure and dysrhythmia were significantly higher in patients with significant CKD progression. This may indicate that these CVD pathologies are the important drivers of renal function decline. As to why classical CKD progression risk factors such as DM and HTN seemed not to be associated with renal function decline; our study did not distinguish well controlled disease from poorly controlled disease which may explain the lack of significant findings. Furthermore, the disease duration was not known in either condition as our study only measured the presence or absence of disease.

10.4.1.5. Renal function testing interval and significant CKD progression

The interval between the first and last eGFR were the same between the significant and non-significant CKD progression groups which may indicate that although outcomes were different between the two groups, they both had a similar period of follow-up.

10.4.1.6. Baseline CKD status and significant CKD progression

Surprisingly, the prevalence of stage 3 to 5 CKD at baseline was lower in patients with significant CKD progression compared to patients with non-significant CKD progression. This finding was supported when the median eGFR decline rate per year was used as the continuous outcome measure. As shown in **Figure 9.10**, patients with a mildly impaired eGFR at baseline had the fastest rate of renal function decline of all the CKD status groups. The inverse picture was true for patients with stage 3 to 5 CKD at baseline who had renal function improvement being especially marked in females with stage 5 CKD. These findings are similar to those published by Gooch *et al*., (2007) who found that rapid CKD progression occurred mainly in a subgroup of NSAID users who had an eGFR of 60-89ml/min/1.73m^2 at baseline.[150] Again, this may suggest that patients with better renal function are more likely to have significant CKD progression and hence an effect of drug use was easier to observe in these individuals. A possible explanation for the findings is that patients with stage 3 to 5 CKD are more likely to have better preventative interventions due to disease recognition and the occurrence of symptoms than patients with well-preserved renal function. This would leave any underlying co-morbidities to cause more marked renal function decline in patients with well-preserved renal function than in the better controlled stage 3 to 5 CKD group.

10.4.2. Drug use and significant CKD progression

10.4.2.1. Single drug use and the risk of significant CKD progression

Single NSAID or paracetamol use at any dose was not significantly associated with significant CKD progression over a two year period. Several studies have found that

normal dose NSAID use is not associated with the progression of CKD. Studies by Yarger *et al*., (2011)[153], Gooch *et al*., (2007)[150] and Hemmelgarn *et al*., (2006)[151] found no significant association between normal dose NSAID use and a rapid eGFR decline of ≥15ml/min/1.73m^2 over a two and a half year period. Equally, the systematic review and meta-analysis based on these studies (*see chapter 6*) reached the same conclusion. However, Gooch *et al*., (2007)[150] also reported that high dose NSAID users were significantly more likely to have rapid CKD progression than non-users. This was not the case in the Yarger *et al*., (2011)[153] study, although the estimate did indicate a possible association; OR= 1.276 (95%CI; 0.844-1.927). This is supported by the systematic review (*chapter 6*) which found an increased risk of accelerated CKD progression in the pooled estimate. Differences between our study and the aforementioned studies are that they both had a larger sample size than our own (10,184 and 34,925) and included older patients (mean age ~75 years).[150,153] Moreover, the definition of high dose was not made clear in the Yarger *et al*., study.[153]

In relation to normal dose paracetamol use, although varying in the definition of "normal dose", Evans *et al*., (2009) found that regular paracetamol users had a significantly slower eGFR decline rate per year compared to none users of the drug. Even amongst users with ≥3000g of paracetamol use, there was no association between use and faster eGFR decline rates.[149] This correlated with our study findings showing no association between paracetamol use and significant CKD progression.

Normal dose aspirin use did not significantly affect the risk of significant CKD progression. However, high dose aspirin use significantly decreased the risk of significant CKD progression during the two year period. Furthermore, on stratification by the baseline

eGFR, it was apparent that the effect was present in patients with normal or mildly impaired eGFR measurements but not in stage 3 to 5 CKD patients. The result is in concordance with similar findings by Evans *et al*., (2008)[149] who reported a slower decline in renal function amongst aspirin users and Kurth *et al*., (2003)[132] who reported that aspirin users without CVD risk factors were significantly less likely to have CKD progression. However, our study also found that the subgroup of patients where aspirin seemed to have a renoprotective effect was in patients with an eGFR ≥60ml/min/1.73m^2. This differed from the Evans *et al*., study where the observed renoprotective effect was in patients with stage 4-5 CKD.[149] On the other hand, Evans *et al*., used a different outcome measure (they reported on the difference in the β co-efficients).[149] Finally, in our study, only 312 patients with stage 3 to 5 CKD had any aspirin use which may have limited the power to detect an effect in this group.

10.4.2.2. Multiple drug use and the risk of significant CKD progression

Multiple drug use was not significantly associated with significant CKD progression. It is unclear why there was a difference in estimates for the risk of developing of stage 3 to 5 CKD and the risk of significant CKD progression in relation to the NSAID and paracetamol group. One explanation is that patients featured in the development of CKD analysis had a normal or mildly impaired eGFR at baseline whilst those featured in the significant CKD progression analysis could have had any of the 5 CKD groups. Therefore, given the overriding picture of greater eGFR decline in patients with normal or mildly impaired eGFR, it may have been easier to detect the change in the development of CKD analysis but not in the significant CKD progression analysis.

10.4.3. Strengths and limitations

The phase 2 results show that single drug use and renal function decline are not significantly associated. Furthermore, the study also explored the effects of multiple drug use on CKD progression adding to the limited evidence base. The outcome measure used (eGFR decline rate of >5ml/min/1.73m^2 per year) is not only clinically relevant but it is based on national UK NICE guidelines.[6] The study has expanded upon the methodologies used for measuring CKD progression by calculating the rate of eGFR decline per year for each patient and using this as the basis for a clinically relevant outcome. Phase 2 subjects had two eGFR measurements placed at least 90 days apart ensuring that stage 3 to 5 CKD was correctly categorised and excluded patients with probable acute renal decline. Finally, using a cohort design and available computerised general practice data, this study has explored the determinants of CKD progression using available covariates and investigated the strength of association between NSAID, aspirin or paracetamol prescription and the clinically important outcome of significant CKD progression.

There are however, some limitations to this part of the study. The eGFR decline rate was calculated using just the first and last eGFR discounting the data recorded between these two points. This makes the outcome more sensitive to relative changes in the values of the first and last eGFR. As mentioned previously, the sample size, study duration, eGFR measurements above 60 and patient censoring could affect the results leading to an underestimation of the true effect of drug use on CKD progression. Although the most common factors that lead to CKD progression were adjusted for, there is a small risk that if the indication for drug use (e.g. gout) was associated with an increased risk of CKD progression, this would lead to confounding and risk overestimation but since our results are not significant; this is unlikely to be the case. However, in our study we did not adjust

for proteinuria or diuretic use. Finally, the number of patients in the high dose user groups with stage 3 to 5 CKD was limited for each of the three drugs.

10.4.4. Conclusions

Normal and high dose NSAID or paracetamol use was not significantly associated with an increased risk of significant CKD progression over two years. Normal dose aspirin use over two years was not significantly associated with significant CKD progression. However, high dose aspirin use over two years significantly decreased the risk of significant CKD progression in patients with a normal or mildly impaired eGFR. Multiple drug use was not significantly associated with CKD progression. Age (>60 years), male gender, a mildly impaired eGFR, ischaemic heart disease, heart failure and dysrhythmia are some of the main determinants of CKD progression.

10.4.5. Recommendations

We have found no evidence that drug use is associated with significant CKD progression over a two year period. However, the lowest effective dose of these drugs should be given as they also have systemic side effects and the long term effects are not known.

Future studies should improve upon the measures of eGFR decline by fitting a regression line to all the data points. Further exploration of the effects of aspirin use on renal decline is required to ascertain its significance. A 5 or 10 year study period with a more substantial sample group would be better suited to evaluating the safety of chronic drug use because renal decline may not become evident over the two year period reported in this study. Finally, the effects of multiple drug use on CKD progression should be studied in greater detail.

10.5. Chapter Summary

- **Characteristics of the CKD population**
    - CKD is easily identifiable using computerised general practice records. Stage 3 to 5 CKD status is associated with increasing age, female gender and deprivation.
    - The burden of co-morbidity and co-drug therapy is high in the CKD population and increases in patients with multiple eGFR measurements. Additionally, co-morbidity and co-drug therapy increases with worsening CKD status.
    - **Strengths**: The use of efficient inclusion criteria. The use of rich general practice data including important co-morbidity and co-drug therapy covariates. The sub-classification of CVD into six disease groups. Generalizability of findings back to clinical practice.
    - **Limitations**: Patient censoring, CKD misclassification and the risk of incomplete data.
    - **Recommendations**: A better understanding of co-morbid disease severity and duration is required.

- **Drug use among the CKD population**
    - One in five patients was prescribed a NSAID during the study period. Most were given relatively small doses of NSAIDS. However, a small group of patients were prescribed substantial amounts of the drug. The prevalence of NSAID prescribing decreased with age and worsening renal function.

- Compared to non-users, NSAID users were more likely to be younger, female with less co-morbidity, co-drug therapy and with better renal function.
- Almost one in three study subjects were prescribed aspirin over two years. Most patients were given therapeutic doses of aspirin. Even patients categorised as 'high dose' users actually had modest daily aspirin use. Aspirin prescription increased with age and decreasing CKD status.
- Aspirin users were more likely to be older, male, more deprived with higher levels of co-morbidity (especially CVD), co-drug therapy and poorer renal function than non-users. High dose aspirin users were less likely to have renal function decline than normal dose aspirin users or non-aspirin users.
- One in five of the included subjects were prescribed paracetamol over two years. Most were given low doses of the drug during that time but a small group of patients had substantial amounts paracetamol prescribed. The prevalence of paracetamol prescribing increased with advancing age and decreasing renal function.
- Paracetamol users were more likely to be older, female, more deprived with higher co-morbidity, co-drug therapy and with poorer renal function than non-users of paracetamol.
- **Strengths:** The use of an internationally recognised, validated dose standardisation system (the DDD). The use of a published definition of standardised normal and high dose NSAID use. The application of standardised normal and high dose definitions to aspirin and paracetamol users.

- **Limitations:** The lack of data on OTC use. Issued and not collected prescriptions.
- **Recommendations:** Future studies should look at the effects of OTC and prescription drug use on CKD.

- **Drug use and stage 3 to 5 CKD**
  - Single or multiple drug use was not significantly associated with stage 3 to 5 CKD over a two year period.
  - Single or multiple drug use was not associated with an increased risk of developing of stage 3 to 5 CKD over a two year period.
  - **Strengths:** Cross-sectional and cohort designs. Clinically relevant outcomes. Study into the effects of both single and multiple drug use.
  - **Limitations:** Limited study period and few patients developed stage 3 to 5 CKD.
  - **Recommendations:** A longer study duration and further study into the effects of multiple drug use on CKD.

- **Drug use and significant CKD progression**
  - Age, male gender, mildly impaired eGFR, ischaemic heart disease, heart failure and dysrhythmia were associated with CKD progression.
  - NSAID or paracetamol use at any dose was not significantly associated with significant CKD progression over a two year period. Although normal dose aspirin did not affect the risk of significant CKD progression, high dose aspirin users with a normal or mildly impaired eGFR were significantly less

likely to have significant CKD progression over a two year period. Multiple drug use was not associated with significant CKD progression.

- **Strengths:** Clinically relevant outcome based on national UK NICE guidelines. Calculation of eGFR decline rate for each patient. Investigation into the effects of multiple drug use on CKD progression.
- **Limitations:** Calculation of eGFR decline rate sensitive to measurement accuracy. Risk of bias by indication. Limited sample size in the high dose user groups.
- **Recommendations:** Use linear regression methods to estimate eGFR decline. Use longer study durations with larger samples. Further explore the significance of the effect of aspirin use on renal decline. Explore the effects of multiple drug use on CKD progression.

Chapter 11. Reflections

11.1. Critical Reflections on Completed Studies and on Ideal Future Observational Study Designs

11.1.1. Defining CKD

CKD is divided into five stages according to the GFR and upon other evidence of renal dysfunction.[4,226] NKF-KDOQI guidelines recommend that a diagnosis of CKD be made where there is evidence of renal dysfunction present on at least 2 occasions for >3 months.[4]

The advantages of the CKD definitions are that the GFR can be estimated using easily attainable variables including age, gender, ethnicity and serum createnine.[4,17] The use of a IDMS-traceable MDRD with standardised serum creatinine assays reduces the amount of inter and intra-laboratory variation.[4,17] It allows for earlier stages of CKD to be identified allowing stratification of patients into low and high risk groups.[4,226] Finally, the definition allows studies to more accurately quantify the association between risk factors of renal disease with earlier CKD stages.

However, there are several disadvantages to the definition of CKD which largely relate to the difficulties in accurately measuring the GFR. Firstly, the assumption that renal dysfunction can wholly be detected by decreasing GFR is not completely accurate.[4] Renal disease can occur without any decline in the GFR.[4] Furthermore, serum creatinine is not an ideal marker of kidney function.[20] Produced during muscle metabolism, its production reflects overall muscle mass thus underestimating renal impairment in patients with low muscle mass.[20] Serum creatinine also increases following protein rich meals and has a degree of biological variability (~5%).[1,20] All the above factors affecting serum creatinine

measurements invariably lead to errors in the eGFR which in turn affect the accuracy of CKD classification.[4] This effect is greatest in subjects with an eGFR >60mL/min/1.73m^2 if using the MDRD equation.[4]

11.1.2. CKD in the UK

Provided below is a brief description of CKD in the UK using Health Survey for England (HSE 2009)[227] data. A large proportion of individuals had an abnormal eGFR (47% males, 49% females).[227] The prevalence of stage 3-5 CKD was 5% in men and 7% in women.[227] However, the majority of individuals in the stage 3-5 CKD group had stage 3 CKD.[227] CKD prevalence was more marked in older individuals and in females.[227] The self-reported prevalence of doctor-diagnosed CKD was 1.4%.[227] Albuminuria was present in 10% of men and 8% of women.[227] As the HSE data demonstrates, CKD continues to be a major health problem in the UK, especially in older individuals. The data underscores the need for continued efforts to identify and manage risk factors. It also highlights the need to test asymptomatic individuals and raise awareness of CKD as a key health problem.

11.1.3. An ideal marker of renal function

The GFR is a measure of the average amount of fluid filtered by all of the renal nephrons.[1] The GFR can be approximated by measuring the renal clearance of any substance which is freely filtered by the kidney and not absorbed or actively secreted.[1] An ideal marker should not undergo any metabolism within the body and its concentration should remain stable such that it is not redistributed or excreted elsewhere.[1] In addition to the physiological considerations, an ideal marker should be practically easy to use.[1] An ideal marker should therefore be cheap, inert, quick to measure and widely available if exogenous.[1]

11.1.4. Defining CKD progression

In general, CKD progression can be defined as an absolute rate of GFR decline per unit time (normally yearly), a percentage GFR change or a decline in CKD stage.[226] Current Kidney Disease – Improving Global Outcomes (KDIGO 2012) guidelines define CKD progression as a decline in CKD stage confirmed by a ≥25% decline in the eGFR from baseline.[226] Rapid CKD progression is defined as a sustained eGFR decline rate >5ml/min/1.73m^2/year.[226] To measure eGFR decline, patients should have at least 1 eGFR estimate per year increasing to ≥4 measurements per year in those with stage 5 CKD.[226]

Definitions of CKD progression use the eGFR and CKD staging classification hence they are easily applicable to clinical practice.[226] Current CKD progression definitions allow patients with clinically significant renal decline to be identified.[226] CKD progression definitions also help research efforts aimed at identifying renal decline risk factors.[226]

However, disadvantages of current definitions are that they assume renal decline is linear which is not usually the case.[226] Renal decline is also different according to the underlying pathology (e.g. DM) and is augmented by treatments (e.g. ACE-i) making the prediction of progression difficult.[226] Most importantly, accurate estimation of eGFR decline rate relies upon extended periods of follow-up and numerous eGFR measurements.[226]

11.1.5. Predictors of CKD progression

There are numerous modifiable and non-modifiable factors associated CKD progression (See *Chapter 3*). Recent KDIGO guidelines listed primary CKD pathology, eGFR level, albuminuria, age, gender, ethnicity, hypertension, hyperglycaemia, dyslipidaemia, smoking, obesity, CVD history and ongoing exposure to nephrotoxic compounds as the

main factors associated with CKD progression.[226] The development of CKD is linked to the presence of initiating pathologies mainly DM, hypertension, glomerulonephritis or tubulointersitial nephritis and inherited renal pathologies (e.g. APKD).[1]

11.1.6. The inclusion of Aspirin and Paracetamol in the study

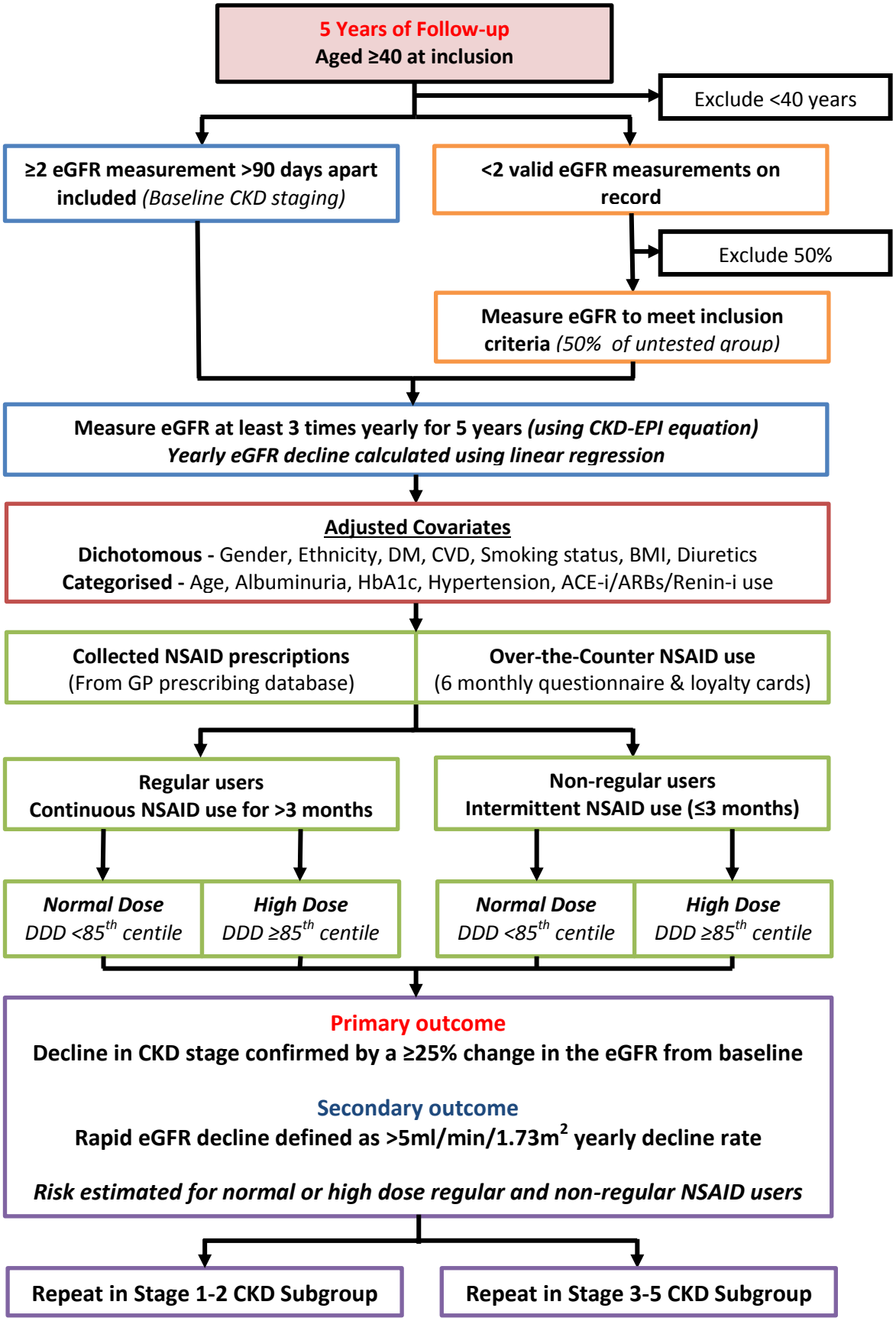
Aspirin has been linked to renal dysfunction in some studies[15] but not others.[3,128,132,139] Its role has changed from that of an analgesic to that of a thromboprophylactic agent.[103] Given its changing role, its wide spread use and the potential for confounding in patients with CVD, it was clear that a new focus on the non-classical NSAID was required.

In settings where NSAID use is contraindicated, paracetamol is often the preferred simple analgesic.[210] Given that paracetamol is a major metabolite of the banned nephrotoxic analgesic phenacetin[110], and its use has been associated in some studies with renal dysfunction[15,128,137,141] but not in others[13,136,137,139,148,149], further study into its effects on renal function was also warranted.

11.1.7. An ideal GP database study

Figure 11.1 below is an idealised large GP database cohort design study designed to more accurately estimate the association between chronic NSAID use and renal function decline. It incorporates confounders (e.g. proteinuria and diuretics) that were not included in my primary study and sets a minimum follow-up period of 5 years. It also includes OTC use and samples untested individuals to be more representative of the general population. Finally, NSAID use behaviour is also accounted for with further stratification of NSAID users into those with continuous use or intermittent use.

Figure 11.1 Ideal GP database linkage cohort design study



11.2. Personal Reflections

Since my pre-clinical years at medical school, I have always wanted to take part in research. This stems from the fascination I have with finding out how things work and is a major reason why I chose to study medicine. I also wanted to have an opportunity to learn new skills that would not only benefit me in my future career as a clinician but would ultimately benefit patients. I was given the perfect opportunity to engage in research in my fourth year with an offer to undertake an intercalated MPhil in renal medicine.

I chose the topic of nephrology because it was an area which I found interesting but also challenging. I wanted to know more about the research opportunities in nephrology as I was interested in applying for specialist training in this area.

Over the last year, I have enjoyed being challenged and learning new things. I have gained a completely new set of skills ranging from critical appraisal and electronic database searching to using citation and statistical software packages. I now have a good understanding of systematic reviewing, meta-analysis, epidemiological study design, statistical analysis and thesis writing. I have had exposure to various topics including computerised consultation and prescription databases, data linkage, READ 5 codes and organising clinical data. I have also had the opportunity to write abstracts, make posters, give presentations and submit a manuscript for publication. Prior to this intercalation year, I had been somewhat apprehensive that research could become somewhat repetitive. However, I have been pleasantly surprised by the diversity of opportunities available. It is this diversity that makes me want to incorporate a research element to my future career as I have found solving new and interesting problems fulfilling.

As well as learning various skills, I have also gained new clinical knowledge on the underlying pathological mechanisms that drive renal function decline in chronic kidney disease. Moreover, I now have an appreciation of the challenges of studying interactions between multi-morbidity and poly-pharmacy.

However, some aspects of the research year have been difficult. I had to be very self-driven and motivated because there are often long intervals between deadlines. Furthermore, the pace of research is not the same as the pace of medical practice and I had to learn to be patient and thoughtful in my approach. As I learned more and more about my subject area, I had to be prepared to make more decisions about the design of the study and ultimately I had to foresee and minimise any problems with the study design given the time critical completion period for the MPhil. I enjoyed the freedom to learn things I felt were important and to think in depth about the problems I had been posed. On the other hand, planning a good study was more demanding that I had anticipated. I was given the freedom to choose the covariates I thought were important for my study but that meant making judgments on what was most important for my study and what was less important. Having to be selective has made me think more critically both about the study question but also about what factors are important in disease pathology. I have begun to appreciate that in research there needs to be a balance between useful clinical outcomes, validity and practicability.

I was encouraged by the degree of team-working present in research both in my own study and within the institute as a whole. I enjoy working with others and find their input invaluable. Numerous aspects of my study have been steered or initiated by conversations or suggestions from my supervisors and peers.

I feel that the intercalation year has offered me the opportunity to diversify my skills set, become more organised, self-driven, decisive and to have a clearer vision of what I want from my future career. In the short term, I hope to apply for an academic foundation post with the aim of continuing to develop the skills learned over the past year and applying them to clinical practice. In the long term, I feel that the academic pathway is the right career choice for me. I hope to continue on as an academic physician and apply the principles I have learned in this year to benefit patients in the future.

Appendices

Appendix 1 - Detailed characteristics of included studies

Study	**Fored *et al.*, 2001[15]**
Study Location	Sweden.
Study Type and Period	Nationwide population-based case-control study, 05/1996 – 05/1998.
Study Population	926 newly diagnosed, physician identified, chronic renal failure patients aged 18-74 years old (creatinine >300µmol/l for men and >250µmol/l for women) vs. 998 age (±10y) and sex matched controls randomly selected from the Swedish Population Register. Patients with pre or post-renal failure or those with a renal transplant were excluded.
Data Collection Methods	Mailed self-administered questionnaire followed by a standardised face-to-face interview. A colour booklet listing 78 major NSAID brands available in Sweden between 1960 -1996 was used as a memory aid.
Analgesic Data	Subjects reported on lifetime use of branded NSAIDs and of aspirin/other analgesia use. Regular analgesic use was defined as more than twice a week for two months. Sporadic use was >20 tablets in their lifetime without regular use. Non-users were defined as <20 tablets in a lifetime. Patients were also asked about symptoms such as pain and about changes in the patterns of use.
Outcomes	Odds ratio for chronic renal failure with exclusive regular paracetamol use was 2.5 (95% CI, 1.7 to 3.6) and 2.5 (95% CI, 1.9 to 3.3) for regular users who took aspirin alone. This risk increased with cumulative lifetime dose. The dose-effect was stronger with paracetamol than with aspirin.
Notes	The eGFR (using the BSA standardised CG-equation) ranged from 2 to 53 ml/min/1.73m^2. The median values for men and women were 22 (creatinine 336µmol/l) and 19ml/min/1.73m^2 (281µmol/l), respectively.

Study	Gooch *et al.*, 2007[150]
Study Location	Alberta, Canada.
Study Type and Period	Community-based elderly population cohort study, 06-12/2001 to 06-12/2003.
Study Population	10,184 subjects aged ≥66 years with a minimum of 2 serum creatinine measurements between July-December/2001 and July-December/2003. Patients with an eGFR of >90ml/min/1.73m^2, those with hospital laboratory measurements or those with >12 measurements over the two six month periods were excluded.
Data Collection Methods	Prescription data, including that taken one year period before the first serum creatinine measurement (up to 31/03/2003), from the provincial administrative Alberta Blue Cross database were used to calculate the NSAID dose. Prescription data was also used to define the patient's co-morbidity score and diabetic status.
Analgesic Data	Two categorisation procedures were employed. In the first, participants were divided into four groups; nonusers, users with at least one prescription of traditional NSAIDs, COX-2 selective NSAIDs or a combination of both. The second approach calculated the total drug exposure and divided the participants into non-users, low-dose users (cumulative dose <90th percentile) and high-dose users (cumulative dose ≥90th percentile). Aspirin exposure was excluded from the study.
Outcomes	The multivariate adjusted OR for an eGFR decline of ≥15ml/min/1.73m^2 was 1.26 (95% CI, 1.04 to 1.53) in high dose users compared to non-users. Stratification by CKD status showed significant interaction between exclusive traditional or COX-2 selective NSAID users but only for those with CKD stage 1 and 2. There was also a dose effect on mean eGFR change in relation to NSAID exposure; each 100-unit increase in the DDD was associated with a 0.08ml/min/1.73m^2 (95% CI 0.01 to 0.16; p=0.04) decrease in the eGFR over the study period. The study found no risk difference between selective and non-selective NSAIDs.
Notes	The eGFR was calculated using the 4-variable MDRD equation. The serum creatinine measurements were calibrated between the two time periods.

Study	Hemmelgarn *et al.*, 2007[151]
Study Location	Alberta, Canada.
Study Type and Period	Community-based elderly population cohort study, 06-12/2001 to 06-12/2003.
Study Population	10,184 subjects years (from a catchment area of 1.1 million) aged >66 with minimum of 2 serum creatinine measurements acquired during two study periods (July-December/2001 and July-December/2003). Patients with an eGFR of >90ml/min/1.73m^2, those with hospital laboratory measurements or those with >12 measurements over the two six month periods were excluded.
Data Collection Methods	Prescription data during the 6 month period before the study start date from the Alberta Blue Cross database was used to identify all the relevant risk factors (including NSAID use).
Analgesic Data	Those prescribed at least one selective or non-selective NSAID 6 months before the first eGFR measurement were considered users.
Outcomes	The primary outcome measure was the OR for a ≥25% decline in the mean eGFR from the baseline measurement. The OR for the primary outcome in NSAID users was 1.0 (95%CI 0.9–1.2).
Notes	The eGFR was calculated using the 4-variable MDRD equation. This study was not primarily designed to assess the association between NSAIDs and CKD. The risk of CKD progression was not stratified by the eGFR. The study did not look for any dose effect. This study may have used the same data set as Gooch *et al*.

Study	Agodoa *et al*., 2008[148]
Study Location	USA.
Study Type and Period	Cross-sectional study, 1999–2002.
Study Population	8,057 non-institutionalised residents (>20 years old) from the NHANES. Patients with missing data, those on dialysis, pregnant women and women in menses were all excluded.
Data Collection Methods	Standardised survey with physical examination at a mobile centre.
Analgesic Data	Ever intake of an analgesic every day for at least a month was defined as habitual use. Analgesics were classified by product (Aspirin, Paracetamol, Ibuprofen and a list of other pre-defined NSAIDs). Participants were also grouped according to duration of analgesic use (<1year, 1-5 years and >5 years)
Outcomes	Albuminuria and reduced eGFR (<60ml/min/1.73m^2) prevalence were the primary outcomes. Multi-variable adjusted OR for reduced eGFR prevalence for habitual use of paracetamol only, ibuprofen only and aspirin only were 1.03 (95% CI, 0.6 to 1.7), 1.21 (95% CI, 0.7 to 2.1), and 0.95 (95% CI, 0.7 to 1.2), respectively. There was no significant association between the length of analgesic use and the primary outcomes.
Notes	The eGFR was calculated using the modified 4-variable MDRD equation using standardized creatinine measurements. Self-reported analgesic use reliability was not checked.

Study	Evans *et al*., 2009[149]
Study Location	Sweden.
Study Type and Period	Population-based cohort study, 05/1996 – 06/2003.
Study Population	801 patients aged 18-74 years old with incident advanced CKD (first elevated serum creatinine >300 µmol/L for men and >250 µmol/L for women) and whose serum creatinine remained above this level were included. Patients with pre and post-renal failure causes of serum creatinine elevation, or renal transplant patients were excluded. Where the diagnosis was in doubt, a repeat measurement was done after 3 months.
Data Collection Methods	Computer-aided face-to-face interviews at study inclusion. Covariates data were collected (BMI, other drug prescriptions, smocking, alcohol, education and work-related exposures). The interview looked at a number of common co-morbidities.
Analgesic Data	Lifetime analgesic use up to the point of inclusion as well as continued use. Patients were categorised into the following groups of lifetime analgesia use; never used (<20 tablets), ≤99g, 100-499, 500-2999 and ≥3000g. Patients were also divided into regular (more than twice a week for 2 months prior to inclusion) and non-regular users.
Outcomes	The median eGFR decline was 5.1ml/min/1.73m^2 per year. Patients with regular paracetamol use prior to the study had a progression rate 0.93ml/min/1.73m^2 per year slower than non-users (95% CI, 0.03 to 1.8), those with continued use during follow-up had an even slower progression rate 1.7ml/min/1.73m^2 (95% CI, 0.6 to 2.8). Similar results were seen with aspirin use 0.80ml/min/1.73m^2 (95% CI, 0.1 to 1.5) and 1.1ml/min/1.73m^2 (95% CI, 0.4 to 1.9) respectively.
Notes	Serum creatinine measurements were used to calculate eGFR using the 4-variable MDRD equation. The mean (SD) eGFR was 16.5ml/min/1.73m^2 (±3.5) [Min = 1.7, Max = 31.3]. Patient follow-up ended if they died or underwent renal replacement therapy. This study used the same data set as Fored *et al*.

Study	Hippisley-Cox and Coupland., 2010[152]
Study Location	England and Wales.
Study Type and Period	Population-based cohort study, 01/2002 – 12/2008.
Study Population	775,091 women and 799,658 men aged 35-74 without pre-existing CKD.
Data Collection Methods	Computerised data from 188 QResearch practices throughout England and Wales.
Analgesic Data	Patients defined as NSAID users if they had 2 or more NSAID prescriptions in a 6 month period before inclusion in study.
Outcomes	The primary outcome was considered to be the first incident of the eGFR being <45ml/min/1.73m^2 (equivalent to CKD stage 3B). The HR for NSAID users vs. non-users was 1.30 (95% CI, 1.27 to 1.34) for men and 1.29 (95% CI, 1.25 to 1.33) for women. NSAID use was seen as predictor of increased CKD stage 3B risk.
Notes	Serum creatinine measurements were used to calculate the eGFR using the 4-variable MDRD equation. The original aim of the study was not to test the effect of NSAIDs on CKD. There was no mention of what NSAIDs were included, what doses patients took or for how long they had been on the drugs. There is no measure of progression and no stratification by eGFR.

Study	Yarger *et al*., 2011[153]
Study Location	USA.
Study Type and Period	Retrospective cohort study, 06-12/2006 to 06-12/2008.
Study Population	34,295 elderly patients (>67 years) within a military healthcare system. Patients with a baseline eGFR representing CKD stage 2 and 3 were included. Patients could only be included if they were continually eligible for TRICARE and had received treatment at a military treatment facility.
Data Collection Methods	Prescription data from the military TRICARE healthcare database was used to define use. The covariates of age, gender, diabetes, hyperlipidaemia and hypertension were also recorded.
Analgesic Data	Data on precise NSAID collection methods are missing. NSAID use was divided into no use, low-medium and high NSAID use.
Outcomes	The primary outcome was a decline in the eGFR of ≥15ml/min/1.73m^2 over the study period. Rapid progression occurred in 10.5% of non-users, 11.2% of low-medium users and 13.4% of high NSAID users. The OR for rapid progression in low-medium users were 1.002 (95% CI, 0.925 to 1.086) for CKD stage 2 and 0.936 (95% CI, 0.782 to 1.122) for stage 3 disease. The OR for rapid progression in high NSAID users were 1.185 (95% CI, 0.994 to 1.413) for CKD stage 2 and 1.276 (95% CI, 0.844 to 1.927) for CKD stage 3.
Notes	The paper did not provide a detailed description of the methodology used in the study and was available only in an abstract form.

Appendix 2 - Detailed characteristics of excluded studies

Study	**Sørenson, 1966**[143]
Study Location	Copenhagen, Denmark.
Study Type and Period	Cohort study, 1958-1960.
Study Population	244 Rheumatoid arthritis (RA) patients and 546 patients with "other diseases". Age range not defined.
Data Collection Methods	Renal function studies, bacteriological studies, kidney biopsy studies and clinic-radiologic studies.
Analgesic Data	Analgesic use of phenacetin containing NSAIDs and of aspirin. Stages of analgesia use divided into no use, consumption under 10 years, consumption over 10 years and over 1g of phenacetin daily for more than 10 years.
Outcomes	There was no significant association between reduced creatinine clearance and analgesic consumption in either the rheumatoid arthritis group or other renal diseases group (p>0.1).
Notes	Analgesic doses not quantified.
Reasons for Exclusion	The outcome measure is creatinine clearance not the GFR The use of phenacetin containing NSAIDs

Study	Lawson DH, 1973[133]
Study Location	Boston, USA.
Study Type and Period	Cohort study, 1968-1971.
Study Population	6,407 hospital patients.
Data Collection Methods	Nurses monitored patients admitted on medical wards using a standardized self-coded data sheet. Patient characteristics, diagnosis, hospital administered drugs and laboratory tests were all recorded.
Analgesic Data	Medication data for the last 3 months before admission to hospital supplemented by information from patient records was used to estimate analgesia use. Patients grouped into four categories; daily oral analgesic consumers, occasional (less than one a day) users, patients taking other drugs but not analgesics and patients not taking any medication.
Outcomes	Of the 234 patients with a diagnosis of renal disease, 4.5% were daily analgesic users, 3.8% of patients took occasional drugs, 3.8% took no drugs and 3.4% took "other drugs"; no significant association was found between analgesic use and renal disease.
Notes	Renal function measure by the blood urea nitrogen (BUN) level. The mean age was 53 years and 36% were female. Some patients with phenacetin consumption were included.
Reasons for Exclusion	The use of the BUN level instead of the GFR. The use of Phenacetin containing NSAIDs.

Study	Dubach *et al*., 1983[129]
Study Location	Switzerland.
Study Type and Period	Prospective cohort study, 1968 – 1979.
Study Population	623 women (30-49y) taking high levels of phenacetin containing analgesics vs. 621 age and parity matched controls with low/no phenacetin intake.
Data Collection Methods	4 phase study. Phase 1, establish the study and control groups (1968) via invitation letters for a health evaluation. Phase 2 (1968), interview on analgesic intake, urinary disorders, smoking and other demographics performed. Phase 3, yearly follow-up interviews up to 1978. Phase 4, mortality survey [1978 and 1979].
Analgesic Data	An average of the 6 urine samples, taken throughout the study, were used to calculate whether the levels of the phenacetin metabolite N-acetyl-*p*-aminophenol (NAPAP) (optical density >0.200 = High, <0.200 = Low).
Outcomes	5 study outcomes reported (total mortality, elevated serum creatinine, specific gravity, haematuria and proteinuria). There was a significant difference between the high-NAPAP group (12.0% incidence of high serum creatinine) vs. low-NAPAP group (1.4%) (p<0.001).
Notes	A psychological interview added before the last follow-up in 1978 resulted in an increase in subject refusal to participate in the study.
Reasons for Exclusion	The outcome measure is serum creatinine not the GFR. The use of phenacetin containing NSAIDs.

Study	Murray *et al*., 1983[136]
Study Location	South-eastern Pennsylvania and New Jersey, USA.
Study Type and Period	Case-control study, 10/1978 - 8/1979.
Study Population	572 ESRD patients with regular analgesic use vs. 1,047 age, sex and race matched controls with no analgesic use.
Data Collection Methods	Trained nurse interviewed patients selected randomly from 18 dialysis units within the study area.
Analgesic Data	List of analgesics available between 1920 to 1979 for a detailed "life history". A detailed analgesic history was taken from participants with daily use or every other day use for ≥ 30 days. Those with <30 day use did not have their exposure explored further. A history of conditions likely to be associated with analgesic use was also taken into account.
Outcomes	The overall relative risk for ESRD was 1.08 (95% CI, 0.86 to 2.64) for users consuming one or more analgesics for more than 3 years compared to non-users. There was no dose effect found as the relative risk for analgesic users of >3kg lifetime use was 1.03 (95% CI, 0.47 to 2.25).
Notes	19% of the patients were <40y, 46% were 40-59y and 35% were 60-79 years old; only 1% ware aged 80 and over. Controls with diagnosis suggestive of high analgesic use (e.g. peptic ulcers) were excluded. 57 % of the patients were "non-white".
Reasons for Exclusion	ESRD was used as the primary outcome. Phenacetin use was included in the study.

Study	Corwin *et al*., 1984[127]
Study Location	Massachusetts, USA.
Study Type and Period	Cohort study, 1/1980-3/1982.
Study Population	26 patients with renal insufficiency.
Data Collection Methods	19 patients recruited by consultation in the renal unit and 7 patients with pericardial pathology identified by chart review with renal insufficiency.
Analgesic Data	Analgesic use described by inpatient days of therapy. NSAIDs examined are Indomethacin, Ibuprofen, Zomepirac, Sulindac and Naproxen. The study details the NSAID indication and other disease factors.
Outcomes	The 26 patients had 27 episodes of deterioration in renal function over the 27 month study period. The mean serum creatinine increased from 1.6 ± 0.1 mg/dL (range 0.7 to 3.1 mg/dL) to a maximum mean value of 3.3 ± 0.3 mg/dL (range 1.1 to 9.8 mg/dL). After discontinuation of the drug, the mean serum creatinine fell to 1.7 ± 0.1 mg/dL (range 1.2 to 3.4 mg/dL).
Notes	The mean age is 66 ± 2. The mean duration of therapy was 4.2 ± 0.7 days. Only one patient, excluded from the statistic above, had an analgesic use of >3 months. Renal insufficiency was attributed to NSAID use only if; there was a temporal correlation between renal deterioration and analgesic use, there was an improvement in the renal function with cessation of use or there no other cause for the renal pathology.
Reasons for Exclusion	The outcome measure is serum creatinine not the GFR. The study had less than 50 patients.

Study	McCredie and Stewart, 1988[134]
Study Location	New South Wales, Australia.
Study Type and Period	Case-control study, 01/1978 – 02/1980.
Study Population	91 patients with a diagnosis of papillary necrosis (RPN) vs.120 clinic controls with other renal diseases.
Data Collection Methods	Interview with an analgesic use questionnaire
Analgesic Data	Lifetime analgesic use up to one year before the diagnosis
Outcomes	For patients with ≥1kg use of phenacetin, the OR for RPN was 19 (95% CI, 10 to 37) compared to those with ≤1kg use. This risk was 0.5 (95% CI, 0.1 to 1.9) for paracetamol users. Those with ≥0.1 kg of phenacetin use or ≥0.1 kg of paracetamol use had a similar OR for RPN.
Notes	The mean age in this study was 47. Less than 3 patients took ≥1kg of paracetamol and all of these were in the control group.
Reasons for Exclusion	The outcome measure is that of RPN; renal function is not measured. Phenacetin use was included in the study.

Study	Sandler *et al*., 1989[141]
Study Location	North Carolina, USA.
Study Type and Period	Multicentre retrospective case-control study, 09/1980 – 08/1982.
Study Population	554 hospitalised patients with newly diagnosed chronic renal failure (serum creatinine consistently ≥ 130μmol/l). 516 matched controls who, if <65 years old, were chosen randomly by random digit dialling but if >65 years old were chosen from Medicare recipient lists.
Data Collection Methods	Telephone interviews on lifestyle, demographics, occupation, environmental exposures, medical history and medication use.
Analgesic Data	Subjects or proxies were given a questionnaire on life conditions associated with NSAID use, NSAID use before 1980 and whether NSAIDs had been obtained over the counter use on at least 10 occasions before 1980 as identified by brand and generic drug lists. Regular daily NSAID use defined as >1 pill per day for at least 360 consecutive days and weekly users as at least once a week for one year. Cumulative consumption for aspirin, paracetamol and phenacetin in kilograms was then calculated.
Outcomes	The adjusted OR for chronic renal disease. Overall risk for frequent users was 2.79 (95% CI, 1.85 to 4.25). The OR for Phenacetin-containing analgesics was 5.11 (95% CI, 1.70 to 14.9). Paracetamol had an OR of 3.21 (95% CI, 1.05 to 9.8) with an OR of 1.32 (95% CI, 0.69 to 2.51) for Aspirin users. An increased frequency of use was associated with an increased risk of renal disease.
Notes	The mean age is 63 for patients and 62 for the controls.
Reasons for Exclusion	The outcome measure is serum creatinine not the GFR. Phenacetin was use was included in the study.

Study	Pommer *et al*., 1989[138]
Study Location	West Berlin, Germany.
Study Type and Period	Case-control study, 1984 to 10/1986.
Study Population	517 ESRD patients vs. 517 age, sex and nationality matched controls. All cases >20 years are recruited.
Data Collection Methods	Face-to-face interviews using a standardised questionnaire and a list of commonly available analgesics.
Analgesic Data	Lifelong analgesic intake, the reasons for use, the use of other drugs and the family history were all recorded. Regular analgesic intake defined as consumption of 15 or more analgesics per month for at least one year.
Outcomes	The relative risk for ESRD for all analgesics was 2.44 (95% CI, 1.77 to 2.39) with a relative risk of 2.65 (95% CI, 1.91 to 3.67) for analgesics consumed in combination. For a lifetime Phenacetin use of ≥1kg, the relative risk was 4.48 (95% CI, 1.32 to 7.68). The relative risk for a lifetime paracetamol, aspirin and phenazones use of >1kg was 4.06 (95% CI, 1.32 to 12.43), 2.42 (95% CI, 1.39 to 4.23) and 3.57 (95% CI, 2.26 to 5.64) respectively. Single analgesic use was not significantly associated with ESRD.
Notes	87.8% patients and 86.3% controls were aged between 30-74 years old. Non-medical interviewers collected the analgesic data. Less than 4% of patients had paracetamol use of >1kg.
Reasons for Exclusion	ESRD is used as the main outcome measure. Phenacetin is included one of the analgesic drugs.

Study	Morlans *et al.*, 1990[14]
Study Location	Spain.
Study Type and Period	Case-control study, 09/1980 – 03/1983.
Study Population	340 ESRD dialysis patients; 673 matched hospital controls.
Data Collection Methods	Standardised structured questionnaires aided by a list of NSAID brand names and sample packages. A history of conditions likely to be treated with NSAIDs was also taken.
Analgesic Data	Daily or every other day analgesia use for 30 days or more was defined as regular use.
Outcomes	OR for ESRD for regular NSAID use was 2.89 (95% CI, 1.78 to 4.68) compared to non-users. For Phenacetin users, the OR was 19.05 (95% CI, 2.31 to 157.4). The OR for Salicylate users was 2.54 (95% CI, 1.24 to 5.20) and 2.16 (95% CI, 0.87 to 5.32) for regular users of Pyrazolones compared to non-users.
Notes	41.5% were 15-44 years old, 52.3% were 45-64 and 6.2% were over 65.
Reasons for Exclusion	ESRD is used as the main outcome measure. Patients with Phenacetin use are included.

Study	Steenland *et al*., 1990[145]
Study Location	Michigan, USA.
Study Type and Period	Case-control study, 1976 – 1984.
Study Population	325 ESRD male aged 30-69 dialysis patients vs. 325 controls identified by random digit dialling.
Data Collection Methods	Telephone interviews. The use of "moonshine", family history of renal disease, education, smoking, lead poisoning, injected antibiotics and environmental exposure to metal solvents was enquired about.
Analgesic Data	Regular NSAID use defined as >1 pill per week for 2 or more years.
Outcomes	Odds ratio for ESRD for Paracetamol or Phenacetin use was 2.66 (95% CI, 1.04 to 6.82) compared to none users. A dose effect was also observed.
Notes	When the OR is recalculated, ignoring the last 5 years of exposure, the result becomes non-significant at 2.47 (95% CI, 0.86 to 7.12).
Reasons for Exclusion	ESRD is used as the main outcome measure. All the patients were male. Patients with Phenacetin use are included.

Study	Murray *et al*., 1990[135]
Study Location	Indianapolis, USA.
Study Type and Period	Retrospective cohort study, 05/1975 – 09/1986.
Study Population	1,908 patients prescribed Ibuprofen and 3,933 Paracetamol users. Patients >18 years were recruited. All patients with other NSAID prescriptions given during the study were excluded. Patients with a serum creatinine measurement of <30µmol/L were also excluded.
Data Collection Methods	Computerized computer records. General medicine clinic data was used to identify patients with renal impairment with additional information from laboratory measurements and imaging. Renal impairment defined by a serum creatinine >110µmol/l after a normal baseline measurement. Patient morbidity determined by visits to the Wishard Memorial Hospital.
Analgesic Data	Computerised Ibuprofen/Paracetamol prescription data from the Regenstrief Medical Records.
Outcomes	The risk of renal impairment was higher for Ibuprofen users compared to Paracetamol users OR 1.05 (95% CI, 0.88 to 1.26). The risk was higher inpatients aged >65 years and those with coronary artery disease with an OR of 1.34 (95% CI, 1.05 to 1.72) and 2.54 (95% CI, 1.38 to 4.68).
Notes	Patients had to have a minimum of two serum creatinine measurements (baseline and post-prescription).
Reasons for Exclusion	Serum creatinine not the GFR is used as a measure of the renal function.

Study	Sandler *et al*., 1991[140]
Study Location	North Carolina, USA.
Study Type and Period	Multicentre case-control study, 09/1980 – 08/1982.
Study Population	554 hospitalised patients (aged 30-79) with newly diagnosed chronic renal dysfunction (serum creatinine consistently ≥130 µmol/l). 516 matched controls, if <65 years old were chosen randomly by random digit dialling but if >65 years old were chosen from Medicare recipient lists.
Data Collection Methods	Telephone interviews on lifestyle, demographics, occupation, environmental exposures, medical history and medication use
Analgesic Data	Subjects or proxies were given a questionnaire on life conditions associated with NSAID use, NSAID use before 1980 and whether NSAIDs had been obtained over the counter use on at least 10 occasions before 1980 as identified by brand and generic drug lists. Regular daily NSAID use defined as >1 pill per day for at least 360 consecutive days and weekly users as at least once a week for one year. Cumulative consumption for aspirin, paracetamol and phenacetin in kilograms was then calculated.
Outcomes	Adjusted OR for chronic renal disease. Overall risk was 2.1 (95% CI, 1.1 to 4.1) for all participants with previous daily use of analgesics. The risk was only significantly higher in men ≥65 years of age with a risk of 10.0 (95% CI, 1.2 to 82.7).
Notes	Only 14 male patients and 1 control were ≥65 years and had a history of regular analgesia use. 55% of the patient group and 10% of the controls had a proxy interview.
Reasons for Exclusion	Serum creatinine not the GFR is used as the measure of renal function.

Study	Segasothy *et al*., 1994[142]
Study Location	Kuala Lumpur, Malaysia.
Study Type and Period	Cohort study, 01/1982 – 12/1992.
Study Population	259 Hospitalised patients with heavy analgesia use. Patients who had medical conditions, such as diabetes mellitus, known to cause renal papillary necrosis were excluded.
Data Collection Methods	Standardised questionnaires.
Analgesic Data	Detailed analgesia use history was obtained in patients admitting to excess analgesic consumption. Analgesia abuse was defined as the use of >1kg of aspirin, phenacetin, paracetamol or other NSAID combinations. Biochemical and radio-graphical investigations were performed on high analgesia use patients.
Outcomes	26.6 % of the patients with heavy analgesia use had radiological evidence of papillary necrosis. Of these, 68.4% had evidence of renal impairment (serum creatinine 126 to 778 µmol/l).
Notes	The mean age was 52 years. 26% of the identified analgesic abuse patients did not contribute to the final analysis. No non-regular NSAID use group was used as a comparison.
Reasons for Exclusion	Serum creatinine not the GFR is used as the measure of renal function. No ORs are given to quantify relative risk of regular analgesia use vs. non-use.

Study	Perneger *et al.*, 1994[137]
Study Location	Maryland, Virginia, West Virginia and Washington DC.
Study Type and Period	Population-based case-control study, 01/1991 – 07/1991.
Study Population	716 dialysis patients treated for ESRD vs. 361 age-matched controls identified by random digit dialling. Patients aged 20-64 were included. Patients without phones, in institutions, those absent from their homes for >2 weeks or those unable to complete the interview were excluded.
Data Collection Methods	Telephone interviews with the aid of a list of the five most commonly used NSAIDs. Paracetamol, aspirin and other NSAID use was assessed.
Analgesic Data	The number of pills per year as well as the lifetime cumulative intake were recorded. A detailed history of analgesic use was obtained from participants who reported talking 10 or more pills within their lifetime.
Outcomes	Odds ratio for ESRD. 0-104 pills/year used as the reference group. For 105-365 pills/year, the OR was 1.4 (95% CI, 0.8 to 2.4). For >366 pills/year the OR was 2.1 (95% CI, 1.1 to 3.7). There was an increase in risk with increasing consumed paracetamol dose.
Notes	Patients taking Phenacetin based medications were adjusted for in the analysis. The NSAID list was based on a review of over the counter NSAIDs sold in Baltimore in 1990 and the North Carolina survey (Sandler et al., 1989).
Reasons for Exclusion	ESRD is used as the main outcome measure.

Study	Elseviers *et al*., 1995[130]
Study Location	Antwerp, Belgium.
Study Type and Period	Prospective cohort study, 01/1984 – 1992.
Study Population	200 analgesic abusers (21 to 86y) vs. 200 matched controls.
Data Collection Methods	Participants had face-to-face interviews using a structured questionnaire as well as undergoing medical examinations and biochemical tests. A psychological test was also used to check the interviewee's mental state.
Analgesic Data	Analgesic abuse defined as a daily intake of at least 1.000 unit (1 unit = 1 tablet/ 1 suppository/ 1 dose of powder) per year.
Outcomes	Subjects with a creatinine clearance below the third centile on two occasions were considered to have decreased renal function; they were then investigated for analgesic nephropathy. The relative risk of reduced renal function was 6.1 (95% CI, 1.4 to 25.9). 6/10 abusers with decreased renal function had analgesic nephropathy.
Notes	The median age amongst abusers was 53 years (range 21 to 86). The creatinine clearance was calculated using the Cockcroft-Gault formulae. Mixed and single analgesics were taken by the participants, these included; salicylic acid, phenacetin, paracetamol and pyrazolone. Inclusion cases were limited to Dutch speaking Belgians. 77% of the participants were female. Patients were referred by family doctors (54%), pharmacists (20%), enrolled analgesic abusers (11%) and others (15%).
Reasons for Exclusion	Creatinine clearance not the GFR is reported. Some of the participants were Phenacetin users.

Study	Murray *et al*., 1995[12]
Study Location	Indianapolis, USA.
Study Type and Period	A three-period randomised cross-over study, study date not reported.
Study Population	29 Community senior citizen centres patients aged >65 with (14) and without (15) renal insufficiency. Patients with diagnosis that place them at risk from NSAID use were excluded.
Data Collection Methods	Two consecutive 24-hour creatinine clearances using the Cockroft-Gault equation were calculated at study inclusion to establish a baseline. Patients had 3-hour inulin clearance and 2-day serum creatinine clearance. Vital signs, compliance, serum creatinine, electrolyte measurements and adverse events were recorded twice weekly. The acute effect of NSAID were assessed on day 4, the chronic effects were assessed on day 36.
Analgesic Data	Each patient received 800 mg of Ibuprofen three times a day, 20 mg of Piroxicam once daily and 200mg Sulindac twice daily for a month. There was a one month wash period between each drug. A 25% decrease in inulin and creatinine clearance was considered clinically significant. Renal insufficiency was defined as a creatinine clearance of 30-70 mL/min.
Outcomes	One month Ibuprofen use was not associated with a change in the creatinine clearance in patients with renal insufficiency 0 ± 3.6mL/min. Patients taking Piroxicam or Sulindac had decreases in creatinine clearance of -7.2 ± 3.62 mL/min.
Notes	The mean age of all the participants was >70 years. The study was stopped if there was a ≥40µmol/l increase in serum cretonne from baseline.
Reasons for Exclusion	There were less than 50 participants. The follow-up period is less than 6 months. Creatinine clearance not the GFR is reported in the chronic NSAID use part of the study.

Study	Rexrode *et al*., 2001[139]
Study Location	USA.
Study Type and Period	Physicians Health cohort study, 09/1982 – 12/1995.
Study Population	11,032 previously healthy physician males from a possible 22071 candidates.
Data Collection Methods	A retrospective analgesic history questionnaire. 8 categories of single and mixed NSAID groups were used. A history of the previous years analgesic use was taken for those who took >12 pills since study enrolment in 1982. Changes in the patterns of use were also recorded. Cumulative data was calculated from both an annual compliance questionnaire and the participants' aspirin/placebo assignment. 910 randomised participants were used to verify self-reported analgesic use data via a telephone interview.
Analgesic Data	4 categories of levels of analgesic intake were used in the analysis. <12 pills (never use), 12-1499 pills, 1500-2499pills and ≥2500 pills over the 14 year period; >7000 pills were examined in the secondary analysis.
Outcomes	Multivariate relative risk for reduced creatinine clearance (<55ml/min) as calculated by the CG equation were not significant for any level of paracetamol, aspirin or other NSAIDs use. For high dose paracetamol, aspirin or other NSAIDs users (≥2500 pills), the OR were 0.78 (95% CI 0.53 to 1.14), 1.40 (95% CI 0.87 to 2.26) and 1.01 (95% CI, 0.73 to 1.41), respectively compared to non-users.
Notes	39% were aged 40-49y, 38% were 50-59y, 20% were 60-69y and 3% were over 70-89y. Neither patients with combined aspirin and paracetamol use nor those with other analgesic combinations were included (237 and 202 respectively). The correlation coefficients between telephone interview and the analgesic questionnaire between 1988 and 1995 were 0.67 for paracetamol, 0.40 for aspirin and 0.46 for other NSAIDs.
Reasons for Exclusion	The study reports on the OR for reduced creatinine clearance not the GFR. All the participants were male.

Study	Strümer *et al.*, 2001[144]
Study Location	Southwest Germany.
Study Type and Period	Cross-sectional study, 01/1995 – 12/1996.
Study Population	809 patients awaiting hip/knee joint replacement for advanced osteoarthritis. Only patients aged <76 years were included.
Data Collection Methods	Participants underwent a face-to-face physician lead interview using a standardised questionnaire accompanied by an examination. Preoperative blood samples were used to measure the serum creatinine.
Analgesic Data	The brand names of all medications taken in the 3 months before hospital admission were recorded. Medications were classified according to the Anatomical Therapeutical Chemical classification system. The drugs were also subdivided by half-lives (less than 4 hours vs. more than 4 hours).
Outcomes	Creatinine clearances less than the 15th percentile (<60ml/min) were considered to be indicative of impaired renal function. The adjusted OR for impaired renal function was 1.4 (95% CI, 0.9 to 2.2) for NSAID users compared to non-users. There was a significantly increased prevalence of impaired renal function in patients taking intermediate-long half-life drugs ≥4 hours; OR= 2.6 (95% CI, 1.2 to 5.7). There was an associated increased risk of impaired renal function in patients taking diuretics 3.5 (95% CI, 1.6 to 7.6) and ACE- i 1.8 (95% CI, 0.8 to 4.4) independent of the risk caused by NSAID use.
Notes	The mean age (SD) was 63 (±9). The creatinine clearance was estimated using the CG formulae. Aspirin was not included within the study definition of NSAIDs thus was not measured for.
Reasons for Exclusion	The use of estimated creatinine clearance instead of the GFR. The CG formula was not adjusted according to the BSA.

Study	Kurth *et al*., 2003[132]
Study Location	USA.
Study Type and Period	Physicians Health cohort study, 09/1982 – 12/1996.
Study Population	4,494 previously healthy physician males from a possible 22,071 candidates aged >40 years old. Patients with evidence of pre-existing CKD were excluded.
Data Collection Methods	A retrospective analgesic history questionnaire. 8 categories of single and mixed NSAID groups were used. A history of the previous years analgesic use was taken for those who took >12 pills since study enrolment in 1982. Changes in the patterns of use were also recorded. Cumulative data was calculated from both an annual compliance questionnaire and the participants' aspirin/placebo assignment. 910 randomised participants were used to verify analgesic use data via telephone interview.
Analgesic Data	4 categories of levels of analgesic intake were used in the analysis. <12 pills (never use), 12-1499 pills, 1500-2499 pills and >2500 pills over the 14 year period; >7000 pills were examined in the secondary analysis.
Outcomes	The study reported on the multivariate OR for a reduction in the eGFR of ≥29ml/min/1.73m^2 over the 14 year study period. The use of >2500 pills of aspirin was associated with an OR of 0.75 (95% CI, 0.35 to 1.57). The ORs for paracetamol and other NSAIDs were 1.22 (95% CI, 0.66 to 2.26) and 1.11 (95% CI, 0.65 to 1.90) respectively compared to non-users. Aspirin appeared to be beneficial to those participants without risks factors for cardiovascular disease.
Notes	The eGFR was calculated by the 4-variable MDRD equation. Correlation coefficients between telephone interview and the analgesic questionnaire varied from 0.40 to 0.76. The baseline eGFRs are not noted thus it is impossible to ascertain whether any of the participants had CKD 3 or worse during the study period.
Reasons for Exclusion	All the participants were male.

Study	Curhan *et al.*, 2004[128]
Study Location	USA.
Study Type and Period	Nurses' Health cohort study, 1989 – 2000.
Study Population	1,697 female nurses aged 30-55 years (in 1976) from 32,826 possible participants. Women with a history of cancer or cardiovascular disease were excluded from blood sample collection.
Data Collection Methods	Analgesic use questionnaires in 1990, 1992 and 1998. Biennial questionnaire were used to collect information relating to any new diagnosis, weight hypertension and diabetes.
Analgesic Data	A detailed analgesic history was taken from nurses reporting aspirin, paracetamol or NSAID use of more than 15 days per month. A questionnaire, given in 1999, detailed the frequency of analgesia use in the 10 previous years and before 1990. Some women with >1501 tablet and some with <1501 tablet intake were randomly selected to give blood samples.
Outcomes	High paracetamol intake was associated with a 30% and ≥30mL/min per 1.73m^2 eGFR decline but aspirin and other NSAIDs were not. The multivariate OR was 2.04 (95% CI, 1.28 to 3.24) for patients with a lifetime consumption of >3000g of paracetamol compared to using <100g. Those consuming >100-499 and 500-2999g of paracetamol also had a statistically increased risk of eGFR decline. The absolute risk increase due to paracetamol use is modest.
Notes	The mean (SD) estimated glomerular filtration rate as measured by the 4-variable MDRD equation decreased from 88 (±17) to 79 (±17) mL/min/1.73m^2 during the study period. Not all the women had their serum creatinine measured.
Reasons for Exclusion	All the participants were female.

Study	Ibañez *et al*., 2005[13]
Study Location	Spain.
Study Type and Period	Case-control study, 6/1995 – 11/1997.
Study Population	583 cases with ESRD vs. 1,190 hospital-based age and sex matched controls. Patients with serious general conditions, those with sensory impairments, those with mental disability or patients with conditions impeding an interview were excluded.
Data Collection Methods	Trained nurse lead interview using a detailed standardised "life history" questionnaire as well as a picture based analgesic brand list from the past 20 years. Diseases associated with NSAID use were also recorded. Patients were categorised per condition that lead to their ESRD according to clinical practice criteria.
Analgesic Data	Patients were classified as users if they used analgesics daily or every other day for 30 days or longer at any point before the first diagnosis of kidney disease. Total exposure was recorded as a DDD.
Outcomes	The primary outcome was ESRD. The overall OR was for ESRD for all analgesics was 1.22 (95% CI, 0.89 to 1.66). Aspirin OR = 1.56 (95% CI, 1.05 to 2.30), other NSAIDs OR = 0.94 (95% CI, 0.57 to 1.56), pyrazolones OR = 1.03 (95% CI, 0.60 to 1.76) and paracetamol OR = 0.80 (95% CI, 0.39 to 1.63). The risk of ESRD increased with the duration of use and with the number of define daily doses taken; however the risk was only statistically significant for a duration of use >5 years of >500 DDD with ORs of 2.07 (95% CI, 1.16 to 3.70) and 2.09 (95% CI, 1.05 to 4.17) respectively.
Notes	16.7% of the participants were 14-45y, 24.2% were 46-60y, 45.1% were 61-75y and 14% were 75y or older. Aspirin was strongly associated with ESRD for patients with vascular nephropathy 2.35 (95% CI, 1.17 to 4.72). Analgesic use in the 2 years prior to the diagnosis of ESRD was disregarded in a separate analysis.
Reasons for Exclusion	ESRD was used as the primary outcome.

Study	van der Woude *et al.*, 2007[146]
Study Location	Germany and Austria.
Study Type and Period	Population-base case-control study, 1/2001 – 12/2004.
Study Population	907 ESRD dialysis patients (<50y) vs. 3,622 age and sex matched controls.
Data Collection Methods	Standardised face-to-face interview. A book of colour photographs of analgesics available since the 1950 was used as a memory aid. Life time use of analgesics was documented by brand name; co-morbidity data was also recorded.
Analgesic Data	A "low use" reference group of participants with less than 1 tablet used per month for 12 months was established. Medium and high dose were those in the 1+2 and 3 tertile of use in grams/month.
Outcomes	Ever and high analgesic use was not associated with an increased OR for ESRD when compared with no or low dose analgesic use; OR= 0.8 (95% CI, 0.7 to 1.0) and 1.0 (95% CI, 0.8 to 1.3) respectively. There was no dose response detected for a cumulative NSAID dose of up to 3.5 kg.
Notes	Analgesic use in the 5 years prior to the diagnosis of ESRD was disregarded in the analysis. All cases and controls had no or very low dose phenacetin use. Extremely high dose users had an excess of other conditions than may cause ESRD.
Reasons for Exclusion	ESRD was used as the primary outcome.

Study	Kuo *et al*., 2010[131]
Study Location	Taiwan.
Study Type and Period	Population based cohort study, 1997-2006.
Study Population	19,163 National Health Insurance (NHI) enrolees with newly diagnosed CKD.
Data Collection Methods	Prescription data extracted from NHI service claims. CKD was defined by International Classification of Disease, 9th revision, Clinical Modification (ICD-9-CM) codes.
Analgesic Data	Aspirin, Paracetamol and other NSAID use standardised to the anatomical therapeutic classification codes and the DDD. Each participant was grouped by the defined daily dose per person-year (DDDPPY) and compared to non-users.
Outcomes	The overall HR for ESRD were for 1.96 (95% CI, 1.62 to 2.36) for Aspirin, 1.56 (95% CI, 1.32 to 1.85) for non-selective NSAIDs, 1.54 (95% CI, 1.08 to 2.20) for selective NSAID and 2.92 (95% CI, 2.47 to 3.45) for Paracetamol. There was a trend of increasing risk with increases in the DDDPPY (p<0.001) for all the above analgesic groups.
Notes	6% were aged 0-19y, 30% were 20-44y, 34% were 46-64y, 17% were 65-74 and 13% were 75y or older. A sensitivity analysis was performed to exclude the possibility of protopathic bias. CKD patients entering ESRD within 1 year of diagnosis and analgesic use 1 year before ESRD were disregarded.
Reasons for Exclusion	ESRD was used as the primary outcome.

Study	Plantinga *et al*., 2011[164]
Study Location	USA.
Study Type and Period	Population based cross-sectional study, 1999-2004.
Study Population	12,065 National Health and Examination Survey respondents aged 20 years or older. Those with stage 5 CKD were excluded.
Data Collection Methods	A questionnaire delivered by via a computer-assisted personal interview regarding the over-the-counter and prescription use of NSAIDs. Self-reported demographics as well as height, weight and blood pressure were recorded. The eGFR (calculated using the modified 4-variable MDRD) and albumin:creatinine ratio were also recorded.
Analgesic Data	Participants were questioned on current and previous over-the-counter and prescription use of analgesics. They were asked in particular about prescription medication taken within the last month. Patients were divided into those with 30 days or more of NSAID use as well as duration of use (<1y and ≥1y).
Outcomes	Participants were divided into no, mild and moderate to severe CKD according to the eGFR. Regular NSAID use was more prevalent with worsening CKD status at 3.5%, 4.3% and 5.7% respectively (p=0.20 across categories).
Notes	No OR measurement is given and causality is not explored. No doses or time periods of analgesia use are given.
Reasons for Exclusion	No acceptable outcome measures are given.

Appendix 3 - ATC/DDD WHO-CCDSM index (2012) for NSAIDs, Aspirin and Paracetamol used in the study

ATC Code	DRUG	WHO DDD (grams)
M01AB16	**ACECLOFENAC**	0.2
M01AB11	**ACEMETACIN**	0.12
B01AC06	**ASPIRIN**	1 tablet
M01AE14	**DEXIBUPROFEN**	0.8
M01AB05	**DICLOFENAC**	0.1
M01AB08	**ETODOLAC**	0.4
M01AH05	**ETORICOXIB**	0.060
M01AE09	**FLURBIPROFEN**	0.2
M01AE01	**IBUPROFEN**	1.2
M01AB01	**INDOMETACIN**	0.1
M01AG01	**MEFENAMIC ACID**	1
M01AC06	**MELOXICAM**	0.015
M01AX01	**NABUMETONE**	1
M01AE02	**NAPROXEN**	0.5
N02BE01	**PARACETAMOL**	3
M01AA01	**PHELYLBUTAZONE**	0.3
M01AC01	**PIROXICAM**	0.020
M01AE11	**TIAPROFENIC ACID**	0.6

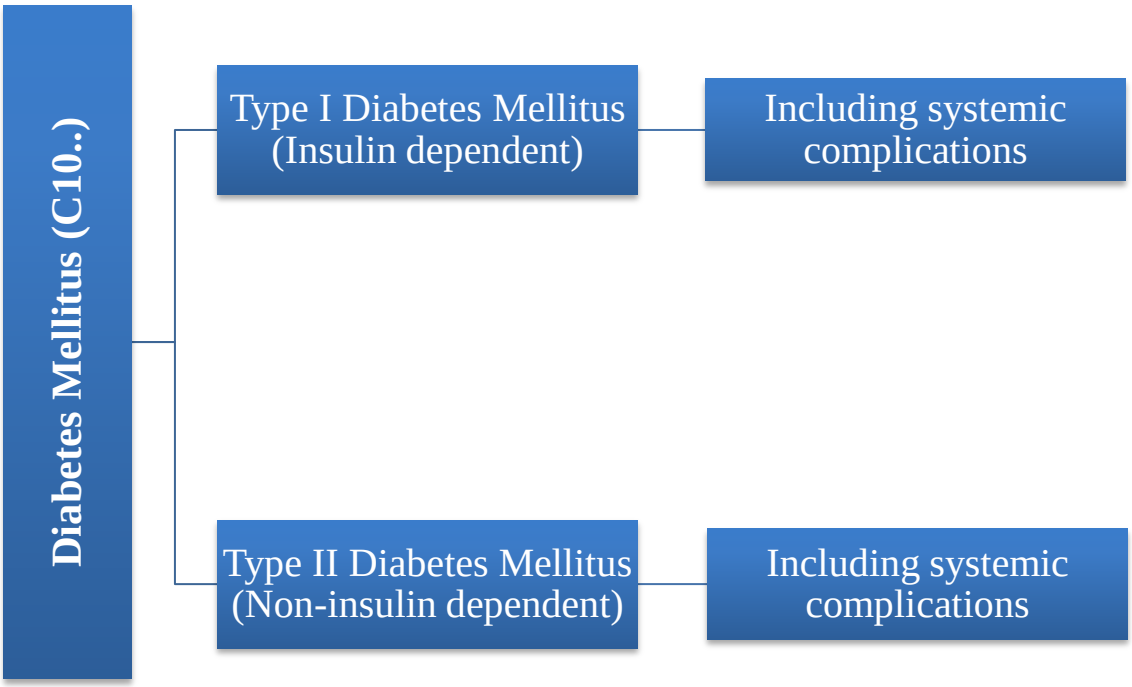
ATC Code Key

B01A ANTITHROMBOTIC AGENTS
- **B01AC** Platelet aggregation inhibitors excl. heparin

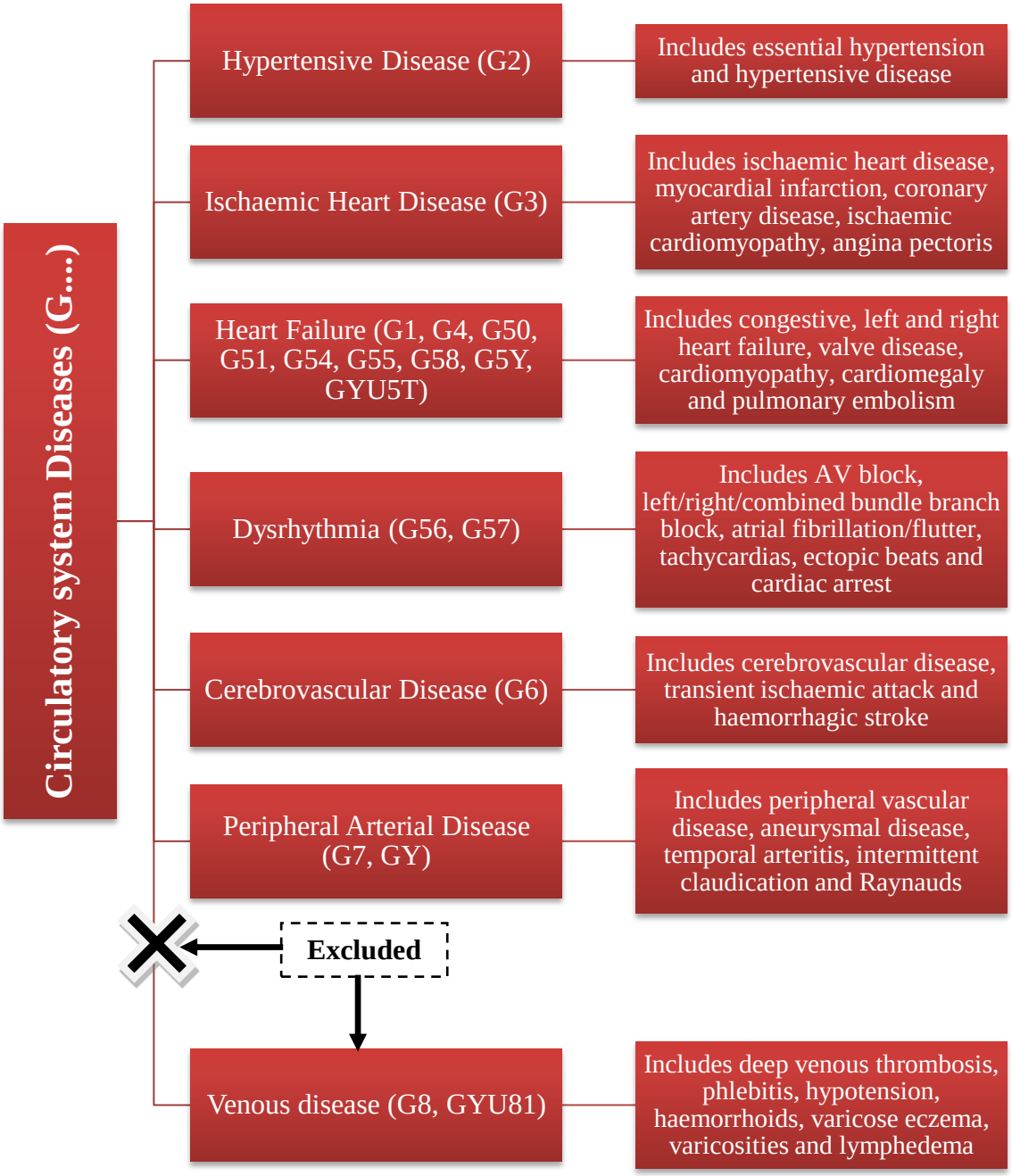
M01A ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
- **M01AA** Butylpyrazolidines
- **M01AB** Acetic acid derivatives and related substances
- **M01AC** Oxicams
- **M01AE** Propionic acid derivatives
- **M01AG** Fenamates
- **M01AH** Coxibs
- **M01AX** Other anti-inflammatory and anti- rheumatic agents, non-steroids

N02B OTHER ANALGESICS AND ANTIPYRETICS
- **N02BE** Anilides

Appendix 4 - Main diabetic pathologies included in the study under the READ 5 (V2) classification (C10..)



Appendix 5 - Major cardiovascular pathologies included/excluded from the study under the READ 5 (V2) classification (G....)



Appendix 6 - Co-morbidity, co-drug therapy and baseline eGFR

Cofactor		eGFR ≥60 N=6639 %	eGFR <60 N=1018 %	*p*-value
[1]**Diabetes** *(n=1323)*	No	**83.3**	**79.2**	**0.001***
	Yes	**16.7**	**20.8**	
All CVD *(n=4038)*	No	**49.2**	**34.4**	**<0.001***
	Yes	**50.8**	**65.6**	
[2]Hypertension *(n=3234)*	No	**59.1**	**49.3**	**<0.001***
	Yes	**40.9**	**50.7**	
[3]Ischaemic Heart Disease *(n=758)*	No	**90.6**	**87.0**	**<0.001***
	Yes	**9.4**	**13.0**	
[4]Heart failure *(n=167)*	No	**98.3**	**94.8**	**<0.001***
	Yes	**1.7**	**5.2**	
[5]Peripheral Vascular Disease *(n=101)*	No	**98.8**	**97.8**	**0.011***
	Yes	**1.2**	**2.2**	
[6]Cerebrovascular disease *(n=379)*	No	**95.6**	**91.3**	**<0.001***
	Yes	**4.4**	**8.7**	
[7]Dysrhythmia *(n=193)*	No	**97.9**	**95.0**	**<0.001***
	Yes	**2.1**	**5.0**	
[8]**ACE-i/ARBs/Renin-i** *(n=3077)*	Non-user	**62.3**	**43.3**	**<0.001***
	User	**37.7**	**56.7**	

READCODES = [1]C10, [2]G2, [3]G3, [4](G1, G4, G50, G51, G54, G55, G58, G5Y, G5UYT), [5]G6, [6](G7, GY), [7](G56, G57). All CVD = 2-7. [8]BNF chapter 2.5.5 and all subsections, *Statistically significant at $p \leq 0.05$..

Appendix 7 - Drug use and baseline eGFR

Analgesia use	eGFR ≥60 N=6639 %	eGFR <60 N=1018 %	*p*-value
[1]**Non users of any of the three drugs** *(n=3360)*	**45.7**	**31.9**	**<0.001***
Non-NSAID users *(n=5981)*	**76.7**	**87.6**	
Normal Dose NSAID users *>0 - <420 DDD (n=1424)*	**19.9**	**9.8**	**<0.001***
High Dose NSAID users *≥420 DDD (n=252)*	**3.4**	**2.6**	
Non-Aspirin users *(n=5401)*	**72.8**	**56.0**	
Normal Dose Aspirin users *>0 - <736 DDD (n=1916)*	**23.2**	**36.6**	**<0.001***
High Dose Aspirin users *≥736 DDD (n=340)*	**4.0**	**7.4**	
Non-Paracetamol users *(n=6031)*	**80.9**	**64.9**	
Normal Dose Paracetamol users *>0 - <300 DDD (n=1375)*	**16.3**	**28.9**	**<0.001***
High Dose Paracetamol users *≥300 DDD (n=251)*	**2.8**	**6.2**	

[1]Non-users of NSAIDs, Aspirin and Paracetamol (n=3360), *Statistically significant at $p \leq 0.05$.

Appendix 8 - Preceding Drug use and baseline eGFR

Analgesia use	eGFR ≥60 N=3478 %	eGFR <60 N=667 %	*p*-value
[1]**Non users of any the three drugs** *(n=1661)*	**41.4**	**33.1**	**<0.001***
Non-NSAID users *(n=3434)*	**81.9**	**88.0**	**0.001***
Normal Dose NSAID users *>0 - <452 DDD (n=605)*	**15.4**	**10.3**	
High Dose NSAID users *≥452 DDD (n=106)*	**2.7**	**1.6**	
Non-Aspirin users *(n=2536)*	**62.8**	**52.6**	**<0.001***
Normal Dose Aspirin users *>0 - <672 DDD (n=1387)*	**32.2**	**40.2**	
High Dose Aspirin users *≥672 DDD (n=222)*	**5.0**	**7.2**	
Non-Paracetamol users *(n=3237)*	**79.9**	**68.5**	**<0.001***
Normal Dose Paracetamol users *>0 - <267 DDD (n=758)*	**16.9**	**25.5**	
High Dose Paracetamol users *≥267 DDD (n=150)*	**3.2**	**6.0**	

[1]Non-users of NSAIDs, Aspirin and Paracetamol (n=1661), *Statistically significant at $p \leq 0.05$.

Appendix 9 - Manuscript Abstract 1

Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely regarded as one of the risk factors which influence Chronic Kidney Disease (CKD) progression. However, previous literature reviews have not quantified the risk in moderate to severe CKD patients. Our systematic review aims to estimate the strength of association between chronic NSAID use and CKD progression using meta-analysis, by identifying general population studies.

Method

Searched electronic databases were MEDLINE, EMBASE, Cochrane, AMED, BNI, and CINAHL until September 31st 2011 without date or language restrictions. Searches also included the reference lists of relevant identified studies, WEB of KNOWLEDGE, openSIGLE, specific journals, the British Library and expert networks. For relevant studies, random effects meta-analysis was used to estimate the association between NSAID use and accelerated CKD progression (defined as a Glomerular Filtration Rate (GFR) decline of $\geq$15ml/min/1.73m^2).

Results

From a possible 768 articles, after screening and selection, seven studies were identified (5 cohort, 1 case-control and 1 cross-sectional). Using 3 cohort studies (total sample size, n=54,663), regular dose NSAID use did not significantly affect the risk of accelerated CKD progression; pooled Odds Ratio (OR) = 0.96 (95%CI; 0.86 to 1.07), but high dose

NSAID use significantly increased the risk of accelerated CKD progression; pooled OR= 1.26 (95%CI; 1.06 to 1.50).

Conclusion

The avoidance of NSAIDs in the medium term is unnecessary in patients with moderate to severe CKD, if not otherwise contraindicated. As the definition of high dose use remains unclear, the lowest effective dose of NSAIDs should be prescribed where indicated.

Appendix 10 - Manuscript Abstract 2

Non-Steroidal Anti-Inflammatory Drug Prescription and Significant Chronic Kidney Disease Progression: A Clinical Linkage Study from General Practice

Introduction

The association between Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Chronic Kidney Disease (CKD) progression is unclear. However, NSAIDs are commonly used by patients with inflammatory musculoskeletal conditions. This study aims to quantify the risk of medium term NSAID prescription on CKD progression.

Methods

A historical cohort was constructed from two population-based general practices in England (UK) linking diagnostic, prescribing and routine clinical data. This dataset included all subjects aged 40 years and over with 2 or more estimated Glomerular Filtration Rate (eGFR) measurements spaced at least 90 days apart between January 1st 2009 and December 31st 2010 (n=4,145).

Cumulative NSAID prescriptions given before the last eGFR test were standardised using the Defined Daily Dose (DDD) and subjects were categorised into non-user (0 DDDs), normal dose (DDDs <85th percentile) and high dose (DDDs ≥85th percentile) groups.

Logistic regression methods were used to explore the associations between NSAID prescription and the outcome of significant CKD progression (defined as eGFR decline

rate >5ml/min/1.73m^2 per year) adjusting for age, gender, deprivation, diabetes, cardiovascular disease, Angiotensin Converting Enzyme inhibitor or Angiotensin Receptor Blockers or Renin inhibitor prescription, Aspirin or Paracetamol prescription and baseline CKD stage.

Results

The prevalence of NSAID prescribing was 17.2% (n=711) and 16.1% (n=667) of the study cohort had stage 3-5 CKD. Significant CKD progression occurred in 928/3434 (27.0%) non-users, 149/605 (24.6%) normal dose and 22/106 (20.8%) high dose users.

There was no significant association between normal dose NSAID prescribing (odds ratio - OR= 1.02, 95%CI: 0.83-1.25) or high dose NSAID prescribing (OR= 0.83, 95%CI: 0.51-1.35) and significant CKD progression.

Conclusions

NSAID prescription over two years does not lead to significant CKD progression. However, the effects of long term NSAID prescription on CKD progression remain uncertain.

Appendix 11 - Presentation Poster 1

Non-Steroidal Anti-Inflammatory Drugs and Chronic Kidney Disease Progression: A Systematic Review and Meta-Analysis

Paul Nderitu[1,2,3], Lucy Doos[1,2], Peter W Jones[1,2], Simon J Davies[1,2], Umesh T Kadam[1,2]

[1]Institute of Science and Technology in Medicine, Keele University, Stoke-on-Trent, UK.
[2]Health Services Research Unit, Keele University, Keele, UK.
[3]Keele University Medical School Keele University, Keele, UK.
p.nderitu@istm.keele.ac.uk

Introduction

- The prevalence of stage 3 to 5 Chronic Kidney Disease (CKD) is 8.5% in the adult UK population and rising.
- CKD is associated with numerous complications (e.g. cardiovascular disease and anaemia).
- Patients with End-Stage Renal Disease (ESRD) requiring renal replacement therapy comprise only 0.05% of the total UK population but consume 1-2% of the total NHS budget.
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are prescribed to patients with chronic inflammatory musculoskeletal conditions.
- NSAIDs can cause tubulo-interstitial nephritis and acute kidney injury.
- However, evidence on the association between NSAIDs and CKD is inconclusive.
- Given the clear clinical, economic and quality of life implications that could result from use of NSAIDs in CKD, a systematic review is required to quantify any possible risks.

Objectives

1. To quantify the effect of NSAID use on CKD progression in patients with stage 3 to 5 CKD.
2. To quantify the effect of NSAID use on the risk of developing stage 3 to 5 CKD.

Methods

Inclusion Criteria

- Population-based studies, ≥6 months duration.
- Sample size ≥50, male and female participants aged 45 and over.
- Participants with stage 3 to 5 CKD.
- All orally administered NSAIDs including Aspirin.
- A measured or estimated Glomerular Filtration Rate (GFR) (using the Modification of Diet in Renal Disease or body-surface-area adjusted Cockroft-Gault equations).
- No language or date of publication restrictions.

Exclusion Criteria

- Phenacetin users.
- ESRD as the primary outcome.

Search Strategy

- Exploded MeSH terms related to NSAIDs, CKD and the GFR.
- Searched databases:
  - MEDLINE, EMBASE, Cochrane, AMED, BNI and CINAHL.
- Other sources:
  - Reference lists, WEB of KNOWLEDGE, openSIGLE, the Lancet Journal, the British Library and a CKD expert.

Figure 1. Study Flow Diagram

- 31 unique articles were identified; 7 were included in the systematic review, of which 3 were also included in the meta-analysis.

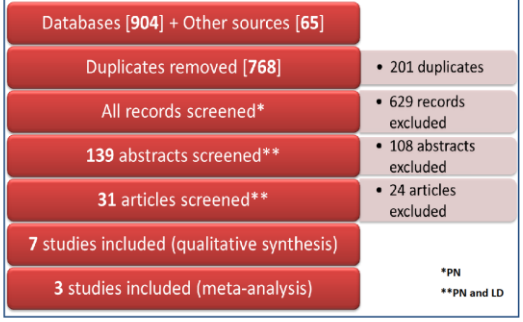


Table 1. Studies reporting the risk of CKD progression or the development of stage 3 to 5 CKD with NSAID use

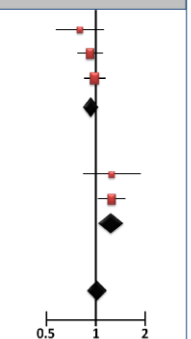
Outcome Measure	Study	Sample size	CKD stage	Dose	Estimate	95% CI
Accelerated CKD Progression (GFR decline of ≥15ml/min/1.73m²)	[1]Gooch *et al.*, 2007	10,184	3	R	0.82	0.59-1.15
			1 to 5	H	1.26	1.04-1.53
	[1]Hemmelgarn *et al.*, 2007	10,184	1 to 5	R	1.00	0.90-1.20
	[1]Yarger *et al.*, 2011	34,295	3	R	0.94	0.78-1.12
			3	H	1.28	0.84-1.93
Difference in the rate of eGFR decline per year	[2]Evans *et al.*, 2009	801	4 to 5	R	+0.80	+0.10, +1.50
Developing stage 3 to 5 CKD	[1]Fored *et al.*, 2001	926 patients vs. 998 controls	4 to 5	R	2.50	1.90-3.30
	[1]Agodoa *et al.*, 2008	8,057	3 to 5	R	1.21	0.70-2.10
	[1]Agodoa *et al.*, 2008	8,057	3 to 5	R	0.95	0.70-1.20
	[3]Hippisley-Cox *et al.*, 2010	1,574,749	3B	R	1.30	1.27-1.32

[1]Odds ratio; [2]Difference in the β coefficients of the user and non-user groups; [3]Hazard ratio; 95% CI - 95% Confidence Interval; R - Regular dose; H - High dose; Purple = Significant result - Regular dose NSAID use; Red = Significant result - High dose NSAID use; Black = non-significant result normal or high dose NSAID use; Green shading = CKD progression studies; Blue shading = Studies reporting on the risk of developing stage 3 to 5 CKD.

Table 2. Random-effects meta-analysis of accelerated CKD progression studies

Subgroup	Study	SE	Weight (IV)	Odds Ratio	95% CI	Forest Plot
Regular dose	Gooch *et al.*,	0.1702	12.7%	0.82	0.59-1.15	
	Yarger *et al.*,	0.0920	25.0%	0.94	0.78-1.12	
	Hemmelgarn *et al.*,	0.0733	29.3%	1.00	0.90-1.20	
	Subtotal		67.0%	0.96	0.86-1.07	
Heterogeneity I^2 = 0%						
Test for overall effect: Z = 0.80 (*p*=0.43)						
High dose	Yarger *et al.*,	0.2106	9.3%	1.28	0.84-1.93	
	Gooch *et al.*,	0.0984	23.7%	1.26	1.04-1.53	
	Subtotal		33.0%	1.26	1.06-1.50	
Heterogeneity I^2 = 0%						
Test for overall effect: Z = 2.62 (*p*=0.009)						
	Total		100%	1.04	0.90-1.20	

Heterogeneity I^2 = 52%
Test for overall effect: Z = 0.49 (*p*=0.63)
Test for subgroup differences (heterogeneity) I^2 = 85.7%



SE - Standard error; IV - Inverse Variance; 95% CI - 95% Confidence Interval; Dark Green = Regular dose NSAID use; Light Green = High dose NSAID use.

Results

NSAIDs and the risk of CKD progression

- Regular dose NSAID use did not significantly increase the risk of accelerated CKD progression; **pooled Odds Ratio (OR)= 0.96 (95%CI; 0.86-1.07) (Table 2).**
- High dose NSAID use significantly increased the risk of accelerated CKD progression; **pooled OR= 1.26 (95%CI; 1.06-1.50) (Table 2).**

NSAIDs and the risk of developing stage 3 to 5 CKD

- Two out of three studies found a significantly increased risk of developing stage 3 to 5 CKD with regular NSAID use (Table 1).

Limitations and Recommendations

- The definition of regular and high dose NSAID use is not standardised.
- The systematic review is based on a small number of observational studies.
- The complete avoidance of NSAIDs is not justified.
- The lowest effective dose of NSAIDs should be given where indicated and renal function should be monitored annually.

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- North Staffordshire Medical Institute

Appendix 12 - Presentation Poster 2

Non-Steroidal Anti-Inflammatory Drug Prescription and Significant Chronic Kidney Disease Progression: A Clinical Linkage Study from General Practice

Paul Nderitu[1,2,3], Lucy Doos[1,2], Vicky Strauss[4], Mark Lambie[1], Simon J Davies[1,2], Umesh T Kadam[1,2]

[1]Institute of Science and Technology in Medicine, Keele University, Stoke-on-Trent, UK.
[2]Health Services Research Unit, Keele University, Keele, UK.
[3]Keele University Medical School Keele University, Keele, UK.
[4]Institute of Primary Care and Health Sciences, Keele University, Keele, UK.
p.nderitu@istm.keele.ac.uk

Introduction

- Chronic kidney disease (CKD) is a major cause of morbidity and mortality worldwide.
- Identifying and avoiding disease progression risk factors is important in the management of CKD.
- Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are widely regarded as one risk factor which influences CKD progression.
- NSAIDs are commonly used by patients with inflammatory musculoskeletal conditions.
- The published literature is conflicting and the association between NSAID use and CKD is unclear.
- This study aims to quantify the risk of medium term NSAID prescription on CKD progression.

Study Objectives

1. To describe the socio-demographic, co-morbidity and co-drug therapy characteristics of NSAID users and non-users.
2. To estimate the prevalence and dose of NSAID prescribing in general practice CKD patients.
3. To quantify the risk of NSAID prescribing on significant CKD progression.

Methods

Study subjects

- Two large general practices in the UK (N= 23,028) between 1st Jan 2009 to 31st Dec 2010.
- Male and female patients aged 40 years and over on the 1st Jan 2009 (N= 13,081).
- At least 2 estimated Glomerular Filtration Rate (eGFR) measurements (N= 4,606).
- At least 90 days between the first and last recorded eGFR (N= 4,145).

Prescription data (PiPCA)

- All NSAID prescribing before the date of the last eGFR measurement.
- Angiotensin Converting Enzyme Inhibitors (ACE-i)/Angiotensin Receptor Blockers (ARBs)/ Renin-inhibitors (Renin-i) prescribing during the study period.
- Aspirin and Paracetamol prescribing before the date of the last eGFR measurement.

Chronic disease registration data (CiPCA)

- Cardiovascular disease (CVD).
  - Hypertension, ischaemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, dysrhythmia.
- Diabetes mellitus (DM).

NSAID dose definition

- Cumulative exposure.
  - Total NSAID prescribing before the last eGFR measure.
- Cumulative Defined Daily Dose (DDD).
  - Cumulative exposure/World Health Organisation (WHO) DDD per NSAID.
- Non-user (0 DDD), normal dose (DDDs <85th percentile), high dose (DDDs ≥85th percentile) user.

Study outcome

- Significant CKD Progression (eGFR decline rate >5ml/min/1.73m^2/year).
  - Calculated as (Last eGFR-First eGFR) x (365/eGFR interval in days).
- The study outcome matches the UK national guidelines (NICE guidelines) for a clinically significant eGFR decline rate.

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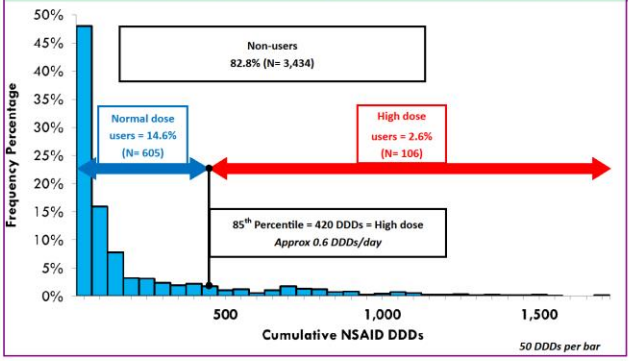
Table 1. Study characteristics of NSAID users and non-users

Variable		Non-users (n=3434)	Normal-dose users (n=605)	High-dose users (n=106)	*p*-value
Mean Age (SD)		67 (12)	62 (12)	61 (10)	<0.001
Gender (%)	M	46.0	43.3	39.6	0.227
	F	54.0	56.7	60.4	
Deprivation (%)	Least Deprived Quartile	24.2	24.0	17.9	0.289
	IMD 2	24.8	27.1	27.4	
	IMD 3	26.6	27.8	24.5	
	Most Deprived Quartile	24.4	21.2	30.2	
All CVD	Yes (%)	71.3	58.3	54.7	<0.001
Diabetes	Yes (%)	26.9	23.6	25.5	0.237
Aspirin	Users (%)	40.6	31.1	26.4	<0.001
Paracetamol	Users (%)	21.2	24.8	28.3	0.039
ACE-i/ARBs/Renin-i	Users (%)	55.9	45.6	37.7	<0.001
Rate of eGFR decline	Median [IQR]	0 [-5.59, +0.84]	0 [-4.93, 0]	0 [-4.18, +1.24]	0.571

SD - Standard deviation; IQR - Interquartile range.

Figure 1. Distribution of Standardised Cumulative NSAID doses (DDD)



Results

NSAID user characteristics and prescribing dosage

- Mean age, CVD prevalence, aspirin, paracetamol and ACE-i/ARBs/Renin-i prescribing differed significantly between NSAID users and non-users. High dose NSAID users had relatively high levels of deprivation compared to non-users (Table 1).
- The prevalence of NSAID prescribing was 17.2% with the majority receiving relatively low doses over two years (Figure 1).

Outcome prevalence characteristics

- Prevalence of stage 3 to 5 CKD at baseline = 16.1% (N=667).
- Overall prevalence of significant CKD progression = 26.5% (N=1,099).
  - Prevalence in non-users = 27.0%, normal dose users = 24.6% and high dose users = 20.8%.
  - There was no significant difference between the rate of eGFR decline between users and non-users (p = 0.571, Table 1)

NSAID prescribing and significant CKD progression

- There was no significant association between normal dose NSAID prescribing and significant CKD progression.
  - Adjusted Odds Ratio (OR)= 1.02 (95%CI: 0.83-1.25).
- There was no significant association between high dose NSAID prescribing and significant CKD progression.
  - Adjusted OR= 0.83 (95%CI: 0.51-1.35).

Limitations and Recommendations

- The sample size within the high dose user group was limited.
- The two year study period may be insufficient to detect the effects of long tern NSAID use.
- The lowest effective dose of NSAIDs should be prescribed where indicated and the eGFR should be monitored annually.
- Future studies should explore the long term effects of normal and high dose NSAID use on CKD progression.

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- Wolfson Foundation
- North Staffordshire Medical Institute

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