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FACULTY OF MEDICINE

Primary Care and Population Sciences

Inequalities, outcomes, and health literacy in people with chronic kidney disease

by

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ABSTRACT

FACULTY OF MEDICINE

Public Health

Thesis for the degree of Doctor of Medicine

INEQUALITIES, OUTCOMES, AND HEALTH LITERACY

IN PEOPLE WITH CHRONIC KIDNEY DISEASE

Simon Douglas Stafford Fraser

Background

Chronic kidney disease (CKD) is common and associated with increased risk of cardiovascular disease (CVD), progression to end stage kidney disease, and other complications. Albuminuria is an independent risk factor for poor outcomes. Socioeconomic inequalities are recognised in progression to renal replacement therapy (RRT). Little is known about socioeconomic inequalities in complications, management, and outcomes in earlier CKD. Lack of adequate health literacy (HL) has been linked to poor health outcomes and inequality, and is potentially modifiable.

Aims / methods:

The studies in this thesis aimed to investigate:

a. Socioeconomic inequalities in low estimated glomerular filtration rate (eGFR) and albuminuria prevalence in the Health Survey for England.
b. Cardiovascular risk, blood pressure (BP) control, albuminuria, and survival in a prospective cohort of 1741 people with CKD stage 3.
c. Process and outcome measures, including CKD identification, albuminuria measurement, acute kidney injury (AKI), RRT and mortality, in a retrospective cohort of 24,000 people with CKD from the Hampshire Health Record (HHR).
d. Prevalence and associations of limited HL in CKD (systematic review)

Results from each component:

a. CKD and albuminuria prevalence were associated with low socioeconomic status (SES).
b. Elevated CVD risk was associated with lower education status and lack of awareness of CKD diagnosis. Suboptimal BP control was common, particularly in those at most risk.
c. CKD was under-recognised and albuminuria assessment under-performed. All-cause mortality was independently associated with lower SES. GP diagnosis of CKD and hypertension were associated with reduced mortality risk. People with comorbidities were at greater risk of mortality, RRT, AKI and emergency hospital admission.
d. Limited HL is common in CKD and associated with low SES.

Conclusions

Low eGFR and albuminuria are more common in people with lower SES. People with lower SES and CKD are at greater risk of CVD and mortality. Aspects of CKD management, particularly identification of CKD, urine testing for albuminuria and BP control could be improved. Improving the limited HL of people with CKD may help reduce inequality gaps and improve outcomes.

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DECLARATION OF AUTHORSHIP

I, Simon Douglas Stafford Fraser declare that the thesis entitled 'Inequalities, outcomes, and health literacy in people with chronic kidney disease' and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- parts of this work have been published as:

  Published papers

  Fraser SD, Roderick PJ, Casey M, Taal MW, Yuen HM, Nutbeam D. Prevalence and associations of limited health literacy in chronic kidney disease: a systematic review. Nephrology Dialysis Transplantation. 2013;28 (1):129-37.

  Fraser SDS, Roderick PJ, McIntyre NJ, Harris S, McIntyre CW, Fluck RJ, Taal MW. Socioeconomic disparities in the distribution of cardiovascular risk in chronic kidney disease stage 3. Nephron Clinical Practice 2012;122:58-65 (doi: 10.1159/000348835)

Fraser SDS, Roderick PJ, McIntyre NJ, Harris S, McIntyre CW, Fluck RJ, Taal MW. Suboptimal blood pressure control in chronic kidney disease stage 3: baseline data from a cohort study in primary care. BMC Family Practice 2013, 14:88 doi:10.1186/1471-2296-14-88. Published: 24 June 2013

Fraser SD, Roderick PJ, Aitken G, Roth M, Mindell JS, Moon G, O'Donoghue D. Chronic kidney disease, albuminuria, and socioeconomic status in the Health Surveys for England 2009 and 2010. Journal of Public Health 2013; doi: 10.1093/pubmed/fdt117

Conference presentations

Limited health literacy prevalence in chronic kidney disease and related disorders; a systematic review. Presented at the Worldwide Universities Network / UK Health Literacy Conference, Southampton, May 2012.

Poster Presentations / Abstracts

Taal MW, Fraser SDS, Roderick PJ, Harris S, McIntyre NJ, Fluck RJ, McIntyre CW. Skin autofluorescence: a non-invasive test to improve mortality risk prediction in chronic kidney disease stage 3. Poster presented at the American Society of Nephrology Conference, Atlanta, Georgia, November 2013.

Fraser SD, Roderick PJ, Aitken G, Roth M, Mindell JS, Moon G, O'Donoghue D. Chronic kidney disease, albuminuria, and socioeconomic status in the Health Surveys for England 2009 and 2010. Poster presented at Public Health England Annual Conference, Warwick, September 2013 and at Society of Social Medicine Annual Conference, Brighton, September 2013.

Fraser SDS, Roderick P, McIntyre N, Harris S, McIntyre C, Fluck R, Taal M. Blood pressure control in patients with CKD Stage 3 in primary care. Poster presented at The British Transplantation Society and the Renal Association joint congress, Bournemouth, March 2013, and at the British Renal Society Conference, Manchester, May 2013.

Fraser SDS, Roderick P, McIntyre N, Harris S, McIntyre C, Fluck R, Taal M. Measurement and associations of albuminuria in people with CKD Stage 3 in primary care. Poster presented at The British Transplantation Society and the Renal Association joint congress, Bournemouth, March 2013.

Fraser SDS, Roderick P, Bailey L, Sanderson H. Novel use of a combined primary and secondary care data resource: investigation of inequalities in chronic kidney disease identification in the UK Hampshire Health Record. Public Health Abstracts. The Lancet Nov 2012. Poster presented at 'Public health science: A national conference dedicated to new research in public health', London, November 2012

Fraser SD, Roderick PJ, Casey M, Taal MW, Yuen HM, Nutbeam D. Prevalence and associations of limited health literacy in chronic kidney disease: a systematic review. Poster presented at the Society of Social Medicine Annual Conference, London, September 2012.

Signed: ……..

Date:……

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Most importantly, this work would not have been possible without the understanding, patience and support of my wife Lindsey and my children James and Rebecca, and to them I dedicate this thesis.

Definitions and Abbreviations

A level	Advanced level
ACE	Angiotensin converting enzyme
AF	Atrial fibrillation
AGE	Advanced glycation end products
AKI	Acute kidney injury
AMI	Acute myocardial infarction
AMNART	American national adult reading test
ARB	Angiotensin II receptor blockers
ARIC	Atherosclerosis risk in communities study
AU	Arbitrary units
AVF	Aterio-venous fistula
BEI	British education index
BMI	Body mass index
BP	Blood pressure
BSAIT	Basic skills agency initial assessment test
CCF	Congestive cardiac failure
CCG	Clinical commissioning group
CHD	Coronary heart disease
Chi2	Chi squared
CKD	Chronic Kidney Disease
CKDEPI	Chronic kidney disease epidemiology collaboration
CKDPC	Chronic kidney disease prognosis consortium
CRF	Chronic renal failure
CRIC	Chronic renal insufficiency cohort
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
Cys C	Cystatin C
DBP	Diastolic blood pressure
EDTA	^{Cr}51-ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EMIS	Egton medical information systems
ESKD	End stage kidney disease

ESRD	End stage renal disease
ESRF	End stage renal failure
GCE	General certificate of education
GCSE	General certificate of secondary education
GFR	Glomerular filtration rate
GLOMMS	Grampian laboratory outcomes morbidity and mortality study
GP	General practitioner
GP2GP	General practitioner to general practitioner record transfer
HALS	Health activities literacy scale
HbA1c	Haemoglobin A1c
HDL	High density lipoprotein
HHR	Hampshire health record
HHRa	Hampshire health record analytics database
HL	Health literacy
HLQ	Health literacy questionnaire
HMIC	Health management information consortium
HR	Hazard ratio
HSE	Health survey for England
HUNT	Nord-Trøndelag health study
IBM SPSS	International business machines statistical package for the social sciences
ICD10	International classification of diseases 10th revision
IDMS	Isotope dilution mass spectrometry
IHD	Ischaemic heart disease
IMD	Indices of multiple deprivation score
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	National Kidney Foundation Kidney Disease Outcome Quality Initiative
KEEP	Kidney early evaluation program
LDL	Low density lipoprotein
LR	Likelihood ratio
LSOA	Lower super output area
LVH	Left ventricular hypertrophy
MAP	Mean arterial pressure
MART	Medical achievement reading test
MDRD	Modified diet in renal disease

MIQUEST	Morbidity information query and export syntax
mm Hg	Millimetres of mercury
NAP	Non-albumin proteinuria
NART	National adult reading test
NEOERICA	New opportunities for early renal intervention by computerised assessment
NHANES	National health and nutrition examination survey
NHS	National health service
NICE	National institute for health and care excellence
NSAID	Non-steroidal anti-inflammatory drugs
NSF	National service framework
NS-SEC	National statistics socio-economic classification
NVQ	National vocational qualification
NVS	Newest vital sign
O level	Ordinary level
OR	Odds ratio
PCT	Primary care trust
PH	Public health
PIAT	Peabody individual achievement test
PRD	Primary renal diagnosis
PVD	Peripheral vascular disease
QICKD	Quality improvement in chronic kidney disease study
QOF	Quality and outcomes framework
QRisk2	Qrisk clinical risk calculator
RAASi	Renin-angiotensin aldosterone system inhibitors
RAGE	Receptor for advanced glycation end products
REGARDS	Reasons for geographic and racial differences in stroke study
REALM	Rapid estimate of adult literacy in medicine
RRID	Renal risk in Derby study
RRT	Renal replacement therapy
SAHLSA	Short assessment of health literacy for Spanish adults
SAIL	Secure anonymised information linkage databank
SBP	Systolic blood pressure
Scr	Serum creatinine
SD	Standard deviation

SES	Socioeconomic status
Skin AF	Skin autofluorescence
STATA	STATAcorp statistics package
STOFHLA	Short form of the test of functional health literacy in adults
THIN	The health improvement network database
TOFHLA	Test of functional health literacy in adults
uACR	Urine albumin:creatinine ratio
UCL	University College London
UHS	University Hospitals Southampton
UK	United Kingdom
uPCR	urinary protein:creatinine ratio
US / USA	United States / United States of America
WHO	World Health Organisation
WRAT	Wide range achievement test
95% CI	Ninety five percent confidence interval

1. Background and aims

Prior to 2002, definitions of a group of conditions characterised by reduction in kidney function and called 'chronic renal failure' (CRF) relied for their definition on sustained levels of serum creatinine above a given threshold (variously ≥300μmol/l, ≥2.0mg/dL, ≥1.7mg/dL, >1.2mg/dL in females and >1.4mg/dL in males).[1-5] More recently, the term chronic renal insufficiency was preferred, and creatinine clearance was used to categorize severity as mild (>50ml/min), moderate (25-50ml/min), severe (10-25ml/min) and end stage renal failure (<10ml/min).[6] In 2002, the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) defined Chronic Kidney Disease (CKD) based on two criteria present for at least three months:

a) Kidney damage, either abnormal structural (pathological samples or imaging studies) or functional (markers of abnormal composition of the urine or blood)

b) Glomerular filtration rate (GFR) <60ml/min/1.73m^2 [27]

CKD, defined by estimated GFR (eGFR), is now recognised as a common long-term condition that represents an important public health issue. At a global level, there is evidence of increasing incidence and prevalence of people requiring renal replacement therapy (RRT, dialysis or transplantation) for end stage kidney disease (ESKD) and high prevalence of earlier stages of CKD. [8] By 2004, the estimated global population of people receiving some form of RRT was 1,783,000 (1,371,000 receiving dialysis, 412,000 with a functioning renal transplant) – an increase from an estimated 158,000 receiving dialysis globally in 1980.[9 10] As well as its association with ESKD and the need for RRT, CKD is linked to several common complications and co-morbidities including cardiovascular disease (CVD) and acute kidney injury (AKI). Much of the increase in the prevalence of CKD and its complications is attributed to the globally increasing prevalence of risk factors, particularly obesity, smoking, hyperlipidaemia, diabetes and hypertension.[8] In addition to this growing burden of disease, there is evidence that CKD and its complications absorb an important proportion of the health budget of many countries, [8 11] In England, the estimated cost of CKD to the National Health Service (NHS) in 2009-10 was between £1.44 and £1.45 billion (about 1.3% of all NHS spending in that year).[12]

Chapter 1 – Background and aims

CKD is frequently asymptomatic, and early stages are often under-recognised by clinicians and by patients themselves. Although the importance of having mild to moderate CKD has been questioned, with some arguing that identifying and labelling a person (particularly an elderly person) as having CKD may be counter-productive, and may even carry risks that outweigh the potential benefits of disease identification and management, there is clear evidence that reduction in kidney function in CKD is associated with poorer outcomes, including in the elderly, and that some complications of CKD are potentially avoidable. [13] There is also evidence that certain aspects of CKD are not distributed evenly across populations, but that people from certain groups bear the brunt of this condition and its complications, particularly the elderly, people from lower socioeconomic groups and people from ethnic minorities. [2,8,11] The association between ethnicity and CKD in the UK have been well described (and were not within the remit of the studies conducted in this thesis), but some aspects of the relationship between socioeconomic status (SES) and CKD are not well understood, particularly with regard to certain outcome measures.

This thesis describes four separate research studies that had an overarching aim to expand knowledge of aspects of CKD epidemiology, and to provide a better understanding of the relationship between SES and CKD in the UK context.

The first chapter will explain the nature and epidemiology of CKD, outline the importance of health inequalities and their role in CKD, and introduce the concept of health literacy (HL) as a potentially important consideration in this context. The chapter will conclude by describing the research questions that the thesis aimed to address and the methods used to do so.

1.1 Kidney function and chronic kidney disease (CKD)

In order to understand the context of this research and the importance of CKD, it is valuable to have an understanding of the basic functions of the kidney, appreciate the definition and classification of CKD, and to understand its descriptive epidemiology. This section provides an outline of the functions of the kidney and the methods by which kidney function is measured. It then describes CKD definition and categorisation, and goes on to describe its epidemiology, and the policy initiatives that have been introduced with the aim of improving CKD outcomes in the UK.

1.1.1 Functions of the kidney

The kidney has several important functions in normal human physiology. These include excretory functions, metabolic functions, and endocrine functions. The excretory functions involve the removal of fluids, waste products of metabolism (nitrogenous waste), electrolytes (sodium and potassium), phosphate, and foreign molecules such as water-soluble medications and toxins. Metabolic functions include acid base homeostasis and regulation of electrolyte concentrations. Key to these functions are the glomeruli, (Figure 1) which act as a blood filtration system, and the renal tubules (Figure 2), which control fluid and electrolyte balance. Endocrine functions include the production of erythropoietin, which stimulates bone marrow to produce red blood cells, conversion of vitamin D to 1-25 hydroxy vitamin D, which is involved in calcium and phosphate homeostasis, catabolism of peptide hormones (including insulin), and production of renin, which controls the formation of angiotensin and influences blood pressure and sodium balance. [14 15]

Figure 1. Simplified diagram of the glomerulus

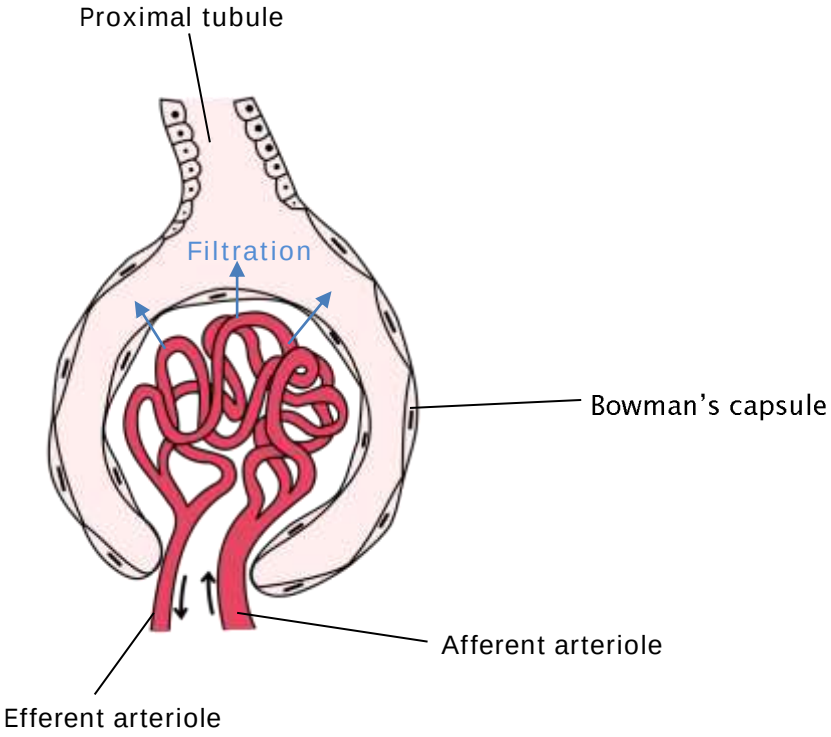

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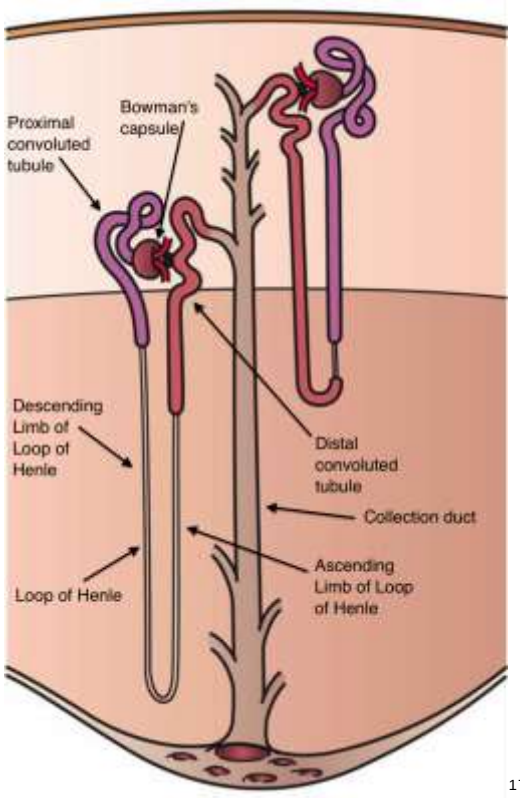
Figure 2. Simplified diagram of the nephron



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In people with renal dysfunction, there is therefore potential for each of these to be disrupted, with subsequent adverse effects on normal physiological processes. Toxic waste products accumulate, (including urea and creatinine, which are routinely measured in clinical practice and used to define the level of kidney function), and metabolic dysfunction can result in abnormal concentrations of electrolytes (which can be associated with important health risks such as cardiac arrhythmia due to hyperkalaemia). Disruption of normal endocrine function can result in anaemia, renal bone disease, osteoporosis, and hypertension.

1.1.2 Measurement of kidney function

Kidney dysfunction is commonly assessed in clinical practice by proxy measures of its excretory function, most commonly through estimation of glomerular filtration rate (GFR). Precise, direct measurement of GFR is difficult because of the lack of a perfect marker substance. Such a marker would be freely filtered at the glomerulus but not secreted or reabsorbed by the renal tubules. [15] Accurate measurement of GFR in the past has relied on assessing the clearance of an inert exogenous substance, inulin, given by infusion. This method is expensive and time consuming, and therefore impractical in routine clinical practice. More recently, radioisotope methods, using $^{Cr}51$-ethylenediaminetetraacetic acid (EDTA), have been used that have been shown to be broadly equivalent to inulin clearance, but are still time consuming and expensive to conduct. [18 19]

Historically therefore, in routine practice, creatinine (and derived creatinine clearance) has been used as a filtration marker. Creatinine is metabolised from creatine in muscle. Creatine is produced in the liver and transported to muscle cells where it is phosphorylated to creatine phosphate which acts as an energy store. Creatinine is freely filtered in the kidney (and not metabolised by the kidney), not bound to protein, and is physiologically inert, making it suitable as marker of filtration.[20 21] Creatinine has several limitations as a marker of kidney function, however. Muscle mass determines the pool of creatine from which creatinine is metabolised. This leads to variation in creatinine production with age (reduced muscle mass with increased age), sex (lower muscle mass in women), ethnicity (higher muscle mass in blacks), comorbidities with muscle wasting (e.g. myotonic dystrophy) and trauma and exercise (increased

creatinine associated with muscle damage). [22 23] Creatinine concentrations have also been shown to vary with diet (reduced in vegetarians, elevated with eating meat). [24 25] In addition to this, active secretion of creatinine by renal tubular cells results in higher creatinine clearance than would be expected at low plasma creatinine concentrations and in renal disease. [26 27] Moreover, in people with CKD, creatinine production exceeds the rate of accumulation in the serum and excretion in the urine ('creatinine deficit'). This creatinine deficit is eliminated by extra-renal creatinine metabolism, mainly involving release into the gut where it is degraded by gut normal flora. [28]

A further important consideration in the measurement of serum creatinine is standardisation of the assay method used. Historically, variation in analysis method between laboratories resulted in non-comparability of creatinine results between different centres (and therefore often between different research studies). Since 2006, isotope dilution mass spectrometry (IDMS) traceable measurements have been in use across the UK in order to calibrate results to a single standardised serum creatinine, thereby reducing this variability. [29]

The estimation of GFR has therefore relied on derivation from creatinine values through the use of estimating equations that try to adjust for muscle mass (age, sex, and race). Several different equations have been used to derive reliable estimated GFR (eGFR) from serum creatinine and other variables. These have included the Cockcroft Gault equation, the 4-variable Modified Diet in Renal Disease (MDRD) equation, and, more recently, the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) equation. [30-32] See Figure 3. It is beyond the scope of this thesis to describe the derivation and characteristics of these formulae in detail, but comparison of the use of the CKDEPI equation with the MDRD equation is explored in more detail in Chapter 2. eGFR is corrected for body surface area (based on a 'standard' body surface area of 1.73m^2) due to the recognition that renal clearance more closely mirrors body surface area than body weight. This has been questioned in the light of increasing body surface area in the general population, but 1.73m^2 is still widely used as the standard.[33 34] The MDRD equation has been shown to have limitations, particularly related to systematic under- estimation of GFR (bias) at higher values compared to the CKDEPI equation, which therefore tends to be a

more accurate estimator of true renal function and to classify people with and without CKD more accurately.[32]

Figure 3. Commonly used formulae for estimating kidney function from serum creatinine

Cockroft and Gault equation

$$\text{Estimated creatinine clearance (ClCr)} = \frac{(140-\text{age}) \times \text{weight} \times 1.2}{\text{SCr}} \times (0.85 \text{ if female})$$

4-variable MDRD equation

$eGFR = 186.3 \times (SCr/88.4)^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$

where SCr = serum creatinine in µmol/l, and age is expressed in years

Modified 4-variable MDRD equation

$eGFR = F \times 175 \times (SCr/88.4)^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$

where F = correction factor, SCr = serum creatinine in µmol/l, and age is expressed in years

CKD-EPI equation

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

where SCr = serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1 and max indicates the maximum of SCr/κ or 1

More recently, there has been interest in the use of (endogenous) cystatin C as a marker to measure GFR. [35] Cystatin C is a non-glycosylated polypeptide that is released from all nucleated cells as part of the response to tissue injury. It is a protease inhibitor, and is freely filtered by the glomerulus and reabsorbed in the proximal tubule where it is catabolised. Elevation in the serum therefore occurs in the context of reduced glomerular filtration. Different assays (latex particle-enhanced nephelometric immunoassays or turbidimetric assays) and different equations have been used to compute eGFR from Cystatin C. [36 37] It has several advantages over serum creatinine as a filtration marker; cystatin C is not influenced by muscle mass, sex, body habitus, age, weight, height, smoking, fever, malignant processes or inflammatory conditions. [38-43] In hypo- and hyperthyroidism, however, cystatin C is subject to variation, meaning that caution must be taken in its interpretation until thyroid function is normalised. [44]

1.1.3 Assessment of proteinuria and albuminuria

The presence of protein in the urine can also be a reflection of renal abnormality. The mechanisms of proteinuria are complex but in simple terms there are four main possibilities: Firstly, proteins cross the glomerular barrier (and are reabsorbed to a greater or lesser extent by tubular cells). Secondly, there is some renal tubular secretion of proteins from the blood. Thirdly, proteins may be synthesized by renal cells and released into the urine, and fourthly, proteinuria may arise from abnormalities further down the urogenital tract (such as urinary infection or transitional cell malignancy).[45] Measurement of the extent (including both quantity of protein and chronicity) of proteinuria is therefore an important element of the assessment of renal function. The traditional clinical standard measure of the extent of proteinuria involves 24 hour urine collection and measurement of protein excretion, however this involves some inconvenience for patients in practice, and other methods have evolved, particularly the measurement of urinary protein:creatinine ratio (uPCR) and albumin:creatinine ratio (uACR). Further simplification for convenience is the widespread use of reagent strips dipped into urine to measure either proteinuria or albuminuria. An extensive literature exists comparing these various methods of proteinuria assessment.[46] Full discussion of this literature is beyond the scope of this thesis, but some further aspects of proteinuria measurement are discussed in sections 1.4.2.3 and 3.4.3. The most recent Kidney Disease Improving Global Outcomes (KDIGO) [47] clinical practice guidelines recommend the use of uACR to evaluate proteinuria, followed by uPCR, with preference for an early morning urine sample being used. [48]

1.1.4 Chronic Kidney Disease – definition and classification

CKD is a non-communicable long-term condition defined by abnormality of kidney structure or function (or both) present for at least three months. [49 50] It is classified by degree of renal function, as measured by eGFR and by the presence or absence of structural kidney abnormality or by other evidence of kidney damage, particularly albuminuria. [49 51] CKD classification is summarised in Table 1

Table 1. Classification of Chronic Kidney Disease

CKD Stage	GFR (ml/min/1.73 m^2)	Description
1	≥ 90	Normal or increased GFR, with other evidence of kidney damage
2	60–89	Slight decrease in GFR, with other evidence of kidney damage
3A	45–59	Moderate decrease in GFR, with or without other evidence of kidney damage
3B	30–44	
4	15–29	Severe decrease in GFR, with or without other evidence of kidney damage
5	< 15	Established renal failure

The relationship between reduced kidney function (as measured by eGFR), level of albuminuria, and CKD prognosis has been helpfully summarised by the KDIGO Foundation (Figure 4). [48] This shows that low eGFR and elevated uACR act both independently and multiplicatively to increase risk of poor outcomes. People with CKD have higher levels of morbidity and mortality than the general population through greater risk of CVD, progression to ESKD, and other complications (hypertension, acute kidney injury (AKI), anaemia, malnutrition, and bone disease).[13 47 52 53]

Figure 4. Diagram showing the relationship between eGFR, level albuminuria, and CKD prognosis (in terms of risk of CKD progression) [48]

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g*	30-300 mg/g	>300 mg/g
				<3 mg/mmol*	3-30 mg/mmol	>30 mg/mmol
GFR categories (ml/min/ 1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk. *uACR measured by different conventions, figures shown are equivalent cut-off values for the different measures.

1.1.5 Causes of CKD

There are two main mechanisms underlying the renal injury associated with CKD; glomerulosclerosis and tubulointerstitial fibrosis. Glomerulosclerosis is similar to atherosclerosis and shares many of its risk factors, including smoking, hypertension and hyperlipidaemia. It involves endothelial damage – injury to the glomerular endothelium initiates glomerular microinflammation

which leads to mesangial cell activation, excessive deposition of extracellular matrix and subsequent glomerular remodelling and scarring and vascular damage. [8] Tubulointerstitial fibrosis is strongly related to proteinuria, whereby excessive resorption of albumin by cells in the proximal tubule results in inflammation, cell death, tubular atrophy and subsequent excessive deposition of extracellular matrix leading to fibrosis. [8 54 55] The European Renal Association and the European Dialysis and Transplant Association produces a set of primary renal diagnosis (PRD) codes that classify causes of kidney disease based on histopathological diagnoses. [56] However, renal biopsy to firmly establish diagnosis is procedure with not inconsiderable risk, and is rarely conducted, particularly in the general population of people with CKD in whom diagnosis is therefore based on eGFR and uACR as described above.[57]

Risk factors for the development of CKD therefore include factors common to other vascular disorders; smoking, obesity, diabetes, hypertension, and hyperlipidaemia, but also chronic inflammatory conditions. [58-60]

1.1.6 CKD epidemiology

1.1.6.1 Prevalence of CKD

Incidence of CKD is difficult to define and identify because of its often silent nature, protracted clinical course, and differences of opinion about the best definition.[61] A summary of the descriptive epidemiology of CKD therefore relies mainly on prevalence studies. In the past, serum creatinine was the only routinely available measure of renal function. In Australia, the AusDiab kidney study used Cockcroft Gault estimated GFR and proteinuria (dipstick proteinuria or uPCR) to describe the prevalence of kidney damage and found that 16% of the adult population had at least one indicator of kidney damage. [62] Data from the US National Health and Nutrition Examination Survey (NHANES) III demonstrated the high prevalence of CKD in the general population using MDRD eGFR and uACR (11% had stage 1–5). [63] The 2010 Health Survey for England (HSE) estimated that approximately 6% of men and 7% of women in England had stage 3-5 CKD based on MDRD eGFR, and that this was strongly positively related to age, with an estimated prevalence of 29% in men and 35% in women over the age of 75.[64] However, the definition of CKD requires chronicity, and the HSE is a cross sectional survey (which may therefore overestimate the prevalence of CKD). Similarly, baseline data from a large cluster-randomised trial in primary care in the UK (n=13,179) has demonstrated a prevalence of CKD of over 56% (95% CI 55.3-57.0) in people aged 75 and over. [65] This study identified higher CKD prevalence in women, people with CVD and people with hypertension. The prevalence of lower eGFR in this elderly population (representing poorer kidney function) was found to be 17.7% for eGFR < 45 (95% CI 17.1-18.4), and 2.7% (95% CI 2.4-2.9) for eGFR < 30. [65] The New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) study used primary care data from over 130,000 adults from different parts of England to estimate the prevalence of CKD based on serum creatinine (using MDRD eGFR). The age standardized prevalence of CKD stage 3 – 5 in NEOERICA was 10.6% for females and 5.8% for males. [66] By contrast, the overall prevalence of CKD stage 3-5 identified by General Practitioners (GPs) and recorded for the Quality and Outcomes Framework (QOF) was about 4% of the adult population in 2011. [67] The disparity between this prevalence and the prevalence of CKD identified in the HSE, NEOERICA, and in cohort studies suggests that, while identification of

CKD in primary care has improved since its inclusion as one of the General Practice QOF chronic diseases, a significant proportion of cases of CKD in the UK may remain unidentified and unquantified.

1.1.7 CKD outcomes

It is beyond the scope of this thesis to list the evidence for all of the potential adverse outcomes that may occur among people with CKD as outlined in section 1.1.1. However, there are key outcomes that are important in the context of this research for which people with CKD are at greater risk than the general population.

Firstly, people with CKD are at increased risk of progression to later stages of kidney disease including ESKD. [69 70] A community-based cohort study in Canada identified that for people with eGFR between 45 and 59ml/min/ 1.73 m^2 and heavy proteinuria, the independent relative risk of ESKD was 4.3 (95%CI 3.1-6.1) compared to people with eGFR of 60ml/min/ 1.73 m^2 and over with heavy proteinuria. [70] There have been similar findings from studies in other countries and in a meta-analysis of nine general population cohorts. [71 72] Such studies have demonstrated graded risk by levels of eGFR and uACR.[71]

Secondly, the risk of all-cause mortality is increased even in people with only moderate decline in renal function. [13 52 53 70 73 74] A systematic review of 39 studies (total 1,371,990 participants) identified an exponential relationship between absolute risk of death and decreasing renal function. [53]

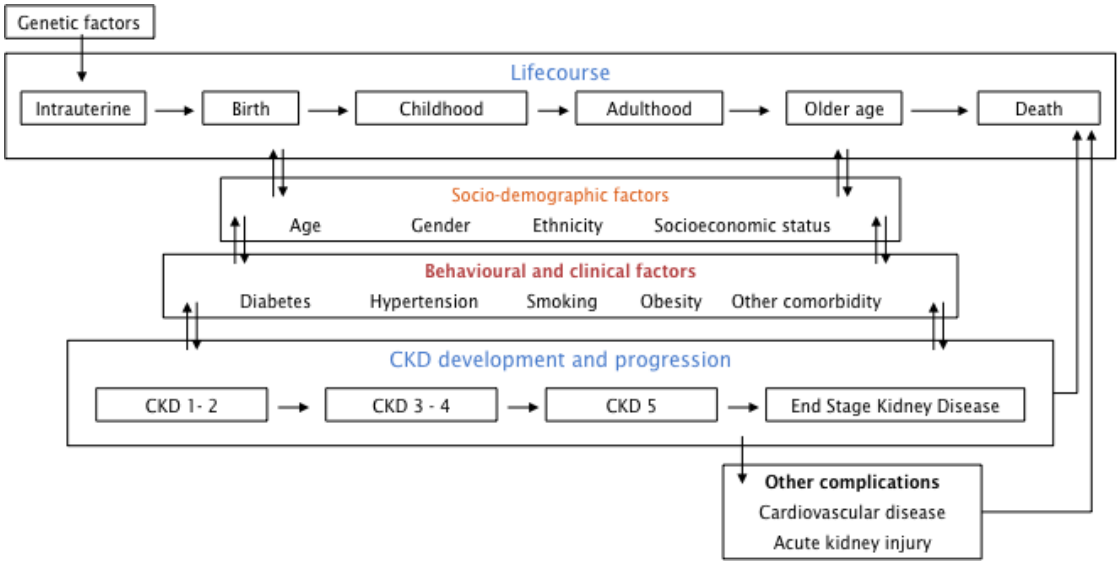
Thirdly, there is increased CVD risk among people with CKD. This has been demonstrated in many studies, including a collaborative meta-analysis of individual patient data from the CKD Prognosis Consortium (CKDPC, a group of investigators who are willing to share data for the purpose of collaborative meta-analyses to study prognosis in CKD), which showed an adjusted hazard ratio for cardiovascular mortality of 2.42 (95%CI 1.92-3.05) for people with eGFR 30-44ml/min/1.73m^2 compared to eGFR 90-104 ml/min/1.73m^2, and 3.06 (95%CI 2.00-4.70) for people in the same range of eGFR with heavy proteinuria. [13] There is substantial evidence for the increased risk of development of vascular disease and the occurrence of cardiovascular events in people with CKD. [52 74-82]

Fourthly, CKD has also been associated with increased risk of hospitalisation and healthcare costs. [12 52] Related to this is the increased risk of AKI among people with CKD. [83] AKI is defined by a reduction in kidney function in a short

period of time measured by relative increase in serum creatinine, absolute increase in serum creatinine, reduction in urine output, and or reduction in eGFR (see Appendix section 7.1). AKI is also an important risk factor for worsening of CKD, development of ESKD, and mortality. [84-87].

A schematic showing the development and progression of CKD across the lifecourse is shown in Figure 5. This is adapted from a similar model developed by Lynch and Kaplan describing socioeconomic influences on CVD.[88]

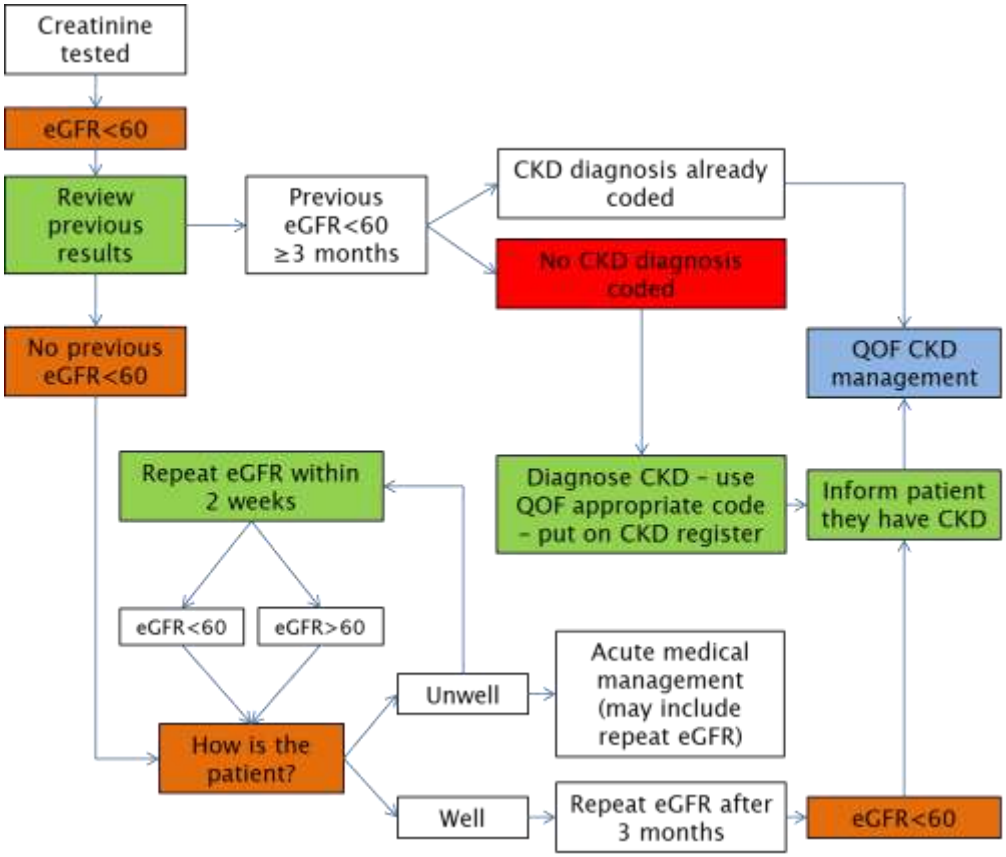
Figure 5. CKD development, progression and outcomes across the lifecourse



1.1.8 CKD diagnosis in practice

The correct identification of CKD is complicated compared to certain other comparable conditions. In hypertension, for example, diagnosis is based on repeat testing not merely on the basis of a single elevated BP, similar to the need for repeat eGFR testing in CKD. However, the KDOQI CKD guideline recommends a gap of at least three months between eGFR values in order to establish chronicity (whereas hypertension requires repeated elevated BP readings, but no time frame is specified, and repeat within a single consultation is considered acceptable).[89] This adds complexity in practice, particularly as low eGFR is also an indication of transient fall in renal function due to AKI, and GPs are recommended to repeat eGFR within two weeks in the context of finding no previous low eGFR.[90] Figure 6 shows an example of the pathway following identification of a low eGFR (<60ml/min/1.73m^2) in primary care. It could therefore potentially be easier for a diagnosis of CKD to be missed than certain other conditions in primary care. Clinicians may also have been confused by the changes in methods of measurement of renal function and definitions of chronic renal disease over time as described in section 1.1.2.

Figure 6. Flow diagram of the clinical management of a low eGFR in primary care



QOF = Quality and Outcomes Framework

1.1.9 CKD policy initiatives in the UK

Data on renal disease, and particularly on RRT, is collected by the UK Renal Registry. Driven mainly by the need to reduce ESKD and progression to dialysis and transplantation, the National Service Framework (NSF) for Renal Services 2004/5 summarised the need for people at increased risk of CKD to be identified, assessed, and managed to preserve kidney function, reduce progression, and reduce complication risk (particularly CVD). [91] Following this, routine reporting of eGFR (derived from serum creatinine by the MDRD equation) to GPs was introduced. In England, since 2004, GPs have been provided with incentive payments to achieve a range of quality standards in chronic disease management (using a detailed set of indicators for each chronic condition) under QOF. CKD has been included as a QOF condition since 2006/7. [92] The 2006/7 revision to QOF required GPs to keep a CKD register (CKD stage 3-5) and to achieve clinical targets in CKD management including

monitoring and control of blood pressure (BP, with achievement of targets). [93] The clinical indicators included in QOF have changed over time. Changes are instigated at the start of each financial year. In some years there were no changes to the CKD indicators. The CKD indicators and their changes are summarised in Table 2.

In 2008 the National Institute for Health and Care Excellence (NICE) also issued guidance on CKD investigation and classification, emphasising the importance of providing patient information and education (including lifestyle advice), identifying progression, referring appropriately to nephrology specialists, using correct and timely pharmacotherapy, identifying risk of CVD, and managing complications.[50]

The Marmot review (2010) is an important document influencing health policy in the UK.[94] It underlined the importance of understanding socioeconomic variations in order to improve health. This will be explored in more detail in the next section, which describes the role of SES in health, focusing on CKD.

Table 2. Changes in QOF CKD Indicators over time

	2006/07	2007/8	2008/9	2009/10	2010/11	2011/12	2012/13
CKD1. The practice can produce a register of patients aged 18 years and over with CKD (US National Kidney Foundation: Stage 3 to 5 CKD)	+	+	+	+	+	+	+
CKD 2. The percentage of patients on the CKD register whose notes have a record of blood pressure in the previous 15 months	+	+	+	+	+	+	+
CKD 3. The percentage patients on the CKD register in whom the last blood pressure reading, measured in last 15 months was 140/85 or less	+	+	+	+	+	+	+
CKD 4. The percentage patients on the CKD register with hypertension who are treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker	+	+	-	-	-	-	-
CKD 5. The percentage of patients on the CKD register with hypertension and proteinuria who are treated with an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) (unless a contraindication or side effects are recorded)	-	-	+	+	+	+	+
CKD 6. The percentage of patients on the CKD register whose notes have a record of a urine albumin: creatinine ratio (or protein: creatinine ratio) test in the previous 15 months	-	-	-	+	+	+	+

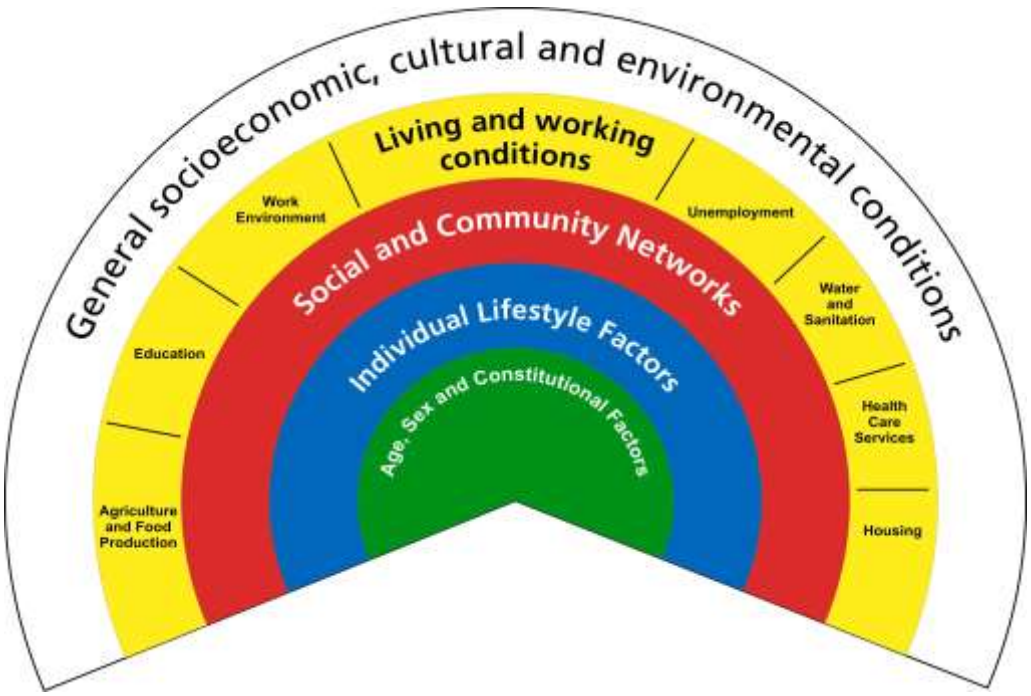
More recently, implementation of the NHS 'Health Check' (Vascular Risk Assessment Programme) has begun in England.[95] The aim is for all adults aged 40-74 to have a vascular risk assessment and stepped intervention according to their level of risk. It includes testing for CKD in those groups at higher risk such as patients with newly diagnosed hypertension. There is potential for this to improve identification of CKD in practice, but uncertainty about how it will affect inequalities if there is disproportionate uptake among people of higher SES.

1.2 Socioeconomic status and health inequalities

SES (or socioeconomic position) and its impact on health has been well documented for many medical conditions. In 1991, Dahlgren and Whitehead first created a schema to show the many influences on health in wider society.[96] See Figure 7. This illustrates that socioeconomic factors influence many aspects of chronic conditions such as CKD, including risk factors for its development, prevalence of the condition, access and use of health services and outcomes.

The distribution and influence of SES in the context of CKD is central to this research. This section provides an introduction to how SES is defined, and then outlines the importance of health inequalities and health inequity generally before focusing on the literature evidence for what is known and what is not known about socioeconomic inequalities in CKD. Inequalities in terms of ethnicity will also be described because of the complex interactions between the effects of SES and ethnicity on health (and some well recognised links between ethnicity and renal disease).[97] However, disparities related specifically to SES will then form a central theme of the rest of the thesis.

Figure 7. The factors that influence health (Dahlgren and Whitehead)



1.2.1 Defining socioeconomic status

SES has been classified in several different ways over time. A key consideration is whether SES is defined by some measure of individual status (such as wealth, or education) or by a measure of area status (such as a measure of poverty of an area).[88] Individual measures of SES have included occupational status, [98] income, [99] education status, [100] and wealth. [101] In the UK, area measures have included measures of area deprivation, such as the Townsend index (a four measure index including unemployment (as a percentage of those aged 16 and over who are economically active), non-car ownership (as a percentage of all households), non-home ownership (as a percentage of all households) and household overcrowding), [102] the Carstairs index (also based on four measures: low social class, lack of car ownership, overcrowding and male unemployment), [103] and the Index of Multiple Deprivation (IMD). The IMD has varied with respect to the variables included over time. The 2010 IMD was based on income, employment, health and disability, education skills and training, barriers to housing and other services, crime and living environment.[104]

Both the individual and the area measures of SES have strengths and weaknesses. Area measures tend to misclassify some individuals as the area level used may be sufficiently large to hide smaller pockets of varying deprivation. In England, the area level used for the IMD is the Lower Super Output Area (LSOA, a small area geography based on approximately 1500 people). This leaves the possibility of drawing incorrect conclusions about individuals based on a population (ecological fallacy).[105] In addition, the nature of an area may change over time, resulting in changes in the deprivation classification of people in that area, regardless of their individual status. Strengths of area measures include the wide availability of data used for their derivation (from census data for example), and their ability to rank and compare different areas across the country. [104]

Individual measures also have strengths and weaknesses. Their strengths include more accurate assessment of an individual's status with respect to a particular domain (such as income or education) at a given point in time, the ability to avoid ecological fallacy, and the possibility of identifying finer variations in SES. Weaknesses are that they tend to reflect only one aspect of a person's status, such as wealth, occupation or education, and that the collection of such data requires individual-level data sources. In addition, the

measures tend to reflect a single point in time. Basing SES on individual measures may therefore misclassify some individuals, if, for example, past education history suggests a lower or higher income than is actually the case. [88]

1.2.2 Health inequality and inequity

The World Health Organisation (WHO) defines Health Inequality as 'differences in health status or in the distribution of health determinants between different population groups'. [106] The association between SES and health has been recognised in many fields of medicine and public health. [88] Large scale (cross sectional and longitudinal) studies between and within countries have demonstrated strong associations between SES (using various measures) and many health outcomes including life expectancy, all cause-mortality, childhood mortality, healthy life years, mental health, and self-reported ill health. [107-110] In addition, risk factors for ill health such as obesity and smoking also have a social gradient, as do many health care processes, such as hospital admission. [107-111]

In England, the Marmot Review (2010) was conducted to summarise the current state of health inequalities in England and to identify areas where action could be taken to reduce the gap in health outcomes between people with high and lower SES. [94] The review confirmed the findings of a substantial body of data (from a wide variety of sources, including the Office for National Statistics) that demonstrates the social gradient in health in this country with people of lower SES experiencing poorer health. [112 113] It concluded that health inequalities arise from social inequalities, that action on health inequalities therefore requires action on the broader social determinants of health, and that focusing on the most disadvantaged alone will not narrow the inequality gap.[94] Moreover, it concluded that fairer societies are not only healthier, but that reducing health inequality benefits society in other ways.

Health inequity has been defined as 'differences which are unnecessary and avoidable but, in addition, are also considered unfair and unjust'.[114] Health equity is closely associated with social justice and fairness. It is different from equality because some disparities in health would not be considered 'unfair' (such as the differences in health experienced by men and women by virtue of their differing biology). [115] In the field of health economics, health equity has

been further characterised as ‘horizontal equity’ (equal health care provision for equal need) and ‘vertical equity’ (unequal health care for unequal need). [116] [117] For example – all eligible adults should have the same opportunity to be screened for bowel cancer (horizontal equity), and, among people attending Accident and Emergency departments, those who are more severely ill should be prioritized above those who are less so (vertical equity). Both principles of equity can be described as ‘fair’ but do not necessarily result in equality of care.

Some of the health inequalities described and identified in this thesis may also represent health inequities. While this distinction is not explored in detail in each case, actions taken to mitigate any of the inequalities identified should also consider health equity as an important factor.

1.3 Health inequalities in CKD

A purposive review of the literature was conducted to identify existing evidence for inequalities in:

a) Risk factors for CKD
b) Prevalence of CKD
c) Progression of CKD
d) Rates of dialysis and kidney transplant
e) Health outcomes for people on renal replacement therapy (RRT).

Method

The following databases were searched using terms for CKD and health inequality:

Medline (1996 onwards), Embase (1980 onwards), Cinahl (1981 onwards).

Earlier records were not searched in order to narrow the field, although I recognised that some literature may have been missed due to this restriction. Searching was undertaken using the Wolters Kluwer OvidSP gateway.

Search terms used were as follows:

- For CKD: CKD, chronic kidney disease, chronic renal disease, chronic renal failure, CRF, haemodialysis, hemodialysis, peritoneal dialysis, renal transplant, kidney transplant, renal replacement, RRT.
- For inequalities: inequality, inequalities, disparity, health disparity, socioeconomic inequality, inequity, ethnicity, ethnic, racial, race.
- Other factors: risk factor, obesity, diabetes, hypertension, smoking, prevalence, process, outcome, progression, mortality, morbidity, death.

A combination of Mesh and free text terms were used. Search times were combined with 'AND' or 'OR' as appropriate to narrow the search. In addition, purposive reference searching was used to identify relevant papers. A summary of the evidence identified is given in Table 3 and the following section describes the literature in more detail.[64 118-126]

Although the main focus of this thesis is the relationship between SES and CKD, the relationship between CKD and inequalities due to ethnicity are also included for descriptive purposes.

Table 3. Inequalities in CKD risk factors, prevalence, progression, renal replacement therapy (RRT), and mortality

		SES (age adjusted)	Age	Sex	Ethnicity
Prevalence of CKD risk factors and CKD	*Obesity*	⇧ in lower SES groups	⇧ in older	⇧ in women	⇧ in women from Black and Pakistani populations
	Diabetes	⇧ in lower SES groups	⇧ in older	⇧ in men	⇧ in Black Africans, Black Caribbeans, and South Asians
	Smoking	⇧ in lower SES groups	⇧ in younger age groups	⇧ in men	⇧ in Bangladeshi and Black Caribbean men
	Primary hypertension	⇧ in lower SES groups	⇧ in older	⇧ in men	⇧ in Black populations and South Asians
	CKD Prevalence	Variable evidence of ⇧ in lower SES groups	⇧ ⇧ in older	⇧ in women	⇧ advanced CKD in South Asians

Table 3 cont

		SES (age adjusted)	Age	Sex	Ethnicity
Progression, management, and complications	*CKD Progression*	?⇧ rapidity in lower SES groups	⇧ in younger	?⇧ rapidity in men	More rapid progression in Black and South Asian
	CVD risk in CKD	Not known	Not known	Not known	⇧ CVD risk in Black populations with CKD
	Aspects of GP CKD management	No significant differences in QOF CKD by practice SE status, but little evidence available from individual patient data. Likely to be a quality gap as people with CKD not on the CKD disease register not recalled for BP and other checks.			
	Acute Kidney Injury in CKD	Not known in UK	⇧ in older peopl e with CKD	⇧ risk in men in US studies. UK not known	⇧ in Black populations in US studies
Dialysis and transplant	Older people >75 (+ more severe CKD) less likely to be referred for dialysis and listed for transplant. More men starting RRT, referred for, and receiving transplant in all age groups.⇧RRT in lower SES groups, also younger and more diabetes-related ESKD, and less able to access transplant. South Asian and Black populations start dialysis younger. Minority ethnic groups wait longer for transplant.				
Mortality	⇧ ESKD in women cancels normal female survival advantage. No variation in survival on RRT by SES. Black populations have increased mortality risk attributable to kidney disease compared to whites.				

⇧ denotes increased risk demonstrated

1.3.1.1 Inequalities in CKD risk factors

The Health Surveys for England (HSEs) are representative population surveys, and they, along with several other sources, provide valuable information on the sociodemographic distribution of factors that are recognised to increase the risk of developing CKD. In considering the independent relationship of CKD with each of these factors, it is important to remember that age is a very powerful determinant in the development of CKD.

1.3.1.1.1 Obesity

Overweight, obesity, and high central body fat increase the risk of developing CKD.[127] This is thought to occur via increased risk of predisposing conditions such as hypertension, diabetes and chronic inflammatory disorders, but there is also emerging evidence of a direct effect through mechanisms predisposing to both CKD and non-alcoholic fatty liver disease.[128 129] The 2011 HSE identified that a similar proportion of men and women in England were obese (24% and 26% respectively), but a higher proportion of men were overweight (41% compared to 33%). [130] Obesity prevalence in the survey increased with increasing levels of deprivation for both men and women. 22% of men and 19% of women in the least deprived quintile were obese, compared with 25% and 30% respectively in the most deprived quintile. Conversely, the pattern was different for overweight, which was higher among people living in the least deprived quintile (both men and women).[130] The survey also identified a trend of increasing prevalence of overweight and obesity (13% of men were obese in 1993 compared to 24% in 2011).[130] In terms of outcome prediction, waist circumference may be a more important measure than BMI. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study in the US, waist circumference was positively associated with risk of all-cause mortality in people with CKD. [131,132] Waist circumference is not yet routinely measured in the UK, but in the 2011 HSE, age standardised prevalence raised waist circumference was higher in households in lower quintiles than higher quintiles of equivalised household income for both men and women. [133]

1.3.1.1.2 Diabetes

Diabetes (both Type 1 and Type 2) is an important risk factor for CKD. [134] In longitudinal analysis of data from NHANES surveys in the US, a direct association has been observed between increased prevalence of diabetic

kidney disease and increasing diabetes prevalence (i.e. with no change in the prevalence of kidney disease among people with diabetes). [135] The cumulative risk of developing diabetic nephropathy has been reported as being between 9 and 25% over 30 years depending on intensity of diabetes treatment. [136] Historically, in people with type 1 diabetes the cumulative incidence of overt nephropathy at 30 years duration is about 40%.[137]

The 2011 HSE identified that diagnosed diabetes increases with age, with less than 3% of men under 45 compared to about 26% of men over 85 having the diagnosis (although this association tails off in the very old). [130] Similarly, less than 3% of women under 45 compared to about 12% of women over 85 have diabetes. Prevalence of diagnosed diabetes is also highest among people with lowest household income (11% of men and 6% of women in lowest quintile of household income compared to 5% of men and 4% of women in the highest quintile) and in the most deprived areas (9% of men and 7% of women in the most deprived index of multiple deprivation (IMD) quintile compared to 5% of men and 2% of women in the highest quintile). The survey identified that 2.3% of the adult population had undiagnosed diabetes (with similar prevalence in men and women, variation by SES was not given). It also identified increasing prevalence of total diabetes (5.5% of men had diabetes in 2003 compared to 9.1% in 2011).[130] The England and Wales National Diabetes Audit 2009/10 showed that the prevalence of Type 2 diabetes rose from about 3% in the least deprived quintile to about 4.5% in the most deprived quintile. [134]

1.3.1.1.3 Smoking

Smoking is also an important independent risk factor for CKD development and progression. [58 138] The Marmot review, Fair Society Healthy Lives, identified that the prevalence of smoking in 2007 was 26% in households of routine/manual workers compared to 15% in households of managerial/professional workers. [94]

The 2009 HSE found that 24% of men and 20% of women aged 16 and over were current cigarette smokers. Cigarette smoking prevalence varied by age (higher among younger adults (32% of men and 26% of women aged 25-34 compared to 11% of men and 8% of women aged 75 and over), and by gender (mean daily cigarette consumption 13.6 for men and 12.6 for women). For both male and female smokers, mean cigarette consumption was higher

among those aged 35 and over. Cigarette smoking prevalence varied by household income, with highest prevalence among people living in the lowest income households (40% of men and 34% of women compared to 14% of men and 11% of women in highest income households). [139]

1.3.1.1.4 Hypertension

Hypertension is also an important CKD risk factor, although causality is difficult to establish as elevated blood pressure is both a cause and a consequence of CKD. [58] The 2011 HSE defined hypertension as either doctor-diagnosed or survey-defined. Hypertension had been diagnosed in 61% of men and 66% of women with survey-defined hypertension. The prevalence of survey-defined hypertension was 31% of men and 28% of women (unchanged since 2003), while the prevalence of untreated hypertension had decreased between 2003 and 2011. However, survey-defined hypertension was more common in lower income households and in people from more deprived areas. 26% of men and 23% of women in the least deprived quintile of IMD had survey-defined hypertension compared to 34% and 30% respectively in the most deprived quintile. [130]

Given this information about social gradient in CKD risk factors, it might be expected that these drive inequalities in the distribution of CKD prevalence.

1.3.1.2 Socioeconomic and ethnic inequalities in CKD prevalence

Analysis of the 2009 and 2010 HSEs showed that CKD prevalence is slightly higher in women (despite the male predominance of smoking, diabetes and hypertension) and mixed evidence for variation of CKD prevalence by area deprivation status (defined by 'Spearhead Primary Care Trusts' (PCTs)) depending on the severity of CKD considered (higher prevalence of CKD 1-5 in Spearhead PCTs, but not CKD 3-5). [64 139] Similar nationally representative studies in the US and Australia have shown variation in prevalence of CKD by country, and, within country, by ethnic group and SES. [121] These studies demonstrated important variations. SES variations in CKD are seen in UK, US non-Hispanic white, and Swedish populations, for example, but similar variations are not seen in all white populations.[62 68 119 120 122 140-142] A population-based case control study in Sweden found an approximately doubled adjusted odds ratio (OR) of having CKD in families with only unskilled workers compared to families with at least one professional. [119] A retrospective cross-sectional

study in the UK of incident CKD found increased adjusted risk of low eGFR (<30ml/min/1.73m^2) in areas with greater socioeconomic deprivation. [141] Data from the Atherosclerosis Risk in Communities (ARIC) study in the US identified an association of CKD incidence with individual SES defined by occupational status.[120] Although data from the Whitehall II cohort showed similar findings in identifying higher adjusted odds of low eGFR in lower occupational grades, this association was attenuated after adjustment for BMI and components of the metabolic syndrome.[140] White and colleagues compared the findings of three nationally representative surveys in the US, Australia, and Thailand and showed variation between countries, and, for the US, between different ethnic groups, in the association between SES and prevalence of CKD 3- 5. Non-Hispanic White and non-Hispanic Black participants with less than 12 years of education remained significantly more likely to have eGFR<60ml/min/1.73m^2. Unemployed non-Hispanic Blacks and Mexican Americans, and non-Hispanic Whites in the lowest income quartile also had higher risk of CKD prevalence compared with employed groups, and those in the highest income quartile respectively after full adjustment. However, no such associations were observed with either education or income in the Australian and Thai populations.[143] A summary of studies investigating inequalities in CKD prevalence is shown in Table 4.

Table 4. Summary of studies investigating inequalities in CKD prevalence.

Author Year Location	Design	Participants	Number	Main findings
Studies with SES variations as the main focus:				
Al-Qaoud 2011 UK	Cross sectional	White participants in Whitehall 2 age 55-79	5,533	Lower occupational grade associated with increased odds of having decreased GFR (OR 1.23 (1.06-1.45) after adjustment)
Bello 2008 UK	Cross sectional	Patients at Sheffield Kidney Institute	1,657	Lowest IMD quintile associated with greater risk for presenting with eGFR<30ml/min/m^2 (OR 4.36 (1.09-17.38) for most vs least deprived after adjustment))
Fored 2003 Sweden	Population-based case control	Incident patients with pre-uraemic CRF. Control drawn from all residents aged 18-74	926 cases, 998 controls	Elevated odds ratio of CRF in families of unskilled workers (OR 2.1, 1.1-4.0) compared to professionals, and in people with <=9 years schooling (OR 1.3, 1.0-1.7) compared to university education
White 2008 USA Australia Thailand	Secondary analysis of 3 surveys (NHANES III, Ausdiab I and InterASIA)	Nationally representative survey respondents	9098 (NHANES) 9329 [142] 5063 (InterASIA)	Prevalence of CKD increased with lower income in US White and non-Hispanic Black population. No SES relationship seen in Australia or Thailand.
Studies with ethnicity and SES variations:				
Shoham 2007 USA	Cohort	Lifecourse Socioeconomic Study (part of ARIC Study)	12,631	Adjusted OR of CKD for working class vs. non-working class at age 30 was 1.4 (1.0 to 2.0) in Whites and 1.9 (1.1 to 3.0) in African Americans

Table 4 cont

Author Year Location	Design	Participants	Number	Main findings
Studies with ethnic variations as the main focus:				
Dreyer 2009 UK	Cross sectional analysis of Read-coded GP data	Adults with diabetes	34,359	CKD stage 3 more prevalent in Whites than South Asians (OR 0.79) and Blacks (OR 0.49), but stage 4 - 5 associated with Black and South Asian ethnicity. Proteinuria more prevalent in Black and South Asian patients
Gujral 1997 UK	Analysis of lab creatinine results and medical records	All elevated Cr values over 200micromol/l in 1991	1,820	Asians and males had twice the prevalence of CRF
Tarver-Carr 2002 USA	Cohort	Adults 30-74, part of NHANES 2	9,082	Incidence of CKD higher in African Americans compared with whites (Fully adjusted RR 1.95 (1.05-3.63)

CRF = Chronic renal failure

1.3.1.3 Socioeconomic and ethnic inequalities in CKD progression

Relatively few studies have examined the relationship between CKD progression and SES. In the UK, a retrospective cross-sectional study in the UK of incident CKD conducted by Bello and colleagues identified that the lowest IMD quintile was independently associated with greater risk for presenting with lower eGFR (OR of presenting with GFR<30ml/min/m^2 4.36 (1.09-17.38) for most vs. least deprived)) after adjusting for age, sex, ethnicity, diabetes and hypertension. [141] This was not explained by increased prevalence of known risk factors, and could represent delay in referral to / presentation at renal services in lower socioeconomic groups.

Several studies have investigated the relationship between ethnicity and CKD progression. A retrospective review of people with diabetic nephropathy in the UK found an increased rate of decline in renal function in people of Indo-Asian origin. [124] A study of data from NHANES III demonstrated increased risk of progression to end stage kidney disease among Blacks, [144] and the ARIC prospective cohort study among adults with diabetes had similar findings (odds ratio for early renal function decline 3.15 (95%CI 1.86-5.33) in Blacks compared to Whites. [145]

A further ARIC study (after 9 years of follow up) identified that, for white men, living in the lowest vs. highest SES-area quartile was associated with a raised hazard ratio for progression of CKD (serum creatinine elevation of >=35micromol/l). However, no such association was found for white women or African-American men or women. [122] Moreover, a study from the CKDPC did not identify gender differences in the association between eGFR rate and albuminuria with end stage renal disease risk. [146] There is therefore little literature evidence concerning socioeconomic inequalities in CKD progression in the UK. A summary of studies investigating inequalities in CKD progression is shown in Table 5.

Table 5. Summary of studies investigating inequalities in CKD progression.

Author Year Location	Design	Participants	Number	Main findings
Studies with ethnicity and SES variations:				
Merkin 2005 USA	Cohort (ARIC study)	9 year follow up of cohort	12,856 adults	For white men: Living in the lowest vs. highest SES-area quartile associated with raised hazard ratio for progression of CKD (SCr elevation of >=35micomol/l). (HR 1.6, 1.0-2.5). No association found for white women or African-American men or women
Studies with ethnic variations as the main focus:				
Hsu 2003 USA	3rd NHANES data birth cohort analysis	New ESRD cases in 1996 and people estimated to have CKD in 1991	21,307 Blacks and 39,016 Whites with incident ESRD in 1996	Adjusted risk of progression from CKD to ESRD higher in Blacks than Whites (RR 4.6; 95% CI, 2.3-10.1),
Krop 1999 USA	Prospective cohort (ARIC study)	Diabetic adults (45-64)	1,434	Early renal function decline (increase in serum creatinine (Scr) of at least 35.4micromol/l more likely to develop in Blacks (OR 3.25, 1.86-5.33) compared to Whites
Earle 2001 UK	Retrospective case-note review	Adults with diabetes attending diabetic clinic	1,684	Rate of decline in renal function (in diabetics), measured by doubling of serum creatinine, higher in Indo-Asian subjects

1.3.1.4 Inequalities in cardiovascular risk in CKD

The association between CKD and CVD is well established, both for ESKD and for earlier stages of CKD. [52 75 147] Increased CVD-related risk in CKD has been identified in several cohort studies in both the US and Europe, [74 76-78 148] and in individual patient data meta-analysis of 39 studies. [53] There is also evidence of an inverse relationship between CVD-related mortality risk and GFR in people with existing heart disease. [149 150] For most people with CKD, the risk of CVD is greater than the risk of progression to ESKD (except for those at late stage). [151]

Whilst there are socio-economic disparities in the prevalence of some shared risk factors for CVD and CKD (such as obesity, diabetes, hypertension and smoking as described in section 1.3.1.1) and for CKD per se, there is little direct evidence about socioeconomic variations in CVD risk among people with CKD, particularly at earlier stages of CKD.

1.3.1.5 Inequalities in CKD management in primary care

1.3.1.5.1 Inequalities and QOF

One UK study has explored the distribution of QOF-defined CKD by SES. [152] However, analysis of QOF data for inequalities in chronic disease management is limited by reporting of aggregated data at practice, rather than individual, level. For example, the 'CKD 3' QOF indicator requires a practice to report the proportion of patients with CKD in whom the last BP reading was 140/85 or less. A practice can achieve the target of 70% of patients falling into this category, but leave much room for residual inequality at patient level. In addition to this, practices can 'exception report' (i.e. exclude people from QOF counts) for a variety of reasons, such as excluding people who decline monitoring or treatment, and those on maximal tolerated therapy.
The following is a summary of guidance on exception reporting:

'Exceptions' relate to registered patients who are on the relevant disease register and would ordinarily be included in the indicator denominator, but are removed from the denominator and numerator for a variety of reasons:

1. Patients who have refused to attend review who have been invited on at least three occasions.

2. Patients for whom it is not appropriate to review the chronic disease parameters due to particular circumstances, for example, terminal illness.
3. Patients who are on maximum tolerated doses of medication whose levels remain sub-optimal for the indicator (e.g. blood pressure in CKD).
4. Patients for whom prescribing a medication is not clinically appropriate e.g. those who have an allergy, contra-indication or have experienced an adverse reaction.
5. Where a patient has not tolerated medication.
6. Where a patient does not agree to investigation or treatment (informed dissent) and this has been recorded in their patient record following a discussion with the patient.
7. Where the patient has a supervening condition which makes treatment of their condition inappropriate e.g. cholesterol reduction where the patient has liver disease.
8. Where an investigative service or secondary care service is unavailable.

In the case of exception reporting on criteria 1 and 2 these patients are removed from the denominator for all indicators in that disease area where the care had not been delivered.[93]
This allows for variation in practice, and the potential for excluding more disadvantaged groups. Studies investigating the impact of QOF on inequalities show little evidence of QOF incentives narrowing inequality gaps. [153] Because of the aggregated nature of QOF data, they provide insufficient information to fully understand inequalities and target efforts to improve quality of CKD management in primary care, identification of CKD progression, and occurrence of complications (particularly CVD and AKI [154]).

There is therefore little patient-level evidence on inequalities in important aspects of CKD disease management such as blood pressure control, identification of albuminuria, and use of renin-angiotensin aldosterone system inhibitors (RAASi) in the UK.

1.3.1.6 Inequalities in Renal Replacement Therapy (RRT) in the UK

A UK study of Renal Registry data from over 10,000 patients showed that socially deprived patients (using the Townsend index) were more likely to be referred late for RRT, were less likely to receive peritoneal dialysis or renal transplant, and were less likely to achieve UK Renal Association clinical standards.[155] Separate Renal Registry studies have demonstrated that people from lower socioeconomic groups were less likely to be placed on a renal transplant waiting list. [156 157] More deprived populations have been shown to have an increased probability of acceptance for RRT, and the rate of *incident* RRT has been demonstrated to follow a linear increase with increasing social deprivation. [126 158] A retrospective study of people accepted for RRT demonstrated a greater likelihood (approximately threefold) of acceptance for RRT among Asian and Black people. [125] A cohort study following people with incident RRT over time showed that increasing age, non-white ethnicity, and presence of diabetes were associated with lower likelihood of renal transplant. [159] Reassuringly, however, there is also some evidence that people from more deprived areas are no less likely to achieve clinical practice guideline standards while on dialysis than people from less deprived areas. [160] Moreover, there is evidence that, although people from South Asian and Black minorities on dialysis tend to be younger and have more diabetic nephropathy, they have better survival than Caucasians. [161] A summary of studies investigating inequalities in RRT is shown in Table 6.

Table 6. Summary of studies investigating inequalities in RRT

Author Year Location	Design	Participants	Number	Main findings
Studies with SES variations as the main focus:				
Caskey 2006 England and Wales	Analysis of UK Renal Registry data	Incident Caucasian patients starting RRT between 1997 and 2004	10,392	Socially deprived patients (using Townsend index) more likely to be referred late, less likely to receive peritoneal dialysis or renal transplant, and less likely to achieve UK RA clinical standards. Poorer survival among people from socially deprived populations.
Dudley 2009 UK	Renal registry data	Prevalent adult dialysis patients	12,401	Social deprivation (Townsend) associated with being listed for transplant
Judge 2012 UK	Analysis of Renal registry data	People >= 20yrs receiving RRT in 2007.	Incident (4,609) + prevalent (36,846)	Adjusted RRT incidence rates higher in most deprived areas (RR 1.4, 1.2-1.6)
Stolzmann 2007 USA	Cohort	Incident ESRD patients starting RRT from 1982 to 2005	22,387	Higher community-level income (HR 1.12 (1.02-1.23) for highest compared to lowest) and education (HR 1.19 (1.10-1.28) for highest compared to lowest) groups more likely to receive transplantation
Studies with ethnicity and SES variations:				
Roderick 1999 England	Retrospective analysis of England renal units' data	Incident RRT aged 16+ 1991&1992	5,715	More deprived populations had an increased rate of acceptance onto renal replacement therapy. Asian and African-Caribbean populations associated with increased acceptance. 1% increase in Asian population associated with 2% increase in risk of ward acceptance

Table 6 cont

Author Year Location	Design	Participants	Number	Main findings
Studies with ethnic variations as the main focus:				
Roderick 1996 England	Retrospective survey of people accepted for RRT	Incident RRT aged 16+ 1991&1992	5,901	Acceptance rates to RRT increased in Asian (RR 3.5) and Black (RR 3.2) populations
Roderick 2009 England and Wales	Renal registry data analyses	Incident RRT between 1997 and 2006	2,495 South Asian. 1,218 Black	These ethnic groups tended to be younger and have more diabetic nephropathy. Less likely to receive a transplant or start peritoneal dialysis. Both had better survival than Caucasians (fully adjusted HR after day 90 on haemodialysis 0.70 (0.55-0.89) for South Asians, and 0.56 (0.41-0.75) for Blacks
Ravanan 2010 UK	Cohort from Renal Registry	Incident RRT between 2003 and 205, followed until 2008	16,202	Age, ethnicity, and primary renal diagnosis were associated with the likelihood of accessing the waiting list or receiving a transplant. (OR for probability of receiving transplant for non-white vs. white 0.47 0.37-0.59)

There remain, therefore, gaps in knowledge of the relationship between some important aspects of CKD and SES. This includes the relationships between CKD prevalence and different measures of SES, between albuminuria and SES, between CVD risk and SES, between certain health care process measures (such as BP control) and SES, and between outcomes (AKI, all cause and cardiovascular mortality) and SES. Such information would be valuable in the appropriate targeting of interventions to improve care and outcomes for people with CKD. Some of these knowledge gaps are addressed in this thesis (see next section).

1.4 Thesis overview; research questions and thesis components

This section introduces the main components of this thesis and summarises the research questions addressed by the studies in each chapter.

1.4.1 Socioeconomic status and CKD in the Health Survey for England

As described above, analysis of the 2009 and 2010 HSEs showed mixed evidence for variation of CKD prevalence by area deprivation status (defined by 'Spearhead Primary Care Trusts' (PCTs)) depending on the severity of CKD considered (higher prevalence of CKD 1-5 in Spearhead PCTs, but not CKD 3-5). [64 139] Studies in other countries have shown mixed results (see section 1.3.1.2).

Data from NHANES III demonstrated association between microalbuminuria and poverty, but no evidence is available in the UK on the relationship between albuminuria and SES.[162] Associations between low SES and increased risk of CKD diagnosis and increased severity of CKD at presentation to renal services have been demonstrated in the UK. [2 141] Any observed variations in CKD prevalence may be explained by differences in lifecourse exposures harmful to the kidney, such as foetal environment, environmental toxins, tobacco, obesity, hypertension, and diabetes; and access to and use of health services. However, consideration needs to be given to the different measures of SES used and limitations of area level proxies.

This study aimed to provide detailed analysis of the associations of several socioeconomic factors (using both area level and individual measures) with CKD stage 3-5, using the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) equation to estimate GFR, and with albuminuria in the 2009 and 2010 HSEs.

As discussed in section 1.1.2, current CKD definitions rely on eGFR derived from serum creatinine-based estimating equations (MDRD and CKDEPI) but serum creatinine levels are affected by several factors including age, muscle mass, race and variation in physiological processes. [31 32] Other events, such as acute illness, may cause a transient rise in serum creatinine and consequent reduction in eGFR. [163] Such inaccuracies can result in misclassification of

patients, and consequent inappropriate clinical decisions. Serum cystatin C is a potential alternative for estimating GFR, with evidence of its improved diagnostic accuracy for impaired renal function compared with serum creatinine. [40 42] In addition, there is growing evidence for the value of combining different measures of renal function (serum cystatin C and creatinine, and uACR) to improve stratification of mortality and renal disease progression risk. [41 164] Such risk stratification is important in the context of concerns about over-diagnosis of CKD resulting in mislabelling people as having a 'disease'.[165]

Nationally representative serum cystatin C levels have been determined in the US by analysis of samples from NHANES III, but population level estimates of cystatin C-derived CKD in other developed countries are limited. [166 167] Analysis of NHANES data between 1988 and 1994 (with additional measurement of cystatin C in 2006 using stored sera) showed that median cystatin C levels increased with age, males, and non-Hispanic whites. Using a threshold level of 1.12mg/L, prevalence of elevated levels were 41% in people over 60, and >50% in people over 80. [167]

Comparison of the prevalence and distribution of CKD in a representative sample in England using creatinine-based equations to calculate eGFR (MDRD and CKDEPI) with estimations using a cystatin C-based equation (the Grubb equation) has not previously been undertaken. [31 32 168] This study also therefore aimed to make these comparisons, and to describe the distribution and associations of elevated cystatin C in these HSEs.

Key research questions for this thesis – see Chapter 2

- What is the relationship between low eGFR prevalence, albuminuria prevalence, and SES in England?
- What is the effect of using other equations and markers (CKDEPI, cystatin C) to define CKD on the prevalence and distribution of CKD?

1.4.2 Assessing risk in people with CKD stage 3 in primary care – a prospective cohort study

1.4.2.1 Cardiovascular risk in CKD

The association between CKD and CVD has been described in section 1.3.1.4. Whilst there are socio-economic disparities in the prevalence of some shared risk factors for CVD and CKD and for CKD per se there is little direct evidence about socioeconomic variations in CVD risk among people with CKD. [118] Identifying such variations may facilitate targeting of interventions aimed at reducing disparities of outcome in people with CKD.

There is also growing evidence that effective chronic disease management involves shared decision making (with appropriate use of decision aids), empowering patients to manage their own condition. [169] Lack of knowledge or understanding of CKD and its associated CVD risk is a potentially modifiable factor that may contribute to poor CKD outcomes and health inequalities. [170] Person-centred care, information provision, and education are key themes of NICE CKD guidance, which also emphasises the importance of accurate assessment of cardiovascular risk in CKD. [50]

The aim of this section of the study was to examine the relationship between CVD risk factors, SES, and CKD diagnosis awareness in patients with CKD stage 3, and to examine the distribution of cardiovascular risk assessed by two scoring systems in use in the UK, the Framingham and QRisk2 predictive instruments. [171-173]

1.4.2.2 Blood pressure control in CKD

Control of hypertension is arguably the most important intervention for reducing the increased risk of CVD in people with CKD, and to slow progression to later stages of CKD. [52 79 81 174 175] However, there is evidence that optimum levels of blood pressure (BP) control are often not achieved among people with CKD, with consistent achievement of BP less than 140/90 mm Hg observed in between 15 and 30% of patients (with as few as 13% achieving a 130/80 threshold). [176-178]

Several national and international guidelines recommend targets for optimal BP control in people with CKD but there are differences between them, including variation of the targets for those at higher risk of outcome (such as people with diabetes and albuminuria). NICE guidelines set a BP control at target <140/90mm Hg for most people with CKD or <130/80 in people with diabetes or high levels of albuminuria (uACR>70mg/mmol), while the QOF CKD BP target is ≤140/85. [50 92] In the US, the National Kidney Foundation KDOQI guidelines set a BP control target at <130/80 for all people with CKD. [179] The 2012 KDIGO guidelines for the management of blood pressure in CKD recommend that both diabetic and non-diabetic people with non-dialysis dependant CKD with hypertension but without albuminuria should have BP controlled ≤140/90, and people with significant albuminuria (microalbuminuria or macroalbuminuria) with or without diabetes should control BP ≤130/80. [180]

Little is known about CKD-related hypertension control in primary care, particularly in individuals at higher risk, such as those with and without diabetes or albuminuria. In England QOF data are aggregated at practice level and do not allow for interpretation at individual level. [67]

This section of the study aimed to evaluate the factors associated with blood pressure control in a population of people with CKD stage 3 in primary care.

1.4.2.3 Albuminuria and non-albumin proteinuria

The assessment of proteinuria is a key element of the investigation of kidney disease but some uncertainty exists regarding the optimal methods to apply. Specific unresolved issues include whether to measure total urinary protein and/or albuminuria and the optimum number of urine specimens required. Proteinuria, most often assessed as albuminuria, is a strong independent predictor of renal, cardiovascular, and mortality risk. [52 181] An increasing level of uACR is independently associated with higher cardiovascular mortality risk and CKD progression. This association exists in both men and women, increases with age, and occurs in people with and without diabetes.[13 70 131 146 182-184] A single uACR measure has been used to derive risk in most cohort studies.[70 131 183 184] Several CKD management guidelines, including those from NICE, KDIGO and KDOQI, recommend identification and quantification of proteinuria using uACR in preference to uPCR. [49-51] In addition, some guidelines recommend repeating uACR measurements for initial identification of albuminuria to avoid over diagnosis due to transient albuminuria changes. [48 50] It has been argued that uPCR is a more sensitive screening test for proteinuria; though uPCR and uACR perform similarly well in predicting adverse outcomes. [185 186] Conversely, it could be argued that assessment of both albuminuria and non-albumin proteinuria (NAP) [68] may provide valuable diagnostic and prognostic information. Albuminuria typically reflects glomerular disease, whereas NAP (including α_2- and β_2-microglobulins) is associated with tubulointerstitial pathology, and a low urinary albumin to total urinary protein ratio (uAPR) demonstrates strong correlation with tubulointerstitial disease on renal biopsy. [187] Some patients have a mixed proteinuria picture reflecting both glomerular and tubular dysfunction, particularly as total protein increases.[187] Little is known about the relative distributions of albuminuria and NAP in people with CKD, or the demographic and clinical associations of NAP or its prognostic significance.

This section of the study aimed to investigate proteinuria assessment in a population of people with CKD stage 3 by determining the prevalence and associations of albuminuria and NAP, and assessing degree of agreement between a single uACR measure and two of three measures to identify albuminuria.

1.4.2.4 Survival, skin autofluorescence and CKD

In the context of CKD, accumulation of advanced glycation end products (AGEs) has been identified as a novel risk factor for CVD.[188] AGEs are a heterogeneous group of compounds formed by the reaction of free amino groups on proteins, lipids, and nucleic acids with reactive carbonyl groups on reducing sugars. They accumulate by endogenous formation through non-enzymatic reaction over time (the Maillard reaction) or from reactive carbonyl products generated by oxidative stress (dicarbonyl stress). Accumulation also occurs from exogenous sources, principally food cooked at high temperature, and AGEs formed by smoking. In addition, because AGEs are normally excreted by the kidneys, they accumulate with decreased renal function. [189-193] In CKD, AGE accumulation may be exacerbated by increased formation, as dicarbonyl and oxidative stress are increased with reduced renal function, and there is increased availability of precursor compounds (such as oxidized ascorbic acid arising in people on haemodialysis). [194] AGE formation is a marker of cumulative metabolic stress, adversely influencing the ageing process and development and progression of chronic disease across the lifecourse.[195-198]

Serum AGEs are subject to fluctuation and have been shown to be a poor indicator of AGE accumulation in tissue compared to skin biopsy.[199] Assessment of AGE accumulation in practice has been considerably simplified by the development of devices that measure skin autofluorescence (skin AF). This allows for non-invasive assessment of tissue AGE deposition by exploiting the close correlation between collagen linked fluorescence and AGE content observed in skin biopsies. [200] Skin AF measurement has been validated against levels of specific AGE molecules in diabetes, CKD, and in healthy controls. [201-204] Increased skin AF is associated with AGE accumulation and the development of a range of vascular complications, as well as all-cause and cardiovascular mortality in people with diabetes. [201-205] In people with ESKD on dialysis, skin AF is associated with arterial stiffness.[206] Skin AF is also independently associated with cardiovascular and all-cause mortality in haemodialysis patients.[206 207]

Potential for reversibility of AGE accumulation has been observed in patients moving from dialysis to renal transplant.[208] In earlier CKD, increased skin AF has been shown to be associated with a wide range of poor prognostic factors, including anaemia, proteinuria, diabetes, age, and eGFR in cross sectional analysis. [191] Dietary modification to reduce exogenous AGE may be important.[193]

However, the relationship between elevated skin AF and subsequent adverse outcomes in earlier stages of CKD is not yet known.
The aim of this section of the study was to examine associations of all-cause mortality with measures of SES (and other demographic and clinical variables). In addition, in view of its future potential to improve risk assessment of people with CKD, and of the potential to intervene to reverse AGE accumulation and improve prognosis, this study also aimed to evaluate the association between skin AF and all-cause mortality (including by SES measures).

Key research questions for this thesis – see Chapter 3

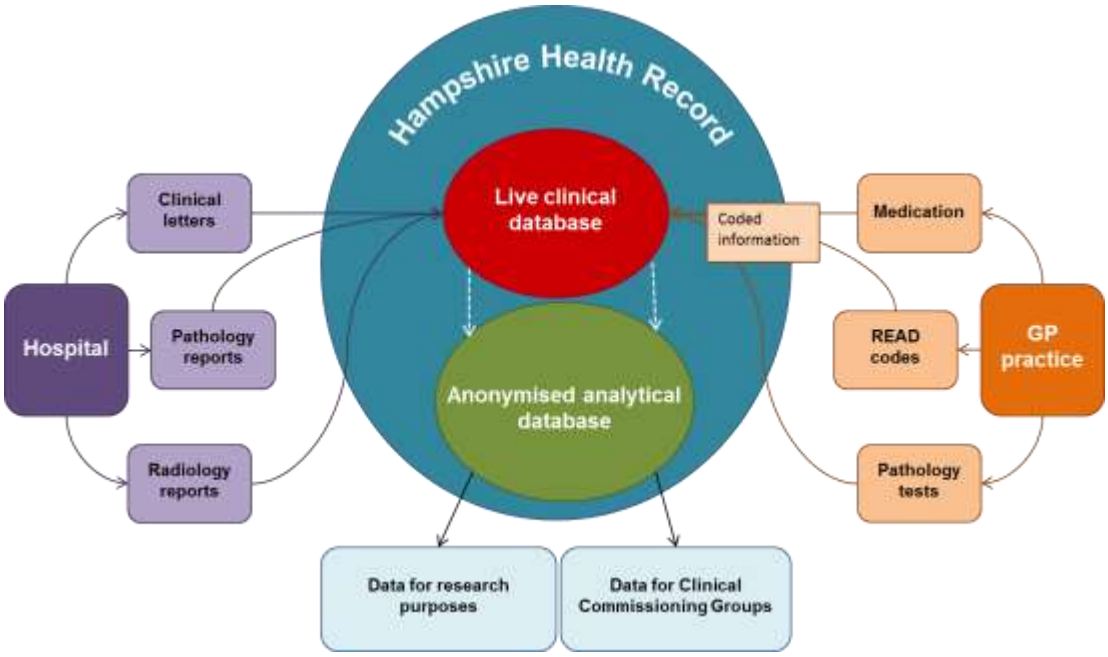
a) What is the relationship between cardiovascular risk and SES and CKD awareness?
b) Is there evidence of socioeconomic inequality in key aspects of CKD management in primary care such as control of blood pressure?
c) What are the associations of albuminuria (an independent risk factor for adverse outcomes in CKD) and non-albumin proteinuria (a measurable factor of uncertain prognostic significance) with SES and clinical factors in CKD?
d) What factors influence survival in CKD? What is the relationship between a novel marker in CKD – skin AF – and all-cause mortality (including the assessment of any SES variation).

1.4.3 Processes and outcomes in CKD: a retrospective cohort study using routine data from the Hampshire Health Record

1.4.3.1 The Hampshire Health Record

The Hampshire Health Record (HHR) is a shared clinical record that holds individual linked extracts of GP and hospital records (including clinic letters, discharge summaries, x-ray, blood test and other pathology reports). [209] A 'live' HHR system is used by GPs and hospital departments across Hampshire and the Isle of Wight to access records during patient appointments and Accident and Emergency attendances. In addition to this live HHR system, there is a monthly data transfer to the Hampshire Health Record Analytics Database (HHRa). During the transfer process all NHS numbers are encrypted and the data becomes pseudonymized (i.e. the clinical information is retained but any patient-identifiable data is removed). The HHRa is therefore a potential resource for patient level data that links both primary and secondary care information while not allowing for patient identification. A schematic for the HHR and the HHRa is shown in
Figure 8.

Figure 8. The Hampshire Health Record



At the end of 2011, 133 GP practices were feeding information to the HHR, representing a total registered patient population of approximately 1.1 million. Technical reasons related to GP practice IT systems preclude some practices from submitting data. During the time of this study, only two hospitals in the region (University Hospital Southampton and Portsmouth Hospitals Trust) were feeding pathology data to the HHR. The HHRa includes patient age, but dates of birth are removed as part of the pseudonimization process. Similarly, the HHRa includes a measure of area SES (IMD) but individual postcodes are removed. Use of the HHR for research is regulated by the Southampton, Hampshire, Isle of Wight and Portsmouth Decision Support Information team. A formal written request to access the data required for a research project (and details of the data needed) is sent to the Decision Support information team. Responsibility for information requests involving extracts of data that is neither patient nor GP practice-identifiable lies with the Head of Information-Decision Support. These governance mechanisms mean that data from the HHRa can be examined without the need for formal ethical approval.
This section of the study aimed to explore the use of the HHRa as a source of routine data to create a retrospective cohort of people with CKD (both prevalent and incident CKD) and follow them over time between 2008 and 2013 to understand variation in various aspects of clinical care and outcomes by SES (using IMD). Because of its access to pathology data, the HHR allows for this cohort of people with CKD to be defined from eGFR measures, rather than being dependent on a clinician having entered a CKD code in the patient record. This would enable comparison of process measures such as CKD registration by GPs for QOF, and measurement of uACR by SES and outcome measures such as mortality and RRT.

Key research questions for this thesis – see Chapter 4

- What is the feasibility of using routine data to investigate the clinical epidemiology of CKD in a defined population?
- Is there evidence of socioeconomic inequality in important aspects of CKD management (process measures) in primary care such as identification of CKD (registration of CKD for QOF chronic disease management purposes) and measurement of uACR?
- Do these aspects of CKD management change over time (in the period since QOF CKD targets were introduced)?

- Is there evidence of socioeconomic inequality in outcomes including mortality, incidence of RRT, and AKI in people with CKD?

1.4.4 Prevalence and associations of limited health literacy in CKD: a systematic literature review

Self-management and shared decision making are important aspects of complication prevention for people with CKD, with emerging evidence of their role in determining certain CKD outcomes. [210 211] Achieving a degree of understanding of the condition is an important component of self-management and shared decision making that may contribute to improved outcomes, as has been suggested for other chronic conditions. [212] Factors such as medication adherence (to achieve blood pressure control, reduction of proteinuria and, where relevant, diabetes control), avoiding potentially nephrotoxic substances (such as non-steroidal anti-inflammatory drugs (NSAIDs)), attending monitoring appointments and avoiding adverse behaviours (such as smoking, high dietary salt intake and lack of exercise), may all be influenced by patient understanding, and play a part in reducing risk of progression and development of complications in CKD. [213]

Health inequalities related to age, gender, SES, and ethnicity have been recognised throughout the CKD pathway, including prevalence of CKD risk factors, prevalence of CKD, risk of progression, and RRT. [118] There is evidence of greater prevalence of CKD in women, older people, [64 214] and lower socio-economic groups, [119-121] and advanced CKD (stages 3b, 4, 5) varies by ethnicity. [145 215] There is also some evidence of more rapid progression in people from more deprived backgrounds and in certain ethnic groups. [122-124 144]

As described in section 1.1.8, CKD is included in the QOF (which incentivises GPs to keep registers of patients with CKD stage 3 and above, and to provide certain standards of care), but little is known about inequalities in health care process and outcome for people with CKD, and the contribution of sub-optimal self-management and shared decision making to clinical outcomes.[93]

There is considerable evidence that an adequate level of HL (defined as 'the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways that promote and maintain good health') [216] is important to the disease management process, and that inadequate HL is a potentially modifiable determinant of poor health outcomes and of health inequalities in people with chronic disease. [217] This has been increasingly recognised with CKD, though to

date, considerably more evidence exists for the role of HL in other chronic diseases such as diabetes. [217-219] European health policy has recognised the inter-related roles of HL, self-management, and shared decision making in the management of chronic conditions and reduction of inequalities in outcome. [220]

1.4.4.1 Definition and measurement of HL

HL has been developing as a construct over approximately two decades. It has achieved recognition as an important, potentially modifiable, independent risk factor for adverse health outcomes, and a possible driver for health inequalities. [217 221 222] The majority of HL research to date has taken place in the USA, and has developed over time in terms of defining HL, and understanding the characteristics, complexity and validity of the various HL measures. [223] HL research in the UK has developed more slowly, perhaps in part due to greater uncertainty of the definition, meaning, and practical application of HL, and how the various measures used to assess degree of HL can be interpreted, both in clinical practice and at a population level. [223 224] HL can be regarded as a subset of literacy, but should be considered as a distinct concept (it is possible to have a high degree of literacy, but to understand little about health or be unable to make appropriate health-related decisions). The understanding of literacy is complex and its measurement is not straightforward. [225] It is possible to measure literacy in absolute terms through assessing the 'task-based' element of literacy (the capacity of a person to be able to read and write basic text), which results in the ability to classify a person as 'literate' or 'illiterate'. [225] Literacy assessed in this way is often referred to as 'functional'. However, to measure the 'skill-based' element of literacy (to include the full range of skills from basic word recognition through to interpreting appropriate meaning from text) is more difficult. Because of its potential to improve understanding and use of written material, and to improve decision making and self-efficacy in many areas of life, improving literacy is an important goal of education and learning (both formal and informal). [221 226] In conditions such as CKD, in which there is evidence of ethnicity-related disparities, it is important to emphasise that limited HL is distinct from poor comprehension due to language barriers. Literacy has been usefully categorised into 'functional' literacy (sufficient basic reading and writing skills to manage in everyday situations), 'interactive' literacy (more advanced cognitive and literacy skills combined with social skills to enable active social participation, extraction of information and derivation of

meaning from different forms of communication), and 'critical' literacy (applied skills enabling analysis of information which allows for greater control over life events and situations). [221]

Similarly, HL is important because of the potential to intervene and improve understanding through health education and health promotion measures, and thereby empower people to make better decisions about their health (i.e. develop interactive and critical skills). [221 224] In the context of chronic disease, an adequate level of HL may improve a person's ability to manage their condition, engage appropriately with health services, and understand the need for (and have the capacity to engage in) specific risk-reducing behaviours. As with literacy, HL is both content and context specific, and its measurement is problematic.

Measurement of HL

Measurement tools such as the Rapid Estimate of Adult Literacy in Medicine (REALM), and the short form of the Test of Functional Health Literacy in Adults (STOFHLA) were primarily developed to enable clinicians and other health educators to assess patients' ability to understand health advice. [227 228] They are therefore best considered as screening tools for clinical contexts that measure an aspect of *health-related* literacy, rather than providing a comprehensive assessment of capacity, or acting as scalable measures of HL for epidemiological or intervention studies. [223]

The measures employ differing constructs and test differing abilities, although there is evidence for good correlation between some, for example, the REALM and the STOFHLA (Spearman correlation between the STOFHLA and REALM 0.80, though important weaknesses acknowledged by the authors involved in the development of the REALM measure, such as reduced correlation for numeracy items). [227] A more complex measure that gave a full understanding of HL would also incorporate the higher levels of skills and motivation required for people to take responsibility and control of their own health. However, measures such as the Health Activities Literacy Scale (HALS), which incorporate a much more detailed assessment of capacity, take approximately one hour to complete, and therefore have limited application in clinical and research contexts. [223] A summary of commonly used measures is given in Table 78 on page 331.

Given these limitations, trying to identify the true prevalence, associations, and effect of limited HL in populations is problematic. Studies identifying the 'prevalence' of limited HL using one of the measurement tools might be better described as identifying the 'screen-positive prevalence' of limited HL, and this should be recognised as a proxy for the true prevalence given the lack of an agreed gold standard test. [229]

Legitimate doubts have been raised about the benefits of screening for limited HL due to the lack of generalisable and effective interventions, and the potential for harm through stigmatization. [230] However, there is a need to understand the potential role that limited HL may play in the context of chronic disease. For CKD this includes, for example, knowledge of risk factors, awareness and understanding of the condition, ability to access appropriate health care and health promotion opportunities, and sharing decision making with clinicians.

The role that limited HL may have in a condition like CKD is therefore not well established. The aim of this section of the thesis was to conduct a systematic literature review of studies that have examined the prevalence of limited HL in CKD and related conditions in order to inform a potential future research agenda.

Key research questions for this thesis – see Chapter 5

- What is the prevalence of limited HL in people with CKD and other chronic vascular conditions?
- What are the associations of limited HL with measures of SES in people with CKD?

1.5 Summary of thesis components

In summary, therefore, the components of this thesis are as follows:

Chapter 2

Analysis of data from the 2009 and 2010 Health Surveys for England to investigate the relationship between risk factors for CKD, prevalence of low eGFR and prevalence of albuminuria, and SES in England. In addition, use of these data to examine the effect of using other equations and markers (CKDEPI, cystatin C) to define CKD on the prevalence and distribution of CKD.

Chapter 3

Analysis of data from a prospective cohort study of people with CKD stage 3 in primary care to examine inequalities in cardiovascular risk, blood pressure control, albuminuria (and non-albumin proteinuria), and mortality in CKD (including skin AF).

Chapter 4

Development and analysis of a retrospective cohort study using data from the Hampshire Health Record to assess the feasibility of using routine data to examine inequalities in aspects of CKD processes and outcomes.

Chapter 5

A systematic literature review to examine the prevalence and associations of limited HL in people with CKD (with a particular interest in associations with measures of SES).

Chapter 6

Summary of findings and discussion.

2. Socioeconomic status and CKD: analysis of data from the Health Surveys for England 2009 and 2010

2.1 Background

This study was conducted in conjunction with Grant Aitken and Graham Moon, Department of Geography and Environment, University of Southampton. It represents further analysis of data from the 2009 and 2010 Health Surveys for England which were joint surveys conducted on behalf of the NHS Information Centre by the National Centre for Social Research and the Department of Epidemiology and Public Health, University College London (UCL). Jenny Mindell and Marilyn Roth of UCL were instrumental in conducting the HSEs used in these analyses. The objective of this study was to analyse data from the 2009 and 2010 Health Surveys for England to investigate the relationship between risk factors for CKD, prevalence of low eGFR and albuminuria, and SES in England. In addition, to examine the effect of using other equations and markers (CKDEPI, cystatin C) to define CKD on the prevalence and distribution of CKD.

2.2 Methods

Full details of the conduct of the HSEs, measurement of non-CKD variables and response rates are given in the HSE Reports. [64 139] A random, nationally-representative sample was selected each year using a stratified, two-stage sample of private addresses. Participants completed an interview questionnaire; most consented to a nurse visit. In the 2009 or 2010 HSE, a valid urine sample was obtained from 88% of men and 86% of women aged 16 and over who had a nurse visit, and a non-fasting blood sample from 77% of men and 73% of women. Approval was obtained from the Oxford B Research Ethics Committee for both surveys (HSE 2009 ref 08/H0605/103, HSE 2010 ref 09/H0605/73)

Socio-economic factors included: i) occupation National Statistics Socio-Economic Classification (NS-SEC, divided into three categories: high (managerial and professional occupations); middle (intermediate occupations) and low (routine and manual occupations)), ii) qualifications (grouped as: degree (NVQ4/NVQ5/Degree or equivalent), below degree (higher education below degree or NVQ3/GCE A Level equivalent or NVQ2/GCE O Level equivalent or NVQ1/CSE other grade), and none (no qualification)) iii) household income tertiles iv) household tenure v) access to motor vehicle (none vs. any), and vi) area level deprivation (using 2007 IMD in national quintiles: 1 least deprived (IMD 0.37-8.32), 2 (8.32-13.75), 3 (13.75-21.22), 4 (21.22-34.42), 5 most deprived (34.42-85.46)). [231] Ethnicity was self-defined using 2001 census categories. Hypertension was defined as doctor-diagnosed (pre-existing diagnosis), survey-defined (identified as having high blood pressure (BP systolic ≥140mmHg and/or diastolic ≥90mmHg and/or taking medication for hypertension) at the survey examination), and 'total' (doctor + survey diagnosed). Diabetes was treated similarly: survey-defined diabetes was HBA1c ≥6.5% at clinic visit. Body mass index (BMI) was defined as normal (<25), overweight (≥25, <30), and obese (≥30). [232] Waist circumference was classified as: <94cm, 94–102cm (high), and >102cm (very high) for men, and <80cm , 80–88cm (high) and >88cm (very high) for women. For South Asians, the waist circumference threshold was 90cm for men and 80cm for women. [232]

Serum creatinine was assayed using an IDMS traceable enzymatic assay in a single laboratory (Clinical Biochemistry Department at the Royal Victoria Infirmary (RVI), Newcastle-upon-Tyne). Albuminuria was assessed using uACR, which was measured on a single random urine sample. Abnormal levels were divided into microalbuminuria (defined as uACR 2.5 to 30mg/mmol in men and 3.5 to 30mg/mmol in women) and macroalbuminuria (uACR>30mg/mmol (in either sex)). [50] CKDEPI eGFR values were derived using the standard equation. [32] Cystatin C levels were obtained using Roche dako immuno-turbidimetric method (rather than the nephelometric method used by several other studies). [39 41] This meant that I was unable to derive the CKEPI cystatin C equation used by these studies. However, comparison between nephelometric and turbidimetric methods have shown similar validity in terms of prediction of outcome, and the the recommended Grubb equation was therefore used to derive eGFR from these cystatin C values. [168 233]

Details of laboratory analysis, internal quality control, and external quality assurance are provided in HSE documentation. [64 139] The KDIGO classification of CKD was used to categorise CKD into stages based on level of eGFR and presence or absence of albuminuria: eGFR 90ml/min/1.73m^2 or more (stage 1), 60-89ml/min/1.73m^2 (stage 2), 45-59ml/min/1.73m^2 (stage 3a), 30-44ml/min/1.73m^2 (stage 3b), 15-29ml/min/1.73m^2 (stage 4), and <15ml/min/1.73m^2 (stage 5). [48] Current guidelines recommend that CKD be defined on the basis of reduced eGFR present for at least 3 months. [48-50] However, because of the cross sectional nature of the HSEs, a single eGFR <60ml/min/1.73m^2 was used to define CKD stage 3 – 5 in these analyses.

Statistics

Descriptive statistics were used to compare the socio-demographic and clinical characteristics of the study population, including the distribution of cystatin C values. Prevalence of CKD 3-5 was compared by eGFR calculation method. Estimated numbers of people with CKD in England was derived for each method using 2011 Census data. Prevalence by CKD stage included only participants with both serum creatinine and uACR. Analyses of CKD and albuminuria associations used all participants with relevant data to maximise power and to allow analysis of albuminuria individually. Logistic regression models were used to examine the relationship between CKD and SES (by various measures), and also between CKD and lifestyle and clinical factors, adjusted for age and sex. Age was categorised as <65 and ≥65. An age x sex interaction term was included in multivariable regression models following identification of an age x sex interaction for CKD 3-5 early in the analyses. Despite low numbers from ethnic minorities, ethnicity is associated with variation in RRT rates,[157 159] and ethnicity was therefore included as a potential confounder in multivariable analyses. Three dichotomised dependent variables were investigated: CKD defined by the CKDEPI equation as eGFR <60ml/min/1.73m^2 (Stage 3-5); the presence of micro- or macro-albuminuria; and CKD Stage 1-2 defined as eGFR >60ml/min/1.73m^2 with evidence of albuminuria. Sensitivity analyses were conducted in the white-only population, and, for albuminuria, in people without diabetes. For CKD 3-5, analyses were also conducted using the MDRD equation to define CKD.

Interactions of socioeconomic variables with age and sex were examined and also with diabetes in the albuminuria models. The final models were i) age, sex

and age*sex, ii) age, sex, ethnicity and age*sex, and iii) age, sex, ethnicity, age*sex, smoking, BMI, doctor diagnosed hypertension, and doctor diagnosed diabetes. Further multivariable analyses of individual socioeconomic characteristics for behavioural and clinical variables (smoking, BMI, hypertension and diabetes) were conducted.

Non-response weights were used in all analyses. Non response weights are used to compensate for the fact that people with certain characteristics are less likely to respond to survey invitations (for example men less than women) in order to ensure representativeness. [234] Obtaining an overall CKD prevalence estimate involves taking into account weighting within gender to allow for gender differences in sampling. Despite low numbers from ethnic minorities, the results suggested lower prevalence of CKD in ethnic minority groups compared to Whites, and ethnicity was therefore included as a potential confounder in multivariable analyses.

For the eGFR model there was a significant age sex interaction (i.e. $p<0.05$) with younger (<65) females having greater odds of CKD compared to younger males but with no difference in older age groups. An age-sex interaction term was included for all SES variables in the eGFR models. Interactions between diabetes and SES were examined in the albuminuria models because of the potential for differentially higher diabetes prevalence in SES sub-groups.

The different methods of estimating eGFR (creatinine (MDRD), creatinine (CKDEPI) and cystatin C (Grubb)) were compared for the different eGFR groups. Prevalence of CKD was compared by eGFR calculation method and CKD stage. A threshold cystatin C level was derived to define CKD in order to compare with CKD defined by eGFR. Individuals in age grouping 16-34 with no hypertension, no diabetes, no albuminuria and not stage 3-5 CKD were selected to determine a cut off value for increased cystatin C levels. This threshold method is similar to that used in analysis of NHANES data. [167]

Univariate, age-sex adjusted, and multivariable logistic regression models were used to examine the associations between cystatin C-defined CKD (using the derived threshold) and a variety of demographic, socio-economic, lifestyle and clinical factors. Age/sex, age/SES, and age/diabetes interactions were tested. Analyses were repeated with a dichotomised dependent variable of eGFR <60ml/min/1.73m2 for cystatin C (Grubb equation).

The distribution of biomarkers in the study population was summarised using a method similar to that used by Peralta et al in a study of the use of cystatin C to aid risk stratification, although I chose step-wise addition of uACR first and then cystatin C to the creatinine-based eGFR in order to better reflect current clinical practice in the UK. [164] Change in the count of the three biomarkers was assessed: CKDEPI Scr eGFR <60ml/min/1.73m^2, cystatin C eGFR <60ml/min/1.73m^2, and uACR>= 3mg/mmol from measuring cystatin C in three groups:

1. CKDEPI Scr eGFR <60ml/min/1.73m^2 and no albuminuria (baseline 1 biomarker, reclassified as 1 or 2 biomarkers)
2. CKDEPI Scr eGFR >=60ml/min/1.73m^2 and albuminuria (baseline 1 biomarker, reclassified as 1 or 2 biomarkers)
3. CKDEPI Scr eGFR <60ml/min/1.73m^2 and albuminuria (baseline 2 biomarkers, reclassified as 2 or 3 biomarkers)

All analyses, adjusted for the complex survey design, were performed using IBM SPSS Statistics version 19.

2.3 Results

2.3.1 Characteristics of the study population

The total combined sample size (unweighted) for the 2009 and 2010 HSE was 13,065 individuals aged 16 and over. Sample characteristics (weighted for non-response) are shown in Table 7. 5799 (44.4%) respondents had a valid serum creatinine value, 7592 (58.1%) had a valid uACR and 5318 (40.7%) had both. Of the unweighted sample of 5799 individuals, 3186 (54.9%) were female (51.2% of the weighted sample). Of those excluded because they lacked a valid serum creatinine, 1994 (27.6%) had no formal qualifications (compared to 20.6% in those included). Of those without valid uACR, 1239 (22.4%) had no access to a motor vehicle and 1660 (30.2%) had no qualifications (compared to 16.7% and 20.3% in those included). Otherwise those included and those excluded were comparable with regard to SES.

2.3.2 Prevalence of CKD and albuminuria

The overall weighted prevalence of CKD stage 3-5 was 303/5786 (5.2%). Prevalence of any albuminuria was 8.2% in men and 7.5% in women (for

macroalbuminuria, 0.3% and 0.5% respectively (only 22 people)). Both CKD 3-5 and albuminuria prevalence was higher in people with low income, no access to a vehicle, and no formal qualifications. Prevalence patterns for CKD1-2 and CKD 3-5 with albuminuria were similar to those for overall albuminuria (although the number of people with CKD stage 3-5 with albuminuria was low (n=66)) (Table 8).

Age-sex adjusted CKD 3-5 was associated with lack of qualifications (odds ratio (OR) 2.27 (95% confidence interval 1.40 - 3.69)), low income (OR 1.50 (1.02 - 2.21)) and renting household tenure (OR 1.36 (1.01 - 1.84) vs. ownership). Tenure remained significant in fully adjusted models. Albuminuria remained significantly associated with several SES measures on full adjustment: low income (OR 1.55 (1.14 - 2.11)), no vehicle (OR 1.38 (1.05 - 1.81)), renting (OR 1.31 (1.03 - 1.67)), most deprived area level quintile (OR 1.55 (1.07 - 2.25)). (Figure 9 and Table 9).

Table 10 shows the prevalence and associations for lifestyle and clinical factors which might act as confounding/explanatory factors for the SES–CKD relationship. This shows slightly different patterns for CKD 3 – 5 and albuminuria. BMI, diabetes and hypertension were positively associated with CKD and albuminuria, whereas total cholesterol was not associated with either. HDL cholesterol was negatively associated with both. All SES measures were associated with smoking, type 2 diabetes, hypertension and obesity after age sex adjustment (Table 11). CKD 1–2 was associated with smoking, BMI, waist circumference, HDL cholesterol, diabetes and hypertension (data not shown).

A significant age*sex interaction ($p<0.05$) was identified in the CKD models, with younger (<65) females having greater odds of CKD compared to younger males but with no difference in older age groups. There were no significant interactions between age and SES in the CKD models or diabetes and SES in the albuminuria models.

There were no differences in these results in the sensitivity analyses for the white-only population, and, for albuminuria, in people without diabetes (data not shown).

Use of the MDRD equation in place of CKDEPI resulted in slightly different associations of CKD 3- 5 with SES, with qualification level and vehicle ownership remaining associated in the fully adjusted model (Table 12).

Table 7. Sociodemographic and clinical characteristics of the weighted study sample

Variable	Category	People with valid serum creatinine value		People with urine albumin creatinine ratio value	
		n	Column %	n	Column %
All	Aged 16+	5799	100	7592	100
Age	Age 16-34	1756	30.3	1949	25.7
	Age 34-54	2037	35.1	2844	37.5
	Age 55-64	856	14.8	1218	16.0
	Age 65-74	615	10.6	871	11.5
	Age 75+	522	9.0	655	8.6
Ethnicity	White	5244	90.4	6884	90.7
	South Asian	243	4.2	285	3.8
	Black	154	2.7	200	2.6
	Other	139	2.4	160	2.1
Sex	Male	2823	48.7	3667	48.3
	Female	2963	51.1	3870	51.0
Income tertile	Lowest	1393	24.0	1517	20.0
	Middle	1617	27.9	1963	25.9
	Highest	1829	31.5	2224	29.3
Access to motor vehicle	Yes	4728	81.5	6280	82.7
	No	1056	18.2	1256	16.5
Qualification	Degree	1295	22.3	1761	23.2
	Below degree	3296	56.8	4238	55.8
	None	1197	20.6	1531	20.2
Occupation (NS-SEC)	High	1894	32.7	2646	34.9
	Middle	1203	20.7	1611	21.2
	Low	2619	45.2	3207	42.2
IMD Quintile	1. Least deprived	1197	20.6	1683	22.2
	2.	1204	20.8	1601	21.1
	3.	1228	21.2	1627	21.4
	4.	1105	19.1	1442	19.0
	5. Most deprived	1051	18.1	1184	15.6

Table 7 cont

Variable	Category	People with valid serum creatinine value		People with urine albumin creatinine ratio value	
		n	Column %	n	Column %
Housing Tenure	Own / Mortgage	3955	68.2	5389	71.0
	Rent/Other	1817	31.3	2148	28.3
Smoking	Never	3126	53.9	4089	53.9
	Ex	1429	24.6	2007	26.4
	Current	1210	20.9	1423	18.7
Body mass index (BMI)	Normal	1956	33.7	2468	32.5
	Overweight	2047	35.3	2683	35.3
	Obese	1314	22.7	1815	23.9
Waist circumference	Low	2120	36.6	2701	35.6
	High	1347	23.2	1761	23.2
	Very High	2242	38.7	2938	38.7
Total Cholesterol	< 5mmol/L	2675	46.1	2984	39.3
	≥ 5mmol/L	3110	53.6	3719	49.0
HDL Cholesterol	< 1.2mmol/l	1301	22.4	1591	21.0
	≥ 1.2mmol	4485	77.3	5809	76.5
Albuminuria	None	4837	83.4	6896	90.8
	Micro	399	6.9	601	7.9
	Macro	22	0.4	39	0.5
Diabetes	No diabetes	5370	92.6	6957	91.6
	Doctor diagnosed[a]	305	5.3	450	5.9
	Survey defined [b]	316	5.4	442	5.8
	Total [c]	429	7.4	581	7.7
Hypertension	No HT	3800	65.5	4854	63.9
	Doctor diagnosed [a]	1387	23.9	1992	26.2
	Survey defined [d]	1542	26.6	2112	27.8
	Total [c]	1980	34.1	2683	35.3
Chronic kidney disease	Yes	303	5.2	-	-
	No	5483	94.6	-	-

[a] Self-reported doctor diagnosis [b] HBA_{1c} ≥6.5% [c] Doctor or survey diagnosed

[d] Identified as high blood pressure (BP systolic ≥140mmHg and/or diastolic ≥90mmHg and/or taking medication for hypertension)

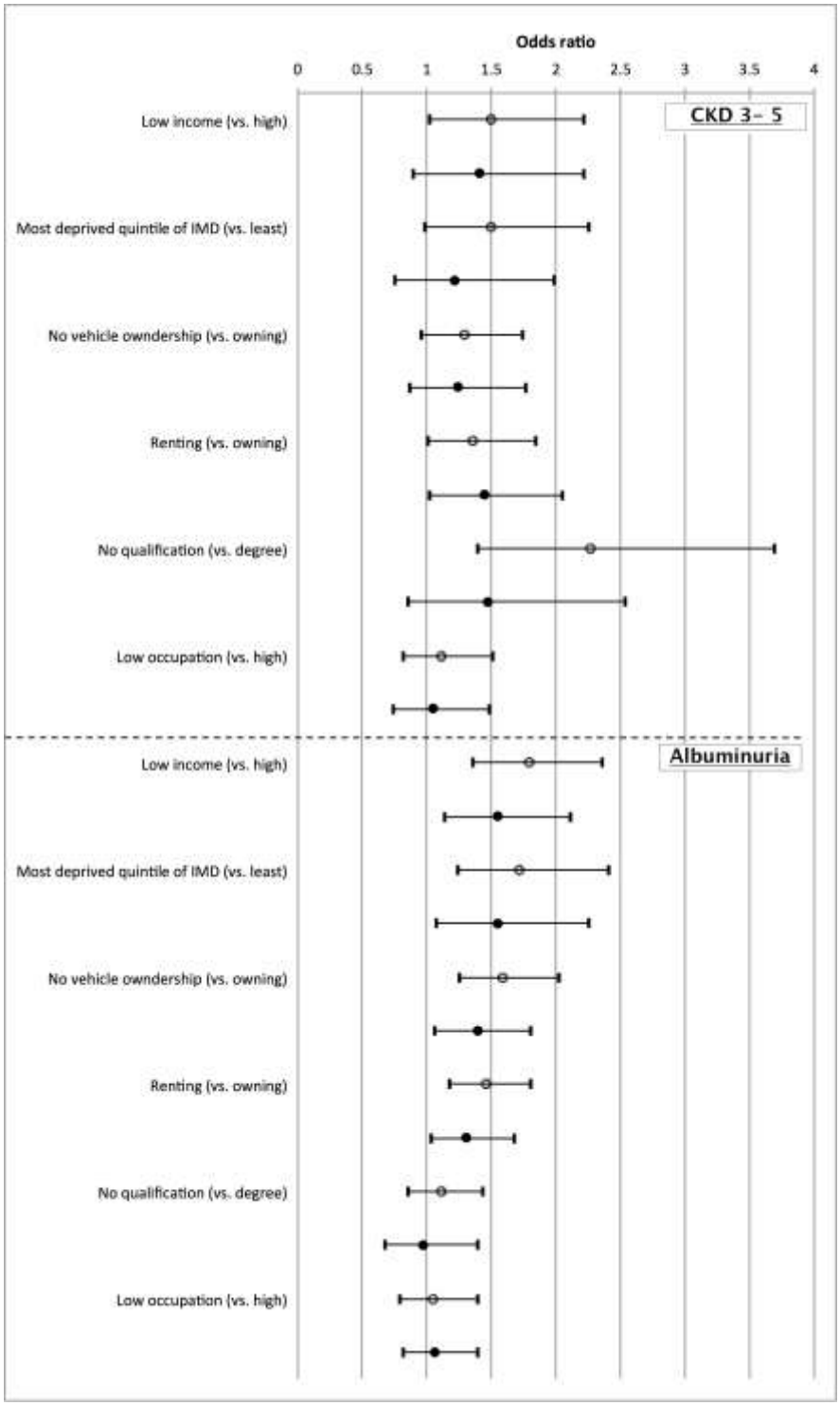
Table 8. Directly age-sex standardised prevalence of CKD stage 3-5 and albuminuria by sociodemographic characteristics

Variable	Category	CKD 3-5 (eGFR <60ml/min/1.73m^2)	Albuminuria (Any)	Albuminuria (CKD 1-2)	Albuminuria (in people with CKD 3-5)	Total n in row
		Weighted n=5786	Weighted n=7529	Weighted n=355	Weighted n=66	
		Prevalence (%)	Prevalence (%)	Prevalence (%)	Prevalence (%)	
All	Aged 16+	5.2	8.0	7.1	1.1	
Ethnicity	White	5.6	8.1	7.2	1.3	5244
	South Asian	1.1	6.4	6.3	0.2	243
	Black	2.7	6.8	6.5	0.6	154
	Other	0.7	6.2	6.2	0.1	137
Income tertile	Lowest	6.5	8.7	7.5	1.5	1393
	Middle	6.0	8.3	7.3	1.4	1617
	Highest	3.0	6.9	6.5	0.6	1830
Access to motor Vehicle	Yes	4.4	7.7	7.0	1.0	4729
	No	8.6	9.2	7.7	2.0	1057
Qualification	Degree	2.5	7.1	6.7	0.5	1295
	Below degree	3.6	7.3	6.7	0.8	3297
	None	12.4	10.8	8.9	2.9	1192
Occupation (NS-SEC)	High	4.6	7.8	7.0	1.1	1894
	Middle	6.1	8.0	7.1	1.3	1203
	Low	5.7	8.2	7.3	1.3	2343

Table 8 cont

Variable	Category	CKD 3-5 (eGFR <60ml/min/1.73m^2)	Albuminuria (Any)	Albuminuria (CKD 1-2)	Albuminuria (in people with CKD 3-5)	Total n in row
		Weighted n=5786	Weighted n=7529	Weighted n=355	Weighted n=66	
		Prevalence (%)	Prevalence (%)	Prevalence (%)	Prevalence (%)	
IMD Quintile	1. (IMD 0.37-8.31) Least deprived	6.0	8.2	7.3	1.4	1196
	2. (IMD 8.32-13.74)	6.3	8.5	7.5	1.4	1204
	3. (IMD 13.75-21.21)	4.8	7.8	7.0	1.1	1229
	4. (IMD 21.22-34.41)	4.6	7.7	6.8	1.1	1105
	5. (IMD 34.42-85.46) Most deprived	3.9	7.5	6.8	0.9	1051
Housing Tenure	Own / Mortgage	5.7	8.1	7.2	1.3	3956
	Rent/Other	3.9	7.6	6.9	0.9	1816

Figure 9. Associations of CKD stage 3- 5 and Albuminuria with measures of SES (age-sex and fully adjusted models)



Open circle marker: age-sex adjusted, closed circle marker: fully adjusted model. Error bars are 95% confidence intervals

Table 9. Associations of CKD stage 3-5 and albuminuria (all albuminuria cases) with socioeconomic factors.

Variable	Category	CKD 3-5 † OR (95% CI)	CKD 3-5 †† OR (95% CI)	CKD 3-5 ††† OR (95% CI)	Albuminuria † OR (95% CI)	Albuminuria †† OR (95% CI)	Albuminuria ††† OR (95% CI)
Age	Under 65	1	1	1	1	1	1
	≥ 65	52.80 (28.33–98.47)**	50.33 (26.95–93.97)**	38.72 (19.06–78.67)**	3.73 (2.78–4.99)**	3.72 (2.77–4.98)**	2.37 (1.69–3.33)**
Sex	Male	1	1	1	1	1	1
	Female	1.02 (0.76–1.37)	1.03 (0.76–1.38)	1.03 (0.73–1.46)	0.60 (0.43–0.85)**	0.60 (0.43–0.85)**	0.59 (0.40–0.88)**
Age*sex	Male <65	1	1	1	1	1	1
	Female <65	2.67 (1.34–5.30)**	2.66 (1.34–5.29)**	3.23 (1.52–6.86)**	1.09 (0.85–1.40)	1.09 (0.85–1.40)	1.05 (0.80–1.36)
	Male ≥ 65	52.81 (28.33–98.47)**	50.33 (26.96–93.97)**	38.72 (19.06–78.67)**	3.73 (2.78–4.99)**	3.72 (2.77–4.99)**	2.37 (1.69–3.33)**
	Female ≥65	53.97 (29.12–100.02)**	51.64 (27.83–95.82)**	40.03 (19.87–80.62)**	2.25 (1.65–3.07)**	2.24 (1.64–3.06)**	1.41 (0.98–2.02)
Occupation / NS-SEC	High	1	1	1	1	1	1
	Middle	1.20 (0.84-1.71)	1.21 (0.84-1.71)	1.13 (0.75-1.71)	1.14 (0.90-1.45)	1.17 (0.92-1.48)	1.06 (0.78-1.44)
	Low	1.11 (0.81-1.51)	1.14 (0.84-1.56)	1.05 (0.74-1.48)	1.05 (0.79-1.39)	1.05 (0.79-1.40)	1.06 (0.82-1.39)

Table 9 cont

Variable	Category	CKD 3-5 † OR (95% CI)	CKD 3-5 †† OR (95% CI)	CKD 3-5 ††† OR (95% CI)	Albuminuria † OR (95% CI)	Albuminuria †† OR (95% CI)	Albuminuria ††† OR (95% CI)
Income	High	1	1	1	1	1	1
	Medium	1.28 (0.87-1.89)	1.28 (0.87-1.89)	1.12 (0.71-1.75)	1.25 (0.89-1.66)	1.25 (0.94-1.66)	1.17 (0.86-1.59)
	Low	1.50 (1.02-2.21)*	1.54 (1.04-2.27)*	1.41 (0.89-2.21)	1.79 (1.35-2.36)**	1.72 (1.30-2.28)**	1.55 (1.14-2.11)**
Qualification	Degree	1	1	1	1	1	1
	Below Degree	1.67 (1.04-2.69)*	1.63 (1.01-2.63)*	1.42 (0.84-2.38)	1.14 (0.86-1.49)	1.13 (0.86-1.48)	1.07 (0.80-1.43)
	None	2.27 (1.40-3.69)**	2.26 (1.39-3.67)**	1.47 (0.85-2.53)	1.27 (0.92-1.75)	1.22 (0.89-1.69)	1.05 (0.74-1.50)
Quintile of IMD	Least deprived	1	1	1	1	1	1
	2nd	0.89 (0.61-1.30)	0.87 (0.60-1.26)	0.78 (0.51-1.20)	1.34 (0.96-1.85)	1.27 (0.92-1.75)	1.33 (0.94-1.88)
	3rd	0.94 (0.63-1.41)	0.90 (0.61-1.33)	0.88 (0.56-1.37)	1.13 (0.80-1.59)	1.06 (0.76-1.49)	1.19 (0.83-1.70)
	4th	1.08 (0.72-1.64)	1.10 (0.74-1.63)	1.02 (0.65-1.62)	1.64 (1.18-2.27)**	1.51 (1.10-2.09)**	1.52 (1.06-2.17)*
	Most deprived	1.49 (0.98-2.25)	1.55 (1.03-2.32)*	1.22 (0.75-1.98)	1.72 (1.24-2.41)**	1.72 (1.23-2.41)**	1.55 (1.07-2.25)*
Vehicle	Yes	1	1	1	1	1	1
	No	1.29 (0.96-1.74)	1.38 (0.99-2.01)	1.24 (0.87-1.77)	1.59 (1.25-2.02)**	1.61 (1.26-2.05)**	1.38 (1.05-1.81)*

Table 9 cont

Variable	Category	CKD 3-5 † OR (95% CI)	CKD 3-5 †† OR (95% CI)	CKD 3-5 ††† OR (95% CI)	Albuminuria † OR (95% CI)	Albuminuria †† OR (95% CI)	Albuminuria ††† OR (95% CI)
Tenure	Own	1	1	1	1	1	1
	Rent	1.36 (1.01-1.84)*	1.45 (1.09-1.93)*	1.45 (1.02-2.05)*	1.46 (1.18-1.81)**	1.42 (1.14-1.76)**	1.31 (1.03-1.67)*

† Adjusted for age, sex, and age*sex

†† Adjusted for age, sex, ethnicity and age*sex

††† Adjusted for age, sex, age*sex, ethnicity, smoking, BMI, Doctor-diagnosed hypertension and diabetes.

* p<0.05 **p<0.01

NS-SEC = National Statistics Socioeconomic Classification

Table 10. Prevalence and age-/sex/age*sex- adjusted associations of CKD stage 3-5 and albuminuria (all albuminuria cases) with behavioural and clinical factors.

Variable	Category	CKD 3 – 5			Albuminuria		
		Prevalence (%)	Odds ratio (95% CI)	p value	Prevalence (%)	Odds ratio (95% CI)	p value
Smoking	Current	4.5	1	0.854	8.4	1	0.048
	Ex	8.9	1.24 (0.80 - 1.92)		9.7	0.85 (0.63 - 1.15)	
	Never	2.4	1.02 (0.62 - 1.65)		6.9	0.76 (0.59 - 0.99)*	
BMI	Normal	2.3	1	0.001	6.6	1	0.048
	Overweight	5.0	1.72 (1.18 - 2.52)		6.7	1.11 (0.86 - 1.43)	
	Obese	7.5	2.75 (1.87 - 4.04)		8.4	1.33 (1.01 - 1.75)*	
Waist circumference	Low	2.1	1	<0.001	6.4	1	
	High	5.5	1.57 (1.05 - 2.34)		7.7	1.10 (0.83 - 1.45)	0.636
	Very High	7.9	1.97 (1.38 - 2.81)		9.2	1.27 (0.99 - 1.62)	0.051
Total Cholesterol	< 5mmol/L	5.6	1	0.092	8.4	1	
	≥ 5mmol/L	4.9	0.80 (0.62 - 1.04)		8.0	0.90 (0.73 - 1.09)	0.251
HDL Cholesterol	< 1.2mmol/l	6.9	1	<0.001	10.0	1	
	≥1.2mmol	4.7	0.55 (0.41 - 0.74)		7.6	0.73 (0.58 - 0.93)**	0.003

Table 10 cont

Variable	Category	CKD 3 – 5			Albuminuria		
		Prevalence (%)	Odds ratio (95% CI)	p value	Prevalence (%)	Odds ratio (95% CI)	p value
Albuminuria	None	4.6	1	<0.001	-	-	-
	Micro	16.0	2.34 (1.65 - 3.31)		-	-	
	Macro	30.0	7.53 (2.22 - 25.5)		-	-	
Diabetes	No diabetes	4.4	1	<0.001	7.0	1	<0.001
	Doctor diagnosed [a]	15.5	3.83 (2.74 - 5.35)		22.9	2.69 (1.95 - 3.70)	
	Survey defined [b]	16.8	4.33 (3.14 - 5.99)		16.8	2.56 (1.93 - 3.41)	
	Total [c]	15.4	3.99 (2.97 - 5.35)		20.4	2.50 (1.89 - 3.66)	
Hypertension	No hypertension	2.1	1	<0.001	5.2	1	<0.001
	Doctor diagnosed [a]	13.1	5.56 (4.37 - 7.09)		14.4	2.25 (1.81 - 2.81)	
	Survey defined [d]	12.4	5.11 (3.99 - 6.56)		9.6	2.13 (1.69 - 2.69)	
	Total [c]	11.3	6.04 (4.64 - 7.88)		13.3	2.04 (1.60 - 2.89)	

[a] Self-reported doctor diagnosis, [b] HBA_{1c} ≥6.5%, [c] Doctor or survey diagnosed

[d] Identified as high blood pressure (BP systolic ≥140mmHg and/or diastolic ≥90mmHg and/or taking medication for hypertension)

Table 11. Age-sex adjusted odds ratios for hypertension, diabetes, smoking and obesity by socio-demographic factors.

Variable	Category	Doctor diagnosed hypertension	Doctor diagnosed diabetes	Smoking	Obesity
Occupation / NS-SEC	High	1	1	1	1
	Middle	1.10 (0.92 – 1.32)	0.83 (0.58 – 1.18)	1.63 (1.34 – 1.98)**	1.05 (0.88 – 1.26)
	Low	1.29 (1.11 – 1.5)**	1.32 (1.01 – 1.72)*	2.15 (1.83 – 2.52)**	1.32 (1.13 – 1.53)**
Income	High	1	1	1	1
	Medium	1.21 (1.02 – 1.44)*	1.50 (1.05 – 2.14)*	1.60 (1.33 – 1.92)**	1.36 (1.15 – 1.6)**
	Low	1.53 (1.28 – 1.84)**	2.41 (1.7 – 3.41)**	2.78 (2.33 – 3.29)**	1.64 (1.38 – 1.96)**
Qualification	Degree	1	1	1	1
	Below Degree	1.49 (1.24 – 1.78)**	1.22 (0.86 – 1.72)**	2.32 (1.93 – 2.8)**	1.56 (1.32 – 1.85)**
	None	1.63 (1.33 – 2.03)**	1.51 (1.03 – 2.21)*	4.29 (3.4 – 5.41)**	1.96 (1.59 – 2.41)**

Table 11 cont

Variable	Category	Doctor diagnosed hypertension	Doctor diagnosed diabetes	Smoking	Obesity
IMD	Least deprived	1	1	1	1
	2nd	1.05 (0.86 – 1.29)	1.18 (0.8 –1.73)	1.70 (1.34 – 2.14)**	1.20 (0.98 – 1.47)
	3rd	1.04 (0.85 – 1.28)	1.47 (1.01–2.15)*	1.98 (1.58 – 2.9)**	1.28 (1.04 – 1.56)*
	4th	1.36 (1.1 – 1.67)**	1.51 (1.02–2.23)*	2.71 (2.16 – 3.39)**	1.51 (1.23 – 1.86)**
	Most deprived	1.86 (1.5 – 2.29)**	2.02 (1.37– 2.96)**	2.72 (2.17 – 3.42)**	1.97 (1.61 – 2.42)**
Vehicle	Yes	1	1	1	1
	No	1.24 (1.04 – 1.47)*	1.72 (1.3 – 2.28)**	2.12 (1.81 – 2.48)**	1.39 (1.17 – 1.64)**
Tenure	Own	1	1	1	1
	Rent	1.24 (1.06 – 1.44)**	1.8 (1.4 – 2.33)**	3.1 (2.7 – 3.56)**	1.50 (1.3 – 1.73)**

* p<0.05 **p<0.01

Table 12. Associations of CKD stage 3-5 defined by the MDRD equation with socioeconomic factors.

Variable	Category	CKD 3-5 † OR (95% CI)	CKD 3-5 †† OR (95% CI)	CKD 3-5 ††† OR (95% CI)
Age	Under 65	1	1	1
	≥ 65	19.76 (12.99–30.08)**	18.49 (12.14–28.17)**	12.76 (7.96–20.44)**
Sex	Male	1	1	1
	Female	1.23 (0.93–1.63)	1.24 (0.94–1.65)	1.31 (0.94–1.82)
Age*sex	Male <65	1	1	1
	Female <65	2.11 (1.36–3.27)**	2.11 (1.36–3.28)**	2.36 (1.48–3.77)**
	Male ≥ 65	19.76 (12.99–30.08)**	18.49 (12.14–28.17)**	12.76 (7.96–20.44)**
	Female ≥65	24.44 (16.30–36.65)**	22.93 (15.28–34.42)**	16.65 (10.59–26.18)**
Occupation / NS-SEC	High	1	1	1
	Middle	1.21 (0.87-1.67)	1.21 (0.88-1.67)	1.17 (0.82-1.67)
	Low	1.10 (0.83-1.46)	1.12 (0.85-1.49)	1.06 (0.78-1.46)
Income	High	1	1	1
	Medium	1.19 (0.85-1.66)	1.18 (0.84-1.65)	1.11 (0.76-1.62)
	Low	1.26 (0.90-1.78)	1.29 (0.91-1.81)	1.35 (0.91-1.98)
Qualification	Degree	1	1	1
	Below Degree	1.58 (1.05-2.38)*	1.53 (1.01-2.31)*	1.39 (0.89-2.16)
	None	2.31 (1.51-3.53)**	2.27 (1.48-3.48)**	2.03 (1.27-3.24)**

Table 12 cont

Variable	Category	CKD 3-5 † OR (95% CI)	CKD 3-5 †† OR (95% CI)	CKD 3-5 ††† OR (95% CI)
Quintile of IMD	Least deprived	1	1	1
	2nd	0.97 (0.69-1.38)	0.96 (0.68-1.36)	0.86 (0.59-1.27)
	3rd	1.09 (0.77-1.55)	1.08 (0.76-1.54)	1.05 (0.71-1.54)
	4th	1.12 (0.78-1.62)	1.15 (0.79-1.66)	1.06 (0.71-1.60)
	Most deprived	1.20 (0.82-1.75)	1.39 (0.95-2.04)	1.12 (0.73-1.73)
Vehicle	Yes	1	1	1
	No	1.39 (1.07-1.80)*	1.52 (1.16-1.98)**	1.41 (1.03-1.93)*
Tenure	Own	1	1	1
	Rent	1.03 (0.79-1.34)	1.08 (0.83-1.42)	1.06 (0.77-1.45)

† Adjusted for age, sex, and age*sex †† Adjusted for age, sex, ethnicity and age*sex ††† Adjusted for age, sex, age*sex, ethnicity, smoking, BMI, Doctor-diagnosed hypertension and diabetes. * p<0.05 **p<0.01

NS-SEC = National Statistics Socioeconomic Classification

2.3.3 Prevalence by MDRD vs. CKDEPI equations

Use of the MDRD equation classified more individuals into a lower CKD category than the CKDEPI equation (17.7% vs. 1.8%). About 1% of all individuals would be classified as having CKD by MDRD equation that would not by the CKDEPI, compared to only 0.2% for CKDEPI equation. There was a net tendency for CKDEPI to classify MDRD CKD 3-5 cases upwards as non CKD 3-5. Out of 269 individuals categorised as CKD 3a (45-59) by MDRD, 57 were categorised as non CKD3-5 by CKDEPI (Table 13). Such re-classified cases were more likely to be female, younger, and less likely to have factors associated with poorer outcome (doctor diagnosed diabetes, hypertension and albuminuria) (Table 14). The prevalence of CKD 3-5 was lower in both sexes using CKDEPI equation (Table 15).

Table 13. Comparison of MDRD and CKDEPI CKD staging (weighted)

		eGFR CKDEPI			
		≥60	45-59	<45	TOTAL
eGFR MDRD	≥60	5426 (93.8%)	11 (0.2%)	0	5437 (94.0%)
	45-59	57 (1.0%)	208 (3.6%)	4 (<0.1%)	269 (4.6%)
	<45	0	2 (<0.1%)	78 (1.4%)	80 (1.4%)
TOTAL		5483 (94.8%)	221 (3.8%)	82 (1.4%)	5786 (100%)

Figures are: number (% of total). (Shaded areas indicate individuals reclassified as a result of changing the equation used to derive eGFR)

Table 14. Sociodemographic and clinical characteristics of people with CKD 3 – 5 defined by eGFR derived from MDRD and CKDEPI equations

		MDRD < 60 ml/min/1.73m²		CKDEPI <60 ml/min/1.73m²	
Total in category		349		303	
Sex	Male	135	38.7%	126	41.6%
	Female	214	61.3%	177	58.4%
Age	16-54	46	13.1%	21	6.9%
	55+	303	86.9%	282	93.1%
Diabetes	(total)	70	20.1%	66	21.9%
Hypertension	(total)	241	61.9%	224	74.2%
Albuminuria	Normal	246	79.1%	207	75.9%
	Micro/macro	65	20.9%	66	24.1%

Table 15. Sociodemographic characteristics of the population surveyed showing the prevalence of CKD as defined by MDRD and CKDEPI equations and albuminuria.

Variable	Category	Number in category	CKDEPI	MDRD	Albuminuria
		Total n = 5799	Prevalence (%)	Prevalence (%)	Prevalence (%)
Age	Age 16-34	1049	0.2	0.2	6
	Age 34-54	2271	2.2	2.2	5.1
	Age 55-64	1051	5.8	5.8	7.9
	Age 65-74	839	15	13.8	11.8
	Age 75+	589	36.6	35.1	19.9
Sex	Male	2613	4.6	4.7	8.2
	Female	3186	7	7.3	7.5
Income tertile	Lowest	1337	7.8	7.9	12
	Middle	1717	7	6.6	7.9
	Highest	1891	3.4	3.4	5.7
Access to motor vehicle	Yes	4858	4.9	5.2	7
	No	940	9.6	9.9	11.9
Qualification	Degree	1278	1.8	2.3	5.9
	Below degree	3221	5	4.6	7.6
	None	1297	19.6	14.2	11
Profession	High	2077	5.2	4.9	7.1
	Middle	1261	6.3	7.3	7.5
	Low	2240	6	6.8	7.2

Table 15 cont

Variable	Category	Number in category Total n = 5799	CKDEPI Prevalence (%)	MDRD Prevalence (%)	Albuminuria Prevalence (%)
IMD quintile	1. (IMD 0.37-8.32) Least deprived	1290	6.7	6.5	6.7
	2. (IMD 8.32-13.75)	1294	6.5	6.6	8
	3. (IMD 13.75-21.22)	1187	5.8	6.2	6.2
	4. (IMD 21.22-34.42)	1086	5.6	5.9	9.1
	5. (IMD 34.42-85.46) Most deprived	942	5.5	5.6	9.5
Housing Tenure	Own/Mortgage	4298	6.7	6.5	7.4
	Rent/Other	1491	4.9	4.9	10.8

2.3.4 Cystatin C

A total of 1538 individuals met the criteria to derive the cystatin C threshold. The mean cystatin C value was 0.87mg/L, median 0.85mg/L. At the 99th centile the cut-off cystatin C value was 1.2mg/L. There were 14 values greater than 1.2 for this age grouping. A (weighted) total of 8.5% of all individuals were above this threshold. Repeating the analyses above after regrouping age to 20-39 (i.e. same age categories as used in NHANES) gave a total of 1399 individuals.[167] The mean cystatin C value was 0.86mg/L, median 0.86mg/L. At the 99th centile the cut-off cystatin C value was 1.2mg/L. There were 13 values greater than 1.2mg/L for this age grouping. Alteration of the age range therefore gave the same threshold, and cystatin C values >1.2mg/L was used as the threshold cystatin C level.

Mean cystatin C was 0.96mg/L, median 0.92mg/L, and both mean and median were higher in males than females. A higher proportion of women had a cystatin C value greater than the 1.2mg/L threshold (8.8 to 8.1%) and a higher proportion had CKD, as calculated by the Grubb equation, (7.5% to 7.9%) compared to men.

Cystatin C distribution varied by age and sex. Males had higher median cystatin C compared to females for the youngest age, but this difference narrowed as the age increased. Cystatin C was higher for males for those aged under 55 (a difference of 0.065mg/L and 0.07mg/L for ages 16-34 and 35-54 respectively). For ages 55-74 males had a slightly higher median cystatin C; a difference of 0.02mg/L and 0.03mg/l for ages 55-64 and 65-74 respectively. For participants aged over 75, females had a slightly higher median cystatin C; 1.18mg/L compared to 1.17mg/L for males. Table 16 shows a comparison of the prevalence of each CKD stage using the different methods of estimating eGFR, and Table 17 shows the proportions of people in each of four eGFR groups reclassified by using cystatin C (Grubb) rather than either the CKDEPI or MDRD equations to derive eGFR.

Table 16. Prevalence of CKD by eGFR calculation method and CKD stage

	Stage of CKD					
Equation	1	2	3A	3B	4/5	TOTAL
Creatinine (CKDEPI)	189 (3.5%)	178 (3.3%)	237 (4.4%)	70 (1.3%)	13 (0.3%)	687 (12.9%)
Creatinine (MDRD)	138 (2.6%)	231 (4.3%)	290 (5.4%)	71 (1.3%)	10 (0.2%)	740 (13.9%)
Cystatin C (Grubb)	198 (3.7%)	141 (2.6%)	285 (5.3%)	129 (2.4%)	37 (0.7%)	790 (14.8%)

Percentages shown are of the total

Table 17. Reclassification of Cystatin C Grubb equation against Serum Creatinine CKDEPI and MDRD equations by eGFR in 4 groupings

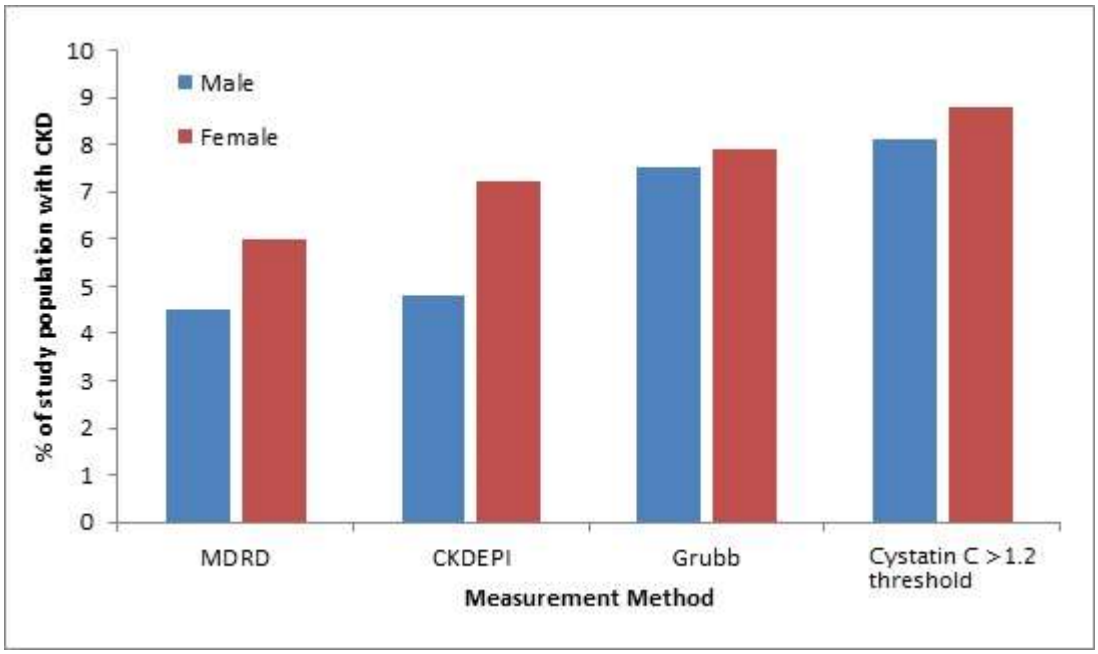
		eGFR cystatin C (Grubb)				TOTAL
		>90	60-89	45-59	<45	
Creatinine eGFR CKDEPI	>90	2658	741 (12.8%)	30 (0.5%)	1 (<0.1%)	3430 (59.2%)
	60-89	770 (13.3%)	1001	187 (3.2%)	50 (0.9%)	2008 (34.7%)
	45-59	20 (0.3%)	82 (1.4%)	86	73 (1.3%)	261 (4.5%)
	<45	2 (<0.1%)	9 (0.2%)	13 (0.2%)	70	94 (1.6%)
TOTAL		3450 (59.6%)	1833 (31.6%)	316 (5.5%)	194 (3.3%)	5793 (100%)

		eGFR cystatin C (Grubb)				TOTAL
		>90	60-89	45-59	<45	
Creatinine eGFR MDRD	>90	2044	496 (8.6%)	25 (0.4%)	1 (<0.1%)	2566 (44.3%)
	60-89	1357 (23.4%)	1213	190 (3.3%)	51 (0.9%)	2811 (48.5%)
	45-59	45 (0.8%)	115 (2%)	87	75 (1.3%)	322 (5.6%)
	<45	3 (0.1%)	9 (0.2%)	13 (0.2%)	67	92 (1.6%)
TOTAL		3449 (59.6%)	1833 (31.7%)	315 (5.4%)	194 (3.4%)	5791 (100%)

Percentages shown are of the total

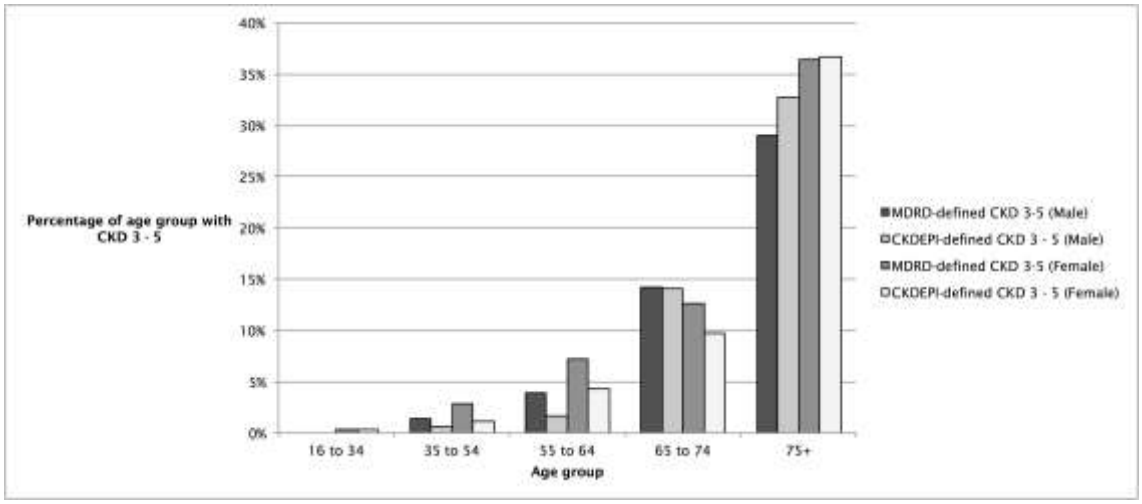
Figure 10 shows the gender variation in CKD 3-5 prevalence using MDRD, CKDEPI, cystatin C (Grubb) and cystatin C threshold to define CKD. Figure 11 shows the change in prevalence of CKD 3- 5 with age between MDRD and CKDEPI.

Figure 10. Comparison of proportion of study participants with CKD stage 3-5 by different measurement methods and by sex



Cystatin C threshold in mg/L

Figure 11. Variation in prevalence of CKD stage 3 – 5 by age, sex, and eGFR estimating equation



CKD defined by Cystatin C also showed socioeconomic variation. Using the Grubb equation to define CKD 3 – 5, Table 18 shows the variation in CKD prevalence by different measures of SES. Further exploration of the SES associations of CKD defined by cystatin C was not a part of this thesis (work being undertaken by Grant Aitken and Graham Moon), but this table suggests higher prevalence of CKD defined by cystatin C in lower SES groups by several measures (no vehicle, no qualifications, occupation, tenure).

Table 18. Variation in prevalence of CKD 3 – 5 (cystatin C, Grubb) by measures of SES

		CKD prevalence (%)
Income	Lowest	11.5
	Middle	7.9
	Highest	3.4
Access to vehicle	Yes	5.8
	No	16.0
Qualification	Degree	2.1
	Below degree	5.3
	None	20.3
Occupation (NS-SEC)	High	5.8
	Middle	8.9
	Low	9.3
IMD	IMD 0.37-8.32 (Least deprived)	7.4
	IMD 8.32-13.75	8.2
	IMD 13.75-21.22	7.2
	IMD 21.22-34.42	7.3
	IMD 34.42-85.46	8.3
Tenure	Own/Mortgage	7.4
	Rent/Other	8.3

2.3.5 Using a triple marker approach in CKD

Peralta and colleagues used a triple marker approach to define CKD and stratify risk. [164] They identified that the presence of abnormal levels of all three biomarkers (serum creatinine, cystatin C, and uACR) identified a group of people at high risk of progression to ESKD and all-cause mortality. Applying a similar stratification process to the weighted HSE population that had valid serum creatinine, cystatin C, and uACR gives groupings as shown in Figure 12. A policy of targeted use of cystatin C measurement in people with CKD 1, 2 and 3a would have an effect on risk stratification as shown in Figure 13.

Figure 12. Chronic kidney disease definitions using a triple marker approach (as per Peralta et al JAMA 2011;305) applied to the HSE data

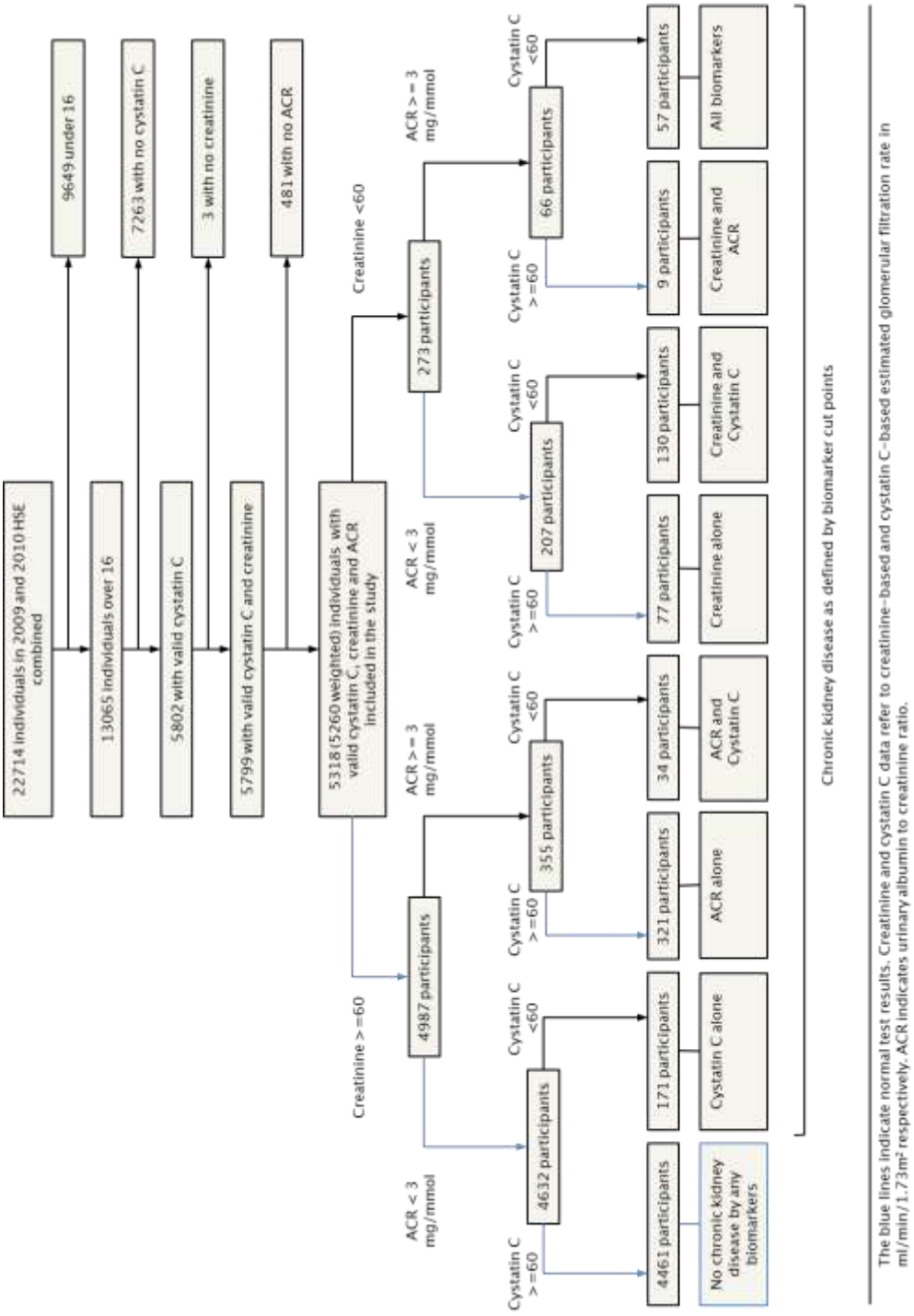
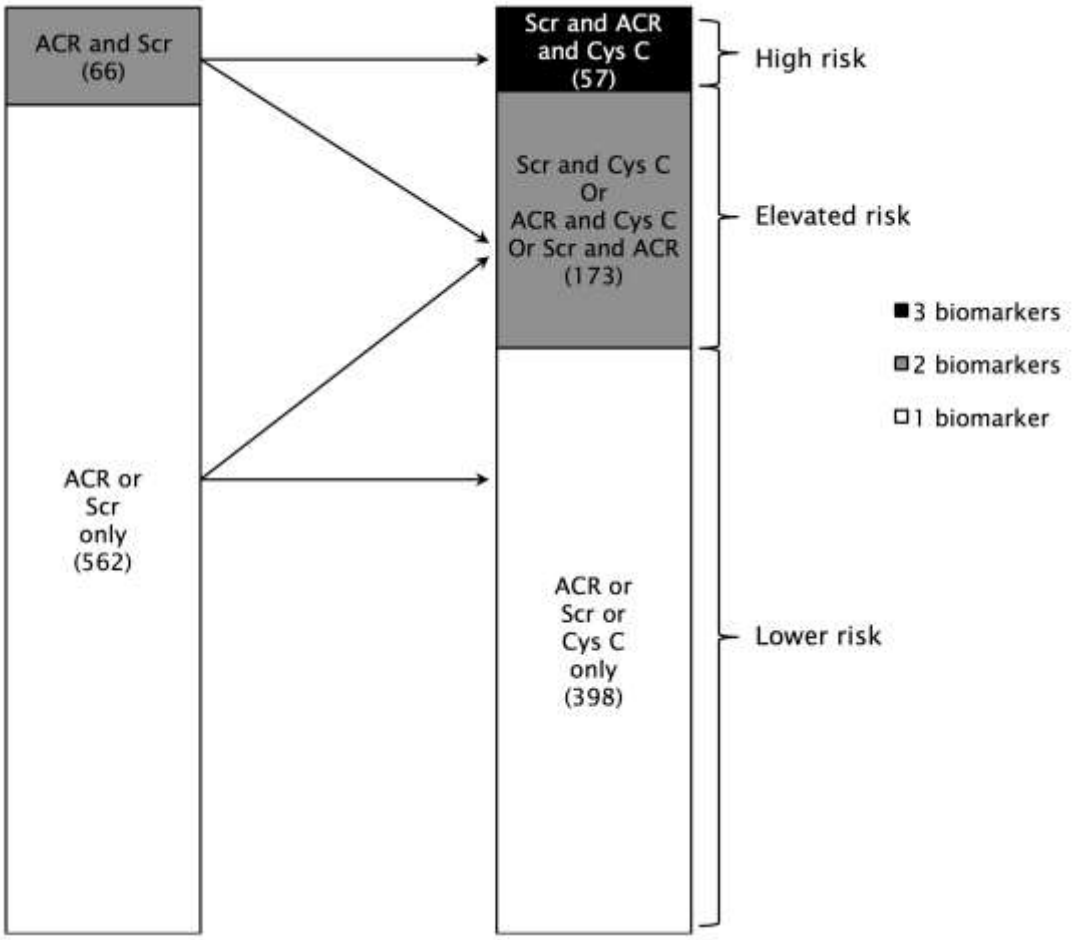


Figure 13. The effect on risk stratification of adding cystatin C testing to people with serum creatinine (Scr) and / or albuminuria (uACR)



This shows that only a small number of people would be identified who had the highest risk and that the majority could be considered as low risk. Additional use of cystatin C therefore clarifies those who are at highest risk by identifying those with three abnormal biomarkers.

2.4 Discussion

This study found socioeconomic disparities in the prevalence of CKD stage 3-5, using the CKDEPI equation to define CKD, for individual measures of SES. It also identified socioeconomic disparities in the prevalence of albuminuria, an independent predictor of poor outcomes, for a wide range of both individual and an area level measure of SES.

Higher CKD 3-5 prevalence was associated with lack of qualifications, low income, and housing tenure (renting) after adjusting for age and sex. These associations were not maintained after further adjustment for ethnicity, lifestyle and clinical variables (obesity, diabetes, hypertension, and smoking), which are likely to be explanatory factors on the causal pathway. Higher albuminuria prevalence was associated with low income, lack of vehicle ownership, housing tenure (renting), and IMD, and these were maintained, though attenuated, after full adjustment, demonstrating independence from these key factors on the causal pathway.

The study suggests that the prevalence of CKD stage 3-5 in England would be lower by 0.8% if the CKDEPI equation was introduced to classify CKD, equivalent to about 375,000 fewer people. It would reduce prevalence in younger and middle aged groups but not in the older people, and would identify a group with higher risk of adverse consequences. Cystatin C-based methods would classify a higher proportion of the population as having CKD 3 – 5 compared to serum creatinine methods, both using the Grubb equation to derive eGFR, or using cystatin C directly with a threshold level, especially in older people.

I identified significant associations between elevated cystatin C and increasing age, qualification, smoking, BMI, diabetes, hypertension, total cholesterol, HDL cholesterol, albuminuria after adjusting for age and sex, although not all of these associations remained on full adjustment. In this study, the associations of elevated cystatin C and Grubb-defined CKD were very similar.

I also showed that selected use of cystatin C may improve risk stratification in certain groups of people with mild CKD. The findings support the findings of several other studies, both from the UK and elsewhere. A population-based case control study in Sweden found an approximately doubled adjusted odds ratio (OR) of having CKD in families with only unskilled workers compared to

families with at least one professional (after adjusting for age, sex, BMI, smoking, alcohol, and aspirin or paracetamol use).[119] A retrospective cross-sectional study in the UK of incident CKD presenting to renal services found increased adjusted risk of low eGFR (<30ml/min/1.73m^2) in areas with greater socioeconomic deprivation. [141] Cross sectional data from the Whitehall II cohort showed similar findings in identifying higher adjusted odds of low eGFR in lower occupational grades, and this association was attenuated after adjustment for BMI and components of the metabolic syndrome; similar to my findings. [140] In the US, the ARIC study identified an association of CKD incidence with individual SES defined by occupational status. [120] By contrast, a national survey in Australia did not demonstrate association of CKD prevalence with SES (measured by education and income) after age-sex adjustment. Reasons for these variations are likely to be complex, but the authors of the study suggest they may relate to differences in health care systems or access to health care and primary prevention. [121] There are limited data on non-developed countries. The numbers of people with CKD from minority ethnic groups was low in these HSEs, so I was unable to draw conclusions about the ethnic distribution of CKD. Patterns of SES-related CKD variation have been found across different ethnic groups in the US as described in section 1.3.1.2. The study by White and colleagues to compare the findings of three nationally representative surveys in the US, Australia, and Thailand showed variation between countries, and, for the US, between different ethnic groups, in the association between SES and prevalence of CKD 3- 5. Non-Hispanic White and non-Hispanic Black participants with less than 12 years of education remained significantly more likely to have eGFR<60ml/min/1.73m^2. Unemployed non-Hispanic Blacks and Mexican Americans, and non-Hispanic Whites in the lowest income quartile also had higher risk of CKD prevalence compared with employed groups, and those in the highest income quartile respectively after full adjustment. [121]

There is little evidence on the relationship between albuminuria and SES. Data from NHANES III demonstrated an association between microalbuminuria and poverty in the US (adjusted OR 1.18, 1.05-1.33), and there is evidence of similar associations with various measures of SES in an Asian (Malay) population. [162 235] To my knowledge, this is the first study to investigate the association between albuminuria and SES in a representative population sample in the UK. As described in section 1.1.4, albuminuria is an independent

predictor of CKD progression and mortality in CKD. [13 72] In unadjusted analyses, these data suggest socioeconomic inequalities in albuminuria distribution, both in those with eGFR <60ml/min/1.73m^2 and those with eGFR above this level, which will influence differential propensity to progress. There are few data on the relationship between SES and CKD progression. The ARIC study in the US identified that, for white men, living in the lowest compared with the highest SES area level quartile was associated with increased risk of CKD progression (hazard ratio for elevated serum creatinine 1.6, (95% CI1.0 to 2.5). [122] The reasons for finding association between SES and CKD and albuminuria may be partly related to the social distribution of underlying factors associated with CKD occurrence and progression, including obesity, smoking, type 2 diabetes, and hypertension. [122 236 237] Persistence of the association for albuminuria after adjustment for confounding factors suggests other causal mechanisms (and or potential residual confounding) may apply. Mechanisms of proteinuria are complex, and the cause of this association warrants future investigation.[45] Albuminuria is a key determinant of progression and poor outcome in CKD, particularly when combined with other risk factors (type 2 diabetes and hypertension), which are more prevalent in lower socioeconomic groups. Other factors such as low birth weight, and health care access (with variation by health system) also show socioeconomic patterns. [238 239]

2.4.1 Strengths and limitations

Strengths of this study include the nationally representative nature of the 2009 and 2010 HSE data, pooled over two years, increasing numbers and precision of estimates, the rigorous nature of HSE methodology with standardised protocols for measurement by trained interviewers and nurses, all samples being tested in the same laboratory with standardised assays, use of non-response weighting to reduce response bias, and use of various SES measures. The study was limited by its cross-sectional nature, reducing the ability to infer causal relationships. Reverse causation was, however, considered unlikely as the majority of people with CKD are asymptomatic. Non-response weighting is an effective method to avoid bias and maintains representativeness of the sample. [240] An important limitation was using single samples to test for serum creatinine and albuminuria. Persistence of reduced eGFR levels and elevated uACR to confirm chronicity could not be shown,

which could lead to non-differential misclassification. The methods were similar to those used in NHANES III, but repeat testing of uACR in NHANES (from the 1988-1994 survey to the 1999-2004 survey) showed reduced albuminuria prevalence. [162 214] Use of single eGFR has also been shown to elevate CKD prevalence estimates. [241] Confirmation in longitudinal studies would therefore be beneficial. There were too few cases from minority ethnic groups to give robust data on ethnic differences in CKD prevalence. South Asians and Blacks have higher rates of RRT but lower prevalence of CKD than Caucasians. [123 125] Prevalence of stage 4/5 CKD is likely to be underestimated as, while the HSE adjusts for non-response among the general population in private households, it may not account for some in whom more severe CKD is more common (people in residential care or those unable to participate because of poor health or hospitalisation) and may therefore miss individuals with ESKD. Further limitations are: lack of data on prevalent CVD and family history, small numbers with macroalbuminuria, lack of information on medication use (differential use of renin angiotensin aldosterone system inhibitors by SES could result in less apparent albuminuria in those with higher SES). Accurately measuring SES in elderly populations is challenging, and non-differential misclassification may bias associations towards the null. [242] Survivor bias may have reduced socioeconomic gradients, with competing risk of mortality from premature deaths in poorer groups. Heterogeneity of these findings in terms of different measures of SES could be considered a limitation. However, given the challenges of accurately measuring SES using any single measure, I believe that the overlap in associations shown here demonstrates support for true association rather than lack of it. A lifecourse approach to assessing SES that is beyond the scope of this study would be needed to fully understand the relationships between different measures and may be an important consideration for future research.[239 243]

3. Assessing risk in people with CKD stage 3 in primary care – a prospective cohort study

3.1 Background: Renal Risk in Derby study.

The Renal Risk in Derby (RRID) Study is a longitudinal prospective cohort study of people with CKD stage 3 conducted from a single nephrology department (The Department of Renal Medicine, Royal Derby Hospital NHS Foundation Trust). The stated aims of the study in the original protocol were as follows:

a) To define the risk of kidney function decline in a cohort of patients with CKD stage 3.
b) To define the risk of CVD in a cohort of patients with CKD stage 3.
c) To develop a comprehensive description of patients with CKD stage 3, who are currently followed up by GPs.
d) To assess the management of patients with CKD stage 3 by GPs compared with Renal Association Clinical Practice Guidelines.
e) To develop care plans to improve the care of patients with CKD stage 3 within primary care.
f) To assess the value of monitoring uACR, urine sodium and urine phosphate in the management of patients with CKD stage 3.
g) To assess associations between CKD and a wide range of previously described risk factors.

Participants were recruited from 32 GP surgeries in Derbyshire. Analyses from this cohort have formed the basis of several previous publications, including an examination of the risk profile of older versus younger patients [244], a study of the relationship between skin AF and cardiovascular and renal risk factors [191], and analysis of the treatment needs and awareness of CKD diagnosis among people with CKD stage 3. [245] The original study design, recruitment, data collection, and analyses for the papers cited above were conducted by Dr Natasha McIntyre, Dr Maarten Taal, Dr Richard Fluck and Dr Christopher McIntyre from Royal Derby Hospital and the University of Nottingham.

Chapter 3– RRID prospective cohort

As described in section 1.4.2, my analyses of data from the RRID study aimed to investigate four aspects of CKD and their relationship to SES. Firstly, the relationship between cardiovascular risk and SES. Secondly, aspects of CKD management in primary care, particularly control of blood pressure. Thirdly, associations of albuminuria and non-albumin proteinuria. And finally, factors influencing survival in CKD (including assessment of a novel marker in CKD – skin AF).

3.2 Methods

3.2.1 Participants and Recruitment

Participants were identified from GP practice databases, either already registered as having CKD or biochemically defined from eGFR. Eligible participants were 18 years or over, met the KDOQI criteria for CKD stage 3 (eGFR of between 30 to 59 ml/min/1.73 m^2 on two or more occasions at least 3 months apart), were able to give informed consent, and were able to attend their GP surgery for assessments. People who had previously had a solid organ transplant or who were terminally ill (expected survival <1 year) were excluded. Eligible patients were invited to participate via a letter sent by their GP and telephoned the coordinating centre to schedule a study visit. Study visits were conducted at participating GP surgeries by the researchers.

3.2.2 Data Collection

Initial study visits were conducted from August 2008 to March 2010. Screening and baseline visits were combined due to the large proportion of elderly participants and the logistical challenges associated with conducting study visits in multiple primary care centres. Participants were sent a medical and dietary questionnaire as well as three urine specimen bottles, and were asked not to eat cooked meat for at least 12 hours before the assessment. SES was defined by two methods. First, using IMD. This is a social deprivation score comprising a composite measure of seven domains that demonstrates a strong relationship to health in all geographical locations. A higher IMD score indicates more social deprivation, and a score of 21.67 (range 2.66 to 80.62) represents average SES in England. [231] Second, self-reported education status was collected, which is an important indicator of SES in elderly populations. [242] Education status was categorised into eight groups (no formal qualifications, General certificate of Secondary Education (GCSE) or equivalent, Advanced level (A level), National Vocational Qualification (NVQ) 1-3, NVQ 4-5, first degree, higher degree, patient refused to answer), subsequently grouped into three for the purposes of analysis (group one: no formal qualifications, group two: GCSE or equivalent, A level, or NVQ 1-3, group three: first or higher degree, NVQ 4-5).

At the assessment, information on questionnaires was checked, anthropomorphic measurements were taken, and urinalysis was performed. . If this suggested a urinary tract infection [246], a specimen was submitted for microscopy and culture. Confirmed UTIs were treated with antibiotics and urine biochemistry was repeated after treatment. Blood specimens were taken and blood and urine specimens were submitted for biochemical analysis. eGFR was calculated using the modified 4-variable Modified Diet in Renal Disease equation and categorised into four groups (>60, 45-59 (stage 3a), 30-44 (stage 3b), < 30 (stages 4 and 5)). [31] Urine specimens were assayed for total protein, albumin and creatinine. Urine total uPCR and uACR were calculated as measures of proteinuria. Non-albumin proteinuria was calculated as the difference between uPCR and uACR. The urine albumin to protein ratio (uAPR) was calculated as the ratio of uACR divided by uPCR. 'At least microalbuminuria' was defined as uACR ≥2.5mg/mmol in men ≥3.5 mg/mmol in women. Proteinuria was defined as uPCR≥17mg/mmol (150mg/g, corresponding to 150mg/day). NAP was defined as uPCR ≥17mg/mmol in two of three specimens and uACR < 2.5mg/mmol (men) and <3.5 mg/mmol (women) in all three specimens. uAPR was calculated from average of three uACRs / average of three uPCRs and uAPR<0.4 was used as a cut off identified as having high sensitivity and specificity for primary tubulointerstitial disorders. [187]

Blood pressure (BP), albuminuria, and pulse wave velocity (PWV) were measured using standardised methods. [247] [248] BMI was calculated from weight in kg divided by height squared in metres and categorised according to WHO categories underweight (<18.5kg/m^2), normal (18.5 – <25kg/m^2), overweight (25-<30kg/m^2), and obese (≥30kg/m^2). [249] Diabetes was defined by having a previous clinical diagnosis in line with World Health Organization [233] criteria. [250] Hypertension was defined as a systolic BP >140 mmHg, diastolic BP >90 mmHg, or current antihypertensive medication. [251] For the purposes of analysis of blood pressure control, hypertension was defined as current antihypertensive medication, but those with a systolic BP >140 mmHg or diastolic BP >90 mmHg at baseline who were not on medication were also identified for descriptive purposes. Target BP threshold was defined according to three evidence-based clinical guidelines: the UK NICE guidelines BP target (<140/90 or <130/80 in people with diabetes and people with uACR>70mg/mmol), and the US KDOQI guidelines BP target (<130/80 for all

people with CKD) [50 179] and the KDIGO BP guidelines (≤140/90 or 130/80 in people with albuminuria). [180]

Previous cardiovascular event was defined as subject-reported myocardial infarction, stroke, transient ischemic attack, revascularization, or amputation due to peripheral vascular disease, or aortic aneurysm. Central fat distribution was defined as a waist to hip ratio of ≥0.9 for men or ≥0.8 for women. [127] Participants were asked 'Were you told that you may have an issue with your kidneys before you were contacted to take part in this study?' Those answering 'yes' were defined as being aware of their CKD diagnosis.

Skin AF was assessed on the left forearm using an AGEReader™ device (DiagnOptics, Groningen, The Netherlands). Three readings were taken and the average calculated. Care was taken to avoid areas of skin that were tattooed or coloured with cosmetics, heavily freckled, or had vessels near to the surface of the skin. It was not possible to conduct skin AF readings on very dark or black skin. According to the manufacturers, the AGE Reader and its software have been validated in patients with skin reflection >6% (Fitzpatrick class 1 to 4). In patients with darker skin colour (Fitzpatrick class 5 to 6, dark brown or black), a correction is made to the skin AF value if the ultraviolet reflectance is between 6 and 8%. If the ultraviolet reflectance is below 6%, the AGE reader gives a warning that the signal is too low for valid results. Skin AF measurement is non-operator dependent. Values are expressed in arbitrary units (AU). Coefficient of variation for 10 skin AF readings obtained on a single patient by a single operator was 7%. Ten readings performed by 10 different operators yielded a coefficient of variation of 8%. [191]

Mortality in the RRID study was examined using extracts of mortality records complied by the Medical Research Information Services (MRIS) from official death notifications. A cut point of the end of February 2013 was used for analysis and those who had not died were censored at the end of February 2013. The main analyses examined all-cause mortality, but cause of death was also explored using death certificate entries. Classification of cause of death was conducted by three people separately (myself, Maarten Taal and Paul Roderick) and discrepancies resolved by three-way discussion. Cause of death was categorised into four groups: 'cardiovascular', 'cancer', 'infection', and 'other' according to the lowest entry of the first section of the death certificate (1a, 1b, and 1c).

The study was approved by the Nottingham Research Ethics Committee 1. All participants provided written consent. The study was included on the National Institute for Health Research (NIHR) Clinical Research Portfolio (NIHR Study ID:6632) and was independently audited by QED Clinical Services in November 2009.

3.2.3 Statistical analyses

3.2.3.1 Cardiovascular risk

Descriptive statistics and logistic regression were used to identify the distribution and associations of cardiovascular risk factors by the SES measures. In eligible subgroups, Framingham and QRisk2 ten year cardiovascular risk prediction scores were calculated to investigate the distribution of elevated CVD risk by SES and CKD diagnosis awareness. Both scores are in common use to assess cardiovascular risk in primary care in the UK. [171 172] The Framingham risk score (eligibility: age 35-74, no previous CVD) incorporates age, sex, smoking, diabetes, left ventricular hypertrophy (LVH), and total/HDL cholesterol ratio. (LVH was not measured; the risks calculated therefore assume lack of LVH). The QRisk2 risk score (eligibility: age 30-84, no previous CVD) incorporates age, sex, ethnicity, postcode, smoking status, diabetes, family history of CVD, CKD, atrial fibrillation, hypertension, rheumatoid arthritis, cholesterol/HDL ratio, systolic BP, height and weight. CKD is defined as stage 3 to 5 in the QRisk2 algorithm. [172] (Family history and atrial fibrillation data were not available and the risks therefore assume their absence). Postcode and positive CKD status were included. Framingham and QRisk2 scores were derived from the University of Edinburgh and QRisk2 online tools. [252 253] Variation in cardiovascular risk (≥20% ten year) by SES, and by CKD diagnosis awareness was assessed using logistic regression modelling. Variables contributing to the CVD risk models (e.g. age) were excluded from multivariable models. Interaction terms were introduced for both education status and awareness of CKD diagnosis by age, gender. SPSS version 18 was used for analyses.

3.2.3.2 Blood pressure control

In the population of people with hypertension on antihypertensive medication, standard descriptive statistics were used to compare the characteristics of

people achieving and not achieving BP control by NICE, KDOQI, and KDIGO BP targets. Univariate and multivariable logistic regression (adjusting for age, sex, albuminuria, diabetes, CVD, and eGFR) were used to identify the factors associated with achievement of the three BP targets. A model excluding CVD was also constructed to assess the effect of this variable on outcomes in view of the potential for CVD to cause lower BP through heart failure. Sensitivity analyses were conducted in participants whose baseline eGFR was <60 ml/min/1.73m^2. The logistic regression analyses were also repeated to examine the associations of people achieving NICE systolic and diastolic targets separately. Interaction terms were introduced for gender by diabetes, age by diabetes, and diabetes by albuminuria because of the effect modification seen among these variables in some studies. [254] Chi squared test for trend was used to examine the degree of BP control by grade of albuminuria in people with and without diabetes. For people on antihypertensive medication or those with elevated BP identified at study registration, multivariable linear regression was used to investigate the association between number of antihypertensive medications and mean arterial BP (MAP). All odds ratios are presented with 95% confidence intervals (CIs) and p values <0.05 are considered statistically significant. IBM SPSS Statistics for Windows version 19 was used to analyse the data.

3.2.3.3 Albuminuria and non-albumin proteinuria

Standard descriptive statistics were used to compare the characteristics of people with and without albuminuria and NAP. Participants were considered to have albuminuria and proteinuria if at least two of three urine specimens were positive by the above criteria. Univariate and multivariate logistic regression was used to identify the associations of albuminuria and NAP. Interactions were assessed for age by gender to test for effect modification in age gender subgroups. Two methods were used to compare a single measurement of uACR (from the first urine specimen) with three measures of uACR from the three specimens collected in this study. Firstly, the Bland Altman method was used to examine the degree of agreement between a single uACR measure and average of three uACR measures, considering albuminuria as a continuous variable. [255] Secondly, considering albuminuria as a categorical variable, comparing a single uACR measure with having at least two of three uACR measures >=2.5mg/mmol in men >=3.5 mg/mmol in women.

3.2.3.4 Survival and skin AF

Descriptive statistics were used to compare those still alive with those who had died by the end of February 2013. Kaplan-Meier plots and Cox regression analysis were used to compare the mortality experience of people from different socio-economic groups defined by education status and IMD. Univariate and multivariable Cox regression analysis was then used to identify clinical factors associated with all-cause mortality. In addition, the relationship between mortality and a novel marker (skin autofluorescence (SAF)), potentially associated with adverse outcome in CKD, was assessed. [191] SAF is a non-invasive method for measuring the accumulation of advanced glycation end products (AGE, an indicator of 'cumulative metabolic stress') using an 'AGE Reader™' (DiagnOptics, Groningen, The Netherlands) applied to the left forearm.[191] For these analyses, eGFR was calculated using the CKDEPI equation.

A Kaplan Meier plot to compare all-cause mortality by differing levels of skin AF was produced by dividing the study population into tertiles of skin AF. Cox regression models were developed with skin AF fitted as a continuous variable with subsequent addition of socio demographic (age, sex) then clinical variables (CVD, diabetes, hypertension, smoking, BMI, central obesity, total:HDL cholesterol ratio, eGFR, uACR haemoglobin). It was found that optimal model fit included skin AF (continuous) and skin AF^2 and both were therefore included in the final model. The primary outcome was all-cause mortality. Interactions between skin AF and diabetes were assessed because of the potential for differential variation of skin AF by diabetes status. Despite meeting the inclusion criteria (and therefore having a clinical diagnosis of CKD stage 3), some participants were found to have baseline eGFR> 60ml/min per $1.73m^2$ (possibly due to strict meat fasted status being observed prior to the baseline measurement). Sensitivity analyses were therefore conducted in those whose baseline eGFR was <60ml/min per $1.73m^2$. Sensitivity analyses were also conducted with the primary outcome of cardiovascular mortality.

3.3 Results

3.3.1 Baseline descriptive data

A summary of the characteristics of the population in this study are given in Figure 14 (population pyramid) and Table 19. These show that the study population was predominantly elderly (67% over 70), white, and had a higher proportion of women (60%). There was a high proportion of people with no formal qualifications (over 50%). A high proportion of people with CKD also had other diagnoses (Figure 16) and greater proportions of people with multimorbidity were seen in lower SES groups (Figure 17 and Figure 18).

Figure 14. Age and gender distribution in the Renal Risk in Derby Study

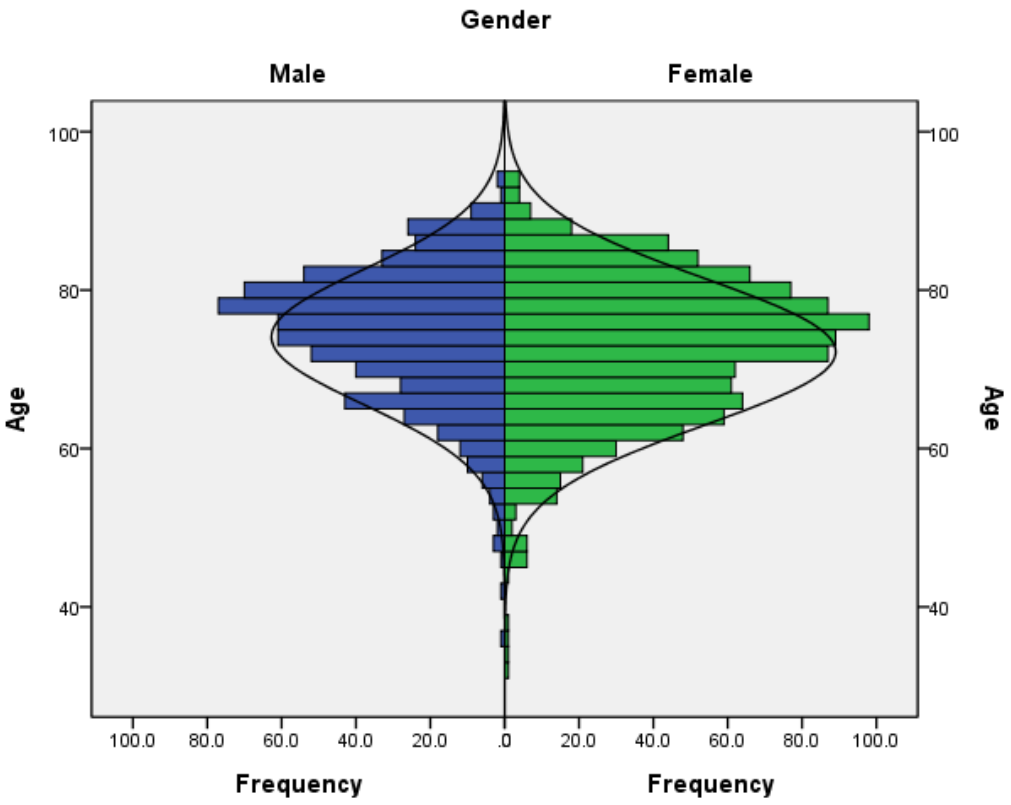


Table 19. Characteristics of people in the RRID study

	Total n = 1741	Categories	n	% of total
Demography	Gender	Male	689	39.6
		Female	1052	60.4
	Age group	30-39	5	0.3
		40-49	23	1.3
		50-59	100	5.7
		60-69	445	25.6
		70-79	761	43.7
		80+	407	23.4
	Age group 4 categories	<60	128	7.4
		60-69	445	25.6
		80+	407	23.4
		70-79	761	43.7
	IMD quintile	Quintile 1 (Most deprived)	151	8.7
		Quintile 2	432	24.8
		Quintile 3	326	18.7
		Quintile 4	447	25.7
		Quintile 5 (Least deprived)	382	21.9
	Ethnicity	White	1698	97.5
		Mixed	6	0.3
		Asian	29	1.7
		African-Caribbean	5	0.3
		Chinese	1	0.1
		Other	1	0.1
		Cypriot	1	0.1
	Education status	None	953	54.7
		GCSE or equivalent	276	15.9
		A level	78	4.5
		NVQ1-3	115	6.6
		NVQ4-5	154	8.8
		First degree	118	6.8
		Higher degree	45	2.6
		Patient refused to answer	2	0.1

Table 19 cont

	Total n = 1741	Categories	n	% of total
	Education status 3 categories	None	953	54.7
		GCSE, A level, NVQ 1-3	469	26.9
		1st or higher degree, NVQ 4-5	317	18.2
Awareness	Knowledge of CKD diagnosis	No	715	41.1
		Yes	1026	58.9
Lifestyle	Smoking	Current	81	4.7
		Ex-smoker	866	49.7
		Never	794	45.6
	BMI	Underweight (<18.5kg/m2)	5	0.3
		Normal (18.5 - <25kg/m2)	348	20.0
		Overweight (25 - <30kg/m2)	738	42.4
		Obese (>=30kg/m2)	650	37.3
	Alcohol consumption	No alcohol	711	40.8
		1-7 units per week	525	30.2
		8-14 units per week	219	12.6
		15-21 (F) 15-28 (M) units per week	133	7.6
		Hazardous (F21-34, M29-49)	50	2.9
		Harmful (F>35, M>50)	15	0.9
Medical history	Diabetes	Yes	294	16.9
		No	1447	83.1
	History of CVD	Angina	334	19.2
		MI	177	10.2
		Heart failure	61	3.5
		Stroke	83	4.8
		TIA	137	7.9
		Narrowed arteries	82	4.7
		Amputation	6	0.3
		Aortic aneurysm	4	0.2
		Any CVD present	592	34.0
		No CVD present	1149	66.0

Table 19 cont

	Total n = 1741	Categories	n	% of total
CKD management	BP control	SBP and DBP under 140/90	1117	64.2
		Either SBP or DBP over threshold	534	30.7
		Both SBP and DBP over threshold	90	5.2
	BP control dichotomised	SBP and DBP under 140/90	1117	64.2
		Either SBP or DBP or both over threshold	624	35.8
	BP130/80	Both SBP and DBP below 130/80	645	37.0
		Either SBP or DBP or both over 130/80 threshold	1096	63.0
	NICE BP target group (diabetes or uACR>70)	In lower BP target group	304	17.5
		Not in lower BP target group	1437	82.5
	ACE / ARB use	No	618	35.5
		Yes	1123	64.5
	Ibuprofen use	No	1695	97.4
		Yes	46	2.6
	Last eGFR categories	eGFR 45-59	1155	66.3
		eGFR >60	161	9.2
		eGFR 30-44	410	23.5
		eGFR 15-29	14	0.8
		eGFR <15	1	0.1
	Last eGFR categories dichotomised	eGFR >45	425	24.4
		eGFR <45	1316	75.6
	Average uACR categories	0 mg/mmol	612	35.2
		1 - 29mg/mmol	1083	62.2
		30 - 69 mg/mmol	28	1.6
		70+ mg/mmol	18	1.0

Table 19 cont

	Total n = 1741	Categories	n	% of total
	Average uACR categories dichotomised	uACR<30mg/mmol	1695	97.4
		uACR>30mg/mmol	46	2.6
Process measures	Seen by a nephrologist	No	1535	88.2
		Yes	206	11.8
	Still under nephrologist	No	1672	96.0
		Yes	69	4.0
	Hospital admission in last year	No	1457	83.7
		Yes planned	133	7.6
		Yes emergency	149	8.6

Only a small proportion of the study population were in the lowest IMD quintile (in contrast to the high proportion with no formal qualifications). Over 70% were either overweight or obese, and a high proportion had a past history of smoking. About 17% had a history of diabetes and 34% had a history of CVD.

The relationship between the two descriptors of SES in this study (IMD and education status) is shown in Figure 15. It can be seen that there is variable correlation between the two measures, reflecting the weakness of IMD (an area measure of SES) as a predictor of individual SES.

Figure 15. Percentage of people with specific qualification category in each Index of Multiple Deprivation quintile in the RRID study

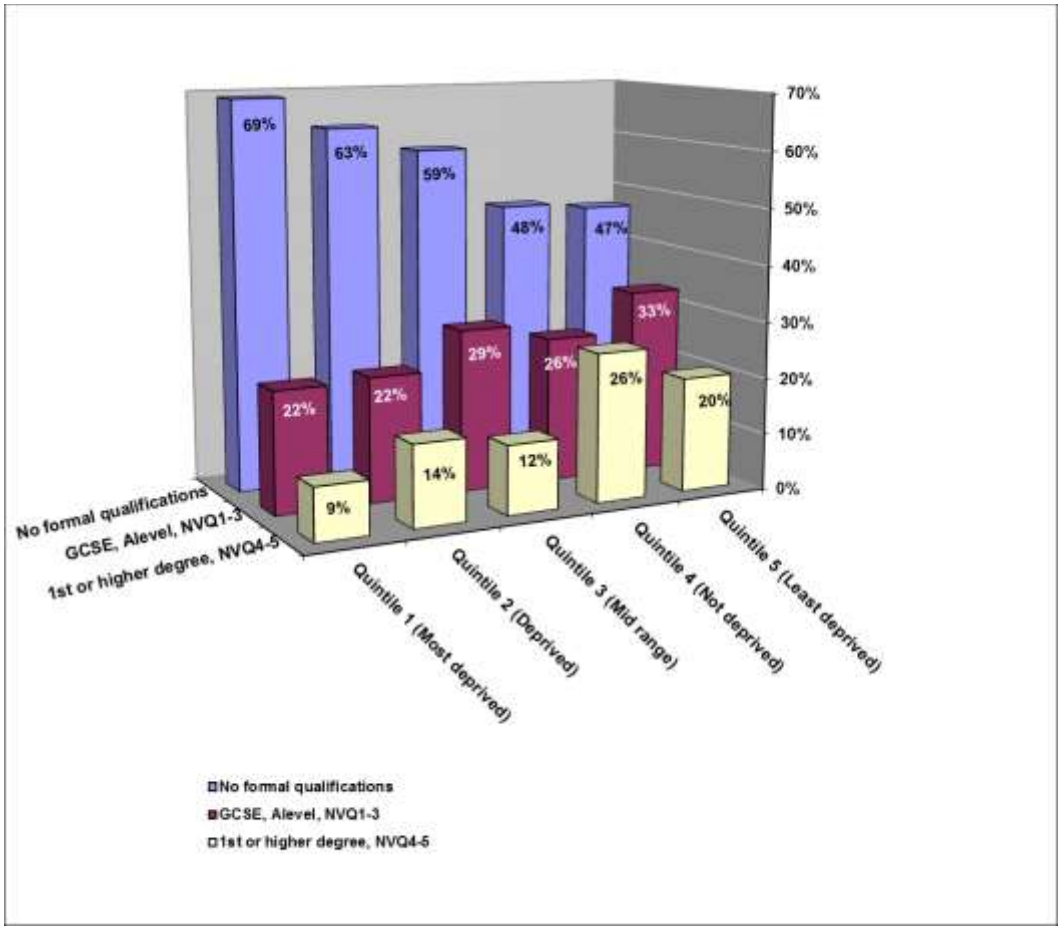
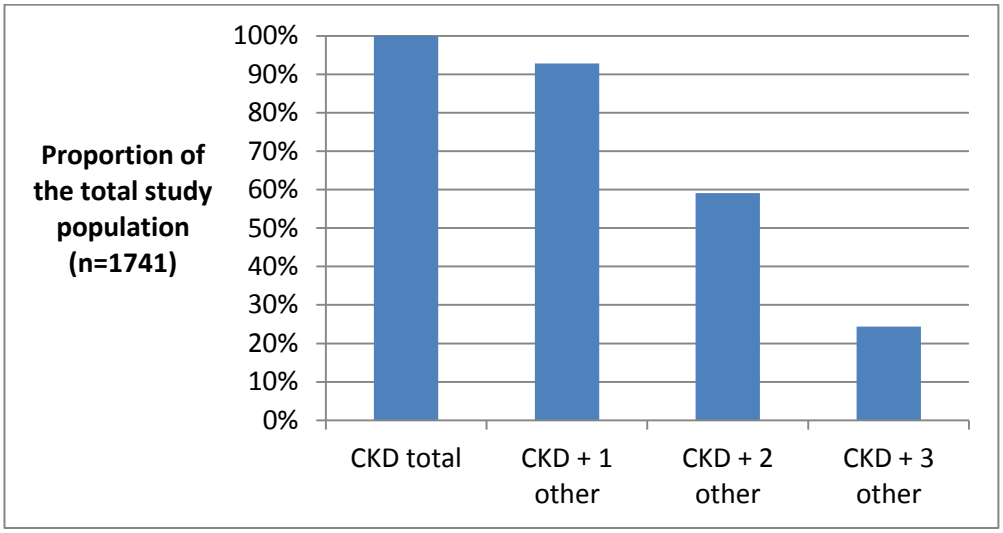


Figure 16. Multimorbidity in the RRID Study



Conditions included: diabetes, hypertension, heart failure, cerebrovascular disease, ischaemic heart disease, peripheral vascular disease, obesity

Figure 17. Proportion of people in each category of education status with different degrees of multimorbidity in the RRID Study

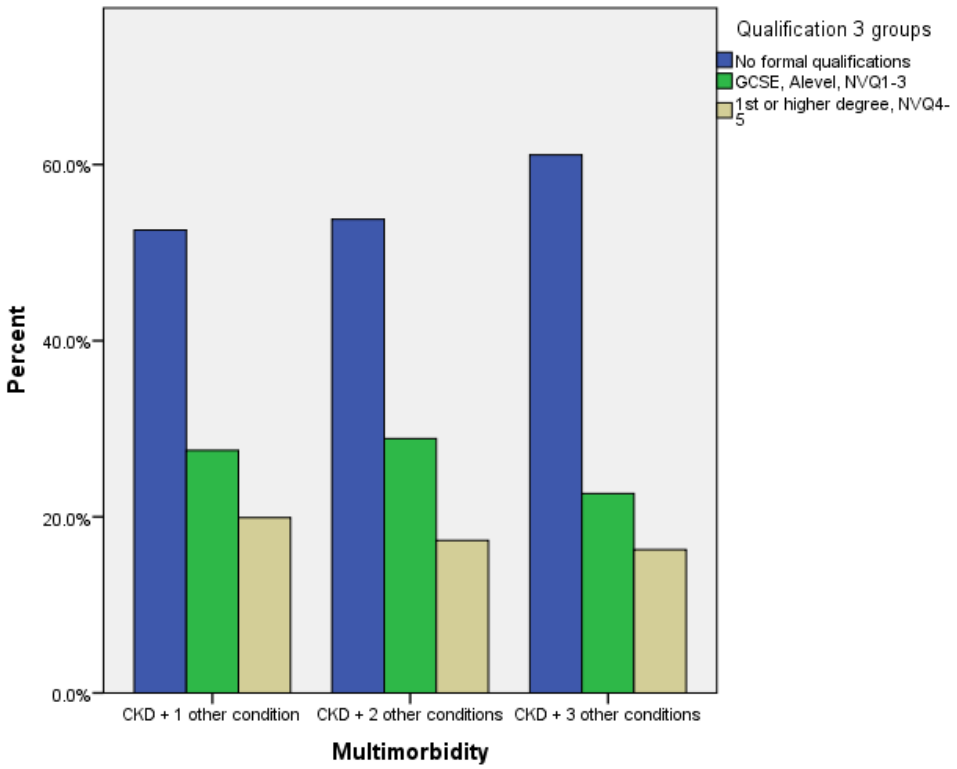


Figure 18. Proportion of people in each quintile of IMD with different degrees of multimorbidity in the RRID Study

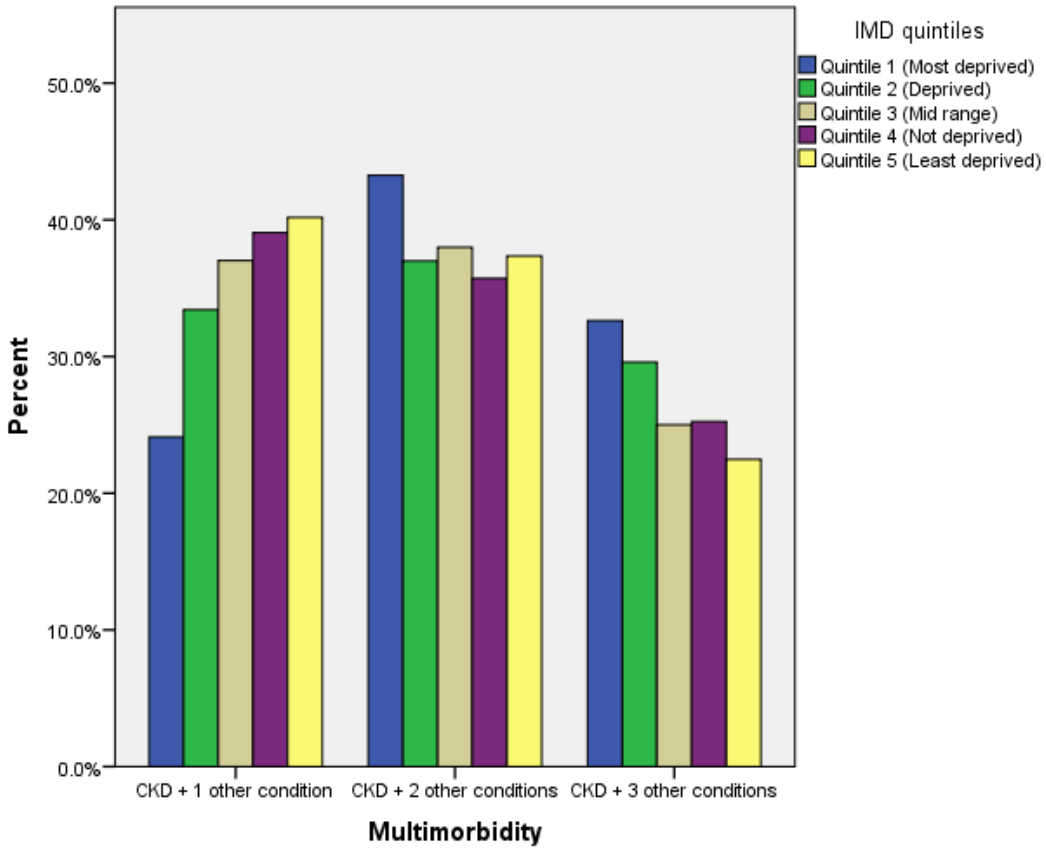


Figure 17 shows that people with no formal qualifications were more likely to have comorbidities than people with other levels of education. Similarly, figure 18 shows that, for IMD higher numbers of comorbidities were more prevalent in people from more deprived areas. For people with only one other condition the reverse pattern was observed. This warrants further investigation by diagnosis, though this was beyond the aims of this thesis.

3.3.2 Cardiovascular risk

Table 20 shows variations in prevalence of cardiovascular risk factors by SES (defined first by IMD and then by education). Higher prevalence of current smoking, history of CVD, diabetes and obesity was seen in more deprived quintiles of IMD. A similar pattern was seen for central obesity, previous CVD and diabetes in those with no formal qualifications. On univariate analysis, greater odds ratios of smoking and diabetes were associated with lower SES measured by IMD. Central obesity, previous CVD, and albuminuria were associated with lower SES measured by education status. Cholesterol/HDL ratio and hypertension were not associated with SES using either measure. Albuminuria was associated with having more qualifications. In multivariate analyses, adjusting for age, gender and diabetes, the associations between smoking and diabetes and deprivation were maintained, as was the association between previous CVD and education status (Table 21).

Table 20. Characteristics of study participants by SES

		Index of multiple deprivation quintiles n (% of column)				
		1 n=151	2 n=432	3 n=326	4 n=447	5 n=382
Gender	Male	60 (40)	170 (39)	120 (37)	181 (41)	157 (41)
	Female	91 (60)	262 (61)	206 (63)	266 (59)	225 (59)
Age	<60	13 (9)	39 (9)	22 (7)	22 (5)	32 (8)
	60-69	36 (24)	118 (27)	95 (29)	114 (26)	81 (21)
	70-79	62 (41)	186 (43)	140 (43)	195 (44)	177 (46)
	80+	40 (27)	89 (22)	69 (21)	116 (26)	92 (24)
Ethnicity	White	139 (92)	424 (98)	320 (98)	442 (99)	370 (97)
	Other	12 (8)	8 (2)	6 (2)	5 (1)	12 (3)
Aware of CKD diagnosis		90 (60)	254 (59)	187 (57)	268 (60)	224 (59)
History of CVD		62 (41)	151 (35)	107 (33)	148 (33)	124 (32)
Diabetes		34 (22)	66 (15)	55 (17)	81 (18)	58 (15)
Hypertension		130 (86)	370 (86)	294 (90)	397 (89)	334 (87)
Smoking	Current	14 (9)	29 (7)	15 (5)	18 (4)	5 (1)
	Ex-smoker	70 (46)	231 (53)	152 (47)	220 (49)	192 (50)
	Never	67 (44)	172 (40)	159 (49)	209 (47)	185 (49)
BMI	Underweight (<18.5)	2 (1)	1 (<1)	0 (0)	1 (<1)	1 (<1)
	Normal (18.5 – 24.99)	26 (17)	77 (18)	65 (20)	100 (22)	80 (21)
	Overweight (25 – 29.99)	55 (36)	178 (41)	139 (43)	191 (43)	173 (45)
	Obese (>=30)	68 (45)	176 (41)	122 (37)	155 (35)	128 (34)
BP	Mean [SD] systolic BP	132 [19]	133 [17]	134 [19]	135 [19]	135 [19]
	Mean [SD] diastolic BP	71 [12]	72 [11]	73 [11]	73 [10]	73 [11]
Central obesity		133(88)	362 (84%)	277 (85)	381 (85)	324 (85)
Total chol:HDL ratio	>4.5	20 (13)	71 (16)	55 (17)	89 (20)	70 (19)
At least microalbuminuria		25 (17)	68 (16)	51 (16)	90 (20)	59 (15)

Table 20 cont

		Education status n (% of column)			
		No formal qualific-ations n=953	GCSE, A level, NVQ 1 – 3 n=469	1st or higher degree, NVQ 4 – 5 n=317	Total n (% of total) n=1740
Gender	Male	323 (34)	178 (38)	187 (59)	689 (40)
	Female	630 (66)	291 (62)	130 (41)	1051 (60)
Age	<60	28 (3)	58 (12)	42 (13)	128 (7)
	60-69	217 (23)	142 (30)	85 (27)	444 (26)
	70-79	446 (47)	191 (41)	123 (39)	760 (44)
	80+	262 (28)	78 (17)	67 (21)	407 (23)
Ethnicity	White	937 (98)	454 (97)	305 (98)	1696 (97)
	Other	16 (2)	15 (3)	12 (2)	44 (3)
Aware of CKD diagnosis		525 (55)	287 (61)	212 (67)	1024 (59)
History of CVD		354 (37)	141 (30)	96 (30)	591 (34)
Diabetes		167 (18)	74 (16)	52 (16)	293 (17)
Hypertension		836 (88)	411 (88)	279 (88)	1526 (88)
Smoking	Current	49 (5)	23 (5)	9 (3)	81 (5)
	Ex-smoker	480 (50)	227 (48)	159 (50)	866 (50)
	Never	424 (45)	219 (47)	149 (47)	792 (45)
BMI	<18.5	5 (<1)	0 (0)	0 (0)	5 (0)
	18.5 – 24.99	182 (19)	90 (19)	76 (24)	348 (20)
	25 – 29.99	390 (41)	211 (45)	137 (43)	736 (42)
	>=30	376 (40)	168 (36)	104 (33)	649 (37)
BP	Mean [SD] systolic BP	135 [19]	133 [18]	133 [17]	134 [18]
	Mean [SD] diastolic BP	72 [11]	74 [11]	75 [11]	73 [11]
Central obesity		827 (87)	390 (83)	261 (82)	1478 (85)
Total chol:HDL ratio >4.5		151 (16)	94 (20)	60 (19)	305 (18)
At least microalbuminuria		155 (16)	65 (14)	72 (23)	292 (17)

Table 21. Associations of cardiovascular risk factors with demographic variables

	Univariate		Multivariate	
CVD risk factor (n, % of total with risk factor)	IMD OR (95% CI) most deprived compared to least deprived	Education status OR (95% CI) people with no qualifications compared to most qualified	IMD OR (95% CI) most deprived compared to least deprived †	Education status OR (95% CI) people with no qualifications compared to most qualified ††
Current smoking (81, 5%)	7.71 (2.72,21.79) **	1.86 (0.90,3.82)	7.99 (2.80,22.83) **	2.84 (1.33,6.09) *
Central obesity (1480, 85%)	1.30 (0.74,2.29)	1.41 (1.00,1.99) *	1.33 (0.75,2.35)	1.36 (0.95,1.94)
Cholesterol / HDL ratio (306, 18%)	0.68 (0.39,1.16)	0.81 (0.58,1.12)	0.67 (0.39,1.15)	1.01 (0.72,1.43)
Previous CVD (592, 34%)	1.45 (0.98,2.14)	1.36 (1.04,1.79) *	1.54 (1.03,2.32) *	1.36 (1.01,1.83) *
Diabetes (294, 17%)	1.62 (1.01,2.61) *	1.08 (0.77,1.52)	1.65 (1.03,2.65) *	1.12 (0.79,1.59)
Hypertension (1528, 88%)	0.89 (0.51,1.54)	0.97 (0.66,1.44)	0.91 (0.52,1.59)	0.88 (0.58,1.35)
Mean uACR >2.5mg/mmol males, >3.5mg/mmol females 282 (17%)	0.94 (0.54,1.64)	0.66 (0.48,0.91) *	1.10 (0.65,1.88)	0.94 (0.67,1.32)

† Adjusted for age and gender

†† Adjusted for age, gender, and diabetes

* $p \leq 0.05$

* $p < 0.001$

3.3.2.1 Cardiovascular risk scores in eligible subgroups

672 people were eligible for Framingham risk scoring, and 1071 for QRisk2 scoring. 219 / 672 (33%) people in the Framingham-scored group, and 862 / 1071 (80%) in the QRisk2-scored group had an estimated ten year CVD risk≥20%. Those eligible for QRisk2 but not Framingham scoring were all over 75, and none had a QRisk2 score <20%. (Table 22). Prevalence of elevated Framingham risk showed a graded relationship with IMD and education status, which was less apparent with QRisk2 (Figure 19 and Figure 20).

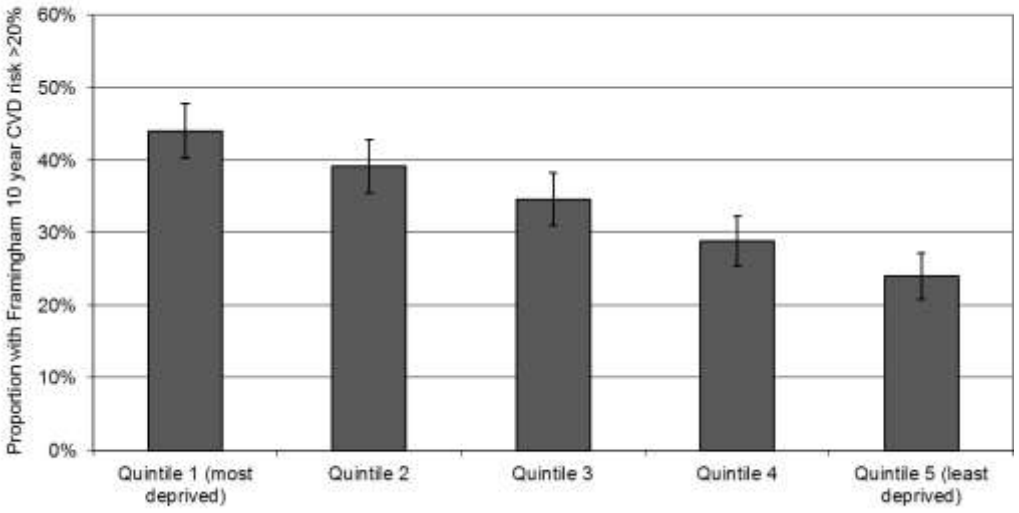
In the Framingham group, elevated CVD risk was associated with greater deprivation, lower education status, and non-awareness of CKD diagnosis. These associations persisted on multivariate analysis, and no interactions were observed (Table 23). In the QRisk2 group, elevated CVD risk was associated with lower education status, and non-awareness of CKD diagnosis, but no association was seen with IMD. On multivariate analysis, the relationships with education status and awareness of CKD were maintained and no interactions were observed.

In the Framingham group, there was no association with gender on age sex adjusted analysis (male vs. female OR 1.03 (95%CI 0.72-1.47), and CVD risk increased with age (within the limits of those eligible) (increased in older age groups OR 1.14 (95%CI 1.10-1.18) per unit (year) increase in age). QRisk2 was associated with male gender (male vs. female OR 6.66 (4.03-11.00) and age (increased in older age groups OR 1.39 (95%CI 1.32-1.46) per unit (year) increase in age). The associations with age were maintained, but the associations with gender were not after adjustment for confounding factors (hypertension, diabetes, CVD, IMD, qualifications, awareness of CKD).

Table 22. Comparison of demographic and clinical characteristics of people with ≥20% 10 year CVD risk assessed by Framingham or QRisk2 prediction tools.

		Framingham tool (eligible age 35-74)	QRisk2 tool (eligible age 30-84)
Characteristic	Category	n (% of Framingham eligible) with 10yr CVD risk >20% n=219	n (% of QRisk2 eligible) with 10yr CVD risk >20% n=862
Gender	Male	69 (32)	344 (40)
	Female	150 (68)	518 (60)
Age group	< 60	12 (5)	27 (3)
	60-69	109 (50)	227 (26)
	70-79	98 (45)	463 (54)
	80 +	-	145 (17)
SES (IMD quintiles)	1 (most deprived)	22 (10)	69 (8)
	2	68 (31)	205 (24)
	3	44 (20)	163 (19)
	4	49 (22)	230 (27)
	5 (least deprived)	36 (59)	193 (22)
Education status	No formal qualifications	130 (59)	476 (55)
	GCSE, A level, NVQ 1- 3	58 (26)	229 (27)
	1st or higher degree, NVQ 4 - 5	31 (14)	156 (18)
CKD awareness	Not aware of CKD diagnosis	91 (42)	356 (41)
Smoking	Current smoker	17 (8)	50 (6)
	Ex-smoker	100 (46)	395 (45)
	Never smoked	102 (47)	425 (49)
Diabetes	Diagnosed diabetes	38 (17)	156 (18)
	No diabetes	181 (83)	706 (82)
Hypertension	Meets hypertension criteria	189 (86)	782 (91)
	No hypertension	30 (14)	80 (9)
Cholesterol / HDL ratio	Ratio > 4.5	47 (21)	187 (22)
	Ratio < 4.5	172 (79)	670 (78)

Figure 19. Percentage with Framingham and QRisk2 10 year CVD risk >20% by national IMD quintiles



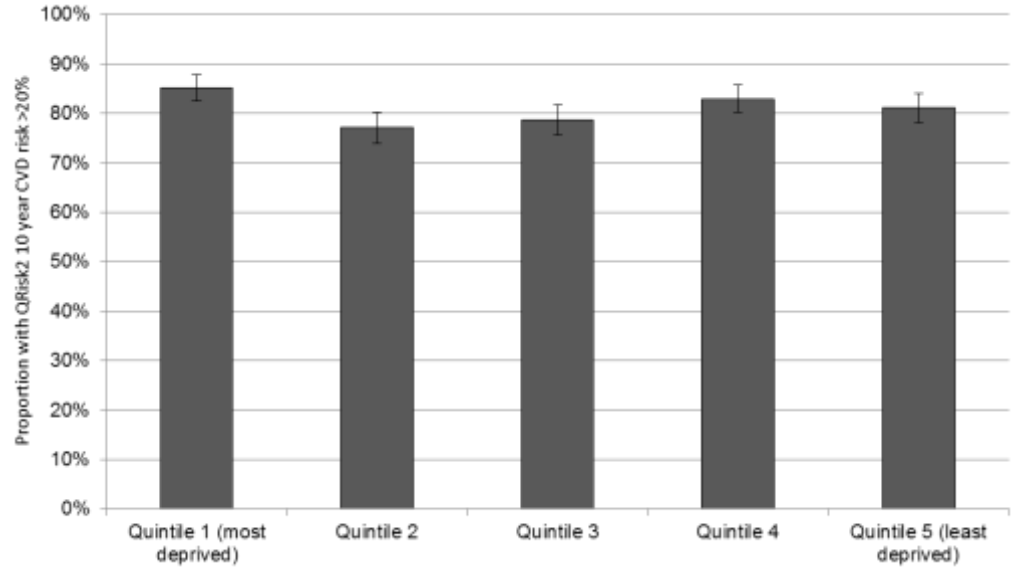


Figure 20. Percentage with Framingham and QRisk2 10 year CVD risk >20% by education status

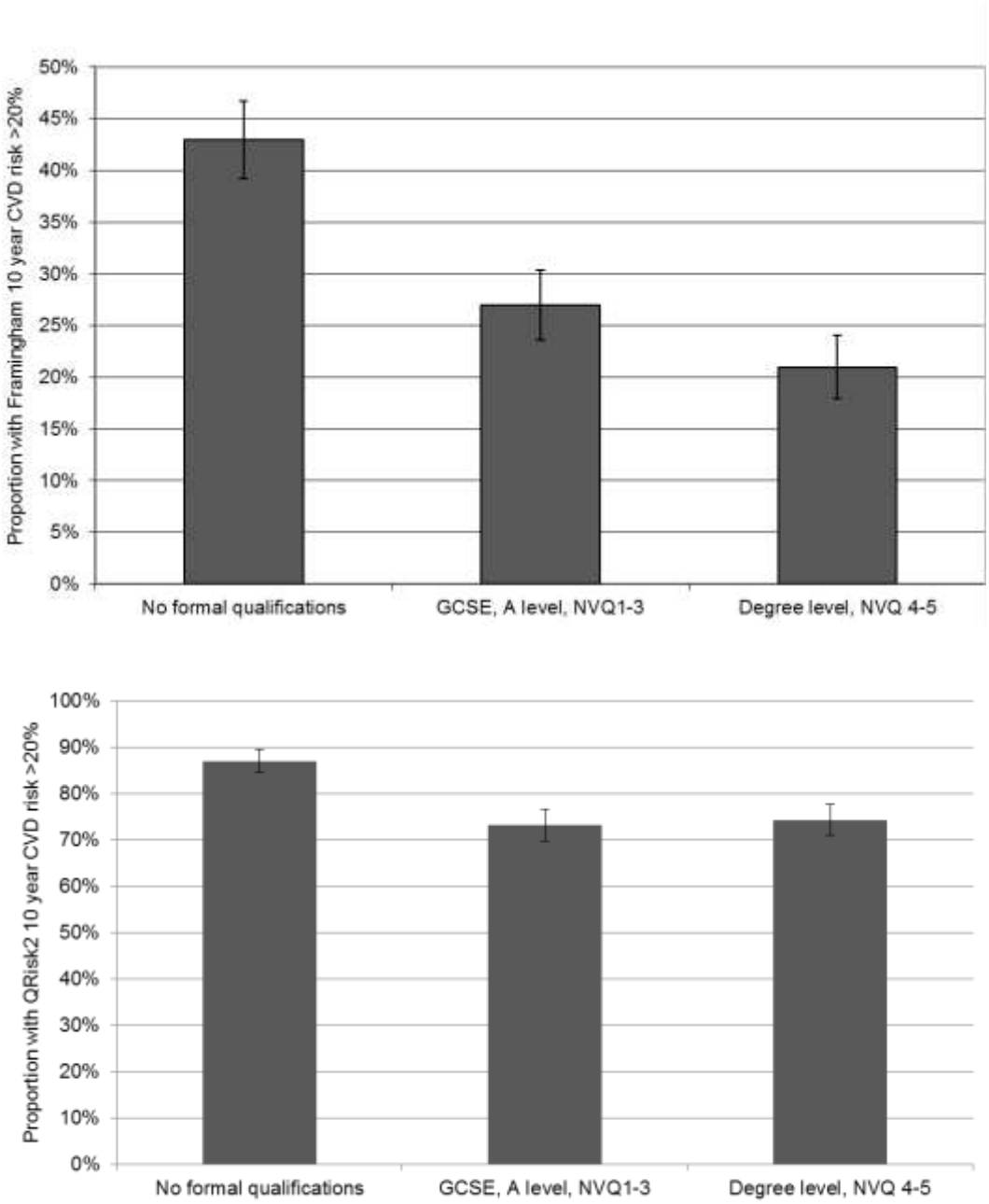


Table 23. Comparison of odds of estimated cardiovascular risk >20% using two risk assessment tools by SES and knowledge of chronic kidney disease diagnosis at baseline

		Odds ratio (95% confidence intervals) of having a 10 year CVD risk >20% using the Framingham tool.		Odds ratio (95% confidence intervals) of having a 10 year CVD risk >20% using the QRisk2 tool.	
		Univariate	Multivariate†	Univariate	Multivariate†
Index of multiple deprivation (Most deprived compared to least deprived quintile)		2.49 (1.27,4.87) *	2.87 (1.41, 5.84) **	1.34 (0.67,2.68)	1.12 (0.55,2.27)
Education status (No qualifications compared to most qualifications)	#Group 1	2.80 (1.77, 4.41) **	2.52 (1.52, 4.00)**	2.32 (1.56, 3.45)**	2.45 (1.63, 3.67)**
	Group 2	1.36 (0.83, 2.23)	1.37 (0.83, 2.26)	0.94 (0.63, 1.41)	0.97 (0.65, 1.44)
CKD diagnosis awareness (Not aware compared to people who know their CKD diagnosis)		1.56 (1.12, 2.18)*	1.54 (1.09, 2.17)*	1.56 (1.13, 2.15)*	1.46 (1.05, 2.03)*

#Group 1: no formal qualifications, group 2: GCSE or equivalent, A level, or NVQ 1-3, group 3: first or higher degree, NVQ 4-5.

† Model adjusting for IMD, education status, or CKD diagnosis awareness

*p<0.05 **p<0.005

3.3.3 BP control

1426 (81.9%) were taking antihypertensive medication and a further 102 (5.9%) had high BP at study assessment.

3.3.3.1 Antihypertensive treatment

In those taking antihypertensive medication, RAASi were the most commonly used (78.8% of patients). Of those on antihypertensives, 85/98 (86.7%) people who met the NICE CKD criteria for requiring RAASi (diabetes with any albuminuria, no diabetes with macroalbuminuria) were taking them. Among people taking only one agent (n=615), 425 (69.1%) were taking RAASi, 62 (10.1%) were taking calcium channel blockers, 61 (9.9%) were taking beta blockers, and 59 (9.6%) were taking thiazide diuretics. Mean (±SD) BP for people on antihypertensive agents was 134 (±18) / 72 (±11) mmHg. The NICE BP control target was achieved in 829/1426 (58.1%), the KDOQI target in 512/1426 (35.9%), and the KDIGO target in 859/1426 (60.2%) (Table 24)

Table 24. Blood pressure control by albuminuria and diabetes status among people on antihypertensive medication

		Diabetes, n=276 n (column %) unless otherwise stated				No diabetes, n=1150 n (column %) unless otherwise stated				Total n (%)
Albuminuria status		None n=195	Micro albuminuria n=63	Macro albuminuria n=18	Subtotal diabetes	None n=981	Micro albuminuria n=149	Macro albuminuria n=20	Subtotal no diabetes	n=1426
Mean BP (SD)	Systolic	132 (17)	140 (20)	155 (22)	135 (19)	133 (18)	136 (19)	141 (18)	135 (18)	134 (18)
	Diastolic	68 (10)	69 (10)	72 (11)	68 (10)	73 (11)	75 (11)	76 (9)	73 (11)	72 (11)
*BP controlled NICE target**	Yes	84 (43)	19 (30)	3 (17)	106 (38)	631 (64)	86 (58)	6 (30)	723 (63)	829 (58)
	No	111 (57)	44 (70)	15 (83)	170 (62)	350 (36)	63 (42)	14 (70)	425 (37)	597 (42)
*BP controlled KDOQI target***	Yes	84 (43)	19 (30)	3 (17)	106 (38)	355 (36)	48 (32)	4 (20)	407 (35)	512 (36)
	No	111 (57)	44 (70)	15 (83)	170 (62)	626 (64)	101 (68)	16 (80)	115 (69)	914 (64)

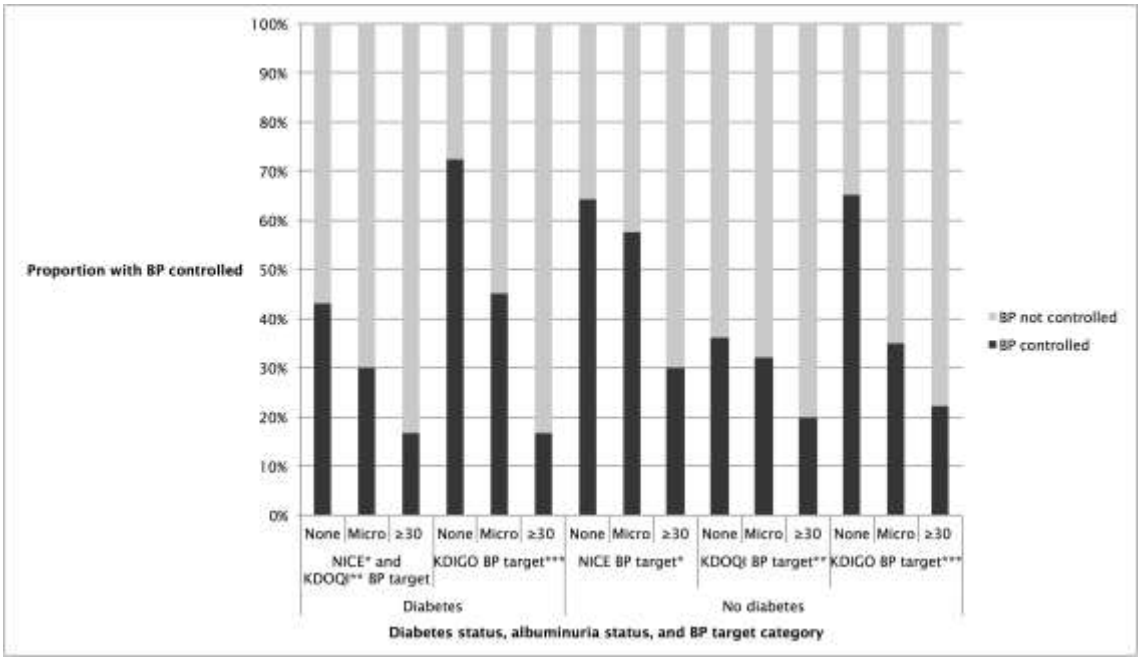
Table 24 cont

		Diabetes, n=276 n (column %) unless otherwise stated				No diabetes, n=1150 n (column %) unless otherwise stated				Total n (%)
Albuminuria status		None n=195	Micro albuminuria n=63	Macro albuminuria n=18	Subtotal diabetes	None n=981	Micro albuminuria n=149	Macro albuminuria n=20	Subtotal no diabetes	n=1426
*BP controlled KDIGO target****	Yes	141 (72)	21 (33)	3 (17)	165 (60)	639 (65)	52 (35)	4 (22)	695 (60)	859 (60)
	No	54 (28)	42 (40)	15 (83)	111 (40)	342 (35)	97 (65)	14 (78)	453 (39)	576 (40)
N° anti-hypertensive agents	1	79 (41)	25 (40)	3 (17)	107 (39)	433 (44)	65 (44)	8 (40)	506 (44)	615 (43)
	2	54 (28)	19 (30)	5 (28)	78 (28)	345 (35)	61 (41)	4 (20)	410 (36)	488 (34)
	≥3	62 (32)	19 (30)	10 (56)	90 (33)	203 (21)	23 (15)	8 (40)	232 (20)	323 (23)
Taking RAASi	Yes	173 (89)	56 (89)	15 (83)	243 (88)	750 (77)	112 (75)	17 (85)	877 (76)	1123 (79)
	No	22 (11)	7 (11)	3 (17)	32 (12)	231 (24)	37 (25)	3 (15)	271 (24)	303 (21)

* <140/90 or <130/80 in people with diabetes and people with uACR>70, ** <130/80 for all people with CKD, ***≤140/90 or 130/80 in people with albuminuria. Microalbuminuria defined as uACR>=2.5mg/mmol (men), >=3.5 mg/mmol (women) in at least two of the three urine specimens. Macroalbuminuria defined as uACR≥30mg/mmol

BP control varied by diabetes status with 106/276 (38.4%) of people with diabetes achieving the NICE or KDOQI target (targets are the same in diabetes). 723/1150 (62.9%), 407/1150 (35.3%) and 695/1150 (60.4%) of people without diabetes achieved the NICE, KDOQI, and KDIGO targets respectively (Table 24 and Figure 21).

Figure 21. BP control by diabetes and albuminuria status in 1426 people with CKD 3 and hypertension



* NICE BP target: <140/90 or <130/80 in people with diabetes and people with uACR>70. ** KDOQI BP target: <130/80 for all people with CKD. ***KDIGO BP target ≤140/90 or 130/80 in people with albuminuria

In people with diabetes and people without, optimal control was less likely in those with albuminuria (Chi-squared test for trend in non-diabetics = 7.68, p=0.006, and in diabetics = 8.59, p=0.003) (Figure 21).

3.3.3.2 Factors associated with suboptimal BP control

On multivariable logistic regression analysis, older patients, those with diabetes, and those with albuminuria were less likely to achieve NICE BP targets whereas those with a history of CVD were more likely to achieve them (Table 25).

Table 25. Factors associated with achievement of BP targets in people on antihypertensive medication.

		Univariate odds ratios of achieving NICE BP targets		Multivariable odds ratios of achieving NICE **BP target ∞**		Univariate odds ratios of achieving KDOQI BP targets		Multivariable odds ratios of achieving KDOQI BP target †	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Sex (male compared to female)		0.91 (0.73, 1.12)	0.359	0.88 (0.71, 1.10)	0.260	0.80 (0.64, 1.00)	0.050	0.76 (0.60, 0.96)	0.023
Age (vs. <60)	60-69	0.60 (0.36, 1.03)	<0.001	0.43 (0.26, 0.71)	<0.001	0.73 (0.46, 1.18)	0.155	0.66 (0.41, 1.08)	0.002
	70-79	0.43 (0.26, 0.71)		0.27 (0.17, 0.43)		0.64 (0.41, 1.01)		0.49 (0.31, 0.79)	
	80+	0.35 (0.21, 0.59)		0.21 (0.13, 0.35)		0.60 (0.38, 0.97)		0.43 (0.26, 0.72)	
Diabetes (vs. people without diabetes)		0.36 (0.28, 0.47)	<0.001	0.32 (0.25, 0.43)	<0.001	1.12 (0.86, 1.17)	0.410	1.08 (0.81, 1.43)	0.601
Albuminuria (vs. none)		0.54 (0.41, 0.72)	<0.001	0.56 (0.42, 0.74)	0.001	0.70 (0.52, 0.95)	0.021	0.65 (0.47, 0.90)	0.009

Table 25 cont

		Univariate odds ratios of achieving NICE BP targets		Multivariable odds ratios of achieving NICE BP **target ∞**		Univariate odds ratios of achieving KDOQI BP targets		Multivariable odds ratios of achieving KDOQI BP target †	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
History of CVD (vs. no CVD)		1.41 (1.13, 1.76)	0.002	1.87 (1.49, 2.35)	<0.001	1.66 (1.33, 2.07)	<0.001	1.89 (1.49, 2.39)	<0.001
eGFR (vs. 45-59)	60+	1.03 (0.81, 1.31)	0.001	0.84 (0.65, 1.09)	0.088	0.78 (0.62, 1.00)	0.145	-	-
	<45	0.66 (0.52, 0.83)		0.77 (0.60, 0.99)		0.92 (0.72, 1.17)			

∞ Model adjusted for age, sex, albuminuria, diabetes, CVD, and eGFR

† Model adjusted for age, sex, albuminuria, diabetes, and CVD

Abbreviations in Table 25:

BP blood pressure

RAASi renin-angiotensin aldosterone system inhibitors

NICE National Institute for Health and Clinical Excellence

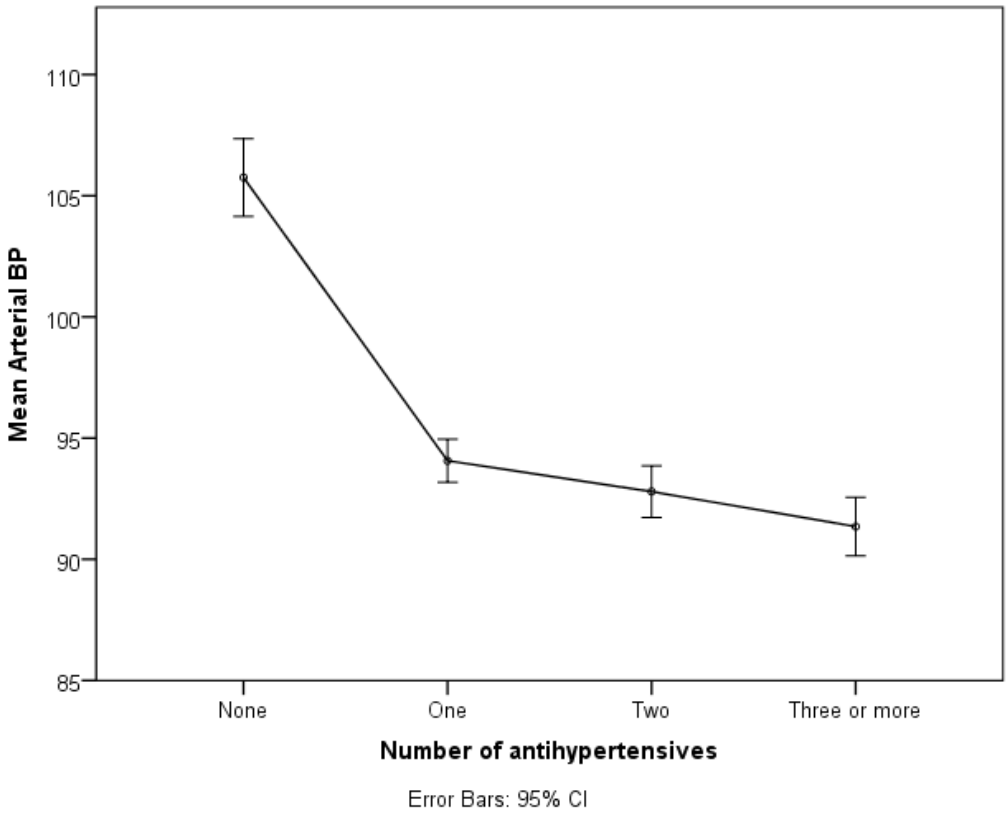
KDOQI National Kidney Foundation Kidney Disease Outcome Quality Initiative

CVD cardiovascular disease

eGFR estimated Glomerular Filtration Rate

No difference was observed in these outcomes when CVD was excluded from the regression model. Findings for age and albuminuria were similar for KDOQI and KDIGO targets. The association with diabetes was not seen with either, but there was an association between lack of achievement of KDOQI target and male gender. All associations did not vary on sensitivity analysis in the population with eGFR<60 at baseline, with the exception of the loss of the gender association with KDOQI targets. No association was seen with SES, ethnicity, awareness of CKD diagnosis, alcohol intake, BMI, central obesity, or taking NSAIDs (data not shown). There was also no association between number of agents and achievement of BP control by any of the targets (NICE OR = 1.12 (95%CI 0.88,1.43), KDOQI OR 1.02 (95%CI 0.80, 1.31), and KDIGO OR 1.05(95%CI 0.80,1.39)). Multivariable linear regression controlling for age, gender, albuminuria, previous CVD, and diabetes identified an association between number of antihypertensive drugs taken and lower MAP. For unit increase in number of antihypertensives, MAP dropped by 2.6 mmHg (95%CI 1.9,3.2, p<0.01) (Figure 22). This effect was consistent when people with previous CVD were excluded from the analysis.

Figure 22. Number of antihypertensive medications and mean arterial BP in people with CKD 3 and hypertension



3.3.3.3 Systolic and diastolic hypertension

Of the 597 people not controlled below the NICE target, 435 (72.9%) had isolated systolic hypertension (≥140), 13 (2.2%) had isolated diastolic hypertension (≥90), and 74 (12.4%) had both systolic and diastolic hypertension. Table 26 shows the distribution of systolic and diastolic blood pressure by age and eGFR in the whole study population. Table 27 shows the variation in systolic and diastolic hypertension (despite treatment) by age, and demonstrates the predominance of systolic hypertension in older age groups. Logistic regression analysis of the associations of achieving NICE systolic and diastolic targets separately demonstrated that older people had a lower odds ratio of achieving systolic targets (OR 0.17 (95%CI 0.09,0.32) $p<0.001$ for over 80), and greater odds ratio of achieving diastolic targets (OR 2.35 (95%CI 1.11,4.96) $p<0.001$ for over 80) compared to those under 60 years.

Table 26. Variation in systolic and diastolic blood pressure by age and eGFR in whole study population

			Age groups							
			<60		60-69		70-79		80+	
			SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
eGFR at baseline	>60	n	40		148		174		56	
		Mean BP (SD)	122 (15)	79 (10)	132 (16)	77 (10)	136 (17)	74 (10)	139 (19)	75 (11)
	45-59.99	n	68		231		412		200	
		Mean BP (SD)	124 (16)	78 (10)	131 (16)	75 (11)	134 (17)	72 (11)	138 (21)	70 (11)
	30-44.99	n	19		63		164		140	
		Mean BP (SD)	126 (22)	79 (13)	134 (17)	75 (12)	135 (21)	69 (11)	138 (21)	69 (11)
	<30	n	1		3		11		11	
		Mean BP (SD)	111	74	138 (13)	68 (16)	134 (14)	73 (9)	136 (19)	65 (5)

SBP = systolic blood pressure DBP = diastolic blood pressure. BP in mm Hg

Table 27. Variation in systolic and diastolic hypertension by age

	Age group			
	<60	60-69	70-79	80+
% with isolated systolic hypertension (SBP >140)	7.8	20.7	32.9	39.8
% with isolated diastolic hypertension (DBP >90)	4.7	1.8	0.7	0.2
% with systolic and diastolic hypertension (SBP >140 and DBP > 90)	7.0	8.1	3.7	4.2
% with normal BP (both SBP < 140 and DBP <90)	80.5	69.4	62.8	55.8
Total	100	100	100	100

SBP = systolic blood pressure, DBP = diastolic blood pressure

3.3.4 Albuminuria and Non-Albumin Proteinuria

Median uACR was 0.33mg/mmol, interquartile range 1.50. Median uPCR was 9.4mg/mmol, interquartile range 7.63.

3.3.4.1 Prevalence of proteinuria

Total proteinuria (any albuminuria and isolated NAP) was present in 365 people (21%) (Figure 23). 280 (16%) had albuminuria based on two of three uACR positive measures (296 (17%) had abnormal uACR on first single uACR). Of these, 88 (5%) had isolated microalbuminuria and 191 (11%) had mixed albuminuria and NAP. 86 (5%) had isolated NAP (on two of three uPCRs). The distribution of uACR and uPCR is shown in Figure 24 with threshold values. These plots demonstrate that there are significant numbers of people (particularly women) with isolated NAP as they fall below the threshold for microalbuminuria. There are also some (more noticeable in men) who have albuminuria and fall below the threshold for proteinuria.

Albumin to protein ratio

Of those with uPCR≥17mg/mmol, 185 (62%) had uAPR<0.4 suggesting primary tubulointerstitial disorder; 45 (24%) were male and 140 (76%) were female.

3.3.4.2 Associations with proteinuria

Univariate associations with albuminuria were male gender, low eGFR, diabetes, hypertension, smoking, history of CVD, raised cholesterol/HDL ratio, and lower educational attainment. In multivariate analysis, the significant positive associations of albuminuria were with male gender, lower eGFR, diabetes, hypertension, and smoking (Table 28). There was no association with SES measured by IMD or education status in the fully adjusted model. Defining albuminuria by single uACR measure or two of three uACRs did not alter these associations.

By contrast, isolated NAP was strongly positively associated with female gender and increasing age, and also associated with elevated cholesterol/HDL ratio, being aware of CKD diagnosis, lower SES (defined by education status), and not taking renin-angiotensin aldosterone system inhibitors (RAASi). The

associations with female gender, age and not taking RAASi remained in the multivariable model. No interactions were observed. (Table 29)
Having both albuminuria and NAP (n=191) was positively associated with male gender, diabetes, hypertension, smoking and being aware of CKD diagnosis, on univariate analysis. The associations with male gender, diabetes, smoking and being aware of CKD diagnosis remained after full adjustment (data not shown).

3.3.4.3 One versus multiple measures of proteinuria

Comparing one vs. average of three measures of uACR, the mean difference was 0.0064 mg/mmol (uACR-average uACR=0.0064, SD 4.69, 95% limits of agreement -9.19 to +9.20 mg/mmol) (Figure 25). In contrast, the mean absolute difference (i.e. ignoring the direction of any difference was 0.837mg/mmol (SD4.62)). In quantifying albuminuria it is the absolute difference that is most relevant. Comparing single and multiple uACR measures as categorical variables there was disagreement between one measure of uACR and three for only 45 /1734 (2.6%). Considering the presence of at least microalbuminuria in at least 2 of 3 specimens as the reference test, the sensitivity of one uACR was 94.6%, specificity 97.9%, and positive predictive value 89.8%. Sensitivity of a single PCR (compared to two of three) for isolated NAP was 81%, specificity was 95%, and positive predictive value was 48% (prevalence of isolated NAP was only 5%).

Table 28. Associations of having at least microalbuminuria in at least two of the three urine samples in the RRID cohort (n with 3 uACR results = 1736)

		Univariate		**Multivariate †**		**Multivariate ††**	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Gender (male compared to female)		4.15 (3.2, 5.5)	<0.001	3.88 (2.92, 5.19)	<0.001	3.83 (2.85, 5.14)	<0.001
Age (compared to 70-79 age group)	<60	1.16 (0.70, 1.93)	0.25	1.56 (0.89, 2.74)	0.27	1.60 (0.90, 2.83)	0.25
	60-69	1.39 (1.01, 1.90)		1.33 (0.94, 1.88)		1.32 (0.93, 1.88)	
	80+	1.10 (0.79, 1.52)		1.13 (0.81, 1.59)		1.22 (0.87, 1.73)	
Deprivation (compared to Quintile 5)	Quintile 1 (most deprived)	1.17 (0.70, 1.98)	0.19				
	Quintile 2	1.15 (0.78, 1.70)					
	Quintile 3	1.08 (0.71, 1.64)					
	Quintile 4	1.53 (1.05, 2.21)					

Table 28 cont

		Univariate		**Multivariate †**		**Multivariate ††**	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Education (compared to Group 1, people with no formal qualifications)	Group 2 (GCSE, A level, NVQ 1-3)	0.68 (0.50, 0.94)	0.02	0.79 (0.56, 1.12)	0.24		
	Group 3 (1st or higher degree, NVQ 4-5)	0.59 (0.41, 0.87)		1.10 (0.77, 1.57)			
eGFR at study entry (compared to eGFR 45-59)	<30	7.59 (2.71, 21.24)	<0.001	5.71 (1.93, 16.92)	<0.001	4.98 (1.69, 14.63)	<0.001
	30-44	2.53 (1.92, 3.33)		2.58 (1.92, 3.45)		2.46 (1.83, 3.32)	
	>60	0.36 (0.17, 0.74)		0.45 (0.21, 0.95)		0.36 (0.17, 0.76)	
Diabetes (compared to people without diabetes)		2.74 (2.04, 3.67)	<0.001			2.50 (1.83, 3.42)	<0.001
Hypertension (compared to people without hypertension)		3.25 (1.83, 5.79)	<0.001			2.32 (1.28, 4.22)	<0.01

Table 28 cont

		Univariate		**Multivariate †**		**Multivariate ††**	
		OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
History of CVD (compared to people without CVD)		1.49 (1.15, 1.94)	<0.01				
Smoking (compared to never smokers)	Current smokers	2.48 (1.44, 4.25)	0.001			2.28 (1.26, 4.11)	0.02
	Ex-smokers	1.62 (1.24, 2.13)				1.11 (0.82, 1.49)	
BMI (compared to normal BMI)	Overweight	0.90 (0.64, 1.26)	0.33				
	Obese	0.80 (0.56, 1.14)					
Central obesity (compared to people not centrally obese)		0.88 (0.62, 1.24)	0.46				
Elevated lipid ratio (compared to people with normal ratio)	Total cholesterol/ HDL >4.5	1.38 (1.00, 1.89)	0.05				

† Model adjusted for age, sex, education, eGFR

†† Model adjusted for age, sex, diabetes, hypertension, smoking, eGFR

Table 29. Associations of having non-albumin proteinuria in the RRID cohort (based on two of three uACRs and two of three uPCRs)

		Univariate		**Multivariate †**		**Multivariate ††**	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Gender (female compared to male)		8.92 (4.31, 18.46)	<0.001	12.57 (5.06, 31.24)	<0.001	10.85 (4.34, 27.16)	<0.001
Age (compared to 70-79 age group)	<60	0.16 (0.02, 1.17)	0.021	0.13 (0.02, 0.96)	0.005	0.16 (0.02, 1.17)	0.022
	60-69	0.85 (0.48, 1.51)		0.77 (0.43, 1.38)		0.80 (0.44, 1.45)	
	80+	1.64 (1.00, 2.70)		1.77 (1.07, 2.93)		1.64 (0.98, 2.73)	
Deprivation (compared to Quintile 5)	Quintile 1 (most deprived)	1.78 (0.81, 3.93)	0.359				
	Quintile 2	1.46 (0.77, 2.77)					
	Quintile 3	1.18 (0.58, 2.39)					
	Quintile 4	0.90 (0.45, 1.81)					
Education (compared to Group 3 (1st or higher degree, NVQ4-5))	No formal qualifications	3.02 (1.37, 6.67)	0.007			1.64 (0.72, 3.71)	0.324
	Group 2 (GCSE, A level, NVQ 1-3)	1.77 (0.73, 4.28)				1.20 (0.49, 2.98)	

Table 29 cont

		Univariate		**Multivariate †**		**Multivariate ††**	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Knowledge of CKD (people aware compared to people not aware of their CKD diagnosis)		1.80 (1.16, 2.78)	0.009			1.46 (0.93, 2.30)	0.099
Diabetes (compared to people without diabetes)		0.87 (0.47, 1.59)	0.643				
Hypertension (compared to people without hypertension)		0.86 (0.46, 1.60)	0.624				
History of CVD (compared to people without CVD)		0.99 (0.63, 1.57)	0.963				
Smoking (compared to never smokers)	Current smokers	0.91 (0.32, 2.61)	0.682				
	Ex-smokers	0.82 (0.53, 1.28)					
BMI (compared to normal BMI)	Over-weight	0.82 (0.46, 1.46)	0.476				
	Obese	0.93 (0.52, 1.66)					
Central obesity (compared to people not centrally obese)		0.90 (0.50, 1.62)	0.731				

Table 29 cont

		Univariate		**Multivariate †**		**Multivariate ††**	
		OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Elevated lipid ratio (compared to people with normal ratio)	Total chol / HDL >4.5	0.40 (0.18,0.87)	0.021			0.52 (0.23, 1.16)	0.111
Taking RAASi (compared to those not taking		0.62 (0.40,0.95)	0.029			0.62 (0.39, 0.97)	0.035
eGFR (compared to 45-59)	60+	1.47 (0.89,2.43)	0.248				
	<45	0.96 (0.55,1.70)					

† Model adjusted for age and gender only

†† Model adjusted for age, gender, education status, knowledge of CKD, cholesterol/HDL ratio, and taking RAASi

Figure 23. The distribution of albumin (based on 2 of 3 uACRs) and non-albumin proteinuria in people with CKD stage 3 in the RRID study

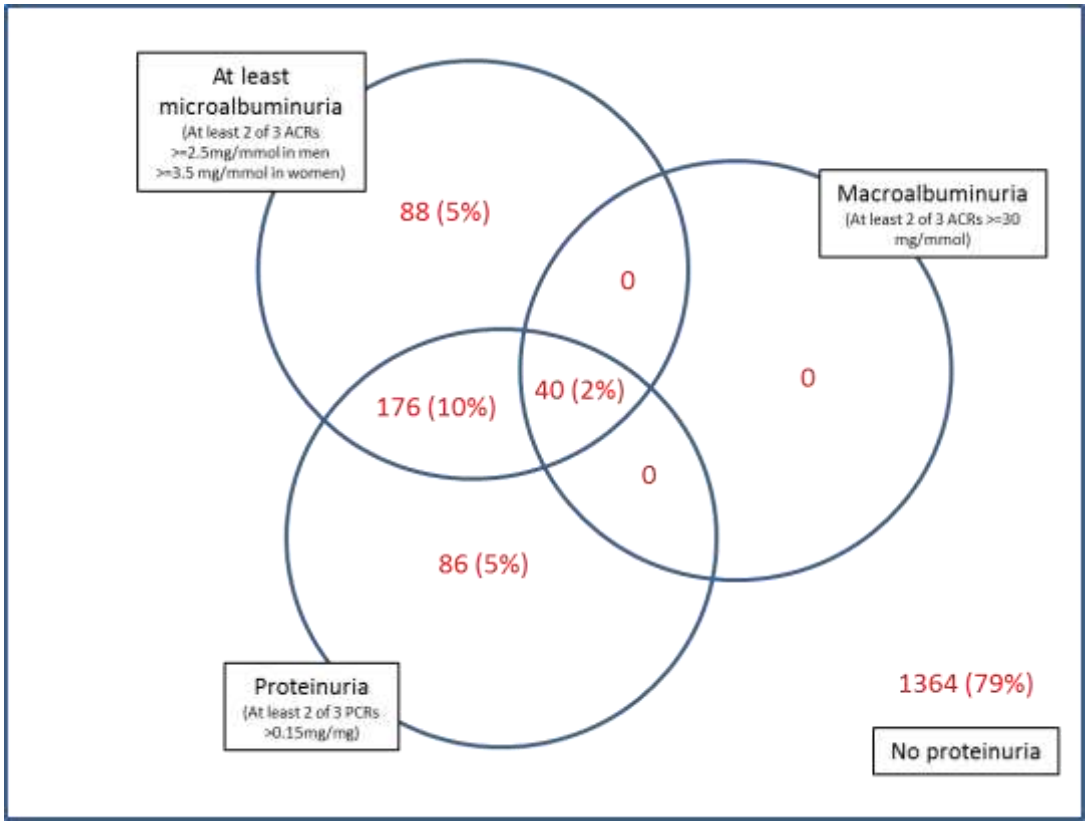
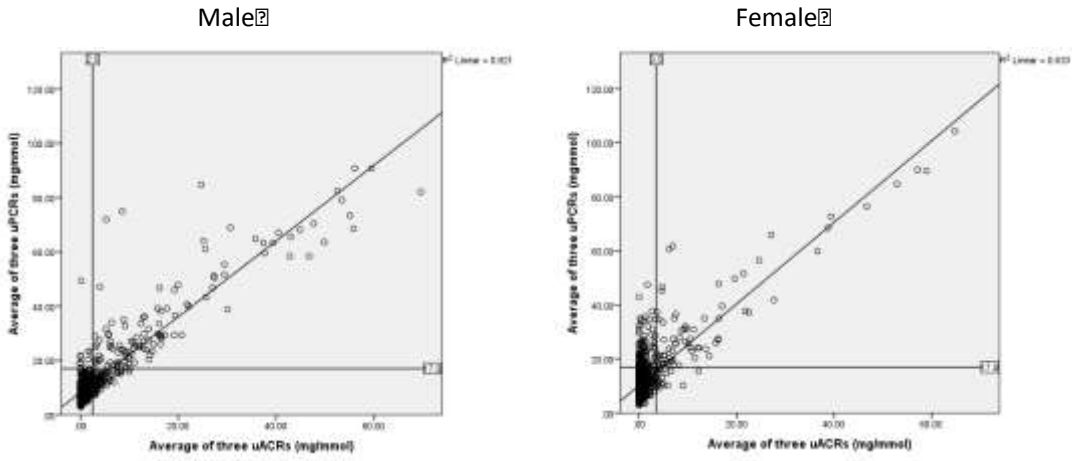
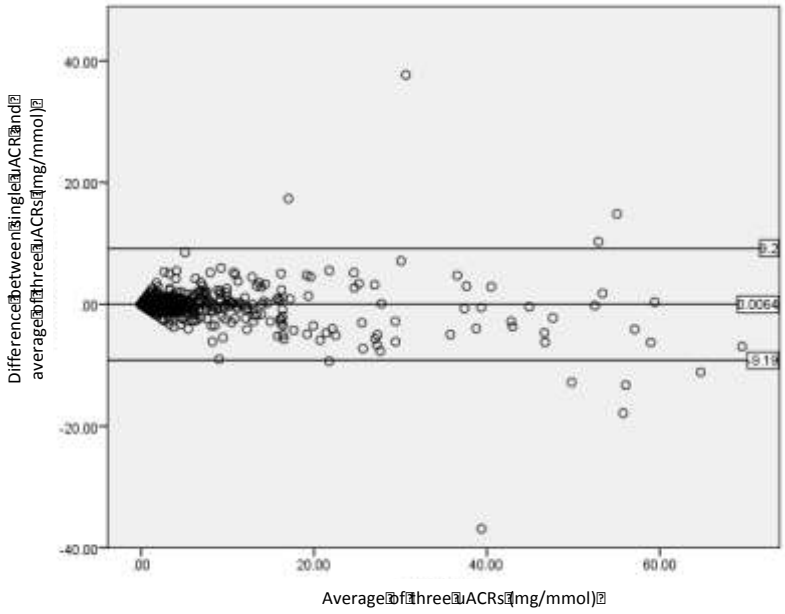


Figure 24. Scatterplots showing the distribution of uACR and uPCR relative to clinically important threshold values (excluding outlier values (uACR over 70mg/mmol and PCR 150mg/mmol))



High values have been excluded (uACR>70mg/mmol and uPCR>150mg/mmol) to better illustrate the relationship at lower levels of proteinuria.

Figure 25. Bland-Altman plot showing the degree of agreement between different methods of identifying albuminuria



3.3.5 Hospital admission

At the point that this study was conducted, the RRID follow up data had not yet been accumulated to allow for analysis of hospital admission. However, hospital admission data for the previous year had been collected at baseline, categorized as emergency or planned. 149 people (10.1%) had experienced (all cause) emergency hospital admission in the preceding year. A greater proportion of males, older people, people with no formal qualifications, ex-smokers, and people with diabetes or history of CVD had experienced emergency hospital admission (Table 30).

Table 30. Characteristics of people with a recent history of emergency hospital admission in the RRID cohort.

		Emergency hospital admission in the year prior to study baseline	
Characteristic	Category	n	Row %
Gender	Male	69	10.0
	Female	80	7.6
Age group	< 60	4	3.1
	60-69	34	7.6
	70-79	71	9.8
	80 +	40	9.3
IMD quintiles	1 (most deprived)	17	11.3
	2	32	7.4
	3	22	6.7
	4	46	10.3
	5 (least deprived)	32	8.4
Education status	No formal qualifications	93	9.8
	GCSE, A level, NVQ 1- 3	32	6.8
	1st or higher degree, NVQ 4 - 5	23	7.3
CKD awareness	Not aware of CKD diagnosis	66	9.2
	Aware of CKD diagnosis	83	8.1
Smoking	Current smoker	4	4.9
	Ex-smoker	86	9.9
	Never smoked	59	7.4
Diabetes	Diagnosed diabetes	34	11.6
	No diabetes	115	7.9
Hypertension	Meets hypertension criteria	130	8.5
	No hypertension	19	8.9
CVD	Any CVD	80	13.5
	No CVD	69	6.0

3.3.6 Survival

By the end of February 2013, 179 (10.2%) people had died. The mean time in the study for all participants was 1317 days (3.61 years (SD 288 days, 0.79 years)). For those still alive at the end of February 2013, the mean time in the study was 1381 days (3.78 years (SD 187 days, 0.51 years)). For those who had died by the end of February 2013, the mean time in the study was 758 days (2.08 years (SD 396 days, 1.08 years)). Table 31 shows descriptive statistics comparing those alive with those who had died by the end of February 2013.

Table 31. Comparison of the characteristics of people in the RRID study who had died with people still alive at the end of February 2013

	Category	Alive at end Feb 2013 n=1566		Died by end Feb 2013 n=179		Total
		n	% of category	n	% of category	n
Gender	Male	592	86%	97	14	689
	Female	974	93%	78	7	1052
Age	<60	128	100%	0	0	128
	60-69	430	97%	15	3	445
	70-79	678	89%	83	11	761
	80+	330	81%	77	19	407
Age (continuous)* Mean (SD)	-	1566	72.24 (9.05)	175	78.44 (6.58)	1741
Ethnicity	White	1529	90%	169	10	1698
	Other	37	86%	6	14	43
Aware of CKD diagnosis	Yes	931	91%	95	9	1026
	No	635	89%	80	11	715
Qualifications	None	846	89%	107	11	953
	GCSE, A level, NVQ1-3	425	91%	44	9	469
	Degree	294	93%	23	7	317
IMD quintiles	1 (most deprived)	136	90%	15	10	151
	2	389	90%	43	10	432
	3	292	90%	34	10	326
	4	397	89%	50	11	447
	5 (least deprived)	349	91%	33	9	382
History of CVD	Yes	487	82%	105	18	592
	No	1079	94%	70	6	1149
Diabetes	Yes	253	86%	41	14	294
	No	1313	91%	134	9	1447

Table 31 cont

	Category	Alive at end Feb 2013 n=1566		Died by end Feb 2013 n=179		Total
		n	% of category	n	% of category	n
Hypertension	Yes	1371	90	157	10	1528
	No	195	92	18	8	213
Smoking	Current	72	89	9	11	81
	Ex-smoker	760	88	106	12	866
	Never	734	92	60	8	794
BMI	Normal (18.5 – 24.99)	306	87	47	13	353
	Overweight (25 – 29.99)	667	90	71	10	738
	Obese (>=30)	593	91	57	9	650
Central obesity	Yes	1334	90	146	10	1480
	No	231	89	29	11	260
Total chol:HDL ratio	>4.5	276	90	30	10	306
	<4.5	1282	90	144	10	1426
At least microalbuminuria	Yes	223	80	57	20	280
	No	1338	92	118	8	1456
uACR >30	Yes	32	80	8	20	40
Isolated NAP	Yes	79	92	7	8	86
eGFR	>60	407	97	11	3	418
	45-59	823	90	88	10	911
	30-45	320	83	66	17	386
	<30	16	62	10	39	26
BP controlled (NICE criteria, in people with hypertension only, n=1528)	Yes	748	90	81	10	829
	No	623	89	76	11	699

3.3.6.1.1 Cause of death

CVD was the commonest cause of death in this cohort, with about 40% of deaths attributable to some form of vascular disease. The results are shown in Table 32.

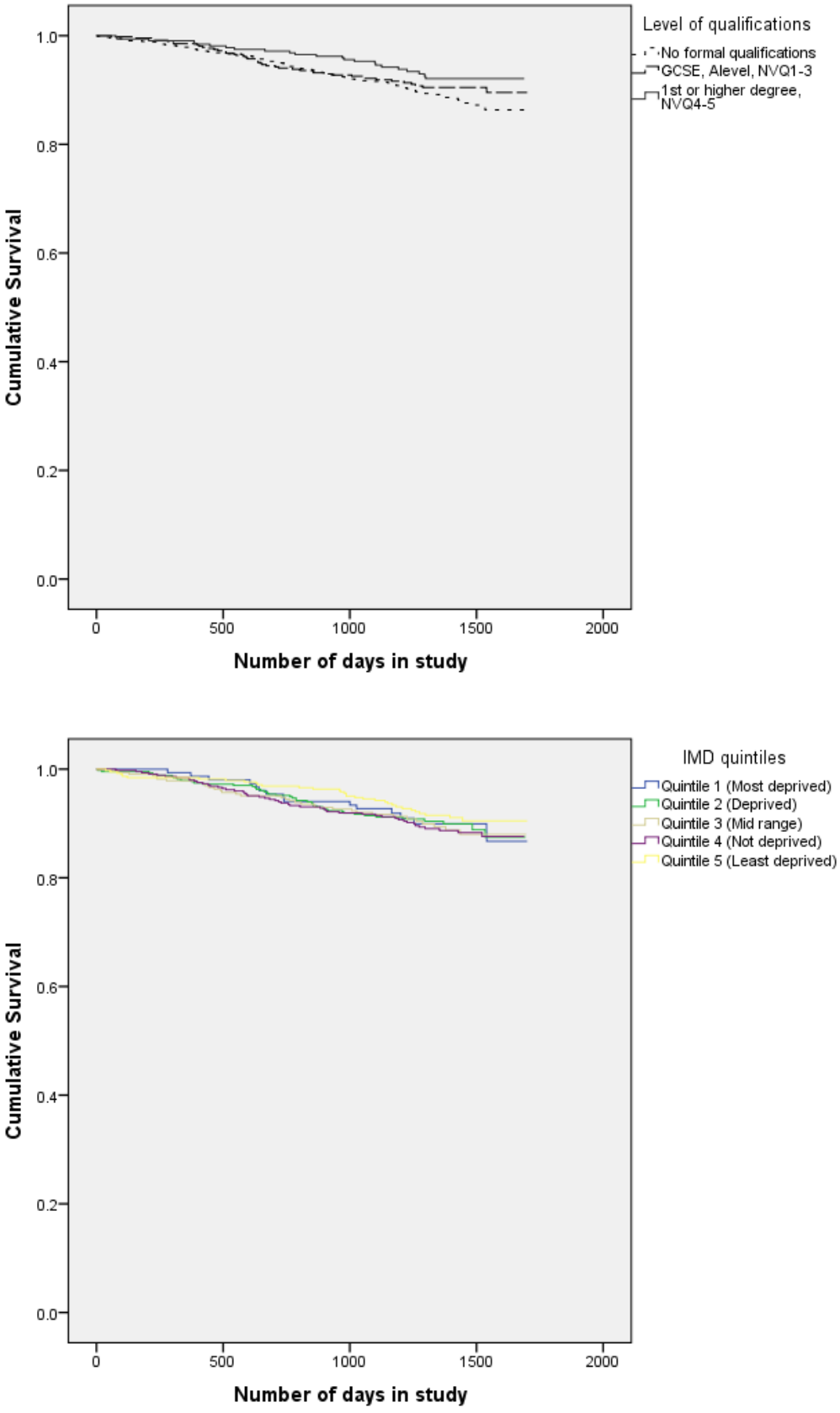
Table 32. Cause of death in the RRID study

Cause of death	Number	% of all who died
CVD	74	41.3%
Cancer	52	29.1%
Infection	24	13.4%
Other	29	16.2%
Total	179	100%

3.3.6.1.2 Survival by SES

Figure 26 shows Kaplan-Meier plots comparing survival between people grouped by education status and IMD. The descriptive statistics (Table 31) and these plots demonstrate that there was little difference in survival experience between people grouped by IMD, but suggest that people with no formal qualifications may have experienced slightly higher mortality compared to others.

Figure 26. Comparison of survival of people with CKD by education status and IMD



Examining this hypothesis further using Cox regression confirmed that there was no statistically significant difference in hazard ratio for all-cause mortality between people resident in different IMD areas. Although there appeared to be a difference in hazard ratio by education status at a univariate level, this was not statistically significant, and was attenuated after adjustment for age and sex. Awareness of CKD at baseline was also not associated with difference in mortality experience (Table 33). Considering education status as a binary variable (none vs. any qualifications), a borderline statistically significant association was identified (hazard ratio, HR 1.35 (95%CI 1.00-1.84, p 0.053, for people with no qualifications compared to those with any). This association was not maintained after adjustment for age and sex (HR 1.22 (95%CI 0.90-1.67, p 0.206, for people with no qualifications compared to those with any).

Table 33. Survival of people with CKD 3 by SES

Variable	Categories	Univariate		Age-sex adjusted	
		HR (95% CI)	p	HR (95% CI)	p
Gender (male vs. female)		1.95 (1.45–2.63)	<0.001	1.73 (1.28-2.33)	<0.001
Age continuous		1.09 (1.07-1.12)	<0.001	1.09 (1.07-1.11)	<0.001
No awareness of CKD diagnosis (vs. aware)		1.22 (0.91–1.64)	0.190	1.08 (0.80-1.46)	0.62
Education (vs. degree level)	No formal qualifications	1.62 (1.03-2.54)	0.093	1.63 (1.03-2.58)	0.103
	GCSE, A-level, NVQ 1-3	1.33 (0.80-2.20)		1.60 (0.96-2.66)	
IMD quintile (vs. least deprived)	1 (most deprived)	1.23 (0.67-2.27)	0.772	1.29 (0.70-2.38)	0.557
	2	1.26 (0.80-1.98)		1.39 (0.88-2.19)	
	3	1.29 (0.80-2.09)		1.44 (0.89-2.32)	
	4	1.32 (0.86-2.06)		1.38 (0.89-2.15)	

3.3.6.1.3 Survival by clinical factors

As indicated in section 1.1.7 above, several factors have been clearly demonstrated to be associated with all-cause mortality in people with CKD. These include poor renal function (reflected in lower eGFR) and higher levels of proteinuria / albuminuria. Multivariable Cox regression was used to examine the risk of all-cause mortality in this cohort from these known factors, and other important clinical considerations such as diabetes, hypertension, and previous CVD.

The results of these analyses are shown in Table 34. This demonstrates significant increased hazard ratios for increasing age, presence of previous CVD, any albuminuria, and lower eGFR. These findings are consistent with the literature from sources such as the CKDPC. [13] No associations were identified between SES and either all-cause or cardiovascular mortality. No interactions were identified.

Table 34. Cox regression models of key clinical factors

Variable	Categories	Univariate		Model 1*		Model 2**	
		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Gender (vs. female)	Male	1.95 (1.45–2.63)	<0.001	1.73 (1.28-2.33)	<0.001	1.29 (0.92-1.79)	0.137
Age continuous	-	1.09 (1.07-1.12)	<0.001	1.09 (1.07-1.11)	<0.001	1.07 (1.05-1.09)	<0.001
No awareness of CKD diagnosis (vs. aware)	Unaware of CKD diagnosis	1.22 (0.91–1.64)	0.190	1.08 (0.80-1.46)	0.62		
Education (vs. degree level)	No formal qualifications	1.62 (1.03-2.54)	0.093	1.63 (1.03-2.58)	0.103		
	GCSE, A-level, NVQ 1-3	1.33 (0.80-2.20)		1.60 (0.96-2.66)			
IMD quintile (vs. least deprived)	1 (most deprived)	1.23 (0.67-2.27)	0.772	1.29 (0.70-2.38)	0.557		
	2	1.26 (0.80-1.98)		1.39 (0.88-2.19)			
	3	1.29 (0.80-2.09)		1.44 (0.89-2.32)			
	4	1.32 (0.86-2.06)		1.38 (0.89-2.15)			
CVD (vs no CVD)	People with CVD	3.15 (2.33-4.26)	<0.001	2.37 (1.74-3.22)	<0.001	2.18 (1.60-2.98)	<0.001
Diabetes (vs. n diabetes)	People with diabetes	1.54 (1.09-2.19)	0.015	1.46 (1.03-2.07)	0.036	1.20 (0.84-1.73)	0.320
Hypertension (vs. no hypertension)	People with hypertension	1.24 (0.76-2.03)	0.380	0.90 (0.55-1.47)	0.67		

Table 34 cont

Variable	Categories	Univariate		Model 1*		Model 2**	
		HR (95% CI)	p	HR (95% CI)	HR (95% CI)	p	HR (95% CI)
Smoking (vs. never smokers)	Current smoker	1.50 (0.74-3.02)	0.006	1.89 (0.93-3.82)	0.062	2.10 (1.02-4.32)	0.116
	Ex-smoker	1.67 (1.22-2.29)		1.40 (1.01-1.95)		1.19 (0.85-1.67)	
BMI (vs. normal)	Overweight	0.71 (0.49-1.03)	0.076	0.65 (0.45-0.95)	0.077	0.75 (0.52-1.10)	0.338
	Obese	0.65 (0.45-0.96)		0.75 (0.51-1.10)		0.84 (0.56-1.25)	
Central obesity (vs.not centrally obese)	Centrally obese	0.89 (0.60-1.32)	0.559	0.85 (0.57-1.27)	0.424		
Elevated total:HDL cholesterol ratio (vs. not elevated)	>4.5	0.95 (0.64-1.41)	0.799	0.97 (0.65-1.44)	0.873		
Albuminuria (vs. no albuminuria)	At least 2 of 3 specimens at least microalbum-inuria (>2.5mg.mmol in men, >3.5mg/mmol in women)	2.74 (1.99-3.75)	<0.001	2.45 (1.76-3.41)	<0.001	1.74 (1.23-2.45)	0.002
eGFR (vs. eGFR 45-59 ml/min/1.73m^2)	>60	0.26 (0.14-0.48)	<0.001	0.31 (0.17-0.59)	<0.001	0.37 (0.20-0.70)	<0.001
	30-45	1.87 (1.36-2.57)		1.60 (1.16-2.20)		1.35 (0.98-1.88)	
	<30	4.85 (2.52-9.34)		4.51 (2.33-8.71)		3.41 (1.75-6.64)	
Non-albumin proteinuria (vs. people without)	Isolated NAP	0.84 (0.39-1.79)	0.649	0.92 (0.42-1.98)	0.82		

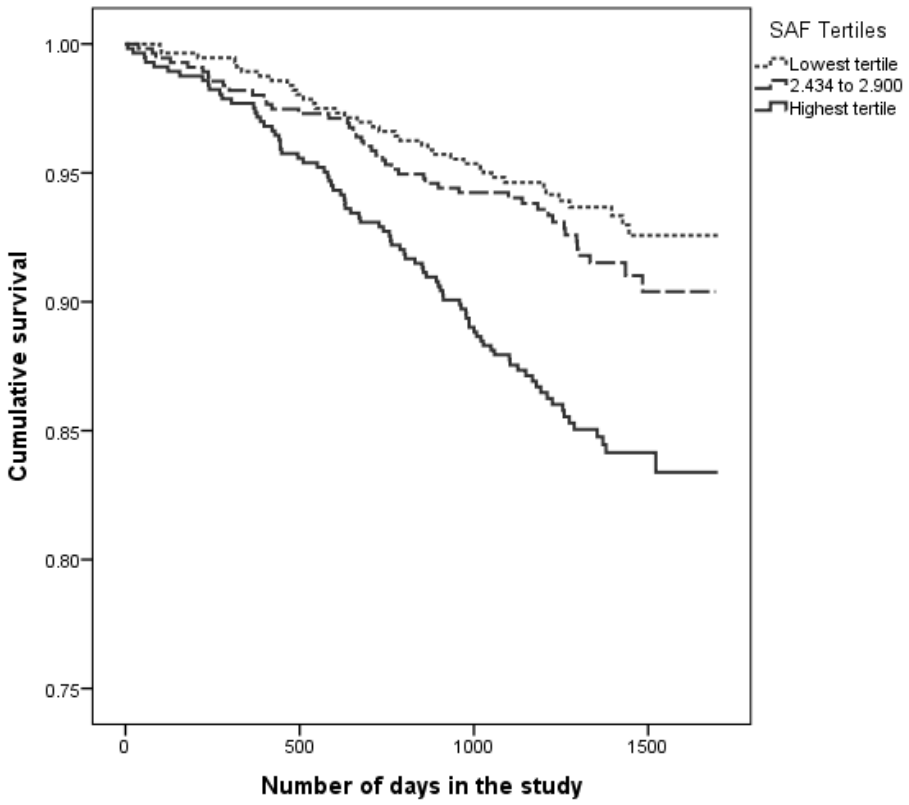
*Model 1 – Age sex adjusted. Tested for age*sex interaction – none. **Model 2 – Adjusted for age, sex, CVD, diabetes, smoking, BMI, any albuminuria, eGFR

3.3.6.1.4 Survival and skin autofluorescence

1707 (98%) had valid measures of skin AF. 34 participants were excluded because skin AF readings could not be obtained due to dark skin colour (n=17) or technical failure (n=17). Mean skin AF was 2.73 AU (SD 0.61) and skin AF was normally distributed. The skin AF of people who died tended to be higher than those who did not (mean 3.0 ±0.8 AU vs 2.7 ± 0.6 AU respectively). The commonest cause of death was CVD (41%) followed by cancer (29%).

The prevalence of several risk factors for death increased across tertiles of skin AF and a Kaplan-Meier plot demonstrated significantly poorer survival in people in the highest tertile of skin AF (log rank 25.9, $p<0.001$, Figure 27). On univariate analysis, skin AF (as a continuous variable), male gender, age, history of CVD, diabetes, smoking (current or previous), decreasing eGFR, albuminuria, and lower haemoglobin were associated with increased risk of all-cause mortality. After age-sex adjustment, the relationship between skin AF (continuous) and all-cause mortality was slightly attenuated (from 2.15 (95% confidence intervals 1.73-2.67) to 1.73 (95% confidence intervals 1.38-2.16, $p<0.001$)). Sequential addition of other potentially confounding variables attenuated but did not remove the association between skin AF as a continuous variable and all-cause mortality. However, the Kaplan Meier plot suggested that the relationship between skin AF and all-cause mortality was not linear Figure 27). The final model (including both skin AF (continuous) and skin AF^2) demonstrated that the effect of increasing skin AF varied by level of skin AF. At lower levels, an increase of 0.5 was protective, whereas, at higher levels, the increase was associated with increase hazard ratio for all-cause mortality (see Table 35 and Figure 28). The fully adjusted hazard ratio for skin AF^2 was 1.32 (95% confidence intervals 1.11-1.57), and for skin AF 0.23 (95% confidence intervals 0.07-0.74).

Figure 27. Kaplan Meier plot showing cumulative survival (all-cause mortality) by tertile of skin autofluoresence



Log rank 25.9, p<0.001

Note – x axis does not intersect y axis at 0 in this figure

Skin autofluorescence measured in arbitrary units (AU)

Table 35. Survival analysis of a novel marker – skin autofluorescence

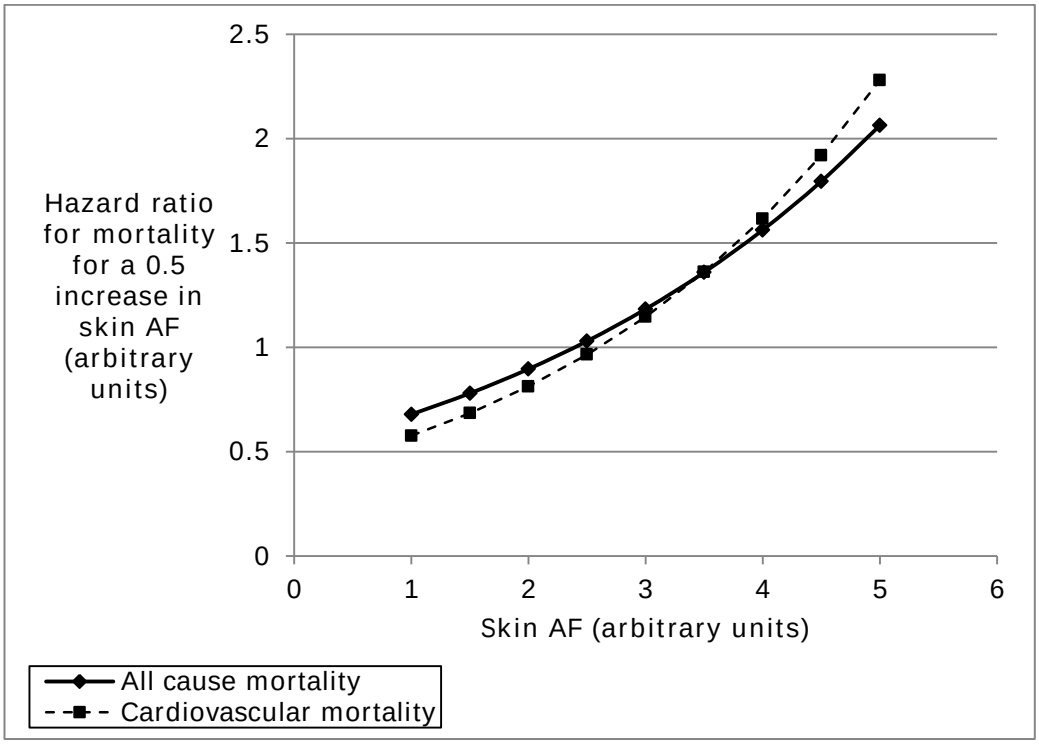
Variable	Univariate		Final model*	
	HR (95% CI)	p	HR (95% CI)	P
Skin autofluorescence [2]	1.13 (1.09-1.16)	<0.001	1.32 (1.11-1.57)	0.002
Skin autofluorescence (as continuous)	2.15 (1.73-2.67)	<0.001	0.23 (0.07-0.74)	0.014
Gender (male vs. female)	1.95 (1.45–2.63)	<0.001	1.17 (0.83-1.64)	0.379
Age(years)	1.09 (1.07-1.12)	<0.001	1.06 (1.03-1.08)	<0.001
CVD (vs no CVD)	3.15 (2.33-4.26)	<0.001	2.11 (1.53-2.91)	<0.001
Diabetes (vs. no diabetes)	1.54 (1.09-2.19)	0.015	1.04 (0.71-1.54)	0.835
Hypertension (vs. no hypertension)	1.24 (0.76-2.03)	0.380		
Smoking (vs. never smokers) Current smoker Ex-smoker	1.50 (0.74-3.02) 1.67 (1.22-2.29)	0.006	1.91 (0.91-3.98) 1.17 (0.83-1.65)	0.178
BMI (kg/m^2)	0.97 (0.94-1.00)	0.054	0.99 (0.96-1.03)	0.770
Central obesity (vs not centrally obese)	0.89(0.60-1.32)	0.559		
Total:HDL cholesterol ratio	0.99 (0.87-1.12)	0.870		
eGFR (continuous)	0.94 (0.93-0.95)	<0.001	0.97 (0.95-0.98)	<0.001
Log average uACR (mg/mmol)	1.35 (1.22-1.51)	<0.001	1.15 (1.03-1.29)	0.014
Haemoglobin (g/dl)	0.80 (0.72-0.89)	<0.001	0.96 (0.86-1.08)	0.529

Table 35 cont

Variable		Univariate		Final model*	
		HR (95% CI)	p	HR (95% CI)	p
Qualifications (vs none)	School level	1.56 (1.00-2.46)	0.118		
	Degree or equivalent	1.27 (0.76-2.11)			
IMD quintiles (vs least deprived)	1 (most deprived)	1.06 (0.55-2.05)	0.747		
	2	1.26 (0.80-1.98)			
	3	1.22 (0.75-1.99)			
	4	1.33 (0.86-2.07)			

*Adjusted for age, sex, CVD, diabetes, smoking, BMI, eGFR, albuminuria and haemoglobin. Model included skin AF as continuous and quadratic for skin AF. All variable are continuous except gender, CVD, diabetes, hypertension, smoking status, and central obesity

Figure 28. Relationship between the hazard ratio for all cause and cardiovascular mortality and increase in skin AF of 0.5 arbitrary units at different levels of skin AF



3.4 Discussion

3.4.1 Cardiovascular risk

In this section of the study, the prevalence of some cardiovascular risk factors, though not all, varied by two different measures of SES, and persisted after adjustment for age, gender and diabetes. Adjusted odds ratios of previous CVD and diabetes were higher in lower socioeconomic groups, though for diabetes the association varied by SES measure (adjusted odds ratio of diabetes higher in more deprived quintile of IMD, but not in people with no qualifications) . Hypertension prevalence showed no clear socio-economic variation but it was almost universal in all groups. Any albuminuria, central obesity and raised cholesterol/HDL ratio showed no significant association with SES after adjustment for confounders. These findings agree with previous research identifying the high burden and social distribution of CVD risk factors among CKD patients.[81 118]

The older age profile of patients included in the QRisk2 subgroup contributed to the higher prevalence of elevated CVD risk compared to the Framingham subgroup. There was variation in CVD risk estimates by SES and by awareness of CKD diagnosis. However, odds ratios differed between the two scores when IMD was used to measure SES. The adjusted odds ratio of elevated Framingham CVD risk was doubled in the lowest deprivation quintile, but there was no clear association with IMD using QRisk2. In contrast, variation in elevated CVD risk by education status was similar between the two measures. Using both, the odds ratio for elevated CVD risk was about one and a half times greater among people unaware of their CKD diagnosis.

Albuminuria and low eGFR have been independently associated with increased CVD risk in elderly populations, and may enhance existing CVD risk prediction tools. [80 257] For UK populations, QRisk2 appears to have better predictive accuracy for CVD than Framingham by incorporating ethnicity, deprivation, and comorbidities, including CKD. [172 258] This study suggests a relationship between CVD risk and education status among people with CKD whether measured by Framingham or QRisk2. Considering all people with CKD as having the same elevated risk is a crude estimation and may hide important variation related to variation in eGFR and uACR. Whilst socioeconomic disparity of CKD prevalence

and of certain outcomes, including disease progression, referral for transplant, and survival has been demonstrated, [122 126] more evidence is needed on the relationships between SES and CKD complications, particularly CVD.

3.4.2 Blood pressure control

In this section of the study, I identified that hypertension was common with a prevalence of 88% and BP control was suboptimal, with 42% not achieving the NICE BP target, 40% not achieving the KDIGO BP target, and 64% not achieving the more strict KDOQI BP target. Presence of diabetes and higher levels of albuminuria were associated with a smaller proportion of people achieving BP control targets. After adjustment for potential confounding factors, poor BP control was associated with increasing age and albuminuria for all three BP target groups and with diabetes in the NICE BP target group. Older age was associated with better diastolic control and poorer systolic control. Better BP control was associated with past history of CVD. The majority of patients were on one or two antihypertensive medications (most commonly RAASi) and taking a greater number of antihypertensive medications was associated with lower MAP.

The prevalence of hypertension in this cohort is similar to other studies. In the Chronic Renal Insufficiency Cohort (CRIC) [259] Study, it was between 82% and 91% in people with eGFR between 30 and 59 mL/min/1.73m^2. [259] In the Kidney Early Evaluation Programme (KEEP) and NHANES, the prevalence of hypertension was between 84 and 92% for people with eGFR between 40 and 60 mL/min/1.73m^2. [175 260] As with previous studies, systolic hypertension predominated in the uncontrolled group with hypertension. [174] The findings of poor BP control in older people, people with diabetes, and people with albuminuria are consistent with previous studies. [251 254 260] For the KDOQI target, I identified similar association with male gender identified in the KEEP cohort, but not the association with obesity identified in KEEP. [178 260] The predominantly white population in this study limited my ability to draw conclusions about the association between CKD-related hypertension and ethnicity identified in other studies. [178 251 260 261]

3.4.3 Albuminuria and non-albumin proteinuria

In the analysis of proteinuria in this study, albuminuria was present in 16% and was associated with NAP in 11%. Isolated NAP was present in 5%. Presence of albuminuria was associated with male gender, diabetes, hypertension, current smoking, and lower eGFR, whereas the pattern of isolated NAP was different – it was associated with female gender and increasing age. A single uACR was sufficient for identification of albuminuria, but due to intra-individual variation in uACR three measurements are preferable for quantification of albuminuria. Albuminuria was relatively uncommon in this cohort suggesting that most people with CKD stage 3 in primary care have tubulo-interstitial and/or vascular rather than glomerular pathology.[187] This low prevalence of albuminuria and the strong association with adverse renal and cardiovascular outcomes underlies the importance of detection to identify the minority of people with CKD who are at increased risk. [13 262 263]

I identified a small number of people with isolated NAP who would not have been identified by use of uACR alone and demonstrated clear differences in albuminuria and NAP distribution patterns in people with CKD 3. I also identified a sub-group of people with both albumin and non-albumin proteinuria. These observations are consistent with albuminuria and NAP reflecting different renal pathologies (glomerular and tubulo-interstitial). The associations observed with albuminuria were similar to those reported from the CRIC study, except for lack of association with BMI in my study. [264] The association between albuminuria and diabetes likely reflects diabetes being a common cause of glomerulopathy. In retrospective analyses of uACR and uPCR in people with CKD, Methven et al identified the high sensitivity of uPCR as a test to identify 'clinically relevant' proteinuria (compared with 24-hour urine collection), and stressed the equivalence of uACR and uPCR in predicting renal outcomes and mortality. [186] In a separate study they reported increased risk of death (HR2.34 (95%CI 1.63-3.35)), renal replacement therapy (HR2.90 (95%CI 1.31-6.43)), and CKD progression (HR for doubled serum creatinine 2.35 (95% CI 1.62-3.40)) among people with discordant (i.e. predominantly non-albumin) proteinuria (low uACR(<30mg/mmol), high PCR (≥50mg/mmol)). [265] However the magnitude of proteinuria in that study was higher than in the RRID study population and different thresholds were used. A study comparing presence of NAP (identified by a low APR) with histology from renal biopsy, confirmed the association with tubulointerstitial pathology. [187] While the prognostic

significance of isolated NAP remains unknown, my findings suggest that identification of NAP may provide additional diagnostic information in certain groups of people, particularly older women. The low positive predictive value of a single uPCR for isolated NAP in this study suggests that future prognostic studies would benefit from using more than one measure.

Use of a single urine specimen uACR to define albuminuria misclassified some individuals in this study compared to using two of three specimens, but sensitivity, specificity and positive predictive value of a single uACR were high. My use of 'two of three' uACRs and uPCRs differs from many studies that have used a single uACR to identify albuminuria and determine prognosis. [13 70 131 183 184] The HUNT 2 study used the mean of three uACR values to define albuminuria, but did not make comparison with a single value. [182] My more restricted definition of albuminuria aimed to improve specificity and better reflect clinical practice (in which albuminuria identified in primary care is confirmed by repeat testing). [50] However, my findings suggest that a single measure of uACR is sufficient to categorise albuminuria for clinical decision-making. Conversely, I have confirmed substantial intra-individual variation in uACR values on consecutive days, suggesting that an average of three uACR measurements is preferable for quantification of albuminuria. The predictive model developed by Tangri et al. for progression of CKD to ESKD was based on a single uACR measure. [69] My results suggest that further research on risk prediction models in CKD should also compare the use of more than one uACR value.

3.4.4 Survival and skin autofluorescence

In this section of the study, I identified no statistically significant associations between all-cause mortality and SES, either by IMD or education status. Although there appeared to be a difference in hazard ratio by education status at a univariate level, this was not statistically significant, and was attenuated after adjustment for age and sex. Awareness of CKD at baseline was also not associated with difference in mortality experience.

I demonstrated that increased levels of skin AF were associated with all-cause mortality independent of well-established risk factors including age, eGFR and uACR. To my knowledge, this is the first report of the association of skin AF with mortality in early stage CKD. I found a similar pattern for cardiovascular

mortality although my study had less power to assess this outcome and hazard ratios were non-significant in the fully adjusted model.

The association between increased skin AF and clinical outcomes has been clearly demonstrated in people with diabetes, with studies showing associations between skin AF and a variety of micro and macrovascular complications including coronary heart disease, cardiovascular and all-cause mortality (in both Type 1 and Type 2 diabetes). [201 203 205] However, a more recent systematic review of the prognostic effect of skin AF in people with diabetes has recommended the need for more prospective studies with longer periods of follow up. [266] The RRID cohort will be followed up for ten years, which will allow for further validation of these findings in the future. It has also been suggested that AGEs may have an important role in the pathogenesis of heart failure and other cardiovascular disorders. [267] In support of this, an association has been shown between AGE accumulation measured as skin AF and peripheral arterial disease independent of diabetes status, and increasing AGEs (measured as serum pentosidine) has been associated with poor prognosis in people with heart failure. [268 269]

In the CKD context, Hartog et al showed correlation between skin AF and poorer diastolic function in a cross sectional study of peritoneal and haemodialysis patients, and Meerwaldt et al identified independent associations between skin AF and cardiovascular as well as all-cause mortality in a prospective cohort of 109 patients on haemodialysis. [201 207] My findings in a larger, prospective cohort of people with CKD support and extend these results to earlier stage CKD. In the cross sectional baseline analysis of this cohort, associations were demonstrated between increased skin AF and several cardiovascular and renal progression risk factors, including age, eGFR and uACR.[191] In this follow up analysis I have demonstrated that the association between all-cause mortality and skin AF is maintained independently from these known risk factors. Univariate association between diabetes and all-cause mortality in this cohort was attenuated on the addition of skin AF to the model, supporting existing evidence that AGE accumulation may be on the causal pathway between diabetes and its complications. [205] Further research is required to evaluate whether AGE accumulation may represent a previously unrecognized mechanism whereby CKD contributes to the pathogenesis of CVD.

There are several proposed mechanisms by which AGE accumulation may influence mortality. [267] Firstly, AGEs cross link extracellular matrix proteins, a mechanism that may be implicated in the development of arterial stiffness associated with old age and diabetes. [270 271] Secondly, AGEs cross-link intracellular proteins, altering their physiological function. For example, AGEs have been shown to affect cardiomyocyte function by causing alterations in intracellular protein function in animal models. [272 273] Thirdly, AGEs bind to cell membrane receptors (particularly the cell receptor for AGEs, RAGE) and may induce several intracellular cascades resulting in the release of cytokines, inflammation, tumour growth, neurodegenerative processes, and amyloidosis. [197 274-277] RAGE has also been implicated in CKD and CVD pathogenesis, and is associated with arterial stiffness. [196 198 200] Although the detail of many such pathophysiological mechanisms is yet to be fully elucidated, these examples suggest that AGEs may influence both cardiovascular and non-CVD processes and mortality.

As discussed chapters 1 and 2, risk factors for CVD and CKD progression are more prevalent in lower socioeconomic groups. Whilst I demonstrated associations between SES and increased cardiovascular risk in the baseline analysis of this cohort, I did not detect an association between all-cause or cardiovascular mortality and measures of SES in this section of the study. [278]

3.4.5 Strengths and limitations

This study had several strengths, including large numbers of people with CKD, being conducted in a primary care setting, standardisation of blood pressure and other measures, and the use of three morning urine samples to assess albuminuria. However, it also has several limitations, including its cross sectional design, which limits the ability to infer causality. A further potential limitation is that a significant proportion of the study population (24%) were found to have an eGFR ≥60 at baseline, which might be considered to question their CKD diagnosis. However, all the participants met the formal definition for CKD prior to inclusion (including chronicity of low eGFR) and, importantly, were therefore on CKD registers in their respective GP practices. I therefore included them in the analyses to improve the generalisability of these findings to normal practice circumstances. There is also potential that non-response to recruitment could have caused selection bias, and that the predominantly

elderly population could result in survivor bias. The potential for selection bias means that caution should be used in application of these results to general populations with CKD. 60% of the study population were women, which is consistent with other similar CKD studies. [241] This study under-represented ethnic minorities and the findings should therefore be interpreted with caution in different ethnic groups. In addition, the study population is not representative of the general population due to the high proportion of older people. However, it included a range of general practices from urban and rural locations, and hence is broadly representative of people with CKD stage 3 in primary care in the UK. Specific limitations of each section of the study are given below.

3.4.5.1 Cardiovascular risk

For the cardiovascular risk aspect, I did not have all variables for the risk models (e.g. left ventricular hypertrophy, LVH) and therefore potentially underestimated socioeconomic disparity if there was a socio-economic gradient in such variables. As a cross sectional study, I was unable to link my findings to cardiovascular outcomes, though this should not bias the association of SES and cardiovascular risk. Misclassification of SES by IMD is possible as IMD is an area measure. This may reduce the chance of finding true associations with SES. The definition of CKD awareness was binary, excluding the potential for assessment of degrees of disease awareness. [245] Lack of data on characteristics of people not responding to recruitment means that I could not exclude selection bias, and in an older prevalence cohort there may be survivor bias, which might narrow socioeconomic gradients. However I found no evidence of an age interaction with SES. Low representation of ethnic minorities reduces generalizability to other ethnic groups.

3.4.5.2 Blood pressure control

In the blood pressure control analyses, it was possible that people taking a single antihypertensive agent were taking it for other reasons, and that the observed relationship between CVD and improved BP control could be a reflection of reverse causality. I checked this among people with heart failure taking only one agent and identified only 25 people whose blood pressure was <140/90. I conclude that the risk of bias from people on single agents for reasons other than hypertension was therefore low. In addition, I cannot

comment on whether people on antihypertensive treatment were receiving adequate doses of medication or adhering to the treatment. Optimisation of drug dosage might therefore represent a potential area of improvement not assessed in this study.

3.4.5.3 Albuminuria and non-albumin proteinuria

The majority of patients were already treated with RAASi at baseline, which may have masked proteinuria and therefore underestimated true proteinuria prevalence. The 2012 KDIGO clinical practice guidelines recommended three categories of albuminuria to grade risk – normal to mildly increased (<3mg/mmol), moderately increased (3 – 30mg/mmol), and severely increased (>30mg/mmol).[48] I chose to examine associations with 'at least microalbuminuria' because the absolute numbers with macroalbuminuria (uACR>30mg/mmol) were small (41 people =2.4%) and increased risk has been demonstrated for all grades of albuminuria.

3.4.5.4 Skin autofluorescence

This study had several limitations. Skin AF can currently not be assessed in people with dark skin, which represents a significant number of those with CKD, particularly in the US. However, a method has been proposed for calculating skin AF independent of skin colour, and this may be an important area of investigation for future research. [279] This was an observational study, and I am therefore cautious in my interpretation of the results with respect to causality. In addition, the primary outcome was all-cause mortality, and so my findings in relation to cardiovascular mortality should be interpreted with caution. In addition, I have not examined the relationship between skin AF and non-fatal CVD events at this stage of follow up.

4. Processes and outcomes in CKD: a retrospective cohort study using routine data from the Hampshire Health Record

4.1 Background

As described in Chapter 1, the Hampshire Health Record (HHR) is a shared clinical record that holds individual linked extracts of GP and hospital records. Over 130 GP practices in Hampshire and the Isle of Wight feed information to the HHR, covering a total registered patient population of over 1.1 million people. This study was conducted using data extracted from the HHRa – the anonymised analytical database to which data is extracted from the live HHR on a monthly basis. I worked with Martin Davis, a data analyst with expertise and experience of using the Hampshire Health Record to identify the practices to include, to identify the study population, and to extract the data.

Other studies of CKD have used routine data from sources such as The Health Improvement Network (THIN) database. [258] These databases have broader coverage than the HHR, with the ability to extract data from practices across the whole country, and therefore cover populations with greater ethnic and social diversity than the HHR. They are therefore potentially more generalisable. However, many are limited with respect to investigation of CKD by a dependence on the identification and coding of a diagnosis of CKD by a clinician in primary care. Some, such as the New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) project, used routinely collected creatinine data in general practices to estimate MDRD eGFR in order to identify quality issues such as recognition of renal disease and prescription of nephrotoxic drugs.[280] The Quality Improvement in CKD (QICKD) trial used routine clinical data from general practice extracted using Morbidity Information Query and Export Syntax (a method of interrogating GP practice databases to extract specific data) to define CKD from eGFR values with a primary aim of investigating quality improvement interventions aimed at improving BP control in CKD. [281 282]

By contrast, in addition to primary care data, the HHRa includes pathology data from two hospitals (Southampton and Portsmouth) and clinical information from those hospitals (including admission data). Collation of these data within a single database eliminates the need to undertake data search and extraction processes in individual practices. It can be used to identify CKD from routine measures of serum creatinine and derived eGFR, and provides the possibility of being able to compare the characteristics and important outcomes (including mortality) of a large population of people with CKD independent of their status with respect to GP identification / QOF registration. This is important for investigating the associations between SES and process and outcome measures if any inequity exists with regard to QOF registration. Moreover, the ability to assess serial eGFRs allows for the element of chronicity to be included in the definition of CKD for the study, rather than defining by single eGFR which is an important limitation of some epidemiological studies of CKD (though not QICKD).[214 282]

This study aimed to construct a retrospective cohort of people with study-defined CKD from the HHRa in order to examine process measures such as aspects of CKD management in primary care (CKD identification and measurement of uACR). It also aimed to investigate outcomes including mortality, need for RRT and hospital admission for AKI. While postcode data is removed from the HHRa to avoid the potential to identify individuals, it includes IMD, which allows for investigation of variation in these process and outcome measures by SES.

This section of the study therefore aimed to explore the use of the HHRa as a source of routine data to create a retrospective cohort of people with CKD (both prevalent and incident CKD) and follow them over time between 2008 and 2013 to understand variation in various aspects of clinical care and outcomes by SES (IMD).

Key research questions to be addressed were:

- What is the feasibility of using routine data to investigate the clinical epidemiology of CKD in a defined population?
- Is there evidence of socioeconomic inequality in important aspects of CKD management (process measures) in primary care such as

identification of CKD (registration of CKD for QOF chronic disease management purposes) and measurement of uACR?

- Do these aspects of CKD management change over time (in the period since QOF CKD targets were introduced)?
- Is there evidence of socioeconomic inequality in outcomes including mortality, incidence of RRT, and AKI in people with CKD?

4.2 Methods

4.2.1 Identification of the study population

As described in section 1.1.4, the identification of CKD stage 3 - 5 requires at least two eGFR values, both below 60 ml/min/1.73m^2 and occurring at least three months apart (without values above 60 ml/min/1.73m^2 in between those values).

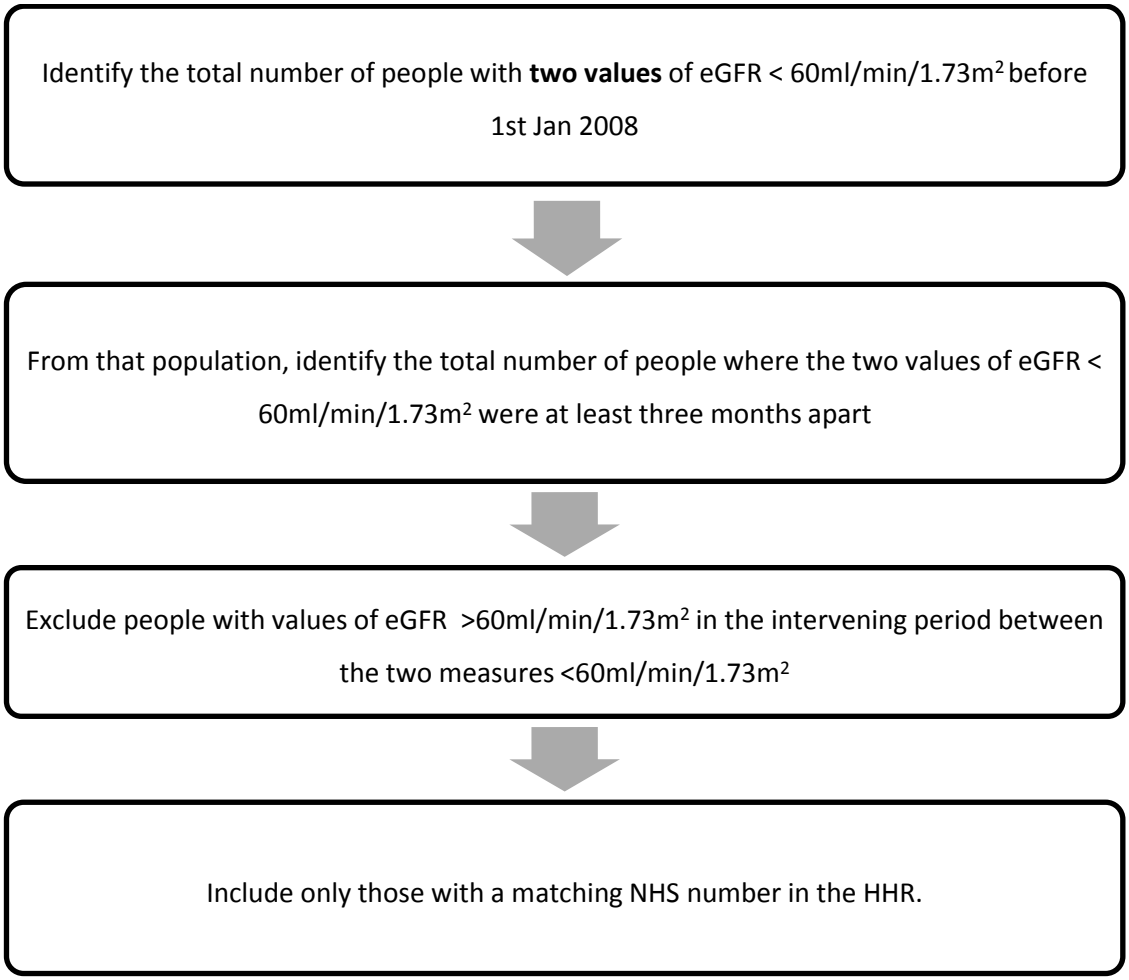
In order to meet the study aims defined above, two cohorts were required:

1. Prevalent CKD cohort – people with study-defined CKD at the start of 2008. Used to investigate process / clinical management measures such as identification of CKD (QOF), measurement of uACR, mortality, and development of AKI and incidence of RRT.
2. Incident CKD cohort – people developing study-defined CKD during the study follow up period. This was needed in order to identify change in identification of CKD (QOF) and measurement of uACR over time.

To identify a prevalent cohort of cases of CKD from the HHRa based on eGFR values, the method used is shown in Figure 29. The index date of CKD was defined as the date of the first eGFR reading below 60 ml/min/1.73m^2 and patients needed to be 18 years and over at their index diagnosis, be alive, and be registered with one of the included practices at the start of observation 01/01/2008.

To identify an incident cohort of cases of CKD, the method was similar, with the index date of CKD defined as the date of the first eGFR reading below 60 ml/min/1.73m^2, but incident cases were defined as those where this occurred during the period 01/01/2008 to the end of follow up. Follow up for both the prevalent and incident cohorts was stopped at the latest time of complete data availability prior to analysis (16/05/2013).

Figure 29. Flow chart of the process used to identify people with prevalent CKD



In order to clarify the rationale for identifying people as having or not having CKD stage 3 – 5, various patterns of eGFR results and their subsequent study classification are shown in Figure 30. The cut off of 3 months was taken from standard guidelines (KDIGO practice guideline for the evaluation and management of CKD define CKD by the presence of a low eGFR for more than three months). [48] In practice, however, eGFR is measured at specific time points, not continuously. It is possible, therefore, that two measures of eGFR, both <60ml/min/1.73m² taken six months apart could represent either CKD or two isolated and separate episodes of transient drop in eGFR due to an acute illness (AKI). NICE guidelines recommend 6 monthly eGFR testing for people with CKD stage 3, but for pragmatic reasons this frequency of eGFR testing may not occur in practice.[50] The QOF targets do not include a target for eGFR testing frequency, and annual eGFR tests are the norm in most practices for

QOF purposes. Therefore, for the purposes of this study, three months was considered the minimum and one year the maximum time between two eGFRs <60ml/min/1.73m^2 to define CKD. It was recognised that this may overestimate the presence of CKD in some individuals with only two eGFR measures, but as most people were anticipated to have more than two measures, this was thought unlikely to represent a major source of bias. See Figure 30.

4.2.1.1 Identification of time of leaving practices

Various aspects of patient administration are captured within primary care information systems. Patient registration events are recorded, as is the date of computerisation of the patient record. Although computerisation is not an actual registration event it provides a date after which records are likely to be computerised and therefore included within the HHR. Although there is likely to be substantial variation across the country, GP Surgeries have been computerising records (including diagnostic codes) since approximately the year 2000. The QOF for primary care and Payments by Results Quality Standards for Acute providers (hospitals) came into being around 2004/5. This means that relying on computerised data between 2008 and 2013 should be robust.

4.2.1.1.1 Start dates

There are three potential events that initiate a period of registration; registration of a new patient, computerisation of a legacy patient's record or (where neither of these exist) the patient's first face to face consultation. These were used (in this priority order) to specify dates of joining.

4.2.1.1.2 End dates

End dates (leaving the practice) are not reliably captured within primary care information systems, although very occasionally a 'GP2GP' patient record transmission will be coded, this is not the norm when a patient de-registers.

In order to identify end dates for periods of registration I therefore used the following information:

1. Whether a patient was still registered at the practice
   The HHR master patient index table details all HHR registered patients currently registered with a practice.
2. Death
   The HHR master patient index table details date of death for all HHR registered patients (though currently cause of death is not available). A limitation of this data is that deaths occurring in people who have left a HHR-submitting practice would not be captured.
3. Migration
   Migratory patients are recorded within the HHRs master patient index table with a default practice code value. This signifies movement to a GP surgery outside of the current HHR catchment area.
4. Last recorded consultation
   When no other dates could be ascertained for a patient I used the last date recorded with a face-to-face consultation.
5. Administration event
   If no face-to-face consultations had taken place I used the last recorded date of any record within the primary care information system (excluding list / population auditing records).

4.2.1.2 Method of identifying people with CKD at start of 2008 (i.e. prevalent cases).

I extracted up to 40 values of eGFR for each person in the study (and the associated test date). Some of the dates that were associated with eGFR values were erroneous (e.g. the year was 1910). This appeared to be for technical reasons in the way that the date was stored in the HHRa, rather than an error occurring in the data extraction process. The total number of cases with erroneous test dates was 592. These tests were discarded because I was unable to verify the correct date associated with the eGFR value. For cases with erroneous tests, any other eGFRs with correct dates were used. I then followed the following procedure to identify prevalent CKD cases (i.e. people with CKD by the start of 2008).

1. Identifying people whose first eGFR was <60ml/min/1.73m^2 by 01/01/2008:

   For each of the possible 40 values, I checked whether it occurred before 01/01/2008, that it was less than 60ml/min/1.73m^2, and that it was not associated with an erroneous test date.

2. Identifying people with an eGFR >60ml/min/1.73m^2 after 2008:

   For each of the possible 40 values, I checked whether it occurred after 01/01/2008, that it was greater than 60ml/min/1.73m^2, and that it was not associated with an erroneous test date.

3. Creating a variable that identified which of the 40 potential eGFRs was <60ml/min/1.73m^2:

   I did this in order to exclude those for whom no eGFR values were under 60ml/min/1.73m^2 in order to check that the population of people included as potential CKD was correct. I also identified for each of the eGFR values individually whether they were under 60ml/min/1.73m^2 or not.

4. Calculating the time difference between eGFRs:

   For each of the gaps, eGFR1 (the first eGFR recorded for an individual) to eGFR2, eGFR2 to eGFR3 etc, I calculated the time difference in days to ensure that I could identify that at least two eGFRs that were less than 60ml/min/1.73m^2.

5. Calculating the time difference between the first eGFR and all others (1-40):

   I calculated the difference in days between the first and subsequent eGFRs.

6. Identifying the baseline prevalent CKD population:

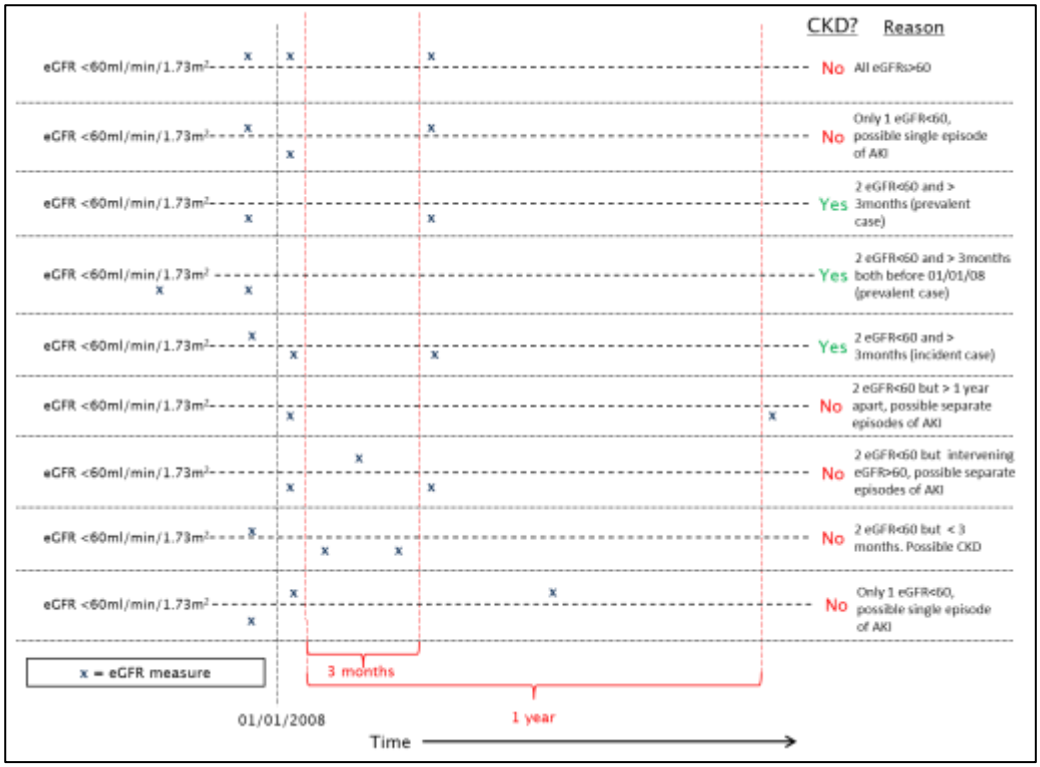
   Using the data defined above, I was then able to identify the prevalent CKD population as follows:

People with CKD at baseline were those who:

- Were still alive at the start of 2008
- Had at least two values of eGFR that were not erroneous
- Had an eGFR1 that was less than 60ml/min/1.73m^2 and occurred before 01/01/2008
- Had a gap between eGFR1 and at least one other that was >90 days (and for non-consecutive values, that there was no intervening eGFR >60ml/min/1.73m^2) and <365 days.

For the incident CKD population, start date in the study was taken as the date of the first eGFR below 60ml/min/1.73m^2 after 2008 (with the same chronicity criteria).

Figure 30. Defining cases of CKD stage 3 – 5 from eGFR patterns



4.2.2 Identifying contributing practices

Due to changes in GP practice information technology systems and/or practice policy, it is possible for practices to change their status over time with regard to submitting data to the HHR. If a practice is inconsistent in submission of data to the HHR over a defined period, it may affect the ability to identify people with eGFR-defined CKD or to reliably identify other variables from the HHRa analytical database.

In addition, at the time of this study, the HHR was receiving pathology data only from two hospital laboratories: University Hospital Southampton and Portsmouth Hospitals. Therefore, practices submitting data to the HHR that do not send all pathology specimens to one of these hospitals would have incomplete data with regard to the pathology results needed for this study. Therefore, in order to reliably derive a population of people with CKD from eGFR results (and be able to identify a denominator population), the method for identifying GP practices needed to meet the following criteria:

1. Submitting practice data to the HHR for the entire study period (2008-2013)
2. Sending all pathology requests to either University Hospital Southampton or Portsmouth Hospitals laboratories for the entire study period.

If practices met these criteria, I could be confident of being able to access to all relevant biochemistry results and routine clinical records for the study period. The denominator population of people aged over 18 from each practice could also be calculated.

The following methods were therefore used:

GP Practice submission of data to the HHR was analysed by year.

- Any practice not submitting data for the entire study period was excluded.
- Any practice not submitting sufficient quantity of records per registered patient was excluded. 'Insufficient quantity' was defined by: a practice with recording level below the lower quartile minus 1.5 times the inter-quartile range of all practices with records in the HHRa. This method was derived from standard methods to identify outliers in boxplots. [283]
- Any practice displaying an abnormal decline in quantity of records per registered patient during the study period was also excluded (again

using the lower quartile minus 1.5 times the inter-quartile range for all practices with records in the HHRa as the lower limit cut off).

It was expected that there would be a drop in the number of submitting practices during the study period due to a change in practice system to EMIS WEB which is not able to submit records to the HHR.

Practices were then identified in which I could be confident that all pathology requests were sent to the relevant hospitals for the entire study period (these were either practices that were within Southampton or Portsmouth city, and / or in which I could demonstrate consistent levels of pathology reporting in the HHR and consistent practice data submission to the HHR during the study period and for one year either side, i.e. 2007-2012). This was achieved as follows:

- Any practice that did not have pathology record data for the entire study period was excluded.

- Any practice with insufficient pathology records per registered patient during the study period was excluded.

- To define the threshold for the level of expected pathology recording, practices within Southampton and Portsmouth Cities Primary Care Trust (PCT) areas (in which I could have a high degree of confidence that all pathology requests would have been analysed at one of these two hospitals) were used. The level of pathology recording was then applied to all surgeries and those not meeting the threshold across the entire study period were excluded. I recognised that this precision of definition improves the internal validity of this study, but may limit the generalisability of findings to all practices.

4.2.2.1 Laboratory confirmation of assay method

I confirmed with consultant biochemists from both Portsmouth and Southampton laboratories that they used standardised Jaffe's assay method for creatinine measurement, and that the method had not changed throughout the study period. I also confirmed that eGFR was calculated using the simplified MDRD equation for estimating eGFR, and creatinine assays with calibration traceable to a standard reference material (IDMS).[284 285]

4.2.3 Identifying variables to extract

A list of Read codes was drawn up to identify the variables needed from the GP data section of the HHRa. These were identified from standard Read code hierarchy lists.[286] These included all codes related to CKD, comorbidities such as diabetes and CVD, behavioural factors such as smoking, prescribing codes and test information (eGFR, uACR, lipids, HbA1c etc). A list of codes extracted is given in Appendix 7.4.

4.2.4 Calculating time spent in the study

It was perceived that, although many people would stay registered with the same GP surgery for the entire study period, there would also be movement between surgeries (both within and out of the HHR catchment area). It was also recognised that there would be potential for loss of data in the gaps between periods of registration (for example if a person had moved to a different part of the country for a period of time and then moved back to one of the study practices). On the other hand, many people would stay registered with a single practice but have no medical activity for prolonged periods of time. In routine data, there is a lack of specific reliable Read code (or other measure) for 'registration' and 'de-registration' with a surgery, and methods were needed to account for this (as described in section 4.2.1.1 above). In addition, some people have time registered at more than one surgery (either because of delay in transfer of records, failure of a practice to de-register a patient when they have moved ('ghosts'), or dual-registration by patients). Given these complexities, it would be possible to inaccurately estimate time spent in the study either by under-estimation (i.e. by excluding all time spent between surgery registration periods, when people may in fact have still been registered

but had no clinical activity) or by over estimation (i.e. by including all time registered in any practice, when there may be duplication of time).

In order to maximise the observable time in the study, registration with up to 10 practices (about 2 practices per year of observation) was considered a reasonable maximum after some exploratory work within the HHR which demonstrated only very small numbers of people registering with more than 8 practices in the time period of interest.

Time in the study was then calculated as:

1. Time from 01/01/2008 to death for those who died during the study period

2. Time from 01/01/2008 to 16/05/2013 for those registered with only one practice for the entire period of follow up.

3. Time from 01/01/2008 to the end of the time spent with the last practice with which an individual was registered for those registered in more than one practice (avoiding overlap between practice times by calculating time in days from the end date of practice n to the end date of practice n+1 for each practice registered). Time of leaving practices was identified as described in section 4.2.1.1.2 above.

In the incident cohort, time in the study was calculated from the first date of eGFR below 60ml/min/1.73m^2.

4.2.5 Defining baseline eGFR and uACR in the CKD cohort

In order to identify a value of eGFR as close to the baseline (01/01/2008) as possible, up to 40 eGFR values were extracted for each person with their associated test date. The closest eGFR values before and after 01/01/2008 were identified. The time difference (in days) was calculated between the dates of these tests and 01/01/2008. Baseline eGFR was then taken as the eGFR value closest to 01/01/2008 (either before or after). A similar method was used to identify uACR (up to 20 values recorded). However, due to very low numbers of people with uACR values prior to 01/01/2008, the mean of any uACR values recorded prior to this date was used as the baseline uACR.
In the incident cohort, the first eGFR <60ml/min/1.73m^2 was used as the baseline, and the date of that first eGFR<60ml/min/1.73m^2 was used as the date of study entry. uACR in the incident cohort was identified as the first

uACR occurring after the first eGFR <60ml/min/1.73m^2 (used to define study entry).

4.2.6 Defining variables

For the prevalent CKD cohort, age was defined as age at 01/01/2008. SES was assessed using England rank of IMD grouped into quintiles (1=most deprived, 5=least deprived) and recorded as a single entry when the data was extracted (i.e. it was not possible to identify changes in IMD across the study period as IMD rank is not recorded for historical addresses in the HHRa). Mortality was defined from death being recorded in the GP or hospital record. Hypertension, diabetes and CVD were defined by having a record (Read code) of the diagnosis in the GP record. For the prevalent cohort, those with the first record of any of these diagnoses occurring before 2008 were identified in order to define baseline comorbidity status. Diabetes included all Type 1 and Type 2 diabetic codes. CVD was defined by the presence of any Read code that included at least one of: cerebral infarct, cerebral thrombosis, ischaemic heart disease (angina or myocardial infarction), heart failure, hypertensive heart disease, intracerebral haemorrhage, stroke, transient ischemic attack and peripheral vascular disease. Smoking was defined as having a history of current or previous smoking in the GP record. Due to a large amount of missing data, it was not possible to precisely identify all smoker or non-smokers (as distinct from people with no record of smoking). For the prevalent CKD cohort, baseline eGFR was defined as the closest eGFR to the start of the study (01/01/2008). For the incident CKD cohort, baseline eGFR was the first eGFR <60ml/min/1.73m^2 occurring in the study period. This also defined the point of study entry in the incident cohort (see section 4.2.5). Microalbuminuria was defined as uACR ≥2.5mg/mmol in men ≥3.5 mg/mmol in women, macroalbuminuria as ≥30mg/mmol in either sex. Type of hospital admission was defined from the relevant hospital coding within the HHRa and classified as 'emergency' or 'routine'. AKI was defined from hospital admission coding of 'acute renal failure' (ICD10 code N17).

It was anticipated that there would be missing data for BMI. For the prevalent CKD cohort, BMI at baseline was defined as a BMI measured within a year of the baseline date. Imputation of BMI was not attempted. BMI categories were

defined according to NICE Obesity guidance: healthy weight (18.5–24.9kg/m^2), overweight (25–29.9 kg/m^2), obese (≥30 kg/m^2).[232]

Incident RRT was defined as presence of new record of dialysis or renal transplant (GP coding or International Classification of Diseases 10th Revision (ICD10) diagnosis code Z99.2 'Dependence on renal dialysis' ICD10 diagnosis code Z94 'Kidney transplant status'). Incident CVD was defined as a new record (GP Read coding) of any of the following: cerebral infarct, cerebral thrombosis, ischaemic heart disease (angina or myocardial infarction), heart failure, hypertensive heart disease, intracerebral haemorrhage, stroke, transient ischemic attack and peripheral vascular disease. Cause of death was not reliably available in the HHR (unless an individual died in hospital), and it was therefore not possible to identify all incident CVD.

AKI was identified by examining up to 15 hospital admissions per case, each with a primary diagnostic code (cause of admission) and up to five further diagnosis codes. Occurrence of the ICD10 code N17 ('Acute kidney failure', used by the CKDPC to identify AKI) was identified in either the primary diagnostic code or any of the subsequent codes for any admission.

QOF CKD status was identified using the relevant Read codes for CKD stage 3 – 5 as indicated in section 4.2.3 above.

Information about medication prescription was obtained for renin angiotensin aldosterone system inhibitors (RAASi) from the GP records within the HHRa.

Statistical analyses

Descriptive statistics:

- Characteristics of the cohorts:
    - Sociodemographic characteristics of the entire population from which the CKD population was drawn.
    - Sociodemographic and clinical variables in the prevalent and incident cohorts.
- Outcomes: Mortality, incident RRT, AKI

    - Numbers and characteristics of people in the prevalent CKD cohort who died, required RRT or developed AKI in the study period.
    - Numbers and characteristics of people who had a GP recorded diagnosis of new CVD or experienced an emergency hospital admission in the study period.
- Processes: QOF CKD recording, uACR testing, RAASi prescription.
    - Characteristics of people in the prevalent CKD cohort with and without QOF CKD recording, uACR testing and RAASi prescription.

Subsequent analysis:

- Processes

Univariate and multivariate binary logistic regression was used to identify the associations of QOF CKD stage 3 – 5 registration and uACR measurement at baseline in the prevalent cohort. Poisson regression analysis was used to identify risk of QOF CKD stage 3 – 5 registration and uACR measurement in the incident cohort. Logistic regression was also used to explore associations of QOF exception reporting in the incident cohort.

Outcomes

Univariate and multivariable Cox regression analysis was used to analyse survival in the prevalent CKD cohort by sociodemographic and clinical variables. Poisson regression analysis was used to identify risk of incident RRT and AKI.

BMI and smoking were not included in final multivariable models (given the high proportion of missing data). Models exploring their effect were constructed and the results presented where relevant.

Cases were censored:

- At death if they died during the follow up period
- If they 'left' the study (i.e. at date of leaving last included practice)
- At the end of the follow up period (16/05/2013)

P values of 0.05 or less were considered statistically significant. In regression analyses, variables with p values of <=0.1 on univariate analysis were included in the multivariable models.

Interactions were examined in regression models where literature evidence or clinical knowledge suggested effect modification may occur (details explained in results in the appropriate section).

IBM SPSS statistics for Windows version 19 was used for most of the descriptive statistics and for the logistic regression. StataCorp STATA version 12.1 as used to conduct the Poisson analyses.

4.3 Results

The results will be presented in the following order:

4.3.1: Identification and characteristics of the study populations

4.3.2: Process measures:

- QOF CKD registration
- uACR measurement
- RAASi prescribing

4.3.3: Outcome measures:

- Mortality and survival analysis
- Incident RRT
- Incident AKI

4.3.1 Identification and characteristics of the study populations

4.3.1.1 Practice selection

Using the methods described above, I identified 88 practices that met the criteria for inclusion. Figure 31 is a flow chart of the practice identification process and Figure 32 is a flow chart of the cohort populations.

Figure 31. Flow chart of practice identification in the HHRa

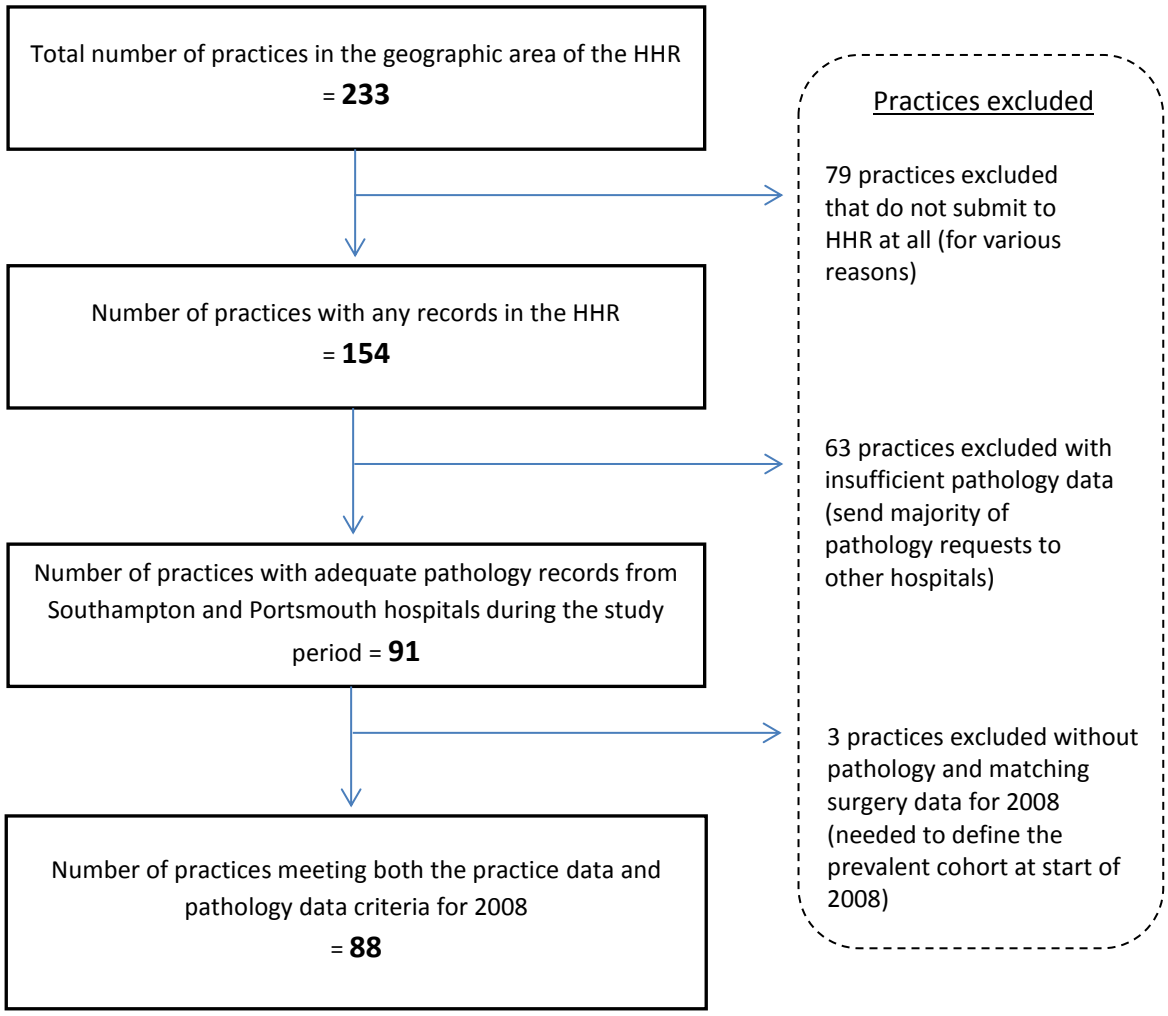
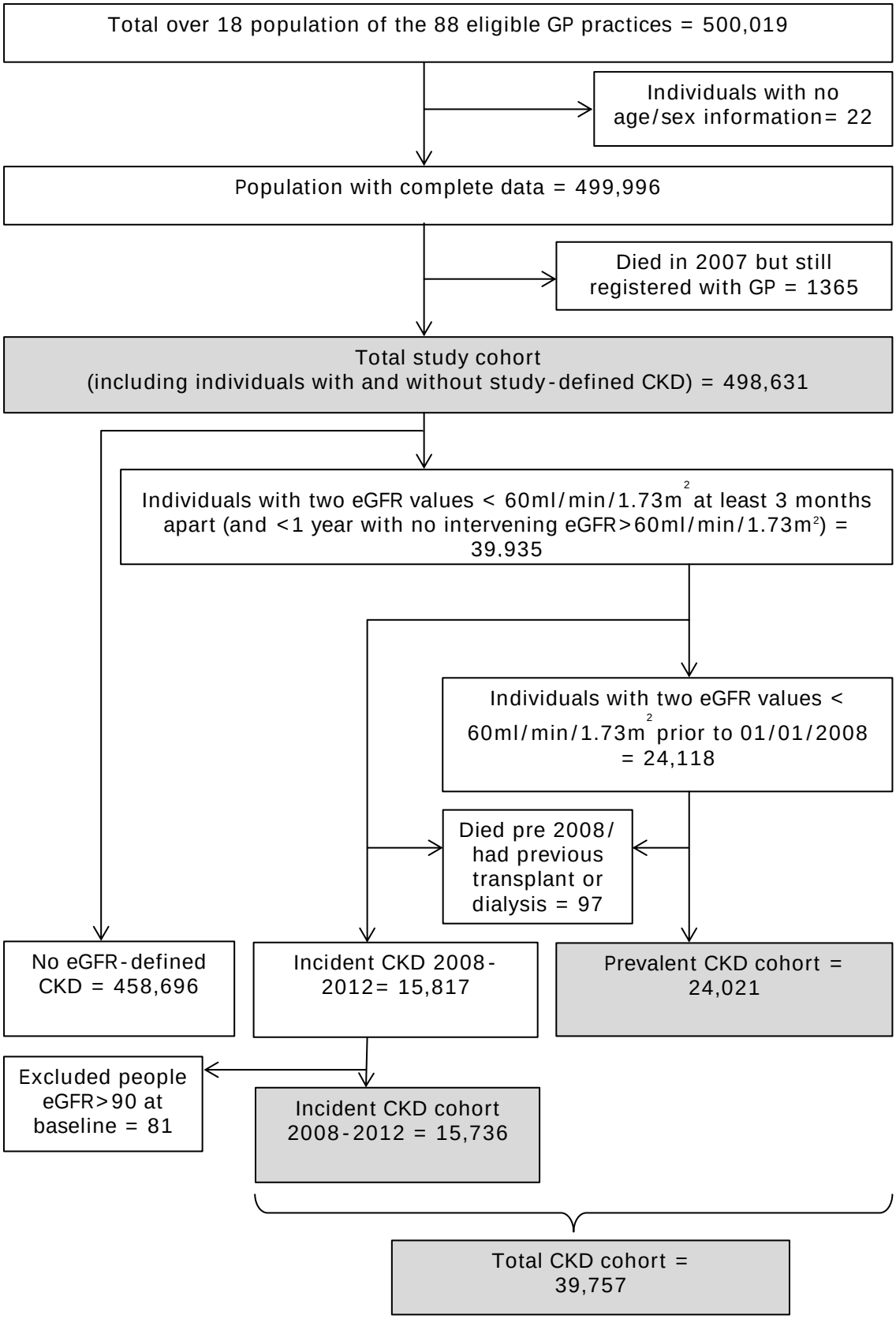


Figure 32. Flow chart of the HHRa CKD study population identification



4.3.1.2 Characteristics of the study population

The total population of people (over 18) from the 88 practices was 499,996 (244,852 male, 255,144 female). Of that population, 39,935 had study-defined CKD and 460,061 did not.

A single main cohort (n=498,631) was extracted from the 88 practices that met the inclusion criteria. This main cohort consisted of all people over 18 registered at the practices during the study period (2008-2013), and therefore included people with and without CKD.Study criteria were applied to this cohort to identify the cohort of people with CKD based on eGFR values ('study-defined CKD').. See Figure 32. Of those with study defined CKD (n=39,935), 24,118 were prevalent cases (i.e. CKD already present at 01/01/2008) and 15,817 were incident cases (new CKD occurring during the follow up period). Of the prevalent cases, 97 had died just prior to the study period, or had had previous dialysis or transplant, leaving 24,021 people with CKD as the prevalent cohort.

For those with prevalent CKD, the mean time spent in the study was 1658 days (SD 526, median 1962, interquartile range 456 days)
For those alive at the end of the study the mean was 1885 days (median 1962 days) , and for those who died during the study it was 1022 days (median 1058 days). Total person years at risk for the prevalent cohort was 109,469, and for the incident cohort 63,832.

378,701 (76%) people in the total cohort stayed registered in a single GP practice for the entire study period. In the prevalent CKD cohort 15,759 (65.6%) stayed in a single practice.

4.3.1.3 Missing data

Ethnicity

Data from the 2011 census showed that the populations of Southampton, Portsmouth and Hampshire were predominantly White, with Asian/Asian British as the next largest ethnic group (Table 36).[287]

Table 36. Proportion of the population in the main ethnic groups in the 2011 census.

	Southampton	Portsmouth	Hampshire
White	85.9%	88.3%	96.0%
Asian / Asian British	8.4%	6.1%	2.0%
Black / African/Caribbean / Black British	2.2%	1.8%	0.4%
Mixed / multiple ethnic groups	2.4%	2.7%	1.3%
Other ethnic group	1.2%	1.0%	0.3%

Furthermore, a recent study using HHRa data in a population of people with diabetes identified that ethnicity was recorded in less than 40% in primary care databases. Of those with any recording of ethnicity, 93% were 'White British', 3.8% were 'Asian' and 0,75% were 'Black'.[288]
While it is recognised that ethnicity is an important factor in CKD, it was not felt that the ethnicity data available in the HHR was robust enough to include in these analyses.

BMI
In the baseline prevalent CKD cohort, 22,379 (93.2%) had a record of ever having had a BMI measured. 12,835 (53.9%) had a record of a BMI value being measured within a year of 01/01/2008. It was not possible to accurately classify appropriate BMI measures for people in the whole study population or in the incident cohort.

Smoking
In the whole study population, 175,305 (35.2%) had a record of ever smoking. In the prevalent CKD cohort, 7656 (31.9%) had a record of ever smoking before 2008. However, among the people with a record of smoking, it was not possible to distinguish between current smokers and ex-smokers. Among people without smoking status recorded, it was not possible to distinguish

never smokers from smoking record not recorded. A variable for 'current smoker' was calculated if the first record of smoking was before 2008 and the last record of smoking was after 2008. This resulted in 6136 (25.5%) of the baseline CKD cohort being current smokers. However, this is likely to be inaccurate as the dates may have been widely spread and it does not account for periods of smoking cessation. In view of the large amount of missing smoking data, it was not included in final multivariable models.

uACR

In the prevalent CKD cohort, 20,127 (83.8%) had no record of a uACR being measured prior to 2008. While this is an important finding in itself, it means that these analyses were unable to reliably adjust for baseline uACR.

Key characteristics of the entire over 18 population of the 88 included practices are shown in Table 37 and for the prevalent CKD cohort are shown in Table 38. People with CKD (both incident and prevalent cases) are compared with those without for descriptive purposes (subsequent analyses separate incident and prevalent CKD). In the total study population, people without CKD were younger (69% were under 60) than those with CKD. In common with the national population distribution in the 2011 Census, there were more females in older age groups.[287] The age sex distribution of the total cohort is shown in Figure 33.

10.7% of the total study population was in the lowest quintile of IMD, and 31.4% was in the highest quintile.

The majority of people (85.1%) in the prevalent CKD cohort had a baseline eGFR in the range 30-59, i.e. CKD stage 3. This proportion was slightly higher but similar in the incident CKD cohort (87.2%).

Figure 33. Age / sex distribution of the total HHRa cohort (n=498,631)

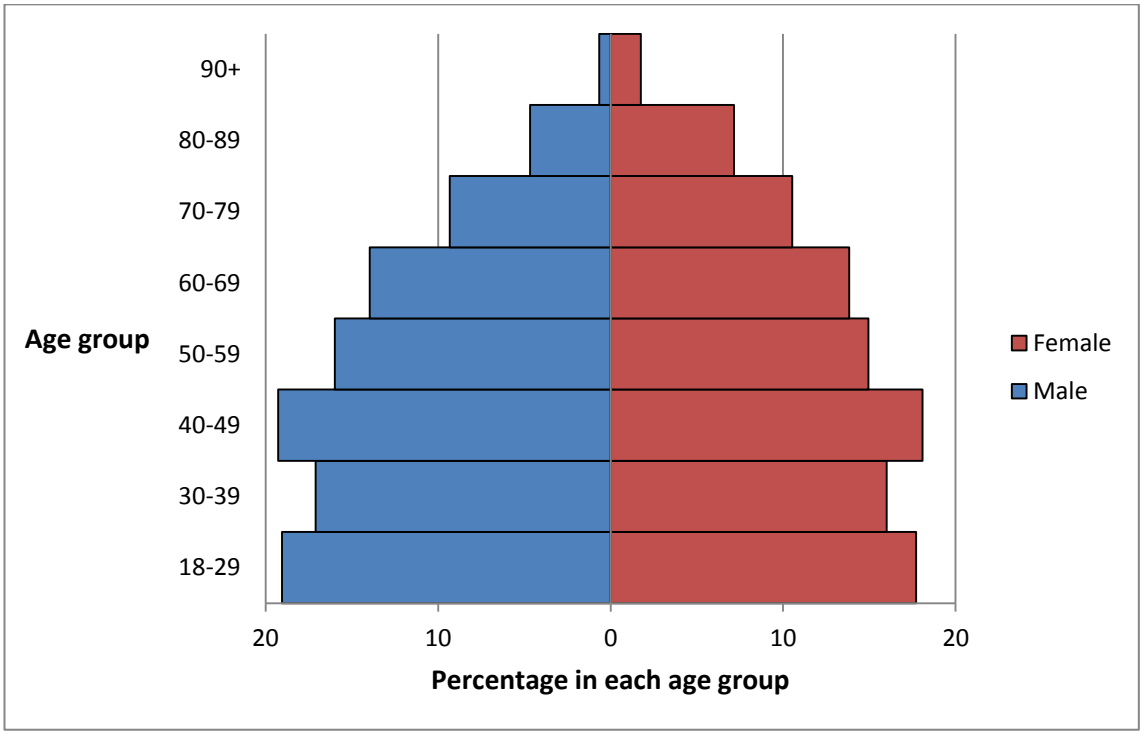


Table 37. Characteristics of the complete cohort

Variable	Category	People with study-defined CKD (incident and prevalent combined)		People without study-defined CKD		Total	
		(n=39,867)		(n=458,764)		(n=498,631)	
		n	%	n	%	n	%
Age at 01/01/2008	18-29	88	0.2	91,432	19.9	91,520	18.4
	30-39	218	0.5	82,243	17.9	82,461	16.5
	40-49	834	2.1	92,229	20.1	93,063	18.7
	50-59	2,249	5.6	74,809	16.3	77,058	15.5
	60-69	6,787	17.0	62,548	13.6	69,335	13.9
	70-79	13,454	33.7	36,071	7.9	49,525	9.9
	80-89	13,355	33.5	16,240	3.5	29,595	5.9
	90+	2,882	7.2	3,192	0.7	6,074	1.2
Sex	M	16,286	40.9	227,917	49.7	244,203	49.0
	F	23,581	59.1	230,847	50.3	254,428	51.0
IMD quintile	1 (most deprived)	3,786	9.5	49,606	10.8	53,392	10.7
	2	5,459	13.7	68,485	14.9	73,944	14.8
	3	8,375	21.0	96,778	21.1	105,153	21.1
	4	9,363	23.5	99,821	21.8	109,184	21.9
	5 (least deprived)	12,850	32.3	143,625	31.3	156,475	31.4
	No record	34	0.1	449	0.1	483	0.1
CKD 3 – 5 QOF registered (GP diagnosed before 2008)	Stage 1 / 2	272	0.7	770	0.2	1,042	0.2
	Stage 3	14,058	35.3	3,484	0.8	17,542	3.5
	Stage 4	1063	2.7	108	0.0	1,171	0.2
	Stage 5	146	0.4	98	0.0	244	0.0
	Exception	650	1.6	179	0.0	829	0.2
	CKD 3- 5	15,077	37.8	3,709	0.8	18,786	3.8
Hypertension	GP diagnosed before 2008	24,900	62.5	62,249	13.6	87,149	17.5

Table 37 cont

Variable	Category	People with study-defined CKD (incident and prevalent combined)		People without study-defined CKD		Total	
		(n=39,867)		(n=458,764)		(n=498,631)	
		n	%	n	%	n	%
Diabetes	GP diagnosed before 2008	7,158	18.0	16,494	3.6	23,652	4.8
CVD *	GP diagnosed before 2008	13,874	34.8	21,139	4.6	35,013	7.0
Smoking	GP record of smoking before 2008	12,923	32.4	162,382	35.4	175,305	35.2
	GP record of smoking but not before 2008	219	0.5	8,522	1.9	8,741	1.8
	No smoking record (missing data)	26,725	67.0	287,860	62.7	314,585	63.1

*CVD includes cerebral infarct, cerebral thrombosis, ischaemic heart disease, heart failure, hypertensive heart disease, intracerebral haemorrhage, stroke, transient ischemic attack, peripheral vascular disease.

Table 38. Characteristics of people in the prevalent CKD cohort (excluding those who had dialysis and transplant prior to 2008)

Variable	Category	Total with CKD (n=24,021)	
		n	% of total
Age at 01/01/ 2008	18-29	40	0.2
	30-39	90	0.4
	40-49	327	1.4
	50-59	1020	4.2
	60-69	3311	13.8
	70-79	7977	33.8
	80-89	9169	38.2
	90+	2087	8.7
Sex	M	9607	40.0
	F	14,414	60.0
IMD quintile	1 (most deprived)	2292	9.5
	2	3229	13.4
	3	5087	21.2
	4	5260	23.4
	5 (least deprived)	7773	32.4
	No record	34	0.1
CKD 3 – 5 QOF registered (GP diagnosed before 2008)	Stage 1 / 2	142	0.6
	Stage 3	12,486	52.0
	Stage 4	1,011	4.2
	Stage 5	100	0.4
	QOF Exception	559	2.3
	CKD 3- 5	13399	55.8
Hypertension	GP diagnosed before 2008	16,504	68.7
Diabetes	GP diagnosed before 2008	4727	19.7
CVD*	GP diagnosed before 2008	9902	41.2
Smoking	GP record of smoking before 2008	7656	31.9
	GP record of smoking but not before 2008	97	0.4
	No GP record of smoking (missing)	16,268	67.7

Table 38 cont

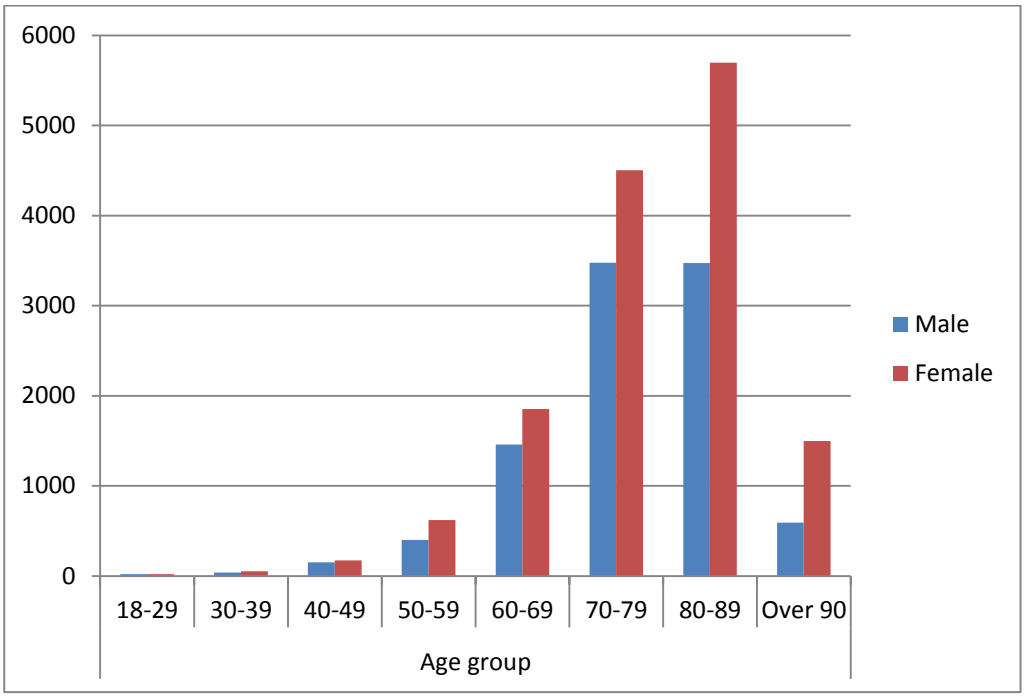
Variable	Category	Total with CKD (n=24,021)	
		n	% of total
BMI at baseline (kg/m^2)	Healthy weight (18.5-24.9)	3713	15.6
	Overweight (25-29.9	4998	21.0
	Obese (≥30)	4124	17.3
	Missing	10,962	46.1
Baseline eGFR ($ml/min/1.73m^2$)	45-59	13,642	56.8
	30-44	6793	28.3
	15-29	1635	6.8
	<15	294	1.2
	>60	1625	6.8

*CVD includes cerebral infarct, cerebral thrombosis, ischaemic heart disease, heart failure, hypertensive heart disease, intracerebral haemorrhage, stroke, transient ischemic attack, peripheral vascular disease.

In the prevalent CKD cohort, there were a greater number (and proportion) of women than men in each ten-year age band. The age / sex distribution of people in the prevalent and incident CKD cohorts is shown in Figure 34. The total CKD cohort (prevalent and incident cases) was older than the non-CKD population in the main cohort with 29,663 people (74.6%) over 70 (compared to 55,503 (12.1%) of the non CKD population). Table 39 shows the distribution of several variables of interest by SES (IMD quintile). A higher proportion of people in the least deprived quintile of IMD were over 80. A higher proportion of people in the most deprived quintile had a history of diabetes, smoking and obesity. Missing smoking data means that the finding of a greater proportion of people smoking in the most deprived quintile of IMD should be interpreted with caution. 16,268 (68%) of people have no smoking data in this cohort.
In the prevalent CKD cohort, 79 (0.3%) had a record of having had dialysis by 01/01/2008, and 36 (0.1%) had a record of kidney transplant.

Figure 34. Age /sex distribution of people in the prevalent and incident CKD cohorts

Prevalent cohort (n=24,021)



Incident cohort (n=15,736)

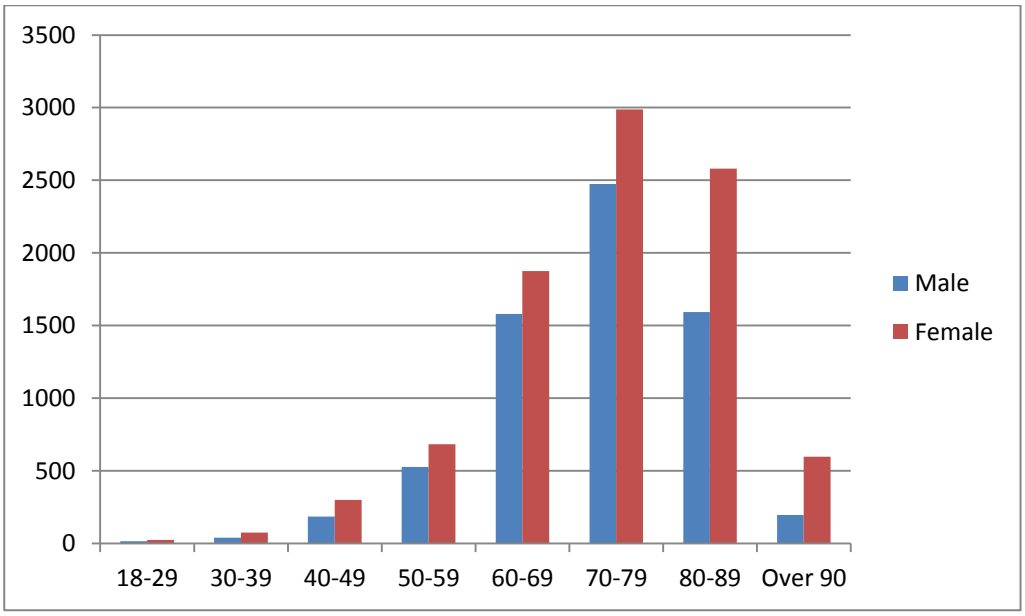


Table 39. Characteristics of people in the prevalent CKD cohort by IMD quintile

IMD Quintile		1 (most deprived)	2	3	4	5	Total
		n (col %)	n (col %)	n (col %)	n (col %)	n (col %)	n (col %)
Male		865 (38)	1195 (37)	1916 (38)	2269 (40)	3357 (43)	9602 (40)
Female		1427(62)	2034 (63)	3171 (62)	3351 (60)	4416 (57)	14,399 (60)
Age group	<50	61 (3)	91 (3)	110 (2)	82 (1)	112 (1)	456 (2)
	50-69	533 (23)	695 (22)	876 (17)	965 (17)	1259 (16)	4328 (18)
	70-79	804 (35)	1036 (32)	1644 (32)	1903 (34)	2582 (33)	7969 (33)
	80+	894 (39)	1407 (44)	2457 (48)	2670 (48)	3820 (49)	11,248 (47)
CKD 3 – 5 QOF registered		1350 (59)	1794 (56)	2780 (55)	3061 (54)	4406 (57)	13,391 (56)
Hypertension		1554 (68)	2184 (68)	3504 (69)	3934 (70)	5313 (68)	16,489 (69)
Diabetes		544 (24)	722 (22)	1015 (20)	1093 (19)	1348 (17)	4722 (20)
CVD		972 (42)	1361 (42)	2085 (41)	2249 (40)	3228 (42)	9895 (41)
History of smoking before 2008		916 (40)	1168 (36)	1581 (31)	1741 (31)	2248 (29)	7654 (32)
BMI (kg/m^2)	18.5-24.9	291 (13)	490 (15)	825 (16)	805 (14)	1300 (17)	3711 (16)
	25-29.9	497 (22)	681 (21)	1002 (20)	1187 (21)	1624 (21)	4991 (21)
	≥30	531 (24)	632 (20)	882 (18)	920 (17)	1157 (15)	4122 (17)
	Missing	936 (42)	1386 (43)	2295 (46)	2644 (48)	3595 (47)	10,856 (45)
Baseline eGFR ($ml/min/1.73m^2$)	45-59	1255 (55)	1797 (56)	2852 (56)	3207 (57)	4518 (58)	13629 (57)
	30-44	623 (27)	970 (30)	1484 (29)	1595 (28)	2115 (27)	6787 (28)
	15-29	168 (8)	231 (7)	340 (7)	356 (6)	540 (7)	1635 (7)
	<15	63 (2)	38 (1)	65 (1)	51 (1)	77 (1)	294 (1)
	>60	179 (8)	185 (6)	341(7)	401 (7)	518 (7)	1624 (7)

Table 40 shows the characteristics of people in the incident CKD cohort (n=15,736), and Table 41 shows the distribution by quintile of IMD. Compared to the prevalent cohort, the incident cohort had a slightly younger age profile, with a smaller proportion of people over 80 years. There was little difference in the distribution of gender or IMD. Similar to the prevalent cohort, a higher proportion of people in the least deprived quintile of IMD were over 80 and a higher proportion of people in the most deprived quintile had a history of diabetes and smoking.

Table 40. Characteristics of people in the incident CKD cohort (n=15,736)

Variable	Category	Incident CKD	
		n	% of total
Age at 01/01/ 2008	18-29	41	0.3
	30-39	117	0.7
	40-49	486	3.1
	50-59	1209	7.7
	60-69	3453	21.9
	70-79	5461	34.7
	80-89	4174	26.5
	90+	795	5.1
Sex	M	6612	42.0
	F	9124	58.0
IMD quintile	1 (most deprived)	1483	9.4
	2	2206	14.0
	3	3266	20.8
	4	3717	23.6
	5 (least deprived)	5050	32.1
	No record	14	0.1
CKD 3 – 5 QOF registered (ever)	Stage 1 / 2	247	1.6
	Stage 3	5661	36.0
	Stage 4	265	1.7
	Stage 5	32	0.2
	QOF Exception	681	4.3
	CKD 3- 5	5876	37.3
Hypertension (ever)	GP diagnosed	9605	61.0
Diabetes (ever)	GP diagnosed	3122	19.8
CVD (ever)	GP diagnosed	5420	34.4
Smoking (ever)	GP record of smoking	5342	33.9
	No GP record of smoking (missing)	10,394	66.1
eGFR at study entry (ml/min/1.73m^2)	≥45	13,614	86.5
	30-44	1594	10.2
	15-29	315	2.0
	<15	126	0.8

Table 41. Characteristics of people in the incident CKD cohort by IMD quintile

IMD Quintile		1 (most deprived)	2	3	4	5	Total
		n (col %)	n (col %)	n (col %)	n (col %)	n (col %)	n (col %)
Male		585 (40)	871 (40)	1363 (42)	1565 (42)	2183 (43)	6567 (40)
Female		888 (60)	1315 (60)	1885 (58)	2134 (58)	2846 (57)	9068 (58)
Age group	<50	116 (8)	102 (5)	138 (4)	133 (4)	139 (3)	628 (4)
	50-69	526 (36)	715 (33)	947 (29)	1047 (28)	1372 (27)	4607 (29)
	70-79	485 (33)	705 (32)	1088 (34)	1323 (36)	1843 (37)	5444 (35)
	80+	346 (23)	664 (30)	1075 (33)	1196 (32)	1675 (33)	4956 (32)
CKD 3 – 5 QOF registered (ever)		555 (38)	832 (38)	1209 (37)	1398 (38)	1858 (37)	5852 (37)
Hypertension (ever)		882 (60)	1331 (61)	1986 (61)	2297 (62)	3051 (61)	9547 (61)
Diabetes (ever)		381 (26)	513 (23)	654 (20)	688 (19)	852 (17)	3088 (20)
CVD (ever)		502 (34)	782 (36)	1121 (35)	1286 (35)	1694 (34)	5385 (34)
History of smoking (ever)		625 (42)	820 (38)	1112 (34)	1193 (32)	1549 (31)	5299 (34)
Baseline eGFR (ml/min/ 1.73m^2)	≥45	1259 (83)	1867 (86)	2793 (86)	3252 (88)	4431 (88)	13,602 (87)
	30-44	155 (11)	247 (11)	353 (11)	368 (10)	470 (9)	1593 (10)
	15-29	26 (2)	52 (2)	80 (2)	60 (2)	97 (2)	315 (2)
	<15	33 (2)	20 (1)	22 (1)	19 (1)	31 (1)	125 (1)

Table 42 shows the age, sex and deprivation characteristics of the incident cohort by year of entry to the study. This shows that greater numbers of people with studydefined CKD were identified in 2008 than any other year and that the numbers added to the cohort fell over time. Table 43 summarises missing data in the prevalent and incident cohorts.

Table 42. Age, sex and deprivation characteristics of the incident CKD cohort by year of study entry

Year of study entry		2008 n (col %)	2009 n (col %)	2010 n (col %)	2011 n (col %)	2012 n (col %)
Sex	Male	3996 (40)	1158 (43)	737 (46)	462 (45)	217 (49)
	Female	5914 (60)	1527 (57)	852 (54)	563 (55)	223 (51)
Age	<50	285 (3)	124 (5)	110 (7)	75 (7)	36 (8)
	50-69	2668 (27)	842 (31)	534 (34)	396 (39)	169 (38)
	70-79	3505 (35)	908 (34)	544 (34)	334 (33)	157 (36)
	80+	3452 (35)	811 (30)	401 (25)	220 (21)	78 (18)
IMD quintile	1 (most deprived)	954 (10)	229 (9)	149 (9)	101 (10)	40 (9)
	2	1361 (14)	375 (14)	242 (15)	146 (14)	62 (14)
	3	2038 (21)	583 (22)	326 (21)	215 (21)	86 (20)
	4	2327 (24)	640 (24)	384 (24)	239 (23)	109 (25)
	5 (least deprived)	3219 (33)	858 (32)	488 (31)	323 (32)	141 (32)
CKD 3 – 5 QOF registered within year		2099 (22)	323 (12)	131 (8)	92 (9)	44 (10)

Table 43. Missing data

	Prevalent cohort		Incident cohort	
	n missing	%	n missing	%
IMD	34	0.1	14	0.1
Smoking	16,327	67.7	10,394	66.1
BMI	10,856	45.2	4976	31.6
uACR	20,127	83.8	8799	56.2

4.3.1.4 Baseline eGFR

In the prevalent CKD cohort, the distribution of baseline eGFRs is shown in Figure 35. The majority (22,364/24,021, 93%) had baseline eGFR <60ml/min/1.73m^2. The mean baseline eGFR value was 46.7 and the median 49.0 ml/min/1.73m^2. The interquartile range was 15 ml/min/1.73m^2 (40-55 ml/min/1.73m^2).

Figure 35. Distribution of baseline eGFR values in the prevalent CKD cohort (excluding people with previous dialysis or kidney transplant)

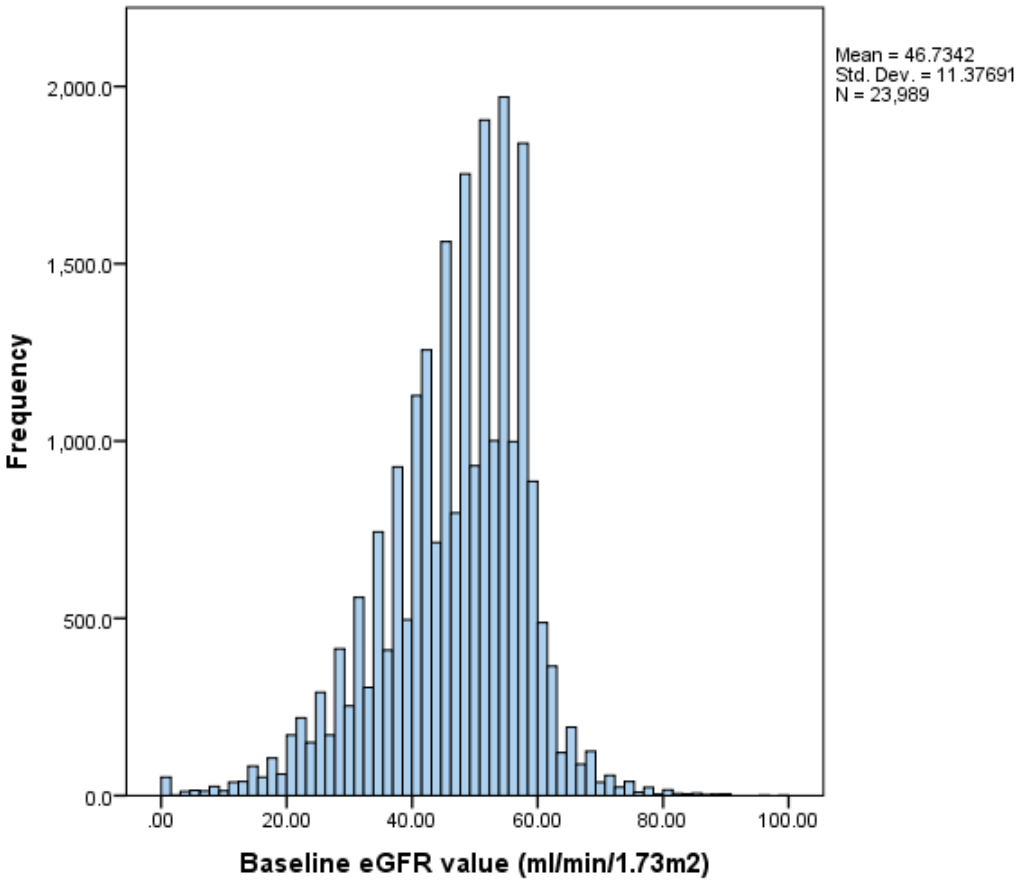


Table 44 shows the number and proportion of people in each CKD category according to their baseline eGFR.

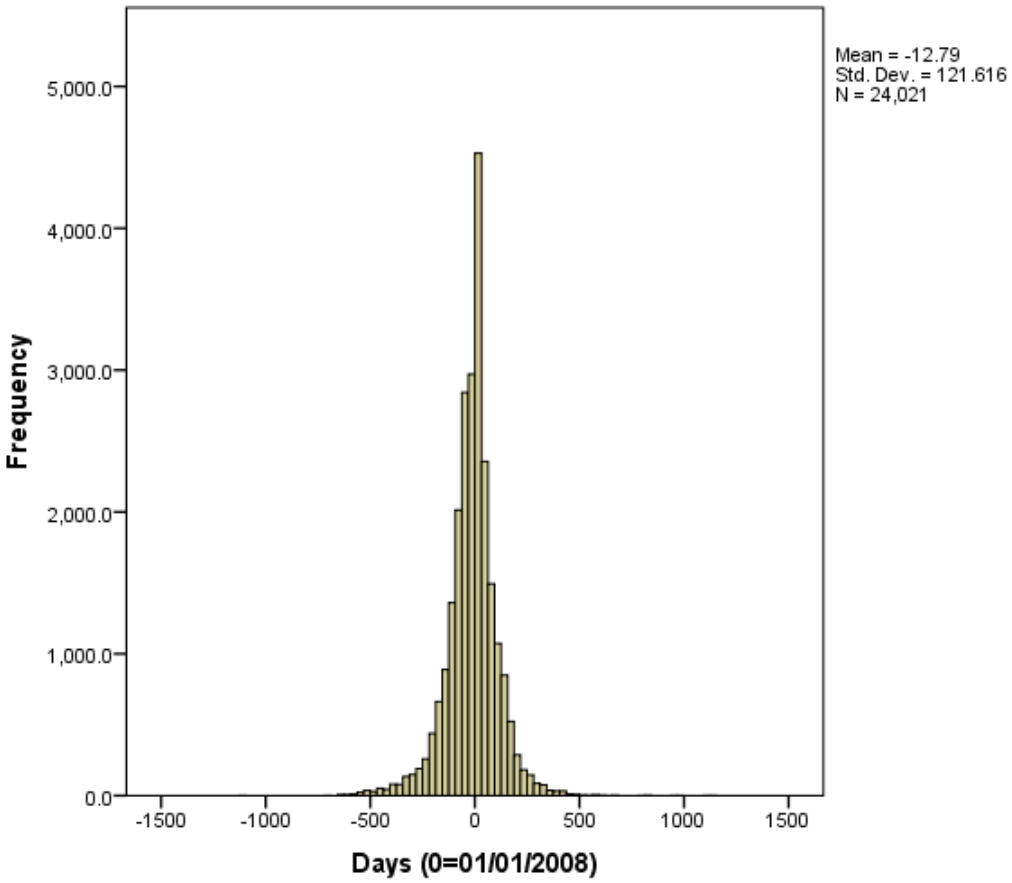
Table 44. Distribution of baseline eGFR values in the prevalent CKD cohort

Baseline eGFR (ml/min/1.73m^2)	Number	Percentage
45-59	13,642	56.8
30-44	6793	28.3
15-29	1635	6.8
<15	294	1.2
>=60	1625	6.8
Missing	32	0.1
Total	24,021	100

This shows that, despite meeting the criteria for study-defined CKD, just under 7% of the population had a baseline eGFR value that was above 60ml/min/1.73m^2 as the closest value to the actual baseline date (01/01/2008). This may reflect variability in eGFR, but it may also reflect the fact that the timing of the baseline eGFR varied considerably from the true baseline in some individuals.

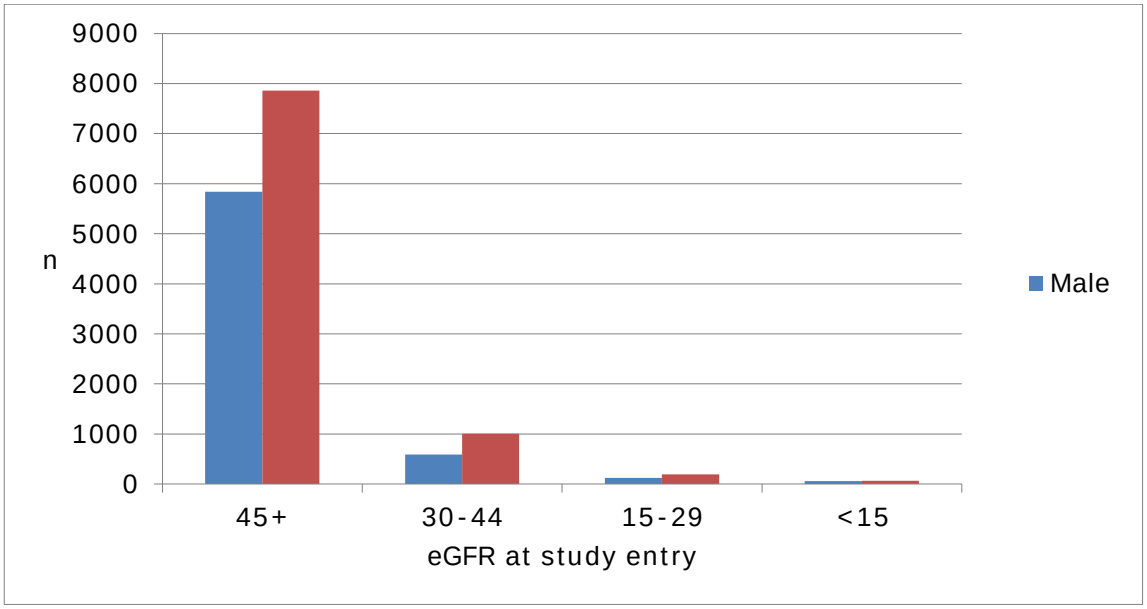
This was explored further by comparing the distribution of the timing of eGFR samples used as the baseline value to the actual baseline date (01/01/2008). This showed a normal distribution with a mean of approximately -13 days (i.e. eGFR result 13 days before baseline), but a standard deviation of 122 days. See Figure 36. This illustrates that, while the majority of eGFRs were quite close to baseline, some were not. This represents a limitation of using routine data such as these.

Figure 36. Distribution of baseline eGFR relative to the true study baseline in the prevalent CKD cohort



In the incident cohort, eGFR at baseline defined the study entry point. The distribution of eGFR at study entry for the incident cohort is shown in Figure 37.

Figure 37. Distribution of eGFR at study entry in the incident cohort.



89 people were excluded from the final incident cohort because none of the eGFRs in the study period were below 60ml/min/1.73m^2.

4.3.2 Process measures

4.3.2.1 QOF CKD registration

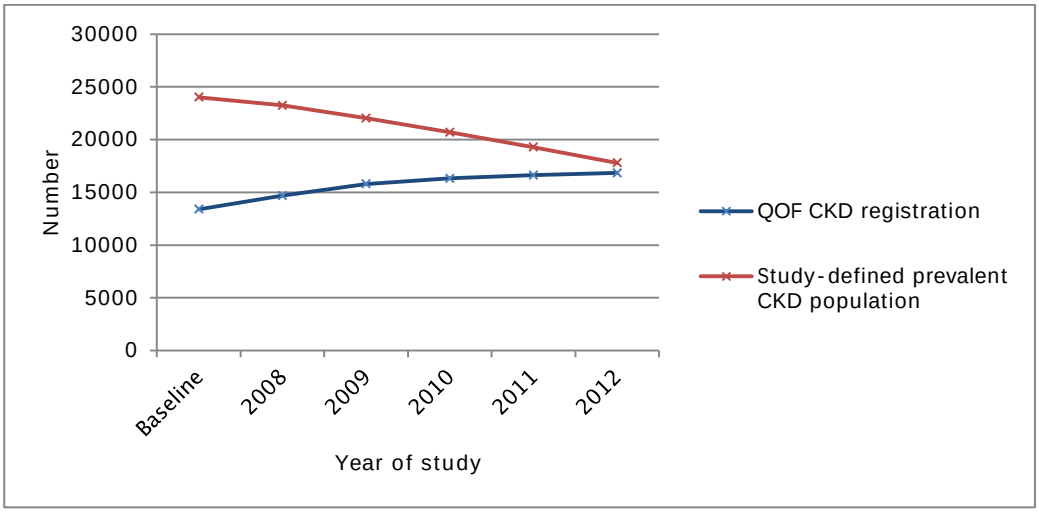
In this section, the terms 'CKD registration' and 'CKD recording' and 'QOF CKD registration' will be used interchangeably to mean a recording of a diagnosis of CKD in the GP record. This recording automatically includes the person on a QOF CKD register in the practice and, as such, registers are defined electronically by searches for appropriate CKD Read codes. QOF CKD registration was introduced in the 2006/07 QOF update.

4.3.2.2 QOF CKD registration in the prevalent cohort

In the prevalent CKD cohort, 13,399 (55.8%) people were registered as having CKD stage 3 – 5 at baseline (at the start of 2008). Descriptive comparison of the characteristics of people with study-defined CKD with and without GP-identified CKD is shown in Table 45. This suggests that a greater proportion of younger people, women, and people without hypertension, diabetes or CVD did not have their CKD either identified or recorded in their GP record. As might be expected, it also suggests that people with higher baseline eGFR were less likely to have a GP record of having CKD. However, a significant proportion of people with much lower eGFRs also did not have a record of CKD (28.1% of all people with a baseline eGFR<30ml/min/1.73m^2).

By the end of 2012, 16,845 (70.1%) of those in the prevalent cohort had been registered as CKD stage 3 – 5 at some point. However, of those registered as having CKD 3 – 5, 4298 died during the study period. The pattern of QOF registration by year allowing for death is shown in Figure 38. This shows that, as the population of people with CKD remaining alive decreased (red line), the proportion registered as CKD for QOF increased (blue line).

Figure 38. Changes in QOF registration status in the prevalent CKD cohort.



The univariate and multivariate odds ratios for QOF CKD registration (by the baseline date) in the prevalent CKD population are shown in Table 46.

The odds ratio of being registered as having CKD was higher in older people compared to younger and higher in men than women, although the association with gender was not maintained on full adjustment. People with hypertension, diabetes, CVD or lower eGFR all had greater odds ratios for QOF CKD registration, and this was maintained in the fully adjusted model.

With regard to SES, a slightly mixed picture was shown by the multivariable model with lower odds ratios of being QOF CKD registered in the 3rd and 4th quintile groups compared to the least deprived and an overall significant test for trend in the fully adjusted model. This suggests that some IMD groups were less likely to be QOF CKD registered, but the strength of association is small and may be explained by unknown confounding (such as variation in uACR).

By the end of 2012, 16,845/24021 (70.1%) had been registered as CKD stage 3 – 5 at some point. Of those registered as having CKD 3 – 5 at some point, 4298 died during the study period.

Table 45. Characteristics of people with and without GP-identified (QOF) CKD in the prevalent CKD cohort

		CKD 3 – 5 QOF registered		CKD not registered		Total
		n	%	n	%	
Age group	<50	209	45.7	248	54.3	457
	50-69	2290	52.9	2041	47.1	4331
	70-79	4543	57.0	3434	43.0	7977
	80+	6357	56.5	4899	43.5	11,256
Sex	M	5494	57.2	4113	42.8	9607
	F	7905	54.8	6509	45.2	14,414
IMD quintiles	1 (most deprived)	1350	58.9	942	41.1	2292
	2	1794	55.6	1435	44.4	3229
	3	2780	54.6	2307	45.4	5087
	4	3061	54.5	2559	45.5	5620
	5	4406	56.7	3367	43.3	7773
Hypertension		9957	60.3	6547	39.7	16,504
No hypertension		3442	45.8	4075	54.2	7517
Diabetes		3133	66.3	1594	33.7	4727
No diabetes		10,266	53.2	9028	46.8	19,294
CVD		6138	62.0	3764	38.0	9902
No CVD		7261	51.4	6858	48.6	14,119
Baseline eGFR (ml/min/1.73m^2)	45-59	6734	49.4	6908	50.6	13,642
	30-44	4537	66.8	2256	33.2	6793
	15-29	1188	72.7	447	27.3	1635
	<15	198	67.3	96	32.7	294
	>=60	721	44.4	904	55.6	1625

Table 46. Associations of QOF CKD registration at baseline in the prevalent cohort

Variable		Univariate		Multivariable+	
		OR (95% CI)	p	OR (95% CI)	p
Age group (vs 18-49)	50-69	1.33 (1.10-1.62	<0.001	1.29 (1.05-1.58	<0.001
	70-79	1.57 (1.30-1.90)		1.31 (1.07-1.60)	
	80+	1.54 (1.28-1.86)		1.16 (0.95-1.41)	
Gender (male vs. female)		1.10 (1.04-1.16)	<0.001	1.04 (0.98-1.10)	0.183
IMD quintiles (vs least deprived)	1 (most deprived)	1.10 (1.00-1.20)	0.001	1.05 (0.95-1.16)	0.001
	2	0.96 (0.88-1.04)		0.91 (0.84-1.00)	
	3	0.92 (0.86-0.99)		0.90 (0.83-0.97)	
	4	0.91 (0.85-0.98)		0.90 (0.83-0.96)	
Hypertension (vs. no hypertension)		1.80 (1.70-1.90)	<0.001	1.72 (1.63-1.82)	<0.001
Diabetes (vs. no diabetes)		1.73 (1.62-1.85)	<0.001	1.53 (1.43-1.64)	<0.001
CVD (vs no CVD)		1.54 (1.46-1.62)	<0.001	1.45 (1.37-1.53)	<0.001
Baseline eGFR (compared to 45-59)	30-44	2.06 (1.94-2.19)	<0.001	1.99 (1.87-2.11)	<0.001
	15-29	2.72 (2.43-3.06)		2.52 (2.24-2.83)	
	<15	2.12 (1.65-2.71)		1.99 (1.55-2.56)	
	>=60	0.82 (0.74-0.91)		0.78 (0.70-0.87)	

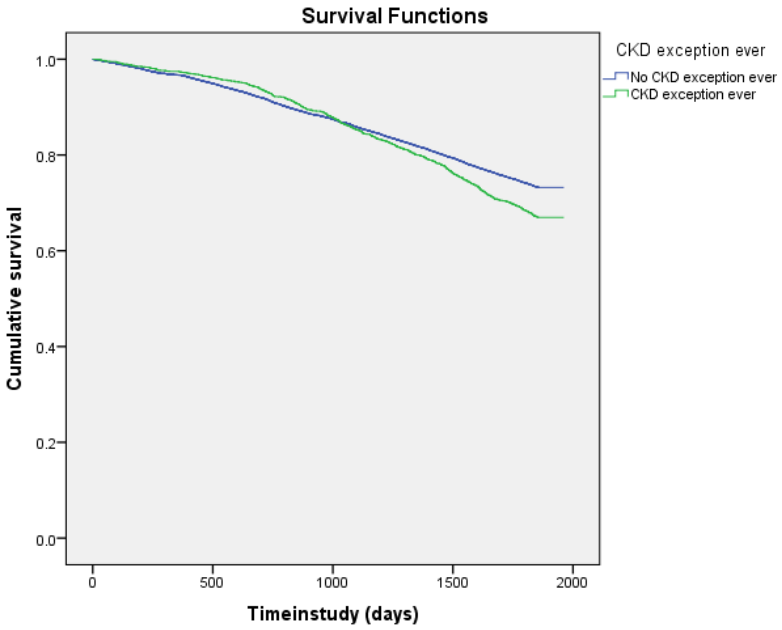
+adjusted for age, sex, IMD, hypertension, diabetes, CVD, and baseline eGFR

There was no evidence of age*sex interaction (p=0.36).

4.3.2.2.1 Exception reporting

As described in section 1.3.1.5, exception reporting is the process of removing people from the denominator and numerator of a QOF indicator for a variety of reasons. In the prevalent cohort, 2271 people had a history of being exception reported at some point for at least one QOF CKD indicator. A Kaplan Meier plot suggests differential survival between those exception reported and those not (Figure 39). However, given that exception reporting is designed to allow for those in whom particular investigations and tests are deemed inappropriate (such as people who are terminally ill), this is perhaps not a surprising finding.

Figure 39. Kaplan Meier plot to compare survival in those with and without a history of exception reporting for CKD QOF indicators



680 people (4.4%) in the incident cohort had a record of being exceptioned for at least one CKD QOF indicator at some point (Table 47). Due to the way that the data were collected (the variables available were: ever exception reported yes/no, first and last exception report dates), I was unable to analyse patterns of exception reporting behaviour by year. On logistic regression in the incident cohort, with exception reporting as a binary outcome, greater likelihood of exception reporting was seen in older age groups, the least deprived quintile of IMD, people with hypertension or CVD, and people with eGFR (at study entry) between 15 and 44ml/min/1.73m^2 (Table 48).

Table 47. Characteristics of people exception reported / not exception reported for at least one of the CKD QOF indicators

		Exception reported at some point		Never exception reported		Row total
		n	Row %	n	Row %	
Sex	Male	275	4.2	6295	95.8	6570
	Female	405	4.5	8674	95.5	9079
Age group	<50	8	1.3	622	98.7	630
	50-69	91	2.0	4518	98.0	4609
	70-79	238	4.4	5210	95.6	5448
	80+	343	6.9	4619	93.1	4962
IMD quintiles	1 (most deprived)	37	2.5	1436	97.5	1473
	2	51	2.3	2135	97.7	2186
	3	147	4.5	3101	95.5	3248
	4	182	4.9	3517	95.1	3699
	5	263	5.2	4766	94.8	5029
Hypertension		483	5.1	9071	94.9	9554
Diabetes		126	4.1	2965	95.9	3091
CVD		315	5.8	5077	94.2	5392
Smoking before 2008		224	4.2	5081	95.8	5305
Baseline eGFR (ml/min/1.73m^2)	45+	541	4.0	13,073	96.0	13,614
	30-44	111	7.0	1483	93.0	1594
	15-29	24	7.6	291	92.4	315
	<15	4	3.2	122	96.8	126

Table 48. Predictors of exception reporting in the incident CKD cohort

Variable		Univariate		Multivariable+	
		OR (95% CI)	p	OR (95% CI)	P
Age group (vs <70)	70-79	2.37 (1.87-3.01)	<0.001	1.31 (1.07-1.60)	<0.001
	80+	3.86 (3.07-4.84)		1.16 (0.95-1.41)	
Gender (male vs. female)		0.94 (0.80-1.09)	0.405	0.98 (0.84-1.15)	0.834
IMD quintiles (vs least deprived)	1 (most deprived)	0.47 (0.33-0.66)	<0.001	0.53 (0.37-0.75)	<0.001
	2	0.43 (0.31-0.59)		0.44 (0.33-0.60)	
	3	0.86 (0.70-1.06)		0.86 (0.69-1.05)	
	4	0.94 (0.77-1.14)		0.94 (0.77-1.14)	
Hypertension (vs. no hypertension)		1.59 (1.35-1.89)	<0.001	1.48 (1.25-1.76)	<0.001
Diabetes (vs. no diabetes)		0.92 (0.76-1.12)	0.413		
CVD (vs no CVD)		1.68 (1.44-1.96)	<0.001	1.43 (1.22-1.68)	<0.001
Baseline eGFR (compared to 45-59)	30-44	1.72 (1.39-2.12)	<0.001	1.54 (1.24-1.91)	<0.001
	15-29	1.89 (1.23-2.89)		1.75 (1.13-2.69)	
	<15	0.75 (0.28-2.04)		1.00 (0.37-2.75)	

+adjusted for age, sex, IMD, hypertension, CVD, and baseline eGFR

4.3.2.3 Cumulative QOF CKD registration in the incident cohort

Registration of CKD status for QOF was calculated for each year of the study (2008-2012) in the incident cohort. If the individual had not died or left the study in subsequent years, they would continue to be registered for QOF and were therefore considered as such. QOF registration by year can therefore be understood as cumulative registration status.

Figure 40 shows that cumulative QOF registration increased over the period of the study. However, even in 2012, only just over 35% of people with study-defined CKD had a CKD code recorded in the GP record. Figure 41 shows the proportion of people with new study defined CKD in each year who were registered as CKD for QOF within a year of the first low eGFR. This shows that, although there was a slight increase in 2009, only a small proportion of people are registered as having CKD within a year of having their first low eGFR.

Figure 40. Cumulative registration of CKD for QOF in the incident cohort

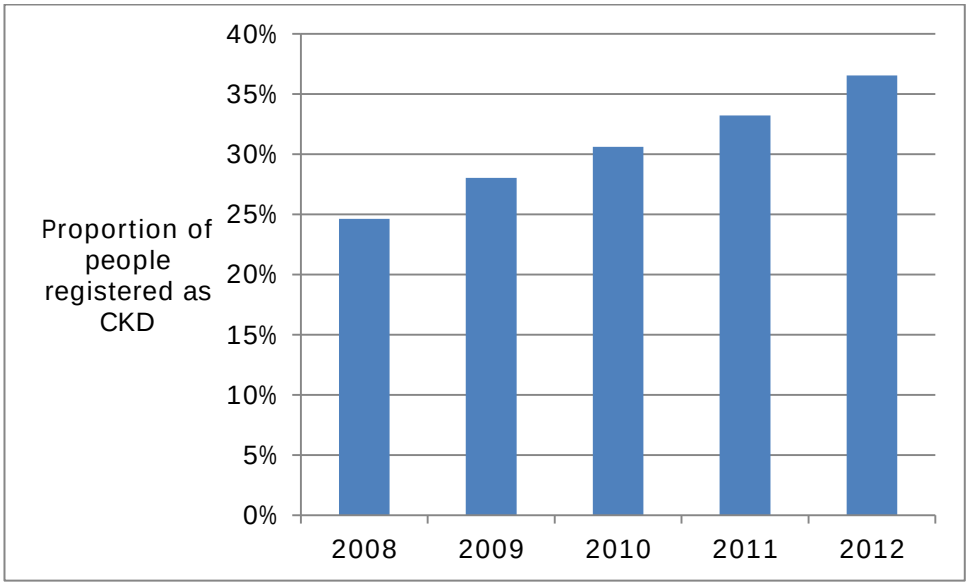
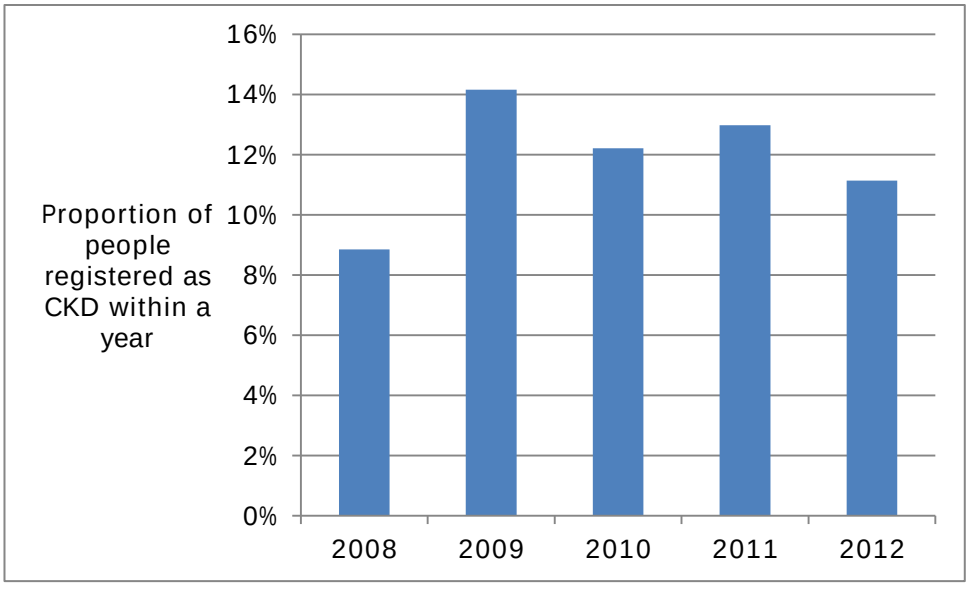
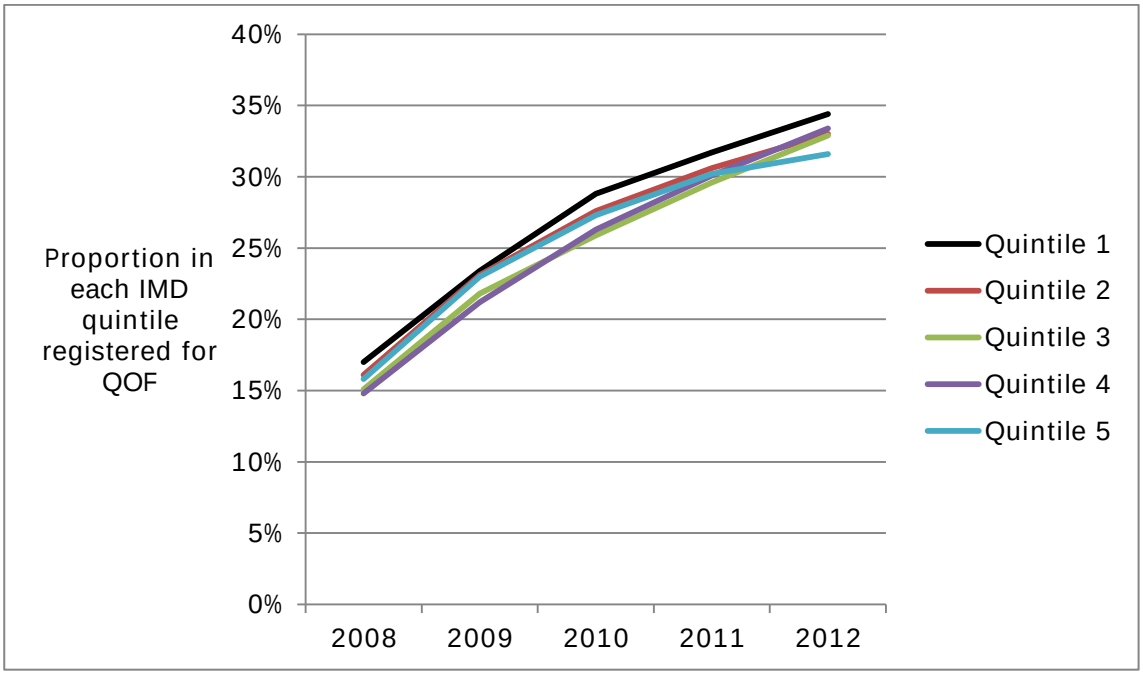


Figure 41. Registration of CKD for QOF within a year of first low eGFR in the incident cohort



Examination of the change in QOF registration status by deprivation status identified an increase in QOF CKD registration in all quintiles of IMD during the study period. There was no evidence of a changing inequality gap over time (Figure 42).QOF CKD registration tended to be higher in lower IMD quintiles.

Figure 42. Change in QOF CKD registration status by IMD quintile in the incident cohort over time.



4.3.2.4 uACR measurement

In the total CKD cohort (both prevalent and incident cases), 22,137 / 39,757 (55.7%) had a record of a uACR ever being recorded. In the prevalent cohort, 14,875/24,021 (61.9%) had a record of ever having a uACR. However, only 3894 (16.2%) of this group had had a uACR measured by the start of the cohort period, the remaining uACRs were taken during the follow up period.
20,127 (83.8%) had no uACR value at baseline, 2266 (9.4%) had had uACR measured and did not have any albuminuria, 1384 (5.8%) had microalbuminuria, and 244 (1%) had macroalbuminuria.
In view of the small proportion of people with uACR values prior to 2008, baseline uACR was considered as the mean of uACRs prior to 2008 for people with any uACR values. The distribution of baseline uACR was positively-skewed (Figure 43). Mean baseline uACR was 9.2, median 2.6, (interquartile range 1.7-5.4) mg/mmol.
A comparison of the characteristics of those with and without a measure of uACR at baseline is shown in Table 49. This shows that, while the great majority of people tested for uACR prior to 2008 had diabetes, not all people with diabetes had been tested. The results of binary logistic regression examining the odds ratios of having a measure of uACR at baseline is shown in Table 50. This clearly demonstrates a strong association between diabetes and likelihood of uACR being measured, with associations also seen with males, people registered as having CKD for QOF, and lower eGFR on multivariable analysis.

Figure 43. Distribution of baseline log uACR in the prevalent CKD cohort

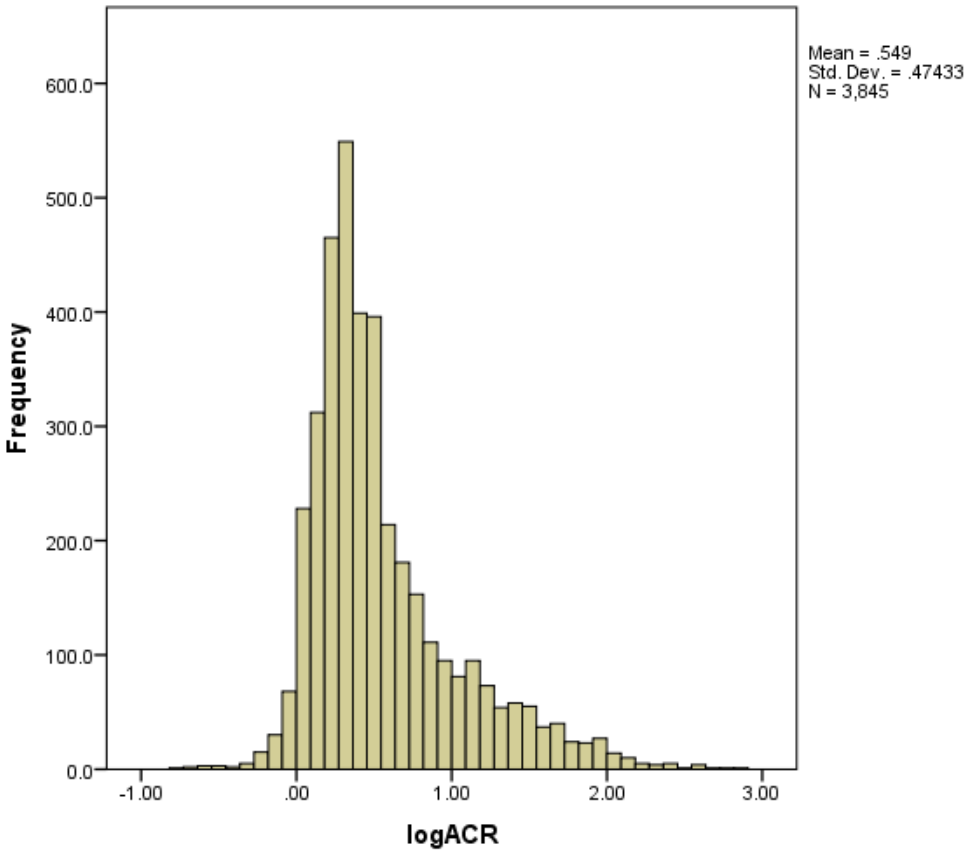


Table 49. Comparison of the characteristics of people in the prevalent CKD cohort with and without a measure of uACR at baseline.

		uACR measured		uACR not measured		Total
		n	Row %	n	Row %	
Sex	Male	1790	18.6	7817	81.4	9607
	Female	2104	14.6	12,310	85.4	14,414
Age	<70	853	17.8	3935	82.2	4788
	70-79	1562	19.6	6415	80.4	7977
	80+	1479	13.1	9777	86.9	11,256
IMD quintile	1 (most deprived)	430	18.8	1862	81.2	2292
	2	557	17.2	2672	82.8	3229
	3	815	16.0	4272	84.0	5087
	4	920	16.4	4700	83.6	5620
	5	1169	15.0	6604	85.0	7773
Hypertension	Yes	2979	18.1	13,525	81.9	16,504
	No	915	12.2	6602	87.8	7517
Diabetes	Yes	3340	70.7	1387	29.3	4727
	No	554	2.9	18,740	97.1	19,294
CVD	Yes	1769	17.9	8133	82.1	9902
	No	2125	15.1	11,994	84.9	14,119
BMI (kg/m^2)	18.5-24.9	499	13.4	3214	86.6	3713
	25-29.9	866	17.3	4132	82.7	4998
	≥30	1037	25.1	3087	74.9	4124
	Missing	1460	13.4	9405	86.6	10,865
Baseline eGFR (ml/min/1.73 m^2)	45-59	1938	14.2	11,704	85.8	13,642
	30-44	1232	18.1	5561	81.8	6793
	15-29	349	20.8	1327	79.2	1676
	<15	42	16.6	211	83.4	253
	>=60	333	20.1	1324	79.9	1657

Table 50. Associations of having a uACR measured by 2008 in the prevalent CKD cohort.

Variable		Univariate		Age Sex adjusted		Multivariable+	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age group (vs 80+)	<70	1.43 (1.31-1.57)	<0.001	1.41 (1.28-1.54)	<0.001		
	70-79	1.61 (1.49-1.74)		1.58 (1.46-1.71)			
Sex (male vs. female)		1.34 (1.25-1.44)	<0.001	1.30 (1.21-1.39)	<0.001	1.19 (1.07-1.32)	0.001
IMD quintiles (vs least deprived)	1 (most)	1.31 (1.16-1.47)	<0.001	1.28 (1.14-1.45)	<0.001	0.90 (0.75-1.08)	0.251
	2	1.18 (1.05-1.32)		1.18 (1.06-1.32)		0.84 (0.71-0.99)	
	3	1.08 (0.98-1.19)		1.09 (0.99-1.21)		0.90 (0.78-1.04)	
	4	1.11 (1.01-1.22)		1.11 (1.01-1.22)		0.99 (0.86-1.14)	
Hypertension (vs. no hypertension)		1.59 (1.47-1.72)	<0.001	1.62 (1.50-1.76)	<0.001	1.08 (0.96-1.21)	0.192

Table 50 cont

Variable		Univariate		Age Sex adjusted		Multivariable+	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Diabetes (vs. no diabetes)		81.50 (73.3-90.5)	<0.001	79.86 (71.9-88.7)	<0.001	79.23 (71.1-88.2)	<0.001
CVD (vs. no CVD)		1.23 (1.15-1.32)	<0.001	1.26 (1.17-1.35)	<0.001		
CKD 3 – 5 QOF registered (vs. not)		1.97 (1.83-2.12)	<0.001	1.98 (1.84-2.13)	<0.001	1.68 (1.51-1.87)	<0.001
Baseline eGFR (vs. 45-59)	>=60	1.49 (1.31-1.70)	<0.001	1.45 (1.34-1.57)	<0.001	1.22 (1.00-1.48)	0.046
	30-44	1.34 (1.24-1.45)		1.75 (1.54-1.99)		1.13 (1.00-1.27)	
	15-29	1.59 (1.39-1.80)		1.19 (0.85-1.67)		1.04 (0.86-1.26)	
	<15	1.27 (0.93-1.72)		1.51 (1.33-1.72)		0.73 (0.46-1.18)	
BMI (vs. 18.5-24.9)	25-29.9	1.34 (1.20-1.52)	<0.001	1.26 (1.12-1.42)	<0.001		
	30+	2.16 (1.92-2.43)		2.04 (1.81-2.30)			
	Missing	0.99 (0.90-1.11)		0.99 (0.89-1.11)			

+adjusted for age, sex, IMD, hypertension, diabetes, CVD, QOF CKD registration, baseline eGFR

Interactions for CVD x Sex, CVD x Age, Diabetes x Sex, Diabetes x Age and Age x Sex were examined using likelihood ratio tests. No Age x Sex, CVD x Sex, Diabetes x Sex or Diabetes x Age interactions were identified.
There was an interaction between Age and CVD (LR Chi^2 15.9, $p<0.001$).
Stratum specific estimates are given in Table 51.

Table 51. Age strata specific estimates for the association between uACR measurement and CVD

Age group	Adjusted odds ratio (95%CI) for the association between uACR measurement and CVD
< 70	0.93 (0.73-1.19)
70-79	0.91 (0.76-1.08)
80+	0.74 (0.63-0.87)

This suggests that the relationship between CVD and uACR measurement varies with age, with older people with CVD less likely to have uACR measured.

This model was also tested including BMI as an explanatory variable. This did not improve the model and made no difference to the associations observed with sex, diabetes and CKD (QOF) registration. However, the association with eGFR was altered, and BMI was therefore excluded from the final model.

4.3.2.5 uACR measurement in the incident cohort

In the incident cohort of 15,649 people, 7217 (46.1%) had a record of ever having an uACR measurement and 8432 (53.9%) did not (Table 52). The associations of ever having uACR tested in the incident cohort are shown in Table 53.

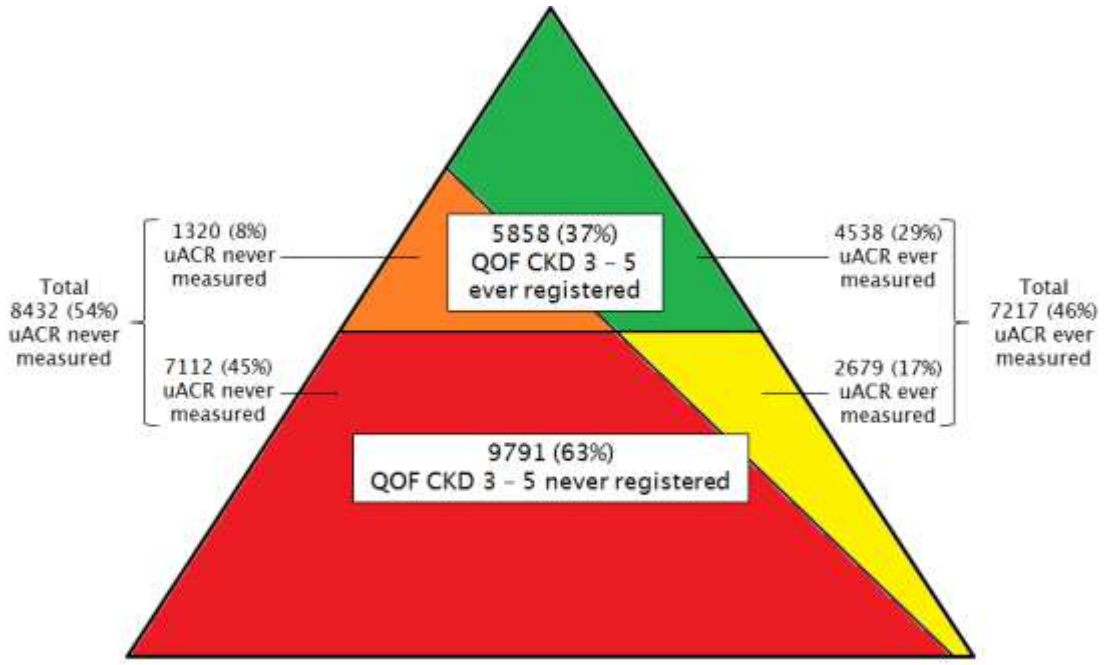
Table 52. Characteristics of people with and without a history of ever having uACR measurement in the incident CKD cohort

		uACR ever measured		uACR never measured		Total
		n	Row %	n	Row %	
Sex	Male	3331	50.7	3239	49.3	6570
	Female	3886	42.8	5193	57.2	9079
Age	<70	2615	49.9	2624	50.1	5239
	70-79	2707	49.7	2741	50.3	5448
	80+	1895	38.2	3067	61.2	4962
IMD quintile	1 (most deprived)	752	51.1	721	48.9	1473
	2	1087	49.7	1099	50.3	2186
	3	1520	46.8	1728	53.2	3248
	4	1636	44.2	2063	55.8	3699
	5	2217	44.1	2812	55.9	5029
Hypertension	Yes	4964	52.0	4590	48.0	9554
	No	2253	37.0	3842	63.0	6095
Diabetes	Yes	2882	93.2	209	6.8	3091
	No	4335	34.5	8223	65.5	12,558
CVD	Yes	2725	50.5	2667	49.5	5392
	No	4492	43.8	5765	56.2	10,257
Baseline eGFR	45-59	6290	46.2	7324	53.8	13,614
	30-44	723	45.4	871	54.6	1594
	15-29	142	45.1	173	54.9	315
	<15	62	49.2	64	50.8	126

This suggests that a higher proportion of people in lower socioeconomic groups than in higher socioeconomic groups are being tested for uACR,

although the overall percentage of people being tested is still low. It is of concern that a high proportion of people with very low eGFR had never been tested for uACR. As with the prevalent cohort, by far the highest proportion of testing took place among people with diabetes. This is perhaps because diabetes has its own QOF indicator for uACR testing (DM 13: The percentage of patients with diabetes who have a record of micro-albuminuria testing in the previous 15 months (exception reporting for patients with proteinuria). The distribution of people in this cohort in terms of ever-registration of CKD for QOF and ever-testing for uACR is shown in Figure 44. This shows that a high proportion of people with study identified CKD were never registered as having CKD for QOF, despite many of them having had uACR tested at some point (of those not QOF registered, but having a uACR test, 1536/2679 (57%) had diabetes). It also illustrates that 4538/5858 (77%) of people with QOF CKD would have a record of uACR testing at some point, although this represents only 29% of the total incident CKD cohort.

Figure 44. Distribution of QOF registration and uACR testing in the incident cohort



(Areas are not in exact proportion. Percentages shown are of the total cohort (n=15,649))

The associations shown in Table 53 indicate that younger people, men, people with diabetes or hypertension, and people registered for QOF are more likely to have ever been tested for uACR. This association is particularly striking for diabetes and QOF registration, even after adjustment for known confounders. The association with deprivation is lost on full adjustment, suggesting that other factors, such as diabetes and QOF registration may be on the causal pathway between deprivation status and uACR testing. This hypothesis is strengthened by use of a simpler model including age, sex, diabetes, IMD and QOF CKD registration, which showed that the association with IMD was lost on the addition of diabetes to the model (data not shown).

Table 53. Associations of having uACR ever measured in the incident cohort

Variable		Univariate		Age Sex adjusted		Multivariable+	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age group (vs 80+)	<70	1.61 (1.49-1.75)	<0.001	1.58 (1.46-1.71)	<0.001	1.78 (1.59-1.99)	<0.001
	70-79	1.60 (1.48-1.73)		1.56 (1.44-1.69)		1.52 (1.37-1.70)	
Sex (male vs. female)		1.37 (1.29-1.46)	<0.001	1.33 (1.25-1.42)	<0.001	1.26 (1.15-1.38)	0.001
IMD quintiles (vs least deprived)	1 (most)	1.32 (1.18-1.49)	<0.001	1.29 (1.14-1.45)	<0.001	1.07 (0.91-1.26)	0.402
	2	1.25 (1.13-1.39)		1.26 (1.13-1.39)		1.10 (0.96-1.27)	
	3	1.12 (1.02-1.22)		1.12 (1.02-1.23)		1.06 (0.94-1.20)	
	4	1.00 (0.92-1.10)		1.00 (0.92-1.10)		0.90 (0.80-1.01)	
Hypertension (vs. no hypertension)		1.84 (1.73-1.97)	<0.001	1.92 (1.79-2.05)	<0.001	1.35 (1.23-1.48)	<0.001
Diabetes (vs. no diabetes)		26.16 (22.6-30.2)	<0.001	25.17 (21.8-29.1)	<0.001	41.35 (35.4-48.3)	<0.001

Table 53 cont

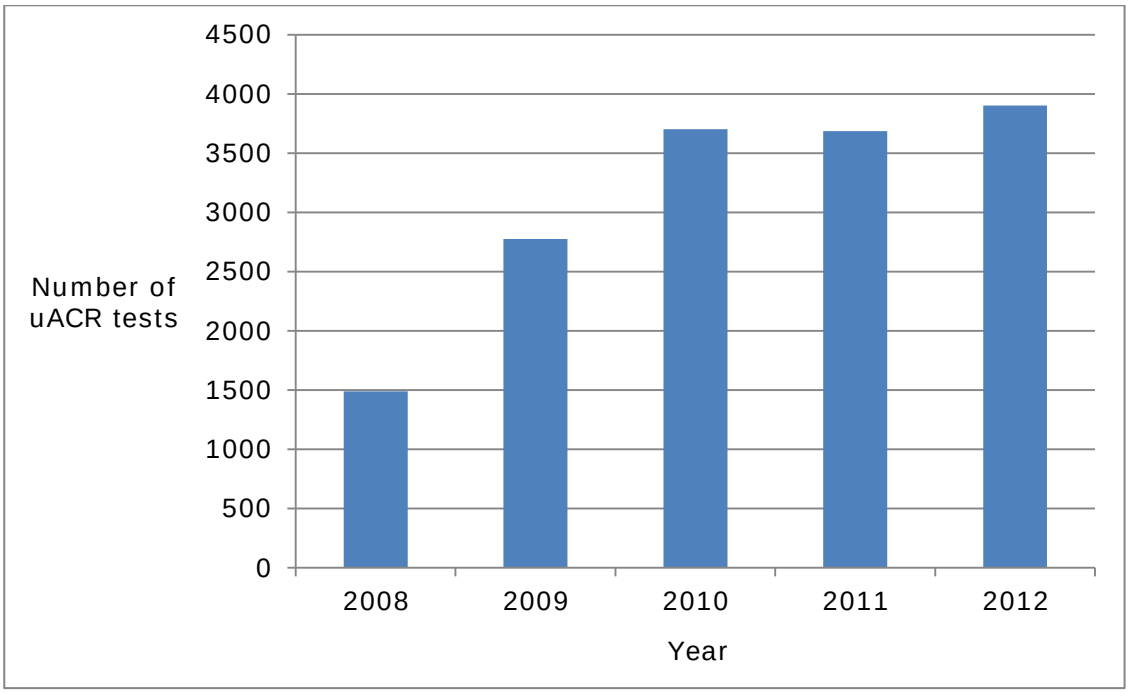
Variable		Univariate		Age Sex adjusted		Multivariable+	
		OR (95% CI)	p	OR (95% CI)	OR (95% CI)	p	OR (95% CI)
CVD (vs no CVD)		1.31 (1.23-1.40)	<0.001	1.38 (1.28-1.47)	<0.001	1.01 (0.92-1.11)	0.859
CKD 3 – 5 QOF registered (vs. not)		9.13 (8.46-9.84)	<0.001	9.64 (8.92-10.4)	<0.001	14.66 (13.4-16.1)	<0.001
Baseline eGFR (compared to 45-59)	30-44	0.97 (0.88-1.08)	0.638	1.07 (0.85-1.34)	0.736	0.81 (0.70-0.93)	0.658
	15-29	0.96 (0.77-1.21)		1.06 (0.75-1.51)		0.70 (0.52-0.94)	
	<15	1.14 (0.80-1.61)		1.04 (0.93-1.15)		0.90 (0.55-1.46)	

+adjusted for age, sex, IMD, hypertension, diabetes, CVD, QOF CKD registration, baseline eGFR

4.3.2.5.1 Changes in uACR measurement over time

In assessing uACR measurement over time, it is important to remember that measurement and recording of uACR in primary care for CKD only became part of the QOF indicator set in 2009/10. From Figure 45 it can be seen that the total number of uACR tests in the incident CKD cohort increased from 1,489 in 2008 to 3901 in 2012 with a considerable increase noticeable between 2009 and 2010 (2775 to 3703 respectively).

Figure 45. Number of uACR tests per year in the incident CKD cohort (total n=15,649)



Examining the change in uACR measurement by proportion of people in the study in each year shows a similar pattern with a gradual upward trend (Figure 46). However, the maximum achieved in each year was about 27% of people with CKD. This is in contrast with national QOF figures that report the achievement of QOF indicator 6 at about 80% (The percentage of patients on the CKD register whose notes have a record of a urine albumin: creatinine ratio (or protein: creatinine ratio) test in the previous 15 months). See Table 54.

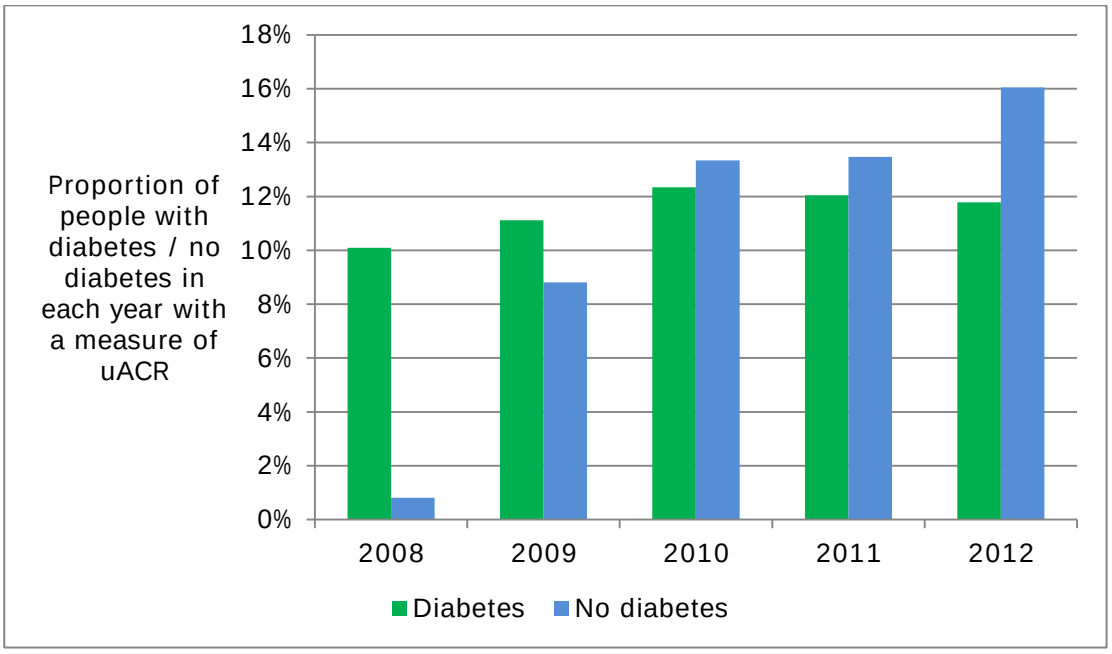
Table 54. Average practice achievement of QOF indicator 6 – measurement of uACR.

	2009	2010	2011	2012
England average practice achievement of QOF indicator 6 (% of those registered with CKD 3-5 who had had uACR measure within 15 months?	77.7%	82.2%	79%	78.8%
Portsmouth practices' average achievement	79.3%	85.0%	83.9%	83.6%
Southampton practices' average achievement	78.3%	81.6%	80.4%	82.4%

Source: Health and Social Care Information Centre [289]

This disparity could arise for a number of reasons, particularly the lack of registration of people for QOF CKD (therefore not included in the denominator of people with CKD for QOF purposes) as discussed in section 4.3.2.3 above. In addition, Table 54 shows the England practice average. More detailed analysis within the practices included in the study would be required to investigate local disparity between QOF achievement and actual uACR measures. For example, variations in exception reporting could affect the recorded QOF achievement. In addition, during the period of this study, the QOF target included uACR measured within 15 months (rather than the year).

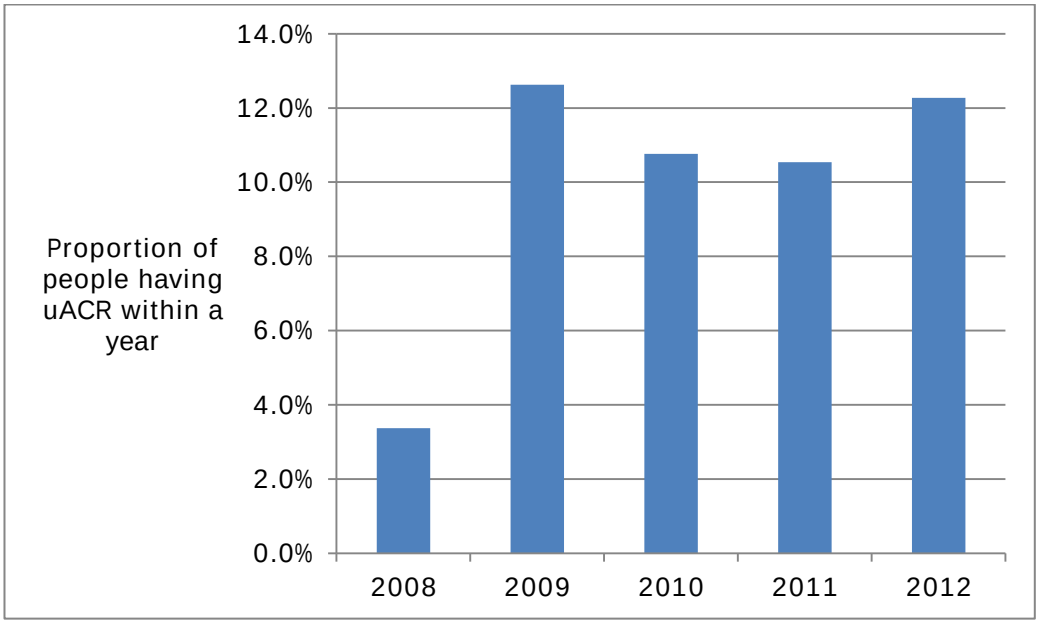
Figure 46. Proportion of people in the incident cohort per year with a measure of uACR in that year.



This demonstrates that, as a proportion of people with or without diabetes in any given year, uACR testing among people with diabetes remained relatively stable over the five years of the study. Testing among people without diabetes increased after 2009 such that the overall increase in the proportion of people tested was almost exclusively due to testing in non-diabetics. This suggests that, as might be expected, testing behaviour in primary care is driven to some extent by changes in QOF indicators.

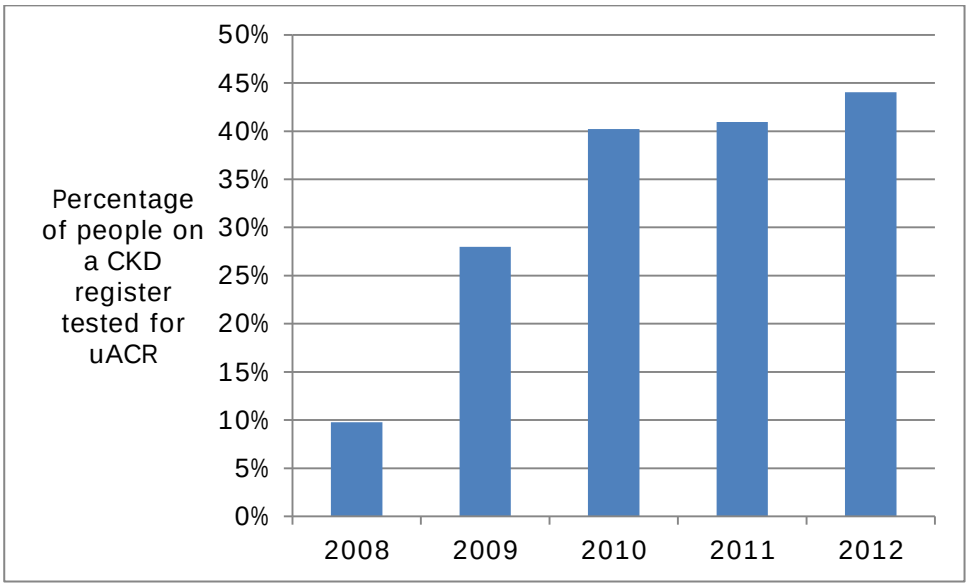
The proportion of people having a uACR measure within a year of their first low eGFR (whether QOF registered or not) is shown in Figure 47. This also suggests that testing improved after 2009, but shows that a low proportion in each year had uACR testing within a year.

Figure 47 Proportion of people in the incident cohort in each year with a measure of uACR taken within a year of their first low eGFR



Examining measurement of uACR by QOF CKD registration status shows a considerably higher proportion of patients registered as having CKD for QOF being tested for uACR in each year (compared to those not registered). It also demonstrates the marked increase in the proportion tested after 2009 (Figure 48).

Figure 48. Trends in any uACR testing in people on a QOF CKD register in the incident cohort.



Examining trends in uACR testing by SES, there is evidence of increased testing over time in all quintiles of IMD with some evidence of a widening inequality gap with more testing in IMD quintiles 1 and 2. (Figure 49) This is likely to be related to the higher proportion of people with diabetes in lower SES groups. In this cohort, 26% of people in the most deprived quintile of IMD had a diagnosis of diabetes compared to 17% in the least deprived quintile, with a graded effect across intervening quintiles (Figure 50).

Figure 49. Change in uACR testing over time by quintile of IMD.

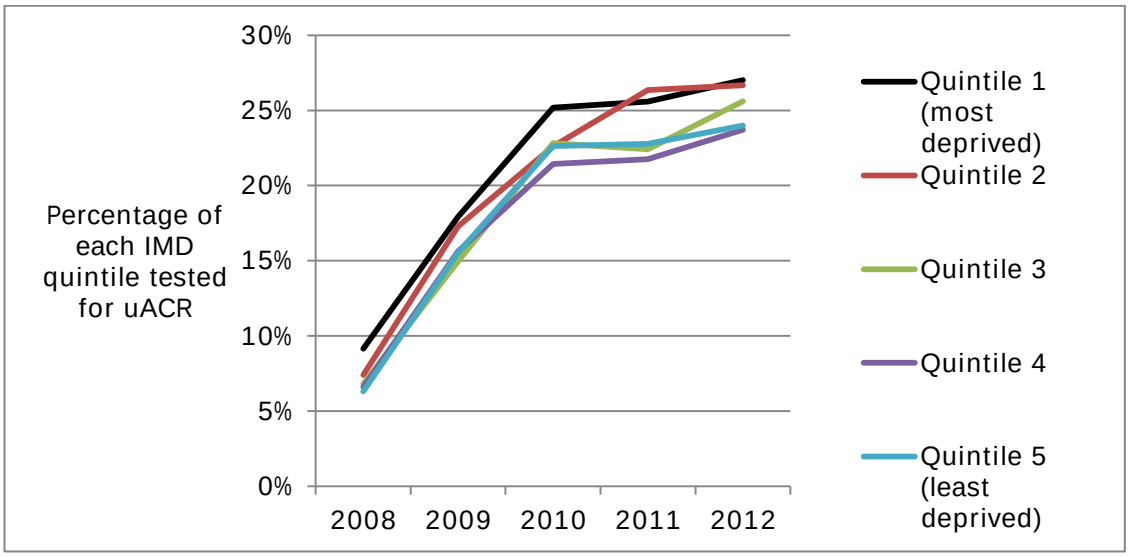
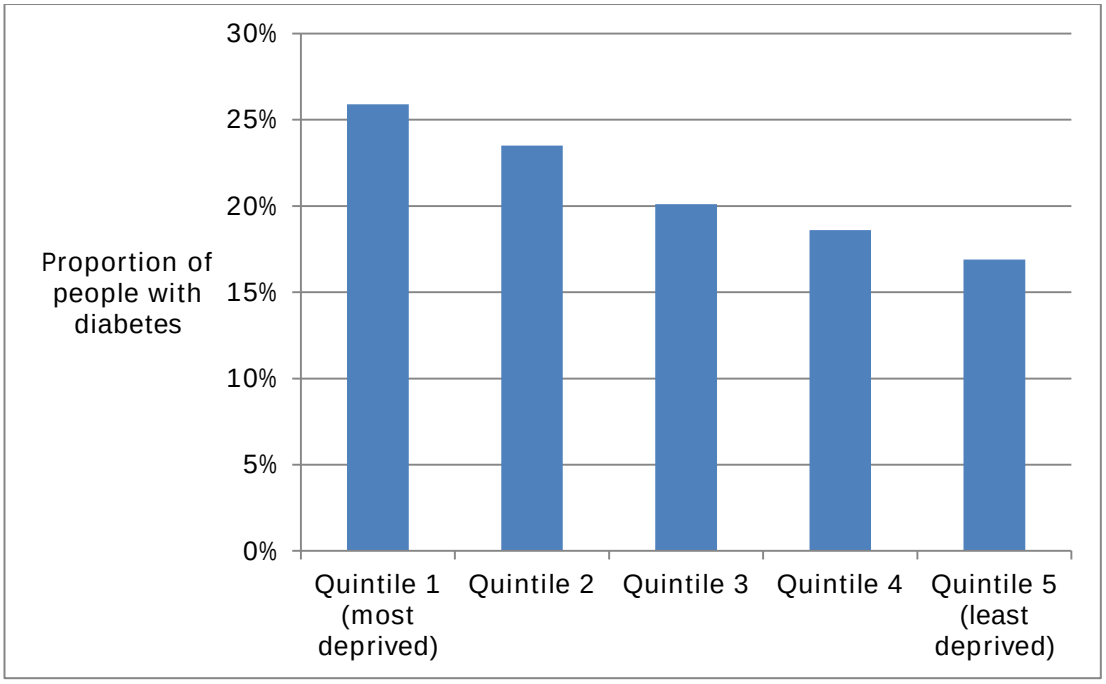


Figure 50. Proportion of people in each IMD quintile with a GP diagnosis of diabetes in the incident cohort.



4.3.2.6 Changes in QOF registration and uACR testing in the incident cohort

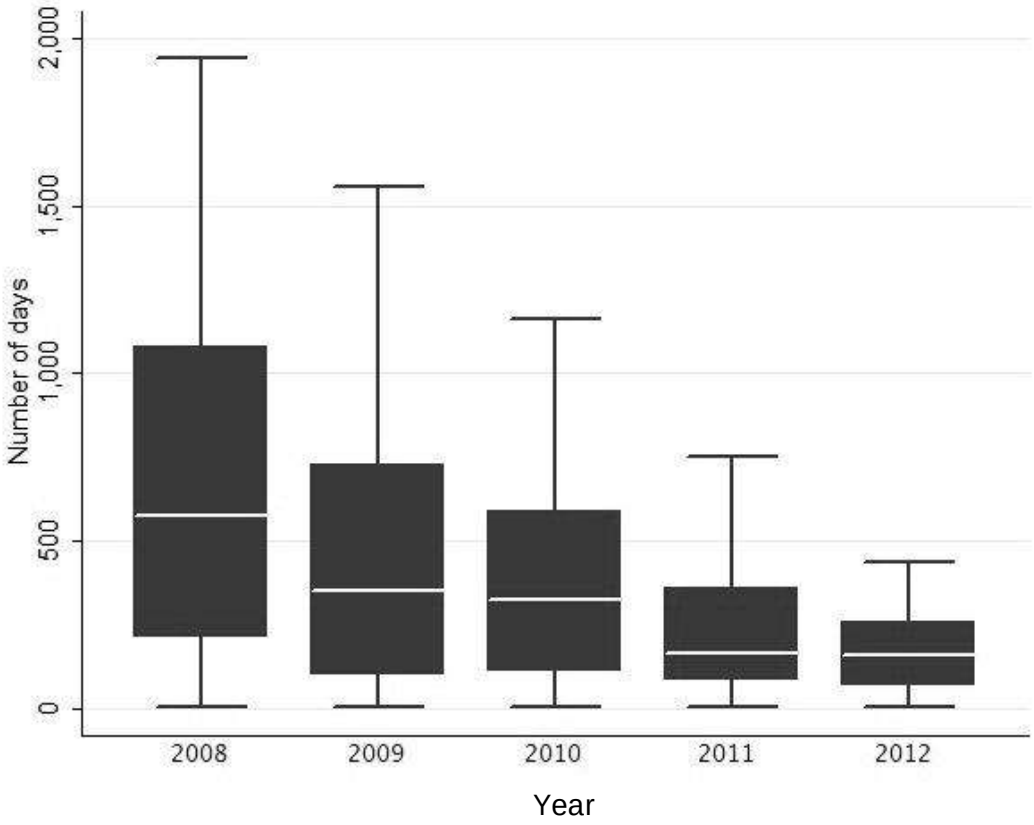
Among those registered for QOF, change in the timing of recognition/registration of CKD for QOF was explored in the incident cohort by

examining the time differences between date of study entry (i.e. first date of low eGFR) and date of QOF registration for each year of the study.
The median time from first eGFR<60ml/min/1.73m^2 to registration of CKD for QOF fell in each year of the study (Table 55). This is shown graphically in Figure 51.

Table 55. Median time (days) from first eGFR<60ml/min/1.73m^2 to registration of CKD

Year of study	Median (days)	Lower quartile	Upper quartile
2008	573	210	1074
2009	349	97	723
2010	321	110	583
2011	166	82	355
2012	159	69	253

Figure 51. Plot showing change in the time between first low eGFR and date of QOF registration of CKD by year of entry to the study.



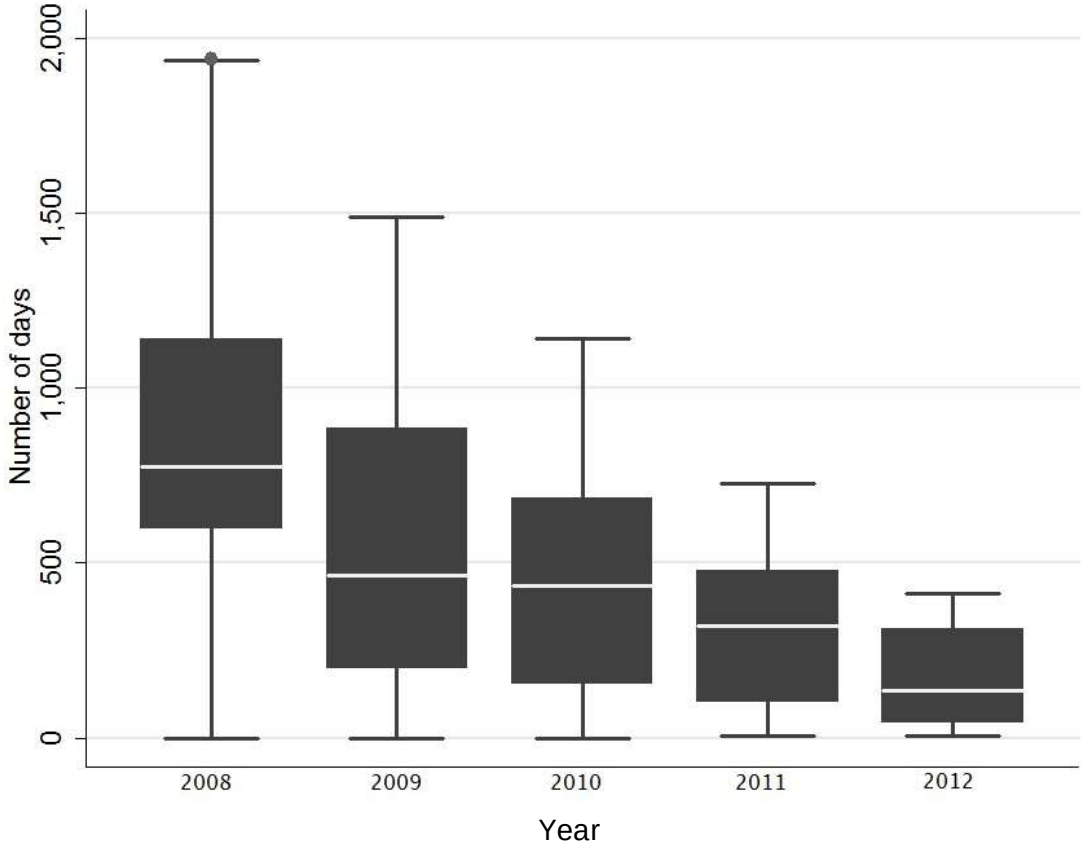
This suggests some improvement in the speed of recognition of CKD over time.

A similar method was applied to uACR testing for those with a measure of uACR in the incident cohort. Median time from entry to study to first uACR test also fell over time (Table 56 and Figure 52)

Table 56. Median time (days) from entry to study to first uACR test

Year of study	Median (days)	Lower quartile	Upper quartile
2008	776	601	1136
2009	463	203	884
2010	434	158	684
2011	321	107	477
2012	137	48	310

Figure 52. Change in time between first low eGFR and first uACR in the incident cohort by year of entry to the study



In addition, in view of the suggestion in QOF exception reporting guidance that patients should have measurements made within three months and delivery of clinical standards within nine months of a diagnosis being made, [93] the proportion of new CKD cases in each year that were registered for QOF or had uACR within 9 months (270 days) of the first eGFR was calculated. This shows that the overall proportion registered for QOF or tested for uACR within 9 months of the first low eGFR was low (Figure 53). This proportion improved for uACR but not for QOF registration (beyond 2009) during the study period.

Figure 53. Changes in QOF registration and uACR testing within 9 months of the first low eGFR over time in the incident cohort

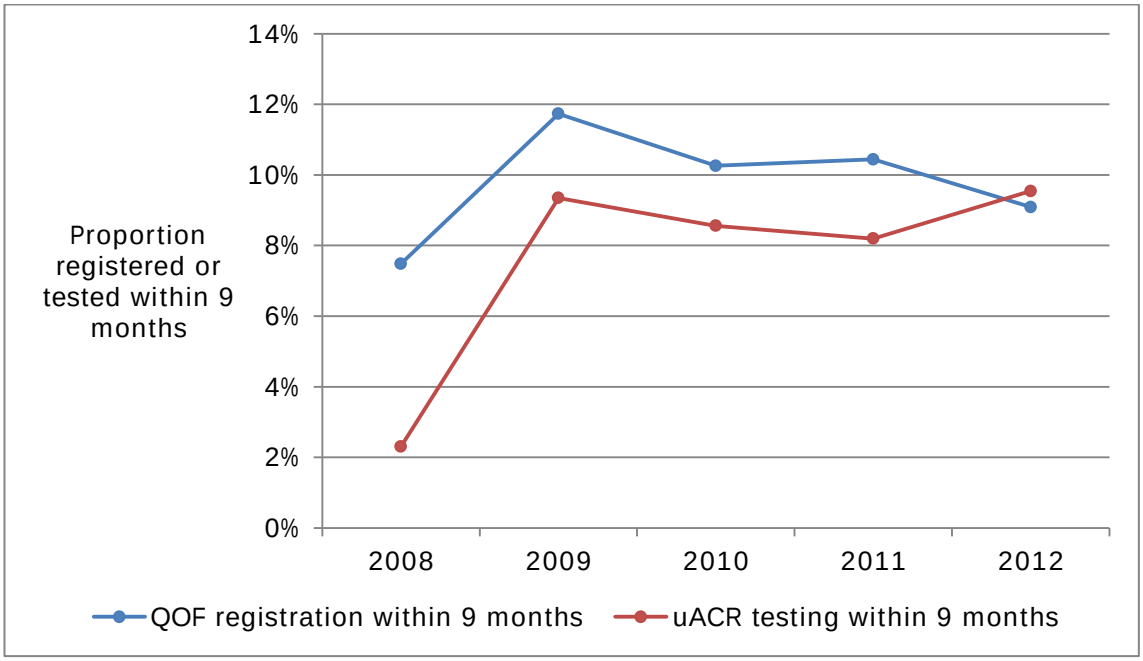


Table 57 shows the characteristics of people with and without QOF CKD registration within 9 months in the incident cohort. On Poisson analysis, greater likelihood of QOF registration within 9 months was associated with male sex, diagnosed hypertension, and lower eGFR (Table 58). It was also associated with joining the cohort in 2009-2011 compared to 2008, suggesting improvement in registration practices over time. Table 59 shows the characteristics of people with and without uACR testing within 9 months in the incident cohort. In contrast to QOF registration, greater likelihood of uACR testing within 9 months was associated with lower age and diabetes, and with joining the cohort after 2008 (Table 60). There was no association of either with SES.

Table 57. Characteristics of people with and without QOF CKD registration within 9 months of entry in the incident CKD cohort

		CKD 3 – 5 QOF registered within 9 months		CKD not registered within 9 months		Total
		n	%	n	%	
Age group	<50	17	2.7	613	97.3	630
	50-69	197	4.3	4412	95.7	4609
	70-79	274	5.0	5174	95.0	5448
	80+	254	5.1	4708	94.9	4962
Sex	M	335	5.1	6235	94.9	6570
	F	407	4.5	8672	95.5	9079
IMD quintiles	1 (most deprived)	65	4.4	1408	95.6	1473
	2	108	4.9	2078	95.1	2186
	3	162	5.0	3086	95.0	3248
	4	161	4.4	3538	95.7	3699
	5	246	4.9	4783	95.1	5029
Hypertension (ever)		509	5.3	9045	94.7	9554
No hypertension		233	3.8	5862	96.2	6095
Diabetes (ever)		143	4.6	2948	95.4	3091
No diabetes		599	4.8	11,959	95.2	12,558
CVD (ever)		294	5.5	5098	94.6	5392
No CVD		448	4.4	9809	95.6	10,257
Baseline eGFR (ml/min/1.73m^2)	45+	600	4.5	13,014	95.5	13,614
	30-44	124	7.8	1470	92.2	1594
	15-29	14	4.4	301	95.6	315
	<15	4	3.2	122	96.8	126

Table 58. Poisson regression analysis of predictors of QOF registration within 9 months of study entry in the incident CKD cohort (n=15,649)

Variable	Category	Univariate		Age sex adjusted		Multivariable *	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Sex (vs. female)	Male	1.24 (1.11-1.37)	<0.001	1.24 (1.11-1.38)	<0.001	1.24 (1.12-1.38)	<0.001
Age (vs. <70 yrs)	70-79	1.00 (0.88-1.13)	0.991	1.00 (0.88-1.13)	0.962	1.04 (0.91-1.19)	0.678
	80+	1.00 (0.87-1.14)		1.01 (0.89-1.16)		1.03 (0.90-1.18)	
IMD quintile (vs. least deprived)	1 (most deprived)	0.96 (0.79-1.17)	0.668	0.97 (0.79-1.18)	0.336		
	2	1.04 (0.88-1.23)		1.05 (0.89-1.24)			
	3	0.97 (0.83-1.12)		0.97 (0.84-1.13)			
	4	0.93 (0.80-1.07)		0.93 (0.81-1.08)			
CVD (vs no CVD)		1.06 (0.95-1.18)	0.317	1.03 (0.92-1.15)	0.651		
Diabetes (vs. n diabetes)		0.99 (0.86-1.13)	0.848	0.97 (0.85-1.11)	0.637		

Table 58 cont

Variable	Category	Univariate		Age sex adjusted		Multivariable *	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Hypertension (vs. no hypertension)		1.15 (1.03-1.28)	0.014	1.15 (1.03-1.29)	0.011	1.21 (1.08-1.35)	0.001
Baseline eGFR (vs. 45-59 ml/min/1.73 m^2)	30-44	2.04 (1.77-2.35)	<0.001	2.08 (1.80-2.40)	<0.001	2.03 (1.76-2.35)	<0.001
	15-29	1.22 (0.83-1.79)		1.23 (0.84-1.81)		1.19 (0.81-1.75)	
	<15	0.78 (0.39-1.57)		0.77 (0.38-1.54)		0.79 (0.39-1.58)	
Year of joining cohort (vs. 2008)	2009	1.53 (1.34-1.74)	<0.001	1.52 (1.34-1.73)	<0.001	1.52 (1.33-1.73)	<0.001
	2010	1.30 (1.10-1.54)		1.29 (1.09-1.53)		1.28 (1.08-1.52)	
	2011	1.30 (1.06-1.59)		1.29 (1.05-1.58)		1.28 (1.05-1.58)	
	2012	1.12 (0.82-1.54)		1.11 (0.81-1.53)		1.09 (0.79-1.50)	

*adjusted for age, sex, hypertension, baseline eGFR, year of joining cohort.

Table 59. Characteristics of people with and without uACR testing within 9 months of study entry in the incident CKD cohort

		uACR testing within 9 months		uACR not tested within 9 months		Total
		n	%	n	%	
Age group	<50	41	6.5	589	93.5	630
	50-69	278	6.0	4331	94.0	4609
	70-79	268	4.9	5180	95.1	5448
	80+	155	3.1	4807	96.9	4962
Sex	M	362	5.5	6208	94.5	6570
	F	380	4.2	8699	95.8	9079
IMD quintiles	1 (most deprived)	69	4.7	1404	95.3	1473
	2	123	5.6	2063	94.4	2186
	3	157	4.8	3091	95.2	3248
	4	162	4.4	3537	95.6	3699
	5	231	4.6	4798	95.4	5029
Hypertension (ever)		440	4.6	9114	95.4	9554
No hypertension		302	5.0	5793	95.0	6095
Diabetes (ever)		261	8.4	2830	91.6	3091
No diabetes		481	3.8	12,077	96.2	12,558
CVD (ever)		233	4.3	5159	95.7	5392
No CVD		509	5.0	9748	95.0	10,257
Baseline eGFR (ml/min/ 1.73m^2)	45+	605	4.4	13,009	95.6	13,614
	30-44	105	6.6	1489	93.4	1594
	15-29	28	8.9	287	91.1	315
	<15	4	3.2	122	96.8	126

Table 60. Poisson regression analysis of predictors of uACR testing within 9 months of study entry in the incident CKD cohort (n=15,649)

Variable	Category	Univariate		Age sex adjusted		Multivariable *	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Sex (vs. female)	Male	1.32 (1.14-1.52)	<0.001	1.28 (1.11-1.48)	0.001	1.14 (0.99-1.32)	0.069
Age (vs. <70 yrs)	70-79	0.83 (0.70-0.97)	<0.001	0.83 (0.70-0.97)	<0.001	0.91 (0.77-1.07)	0.001
	80+	0.58 (0.48-0.70)		0.59 (0.49-0.72)		0.72 (0.59-0.87)	
IMD quintile (vs. least deprived)	1 (most deprived)	1.02 (0.78-1.33)	0.317	0.97 (0.74-1.27)	0.571		
	2	1.21 (0.98-1.52)		1.20 (0.96-1.50)			
	3	1.05 (0.86-1.29)		1.05 (0.85-1.28)			
	4	0.95 (0.78-1.16)		0.94 (0.77-1.15)			
CVD (vs. no CVD)		0.91 (0.78-1.06)	0.214	0.94 (0.80-1.10)	0.446		
Diabetes (vs. n diabetes)		2.20 (1.89-2.55)	<0.001	2.08 (1.78-2.42)	<0.001	2.32 (1.99-2.71)	<0.001

Table 60 cont

Variable	Category	Univariate		Age sex adjusted		Multivariable *	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Hypertension (vs. no hypertension)		0.92 (0.79-1.06)	0.254	0.95 (0.82-1.10)	0.488		
Baseline eGFR (vs. 45-59 ml/min/1.73m^2)	30-44	1.64 (1.33-2.02)	<0.001	1.78 (1.44-2.20)	<0.001	1.59 (1.29-1.97)	<0.001
	15-29	2.31 (1.58-3.37)		2.49 (1.70-3.64)		2.00 (1.36-2.93)	
	<15	0.71 (0.27-1.91)		0.66 (0.25-1.77)		0.78 (0.29-2.08)	
Year of joining cohort (vs. 2008)	2009	3.94 (3.29-4.71)	<0.001	3.85 (3.22-4.61)	<0.001	4.05 (3.38-4.85)	<0.001
	2010	3.51 (2.84-4.35)		3.37 (2.72-4.17)		3.46 (2.79-4.29)	
	2011	3.30 (2.57-4.24)		3.13 (2.44-4.02)		3.30 (2.56-4.24)	
	2012	3.82 (2.75-5.31)		3.57 (2.56-4.96)		3.73 (2.67-5.20)	

*adjusted for age, sex, diabetes, baseline eGFR, year of joining cohort.

4.3.2.7 Use of renin angiotensin aldosterone system inhibitors

In the prevalent CKD cohort, people were identified who should be administered renin angiotensin aldosterone system inhibitors (RAASi) according to NICE guidelines. This includes:

- People without diabetes, but with hypertension and macroalbuminuria (uACR>=30mg/mmol)
- People with diabetes and hypertension with any albuminuria
- People without diabetes, with or without hypertension, with albuminuria >=70mg/mmol)

1326/24,021 (5.5%) of the population of this cohort fell into this category. This is likely to be an underestimate because of inability to assess albuminuria status in the majority with low numbers of people having had uACR testing. 17,344/24,021 people (72%) had been prescribed RAASi at some point. The characteristics of people in the prevalent cohort with and without a history of RAASi prescription are shown in Table 61. This shows that a higher proportion of people with no history of RAASi prescribing were women, over 80, and those with higher baseline eGFR. RAASi prescribing was more common in people with a history of CVD, hypertension or diabetes and lower baseline eGFR. It is difficult to separate prescribing indication in these people (such as primary use of RAASi for hypertension and heart failure) and it was not attempted in this study. Combining this aspect with the low numbers of people with uACR measures, it was not possible to investigate 'appropriate RAASi prescribing' as a process measure.

62% of people with a history of RAASi were CKD QOF registered (compared to 40% of those with no history of RAASi prescribing). Stated by percentage of people with and without CKD QOF registration, 80% of people registered for QOF had had RAASi at some point, compared to 62% of people not registered. Among those in with a value for uACR (n=3894), 3436 (88%) had a history of RAASi prescription. Of those with microalbuminuria, this proportion was 91%, and macroalbuminuria 93%. In the incident cohort, 3634/15649 (23.2%) were identified as having at least one measure of uACR that was above the microalbuminuria threshold. Of those who had a record of any albuminuria, 2939 (81%) had had RAASi at some point.

Table 61. Characteristics of people in the prevalent cohort with and without a history of RAASi prescription

		Ever had RAASi (n=17,344)		No record of RAASi (n=6774)		Row total
		n	Column %	n	Column %	
Sex	Male	7282	42.0	2358	34.8	9640
	Female	10,062	58.0	4416	65.2	14,478
Age group	<50	263	1.5	194	2.9	457
	50-69	3144	18.1	1187	17.8	4331
	70-79	6191	35.7	1786	26.8	7977
	80+	7746	44.7	3510	52.6	11,256
IMD quintiles	1 (most deprived)	1726	10.0	566	8.5	2292
	2	2334	13.5	895	13.4	3229
	3	3621	20.9	1466	22.0	5087
	4	4053	23.4	1567	23.5	5620
	5	5596	32.3	2177	32.6	7773
CKD 3 – 5 QOF registered		10,742	61.9	2657	39.8	13,399
Hypertension		13,688	78.9	2816	42.2	16,504
Diabetes		4184	24.1	543	8.1	4727
CVD		7777	44.8	2125	31.8	9902
Smoking history		5503	31.7	2153	32.3	7656
Baseline eGFR (ml/min/1.73m^2)	45-59	9556	55.1	4086	61.2	13,642
	30-44	5136	29.6	1657	24.8	6793
	15-29	1318	7.6	358	5.4	1676
	<15	178	1.0	75	1.1	253
	>60	1156	6.7	501	7.5	1657

4.3.3 Outcome measures

4.3.3.1 Mortality

Of the whole study population (n=498,631), 25,878 (5.2%) people died during the five years of follow up. Of the prevalent CKD cohort (n=24,021), 6352 (26.4%) died during follow up.The characteristics of people who died in the prevalent CKD cohort are shown in Table 62. People who died tended to be older, had more CVD, and had poorer renal function. There was little observable difference in terms of the proportion in each quintile of IMD between those who died and those still alive.
In the incident cohort, 2503 people (16.0%) died during the follow up period (Table 63).

Table 62. Comparison of the characteristics of people in the prevalent CKD cohort (n=24,021) who died / did not die during the follow up period

		Alive		Died		Row total
		n	Column %	n	Column %	
Sex	Male	6905	39.1	2702	42.5	9607
	Female	10,764	60.9	3650	57.5	14,414
Age group	<50	433	2.5	24	0.4	457
	50-69	3962	22.4	369	5.8	4331
	70-79	6643	37.6	1334	21.0	7977
	80+	6631	37.5	4625	72.8	11,256
IMD quintiles	1 (most deprived)	1685	9.5	607	9.6	2292
	2	2392	13.5	837	13.2	3229
	3	3623	20.5	1464	23.0	5087
	4	4207	23.5	1413	22.2	5620
	5	5742	32.5	2031	32.0	7773
CKD 3 – 5 QOF registered (by 2008)		9786	55.4	3613	56.9	13,399
Hypertension (by 2008)		12,281	69.5	4223	66.5	16,504
Diabetes (by 2008)		3356	19.0	1371	21.6	4727
CVD (by 2008)		6484	36.7	3418	53.8	9902
Smoking (before 2008)		5369	30.4	2287	36.0	7656
BMI (kg/m^2)	18.5-24.9	2535	14.5	1178	19.0	3713
	25-29.9	3940	22.5	1058	17.1	4998
	≥30	3413	19.5	711	11.5	4124
	Missing	7623	43.5	3242	52.4	10,865
Baseline eGFR ($ml/min/1.73m^2$)	45-59	10,873	61.5	2769	43.6	13,642
	30-44	4448	25.2	2345	36.9	6793
	15-29	853	4.8	782	12.3	1635
	<15	174	1.0	120	1.9	294
	>60	1303	7.4	322	5.1	1625

Table 63. Comparison of the characteristics of people in the incident CKD cohort who died / did not die during the follow up period (n=15,649)

		Alive		Died		Row total
		n	Column %	n	Column %	
Sex	Male	5506	41.9	1064	42.5	6570
	Female	7638	58.1	1441	57.5	9079
Age group	<50	611	4.7	19	0.8	630
	50-69	4370	33.3	239	9.5	4609
	70-79	4813	36.6	635	25.4	5448
	80+	3350	25.5	1612	64.4	4962
IMD quintiles	1 (most deprived)	1241	9.5	232	9.3	1473
	2	1846	14.1	340	13.6	2186
	3	2702	20.6	546	21.8	3248
	4	3122	23.8	577	23.0	3699
	5	4219	32.1	810	32.3	5029
CKD 3 – 5 QOF registered (ever)		4962	37.8	896	35.8	5858
Hypertension (ever)		8143	62.0	1411	56.3	9554
Diabetes (ever)		2635	20.1	456	18.2	3091
CVD (ever)		4212	32.1	1180	47.1	5392
Baseline eGFR (ml/min/1.73m^2)	45+	11,700	74.8	1914	76.4	13,614
	30-44	1136	8.6	458	18.3	1594
	15-29	195	1.5	120	4.8	315
	<15	113	0.9	13	0.5	126

4.3.3.2 Survival analysis

In the prevalent CKD cohort, univariate and multivariable Cox regression models were used to examine the risk of all-cause mortality among people with CKD.

On univariate analysis, elevated hazard ratios were associated with male gender, increasing age, lower IMD quintile, previous (diagnosed) CVD, previous diabetes, previous smoking, and lower baseline eGFR. Previous hypertension was associated with reduced risk of death. These associations were maintained after age-sex adjustment and further adjustment for IMD, hypertension, diabetes, CVD, smoking, GP CKD diagnosis and baseline eGFR.

GP QOF CKD diagnosis / registration was associated with lower risk of death after inclusion of baseline eGFR in the model.

The results of the survival analysis for all-cause mortality in the prevalent cohort are shown in Table 64. Very similar results were seen in the incident cohort with increasing age, male sex, lower quintile of IMD, diabetes, CVD and lower eGFR all associated with higher hazard ratios for mortality, whereas CKD QOF registration and hypertension were associated with lower hazard ratios (Table 65).

Proportional hazards assumptions were met in both cohorts for key variables (tested using Nelson-Aalen cumulative hazard plots).

Univariate and age-sex adjusted Hazard ratios for log uACR (as continuous) were 1.74 (95%CI 1.57-1.94), $p < 0.001$ and 1.95 (95%CI 1.73-2.19), $p < 0.001$ respectively, suggesting that increasing albuminuria was associated with increased mortality risk. However, due to the large amount of missing data for uACR (only 3894 (16.2%) had a value for baseline uACR), uACR was not included in the final multivariable model.

Table 64. Prevalent CKD cohort survival analyses

Variable	Category	Univariate		Age sex adjusted		Multivariable *	
		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Sex (male vs. female)		1.13 (1.07–1.19)	<0.001	1.34 (1.27 - 1.41)	<0.001	1.26 (1.20 - 1.33)	<0.001
Age in years continuous		1.09 (1.09 - 1.10)	<0.001	1.10 (1.09 - 1.10)	<0.001	1.09 (1.09 - 1.09)	<0.001
IMD quintile (vs. least deprived)	1 (most deprived)	1.00 (0.92 - 1.10)	<0.001	1.24 (1.14 - 1.36)	<0.001	1.18 (1.08 - 1.30)	<0.001
	2	0.97 (0.90 - 1.05)		1.09 (1.01 - 1.18)		1.06 (0.97 - 1.14)	
	3	1.10 (1.03 - 1.18)		1.16 (1.08 - 1.24)		1.15 (1.07 - 1.23)	
	4	0.94 (0.87 - 1.00)		0.95 (0.89 - 1.02)		0.96 (0.90 - 1.03)	
CVD (vs no CVD)		1.83 (1.74 - 1.92)	<0.001	1.41 (1.34 - 1.48)	<0.001	1.35 (1.28 - 1.42)	<0.001
Diabetes (vs. n diabetes)		1.15 (1.08 - 1.22)	<0.001	1.35 (1.27 - 1.43)	<0.001	1.32 (1.24 - 1.40)	<0.001
Hypertension (vs. no hypertension)		0.88 (0.84 - 0.93)	<0.001	0.86 (0.81 - 0.91)	<0.001	0.83 (0.79 - 0.88)	<0.001

Table 64 cont

Variable	Univariate		Age sex adjusted		Multivariable *	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
CKD 3 – 5 QOF registered by 2008 (vs. not)	1.05 (1.00-1.10)	0.057	1.03 (0.98-1.08)	<0.001	0.89 (0.85-0.94)	<0.001
Baseline eGFR ((ml/min/1.73m^2) as continuous)	0.97 (0.97-0.97)	<0.001	0.98 (0.97-0.98)	<0.001	0.98 (0.97-0.98)	<0.001

*adjusting for age, sex, IMD, hypertension, diabetes, CVD, GP diagnosed CKD and baseline eGFR

The pattern for survival by IMD in the prevalent cohort was not completely clear, with evidence of quintile 3 experiencing poorer survival than quintile 2, for example. This is illustrated in the Kaplan-Meier plot of survival by IMD quintile (Figure 54).

Figure 54. Kaplan-Meier plot of survival by IMD quintile in the prevalent CKD cohort

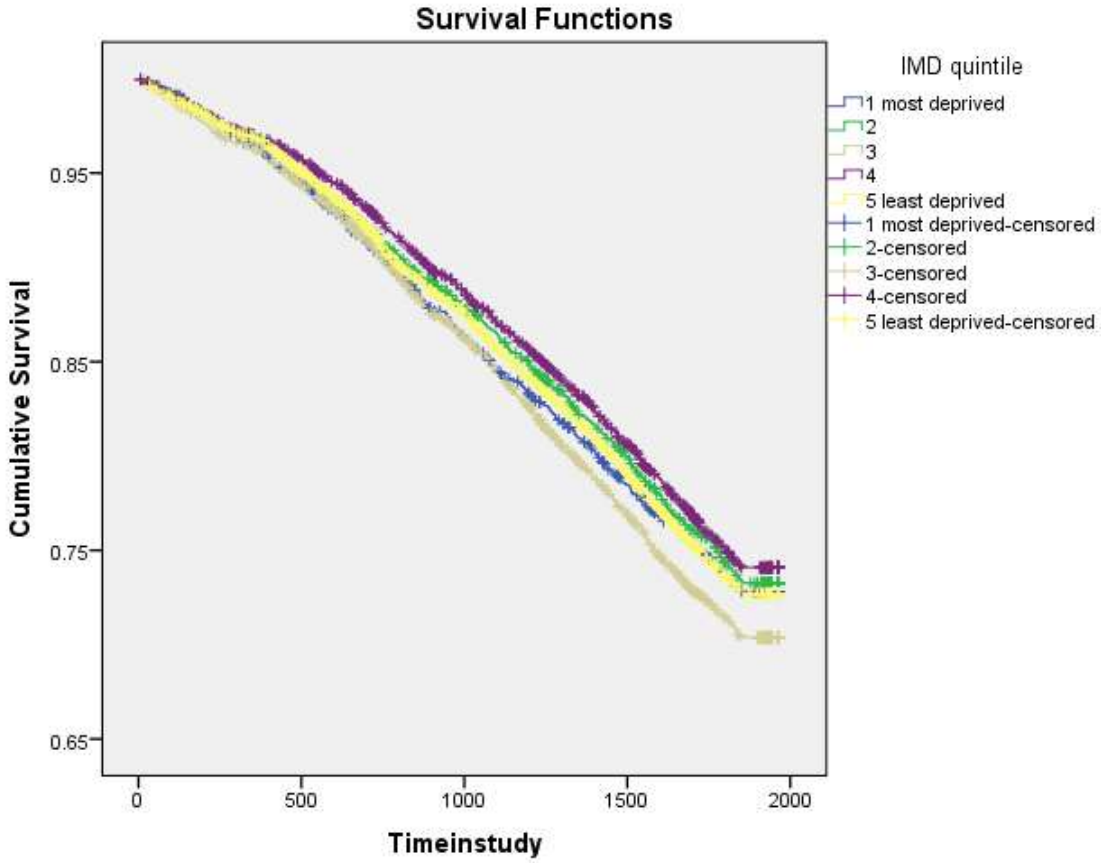


Table 65. Incident CKD cohort survival analyses

Outcome – all cause mortality. n= 15,649. n with event=2503

Variable	Category	Univariate		Age sex adjusted		Multivariable model*	
		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Sex (male vs. female)		1.02 (0.94-1.11)	0.598	1.24 (1.14-1.34)	<0.001	1.20 (1.11-1.31)	<0.001
Age in years continuous		1.10 (1.09–1.10)	<0.001	1.10 (1.09-1.10)	<0.001	1.09 (1.09-1.10)	<0.001
IMD quintile (vs. least deprived)	1 (most deprived)	0.98 (0.84-1.13)	0.674	1.31 (1.13-1.52)	0.001	1.28 (1.10-1.48)	0.001
	2	0.96 (0.84-1.09)		1.07 (0.94-1.21)		1.04 (0.92-1.18)	
	3	1.04 (0.93-1.16)		1.08 (0.97-1.21)		1.05 (0.94-1.17)	
	4	0.96 (0.86-1.07)		1.00 (0.90-1.11)		0.99 (0.89-1.10)	
CVD (vs no CVD)		1.76 (1.63-1.91)	<0.001	1.30 (1.20-1.41)	<0.001	1.35 (1.24-1.46)	<0.001
Diabetes (vs. n diabetes)		0.90 (0.81-1.00)	0.040	1.15 (1.03-1.27)	0.010	1.18 (1.06-1.31)	0.002
Hypertension (vs. no hypertension)		0.81 (0.75-0.88)	<0.001	0.75 (0.69-0.81)	<0.001	0.75 (0.69-0.81)	<0.001

Table 65 cont

Variable	Univariate		Age sex adjusted		Multivariable model*	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
CKD 3 – 5 QOF registered by 2008 (vs. not)	0.93 (0.85-1.00)	0.064	0.93 (0.85-1.00)	0.062	0.89 (0.82-0.97)	0.006
Baseline eGFR ((ml/min/1.73m^2) as continuous)	0.98 (0.98-0.98)	<0.001	0.98 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.001

*adjusting for age, sex, IMD, hypertension, diabetes, CVD, GP diagnosed CKD and baseline eGFR

4.3.3.3 Incident Renal Replacement Therapy

In the prevalent CKD cohort people with a history of new RRT (after 2008) were identified. The number of people who required incident RRT in the follow up period was 284/24,021 (1.2%). In terms of numbers of cases occurring the study period, this equates to a rate of 2.6 per thousand person years).
A higher proportion of men and younger people had new RRT during the study period, and a slightly higher proportion of people from lower socioeconomic groups (although larger absolute numbers of people from higher socioeconomic groups). Similarly, a higher proportion of people with hypertension or diabetes had new RRT during the study period, but absolute numbers were greater among people without diabetes (Table 66).
Unsurprisingly, a higher proportion of people with very low eGFR required RRT during the follow up period.

Table 66. Characteristics of people in the prevalent CKD cohort who received incident RRT during the study period.

Characteristic		New RRT		Total
		n	%	
Sex	Male	180	1.9	9607
	Female	104	0.7	14,414
Age group	<50	52	11.4	457
	50-69	115	2.7	4331
	70-79	78	1.0	7977
	80+	39	0.3	11,256
IMD	1 (most deprived)	40	1.7	2292
	2	42	1.3	3229
	3	72	1.4	5087
	4	53	0.9	5620
	5	77	1.0	7773
Hypertension	Present	227	1.4	16,504
	Absent	57	0.8	7517
Diabetes	Present	100	2.1	4727
	Absent	184	1.0	19,294
CVD	Present	110	1.1	9902
	Absent	174	1.2	14,119
Smoking	Missing data	166	1.0	16,268
	Record of smoking	117	1.5	7656
CKD 3 – 5 QOF registered	GP QOF CKD	197	1.5	13,399
	Not GP QOF CKD	87	0.8	10,622
Baseline eGFR (ml/min/1.73m^2)	45-59	41	0.3	13,642
	30-44	67	1.0	6793
	15-29	89	5.4	1635
	<15	82	27.9	294
	>60	4	0.2	1625

Table 66 cont

Characteristic		New RRT		Total
		n	%	
BMI (kg/m^2)	18.5-24.9	38	1.0	3713
	25-29.9	57	1.1	4998
	≥30	66	1.6	4124
	Missing	120	1.1	10,865

In the prevalent CKD cohort, Poisson regression analysis to identify the associations of new RRT during the study period found that presence of albuminuria at baseline was associated with greater risk of new RRT on univariate and age sex adjusted analyses (RR 4.12 (95%CI 3.11-5.45) and 3.24 (95%CI 2.44-4.30) respectively), but uACR was omitted from the fully adjusted model due to extensive missing data.

On full adjustment, males, younger people, people with diabetes or hypertension, and people with lower eGFR were more likely to have received new RRT during the study period. Baseline CKD registration status and IMD were not associated with incident RRT after full adjustment (Table 67).

Table 67. Poisson regression analysis of new RRT in the prevalent CKD cohort (n=24,021)

Variable	Category	Univariate		Age sex adjusted		Multivariable*	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Sex (vs. female)	Male	2.63 (2.07-3.35)	<0.001	2.38 (1.87-3.03)	<0.001	1.86 (1.45-2.39)	<0.001
Age (continuous)		0.93 (0.92-0.94)	<0.001	0.93 (0.92-0.94)	<0.001	0.95 (0.94-0.95)	<0.001
IMD quintile (vs. least deprived)	1 (most deprived)	1.75 (1.19-2.56)	0.008	1.36 (0.93-2.00)	0.087	0.90 (0.61-1.33)	0.672
	2	1.29 (0.89-1.88)		1.10 (0.76-1.61)		0.92 (0.63-1.35)	
	3	1.43 (1.04-1.97)		1.32 (0.96-1.83)		1.09 (0.79-1.51)	
	4	0.93 (0.65-1.32)		0.97 (0.68-1.37)		0.83 (0.59-1.19)	
CVD (vs no CVD)		0.98 (0.77-1.25)	0.873	1.50 (1.16-1.95)	0.002	1.20 (0.92-1.56)	0.179
Diabetes (vs. n diabetes)		2.26 (1.77-2.88)	<0.001	2.22 (1.73-2.83)	<0.001	1.90 (1.48-2.44)	<0.001
Hypertension (vs. no hypertension)		1.77 (1.32-2.37)	<0.001	2.25 (1.68-3.02)	<0.001	1.51 (1.12-2.03)	0.007

Table 67 cont

Variable	Category	Univariate		Age sex adjusted		Multivariable*	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
CKD 3 – 5 QOF registered by 2008 (vs. not)		1.80 (1.40-2.32)	<0.001	1.95 (1.51-2.51)	<0.001	1.12 (0.86-1.45)	0.388
Baseline eGFR (vs. 45-59ml/min/1.73m^2)	30-44	3.60 (2.44-5.31)	<0.001	4.21 (2.86-6.22)	<0.001	3.79 (2.56-5.62)	<0.001
	15-29	24.31 (16.88-35.00)		22.96 (15.92-33.13)		19.94 (13.74-28.94)	
	<15	112.80 (76.94-165.36)		67.01 (45.20-99.49)		60.74 (40.77-90.51)	
eGFR as continuous (in place of categorical)		0.90 (0.90-0.91)	<0.001	0.91 (0.90-0.92)	<0.001	0.91 (0.90-0.92)	<0.001

*adjusted for age, sex, IMD, CVD, diabetes, hypertension, GP CKD3-5, baseline eGFR.

4.3.3.4 Acute Kidney Injury

In the prevalent CKD cohort, 224 people had the N17 code for acute renal failure recorded in at least one of up to 15 hospital admissions. This represents a rate of 2.0 per 1000 person years. In 18 of the admissions, AKI was the primary diagnosis.

The characteristics of people with a record of AKI in the prevalent cohort are shown in Table 68. This shows that a higher proportion of males, older people, smokers, and people with a history of diabetes, hypertension or CVD developed AKI, as did people with lower baseline eGFR. It suggests that a higher proportion of obese people developed AKI.

On Poisson analysis, a greater risk of AKI occurring in the prevalent cohort was observed in men, people with diabetes, people with lower baseline eGFR and people who had ever received RAASi after age sex adjustment. Apart from the association with taking RAASi, these associations remained after further adjustment for diabetes and baseline eGFR. There was no relationship observed with SES on univariate or multivariable analysis (Table 69).

Table 68. Comparison of the characteristics of people in the prevalent CKD cohort (n=24,021) with a record of AKI during the follow up period

Characteristic		AKI (n=224)		No record of AKI (n=23,797)		Row total
		n	Column %	n	Column %	
Sex	Male	117	52.2	9490	39.9	9607
	Female	107	47.8	14,307	60.1	14,414
Age group	<50	3	1.3	454	1.9	457
	50-69	44	19.6	4287	18.0	4331
	70-79	67	29.9	7910	33.2	7977
	80+	110	49.1	11,146	46.8	11,256
IMD quintiles	1 (most deprived)	25	11.2	2267	9.5	2292
	2	29	12.9	3200	13.5	3229
	3	48	21.4	5039	21.2	5087
	4	49	21.9	5571	23.4	5620
	5	73	32.6	7700	32.4	7773
CKD 3 – 5 QOF registered		126	56.3	13,273	55.8	13,399
Hypertension		161	71.9	16,343	68.7	16,504
Diabetes		76	33.9	4651	19.5	4727
CVD		106	47.3	9796	41.2	9902
Had RAASi ever		179	79.9	17,167	71.9	17,346
Smoking before 2008		89	39.7	7567	31.8	7656
Baseline eGFR (ml/min/1.73m^2)	45-59	112	50.0	13,530	56.9	13,642
	30-44	72	32.1	6721	28.2	6793
	15-29	27	12.1	1608	6.8	1635
	<15	7	3.1	287	1.2	294
	>60	5	2.2	1620	6.8	1625
Baseline uACR	No measure	169	75.5	19,958	83.9	20,127
	No albuminuria	20	8.9	2246	9.4	2266
	Microalbuminuria	28	12.5	1356	5.7	1384
	Macroalbuminuria	7	3.1	237	1.0	244
BMI (kg/m^2)	18.5-24.9	30	13.5	3683	15.6	3713
	25-29.9	45	20.2	4953	21.0	4998
	≥30	48	21.5	4076	17.3	4124
	Missing	100	44.8	10862	46.1	10,962

Table 69. Poisson regression analysis of AKI in the prevalent CKD cohort (n=24,021)

Variable	Category	Univariate		Age sex adjusted		Multivariable*	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Sex (vs. female)	Male	1.66 (1.28-2.16)	<0.001	1.71 (1.31-2.22)	<0.001	1.63 (1.25-2.12)	<0.001
Age (compared to <70 yrs)	70-79	0.89 (0.61-1.73)	0.119	0.88 (0.61-1.28)	0.183	0.87 (0.60-1.27)	0.221
	80+	1.21 (0.86-1.70)		1.26 (0.90-1.78)		1.24 (0.88-1.76)	
IMD quintile (vs. least deprived)	1 (most deprived)	1.15 (0.73-1.81)	0.904	1.22 (0.77-1.92)	0.402		
	2	0.94 (0.61-1.45)		0.99 (0.64-1.52)			
	3	1.01 (0.70-1.45)		1.04 (0.72-1.49)			
	4	0.91 (0.63-1.30)		0.92 (0.64-1.32)			
CVD (vs no CVD)		1.39 (1.07-1.81)	0.014	1.26 (0.96-1.66)	0.090		
Diabetes (vs. n diabetes)		2.13 (1.62-2.81)	<0.001	2.15 (1.62-2.84)	<0.001	2.03 (1.53-2.71)	<0.001

Table 69 cont

Variable	Category	Univariate		Age sex adjusted		Multivariable*	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Hypertension (vs. no hypertension)		1.14 (0.85-1.52)	0.386	1.17 (0.87-1.56)	0.303		
CKD 3 – 5 QOF registered by 2008 (vs. not)		1.02 (0.79-1.33)	0.869	1.01 (0.77-1.31)	0.961		
Baseline eGFR (compared to 45-59ml/min/1.73 m^2)	30-44	1.42 (1.05-1.90)	<0.001	1.38 (1.02-1.86)	<0.001	1.31 (0.97-1.77)	<0.001
	15-29	2.54 (1.68-3.85)		2.43 (1.60-3.68)		2.23 (1.47-3.39)	
	<15	3.39 (1.49-7.72)		3.32 (1.46-7.56)		3.19 (1.40-7.28)	
Ever had RAASi (compared to never)		1.43 (1.03-1.98)	0.032	1.41 (1.01-1.95)	0.041	1.17 (0.84-1.64)	0.362

*adjusted for age, sex, diabetes, baseline eGFR, ever had RAASi

In the incident CKD cohort, 134 people had a record of AKI. This represents a rate of 2.1 per 1000 person years. In 6 of these admissions, AKI was the primary diagnosis. The characteristics of people with a record of AKI in the incident cohort is shown in Table 70. This shows that a higher proportion of males, smokers, and people with a history of diabetes, CVD and QOF CKD developed AKI, as did people with lower baseline eGFR. The relationship with age was not clear in this cohort. On Poisson analysis, a greater risk of AKI occurring in the incident cohort was observed in men, people with diabetes and people with lower baseline eGFR after age sex adjustment, and these associations remained after further adjustment. There was no relationship observed with SES on univariate or multivariable analysis (Table 71).

Table 70. Comparison of the characteristics of people in the incident CKD cohort (n=15,649) with a record of AKI during the follow up period

Characteristic		AKI (n=134)		No record of AKI (n=15,515)		Row total
		n	Column %	n	Column %	
Sex	Male	69	51.5	6501	41.9	6570
	Female	65	48.5	9014	58.1	9079
Age group	<50	4	3.0	626	4.0	630
	50-69	44	32.8	4565	29.4	4609
	70-79	45	33.6	5403	34.8	5448
	80+	41	30.6	4921	31.7	4962
IMD quintiles	1 (most deprived)	15	11.3	1458	9.4	1473
	2	12	9.0	2174	14.0	2186
	3	24	18.1	3224	20.8	3248
	4	35	26.3	3664	23.6	3699
	5	47	35.3	4982	32.1	5029
CKD 3 – 5 QOF registered		55	41.0	5803	37.4	5858
Hypertension		83	61.9	9471	61.0	9554
Diabetes		38	28.4	3053	19.7	3091
CVD		54	40.3	5338	34.4	5392
Smoking (ever)		61	45.5	5244	33.8	5305
Baseline eGFR (ml/min/1.73m^2)	45+	102	76.1	13,512	87.1	12,053
	30-44	14	10.5	1580	10.2	1594
	15-29	13	9.7	302	2.0	315
	<15	5	3.7	121	0.8	126

Table 71. Poisson regression analysis of AKI in the incident CKD cohort (n=15,649)

Variable	Category	Univariate		Age sex adjusted		Multivariable*	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Sex (male vs. female)		1.47 (1.05-2.06)	0.026	1.48 (1.05-2.08)	0.024	1.45 (1.03-2.04)	0.033
Age (compared to <70 yrs)	70-79	0.92 (0.61-1.39)	0.882	0.92 (0.61-1.38)	0.799	0.99 (0.66-1.48)	0.947
	80+	1.02 (0.67-1.55)		1.06 (0.70-1.60)		1.13 (0.74-1.73)	
IMD quintile (vs. least deprived)	1 (most deprived)	1.09 (0.61-1.94)	0.348	1.11 (0.62-1.98)	0.350		
	2	0.58 (0.31-1.10)		0.59 (0.31-1.12)			
	3	0.79 (0.48-1.29)		0.79 (0.48-1.29)			
	4	1.01 (0.65-1.56)		1.01 (0.65-1.56)			
CVD (vs no CVD)		1.34 (0.95-1.89)	0.103	1.28 (0.90-1.83)	0.174		
Diabetes (vs. n diabetes)		1.60 (1.10-2.33)	0.018	1.44 (1.02-2.02)	0.037	1.61 (1.07-2.43)	0.019

Table 71 cont

Variable	Category	Univariate		Age sex adjusted		Multivariable*	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Hypertension (vs. no hypertension)		1.03 (0.72-1.45)	0.888	1.04 (0.73-1.47)	0.843		
CKD 3 – 5 QOF registered (vs. not)		1.16 (0.82-1.64)	0.398	1.15 (0.81-1.62)	0.431		
Baseline eGFR (compared to 45-59ml/min/1.73m^2)	30-44	1.26 (0.72-2.20)	<0.001	1.27 (0.72-2.24)	<0.001	1.28 (0.73-2.25)	<0.001
	15-29	6.17 (3.45-11.02)		6.16 (3.43-11.06)		6.14 (3.43-11.02)	
	<15	5.14 (2.09-12.64)		4.99 (2.03-12.31)		5.08 (2.06-12.53)	

*adjusted for age, sex, diabetes, baseline eGFR.

4.3.3.4.1 Incident CVD

In the prevalent CKD cohort, 2795/24,021 (11.6%) people were identified who had a new diagnosis of a cardiovascular condition made by their GP during the follow up period. This was based on GP coding of a diagnosis of ischaemic heart disease, hypertensive heart disease, heart failure, stroke, transient ischaemic episode, or peripheral vascular disease. Of this population, 1140/24,021 (4.8%) had had a prior diagnosis of CVD and 1655/24,021 (6.8%) had not.

Unfortunately, the lack of data on cause of death meant that I was unable to conduct full analysis of incident CVD that included CVD deaths. Some analysis was conducted using GP diagnosis of CVD as the outcome of interest. This information is presented in Appendix 7.2. but extending this to include CVD deaths (when cause of death becomes available) is an aim for future HHR research.

4.3.3.4.2 Emergency hospital admission

In the prevalent CKD cohort, all-cause emergency hospital admission was explored. 1530 people had one or more emergency admissions at some point during the study period (Table 72). A slightly higher proportion of people from the lowest quintile of IMD experienced an emergency hospital admission during the follow up period (7.3% vs. 6.5% in the least deprived quintile).

Poisson analysis demonstrated that males, older people, people with diabetes, past CVD history, and lower eGFR were associated with increased risk of emergency hospital admission. No association was found with IMD. The details are given in Appendix 7.3. Again, future work to investigate cause of hospital admission is intended.

Table 72. Characteristics of people in the prevalent CKD cohort experiencing at least one emergency hospital admission during the study period.

Characteristic		Emergency admission		Total
		n	row %	
Sex	Male	687	7.2	9607
	Female	843	5.9	14,414
Age group	<50	28	6.1	457
	50-69	230	5.3	4331
	70-79	503	6.3	7977
	80+	769	6.8	11,256
IMD	1 (most deprived)	168	7.3	2292
	2	184	5.7	3229
	3	327	6.4	5087
	4	348	6.2	5620
	5 (least)	502	6.5	7773
Hypertension	Present	1082	6.6	16,504
	Absent	448	6.0	7517
Diabetes	Present	414	8.8	4727
	Absent	1116	5.8	19,294
CVD	Present	720	7.3	9902
	Absent	810	5.7	14,119
Smoking	No record	979	6.0	16,268
	Record of smoking	540	7.1	7656
CKD 3 – 5 QOF registered	GP CKD record	881	6.6	13,399
	No CKD record	649	6.1	10,622
Baseline eGFR ($ml/min/1.73m^2$)	45-59	798	5.95	13,642
	30-44	503	7.4	6793
	15-29	111	6.6	1676
	<15	25	9.9	294
	>60	93	5.6	1657

4.4 Discussion

4.4.1 Feasibility of using the Hampshire Health Record to study CKD

This study has demonstrated that the use of a database that combines routine data from primary care, secondary care and laboratory data is feasible and has the potential to be a powerful research and service evaluation tool to explore process and outcome measures in CKD. The ability to identify a cohort of people with biochemically-defined eGFR (i.e. CKD defined separately from QOF CKD registration) and to follow them over a five-year period meant that I was able to investigate some important aspects of CKD management, such as QOF CKD registration, that would not have been possible in a study using a GP-diagnosed/QOF registered CKD population. Moreover, the ability to explore process and outcome measures in a population of 24,000 people with prevalent CKD and 15,000 people with incident CKD has led to a less costly and more statistically powerful study than would be possible in a standard prospective cohort study. There are, however, important limitations to this study and challenges of using routine data and this database in particular.

4.4.1.1 Challenges of using the Hampshire Health Record to study CKD

The challenges associated with conducting this study using the HHR fall into two broad groups: those related to the use of routine data generally and those related specifically to use of the HHR.

4.4.1.1.1 Strengths and limitations of routine data

There are several well-recognised strengths of using routine data of this kind in epidemiological research. These include low cost, consistency across different GP practices (because of the national nature of the requirements of QOF) and the timeliness of the data compared to conducting a prospective research study. Disadvantages include the limitations imposed by the limited number of variables available to address important questions (such as the lack of uACR data in this study), the variable quality of recording in both primary and secondary care, uncertainties about accuracy of data, and the understandable limitation to access of confidential data.[290]

An important consideration is that of missing data. Missing data can arise because of incompleteness of recording or of coding medical events or

behavioural aspects, such as smoking. It can also arise because of inaccuracy of coding. For example – clinicians can use Read code hierarchies to record medical events in a variety of ways. A stroke, for example, could be coded as the diagnosis 'Stroke' but also as a symptom 'Weakness of arm' or an action code 'Referral to stroke clinic', or even a more general code such as 'Seen in GP surgery' (with the details of the consultation following in free text). Each of these could be regarded as correct recordings from a medical / medicolegal perspective, but only the first may be captured in any analysis of stroke. The introduction of QOF has led to the need for greater precision of recording accurate codes in general practice because they are the link to incentive payment. However, there is still the issue of limited information on potential confounding variables because many of these may not be accurately or completely recorded. I attempted to minimise the effect of this by including a wide range of codes for each potential outcome (see section 7.1). There remained, however, important missing data in this study, particularly ethnicity, smoking, and BMI. Each of these represents a potential source of unexplained confounding in these analyses.

A further limitation of using routine data is that it relies on individuals having contact with health services in order to detect and event. Events that are managed by an individual at home, or occurring in other health systems will not be captured. This study relied on measure of creatinine and estimated eGFR to define the study population. While this resulted in a more complete CKD population than using QOF CKD recording alone, potential remains for this to underestimate the true prevalence of CKD in this population because of CKD occurring in people who have never been tested.

A specific limitation of using routine data in the UK to study CKD is that the MDRD equation is currently the standard equation used to define eGFR. As discussed in sections 1.4.1 and 2.4, the CKDEPI equation more accurately classifies people with CKD. It is possible that routine use of CKDEPI in the UK would affect some of the associations identified in this study by defining a higher risk population as having CKD (compared to MDRD-defined).

4.4.1.1.2 Limitations of particular relevance to the HHR

Some of the challenges associated specifically with the HHR are described in 4.2.1 and 4.2.1 above on the issues of identifying the practices from which

to extract data and identification of those individuals meeting the criteria for CKD.

Other important considerations are:

4.4.1.1.2.1 Access to data

Access to the HHR for the data relied on colleagues with expertise in Structured Query programming Language on which the HHR is based. Considerable time was taken in translating the aims of the study into the relevant code to extract the correct data from the HHRa database.

4.4.1.1.2.2 Governance issues

The data extracted for these analyses are pseudonymised (i.e. non-patient identifiable). This is a strength because it reduces the need for ethical approval to conduct analyses such as this, but also a limitation. It means, for example, that studies requiring detailed exploration of individuals' patient records are not possible using these data.

4.4.1.1.2.3 Usability of and cleaning the data

Initially, some of the data as they were transferred across contained inaccuracies, for example, in some of the dates allocated to certain variables. This took considerable time to reconcile, and data needed to be downloaded on more than one occasion for certain variables in order to ensure that all fields were correct.

4.4.1.1.2.4 Handling the volume of data

Using a database with about 500,000 people slowed computer speed, limiting the analyses that could be achieved in the available time.

4.4.1.1.2.5 Generalisability

The HHR covers Hampshire and the Isle of Wight - an area with a limited ethnic mix. Given the limitations of routine data with respect to recording of ethnicity, it was not possible to explore this in detail, but the findings of studies using the HHR may not be generalisable to populations with higher proportions of ethnic minorities for example.

4.4.1.1.2.6 Limited measures of SES

The method by which the HHRa is anonymised means that the only measure of SES available is IMD, either as England rank (which was used in these analyses to derive quintiles) or as England deciles. It is well recognised that IMD, as an area measure of SES, has limitations at individual level. This is particularly true of an elderly population, including most populations with CKD. [242] It is also important to recognise that SES in this study was based on IMD at the time of data extraction. It is possible that some individuals were therefore misclassified if they had moved during the study period.

4.4.1.1.2.7 Baseline eGFR

An important limitation was that, because routine data were being used, the baseline eGFR value was not taken exactly on the true study baseline of 1st January 2008. 95% of eGFRs were within eight months of the baseline date, but some were more than a year from true baseline. The normal distribution of values around the baseline date makes it unlikely that this variation introduced specific bias, but there may be differences in the characteristics of people with infrequent creatinine testing compared to those being tested frequently. Conversely, the reliance on eGFR to define CKD and the ability to include chronicity by ensuring that those defined as CKD had a least two eGFR readings at least 90 days apart, improved the accuracy of CKD diagnosis compared to studies using either GP coding or a single measure of eGFR to define CKD (including the HSE study described in Chapter 2). It is possible, however, that cases of CKD were missed because of the criteria used for CKD definition. For example, people were excluded who only one eGFR value below 60ml/min/1.73m^2. Some of these individuals would have had a transient drop in eGFR (most likely AKI) and some may have had CKD which was not ever identified by a second eGFR. Future use of this dataset might usefully include description of those with each of the patterns of eGFR described in Figure 30 and exploration of outcomes in people with different eGFR patterns.

4.4.1.1.2.8 Bias due to assumptions about patient registration end dates

Use of the last consultation date to indicate the date at which a patient left a practice may have been a somewhat conservative, i.e. it would potentially underestimate time in practice. Similarly, in the situation where no face to face consultations had taken place and the last record of any kind (including

administration codes) was used to indicate end date, underestimation of time spent in a practice could cause bias, particularly in young people. This problem is likely to affect older people less as they are more likely to consult and less likely to move.[291]

4.4.1.1.2.9 Missing practices

Our method of identifying practices that had been continuously receiving pathology data from the two hospitals (Southampton and Portsmouth) for the five years of the study meant that a significant number of practices in the HHRa were excluded. This reduced the population from which the sample was drawn, but was felt necessary to maximise the reliability of the data. Future development of the HHRa as a research tool could usefully include efforts to expand the number of hospitals submitting pathology data.

4.4.1.1.2.10 Lack of cause of death data

At the time of these analyses, the HHRa does not link to any source providing cause of death. It is hoped in the future that data linkage with the ONS / Registrars General will allow for cause of death, based on death certificates, to be available.

This study suggests that combined databases, such as the HHRa, are therefore particularly useful for studies investigating aspects of process, such as registration of a condition for QOF (where an alternative method of identifying the condition is available, such as eGFR used here), identifying medication use (which could be explored in more detail than I was able to achieve in this study). The HHRa was also valuable for studying all-cause mortality (and the addition of cause of death data is an important potential development for this database) and for identifying events that are well-captured in routine practice. Events that are not well captured (such as AKI) would be better analysed using creatinine data rather than hospital coding. The HHR has the potential to allow for such analyses, but I was unable to achieve this in the time available for this study. A further research development would be to extend the analyses to identify a non-CKD control group for comparisons to be made with the CKD cohort.

4.4.2 Other UK studies using routine data

Previous research in the UK has used primary care datasets to study CKD. Collins and Altman used The Health Information Network (THIN) database to validate the QKidney CKD risk scoring system; the QICKD study used information from GP databases to explore the role of creatinine fluctuation in the prevalence of CKD; other studies have used the Morbidity Information Query and Export Syntax (MIQUEST) software to explore issues such as CKD prevalence in hypertension. [241 258 261 280] The NEOERICA study was similar to this study in using pathology data to derive prevalence of CKD and improve its identification in primary care. [66] A study by Walker et al used QOF data to identify the associations of CKD recording. It found that higher CKD recording rates were associated with higher recording rates for hypertension and stroke and practices in areas of lower deprivation. [292] Hippisley-Cox and colleagues have used large primary care datasets to validate QKidney risk scores (which includes the risk of ESKD).[293] To my knowledge, this study is the first use of an established combined primary and secondary care database to construct a retrospective cohort study to investigate process and outcome measures in CKD in the UK. A summary of previous studies is given in Table 73.

Table 73. Studies using primary care data to investigate CKD in the UK

Author / Study	Year	Data source used	Design / setting / number	Used to address
de Lusignan (NEOERICA)	2005	Pathology and clinical data via MIQUEST extraction from primary care	Cross sectional using routine data from 12 GP practices. n=28,862 with creatinine values	Identification of undiagnosed renal disease using eGFR
Stevens (NEOERICA)	2007	Pathology and clinical data via MIQUEST extraction from primary care	Cohort using routine data from 17 GP practices. n=38,262 with creatinine values	Identification, prevalence and BP control in CKD
Hippisley-Cox (Qkidney)	2010	QResearch derivation cohort and THIN database	Cohort from 368 GP practices (QResearch – derivation cohort of about 8 million people) and 364 THIN database GP practices	To develop and validate QKidney risk algortihms (including risk of developing ESKD)
Hull	2011	Pathology and clinical data via MIQUEST extraction from primary care	Cross sectional using routine data from 148 GP practices. n=49,203 with hypertension	Relationship between ethnicity, hypertension and CKD prevalence
de Lusignan (QICKD)	2011	Pathology and clinical data via MIQUEST extraction from primary care	Cross sectional using routine data from 129 GP practices. n= 930,997 (50,331 with CKD)	CKD prevalence

Table 73 cont

Author / Study	Year	Data source used	Design / setting / number	Used to address
Walker	2011	QOF reports via the NHS Information Centre	Cross sectional QOF data from 230 GP practices.	Practice and patient characteristics associated with CKD recording in primary care
Collins and Altman	2012	THIN database	Cohort of 1.6 million aged 35-74 n= 41,119 with incident CKD from THIN database GP practices.	Validation of Qkidney risk score

In contrast to some of these studies, this HHR study, by combining a cohort design with characterisation of CKD using biochemistry results (rather than CKD GP (QOF) diagnosis), allowed for the assessment of process and outcome measures in a large population of people (for both prevalent and incident CKD). An important difference between the studies using MIQUEST and this HHR study is that MIQUEST methods requires bespoke searches to be conducted in the database of each participating practice, whereas the HHRa is collected centrally, thereby requiring only one extraction of data for all practices.

4.4.3 Summary of main findings

4.4.3.1 Processes

4.4.3.1.1 QOF CKD registration

Identification of CKD (and therefore registration for QOF) in primary care is key to ensuring that correct chronic disease management and follow up occurs, particularly informing the patient of their diagnosis, uACR testing, BP monitoring and control, and appropriate prescribing (avoiding nephrotoxic medication such as non-steroidal anti-inflammatory drugs (NSAIDs) and using RAASi appropriately). In the prevalent CKD cohort, only 56% of those with study-defined CKD were registered as having a CKD diagnosis in the GP records at the start of the study. Those more likely to have their CKD identified were older, or had hypertension, diabetes, CVD or lower eGFR at baseline. A higher number (and proportion) of people from lower IMD quintiles had a record of CKD diagnosis. On univariate analysis, the likelihood of CKD recording was higher in the lowest quintile of IMD, but there was no clear pattern on multivariable analysis. This again suggests that factors on the causal pathway between SES and CKD (such as diabetes) may explain the univariate associations observed.

As CKD was only included in QOF targets from 2006/2007, analysis of subsequent recognition of CKD was also important. Over time, CKD registration in the incident cohort increased in all IMD quintiles with no evidence of an inequality gap. However, overall proportion of people registered as having CKD was still low with just over 30% of people with study-defined CKD registered as having CKD by their GP. Cumulative QOF registration increased year on year between 2008 and 2012, and there was improvement (reduction) in the median time taken between the first recorded low eGFR and registration of CKD for QOF, and between the first recorded low eGFR and first record of uACR testing. However, even in 2012, only about 10% cases were registered and or tested within 9 months of a first low eGFR.

CKD studies using primary care data that have that were conducted since the inclusion of CKD in QOF (of those shown in Table 73 above) have not compared study-defined CKD prevalence with QOF-registered CKD prevalence.[241 258 261 292 293] These studies have also not looked at time between first low eGFR and subsequent CKD registration for QOF.

My findings with regard to QOF CKD registration are consistent with the observation that about 40% of people with CKD in primary care may be unaware of their CKD diagnosis.[245]

4.4.3.1.2 uACR measurement

As described in sections 1.1.3 and 3.4.3, albuminuria is an independent determinant of poor outcomes in CKD. Measurement of uACR in CKD should therefore be a central part of the correct management of CKD in primary care. In general terms, measurement of uACR was poor in the CKD population in this study. Only 16% of the baseline CKD population had had a uACR measured by the start of 2008. Although this improved by the end of the follow up period, only 62% had ever had their uACR measured by the end of follow up. In the incident cohort, the mean proportion of people having a uACR measurement within each year between 2010 and 2012 was 26%.

The strongest positive association of uACR testing was in people with diabetes. In the incident cohort, there was also a strong positive association with QOF CKD registration.

Prior to 2009, uACR measurement was predominantly performed in people with diabetes, suggesting that ACR testing was driven more by diabetes guidelines (and diabetes QOF requirements) than by CKD guidelines. People with diabetes or hypertension were more likely to have uACR testing in fully adjusted models. As albuminuria is associated with increased risk of CVD, it is of concern that people with CVD were less likely to have uACR measurement in the fully adjusted model.

On univariate analysis, there was an association between lower SES and uACR measurement with greater likelihood of measurement in the lowest quintile of IMD. This association is not maintained on adjustment for potential confounding factors, suggesting that the association is due to other factors, most likely the higher prevalence of diabetes demonstrated in lower IMD groups. There is some evidence of a widening gap in uACR measurement over time, but this is potentially related to higher diabetes prevalence in more deprived groups and may not represent true inequity.

There is little literature evidence in the UK on the degree of measurement of uACR as a process measure. As far as I am aware, this was the first study to

examine uACR measurement in a large cohort using routine data. Comparing the findings of this study with QOF data, there is a marked contrast between the average practice achievement of QOF indicator 6 (measurement of uACR) and the patient-level achievement identified in this study. For example, as shown in Table 54, the average practice achievement of this indicator in 2010 was 82.2% (Portsmouth practices' average was 85% and Southampton 81.6%) compared to the study finding of only about 13% of people having uACR tested in 2010. This large discrepancy may be due to:

- Differences between the QOF prevalence of CKD compared to true prevalence (a lower recorded prevalence than the true prevalence would result in higher proportion achieving target). This is quite likely to be an important cause given the low level of QOF CKD registration.
- Exception reporting (exception reporting will reduce the number of people in a practice with CKD who are 'eligible' for the achievement of the QOF target)
- QOF reporting at aggregate practice level rather than individual (practice achievement of a target does not reflect individual achievement as certain people may comply with testing on a regular basis while others may never have been tested)
- The fact that, during the time of this study, the QOF achievement allowed for measurement in the last 15 months rather than 12 months (resulting in a higher proportional achievement and potential overlap between years)[294].

4.4.3.1.3 Exception reporting

Exception reporting was not particularly common. In the incident cohort, 680 people (4.4%) had a record of being exceptioned at some point. This is, however, a generalisation, as exception reporting is indicator specific. For example, the average proportion of people exception reported for QOF CKD indicator 6 (uACR measurement) in Southampton practices in 2010 was 3.2%, whereas for CKD indicator 3 (BP control) it was 8%. [289] In the data extracted for this study, it was not possible to distinguish between the different indicators; this would be a valuable area of future exploration. Greater likelihood of overall exception reporting in the study was seen in older age groups, the least deprived quintile of IMD, people with hypertension or CVD, and people with eGFR (at study entry) between 15 and 44ml/min/1.73m^2. While it is reassuring

from an inequalities perspective that people from lower SES groups do not seem to have a greater likelihood of exception reporting, it is of concern that those with comorbidities and people with CKD stages 3b and 4 may be more likely to be exceptioned from QOF targets. There is some evidence in the literature that exception reporting may increase inequity.[295] However, a study by Doran et al suggested that only about 2.7% of the variance in exception reporting could be attributed to patient or practice characteristics.[294] Potential reasons for exception reporting were discussed in section 1.3.1.5.1 on page 39. In the context of CKD, it is of concern that people with comorbidities and low eGFR may be among those more likely to be exception reported as they represent important higher risk groups.

4.4.3.1.4 RAASi prescribing

Current UK guidelines recommend RAASi use in people with diabetes and any albuminuria or in people with high levels of proteinuria with or without diabetes.[50] It was not possible to fully assess whether RAASi were being appropriately prescribed in CKD because of low numbers of people with uACR testing and the high prevalence of comorbidities that might represent alternative (or combined) reasons for their use. A lower proportion of women, older people, and people with higher eGFR had a history of being prescribed RAASi. Overall, 72% of people in the prevalent cohort had ever been treated with RAASi. This is similar to findings in the US from the CRIC study, where 74% of people with CKD had ever been prescribed RAASi.[259]

A summary of the findings of this study with regard to the process measures investigated is shown in Table 74. This demonstrates that there was little evidence of socioeconomic inequalities with regard to the process measures assessed. The study suggests that it may in fact be less deprived groups who are less likely to achieve care quality measures.

Table 74. Summary of process measure findings

	Process measure			
	Less likely to be registered as having CKD for QOF	Less likely to have urine testing for uACR	More likely to be QOF CKD exception reported	Lower proportion prescribed RAASi
Age	Younger people	Older people with CVD	Older people	Older people
Sex	-	Females	-	Females
SES	-	Possibly people from higher SES groups	Less deprived groups	-
Comorbidities	People without comorbidities (hypertension, diabetes, CVD)	People without diabetes	People with hypertension or CVD	-
eGFR	-	People with eGFR 45-59ml/min/1.73m^2	People with eGFR 15-44ml/min/1.73m^2	People with higher eGFR
Other	-	People not on QOF CKD register	-	-

4.4.3.2 Outcomes

4.4.3.2.1 Mortality

The survival analysis in the prevalent CKD cohort showed that people who died were more likely to be men, older, in a lower IMD quintile, having a previous diagnosis of CVD or diabetes and lower baseline eGFR. eGFR is an independent predictor of mortality. The Grampian Laboratory Outcomes Morbidity and Mortality Study (GLOMMS-1) study in Scotland has identified that age sex standardized mortality rate in a large CKD population was 4.7 times higher than in the general population, with non-cardiovascular causes accounting for about 50% of cases.[296] In a systematic review and meta-analysis of 39 studies,

Tonelli et al confirm the higher all-cause (and cardiovascular) mortality risk of people with CKD compared to people without.[53] Further exploration of mortality in the non-CKD population of this HHR cohort would be valuable to assess the relative deprivation effect (i.e. in people with and without CKD), which has not been explored in detail in the UK.

In the HHR study, previous hypertension was associated with reduced risk of death. This is consistent with the findings of the CKDPC meta-analysis that identified lower hazard ratios for all-cause mortality in people with hypertension and eGFR<60ml/min/1.73m^2 compared to people without hypertension. [263] The CKDPC proposes that this may be related to the presence of comorbid disorders, such as heart failure, which predispose people to increased mortality risk, but may not be associated with blood pressure increase. They also suggest that antihypertensive treatment could affect concentrations of serum creatinine and albuminuria, thereby reducing the risk of mortality.[263] GP diagnosis of CKD (QOF registration) was associated with lower risk of death after inclusion of baseline eGFR in the model suggesting that recognition and appropriate treatment of CKD may be associated with lower mortality risk. However, selection bias needs to be considered. For example, those more likely to be QOF CKD registered may be those more likely to attend their GP, take up health promotion opportunities and comply with treatment, and therefore be at lower risk.

4.4.3.2.2 Incident RRT

About 0.2% of the prevalent CKD population required RRT in each year of follow up (compared to an average of 5.6% of the population dying each year). Males, younger people, people with diabetes or hypertension, and people with lower eGFR were more likely to require new RRT after adjustment for potential confounding factors. However, low numbers of people with any uACR measurement precluded reliable assessment by albuminuria status. The finding that younger people are more likely to receive RRT is in contrast to previous studies in the UK that have demonstrated an increase in acceptance onto RRT with increasing age (although this tails off at very old age). [126] The findings with regard to eGFR and diabetes are consistent with larger studies of RRT outcome in CKD. [297] However, my finding of association between hypertension and starting RRT is in contrast to a large meta-analysis that has demonstrated no significant difference in risk of progression to ESRD (defined

by starting RRT) with hypertensive status. [263] It is possible that, because I used coding for RRT as the outcome variable in these analyses rather than progression, reverse causality explains the association identified with hypertension (i.e. those starting RRT may be more likely to have a diagnosis of hypertension made). Predictive models for CKD progression that include only age and gender have been shown to perform poorly compared to those including eGFR. [69] My findings are consistent with a similar cohort in Scotland that identified reduced risk of RRT in women and increased risk in more advanced CKD. [298]

4.4.3.2.3 AKI

In the combined populations of the prevalent and incident cohorts, 358/39670 people (0.8%) had a record of AKI identified by hospital coding of acute renal failure ('N17'). In the incident cohort, this figure was 134/15,649 over the five years of the study. Although exact figures for the denominator population in each of the five years of the study was not known, this represents approximately 54 per million population (over 18) per year. The incidence of AKI has been estimated in a large study in Scotland at about 1800 per million population (in people where AKI was identified by change in serum creatinine / eGFR). [84] My findings are therefore likely to represent a significant underestimate of the true incidence of AKI in this population. In this study, AKI was more likely to have occurred in older people, people with lower eGFR, and people with diabetes. Use of the hospital code to identify AKI is likely to be a very specific measure, but not sensitive. More sensitive indicators would be eGFR and albuminuria. Findings from the CKDPC show that lower eGFR and higher albuminuria are independent predictors of AKI risk.[72] CKD is therefore a major risk factor for AKI. As discussed in section 1.1.7, AKI is important because it is a significant cost to health services and a high proportion is potentially preventable by relatively simple interventions such as appropriate fluid management, avoidance of nephrotoxins and early treatment of sepsis.[85] [299] Higher risk of AKI has been associated with RAASi use in other studies.[300] I identified similar findings in univariate and age sex adjusted models in the prevalent cohort, but the association did not remain after adjustment for diabetes and baseline eGFR. Future work to explore this in the incident cohort using more sensitive methods of identifying AKI would be beneficial.

4.4.3.2.4 Emergency hospital admission

A slightly higher proportion of people from the lowest quintile of IMD experienced an emergency hospital admission during the follow up period, but no social gradient was demonstrated in either univariate or multivariable Poisson regression analyses.

Older people, people with diabetes or CVD, and people with lower eGFR were more likely to have an emergency hospital admission during the follow up period. These findings are consistent with a recent UK study demonstrating increased risk of hospital admission in older people, people with lower eGFR, and people with proteinuria. [301] I was unable to demonstrate any association with albuminuria because of incomplete data.

A summary of the main outcome measure findings is shown in Table 75.

Table 75. Summary of outcome measure findings

	Outcome measure – associations of elevated risk		
	Mortality	RRT	AKI
Age	Older people	Younger people	Older people
Sex	Males	Males	-
SES	More deprived groups	-	-
Comorbidities	People with previous CVD or diabetes	People with previous diabetes or hypertension	People with previous diabetes
eGFR	People with lower eGFR	People with lower eGFR	People with lower eGFR
Other	Decreased risk in people with hypertension or on QOF CKD register	-	-

4.4.3.3 Socioeconomic inequalities and CKD in the HHR study

I did not identify a great deal of evidence of socioeconomic inequalities in the process and outcome measures investigated in this study. A higher risk of mortality was identified in lower SES groups (defined by IMD), but excess mortality risk compared to the non-CKD population was not explored. Some process measures (uACR measurement, exception reporting) seemed to be more common in less deprived groups. The other outcomes investigated (RRT, AKI) did not show socioeconomic variation.

It is reassuring that this study did not identify evidence of inequality. Further research is needed to explore the reasons for observed variation in RRT and transplant by SES.

4.4.3.4 Implications for primary care

4.4.3.4.1 Process measures:

This study identified low levels of QOF CKD registration and uACR testing. This has implications for the identification and management of CKD in primary care including:

1. A need for audit –based work with practices (based on eGFR) to improve identification of CKD in practice lists, similar to that used in the QICKD study with respect to BP control.[302]
2. A need for education programmes for clinicians to improve understanding of the importance of uACR testing (including appropriate management of abnormal results), particularly in people with moderately low eGFR (CKD3a) and people without diabetes.
3. The potential to improve time from diagnosis to first registration and uACR testing.
4. Recognition that younger people and people without comorbidities are less likely to be QOF CKD registered. The fact that younger people are less likely to be QOF registered is of concern because they have potentially longer to live with the condition and are therefore at greater risk of complications/progression. There is a need for early identification and risk stratification (including uACR testing and consideration of nephrology referral) in younger people with CKD

When combined with the evidence about suboptimal BP control from the RRID study (section 3.3.3), there is therefore potential to improve the following key aspects of CKD management in primary care:

- Understanding and clarity about the management of abnormal eGFR (see section 1.1.8)
- Identification of CKD and inclusion on a chronic disease register (QOF)
- Early testing for uACR and appropriate management
- Appropriate use of RAASi and other antihypertensives
- Critical review of exception reporting in people with low eGFR, co-existent CVD or hypertension, as these indicate higher risk.
- Prevention of AKI

4.4.3.4.2 Outcome measures

This study has identified that men with CKD are at greater risk of mortality and need for RRT. There is therefore an opportunity for GPs and others in primary care to consider men to be potentially more at risk of adverse outcomes and to target men with health promotion messages and interventions to reduce risk. Gender-specific risk of RRT has been explored in a study by the CKDPC. This demonstrated overlap for men and women in the association of eGFR with rate of ESKD. [146] In that study, ESKD was defined as initiation of RRT or death due to kidney disease. I was unable to explore cause of death, and so may have missed cases of ESKD.

We have also identified that recognition of CKD (indicated by QOF registration) is associated with reduced mortality risk. This suggests that QOF-related disease management strategies such as blood pressure control may be having a positive impact on outcomes. However, this finding may be influenced by selection bias (with lower risk in people who attend for checks, comply with medication etc). It does, however, support the need to improve methods to identify people with CKD in primary care.[280] Prioritising CVD risk is important in this regard, although recent research has identified the risk of non-cardiovascular death in people with CKD, particularly related falls and dementia. [296] Frailty is therefore an important consideration in CKD

populations, who are predominantly elderly (in this study, about 74% of the combined prevalent and incident CKD cohorts were over 70).

As part of identification of groups at greater risk, it is important to act in accordance with NICE guidance to consider referral of people with low eGFR, diabetes, CVD, albuminuria to nephrologists for specialist advice. [303] There may also be a case for increased use of CVD risk stratification tools that include CKD such as QRisk2 in order to reduce mortality risk by targeting effective interventions such as statins.[172]

This study supports calls for increased awareness of the risk of AKI in the community, particularly in older people, people with diabetes and people with lower eGFR. [299] It is a concern that elevated uACR is a strong predictor of AKI, and yet this study shows it is not being measured sufficiently in primary care. Use of RAASi has been associated with higher risk of AKI in an ecological study. [300] I did not assess the combined use of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), but use of this combination has recently been shown to be associated with increased risk of adverse events, including hyperkalaemia and AKI in people with diabetic nephropathy.[304]

4.4.3.5 Implications for public health

4.4.3.5.1 Process measures:

The recognition in this study that CKD identification in younger people is suboptimal underlines the potential importance of the NHS vascular health check in early diagnosis. Current recommendations in the programme are that people with newly diagnosed hypertension are screened for kidney disease. This study suggests that consideration should be given to screening all NHS vascular check participants for CKD (i.e having creatinine as well as having routine fasting lipid levels assessed) in order to improve identification of those without comorbidities.[95]

Clinical Commissioning Group (CCG) Kidney Disease Profiles produced by NHS Kidney Care (derived from comparison between HSE and QOF data) give an indication that there is a clear gap between observed and expected prevalence of CKD for many areas of the UK, including Southampton, Hampshire and Portsmouth.[305]. The observed prevalence of CKD (based on 2012 QOF data) for

England was 4.3%, whereas the 2009 HSE estimated prevalence was 6.4%, with almost identical results for Southampton CCG.[305] The HHR study shows a similar discrepancy between QOF-defined and study-defined CKD. However, my study 'prevalence' is likely to represent an underestimate as it relied on routine blood tests, so would not have identified those with CKD who had not been tested. It does, however, add to the weight of evidence indicating that CKD is under-diagnosed in the UK.

There is also a need to improve the testing of uACR in people with CKD. There may be a role for public health teams in working across primary and secondary care boundaries to improve both CKD identification and uACR testing. A National CKD Audit, funded by the Healthcare Quality Improvement Partnership, is ongoing, and will provide further evidence to inform such efforts.

This study has identified several process and outcome measures that are worse for people with multimorbidity. For example, greater likelihood of QOF exception reporting, and increased risk of mortality, RRT and AKI occurs in people with at least one comorbidity. There is therefore a need for better guidelines for clinicians dealing with people with comorbidities to improve risk stratification and help prioritisation of interventions.[306]

4.4.3.5.2 Outcome measures:

The finding that men are at greater risk of mortality and RRT supports the need for men's health programmes that address cardiovascular risk. There is also a need for awareness-raising of risk factors for progression / CVD mortality among people with CKD.

In view of the increased risk of AKI in older people, a population-level approach may be needed to raise awareness of the risks of AKI and on issues such as avoiding dehydration when unwell, the importance of flu and pneumococcal vaccination, avoiding NSAIDs, inappropriate use of RAASi and 'sick day rules' (stopping certain medications such as RAASi, metformin when unwell) .

There is potential to reduce some avoidable hospital admissions by improving resources (including education) for community management of potential AKI.

4.4.3.6 Implications for research

There is considerable potential for using these HHR data to explore further research questions. Examples include investigating incidence and association of AKI using changes in serum creatinine values (rather than relying solely on hospital coding), investigating use of NSAIDs in people with CKD, exploring associations and outcomes of multimorbidity, and examining other CKD associations (such as fractures and depression). Identifying a control group from the total cohort population and extending these analyses to compare risk of outcomes (such as fracture risk) with the non-CKD population would also be valuable.

There is a need for better risk stratification tools to assess community risk of AKI in feasible time frames (and with limited equipment), particularly in the elderly (including consideration of ability to risk stratify in the housebound setting). Associated with this is the need to improve understanding of the appropriate management of potential AKI when identified (e.g. stopping nephrotoxic drugs).

Further research into the best methods of increasing uACR testing in primary care and improving CKD identification is also needed. [280]

5. Prevalence and associations of limited health literacy in CKD: a systematic literature review

5.1 Background and aims.

The studies in this thesis have identified some evidence of socioeconomic inequalities in various aspects of CKD, including prevalence of CKD risk factors, prevalence of CKD itself (and albuminuria), cardiovascular risk, and all-cause mortality. I have not demonstrated a social gradient in other aspects of CKD, including process measures such as blood pressure control, registration of CKD for QOF, uACR testing and outcomes (AKI and RRT). Reasons for these variations are likely to be complex. However, one aspect I wished to explore in this thesis was the role that HL might play in the context of a chronic condition such as CKD. As described in section 1.4.4, HL is defined as 'the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways that promote and maintain good health'. [216] One conceptual model of HL considers it as a 'risk' that needs to be managed in order to provide effective clinical care. [307] This approach focuses on the individual and system factors that may act independently to influence clinical outcomes. Another model considers it as an 'asset'; a means of enabling and empowering people to take greater control of their health. [307] The logical extension of the 'risk' model is for clinicians to improve patient comprehension by such means as avoidance of jargon, use of simple sentence structure, being specific, using varied forms of communication, creating an environment in which patients can ask questions, and confirming comprehension ('the teach back' strategy). [308] It is possible that a limited level of HL may be an important risk factor in the development, management (including self-management and interaction with health services) and outcomes in CKD. Conversely, limited HL is potentially modifiable and good HL may be an invaluable asset to improve outcomes and reduce inequalities. Limited HL (or 'high risk of limited HL') is defined by achievement below a threshold level of one of the HL measures. The aim of this section of the thesis was therefore to conduct a systematic literature review of studies examining the prevalence of limited HL (by whichever measure) in CKD and related

conditions in order to summarise current knowledge and inform a potential future research agenda.

Key research question to be addressed were:

- What is the prevalence of limited HL in people with CKD and other chronic vascular conditions?
- What are the associations of limited HL with measures of SES in people with CKD?

5.1.1 HL in chronic vascular diseases

Prior to conducting a systematic review on the prevalence of limited HL in CKD, I perceived that the quantity of research that had been conducted on the subject of HL prevalence in chronic disease may be small, particularly UK studies. I therefore conducted a review of the literature on the prevalence of limited HL in several cardiovascular-related conditions to explore this further.

Methods

The aim of the search strategy was to identify studies which had measured HL in people with a chronic vascular-related disorder, and recorded a prevalence of limited HL (defined as 'low', 'inadequate' or 'marginal' HL). The specific outcomes of interest were: an objectively measured prevalence of limited HL in a population with a vascular disorder or a risk factor (i.e. on the causal pathway) for vascular disorders, and the measure by which that level of HL was obtained. The indices most frequently used to measure HL include the Rapid Estimate of Adult Literacy in Medicine (REALM) and derivatives, the Test of Functional Health Literacy in adults (TOFHLA) and derivatives (including the short form, STOFHLA), the Short Assessment of Health Literacy for Spanish-speaking Adults (SAHLSA), and the Newest Vital Sign (NVS). Other measures assessing literacy include the Basic Skills Assessment Initial Test (BSAIT) and the Wide Range Achievement Test (WRAT).

In view of the differences between STOFHLA and TOFHLA in terms of the average duration to complete them and the number of items, they were considered separately, but REALM derivatives (seeking correct pronunciation of disease-specific words) were considered together because the basic structure of the tool was the same.

The exposures of interest included the presence of one or more chronic vascular related disease (or condition acting as a risk factor) including diabetes, chronic kidney disease, hypertension, hyperlipidaemia, cerebrovascular disease, coronary heart disease, heart failure, and peripheral vascular disease.

All study designs were included and a minimum study population of 50 participants (adults or adolescents) was used in order to identify studies with a predominantly quantitative rather than qualitative focus. Studies were included that reported a prevalence measure of low or limited HL assessed by a validated measurement tool.

Search strategy

The databases searched were as follows:

- Medline 1948 onwards
- Health Management Information Consortium (HMIC) 1979 onwards
- Embase 1980 onwards
- Cinahl 1981 onwards
- Ovidfulltext including Psycharticles
- Psychinfo 1806 onwards
- British Education Index (BEI)

Searching was undertaken using the Wolters Kluwer OvidSP gateway for the Medline, HMIC, Embase, Cinahl, Ovidfulltext and Psycharticles searches. The Psychinfo and BEI searches were undertaken directly via their internet access portals. Search terms were used for HL and for each of the disorders under consideration. HL terms were drawn from a previous review of prevalence of HL, updated with more recent HL measures.[229] Terms used were: Health, literacy, numeracy, HL, TOFHLA, Rapid Estimate of Adult Literacy in Medicine, REALM AND read, Wide Range Achievement Test, WRAT, Slosson oral reading test, SORT AND read, Peabody Individual Achievement Test, PIAT, National Adult Reading Test, NART, AMNART, Woodcock- Johnson AND test, medical terminology AND achievement, MART AND read, literacy assessment for diabetes, and adult basic education test, Newest Vital Sign, NVS, STOFHLA,

Short Assessment of Health Literacy for Spanish Adults, SAHLSA. These terms were searched as title, abstract or keyword. They were searched with chronic disease / risk factor terms for cardiovascular, cerebrovascular, and peripheral vascular disease, CKD, hypertension, hyperlipidaemia and diabetes. (Table 76) These terms were combined with 'prevalence' to narrow the field. A combination of Mesh and free text terms were used.

Table 76 Chronic vascular disease and risk factor search terms

Chronic condition	Search terms used
Atrial fibrillation	atrial fibrillation, atrial, fibrillation, af
Heart failure	heart failure, ccf, cardiac failure, chronic heart failure, lvf, left ventricular failure
Ischaemic heart disease	ami, angina, angina pectoris, artery, atherosclerosis, chd, coronary, coronary artery disease, coronary atherosclerosis, coronary heart disease, heart, ihd, infarction, ischaemic, ischaemic heart disease, literacy, mi, myocardial, myocardial infarction
Stroke	stroke, cva, cerebrovascular accident, cerebrovascular disease, cerebral thrombosis, cerebral embolism, cerebral haemorrhage
Peripheral vascular disease	Peripheral vascular disease, PVD, intermittent claudication, arterial embolism
Renal disease	chronic renal failure, ckd, crf, failure, kidney, kidney disease, renal, renal disease, chronic kidney disease, CKD
Hypertension	hypertension, high bp, blood pressure, blood pressure
Hyperlipidaemia	hyperlipidaemia, lipids, LDL, HDL, cholesterol
Diabetes	diabetes, diabetes mellitus, type 1 diabetes, type 2 diabetes

Limited grey literature searching was done by trying to identify otherwise unpublished conference abstracts.
Two reviewers (myself and Marie Casey) assessed the inclusion of articles and quality assessment and disagreements were resolved by discussion.
Abstracts were assessed for the following criteria:
1) The study included a population of at least 50 people with a chronic disease relevant to the research question,
2) The study used a measure of HL for which there was literature evidence of validity,
3) The study reported a prevalence (number, proportion, or percentage) of people with marginal or inadequate HL.
Full text articles were obtained if the first of these criteria and either of the other two criteria were evident from the abstract. Reference follow up was undertaken in the full text articles accessed. Study quality was assessed using the following criteria: study design, study setting, sampling method, population studied, HL measure used, main outcome variables, potential for bias, potential unrecognised confounders, presence of a sample size calculation, recognition of limitations of the study by authors.

Statistical analysis

A prevalence value for limited HL was extracted from each of the studies. 95% confidence intervals were calculated for each prevalence value of limited HL. For those studies with mixed but identifiable diseases, each sample was split accordingly into mutually exclusive sub-samples and then individual prevalence and 95% CI values were calculated. Meta-analysis was performed to analyse and summarise the observations using the 'metan' command in STATA (version 11).

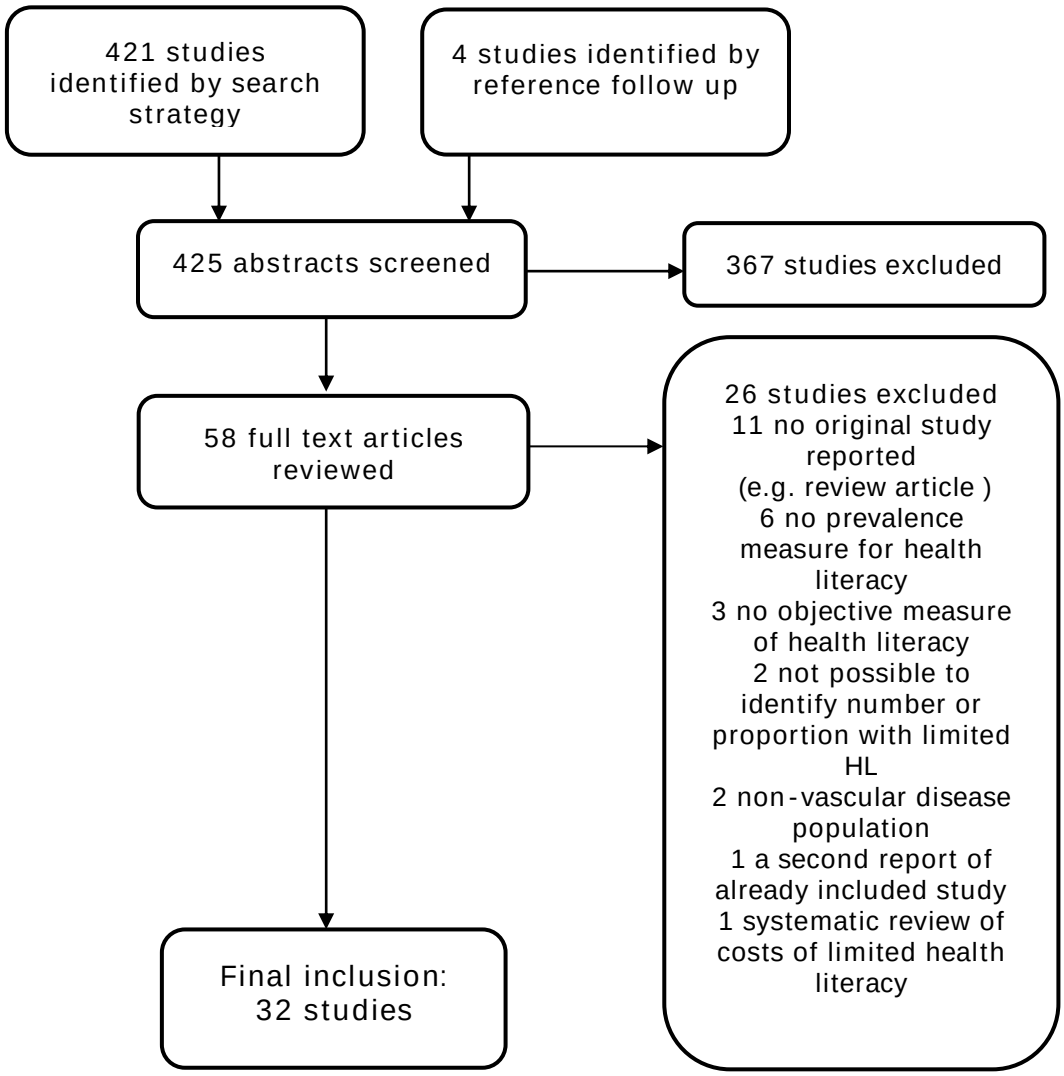
It was perceived a priori that there may be a high degree of heterogeneity in the studies identified due to variations in the methodology of studies, the populations studied, the HL measure used, and the different disease groups identified. The prevalence values were therefore combined using random effect model to give an overall prevalence value, as well as by disease groups and by HL measure used. The summarised values were aiming to give a rough idea about the limited level of HL knowing the variation in the data. The degree of heterogeneity was indicated using the I^2 statistic (the percentage of total

variation in the estimated effects across studies that is due to heterogeneity rather than to chance). [309] These results were presented using Forest plots.

Results

421 studies were identified from the initial search strategy. 367 did not meet inclusion criteria on abstract review, leaving 54 studies of which 25 were excluded on full text review. A further four potential studies were identified from reference follow up, of which one was excluded on full text examination, leaving a final inclusion of 32 studies. [154 222 310-339] See Figure 55.

Figure 55. Flow chart of study selection for systematic review of limited HL in vascular disorders



The main reasons for exclusion on full text review were – no original study reported (e.g. review article), no objective measure of HL, no prevalence measure for HL (e.g. results were all correlates of HL with other factors), study not in vascular disease-related population.

Of the 32 studies, 29 were conducted in the US, two in the UK, and one in the Netherlands. All were in English language. Six were only available as conference abstracts, not fully published.

26 were cross sectional studies, five were baseline data from cohort studies, and one was baseline data of a randomised controlled trial. Six were conducted in a community setting, four in primary care, one in both primary and secondary care, and 15 in secondary care (outpatients), four in hospital inpatients, one in a diabetes education session, and one in an emergency department. All of the studies involved adults (18 years old or above). A summary of the included studies is shown in Appendix 7.5 [154 222 312-332 334-339]

Methodological quality of included studies

I identified the following weaknesses in study design:

Sampling

Five of the studies used random sampling, for ten it was not possible to assess the method used, six used consecutive sampling, and eleven used convenience sampling (e.g. attending a clinic)

Population studied

Nine of the studies were conducted in specifically defined subsets of chronic disease populations, for example 'cardiac inpatients'. Six studies selected people from an inpatient setting. In four of the nine studies, the population selected was judged to have a potentially important impact on the prevalence of limited HL. Two studies selected patients of low socio-economic status, and two studies selected populations with poor glycaemic control.

Bias

Potential for selection bias was identified in 27 of the studies. Many of the studies excluded non-English speakers, people with cognitive impairment, people living in nursing homes, and people with poor vision, but in addition to this, the sampling method used introduced the possibility of volunteer bias for many studies. Non responder bias was a possibility in at least 18 studies. Measurement bias was considered a possibility in two studies that relied on self-report of chronic disease status.

Confounding

Residual confounding was considered a problem in 13 studies. The most important confounders omitted were considered to be education status and income.

Sample size calculation

Only five studies reported a sample size calculation.

Limitations

The majority of studies appropriately recognised their limitations. It was not possible to fully assess this aspect in the six studies where only the abstract was available.

Only four of the studies were conducted in a population of people with chronic kidney disease, ten were conducted in populations of people with heart disease (coronary heart disease and heart failure), twelve in a population with diabetes, one in a population with hypertension, and five in populations with combinations of the above. In two of the studies of combined populations, it was not possible to tell how many people there were with each of the conditions considered, but all conditions were vascular-related, so these studies were still included and considered as a 'mixed' population. No studies were identified in populations with hyperlipidaemia, peripheral vascular disease or stroke.

The total number of people in all studies was 12,429 (8% with chronic kidney disease, 8% with hypertension, 36% with diabetes, 18% with heart disease, and 30% with one or more of the above conditions, but exact numbers of each were not specified). Among the four studies in people with CKD, two were

conducted in people on haemodialysis (Cavanaugh [154], Grubbs[321]), one was conducted in kidney transplant recipients, (Gordon[320]), one in people with CKD of all stages from a nephrology clinic (Wright[339]), All CKD studies were conducted in the USA.

To assess literacy and numeracy, several of the studies used more than one measure. 17 studies used STOFHLA alone, two used TOFHLA alone, eight used REALM alone, one used REALM-R, one used REALM and Basic Skills Agency Initial Assessment Test (BSAIT), one used REALM, WRAT and a diabetes numeracy test, one used STOFHLA and REALM-T (specific for transplant patients), and one used REALM and NVS.

The results of this study are not adjusted for age differences, and it is therefore not possible to derive a directly standardised prevalence. This would require age-specific prevalence and different age ranges in the studies
The overall prevalence of limited HL in all studies, including all chronic vascular related conditions (including both those with 'inadequate' and 'marginal' HL where this distinction was made in the studies) was 32% (95% CI 31%, 33%). This reflected 24% (95% CI 22%, 27%) of those with chronic kidney disease (CKD), 40% (95% CI 37%, 43%) of those with hypertension (HTN), 35% (95% CI 33%, 36%) of those with heart disease, 27% (95% CI 26%, 28%) of those with diabetes, and 36% (95% CI 34%, 37%) of those in the mixed population studies. The combined prevalence by disease group is shown in Figure 56, and by measure in Figure 57 and Table 77. The majority of the studies (24/32) showed a screen positive prevalence of limited HL between the range of 10% and 40%. The results show no trend in screen positive prevalence toward a particular disease population, but studies using the TOFHLA measure generally gave a higher screen positive prevalence of limited HL.
Significant heterogeneity was identified in the studies (I^2 for all studies was 98%).

Figure 56. Combined prevalence of limited HL by vascular condition

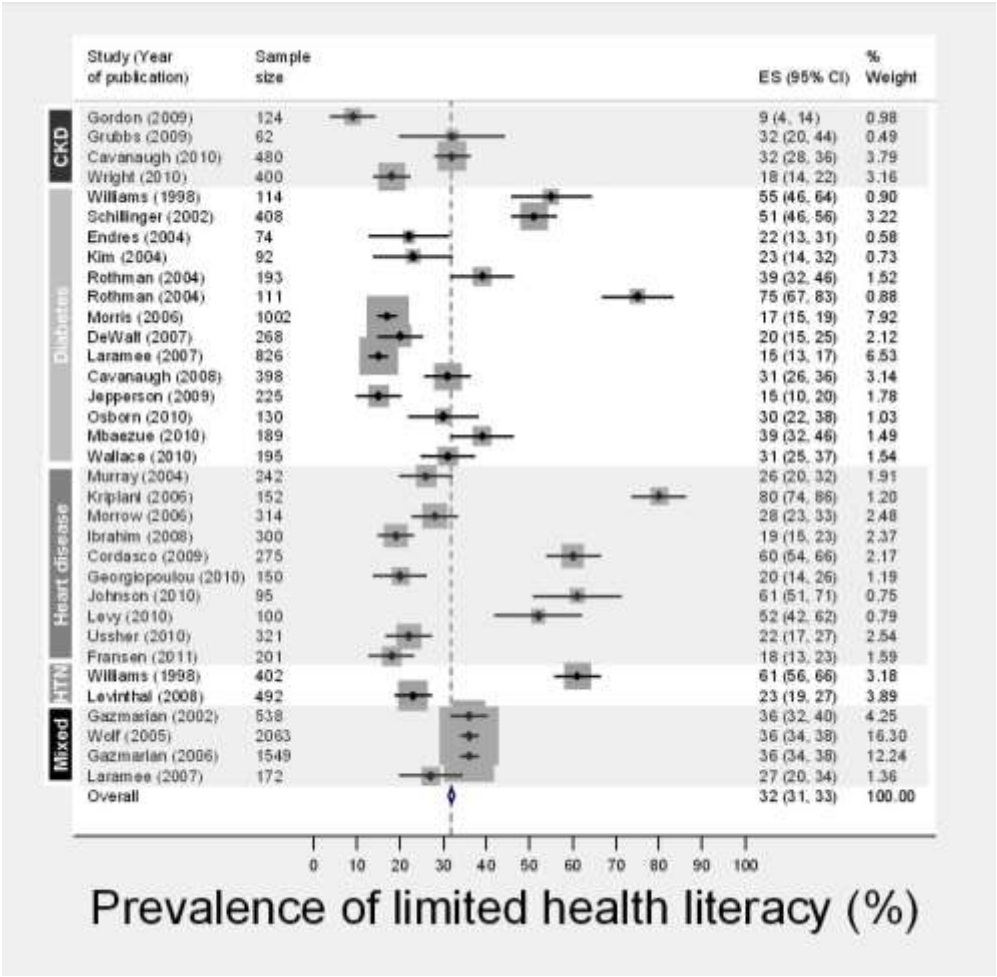


Figure 57. Combined prevalence of limited HL by HL measure

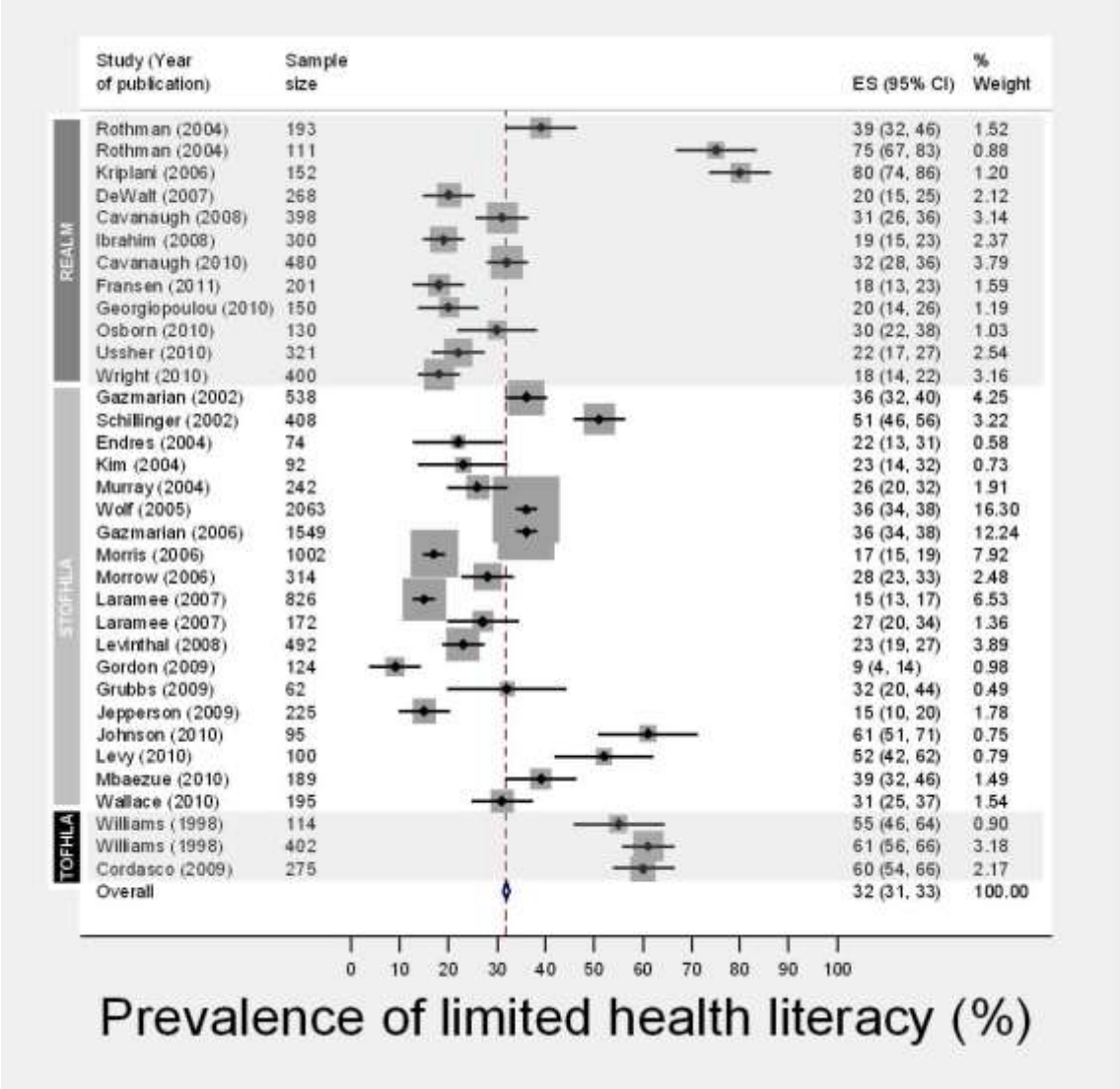


Table 77. Estimated prevalence of limited HL by HL measures used

HL measure used	Number of studies using this measure	Estimated prevalence (%)	95% CI	I^2
REALM	12	30%	(28, 31)	98%
STOFHLA	19	30%	(29, 31)	98%
TOFHLA	3	60%	(56, 63)	0%
Overall	32 individual studies	32%	(31, 33)	98%

Principal findings

The overall prevalence of limited HL in the combined populations of all the studies included in this review was about 30%, and the combined prevalence in CKD populations was about 25%. The limitations of the screening measures, the absence of a gold standard test, and the significant heterogeneity identified between studies mean that this combined prevalence estimate should be interpreted with caution. The populations in the CKD studies included people on haemodialysis, transplant recipients, and one broader CKD outpatient group. In addition, some of the patients classified with hypertension, diabetes and heart disease may also have had CKD.

Strengths and weaknesses

Strengths of this review included a broad search strategy that included multiple databases, more than one disease group, and multiple search terms for many aspects of HL. However, this review also had some important limitations. Firstly, the search strategy may not have covered all potential studies from education databases. Secondly, it may have missed studies by inclusion of the word 'prevalence' in the search strategy. This was used to limit the field of searching, but may have resulted in an over narrow result. Thirdly, several studies were reported in abstract format only, and I was unable to obtain full reports. The grey literature searching was limited, and may therefore have missed studies, particularly any reported at conferences with a primary focus

on education. This raises the possibility that this review is subject to publication bias, although this is less likely for studies of prevalence for which there is no positive or negative outcome that would influence likelihood of publication. The majority of studies identified were from the US, which reduces the generalisability of the findings of this review to other countries, particularly given differences in ethnicity and language variables, and the non-comparability of health systems. There is also a need to recognise the limitations of the HL measurement tools.

This literature review found that suspected limited HL is common among people with chronic vascular-related diseases using any of the commonly used screening measures. Limited HL identified in this way has been independently associated with poorer health outcomes, may adversely impact self-management efforts, and may therefore represent an important determinant of inequality of outcomes in chronic disease. However, in view of the majority of CKD studies having been conducted in people on renal replacement therapy, I suspected that the CKD search terms used in this review were not broad enough, and may have omitted studies. A more in depth review of limited HL in CKD was therefore conducted as part of this thesis.

The aim of the more specific review was to synthesise and critically appraise the literature evidence on the prevalence and associations of limited HL in CKD.

5.2 Methods

I aimed to identify studies that had measured HL in people with CKD, and recorded a prevalence of limited HL (defined as 'low', 'inadequate' or 'marginal' HL – see Table 78). The specific outcomes of interest were: an objectively measured prevalence of limited HL in a population with CKD, the measure by which that level of HL was obtained, and the associations of limited HL. The indices most frequently used include the Rapid Estimate of Adult Literacy in Medicine (REALM) and derivatives, the Test of Functional Health Literacy in adults (TOFHLA) and derivatives (including the short form, STOFHLA), the Short Assessment of Health Literacy for Spanish-speaking Adults (SAHLSA), and the Newest Vital Sign (NVS). A summary of these measures is given in Table 78. In view of the differences between STOFHLA and

TOFHLA in terms of the average duration of time to complete them and the number of items, they were considered separately, but REALM derivatives (seeking correct pronunciation of disease-specific words) were considered together because the basic structure of the tool was the same.

Table 78. Common health literacy measures

Instrument / how administered	Description	Time taken (min)	Scoring	Definition of low HL
Rapid Estimate of Adult Literacy in Medicine (REALM) Interview administered	Assessing correct pronunciation of 125 words from primary care materials. (More commonly used short form is 66 words) Point allocated for correct pronunciation of each word	3 – 5	Score between 0-66 converted to US school grade	0-44: Inadequate HL 45-60: Marginal HL 61-66: Adequate
Test of Functional Health Literacy in Adults (TOFHLA) Numeracy section interview administered	3 passages of text, uses modified Cloze procedure where every 5 -7th word omitted and respondent selects from four options. Interviewer administered 17 item numeracy component	20	Literacy 0-50. Numeracy 0-50. Total 0-100	0-59 : Inadequate HL 60-74: Marginal HL 75-100: Adequate HL
Short form TOFHLA (STOFHLA) Numeracy section interview administered	36 reading comprehension and 4 numeracy items	<10	Total weighted score 0-100	0-53: Inadequate HL 54-66: Marginal HL 67-100: Adequate HL

Table 78 cont

Instrument / how administered	Description	Time taken (min)	Scoring	Definition of low HL
Newest Vital Sign (NVS) Interview administered	6 questions relating to nutrition information from an ice cream container	3	0-6	0-1: High likelihood of marginal / inadequate HL 2-3: Possibility of marginal / inadequate HL 4-6: Adequate HL

The exposure of interest was a diagnosis of CKD, and studies investigating any stage of CKD were included. I included cross sectional, cohort and randomised controlled study designs that contained a cross sectional or baseline assessment of the proportion of people with limited HL in order to derive prevalence. I chose a minimum study population of 50 participants in order to identify studies with a predominantly quantitative rather than qualitative focus, and restricted the age to adults over 18 years. I included only studies that measured HL using a validated measurement tool.

Database searching was conducted in February 2012. The databases searched were as follows:

Medline (1996 onwards), Health Management Information Consortium (HMIC, 1979 onwards), Embase (1980 onwards), Cinahl (1981 onwards), Ovidfulltext (including Psycharticles), Psychinfo (1995 onwards), and the British Education Index (BEI). Searching was undertaken using the Wolters Kluwer OvidSP gateway for the Medline, Health Management Information Consortium (HMIC),

Embase, Cinahl, Ovidfulltext and Psycharticles searches. The Psychinfo and BEI searches were undertaken directly via their internet access portals.

Search terms were used for HL and for CKD. HL terms were drawn from a previous review of prevalence of HL, updated with more recent HL measures. [229] CKD terms were drawn from renal reviews identified through the Cochrane Renal Group website. [340]

Terms used were: Health, literacy, numeracy, HL, TOFHLA, Rapid Estimate of Adult Literacy in Medicine, REALM AND read, Wide Range Achievement Test, WRAT, Slosson oral reading test, SORT AND read, Peabody Individual Achievement Test, PIAT, National Adult Reading Test, NART, AMNART, Woodcock- Johnson AND test, medical terminology AND achievement, MART AND read, literacy assessment for diabetes, and adult basic education test, Newest Vital Sign, NVS, STOFHLA, SAHLSA, Short Assessment of Health Literacy for Spanish Speaking Adults. These terms were searched as title, abstract or keyword. A combination of Mesh and free text terms were used. They were searched against chronic disease terms for CKD (renal disease, kidney disease, kidney failure chronic, chronic kidney failure, chronic renal failure, CKD, CRF, renal replacement therapy, haemodialysis, hemodialysis, renal transplant, peritoneal dialysis, end stage renal disease, end stage renal failure, end stage kidney disease, ESKD, ESRD, ESRF). I also hand searched reference lists of review articles and included studies, and conference proceedings abstracts. I contacted authors for full study information where this was lacking.

Two reviewers (myself and Dr Marie Casey) assessed inclusion of articles and quality assessment. Disagreements were resolved by discussion.

Abstracts were assessed for the following criteria:

1) The study included a population of at least 50 people with CKD (in order to identify studies that were predominantly quantitative rather than qualitative in design)

2) The study used a measure of HL for which there was literature evidence of validity

3) The study reported a prevalence (or ability to calculate prevalence) of people with marginal or inadequate HL.

Full text articles were obtained if the first of these criteria and either of the other two criteria were evident from the abstract. Final study inclusion required all three criteria to be met on full text review. Duplicate publications were excluded. Study quality was assessed using the following criteria, (guided by a review of tools for assessing quality of observational studies) [341]: setting of sample (e.g. primary or secondary care), definition of nature of sample, sampling method, response rate, validity of HL measure used, main outcome variables, potential for bias, potential for unrecognised confounders (assessed by identifying variables known to be associated with HL in other studies not controlled for in the analyses), and statistical methods (including whether the prevalence estimates were age standardised, presence of a sample size calculation, measure of precision of HL prevalence).

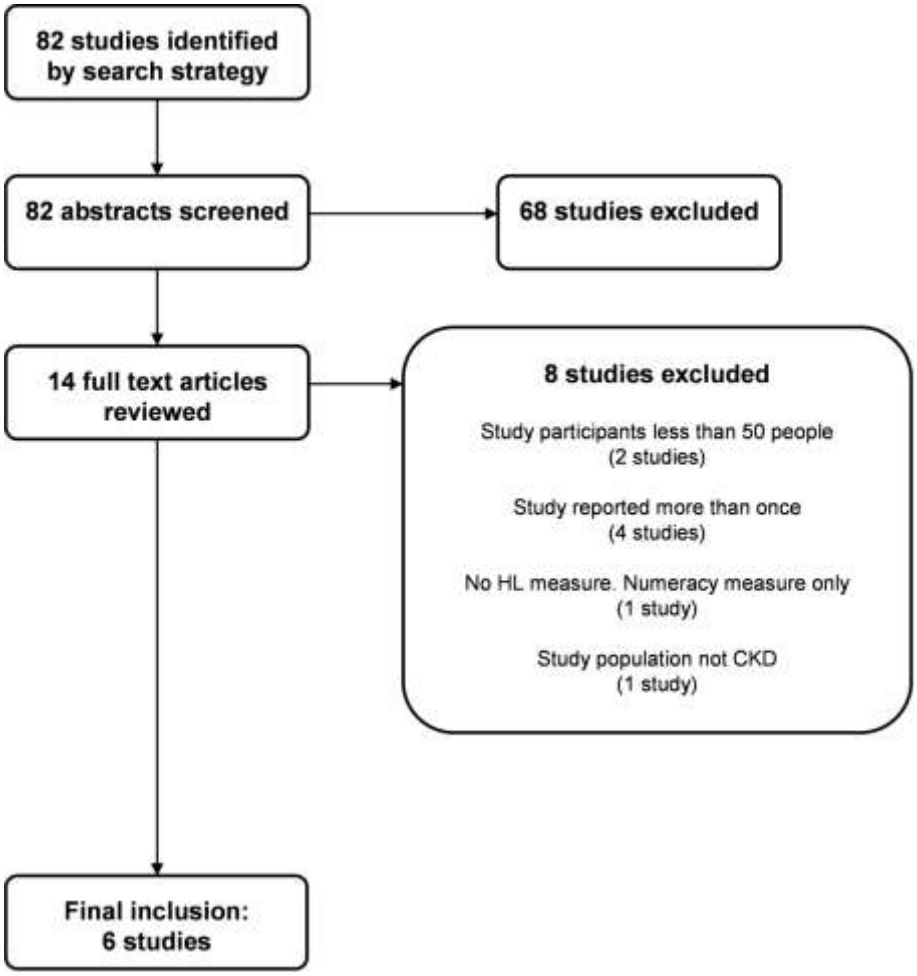
Statistical analysis

A prevalence value for limited HL was extracted from each of the studies and 95% confidence intervals calculated. Meta-analysis was performed to analyse and summarise the observations using the 'metan' command in Stata (version 11), using a random effects model to allow for between and within study heterogeneity, to give an overall prevalence value. The degree of heterogeneity was indicated using the I^2 statistic.[309]

5.3 Results

82 studies were identified from the search strategy. 68 did not meet inclusion criteria on abstract review, leaving 14 studies of which eight were excluded on full text review, leaving a final inclusion of six studies (four of these had also been identified in the first systematic review of HL in chronic vascular conditions). SeeFigure 58. [154 170 218 320 321 342]

Figure 58 Flow chart of study selection



A summary of the included studies is shown in Table 79. All studies were conducted in the U.S, all were in English language. Four studies used the REALM to measure HL, and two studies used STOFHLA (one of which also used an adapted REALM measure specific for transplant patients).

Five were cross sectional studies and one baseline data from a cohort study).

Five were conducted in dialysis units, and one in a nephrology clinic setting. The total number of patients in all studies was 1,405 (median study size 206, range 50-480 participants).

Table 79.Characteristics of studies included in the review

Study Date of Publication Location	n	Median age (yrs) [Mean]	Main aim	Study design	Setting
Cavanaugh 1 2010 US	480	62	Characterise prevalence and associations of limited HL + risk of all-cause mortality in patients initiating chronic haemodialysis	Cohort	77 Dialysis units across US
Cavanaugh 2 (conference abstract only) 2010 US	50	[51]	Association between HL and type of dialysis access used	Cross sectional	Dialysis unit
Gordon 2009 US	124	[47]	Relationship between HL, transplant knowledge and graft function	Cross sectional	Post transplant clinic visit
Green 2011 US	288	64	Prevalence and associations of limited HL in haemodialysis patients	Cross sectional	9 outpatient dialysis units
Grubbs 2009 US	62	[52.4]	Association of poor HL with access to kidney transplant	Cross sectional	5 outpatient dialysis units
Wright 2010 US	401	58	Awareness and knowledge of CKD in patients seeing nephrologists (developing CKD knowledge survey tool)	Cross sectional	Nephrology clinic

Table 79 cont– further characteristics of the same studies

Study Date of Publication Location	Participants	HL measure used	Main outcome variables	Prevalence of limited HL	Associations of limited HL
Cavanaugh 1 2010 US	Adults>18 on haemodialysis 'eligible for patient education programme'	REALM	HL, survival (adjusted HR)	32%	Males, non-white, less education, not married status, lower serum albumin, mortality
Cavanaugh 2 (conference abstract only) 2010 US	Adults on haemodialysis	REALM	Prevalence of limited HL, catheter use for dialysis (vs AVF / graft)	32%	Males, greater likelihood of catheter use
Gordon 2009 US	Adults > 18 taking immune-suppressants post kidney transplant	STOFHLA and REALM-T (relevant to transplant)	Association between HL measures and demographic variables and graft function measures	9%	Less education, lower income, and non-married status

Table 79 cont

Study Date of Publication Location	Participants	HL measure used	Main outcome variables	Prevalence of limited HL	Associations of limited HL
Green 2011 US	>17, English speaking, outpatients on dialysis	REALM	HL, association with ethnicity, education, income, veteran status, comorbidity	16%	African American race, less education, lower income, veteran status
Grubbs 2009 US	21-75 year old, black and white only, maintenance dialysis for at least 9 months	STOFHLA	HL, referral for transplant evaluation, wait-listed for transplant	32%	Older, lower income, less education, and lower likelihood transplant referral
Wright 2010 US	Adults with all stages of CKD seen at least once in a nephrology clinic in the past	REALM	Awareness of CKD by grade of CKD, literacy	18%	Kidney disease knowledge

5.3.1 Methodological quality of included studies

Sampling

None of the studies used a random sampling procedure. One used consecutive sampling, one convenience sampling (attending a nephrology clinic), three used volunteer samples, and for one it was not possible to define the sampling method.

Non response or selection bias

All of the studies were identified as having potential for selection bias. For example, in the cohort study, participants were selected if they were deemed 'eligible to participate in a patient education programme by local nephrology clinical care staff'. [154] This is recognised as a potential weakness by the authors. Many of the studies excluded non-English speakers, people with cognitive impairment, people living in nursing homes, and people with poor vision. Response rate was available for four of the studies and ranged from 26% [321] to 67% [170] leading to the possibility of non-responder bias in these studies. Overall, the risk of bias was considered to be high within these studies.

Confounding

All studies only reported overall prevalence with no age sex standardisation.

Residual confounding was considered unlikely to influence the prevalence of limited HL. However, with regard to the associations identified, some studies did not appear to control for potentially important confounding factors such as education status and income (see Table 80).

Table 80. Associations of limited HL in people with CKD

Study	Male	Older age	Race	Lower education attainment	Lower income	Veteran status	Non married status	Lower serum albumin	Catheter use for haemodialysis in preference to fistula / graft	Fistula / graft use for haemodialysis in preference to catheter use	Greater level of co-morbidity	Kidney disease knowledge	Lower likelihood of referral for transplant	Mortality
Cavanaugh 1	● a		Non-white ● a	● a				●						● b
Cavanaugh 2	● c								● c					
Gordon				● d	● d		● d							
Green			African American ● e	● e	●	● e				●	●			
Grubbs		● f		● f	● f								● f	
Wright												● g		

Marker = independent association identified with $p<0.05$

Key to Table 80

- Univariate

a Multivariate – adjusted for age, gender, race, education, marital status, diabetes mellitus status, body mass index, dialysis adequacy (Kt/V), and serum albumin

b Multivariate – adjusted for age, gender, race, and diabetes mellitus status

c Multivariate – adjusted for age, gender, race, and years of dialysis

d Multivariate – adjusted for age, gender, race, education, income, employment, time after transplant, donor source, number of transplants

e Multivariate – adjusted for race, education, income, and veteran status

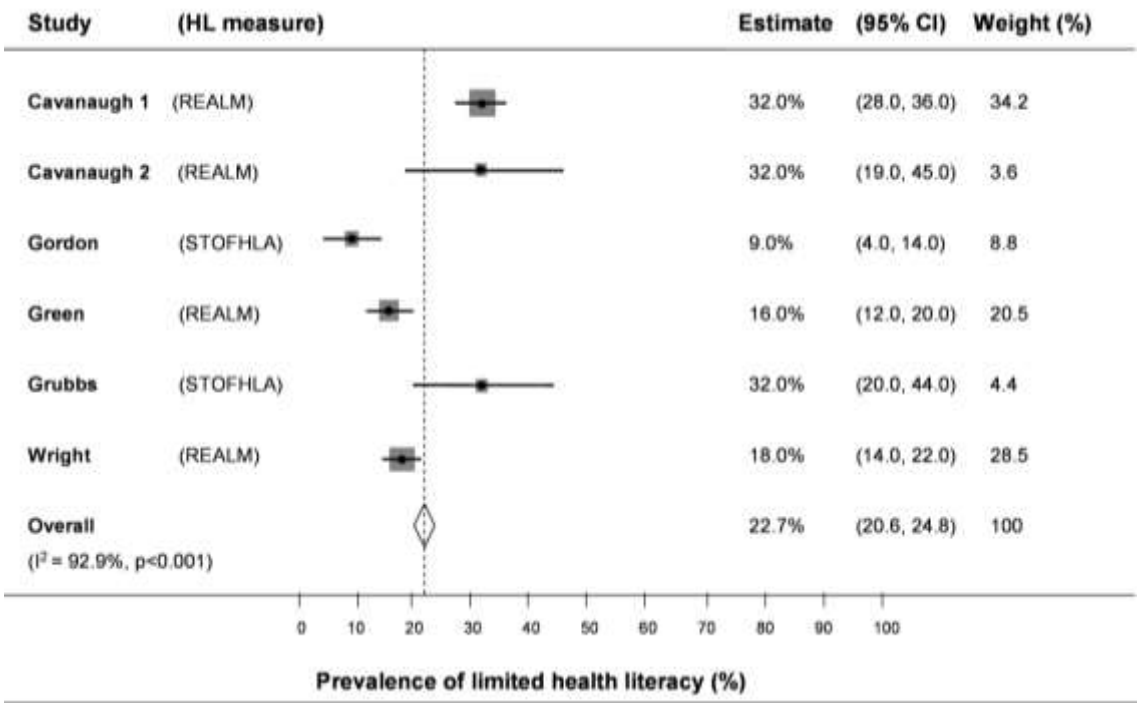
f Multivariate – adjusted for age, gender, race, income, age at start of dialysis, co morbidity, and support

g Multivariate – adjusted for age, CKD stage, participation in kidney education class, awareness of CKD diagnosis, knowing someone with CKD

Prevalence of limited HL (see Table 78 for definitions of HL levels)

Prevalence of limited HL varied from 9% to 32% (median 25%, inter-quartile range 16%) and there was significant heterogeneity (I^2 = 92.9%). The pooled prevalence of limited HL in all studies was 22.7% (95% CI 20.6%, 24.8%).(Figure 59)

Figure 59. Pooled prevalence of limited HL



Compared with the pooled prevalence of limited HL identified in the first systematic review (Figures 56 and 57) this suggests a slightly lower prevalence in CKD. However, the heterogeneity of the studies and measures mean that such comparisons should be interpreted with caution.

5.3.2 Associations of limited HL

The associations of limited HL identified in the studies are shown in Table 80.

Four studies identified associations of limited HL with lower educational attainment, and three with lower income. Two studies identified associations of limited HL with male gender, and two with non-white populations. Other associations, including veteran status, non-married status, and greater level of co morbidity were identified in individual studies. There was conflict between two studies over association with catheter vs. fistula/graft use for dialysis. Within the cohort study limited HL was associated with increased mortality in ESKD. [154]

5.4 Discussion

These systematic reviews found that limited HL is common in CKD as with several other chronic conditions, with an overall prevalence in the CKD studies of about 23%. However the significant heterogeneity between studies, and the paucity of HL research to date in CKD, means this estimate should be interpreted as indicative of magnitude rather than a precise measure. Independent associations of limited HL in CKD populations common to several studies included lower education attainment and low income, raising the possibility of an important role for limited HL in contributing to socioeconomic inequalities. Other important associations of limited HL in individual studies were lower levels of kidney disease knowledge [170], lower likelihood of referral for transplant [321], and higher mortality. [229]

No previous review of HL prevalence in studies of CKD or associated vascular-related disease was identified on literature searching. A previous systematic review aiming to identify the prevalence of low or marginal HL in the USA identified 85 studies in a wide variety of populations and gave a weighted prevalence of 26% with a very wide range (0%-68%). [229] The reviewers recognised that they could not conclude that this was a nationally representative prevalence estimate. A UK-wide survey in 759 adults, identified using random location sampling, used TOFHLA to measure HL, and gave a prevalence of 11.4% for marginal or inadequate HL.[343] The authors caution against imputing general population estimates of limited HL prevalence from clinical populations. This review supports this by demonstrating the wide variation in limited HL prevalence between studies of clinical populations.

It is possible that limited HL is more common in populations of people with CKD than the general population, due to the increased prevalence of CKD in older populations and in populations with a lower socio-economic profile, although this has not been demonstrated conclusively by this review. [118]

Overall, the risk of bias was considered to be high within these studies and the results should therefore be interpreted with caution. There was considerable variation in population characteristics such as age and diagnosis, study size, and study design, in the studies included in this review. These differences may account for much of the variation in HL prevalence identified. The prevalence of limited HL also varied depending on the measure of HL used with the two

studies using TOFHLA finding a higher prevalence of limited HL than those using the other measurement tools. There was also considerable within-study variation of prevalence of limited HL with age. For example, in the study by Cordasco et al., the prevalence of inadequate HL was about 87% in older people, compared with 26% in younger people. [313] The majority of studies controlled for age and gender in their analysis, although this may have been a residual explanation in a small number of studies (for example where it was difficult to be certain of the variables included in regression models). There appeared to be adequate adjustment for confounders in the CKD studies (age, gender, race, education, income, employment, co-morbidities, transplant status). [154 320 321 339]

Variation was also seen in the prevalence of limited HL by measure used within studies. For example, the Dutch study showed a prevalence of limited HL of 18% with REALM-S and 52% with NVS. [316] These differences add to existing uncertainty about the comparability of the different measures, and mean that it is difficult to draw inference about a true prevalence of limited HL in the population of people with chronic vascular-related disease.

5.4.1 Limitations of measures of HL

There are limitations of the HL measures, as discussed in section 1.4.4.1. The prevalence of limited HL in the studies included in this review varied with the measure of HL used. It may be that the 'prevalence' measured in the studies in this review should therefore more correctly be considered as the 'screen positive' prevalence using the particular screening tool in question. It may also be important for future research to include the development of more specific tools for the early CKD context as has already been developed for transplant patients.[320]

5.4.2 Heterogeneity

There was considerable variation in population characteristics (such as age distribution and stage of CKD), study size, and study design, setting and study quality, particularly weaknesses of sampling and non–response (Table 79). Non response and exclusions are likely to underestimate the true prevalence as it is likely that those with limited HL were less likely to be included.

The prevalence data reported in this review are not adjusted for age differences, and it is therefore hard to compare between them, and not possible to derive an overall directly standardised prevalence of limited HL. This would require age-specific prevalence in the individual studies.

5.4.3 Generalisibility

The small number of studies in this area reduces generalisability. In addition, all studies identified were from the USA, which reduces the generalisability of the findings to other countries, particularly given differences in ethnicity and language variables, the non-comparability of health systems, and uncertainty about the validity of HL measures in other countries. Moreover, variations in ethnicity distribution between the studies reduce generalisability even within the USA.

Most of the studies were conducted in secondary care with populations that included people on haemodialysis, transplant recipients, and only one study in a broader CKD outpatient group.

5.4.4 Further research

There is a need for studies that include populations of people with pre-end stage CKD, and also for non-US studies. HL is important throughout the whole care pathway in CKD, and information needs vary at different stages of CKD. An inadequate level of HL is potentially modifiable through educational interventions, and other measures that improve self-care, and facilitate access to health care and the appropriate uptake and use of health services. Such measures can empower patients to manage their own condition. Understanding the role of limited HL in adversely affecting disease process and outcomes in CKD is therefore an important goal for health services in many countries, and for future research. Whilst CKD is more common in lower socio-economic groups and certain ethnic minorities, [118] more evidence is needed on socio-economic disparities in CKD process and outcome (particularly in pre-ESKD stages of CKD) and consideration of the role of limited HL in adversely influencing self-management and shared decision making earlier in the CKD disease process. [344-346] There is some evidence that community-based chronic disease self-management education programmes can improve health behaviours and reduce hospital admissions, and that providing information for

patients in an accessible format may improve clinical outcomes. [347-349] This review supports the need to develop and evaluate such interventions in CKD. One study identified, but not included, in this review had investigated numeracy skills in people with CKD, and identified that poor numeracy skills are common. [350] This remains an important and under-explored area in CKD where understanding numerical concepts may be vital to informed decision making. Uncertainties remain about the measurement of HL, the value of measuring HL in clinical contexts, and the appropriate interpretation of the results of the different measures (including decisions to adopt a 'population' or 'at risk' approach). In the context of demographic transition and growing prevalence of CKD, HL, self-management, and shared decision making are set to become increasingly important. This should include an understanding of CKD-related HL as an asset that can improve capacity for self-care, facilitate navigation of the health system, and improve the quality of clinician-patient interactions.

5.4.5 Strengths and weaknesses

Strengths of this review included a broad search strategy that included multiple databases, clear eligibility criteria, assessment of study quality, and multiple search terms for many aspects of HL. However, there were some important limitations. Firstly, the search strategy may not have covered all potential studies from education databases, though this is considered unlikely for clinical conditions. Secondly, one study was reported in abstract format only, and I was unable to obtain full reports. Unpublished literature searching was limited, and studies may therefore have been missed, particularly any reported at conferences with a primary focus on education. This raises the possibility that this review is subject to publication bias, although this is less likely for studies of prevalence for which there is no positive or negative outcome that would influence likelihood of publication.

6. Discussion

6.1 Overview

The overarching aim of this thesis was to conduct a series of studies that would explore several aspects of CKD epidemiology, with a particular focus on relationship between SES and CKD. I addressed this aim by investigating aspects of socioeconomic inequalities in CKD in three separate populations. Firstly, I explored variations in the social distribution of CKD in the nationally representative populations of the Health Surveys for England 2009 and 2010. Secondly, I examined variation in cardiovascular risk, blood pressure control, proteinuria and survival in a prospective cohort study of people with CKD stage 3 recruited from primary care (in terms of SES, patient awareness of CKD diagnosis at baseline, and other clinical variables). Thirdly, through the creation and investigation of a large retrospective cohort of people with CKD identified through routine biochemistry tests in the Hampshire Health Record, I investigated the relationship between SES and aspects of clinical process (registration of CKD for QOF in primary care, testing of uACR, QOF exception reporting and use of RAASi) and outcome (mortality, RRT, AKI and emergency hospital admission). Finally, through a systematic literature review, I raised the possibility that HL might be relevant in the link between SES and certain aspects of CKD.

This chapter will summarise the findings from each of the chapters, explore what this thesis has added to existing knowledge, describe the potential implications for public health policy and NHS practice in the care of people with CKD, and identify areas for future research.

6.2 Summary of main findings

6.2.1 SES and CKD in the Health Surveys for England 2009 and 2010

In the analysis of data from these two Health Surveys for England in Chapter 2, I identified that CKD (defined by eGFR) and albuminuria prevalence both varied by several measures of SES (with higher prevalence in lower SES groups). For albuminuria this was maintained after adjusting for factors that might act as either confounders or factors on the causal pathway between SES and albuminuria prevalence, suggesting that there is an important independent relationship between the two. I also identified that greater prevalence of several CKD risk factors (hypertension, diabetes, smoking and obesity) was associated with lower SES. Furthermore, I identified that the prevalence of CKD would be lower and more accurate using the CKDEPI equation rather than the MDRD, and I explored the potential additional use of cystatin C as a targeted marker to improve risk stratification in CKD.

6.2.2 Assessing risk in people with CKD stage 3 in primary care: a prospective cohort study

In the series of studies conducted in the RRID cohort described in Chapter 1, I identified a relationship between greater cardiovascular risk and lower SES as measured by educational attainment, and also a relationship between lack of awareness of CKD diagnosis and increased cardiovascular risk. Blood pressure control, albuminuria, non-albumin proteinuria and all-cause mortality were not found to have a social gradient in this population or an association with CKD awareness. While this is reassuring in some respects, important clinical associations were identified that suggested that management of CKD in primary care may be suboptimal (such as the finding that good BP control was least likely in those at greatest risk of complications, particularly those with diabetes and albuminuria). This suggests that important aspects of care may need to be addressed in certain groups, and supports the need for better risk stratification in early CKD (in order to improve efforts to reduce progression/complications such as BP control and use of RAASi). Associated with this, an interesting new potential marker of risk, skin autofluorescence, was explored in this population and found to have an independent association with mortality. These findings may contribute to efforts to improve risk

stratification of people with CKD stage 3 in the future. The identification of albuminuria is important to determine prognosis and guide intervention in CKD (such as use of RAASi). In this study, I identified that albuminuria and isolated NAP have distinct associations in people with CKD stage 3, likely reflecting glomerular and tubulo-interstitial pathology respectively. The prognostic significance of isolated NAP needs further assessment. The study also suggested that a single measure of uACR is sufficient to categorise albuminuria but three uACR measurements are preferable for quantification. This is in line with current recommendations. [50]

6.2.3 Processes and outcomes in CKD: a retrospective cohort study using routine data

In the studies of people with CKD in the HHR, I showed that it was feasible to identify a large population of people with CKD using routine laboratory data and to undertake analyses using the combined primary and secondary care data in this database. I found that identification of CKD (and registration for QOF) was low. Overall, 56% of people in the prevalent CKD cohort had been registered for QOF as having CKD. In the incident cohort, QOF registration (within the year of study CKD identification) was even lower. I demonstrated socioeconomic variation in the QOF registration of people with CKD (with people from more deprived groups more likely to be QOF- registered) and, on univariate analysis, in testing for uACR in primary care (with people from lower SES groups more likely to be identified and tested). The association was not maintained on multivariable analyses, and, for uACR, this was thought to be because of higher prevalence of risk factors such as diabetes in lower SES groups. QOF CKD registration in the incident cohort was strongly associated with having uACR measured. The extent of QOF registration and uACR testing improved over time across all deprivation quintiles, but remained suboptimal. A greater likelihood of exception reporting was independently associated with older age groups, the least deprived quintile of IMD, people with hypertension or CVD, and people with eGFR (at study entry) between 15 and 44ml/min/1.73m^2. An independent association was identified between SES and all-cause mortality in CKD (with higher mortality in lower socioeconomic groups), but no social gradient was identified in other important CKD outcomes such as RRT or AKI. Perhaps the most important finding of this HHR study was the lack of albuminuria testing in people with CKD in primary care.

Given the finding in the HSE that albuminuria prevalence is greater in lower SES groups, and knowledge that albuminuria is an independent risk factor for poor outcomes, this is of particular concern.

6.2.4 Prevalence and associations of limited HL in CKD: a systematic literature review

In this literature review, I identified six studies that had addressed the question of the prevalence of limited HL in CKD. Using standardized, validated measures, limited HL was found to be common in CKD and linked to measures of SES in some studies (including low educational attainment and low income), but most were conducted in dialysis and transplant patients, so there remains little evidence on this question in people at earlier stages of CKD. This is an important area where further development could lead to educational interventions (both for clinicians and patients) that improve CKD understanding, self-management and shared decision making for people with CKD.

The following discussion relates these findings to the existing literature and goes on to explore the implications of the findings of this thesis for clinicians, for policy and for future research.

6.3 Findings of this thesis in the context of the current literature

6.3.1 CKD and socioeconomic inequalities

6.3.1.1 SES, CKD and albuminuria prevalence

As discussed in section 1.3.1.2 and summarised in Table 4 (page 35), socioeconomic variation in CKD prevalence has been identified in several, but not all studies. The reasons for the association between SES and CKD appear to be partly related to the social distribution of underlying factors associated with CKD occurrence, including obesity, smoking, hypertension, and type 2 diabetes, but the persistent association even after adjustment suggests other causal mechanisms may apply, as well as residual confounding (for example poor adjustment for lifetime smoking). [351 352] In the 2011 HSE, The prevalence of hypertension increased from 26% of men and 23% of women in the least deprived IMD quintile to 34% and 30% respectively in the most deprived quintile. [133] Other factors such as low birth weight, exposure to environmental and occupational nephrotoxins, and health care access are also associated with lower SES. [238 239] Low birth weight has been linked to greater risk of subsequent CKD in a meta-analysis of 31 observational studies.[353] There is also growing evidence of social disparities in multimorbidity, including greater prevalence among people from lower SES groups and occurrence at younger age, which may adversely impact risk of CKD and its complications.[306]

There are few data on the relationship between SES and CKD progression. The (ARIC) study in the US identified that, for white men, living in the lowest compared to the highest SES-area quartile was associated with increased risk of CKD progression (hazard ratio for elevated serum creatinine 1.6, (95% CI1.0-2.5). [122] The impact of factors across the lifecourse, including low birth weight, differential exposure to nephrotoxins, behavioural aspects such as smoking and the impact of limited HL (including differential access to healthcare in the US), are all potential explanations for such variation, but more research is needed to improve understanding of this relationship (see Figure 5 on page 15). More recently, a hospital-based retrospective study in the UK has identified independent associations between area level deprivation and CKD progression.[354]

6.3.1.2 Cardiovascular risk in CKD

The combined findings of the RRID study and the HL systematic review suggest that patients with CKD need tailored information on diagnosis, risk, medication, and behaviour change (e.g. smoking), in order assist self-management and inform decision making.[50 355] Poor HL has been recognised as a barrier to patient participation in their own care. [224] Education interventions informing patients of their CKD diagnosis and providing advice about risk reduction may also be important in reducing disparities in outcomes, with growing evidence of under-recognition of CKD in primary care, and the benefits of appropriate targeting of CVD risk-reducing interventions. [356-358] NICE guidance prioritises person-centred care, emphasising that 'People with chronic kidney disease should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals', and 'Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the person's needs. Treatment and care, and the information people are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English'.[50] Explaining risk is an important component of the management of people with CKD, and these aspects need to be taken into consideration in advising patients about risk reduction, and advising about interventions such as use of statins and RAASi.

6.3.2 CKD processes and outcomes

6.3.2.1 Processes

6.3.2.1.1 Identification of CKD

There are two issues with regard to identification of CKD that were addressed in this thesis. The first is the recognition of CKD by clinicians (particularly GPs), and the second is the communication of the diagnosis of CKD to the patient.

Previous studies have identified low levels of kidney disease diagnosis in primary care (including comparisons of QOF reports with prevalence studies using individual patient measures), but I am not aware of other analyses in the post-QOF CKD period that have compared patient-level GP-identified CKD

with eGFR-defined CKD. [280 292] I therefore believe that this is new information that may be important if CKD identification and management is to improve in England. Qualitative work undertaken with clinicians has provided very useful information about the reasons for under-identification/registration of CKD, including anxiety about disclosure of CKD to patients and organisation of care. [359] Such barriers need to be addressed in order to facilitate the optimum management of CKD. Education interventions for clinicians aimed at improving communication of risk in the context of CKD would be valuable.[360 361]

Secondly, in the RRID study, 41% of participants were unaware of their CKD diagnosis at baseline, and subsequently I showed that patients who were unaware of their diagnosis were also at greater risk of CVD. [245 278] This raises important issues about the need for effective communication strategies to inform patients of the diagnosis in order to facilitate risk-reducing interventions such as BP control and efforts to prevent AKI.

6.3.2.1.2 Exception reporting in QOF

As discussed in section 1.3.1.5.1, the intended aim of exception reporting is to protect individuals from unnecessary investigation and intervention (such as intensive BP control) in whom such activity may be inappropriate (for example, the terminally ill). Therefore, the elderly and people with many comorbidities may be appropriate people to exclude from QOF targets. I was unable to tell from this study, for example, the number of people who were terminally ill. However, there is also potential for the exception process to be subject to 'gaming' (inappropriate exclusion of patients for whom targets have been missed). A large study by Doran et al examining exception reporting behaviour across the whole of England concluded that exclusions were more likely to be among indicators related to provision of treatments and achievement of intermediate outcome targets, rather than those relating to routine checks.[294] However, although this provides reassurance in principle that inequality arising from exception practices may be unlikely, it is worth noting that their analysis was conducted on data from 2005 and 2006, before CKD was introduced as a QOF condition. From this HHR study, it appears that less deprived groups may be more at risk from lack of appropriate checks and treatment due to exception reporting. This is an area that warrants further investigation. I also did not conduct analyses on variation in exception reporting behaviour at practice level, which would also be of interest.

6.3.2.1.3 Measurement of uACR

The low level of uACR testing among people with CKD in primary care is of concern for three main reasons. Firstly, as described in section 1.4.2.3 there is strong evidence that any degree of albuminuria is linked to poor outcomes, including CVD, all-cause and cardiovascular mortality, ESKD and AKI. [13 72 80 83 131 146 182-184 362] Secondly, lack of an albuminuria measure restricts the ability to accurately risk stratify people with CKD and to appropriately intervene (for example with appropriate monitoring or prescription of RAASi). Thirdly, I have identified in the HSE study that albuminuria is independently associated with lower SES, and there is therefore potential to widen inequality gaps in CKD outcome if uACR is not routinely measured in people with CKD. I am not aware of other studies that have explored the degree of uACR testing and linked it to SES using routine data in the UK. A retrospective study of primary care records in London (prior to the inception of QOF) identified that only 29% of people with hypertension or diabetes had a record of proteinuria testing within 12 months.[363] In the HHR study, I found that people with diabetes were more likely to have had uACR measured, but also that QOF targets did seem to influence testing behaviour in people with CKD without diabetes. QOF registration was associated with greater uACR testing, suggesting that recognition of CKD is an important determinant of having uACR measured. uACR testing within 9 months of a low eGFR improved over the time of the study, but remained low overall. Identifying methods to improve the degree of routine uACR testing among people with CKD therefore represents an important goal for future research and clinical practice in the UK. There is a need to understand the potential barriers to uACR testing, such as understanding of its importance and correct interpretation of the results by clinical staff, particularly in primary care.

6.3.2.1.4 Blood pressure control and use of RAASi

Failure to achieve BP targets was common in CKD patients with hypertension in the RRID prospective cohort study, particularly in those at highest risk, and systolic hypertension predominated in those with uncontrolled BP. These findings suggest that there is scope for improving BP control in CKD stage 3 in primary care, possibly using more antihypertensive agents in combination, though there is a need to weigh potential side effects and costs.

In the light of the findings on cardiovascular risk, the main concern raised by this section of the research was that people at greater CVD risk (older people and people with diabetes and/or albuminuria) and people at greater progression risk (those with diabetes and albuminuria) were less likely to achieve BP targets. In the UK in 2010/11, the mean practice-level achievement of the QOF target for blood pressure control in CKD patients was 74.9% (standard deviation (SD) 8.2%), and the median 74.7%. [67] The RRID study has shown that BP control may be considerably worse than that when individual patient data are analysed and more robust targets are adopted. [50 179] There are several reasons why these patient-level study data may vary from QOF data, including variations in exception reporting and under-identification of CKD in practice.

In the UK, diabetic nephropathy is the commonest reason for starting RRT.[364] Recent data from the National Diabetes Audit in England showed that only 36.4% of people with diabetes were achieving target blood pressure (<140/80 if no co-morbidity, <130/80 with comorbidity, including CKD). [365] The RRID study findings were very similar (38.0% of people with diabetes achieving BP targets) and add information on BP control by albuminuria status and in people without diabetes.

There is evidence that RAASi reduce progression of CKD in patients with diabetic nephropathy and in those with non-diabetic CKD and macroalbuminuria. [366 367] A recent Cochrane review has not been able to identify sufficient evidence to determine the effectiveness of RAASi in patients with stage 1 to 3 CKD who do not have diabetes, although the included studies varied considerably with regard to severity of proteinuria. [368] In the UK, NICE guidelines recommend offering RAASi to non-diabetic people with CKD and hypertension if they have macroalbuminuria (uACR>=30mg/mmol), or to people with diabetic nephropathy who have uACR >2.5mg/mmol in men or 3.5/mmol in women. [50] RAASi were being taken by the majority of relevant participants in the RRID study, but I was unable to fully evaluate this in the HHR study.

Despite not finding a significant association between numbers of hypertensive agents and achievement of optimal BP control, the RRID study demonstrated that a large proportion of people were only taking one agent. Furthermore, there was an independent association between a higher number of antihypertensives and lower mean arterial blood pressure, even when previous

CVD was excluded (to remove indication bias). This suggests there is scope for improving BP control by the use of more antihypertensive agents in combination. The lack of association of agent number and optimal control may be as a result of indication bias, as many older patients have multiple co-morbidities. In recommendations to add more agents, risk of side effects, impact on quality of life and costs all need to be considered, as well as issues of medication adherence. The potential for RAASi to precipitate AKI, for example, is an important factor requiring evaluation in this context.[300] BP control and these related concerns will be important aspects for the ongoing UK national CKD audit in primary care.

Optimal targets for BP control remain the subject of debate. Furthermore the correct management of isolated systolic hypertension is uncertain and very low blood pressure has been associated with poor outcomes, particularly in diabetes. [369] Further research, including (initially) a systematic review of studies linking different treatment strategies for those with isolated systolic hypertension with important outcomes such as CVD and AKI, would be valuable in people with CKD. In the RRID analysis I applied the two most widely applied evidence-based guidelines in use at the time that the study was conducted, NICE and KDOQI, and added analysis for the KDIGO guidelines in view of their current relevance.

RAASi prescription is also important in the management of albuminuria. KDIGO and NICE guidelines make similar recommendations about RAASi prescription in people with diabetes (KDIGO: albuminuria ≥ 30-300mg/24hr, NICE: ≥2.5mg/mmol (men),3.5mg/mmol (women)) and without diabetes (KDIGO: >300mg/24hr, NICE: >30mg/mmol (hypertensive), >70mg/mmol (non-hypertensive)).[48 50] In the HHR study, I was unable to fully assess the appropriateness of RAASi prescribing among people with CKD due to a lack of uACR data. Optimising the balance between controlling hypertension and managing albuminuria to reduce risk of ESKD and CVD, while at the same time avoiding complications such as hypotensive falls (in this predominantly elderly population) and AKI, remains an important area for future research.

6.3.2.2 Outcomes

6.3.2.2.1 Mortality

In the RRID study described in chapter 1, I identified that the majority of deaths occurred due to CVD (41%). However, it was also recognised that a significant proportion were due to other causes, particularly cancer (29%) and infection (13%). This is similar to recent data from GLOMMS-1, a community cohort of over 3000 people with CKD in Scotland, which identified that non-cardiovascular causes of death accounted for more than half of all deaths. [296] Similarly, Fried and colleagues identified an independent association between poor kidney function (measured by both cystatin C and eGFR) and non-cardiac death in older people.[370] Unfortunately, I did not have access to cause of death for the HHR study, so was unable to confirm this in this large CKD cohort. Through patient-level meta-analysis of over 100,000 people from 14 studies, the CKDPC has clarified that low eGFR and raised uACR are both independent predictors of all-cause and cardiovascular mortality.[13] My findings were similar in the RRID study, with increased all-cause mortality risk in people with albuminuria or lower eGFR. Age has an effect on this relationship with moderation of relative risk in older people (though higher absolute risk of mortality). I was unable to assess uACR in the HHR study due to the large proportion of missing data, but there was an independent association between lower eGFR and increased mortality risk.

I also identified an independent association of mortality with SES (measured by IMD) in the HHR study (but not in the RRID study). While the limitations of IMD as a measure of SES are recognised (see Section 1.2.1), this adds to limited existing knowledge on the relationship between SES and mortality in CKD. In the dialysis population, survival has not been shown to be related to SES after adjustment for comorbidity.[155] A further issue worthy of exploration in the HHR cohort is that of relative mortality risk (i.e. the additional risk to mortality conferred by CKD when compared with the general population) as has been described in relation to cancer survival in the UK.[371]

6.3.2.2.2 Advanced glycation end product (AGE) accumulation, skin autofluorescence and CKD outcomes

My findings in the RRID study suggest that skin AF measurement might be a simple non-invasive method to improve risk stratification in CKD, although

further evaluation is needed. Current risk stratification models, such as that proposed by Tangri et al, are potentially useful for prediction of CKD progression, but less so for cardiovascular risk and all-cause mortality prediction.[69] When considering cardiovascular risk, for UK populations, the QRisk2 score appears to achieve better predictive accuracy for CVD than the Framingham score by incorporating other comorbidities, including CKD (although CKD is treated as a simple dichotomous variable in QRisk2 and does not include variation by CKD stage or presence of albuminuria). [69 172 258] There is potential for skin AF to form a useful part of such risk prediction models in CKD as an 'integrated' risk marker that is influenced by several pathological processes. [202 372] Better cardiovascular risk prediction in people with CKD would help in the targeting of interventions such as statins and antiplatelet drugs. However, the skin AF analyses in the RRID study described in section 3.3.6.1.4 do not provide sufficient evidence to develop a risk score incorporating skin AF. Future research involving studies with sufficient sample size for development and validation of risk scores incorporating skin AF would be valuable.

There is also a need for more evidence around interventions to reduce AGE accumulation and their link to clinical outcomes. Dietary modification (for example by reducing carbohydrates, animal fat and protein content, and adjusting cooking temperature) to lower AGE content has been linked to an improvement of renal function in animal and small clinical studies. [373-375] From a clinical and from a public health perspective, interventions (such as a low AGE diet, smoking cessation) to reduce AGE accumulation may become interventions to reduce risk in the CKD population, but more evidence of their place on the causal pathway is needed.

6.3.2.2.3 RRT

In the GLOMMS-I study, people with CKD were followed over six years to compare the initiation of RRT with progression of CKD.[296] It found that females had lower progression and RRT initiation rates than males and that RRT initiation was associated with CKD stage (whereas progression rate was not). [376] I also found that males were more likely to initiate RRT in the HHR study. In the CKDPC, higher risk for all–cause and cardiovascular mortality has been identified at all levels of eGFR and uACR.[146]

Deprivation has been associated with acceptance onto RRT in the UK in ecological studies, with greater acceptance among more deprived areas (but poorer access to transplant waiting lists). [126 157] In the HHR study I did not demonstrate a relationship between starting RRT and SES. [2]The HHR study was limited by having IMD as the only measure of SES and by inability to control for all potential confounders (particularly albuminuria) due to missing data. A further important issue in this context, not explored in detail in this thesis, is the issue of competing risk (where an event that is not the event of primary interest alters the probability of the event of interest). In people with CKD, mortality and RRT represent competing risks, and this can be challenging in the analysis of outcome data.[377] Fine and Gray have reported a methodology that allows for assessment of competing risk in survival analyses. [378] Such methods were not used in these analyses as cause-specific mortality data was not available (precluding the need to consider competing risks of different causes of death). Future consideration of the role of competing risk in the analysis of progression to ESKD and RRT in the HHR cohort would be valuable to avoid misinterpretation of these outcomes.

6.3.2.2.4 AKI

In the HHR study, I identified that older people, people with lower eGFR at baseline, and people with diabetes were at greater risk of AKI (identified by hospital coding). I recognised that the numbers in my study were likely to represent an underestimate of the true incidence of AKI (and I was limited by the lack of uACR data), but the findings were consistent with previous research that has identified associations of AKI with eGFR, age and diabetes.[83-85] I did not identify any variation in AKI by SES. An important limitation was missing uACR data. An area for future research is further analysis of the HHR dataset to identify AKI from changes in creatinine rather than relying on AKI coding. This would be valuable in order to fully understand the relationship between SES and AKI and get a better understanding of the frequency, recurrence, severity, outcomes and associations with AKI. Stevens et al showed that between a third and a half of cases of AKI were potentially preventable, and the HHR data has the potential to replicate and expand on some aspects of their study in a population of people with CKD.[379] It is also possible that follow up data in the RRID study will allow for analysis of AKI incidence with measures of SES (IMD and education status). Prevention of AKI in people with diabetes and CKD is of

particular importance and would form an important aspect of these future studies.

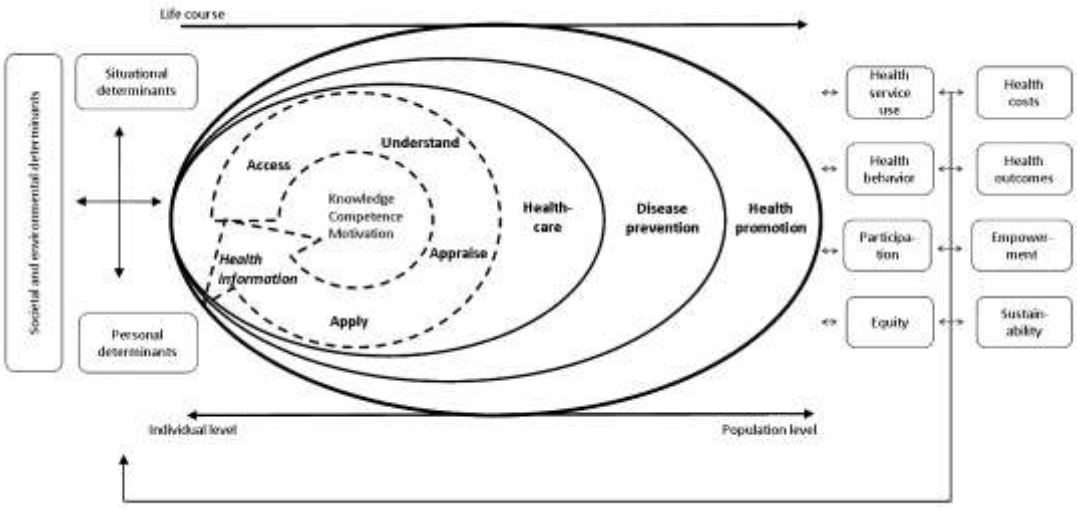
All-cause emergency hospital admission was also considered in the HHR study as an important consideration for health systems such as the NHS (with its current policy emphasis on reducing unnecessary hospital admission and transfer of care to community health services). [380] I identified similar groups at greater risk of emergency hospital admission to the AKI findings (elderly, people with comorbidities, lower eGFR). CKD has been included in the QAdmissions score - a prediction tool assessing risk of emergency hospital admission (CKD yes/no is a binary input to this risk score, which does not allow for inclusion of uACR). [381] Further analysis of cause of emergency admission in the HHR study would be a valuable contribution to the understanding of risk in CKD. Of particular interest is the link between CKD, AKI and infection as causes of emergency admission (sepsis being a cause of AKI). For example, there is evidence that influenza may precipitate AKI and hospital admission, and investigation of uptake of influenza and pneumococcal vaccination and its link to admissions would be valuable in this large CKD cohort.[85 299 382]

6.3.3 Health literacy and CKD

In the literature review described in chapter 5, I found that limited HL is common among people with CKD using commonly used HL measures. I identified several studies showing associations between limited HL and socioeconomic factors (lower education attainment, lower income), and individual studies showing association of limited HL with certain process and outcome measures (lower likelihood of referral for transplant, higher morbidity). Despite the weaknesses identified in the design of the included studies, the review suggested that limited HL may represent an important determinant of poor outcomes in CKD though a better understanding of causal mechanisms and the effectiveness of interventions to address HL is required. The model depicted in Figure 5 on page 15 shows the development and progression of CKD across the lifecourse. HL could be considered as influencing many parts of this pathway from antenatal care, through childcare, behavioural aspects and so on. At many stages, limited HL could contribute adversely (as a risk) to the development and progression of CKD, and (as an

asset) HL could be considered as an opportunity to intervene to improve outcomes. Since the inception of this thesis, a model of HL has been proposed based on integration of previous definitions and models. [383] This model summarises HL as the ability to access, understand, appraise, and apply health information in three contexts: i) as a person who is ill / a patient in a healthcare setting ii) as a person at risk of disease in a 'disease prevention system' and iii) as a citizen in relation to health promotion efforts in society. This is a helpful construct because it allows for HL in the context of a condition like CKD to be considered in terms of healthcare, but also in terms of the wider determinants of health.[383] The conceptual model is shown in Figure 60.

Figure 60. Integrated model of HL (Sorenson et al)[383]



Future research directions could usefully investigate the role of HL in CKD as a capacity to adopt practices that aid the prevention of complications and progression, including aspects of awareness and understanding, risk assessment and reduction, engagement with health services and uptake of health improvement opportunities.

There is evidence that community based chronic disease self-management education programmes can improve health behaviours and reduce hospital admissions. [347 348 384] There is increasing evidence of the contribution of self-care to outcomes in vascular conditions, and that providing information for

patients in an accessible format, not just printed material, may be important in facilitating this process. [349] The suggestion from this review that a third of people with vascular-related disorders have limited HL supports the need for accessible information and the value of tailored education programmes.

However, it needs to be remembered that, as identified in a recent systematic review of HL measures, there is wide variability in the composition of underlying constructs and content of the different measures, and the authors conclude that 'none appeared to full measure a person's ability to seek, understand, and use health information' [385] This between-measure variability may explain some of the heterogeneity seen in the results of my review. Including a measure of HL in a prospective study of people with CKD in the UK context is a potentially important future research aim. Using a more comprehensive HL measure such as the recently developed 'Health Literacy Questionnaire' (that attempts to incorporate many of these aspects) would be beneficial in such research.[386]

There is only limited evidence on the extent to which HL explains SES-related variations in health. Howard et al demonstrated that, in an elderly population, variation in HL explains some of the variation normally attributed to SES.[387] Their study was in a Medicare population in the US, and similar investigation in a UK setting would be valuable.

As discussed in section 1.1.8, CKD diagnosis is complex in practice, and clinicians are often anxious about communicating the diagnosis to patients. [359] Moreover, CKD is complex to manage, with high levels of comorbidity and many potential complications (see section 1.1.7). Communicating issues of risk, dietary advice, medication management, disease monitoring and complication prevention actions (such as flu vaccination) within the limited time frame available in most GP consultations is extremely challenging. This is particularly true in the context of an often elderly population with CKD (including greater potential for cognitive impairment in ageing populations). Further exploration of the prevalence and associations of cognitive impairment in CKD and their relationship to HL would therefore be valuable. [388]

Consideration of the 'cumulative complexity' model can be helpful in explaining some of the challenges faced by CKD patients.[389] In this model, the balance between patient 'workload' (i.e. the demands on patient's time and

energy) and 'capacity' (i.e. functioning, financial and social resources, literacy) are considered. Imbalance of workload and capacity can lead to increasing complexity over time. Methods of assessing capacity (including HL) and managing workload are an important consideration for clinicians, health services and research for people with CKD and multimorbidity.

6.4 What has this thesis added?

In summary, the research contained in this thesis has filled in some of the gaps in knowledge outlined in section 1.3 and summarised in Table 3.

- It has increased the understanding of the socioeconomic distribution of CKD prevalence and added new knowledge about the distribution of albuminuria.
- It has confirmed the findings of previous research about the social distribution of several CKD risk factors, such as diabetes, obesity and smoking.
- It has identified socioeconomic variation in cardiovascular risk in people with CKD stage 3 and has highlighted some areas of the management of CKD in primary care, particularly identification of CKD, measurement of uACR, and control of BP where improvements in care are needed. In addition, it has found that people at greatest cardiovascular risk are less likely to be aware of their CKD, and that people with poor BP control are more likely to have other risk factors for poor outcome, particularly diabetes and albuminuria.
- It has identified socioeconomic variation in mortality in people with CKD (though this could reflect the expected pattern seen in people without CKD)
- It has explored the potential of cystatin C in combination with creatinine based eGFR and uACR to act as tools for risk stratification in CKD, and has identified a novel marker (skin autofluorescence) that is linked to mortality and may also play a future role in risk stratification.
- It has demonstrated the value and potential of shared databases such as the Hampshire Health Record as useful tools in applied epidemiological and health care research.
- Finally, it has raised the possibility that limited HL, which encompasses aspects of self-management and shared decision making, which may be

an important, and potentially modifiable factor influencing some of the socioeconomic disparities identified.

Table 81 is a copy of Table 3 annotated in red with the findings of this thesis to summarise the additions to knowledge of inequalities in CKD.

Table 81. Inequalities in CKD risk factors, prevalence, progression, renal replacement therapy (RRT), and mortality – updated Table 3 with evidence from this thesis

		SES (age adjusted)	Age	Sex	Ethnicity
Prevalence of CKD risk factors and CKD	*Obesity*	⇧ in lower SES groups Confirmed this in the HSE using several SES measures	⇧ in older	⇧ in women	⇧ in Black and Pakistani women
	Diabetes	⇧ in lower SES groups Confirmed this in the HSE using several SES measures	⇧ in older	⇧ in men	⇧ in Blacks and South Asians
	Smoking	⇧ in lower SES groups Confirmed this in the HSE using several SES measures	⇧ in younger age groups	⇧ in men	⇧ in Bangladeshi and Black Caribbean men
	Primary hypertension	⇧ in lower SES groups Confirmed this in the HSE using several SES measures	⇧ in older	⇧ in men	⇧ in Black populations and South Asians

Table 81 cont

		SES (age adjusted)	Age	Sex	Ethnicity
Prevalence of CKD risk factors and CKD	*CKD Prevalence*	Variable evidence of ⇧ in lower SES groups CKD prevalence ⇧ in lower SES groups in the HSE, but explained by factors on causal pathway	⇧ ⇧ in older	⇧ in women	⇧ advanced CKD in South Asians
			Age*sex interaction identified in HSE: younger (<65) females having greater odds of CKD compared to younger males but with no difference in older age groups		
	Prevalence of albuminuria	⇧ prevalence in lower SES groups by several SES measures in HSE	⇧ in older	⇧ in men	Not known
Progression, management, and complications	*CKD Progression*	?⇧ rapidity in lower SES groups	⇧ in younger	?⇧ rapidity in men	? more rapid progression in Black and South Asian
	CVD risk in CKD	⇧ in lower SES groups in the RRID cohort	⇧ with age within age limits of risk scores in the RRID cohort.	No association with gender identified in the RRID cohort.	⇧ CVD risk in Black populations with CKD

Table 81 cont

		SES (age adjusted)	Age	Sex	Ethnicity
Progression, management, and complications	*CKD GP diagnosis*	⇧ in lower SES groups in the HHR study	⇧ in older in HHR study	No gender difference in HHR study	-
	uACR measurement	More measurement in lower SES groups (univariate) in the HHR study ?explained by ⇧ diabetes prevalence	More measurement in younger in HHR study after adjustment for confounders	More measure-ment in men in HHR study	-
	BP control	No SES associations with BP control in RRID study	⇧ poor control with age in RRID study	⇧ poor control in men for stricter BP target in RRID study	-
	AKI in CKD	No SES association shown in HHR study	⇧ in older people with CKD Confirmed this in the HHR study	⇧ risk in men in US studies. No gender difference seen in HHR study	⇧ in Black populations in US studies

Table 81 cont

	SES (age adjusted)	Age	Sex	Ethnicity
Dialysis and transplant	Older people >75 (+ more severe CKD) less likely to be referred for dialysis and listed for transplant. More men starting RRT, referred for and receiving transplant in all age groups.⇧RRT in lower SES groups, also younger and more diabetes-related ESKD, and less able to access transplant. South Asian and Black populations start dialysis younger. Minority ethnic groups wait longer for transplant. Incident RRT ⇧ in men and lower age groups, but no SES variation in incident RRT in the HHR study.			
Mortality	⇧ ESKD in women cancels normal female survival advantage. No variation in survival on RRT by SES. Black populations have increased mortality risk attributable to kidney disease compared to whites. ⇧ all-cause mortality in men, increasing age and lowest quintile of IMD in the HHR study ⇧ all-cause mortality with increasing age, albuminuria and lower eGFR in the RRID study. No SES association identified in the RRID study.			
Health literacy	Low HL common in CKD. Linked to measures of SES in some studies (including low educational attainment and low income), but most were conducted in dialysis and transplant patients.			

⇧ denotes increased risk demonstrated

6.5 Strengths and limitations

6.5.1 Strengths and limitations of the studies

The specific strengths and limitations of the individual studies included in this thesis have been outlined in the relevant sections:

Health Survey for England analyses: Section 2.4.1 , Page 99

Renal Risk in Derby analyses: Section 3.4.5 , Page 175

Hampshire Health Record CKD study: Section 4.4.1.1 , Page 292

HL in CKD systematic review: Section 5.4.5, Page 348

The following section will consider the strengths and limitations of the thesis as a whole.

6.5.2 Strengths and limitations of the thesis

6.5.2.1 Strengths

6.5.2.1.1 Populations studied

Overall, this thesis covered a broad series of questions related to the relationship between CKD and socioeconomic inequalities. It also expanded knowledge of CKD epidemiology by examining new tests and markers in CKD. It has expanded several areas of knowledge (Table 81) by examining three separate populations of people: a nationally representative population in two HSEs, a prospective cohort of people with CKD in the RRID study, and a large retrospective cohort in the HHR. It has also provided new information on the developing area of HL in the context of CKD.

6.5.2.1.2 Methodology

In terms of the methods used, the inclusion of cross sectional data has allowed for analysis of prevalence, while the use of prospective and retrospective cohorts has allowed for analysis of both prevalent and incident cohorts, and included survival analyses and improved understanding of process and outcome measures through longitudinal methods. The methods involved in the creation of a retrospective cohort of people with CKD have demonstrated the

feasibility and potential value of routine data in this context, and will allow for further development and analysis of this and other cohorts from the HHR in the future. There is potential for future collaboration with other similar UK datasets (including the Dundee Tayside database, the Salford Integrated Record, the Welsh secure anonymised information linkage databank (SAIL) databank).[306 390 391] Defining people with CKD in the HHR using routine biochemistry results (and not on clinical diagnosis and coding) has allowed for analysis of process measures that would not otherwise have been possible. Undertaking a formal systematic review with broad inclusion criteria on the subject of HL in CKD formed a useful starting point for future research in this area.

6.5.2.1.3 Primary care / population focus

As stated elsewhere, the majority of people with mild and moderate CKD are managed in primary care in the UK. Much renal research to date has taken place in secondary care settings and in people with more severe stages of CKD. The research presented in this thesis represents an important expansion of knowledge of CKD in the primary care setting, particularly in the RRID and HHR studies. The potential for improving risk stratification in CKD with targeted use of markers (cystatin C), and potential new techniques such as skin AF, may begin to address concerns about inappropriate over diagnosis of CKD in the population. [165]

6.5.2.1.4 SES measures

In considering the relationship between CKD and SES, the thesis has benefitted from the variety of SES measures available in the included studies. The detail of different measures of SES in the HSE study has afforded unprecedented insights into the SES/CKD prevalence relationship. In the RRID study, the detailed recording of education status provided a very informative addition to IMD, providing contrasting results in some places and illustrating the difficulties of accurately measuring SES in elderly populations. The HHR study was limited by only having IMD as a measure of SES, but this disadvantage is balanced by the power of such a large cohort that would have been impracticable to develop as a traditional cohort study.

6.5.2.2 Limitations

6.5.2.2.1 Ethnicity

An important limitation common to each of the studies in this thesis is a lack of data on ethnicity. The HSE study, although representative of the population of England, had low absolute numbers of people from ethnic minorities, precluding detailed analyses. The RRID study drew participants from practices in and around Derby, an area with a predominantly white population. The HHR study, in relying on routine data, suffered from such poor recording of ethnicity that reliable analyses that included ethnicity were not possible (it also covers an area of low ethnic minority population density). It is well recognised that ethnicity and SES are closely related, with a greater proportion of ethnic minorities represented in lower SES groups.[97] It is also well recognised that ethnicity has important effects in the context of kidney disease, including the prevalence of risk factors, the prevalence and severity of CKD itself, and the relationships between ethnicity and process and outcome measures (such as access to RRT, progression to ESKD, attainment of clinical practice guideline standards and competing mortality risk).[123 157 160 261] The lack of ethnicity data in these studies therefore reduces their generalisability to many populations with different ethnic distributions. As discussed in section 1.4.4.1, when discussing HL, it is important to distinguish the lack of knowledge or understanding of health issues from language difficulties. While language barriers present their own important challenge to health services, they are distinct from HL. Low levels of HL can exist completely independent of the understanding of language and should be considered separately. [225 307]

6.5.2.2.2 HL and SES

A limitation of the studies in this thesis is that they did not allow for a direct comparison between factors associated with limited HL and those associated with levels of SES. HL was not measured in either the HSE or the RRID studies, and HL is not routinely measured in health care settings in the UK to allow for analysis in routine data. The systematic review identified studies that had found associations between low levels of HL and measures of SES (particularly low educational attainment and low income), but they were conducted mainly in dialysis and transplant patients in the US, so their generalisability is uncertain.

6.5.2.2.3 Study methods

The studies in this thesis were observational in nature (cross sectional and cohort studies). It is therefore important to treat the results with caution in terms of attributing causality. HL is a developing field, and new studies may have been reported since the systematic review was undertaken.

6.5.2.2.4 Generalisability

By their nature, the studies in this thesis (with the exception of the systematic review) had a UK focus. Their generalisability to other populations may therefore be limited and their interpretation in other contexts should be approached cautiously. Despite some variations in the predominant pathological mechanisms underlying CKD in different countries, however, many are common across populations, and many of the study findings are therefore largely generalisable. [8]

6.6 Recommendations

6.6.1 Implications for the NHS

There are some key recommendations for the health service that arise from this research.

6.6.1.1 Identification of CKD

This research has found similar results to studies from other developed countries showing that CKD and albuminuria are common and associated with adverse outcomes.[143 214] It has shown that both are associated with greater prevalence in lower SES populations in England, which is consistent with previous research showing that CKD cases referred to hospitals are more likely to come from deprived areas.[152] The introduction of CKD targets to QOF in 2006/7 has undoubtedly increased the diagnosis and recognition of CKD in primary care, but these studies confirm findings from the QICKD study that many cases of CKD in the UK remain undiagnosed. [282] It also adds new information about the low levels of uACR testing among people with CKD (and the associations with lack of testing) – an important quality issue in CKD management. In the HHR study, I found that recognition of CKD was associated with reduced mortality risk. This is potentially due to the risk reduction

associated with increased monitoring and attention to control of blood pressure, use of RAASi etc among people whose CKD is recognised. This hypothesis could be explored further in the HHR. However, it is not possible to exclude selection bias as an explanation for this finding (if GPs' register 'better' patients for QOF), so this conclusion should be treated with caution.

Summary NHS need:

- Improved identification of CKD in primary care

6.6.1.2 Risk stratification in CKD

This thesis has highlighted a need for better methods to ensure that uACR testing is performed in people with CKD as a vital part of risk stratification in primary care. In common with other studies, I have shown that use of the CKDEPI equation to derive eGFR and define CKD will reduce the overall prevalence, but improve the risk stratification of those identified. [392] I also showed that use of cystatin C in combination with other markers may help to risk stratify in people with mild CKD, and that CVD risk is worse in lower SES groups in people with CKD and that men and people with diabetes appear to be at greater risk of adverse associations in a number of process and outcome measures.

Summary NHS needs:

- Better testing of uACR in CKD in primary care
- Use of the CKDEPI equation to derive eGFR
- Consideration of focused cystatin C use in risk stratification of people with mild CKD (a group in whom there is concern about over-diagnosis)
- Strategies that target cardiovascular risk reduction at high risk individuals, including people from lower SES groups, men, and people with diabetes.

6.6.1.3 Clinical management of CKD

I have shown that BP control is suboptimal in people with CKD in primary care. There is a need for improved BP control in the general population of people with CKD (population approach) and for BP control to be focused on people with diabetes and/or albuminuria (high risk approach). The results of the HHR study suggest that QOF exception reporting in CKD should be under regular

review to assess whether higher risk people may be being exception reported. This could be achieved by regular audit. In common with other research, the HHR study also suggested that recognition and coding of AKI in secondary care needs to improve. Better understanding of AKI in the UK, including the contribution of CKD to the burden of disease, requires standardised definition and recording in the NHS.

Summary NHS needs:

- Improved BP control in CKD in primary care, particularly in people with diabetes and/or albuminuria.
- Regular audit of people with CKD who have been exception reported for QOF.
- Improved methods to identify and record people with AKI in hospital (and in the community, along with better ways of preventing AKI in CKD patients).

6.6.1.4 Diagnostic awareness and HL in CKD

The findings from the RRID study about CKD awareness, and the HL findings underline the importance of good communication with patients and the need for information resources to help people understand CKD and the actions they can take to reduce risk of adverse events. As a result of this, a letter was drafted that could be used by GPs to inform patients of the finding of reduced eGFR and invite them to discuss this with their GP or practice nurse (see Appendix 7.6). Such interventions would benefit from evaluation in qualitative studies. The language used in CKD is an important consideration. Labelling CKD a 'disease' is an important part of this discussion as it may form a barrier to patients' understanding and management of the condition.[359]

Efforts to improve HL in the UK have included the NHS Expert Patient Programme, information provided by specific disease charities and interest groups (such as the UK National Kidney Federation), and a growth in interactive web-based interventions such as the NHS Choices kidney disease check. [393] In the context of demographic transition and growing prevalence of chronic vascular related disease, including CKD, self-management is set to become increasingly important, and greater efforts to ensure patient and public understanding are needed. This should include an understanding of HL as an

asset that can improve capacity for self-care and navigation of the health system.

Summary NHS need:

- Improved communication strategies to inform people of their CKD and encourage understanding of ways to reduce their risk
- Education programmes / resources to facilitate better self-management of chronic conditions including CKD (with extension to milder CKD)

6.6.2 Policy implications

The policy implications arising from this thesis can be considered as 'high risk' and 'population level' strategies in CKD.[394]

High risk

This thesis has underlined the need for better identification and risk stratification of people with CKD and has proposed ways in which this might be achieved such as using better markers and communicating more effectively with patients. It also includes the need to establish policies that allow for the appropriate targeting of interventions such as BP control, use of statins and RAASi, and messages about AKI prevention in high risk people once identified.

There is also potential to develop policies with the aim of reducing unnecessary hospital admissions by earlier recognition of AKI in the community, but such efforts must be supported by adequate infrastructure to allow for better monitoring such as urgent and repeated testing of creatinine at home.

Population level

At a population level, greater awareness and understanding of CKD and its determinants would facilitate testing strategies. Education efforts related to self-care and appropriate access of the health system, and policies related to population level prevention strategies to reduce smoking, hypertension, diabetes and obesity are important. More information is needed about other dietary interventions such as population-level advice on appropriate fluid intake (particularly for the elderly).

Policies guiding the identification and management of CKD should take account of the potential benefits of changing to use of the CKDEPI equation to derive eGFR, and should prioritise the need to assess albuminuria by the measurement of uACR. Efforts should be made to address social inequalities in the risk of CKD progression and complications, notably CVD risk. Mechanisms to monitor socioeconomic inequity in aspects of primary prevention, care, and outcomes of CKD would usefully inform such efforts. In addition, policies directing management of CKD in primary care need to ensure that albuminuria identification, blood pressure control, and use of renin-angiotensin aldosterone system inhibitors is targeted to help reduce inequity in outcomes. The forthcoming UK national CKD audit also needs to explore these considerations.

6.6.2.1 Multimorbidity in CKD

An important consideration in the context of CKD is the potential impact of comorbidities on patients and populations, rather than considering only the index condition. This is particularly true when trying to understand the impact of SES and HL on process and outcomes. A recent cross sectional study of over 1.7 million people in Scotland identified that over 23% had more than one long term condition, increasing to about 65% in people over 65.[306] Multimorbidity prevalence increases substantially with age, but there is good evidence that multimorbidity is not simply a problem of the elderly, with a significant burden (in terms of absolute numbers) in the under 65s. [306 395] Multimorbidity is associated with poor outcomes, including high overall and premature mortality, poor quality of life, and impaired functional status. [306 396-399] People with multimorbidity are higher users of ambulatory and inpatient care than people without, including higher consultation rate in primary care, emergency department attendance, and both hospital admission and readmission. [400 401] Recent evidence from a large UK primary care database study showed that levels of multimorbidity are strongly positively associated with healthcare costs. [402]

Multimorbidity disproportionately affects the disadvantaged in society as assessed by a variety of measures of SES. People with lower educational qualifications, those with lower SES using area deprivation indices, and those with greater disadvantage assessed by lifecourse measures such as childhood financial hardship and lifetime earnings have all been shown to have a greater

burden of multimorbidity. [306 399 403-405] There is also evidence that the onset of multimorbidity occurs at a younger age among people from more deprived areas and of the high prevalence of depression as a comorbidity in those with multiple conditions.[306 402]

The measurement and definition of multimorbidity has varied over time, both in medical practice and in the research literature.[406 407] Commonly used definitions rely on the presence of two or more simultaneously occurring chronic conditions in the same person. [408] The assumption that one condition is the 'index' condition and others are 'comorbidities' has been challenged, however, with the suggestion that, from the patient's perspective, one condition may not necessarily be more central than others. Conversely, it has been argued that the definition should be context-specific, with some conditions very obviously being dominant and others therefore rightly being considered 'comorbidities' in a clinical care setting.[409] In the context of CKD, particularly mild to moderate CKD, it may well not be considered the index condition by either patient or clinician, particularly because it is largely asymptomatic until an advanced stage. Diabetes or hypertension may, for example, be considered the more important diagnosis. However, this thesis suggests that identification and appropriate monitoring of CKD and its comorbidities can be associated with reduced risk. Conversely, ignoring CKD may lead to increased morbidity, mortality and health and social care costs (for example hospital admissions due to community-acquired AKI). It is therefore important to increase the awareness and prioritisation of CKD in the context of multimorbidity among both clinicians and patients. This relates to the discussion about HL in CKD above. Although not a central aim of the study (and limited to those chronic conditions identified in the study protocol), examination of multimorbidity in the prospective cohort study in Chapter 3 showed that most participants had more than one chronic condition (see Figure 16). In addition, there appeared to be variation in the prevalence of multimorbidity by SES, with a greater proportion in people with no formal education and from lower IMD quintile areas (see Figure 17 and Figure 18).

Despite the increasing prevalence of multimorbidity, and the growing recognition of its implications for patients, clinicians and health services, the majority of current guidelines, including those for CKD, focus on single diseases with little to guide clinical management or priority setting in the

context of multimorbidity. [50 303] There is also some evidence of harm arising from the application of conflicting individual disease guidance in the context of multimorbidity.[410] As with clinical guidelines, QOF is dominated by targets relating to single conditions, although there have also been efforts in UK primary care (including use of incentive payments to GPs) to identify and case manage people with complex care needs. More evidence is needed to guide primary care teams on the management of people with multimorbidity. More disadvantaged patients may be those least well equipped to fill the gap between guidelines, clinical advice and their personal experience of managing several conditions, possibly mediated by lower levels of HL. [221] This is an important public health issue both for populations of people with CKD and other chronic conditions, and one that is likely to grow as the prevalence of multimorbidity increases.

6.6.3 Implications for future research

Recommendations for future research arising from this thesis can be considered under the themes of risk stratification in CKD, interventions in CKD, comorbidity and CKD, inequalities and CKD, and HL in CKD.

Risk stratification in CKD:

- There is a need for full evaluation (to include economic evaluation) of the additional, targeted role of cystatin C compared to CKDEPI / albuminuria alone in prospective studies of CKD 1-3.
- Further evaluation (to include development of risk stratification models) of the role of novel markers such as skin AF in CKD as predictors of all-cause and cardiovascular mortality.
- Improved understanding in prospective studies of the optimum levels of BP control in elderly people with CKD.
- Better understanding of the prognostic significance of NAP

Interventions in CKD

- Evaluation of education / audit interventions to improve CKD identification and uACR testing in primary care. This could include a qualitative study with GPs and practice nurses to improve understanding of the reasons behind poor testing rates, and intervention studies, such

as use of a similar audit based education method as that used to influence BP control in QICKD.[302]

- Qualitative research to explore GP views of communicating CKD diagnosis with patients.
- Exploration of other methods to increase patient knowledge and understanding of CKD, such as peer education, in high risk groups. [411]
- Systematic review of studies investigating treatment strategies for people with isolated systolic hypertension and CKD.
- Evaluation of primary care interventions to reduce risk of AKI, such as optimum fluid intake in the elderly, optimum management of acute illness (such as stopping RAASi), measurement of uACR (and appropriate action), uptake of vaccinations.

CKD and comorbidity

Research to improve understanding of the role of CKD in driving poor outcomes in multimorbidity could usefully include:

- Better understanding of the incidence and associations of AKI in people with multimorbidity including CKD
- The role of multimorbidity in driving inequalities in CKD process and outcomes.
- The association between HL, multimorbidity and SES

CKD and inequalities

There are several unanswered questions about CKD and inequality that could potentially be addressed by further analysis of HHRa data:

- There is an ongoing need to better understand the relationships between CKD progression and SES.
- Exploration of relative mortality (CKD vs. control group) and cause of death.
- Exploration of the relationship between AKI (defined by biochemical measures) and SES (and other clinical factors such as RAASi use) in the HHRa.
- Examination of emergency admissions by cause of admission (assessing role of influenza and pneumococcal vaccination uptake) in the HHRa

- Exploration of the association between deprivation, QOF exception reporting and prognosis.

HL in CKD

Uncertainties remain about the measurement, nature, and importance of HL and of its role in CKD.

- More evidence is needed on socio-economic disparities in CKD process and outcome (particularly in pre-ESKD stages of CKD) and consideration of the role of limited HL in adversely influencing self-management.
- A more comprehensive gold standard measure of HL may help by drawing out the different facets of HL (functional, interactive, and critical) that play a part in facilitating self-management of chronic disease. Use of the Osborne Health Literacy Questionnaire in a population with CKD would be valuable. [386]
- Further research into the relationship between CKD and HL is required before the development of interventions can be considered.

6.7 Conclusion

In this thesis, I have conducted a series of studies that aimed to provide a better understanding of the relationship between SES and CKD and to expand knowledge on various aspects of CKD epidemiology.

The first study explored variations in the social distribution of CKD and albuminuria in the nationally representative populations of the Health Surveys for England 2009 and 2010. I found that CKD (defined by eGFR) and albuminuria prevalence both varied by several measures of SES and that greater prevalence of several CKD risk factors (hypertension, diabetes, smoking and obesity) were associated with lower SES. I also identified that the prevalence of CKD would be lower and more accurate using the CKDEPI equation rather than the MDRD, and I explored the potential additional use of cystatin C as a targeted marker to improve risk stratification in CKD.

The second study examined variation in cardiovascular risk, blood pressure control, proteinuria and survival in a prospective cohort study of people with CKD stage 3 recruited from primary care (in terms of SES, patient awareness of CKD diagnosis at baseline, and other clinical variables). I identified a relationship between greater cardiovascular risk and lower SES as measured by educational attainment, and also a relationship between lack of awareness of CKD diagnosis and increased cardiovascular risk. Blood pressure control, albuminuria, non-albumin proteinuria and all-cause mortality were not found to have a social gradient in this population or an association with CKD awareness. Clinical associations were identified that suggested that management of CKD in primary care may be suboptimal (such as good BP control being least likely in those at greatest risk of complications, particularly those with diabetes and albuminuria). I concluded that important aspects of care may need to be addressed in certain groups and recognised a need for better risk stratification in early CKD. Associated with this, an interesting new potential marker of risk, skin autofluorescence, was explored in this population and found to have an independent association with mortality.

The third study involved creation and investigation of a large retrospective cohort of people with CKD identified through routine biochemistry tests in the Hampshire Health Record. In this study, I investigated the relationship between SES and aspects of clinical process (registration of CKD for QOF in primary

care, testing of uACR, QOF exception reporting and use of RAASi) and outcome (mortality, RRT and AKI). I demonstrated socioeconomic variation in the QOF registration of people with CKD and, on univariate analysis, in testing for uACR in primary care (with people from lower SES groups more likely to be identified and tested). The association was not maintained on multivariable analyses, and, for uACR, this was thought to be because of higher prevalence of risk factors such as diabetes in lower SES groups. The lack of identification of CKD and albuminuria testing in people with CKD in primary care was an important finding in this study. The extent of QOF registration and uACR testing improved over time, but remained suboptimal. An independent association was identified between SES and all-cause mortality in CKD, but no social gradient was identified in other important CKD outcomes such as RRT or AKI.

Finally, through a systematic literature review, I examined the possibility that at least some of the socioeconomic variation identified in CKD outcomes might be related to low levels of HL in people with CKD. I found limited HL to be common in CKD and linked to measures of SES in some studies, but most were conducted in dialysis and transplant patients, so there remains little evidence on this question in people at earlier stages of CKD.

In conclusion, this thesis has increased the knowledge base on several aspects of CKD epidemiology and on the relationship between various aspects of CKD and socioeconomic inequalities and has explored the possibility that improving HL may be one way of narrowing inequality gaps. Implications have been drawn for public health policy, for the clinical care of people with CKD and for future research needs.

7. Appendices

7.1 Appendix 1 – Acute Kidney Injury

Three main definitions have been in use for AKI :

1. Acute Dialysis Quality Initiative (RIFLE criteria)
2. Acute Kidney Injury Network (AKIN)
3. Kidney Disease Improving Global Outcomes

The criteria used to identify AKI within each of these definitions are given in Table 82 below.

Appendices

Table 82. Comparison of the three common definitions of acute kidney injury

	ADQI (RIFLE)	AKIN	KDIGO
Date published	2004	2007	2012
Stages of AKI	5	3	3
Relative increase in serum creatinine	1.5x (R) 2x (I) 3x (F)	1.5 - 2x (Stage 1) 2 - 3x (Stage 2) >3x (Stage 3)	1.5 - 1.9x (Stage 1) 2 - 2.9x (Stage 2) 3x (Stage 3)
Absolute increase in serum creatinine	-	0.3mg/dl(26.5µmol/l) (Stage 1) ≥4.0 mg/dl (≥ 354 µmol/l) (Stage 3)	0.3mg/dl(26.5µmol/l) (Stage 1) >4.0 mg/dl (353.6 mcmol/l) (Stage 3)
Reduction in urine output	<0.5 ml/kg/h for 6 hours (R) <0.5 ml/kg/h for 12 hours (I) UO <0.3 ml/kg/h for 24 hours (F)	<0.5 ml/kg/h for >6h (Stage 1) < 0.5 ml/kg/h for >12h (Stage 2) UO < 0.3 ml/kg/h for 24h (Stage 3)	<0.5 ml/kg per hour for 6-12h (Stage 1) < 0.5 ml/kg/h for >12h (Stage 2) UO < 0.3 ml/kg/h for 24h (Stage 3)
Reduction in eGFR	GFR decrease >25% (R) GFR decrease >50% (I) GFR decrease >75% (F)	-	-

7.2 Appendix 2 – Incident CVD in the HHR prevalent CKD cohort

Treating incident CVD as these 1655 new cases recorded by the GP with no prior history of CVD ('primary CVD'), the number and proportion increased with age, hypertension and diabetes (Table 83).

On univariate and age sex adjusted analyses, incident CVD was associated with increasing age, hypertension and smoking. There was no clear evidence of variation by IMD.

It was also associated with any albuminuria (univariate RR 1.27 (95% CI 1.07-1.52, p=0.007), age-sex adjusted RR 1.32 (95%CI 1.10-1.57)) in those for whom uACR was available.

On multivariable analysis, adjusting for age, sex, diabetes, hypertension, smoking and baseline eGFR, incident CVD remained associated with age, hypertension, and smoking (Table 84).

When this analysis was repeated to include secondary CVD (i.e. CVD occurring in those with an existing record of CVD prior to 2008), incident CVD was associated with males, older people, diabetes, smoking, GP diagnosis of CKD, and lower baseline eGFR. People with previous CVD were slightly less likely to have an incident CVD event than people without (Table 85). There was no clear evidence of variation by IMD.

Appendices

Table 83. Characteristics of people with first ever CVD episode recorded by GP

		Incident CVD		Total
		n	Row %	
Sex	Male	648	6.7%	9607
	Female	1007	7.0%	14,414
Age group	<50	12	2.6%	457
	50-69	228	5.3%	4331
	70-79	541	6.8%	7977
	80+	874	7.8%	11,256
IMD	1 (most deprived)	158	6.9%	2292
	2	211	6.5%	3229
	3	377	7.4%	5087
	4	408	7.3%	5620
	5 (least)	500	6.4%	7773
Hypertension	Present	1200	7.3%	16,504
	Absent	455	6.1%	7517
Diabetes	Present	343	7.3%	4727
	Absent	1312	6.8%	19,294
Smoking	No record of smoking	1142	7.0%	16,268
	Record of smoking	513	6.6%	7753
CKD 3 – 5 GP diagnosed	GP record of CKD	901	6.72%	13,399
	No GP record of CKD	754	7.1%	10,622
Baseline eGFR (ml/min/1.73m^2)	45-59	936	6.9%	13,642
	30-44	473	7.0%	6793
	15-29	106	6.5%	1635
	<15	23	7.8%	294
	>=60	117	7.2%	1625
Baseline uACR (mg/mmol)	No uACR value	1380	6.9%	20,127
	No albuminuria	141	6.2%	2266
	Any albuminuria	134	8.2%	1628

Table 84. Poisson analysis of new CVD in the baseline CKD cohort

Variable	Categories	Univariate		Age sex adjusted		Multivariable model*	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Sex (vs. female)	Male	0.98 (0.89-1.08)	0.682	1.01 (0.92-1.12)	0.819	1.01 (0.91-1.11)	0.89
Age (compared to <70 yrs)	70-79	1.40 (1.21-1.63)	<0.001	1.40 (1.20-1.63)	<0.001	1.39 (1.19-1.62)	<0.001
	80+	1.88 (1.63-2.17)		1.89 (1.63-2.18)		1.88 (1.63-2.17)	
IMD quintile (vs. least deprived)	1 (most deprived)	1.06 (0.89-1.27)	0.226	1.12 (0.94-1.34)	0.206	-	-
	2	1.00 (0.85-1.17)		1.04 (0.88-1.21)	0.676	-	-
	3	1.15 (1.01-1.32		1.17 (1.02-1.33)	0.025	-	-
	4	1.10 (0.97-1.25)		1.11 (0.97-1.26)	0.127	-	-
Diabetes (vs. n diabetes)	People with diabetes	1.09 (0.96-1.22)	0.175	1.13 (1.00-1.27)	0.050	1.11 (0.99-1.26)	0.078
Hypertension (vs. no hypertension)	People with hypertension	1.17 (1.05-1.31)	0.004	1.14 (1.02-1.27)	0.018	1.13 (1.02-1.26)	0.024
Smoking (vs. no smoking record before 2008)	Record of smoking before 2008	2.06 (1.19-3.56)	0.010	2.10 (1.22-3.63)	0.008	2.11 (1.22-3.65)	0.007
CKD 3 – 5 GP diagnosed (vs. not CKD diagnosed)	Record of CKD 3 – 5 Read code before 2008	0.95 (0.86-1.05)	0.302	0.94 (0.85-1.03)	0.193	-	-
Baseline eGFR (as continous)		0.99 (0.99-1.00)	0.001	1.00 (0.99-1.00)	0.066	1.00 (0.99-1.00)	0.129

* adjusted for age, sex, diabetes, hypertension, smoking and baseline eGFR

Table 85. Poisson analysis of new CVD in the baseline CKD cohort (including secondary CVD, i.e. new CVD occurring in people with previous CVD)

Variable	Categories	Univariate		Multivariable model*	
		RR (95% CI)	p	RR (95% CI)	p
Sex (vs. female)	Male	1.14 (1.05-1.23)	0.001	1.16 (1.07-1.25)	<0.001
Age (compared to <70 yrs)	70-79	1.55 (1.37-1.75)	<0.001	1.56 (1.38-1.76)	<0.001
	80+	2.20 (1.96-2.47)	<0.001	2.27 (2.02-2.55)	
IMD quintile (vs. least deprived)	1 (most deprived)	1.08 (0.95-1.24)	0.247	1.13 (0.99-1.29)	0.080
	2	0.96 (0.85-1.09)	0.526	0.98 (0.87-1.11)	0.802
	3	1.13 (1.02-1.25)	0.022	1.13 (1.02-1.26)	0.016
	4	1.00 (0.90-1.10)	0.955	1.00 (0.90-1.11)	0.993
CVD (vs no CVD)	People with existing CVD	1.07 (0.99-1.15)	0.085	0.91 (0.84-0.98)	0.014
Diabetes (vs. n diabetes)	People with diabetes	1.32 (1.21-1.43)	<0.001	1.34 (1.23-1.46)	<0.001
Hypertension (vs. no hypertension)	People with hypertension	1.15 (1.06-1.24)	0.001	1.07 (0.99-1.17)	0.099
Smoking (vs. no smoking record before 2008)	Record of smoking before 2008	1.64 (1.02-2.65)	0.041	1.65 (1.02-2.65)	0.041
CKD 3 – 5 GP diagnosed (vs. not CKD diagnosed)	Record of CKD 3 – 5 Read code before 2008	1.17 (1.08-1.26)	<0.001	1.08 (1.00-1.17)	0.048
Baseline eGFR (as continous)		0.99 (0.98-0.99)	<0.001	0.99 (0.99-1.00)	0.001

*adjusted for age, sex, IMD, CVD, diabetes, hypertension, GP CKD3-5, baseline eGFR.

7.3 Appendix 3 - Poisson analysis of emergency hospital admission in the prevalent CKD cohort

Table 86. Poisson analysis of emergency hospital admission in the prevalent CKD cohort

Variable	Categories	Univariate		Multivariable model*	
		RR (95% CI)	p	RR (95% CI)	p
Sex (vs. female)	Male	1.24 (1.12-1.37)	0.001	1.21 (1.09-1.34)	<0.001
Age (compared to <70 yrs)	70-79	1.21 (1.04-1.41)	<0.001	1.16 (0.99-1.35)	<0.001
	80+	1.54 (1.34-1.78)		1.48 (1.28-1.72)	
IMD quintile (vs. least deprived)	1 (most deprived)	1.12 (0.94-1.34)	0.099	1.14 (0.95-1.35)	0.403
	2	0.87 (0.73-1.03)		0.87 (0.74-1.04)	
	3	1.00 (0.87-1.15)		1.00 (0.87-1.15)	
	4	0.93 (0.82-1.07)		0.94 (0.82-1.08)	
CVD (vs no CVD)	People with existing CVD	1.38 (1.25-1.52)	<0.001	1.22 (1.10-1.35)	<0.001
Diabetes (vs. n diabetes)	People with diabetes	1.54 (1.38-1.73)	<0.001	1.52 (1.36-1.71)	<0.001
Hypertension (vs. no hypertension)	People with hypertension	1.07 (0.96-1.20)	0.205	-	-
CKD 3 – 5 GP diagnosed (vs. not CKD diagnosed)	Record of CKD 3 – 5 Read code before 2008	1.08 (0.98-1.19)	0.139	-	-
Baseline eGFR (as continous)		0.99 (0.98-0.99)	<0.001	0.99 (0.99-0.99)	<0.001

*adjusted for age, sex, IMD, CVD, diabetes, baseline eGFR.

7.4 Appendix 4 - Read codes and other variables used in the HHR

Variable	Read code (where relevant)
Gender	
Age, year of birth, date of death	
Practice (s) registered during study period	
Hypertension	G2..
	G20..%
	G24..-G2z..(excluding G24z1)
Ischaemic heart disease	G3%
Heart failure	G58%
Hypertensive heart disease	G21..%
Diabetes	C10..
NIDDM with nephropathy	C109C
Type 2 diabetes with renal complications	C10F0
Type 2 diabetes with nephropathy	C10FC
Liver disease	J61%
Intracerebral haemorrhage	G61..
Stroke and CVA	G66%
Cerebral infarct codes	G63y0
	G63y1
Cerebral thrombosis	G64..
	G640.
Other IC haemorrhage	Gyu62
	Gyu63
	Gyu64
	Gyu65
	Gyu66
	Gyu6F
	Gyu6G
TIA	G65..
	G65z.
	G65zz.
CKD3-5	1Z12.

	1Z13.
	1Z14.
	1Z15.
	1Z16.
	1Z1B-1Z1L.
	1Z1B.
	1Z1C.
	1Z1D.
	1Z1E.
	1Z1F.
	1Z1G.
	1Z1H.
	1Z1J.
	1Z1K.
	1Z1L.
CKD1-2	1Z10.
	1Z11.
	1Z17.-1Z1A.
CKD exception reporting codes	9hE1.
	9hE0.
Proteinuria	1Z1B.
	1Z1D.
	1Z1F.
	1Z1H.
	1Z1K.
	R110.
	R1100
	R1103
	R110z
Albumin : creatinine	44lD.
Protein : creatinine ratio	46TC.
Smoking	137..%
Alcohol intake	
Weight	
Height	
BMI	22K.
Smoking cessation advice	8CAL.

ACE inhibitor prescription	bi...%
	bA...%
	bk6..%
A2 prescription	bk..-bk5z.
	bk7..-bk9z.
	bkB..%,bkD..%
ACE inhibitor contraindications	14LM.
	U60C4
	TJC77 – TJC79
	ZV14D
A2 contraindications	14LN.
	U60CB
	ZV14E
Statin prescribing	bx...%
Flu vaccination codes	65E5.
	65E6
	65E7
	65E8
	65E9
	65EA
	65EB
	65EC
	n47%
Pneumonia vaccine	
eGFR	
Creatinine	
Albumin creatinine ratio	
Protein creatinine ratio	
Urinalysis (proteinuria)	
Cholesterol (total)	
Cholesterol/HDL ratio	
HbA1c	
Hospital admission (including type of admission and diagnoses)	
A&E attendances	

7.5 Appendix 5 - Summary of studies included in the systematic review of limited HL in vascular disorders

Study	Date of publication	Location	Chronic condition	n (with vascular relevant disease)	Main aim	Study design	Setting	Participants	Health literacy measure used	Main results	Prevalence of limited HL
Levinthal	2008	US	Hypertension	492	Role of cognitive and sensory abilities in determining FHL	Cross sectional	Community	Adults aged 21 to 92 with doctor diagnosed hypertension. 68% African American, 30% white	STOFHLA	Significant associations of variation in HL score with gender, race, education and other cognitive measures	23%
Gordon	2009	US	CKD	124	Relationship between HL, transplant knowledge and graft function	Cross sectional	Post transplant clinic visit	Adults > 18 taking immunosuppressants post kidney transplant	STOFHLA and REALM-T (relevant to transplant)	HL positively correlated with education, income, marital status. HL measures not significantly related to graft function measures	9%
Wright (conference abstract only)	2010	US	CKD	400	Describing awareness of CKD in patients seeing nephrologists	Cross sectional	Community	Adults with all stages of CKD seen at least once in a nephrology clinic in the past	REALM	28% unaware they had CKD. 45% stage 1 - 2 unaware, 22% stage 3 - 5 unaware	18%
Cavanaugh / Wingard	2010	US	CKD	480	Characterise prevalence and associations of limited HL + risk of all cause mortality in patients initiating chronic haemodialysis	Cohort	86 Dialysis units across US	Adults>18 'eligible for patient education programme'	REALM	Low HL associated with non-white, less education, not married. Low HI associated with reduced survival HR 1.5, but significance disappears when adjusting for age, gender, race, diabetes and baseline albumin	32%
Grubbs	2009	US	CKD	62	Association of poor HL with access to kidney transplant	Cross sectional	5 outpatient dialysis units	21-75 year old, black and white only, maintenance dialysis for at least 9 months, never had renal transplant, excluded cog dysfunction	STOFHLA	Lower hazard for referral for transplant in lower HL group. No association with wait-listing for transplant	32%
Cavanaugh / Huizinga	2008	US	Diabetes	398	Association between diabetes-related numeracy and glycaemic control	Cross sectional	2 primary care and 2 diabetes clinics	Adults 18-85, Type 1 or 2 diabetics	REALM and WRAT-3 and Diabetes Numeracy Test	Weak relationship between diabetes numeracy score and glycaemic control. DNT linked to REALM score	31%
DeWalt	2007	US	Diabetes	268	Relationship between literacy and trust, self-efficacy and participation in decision making	Cross sectional	General internal medicine practice	Adults >18, type 2 diabetic on medication	REALM	No relationship between literacy and trust, self-efficacy, and facilitation of patient involvement. People with low literacy less likely to want to be involved in decision making	20%

Study	Date of publication	Location	Chronic condition	n (with vascular relevant disease)	Main aim	Study design	Setting	Participants	Health literacy measure used	Main results	Prevalence of limited HL
Endres	2004	US	Diabetes	74	Association between functional HL and 'markers of pregnancy preparedness' in women with pregestational diabetes	Cross sectional pilot study with birth outcomes	University clinics, high risk community clinic	Women with pregestational diabetes	STOFHLA	Lower pregnancy preparedness in those with lower health literacy	22%
Jepperson	2009	US	Diabetes	225	Identifying questions and demographics that predict limited HL	Cross sectional	Primary care	Adults	STOFHLA	Limited HL associated with lower self-rated reading ability, lower educational attainment and need for help with written materials	15%
Kim	2004	US	Diabetes	92	Association between HL and self-management behaviour in diabetics	Cohort	Hospital diabetes education classes	Adults with diabetes >18	STOFHLA	Prevalence of low HL. Change in diabetes understanding with education sessions	23%
Mbaezue	2010	US	Diabetes	189	Relationship between HL and self monitoring of glucose	Cross sectional	Hospital clinic	Adults 18-65	STOFHLA	No relationship between HL and self monitoring og blood glucose	39%
Morris	2006	US	Diabetes	1002	Relationship between HL and diabetes control and complications	Cross sectional	Primary care	Adults	STOFHLA	No relationship between HL and diabetic control measures, BP, LDL or complications	17%
Osborn	2010	US	Diabetes	130	Relationship between HL, determinants of diabetes self-care, and glycaemic control	Cross sectional	Outpatients	Adults >18 with type 2 diabetes	REALM R	No relationship between HL and diabetes knowledge, self care or glycaemic control. HL related to social support.	30%
Rothman / DeWalt	2004	US	Diabetes	193	Examine role of literacy on effectiveness of a diabetes disease management programme	RCT	University gen int medicine clinic	Adults>18 with type 2 diabetes	REALM	Low literacy group had greater improvement in diabetes outcomes than high literacy group after adjusting for potential confounders	39%

Study	Date of publication	Location	Chronic condition	n (with vascular relevant disease)	Main aim	Study design	Setting	Participants	Health literacy measure used	Main results	Prevalence of limited HL
Rothman / Malone	2004	US	Diabetes	111	Role of literacy in patients with poorly controlled diabetes participating in a disease management programme	Cohort	Pharmacy-led diabetes management programme	Adults with type 2	REALM	Both low and higher literacy groups improved after the intervention. No significant difference in improvement between low and high literacy groups.	75%
Schillinger	2002	US	Diabetes	408	Relationship between HL and diabetes outcomes	Cross sectional	Primary care	Adults>30 with type 2	STOFHLA	Patients with low HL less likely to achieve tight DM control after adjusting for sociodemographic factors, depression, social support, treatment regime, duration of diabetes, and more likely to have retinopathy	51%
Wallace	2010	US	Diabetes	195	Identify factors associated with experiences of self-management support in primary care encounters	Cross sectional	Internal medicine clinic	Adults>18 with type 2 diabetes	STOFHLA	Adequate HL associated with higher self management score	31%
Cordasco	2009	US	Heart disease	275	Evaluate relationship between HL and age in inpatients with CHD or CHF	Cross sectional	Inpatients	Adults>18 with CHD or CHF	TOFHLA	Prevalence in inadequate HL increased with age	60%
Fransen	2011	Netherlands	Heart disease	201	Prevalence of low HL in coronary heart disease patients	Cross sectional	Outpatients	Adults with coronary heart disease	NVS and REALM	Low HL prevalence varies between measures. Low HL associated with worse CHD riskscore	NVS 52%, REALM 18%
Georgiopoulou (conference abstract only)	2010	US	Heart disease	150	Assess HL levels and outcomes in HF patients	Cross sectional at start of cohort	Outpatients	Adults with heart failure	REALM	Some correlation of REALM with self-report of education. Patients with suboptimal REALM score had increased risk (HR 2.2) of adverse event	20%
Ibrahim	2008	UK	Heart disease	300	To validate REALM for use in UK population	Cross sectional	Inpatients	Adults>18 admitted for Ix of CHD	REALM and BSAIT	REALM significantly correlated with BSAIT	19%

Study	Date of publication	Location	Chronic condition	n (with vascular relevant disease)	Main aim	Study design	Setting	Participants	Health literacy measure used	Main results	Prevalence of limited HL
Johnson (conference abstract only)	2010	US	Heart disease	95	Prevalence of inadequate HL and association with HF knowledge, self-care and readmission rate	Cross sectional	Inpatients	Adults admitted with primary diagnosis of HF	STOFHLA	Self care maintenance, management and readmission did not vary by HL level	61%
Kriplani	2006	US	Heart disease	152	Evaluate effects of HL and others on medication self management	Cross sectional at start of RCT	Outpatients	Adults with CHD	REALM	DRUGS score and ability to identify drugs increased with REALM score	80%
Levy (conference abstract only)	2010	US	Heart disease	100	Effect of HL as modifier for interaction between behaviours and beliefs in HF	Cross sectional	Emergency department	Adults with CCF	STOFHLA	HF illness beliefs did not correlate with HL	52%
Morrow	2006	US	Heart disease	314	Relationship between HL and cognitive and sensory abilities	Cross sectional	Community	Adults with CCF	STOFHLA	Education and cognitive ability independently associated with STOFHLA and these explained age and race differences in HL	28%
Murray (conference abstract only)	2004	US	Heart disease	242	Association between HL and medication aherence	Cohort	Community	Adults with cardiovascular diease	STOFHLA	HL independently predicted medication adherence	26%
Ussher	2010	UK	Heart disease	321	Psychosocial correlates of health literacy	Cross sectional	Inpatients	Adults>18 with CHD	REALM	4 psychosocial variables related to REALM after adjustment for ethnicity, age, gender and education.	22%

Study	Date of publication	Location	Chronic condition	n (with vascular relevant disease)	Main aim	Study design	Setting	Participants	Health literacy measure used	Main results	Prevalence of limited HL
Gazmarian / Kriplani	2006	US	Heart disease, hypertension, diabetes, hyperlipidaemia	1549	Relationship between HL and medication refill adherence	Cohort	Outpatients	Adults >65 with CHD, HT, DM, hyperlipidaemia	STOFHLA	Relationship between HL and medication adherence not sustained after adjustment for age, race, gender, education, and regimen complexity	36%
Gazmarian / Williams	2003	US	Diabetes, asthma, heart disease, hypertension (Total study pop 653)	538	Relationship between HL and knowledge of disease	Cross sectional	Outpatients	Adults >65 with diabetes, asthma, HT or CCF (84% had only 1 condition)	STOFHLA	People with low HL knew less about their disease	36%
Laramee	2007	US	Diabetes, heart failure	998	Prevalence of limited HL in diabetics with and wihout HF	Cross sectional	Primary care	Adults with diabetes +/-HF	STOFHLA	Relationship between HL and presence of HF disappeared when education was added to the model.	DM + HF: 27% DM only: 15%
Wolf	2005	US	Diabetes, hypertension, heart disease, COPD, asthma, arthritis, cancer (Total study pop 2923)	2063	Association between HL and physical and MH functioning	Cross sectional	Community	Adults with DM, HT, CHD, COPD, arthritis, Cancer	STOFHLA	Low HL associated with poor physical function and mental health, ADL, etc	36%
Williams	1998	US	Diabetes, hypertension	516	Association between FHL and knowledge of chronic disease	Cross sectional	Outpatients	Adults with DM or HT	TOFHLA	Correlation between HL and disease knowledge, but no difference in disease outcomes	HT 61% DM 55%

7.6 Appendix 6 – Letter to patients with newly identified CKD

Dear…,

I am writing to you because you have had blood tests which show that your kidneys may not be working quite as well as they used to. It might be helpful for you to discuss this with your doctor or nurse.

'Kidney disease' is a term used by doctors to include any abnormality of the kidneys, even if there is only a very slight problem. 'Chronic' means a condition that does not get completely better. So if you hear a doctor or nurse saying 'Chronic Kidney Disease' (CKD), it does not necessarily mean that there is a major problem. Most cases do not cause symptoms and do not progress. However, people with CKD do have an increased risk of developing other problems (such as heart problems). This is why it is important to detect mild CKD, as treatment slows down the progression of the CKD as well as reducing the risk of getting heart problems or a stroke.

You can help look after your kidneys and your heart:

- Avoid medicines that put a strain on the kidneys, e.g. painkillers (NSAIDs) such as ibuprofen. Paracetamol is completely safe. Talk to your doctor or pharmacist (chemist) if you are not sure
- Lose any excess weight and exercise regularly
- Stop smoking
- Eat a healthy, balanced diet (see www.bhf.org.uk for advice – click 'prevention' then 'healthy eating'
- Reduce the amount of salt in your diet to help keep your blood pressure down
- Make sure you take your blood pressure tablets every day if you have high blood pressure
- Keep your blood sugar under control if you have diabetes
- Drink water normally and when you feel you want to, unless you've been advised otherwise by a doctor. (There's no evidence that drinking extra water or fluids will help if you have kidney disease).

We have identified that you may have CKD Stage 3. Because of this result you have been added to our kidney monitoring register. We will send you an annual invitation to have a repeat blood test and a health check. If you would like more information, please make an appointment to discuss it with us, or look at this website:

http://www.kidney.org.uk/Medical-Info/ckd-info/

Yours sincerely

Dr….

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