Chronic Kidney Disease: Determining chronicity, prevalence, variation and survival in a community chronic kidney disease (CKD) cohort

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Abstract

Chronic kidney disease (CKD) is insidious and most cases are diagnosed through opportunistic serum creatinine (SCr) testing before symptoms develop. However, efforts to accurately assess prevalence have been hampered by the lack of a universally agreed definition of SCr thresholds for the diagnosis of CKD. At the turn of the millennium, two crucial developments occurred. The first was the description of the Modification of Diet in Renal Disease estimated Glomerular Filtration Rate (eGFR) which closely correlated to cumbersome measured GFR and could be used instead in daily clinical practice. The second was the publication of the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline for the evaluation, classification and stratification of CKD detailing a new definition of CKD based on GFR thresholds. Together, these two developments formed the basis of CKD as we know it today.

Prevalence of CKD varies, and accurate prevalence estimates are difficult to obtain especially with respect to fulfilling the chronicity criterion (reduced eGFR $\geq$ 90 days). Traditional risk factors for CKD are well described and non-traditional risk factors such as socio-economic status (SES), health literacy and rurality are gaining interest. SCr sampling patterns in the community mean that most individuals with CKD are tested routinely every year. This information may not be considered in its entirety by primary care providers (PCP) which may explain inaccuracies in PCP CKD registers. Accurate identification is important to direct evidence based clinical interventions to this patient group.

In chapter 2, a novel algorithm for detecting CKD and confirming chronicity from a laboratory database was developed to identify a CKD cohort of the population served by NHS Ayrshire & Arran. Data linkage of additional laboratory data, Scottish Morbidity Records for co-morbidity, statin dispensing information from Prescribing Information Scotland, area SES, rurality and deaths from Information Services Division Scotland enriched the cohort. Patients on renal replacement therapy were identified and excluded through the Scottish Renal Registry. Multiple imputations were applied where appropriate to address missing values. There were 21,037 individuals from 2010 to 2012 fulfilling the definition of CKD stage 3 – 5. Prevalence of adults with CKD was 5.6% – 5.8%. Average age (± SD) of the cohort was 75 ± 11 years. 64.6% were female and average eGFR for the cohort was 47.32 ± 11.53 mL/min/1.73m^2.

In chapter 3, laboratory ascertainment of CKD identified 7% more cases than PCP CKD registers. Furthermore, around 25% of patients on PCP CKD registers may be wrongly coded as having CKD. There was a 3.9-fold variation in CKD prevalence amongst PCPs, ranging from 2.8% - 11.0%. Variation fell to 3-fold with laboratory ascertainment, ranging from 3.0% - 9.1%. This fell further with age and gender stratification. Stratified laboratory CKD prevalence was positively associated with SES and rurality, a novel finding, but in multivariate linear regression, only SES, in addition to age and gender, were significant predictors for CKD prevalence.

Chapter 4 explored the association between SES, eGFR and all-cause mortality. One-way ANOVA demonstrates a linear relationship between eGFR and SES ($F(4,15078) = 2.52$, $p = 0.039$) with a mean difference in eGFR of 0.83 mL/min/1.73m^2 between the lowest and the highest SES quintile. However, linear regression modelling found proteinuria, hypertension, peripheral arterial disease, age, gender and serum albumin to be significant predictors for eGFR, but not SES. After adjustment for age and gender imbalance, survival demonstrated substantial influence by SES, but weakened in effect with full adjustment with only Scottish Index of Multiple Deprivation (SIMD) quintile 3 demonstrating a 13% increased risk (HR 1.13, 95% CI 1.03 to 1.24) with no progressive increase in risk associated with lower levels of SES.

As a quality of care marker, the dispensing of statin was examined in chapter 5. Having another diagnosis where statins are indicated, male gender, higher serum albumin, CKD stage 3B and age between 65 – 80 were associated with higher odds ratio for statin dispensing. 64% of the cohort was dispensed a statin in 2010, but the proportion fell by 5% to 58% in 2012. This fall in dispensing disproportionately affected younger and less co-morbid CKD patients who were all eligible for a statin. SES and gender did not appear to be a factor in falling dispensing rates. Average LDL levels were lower in the statin group by (mean difference) 0.78 mmol/L (95% CI 0.74 to 0.81) in 2010 and 0.93 mmol/L (0.90 to 0.97) in 2012. 37.2% of all statin prescriptions was for Simvastatin 40 mg.

Statins reduce cardiovascular events and mortality in CKD. However, in older patients typical of CKD, evidence is lacking. Chapter 6 examines survival in those dispensed a statin. Those dispensed a statin were younger, more likely to be male, had higher serum albumin and more co-morbid. After full adjustment, statin dispensing was associated with a 24% lower risk of death (HR 0.76, 95% CI 0.71 to 0.83) overall, 18% benefit for primary prevention (no prior coronary heart disease or cerebrovascular disease) (0.82, 0.74 to 0.91),

32% benefit in secondary prevention (0.68, 0.60 to 0.77), 22% benefit in younger (<76 years) CKD patients (0.78, 0.67 to 0.92) and 22% benefit in the older (≥ 76 years) CKD patients (0.78, 0.71 to 0.85) over 4.5 years follow-up. To illustrate absolute risk reduction, the number needed to treat to avoid one death for all patients is 15.8 (95% CI 12.3 to 22.2) and 12.4 (9.3 to 18.5) for older CKD patients.

This thesis demonstrates that centralised ascertainment of CKD is better at case finding, than existing PCP CKD registers. The linkage of additional, routinely collated healthcare data can develop CKD registers into a powerful tool for monitoring quality of care, efficacy of therapy and hypothesis generation which can, and should be, integrated into clinical IT systems with the appropriate information governance oversight in place.

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Author's Declaration

The work presented in this thesis was that of the author and his supervisors, including all statistical analyses unless specifically stated otherwise.

I declare that this thesis has been composed by myself and has not previously been submitted for a higher degree. Parts of this thesis have been presented at local and international meetings and published in peer-reviewed journals as listed separately.

Beng Hock So, January 2018.

Definitions/Abbreviations

4D	Deutsche Diabetes Dialyse Studie
A&A	NHS Ayrshire and Arran Health Board
ABPM	Ambulatory Blood Pressure Monitoring
ACEi	Angiotensin converting enzyme inhibitor
AGP	Age and Gender stratified prevalence of CKD stage 3 – 5 by Primary Care Practices in A&A
AKI	Acute kidney injury
ASCOT-LLA	Anglo Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
BP	Blood pressure
BSA	Body surface area
CARE	Cholesterol and Recurrent Events trial
CHD	Coronary Heart Disease
CHI	Community Health Index
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	CKD Epidemiology Collaboration equation
CKDPC	Chronic Kidney Disease Prognosis Consortium

COPD	Chronic obstructive pulmonary disease
CrCl	Cockcroft and Gault creatinine clearance
CRIC	Chronic Renal Insufficiency Cohort Study
CVD	Cerebrovascular disease
DM	Diabetes Mellitus
eGFR	Estimated glomerular filtration rate
ESRF	End-stage renal failure
FEV_1	Forced expiratory volume in the first second
FSGS	Focal Segmental Glomerulosclerosis
GFR	Glomerular filtration rate
GP	General Practitioner
HBPM	Home Blood Pressure Monitoring
HL	Health Literacy
HQIP	Healthcare Quality Improvement Partnership
HR	Hazard Ratio
IDMS	Isotope dilution mass spectrometry
IHD	Ischaemic Heart Disease
IQR	Inter quartile range
ISDS	Information Services Division Scotland

JUPITER	Justification for the Use of Statins in Prevention – an Intervention Trial Evaluating Rosuvastatin
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
LabP	Laboratory ascertained prevalence of CKD stage 3 – 5
LIPID	Long-Term Intervention with Pravastatin in Ischaemic Disease
MCAR	Missing completely at random
MDRD	Modification of Diet in Renal Disease Study
MRFIT	Multiple Risk Factor Intervention Trial
NHANES	National Health and Nutrition Examination Survey
NHS	The National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
P4P	Pay for performance
PAD	Peripheral arterial disease
PCP	Primary Care Practice
PGR	Number of patients to full-time-equivalent GP ratio
PIS	Prescribing Information Service for Scotland
QALY	Quality Adjusted Life Years

QOF	Quality and outcome framework
RAS	Renin-angiotensin system
RCT	Randomised controlled trial
RR	Relative risk
RRT	Renal replacement therapy
SCI-store	Scottish Care Information store
SCr	Serum creatinine (µmol/L)
SD	Standard deviation (usually presented as 2 SD either side of the mean unless stated otherwise)
SES	Socio-economic status
SHARP	Study of Heart and Renal Protection
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
SMR	Scottish Morbidity Records
SRR	Scottish Renal Registry
Statin	HMG Co-A reductase inhibitor
uACR	Urinary albumin to creatinine ratio
UK	United Kingdom of Great Britain and Northern Ireland
uPCR	Urinary protein to creatinine ratio
US	United States of America

WOSCOPS	West of Scotland Coronary Prevention Study

1 CHAPTER 1 INTRODUCTION

1.1 Defining CKD

1.1.1 Measuring kidney function

It is an often-repeated quote that each human kidney consists of approximately 1 million glomeruli at birth.(1) This derives from the work of RA Moore in 1931 on glomeruli count in a cross section of kidneys at autopsy. He made four important conclusions: the first being that a forty-year-old man has approximately 800,000 to 1,000,000 glomeruli in each kidney, the second that postnatal nephrogenesis does not occur, the third that there is senile loss of glomeruli in man, similar to that of rats, and the fourth that the two kidneys of one individual contain approximately the same number of glomeruli. The first three of his conclusions, made 85 years ago, continue to inform research in the 21st century and is certainly pertinent to the work laid out in the following pages.

Chronic kidney disease (CKD) is insidious and develops well before any appreciable symptoms develop (Figure 1-1).(2) In order to determine if an individual has CKD, we require the means to determine and quantify dysfunction of the organ. The kidney has multiple functions but the excretion of metabolic waste products is the function most are familiar with.(3) Since the 1970's the gold standard for the measurement of kidney function or glomerular filtration rate (GFR) has been widely accepted as inulin clearance.(4) This is because it has the characteristics of a perfect filtration marker; it is not protein bound, is freely filtered at the glomerulus, not secreted, absorbed or metabolised by the renal tubule, and is non-toxic and physiologically inert. It is also generally accepted as being impractical for widespread clinical use due to its cumbersome and time-consuming execution.(5)

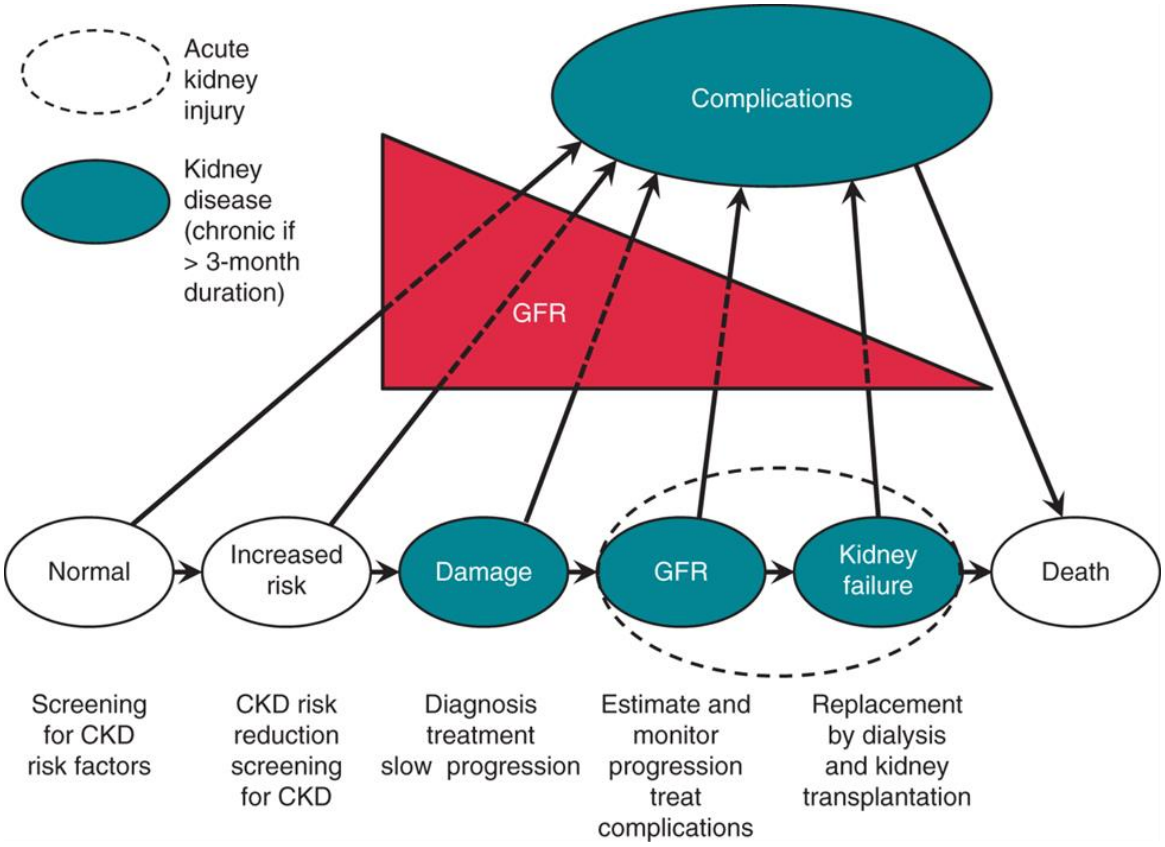


Figure 1-1. Stages of the development and progression of chronic kidney disease (CKD), including complications and strategies to improve outcomes.(2) Reproduced with permission © EP Europace 2015.

Measured GFR such as creatinine clearance, iohexol, iothalamate, chromium-51 labelled ethylenediamine tetraacetic acid (Cr-EDTA) and diethylenetriamine pentaacetate (DTPA) are mainly used for live kidney donor assessment or chemotherapy dosing when accurate GFR measurement is desirable. However, these and other measured GFR methods are also cumbersome, costly, involves exposure to radioactivity and iodinated contrast with performances that fall short when benchmarked against inulin clearance.(6, 7)

Serum creatinine (SCr) as an endogenous marker, fulfils many of the conditions of a perfect filtration marker: it is not protein bound, is freely filtered, not metabolised by the tubules, and is physiologically inert. However, with declining kidney function up to 60% of the total SCr secreted by the kidneys occurs via the proximal tubules and this process can be inhibited by drugs such as cimetidine and trimethoprim.(8) Furthermore, creatinine is formed from muscle creatine and the size of this pool can be affected by diet, drugs and illness. In 1994 the US National Institute of Health released a consensus statement with the aim of providing a pragmatic definition of chronic renal insufficiency. It suggested a threshold of SCr $\geq$ 1.5mg/dL and $\geq$ 2.0mg/dL for referral to a Nephrologist for male and female patients respectively.(9) With the benefit of hindsight, this recommendation for a higher SCr referral threshold for female patients would be unthinkable now, but such was

the lack of research and understanding of pre-dialysis CKD at a population level that absolute SCr thresholds were used without accounting for differences in age, gender and even race.

To overcome the inherent weakness of using an absolute SCr value to diagnose chronic renal insufficiency or CKD, mathematical models of GFR estimation were developed. One of the earliest eGFR formulae was the Cockcroft and Gault creatinine clearance (CrCl).(10) This formula used SCr, age, gender and weight to predict CrCl. Due to its reliance on unstandardized SCr, it was prone to overestimation of GFR. Over the subsequent 23 years, until the advent of the Modification of Diet in Renal Disease (MDRD) formulae, there were other formulae proposed and in use, but the Cockcroft and Gault equation remained the most popular.(11)

Although eGFR derived from the MDRD formula is thought to be inferior to measured GFR, it more than makes up for its inadequacies by being convenient and accessible which allows for multiple measurements over time to determine temporal trends. Other recent advances such as the CKD epidemiology collaboration (CKD-EPI) equation for predicting eGFR and cystatin-C measurement and its incorporation into various eGFR formulae further enhances its accuracy.(12, 13) eGFR has also been shown to be equal or superior at predicting death, cardiovascular events or kidney failure than some measured GFR methods.(14, 15)

1.1.2 CKD in the 21st century

eGFR as we currently know it, was first described in 1999 by Levey et al. in a paper describing a new equation for predicting glomerular filtration rate in 1,628 participants with chronic renal disease from the MDRD study.(16) This equation used SCr, serum urea, serum albumin, age, gender and ethnicity and became known as the 6-variable MDRD. They demonstrated a high correlation ($R^2 = 0.903$) for the equation when compared to measured GFR by ^{125}I-iothalamate excretion. They were able to predict GFR to within 30% of measured GFRs, 91% of the time. The 6 variable MDRD formula was quickly followed by the simplified 5-variable and 4-variable equations, developed in the same population which made do without serum albumin and serum urea respectively but with only a small trade off in accuracy (Figure 1-2). Correlation co-efficient of determination (R^2) for the simplified equations were 0.899 and 0.892 for the 5-variable and 4-variable equations respectively. This work was only published in abstract form.(17) Following this

the 4-variable MDRD equation was incorporated into the 2002 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline for the evaluation, classification and stratification of CKD.(18)

This document also proposed a CKD classification based on GFR threshold which formed

MDRD 6 eGFR = $170 \times SCr^{-0.999} \times Age^{-0.176} \times (1.180 \text{ if black}) \times (0.762 \text{ if female}) \times \text{Serum urea}^{-0.170} \times \text{Serum albumin}^{+0.318}$

MDRD 5 eGFR = $270 \times SCr^{-1.007} \times Age^{-0.180} \times (1.178 \text{ if black}) \times (0.755 \text{ if female}) \times \text{Serum urea}^{-0.169}$

MDRD 4 eGFR = $186 \times SCr^{-1.154} \times Age^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$

Figure 1-2. The original MDRD 6, 5 and 4 variable formulae as proposed by Levey et al.(16)

the basis of CKD definition that we are familiar with today (Figure 1-3). Proteinuria, although mentioned in the guideline was not an explicit component of the original proposed CKD definition.(19) Prior to the publication of this document, there was no internationally accepted definition of CKD. In a paper titled ‘Chronic Renal Confusion: Insufficiency, Failure, Dysfunction or Disease’ by Hsu et al. published in 2000, the authors document up to 23 different terms used to describe CKD in abstracts submitted to an annual nephrology meeting held in the United States of America (US).(20) They also found that these terms covered a range of severity from those with creatinine clearance as high as 75 mL/min to those so low as to require dialysis. The biochemical characteristics of the populations described were equally heterogeneous and encompassed SCr thresholds greater than 150 µmol/L or 1.5 mg/dL (equivalent to 132 µmol/L) and included patients on haemodialysis.

Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Figure 1-3. The very first NKF/KDOQI proposed classification of CKD in 2002.

The 2002 KDOQI guidelines also recommended the standardisation of SCr assays used in GFR estimation. This, along with a modified MDRD 4 equation, was thought to increase the accuracy at higher estimates of eGFR.(21) However, the overall performance of the equation compared to within 30% of measured GFR using ^{125}I-iothalamate excretion was largely unchanged, with an accuracy of approximately 90%.(22)

In 2004, Kidney Disease: Improving Global Outcomes (KDIGO), a non-profit international foundation, conducted a survey of 10,000 nephrologists internationally (12% response rate) on the KDOQI 2002 guidelines and hosted a Controversies Conferences in 2004 resulting in the endorsement of the guidelines.(23) In 2006, a second Controversies Conference was convened following which the CKD classification was modified to include the suffix 'T' for kidney transplant patients at all levels of GFR and 'D' for those with stage 5 CKD in receipt of dialysis. It also strengthened the global endorsement of the KDOQI guidelines along with amendments from KDIGO summarised in a joint position statement published in 2009.(24)

A third Controversies Conference was convened by KDIGO in 2009, during which it was recommended that stage 3 (eGFR 30 – 59) be subdivided into 3A (45 – 59) and 3B (30 – 44), the addition of albuminuria stage, and an emphasis on establishing a diagnosis of the underlying renal pathology leading to reduced eGFR.(25)

In the intervening years since the KDOQI classification was proposed in 2002, emerging evidence from cohort studies suggested strong independent associations between albuminuria and eGFR with mortality.(26, 27) To justify these amendments and shift the focus of the classification system to include prognostic information, a meta-analysis of 45 cohorts of general, high risk and kidney disease populations which included 1.5 million individuals was conducted to estimate mortality, end-stage renal failure (ESRF) and acute kidney injury (AKI) risk from CKD (Figure 1-4).

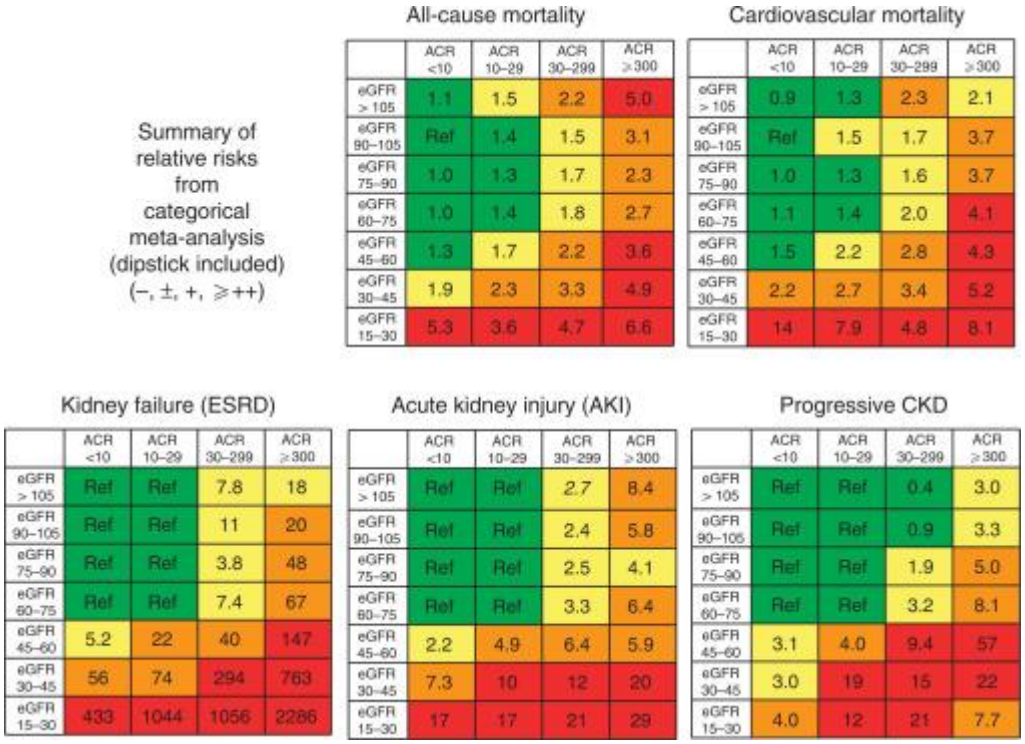


Figure 1-4. Meta-analyses of relative risk by amount of proteinuria, stratified by CKD stage. Adapted from Levey et al.(24) Reproduced with permission © Kidney International 2011.

The KDOQI classification was quickly incorporated into national guidelines in the UK where joint guidelines from the Royal College of Physicians of London and the Renal Association were published in 2005.(28) This was followed by the National Institute for Health and Care Excellence (NICE) guidelines for England and Wales, and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines, both published in 2008. (28-30)

The key to the introduction of these guidelines was the implementation of a programme nationally in 2006 to prepare UK laboratories to automatically report eGFR from SCr measurement with calibration traceable to isotope dilution mass spectrometry (IDMS) reference on all SCr sample requests.(31, 32) Due to the lack of accuracy at higher levels of eGFR, only estimates of < 60 mL/min/1.73m2 would be reported and higher values would only be reported as "≥ 60 mL/min/1.73m2". The laboratory roll-out of eGFR

reporting was paired with the introduction CKD as a new indicator in the primary care pay-for-performance initiative, the quality outcomes framework (QOF) in 2006.(33) This scheme provided financial incentives to primary care practices for creating and maintaining a register for all their patients with eGFR < 60 mL/min/1.73m^2.

1.1.3 Critique of CKD

Although generally well received by nephrologist, who welcomed a standardised definition for non-dialysis CKD and its potential thereby to increase awareness, encourage earlier referral, facilitate research and development of public health policy, there were also detractors.(34, 35) Hallan and Orth summed up the major criticisms succinctly in a 2010 editorial stating "eGFR is the backbone, but also the soft spot, of the current CKD classification".(36) Many critics held the view that eGFR was inaccurate, especially in those with better function and would lead to many being unnecessarily misclassified as having CKD stage 3 (eGFR 30 – 59). This is an inherent flaw in the MDRD formula as it was developed in a cohort of patients with known reduction in GFR. In a 2009 paper examining the accuracy of the MDRD4 equation in those with GFR ≥ 60 mL/min/1.73m^2, Levey et. al. found a median difference of 10.6 (9.8 – 11.0) mL/min/1.73m^2 between MDRD4 compared to measured GFR (^{125}I-iothalamate). They proposed a new eGFR equation that reduced this bias to -4 mL/min/1.73m^2 which they called the CKD Epidemiology Collaboration equation (CKD-EPI).(37)

A study carried out in NHS Ayrshire and Arran (A&A), examining the impact on population prevalence in 2009 of switching from MDRD4 to CKD-EPI found a 0.69% reduction in the overall CKD 3 – 5 prevalence from 5.63% to 4.94%.(38) The majority of those were reclassified to eGFR ≥ 60 mL/min/1.73m^2, with relatively few in the lower levels of eGFR reclassified to milder stages of CKD. However, the authors also cautioned that converting to CKD-EPI from MDRD4 would reclassify 1.8%, of mostly elderly female patients, to a more severe stage of CKD.

Regardless of whether eGFR is estimated using the MDRD or CKD-EPI formulae, the estimates are indexed to a body surface area (BSA) of 1.73 m^2 by convention. This is so thresholds of eGFR can be applied across populations with varying BSA such as the obese or anorexic. However, this indexing of eGFR to BSA is likely to underestimate the GFR of the obese and overestimate it in the anorexic individual.(39) Although, in general clinical practice this is unlikely to have much of an impact, this issue can have important clinical

consequences in certain circumstances, such as for drug dosing or when deciding on the eligibility of a potential living kidney donor.(40, 41)

Another criticism is the use of the word ‘disease’ as opposed to ‘insufficiency’ or ‘impairment’ and the division of CKD into sequential stages of 1 to 5 which suggests a certain inevitable descent towards RRT once the label of CKD is applied.(19, 42) This is despite contemporary research showing a progression rate of only 1-2% in the vast majority who are labelled with CKD stage 3 (eGFR 30 – 59 ml/min/1.73m^2) over a follow-up period of between 5 to 8 years.(43, 44)

CKD stage 3 as it was originally proposed, encompassed all those whose eGFR fell between 30 and 59 mL/min/1.73m^2 and was indiscriminately broad. For example, in a 2003 study to estimate the US prevalence of CKD using data from the NHANES study, Coresh et al. estimates that 8.3 million individuals in the US aged over 20 have an eGFR < 60 mL/min/1.73m^2. Of these, 7.6 million or 92% fell into CKD stage 3(45). The division of stage 3 into 3A (eGFR 45 – 59) and 3B (eGFR 30 – 44) was mooted at the 2007 UK consensus conference on Early Chronic Kidney Disease and subsequently adopted by SIGN and NICE in their respective 2008 CKD guidelines to reflect the difference in mortality risk between the two groups.(30, 46, 47)

This change was subsequently endorsed by KDIGO in 2011.(25) This move did not allay concerns that there might still be too many mislabelled with CKD. Critics maintain that many individuals, especially the old, will be mislabelled as having CKD when they simply have age related senescence of nephron mass. They justify this by the low incidence of progression to RRT especially in those labelled as CKD stage 3.(34, 48-50) However, these arguments often ignore the strong evidence of a stepwise and independent increase in mortality associated with declining eGFR even in the elderly.(51, 52) Also, that in this population CKD is prevalent and associated with manageable metabolic complications.(53)

The projected rise in CKD incidence and prevalence also raised concerns about the ability of Nephrology services to cope with a surge in demand following the introduction of eGFR reporting. Population studies examining this trend document a significant increase in referrals to Nephrology services of between 1.5 to 2.7 times the base rate in the months immediately following the introduction of automated eGFR reporting.(54-57) However, with the creation and dissemination of local guidelines for management in primary care

and referral criteria, referral rates fell and improved in appropriateness to manageable levels.(54, 55)

Commentators and epidemiological studies in the years following the introduction of the KDOQI CKD definition frequently refer to an epidemic of CKD. This stemmed from a publication by Levey et al. in 2003, in the American Journal of Kidney Disease titled "Prevalence of Chronic Kidney Disease and Decreased Kidney Function in the Adult US Population: Third National Health and Nutrition Examination Survey" which applied the MDRD4 formulae to the recurring National Health and Nutrition Epidemiological Study cohort (NHANES III) and concluded that 10-13% of the population fulfilled the KDOQI definitions of CKD stage 1 – 5.(45) This was a major rise from the 3.0% national prevalence estimate quoted in the same cohort using absolute SCr cut off of 141 µmol/L (1.6 mg/dL) for men and 124 µmol/L (1.4 mg/dL) for women that was published earlier in 2001.(58)

Critics derided the KDIGO definitions as a made-up construct which, overnight, labelled a large proportion of the populace with CKD to increase activity and thereby revenue for Nephrologist and was a prime example of "overdiagnosis" in medicine.(34, 48, 49) In spite of the these early criticisms, the KDIGO-CKD guidelines have been effective in identifying a population at risk of incapacity and death from cardiovascular events that are preventable, and also for reducing the number of people requiring RRT presenting late to Nephrology services.(52, 54, 59, 60)

1.1.4 Changing incidence and prevalence

Before the introduction of the KDOQI CKD definitions, there were few large-scale population studies examining the prevalence of non-dialysis CKD. This was in part, hampered by the lack of a universally accepted definition for CKD and a general lack of awareness of the problem.(20) A study by Culleton et al. in 1999, with SCr measurements in 6,233 adults found 8.9% of men and 8.0% of women had a SCr of greater than 136 µmol/L (1.5 g/dL) and 120 µmol/L (1.4 mg/dL) respectively.(61) Another US study published in 2001 using a sex specific threshold of 1.2 mg/dL (106 µmol/L) for women and 1.4 mg/dL (124 µmol/L) for men, involving a large health care organisation in the US with more than 150,000 members, estimated the prevalence of CKD to be 3.7%, equating to 9.1 million individuals across the US.(62)

One of the most widely quoted source of CKD population prevalence estimates before the millennium was from the NHANES III study. This population survey was conducted between 1988 and 1994 and involved 18,723 non-institutionalised participants aged 12 years and over with 69% providing a SCr measurement. One of the earliest studies studying this cohort was by Jones et al. who defined chronic renal dysfunction using an absolute SCr cut off of > 1.5 mg/dL (133 µmol/L), > 1.7 mg/dL (150 µmol/L) and > 2.0 mg/dL (177 µmol/L) and found that 10.9 million, 3.0 million and 0.8 million people respectively in the US would have these SCr levels.(63) Expressed in percentage terms, this equates to 9.7% of men and 1.8% of women with SCr > 1.5mg/dL (133 µmol/L). A later reanalysis of this same dataset by Coresh et al. in 2001, but using sex specific SCr threshold of ≥ 141 µmol/L (1.6 mg/dL) for men and ≥ 124 µmol/L (1.4 mg/dL) for women estimated the total US population prevalence of chronic renal disease to be 3.0% (5.6 million adults).(58) When divided by gender, it was 3.3% male and 2.7% females age ≥ 17 years.

This same dataset was again used to estimate population prevalence in 2002, but this time using the MDRD formula proposed by Levey et al. 3 years earlier and only including non-diabetic individuals.(16, 64) In this study, an estimated 13% of the US population age ≥ 20 years had eGFR by MDRD of < 60 mL/min 1.73m^2 and was described in the paper as "unexpectedly high".(64) The authors postulate that this higher than expected estimate was due to interlaboratory variation in SCr assay. In the same year, SCr from the MDRD and NHANES III study was reanalysed together and concluded that NHANES III laboratory produced on average 0.23 mg/dL (20 µmol/L) higher SCr values than the laboratory used in the MDRD study.(21)

When Clase et al. took this correction of 0.2 mg/dL (17 µmol/L) into consideration, the estimated population prevalence of those with eGFR < 60 mL/min/1.73m^2, fell from 13% to 4%.(64) It became clear that interlaboratory variability in measuring SCr, even between the same assay methods, was a significant cause of inaccuracy in eGFR reporting and subsequently huge effort was made by national bodies to standardise SCr across laboratories and analysers.(22, 32)

Using the NHANES III cohort again, but this time with calibrated SCr and with repeat albuminuria results, Levey et al. estimated 4.7% (8.3 million individuals) of the US population fulfil the definition of CKD stage 3 – 5.(45) An additional 6.3% (11.2 million) had eGFR > 60ml/min/1.73m2 and persistent albuminuria corresponding to CKD stage 1 –

2. Persistent albuminuria was determined by repeat testing of spot urine albumin creatinine ratio in a subset of 1,241 subjects out of the original 15,625 subjects within a two-month window. This study highlighted the potential size of the problem with contemporary commentators claiming this amounted to an epidemic.(34, 65) Sceptics also warned of the implication of labelling millions with a disease label who would unlikely progress to requiring RRT. However, a seminal paper by Go et al. demonstrated that people with reduced eGFR are at substantially increased risk of death, hospitalisation and cardiovascular events, effectively framing CKD as a major risk factor for health and mortality and not just a tool for identifying those at risk of progressive renal failure (Figure 1-5).(66)

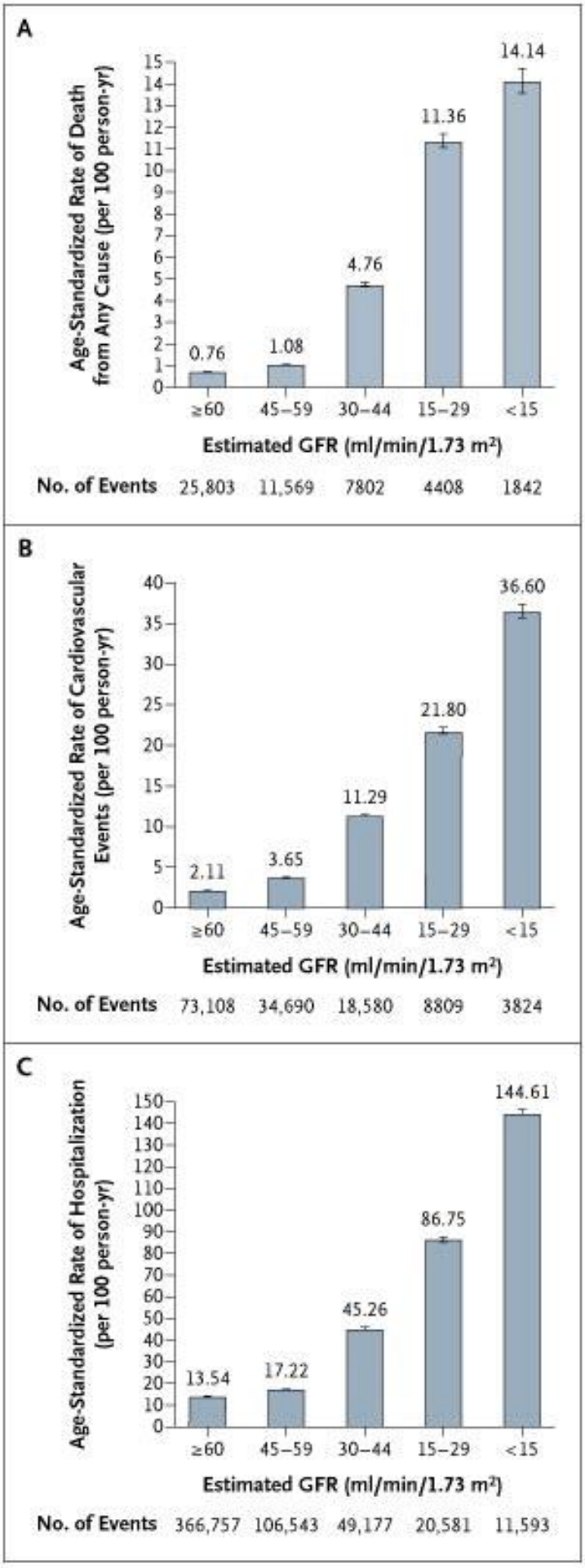


Figure 1-5. Age-Standardized Rates of Death from Any Cause (Panel A), Cardiovascular Events (Panel B), and Hospitalization (Panel C), According to the Estimated GFR among 1,120,295 Ambulatory Adults.(66) Reproduced with permission © New England Journal of Medicine 2004.

In the UK, population prevalence estimates of CKD predating the KDOQI definitions were few and restricted to advanced kidney disease. In 1972, Pendrigh et. al. published the results of a Scottish national survey, examining the prevalence of chronic renal failure in those known to have a blood-urea concentration of greater than 100 mg/dL (35.7 mmol/L). The authors determined that in a population of 5.2 million, 775 individuals aged less than 65 years had chronic renal failure. This equates to a national prevalence of 0.015% with advanced CKD.(67) A more contemporary study by John et. al. examining the laboratory records of a population of 688,193 from the south-east of England between October 2000 to September 2001 using SCr threshold of ≥ 180 µmol/L in men and ≥ 135 µmol/L in women found a population prevalence of 0.56%.(68)

After the introduction of the NKF/KDOQI definition, there were several large population studies utilizing primary care databases to estimate the UK prevalence of CKD 3 – 5. The range of estimates for CKD stage 3 – 5 in the earliest studies using eGFR estimates were between 4.4% and 8.5%.(69, 70) None of these studies assessed chronicity, and they largely relied on a single eGFR estimate. An influential study, conducted with the primary care records of 130 226 individuals, aged ≥ 18 years, over a 5-year period from 1998 to 2005 estimated the overall prevalence of CKD 3 – 5 to be 8.5%.(70) The NEw Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) study conducted in Kent, Manchester and Surrey estimated CKD 3 – 5 prevalence for women at 10.6% and men at 5.8%. However, this study was based on a single recorded SCr and contained more adults aged ≥ 75 years than the national average, both of which may lead to an overestimation in the prevalence of CKD.

The Health Survey for England (HSE), on the other hand, was a large population survey looking at non-institutionalised individuals.(71) Although the sample population with CKD was small, it was subsequently strengthened by combining the survey results from subsequent years (combined 2009 and 2010 HSE, n = 13,065) and given that it was less likely to be prone to selection bias, would produce a more representative sample estimate of the national CKD prevalence.(72) It estimated the prevalence of CKD stage 3 – 5 to be 5.2% nationally. The prevalence of any albuminuria was 7.5% and 8.2% in women and men respectively. Similar to NEOERICA, HSE only used single SCr readings and was thus prone to overestimation from the inclusion of individuals with a transient SCr elevation. On the other hand, the survey method employed in the study would avoid institutionalised individuals and those with advanced CKD and perhaps underestimate the population prevalence. Results from the HSE were used by Public Health England to estimate that in

2036, CKD is projected to affect 4,199,203 individuals, largely due to an increasing aging population.(73) This is a rise of over 50% from a base of 2,623,504 individuals estimated in 2011 and assumes that there are no improvements in the prevention and management of CKD over that period.

Internationally, CKD prevalence estimates utilising both MDRD and CKD-EPI formulae were beginning to emerge. Prevalence estimates for population prevalence with eGFR < 60 mL/min/1.73m^2 range from 1.6% in India to 8.1% in the US with estimates from other countries listed in table 1-1.(74) Regional influences such as demographic make-up, co-morbidity, smoking and obesity rates affecting prevalence. Although the debate continues as to which method of GFR estimation is most accurate, it is undeniable that the advent of the KDOQI definitions, with all their flaws, have provided a simplified framework to carry out comparative epidemiological studies regionally and internationally.

Country	[city or area]	Period (year)	*N*	PR (%)	Mean age (years)	Obesity (%)	DM (%)	HTN (%)	eGFR equation	CKD (%)	CKD by stage (%) Stages G1–2 Stages G3–4
Poland		2011	2413	67	51	NR	6.7	31.9	CKD-EPI	5.8	3.9 1.9
Tanzania	[Moshi area]	2014	481	70	45	NR	12.7	28.0	MDRD	7.0	5.3 1.7
Italy		2008–12	7552	84	57	26.4	11.8	50.1	CKD-EPI	7.1	4.2 2.9
India	[Delhi, Chennai]	2010–11	9797	76	43	17.8	19.0	32.5	CKD-EPI	7.5	5.9 1.6
Spain		2004–08	2746	21	50	26.1	9.2	24.1	MDRD	9.1	2.3 6.8
Malaysia	[Western area]	2011	876	76	43	NR	19.6	38.4	CKD-EPI	9.1	6.2 2.9
Switzerland	[Lausanne]	2003–06	6317	67	52	15.7	3.4	37.0	CKD-EPI	10.0	5.5 4.5
Norway	[Trøndelag]	1995–97	65 181	70	50	15.9	3.4	44.8	MDRD	10.3	5.9 4.4
Netherlands	[Groningen]	1997–98	2489	29	49	NR	NR	NR	MDRD	10.4	5.1 5.3
China		2007–10	47 204	93	50	NR	7.4	35.4	MDRD modified	10.8	9.1 1.7
Australia		1999–2000	10 949	54	51	21.2	8.5	29.0	CKD-EPI	11.5	5.7 5.8
England		2009–10	5799	67	50	24.7	7.4	34.1	CKD-EPI	11.9	6.7 5.2
Canada		2007–09	3689	45	52	23.0	6.3	16.3	CKD-EPI	12.5	9.4 3.1
USA		1999–2004	13 233	78	46	30.8	6.8	27.1	MDRD	13.1	5.0 8.1

PR, participation rate, that is, percentage of individuals completing screening out of the planned sample; DM, diabetes mellitus; HTN, hypertension; NR, not reported.
[a]Data are from national surveys (or, if not available, from local areas) providing information on a whole spectrum of CKD. Countries are grouped by ranking CKD prevalence in low (white area), intermediate (light grey) and high (dark grey) prevalence.

Table 1-1. Worldwide CKD prevalence, overall and by stage, in the general adult population.(73) Reproduced with permission © Nephrology Dialysis Transplantation 2016.

1.1.5 Progression to RRT

Predating the KDOQI CKD definition, estimates of CKD population burden were few and predominantly focused on incidence of advanced disease and prevalence of ESRF with the aim of informing service planning for RRT.(67, 75, 76) Methods used for these estimates involved either death certificate reviews or surveys of physicians. In these surveys, chronic renal failure was defined as a serum urea greater than 100 mg per 100ml (approximately 35 mmol/L) or SCr of > 500 µmol/L. Unsurprisingly, the rate of progression to RRT was high. In a 1990 Scottish national survey by Feest et al., 65% of the 210 patients identified (equating to 148 per-million population) with advanced chronic renal failure went on to have RRT.(75)

One of the earliest post KDOQI studies examining the rate of progression to ESRF in earlier stages of CKD was by Keith et al. in 2004.(44) This study utilised the electronic administrative and clinical database of a large north American health maintenance organisation and retrospectively identified 42,293 enrolled patients in 1996 with an eGFR of < 60 mL/min/1.73m^2 who were > 17 years of age and linked these individuals to the outcomes of death or RRT. They found that over a 5½ year period 24.3% those with stage 3 CKD (eGFR 30 – 59 mL/min/1.73m^2) died without RRT whilst only 1.3% of the cohort progressed to requiring RRT. Even in the cohort with much lower renal function, CKD stage 4 (eGFR 15 – 29 mL/min/1.73m^2), the predominant risk during follow-up was of death without RRT at 45.7% compared to the 19.9% who had RRT. This was thrown into sharp relief when compared to a control group with no proteinuria and eGFR between 60 – 89 mL/min/1.73m^2, in whom at the end of follow-up, only 10.2% died and 0.07% required RRT. This study established that for most individuals with CKD, their predominant risk was that of death rather than ESRF.

1.1.6 Morbidity risk of CKD

It is a long-held view that CKD is asymptomatic until it is in the advanced stages. Before the widespread adoption of the KDOQI CKD definitions, there were few studies examining this received wisdom.(77-81) The standardisation of CKD definition has facilitated large scale population studies that have demonstrated a substantially higher risk of hospitalisation in populations with mild reduction in eGFR and microalbuminuria.(66) This risk increases with falling eGFR and rising albuminuria. The cardiovascular events frequently examined in these observational studies are myocardial infarction, ischaemic

strokes, heart failure and arrhythmias. In the general population, survival and quality of life is poor after the first cardiovascular event.(82-86)

Some early studies found no increased risk of cardiovascular events in CKD. An example of which was a subgroup analysis of the Framingham Heart Study in 1999 by Cullerton et al. examining 516 subjects with mild renal insufficiency defined as SCr of 136 to 265 µmol/L in men and 120 to 265 µmol/L in women and used the remainder of the cohort as control (n = 5,707). Mean follow-up was 11 years, during which the authors found no association between mild renal impairment with an increase in cardiovascular events after adjusting for baseline differences (HR 1.04, 95% CI 0.79 to 1.37).

However, a *post-hoc* analysis of the Heart Outcomes Prevention Evaluation (HOPE) study by Mann et al. in 2001, demonstrated an increased risk of cardiovascular death, myocardial infarction or stroke in a larger subgroup of 980 participants identified as having mild renal insufficiency by a SCr of between 124 and 200 µmol/L. This group had a HR of 1.90 (95% CI, 1.54 to 2.17) after adjusting for Ramipril use. Similarly, hospitalisation for heart failure was also worse in the mild renal insufficiency group with a HR of 2.11 (1.56 to 2.81).(81)

Another *post-hoc* analysis, this time using the Hypertension Optimal Treatment (HOT) study involving 18,597 participants from 26 countries found a higher adjusted relative risk (RR) of 1.58 (95% CI 1.29 to 1.95) for major cardiovascular events (non-fatal strokes and MIs, and all cardiovascular deaths) in those with a baseline CrCl of < 60 mL/min compared to those ≥ 60 mL/min.(78)

Acute kidney injury (AKI) is a risk factor for developing CKD and the risk of developing AKI is high in individuals with CKD.(87-89) Developing AKI in individuals with pre-existing CKD is associated with higher mortality and higher rates of requiring RRT.(90, 91) However, this is not clear-cut as an ICU based study on AKI reported lower mortality rates in patients with AKI superimposed on CKD compared to controls without pre-existing CKD.(92)

Mineral bone disease because of CKD is also present in mild to moderate renal impairment. Pitts et al. demonstrated in 1988 that individuals with mild and moderately impaired CrCl of > 40 mL/min and 20 – 40 mL/min respectively had significantly lower average levels of 1,25 dihydroxyvitamin D despite similar levels of 25 hydroxyvitamin D compared to a control group with normal renal function.(80) This suggests that impaired 1-

hydroxylation of vitamin D occurs at higher levels of eGFR than previously thought. Those with moderate renal impairment were also found to have significantly lower total and ionised serum calcium, higher plasma PTH and fractional excretion of phosphate.

Anaemia in individuals with mild renal insufficiency was also examined by Hsu et al. in 2001 by utilising the NHANES III (1988 to 1994) survey dataset which included 15,791 individuals.(93) The authors found that those with a CrCl of < 80 mL/min were more likely to be anaemic, and the lower the CrCl, the higher the proportion of individuals with more severe anaemia. Prevalence of anaemia (< 12 g/L) in men for CrCl ≥ 80mL/min, 40 – 50 mL/min and 20 – 30mL/min in those age 61 – 70 years was 3, 4 and 12 % respectively. This was compared to women who had prevalences of 7, 10 and 25% for the same CrCl and age categories.

The risk of infections is also known to be higher in dialysis patients compared to those with normal renal function, but this is also true in CKD patients. USRDS data shows that compared to non-CKD populations, those with CKD or on dialysis had higher hospitalisation rates of pneumonia, bacteraemia/sepsis and UTI.(94) The incidence of pneumonia was 3 times higher in the CKD compared to the non-CKD group and was also associated with hospital stays that were 4 – 6 times longer.

Severity of infections and associated mortality is also higher in CKD populations. Viasus et al. prospectively collated data on 3,800 patients hospitalised for pneumonia in a Spanish hospital between 1995 and 2010. Those with an eGFR < 60mL/min/1.73m^2 (n = 203) were more frequently classed as ‘high-risk’ (89.6% vs 57%, p < 0.001) and had higher overall mortality (15.8% vs 8.3%, p < 0.001) which did not differ by CKD stage when compared to those with eGFR > 60m l/min/1.73m^2. However, in a large Canadian population cohort study of 25,675 individuals aged 65 years and older, lower levels of eGFR was associated with poorer outcomes.(95) During a median follow-up of 3.2 year, eGFR between 45 – 59, 30 – 44 and < 30 mL/min/1.73m^2 was associated with HRs for any bloodstream infection of 1.24 (1.01 – 1.52), 1.59 (1.24 – 2.04) and 3.54 (2.69 – 4.69) respectively compared to individuals with eGFR ≥ 60mL/min/1.73m^2.

One of the earliest and largest studies examining the morbidity associated with CKD in the eGFR era was by Go et al. in 2004, and involved 1.12 million individuals.(66) They showed that compared to those with an eGFR of ≥ 60 mL/min/1.73m^2, those with an

eGFR < 60 mL/min/1.73m^2 were associated with an increasing risk of hospitalization for any cause, cardiovascular events and death (Table 1-2).

Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.*

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	adjusted hazard ratio (95 percent confidence interval)		
≥60 ml/min/1.73 m²†	1.00	1.00	1.00
45–59 ml/min/1.73 m²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m²	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)

* The analyses were adjusted for age, sex, income, education, use or nonuse of dialysis, and the presence or absence of prior coronary heart disease, prior chronic heart failure, prior ischemic stroke or transient ischemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations.
† This group served as the reference group.

Table 1-2. Adjusted HR for death from any cause, cardiovascular events and hospitalisation amongst 1,120,295 ambulatory adults according to the estimated GFR.(66) Reproduced with permission © Massachusetts Medical Society 2004

There have been several studies examining the quality of life of individuals with non-dialysis CKD.(96-98) These usually employ validated questionnaires and checklists such as The Medical Outcomes Study Short Form-36, Health Utilities Index-3, The Quality of Wellbeing Scale and The Symptom Checklist-90R. These questionnaires and checklist measure both physical and mental wellbeing, and all demonstrate that lower eGFR or CrCl was associated with lower quality of life.

When using the Health Utilities Index-3 questionnaire scores to compare CKD sufferers to a broad range of populations with other chronic ill health conditions, CKD stage 3 (eGFR between 30 – 60 mL/min/1.73m^2) scored lower on average than those suffering with arthritis, brain cancer, hepatitis, colorectal cancer and coronary heart disease to name but a few.(96)

1.1.7 Mortality risk of CKD

A key characteristic of the CKD stages as defined by KDOQI is the association with increased mortality. A 2004 study by Go et al. found that, compared to those with eGFR of ≥ 60 mL/min/1.73m^2, the HRs for death for CKD stage 3A, 3B, 4 and 5 was 1.2, 1.8, 3.2, and 5.9 respectively.(66) A definitive study of this kind was only made possible following the simultaneous development of a standardised definition of CKD and the widespread adoption of automated eGFR reporting with SCr testing.

Before the arrival of the KDOQI CKD definitions and automated eGFR reporting, there were few studies examining the rates of mortality in non-dialysis CKD patients. The handful of studies examining mortality rates in non-dialysis CKD patients demonstrated a higher mortality rate, but often had small sample sizes and were limited to those attending secondary care with very advanced disease or in receipt of RRT. For example, a Danish study by Damsgaard et al. in 1990, examined the risk of death amongst 223 elderly subjects aged between 60 – 74 years with microalbuminuria. Over a follow-up period that ranged from 62 – 883 months, they found that urinary albumin excretion rate and a high SCr was associated with an odds ratio (OR) for death of 2.94 (95% CI 1.31 to 6.64) and 4.16 (1.52 to 11.36) respectively, after adjustment for gender and hypertension.(77)

This association with mortality was further cemented by Shlipak et al. in a 2005 study comparing the predictive ability of SCr, eGFR or cystatin-C in 4,637 participants of The Cardiovascular Health Study.(99) This was a study that only enrolled participants ≥ 65 years of age. Dividing the cohort into sex specific SCr quintiles, they demonstrated a J-shaped association with all-cause mortality for SCr and eGFR quintiles but a more linear association with cystatin-C. By tertiles of cystatin-C levels of < 1.00 mg/L (low), 1.00 – 1.28 mg/L (intermediate) and > 1.28 mg/L (high) associated HRs for all-cause mortality of intermediate and high risk was 1.23 (95% CI 1.07 to 1.43) and 2.05 (1.74 to 2.40) after adjustment for age, gender, diabetes, self-reported health status, left ventricular hypertrophy, fibrinogen level, log C-reactive protein, myocardial infarction, cerebrovascular disease and heart failure.

The association between rising mortality with decreasing eGFR and its generalisability to a non-caucasian population was also examined in a Taiwanese retrospective cohort study, again using routinely collected data from a large health maintenance organisation of 462,293 individuals aged ≥ 20 years from 1994 to 2006.(52) HR for all-cause mortality in

this study for CKD stage 3A, 3B, 4 and 5 were 1.5, 3.0, 5.3 and 9.1 respectively. Additionally, this study also examined whether individuals were aware of having a diagnosis of CKD and found that < 3.5% of the cohort had an awareness of either a nephritis or CKD.

This study also demonstrated a 'J' shaped mortality curve with the higher eGFR (> 90 mL/min/1.73m^2) groups also demonstrating higher mortality.(Figure 1-6) HR of individuals in this cohort with an estimated eGFR of 105 – 119 mL/min/1.73m^2 and no proteinuria was 1.2 (95% CI 1.0 to 1.5). HRs for those with minimal or overt proteinuria was much higher at 1.8 (1.2 to 2.8) and 11.1 (6.1 to 20.0) respectively. The reasons for this observation were not commented upon by the authors in the study.

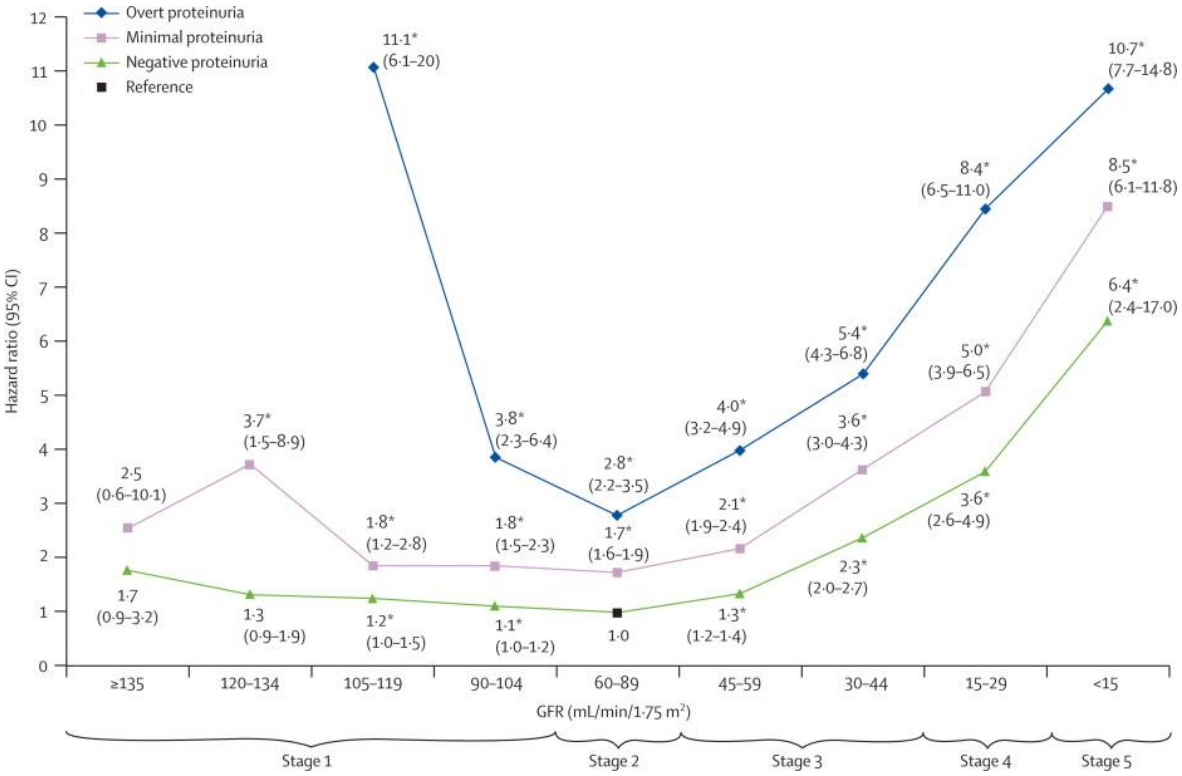


Figure 1-6. Hazard ratios (HR) for all-cause mortality by stages of chronic kidney disease in a prospective Taiwanese cohort.(52) For the HRs, comparison was made with participants with negative urine protein and glomerular filtration rate (GFR) between 60 and 89 mL/min/1·73 m2 as reference group, by adjustment for age, sex, smoking, systolic blood pressure, triglyceride, glucose, body-mass index, and cholesterol in a multivariate Cox model with continuous variables whenever appropriate. Minimal proteinuria defined as trace or one plus; overt proteinuria defined as two or more pluses. *p<0·05. Reproduced with permission © The Lancet 2006.

Similar J-shaped mortality curves associated with eGFR was also described by Shlipak et al. in 2005 from the Chronic Kidney Disease Prognosis Consortium (CKDPC) and Matsushita et. al. in 2010.(99-101) The authors of these studies postulate that this is due to the inaccuracies of eGFR estimation at levels > 60mL/min/1.73m^2. In addition, a high eGFR as a result of low SCr due to muscle wasting from ill health may be another explanation. These higher readings may also reflect a sampling bias for co-morbid individuals with obesity and diabetes, conditions that lead to renal hyperfiltration, that have inherently higher associated co-morbidity and mortality. Cystatin-C which is produced by all nucleated cells and not just dependent on relative muscle mass did not demonstrate the same J-shaped association with mortality, as with the SCr derived eGFR and has a more linear association with mortality risk.(99)

The CKDPC in its debut publication in 2010 meta-analysed 21 international studies totalling 1,234,182 participants with a median follow-up of 7.9 years.(100) Since then, the consortium have updated this work by including more international cohorts and in its last publication in 2013, examined the association of eGFR and albuminuria with sex specific mortality that included 46 cohorts consisting of 2,051,158 participants of which 54% were women.(102) This study used the CKD-EPI equation for eGFR and HRs were adjusted for age, sex, race, smoking status, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and estimated glomerular filtration rate splines or albuminuria. At baseline (eGFR 95 mL/min/1.73m^2) men had a 60% higher risk of all-cause mortality then women (adjusted HR 1.60, 95% CI 1.52 to 1.69) and as eGFR fell, the adjusted HRs rose, but for women the rise was more pronounced (Figure 1-7).

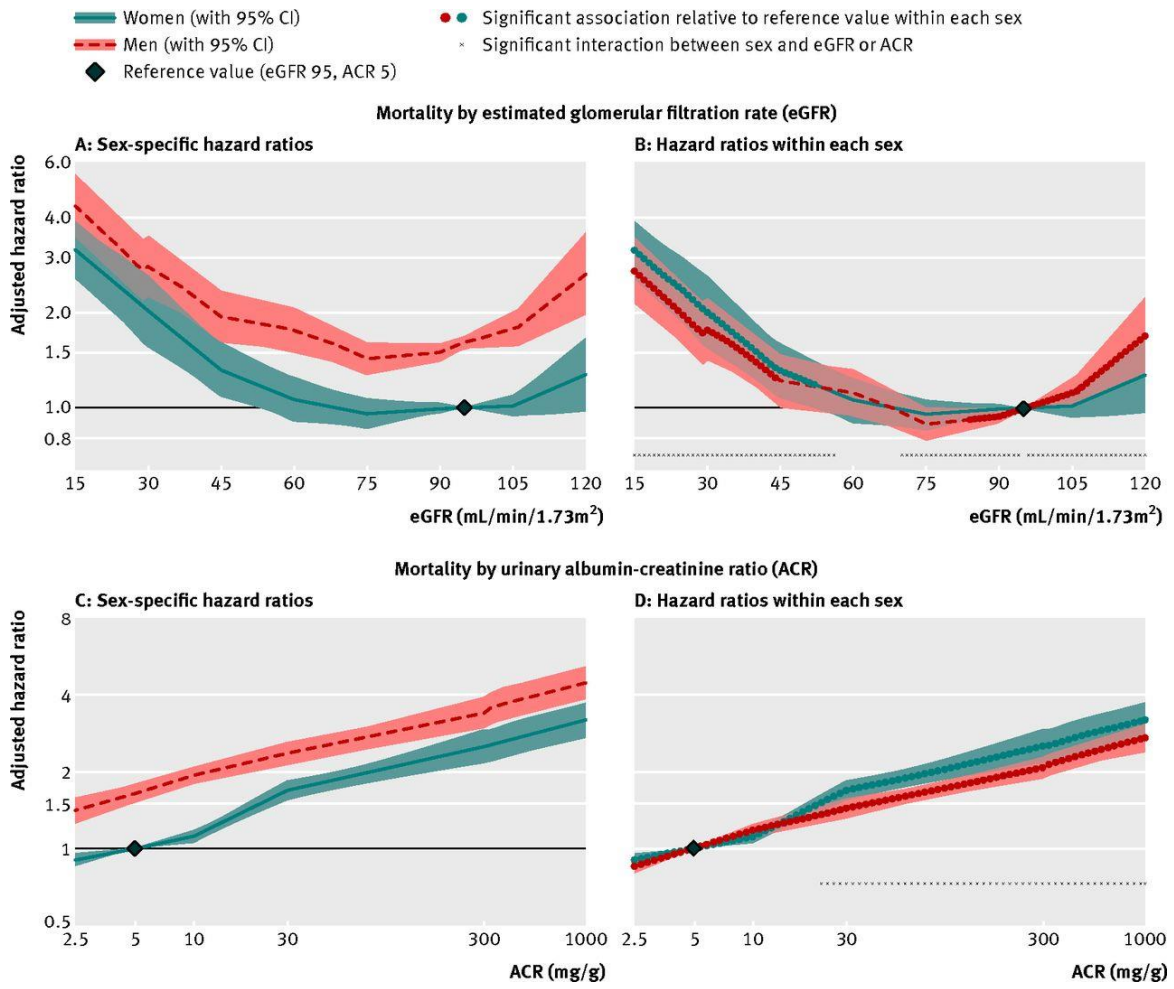


Figure 1-7. HRs of all-cause mortality according to estimated glomerular filtration rate (A and B) and urinary albumin-creatinine ratio (C and D) in men versus women in general population cohorts and high cardiovascular risk cohorts.(102) Panels A and C show sex-specific HRs including a main effect for male sex at the reference point. Panels B and D show HRs within each sex, thus visually removing the baseline difference between men and women. Reproduced with permission © British Medical Journal 2013.

1.1.8 Economic cost of CKD

The longitudinal studies examining progression of CKD stage 3 through to ESRD quote a 5-year cumulative incidence of 1.3% and a 10-year cumulative incidence of 4%.(44, 103) It is estimated that CKD accounts for 1-2% of all NHS spending and approximately half of this amount is spent on RRT.(104, 105) The different modalities of RRT have significant varying costs. In a 2008 multi-centre Welsh study, it was estimated that hospital based dialysis and satellite dialysis costs on average £35,023 and £32,669 per annum respectively.(106) Home based therapies such as home haemodialysis, continuous ambulatory peritoneal dialysis and automated peritoneal dialysis was estimated to costs on average £20,764, £15,570 and £21,655 respectively, per annum. These estimates were conducted to include all aspects of maintenance dialysis care and included patient transport, medication costs and overheads. Thus RRT, when it is required, consumes a

large proportion of the healthcare budget. Between 2011 and 2015, the prevalence of RRT in the UK increased by 12%.(107) This was largely driven by a 20% rise in the prevalent population with a functioning kidney transplant, whereas over that same period, all modes of dialysis only saw a 3% rise.

Kidney transplantation, if patients are eligible, is a much more cost-effective modality which also provides better patient outcomes.(108) The average annual cost over 5 years is £14,618 per patient.(104) Of the 61,256 adult patients in the UK receiving RRT in 2015, a functioning kidney transplant was the most prevalent modality at 53%, followed by haemodialysis at 41% and peritoneal dialysis at 6%.(107) However, to merely focus on the RRT population may be missing the wider picture of the morbidity burden and associated costs incurred by the non-dialysis CKD population.

In 2012, Kerr et al. published a wide-ranging study estimating the costs to the English NHS of CKD.(104) The costs to primary care for identifying and maintaining CKD registers, including nursing costs, blood pressure and proteinuria monitoring costs across the English NHS were approximately £143 million. The additional anti-hypertensives alone costs £152 million, and the costs of CKD specific prescriptions such as erythropoiesis stimulating agents, vitamin D analogues and phosphate binders combined amounted to a further £27 million. Outpatient care, not including RRT patients, totalled £53 million. Hospital admissions, with longer stay, excess Strokes, Myocardial Infarction and MRSA infections were all included in the final estimate totalling £1.44 to £1.45 billion in 2009-2010 which equates to an average of £795 for each patient with CKD.

1.2 Estimating prevalence and incidence in the UK

1.2.1 Population sampling patterns

NICE, in their 2014 clinical guideline “Chronic Kidney Disease in adults: assessment and management” suggests monitoring eGFR annually in those who are on potentially nephrotoxic drugs and offering testing with eGFR and uACR in those with: diabetes, hypertension, acute kidney injury, cardiovascular disease, structural renal tract disease, multisystem disease with the potential for kidney involvement, family history of end-stage kidney disease and opportunistic detection of haematuria.(109) The primary care QOF also incentivised screening in select patient populations such as hypertensive and diabetic patients through uACR screening.(110)

The number of SCr tests carried out each year and the proportion of the population subjected to it is rising, but in accordance with the law of diminishing returns, untargeted screening has led to a much lower yield of new CKD cases documented.(38, 111) Screening of high risk populations would identify one case of CKD for every three to six screened, but in non-targeted screening this would fall to one in every 16 to 21 screened.(112) Population based screening is also prohibitively expensive. A 2010 Canadian cost utility analysis of population screening for CKD, estimated the cost per QALY gained at $C104,900 (£58,972 using the average 2010 exchange rates). (112) In high risk subgroups such as diabetics, the cost per QALY gained was acceptable at $C22,600 (£12,705) but prohibitively expensive in non-diabetic populations at $C572,000 (£321,564).

It is estimated that 93.2% of CKD in a population can be detected by targeted screening of those with diabetes, hypertension or age ≥ 55 years.(113) This represents a number needed to screen of 8.7 (95% CI of 8.5 to 9.0). Indiscriminate screening in the UK has been shown to be poor utilisation of resources. A retrospective cross-sectional study by Gifford et al. demonstrated that a substantial proportion of the UK population may be inadvertently getting CKD screening from 'routine' medical activity.(38) By comparing the SCr testing of a well-defined population in Scotland from 2004 to 2009, they found that the number of SCr tests rose from 341,928 to 438,872 and despite the proportion of the adult population tested rising by 20%, the proportion of CKD stage 3 – 5 cases identified, only increased by 0.2% from 5.44% to 5.63%.

1.2.2 Establishing chronicity

A key criterion of the KDOQI definition of CKD is that it is indeed "chronic" which is arbitrarily defined as being present for ≥ 90 days or 3 months. And rightly, this has been criticised by commentators that this aspect is frequently lacking in most epidemiological studies which utilise single eGFR measurement and so, are prone to overestimation of the size of the population affected.(34)

In the NHANES III study, a small proportion of patients who had repeat SCR testing a median of 2 weeks later found only 77% of 98 individuals with an in initial eGFR < 60 mL/min/1.73m^2 were classified the same again.(45) A good example of an epidemiological study which accounts for chronicity is by Eriksen et al. who found that, from their initial cohort of 6,863 who had an eGFR of < 60 mL/min/1.73m^2, a third of the group (n = 2,175)

no longer fulfilled the criteria 3 months later.(103) A further fifth (n = 1,526) did not have a repeat SCr more than 3 months after the first. The authors also examined the effect of extending the 3 month chronicity duration to 6, 9 and 12 months, and found that the longer intervals were no better at predicting renal failure in CKD stage 3.

A 2011 study examining primary care records and the impact of single eGFR measurements versus two measurements, ethnicity or the use of different eGFR calculators found that confirming chronicity with at least two measurements provided the most accurate measure of population prevalence of CKD stage 3 – 5 than any of the other measures.(114, 115) de Lusignan et al. found that when only taking into account the latest eGFR, the prevalence of CKD 3 – 5 in the QICKD study population was 8.01% but when taking two SCr measurements into account was only 6.76%.

1.2.3 Measuring proteinuria

Proteinuria is usually detected on urine dipstick when screening for kidney disease and in many countries, forms part of routine public health measures where regular testing is carried out in school children, at workplace screening and age determined health check-ups.(116) The presence of albuminuria even at low levels may represent glomerular damage and is useful in screening diabetic patients for early laboratory markers of diabetic nephropathy. Urine dipstick is by far the commonest method for detecting albuminuria in clinical practice and has high specificity for detecting albumin but has questionable sensitivity to low but clinically significant levels of albuminuria.(117, 118) However, albuminuria can be transient, as demonstrated by the NHANES III survey when a subsample of 1,241 albuminuric individuals was retested after 2 months, only 63.2% had persistent albuminuria.(45)

Total proteinuria and albuminuria was historically measured using timed, usually 24-hour, urine collections. This was time consuming and sample collection was frequently incomplete. Current practice is to use a spot urine sample for estimating proteinuria from the ratio of protein or albumin to creatinine concentration.(118) Spot uPCR and uACR are closely correlated with protein estimation from timed urine collections, and therefore reliably predict 24-hour urine protein excretion.(119)

In primary care, regular proteinuria testing is recommended for diabetics and is incentivised under the QOF.(120) Practices were also incentivised to identify proteinuria in

patients with CKD between 2009-2015. The presence and degree of proteinuria is important for stratifying risk, targeting interventions and monitoring response to therapy.(120, 121)

1.2.4 Awareness of CKD

Patient awareness of CKD is low due to the asymptomatic nature of the condition. In a 2008 Taiwanese study of 462,293 individuals participating in national health screening, only 3.94% (95% CI 3.37% to 3.68%) of a national prevalence of CKD stage 1 – 5 of 11.93% (11.66% to 12.28%) reported awareness of having a nephritis or kidney disease.

The north American survey, the NHANES in 1999 - 2000, had the question "Have you ever been told by a doctor or other health professional that you have weak or failing kidneys?" and found awareness rates amongst those with CKD stage 1, 2, 3 and 4 at 40.5%, 29.3%, 22.0% and 44.5% respectively.(122)

In the UK, the 2010 HSE asked 6,000 participants "Do you yourself now have, or have you ever had CKD? And if so, were you told by a doctor that you had CKD?".(71) Overall, only 1.1% of participants reported a doctor diagnosis of CKD, and of those 40% had normal renal function and 35% had stage 3A/3B survey defined CKD. The prevalence of CKD stage 3A/3B in the survey was 6% of men and 7% of women, but only 5% of men and 6% of women were aware of their diagnosis.

The accuracy of diagnostic coding by healthcare professionals is also questionable. A Dutch study examining the quality of care in 47 primary care practices examined using medical records.(123) Of the 59,728 adults with valid SCr or albuminuria data, 8,795 had CKD and were under the care of a general practitioner. Of those, only 31.4% were documented as having CKD.

1.3 CKD risk factors

1.3.1 Conventional cardiovascular risks in CKD

These are "traditional" risk factors described in the earliest Framingham Heart Study publications.

1.3.1.1 Smoking

In the general population, smoking is the single most preventable cause of death worldwide and is a risk factor for six of the eight leading causes of death in the world.(124) In CKD patients, smoking is associated with an 84% increased risk of ESRF in men aged 35 to 57 years over a 25 year observation period in the 'Multiple Risk Factor Intervention Trial' (MRFIT).(125) A reduced risk of CKD progression with hazard ratios (HR) of 0.68 (95% CI 0.55 to 0.84) over 4 years was also observed in non-smokers in the 'Chronic Renal Insufficiency Cohort study' (CRIC).(126)

Smoking amongst CKD patients also significantly increases the risk of vascular and non-vascular morbidity and mortality. A *post-hoc* analysis of the 'Study of Heart and Renal Protection' trial (SHARP) at baseline found 13% of the participants identified as current smokers. (127) Amongst smokers, vascular events, cancer and all-cause mortality was significantly higher. The prevalence of smoking within CKD populations varies from 10% to 15% and reducing the prevalence of smoking is a public health priority.(128)

1.3.1.2 Hypertension

Hypertension begets kidney disease and kidney disease begets hypertension. Systemic hypertension causes increased glomerular capillary pressure which leads to kidney damage and accelerated decline.(129) The reverse is also true, as kidney damage leads to the development of hypertension via sodium retention and activation of the renin-angiotensin system.(130) The prevalence of hypertension amongst individuals with CKD in primary care is variable internationally, with reported prevalence as high as 75% in the UK and 60.5% in China, but lower at 43% in Taiwan, 37.4% in the US and 24.4% in Canada.(44, 52, 70, 131, 132) Regardless of the aetiology of the hypertension, multiple studies have shown that lowering blood pressure (BP) reduces cardiovascular risk, mortality and progressive CKD.

In the non-CKD population, there is a well established association between lower BP and lower cardiovascular risk. A 2002 meta-analysis of nearly 1 million participants from 61 international studies found that between the ages of 40 – 69 years, each 20 mm Hg reduction in systolic BP is associated with a twofold difference in stroke death rate, and a twofold difference in death rates from ischaemic heart disease (IHD) and other vascular causes.(133) A 2013 meta-analysis of randomised trials, found no difference in the risk reduction of BP lowering in people with and without CKD. (134) The investigators found a

17% risk reduction in major cardiovascular events for every 5 mm Hg reduction in systolic BP in those with (HR 0.83, 95% CI 0.76 to 0.90) and without (0.83, 0.79 to 0.88) reduction in eGFR. However, the net absolute effect for those with lower eGFR was higher due to their higher risk with a NNT = 35 or 53 for those with an eGFR < 60 or ≥ 60 mL/min/1.73m2 respectively.

In the general population, BP lowering therapy did not reduce the incidence of ESRF requiring dialysis, transplantation or resulting in death.(303) In CKD patients, there is some evidence that good BP control preserves renal function, especially in those with proteinuria.(135, 136) However, the target BP to aim for in individuals with CKD is debatable. Most guidelines recommend a BP target of ≤ 140/90 mmHg, but some suggest a more intensive target of ≤ 130/80 mmHg if albuminuria is >30mg/g; however, these suggestions are often based on weak or low-quality evidence.(137, 138)

Although the rationale for individualised BP targets is compelling, the lack of high quality supporting evidence has meant that the recommendation has garnered some controversy.(139, 140) In the SPRINT trial, which was stopped early, the composite renal outcomes of ≥ 50% reduction in eGFR, dialysis and incident albuminuria were not reduced in the intensively treated group (systolic BP < 120 mmHg) with CKD, but increased the risk of acute kidney injury.(141) The intensive therapy arm also recorded a significantly higher rate of individuals with a 30% fall in eGFR, to a value of < 60 mL/min/1.73m^2, compared to the control (< 140 mmHg) arm (HR 3.49, 95% CI 2.44 to 5.10).

Regardless of the above findings, a secondary analysis by Beddhu et al. of the participants without baseline CKD found that despite developing incident CKD (a > 30% fall in eGFR to < 60 mL/min/1.73m^2), the intensively treated group demonstrated a reduction in the primary outcomes of first major cardiovascular event, death from any cause, and incident albuminuria.(306) A subsequent meta-analysis of 9 trials with data for 8,127 individuals, including participants from the SPRINT trial, found no additional benefit for lowering BP below the conventional target of < 140/90 mmHg.(304) Amongst participants of the SPRINT trial, with baseline CKD, the intervention group did not demonstrate a reduction in primary CVD or kidney outcomes, but did reduce all cause mortality.(307) In subgroup analysis, older patients (≥ 75 years) randomised to the intensive BP target had reduced primary CVD outcomes and all-cause mortality.

The methods used for measuring blood pressure were also given a thorough review in the last NICE hypertension guideline issued in 2011.(142) In its evidence review, NICE concludes that both Ambulatory BP measurements (ABPM) and home BP measurements (HBPM) are superior at predicting prognosis than compared to clinic BP readings. Of the two, ABPM was adjudged to be superior to HBPM. An analysis in that same report also assessed ABPM as the most cost-effective method for diagnosing hypertension in primary care. It is also important to point out that the SPRINT trial, mentioned earlier, utilised a novel BP measurement method, whereby participants were seated quietly in a room for 5 minutes before recording three BP readings without an observer in the room.(141) Compared to supine BP measured by healthcare worker, this method provided systolic BP readings that were approximately 12.7 mmHg lower and 7.9 mmHg lower when compared to daytime ambulatory BP monitoring.(305)

1.3.1.3 Dyslipidaemia

The benefit for treatment with statins for primary prevention of cardiovascular events and mortality in the non-CKD population is compelling, but treatment of low risk individuals has been controversial.(143, 144) Overall, statins reduce the need for revascularisation (RR 0.62, 95% CI 0.54 to 0.72), major cardiovascular events (RR 0.73, 95% CI 0.67 to 0.80) and all-cause mortality (OR 0.86%, 95% CI 0.79 to 0.94).

In CKD patients, the focus of earlier randomised clinical trials was predominantly focused on ESRF populations. These were the 2004 ‘Deutsche Diabetes Dialyse Studie’ (4D) and the 2009 ‘A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events study’ (AURORA) which enrolled 1,255 diabetic dialysis and 2,773 dialysis patients respectively.(145, 146) These studies and others, when considered together, found no reduction in major cardiovascular events or mortality benefit favouring statins despite achieving an average 1.2 mmol/L LDL reduction compared to placebo.(147) So, it would seem that the process of endothelial damage, lipid filled atherosclerotic plaque formation and plaque rupture may not be the same pathophysiological process leading to cardiovascular events and mortality in dialysis patients.

When considering the effects of statins in non-dialysis CKD patients, the majority of trials in this population were *post-hoc* analysis of large statin trials on the general population that included participants with varying degrees of CKD. The largest of these were the *post-hoc*

analysis of 4,491 participant with CKD stage 3 – 5 from the pravastatin pooling project which was a combination of three randomised controlled trials (RCT): 'Cholesterol and Recurrent Events trial' (CARE), 'Long-Term Intervention with Pravastatin in Ischaemic Disease' (LIPID) and the 'West of Scotland Coronary Prevention Study' (WOSCOPS) which found that pravastatin 40 mg reduced cardiovascular events (HR 0.77, 95% CI 0.68 to 0.86) to an extent similar to that of the general population and reduced all-cause mortality (adjusted HR 0.86, 95% CI 0.74 to 1.00, P = 0.045).(148)

The 2011 SHARP trial included 3,023 dialysis and 6,247 individuals with SCr ≥ 150 µmol/L in men and ≥ 130 µmol/L in women, and was the first RCT to specifically examine a large non-dialysis CKD population.(149) SHARP found that a combination of simvastatin 20 mg and ezetimibe 10 mg compared to placebo reduced the primary outcome of first major atherosclerotic cardiovascular event and need for revascularisation. Coupled with the aforementioned lack of benefit of statins in dialysis patients, this demonstrates that as CKD progresses there is a transition point where traditional cardiovascular risk factors pale and "uraemic" risk factors prevail. This was demonstrated in a meta-analysis by Hou et al., examining the effect of statins by CKD stages.(308) With advancing CKD stage, the number needed to treat (NNT) increased from 24 (19 – 32) for stages 2 and 3, 36 (19 – 330) for stage 4, and 46 (25 – 257) for stage 5.

A Cochrane meta-analysis considering the role of statins for people with CKD not requiring dialysis was originally published in 2009 and updated in 2014 to incorporate a total of 38 studies with a total of 37,274 participants in its analysis.(150) It concluded that compared to placebo, statins consistently prevented major cardiovascular events (RR 0.72, 95% CI 0.66 to 0.79), all-cause mortality (RR 0.79, 95% CI 0.69 to 0.91), cardiovascular death (RR 0.77, 95% CI 0.69 to 0.87) and myocardial infarction (RR 0.55, 95% CI 0.42 to 0.72). The analysis also notes a significant reduction in proteinuria (MD -0.47 g/24h, 95% CI -0.75 to -0.19) associated with statin use, but found no significant effect on renal function.

1.3.1.4 Glycaemia and diabetes

Diabetic nephropathy is a leading cause of ESRF and its incidence is rising.(151) In the UK, registry data from Scotland demonstrates that 28% of those commencing dialysis between 2012 and 2016 did so due to diabetes.(152) In England and Wales the proportion of incident RRT patients with diabetic nephropathy for 2015 was similar at 27.5%.(153)

Internationally, this rate varies and is often higher, however the median age of development of ESRF also varies substantially which may influence the overall incidence rate in other countries.(151) Good glycaemic control whether in type I or type II diabetes, has been shown (in the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study) respectively to prevent or delay the onset of kidney disease.(154, 155)

Diabetes, whether type I or type II, is associated with a higher risk of death than the background population from which the cohort is selected from. (156) Patients with diabetic nephropathy (proteinuria) and hypertension fare much worse still, with Wang et al. estimating a 5-fold increase in all-cause mortality for men and 8-fold increase for women with non-insulin dependent diabetes mellitus. Targeting the Renin-Angiotensin system (RAS) and achieving tight blood pressure control remains the mainstay of treatment for attenuating progressive kidney damage and delaying the onset of ESRF in those with diabetic nephropathy.(81, 157, 158)

1.3.1.5 Obesity and Indolence

Obesity is associated with glomerulopathy in the form of focal segmental glomerulosclerosis (FSGS) in a minority of individuals, but the incidence of this is growing.(159) Pathological studies of kidney tissue from obese individuals found evidence of glomerular hyperfiltration leading to glomerular enlargement, reduced podocyte number and widespread foot-process effacement.(160)

In the broader CKD population, obesity is associated with a higher incidence of developing CKD, faster progression to ESRF and increased risk of death in CKD patients.(161-163) Paradoxically, in ESRF patients on haemodialysis, overweight or obesity is associated with lower mortality compared with standard weight.(164) In renal transplantation, the impact of obesity appears to be limited to early post-operative complications with some studies identifying an association with delayed graft function and graft loss.(165, 166) Longer term outcomes however, appear unaffected as patients classed as obese pre-transplantation do not appear to have significantly worse outcomes when observed up to 5-years post-transplant compared to non-obese individuals.(167)

1.3.2 Socio-economic status, a novel CKD risk factor

Uraemic cardiomyopathy, anaemia, CKD mineral bone disease, hyperuricaemia and proteinuria are a constellation of non-conventional cardiovascular risk factors in the CKD

milieu that influence morbidity and survival.(168-173) Added to that mix is the effect low socio-economic status (SES) has on CKD. Low SES in the general population is associated with increased cardiovascular, cancer and premature deaths than higher SES controls.(174) There is emerging evidence from observational studies that lower SES is associated with higher prevalence of CKD, lower eGFR, higher prevalence of proteinuria and poorer outcomes.(175, 176)

It is not clear if health behaviours such as smoking and alcohol, or comorbid conditions such as diabetes and hypertension, which are individually associated with higher mortality and morbidity, act as confounding factors to which low SES acts as a surrogate marker.(177) Or if the associated health behaviours and comorbidity, act as mediators for low SES. In support of the role low SES has as an independent risk factor in CKD are studies which identify low SES as an independent risk factor for adverse outcomes despite adjusting for the confounding factors: diabetes, hypertension, smoking and alcohol.(178-180)

The mechanism for low SES in mediating poor health is likely to be multifactorial and complex, beginning antenatally and extending into adulthood.(181, 182) Another complication that arises when studying SES is the lack of a standardised definition with many studies using income, educational attainment, tenancy, occupation, area deprivation or a composite marker for measuring SES.(176) The commonest measure used is income, which is associated with access to healthcare especially preventative care, lifestyle and educational attainment.(183)

Low SES is also correlated with poor health literacy (HL).(184, 185) Poor 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" and has been proposed as a mechanism driving poorer outcomes in those with low SES.(184) Limited HL is common in CKD being present in approximately 25% of CKD cohorts and is associated with lower educational attainment, low income, lower likelihood of referral for renal transplantation and higher mortality.(185, 309)

1.4 Quality and outcomes framework

Pay for performance (P4P) arrangements in single payer healthcare settings are commonplace. The principle being that primary care providers are incentivised to meet

targets for implementing best practice interventions or evidence based care bundles to all those under their care for whom it is indicated.(186) These arrangements usually target chronic conditions such as diabetes or COPD. For example, setting targets for retinopathy, neuropathy and proteinuria screening, and blood pressure targets in diabetic patients or smoking cessation advice, FEV_1, oxygen saturation monitoring and influenza vaccination in COPD patients. It remains contentious whether P4P schemes have had the desired influence of propagating best clinical practice with frequent criticism levelled at the vulnerability of such schemes to gaming.(187, 188)

The UK introduced a P4P system, the quality and outcomes framework, for the majority of primary care providers in 2004. A QOF domain for CKD was introduced in 2006 with automated eGFR reporting introduced throughout the UK to coincide with its launch.(33) The QOF domain required primary care practices to maintain a register of all patients with CKD stages 3 – 5 identified from routine testing but did not advocate population screening. However, there were many centres with significant discrepancies between the expected and reported prevalence of CKD, leading to initiatives to facilitate better case finding amongst primary care providers to address this gap.(189)

The response to QOF has been mixed. Some have concluded that it has had no discernible benefit to patient care.(190) Others, especially in relation to CKD, have found improved markers of care for chronic conditions such as better BP control, increased lipid modifying therapy, a reduction in cardiovascular comorbidities with time and better recognition of the condition.(191-193) It has also been postulated that the observed steady decline of patients with kidney disease presenting late (within 90 days or requiring RRT) from 28.6% of all incident RRT patient in 2005 to 22.2% in 2008 may be attributable to the increased awareness of primary care physicians from the introduction of QOF CKD indicators.(194)

1.4.1 Early referral to specialist services

Benefits of early Nephrology referral to the patient is well documented in many longitudinal studies and consolidated in a recent Cochrane meta-analysis.(195) These benefits include: lower mortality at 3 months (RR 0.61, 95% CI 0.55 to 0.67) which persisted at 5 years (RR 0.66, 95% CI 0.60 to 0.71), reduction in hospitalisation by an average of 9.12 days (95% CI -10.92 to -7.32 days), higher likelihood of choosing peritoneal dialysis (RR 1.74, 95% CI 1.64 to 1.84), lower rates of temporary vascular access (RR 0.47, 95% CI 0.45 to 0.50) and better blood pressure control. These

observations may be influenced by unmeasured confounders, such as poor health literacy, increased co-morbidity or inadequate primary care provision that could operate in a causal pathway leading to worse outcomes.

Late presenters (referral time < 90 days before starting RRT), frequently include those with *de novo* AKI or AKI on a background of CKD, and are often older and more co-morbid.(310) Udayaraj et al. examined a cohort of 894 patients who commenced RRT in a single centre between 2003 – 2008, and identified 24.3% as late presenters.(310) This group had a fully adjusted HR of 1.57 (95% CI 1.14 – 2.14) compared to those referred ≥ 365 days before starting RRT. When the late presenters with AKI were excluded, the adjusted HR comparing those who presented < 365 vs. ≥ 365 was 1.46 (95% CI 1.07 – 1.99).

Early referral is also associated with cost savings to the healthcare service. A Korean prospective study examining 879 patients found that those referred to a Nephrologist more than 1 year prior to commencing dialysis, and with at least 2 Nephrology clinic visits, was associated with healthcare cost savings of USD $2,534.00 (SD ± 436.2, $p < 0.001$) in the preceding 12 months before, and USD $428.50 (SD ± 172.30, $p = 0.013$) in the first month after initiating RRT, compared to those referred within 1 year of starting.(196)

Markov modelling by Black et al. suggests that a policy which refers everyone with an eGFR < 60 mL/min/1.73m^2 to a Nephrologist generated the most Quality Adjusted Life Years (QALY) and when compared to a policy which only referred stage 4 CKD patients could be associated with an incremental cost-effectiveness ratio of £3,086.00 per QALY.(197) However, the authors concede that the modelling was based on multiple assumptions and was limited by the lack of published data on the natural history of individuals with non-diabetic CKD.

1.5 Hypothesis and aims

The epidemiology of CKD is predominantly influenced by the age and gender constitution of a population but has a complex relationship with other demographic factors. The true prevalence, disease progression and accurate detection of which is influenced by primary care sampling practices which in turn is influenced by health beliefs often shaped by the socio-economic status of the population in question. This is also true of the health care

providers and this is evident in the varying quality of disease registers and approach to the adoption of primary prevention measures.

The aims of this thesis are as follows:

1. Develop and demonstrate the feasibility and accuracy of central laboratory ascertainment of CKD prevalence down to primary care practice level.

2. Determine the demographic factors that influence CKD prevalence at primary care practice level.

3. Assess the impact of socio-economic deprivation on disease prevalence, severity and survival.

4. Measure indicators of quality of care in CKD and temporal trends through the utilisation of routinely collated healthcare data and data linkage.

5. Demonstrate the utility of harnessing routinely collated healthcare data to inform and monitor efficacy of therapies, inform management priorities and improve patient outcomes.

2 CHAPTER 2 METHODS

2.1 Developing a CKD cohort

2.1.1 Population

The cohort is based around the geographical boundary served by NHS Ayrshire & Arran health board (A&A) identified in figure 2-1. It encompasses 2,931 square kilometres with a large coastline to the west and includes the islands of Arran and The Cumbraes. It is further divided into three council areas; North, South and East Ayrshire.

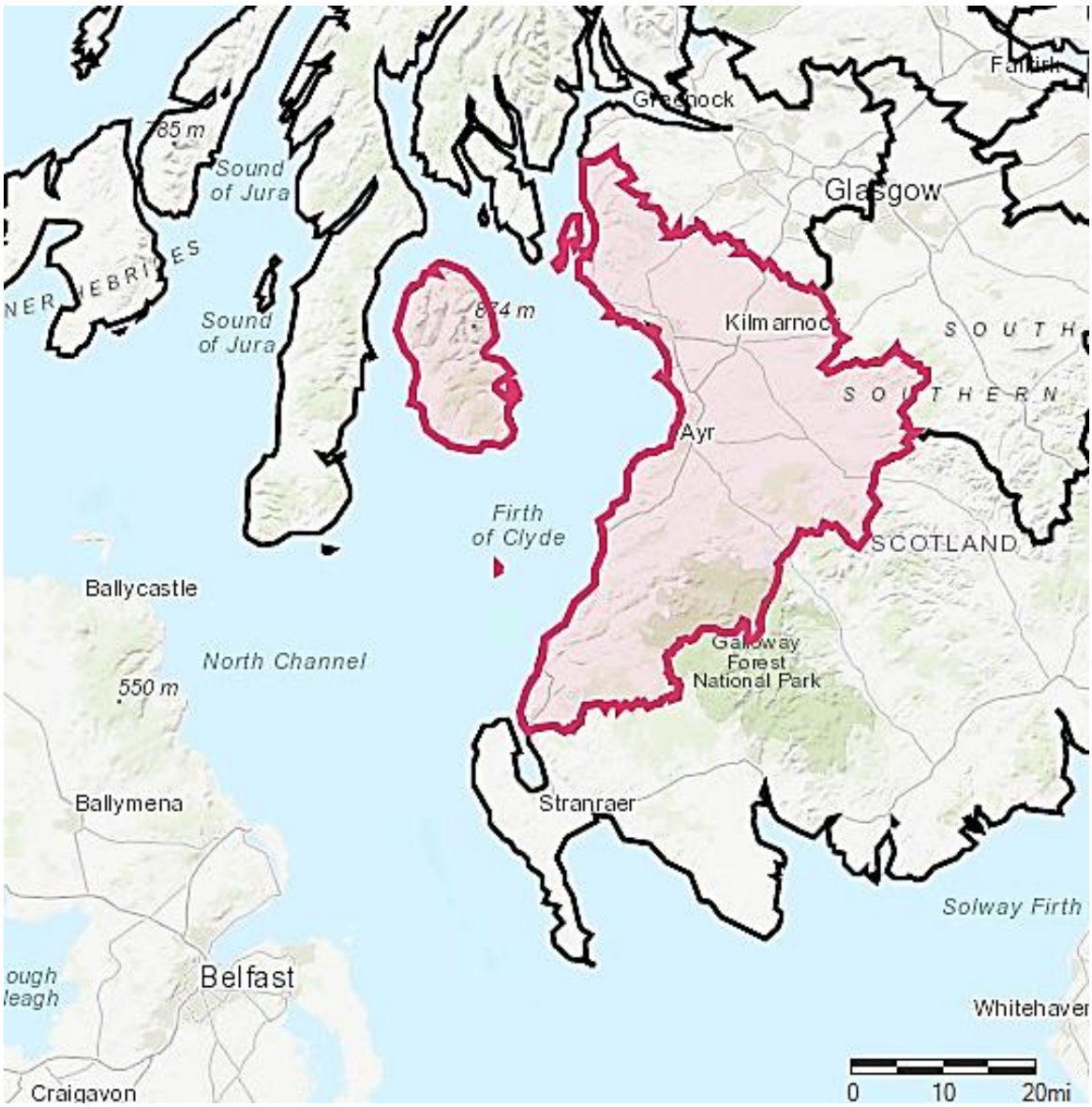


Figure 2-1. Map of south west Scotland with the area served by NHS Ayrshire & Arran outlined.

Its most populous centres are Ayr, Kilmarnock and Irvine. The area is a mix of rural, urban and island populations. In the 2011 census, the population served by A&A was approximately 373,712.(198) Of this, 299,772 were adults aged ≥ 18 years of age with a

slight preponderance of the elderly compared to the Scottish average (Figure 2-2). There were 288 GPs serving in A&A, equating to a ratio of 1,298 individuals per GP. The female to male ratio of the population was 1.1:1 which is similar to the Scottish average. Ethnicity is not routinely recorded however, the population is predominantly white (98.84% white, 0.37% Indo-Asian, 0.24% Chinese, 0.23% mixed ethnicity, 0.12% African or Caribbean origin).(198)

The PCPs are independent contractors to the health board, and are responsible for the primary care needs of their registered patients. Almost the entire population is registered with a PCP. There were 57 primary care practices that amalgamated into 55 practices in 2011. These were spread out across 77 sites within the health board area. Each practice serves a median catchment population of 6,533 (IQR 4079 – 9098; range 1,280 – 4,804).(199)

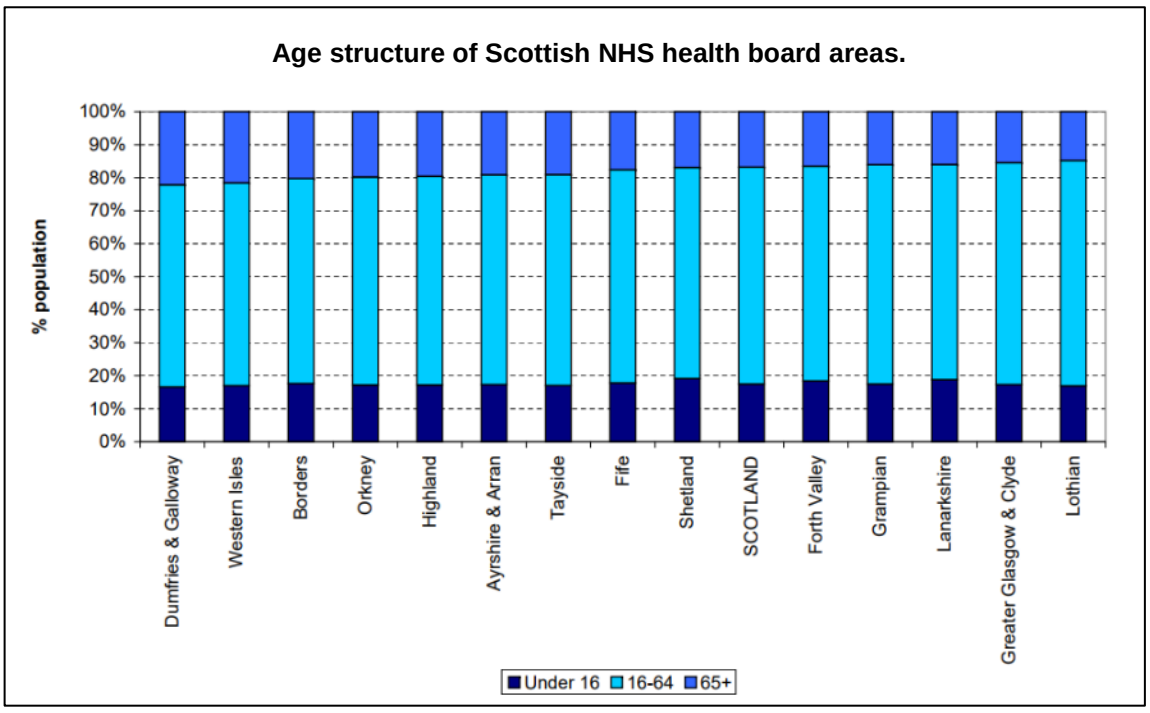


Figure 2-2. Age structure of NHS health board areas on the 30th June 2010 by percentage population aged; under 16, 16 to 64 and ≥ 65. Ranked by percentage aged ≥ 65.

2.1.2 Organisation of laboratory services and data storage

The health informatic architecture of the Scottish health boards share a common infrastructure, the Scottish Care Information or SCI-store. Nationally, Scotland has 14 geographical health boards with 14 corresponding SCI-stores. Each is a network of servers hosted locally, which functions as a repository for laboratory data which can be accessed securely by clinicians throughout the health board. This centralised repository contains a wealth of historic and real-time data with the potential to facilitate the automatic

identification of adults with CKD, without the need for time consuming and laborious manual review of individual SCr results.

Laboratory services are centralised to the two major district general hospitals of University Hospital Crosshouse and University Hospital Ayr. Primary care practices, without exception, utilise the nearest laboratory for SCr testing. One PCP situated in the north of A&A uses laboratory services in another health board and was therefore excluded from statistical analysis. For the remaining 54 PCPs, all samples for SCr estimation are sent to either one of the two main regional laboratories at Ayr or Crosshouse.

The laboratories use the Jaffe assay SCr method, performed using Roche Modular P Units and calibrated to the UK National External Quality Assessment Service adjustment for isotope dilution mass spectrometry (IDMS) traceability.(32) eGFR was calculated using the IDMS traceable 4 variable Modification of Diet in Renal Disease equation, which is the method stipulated for QOF reporting.(199) Calibration and maintenance protocols are standardised across both sites to ensure consistency. eGFR was reported automatically for all SCr samples if subjects were aged ≥ 18 years and to a upper threshold of ≥ 60 mL/min/1.73m^2.

2.2 Determining the chronicity of eGFR impairment

2.2.1 Algorithm for identifying non-dialysis CKD stage 3 – 5

Following the acceptance of eGFR based CKD classification, with the exception of CKD stages 1 and 2, stages 3 to 5 is based predominantly on eGFR.(24) There are several apparent challenges when attempting to classify serial SCr measurement into corresponding CKD stages, whilst respecting the principal tenet that the reductions in function has to be present for > 90 days and therefore ‘chronic’.(18) The inherent characteristics of the metabolite SCr, from skeletal muscle creatine and phosphocreatine, and its propensity to vary with diet, hydration, drugs, sarcopenia, tubular reabsorption and inter assay variation will result in variations in SCr of up to 8% daily, and thus varying eGFR estimates for an individual despite stable function.(200)

Utilizing single eGFR measurements will result in overestimation of prevalence, by the inclusion of a significant proportion who have a transient fall in eGFR.(114) Therefore, using two or more readings would provide a more accurate assessment of population prevalence. However, accurate identification of individuals with CKD using this method

would be highly dependent on the timepoints selected and may exclude those whose results lie outside these chosen timepoints or ignore the temporal fluctuations of their eGFR readings.

In clinical practice, it is easy to diagnose CKD in individuals who have eGFR estimates consistently below the 60 mL/min/1.73m^2 threshold. In those who have milder stages of CKD however, this can be much more difficult to gauge. Practically, clinicians approach borderline CKD cases by assessing historic results and intuitively gauging if the majority of the data points lie below the eGFR threshold of 60 mL/min/1.73m^2.(201). However, PCP IT systems usually record only the test results that are reported directly to the PCPs. This may result in PCPs only considering a small number of available serum creatinine readings for patients who may have testing elsewhere, i.e. through secondary care interactions. Thus, this approach is not robust, and some PCP CKD registers in A&A examined by Methven et al., contained, on average, 11% (46 of 411) of incorrectly coded cases.(202) These individuals all had serum creatinine measurements > 60 mL/min/1.73m^2 in the preceding year of the study. To automate and mimic clinical decision making, and take into account all the available serum creatinine results for an individual, we developed a decision tree to facilitate automated case finding in large databases (Figure 2-3).

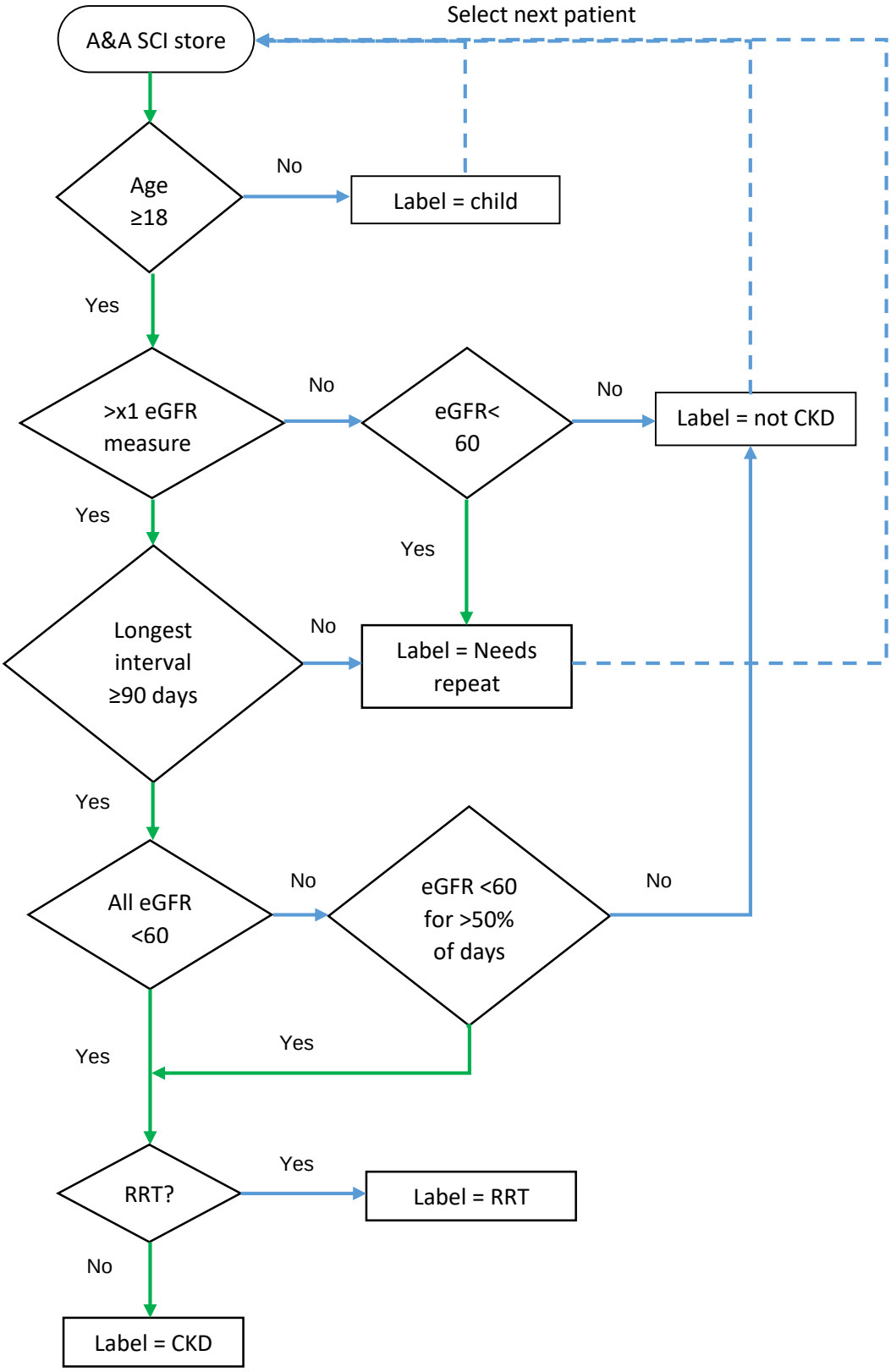


Figure 2-3. Algorithm for automated identification of individuals with non-dialysis stage 3-5 CKD and confirmation of chronicity from databases with multiple serial estimates of eGFR.

If a patient's eGFR was < 60 mL/min/1.73m^2 on ≥ 2 occasions they were considered to have CKD 3 – 5. If eGFR was ≥ 60 mL/min/1.73m^2 on all measurements during the study period, they were not considered to have CKD 3 – 5. However, if a patient had eGFR measurements both, above and below 60 mL/min/1.73m^2 during the study period, further consideration was given as follows; the number of days between SCr results was calculated for each individual, and any changes in eGFR across the 60 mL/min/1.73m^2 threshold were noted. It was assumed that changes in eGFR across the threshold occurred at the midpoint between the sample dates. CKD was diagnosed when eGFR was < 60 mL/min/1.73m^2 for > 50% of the time. We believe that this method accounts for chronicity and approximates real-world decision-making. The approach is illustrated in figure 2-4.

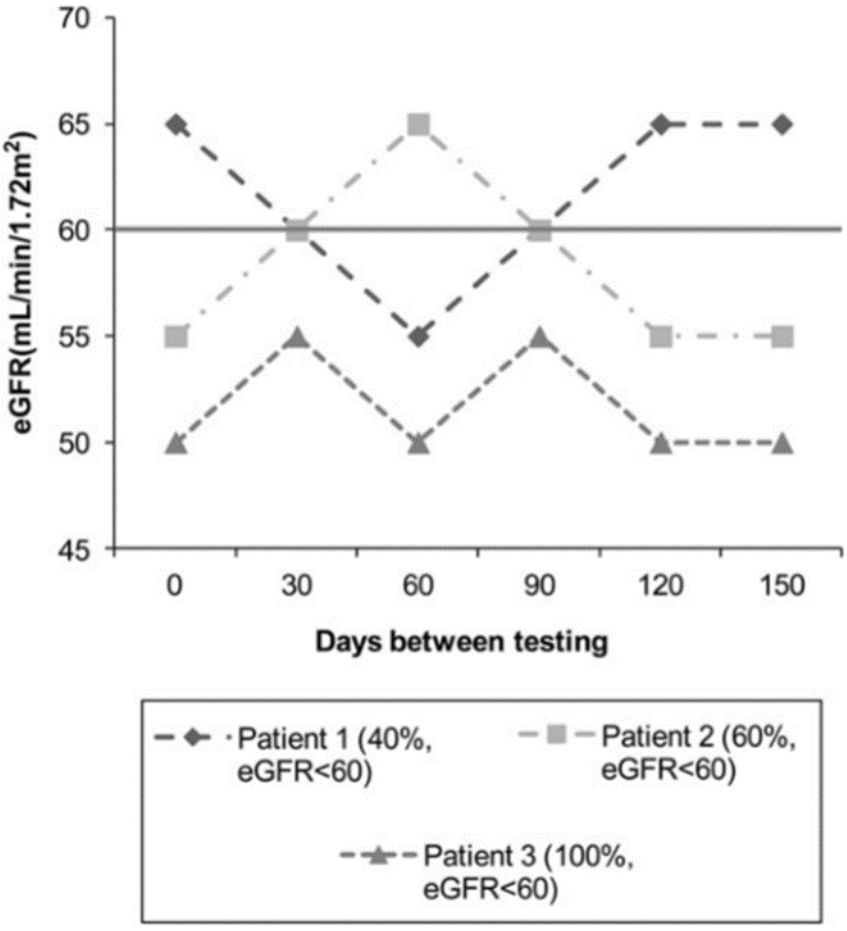


Figure 2-4. Diagrammatical representation of serial SCr measurements for 3 fictional individuals and the method used for determining chronicity. Patients 2 and 3 would be considered to have stage 3 – 5 CKD whereas patient 1 would not.

This approach has the benefit of excluding those with AKI and accurately identifying individuals in any database of SCr for individuals with CKD 3 – 5 and discriminating between those whose results straddle the 60 mL/min/1.73m^2 threshold. The accuracy of this method was assessed in non-sequential clusters totalling 200 individuals identified through our algorithm as having CKD and those without. From this small sample, this approach identified individuals with CKD accurately in 98.5% of the cases. Of those misclassified, were 3 individuals who were identified as having CKD due to repeated episodes of AKI spanning > 90 days apart with a paucity of SCr measurements prior the index illness.

2.3 Sources for data linkage

2.3.1 Community Health Index

The Community Health Index or CHI, is an individual's unique identification number for all matters pertaining to healthcare in Scotland. This nationally endorsed identifier is allocated to residents at birth or on registration with a primary care provider. This 10-digit number is retained by an individual for life. The CHI number is in use by > 97% of the population and it was this widespread use that facilitated the data linkage of the various large datasets of routinely collated healthcare data listed below.(203) As the CHI is unique to an individual and thus has the potential to identify, once data linkage was complete, the CHI numbers were anonymised prior to statistical analysis or reporting.

2.3.2 Mortality data

Survival analysis requires the accurate and timely identification of deaths of participants within the cohort of interest. All health boards maintain a register of deaths locally and is regularly updated. However, this data source has the disadvantage of potentially missing deaths that occur outside the health board. For example, following a transfer for treatment to a tertiary centre or relocation prior to death. To ensure complete capture of deaths from our cohort, we obtained data from the Information Services Division Scotland (ISDS) using the CHI number. ISDS collate and maintain a register of all deaths of Scottish residents and was able to identify all deaths within our cohort up to and including the 26th June 2014.

2.3.3 Patients in receipt of renal replacement therapy

Although patients with CKD are at risk of progressing to ESRF and may require RRT, this risk is tiered and increases with declining eGFR.(44) However, patients in receipt of RRT differ substantially to the non-dialysis CKD population.(204) They tend to be younger, more likely to have had a condition which warrants treatment with immunosuppression, may be in receipt of a kidney transplant or undergoing dialysis with associated risks from the modality or dialysis access. For these reasons, patients in receipt of RRT carry substantially higher risks than those faced by patients with CKD stage 3 – 5.

As such, we planned from the outset to exclude those in receipt of RRT from the cohort. To identify these patients, we referenced the Scottish Renal Registry (SRR) for all patients in receipt of haemodialysis, peritoneal dialysis or in receipt of a kidney transplant within A&A. We used the CHI number to ensure all those resident within A&A who were in receipt of RRT between 2009 and 2012 were correctly identified in the cohort.

2.3.4 Co-morbidity data

Given the heterogeneous nature of the subjects we would be examining, it was essential that we enriched the cohort with co-morbidity data. As our intention was to examine mortality risk in our CKD cohort, we limited the co-morbidities of interest to CHD, CVD, PAD, DM and hypertension. We initially explored the possibility of accessing co-morbidity data from primary care records, but this would have required data sharing agreements from each of the 55 primary care practices within the health board and the not inconsequential demands of reconciling the differing IT infrastructure, filing and coding systems which was beyond our resources.

It is common for large epidemiological studies to use either billing records or admission diagnostic coding. Billing records are usually only available in privately funded health care systems such as in the US. In Scotland, the Scottish Morbidity Records (SMR) requires every elective or emergency hospital admission to be attributed with ICD-10 diagnostic codes. Up to six codes may be recorded per admission and is a validated source of co-morbidity data.(205) It is however, limited to six diagnostic codes per admission and may miss out less acute diagnoses. To ensure the widest capture of co-morbidity data for our dataset we requested SMR data for a period of ten years earlier. By referencing the CHI numbers from our cohort, we retrieved the relevant ICD-10 codes from ISDS.

The ICD-10 codes of interest were:

Coronary heart disease	I20 to I25
Cerebrovascular disease	I60 to I69
Transient cerebral ischaemic attacks	G45
Vascular cerebral syndromes	G46
Diabetes Mellitus	E10 to E14
Hypertension	I10 to I15
Peripheral arterial disease	I70 to I73

These data were utilised in chapters four, five and six where individual risk and associated factors were under examination and so it was essential that potential competing risk factors were adjusted for in the analyses.

2.3.5 Prescribing data

NHS Scotland collates dispensing data from all community pharmacists through the Prescribing Information Service for Scotland (PIS), a division of ISDS.(206) Prescription charges were abolished across Scotland in 2011 and to ensure accurate dispenser reimbursement for the drugs dispensed in the community, dispensing data was routinely submitted, linked to an individual's CHI number, to PIS in preparation. This data was consistently submitted across A&A from the 1st April 2009. We obtained PIS data for our cohort up until the 17th of October 2013.

In chapters five and six, this data was used to examine the temporal trends in Statin dispensing as a marker of quality of care in CKD patients and assess its long-term effects on all-cause mortality. This rich source of verified dispensing data is perhaps more useful than prescribing data as not all prescriptions are redeemed and so using data on actual dispensed medications, although not guaranteed, is more likely to represent the actual drug administration.(207) PIS was approached and requests made for dispensing data pertaining to our cohort for drugs known to alter LDL-cholesterol.

These were:

i. Sevelamer Hydrochloride and Carbonate.(208)

ii. Bile acid sequestrants – Colestyramine, Colesevelam and Colestipol.(209)

iii. Nicotinic acid.

iv. Omega-3-fatty acids.

v. Fibrates – Gemfibrozil, Finofibrate, Bezafibrate and Ciprofibrate.

vi. Ezetimibe.

vii. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (Statins): simvastatin, atorvastatin, pravastatin, rosuvastatin and fluvastatin.

2.3.6 Socio-economic status

We used an area deprivation index, the Scottish Index of Multiple Deprivation (SIMD) ranked into quintiles of deprivation, as a proxy for individual socio-economic status. Where individual level data for socio-economic status (SES) is unavailable, the use of area level deprivation has been demonstrated to perform as well in predicting clinically relevant outcomes.(210, 211) When it comes to CKD, some have demonstrated area SES to be superior to individual level SES for predicting prevalence and progression of CKD.(212, 213)

SIMD is the Scottish Government's official measurement of concentrations of deprivation. It incorporates several different aspects of deprivation into a single index by measuring 38 indicators across 7 domains.(214) The domains are income, employment, education, health, access to services, crime and housing. It is organised around small geographical units or datazones, each containing 500 to 1000 residents (average in our study area was 870 individuals) or approximately 350 households, but can vary depending on housing density.(214) Despite having only 480 datazones, A&A has 129 of the nation's 20% most deprived areas. Over time, this index has been updated and altered in response to demographic changes and changes to population density following urban housing developments.

In chapters three and four, we used version two of the 2009 SIMD index as it was the most recent iteration at the time of data collection which was based on the 2001 boundaries consisting of 6,976 datazones. The boundaries were reviewed and redrawn in 2011 and the number of datazones was reduced to 6,505. This was termed the 2011 datazone version and it was this version that was used in the subsequent analysis of chapters five and six to allow for a larger proportion of the cohort to be mapped to a SIMD rank. Each SIMD rank was mapped using postcodes, with ranking available for 85 – 88% of the cohort over the three years. In the 2009 version of SIMD, ranking of datazones was in descending order of increasing deprivation, hence when divided into quintiles; SIMD 1 = highest SES and 5 = lowest SES. However, in the 2011 iteration, this was reversed.

2.3.7 Rurality index

As the population we are studying encompassed a large number of rural population clusters, we were interested in examining the effect rurality had on the epidemiology of CKD. In chapters three and four we included rurality in our regression analysis using the Scottish Government's own Urban/Rural classification first developed in 2003 by the office of the Chief Statistician department for the Scottish Executive (Table 2-1).(215)

The 8-fold urban/rural classification used is as follows:

Scottish Government 8-fold Urban Rural Classification	
1 Large Urban Areas	Settlements of 125,000 or more people.
2 Other Urban Areas	Settlements of 10,000 to 124,999 people.
3 Accessible small Towns	Settlements of 3,000 to 9,999 people and with a drive time of less than 30 minutes to a settlement of 10,000 or more.
4 Remote Small Towns	Settlements of between 3,000 to 9,999 people and with a drive time of over 30 minutes to a settlement of 10,000 or more.
5 Very Remote Small Towns	Settlements of 3,000 to 9,999 people and with a drive time of over 60 minutes to a settlement of 10,000 or more.
6 Accessible Rural	Areas with a population of less than 3,000 people, and with a drive time of less than 30 minutes to a settlement of 10,000 or more.
7 Remote Rural	Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes but less than 60 minutes to a settlement of 10,000 or more.
8 Very Remote Rural	Areas with a population of less than 3,000 people, and with a drive time of over 60 minutes to a settlement of 10,000 or more.

Table 2-1. Scottish Government 8-fold urban rural classification.

2.4 Ethics

Following consultation with the West of Scotland Regional Ethics Chair, we were advised that no formal ethics approval was required for the studies. Caldicott guardian approval was sought and received for the access to routinely collected patient data within A&A.

3 CHAPTER 3: SOCIO-ECONOMIC STATUS INFLUENCES CHRONIC KIDNEY DISEASE PREVALENCE IN PRIMARY CARE: A COMMUNITY BASED CROSS-SECTIONAL ANALYSIS

3.1 Introduction

Chronic kidney disease (CKD) is common.(38, 70, 71, 216, 217) It is also a major public health concern as it is associated with increased cardiovascular risk and, in subgroups, an increased risk of progressive renal decline.(44, 66, 71, 217) CKD stages 3 – 5 (CKD 3 – 5) is a laboratory diagnosis, based on estimated glomerular filtration rates (eGFR) of < 60 mL/min/1.73m^2. UK laboratories have reported eGFR routinely along with serum creatinine measurement in adults since 2006.(218) However, to fulfil the chronicity criterion, the reduced eGFR must be present for ≥ 90 days, an important aspect which is often neglected in epidemiological studies.

CKD 3 – 5 has been a domain in the UK General Practice Quality and Outcomes Framework (QOF) since 2006.(219) Primary care practices (PCP) receive performance-related payments to maintain a register of adult patients with CKD 3 – 5. The prevalence of CKD 3 – 5 registered by PCPs rose from 1.8% of the total Scottish population in 2006-07 (the first year CKD 3 – 5 was included in the QOF), to 3.3% in 2010-11, due to increasing ascertainment. Prevalence has now reached a plateau, most recently at 3.2% in 2012-13.(119)

This national prevalence rate masks substantial variation. In 2012-13, prevalence ranged from 2.5% in NHS Lothian health board, to 4.9% in A&A.(199) Within health boards, there were large variations between PCPs. For example, in A&A, prevalence in individual PCPs varied from 1.7% to 10.5%. We hypothesised that these large variations were due to differences in population characteristics. Therefore, the aim of this study was to establish the prevalence of CKD 3 – 5 using laboratory data (including the chronicity criterion), and to identify population level factors that explain the variation in prevalence between PCPs.

3.2 Methods

3.2.1 Participants and setting

A&A is a health board in the West of Scotland and is responsible for commissioning and providing healthcare for its geographically defined population of 373,712 residents (2011 census data).(198) This is further detailed in chapter two.

3.2.2 Laboratory data

We extracted all serum creatinine results recorded within the A&A laboratory database from 1st January 2009 to 31st March 2012 (39 months). All patients with one or more eGFR results < 60 mL/min/1.73m^2 during the period were included. We excluded those who were not residents of A&A, did not have a CHI number, or did not have two or more serum creatinine samples more than 90 days apart at any point during the index period. The CHI was used to identify individuals' PCP. Patients who died before the census date for each year (1st April) were excluded from the annual prevalence figures.

Assessment of chronicity of kidney disease was then performed. This is detailed in chapter two. We identified our cohort from the 1st April 2010 to the 31st March 2011. For annual assessment of prevalence, the QOF allows the inclusion of data from the preceding 15-month period. Therefore, to avoid excluding genuine CKD 3 – 5 patients in the year of interest, we also used laboratory data from 2009-10. We replicated this approach for the following year (2011-12) to ensure reproducibility.

3.2.3 Primary care practice data

QOF data is published annually by ISDS, and includes CKD 3 – 5 prevalence by PCP.(199) ISDS report CKD prevalence as a percentage of the total population. We obtained the number of registered patients in each PCP, by age and gender (as of October 2011) from ISDS, and adjusted the denominator to the adult population, which is used throughout the analysis. Practice level data including SES, rurality, mean patient age, patient gender split, practice list size and number of GPs in post expressed as patient to GP ratio (PGR) is detailed in chapter two.

3.2.4 Statistical analysis

Statistical analysis was carried out using the statistics software, SPSS version 16. Data are presented as mean ± standard deviation or median (interquartile range) as appropriate. Univariate and stepwise multivariate regression analyses were carried out as described in the text.

3.3 Results

3.3.1 Study population

The study population is described in a flowchart in figure 3-1. From the laboratory database all adults (age ≥ 18 years) with an eGFR of < 60 mL/min/1.73m^2 over a 39-month period from the 1st of January 2009 were identified to form an initial cohort of 46,129 individuals. Of these, 1,863 were excluded for not having a second SCr measurement, being non-resident or have a CHI number. A further 23,229 individuals were excluded for not having SCr spanning ≥ 90 days or fulfilling the chronicity criterion according to the algorithm previously described in chapter two. It is worth noting that a substantial proportion of individuals excluded at this level appear to have had at least one episode of AKI.

Based on laboratory data, and using the chronicity criterion, the prevalence of CKD 3 - 5 was 5.8% of adults (range 3.0 – 9.1%). The prevalence for females was 7.3% and males 4.2%. In Scotland, the QOF reports CKD 3 - 5 prevalence as 4.3%, but used the total population as the denominator. Once expressed using the adult population as the denominator, prevalence was 5.4% (range between PCPs 2.8 - 11.0%).

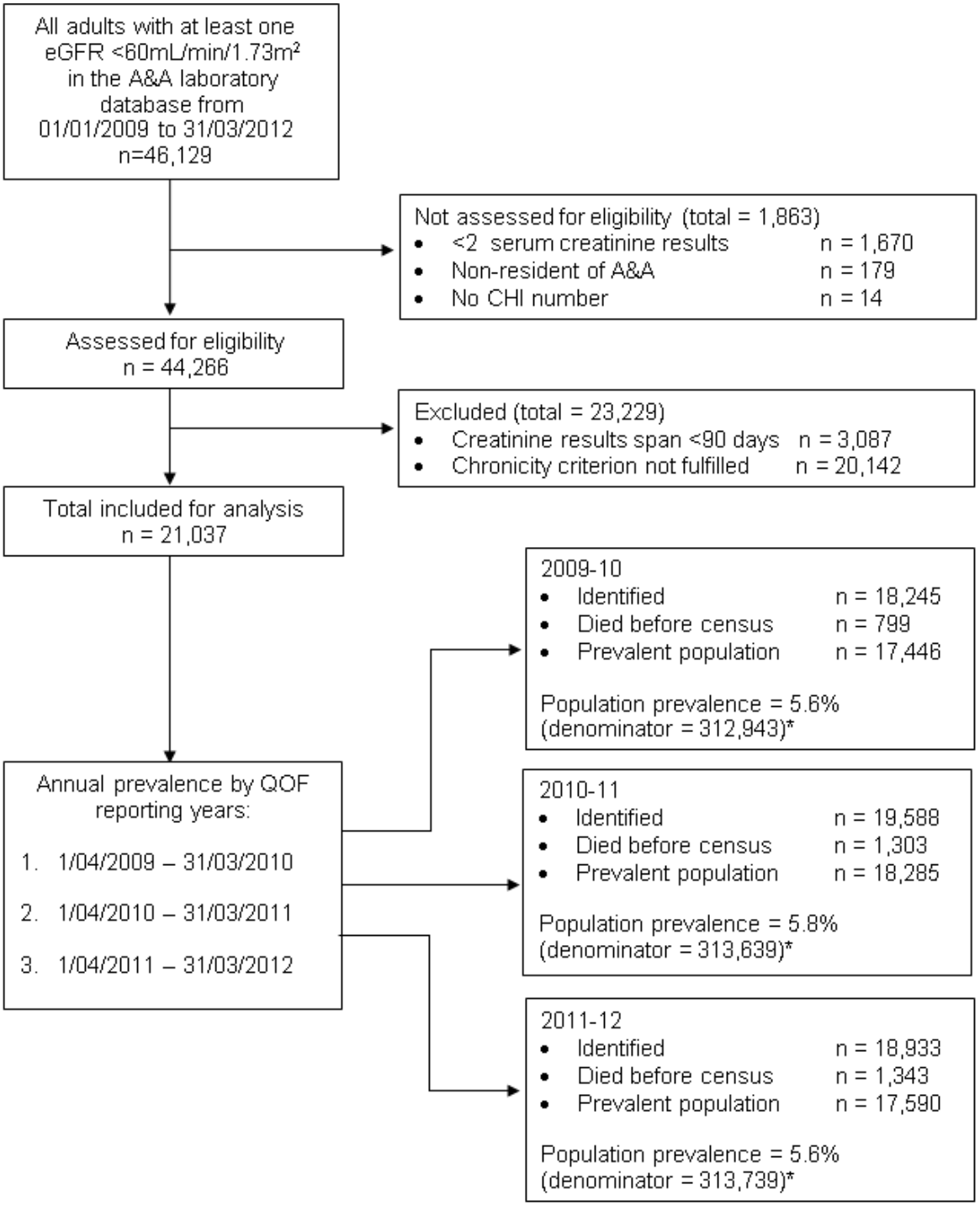


Figure 3-1. Flowchart of study population and exclusions. eGFR – estimated glomerular filtration rate; A&A – NHS Ayrshire & Arran; CHI – community health index; QOF – Quality Outcomes Framework. *Patients registered with PCPs in A&A on the 1st October in each corresponding year.(220)

This report focuses on the cohort from 2010 to 2011 with population demographic for the year in comparison with the Scottish and A&A average presented in table 3-1. Overall, the CKD population of A&A were much older and had higher proportions of women. A&A had more deprivation overall compared to the Scottish average, and the CKD cohort average SES was almost identical to its base population.

	Scotland	A&A adults	A&A adult with CKD 3-5
Female (%)	52.2	51.4	64.6
Mean Age ± SD*	48 ± 18	50 ± 18	75 ± 11
Mean SIMD quintile ± SD**	3.0 ± 1.4	3.4 ± 1.4	3.4 ± 1.3
Proportion of population† (%)			
65 and over	20.9	22.6	84.5
75 and over	9.6	10.1	57.4
85 and over	2.5	2.6	18.6

Table 3-1. Population characteristics for 2010-11 A&A CKD cohort. SD = standard deviation. *Excludes population age < 18. **Scottish Index of Multiple Deprivation scale, 1 = least socio-economically disadvantaged and 5 = most disadvantaged. †Denominator for Scotland = 4,252,806, A&A = 313,639, A&A CKD3 - 5 = 18,285.

The age structure of the CKD cohort in relation to the Scottish and A&A population structure including the proportion of the A&A population who had SCr testing is detailed in figure 3-2. In A&A, 56% of everyone age > 45 and 75% of those age > 65 years have had at least one SCr sample test carried out in 2009. There were no screening programmes for CKD in place during this period and so sampling patterns were driven by the requesting practices of individual physicians.

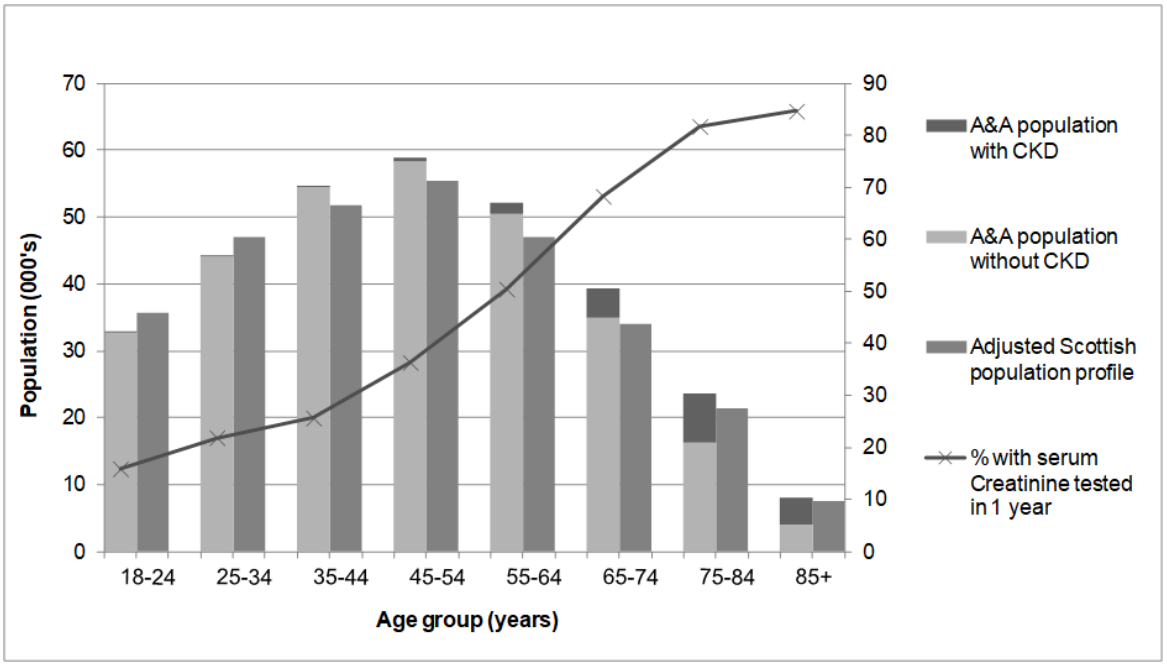


Figure 3-2. Age structure of the adult population of NHS Ayrshire & Arran, with and without CKD stages 3 - 5 in 2010-11. The percentage of the population who had serum creatinine tested in 2009-10 (secondary axis) is also shown.(38) The age distribution of the standardised Scottish population (2011) is also shown for comparison.

3.3.2 Variation in practice level CKD prevalence

Laboratory data confirmed variation in CKD prevalence at PCP level, but to a lesser degree than the QOF data. There was strong correlation between CKD laboratory prevalence (LabP) and age (Pearson's $r = 0.69$, $p < 0.001$). We therefore generated CKD prevalences for each PCP, stratified to the age and gender structure of A&A's population (AGP), prior to further analyses.

Variations in age and gender composition can act as a confounder when comparing the prevalence of disease between areas. Stratification removes this effect. For each PCP, we calculated the fraction for each of the age bands presented in figure 3-2 by gender, using the total adult population of A&A as the denominator, then multiplying this with the actual PCP prevalence rate for each age and gender stratum. The sum of these is the standardised age and gender prevalence for each PCP.

After standardisation for age and gender, SES was found to have a strong positive association with CKD prevalence (Figure 3-3). There were complex interactions between SES and other primary care practice demographic factors; level of rurality, mean age and PGR (Table 3-2).

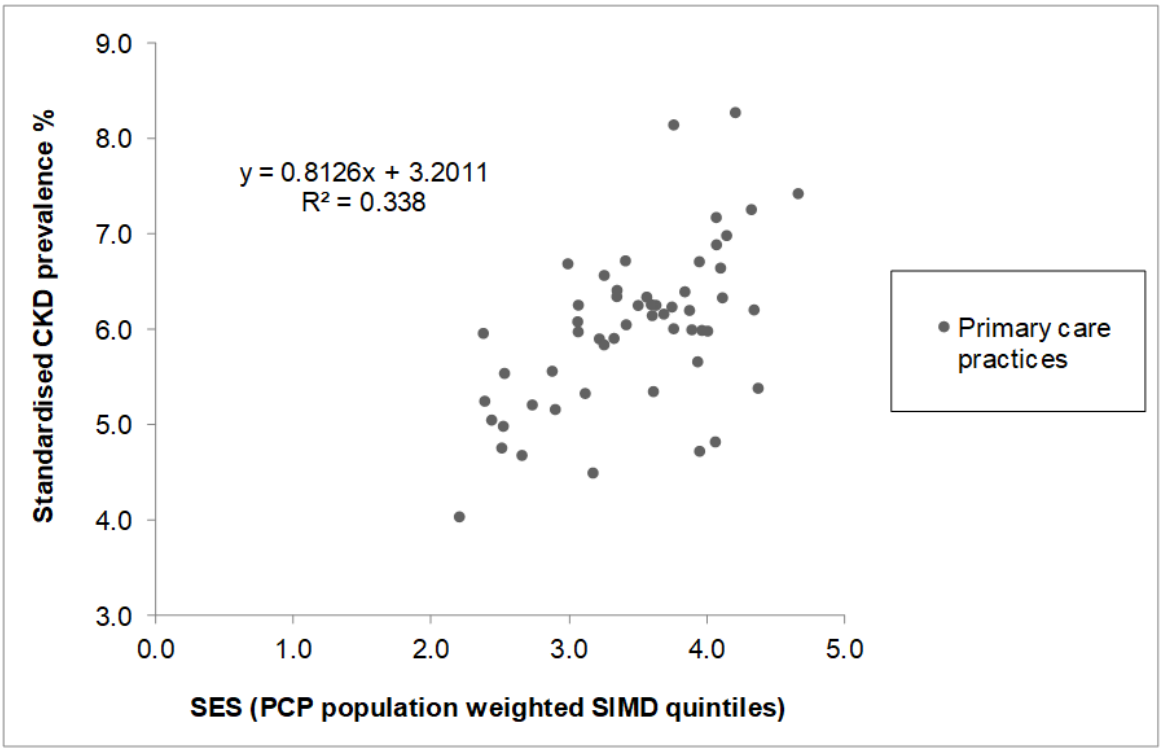


Figure 3-3. Relationship between CKD prevalence (age and gender standardised) and SES (SIMD quintiles weighted for PCP population profile). SIMD 1 = least deprived; 5 = most deprived.

N=54	Mean Age	PGR†	SES†	Rurality‡
AGP	-0.262	0.060	0.581**	0.270*
Mean age		-0.461**	0.389**	0.363**
PGR			-0.037	-0.430**
SES				0.233

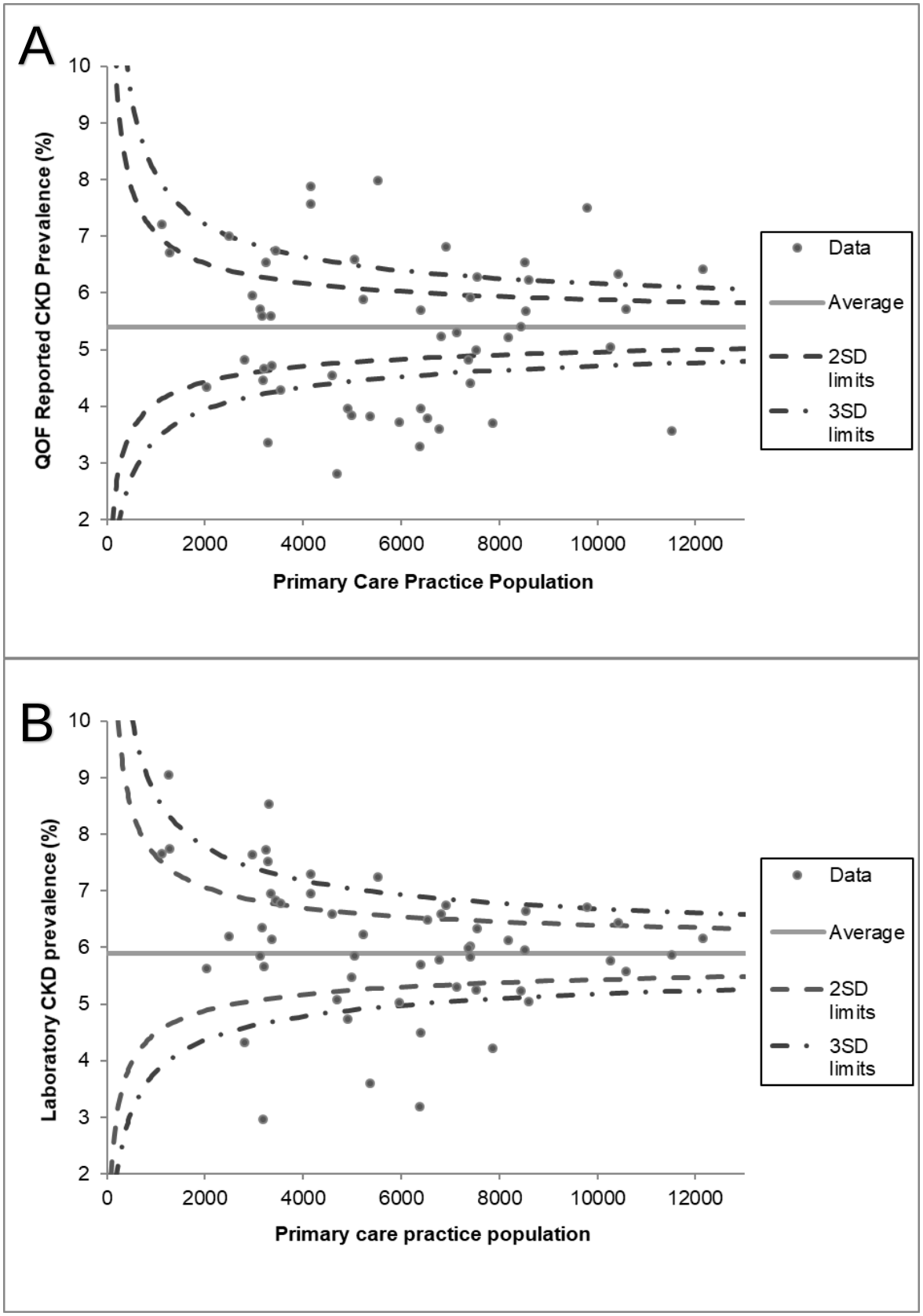
Table 3-2. Univariate relationships between primary care practice demographic factors and laboratory chronic kidney disease prevalence after adjustment for age and gender (AGP). * p < 0.05. **p < 0.01. † Pearson's. ‡ Spearman's rho.

In a stepwise multivariate regression model, SES, rurality, mean age, and PGR were included as independent variables against the dependent variable, AGP. The strongest and most parsimonious model to emerge features only SES, rurality and PGR (Table 3-3) The coefficients are positive indicating that higher standardised CKD prevalence is associated with poorer SES and rurality, and with higher PGR. These three factors combined explained 39% (adjusted $R^2 = 0.392$) of the variability in prevalence ($F(3,50) = 12.37$, $p < 0.001$). SES was the single most influential predictor, accounting for 25% of the variability.

	B (s.e.)	Standardised β	t	95% CI	Part Correlation
(Constant)	2.053 (0.728)		2.822**	0.592, 3.515	
SES	0.714 (0.155)	0.512	4.635**	0.406, 1.027	0.497
Rurality	0.163 (0.061)	0.356	2.662**	0.040, 0.287	0.285
PGR	0.088 (0.041)	0.279	2.139*	0.005, 0.171	0.229

Table 3-3. Predictors of age and gender standardised CKD prevalence at primary care practice level: regression coefficients. SES: Socio-economic status. PGR: Patients (hundreds) to GP ratio. * p < 0.05. **p < 0.01.

By applying the coefficient from the univariate regression of AGP and SES, we created funnel plots of CKD prevalence (LabP) before and after adjusting for age and sex then SES (Figure 3-4: A-D). Adjusting for age and gender, and then SES reduces the number of PCPs outwith three standard deviations from 15 to 7 to 6. For PCPs between two and three standard deviations, the number of practices fell from 16 to 13 to 5. Variation in prevalence between practices was 3.9-fold for QOF prevalences, 3.1 for laboratory prevalences, 2.1 for age and gender adjusted laboratory prevalences and 1.8 for age, gender and SES adjusted laboratory prevalences.


A
QOF Reported CKD Prevalence (%)
Primary Care Practice Population
Data
Average
2SD limits
3SD limits
B
Laboratory CKD prevalence (%)
Primary care practice population
Data
Average
2SD limits
3SD limits

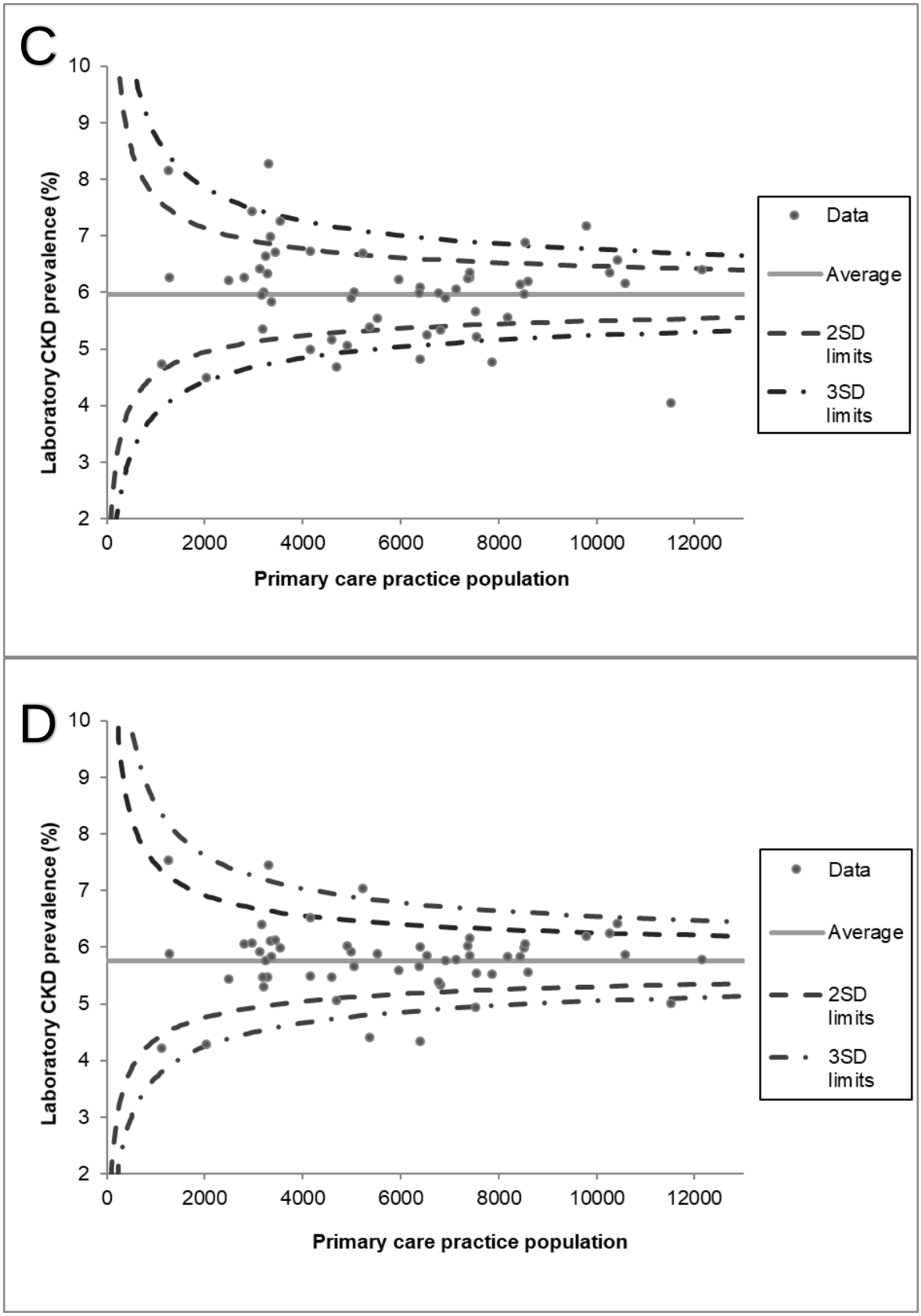


Figure 3-4. Funnel plots of CKD 3 - 5 prevalence by primary care practice population (A to D). (A) Funnel plot constructed using primary care practice QOF reported CKD stage 3 - 5, unadjusted prevalences. (B) Funnel plot constructed using primary care practice unadjusted laboratory ascertained CKD stage 3 - 5 prevalences. (C) Funnel plot constructed using primary care practice laboratory prevalences, adjusted for population age and gender profile. (D) Funnel plot constructed using primary care practice laboratory prevalences; adjusted for age, gender and socio-economic status.

3.4 Discussion

3.4.1 Main findings

Using existing laboratory data, all patients with CKD stage 3 – 5 in a large geographically well-defined Scottish population, could be identified reliably taking into account chronicity of the eGFR impairment (i.e. persistence of reduced eGFR ≥ 90 days). CKD prevalence remained stable at 5.6 – 5.8% of adults from 2009-10 to 2011-12. This study had three main findings.

First, a laboratory case-finding approach was practical, and identified more patients than PCP registers, equating to an additional 1,255 patients (7% of the CKD population). There was a 3.9-fold variation in CKD prevalence between PCPs using QOF registers, ranging from 2.8 - 11.0%.

The second main finding was to demonstrate a reduction in variation to three-fold by using laboratory defined prevalence (3.0 - 9.1%). However, substantial variation persisted, suggesting it cannot simply be explained by clinical practice variation in recognising and registering disease alone. Age and gender are well established predictors of CKD prevalence and the demographics of PCPs differ substantially which results in age and gender acting as both confounders and effect modifiers in the relationship between PCPs and CKD prevalence.(70, 71) Adjusting for age and gender reduced this variation between PCPs substantially.

The third finding was that after age and gender, PCP population weighted SES was the single most important factor for explaining the residual variation in CKD prevalence amongst PCPs.

Others have used a variety of case-finding approaches to investigate CKD prevalence: population surveys, laboratory based case-finding, primary care record searches or PCP registers.(45, 70, 71, 114, 115, 221-223) However, there has been relatively limited attention to describing and understanding the variation in prevalence between PCPs.

In England, the NHS Atlas of Variation has examined variation in CKD prevalence as reported on QOF registers, and has benchmarked this against age and gender adjusted expected prevalences.(189) In 2008 - 09, the observed/expected ratio was 0.2 - 0.9 in primary care trusts, a 4.5-fold variation. When benchmarked against the NEOERICA

study, which used primary care records and a single eGFR estimate, variation at individual practice level was 10-fold.(70) When benchmarked against the Health Survey for England, which uses a population survey approach based on a single eGFR and excluding institutionalised adults, the observed/expected ratios in 2011 demonstrated a 4.7 fold variation from 0.3 to 1.4.(224) Underlying explanatory factors for the variation were not sought in these studies.

A national CKD audit by the Healthcare Quality Improvement Partnership (HQIP) was published in 2 parts in 2017.(316) The first part, published in January, focused on the accuracy of PCP diagnostic coding of CKD from a sample of 459 PCP in Wales and 1267 PCP in England. Their work on diagnostic accuracy mirrors some of the work presented in this chapter which predates the HQIP report by 2 years.(175) In the HQIP report, they found that a diagnosis of CKD 3-5 was coded for 4.4% of the population sampled age ≥ 18, but 11% of them did not have recorded test results to support this. This miscoding rate is very similar to that found by Methven et al.(202) They also demonstrate that a further 1.2% of PCP population should have a CKD 3-5 diagnostic code based on existing serum creatinine results recorded on PCP IT systems. PCP IT systems do not routinely record serum creatinine results requested in secondary care and our work demonstrates that this results in reduced ascertainment of CKD. This reliance solely on PCP patient records was not addressed in the HQIP report.

A novel finding from our study was that rurality was associated with higher CKD prevalence and this association persisted after stratifying for age and gender profile of the population. No other studies were found replicating this with regards to CKD, but there was a study by Dunlop et al. describing rurality as a barrier to healthcare.(225) There are complex interactions between age, socio-economic status and rurality, but each added to the model and remained significant in our multivariate model (Table 3-3)

The association between CKD prevalence and SES has been described elsewhere but with differences in methods and indicators used to indicate level of SES. In a Swedish case-control study, individual level SES as defined by occupation class or educational attainment was negatively associated with an increased risk of chronic renal failure (approximating to CKD stage 4) after adjusting for age, sex, BMI, smoking, alcohol and analgesic use.(226) In an English laboratory-based study, incidence of CKD 3 – 5 was associated with area-level SES with the highest SES group having a RR of 0.80 (0.69 – 0.93) and for the lowest SES quintile a RR of 1.17 (1.02 – 1.33).(227)

The lower SES quintiles also had worse outcomes. Studies from a UK secondary care population demonstrated an association between lower SES with increased referrals for CKD and also lower eGFR at presentation.(179, 228) An English study using a population survey found an increased risk of age and sex adjusted CKD with several individual level socio-economic markers. However, after adjustment for ethnicity, smoking, BMI, hypertension and diabetes mellitus, only household tenure of renting versus ownership remained significant predictors.(72) A large UK study based on primary care records, showed an OR of 0.92 for SES and CKD prevalence after multivariate analysis.(217) However, the authors considered this insignificant having pre-specified a clinically significant effect as an OR < 0.67 or >1.49. We found a linear relationship between CKD prevalence and the mean SES of the population served by PCPs. Whether the linear relationship we identified applies to other populations in the UK and beyond requires confirmation.

Laboratory information is sufficient to identify most, if not all, patients with CKD 3 – 5. We have shown that laboratory case-finding is technically feasible and desirable. The methods described in this paper are easily replicable throughout the UK, and any other health system with high quality information systems at population level. Implementation would improve the accuracy and completeness of CKD registers which may lead to improved care and outcomes.

There are very few studies in CKD examining the impact of QOF on outcomes, with one study demonstrating a sustained improvement in the mean blood pressure of CKD patients after the introduction of QOF.(191) Another study found that the proportion attaining blood pressure targets, along with diabetes prevalence, age and ethnicity combined influenced 40% of the variation in incidence of renal replacement therapy.(229)

A similar laboratory based approach could also be applied to proteinuria, as laboratory quantification is the recommended screening test.(29, 30) However, ascertainment will be less complete, as a smaller proportion of the population is tested. Even amongst patients with CKD 3 – 5 where incentives exist for testing, only 82% have had proteinuria quantified.(199)

The mechanism by which low SES is associated with increased CKD prevalence is not clear. Other factors associated with CKD are known to be more common in lower SES which includes obesity, smoking, diabetes mellitus and vascular disease and so low SES

may simply be a composite marker for these.(230) The Whitehall II study demonstrated that in white London civil servants, 25% of the observed association between SES and decreased GFR could be explained by the combined effect of obesity and metabolic syndrome.(178) However, even after adjustment for known risk factors, residual increased risk remained associated with low SES.(231)

On a more practical level, others have assumed that an age and gender adjusted prevalence is a reasonable benchmark to use for PCPs or regions, with the assumption that those with lower than expected prevalence are failing to identify or register patients.(224) Our study shows the importance of also including SES when benchmarking, as the number of statistical outliers (> 2 S.D from the mean) fell from 20 to 11 practices. Using this approach will allow further investigation and resources to be targeted at a smaller group of outliers.

Identification of patients with CKD 3 - 5 is the first step in optimising the renal health of the population. Patients with CKD but not on the register may not receive appropriately targeted monitoring, referral and treatment. Patients incorrectly on the register may receive inappropriate interventions. Currently, the UK relies on populating CKD registers with patients identified and coded by PCPs. Some PCPs perform this task manually, while others use software packages which interrogate PCP electronic records, but do not correct the serum creatinine for IDMS standardisation. Furthermore, a large proportion of serum creatinine results carried out by other community health services or in secondary care is mostly not included in these searches further increasing the risk of misdiagnosis.

3.4.2 Study limitations

We assumed that those with no serum creatinine results did not have CKD. We have also assumed that those with a reduced eGFR, but no confirmatory sample ≥ 90 days later, did not have CKD. Both assumptions could lead to an underestimate of CKD prevalence, and a population survey with repeated eGFR estimates would be necessary to address those flaws. However, the logistics and cost of such a study would be prohibitive. Most CKD occurs in older people, and we have shown that 75% of > 65 year olds had a SCr checked in a single year (Figure 3-2). Others have shown that despite a 20% rise in the A&A population being bled between 2004 and 2010, that there was no change in CKD prevalence.(38) We therefore believe relatively few cases of CKD have been missed.

We developed a particular method of defining chronicity, which we believe mimics clinical decision making. Other methods are possible. de Lusignan et al examined a variety of approaches to defining CKD prevalence.(114) When they required two eGFRs > 90 days apart, with no intervening results > 60 mL/min/1.73m^2, they found a prevalence of CKD 3 – 5 of 5.41%. If intervening results were ignored, this rose to 5.55%. Our approach is different again, but likely to give an intermediate value. More importantly, many CKD prevalence studies are based on a single eGFR reading, with no attempt at confirming chronicity.(38, 45, 70, 71) This can lead to an overestimate of prevalence (6.41% in the study above).

In our study, we demonstrate the practical application of the chronicity criterion in a large cohort with multiple serial results at varied intervals. This approach avoids misclassifying a large group with transient fall in eGFR to < 60 mL/min/1.73m^2 as chronic kidney disease. This may explain the significant errors of classification found in PCP CKD registers in A&A.(202) The method utilised in this study is one approach of classifying 'borderline' cases when eGFR measurements fluctuate close to the 60 mL/min/1.73m^2 threshold, in a fashion that mimics clinical decision making.

The difference between the QOF reported prevalence and LabP range from -4.2% to 2.5%. However, for information governance reasons, we were unable to access PCP registers, to directly access their accuracy compared to laboratory data. This means that the discrepancy between PCP registers and our laboratory derived register may be larger still.

It is worthwhile noting however, that within the limitation of the data presented, there appears to be both under and over reporting within PCP registers which appears unintentional and generally reflects the inefficiencies of the systems currently in place. When examining 8 A&A PCP CKD registers in detail, Methven el al. previously found that 11% of patients in those CKD registers did not have an eGFR < 60 mL/min/1.73m^2.(202) If this finding is generalisable across A&A, it could mean that approximately 1,800 patients listed on PCP CKD registers are inappropriately coded as such. This problem could be addressed by central laboratory ascertainment of CKD 3 – 5.

4 CHAPTER 4: SOCIO-ECONOMIC STATUS, eGFR AND SURVIVAL: RESULTS FROM A COMMUNITY-BASED CKD COHORT

4.1 Introduction

Studies examining the influence of low socio-economic status (SES) on Chronic Kidney Disease (CKD) have often been confounded by ethnicity, especially those conducted in North America.(232-235) These studies frequently cite poor access to health-care, income or racial disparities to account for the apparent association between CKD and low SES. Figure 4-1 illustrates the various factors by which SES could influence health and illness. (177) It demonstrates the multitude of interacting factors that may lead to the development of ill health in an individual or population. Despite the provision of universal healthcare in the UK, these factors may play a role in the variation of health outcomes in a population.

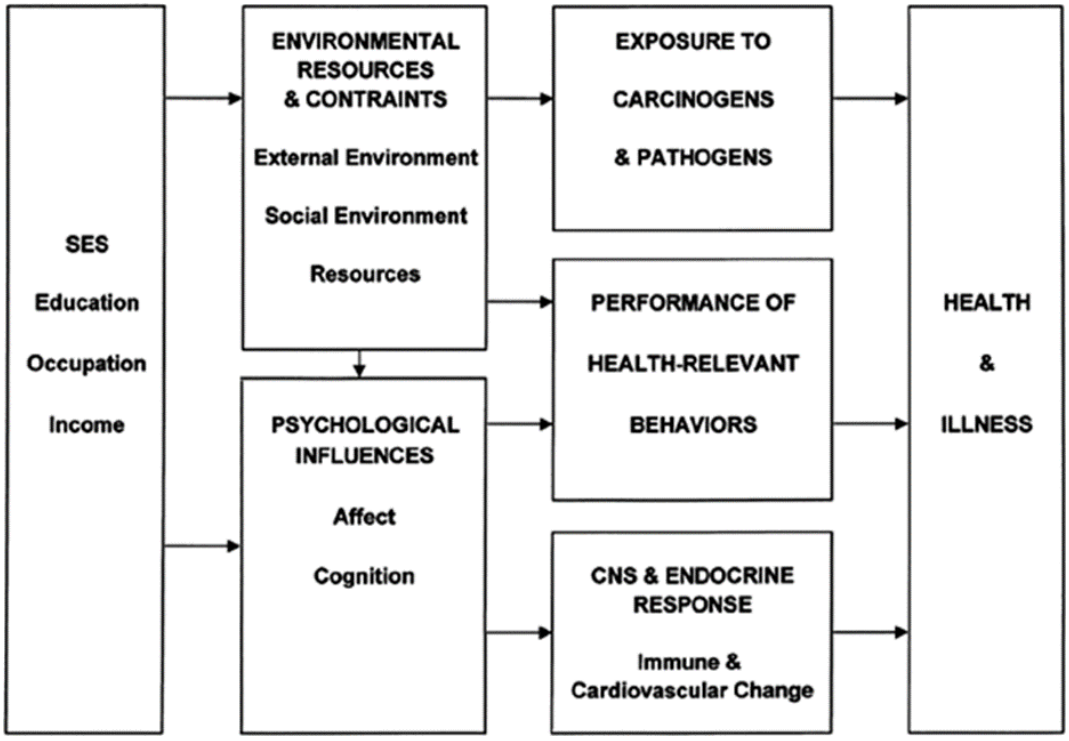


Figure 4-1. Model of pathways by which SES influences health. Reproduced with permission © Ann N Y Acad Sci 1999.

In the UK, a pay for performance scheme, the Quality and Outcomes Framework (QOF), was introduced in 2004 with the aim of improving health inequalities with some success.(187) Since the introduction of CKD as a QOF indicator in 2007, the UK has seen the establishment of CKD registers in all primary care practices in Scotland. Prevalence rates rose from 2.1% in the index year to a plateau of between 4.5 and 5.0% since 2012.(110)

CKD prevalence is higher in areas with lower SES.(72, 175, 226) The relationship between poor SES and renal function was well characterised by Bello et al. for a cohort presenting to Nephrology services.(179) They showed that individuals from the lowest quintile of SES had a OR of 4.36 (95% CI 1.09 to 17.38) for lower eGFR (< 30 mL/min/1.73m^2) compared to the most affluent SES quintile even after adjusting for sociodemographic, smoking and clinical factors.

An association between SES and poorer survival was described by Drey et al. in 2003.(227) In this study of 4,228 cases of kidney disease, the focus was on incident CKD as defined by a new serum creatinine result greater than 1.7 mg/dL (150 µmol/L) with no fall within 6 months in the preceding two-year period. The study found that lower SES as defined by the Townsend deprivation quintiles were associated with 20% worse survival after adjusting for age, gender and SCr. They also examined death certificates and found cardiovascular causes accounted for 46% of deaths and only 4% received RRT. This study did not adjust for co-morbidity or other laboratory markers of CKD severity.

We hypothesised that in this study, lower SES would be associated with poorer kidney function and impact survival negatively. Using an established community cohort of prevalent CKD patients, which is racially homogenous and has unfettered access to healthcare, we assessed the relationship between estimated glomerular filtration rate (eGFR), SES and survival while taking account the co-morbidity mix.

4.2 Method

4.2.1 Participants and settings

The demographic make-up of A&A is detailed in chapter two. All routinely collated healthcare data is stored in a central server, the SCI-store. Using the algorithm described in chapter two, we identified all patients between 2009 and 2012 within A&A with CKD 3 – 5 accounting for chronicity (i.e. ≥ 90 days duration) and excluding those in receipt of renal replacement therapy.(175) Data regarding individuals who commenced RRT was obtained from the SRR. For this study, we selected a cohort identified as having CKD stage 3 to 5 from one calendar year starting from the 1st of January 2009.

Serum albumin, protein-to-creatinine ratio (PCR) and albumin-to-creatinine ratio (ACR) were obtained from the A&A SCI-store. Only values recorded in the corresponding year were included as the individual's baseline characteristic. Proteinuria and albuminuria was grouped according to Kidney Disease Improving Global Outcomes (KDIGO) proteinuria stage i.e. A1 = ACR < 3 mg/mmol or PCR < 15 mg/mmol, A2 = ACR 3 – 30 mg/mmol or PCR 15 – 50 mg/mmol and A3 = ACR > 30 mg/mmol or PCR > 50mg/mmol. SMR together with dates of death was obtained from ISDS. The ICD-10 codes selected for this study is listed in chapter two.

4.2.2 Socio-economic status and survival data

SES was measure using the 2009 SIMD rankings detailed in chapter two.(214) We mapped datazones to individual postcodes using the CHI and subdivided patients by SIMD rank into five SES quintiles with 1 representing the least affluent, and 5 the most affluent. In CKD, area SES has been demonstrated to be superior to individual SES for predicting prevalence and progression.(212, 213)

To compare survival, we linked date of death obtained from ISDS up to the censor date of 27th June 2014. Comparisons were made between the top and bottom, as well as all SES quintiles, before and after adjustment for demographic factors, co-morbidities and biomarkers.

4.2.3 Statistical analysis

Demographic differences between groups were assessed using t-test or one-way ANOVA for continuous variables and χ^2 for categorical variables. Associations between categorical and continuous variables were assessed using univariate ANOVA or Spearman's rank correlation co-efficient. Unadjusted comparison of survival was assessed using Kaplan-Meier method and multivariate adjustments for differences between groups with Cox proportional hazards model. Cox and Snell R^2 method was used to assess model fit for the different Cox models. Statistical analysis was carried out using SPSS statistics package v24. (ref IBM)

4.2.4 Missing values

There were 11.7% (n = 2,015) missing values for serum albumin, 12.4% (n = 2,130) for SIMD rank and 34.3% (n = 5,898) for Proteinuria. Little's tests for variables missing completely at random (MCAR) was χ^2 = 1,414.90, df = 23, p < 0.001. After univariate statistics and estimated means analysis the conclusion was that the data was missing at random. Although not necessary, imputation of missing variables was carried out as a form of sensitivity analysis. Pattern analysis suggests the dataset was non-monotone. Therefore, it would be appropriate to apply multiple imputation of missing variables to this dataset.

However, only serum albumin was subjected to multiple imputation as missing values for both proteinuria and SIMD appeared to be influenced by better health (higher serum albumin, eGFR and lower co-morbidity count) and younger age. Random seed generator was set arbitrarily at 2,000,001 to enable replication. Proteinuria was also omitted from the final model after Cox and Snell R^2 analysis. Analyses of the imputed datasets are presented as pooled HRs.

4.3 Results

4.3.1 Cohort characteristics

We identified a cohort of 17,209 individuals with CKD stage 3 to 5 who were not in receipt of dialysis or transplantation at the time. Their baseline characteristics are displayed in table 4-1. The cohort was elderly with an average age of 75 years, predominantly female and the average eGFR for the cohort was 47.32 mL/min/1.73m^2. Due to the missing values described above, the number of individuals with a complete dataset was n = 11,311, but without proteinuria it was n = 13,379.

Cohort characteristics (n = 17,209)			
Variables		Value	n
Age (years) (median, IQR)		75 (68 - 82)	17,209
Follow-up (days) (median, IQR)		1,857 (1645 - 1949)	17,209
eGFR (mL/min/1.73m^2) (mean ± SD)		47.32 ± 11.53	17,209
Albumin (g/L) (mean ± SD)		42.16 ± 3.70	15,193
Sex (male) (%)		35.7	17,209
Hypertension (%)		40.1	17,209
Coronary heart disease (%)		25.6	17,209
Diabetes mellitus (%)		14.1	17,209
Cerebrovascular disease (%)		8.1	17,209
Peripheral arterial disease (%)		4.0	17,209
Proteinuria (%)	A1	47.3	8,144
	A2	14.7	2,537
	A3	3.7	530
SES quintiles (%)	1	20.1	3,024
	2	20.0	3,018
	3	20.1	3,027
	4	19.9	3,005
	5	19.9	3,005

Table 4-1. Baseline cohort characteristics. Proteinuria categories: A1 = ACR < 3 mg/mmol or PCR < 15 mg/mmol, A2 = ACR 3-30 mg/mmol or PCR 15-50 mg/mmol, A3 = ACR > 30 mg/mmol or PCR > 50 mg/mmol. SIMD 1 = most deprived SES quintile and 5 = least deprived.

To examine the variable of interest; deprivation, the cohort was grouped by SES quintiles outlined in table 4-2. The least affluent SES quintiles was associated with lower age, eGFR and serum albumin. It was also associated with higher proportion of females, incident RRT, proteinuria, hypertension, coronary heart disease and diabetes.

		SES (quintiles)					p-value (χ^2 or one-way ANOVA)
		1	2	3	4	5	
Age (years) (mean ± SD)		73.6 ± 10.8	74.7 ± 10.0	75.2 ± 10.3	75.2 ± 10.4	75.9 ± 10.5	< 0.001
eGFR (mL/min/1.73m^2) (mean ± SD)		46.7 ± 12.2	47.0 ± 11.9	46.9 ± 11.9	47.3 ± 11.8	47.5 ± 11.3	0.039
Survival (days) (mean ± SD)		1,632 ± 467	1,638 ± 460	1,618 ± 476	1,637 ± 466	1,636 ± 469	0.430
Albumin (g/L) (mean ± SD)		41.8 ± 3.9	41.8 ± 3.8	42.1 ± 3.7	42.0 ± 3.7	42.2 ± 3.7	< 0.001
Male (%)		35.3	34.8	35.1	36.6	39.3	0.001
Incident RRT (n) (%)		49 (1.6)	30 (1.0)	22 (0.7)	27 (0.9)	18 (0.6)	0.001
Proteinuria category (%)	A1 (< 3 mg/mmol)	69.6	70.3	71.5	70.6	70.6	0.005
	A2 (30 - 300 mg/mmol)	22.4	23.5	23.6	23.9	24.2	
	A3 (> 300 mg/mmol)	8.0	6.2	4.9	5.5	5.2	
Hypertension (%)		49.1	47.8	46.0	43.0	42.8	< 0.001
Coronary Heart Disease (%)		31.8	30.3	30.4	27.4	26.0	< 0.001
Diabetes (%)		18.2	18.5	15.6	14.0	13.8	< 0.001
Cerebrovascular Disease (%)		9.8	9.2	10.0	8.0	9.0	0.061
Peripheral Arterial Disease (%)		4.0	3.9	4.6	4.5	4.3	0.619

Table 4-2. Cohort characteristics subdivided by SES quintiles. SIMD 1 = most deprived SES quintile and SIMD 5 = least deprived.

4.3.2 Socio-economic status and eGFR

Spearman's rank correlation of SES and eGFR demonstrated a very small but significant correlation (rho = 0.022, $p < 0.001$). In figure 4-2, the one-way ANOVA demonstrates the linear relationship between eGFR and SES ($F(4,15078) = 2.52$, $p = 0.039$) with a mean difference in eGFR of 0.83 mL/min/1.73m^2 between the lowest and the highest SES quintile.

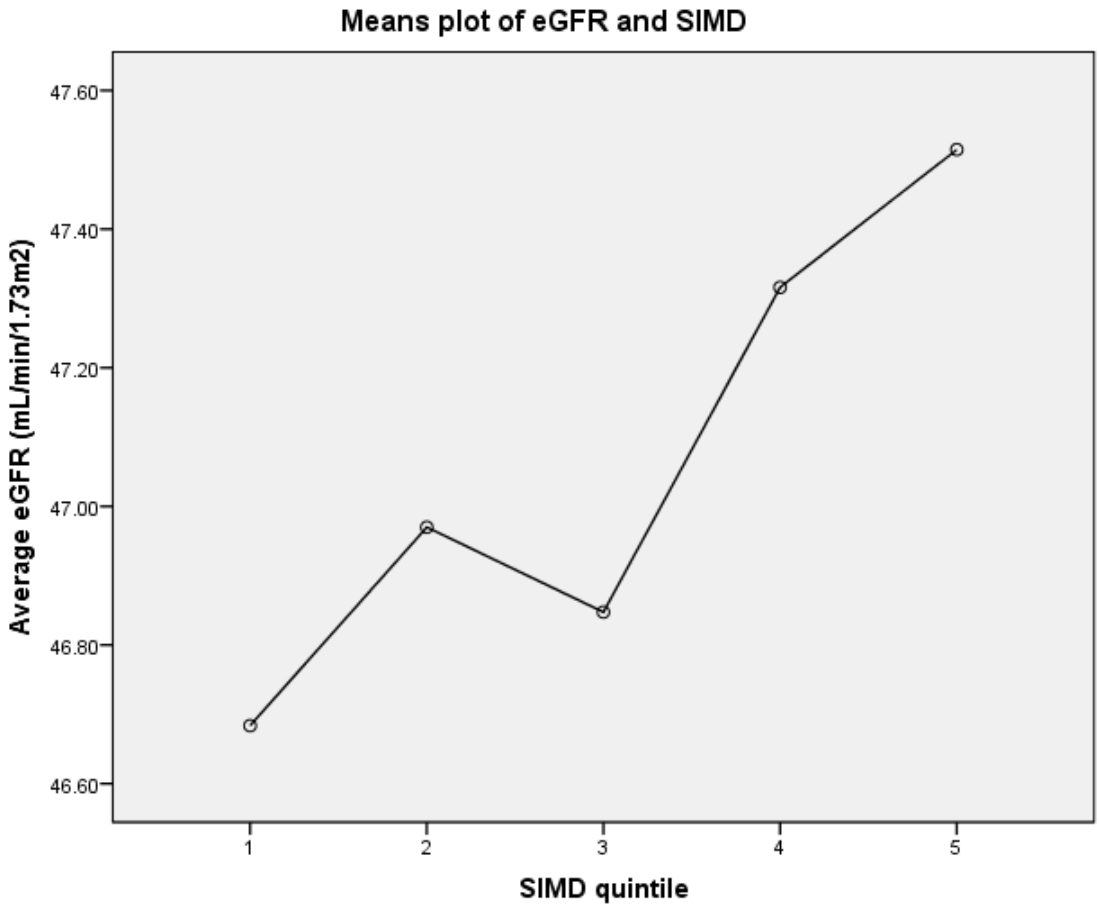


Figure 4-2. Means plot of SES and average eGFR (mL/min/1.73m^2) of the cohort. SIMD 1 = most deprived SES quintile and SIMD 5 = least deprived.

However, when we applied linear regression modelling to predict eGFR, only age, sex, serum albumin, proteinuria, a previous diagnosis of hypertension, and peripheral vascular disease emerged as significant variables [$R^2 = 0.090$ ($F(6,9031) = 150.36$, $p < 0.001$)]. SES was found to be a very weak and statistically non-significant predictor and rejected from the final model.

4.3.3 Socio-economic status and survival

Before adjustment, difference in survival (all-cause mortality) between the 20% most affluent (n = 3,005) and the 20% least affluent (n = 3,024) was on average 10 days longer by Kaplan-Meier method (Figure 4-3). However, this difference was not statistically significant with estimate means for survival of 1,704 (95% CI 1,686 to 1,722) vs. 1,714 (95% CI 1,696 to 1,732) days, p (log-rank) = 0.198.

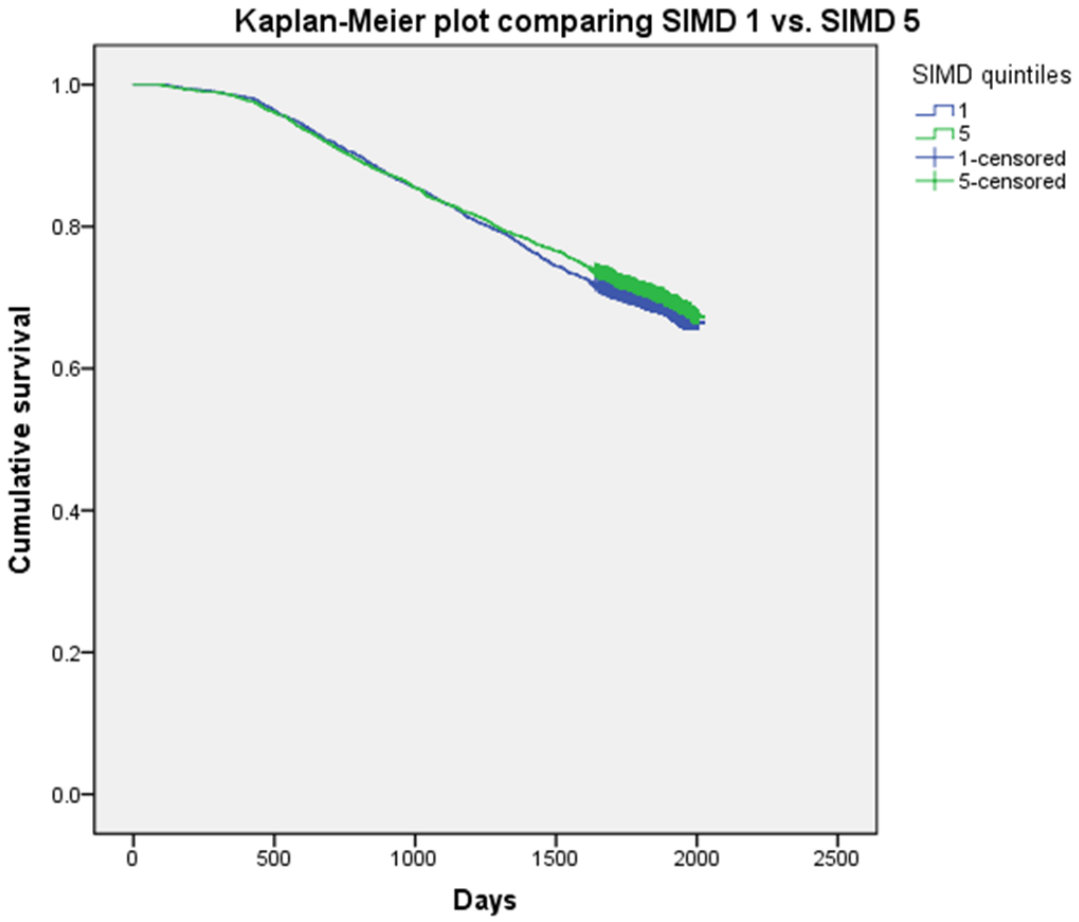


Figure 4-3. Kaplan-Meier survival plot comparing survival between SES quintile 1 (blue) = least affluent and quintile 5 (green) = most affluent.

After adjustment for the demographic factors of age and sex, the least affluent 1st, 2nd and 3rd SES quintiles were associated with a progressively increasing risk of death, when compared with the most affluent SES quintile (Table 4-3). This limited adjustment was associated with an increased HR for those belonging to a less affluent SES quintile when compared to the most affluent 20%. To obtain an estimate of the goodness-of-fit to subsequent changes to the model we used Cox and Snell R^2 logistic regression method and for this initial model, attributed a value of 12.8%.

Variables in the equation	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age (decades)	0.76	0.02	1,770.52	1	<0.001	2.14	2.07	2.22
Sex (male)	0.25	0.03	70.63	1	<0.001	1.29	1.21	1.37
SES quintile 5 (ref)			27.32	4	<0.001			
SES quintile 4	0.09	0.05	3.57	1	0.059	1.09	1.00	1.20
SES quintile 3	0.18	0.05	14.99	1	<0.001	1.19	1.09	1.31
SES quintile 2	0.14	0.05	9.15	1	0.002	1.15	1.05	1.26
SES quintile 1	0.22	0.05	22.90	1	<0.001	1.25	1.14	1.37

Table 4-3. Cox proportional hazards model of the influence of age and sex on SES. Age was recorded in decades. Female = 0 and male = 1. SES 1 = most deprived SES quintile and 5 = the least.

The addition of eGFR, serum albumin, proteinuria and co-morbidities (hypertension, diabetes, coronary heart disease, cerebrovascular disease and peripheral vascular disease) diminished the role of SES to just the 3rd quintile exerting a statistically significant HR of 1.13 (95% CI 1.03 to 1.24) when compared to the most affluent SES group (Table 4-4).

Variables in the equation	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age (decades)	0.61	0.02	1,007.73	1	<0.001	1.85	1.78	1.92
Sex	0.24	0.03	53.94	1	<0.001	1.27	1.19	1.35
SES quintile 5 (ref)			9.29	4	0.054			
SES quintile 4	0.04	0.05	0.62	1	0.431	1.04	0.94	1.15
SES quintile 3	0.12	0.05	6.46	1	0.011	1.13	1.03	1.24
SES quintile 2	0.01	0.05	0.05	1	0.820	1.01	0.92	1.11
SES quintile 1	0.09	0.05	3.02	1	0.082	1.09	0.99	1.20
eGFR	-0.01	<0.01	102.00	1	<0.001	0.99	0.98	0.99
Albumin	-0.13	<0.01	1,194.98	1	<0.001	0.88	0.88	0.89
Coronary heart disease	0.26	0.03	59.81	1	<0.001	1.29	1.21	1.38
CVA&TIA	0.27	0.05	33.48	1	<0.001	1.30	1.19	1.43
Diabetes	0.24	0.04	36.43	1	<0.001	1.27	1.18	1.37
Hypertension	-0.11	.003	11.11	1	0.001	0.90	0.84	0.96
Peripheral vascular disease	0.43	0.06	48.74	1	<0.001	1.54	1.36	1.73

Table 4-4. Cox proportional hazards model demonstrating the influence on survival of age and sex on SES with the inclusion of existing co-morbidities. Hypertension, Diabetes, Coronary Heart Disease (CHD), Cerebrovascular disease including Transient Ischaemia Attack (CVD & TIA) and Peripheral Vascular Disease (PVD) were dichotomised, 0 = no previous record or 1 = prior recorded diagnosis in SMR in the preceding 10 years.

Cox and Snell R^2 for this model was higher at 18.5% compared to the initial model with adjustment only for age and gender. However, with the removal of proteinuria from the model, the resultant Cox and Snell R^2 improved to 21.3% and the HR of all the remaining variables remain essentially the same. Therefore, the final Cox proportional hazards model

presented in table 4-4 excludes the variable, proteinuria. To ensure these results were not biased by missing values, missing values analyses were conducted.

4.3.4 Missing values and multiple imputation.

As pre-specified in the methods section, we carried out a maximum of 5 imputations of the missing serum albumin values (Table 4-5). Following imputation, the cohort size increased from 13,379 to 15,079. We repeated the same Cox proportional hazards modelling to the larger, imputed cohort.

Data	Imputation	n	Mean	Std. Deviation	Minimum	Maximum
Original Data		15,194	42.16	3.70	18.00	56.50
Imputed Values	1	2,015	42.27	3.82	29.30	54.96
	2	2,015	42.07	3.72	28.54	54.33
	3	2,015	42.30	3.80	29.70	53.89
	4	2,015	42.37	3.65	29.70	57.31
	5	2,015	42.27	3.71	29.42	57.52
Complete Data After Imputation	1	17,209	42.17	3.71	18.00	56.50
	2	17,209	42.15	3.70	18.00	56.50
	3	17,209	42.17	3.71	18.00	56.50
	4	17,209	42.18	3.69	18.00	57.31
	5	17,209	42.17	3.70	18.00	57.52

Table 4-5. Descriptive statistics of imputed missing serum albumin (mg/dL) values.

The only change from the analyses of the original cohort was that in the pooled imputed dataset, HR for the most deprived SES quintile was significant with a HR of 1.11 (95% CI 1.01 to 1.22) and the 3rd SES quintile remained similar to the pre-imputation model with a HR of 1.14 (95% CI 1.04 to 1.25) for an increased risk of mortality. HRs for the remaining variables remained broadly similar to the original pre-imputation dataset without altering the conclusions.

4.4 Discussion

4.4.1 Main findings

The influence of SES on health and survival is complex and studies examining this have variously attributed it to racial disparities, limited access to health care, income inequality or more recently, reduced health literacy (HL).(177, 236) A systematic review of HL in

CKD by Fraser et al. found a pooled prevalence of limited HL to be 22.7% (95% CI 20.6% to 24.8%) amongst CKD patients from the 8 north American studies identified.(185) They also found that limited HL was independently associated with lower SES and poorer health outcomes.

In this study, we examined the effects of disparities in area SES, in a racially homogenous population with unfettered access to healthcare, on the severity of CKD and outcome (all-cause mortality). Indeed, up to the age of 75 years, patients from the lower SES quintile account for the highest number of GP and practice nurse consultations than patients of any other SES quintile (Figure 4-4).(237) Above the age of 75 the pattern is reversed: greater numbers of patients from the highest SES quintile attend their primary care teams more often. This phenomenon is likely to be a manifestation of survival bias in those from a more affluent SES group living longer into old age and accruing more health conditions.

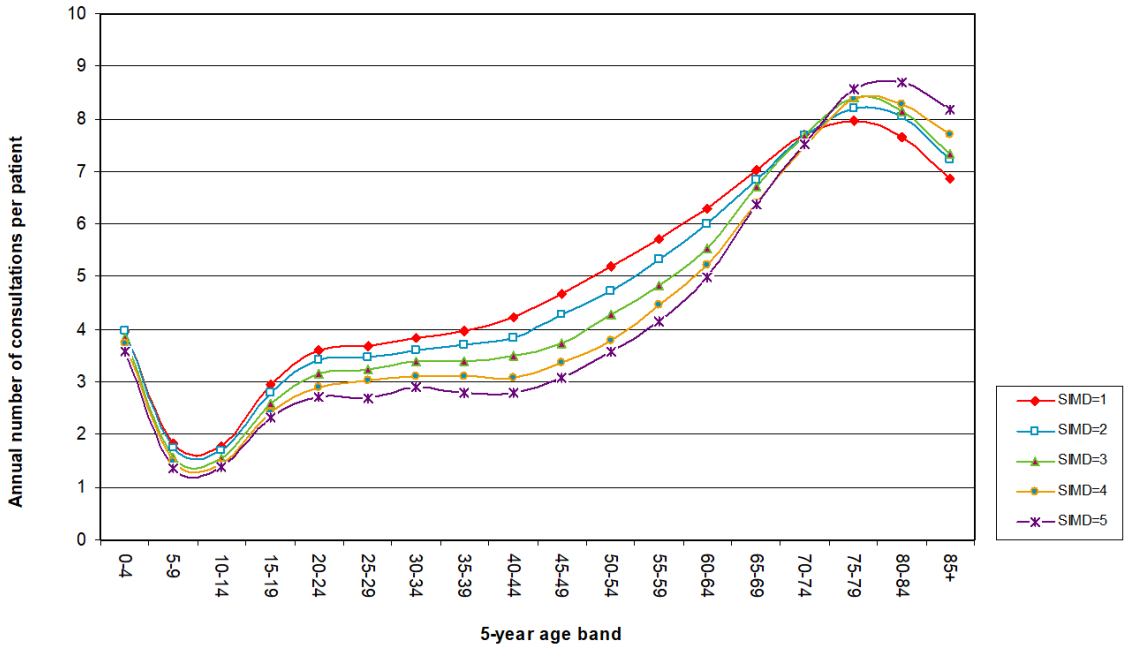


Figure 4-4. Estimated number of consultations per patient with a GP or practice nurse. Over all ages; by 5-year age groups and SIMD quintiles. Sampled from 6% of Scottish practices participating in the Practice Team Information programme. Scottish Index of Multiple Deprivation (SIMD) quintile 1 = most deprived, quintile 5 = least deprived.

In our heterogeneous community CKD cohort, there appeared to be a significant correlation between lower SES and lower average eGFR. We accounted for the heterogeneity of the cohort through multivariate linear regression modelling of the effect of SES in predicting eGFR. In a backwards regression model, the effects of SES in predicting CKD was non-significant, raising the possibility that SES was simply a confounder. The

diagnosis of hypertension, peripheral arterial disease, proteinuria, serum albumin level, age and gender were the main predictors of eGFR in our cohort. This contrasts with the conclusions of Bello et al. who examined this same association in a cohort of CKD patients referred to Nephrology services in Sheffield.(179) In this cross-sectional analysis, they used a similar SES measure, the index of multiple deprivation quintiles, but used a secondary care cohort (n = 1,657) with a predominance of men (57.7%), a much younger average age (58.2 ± 17.2), lower average eGFR (35.6 ± 23.3 mL/min/1.73m^2) and had other methodological differences to our study.

When it comes to survival, the story is similar. In unadjusted analysis, the lower SES group had a higher prevalence of characteristics associated with negative outcomes such as lower eGFR, higher proteinuria, lower serum albumin, higher prevalence of hypertension, CHD, CVD and diabetes, all at a younger age. Lower SES was also associated with poorer outcomes such as a higher incidence of RRT and higher proportion of all-cause mortality on follow-up.

In order to better assess the independent impact of SES on all-cause mortality, we adjusted initially for age and gender, then included co-morbidities, eGFR and serum albumin in a stepwise manner. Proteinuria is traditionally a marker for severity and prognosis, but our pseudo-R^2 analysis suggests this variable added little and changed little to the overall model and hence excluded. We then found that with every iteration, the role of SES becomes less significant. Although SES quintile 3 did demonstrate a statistically significant increased HR of 1.13 in table 4-4, no progressive association was found with the increasing quintiles of deprivation even after imputation of the missing values.

Our *a priori* hypothesis was that our cohort would demonstrate increasing CKD severity and poorer outcomes with lower SES, in keeping with other cohort studies.(179, 227) The relatively small influence of SES in our cohort in relation to average eGFR and all-cause mortality may be down to the differences in study design. In a primary care cohort study by Drey et al., although reporting a similar age profile (median, 77 years), had a greater preponderance of men (60%) in their cohort.(227) This may be due to the use of a non-gender specific serum creatinine threshold of ≥ 1.7 mg/dL (150 μmol/L) for the diagnosis of CKD.

A bias towards under referring and under treating women and the elderly, who are often from lower SES groups, is well documented and may explain the differing conclusions to

our study.(238, 239) Thus, we believe that our cohort more accurately represents the true prevalence and clinical course of population CKD in primary care.

Outside of the UK, many studies have documented a strong association between SES and CKD outcomes, we postulate that the reason SES had little effect on outcomes in our cohort may be due to the unfettered access to immediate and preventative healthcare of our population through the single-payer model, that is the National Health Service.(212, 213, 234, 240-242) In contrast, in multi-payer models the ability to access healthcare, either through insurance or direct payment is correlated to employment or wealth, which would lead to wider socio-economic gradient and thus, a more pronounced effect between SES quintiles.

4.4.2 Study limitations

The weakness of this study largely rests on its design as an observational cohort and that any statistical adjustment for cohort heterogeneity will be prone to error. We obtained co-morbidity data from the SMR. The accuracy of SMR diagnosis was assessed in a systematic review of discharge coding in Great Britain by Burns et al., who found SMR data had an overall median accuracy of 83.2% (IQR 67.3 – 92.1%).(243) Although comprehensive, the SMR may be prone to underreporting as this data is only collated in association with an urgent or elective hospital admission.

In our cohort the prevalence of hypertension is probably underrepresented at around 40% compared to the 70% prevalence reported by Methven et al. in a cohort of 411 CKD patients sampled form this same population.(202) Otherwise, our reported prevalence of diabetes and CHD was not dissimilar to that of a CKD cohort from a neighbouring health board.(244)

We also recognise an interesting but questionable positive survival relationship in the Cox model associated with a diagnosis of hypertension. In our complete adjustment model in table 4-4, this was attributed with a 10% better survival (HR 0.90, 95% CI 0.84 to 0.86). We hypothesise that this may again, be down to our use of the SMR as the source of our co-morbidity data. As the SMR records no more than 6 relevant diagnoses related to a hospital admission, it may be biased towards the recording of diagnoses that are more life limiting, thus, only recording the diagnosis of hypertension in those with fewer prognostically poorer diagnoses.

We identified a proportion of missing values in the cohort which may influence our conclusions and attempted to address these using the multiple imputations method where appropriate. After imputing serum albumin to a total of 5 datasets and repeating the survival analyses, we found little change in the overall adjusted survival model.

5 CHAPTER 5: PREVALENCE OF STATIN USAGE IN A COMMUNITY CKD COHORT: A 3-YEAR TREND ANALYSIS

Introduction

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are one of the few evidence based therapies in non-dialysis chronic kidney disease (CKD). In 2004, a post hoc analysis of three pravastatin studies in the general population identified a 23% RR reduction in cardiovascular events, and a 14% RR reduction in all-cause mortality in a subset of participants with CKD.(148) In 2011, the pivotal SHARP study demonstrated a 17% reduction in major cardiovascular events, compared to placebo.(149) A subsequent Cochrane meta-analysis update of statins in non-dialysis CKD demonstrated a 21% reduction in all-cause mortality, and a 28% reduction in major cardiovascular events.(150)

International guidelines recommend statins for primary prevention in all patients ≥ 50 years old with CKD excluding those in receipt of RRT, and in those < 50 years old if 10-year risk of cardiac events exceeds 10%, or they have diabetes mellitus.(245) UK guidelines recommend treating all patients with CKD (excluding those on RRT) with statins.(246)

Little has been published on whether current evidence in this field is being implemented. Using an established community CKD cohort, we aim to identify and characterise those receiving lipid lowering therapy. We also examined prescribing trends for statins in this population, over three consecutive years (2010-2012)

5.1 Methods

5.1.1 Participants and setting

Healthcare in Scotland is free at the point of use, funded through general taxation. A&A is the health board responsible for commissioning and provision of all health care for the region and the population it serves is detailed in chapter two.

The methods for identifying our cohort of CKD patients within the adult population of A&A is described in chapter two, and included determination of persistence of reduced estimated glomerular filtration rate for ≥ 90 days, and excluded patients on RRT. Cohorts for each year began on the 1st of April in the preceding year through to the 31st of March i.e. the 2010 cohort refers to the prevalent CKD population from the 1st of April 2009 to the 31st of March 2010.

Relative socio-economic status (SES) is measured using the Scottish Index of Multiple Deprivation (SIMD) and divided into equal quintiles. This indicator is described in detail in chapter two.

5.1.2 Laboratory data

All lipid profile tests are sent to one of two regional laboratories running identical assays and the results are stored centrally in the A&A Scottish Care Information database. Total cholesterol, high-density lipoprotein (HDL) and triglycerides were measured on a Roche Modular analyser using routine automated methods according to the manufacturer's instructions.

The laboratory is accredited (Clinical Pathology Accreditation, UK) and participates in regular external quality assurance schemes. The analytical coefficients of variation were 2.7%, 2.0% and 2.5% respectively. If multiple lipid profiles were available for an individual, the last value for each year was used. Low-density lipoprotein levels (LDL) was derived from the Friedewald equation.(247)

Serum albumin was frequently measured in our cohort (90.2%, 85.7% and 85.3% of cohort had one or more measurements in 2010, 2011 and 2012 respectively) and was included as a surrogate marker for illness. Approximately one third had serum albumin measured more than once, in which case the average was used.

Laboratory proteinuria values were recorded as albumin creatinine ratio (uACR) or protein creatinine ratio (uPCR). Only the first proteinuria reading for the corresponding year was included. Proteinuria was coded in accordance with the 2012 Kidney Disease Improving Global Outcomes proteinuria classification.(249) Where no uACR was available, uPCR was used and equivalence approximated.(311) Proteinuria or albuminuria > 2 g/day were excluded to avoid including transient dyslipidaemia secondary to heavy proteinuria.(248) This was to ensure that the lipid profiles analysed and presented accurately reflect those of the majority of CKD patients.

5.1.3 Co-morbidity data

SMR data requested is detailed in chapter two and was obtained from ISDS.(250) Deaths from our cohort was also provided by ISDS. Both SMR and death were identified using the CHI. The prevalent population was censored for death on the 31st of March of each year.

5.1.4 Dispensing data

Prescription-only medications, such as lipid-lowering medication, are prescribed by a general practitioner, and usually dispensed by a community pharmacy with no charges or co-payments. Simvastatin 10 mg daily is also available without prescription from pharmacies but attracts an out-of-pocket charge to the patient. Guidance on supply of over the counter statins states that all patients with renal disease should be referred to their primary care practice.

Medication dispensing data was obtained from the Prescribing Information System for Scotland (PIS).(206) PIS collates all dispensing data such as medication name, dose and quantities supplied, to facilitate disbursements to community pharmacies. All pharmacies in our area contribute to PIS.

Information was requested on all medications listed in the lipid-regulating drugs chapter of the British National Formulary, and also sevelamer.(251) Patients dispensed lipid-lowering therapies within 56 days preceding the census date (31st of March 2010, 2011 and 2012) were deemed to be on lipid-lowering therapy that year. We chose this time period as 61.2% of all dispensed statin prescriptions were for 56 tablets (IQR 28 – 56), or approximately a two-month supply which is common practice for stable dosing.

5.1.5 Missing values

There were missing values for serum albumin (range 10% to 14%), proteinuria (30% to 35%) and SES (13% to 16%). Inspection of the missing value patterns suggests these were missing at random. Therefore, we presented the original data without imputation of missing values.

5.1.6 Statistical analysis

We linked our laboratory-derived cohort of CKD patients with PIS dispensing data, SMR comorbidity data and death records with the CHI as the primary key. All patient identifiable data were anonymised after linkage.

Statistical analysis was carried out using IBM SPSS Statistics, version 22. Analysis of variance was applied for parametric variables and χ^2 test for non-parametric variables including trends across the three years. Logistic regression was used to calculate the OR

for variables associated with statin dispensing in the 2012 cohort. Log-linear models were used to test for 3-way interactions.

5.2 Results

5.2.1 Cohort characteristics

The cohort characteristics are presented in table 5-1. The results of statistical analysis for 2010 and 2012 were similar to the analysis for all three years and so the 2011 summary data was omitted for clarity of layout. Our cohort of CKD 3 – 5 patients was 5.3% and did not vary significantly over the 3-years due to a stable background population with very little migration. Gender split also remined the same at 65% female. However, average age of the cohort increased by 1.6 years, along with the proportion with a diagnosis of hypertension and CVD. Crucially, statin dispensing fell 5% over the 3 years from 63.8% to 58.8%.

Year		2010		2012		p value & effect size (r or OR)
CKD population		16,532		16,491		
Prevalence (% of adult population)		5.3		5.3		
Mean age (± SD)		74.4 (± 10.5)		76.0 (± 10.5)		p < 0.001, r = 0.08
Female (%)		64.3		65.2		p = 0.07
Hypertension (%)		41.1		45.9		p < 0.001, OR = 1.20
Coronary heart disease (%)		25.9		26.4		p = 0.337
Diabetes mellitus (%)		14.2		14.7		p = 0.200
Cerebrovascular disease (%)		8.3		9.1		p = 0.011, OR = 1.10
Peripheral arterial disease (%)		4.2		4.4		p = 0.317
Proteinuria (%)*	A1	72.6		73.0		p = 0.216
	A2	22.8		22.8		
	A3	4.7		4.2		
	No data available	n= 5,801 (35.1%)		n = 4,808 (29.2%)		
Statin treatment (%)		Yes (63.8)	No (36.2)	Yes (58.8)	No (41.2)	p < 0.001, OR = 0.81
Mean age (± SD)		73.7 (± 9.3)	75.5 (± 12.1)	75.6 (± 9.2)	76.4 (± 12.1)	p < 0.001, r = 0.02†
% Female		61.3	69.3	61.6	70.2	p = 0.55††
Serum Albumin (g/L) (mean ± SD)**		42.5 ± 3.4	41.5 ± 4.0	42.0 ± 3.4	41.2 ± 3.8	p < 0.001, r = 0.02

Table 5-1. Cohort descriptive data for the years 2010 and 2012 (after exclusion of individuals in receipt of non-statin lipid lowering drugs). Proteinuria categories: A1 = urine protein:creatinine ratio (uPCR) < 15 mg/mmol or urine albumin:creatinine ratio (uACR) < 3 mg/mmol; A2 = uPCR 15-50 mg/mmol or uACR 3-30 mg/mmol; A3 = uPCR > 50 mg/mmol or uACR > 30 mg/mmol.(311) **For 2010 90% and 2012 85% complete data. †For 3-way interaction between age, statin use and year. For 2-way interaction between statin use and age p < 0.001, r = 0.05; statin users are younger. ††For 3-way interaction between gender, statin use and year. For 2-way interaction between statin use and gender p < 0.001, OR = 1.47; males are 1.47 times more likely than females be on statins.

5.2.2 Statin dispensing characteristics

A small number of patients (n = 813, 706 and 393 for the year 2010, 2011 and 2012 respectively) were dispensed non-statin medications for treatment of dyslipidaemia. These were fibrates (n = 227, 221 and 197), ezetimibe (n = 487, 424 and 140), bile acid sequestrants (n = 33, 23 and 19), omega-3-fatty acids (n = 13, 15 and 12), with no one dispensed nicotinic acids. Some were also taking sevelamer, a phosphate binder with lipid-lowering properties (n = 90, 50 and 33). Given the small numbers receiving these agents, they were excluded, unless concurrently on statins (n = 550, 463 and 206).

Logistic regression of statin usage on the 2012 cohort with the variables listed in table 5-1 as predictors, resulted in $R^2 = 0.13$, $p < 0.001$, with the ORs presented in figure 5-1. Having another diagnosis, such as CHD (OR 3.04, 95% CI 2.73 to 3.37), DM (OR 2.61, 2.30 to 2.96), CVD (OR 2.27, 1.91 to 2.69) or PAD (OR 2.30, 1.78 to 2.98), for which treatment with a statin would also be indicated was associated with higher ORs favouring statin dispensing. Higher serum albumin (≥ 35 g/L, OR 2.56, 2.08 to 3.15), male gender (OR 1.21, 1.10 to 1.33) and CKD stage 3B (OR 1.17, 1.05 to 1.29) were also associated with higher odds for statin dispensing. Age and statin dispensing was complex and demonstrated an inverted J-shaped relationship with those aged 65-79 most likely to be dispensed a statin whilst those ≥ 85 years of age were significantly less likely.

Variables	OR (95% CI)
Male gender	1.21 (1.10,1.33)
Proteinuria A1 (reference)	1
Proteinuria A2	0.95 (0.85, 1.06)
Proteinuria A3	0.86 (0.70, 1.10)
SIMD quintile 1 (reference)	1
SIMD quintile 2	0.92 (0.80, 1.05)
SIMD quintile 3	0.83 (0.72, 0.95)
SIMD quintile 4	0.85 (0.73, 0.97)
SIMD quintile 5	0.84 (0.72, 0.97)
Hypertension	0.99 (0.90, 1.09)
Coronary heart disease	3.04 (2.73, 3.37)
Diabetes mellitus	2.61 (2.30, 2.96)
Cerebrovascular disease	2.27 (1.91, 2.69)
Peripheral arterial disease	2.30 (1.78, 2.98)
Serum albumin (≥35mg/L)	2.56 (2.08, 3.15)
CKD stage 3a (reference)	1
CKD stage 3b	1.17 (1.05, 1.29)
CKD stage 4	1.10 (0.91, 1.32)
CKD stage 5	0.69 (0.34, 1.38)
Age <65 (reference)	1
Age 65-69	1.44 (1.19, 1.75)
Age 70-74	1.47 (1.24, 1.75)
Age 75-79	1.44 (1.22, 1.69)
Age 80-84	1.04 (0.89, 1.22)
Age ≥85	0.57 (0.49, 0.67)

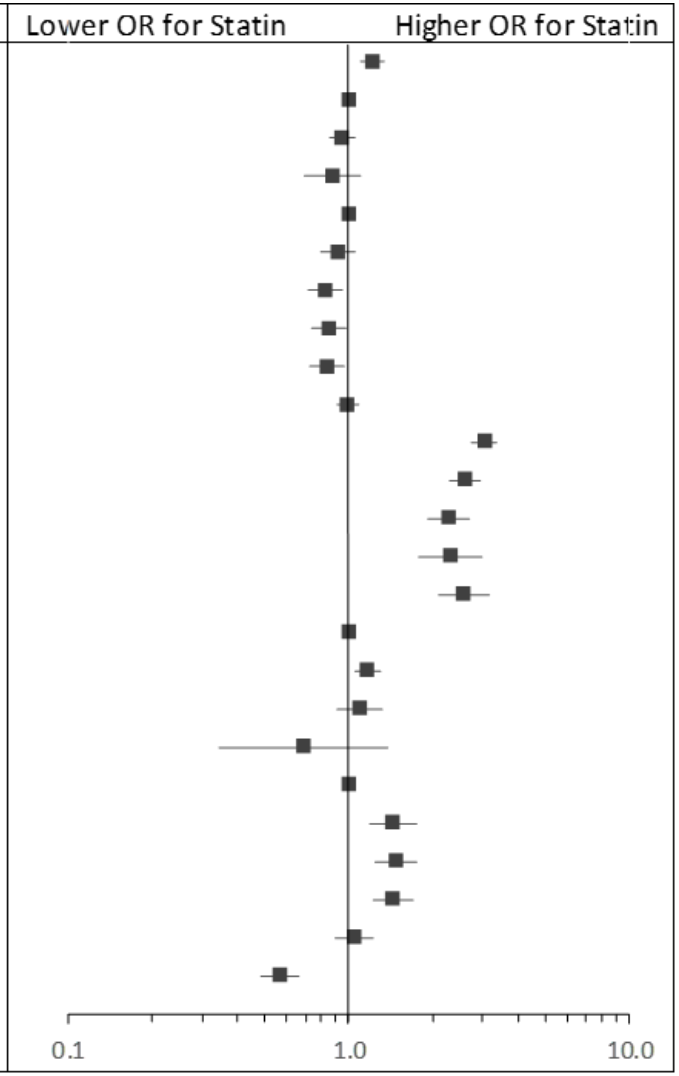


Figure 5-1. Forest plot of ORs (with 95% CI bars) of variables associated with dispensing of statins for the 2012 cohort. SIMD 1 is least deprived and SIMD 5 is most.

5.2.3 Statin dispensing by age and CKD stage

CKD stage, for the purpose of this analysis was determined by average eGFR. As a result, some were classified as CKD stage 2 simply because their average eGFR was ≥ 60 mL/min/1.73m^2, but did not take into account the duration between measurements. Of all CKD patients in 2010, 7.5% were stage 2, 56.9% stage 3a, 27.6% stage 3b, 7.0% stage 4 and 1.0% stage 5. The proportion dispensed a statin by CKD stage was 59.4% of stage 2, 63.2% of stage 3a, 65.6% of stage 3b, 66.5% f stage 4 and 58.8% of stage 5. Between 2010-12, there was a fall in statin dispensing (χ^2 (1) = 87.9, p < 0.001, r= -0.04) for all CKD stages except stage 5 which remained unchanged. Stage 3a was most affected, falling from 63.2% (5,947 of 9,405 individuals) in 2010 to 57.9% (5,825 of 10,069 individuals) in 2012.

The age of those dispensed a statin rose over the 3 observed years, from 73.7 ± 9.3 to 75.6 ± 9.2 years. Subdivision by age reveals that this rise was accounted for by a disproportionate fall in the proportion of younger patients being dispensed a statin over the three years (Figure 5-2). Few of these patients were aged ≤ 50 years. In 2010, 2011 and 2012 there were 441, 390 and 370 individuals, of which 41%, 35% and 31% respectively were dispensed a statin.

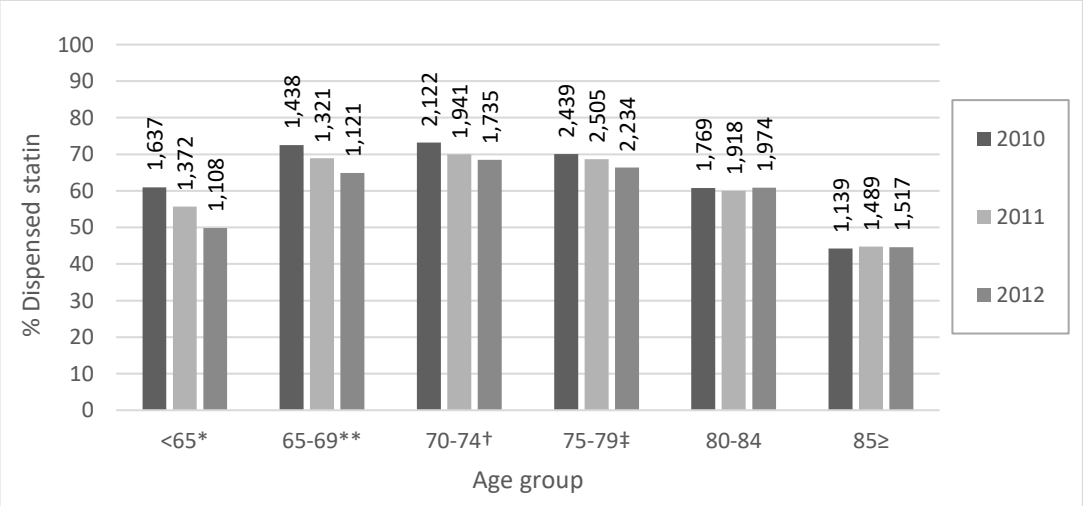


Figure 5-2. Proportion of CKD patients dispensed a statin by age group, between 2010-2012. * Age < 65 year χ^2 (1) = 62.5, p < 0.001, r = -0.09. ** Age 65-69 χ^2 (1) = 24.2, p < 0.001, r = -0.07. † Age 70-74 χ^2 (1) = 14.7, p < 0.001, r = -0.04. ‡ Age 75-79 χ^2 (1) = 10.4, p = 0.001, r= -0.03.

5.2.4 Statin dispensing by co-morbidity

Approximately half of patients prescribed a statin had another indication in addition to CKD. Hypertension was not included as it is not a clinical indication for statins *per se*. Of those with CKD and no additional indicators for a statin, approximately 49.8% were dispensed one across the three years. Contrast this to those with additional co-morbidities and it was 82.0% for DM, 78.9% for CHD, 81.1% for CVD and 83.5% for PAD.

In 2010 the proportion of patients with CKD alone that was dispensed a statin was 51.3% but fell significantly to 49.7% and 46.4% for 2011 and 2012 respectively (χ^2 (1) = 90.34, p < 0.001, r = -054). There was a similar but smaller fall for those with 1 additional comorbidity (78.2% to 76.9% to 74.3%, χ^2 (1) = 19.03, p < 0.001, r = -037). There were no significant reductions for those with 2 or more comorbidities (Figure 5-3).

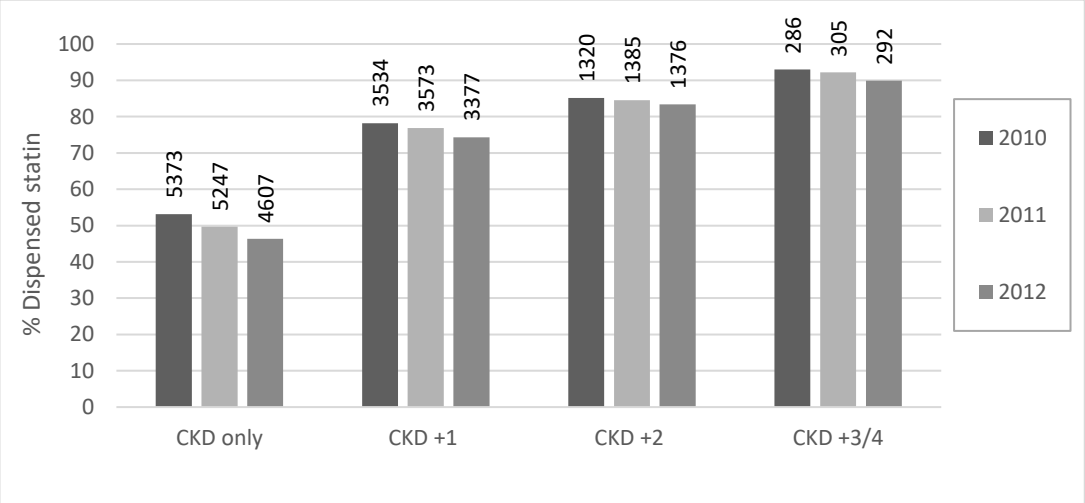


Figure 5-3. Absolute number and proportions of patients dispensed a statin by number of additional co-morbidities.

5.2.5 Statin dispensing by socioeconomic status

The relative deprivation mix of the CKD population did not change between 2010 and 2012 (χ^2 (1) = 1.87, p = 0.17). In each of the three years observed, statin dispensing rates were higher in those with higher relative deprivation (SIMD 1) than those with lower deprivation (SIMD 5); 65.6% vs 58.0% respectively (χ^2 (1) = 131.07, p < 0.001, R = -0.06) (Table 5-2). Over the three years observed, statin dispensing rates fell uniformly in all SIMD categories. A log-linear analysis of statin use, SIMD quintile and year, suggested no evidence of a 3-way interaction (χ^2 (8) = 0.98, p =0.99).

A multilinear regression of morbidity count and age categories as predictors for SES quintiles were statistically significant (F (2) = 68.09, p < 0.001), but small. SES quintile was equal to 2.80 (constant) – 0.13 (co-morbidity count) + 0.06 (age category). Adjusted R^2 was 0.01, thus only accounting for 1% of the variance observed in this population.

When examining the predictors for patients dispensed a statin, SES quintiles, co-morbidity count and age category were all significant predictors (F (3) = 606.97, p < 0.001). Receiving a statin was equal to 0.60 (constant) + 0.20 (co-morbidity count) – 0.02 (age category) – 0.01 (SES quintile). The adjusted R^2 for the model was 0.12, explaining approximately 12% of the variance in statin dispensing. Although a lower SES was weakly associated with a higher co-morbidity count and age, it was also independently associated with higher rates of statin dispensing.

SIMD*	2010		2011		2012		Total	
	n	On statins (%)	n	On statins (%)	n	On statins (%)	n	On statins (%)
1	2,812	1,905 (68)	2,848	1,869 (66)	2,660	1,688 (63)	8,320	5,462 (66)
2	3,268	2,161 (66)	3,286	2,109 (64)	3,107	1,924 (62)	9,661	6,194 (64)
3	3,114	1,983 (64)	3,180	1,972 (62)	2,998	1,770 (59)	9,292	5,725 (62)
4	2,804	1,748 (62)	2,840	1,688 (59)	2,708	1,570 (58)	8,352	5,006 (60)
5	2,446	1,482 (61)	2,560	1,483 (58)	2,438	1,352 (56)	7,444	4,317 (58)
Total	14,444	9,279 (64)	14,714	9,121 (62)	13,911	8,304 (60)	43,069	26,704 (62)

Table 5-2. The proportion of CKD patients dispensed a statin according to socio-economic status and the proportions whose sole indicator for statin treatment in CKD. *SIMD 1 = highest relative deprivation and 5 = the lowest.

5.2.6 3-year trends of lipid profiles

In each of the 3 years, patients on statins were more likely to have their lipid profile tested, ranging from 48 – 55% for those dispensed a statin vs 21 – 22% of those not. However, the proportion who had lipid profile testing fell linearly year-on-year from 54.5% in 2010 to 48.4% in 2012. Whilst the absolute number of patients not dispensed a statin but had lipid profile measurement remained consistent at around 3,600, the absolute fall in individuals who had their lipid profiles tested fell by around 1,000 individuals. This number is much higher than the absolute reduction in statin dispensing (approximately 825 individuals) and represents an overall fall in lipid profile testing in those being dispensed a statin.

Serum total and LDL cholesterol was lower in the group dispensed a statin than those who were not. Mean difference in LDL was 0.78 mmol/L (95% CI, 0.74 to 0.81), 0.86 mmol/L (0.82 to 0.89) and 0.93 mmol/L (0.90 to 0.97) in 2010, 2011 and 2012 respectively (Table 5-3). The mean difference for total cholesterol and LDL between the treated and untreated groups grew over the three years. This was driven by a rise in the average total cholesterol in the untreated cohort from 5.08 ± 1.07 mmol/L to 5.25 ± 1.06, whilst the treatment group remained stable over 3 years at around 4.03 ± 1.06.

Average HDL cholesterol in our cohort, who were in receipt of a statin (1.32 ± 0.41), compares favourably to the treatment arm of the SHARP trial (1.12 ± 0.35). (149) This difference is explained by the cohort make-up of the SHARP study, a third of whom were dialysis patients who have much lower HDL cholesterol levels than non-dialysis CKD patients.(313)

Year		2010		2011		2012	
CKD population (n)		16,533		17,213		16,493	
Statin treatment		Yes	No	Yes	No	Yes	No
Lipid profile tested (% of n)		9,006 (54.5)	3,639 (22.0)	8,757 (50.9)	3,583 (20.8)	7,986 (48.4)	3,653 (22.1)
Lipid profile (mmol/L) (mean ± SD)	Cholesterol	4.30 ± 1.06	5.08 ± 1.07	4.35 ± 1.06	5.22 ± 1.08	4.30 ± 1.06	5.25 ± 1.06
	HDL	1.32 ± 0.41	1.40 ± 0.45	1.32 ± 0.41	1.40 ± 0.43	1.32 ± 0.41	1.40 ± 0.44
	LDL*	2.16 ± 0.87	2.94 ± 0.89	2.20 ± 0.87	3.06 ± 0.89	2.16 ± 0.87	3.09 ± 0.88
	Triglycerides	1.83 ± 1.02	1.64 ± 0.82	1.83 ± 1.01	1.66 ± 0.88	1.82 ± 1.01	1.69 ± 0.93

Table 5-3. Average lipid profiles of patients with non-dialysis CKD over three years, divided by statin therapy with patients on non-statin lipid lowering drugs excluded unless co-administered with a statin. Renal transplant patients were also excluded. *Calculated LDL values were not available in 2% of cases due to measured triglycerides levels exceeding the Friedewald equation threshold 4.52mmol/L.

5.2.7 Statin type and dose

During the last observed year (1st of April 2011 to 31st March 2012), 3,250,019 doses from 71,229 prescriptions for statins were dispensed. Table 5-4 details the commonest type of statin and dosage dispensed. The dose dispensed may not always reflect actual consumed dose, as two 10 mg tablets may be prescribed to make up 20 mg and so forth. However, this practice was unusual.

Statin (n=prescriptions)	% of all prescriptions	Tablet strength (mg)	% of each statin
Simvastatin (46,951)	66.8	10	8.4
		20	32.6
		40	56.4
		Other	2.6
Atorvastatin (16,389)	23.2	10	31.8
		20	30.5
		40	28.4
		80	7.3
		Other	2.0
Pravastatin (5,470)	7.1	10	18.1
		20	34.0
		40	47.5
		Other	0.4
Rosuvastatin (2,130)	2.5	5	25.7
		10	45.9
		20	22.8
		40	4.5
		Other	1.1
Fluvastatin (289)	0.4	20	29.5
		40	59.1
		80	9.1
		Other	2.3

Table 5-4. The types of statin and common doses dispensed to patients with CKD.

Simvastatin was by far the most common statin prescribed (66.8% of all prescription) with most patients (56.4%) being dispensed a dose of 40 mg daily. Atorvastatin was the second most common (23.2%), but by a large margin. The dosage of Atorvastatin was spread

fairly evenly, with approximately 30% each taking 10 mg, 20 mg and 40 mg daily. 37.2% of all statins dispensed was for Simvastatin 40 mg.

5.3 Discussion

5.3.1 Main finding

Our study is a large, community-based population study utilising actual dispensing data, and so reflects delivered population care. CKD is associated with a high risk of cardiovascular events and death, for which statins are an evidence-based intervention.(149, 150) In this community-based cohort of CKD patients, 64% were receiving statins in 2010, but declined to 59% over the three years studied. This is despite a backdrop of strengthening published evidence of benefit.(149, 150) Patients with additional co-morbidities were more likely to receive statins, suggesting that CKD may not be the main driver for initiating statins. There was a fall in statin usage over time in all co-morbidity subgroups (non-significant for PAD and CVD), but this trend was more pronounced in patients with CKD alone.

Statin usage showed an inverted J-shaped relationship with age, with those aged 65-79 years more likely to be dispensed one. Overall however, statin use declined over time in all patients under 80 years, with a statistically significant marked decline for the younger patients. Men were more likely to receive statins than women, and this gender bias was maintained over time despite a preponderance of women in the cohort. Gender bias is not unique to CKD and is well documented in other disease conditions.(256, 257) These reasons may also explain the association between receipt of a statin and a higher serum albumin demonstrated in table 5-1 and figure 5-1.(312)

A higher proportion of more deprived patients received statins compared to less deprived patients and the distribution was maintained over time despite a fall in absolute numbers getting a statin. SES was a weak predictor of increasing co-morbidity, but this may be explained by the lack of smoking data and the relatively low health inequality in a comprehensive state delivered healthcare system. The falling rate of dispensing was not influenced by CKD stage.

LDL cholesterol was 0.93 mmol/L lower in patients receiving statins, similar to the 0.85 mmol/L reduction achieved in the SHARP trial which used a combination of simvastatin

20mg and ezetimibe 10 mg daily.(149) Simvastatin and atorvastatin were by far the most common statins dispensed, reflecting prescribing trends in the general population.(258) Higher doses of rosuvastatin and atorvastatin were less commonly dispensed. Few other lipid lowering agents were used, and in particular ezetimibe was rarely used either alone or in combination with a statin, despite its use in the SHARP trial.(149) For example, in the 2010 cohort, only 2.9% of those dispensed a statin was also dispensed ezetimibe.

We identified only two other studies on the use of lipid-lowering therapies in a community-based CKD cohort. The first, reported statin use in their CKD cohort with concurrent diabetes (60%) and cardiovascular disease (51%), but did not comment on patients with CKD alone.(70) The second, reported 55.7% of their cohort of 184,557 individuals with CKD were prescribed a statin.(314) In dialysis patients in the US, statins were used by 34.2%, and the commonest statin prescribed was atorvastatin (49%), followed by simvastatin (33%).(259)

In population studies examining the general population, such as the National Health and Nutrition Examination Surveys of 2003-2004 and 2011-2012 revealed that in adults over 40 years of age, statin use rose from 16.3% to 23.2%.(258) The commonest statins used were simvastatin (42.0%) and atorvastatin (20.2%). Prescribing increased linearly with age and did not differ by gender or race. In adults with doctor-diagnosed cardiovascular disease 71% were treated with cholesterol-lowering medications, as were 63% of patients with diabetes mellitus. Within two years of diagnosis, 68% of an incident Scottish cohort with diabetes mellitus were prescribed a statin.(260)

Current international guidelines (KDIGO 2013) recommend statins for primary prevention in all patients ≥ 50 years old with CKD (excluding those on RRT), and in those under 50 if their 10 year risk of cardiac events exceeds 10%, or they have diabetes mellitus.(245) UK guidelines (NICE 2014) recommend treating all patients with non-dialysis CKD with statins. If current guidelines were being followed, then almost all patients in our cohort would be eligible for treatment with lipid-lowering therapy, save for those with a genuine intolerance to the drug.

Cardiovascular risk calculators are widely used in primary care in the UK, to guide prescription of primary prevention therapies. The ASSIGN calculator used in Scotland does not include CKD in its risk model.(261) The QRISK2 calculator used in England contains CKD as a dichotomous variable.(262) Contemporary guidelines (SIGN guideline

103) recommended the use of statins in CKD stage 1-3 if 10-year cardiovascular risk exceeded 20%, however in CKD patients cardiovascular risk was underestimated by existing calculators.(30, 263) Thus primary care doctors and patients would be using underestimates of cardiovascular risk to inform decision-making around starting a statin.

Despite evidence supporting the prescription of statins to this population, we found that the proportion of CKD patients dispensed a statin fell over three consecutive years in our community-based population cohort. Primary care physicians in Scotland receive performance related payments (Quality and Outcomes Framework) to identify and keep a register of patients with CKD.(264) Further actions such as monitoring and treating blood pressure, monitoring proteinuria and prescription of angiotensin converting enzyme inhibitors in proteinuric patients are also incentivised.

Checking lipid profiles and commencing a statin in patients with CKD is not included in the QOF scheme. However, the QOF does stipulate a target total cholesterol of less than 5 mmol/L in diabetics and as a result, 80% of CKD patients in our cohort with diabetes were dispensed a statin. The QOF may have inadvertently contributed to the fall in newly diagnosed CKD patients being started on statins by the lack of incentives, or as a consequence of the increased workload associated with fulfilling other QOF indicators (i.e. an opportunity cost).

We have shown that women, younger patients and less co-morbid patients were less likely to be dispensed a statin. In the absence of reliable risk calculators that incorporate both eGFR and albuminuria, clinicians may perceive that these patients as low risk. For example, the widely used QRISK score for calculating CV risk did not include CKD in its original iteration, published in 2007.(279) An updated score, the QRISK 2, followed in 2008 included renal failure as a dichotomised variable, not discriminating between those with mild or severe renal failure.(262) Subsequent updates have not addressed this issue and continue to regard CKD as a binary risk factor.(315)

We also find a worrying trend for younger patients of the cohort, regardless of gender, were less likely to be dispensed a statin. Perhaps, individuals newly diagnosed with CKD were not being offered, or were disinclined to accept a statin. This may be because of opinions expressed in the popular press and mass media conflating the controversies surrounding statin use in low-risk populations with statin use in well-evidenced high-risk groups such as CKD.(265)

The oldest patients (≥ 85 years old) were also less likely to receive statins. These patients will have high absolute risk and therefore more likely to gain, but clinicians may be unconvinced that they will benefit from treatment or may be of the opinion that they may be more prone to drug side effects. Furthermore, such patients are rarely represented in drug trials, resulting in a paucity of evidence on which to base clinical practice. However, the average 85-year old Scot is expected to have a life expectancy of a further 6.0 (male) or 6.5 years (female), which may be longer than many clinicians expect.(266) Low SES is associated with poorer outcomes in cardiovascular conditions and in CKD.(227) Reassuringly, we found that patients with lower SES were marginally more likely to be dispensed a statin (Table 5-2).

What explains the decline in statin usage in our population? Campaigns to reduce over-diagnosis and overtreatment have become increasingly prominent.(48, 267, 268) In particular, there is a view that the benefits from statins are much less impressive, when expressed as absolute rather than relative risk reductions. Side effects are perhaps under-reported, and historically there have been specific concerns about the safety of statins, specifically cerivastatin and rosuvastatin.(269)

Multi-morbidity is increasingly prevalent, and these patients may suffer from overly complex therapeutic regimens.(270) Some believe that CKD, particularly in the elderly, is a manifestation of normal ageing and hence, another facet of over diagnosis.(49) These vocal campaigns could potentially explain the decline in statin usage in our population, as the reporting of negative statin related news in mass media is associated with the discontinuation of statin therapy in some patients.(265, 271, 272)

5.3.2 Study limitations

If patients were prescribed statins by their general practitioners but did not collect a prescription, they would not show up in the dispensing data. Studies examining prescribing to dispensing rates demonstrate that 93% of prescriptions are usually dispensed within a week of issue.(273) We also cannot identify patients who collected prescriptions, but did not actually take the statin. However, the lower serum cholesterol levels suggest that most patients dispensed a statin were taking the medication. It is possible that some who were prescribed a statin did not have it dispensed.

It is also possible that patients were not receiving a statin because of intolerance. However, 41% of our population were not dispensed a statin, whereas intolerance rates are typically reported to be between 10 – 20%.(274-276) If the reason for non-dispensing was due to intolerance of statins, then one might expect to see greater use of non-statin medications. We also demonstrated, in higher risk groups within our cohort, statin dispensing rates exceeding 80%. A study of diabetic patients in A&A reported statin prescribing rates of approximately 85% in type 2 diabetics.(277) Furthermore, a recent study examining the adverse event rates in the 'Anglo Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm' (ASCOT-LLA) trial following un-blinding, called into question the high reported rates of statin associated myopathy which the authors attribute to the 'nocebo' effect.(278)

The diagnosis of CKD in our cohort was based on laboratory data from ad-hoc testing and may have missed individuals with CKD. However, with a high proportion of the population having serum creatinine testing through routine medical care, we expect our stated prevalence to be very close to the true population prevalence and certainly more accurate than those ascertained from diagnostic codes or registers.(175) We have previously shown that a high proportion of our population at risk of CKD have had renal function measured and the prevalence of CKD did not rise despite an increasing proportion of the population being tested, suggesting an already high ascertainment rate.(38)

We identified co-morbidities through hospital diagnostic coding, but did not have access to primary care coded data, and so may be at risk of under-reporting co-morbidities. Ideally, we would estimate individual patient risk using a score such as ASSIGN or QRISK, as used by general practitioners, but did not have sufficient information.(261, 279) This would allow us to see if patients not receiving statins were assessed using these scores to have lower risk profiles.

Our work is based on a single geographical area with a predominantly white and elderly population, and so may not be generalizable. Although the health board (A&A) is a single managed entity, there are 55 general practices, which are independent contractors who are free to set their own service priorities.

6 CHAPTER 6: STATIN DISPENSING AND SURVIVAL IN A NON-DIALYSIS CKD COHORT: A RETROSPECTIVE STUDY

6.1 Introduction

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) have an evidence based role in the prevention of cardiovascular events in patients with non-dialysis chronic kidney disease (CKD). This was demonstrated in the 2011 publication of the SHARP study whose results further bolstered the updated 2014 Cochrane metanalysis which concludes with confidence, that compared to placebo, statins were associated with a 28% reduction in major cardiovascular events (RR 0.72, 95% CI 0.66 to 0.79) and 21% reduction in all-cause mortality (RR 0.79, 95% CI, 0.69 to 0.91) in individuals with non-dialysis CKD.(149, 150)

However, striking results obtained in controlled clinical trials can often disappoint when put into routine clinical practice.(280) Moreover, study populations are often younger and made up of more men which is unrepresentative of the general CKD population where the opposite is often true. We also demonstrated in chapter five that the incorporation of this evidence into routine clinical practice has been poor. Especially when statin use in other chronic conditions, such as diabetes, is higher and regarded as a maker of quality of care.(260, 281) There is also a worrying trend of falling statin dispensing rates for CKD patients over a 3-year period from 2010 to 2012, perhaps fuelled by scepticism about the benefits of statin therapy or by disproportionate reporting of statin side-effects.(265, 272, 282)

In light of the uncertainty surrounding the effect of statins in a more elderly and female population that is more representative of CKD patients outside of trial settings, we aim to utilise our well-defined community cohort of CKD patients from the west of Scotland to gauge the efficacy of those dispensed a statin in reducing all-cause mortality. Of special interests is the impact of statins in the elderly (age > 75 years), women and for secondary prevention.

6.2 Methods

6.2.1 Participants and settings

The study was set in NHS Ayrshire and Arran (A&A), the health board responsible for the commissioning and provision of healthcare services for the region. We identified all those within A&A who fulfil the KDIGO classification for CKD stage 3-5 from a centralised

laboratory database using an algorithm for determining chronicity.(175) This is detailed in chapter two.

We started with an initial cohort of 21,037 with CKD stage 3-5, age ≥ 18 years from the 1st April 2009 to the 31th of March 2012. We subsequently excluded those who were in receipt of renal replacement therapy (RRT), taking a non-statin lipid lowering drug if not concurrently on a statin as well and those with proteinuria > 2 g/day. Resulting in a final cohort of 16,588 individuals.

Individuals were deemed to be on a statin if they were dispensed at least 56 tablets of a statin or 2 consecutive months if the prescription was for 28 days as this was the practice in A&A for patients on stable dosing regimens. This number of prescriptions made-up 61.2% of all dispensed prescriptions of any statin.

6.2.2 Demographic data

Additional demographic, socioeconomic status, co-morbid conditions, statin dispensing and mortality from separate databases were linked to the cohort using each patient's unique community health index number. The first SIMD rank recorded during the index and follow-up was used. Details of the cohort demographics and databases used are provided in chapter 2.

6.2.3 Laboratory data

Proteinuria level was the first reading recorded at any point during study period and categorised according to KDIGO CKD staging. For serum albumin, only values from the index year was used. If more than one value was available, the readings were averaged. Details regarding laboratory set-up is provided in chapter 2 and cholesterol assay in chapter 5.

6.2.4 Missing values

In total, there were 31.3% of cases with at least one missing value. The variables proteinuria, SES and serum albumin had 13.8%, 12.6% and 9.9% missing values respectively. This is different from the proportions reported in chapter five, due to the difference in cohort selection highlighted above. Each of these variables were assessed for missing completely at random, missing at random or systematically missing. Results

reported exclude the missing cases. Multiple imputation was used to address the missing serum albumin values as a form of sensitivity analyses with pooled HRs presented.

6.2.5 Statistical analysis

Parametric mean differences were analysed using student's t-test and non-parametric proportions with chi-square. Adjusted survival analysis was conducted with Cox proportional hazards model. We used the statistics package SPSS v24 (IBM). Number needed to treat (NNT) along with 95% confidence intervals, where quoted, was calculated by the Newcombe-Wilson hybrid score method using a programme created by Professor Dan Tandberg.(283)

6.3 Results

6.3.1 Cohort characteristics

There were 16,588 patients in the cohort with a mean follow-up of 4.54 (SD ± 1.23) years. Of these 10,512 were dispensed a statin and 6,076 were not. Table 6-1 lists the cohort characteristics by statin dispensing status. The demographic factors favouring statin dispensing were younger age (mean difference -1.96 years, 95% CI -2.29 to -1.63), a higher proportion of men and higher levels of relative deprivation. Clinical parameters favouring statin dispensing were lower eGFR (mean difference -0.83 mL/min/1.73m^2, -1.19 to -0.47), higher serum albumin (mean difference 1.16 g/L, 1.04 to 1.29) and higher co-morbidity.

Variables		Statin (No)	Statin (Yes)	p-value
AGE (years) (mean ± SD)		75.66 ± 12.02	73.70 ± 9.34	< 0.001
eGFR (mL/min/1.73m^2) (mean ± SD)		47.96 ± 11.56	47.13 ± 11.29	< 0.001
serum albumin (g/L) (mean ± SD)		41.37 ± 4.11	42.54 ± 3.39	< 0.001
Female (n) (%)		4,216 (69%)	6,441 (61%)	< 0.001
Follow-up (days) (mean ± SD)		1574 ± 516	1705 ± 398	< 0.001
SES (n) (%)	1	963 (18%)	1,956 (21%)	< 0.001
	2	979 (19%)	1,928 (21%)	
	3	1,064 (20%)	1,840 (20%)	
	4	1,093 (21%)	1,817 (20%)	
	5	1,157 (22%)	1,707 (18%)	
Proteinuria category (n) (%)	A1	3,410 (73%)	6,938 (72%)	0.092
	A2	1,090 (23%)	2,207 (23%)	
	A3	187 (4%)	461 (5%)	
Hypertension (n) (%)		2,120 (35%)	4,729 (45%)	< 0.001
Coronary heart disease (n) (%)		839 (14%)	3,489 (33%)	< 0.001
Diabetes mellitus (n) (%)		392 (7%)	1,971 (19%)	< 0.001
Cerebrovascular event (n) (%)		292 (5%)	1,097 (10%)	< 0.001
Peripheral vascular disease (n) (%)		120 (2%)	583 (5%)	< 0.001
Events (n) (%)		2,042 (34%)	2,699 (26%)	< 0.001

Table 6-1. Cohort characteristics divided by those dispensed a statin and those who were not. Proteinuria categories were: A1 = urine protein:creatinine ratio (uPCR) < 15 mg/mmol or urine albumin:creatinine ratio (uACR) < 3 mg/mmol; A2 = uPCR 15-50 mg/mmol or uACR 3-30 mg/mmol; A3 = uPCR > 50 mg/mmol or uACR > 30 mg/mmol. SIMD 1 = highest relative deprivation and 5 = the lowest. P-values stated were for Pearson's X^2 when variables were non-parametric and Student's t-test for parametric variables.

6.3.2 Statins for primary and secondary prevention

Patient who had no prior diagnosis of CHD or CVA were categorised as primary prevention and those who did, as secondary prevention. Compared to the secondary prevention group, the primary prevention group was significantly younger (mean difference -3.18 years, 95% CI -3.53 to -2.84), had higher eGFR (1.78 mL/min/1.73m^2, 1.40 to 2.15), higher serum albumin (1.12 g/L, 1.00 to 1.25), higher proportion of females (67% vs. 57%), had lower SES (SIMD quintile 1, 19% vs 22%) and less co-morbid. Excluding CHD and CVA, the primary prevention group had significantly less hypertension (31% vs. 66%), diabetes (11% vs. 22%) and PVD (2% vs. 9%).

The primary and secondary prevention cohorts were further subdivided into those dispensed a statin and those not and detailed in table 6-2. There were 11,505 individuals in the primary prevention cohort, of whom 6,450 (56%) were dispensed a statin. In the secondary prevention cohort, there were 5,083 individuals of which, 4,062 (80%) were dispensed a statin.

Of note, in the primary prevention group average eGFR was significantly lower in the statin dispensing group, but this relationship was reversed in the secondary prevention group. In both the primary and secondary prevention groups, those dispensed a statin had higher deprivation, a larger proportion of men and more co-morbidity, especially diabetes, then the non-statin dispensing group. These demographic differences should favour a lower average eGFR as demonstrated in the primary prevention group dispensed a statin. The reason the observation does not hold true in the secondary prevention cohort, may be attributable to the larger age difference between the groups in this cohort.

In the primary prevention cohort, there were 4,218 (37%) cases with missing values. For the variables proteinuria, SES and serum albumin there were 13.5%, 18.1% and 11.4% missing values respectively. In the secondary prevention cohort, there were 981 (19%) cases with missing values. For the variables proteinuria and serum albumin, there were 14.5% and 6.4% missing values respectively.

Variables		Primary prevention		p-value	Secondary prevention		p-value
		Statin (No)	Statins (Yes)		Statin (No)	Statin (Yes)	
AGE (mean ± SD)		74.57 ± 12.26	72.57 ± 9.50	< 0.001	81.09 ± 8.96	75.71 ± 8.79	< 0.001
eGFR (mean ± SD)		48.41 ± 11.33	47.64 ± 10.97	< 0.001	45.75 ± 12.44	46.32 ± 11.73	< 0.001
serum albumin (mean ± SD)		41.75 ± 3.92	43.03 ± 3.14	< 0.001	39.66 ± 4.52	41.78 ± 3.62	< 0.001
Female (n) (%)		3,548 (70%)	4,209 (65%)	< 0.001	668 (65%)	2,232 (55%)	< 0.001
Follow-up (days) (mean ± SD)		1,633 ± 472	1,757 ± 341	< 0.001	1,282 ± 619	1,622 ± 463	< 0.001
SES (n) (%)	1	759 (18%)	1,051 (20%)		204 (20%)	905 (22%)	
	2	781 (18%)	1,094 (21%)		198 (19%)	834 (21%)	
	3	837 (20%)	1,010 (20%)	< 0.001	227 (22%)	830 (20%)	0.266
	4	902 (21%)	1,051 (20%)		191 (19%)	766 (19%)	
	5	956 (23%)	980 (19%)		201 (20%)	727 (18%)	
Proteinuria category (n) (%)	A1	2,950 (74%)	4,464 (75%)		460 (64%)	2,474 (68%)	
	A2	876 (22%)	1,246 (21%)	0.121	214 (30%)	961 (27%)	0.063
	A3	145 (4%)	267 (5%)		42 (6%)	194 (5%)	
Hypertension (n) (%)		1,492 (30%)	2,025 (31%)	0.030	628 (62%)	2,704 (67%)	0.002
Coronary heart disease (n) (%)		x	x		839 (82%)	3,489 (86%)	0.003
Diabetes mellitus (n) (%)		259 (5%)	973 (15%)	< 0.001	133 (13%)	998 (25%)	< 0.001
Cerebrovascular event (n) (%)		x	x		292 (29%)	1,097 (27%)	0.307
Peripheral vascular disease (n) (%)		52 (1%)	182 (3%)	< 0.001	68 (7%)	401 (10%)	0.002
Events (n) (%)		1,425 (28%)	1,229 (19%)	< 0.001	617 (60%)	1,470 (36%)	< 0.001

Table 6-2. Cohort characteristics divided by primary and secondary prevention, and by statin dispensing status. P-values are for Pearson's X^2 for non-parametric variables and student's t-test for parametric variables.

6.3.3 Statins for the older CKD patient

Older patients are an often-neglected group. To determine the effect of statin dispensing on all-cause mortality in elderly CKD patients, we divided the cohort into two roughly equal groups. There were 8,257 who were < 76 year of age of which, 5,684 (69%) were dispensed a statin. There were 8,331 individuals ≥ 76 years of age of which, 4,828 (58%) were dispensed a statin. Average age of the younger vs. older group, irrespective of statin dispensing status, was (mean ± SD) 66.30 ± years 7.99 vs. 82.47 ± 4.88. respectively.

Table 6-3 details the group characteristic by age group and treatment status. In both the older and younger groups, the number of cases with at least one missing value was similar at 31.3%. The distribution of missing values for the variables proteinuria, serum albumin and SES were broadly similar in both groups.

Variables		Age <76 years		p-value	Age ≥76 years		p-value
		Statin (No)	Statins (Yes)		Statin (No)	Statin (Yes)	
AGE (mean ± SD)		64.55 ± 9.48	67.09 ± 7.07	< 0.001	83.82 ± 5.23	81.49 ± 4.35	< 0.001
eGFR (mean ± SD)		50.21 ± 10.78	48.45 ± 10.94	< 0.001	46.31 ± 11.84	45.58 ± 11.50	0.005
serum albumin (mean ± SD)		42.53 ± 3.91	43.11 ± 3.27	< 0.001	40.53 ± 4.06	41.86 ± 3.41	< 0.001
Female (n) (%)		1,757 (32%)	2,394 (58%)	< 0.001	1,044 (30%)	1,681 (35%)	< 0.001
Follow-up (days) (mean ± SD)		1,736 ± 398	1,788 ± 317	< 0.001	1,456 ± 559	1,608 ± 457	< 0.001
SES (n) (%)	1	418 (20%)	1,097 (23%)	< 0.001	545 (17%)	859 (19%)	0.010
	2	394 (19%)	1,040 (22%)		585 (18%)	888 (20%)	
	3	420 (20%)	934 (20%)		644 (20%)	906 (20%)	
	4	436 (21%)	934 (20%)		657 (21%)	883 (20%)	
	5	413 (20%)	780 (16%)		744 (23%)	927 (21%)	
Proteinuria category (n) (%)	A1	1,645 (79%)	3,948 (74%)	0.001	1,765 (68%)	2,990 (69%)	0.112
	A2	346 (16%)	1,062 (20%)		744 (29%)	1,145 (27%)	
	A3	99 (5%)	291 (6%)		88 (3%)	170 (4%)	
Hypertension (n) (%)		711 (28%)	2,367 (42%)	< 0.001	1,409 (40%)	2,362 (49%)	< 0.001
Coronary heart disease (n) (%)		208 (8%)	1,616 (28%)	< 0.001	631 (18%)	1,873 (39%)	< 0.001
Diabetes mellitus (n) (%)		156 (6%)	1,187 (21%)	< 0.001	236 (7%)	784 (16%)	< 0.001
Cerebrovascular event (n) (%)		65 (3%)	479 (8%)	< 0.001	227 (6%)	618 (13%)	< 0.001
Peripheral vascular disease (n) (%)		29 (1%)	286 (5%)	< 0.001	91 (3%)	297 (6%)	< 0.001
Events (n) (%)		401 (16%)	883 (16%)	0.954	1,641 (47%)	1,816 (38%)	< 0.001

Table 6-3. Cohort characteristics divided by age (< 76 and ≥ 76-year-old) and by statin dispensing status. P-values are for Pearson's X^2 for non-parametric variables and student's t-test for parametric variables.

6.3.4 Statins by gender

There were 10,657 females in the cohort and 5,931 males. The demographic differences and variation by treatment status are presented in table 6-4. Amongst female patients, 60% (n = 6,441) were dispensed a statin compared to a higher proportion of males at 69% (n = 4,071) of patients.

In the female cohort, there were 33.0% of cases with at least one missing value. For the variables proteinuria, SES and serum albumin there were 14.6%, 13.3% and 10.4% missing values respectively. Of the male subjects, there were 28.3% of cases with missing values. For the variables proteinuria, SES and serum albumin there were 12.5%, 11.2% and 8.9% missing values respectively.

Variables		Female		p-value	Male		p-value
		Statin (No)	Statin (Yes)		Statin (No)	Statin (Yes)	
AGE (mean ± SD)		75.98 ± 12.13	74.30 ± 9.38	<0.001	74.94 ± 11.73	72.76 ± 9.19	<0.001
eGFR (mean ± SD)		48.01 ± 11.34	47.05 ± 11.28	<0.001	47.84 ± 12.06	47.26 ± 11.30	0.071
serum albumin (g/L) (mean ± SD)		41.35 ± 4.01	42.47 ± 3.42	<0.001	41.43 ± 4.34	42.65 ± 3.35	<0.001
Primary prevention (n) (%)		3,548 (84%)	4,209 (65%)	<0.001	1,507 (81%)	2,241 (55%)	<0.001
Follow-up (days) (mean ± SD)		1,596 ± 501	1715 ± 389	<0.001	1,525 ± 547	1690 ± 413	<0.001
SES (n) (%)	1	648 (18%)	1,241 (22%)	<0.001	315 (19%)	715 (20%)	0.094
	2	697 (19%)	1,195 (21%)		282 (17%)	733 (20%)	
	3	731 (20%)	1,147 (20%)		333 (20%)	693 (19%)	
	4	747 (21%)	1,100 (20%)		346 (21%)	717 (20%)	
	5	791 (22%)	938 (17%)		366 (22%)	769 (21%)	
Proteinuria category (n) (%)	A1	2,463 (76%)	4,426 (76%)	0.703	947 (66%)	2,512 (67%)	0.179
	A2	686 (21%)	1,243 (21%)		404 (28%)	964 (26%)	
	A3	95 (3%)	190 (3%)		92 (6%)	271 (7%)	
Hypertension (n) (%)		1,462 (35%)	2,926 (45%)	<0.001	658 (35%)	1,803 (44%)	<0.001
Coronary heart disease (n) (%)		550 (13%)	1,890 (29%)	<0.001	289 (16%)	1,599 (39%)	<0.001
Diabetes mellitus (n) (%)		220 (5%)	1,102 (17%)	<0.001	172 (9%)	869 (21%)	<0.001
Cerebrovascular event (n) (%)		182 (4%)	635 (10%)	<0.001	110 (6%)	462 (11%)	<0.001
Peripheral vascular disease (n) (%)		62 (2%)	280 (4%)	<0.001	58 (3%)	303 (7%)	<0.001
Events (n) (%)		1,341 (32%)	1,577 (25%)	<0.001	701 (38%)	1,122 (28%)	<0.001

Table 6-4. Cohort characteristics divided by gender and statin dispensing status. P-values are for Pearson's X^2 for non-parametric variables and student's t-test for parametric variables.

6.3.5 Survival

There were 2,699 (25.7%%) deaths in statin recipients and 2,042 (33.6%) in non-recipients. The crude death rate per 100 patient years was 7.8 in non-recipients and 5.5 in the recipients. Unadjusted survival analyses comparing statin recipients to non-recipients yielded a mean survival of 4.89 years (95% CI 4.87 to 4.91) and 4.53 years (95% CI 4.49 to 4.57) respectively, p (log-rank) < 0.001. To account for the case-mix, adjustment for age, gender, serum albumin, eGFR, Proteinuria, SES and co-morbidities were carried out using Cox proportional hazards model.

The Cox proportional hazards model assumes that the hazards are consistent and do not vary substantially over time. To assess proportionality, we plot the log(-log(survival)) for the treatment group and the non-treatment group versus the survival time (Figure 6-1). Inspection of the log minus log plot confirms proportionality of the model and appropriateness of this method.

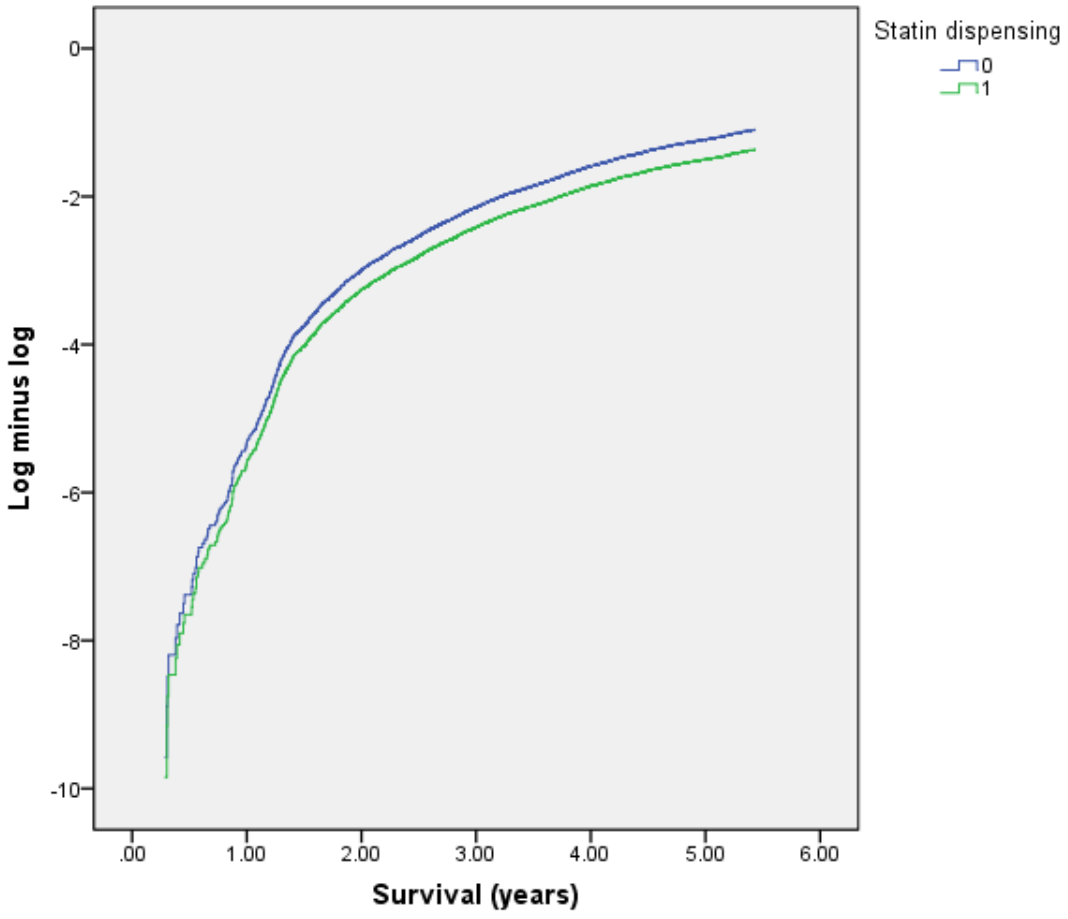


Figure 6-1. Log minus log plot demonstrating proportionality. Those dispensed statin = 1 and those not dispensed a statin = 0.

Fully adjusted HR for those dispensed a statin was 0.76 (95% CI 0.71 to 0.83). We present the fully adjusted HRs and 95% CI for the subgroups by indication, age and gender summarised as a Forest plot in figure 6-2. In addition, to assists in clinical decision making, adjusted HRs for clinically relevant subgroups were also presented.

Subgroups	n	Events	Hazard Ratio (95% CI)
Indication for statin			
Primary prevention	7,287	1,696	0.82 (0.74 - 0.91)
Secondary prevention	4,102	1,488	0.68 (0.60 - 0.77)
Age			
Age < 76	5,671	936	0.78 (0.67 - 0.92)
Age ≥ 76	5,718	2,248	0.78 (0.71 - 0.85)
Gender			
Female	7,137	1,904	0.79 (0.71 - 0.87)
Male	4,252	1,280	0.73 (0.64 - 0.83)
Indication, age and gender			
Primary prevention, female and <76	2,453	313	0.73 (0.57 - 0.93)
Pirmary prevention, female and ≥76	2,393	787	0.86 (0.74 - 1.00)
Primary prevention, male and <76	1,388	204	0.99 (0.72 - 1.38)
Primary prevention, male and ≥76	1,053	392	0.78 (0.63 - 0.97)
Secondary prevention, female and <76	941	179	0.86 (0.55 - 1.36)
Secondary prevention, female and ≥76	1,350	625	0.74 (0.62 - 0.89)
Secondary prevention, male and <76	889	240	0.45 (0.30 - 0.67)
Secondary prevention, male and ≥76	922	444	0.65 (0.51 - 0.81)
Overall	11,389	3,184	0.76 (0.71 - 0.83)

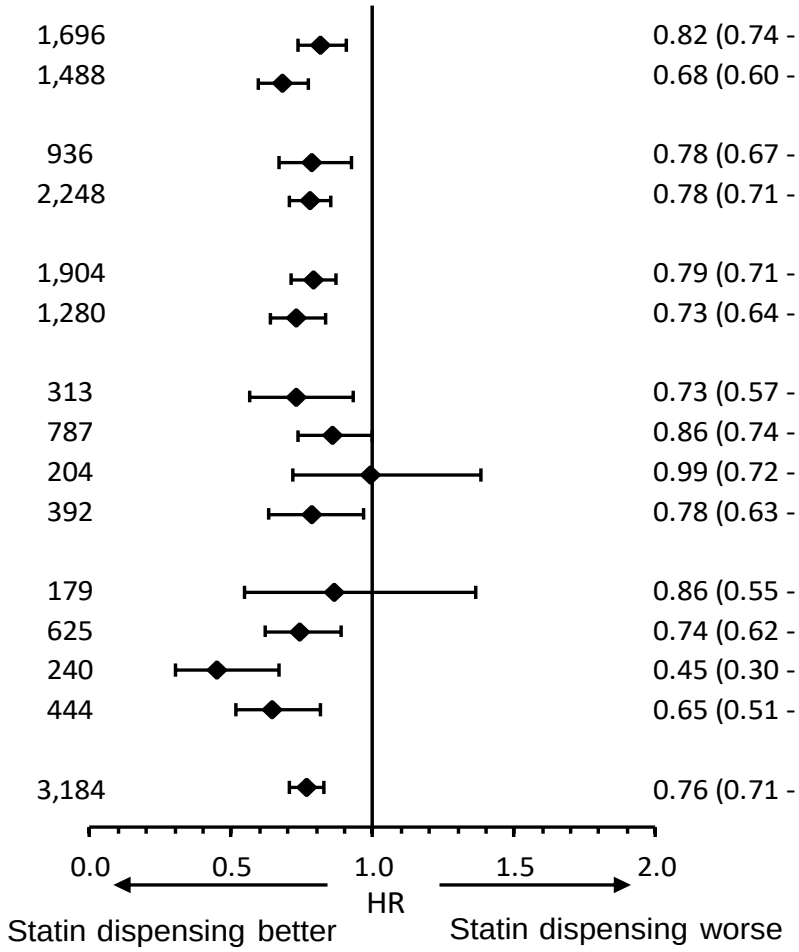


Figure 6-2. Forest plot of adjusted HRs adjusted for age, gender, serum albumin, eGFR, proteinuria category, SES and co-morbidities by subgroups.

6.3.6 Missing values and multiple imputation

There were 31.3% of cases with at least one missing value. The variables with missing values were serum albumin (9.9%), SES (12.6%) and proteinuria (13.8%). The p-value for Little's MCAR test was < 0.001, indicating that the missing data were not wholly MCAR and therefore cannot simply be excluded without additional analysis. The individuals with missing values for SES and proteinuria were substantially different in age, gender split and comorbidity than the rest of the cohort, but this was not the case for serum albumin.

Missing cases were adjudged to be missing at random and therefore excluded from the initial analyses. However, cases with missing serum albumin values were non-contiguous and so subjected to multiple imputation. A total of 5 imputations were generated using a Mersenne twister random number generator with a seed set at 20,000,001, to enable replication. After imputation, the number of complete cases for analyses increased by 9.1% (n = 1,039) and total deaths by 7.4% (n = 236). The subgroup analyses in figure 6-2 was repeated with this expanded cohort and apart from older women in receipt of a statin for primary prevention, the pooled HRs were largely unchanged (Figure 6-3).

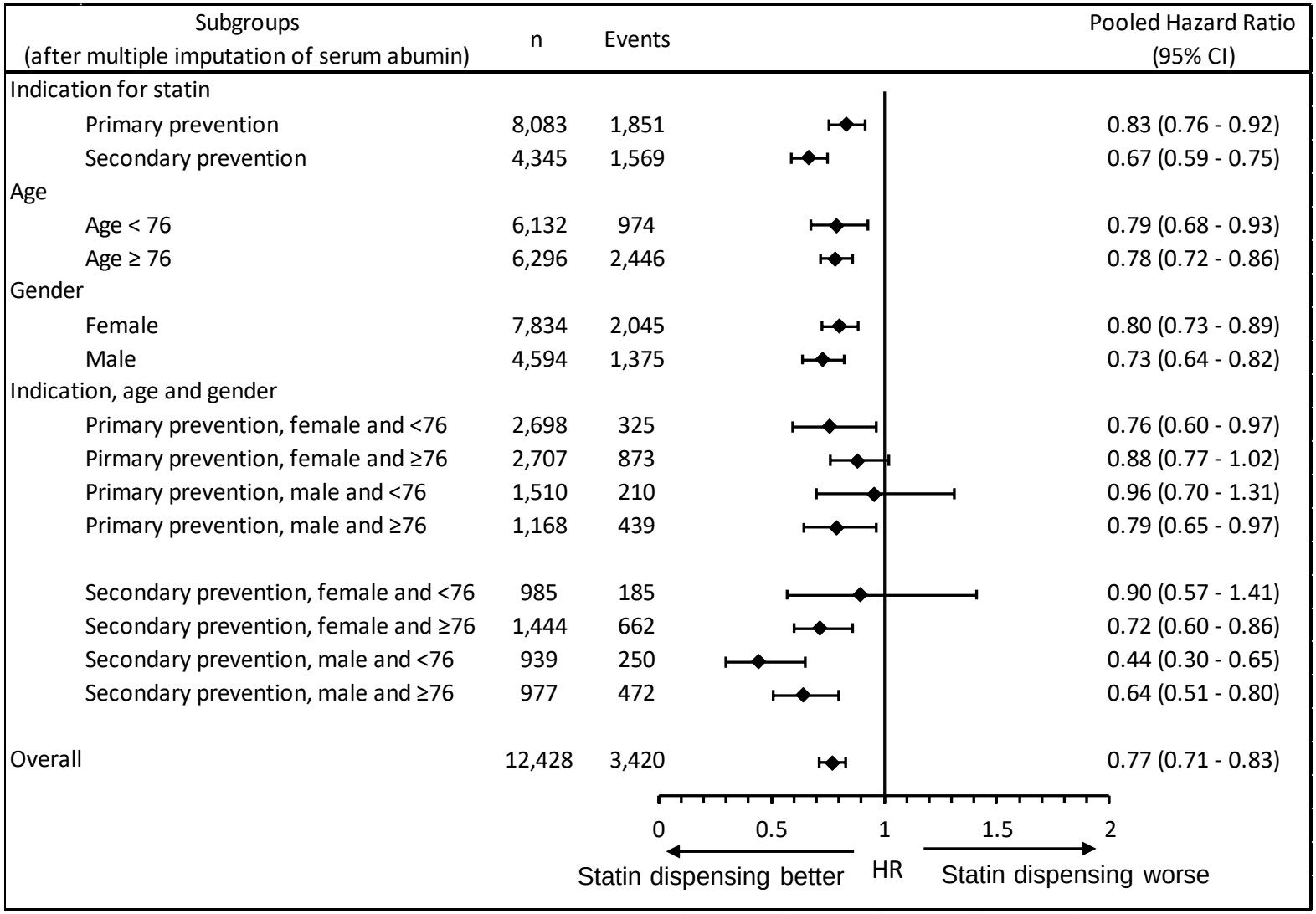


Figure 6-3. Repeat subgroup analyses after multiple imputation of missing serum albumin levels. Pooled HRs adjusted for age, gender, serum albumin, eGFR, proteinuria category, SES and co-morbidity.

6.4 Discussion

6.4.1 Main findings

In just under 5 years of follow-up, those in our community CKD cohort being dispensed a statin derived a similar magnitude of benefit for reduction in all-cause mortality in line with the 2014 Cochrane meta-analysis by Palmer et al.(150) Overall, a 34% survival advantage was associated with those receiving a statin and in subgroup analyses those receiving statins for primary prevention was associated with an overall 18% reduction in all-cause mortality. Although this benefit is not consistent for the whole group with younger (<76 years) men, and perhaps, older (≥ 76 years) women not deriving the same benefit.

The evidence for the use of statins for primary prevention of cardiovascular events and death in non-dialysis CKD patients is incontrovertible.(150) The case for secondary prevention of cardiovascular events in CKD however, is largely derived from post-hoc studies of statin trials that included some patients with mild CKD.(284, 285) These studies usually include a younger population (mean age in the Tonelli et al. and Shepherd et al. studies were 64.3 ± 6.8 and 65.5 ± 7.0 years respectively) and have milder stages of renal impairment (mean CrCl 61.3 ± 10.1 mL/min and MDRD 52.9 ± 6.5 mL/min/1.73m^2 respectively) than is representative of the general population with CKD. Here we demonstrate, in a real-world cohort of CKD patients, that being dispensed a statin for secondary prevention is associated with a 32% survival benefit over those who were not.

There is also little evidence to support the use of statins in the elderly CKD patient despite the high absolute risk in this group. The only clinical study with an elderly cohort was a secondary analysis of the 'Justification for the Use of Statins in Prevention - an Intervention Trial Evaluating Rosuvastatin' (JUPITER) looking at the effect of Rosuvastatin in a subset of patients with mild CKD.(286) The median age of this cohort was 70 years (IQR 65 – 75) with a median eGFR of 56 mL/min/1.73m^2 (51 – 58). Although this cohort was more representative of the general population at risk, the average CKD patient is still much older and with poorer renal function. For example, in our cohort the median age was 76 years (68 – 82) with a median eGFR of 49 mL/min/1.73m^2 (41 – 55), which is similar to other UK community CKD cohorts.(70, 287) Our subgroup analyses of an elderly cohort (age ≥ 76 years), who had a median age of 82 years (78 – 86), was just as likely to benefit from the dispensing of a statin as the cohort with a median age

15 years younger. This effect persisted for both gender and regardless of a previous history of CHD or CVD.

Men appeared to derive a larger benefit overall, with a 27% lower associated risk of all-cause mortality compared to 20% lower risk for women. However, in male patients who were younger and in receipt of a statin for primary prevention there appeared to be no statistically significant benefit. This contrasts with older men and women of all ages. The reasons for this is unclear.

Although not a controlled study, a similar magnitude of benefit was demonstrated in this community CKD cohort to that of clinical trials of statins in non-dialysis CKD patients. In table 6-5, we calculated the number needed to treat for this cohort along with the aforementioned subgroups to provide some context for the effect sizes in figure 6-2. This suggests an overall NNT of 15.8 over 4.5 years to prevent one death. This NNT falls for the higher risk groups especially those with a history of CHD or CVA to between 5.0 and 6.6. However, this analysis was based on much smaller numbers.

This study was based on records of drugs actually dispensed to patients from a pharmacy, while not a guarantee of compliance, is more likely to be representative of actual administration than if we had only obtained prescription data.(273) While 93% of new prescriptions get dispensed within a week of issue, long term adherence to therapies are frequently lower. Only 50% of patients managed to get their prescriptions dispensed ≥ 80% of the time in a 15-month period. Thus, dispensing data is a much better indicator of adherence than prescribing data.

Subgroups	Statin (No)		Statin (Yes)		NNT (at 4.5 years)
	Deaths	n	Deaths	n	
Indication for statin					
Primary prevention	796	2,867	900	4,420	13.5 (10.6 - 18.6)
Secondary prevention	345	664	1,143	3,438	5.3 (4.4 - 6.9)
Age					
<76	228	1,478	708	4,193	NS
≥76	913	2,053	1,335	3,665	12.4 (9.3 - 18.5)
Gender					
Female	741	2,405	1,163	4,732	16.0 (11.8 - 24.8)
Male	400	1,126	880	3,126	13.6 (9.4 - 23.8)
Indication, gender and age					
Primary prevention, female and <76	119	874	194	1,579	NS
Primary prevention, female and ≥76	416	1,109	371	1,284	11.6 (8.1 - 20.7)
Primary prevention, male and <76	58	416	146	972	NS
Primary prevention, male and ≥76	203	468	189	585	9.0 (5.9 - 19.3)
Secondary prevention, female and <76	22	117	157	824	NS
Secondary prevention, female and ≥76	184	305	441	1,045	5.5 (4.1 - 8.5)
Secondary prevention, male and <76	29	71	211	818	6.6 (3.7 - 25.4)
Secondary prevention, male and ≥76	110	171	334	751	5.0 (3.6 - 25.4)
Overall	1,141	3,531	2,043	7,858	15.8 (12.3 - 22.2)

Table 6-5. Number needed to treat (NNT) for dispensing statins by subgroup and for the cohort as a whole.

6.4.2 Study limitations

Our study was an observational retrospective cohort study which would have limited our ability to control for confounding. We also assume that statin use at the time the cohort was established, persisted throughout follow-up. To minimise the effect of drug discontinuation, we only selected those who had > 2 months of consecutive dispensing when the average prescription was for 28 days or in receipt of 56 days worth of medications which is the routine practice of patients on stable dosing. We were reassured by the significant reduction in total cholesterol between those earmarked as being on a statin compared to those not, presented in chapter 5.

It is possible that our co-morbidity data is incomplete as it was based on SMR which only captures those individuals who have had reason for inpatient treatment or investigations. This is likely to exclude a proportion of those who have had no reason for hospital admission. To increase capture, we interrogated the SMR database as far back as 1st of January 1999. Others have found the SMR to be reasonably robust as a data source for studies.(205) Obtaining this data from primary care records would have been the ideal, but outwith the resources of this study.

It is possible that those not dispensed a statin could have been offered but were intolerant of a statin. Of course, no population is likely to achieve complete medication coverage but in type 2 diabetic patients in A&A the prevalence of statin use is approximately 85%.(277) Even within this cohort there is a large discrepancy in the proportion of patients in receipt of a statin for secondary prevention (80%) and primary prevention (56%). It is also often the case that statin dosage is much higher for secondary prevention and here it appears well tolerated. Furthermore, trial data estimates statin intolerance to be around 10 – 20% of individuals but has also been brought into question by a recent study where reported adverse events only increased following study un-blinding.(274-276, 278)

7 CHAPTER 7: DISCUSSION

7.1 Summary of the main findings

In this thesis, the key findings were:

- The development of a novel method for identifying individuals with CKD stage 3 – 5 from a large database of serial serum creatinine measurements reliably, while accounting for chronicity that mimics clinical decision making. Due to serum creatinine testing patterns in the UK, the overwhelming majority of individuals with CKD are being routinely tested and this algorithm provides a robust mechanism to reliably identify these individuals.

- Laboratory ascertainment of individuals with CKD is desirable as it is more accurate and efficient than the current system, whereby this exclusively laboratory based diagnosis, is entirely determined manually by PCPs. Central laboratory ascertainment identified more individuals with CKD and also reduced the variation in prevalence (outside 3 SD) from 22, down to 15 out of a total of 54 PCPs when compared to the QOF CKD register.

- That the variation in prevalence of CKD in a defined locality is heavily influenced by the demographic factors of age and gender, but is also significantly influenced by socio-economic status and rurality of the area. Although this impact is small, most rural communities are deprived and often overrepresented by the elderly, and should therefore have these factors taken into consideration when targeting resources. Adjusting for age, gender and SES reduced variations in prevalence of outlier (outside 3 SD) from 15 to 6.

- Socio-economic status in univariate analyses is associated with lower eGFR, but this association is lost in multivariate modelling, behaving as a confounding factor. SES is also associated with a higher number of co-morbidities and thus, may explain the associated lower average eGFR.

- In survival analysis, this confounding may also explain a large part of the higher mortality apparently associated with CKD. The associated mortality risk between SES and CKD weakened substantially when fully adjusted for between group differences. When considered in the context of international studies examining this same issue, the lack of association to excess mortality from lower SES may be

attributable to the unfettered access to comprehensive healthcare, regardless of means, provided by the NHS.

- A well linked and continually updated database of prevalent CKD patients can provide performance data on quality measures such as the appropriate dispensing of evidence based treatments. An example of such a system in use is the SCI-diabetes network, which has a proven track record of successfully improving the care of diabetic patients in Scotland.(288)

- In chapter five, we used statin dispensing as a marker of quality of care and revealed a concerning trend of falling dispensing rates between 2010 and 2012 in A&A. This trend affects the young and the elderly especially and should warrant root cause analysis and a plan of action to reverse this decline.

- Statins are associated with a reduction in all-cause mortality, to a similar magnitude as that demonstrated in clinical trials, in a real-world community cohort of CKD patients who were being dispensed one.

- There is systemic under recognition of risk and under treatment of women with statins in our CKD cohort, which has been well documented in the literature from other branches of medicine. This is despite evidence that demonstrates significant clinical efficacy in this patient population.

- That a comprehensive and enriched database with longitudinal data can generate useful hypothesis and inform clinical practice. An example of this is the novel observation that, in the older CKD patient (≥ 76 years old), statin dispensing is also associated with significant improved survival.

7.2 Centralised laboratory CKD ascertainment

Detailed in chapter two, was a novel algorithm developed to identify CKD stage 3 – 5 from existing serum creatinine results stored in a central laboratory database. The algorithm accounted for chronicity even in fluctuating, borderline cases. It performed better than current PCP CKD registers by identifying many more individuals, in absolute numbers, than those reported by the QOF CKD registers. Furthermore, this method of case finding reduced some of the variation in prevalence as compared to the QOF CKD prevalence.

In chapter three, the use of a central laboratory based case-finding approach identified more patients than that reported in the QOF CKD registers. This approach also reduces the observed variation in CKD prevalence between PCPs CKD registers. Using such an approach to facilitate case finding is both practical, and will improve the accuracy and completeness of PCP CKD registers. Accurate and complete CKD registers will greatly improve the efficiency of monitoring, targeted interventions and appropriate and timely referral to Nephrology services.(194)

7.3 Socio-economic status and disease prevalence

There are well documented associations between lower SES and higher CKD prevalence.(72, 226, 227) Chapter three demonstrates the importance of adjusting for socio-economic status when examining variations in CKD prevalence. This is an important consideration when examining differences between PCPs to detect genuine unwarranted variations in CKD prevalence over and above demographic differences.

In addition, a novel, but small association between higher CKD prevalence and more rural areas after adjustment for age, gender and SES, was found. More rural areas are often associated with poorer SES, but this effect appears independent of area SES in multivariate modelling. However, the effect of rurality was small and did not have a significant effect on variation of CKD prevalence.

7.4 Socio-economic status and disease severity

Chapter four demonstrates that a lower SES is associated with lower average eGFR in univariate analysis. Unsurprisingly, those with lower SES had higher prevalence of hypertension, diabetes, coronary heart disease, lower average serum albumin and a demographic make-up consisting of a higher proportion of women and a younger average age.

Following multivariate regression modelling, SES as a predictor of eGFR lost its effect and was statistically non-significant. This suggests SES was behaving as a confounder and had little effect on eGFR beyond its association with higher levels of co-morbidities at a younger age. This contrasts with findings from another UK CKD cohort that examined this issue. However, this study from Sheffield utilised different methods and a cohort that had

been referred to specialist nephrology services.(179) Notwithstanding the smaller sample size, in effect, this study examined a different population of CKD patients.

7.5 Socio-economic status and disease outcomes

Lower SES in this CKD cohort was associated with a stepwise, incremental risks for all-cause mortality when differences in age and gender were accounted for. However, following further adjustment for co-morbidity mix and renal disease severity markers, this association is attenuated and its effect on outcome became questionable. This is not in keeping with previous studies that have reported a strong association between lower SES and worse outcomes after adjustment for demographic and clinical factors.(212, 213, 234, 242) It is worth noting that the majority of studies reporting a link between SES and worse outcomes in CKD are often based in North America where access to healthcare is linked to income and employment.

It may well be that the higher co-morbidity associated with lower SES is the mechanism for higher mortality, but is not itself independently associated with an incremental mortality risk in CKD patients. Instead, it may be that access to healthcare is the significant determinant for increased mortality in CKD and in the UK where access to healthcare is not reliant on SES, it has a much smaller effect than previously reported.(234, 240, 241)

7.6 Statin dispensing in CKD

Statins use in CKD was first demonstrated to be effective in a 2004 post-hoc analysis of pravastatin trials in the general population.(148) In 2011, the SHARP trial used a combination of simvastatin with ezetimibe compared to placebo and demonstrated a 17% RR reduction in major cardiovascular events in a cohort of CKD and RRT patients.(149) A 2009 Cochrane meta-analysis published at the beginning of our study period concluded that statins were associated with a 19% RR reduction in all-cause mortality and 25% reduction in non-fatal cardiovascular events.(255) These findings have been strengthened by an updated Cochrane meta-analysis published in 2014, which included data from the SHARP study.(150)

Given the high-quality evidence available at the time of this CKD cohort's creation, the expectation a priori, was that statin dispensing rates would be high. As many as 40% of patients with CKD were not being treated with lipid-lowering therapy, a proven

intervention to reduce the risk of cardiovascular events. Drug intolerance cannot account for this 40% gap which is typically estimated to be between 10 – 20%.(274-276) Those within the cohort with a diagnostic code for prior diabetes, CHD or CVD were being dispensed a statin at rates of around 80%. They were also receiving larger doses than those typically recommended for primary prevention. Statin prescribing in type 2 diabetic in A&A also fare better, at approximately 85%.(277)

It is not clear why dispensing rates of statins in this cohort of high risk patients was low. It may be that awareness amongst clinicians regarding the heightened cardiovascular risk in CKD is low and so perhaps, better individualised risk estimates that fully incorporate markers of CKD are required to allow for informed decision-making by patients and clinicians. Cardiovascular risk calculators do not incorporate eGFR or urinary albumin:creatinine ratios and need to be developed to provide a more accurate risk estimates in CKD patients to facilitate shared decision making.(289) Whether this would increase statin usage in CKD remains unknown.

7.7 Statins dispensing trends over a 3-year period

Statin dispensing fell by 5% over a 3-year period. Reversing this decline and increasing the utilisation of statins, has the potential to improve survival significantly in this patient group, and reduce the number of cardiovascular events. It was not clear as to why substantial numbers of patients were not being prescribed an evidence-based therapy. It may be that the conflated accounts in the popular press and medical journals may have influenced attitudes of patients and physicians alike to avoid initiating this class of drugs in all patients, even though the evidence for its use in CKD is not in question.(144, 265, 282)

Qualitative research with patients and prescribers may provide a more conclusive understanding of the underlying reasons for falling dispensing rates. It will be of interest to see if the declining trend in statin usage is maintained despite the publication of guidelines after the period of study, in 2013 and 2014, unequivocally recommending their use in this population. It will require replication of this work in other populations to show if this negative trend is pervasive.

7.8 The influence of statins on survival in a CKD cohort

In chapter six, being dispensed a statin was found to achieve a similar magnitude of risk reduction as demonstrated in the 2014 Cochrane meta-analysis.(150) A novel finding was that this effect is consistent even in the oldest patients (82.47 years (mean) ± 4.88 (SD)) which are more typical or 'real-world' clinical encounters than that represented in clinical trials.

Assuming that this effect was consistent and reproducible, the estimated NNT over 4.5 years is modest at 15.8 to avoid one death and improves substantially to 5.0 for the highest risk groups. This is an example of how large clinical databases can be used to conduct clinically useful research, drug efficacy monitoring and quality improvement through better targeting of therapy and identifying changing trends in care.

7.9 Limitations of these studies

The main limitation of this thesis are the sources of data. Reliance on single sources of data does not allow for verification. This may not be avoidable if only one source of data exists, but by definition that source is then regarded as the reference. However, healthcare data is often stored in parts in multiple repositories and re-recorded whether for clinical or administrative purposes. Poor interoperability is rife, even amongst primary care providers there is a multitude of EPRs in use, although a system (GP2GP) exist for the transfer of health records when patients move practices.(290) However, the sharing of data between primary and secondary care in the UK remains severely undeveloped. The major challenges and strategies to improve this was outlined in a 2014 policy document "Personalised Health and Care 2020" by the department of health.(291) Also, data quality standards may be inconsistent and one approach to improving the accuracy of such population studies is to have access to multiple sources of data for verification.

Dispensing data is not the same as actual prescribing data and so caution is required when examining and making inferences regarding statin prescribing rates. While the proportion of prescriptions that are fulfilled is very high (93% within a week), the adherence to long term prescriptions may be as low as 50% over 15 months.(273) While drug dispensing data is better for measuring adherence, and this was demonstrated by the significantly lower cholesterol levels of the statin dispensing group in chapter five, it is possible that a degree

of non-fulfilment of prescriptions could affect the conclusions regarding falling dispensing rates over time.(292)

The true discrepancy between the CKD cohort that we identified through central laboratory ascertainment using our algorithm, could not be examined directly against the CKD registers maintained by PCPs for the purposes of QOF due to a lack of access to individual primary care databases. However, the algorithm and laboratory ascertainment identified an additional 1,255 individuals with CKD over and above the absolute QOF figures published for that same year. Furthermore, work by Methven et al. found that PCP CKD registers in A&A may include up to 11% of individuals misdiagnosed with CKD who did not have an eGFR < 60 mL/min/1.73m^2 in the preceding year.(202) If this is generalisable across the health board, the gulf between those on the PCP CKD register with actual CKD 3-5, and our laboratory ascertained figures could be larger still.

We used the SMR for co-morbidity data, while shown to be an accurate source for populations studies, will have excluded those who have avoided hospital admissions in the previous 10 years.(243)

Another issue with the SMR may be its propensity to underreport more ‘minor’ health conditions as it is only limited to six codes per admission and in our cohort with high levels of co-morbidities, the prevalence of hypertension appears underrepresented at around 40% compared to the 70% prevalence reported by Methven et al. in a cohort of 411 CKD patients sampled form this same population.(202) Otherwise, the reported prevalence of diabetes and CHD for this CKD cohort was not dissimilar to that of a CKD cohort from a neighbouring health board.(244)

The population make-up of our cohort was predominantly Caucasians (98.84% white from the 2011 national census) from the west of Scotland and so may not be generalisable to other parts of the UK with a higher proportion of ethnic minorities.(198)

7.10 Future studies

In this thesis the complex association between SES and CKD was examined. It is not yet clear how low SES affects health, or even how much of ill health and the experience of it that perpetuates lower SES. In chapter four, SES disparities may be associated with a higher burden of co-morbid conditions, but this is largely offset by having unimpeded

access to health care. Low SES is increasingly associated with low HL, and it may be that HL is a mediator for higher disease prevalence and poorer outcomes.(184, 185, 293) Any future work should examine the complex interaction between HL, SES with healthcare provision and its effect on perceived health and clinical outcomes in CKD.

The data already exists for using routinely collated data to inform clinical practice for our specific patient population. This approach could also be utilised for other drugs, real-time pharmacovigilance as well as other, non-drug therapies. A well linked database can also enhance trial recruitment and monitoring with the appropriate data governance oversight and patient participation in its development.

7.11 Implementation into clinical practice

AKI e-alerts are already in place or are being rolled out in many health trusts nationally.(294, 295) The poor outcomes associated with AKI is well described, with accurate and timely recognition potentially affecting clinical outcomes.(296) Similarly in CKD, targeted therapies improve QOL, morbidity and mortality and so the ability to accurately identify these individuals at risk should be considered a clinical priority on par with inpatient AKI e-alerts. In this thesis, both the feasibility and practicalities of introducing laboratory ascertainment of CKD in the community as well as the potential public health benefits of such a system have been demonstrated.

An example of such a system in use is the HQIP National CKD Audit.(316) This quality improvement programme aims to improve the accuracy of disease coding in PCP in England and Wales. Of an estimated 5.8% population prevalence of CKD 3-5, only 4.2% were accurately coded. Uncoded cases resulted in an electronic prompt to the PCP. This audit also demonstrated an association between uncoded CKD with higher rates of adverse outcomes including hospital admissions, intensive care unit admissions, CV events and mortality. It is important to note that this audit only relied on GP records for the diagnosis of CKD, and as demonstrated by chapters 2 and 3, would result in under ascertainment by not including serum creatinine testing conducted in secondary care.

Any future IT health record programme should also aim to incorporate the linkage of relevant datasets, for example diagnostic codes from multiple sources to improve accuracy and completeness, prescription and dispensing data, and other clinically relevant data such as BP measurements or smoking status. In the many healthcare interactions that an

individual currently has with the NHS, this data is already being routinely collated but often accumulates in virtual silos with little or no interoperability due to a lack of data sharing, IT infrastructure and an overarching information governance structure.

Surveys highlight the public's appetite and expectation that healthcare data is used to improve care.(297) The majority of people surveyed were happy for electronic health records to record patient identifiable data and also for these records to be used for identifying and contacting individuals for health screening.(298) Also, most do not view the inclusion of patient identifiable data into disease registries as an invasion of privacy, if the purpose was for improving care.(299) A consistent theme in surveys, highlighting the fears of the public, is regarding the potential for security and confidentiality breaches of their sensitive data.(300) In general, public support for research that involves data sharing and linkage is high as long as this work leads to actual or potential public benefits, with the caveat that adequate oversight and data guardianship measures are in place.(301)

At present, the data generated by human activity is increasing exponentially. The technology giant IBM, stated in 2013 that "90% of the data in the world today was created in the last two years".(302) The generation of this vast amount of data has been termed 'big data' and is constantly being harvested and utilised for: marketing, scientific research, logistics, product design, business operations, crime reduction and is rapidly driving societal change. Thus, it is imperative that the vast amounts of routinely collated healthcare data in a large organisation such as the NHS is utilised to its full potential to improve the efficiency and accuracy of service delivery in an environment with increasingly constrained resources. This would represent a paradigm shift from the current piecemeal use of data within the NHS.

7.12 Conclusions

Throughout this thesis the aim was to demonstrate the feasibility of large scale, automated diagnosis of CKD stage 3 – 5 and its ability to inform clinical care, utilising data that already exists within the NHS. This can be done with little investment or change to existing laboratory systems. A novel algorithm for identifying individuals with CKD was developed to address a major weakness of laboratory ascertainment of CKD, the determination of chronicity of an individual's reduced eGFR.

Lab ascertainment is superior to current QOF CKD registers and found 7% more cases than the QOF reported for the same period and the discrepancy could be higher still. SES and rurality effects CKD prevalence over and above age and gender. However, SES was not a strong predictor of lower eGFR or poorer outcomes, contrary to received wisdom.

Statin dispensing in CKD fell by 5% over a three-year period from 2011 to 2012 despite strengthening evidence base for its use. CKD patients dispensed a statin demonstrate an association with lower all-cause mortality in primary and secondary prevention even in the elderly (≥ 76 years) who are unlikely to be enrolled in drug trials. This approach can and should be integrated into clinical systems to regularly yield clinically meaningful insights and improve care.

Publications and presentations

Publications containing work undertaken for this thesis

Socio-economic status influences chronic kidney disease prevalence in primary care: a community-based cross-sectional analysis.
So BH, Methven S, Hair MD, Jardine AG & MacGregor MS.
Nephrology Dialysis Transplantation 2015, vol 30(6), pp. 1010-1017
https://doi.org/10.1093/ndt/gfu408

Presentation to learned societies of work undertaken for this thesis

Statins for primary or secondary prevention improves survival in CKD 3 to 5.
So BH, Blackwell S, Hair MD, Jardine AG & MacGregor MS.
Poster presentation, American Society of Nephrology, November 2014:

Socio-economic status influences survival in CKD.
So BH, Traynor JP, Hair MD, Jardine AG & MacGregor MS.
Poster presentation, American Society of Nephrology, November 2014.

Statins for primary or secondary prevention improves survival in non-dialysis CKD 3 to 5.
So BH, Blackwell S, Hair MD, Jardine AG & MacGregor MS.
Awarded the best medical oral abstract, Royal College of Physicians Edinburgh and Scottish Renal Association Joint Symposium, September 2014.

The lipid profiles and treatment of CKD patients. A community base cohort study.
So BH, Blackwell S, Hair MD, Jardine AG & MacGregor MS.
Poster presentation, European Renal Association-European Dialysis and Transplantation Association, May 2014.

Socio-economic deprivation influences survival and eGFR.
So BH, Traynor JP, Hair MD, Jardine AG & MacGregor MS.
Oral presentation, Joint Renal Association and British Renal Society UK Kidney Week, May 2014.

Understanding variation in CKD prevalence amongst Scottish Health Boards.
So BH, Methven S, Hair MD, Jardine AG & MacGregor MS.
Poster presentation, American Society of Nephrology, November 2013.

Improving Ascertainment of chronic kidney disease with laboratory-based case finding
So BH, Methven S, Hair MD, Jardine AG & MacGregor MS.
Poster presentation, European Renal Association-European Dialysis and Transplantation Association, May 2013.

Appendices

Appendix 1: Scottish Index of Multiple Deprivation (SIMD) domains in detail.

Income Domain:

Count or proportion of people defined as income deprived. This is a combined count of claimants on the following benefits:

- Adults and Children in Income Support (IS) or Income-based Employment and Support Allowance Households;
- Adults and Children in Job Seekers Allowance (JSA) households;
- Adults in Guarantee Pension Credit Households;
- Adults and Children in Tax Credit Households on low incomes.

Each person will only be counted once.

Employment Domain:

Count or proportion of people defined as employment deprived. This is a combined count of claimants on the following benefits:

- Working Age Unemployment Claimant Count averaged over 12 months;
- Working Age Incapacity Benefit claimants, or Employment and Support Allowance recipients;
- Working Age Severe Disablement Allowance claimants.

Each person will only be counted once.

Crime Domain:

Rate of recorded crime taken from the following:

- Recorded Crimes of Violence;
- Recorded Sexual Offences;
- Recorded Domestic housebreaking;
- Recorded Vandalism;
- Recorded Drugs Offences;
- Recorded Common Assault.

Sum of the recorded crimes/offences in each of the above indicators.

Education Domain:

The Education Domain gives an education deprivation rank using the following indicators:

- School pupil absences;
- Pupil performance on SQA at stage 4;
- Working age people with no qualifications;
- 17-21 year olds enrolling into higher education;
- People aged 16-19 not in education, employment or training.

Health Domain:

The Health Domain gives a Health deprivation rank using the following indicators:

- Standardised Mortality Ratio;
- Hospital stays related to alcohol use;
- Hospital stays related to drug use;
- Comparative Illness Factor;
- Emergency stays in hospital;
- Estimated proportion of population being prescribed drugs for anxiety, depression or psychosis;
- Proportion of live singleton births of low birth weight.

Housing Domain:

The Housing Domain uses rates for the following:

- Persons in households without central heating;
- Persons in households that are overcrowded.

To calculate housing deprivation.

Geographical Access to services Domain:

This indicator is intended to capture the issues of financial cost, time and inconvenience of having to travel to access basic services and uses the population weighted average drive time in minutes as a measure of geographical access to services. This is based on

- drive time to: GPs, shopping facilities, a petrol station, schools and a post office and
- public transport time to GPs, a post office and to shopping facilities.

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