BMJ Open

Associations and mitigations: an analysis of the changing risk factor landscape for chronic kidney disease in primary care using national general practice level data

Mike Stedman,[1] Adrian Heald ,[2,3] Adam Robinson,[2] Mark Davies ,[1] Patrick Harnett[4]

To cite: Stedman M, Heald A, Robinson A, *et al*. Associations and mitigations: an analysis of the changing risk factor landscape for chronic kidney disease in primary care using national general practice level data. *BMJ Open* 2022;**12**:e064723. doi:10.1136/bmjopen-2022-064723

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-064723).

Received 23 May 2022
Accepted 08 November 2022

[1]Res Consortium, Andover, UK
[2]University of Manchester, Manchester, UK
[3]Department of Diabetes and Endocrinology, Salford Royal Hospital, Salford, UK
[4]Department of Renal Medicine, Princess Elizabeth Hospital, Saint Andrews, Guernsey

Correspondence to
Dr Adrian Heald;
adrian.heald@manchester.ac.uk

ABSTRACT

Objectives Early recognition of chronic kidney disease (CKD) should be achieved by every modern healthcare system. The objective of this study was to investigate CKD risk factor trends in England using general practice level data.

Design Observational analysis of data at practice level for all general practices in England. Practice characteristics identified as potential CKD risk factors included comorbidities and local demography. Data were analysed using both univariate and multivariate analysis to identify significant factors that were associated with CKD diagnosis for the period 1 April 2019 to 31 March 2020.

Setting Publicly available data from UK primary care sources including Primary Care Quality and Outcomes Framework database, practice-level prescribing data from the British National Formulary and Public Health England health outcome data.

Participants All data submitted from 6471 medium to large practices in England were included (over 46 million patients).

Risk factor analysis Potential risk factors were grouped into four classes based on existing literature: demographic factors, comorbidities, service and practice outcome factors, and prescribing data effects.

Results The original model's prediction of CKD improved from r^2 0.38 to an r^2 of 0.66 when updated factors were included. Positive associations included known risk factors with higher relative risk such as hypertension and diabetes, along with less recognised factors such as depression and use of opiates. Negative associations included NSAIDs which are traditionally associated with increased CKD risk, and prescribing of antibiotics, along with more northerly locations.

Conclusions CKD is a preventable disease with high costs and consequences. These data and novel analysis give clearer relative risk values for different patient characteristics with some unexpected findings such as potential harmful association between CKD and opiates, and a more benign association with NSAIDs. A deeper understanding of CKD risk factors is important to update and implement local and national management strategies. Further research is required to establish the causal nature of these associations and to refine location appropriate actions to minimise harm from CKD on regional and local levels.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study looks at large, high-quality data and demonstrates some important novel associations between risk factors and the prevalence of chronic kidney disease (CKD). Causation and the mechanism behind these associations cannot be stated as this is an observational study.
⇒ Guidelines and common practice dictate that these drugs should be avoided in patients with CKD, implying fewer prescriptions will appear in practices with high levels of CKD.
⇒ Analysis was of national cross-sectional prescribing data, permitting an estimate of the point prevalence of comorbidities and risk factors. This is at general practice not individual patient level. The cross-sectional analysis of individual practices makes it more likely that confounding variables not measured could affect the outcome (eg, different prescribing practices).
⇒ More prescriptions may be seen in practices with lower proportions of CKD and may explain some of the apparent 'protective' effect suggested by the regression analysis
⇒ Disaggregation of some risk factors such as diabetes and obesity was not possible due to the nature of the data.

INTRODUCTION

Chronic kidney disease (CKD) is common in the UK.[1] The CKD prevalence model provides estimates of total CKD prevalence for adults aged 16 and over in England.[1] Estimates of prevalence for all CKD (mild to severe, stages 1–5) is 14% in males and 13% in females. Moderate-to-advanced stage CKD (stages 3–5) is estimated at 6% and advanced

disease (stages 4 and 5) in 0.15% of the adult population.[2 3] The incidence of CKD increases with age and with multimorbidity. The most frequent cause of dialysis-dependant CKD in the UK is diabetes, with hypertension and vascular disease also related to high proportions of dialysis-dependent disease.[4] Overall, a small proportion of people with CKD will progress to require renal replacement therapy (RRT), with most patients with CKD not reaching the degree of severity to require dialysis or transplantation.[5]

Treatment of advanced CKD is expensive and associated with complications, reduced quality of life and decreased life expectancy.[6] There is a large body of evidence showing that many forms of CKD respond to treatments which reduce progression of CKD.[7 8] Early recognition is therefore potentially beneficial to individuals with an increased lifetime risk of developing advanced CKD. Conventional models for prediction of CKD rely mainly on age, laboratory tests and comorbidity.[9] Guidance on which individuals to target for CKD screening and monitoring is based on these measures.[10]

National-level data in England regarding primary care management and prescribing practices are routinely collected in addition to comorbidity. Numerous commonly used medications are associated with increased risk of CKD. For example, non-steroidal anti-inflammatory drugs (NSAIDs) are known to have adverse effects on kidney function. The UK 2014 National institute of Clinical Excellence (NICE) guidance on CKD advises that NSAIDs should be considered when making decisions about monitoring of CKD, and that caution should be exercised in their use in patients with CKD.[10]

The chronic renal insufficiency cohort (CRIC) study[11] examined and quantified the strength of associations between the use of opiate analgesics and NSAIDs in patients with established CKD in a large, multicentre, long term follow-up study of patients with CKD. The study was conducted in the USA, where the opiate epidemic has resulted in large scale adverse health outcomes. More adverse renal outcomes were strongly associated with opiate use with a weak association at subgroup level with NSAIDs.

No such study has previously been conducted in the UK. Consideration of additional parameters that may have effects on development and outcome in CKD, such as analgesic use, could benefit and refine predictive models. The aim of this study was to examine medical data systematically collected in primary care in England to establish strength and magnitude of association of recorded medical data items in existing registries. Specific data items included CKD recorded in primary care quality outcome data, demographic data, public health data and practice-level prescribing data. These data were analysed to demonstrate the level of association between a range of potential risk factors for CKD and the practice-level records of incidence of CKD.

METHODS

Local data were analysed at practice level for general practices in England that had submitted information for more than 1000 patients into the Quality and Outcomes Framework (QOF) data set. No individual patient data were accessed, and the aggregated data were publicly available, so ethics committee approval was not sought for the study. Patient and public involvement in terms of the analysis done was also deemed not to be required.

CKD was defined as estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m^2. Social deprivation was defined using the Index of Multiple Deprivation (IMD). Data were collected for the year 1 April 2019–31 March 2020 from the following sources:

a. *QOF*[12]—the QOF is an incentivised voluntary scheme for primary care in the UK that aims to support primary care practitioners to deliver good quality care by collecting and publishing data relating to medical conditions in primary care in the UK.
b. *Public Health England (PHE) Fingertips*[13]—this is a web-based platform that provides easy access to indicators across a range of health and well-being topics. Data in Fingertips are organised into thematic practice demographics (age, gender, ethnicity) obtained from the online resource provided by PHE.
c. *Prescribing in general practice*—by each British National Formulary (BNF) code[14] which distinguishes between the various prescribed agents. Average prescriptions per patient were calculated using the total annual average daily quantities per person by therapy.
d. *Expected CKD prevalence* was taken by applying the factors from the 2014 PHE model[1] to patient numbers in practices by age and sex.

Potential risk factors for CKD were grouped into four classes based on existing literature:

- *Demographic factors*—including:
  - Age and sex were incorporated by calculating expected CKD by applying the PHE prevalence model.
  - Latitude and longitude of the GP practice (GPP) defined by north/south and east/west.
  - % population from minority (non-white) ethnic groups was taken from the GPP patient survey.
  - Level of urban/rural type was evaluated as the population density in thousands/square kilometre local to the GPP.
  - Deprivation score for the practice calculated using IMD 2019 data.
  - % Age>16 recorded as smoking.
  - Population % body mass index (BMI)>30 for age 17+.
- *Comorbidities*—including:
  - Local long-term health conditions and comorbidities.
  - Local level of CKD taken as percentage of patients aged 18 or over with reported classification of CKD categories G3a to G5 (an eGFR<60 mL/min/1.73 m^2).

  - For hypertension, depression, asthma, diabetes, coronary heart disease, cancer, atrial fibrillation, chronic obstructive pulmonary disease, heart failure, dementia the reported practice % prevalence in the QOF was used.
- *Service performance context* —which reflected the wider performance including outcomes achieved by the practice and local hospital, including:
  - Involvement of local people in the process/priority given to CKD was estimated by calculating the average identification of CKD in the local health economy (CCG) as measured by the total actual register (excluding the practice being evaluated) divided by the total expected age/sex model prevalence.
  - Patient experience from national GPP surveys taken as the % reporting 'Overall Good Experience'.
  - Patient confidence in long-term condition management taken from national GPP surveys as % reporting that were 'Confident'.
  - Control of blood pressure taken from QOF hypertension as % BP within reference range (controlled hypertension was defined as BP of<150/90 mm Hg).
  - The control of diabetes was taken from the National Diabetes Audit for type 2 diabetes as % of last HbA1c results<58 mmol/mol.
- *Medication*—the use of selected medication classes that could have significant renal impact both protective and impairing were included by evaluating the number of prescriptions issued divided by the adult population, including:
  - Lipid regulating (BNF 2.12).
  - ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) (BNF 2.5.5).
  - Proton-pump inhibitors (PPIs) (BNF 1.3.5).
  - Drugs used in diabetes (BNF 6.1).
  - Antibacterial drugs (BNF 5.1).
  - Opiate analgesics (BNF 4.7.2).
  - NSAID BNF 10.1.1.

Patient and public involvement

There was no patient involved.

Statistics

The analysis was carried out on MS Excel using the *Analyse-it* add-in. Multivariate cross-sectional analysis of the local GPP data was carried out with target outcome taken as the % of CKD and then stepwise removing factors, with highest p value ranked until all p values were below 0.05. This was first done for the factors within each class and once again over all the factors combined. Finally, the effect of local advocacy was highlighted by running the model without that factor. As renal damage is cumulative over a long time period an assumption was made that current levels reflect historical exposure to risk factors.

RESULTS

Six thousand four hundred seventy-one general practices with practice patient lists were included in the analysis as these had both data for all the items required along with>1000 patients submitted. This patient number threshold was used in order to reduce the effect of potential outliers which could occur if practices with smaller list numbers were included. These practices supported a total population of 46 958 680 equivalent to 81% of the total England population, with a reported total of 1 898 427 patients on their chronic disease register defined as patients aged 18 or over with CKD classification of categories G3a to G5 (an eGFR<60 mL/min/1.73 m^2).

The average and SD plus median and quartile values are given for factors used in table 1. The level of spread in each factor is indicated by showing the IQR as % of median. The change in overall prevalence recorded in QOF for the various conditions versus 2010 value (=100) (figure 1) suggested that although prevalence of many disorders increased from 2010 to 2020, the prevalence of CKD remained relatively stable.

When the actual values were linked to the predicted values based on the public health age and gender prevalence model, the overall average identification was 71% and the r^2 was 0.38 suggesting that many sources of variation in CKD are not being captured within the model (figure 2A). However, with the addition of the 22 factors identified to the model, the r^2 increased to 0.66. Positive and negative associations with CKD included:

Positive association—CKD local priority, expected CKD prevalence, hypertension prevalence, heart failure prevalence, use of BNF 2.12: lipid-regulating drugs, diabetes prevalence, depression prevalence, dementia prevalence, atrial fibrillation prevalence, cancer prevalence, obesity.

Negative associations—use of BNF 4.7.2: opioid analgesics, east/west location, blood pressure control in hypertension, HbA1c control in diabetes, use of BNF 10.1.1: NSAIDs, level of smoking, use of BNF 1.3.5: PPIs, use of BNF 5.1: antibacterial drugs, north/south location, use of BNF 6.1: drugs used in diabetes.

The prescribing rates for the principal agents are given below in table 2. The most commonly prescribed agents were atorvastatin, ramipril, omeprazole and metformin.

The r^2 value gives an indication of the amount of variation being captured and the standard beta values give the relative impact of each factor. By including the expected value based on age and gender this allowed for a profile of the basic population mix within each practice.

Including demographic factors with an overall model r^2 of 0.48 (figure 3A) the strongest association was with obesity, while other factors such as ethnicity, urban/rural living did not show significant association to levels of CKD. For comorbidities, the model showed an overall r^2 of 0.52 (figure 3B), while heart failure, hypertension and atrial fibrillation all had strong positive associations with recorded prevalent CKD.

For medication and service factors with an overall r^2 of 0.56 (figure 3C), association with lower QOF register

Table 1 General practitioner (GP) practice measures applied within analysis and values for 2019–2020

Measure	Metric	Class	Note	Mean	SD	Median	25%ile	75%ile	IQR % Median
General practitioner practice (GPP) size	Total list	Size	1	7257	4805	6319	4042	9247	82%
Chronic kidney disease (CKD) prevalence	Register % GPP list	Outcome	2	4.1%	2.0%	4.1%	2.6%	5.3%	65%
Expected CKD prevalence	PHE model age by sex	Location	3	5.2%	1.7%	5.2%	4.0%	6.3%	45%
North/south	GPP location latitude	Location	2	52.42	1.13	52.42	51.50	53.42	4%
East/west	GPP location longitude	Location	2	–1.21	1.20	–1.21	–2.10	–0.20	–158%
Ethnicity	% Minority ethnicity	Location	4	14	8.61	14	0.05	0.38	232%
Urban/rural	GPP local population density	Location	2	4221	4156	4221	1251	5623	104%
Deprivation	Location IMD 2019 score	Location	4	23	12	23	14	30	70%
Smoking	Smoking % age>16	Location	2	16.6%	5.7%	16.6%	12.4%	20.0%	46%
BMI	Population BMI>30% age 17+	Location	2	10.9%	4.0%	10.9%	8.2%	13.3%	47%
Hypertension	GPP register % GPP list	Health	2	18.1%	4.6%	18.1%	15.7%	20.9%	29%
Depression	GPP register % GPP list	Health	2	11.5%	4.4%	11.5%	8.5%	14.0%	48%
Asthma	GPP register % GPP list	Health	2	8.2%	1.9%	8.2%	7.2%	9.4%	27%
Diabetes	GPP register % GPP list	Health	2	7.5%	2.3%	7.5%	6.3%	8.6%	30%
Coronary heart disease	GPP register % GPP list	Health	2	4.0%	1.3%	4.0%	3.1%	4.8%	43%
Cancer	GPP register % GPP list	Health	2	3.9%	1.4%	3.9%	2.9%	4.9%	51%
Atrial fibrillation	GPP register % GPP list	Health	2	2.5%	1.1%	2.5%	1.7%	3.3%	61%
Chronic obstructive pulmonary disease (COPD)	GPP register % GPP list	Health	2	2.5%	1.2%	2.5%	1.7%	3.2%	62%
Heart failure	GPP register % GPP list	Health	2	1.1%	0.5%	1.1%	0.8%	1.4%	57%
Dementia	GPP register % GPP list	Health	2	1.0%	0.9%	1.0%	0.6%	1.2%	65%
CKD local priority	CCG % CKD identification	Service	2	62.9%	14.1%	62.9%	53.5%	69.6%	25%
Patient experience	GPP survey % good experience	Service	3	83.2%	8.4%	83.2%	78.4%	89.3%	13%
Long-term condition patient confidence	GPP survey LTC % confident	Service	3	83.5%	9.9%	83.5%	77.6%	90.9%	16%
Blood pressure control	Hypertension % BP in control	Service	2	75.5%	7.5%	75.5%	70.7%	80.7%	13%
HbA1c control	NDA T2 Hba1c % <58	Service	5	66.3%	5.9%	66.3%	62.5%	70.2%	12%
BNF 2.12: lipid regulating	Prescriptions/GPP list	Medication	6	1.32	0.54	1.32	0.94	1.65	54%
BNF 2.5.5: ACEI and ARB	Prescriptions/GPP list	Medication	6	1.12	0.45	1.12	0.80	1.39	53%
BNF 1.3.5: proton-pump inhibitors	Prescriptions/GPP list	Medication	6	1.07	0.44	1.07	0.75	1.35	56%
BNF 6.1: drugs used in diabetes prescriptions	Prescriptions/GPP list	Medication	6	0.99	0.39	0.99	0.74	1.18	45%
BNF 5.1: antibacterial drugs	Prescriptions/GPP list	Medication	6	0.48	0.15	0.48	0.40	0.57	36%

Continued

Table 1 Continued

Measure	Metric	Class	Note	Mean	SD	Median	25%ile	75%ile	IQR % Median
BNF 4.7.2: opiate analgesics	Prescriptions/GPP list	Medication	6	0.38	0.23	0.38	0.21	0.50	75%
BNF 10.1.1: NSAID	Prescriptions/GPP list	Medication	6	0.18	0.08	0.18	0.12	0.22	58%

1 Practice list by age and sex/2 Quality and outcomes framework 2020/3 PHE CKD prevalence/4 Fingertips GP practice data/5 National Diabetes Audit (NDA)/6 GPP Prescribing Monthly.
ACEI, ACE inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BNF, British National Formulary; NSAID, non-steroidal anti-inflammatory drugs; PHE, Public Health England.

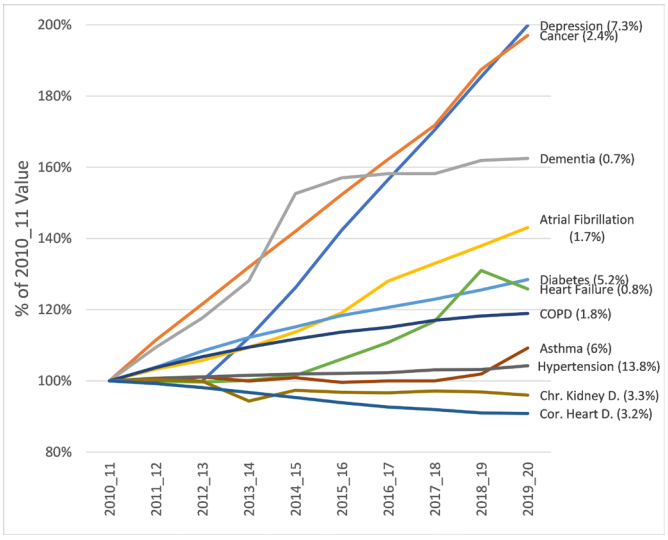

Figure 1 Overall prevalence by major disease register in Quality and Outcomes Framework over last 10 years highlights that while the population has been ageing the chronic kidney disease register has not been increasing. COPD, chronic obstructive pulmonary disease.

recording of CKD was seen with prescription of NSAIDs and a higher rate with prescription of ACEIs/ARBs, with a lower rate of CKD recorded with prescription of PPIs.

In the final regression model (figure 4), an r^2 of 0.66 for all factors taken together was demonstrated with an independent relation being found between prioritisation of CKD by the local CCG and prevalent CKD, with opiate prescribing and greater levels of obesity also positively associated. Prescription of PPIs was negatively associated with CKD prevalence.

DISCUSSION

Recorded levels of CKD in English national primary care registers (QOF) vary with age, comorbidity, prescribing practice and primary care quality markers.[1] The multivariate regression analysis described in this paper evaluated a broad variety of factors that are potentially associated with CKD recording rates, including those less expected such as obesity and the negative association with NSAID prescribing, with an intriguing lower rate of CKD recording in practices using more PPIs. Current smoking status was associated with higher rates of recorded CKD—this does not take into account the effects of previous cigarette consumption on current renovascular disease.

Of note is that not all factors analysed in the study were 100% independent of each other. However, the stepwise regression analysis mitigates against this to some extent by identifying factors with most significant impact and allocate marginal effects to the other factors.

The QOF register analysis over time showed no overall change in the quantity of recorded CKD over the 10-year interval from 2010 (figure 1). Paradoxically, the numbers of patients in the UK requiring RRT over a similar period increased from 47525 at the end of 2008[15] to 66612 at

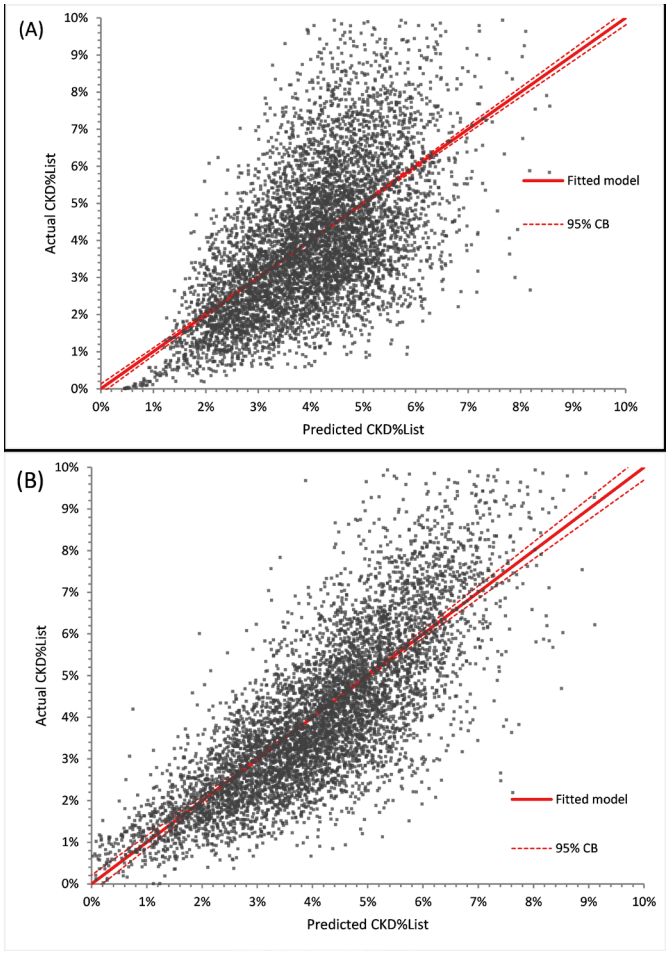

Figure 2 (A) Link between public health age and sex chronic kidney disease (CKD) model prediction and actual registered CKD R2=0.38. (B) Link between CKD model prediction updated in this paper to include the final demographic, comorbidity, medication and service factors as listed in figure 4 and actual registered CKD model R2=0.66.

the end of 2018[4]—an overall increase of 40% over a similar period. Despite the stability or even slight decline in recorded CKD cases in primary care, the absolute numbers of patients receiving intervention for advanced CKD has increased substantially, with consequent effects on survival, quality of life and healthcare resources. Therefore, although absolute numbers of patients with CKD may have declined slightly, the subset of severe CKD including those patients that require intervention has increased substantially due either to greater absolute levels of severity of CKD, and/or lower thresholds for treatment.

The strongest associations with recorded CKD were seen for age, hypertension, heart failure and atrial fibrillation (figure 3B). These are well recognised risk associations with CKD and advice regarding screening and management is embedded in UK CKD NICE guidelines[16] on management and screening. Adjustment of frequency of monitoring for CKD through eGFR is also recommended in patients that take NSAIDs.[16] Such detailed data can be of use to commissioners and providers of healthcare to implement and measure the effectiveness of preventative strategies. An important note here is that in relation to the years leading up to the study period, the use of GLP-1 agonists and SGLT2-inhibitors was relatively low and not materially impactful. This theme will be the subject of a subsequent analysis.

NICE CKD guidance specifically states that obesity in the absence of diabetes or the metabolic syndrome should not be used as an indication to test for eGFR.[16] Obesity is a major public health problem worldwide, and is increasingly recognised as an independent risk factor for the development of CKD.[17] Projections for prevalence levels of obesity in the USA are that 30% of adults will be obese by the year 2030. New therapeutic options for obesity include lifestyle measures, pharmaceutical agents and surgery.[18] The prevalence of patients with a high BMI is rising. The QOF register used in this analysis estimates the total number of patients with a BMI of over 30 as 4.8 million. With a beta value of 0.1 for this highly prevalent risk factor, this indicates that 185 000 patients will develop CKD with obesity as a contributing factor. This suggests that obesity management should become an important focus for prevention and treatment of CKD.

In the final regression analysis, the proportion of people with HbA1c≤58 mmol/mol (≤7.5%) was associated with a higher recorded rate of CKD at GPP level, while the proportion of people over the age of 15 recorded as smokers was independently associated with a lower rate of recorded CKD. This may relate to the way that some practices are more efficient at recording details of individual patient medical histories. This phenomenon was intepreted as a proxy marker for the organisational efficiency of an individual practice as is the proportion of people at target blood glucose control.[19 20] Also current smoking status does not take into account the effects of previous cigarette consumption on current renovascular disease.

Patients with CKD often have other illnesses and frequently require analgesic medication. Guidelines urge caution with the use of NSAIDs in CKD.[10] A small but significant beneficial effect in reduced QOF levels of CKD recording was seen in association with higher use of NSAIDs. This may relate to the fact that NSAID use should be avoided in people with significant CKD where possible. NSAIDs are linked to adverse effects on renal function.[21 22] A Cochrane collaboration analysis of outcomes of NSAIDs in specific clinical scenarios (post surgery) did not demonstrate clear evidence of harm,[23] while the large scale CRIC Study analysed associations with NSAID use and renal outcomes in patients with established CKD and found possible protective effects in some subsets and some harm in other groups[11] which accords with findings in this study.

The reported association here between higher PPI prescribing at GPP level and lower recorded CKD (figure 3D and figure 4) differs from reports from the atherosclerosis risk in a community study of an associated higher risk of prevalent CKD with PPI prescribing.[24]

Table 2 Total prescriptions and average medication classes included and top 5 agents within each class and number of practices prescribing

Class and agent	Used in practices	Prescriptions issued	Average daily quantity
BNF 2.12: lipid-regulating (statin) total	**6471**	73 857 463	**3 001 334 710**
Atorvastatin	6471	45 194 000	2 131 360 329
Simvastatin	6470	20 472 070	642 169 739
Rosuvastatin calcium	6461	2 530 023	78 430 469
Pravastatin sodium	6444	2 430 463	59 981 766
Ezetimibe	6448	1 805 262	58 051 080
BNF 2.5.5: ACEI and ARB Total	**6471**	63 352 565	**2 479 790 466**
Ramipril	6471	28 480 214	1 010 158 662
Losartan potassium	6471	10 083 813	413 543 173
Lisinopril	6469	8 291 249	335 655 523
Candesartan cilexetil	6469	6 922 000	319 055 828
Perindopril erbumine	6454	4 189 707	173 755 891
BNF 1.3.5: proton-pump inhibitors total	**6471**	60 951 098	**2 437 454 659**
Omeprazole	6471	31 165 710	1 143 830 363
Lansoprazole	6471	26 123 691	1 109 573 251
Esomeprazole	6441	2 024 323	120 463 411
Pantoprazole	6387	1 294 327	49 938 514
Rabeprazole sodium	5330	342 898	13 649 120
BNF 6.1: drugs used in diabetes total	**6471**	54 991 271	817 078 827
Metformin hydrochloride	6471	21 702 077	651 797 145
Gliclazide	6470	6 478 722	213 956
Glucose blood testing reagents	6471	6 406 935	
Sitagliptin	6438	2 349 731	58 603 534
Linagliptin	6379	2 101 797	NA
BNF 5.1: antibacterial drugs total	**6471**	27 996 867	169 264 544
Amoxicillin	6471	6 668 919	98 717 127
Nitrofurantoin	6470	3 715 981	1996
Flucloxacillin sodium	6470	3 291 202	NA
Doxycycline hyclate	6471	2 856 834	38 509 595
Phenoxymethylpenicillin (penicillin V)	6471	1 887 395	Not available
BNF 10.1.1: NSAID total	**6471**	10 159 089	271 424 296
Naproxen	6471	6 509 904	216 354 819
Ibuprofen	6467	1 480 953	2 414 740
Diclofenac sodium	6391	516 036	6 268 739
Meloxicam	5519	467 625	25 341 612
Etoricoxib	6019	375 068	10 846 381
BNF 4.7.2: opiate analgesics total	**6471**	22 061 797	101 173 320
Tramadol hydrochloride	6468	5 762 921	15 403 063
Morphine sulfate	6465	4 823 795	14 987 228
Codeine phosphate	6469	4 725 190	2 217 533
Buprenorphine	6438	2 231 007	28 845 280
Oxycodone hydrochloride	6415	1 698 176	9 285 385

ACEI, ACE inhibitors; ARB, angiotensin II receptor blockers; BNF, British National Formulary; NSAID, non-steroidal anti-inflammatory drugs.

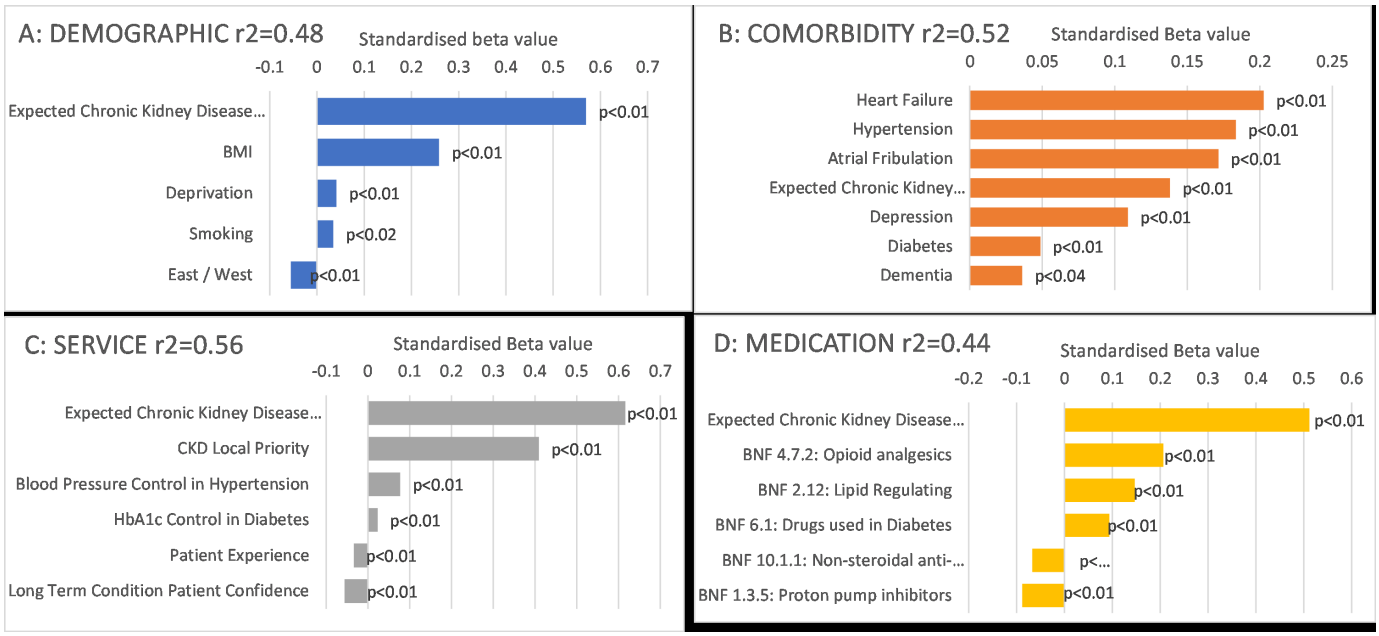

Figure 3 Multiple regression across the factors under the four classes. BMI, body mass index; BNF, British National Formulary; CKD, chronic kidney disease.

Furthermore, in an observational cohort of patients with established CKD, PPI use was associated with progression to major adverse renal events.[25]

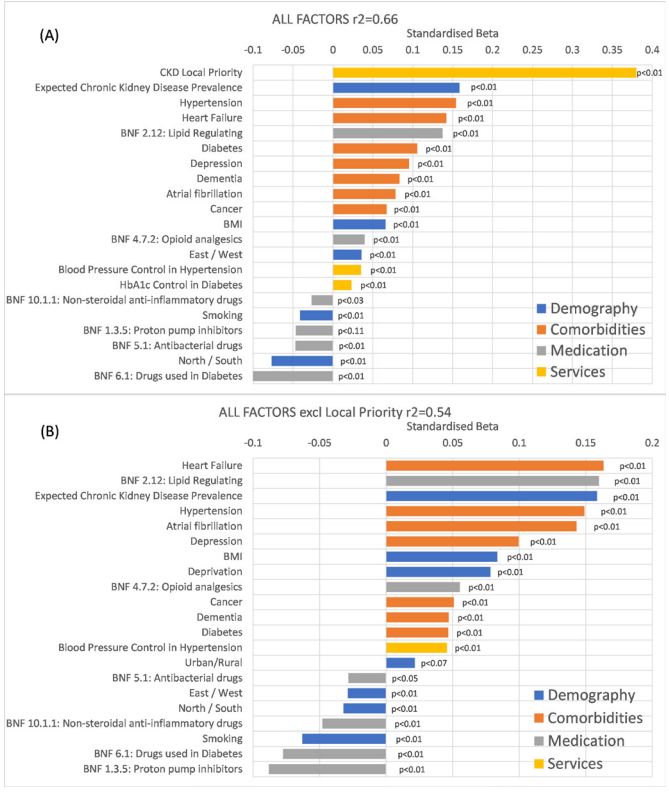

Figure 4 Multiple regression analysis to include (A) all factors significantly related to reported local prevalence chronic kidney disease (CKD). (B) All factors excluding local advocacy/priority. BMI, body mass index; BNF, British National Formulary.

The opiate epidemic in the USA was recognised as a public health emergency by the US Department of Health and Human Services in 2017. In 2019, they estimated the number of deaths attributable to opiate overdose in the USA at 70 630.[26] The CRIC study examined the association between use of opiate analgesics and adverse effects in patients with existing CKD. The relative risk for adverse outcomes with opiate use was greater in CKD when compared with use of NSAIDs, which accords with our findings here. Our regression analysis demonstrates an association between opiate use and quantity of recorded CKD on the QOF register. Opiates are widely prescribed in the UK and the quantity of opiate prescription in the UK has increased over time.[27] The size and severity of opiate misuse have not reached the proportions seen in in the USA. Detailed recent analysis of opiate prescription at practice level demonstrated 2 million new prescriptions of opiates in patients without cancer in the UK over a 12-year period, with 14% of this group becoming long-term users.[28]

Estimates from our analysis put the amount of CKD that may be associated with opiate use as 91 000 patients. Inclusion of opiate use in this analysis improves the explanatory power and predictive value of this analysis. This effect was independent of comorbidity, demographics and other potential confounding factors (figure 4) which implies a direct nephrotoxic effect of opiates. Such direct effects of opiates and their metabolites have been demonstrated on the kidney in animal models.[29] Toxic effects of opiates and their metabolites on cellular components of the kidney (glomerular mesangial cells), and increased renal fibrosis have also been demonstrated in vitro and in vivo.[30] The proposition that opiates have a direct adverse effect is supported by this analysis and other observational data,

with these medications potentially contributing significantly to the burden of CKD nationally if not prescribed appropriately.

We accept that the current study design is different from the CRIC study.[11] Specifically, we have looked at the outcome of recorded CKD and not incident CKD or end-stage kidney disease. Furthermore, this is not a prospective study but a cross-sectional analysis of individual practices which makes it more likely that confounding variables not measured could affect the outcome (eg. different prescribing practices). Finally, some of the findings which contradict current literature such as lower recorded CKD with higher NSAID use and higher tobacco use, and higher recorded CKD with better blood glucose control are here attributed to differences in recording at practice level or practice patterns such as avoidance of NSAIDs in patients with CKD. The same could be said about opiates as well as clinicians are more likely to use them for pain control rather than NSAIDs if a patient has CKD.

CONCLUSION

CKD is a preventable disease with high costs and consequences. These data and novel analysis give clearer relative risk values for different patient characteristics with some unexpected findings such as a positive CKD risk associations with opiates and depression, and a more benign association with NSAIDs, antibiotic prescribing and living further north. A deeper understanding of CKD risk factors is important to update and implement local and national management strategies. Further research is required to establish the causal nature of these associations and to refine location appropriate actions to minimise harm from CKD on regional and local levels.

Contributors MD and PH conceived the research project and suggested the structure of the manuscript while contributing at all stages to the writing of the paper. MS compiled the data for analysis and conducted the analysis and put compiled the tables and figures. AH and AR provided expert clinical insight and interpretation of the results while also contributing to the writing of all sections as did MD, PH and MS.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. No data are available. No additional data available.

ORCID iDs

Adrian Heald http://orcid.org/0000-0002-9537-4050

Mark Davies http://orcid.org/0000-0001-9993-9007

REFERENCES

1 Public Health England. Chronic kidney disease prevalence model About Public Health England. *Public Heal Engl*. 2014. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/612303/ChronickidneydiseaseCKDprevalencemodelbriefing.pdf
2 Roderick P, Roth M, Mindell J. Prevalence of chronic kidney disease in England: findings from the 2009 health survey for England. *J Epidemiol Community Heal* 2011;65:A12
3 Hirst JA, Hill N, Callaghan CAO. Prevalence of chronic kidney disease in the community using data from OxRen. *Br Journal Gen Pract* 2020;1:285–93.
4 UK Renal Registry. Adults on renal replacement therapy (RRT) in the UK at the end of 2017. *UK Ren Regist 21st Annu Rep* 2017.
5 Go AS, Chertow GM, Fan D, *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–305.
6 GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2020;395:709–33.
7 Parving HH, Lehnert H, Bröchner-Mortensen J, *et al*. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870–8.
8 Perkovic V, Jardine MJ, Neal B, *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295–306.
9 Shih C-C, Lu C-J, Chen G-D, *et al*. Risk prediction for early chronic kidney disease: results from an adult health examination program of 19,270 individuals. *Int J Environ Res Public Health* 2020;17:4973–11.
10 Forbes A, Gallagher H. Chronic kidney disease in adults: assessment and management. *Clin Med* 2020;20:128–32.
11 Zhan M, Doerfler RM, Xie D, *et al*. Association of Opioids and Nonsteroidal Anti-inflammatory Drugs With Outcomes in CKD: Findings From the CRIC (Chronic Renal Insufficiency Cohort) Study. *Am J Kidney Dis* 2020;76:184–93.
12 NHS Digital. Quality and outcomes framework prevalence. Available: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data
13 Public Health England PHE. GP practice public health profiles. Available: http://fingertips.phe.org.uk/
14 English GP practice prescribing dataset. Available: https://opendata.nhsbsa.net/dataset/english-prescribing-data-epd
15 Byrne C, Steenkamp R, Castledine C, *et al*. Chapter 4: UK ESRD prevalent rates in 2008: national and centre-specific analyses. *Nephron Clin Pract* 2010;115:c41–68.
16 NICE. Chronic kidney disease: assessment and management NICE guideline, 2021. Available: www.nice.org.uk/guidance/ng203
17 García-Carro C, Vergara A, Bermejo S, *et al*. A nephrologist perspective on obesity: from kidney injury to clinical management. *Front Med* 2021;8:655871.
18 Ruban A, Stoenchev K, Ashrafian H, *et al*. Current treatments for obesity. *Clin Med* 2019;19:205–12.
19 Heald AH, Livingston M, Fryer A, *et al*. Route to improving type 1 diabetes mellitus glycaemic outcomes: real-world evidence taken from the National diabetes audit. *Diabet Med* 2018;35:63–71.
20 Heald AH, Livingston M, Malipatil N, *et al*. Improving type 2 diabetes mellitus glycaemic outcomes is possible without spending more on medication: lessons from the UK national diabetes audit. *Diabetes Obes Metab* 2018;20:185–94.
21 Baker M, Perazella MA. Nsaids in CKD: are they safe? *Am J Kidney Dis* 2020;76:546–57.
22 Möller B, Pruijm M, Adler S, *et al*. Chronic NSAID use and long-term decline of renal function in a prospective rheumatoid arthritis cohort study. *Ann Rheum Dis* 2015;74:718–23.
23 Bell S, Rennie T, Marwick CA, *et al*. Effects of peri-operative nonsteroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function. *Cochrane Database Syst Rev* 2018;2018;68.
24 Lazarus B, Chen Y, Wilson FP, *et al*. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med* 2016;176:238–46.
25 Grant CH, Gillis KA, Lees JS, *et al*. Proton pump inhibitor use and progression to major adverse renal events: a competing risk analysis. *QJM* 2019;112:835–40.

26 Florence C, Luo F, Rice K. The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017. *Drug Alcohol Depend* 2021;218:108350.
27 Curtis HJ, Croker R, Walker AJ, *et al*. Opioid prescribing trends and geographical variation in England, 1998-2018: a retrospective database study. *Lancet Psychiatry* 2019;6:140–50.
28 Jani M, Birlie Yimer B, Sheppard T, *et al*. Time trends and prescribing patterns of opioid drugs in UK primary care patients with non-cancer pain: a retrospective cohort study. *PLoS Med* 2020;17:1–16.
29 Danesh S, Walker LA. Effects of central administration of morphine on renal function in conscious rats. *J Pharmacol Exp Ther* 1988;244:640–5.
30 Mercadante S, Arcuri E. Opioids and renal function. *J Pain* 2004;5:2–19.