BMJ Open

Trends in kidney function testing in UK primary care since the introduction of the Quality and Outcomes Framework: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028062
Article Type:	Research
Date Submitted by the Author:	22-Nov-2018
Complete List of Authors:	Feakins, Benjamin; Medical Statistics Group, University of Oxford, UK, Nuffield Department of Primary Care Health Sciences Oke, Jason; University of Oxford, Nuffiled Department of Primary Care Health Sciences McFadden, Emily; University of Oxford, Nuffield Department of Primary Care Health Sciences Aronson, Jeffrey; University of Oxford, Clinical Pharmacology Lasserson, Daniel; University of Birmingham, Institute of Applied Health Research; University of Oxford, Nuffield Department of Medicine O'Callaghan, Christopher; University of Oxford, Nuffield Department of Clinical Medicine; Oxford Radcliffe Hospitals Trust, John Radcliffe Hospital Taylor, Clare; University of Birmingham, Nuffield Department of Primary Care Health Sciences Hill, Nathan; Bristol-Meyers Squibb Pharmaceuticals Limited Stevens, Richard; University of Oxford, Nuffield Dept Primary Care Health Sciences Perera, Rafael; University of Oxford, Primary Health Care
Keywords:	Serum creatinine, Proteinuria, Kidney function, PRIMARY CARE, Monitoring, Chronic Kidney Disease

Trends in kidney function testing in UK primary care since the introduction of the Quality and Outcomes Framework: a retrospective cohort study using CPRD

Benjamin G. Feakins[1] (benjamin.feakins@phc.ox.ac.uk), Jason L. Oke[1] (jason.oke@phc.ox.ac.uk), Emily C. McFadden[1] (emily.mcfadden@phc.ox.ac.uk), Jeffrey K. Aronson[1] (jeffrey.aronson@phc.ox.ac.uk), Daniel S. Lasserson[2,3] (d.s.lasserson@bham.ac.uk), Chris A. O'Callaghan[3] (chris.ocallaghan@ndm.ox.ac.uk), Clare J. Taylor[1] (clare.taylor@phc.ox.ac.uk), Nathan R. Hill[4] (nathan.hill@bms.com), Richard J. Stevens[1] (richard.stevens@phc.ox.ac.uk), Rafael Perera[1] (rafael.perera@phc.ox.ac.uk)

[1] Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.

[2] Institute of Applied Health Research, University of Birmingham, Birmingham, UK.

[3] Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

[4] Bristol-Meyers Squibb Pharmaceuticals Limited, Uxbridge, UK

Word count:

Abstract: 300

Main text: 4,425

Corresponding author:

Jason Oke, DPhil (jason.oke@phc.ox.ac.uk)
Nuffield Department of Primary Care Health Sciences
Radcliffe Observatory Quarter, Woodstock Road
Oxford
OX2 6GG

Abstract

Objectives: To characterise serum creatinine and urinary protein testing in UK general practices from 2005 to 2013, and to examine how the frequency of testing varies across demographic factors, with the presence of chronic conditions, and with the prescribing of drugs for which kidney function monitoring is recommended.

Design: An open cohort study.

Setting: Routinely collected data from 630 UK general practices contributing to the Clinical Practice Research Datalink.

Participants: 4,573,275 patients aged over 18 years registered at up-to-standard practices between 1st April 2005 and 31st March 2013. At study entry, no patients were kidney transplant donors or recipients, pregnant, or on dialysis.

Primary outcome measures: The rate of serum creatinine and urinary protein testing per year, and the percentage of patients with isolated and repeated testing per year.

Results: The rate of serum creatinine testing increased linearly across all age groups. The rate of proteinuria testing increased sharply in the 2009-10 financial year, but only for patients aged 60 or over. For patients with established chronic kidney disease (CKD), creatinine testing increased rapidly in 2005-06 and 2006-07, and proteinuria testing in 2009-10, reflecting the introduction of Quality and Outcomes Framework indicators. In adjusted analyses, CKD Read codes were associated with up to a two-fold increase in the rate of serum creatinine testing, while other chronic conditions and potentially nephrotoxic drugs were associated with up to a six-fold increase. Regional variation in serum creatinine testing reflected country boundaries.

Conclusions: Over a nine-year period, there have been increases in the numbers of patients having kidney function tests annually and in the frequency of testing. Changes in the recommended management of CKD in primary care were the primary determinant, and increases persist even after controlling for demographic and patient-level factors. Future studies should address whether increased testing has led to better outcomes.

Keywords: Serum creatinine, proteinuria, kidney function, primary care, monitoring, chronic kidney disease.

Article summary

Strengths and limitations of this study

- To date, this is the largest population study of trends in renal function testing in primary care.
- The data source did not permit us to ascertain why a kidney function test was performed.

- The transitioning of 'high risk' patients from primary to secondary care means the estimates in this study may be liable to underestimate the amount of testing performed in certain patient subgroups.

Introduction

Kidney function testing in primary care is used to diagnose and monitor chronic kidney disease (CKD). Testing is recommended at baseline, and after initiation of some drugs such as antihypertensives [1]. Kidney function is usually tested by measuring serum creatinine, and screening for glomerular disease is undertaken by measuring urine albumin or protein concentrations.

In 2002 the Kidney Disease Outcomes and Quality (K/DOQI) Initiative published clinical guidelines advocating that CKD be categorised into five stages [2]. Two years later, these stages were adopted by the UK Quality and Outcomes Framework (QOF), which is a set of business rules that include financial incentives to regularly monitor and test certain subsets of patients, and to record their data [3]. The 2006-07 financial year saw an extension to QOF that required general practitioners to maintain a register of patients with CKD stages 3-5 [4]. In 2008, the National Institute for Health and Care Excellence (NICE) recommended monitoring eGFR levels in high risk patients [5]. Then in the 2009-10 financial year a further QOF extension incentivised the monitoring urinary markers of kidney disease (such as proteinuria) in patients on the CKD register [6]. Current NICE recommendations on the frequency of testing are based on the underlying cause of CKD, previous test results, comorbidities, and the treatments being used. Monitoring is recommended annually in patients with mild to moderate reductions in kidney function and every three months in patients with more advanced disease [1].

National rates of kidney function testing and potential differences between different populations have not been characterised. In contrast, rates of kidney function testing in patients with diabetes have been well documented. A cohort study of adults with diabetes showed that under 13% had incomplete CKD screening and just 4.4% had no serum creatinine measurement on record in the two and half years before the start of the study, whereas the albumin-creatinine ratio (ACR) was not monitored in 37% during the same period [7]. Similarly, high frequencies of creatinine testing have been observed among patients with diabetes in studies looking at individual health regions, but with more variable levels of recording in patients without diabetes across different ages, genders and ethnic groups [8].

There has been a dramatic increase in the use of laboratory testing over recent decades, particularly repeated testing or monitoring [9,10]. However, it is unclear whether this increase is appropriate and consistent with guideline recommendations or whether it represents over-testing. Appropriate testing of kidney function might be of value in planning management to slow the progression of the disease and, therefore, lead to tangible patient benefit. However, over-use of tests provides little patient benefit and adds to the financial burden of healthcare systems. A recent meta-analysis of the use of laboratory tests during the last 15 years showed that under-use of high-volume tests (such as creatinine) was more likely than over-use [11]. A cross-sectional survey of US physicians' patterns of care in patients with CKD showed that 85% of physicians recommended one additional test, which was not recommended in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [12]. These tests were most likely to be magnetic resonance angiography of renal arteries or serum protein electrophoresis, rather than blood or urinary measurements [13]. It is, of course, possible that over-use and under-use may co-exist, with some patients receiving more tests than indicated and other patients not receiving tests warranted by their clinical history, recent health, and age.

The aim of this study is to describe rates of kidney function testing since the introduction of the QOF in UK general practice. Specifically, we have examined the numbers of serum creatinine and proteinuria tests requested in each financial year during the nine years from 2005 to 2013 by: age category, gender, ethnicity, index of multiple deprivation (IMD), Strategic Health Authority (SHA), CKD stage, the presence or absence of major comorbidities (such as diabetes, hypertension, cardiovascular disease, atrial fibrillation), and the prescription of nephrotoxic drugs.

Methods

Data

We used the Clinical Practice Research Practice Datalink (CPRD) [14] to construct an open cohort study of adults (≥ 18 years of age) registered at UK general practices whose data quality was deemed to be "up-to-standard", i.e. the data committed by general practices has reached a standard suitable for research (based on a CPRD algorithm that primarily focusses on death recording and gaps in the data). The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (protocol number 14_150R) and the approved protocol was made available to the journal and reviewers during peer review. Ethical approval for observational research using the CPRD with approval from ISAC has been granted by a National Research Ethics Service committee (Trent MultiResearch Ethics Committee, REC reference number 05/MRE04/87).

Study period

We selected a start date of 1st April 2005, which post-dated the publication of the K/DOQI guidelines for classification of CKD in 2002 [2], and the introduction of QOF targets in UK primary care in 2004 [3]. The study end date was 31st March 2013.

Inclusion and exclusion criteria

Eligible patients had to have been registered with their practice for a minimum of 12 months before their study entry to ensure adequate recording of baseline covariates. The study entry date was defined as the latest of either the study start date (1st April 2005) or the date of the patient's current registration date + 12 months. We excluded patients who were living kidney donors, had a renal transplant, ever underwent dialysis, or women who were pregnant in the 12 months prior to study entry. Follow-up ended at the study end date, unless preceded by the patient's death, transfer out of CPRD, the last available linked data, or (where applicable) pregnancy, renal transplantation/donation, or dialysis. For any given financial year, patient records were excluded if their data were incomplete/censored.

Outcomes

A serum creatinine test was deemed to have occurred when a patient test record contained a valid date, an entity type associated with serum creatinine testing or blood/serum biochemistry, and a Read code for serum creatinine testing (Supplementary Table 1).

A proteinuria test was deemed to have occurred when a patient test record contained a valid date, an entity type associated with urine biochemistry tests and a Read code for albuminuria or proteinuria testing (Supplementary Table 2).

Subsequent tests recorded per patient on the same day were discarded, under the assumption that they were data entry errors.

Variables

Nominal CKD stage was identified by Read codes (Supplementary Table 1). Albuminuria status was derived using either ACR or protein: creatinine ratio (PCR). When these were unavailable, raw albumin excretion rate or protein excretion rate were used. Normoalbuminuria (albuminuria stage A1) was defined as <3 mg/mmol, microalbuminuria (albuminuria stage A2) was defined as 3-30 mg/mmol, and macroalbuminuria (albuminuria stage A3) as >30 mg/mmol, in accordance with the 2012 KDIGO guidelines for evaluation and management of CKD [12]. Estimated glomerular filtration rate (eGFR) was calculated using the four-part Modification of Diet in Renal Disease (MDRD) equation based on recorded values of serum creatinine, sex, age at test, and ethnicity [15]. The four-part MDRD equation was used in place of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16], more recently advocated by NICE, as this was the equation that would predominantly have been used to monitor patients during the follow-up period.

Prevalence data for the comorbidities of: atrial fibrillation, cancer, diabetes, heart failure, hypertension, ischaemic heart disease, peripheral vascular disease, stroke or transient ischaemic attack, and thyroid disease, were assessed by the presence of diagnostic Read codes in patient clinical records.

Pharmacotherapies that were either nephrotoxic, excreted by the kidneys or that affected serum potassium were established through consensus between the general practitioners/pharmacologists (JA, CO'C and CT). These consisted of: angiotensin-converting enzyme inhibitors (ACE-is), angiotensin receptor blockers (ARBs), amiodarone/dronedarone, digoxin, diuretics, gold, immunosuppressants, lithium, mesalazine, non-steroidal anti-inflammatory drugs (NSAIDs) and oral-anticoagulants (OACs).

Patient demographic data were also extracted, including, age, gender, ethnicity, deprivation, and region. Within these variables, age was categorised into seven levels (18-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+), ethnicity was divided into six categories ("white", "Asian", "black", "mixed", "other" or "missing"), deprivation was categorised into six levels (representing quintiles of IMD data plus a "missing" level), and region was divided into 13 categories (aligning with the 10 SHAs of England, and the countries of Northern Ireland, Scotland and Wales).

Analyses

Trends across kidney disease categorisations

Adherence to the most current NICE guidelines [1] was evaluated by stratifying crude rates of serum creatinine and proteinuria testing (herein jointly referred to as "kidney function testing") by CKD stage, and eGFR and albuminuria categories. We present these rates as tile and line plots.

Trends over time

We calculated crude rates of kidney function tests, stratified by financial year, and further stratified by CKD stage, demographic factors (such as age, ethnicity and deprivation), the presence of various comorbidities and concurrent prescriptions for nephrotoxic drugs. We present the percentage of patients with 1, 2, 3, 4 and >4 tests per financial year for serum creatinine and urinary albumin/protein as bar plots.

Factors associated with kidney function testing

We examined factors associated with serum creatinine testing in CPRD. We used a negative binomial regression model to assess the relationship between demographic factors, the presence of markers for CKD and other chronic conditions, and indicators of drug therapy. We fitted age and year of entry into the study as categorical factors in order to model non-linear associations. The presence of Read codes for CKD was used as markers of kidney disease. We studied 13 geographic regions corresponding to the SHAs of England, and the countries of Scotland, Northern Ireland and Wales. The model was adjusted for the presence of chronic conditions and medications. These were added to the models as binary covariates if a Read code or Gemscript code was present within the eligible data preceding the study entry date for that patient. The outcome of the model was the number of serum creatinine tests on record following study entry with the log person-years of follow-up used as the offset term. The model, therefore, estimates the natural log rates of serum creatinine testing, and covariate effects are log incidence rate ratios (IRRs). We have presented results from unadjusted, i.e. univariable, minimally adjusted, i.e. adjusted for gender, age, ethnicity, deprivation, region and year of entry, and fully adjusted, i.e. adjusted for all extracted variables, models on a natural scale, as IRRs with 95% confidence intervals.

Statistical software and packages

All analyses were conducted in R (version 3.5.1) [17]. Plots were produced using the *ggplot2* package [18]. Crude rates and their 95% confidence intervals were calculated via the skewness-corrected asymptotic score method [19] implemented in the `scaspci()` function of the *ratesci* package [20]. Negative binomial models were fit using the `glm.nb()` function of the *MASS* package [21].

Patient and public involvement

This project has been reviewed by individuals with long term conditions that require frequent monitoring, as well as nurse practitioners and general practice commissioners. Patient and public involvement members have also been invited to the steering and senior management groups. A patient and public involvement expert was also involved as a strategic consultant in a programme of work including this project.

Results

Baseline Demographics

We identified 4,573,275 patients from 630 practices with 26,496,643 person-years of eligible follow-up data, containing a total of 15,049,063 serum creatinine tests and 995,524 proteinuria tests. The

median length of follow up was 6.1 (interquartile range (IQR) 3.5 to 9.0) years. The cohort comprised 49.7% men and 50.3% women. The median (IQR) age was 46 (34 to 61) years (Table 1).

Table 1 - Characteristics of the cohort at study entry. (Note: only recorded characteristics reported).

Characteristic	Female (N = 2,279,097)	Male (N = 2,294,178)	Everyone (N =4,573,275)
Age (years)			
18-39	807,015 (35.4%)	904,018 (39.4%)	1,711,033 (37.4%)
40-49	437,734 (19.2%)	475,130 (20.7%)	912,864 (20.0%)
50-59	370,235 (16.2%)	379,112 (16.5%)	749,347 (16.4%)
60-69	286,951 (12.6%)	278,903 (12.2%)	565,854 (12.4%)
70-79	212,826 (9.3%)	174,193 (7.6%)	387,019 (8.5%)
80-89	132,990 (5.8%)	73,456 (3.2%)	206,446 (4.5%)
≥90	31,346 (1.4%)	9,366 (0.4%)	40,712 (0.9%)
Ethnicity			
White	512,088 (22.5%)	441,467 (19.2%)	953,555 (20.9%)
Asian	42,888 (1.9%)	43,623 (1.9%)	86,511 (1.9%)
Black	19,819 (0.9%)	17,302 (0.8%)	37,121 (0.8%)
Mixed	316,792 (13.9%)	303,891 (13.2%)	620,683 (13.6%)
Other	13,933 (0.6%)	14,310 (0.6%)	28,243 (0.6%)
Index of multiple deprivation			
1 (least deprived)	334,473 (14.7%)	337,305 (14.7%)	671,778 (14.7%)
2	340,977 (15.0%)	337,861 (14.7%)	678,838 (14.8%)
3	293,127 (12.9%)	294,250 (12.8%)	587,377 (12.8%)
4	269,680 (11.8%)	277,279 (12.1%)	546,959 (12.0%)
5 (most deprived)	206,571 (9.1%)	217,148 (9.5%)	423,719 (9.3%)
Chronic kidney disease stage			
1	699 (0.0%)	608 (0.0%)	1,307 (0.0%)
2	2,512 (0.1%)	2,009 (0.1%)	4,521 (0.1%)
3	8,149 (0.4%)	4,760 (0.2%)	12,909 (0.3%)
4	687 (0.0%)	459 (0.0%)	1,146 (0.0%)
5	73 (0.0%)	75 (0.0%)	148 (0.0%)
Estimated glomerular filtration rate (mL/min/1.73m^2)			
≥90	142,918 (6.3%)	154,064 (6.7%)	296,982 (6.5%)
60-89	512,731 (22.5%)	459,469 (20.0%)	972,200 (21.3%)
45-59	188,796 (8.3%)	95,043 (4.1%)	283,839 (6.2%)
30-44	52,765 (2.3%)	23,242 (1.0%)	76,007 (1.7%)
15-29	10,543 (0.5%)	5,782 (0.3%)	16,325 (0.4%)
<15	833 (0.0%)	480 (0.0%)	1,313 (0.0%)
Albuminuria (mg/mmol)			
<3.0	39,442 (1.7%)	42,665 (1.9%)	82,107 (1.8%)
3-30	11,978 (0.5%)	14,489 (0.6%)	26,467 (0.6%)
>30	3,096 (0.1%)	3,757 (0.2%)	6,853 (0.1%)
Comorbidities			
Atrial fibrillation	37,041 (1.6%)	28,662 (1.2%)	65,703 (1.4%)
Cancer	44,136 (1.9%)	52,068 (2.3%)	96,204 (2.1%)
Diabetes	267,791 (11.7%)	238,922 (10.4%)	506,713 (11.1%)
Heart failure	12,692 (0.6%)	12,964 (0.6%)	25,656 (0.6%)
Hypertension	21,381 (0.9%)	21,497 (0.9%)	42,878 (0.9%)
Ischaemic heard disease	49,227 (2.2%)	59,621 (2.6%)	108,848 (2.4%)
Peripheral vascular disease	19,153 (0.8%)	21,166 (0.9%)	40,319 (0.9%)

Stroke/Transient ischaemic attack	21,988 (1.0%)	21,774 (0.9%)	43,762 (1.0%)
Thyroid disease	73,289 (3.2%)	16,009 (0.7%)	89,298 (2.0%)

Trends across kidney disease categorisations

Chronic kidney disease categories

When categorising kidney disease according to CKD stages, the highest rates of kidney function testing were found in patients with CKD stage 4 (Figure 1). The lowest rates of testing were observed in patients without a Read code for CKD, however, such patients were still receiving roughly one serum creatinine test every two years and one proteinuria test every nine years. Rates of serum creatinine testing were roughly in line with NICE guidelines for CKD stages 1-4, but fell below recommendation in stage 5 [1].

Figure 1 - Rates of kidney function testing (per year), stratified by CKD stage.

Estimated glomerular filtration rate and albuminuria categories

The rates of serum creatinine testing observed in the data were higher than those advocated by NICE [1] and KDIGO [22] in all eGFR-albuminuria subcategories (Figure 2). The highest rates of serum creatinine testing were in patients with eGFR stage G5. Patterns of proteinuria testing were less consistent, with patients with eGFR stage G5 or albuminuria stage A3 both exhibiting high rates of proteinuria testing. Rates of kidney function testing were generally higher than expected for individuals with either no eGFR or proteinuria stage assigned. For instance, patients with no assignable eGFR category and normal (A1) albuminuria levels were still receiving 0.84 (95% CI: 0.84, 0.85) tests per year, while patients with no assignable albuminuria level and normal (G1) eGFR levels were still receiving 0.25 (95% CI: 0.25, 0.25) proteinuria tests per year.

Figure 2 - Rates of kidney function testing (per year), stratified by eGFR and albuminuria categories.

Trends over time

Trends across CKD categories

Figure 3 shows trends in serum creatinine (left-panel) and urinary protein testing (right-panel), stratified by stage of CKD for the same period. Rates of kidney function testing increased with CKD stage up to stage 4, though rates in CKD stage 5 were lower or similar to rates in CKD stage 4. For patients in stages 2-5, rapid increases in the number of serum creatinine tests coincided with the inclusion of CKD management in QOF in 2006-07 [4] and then stabilised after 2007-08. Sharp increases in proteinuria testing for patients with CKD stages 2-5 also coincided with the incorporation of proteinuria testing into QOF guidelines for the monitoring of CKD in 2009-10 [6].

Figure 3 - Rates of kidney function testing per financial year, stratified by CKD stage.

General trends in testing

The percentage of patients receiving kidney function tests has been steadily increasing year on year (Figure 4). In the 2005-06 financial year, 27.2% of patients received a serum creatinine test, while 7.5% of patients received a proteinuria test. In the 2012-13 financial year, these figures were 38.1% and 11.8%, respectively. These increases appear to be driven by increases in the number of patients with isolated kidney function testing, i.e. patients receiving one test per year, which for serum creatinine tests increased from 18.5% in 2005-06 to 25.2% in 2012-13. For proteinuria testing isolated testing increased from 5.6% in 2005-06 to 9.1% in 2012-13. In the same time period, the percentage of patients with repeated serum creatinine testing, i.e. two or more tests per year, increased from 8.7% to 12.9%, while the percentage of patients with repeated proteinuria testing increased from 2.0% to 2.7%.

Figure 4 - Percentage of patients that have had 1, 2 ,3, 4, or more than 4 kidney function tests per financial year.

Trends in testing across demographic data

Figure 5 shows the yearly trend in testing for serum creatinine (left panel) stratified by age and the equivalent trends in urinary protein tests (right panel). In general, rates of testing were higher with higher age, up to age 80-89 years, but note that rates in the 90+ years age group are not the highest. Serum creatinine test rates increased approximately linearly over time within each decile of age. In contrast, urinary protein test rates were constant over time in age groups less than 60 years, and increased over time for patients over 60 years of age, with a sharp increase in the year 2009-10.

Figure 5 - Rates of kidney function testing per financial year, stratified by age category.

Differences between the rates of kidney function testing were much lower when stratifying by gender (Supplementary Figure 1), ethnicity (Supplementary Figure 2), IMD quintile (Supplementary Figure 3), and geographic region (Supplementary Figure 4). Testing was marginally higher in women than men for both serum creatinine and proteinuria tests, with rate differences of roughly 0.1 tests per year and 0.02 tests per year, respectively. These differences remained relatively constant throughout the follow-up period. Testing remained higher in patients coded in the CPRD as white or mixed ethnicity, with patients of black or Asian ethnicity having lower rates of testing. A similar pattern was found in proteinuria testing. Rates of kidney function testing were similar when stratifying by IMD quintile, with rates being lowest in the lowest (most affluent) IMD quintile, for both markers of kidney function. Stratification by SHA region resulted in slightly larger differences in testing rates of up to 0.25 tests per year for serum creatinine and 0.14 tests per year for proteinuria. London demonstrated the lowest rates of kidney function testing for the majority of the study observation period. The highest rates of serum creatinine testing were initially seen in North-East England, being surpassed by Northern Ireland in 2007-08. Rates of serum creatinine testing were initially lowest in Scotland and London, until 2010-11, where rates of testing in Scotland increased. Conversely, the highest rates of proteinuria testing were present in the English East Midlands.

Trends in testing across comorbidities and pharmacotherapies

For all evaluated comorbidities, rates of kidney function testing were elevated when compared to a population for whom these comorbidities were absent (Figure 6). Testing appears to have increased across all comorbidities with time, with the exception of diabetes, where the rate of testing appears to have decreased. The highest rates of serum creatinine testing were present in patients with heart failure and diabetes, however, all comorbidities were associated with at least one serum creatinine test per year by 2007-08. The highest rates of proteinuria testing were present in patients with diabetes.

Figure 6 - Rates of kidney function testing per financial year, stratified by comorbidity. Key: AFib = atrial fibrillation; HF = heart failure; HTN = hypertension; IHD = ischaemic heart disease; PVD = peripheral vascular disease; TIA = transient ischaemic attack; THY = thyroid.

Across all evaluated pharmacotherapies, rates of kidney function testing were higher than in patients for whom prescriptions of these therapies were absent (Figure 7). Rates of kidney function testing were relatively stable across time for most comorbidities with a few notable exceptions. For patients receiving prescriptions for gold, methotrexate or other immunosuppressants, serum creatinine testing appears to have increased with time. Proteinuria testing was elevated in patients prescribed gold but was generally less than 0.5 tests/year for all other pharmacotherapies.

Figure 7 - Rates of kidney function testing per financial year, stratified by concomitant pharmacotherapy. Key: ACE-is = angiotensin-converting-enzyme inhibitors; ARBs = angiotensin II receptor blockers; Darones = amiodarone or dronedarone; OACs = oral anticoagulants; Immuno = other (non-methotrexate) immunosuppressants; NSAIDs = nonsteroidal anti-inflammatory drugs.

Factors associated with serum creatinine testing

The presence of a Read code for CKD was independently associated with more frequent serum creatinine testing in primary care, with stage 4 CKD conferring the highest rates of testing (Table 2). Testing frequency increased with age up to a peak at ages 80-89. Variation in testing between the SHA regions of England was quite low, with the exception of the North-East and the South-West, where the rates of testing were roughly 20% higher than that of London. Rates in Northern Ireland, Scotland and Wales were 21-48% greater than those of London, possibly reflecting differences in clinical guidelines between England and other countries. In our adjusted model of testing frequency, the extent of testing in men and women differed by 14% IRR 1.14, (95% CI: 1.14, 1.14). All assessed comorbidities were significantly associated with elevated rates of serum creatinine testing with the exception of atrial fibrillation. With the exception of ethambutol, for all analysed pharmacotherapies, serum creatinine testing increased independently of other factors and was most marked in patients taking methotrexate, other immunosuppressants, gold and lithium.

Table 2 - Results of regression models describing the demographic characteristics, the presence/absence of chronic conditions and drug prescription, and associations with the frequency of serum creatinine testing in primary care.

Characteristic	Univariable IRR (95%CI)	Minimally Adjusted IRR (95%CI)	Fully Adjusted IRR (95%CI)
Gender			

Female	1.20 (1.20, 1.21)	1.18 (1.18, 1.18)	1.14 (1.14, 1.14)
Age (years)			
40-49	2.09 (2.08, 2.10)	2.10 (2.09, 2.11)	1.92 (1.91, 1.92)
50-59	3.50 (3.49, 3.51)	3.53 (3.52, 3.54)	2.87 (2.86, 2.88)
60-69	5.38 (5.36, 5.40)	5.39 (5.37, 5.41)	3.94 (3.93, 3.96)
70-79	7.25 (7.22, 7.27)	7.23 (7.20, 7.26)	4.83 (4.81, 4.85)
80-89	7.57 (7.53, 7.61)	7.47 (7.43, 7.51)	4.86 (4.83, 4.88)
≥90	6.17 (6.10, 6.25)	5.94 (5.87, 6.01)	4.05 (4.00, 4.10)
Ethnicity			
Asian	0.78 (0.77, 0.79)	1.25 (1.24, 1.27)	1.23 (1.22, 1.24)
Black	0.77 (0.76, 0.78)	1.19 (1.18, 1.21)	1.16 (1.14, 1.17)
Mixed	0.96 (0.96, 0.97)	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)
Other	0.71 (0.69, 0.72)	1.05 (1.03, 1.06)	1.04 (1.02, 1.05)
Not recorded	0.83 (0.83, 0.83)	0.84 (0.84, 0.84)	0.84 (0.84, 0.84)
Index of multiple deprivation			
2	1.07 (1.06, 1.07)	1.04 (1.04, 1.05)	1.03 (1.02, 1.03)
3	1.07 (1.06, 1.07)	1.07 (1.06, 1.07)	1.04 (1.04, 1.04)
4	1.03 (1.03, 1.04)	1.11 (1.11, 1.12)	1.08 (1.07, 1.08)
5 (most deprived)	1.04 (1.03, 1.04)	1.14 (1.13, 1.14)	1.09 (1.08, 1.09)
Not recorded	1.05 (1.05, 1.05)	1.07 (1.07, 1.08)	1.03 (1.03, 1.04)
Year of Study Entry			
2006	0.72 (0.71, 0.72)	0.96 (0.95, 0.96)	1.08 (1.08, 1.09)
2007	0.78 (0.77, 0.78)	0.96 (0.95, 0.96)	1.10 (1.09, 1.10)
2008	0.81 (0.80, 0.81)	0.99 (0.98, 1.00)	1.13 (1.13, 1.14)
2009	0.77 (0.76, 0.78)	1.00 (0.99, 1.01)	1.13 (1.12, 1.14)
2010	0.83 (0.82, 0.83)	1.04 (1.03, 1.04)	1.17 (1.17, 1.18)
2011	0.92 (0.92, 0.93)	1.11 (1.10, 1.12)	1.29 (1.28, 1.30)
2012	0.96 (0.95, 0.97)	1.18 (1.16, 1.19)	1.34 (1.33, 1.35)
Region			
East Midlands	1.29 (1.28, 1.30)	1.18 (1.17, 1.19)	1.07 (1.07, 1.08)
East of England	1.18 (1.17, 1.18)	1.09 (1.09, 1.10)	1.04 (1.04, 1.05)
North-East	1.44 (1.42, 1.45)	1.27 (1.26, 1.28)	1.20 (1.19, 1.21)
North-West	1.30 (1.29, 1.31)	1.18 (1.18, 1.19)	1.10 (1.10, 1.11)
South Central	1.21 (1.20, 1.22)	1.14 (1.13, 1.14)	1.10 (1.09, 1.10)
South-East Coast	1.23 (1.22, 1.24)	1.12 (1.11, 1.12)	1.10 (1.10, 1.11)
South-West	1.43 (1.42, 1.44)	1.22 (1.22, 1.23)	1.17 (1.17, 1.18)
West Midlands	1.24 (1.24, 1.25)	1.14 (1.13, 1.15)	1.08 (1.07, 1.08)
Yorkshire & The Humber	1.24 (1.23, 1.25)	1.08 (1.07, 1.09)	0.97 (0.96, 0.97)
Northern Ireland	1.51 (1.50, 1.53)	1.55 (1.54, 1.57)	1.48 (1.47, 1.49)
Scotland	1.21 (1.20, 1.22)	1.22 (1.21, 1.22)	1.21 (1.20, 1.22)
Wales	1.33 (1.32, 1.34)	1.26 (1.26, 1.27)	1.22 (1.21, 1.22)
Chronic kidney disease stage			
1	1.93 (1.76, 2.11)	2.18 (2.03, 2.35)	2.05 (1.92, 2.19)
2	2.30 (2.21, 2.40)	1.82 (1.76, 1.88)	1.93 (1.87, 1.99)
3	3.32 (3.25, 3.40)	1.67 (1.64, 1.70)	1.48 (1.46, 1.51)
4	4.98 (4.60, 5.39)	2.61 (2.45, 2.77)	2.17 (2.05, 2.30)
5	3.92 (3.05, 5.03)	2.37 (1.94, 2.89)	1.74 (1.45, 2.09)
Comorbidities			
Atrial fibrillation	3.09 (3.04, 3.13)		1.00 (0.99, 1.02)
Cancer	2.14 (2.12, 2.17)		1.15 (1.14, 1.16)
Diabetes	3.48 (3.45, 3.51)		1.98 (1.97, 1.99)

Heart failure	3.89 (3.83, 3.95)		1.07 (1.05, 1.08)
Hypertension	2.37 (2.37, 2.38)		1.28 (1.28, 1.29)
Ischaemic heard disease	2.76 (2.73, 2.78)		1.23 (1.23, 1.24)
Peripheral vascular disease	2.55 (2.52, 2.58)		1.20 (1.19, 1.21)
Stroke/Transient ischaemic attack	2.85 (2.81, 2.88)		1.14 (1.13, 1.15)
Thyroid disease	2.09 (2.07, 2.11)		1.31 (1.30, 1.32)
Pharmacotherapies			
ACE Inhibitors	3.20 (3.18, 3.21)		1.41 (1.41, 1.42)
ARBs	2.98 (2.96, 3.00)		1.25 (1.24, 1.26)
Amiodarone/Dronedarone	3.49 (3.41, 3.56)		1.15 (1.13, 1.17)
Digoxin	3.39 (3.34, 3.44)		1.17 (1.16, 1.19)
Diuretics	3.27 (3.25, 3.28)		1.46 (1.46, 1.47)
Ethambutol	1.37 (1.09, 1.73)		1.16 (0.97, 1.40)
Gold	11.11 (9.59, 12.88)		5.48 (4.95, 6.07)
Immunosuppressants (Not Inc. Methotrexate)	5.06 (4.97, 5.15)		3.44 (3.40, 3.49)
Lithium	4.14 (4.00, 4.28)		4.42 (4.32, 4.52)
Mesalazine	2.44 (2.37, 2.50)		2.23 (2.19, 2.28)
Methotrexate	9.41 (9.19, 9.64)		6.17 (6.07, 6.28)
NSAIDs	1.55 (1.55, 1.56)		1.25 (1.25, 1.25)
Oral Anticoagulants	2.93 (2.89, 2.96)		1.17 (1.16, 1.18)

Discussion

Key results

This is the first study to evaluate the rates of kidney function testing over a nine-year period following the introduction of the QOF in a large UK primary care database. Over the course of this study, rates of serum creatinine and proteinuria testing increased by 40% and 36%, respectively, and by 2012-13 almost four in every 10 people were receiving at least one serum creatinine test per year and over one in every 10 people were receiving at least one proteinuria test per year.

Across most strata evaluated, rates of kidney function testing appear to have either remained constant or increased with time. One notable exception to this was diabetes, where rates appear to have decreased with time. Women appear to be tested more than men, receiving roughly an extra 0.1 serum creatinine tests per year and an extra 0.02 proteinuria tests per year. When stratifying by age, rates of kidney function testing increased between successive age categories up to age 80-89, with patients aged ≥90 typically having lower rates of testing than patients aged 70-79. Serum creatinine and urinary protein testing have both increased across all ethnic groups, but patients of white and mixed ethnicities still have higher rates of testing than patients of black and Asian ethnicity. Stratification by IMD quintile demonstrated minimal differences in testing rates. Conversely, stratification by comorbidity revealed the highest rates of both serum creatinine and proteinuria testing to be present in patients with heart failure or diabetes, while stratification by concomitant pharmacotherapy, revealed the highest rates of kidney function testing to be present in patients or prescribed gold. Serum creatinine testing was more frequent in patients prescribed immunosuppressants.

The effects of pay-for-performance indicators are visible in most plots present in this paper with noticeable increases in the rates of serum creatinine testing in 2006-07 and of proteinuria testing in 2009-10. The former of these coincided with the requirement that general practices maintain a register of patients with CKD stages 3-5 [4], while that latter coincided with the inclusion of the monitoring of secondary markers of kidney disease via ACR and PCR tests in patients on the CKD register [5]. There was no obvious impact in any of the plots from the 2008-09 NICE guidelines which recommended monitoring eGFR levels in high risk patients [5].

Frequency of serum creatinine testing was strongly associated with increasing age and the presence of a Read code for CKD in adjusted analyses. Testing frequency was also independently associated with chronic conditions and prescription of potentially nephrotoxic drugs but has risen year on year, even after accounting for age, chronic conditions, and prescription of drugs that require monitoring of kidney function.

Strengths and limitations

To date, this is the largest population-based study of trends in renal function testing in primary care. The study population was an unselected sample of over 4.5 million patients from over 600 general practices across the UK included in the CPRD database, which has been shown to be representative of the UK. The scale and design of the study allowed us to test associations adjusted for many important potential explanatory and confounding factors. Our study has limitations, some of which are inherent in the CPRD database. We were not able to ascertain why the tests were performed. Even though the CPRD contains consultation codes, these provide only a very broad classification of the time and type of consultation (e.g. Clinic, Night visit, Home visit). An in-depth analysis of Read codes or mining of the consultation free text would be required to start to explain the reasons for test ordering, which is beyond the scope of this study. Finally, the use of the MDRD equation could be challenged. It was the formula in use during the period of the study but is now considered inferior to the CKD-EPI formula. However, we have used MDRD, because we wanted the analysis to reflect the clinical decision made at the time of the study.

Relationship to the literature

The rise in the number of patients having serum creatinine concentration measurements and the increased frequency of testing for those being tested can be interpreted in two ways. CKD has gained more attention since the incorporation of CKD into the QOF in 2006-07. The establishment of a register in 2006-07 and its subsequent extension has encouraged renal function testing to identify those with CKD who may benefit from risk factor modification. From the viewpoint of patient safety, our results are encouraging and show that, for all the therapies we examined, the prescription of drugs that are potentially nephrotoxic is associated with more frequent monitoring.

Our results could be interpreted in a different light. There is little direct evidence that extra testing has improved outcomes in the short term or long term [23]. Additional testing has increased the apparent prevalence of CKD from 0.12% to 6.51%, but as yet, there has been no change in long-term outcomes, such as patients requiring renal replacement therapy [24,25]. Increases in consultations with general practitioners or practice nurses for either newly diagnosed disease or monitoring, with associated laboratory tests, place further strain on limited healthcare resources and increase

expenditure. The very substantial costs of renal replacement therapy or cardiovascular complications [25] mean that testing might be cost-effective, even if it results in only modest reductions in the number of patients who progress to this stage, but whether this is the case is unclear. In a report from one NHS trust in the period following the introduction of renal QOF there was an abrupt 61% increase in the number of new referrals to nephrology, 54% of which were classified as inappropriate and a further 22% as inadequate [26]. Inappropriate referrals use up resources and may cause unnecessary distress to patients and their carers [27].

Implications for practice

Rates of testing have increased over the observation period in our study. Much of these increases appear to be driven by financial incentivisation schemes, such as the QOF. However, the increases were found to be independent of comorbidities, age and prescriptions for 'high risk' drugs. Much of the increase in testing appears to have occurred in patients with mildly to moderately impaired kidney function (CKD stages 2-3). However, there is limited evidence to suggest any benefit from interventions delivered in the early stages of CKD [28]. Moreover, studies in cholesterol monitoring have shown that more frequent testing can have negative consequences [29] - particularly in biomarkers that exhibit high within-person variability, such as serum creatinine [30], where there will be an increased likelihood of raising false alarms for acute kidney injury or elevation in CKD severity. Hence, a more targeted approach could prove beneficial for most patients.

Increases in testing are also likely to have knock-on effects to other aspects of healthcare, including the financial burden on the NHS, the time burden on general practitioners, and laboratory workloads; potentially resulting in delayed or missed diagnosis [31]. Reducing the amount of serum creatinine testing performed as part of kidney function monitoring could ease some of these burdens, although we acknowledge that a reasonable amount of serum creatinine testing is performed as part of test batches not directly related to the assessment of kidney function and including other tests such as full blood counts [32].

Conclusion

The observed increase in kidney function testing could be attributable to any or all of several changes that have occurred over the period of the study. The introduction of pay-for-performance indicators, the establishment of a CKD register, national guidelines promoting monitoring of renal function in high-risk groups, and linkage of pathology laboratories to practice systems have potentially all raised the profile of CKD in primary care and contributed to the observed increases in testing. While it is clear that these initiatives have changed process measures, it is still not clear whether clinical outcomes have improved as a consequence.

Statements

Funding

This article presents independent research funded by the National Institute for Health Research (NIHR) under the programme grants for applied research programme (RP-PG-1210-12003). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the

Department of Health and Social Care. RP receives funding from the NIHR Oxford Biomedical Research Centre Program, the NIHR Program for Applied Research, the NIHR Health Protection Research Unit (HPRU) Gastrointestinal Infections Group, and the NIHR Diagnostic Evidence Co-operative (DEC).

Competing interests

NH is currently employed by Bristol-Meyers Squibb Limited; a company that manufactures ACE inhibitors, which are drugs indicated in the treatment of CKD, when present in conjunction with other comorbidities such as type 2 diabetes. All other authors declare no conflicts of interest.

Author contributions

RP and RS provided substantial contributions to the concept and design of the study. JO, BF, RS, RP and EM provided statistical expertise, while JA, CT, CO'C and DL lent clinical and pharmacological expertise. Any coding work necessary for the project was performed by BF, JO, EM and NH. All authors contributed to the drafting and critical appraisal of the manuscript. Final approval for the version to be published was given by RP.

Patient consent and ethical approval

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (protocol number 14_150R), and the approved protocol was made available to the journal and reviewers during peer review. Ethical approval for observational research using the CPRD with approval from ISAC has been granted by a National Research Ethics Service committee (Trent MultiResearch Ethics Committee, REC reference number 05/MRE04/87).

Data sharing

The data that support the findings of this study are available from the Medicines and Healthcare Products Regulatory Agency, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. Data are, however, available from the Medicines and Healthcare Products Regulatory Agency, subject to approval from ISAC.

Acknowledgements

We would like to thank Alice Fuller and Dr Sarah Lay-Flurrie for their hard work in providing much of the initial data management for this project.

Suggested reviewers

Prof Simon de Lusignan (s.lusignan@surrey.ac.uk)

Professor of Primary Care & Clinical Informatics / Chair in Health Care Management / Head of the Department of Clinical and Experimental Medicine.

Prof Martin Gulliford (martin.gulliford@kcl.ac.uk)

Professor of Public Health

Bibliography

1 National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. Clinical guideline [CG182]. 2014.https://www.nice.org.uk/guidance/cg182

2 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**:S1–266.

3 Department of Health. The National Services Framework for Renal Services. Part One: Dialysis and Transplantation. 2004.

4 British Medical Association. Revisions to the GMS contract 2006/07. 2006.http://www.nhsemployers.org/-/media/Employers/Documents/Primary-care-contracts/QOF/2006-07/Revisions-to-the-GMS-contract-200607---Delivering-investments-in-general-practice.pdf?la=en&hash=C4949A6E6518C75287E55BCB13A8D311AD0DF3E4

5 National Institute for Health and Care Excellence. NICE Clinical Guideline 73: Chronic Kidney Disease: Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care. 2008.https://www.nice.org.uk/guidance/CG73

6 British Medical Association. Quality and Outcomes Framework guidance for GMS contract 2009/10. 2009.http://www.nhsemployers.org/~/media/Employers/Documents/Primary care contracts/QOF/2010-11/Quality and Outcomes Framework guidance for GMS contract 200910 - Delivering investment in general practice.pdf

7 McGovern AP, Rusholme B, Jones S, *et al.* Association of chronic kidney disease (CKD) and failure to monitor renal function with adverse outcomes in people with diabetes: a primary care cohort study. *BMC Nephrol* 2013;**14**:198. doi:10.1186/1471-2369-14-198

8 de Lusignan S, Nitsch D, Belsey J, *et al.* Disparities in testing for renal function in UK primary care: cross-sectional study. *Fam Pract* 2011;**28**:638–46. doi:10.1093/fampra/cmr036

9 Doll H, Shine B, Kay J, *et al.* The rise of cholesterol testing: how much is unnecessary. *Br J Gen Pract* 2011;**61**:e81-8. doi:10.3399/bjgp11X556245

10 Oke J, Shine B, McFadden E, *et al.* Trends in serum creatinine testing in Oxfordshire, UK, 1993-2013: a population-based cohort study. *BMJ Open* 2015;**5**:e009459. doi:10.1136/bmjopen-2015-009459

11 Zhi M, Ding EL, Theisen-Toupal J, *et al.* The landscape of inappropriate laboratory testing: a 15-year meta-analysis. *PLoS One* 2013;**8**:e78962. doi:10.1371/journal.pone.0078962

12 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013;**3**:1–150.

13 Charles RF, Powe NR, Jaar BG, *et al.* Clinical Testing Patterns and Cost Implications of Variation in the Evaluation of CKD Among US Physicians. *Am J Kidney Dis* 2009;**54**:227–37. doi:10.1053/j.ajkd.2008.12.044

14 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;**44**:827–36. doi:10.1093/ije/dyv098

15 Levey AS, Bosch JP, Lewis JB, *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461–70. doi:10.7326/0003-4819-130-6-199903160-

00002

16 Levey AS, Stevens LA, Schmid CH, *et al.* A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* 2009;**150**:604–12. doi:10.7326/0003-4819-150-9-200905050-00006

17 R Core Team. R: A Language and Environment for Statistical Computing. 2018.https://www.r-project.org

18 Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York: : Springer-Verlag 2016. http://ggplot2.org

19 Laud PJ. Equal-tailed confidence intervals for comparison of rates. *Pharm Stat* 2017;**16**:334–48. doi:10.1002/pst.1813

20 Laud PJ. ratesci: Confidence Intervals for Comparisons of Binomial or Poisson Rates. 2018.

21 Venables WN, Ripley BD. *Modern Applied Statistics with S*. Fourth. New York: : Springer 2002. http://www.stats.ox.ac.uk/pub/MASS4

22 KDIGO. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013;**3**:136–50.

23 Inker LA, Astor BC, Fox CH, *et al.* KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD. *Am J Kidney Dis* 2014;**63**:713–35. doi:10.1053/j.ajkd.2014.01.416

24 Byrne C, Caskey F, Dawnay CC, *et al.* UK Renal Registry UK Renal Registry 19th Annual Report of the Renal Association. *Nephron* 2017;**137**.

25 Kerr M, Bray B, Medcalf J, *et al.* Estimating the Financial Cost of Chronic Kidney Disease to the NHS in England. *Nephrol Dial Transplant* 2012;**27**:iii73-80. doi:10.1093/ndt/gfs269

26 O'Callaghan CA, Shine B, Lasserson DS. Chronic Kidney Disease: A Large-Scale Population-Based Study of the Effects of Introducing the CKD-EPI Formula for eGFR Reporting. *BMJ Open* 2011;**1**:e000308. doi:10.1136/bmjopen-2011-000308

27 Glassock RJ, Winearls C. Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol* 2008;**3**:1563–8. doi:10.2215/CJN.00960208

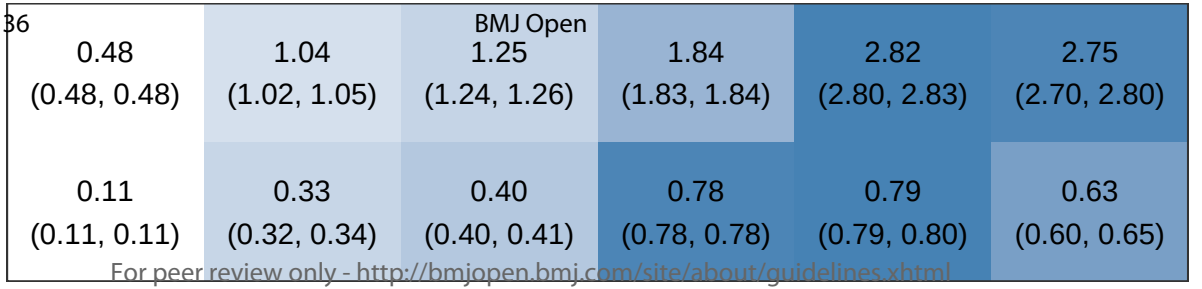
28 Fink HA, Ishani A, Taylor BC, *et al.* Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: a systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2012;**156**:570–81. doi:10.7326/0003-4819-156-8-201204170-00004

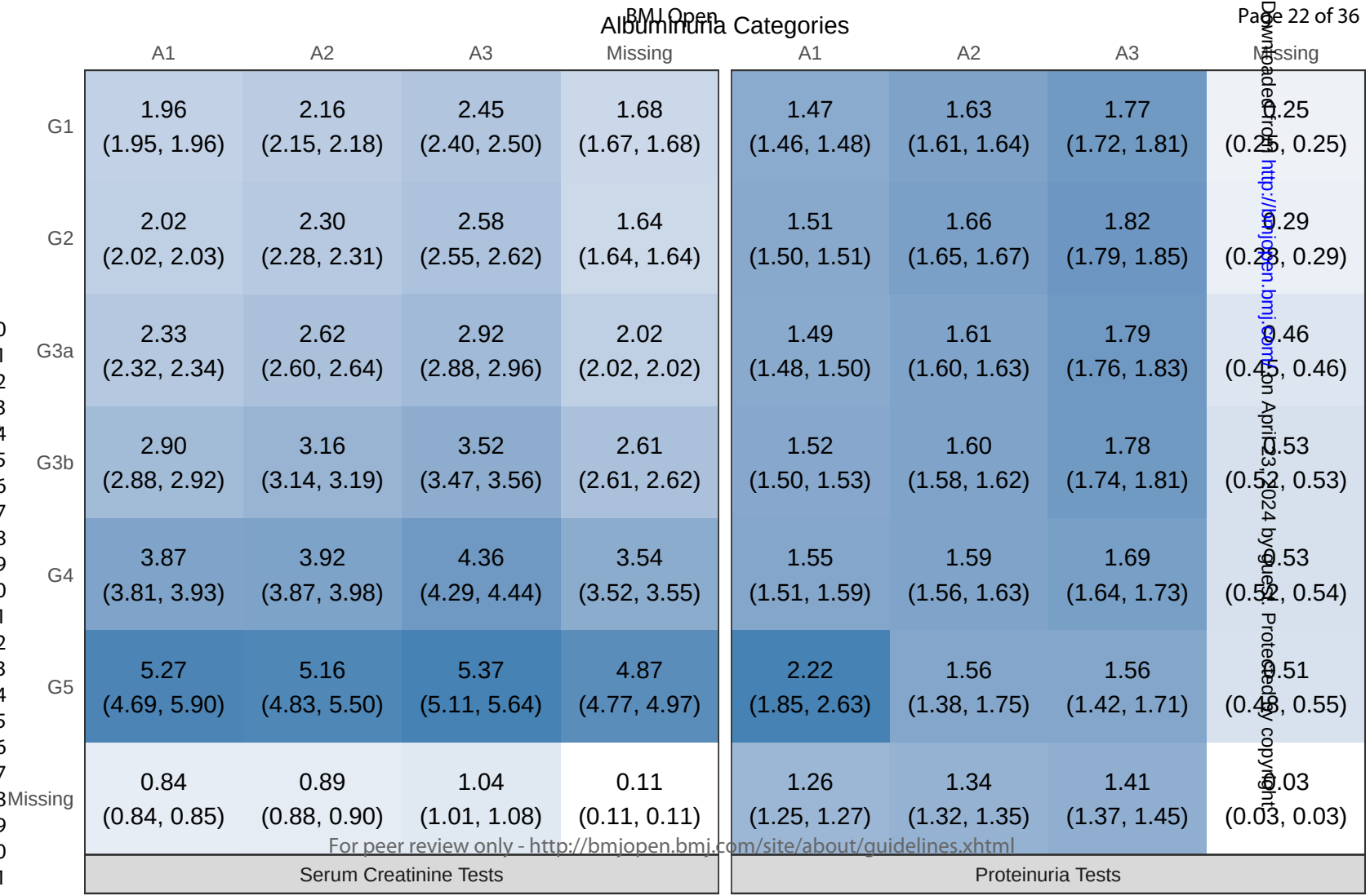
29 Glasziou PP, Irwig L, Heritier S, *et al.* Monitoring Cholesterol Levels: Measurement Error or True Change? *Ann Intern Med* 2008;**148**:656–61.

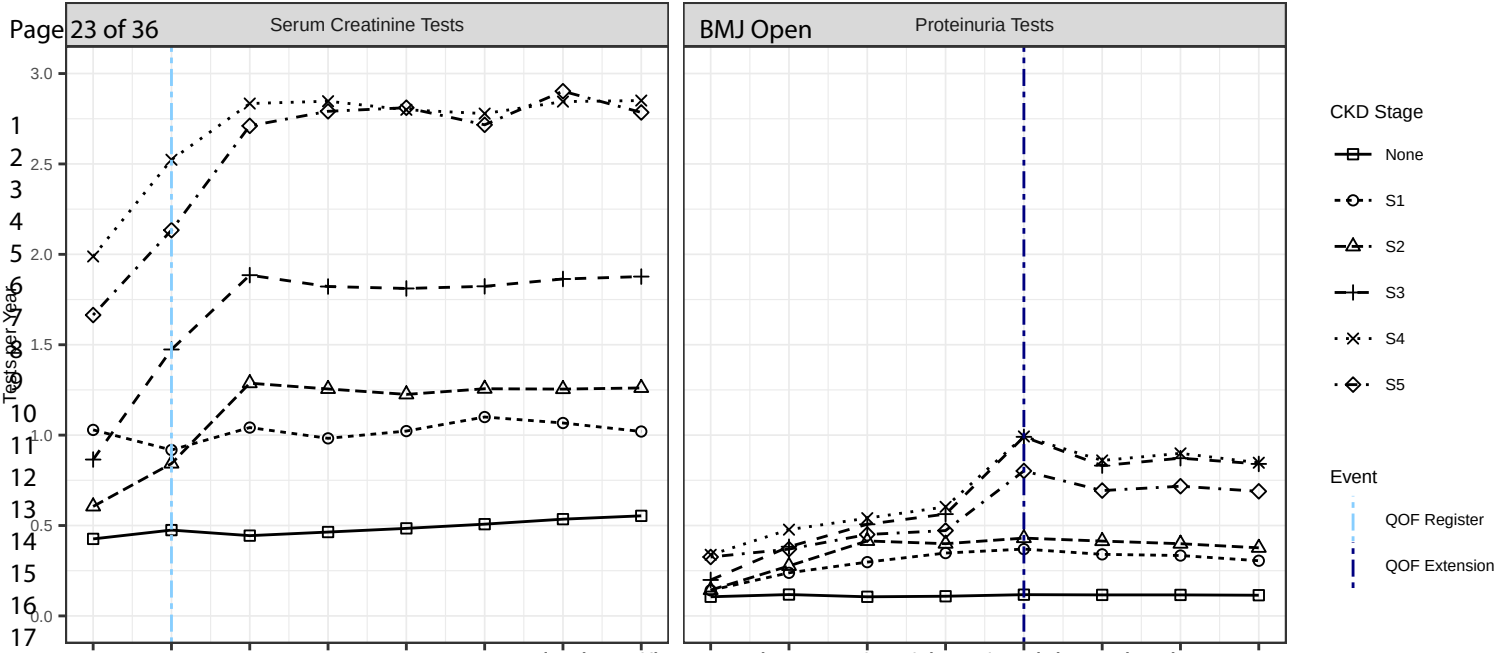
30 Lamb EJ, Brettell EA, Cockwell P, *et al.* The eGFR-C study: Accuracy of Glomerular Filtration Rate (GFR) Estimation Using Creatinine and Cystatin C and Albuminuria for Monitoring Disease Progression in Patients with Stage 3 Chronic Kidney Disease - Prospective Longitudinal Study in a Multiethnic . *BMC Nephrol* 2014;**15**:13. doi:10.1186/1471-2369-15-13

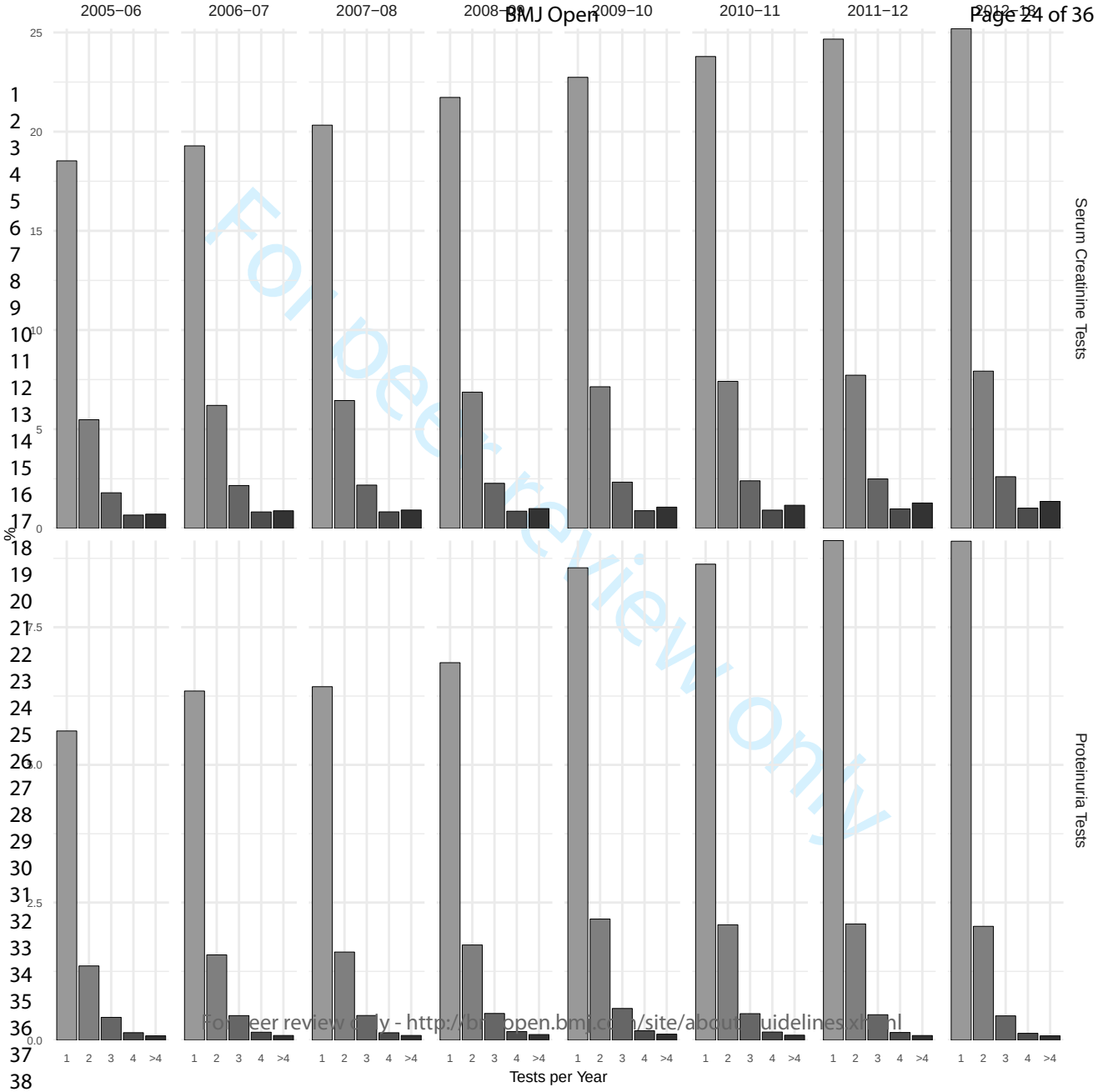
31 Gandhi TK, Kachalia A, Thomas EJ, *et al.* Missed and Delayed Diagnoses in the Ambulatory Setting: A Study of Closed Malpractice Claims. *Ann Intern Med* 2006;**145**:488–96.

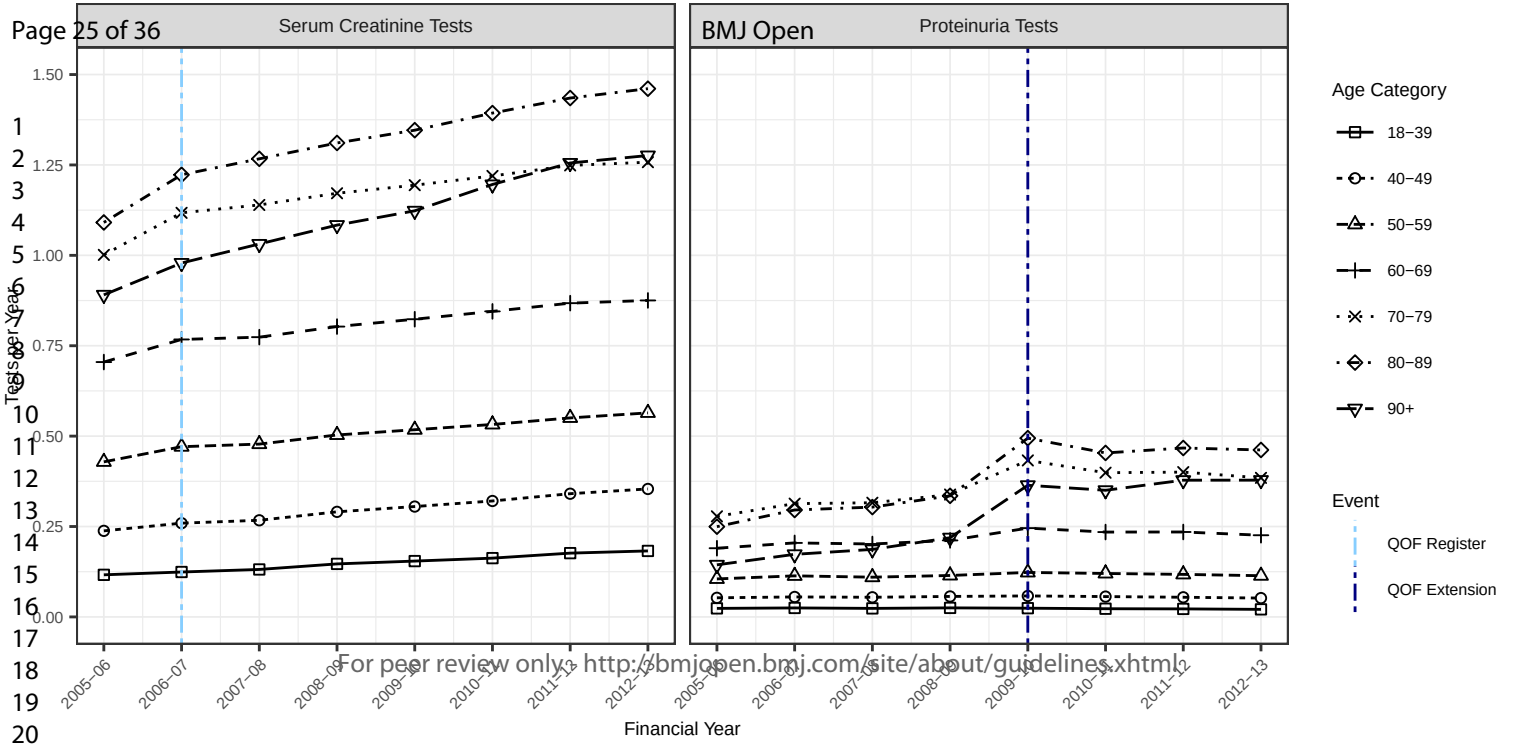
32 Fanshawe TR, Ordóñez-Mena JM, Turner PJ, *et al.* Frequencies and Patterns of Laboratory Test Requests From General Practice: A Service Evaluation to Inform Point-of-Care Testing. *J Clin Pathol* 2018;**0**:1–6. doi:10.1136/jclinpath-2018-205242

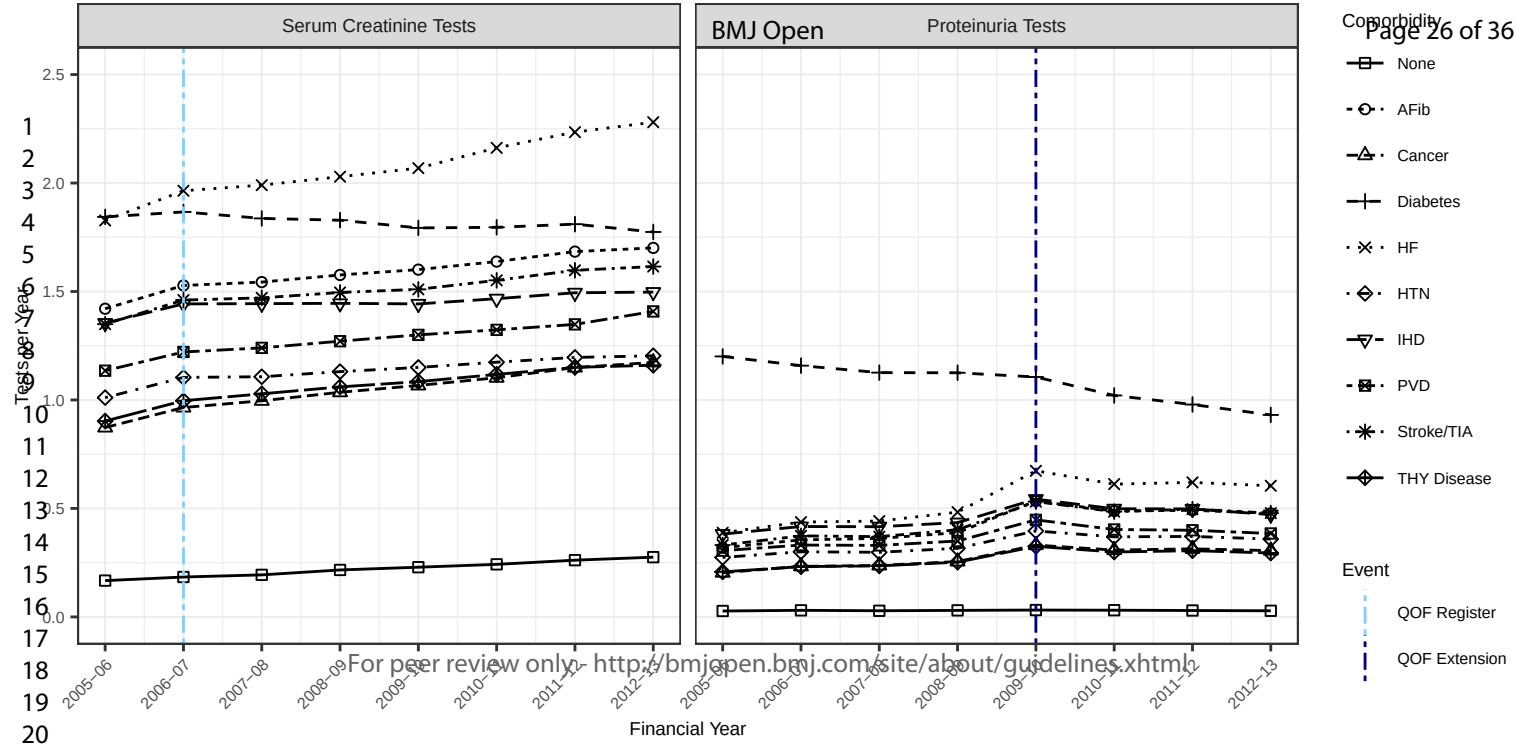


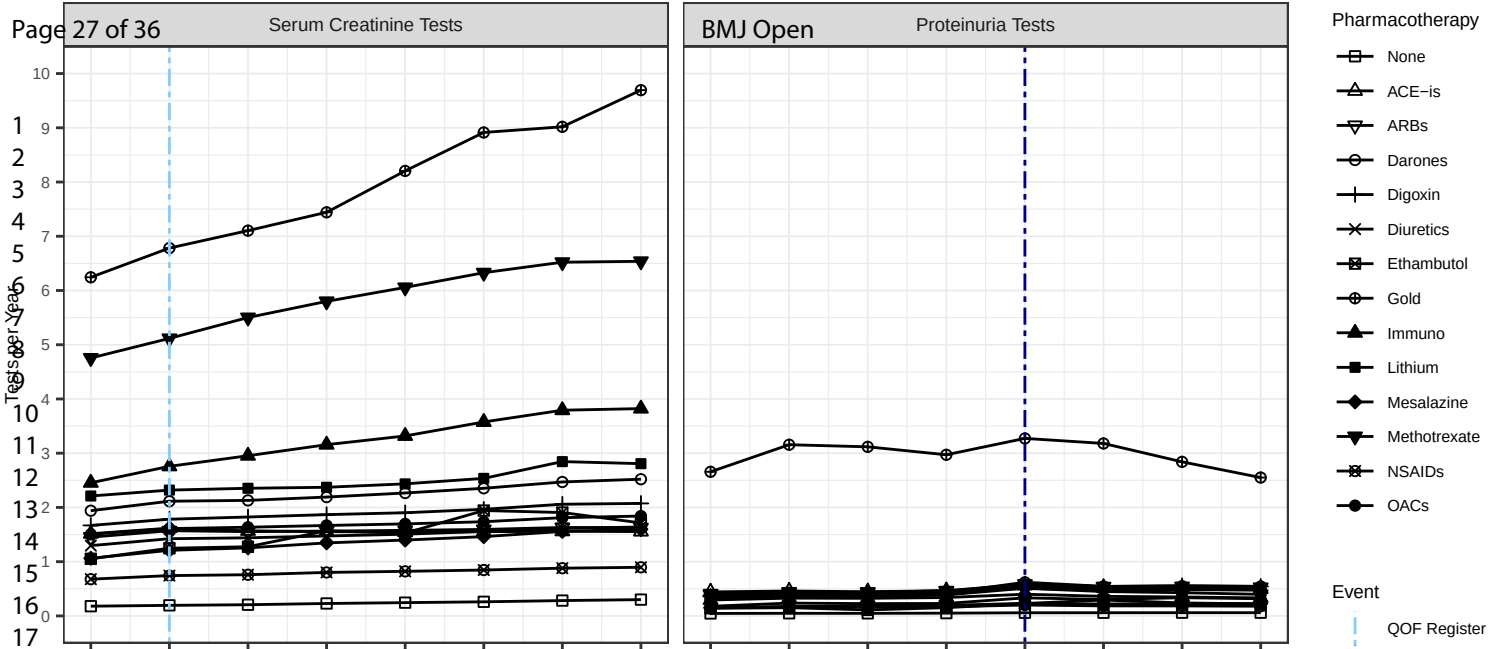












Supplementary material

Serum creatinine test Read codes

Supplementary Table 1 - Serum creatinine testing Read codes.

Medical Code	Read Code	Read Term
5	44J3.00	Serum creatinine
3927	44J3300	Serum creatinine raised
13736	44JF.00	Plasma creatinine level
26903	44J3200	Serum creatinine normal
31277	44J3000	Serum creatinine abnormal
35545	44J3100	Serum creatinine low
42345	44J3z00	Serum creatinine NOS
45096	44JD.00	Corrected serum creatinine level
62062	44JC.00	Corrected plasma creatinine level

Proteinuria test Read codes

Supplementary Table 2 - Proteinuria testing Read codes.

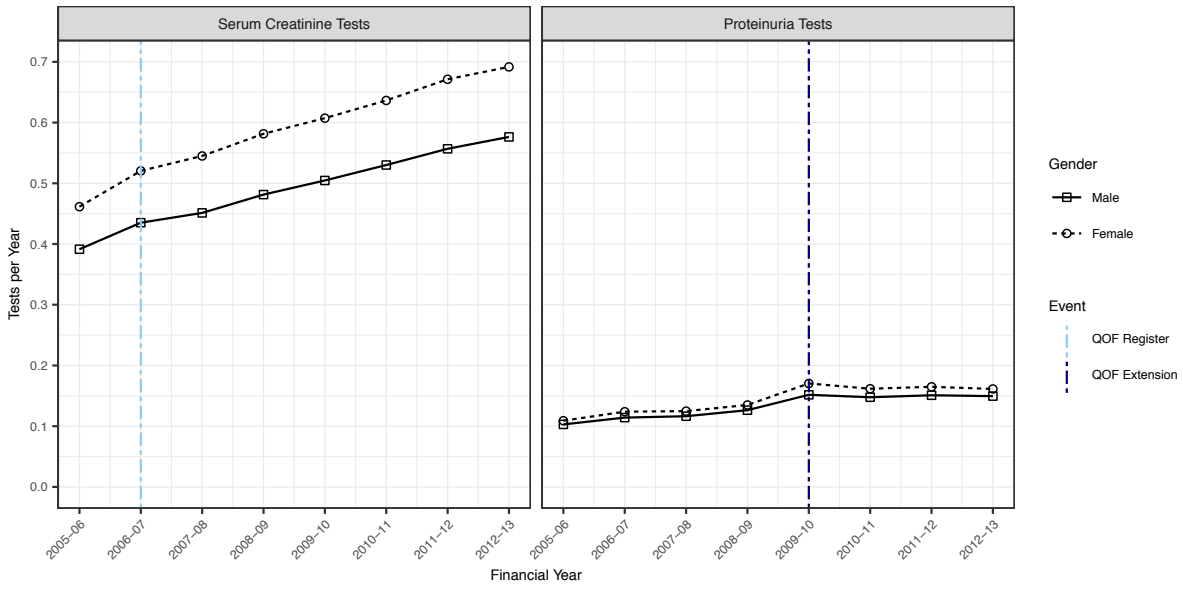
Medical Code	Read Code	Read Term
43	467..00	Urine protein test
1802	4678	Proteinuria
2482	D011100	Vit B12 defic anaemia due to malabsorption with proteinuria
2607	46TC.00	Urine albumin:creatinine ratio
5451	R110000	[D]Albuminuria
8482	467A.00	24 hour urine protein output
9430	4679	Urine dipstick for protein
10924	R110300	[D]Microalbuminuria
11248	R110.00	[D]Proteinuria
13590	4674	Urine protein test = +
13600	4677	Urine protein test = ++++
13611	4675	Urine protein test = ++
13612	4673	Urine protein test = trace
13613	46N2.00	Urine protein abnormal
13621	4676	Urine protein test = +++
14091	4672	Urine protein test negative
14092	4671	Urine protein test not done
14094	467E.00	Urine protein level
14113	44J7.00	Albumin / creatinine ratio
14382	46N1.00	Urine protein normal

Medical Code	Read Code	Read Term
14389	46N5.00	24 hour urine protein excretion test
14391	46TD.00	Urine microalbumin:creatinine ratio
14395	46N..00	Urine protein
14405	46N6.00	24 hour urine albumin output
14410	46N4.00	Urine albumin
14411	46M7.00	Urine creatinine
14429	46N3.00	Urine total protein
14434	46MD.00	24 hour urine creatinine output
14563	46W..00	Urine microalbumin
14564	46W2.00	Microalbumin excretion rate
14901	K136.00	Benign postural proteinuria
16465	K190X00	Persistent proteinuria, unspecified
17106	46W1.00	Urine microalbumin negative
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
23281	44J6.00	Albumin excretion rate
23334	L162.11	Albuminuria in pregnancy without hypertension
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
27059	467Z.00	Urine protein test NOS
27214	46NZ.00	Urine protein NOS
27266	44lD.00	Urine protein/creatinine ratio
28180	46W0.00	Urine microalbumin positive
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
34173	L12B.00	Proteinuric hypertension of pregnancy
34265	L16C000	Gestational proteinuria
34680	R110200	[D]Exercise proteinuria
36243	K136.11	Orthostatic proteinuria
36394	L16C.00	Pregnancy induced oedema+proteinuria without hypertension
37201	L16C100	Gestational oedema with proteinuria
38284	R110z00	[D]Proteinuria NOS
39248	46N8.00	Urine microalbumin profile
43262	467H.00	Random urine protein level
43524	44JG.00	Overnight albumin excretion rate
43611	K0A4.00	Isolated proteinuria with specified morphological lesion
44179	46N7.00	Urine protein/creatinine index
49741	68K2.00	Urine screen for protein
59992	K0A4W00	Isolated proteinuria, with unspecified morpholog changes
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
61470	66Al.00	Diabetic monitoring - higher risk albumin excretion
64030	Kyu5G00	[X]Persistent proteinuria, unspecified

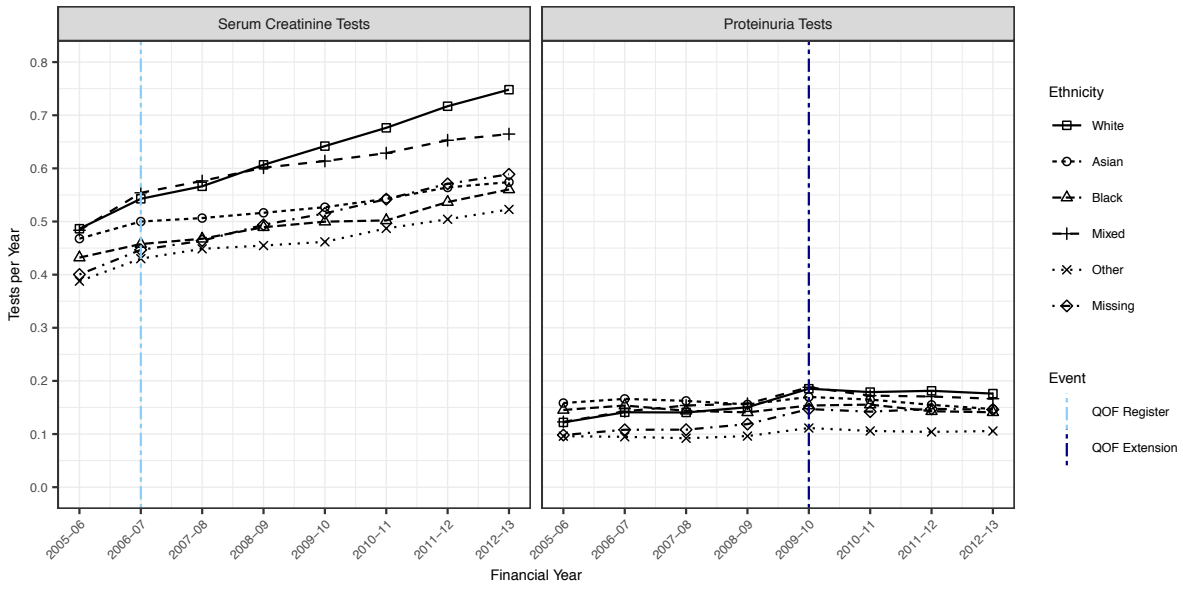
Medical Code	Read Code	Read Term
66475	66Ak.00	Diabetic monitoring - lower risk albumin excretion
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
92998	Lyu1.00	[X]Oedema,proteinuria+hypertens in pregnancy,childbrth,puerp
94789	1Z17.00	Chronic kidney disease stage 1 with proteinuria
94793	1Z1B.00	Chronic kidney disease stage 3 with proteinuria
95121	1Z1A.00	Chronic kidney disease stage 2 without proteinuria
95122	1Z1H.00	Chronic kidney disease stage 4 with proteinuria
95123	1Z1C.00	Chronic kidney disease stage 3 without proteinuria
95145	1Z1B.11	CKD stage 3 with proteinuria
95146	1Z19.00	Chronic kidney disease stage 2 with proteinuria
95175	1Z1E.00	Chronic kidney disease stage 3A without proteinuria
95176	1Z1E.11	CKD stage 3A without proteinuria
95177	1Z1G.00	Chronic kidney disease stage 3B without proteinuria
95178	1Z1F.00	Chronic kidney disease stage 3B with proteinuria
95180	1Z1F.11	CKD stage 3B with proteinuria
95188	1Z1C.11	CKD stage 3 without proteinuria
95405	1Z1L.00	Chronic kidney disease stage 5 without proteinuria
95406	1Z1J.00	Chronic kidney disease stage 4 without proteinuria
95408	1Z1D.00	Chronic kidney disease stage 3A with proteinuria
95508	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
95571	1Z1D.11	CKD stage 3A with proteinuria
95572	1Z18.00	Chronic kidney disease stage 1 without proteinuria
97587	1Z1J.11	CKD stage 4 without proteinuria
97683	1Z1L.11	CKD stage 5 without proteinuria
97978	1Z1A.11	CKD stage 2 without proteinuria
97979	1Z19.11	CKD stage 2 with proteinuria
97980	1Z17.11	CKD stage 1 with proteinuria
99160	1Z1K.11	CKD stage 5 with proteinuria
99312	1Z1H.11	CKD stage 4 with proteinuria
100633	1Z1G.11	CKD stage 3B without proteinuria
101572	K0A4X00	Isolated proteinuria, with oth specif morpholog changes
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria
104677	2126A00	Proteinuria resolved
105302	K08yA00	Proteinuric diabetic nephropathy
108916	44lzX00	Random urine protein:creatinine ratio
109657	1Z1Y.00	CKD with GFR category G3b & albuminuria category A2
109804	1Z1T.00	CKD with GFR category G3a & albuminuria category A1
109805	1Z1V.00	CKD with GFR category G3a & albuminuria category A2
109904	1Z1b.00	CKD with GFR category G4 & albuminuria category A2
109905	1Z1W.00	CKD with GFR category G3a & albuminuria category A3

Medical Code	Read Code	Read Term
109963	1Z1X.00	CKD with GFR category G3b & albuminuria category A1
109980	1Z1a.00	CKD with GFR category G4 & albuminuria category A1
109981	1Z1e.00	CKD with GFR category G5 & albuminuria category A2
109990	1Z1Z.00	CKD with GFR category G3b & albuminuria category A3
110003	1Z1N.00	CKD with GFR category G1 & albuminuria category A2
110033	1Z1M.00	CKD with GFR category G1 & albuminuria category A1
110108	1Z1R.00	CKD with GFR category G2 & albuminuria category A2
110133	1Z1d.00	CKD with GFR category G5 & albuminuria category A1
110251	1Z1S.00	CKD with GFR category G2 & albuminuria category A3
110269	1Z1Q.00	CKD with GFR category G2 & albuminuria category A1
110467	1Z1f.00	CKD with GFR category G5 & albuminuria category A3
110484	1Z1P.00	CKD with GFR category G1 & albuminuria category A3
110626	1Z1c.00	CKD with GFR category G4 & albuminuria category A3
111022	1Z18.11	CKD stage 1 without proteinuria

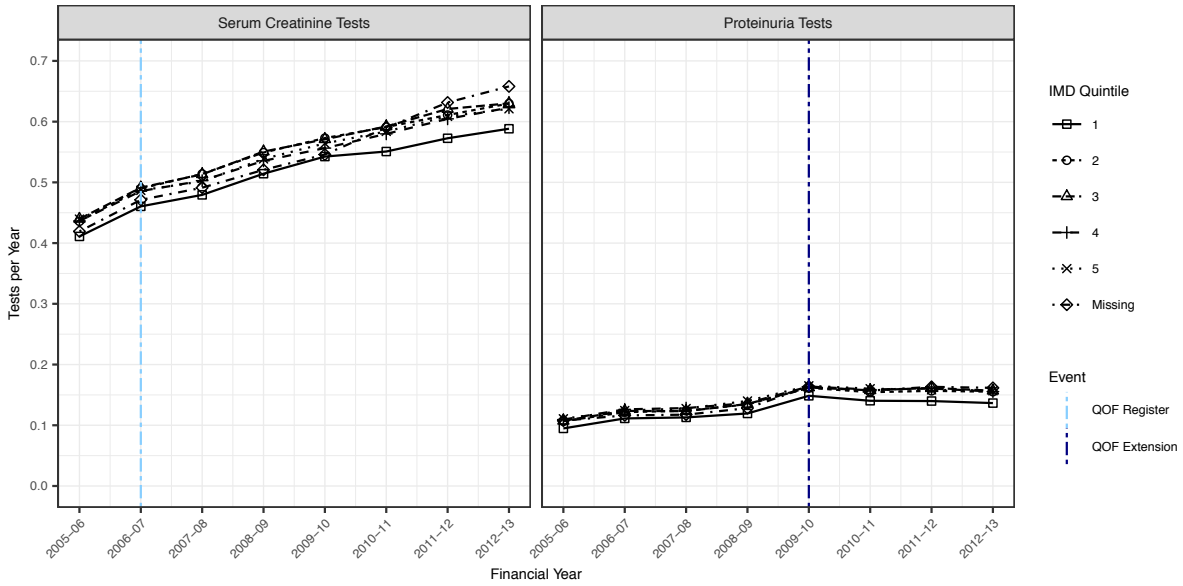
Trends over time



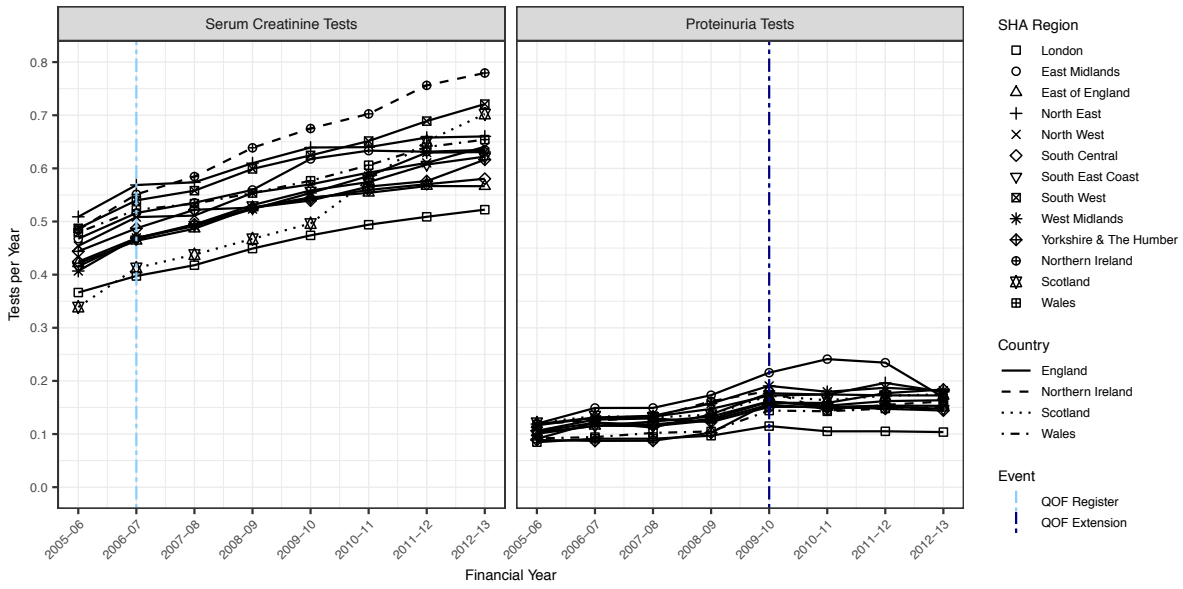
Supplementary Figure 1 - Rates of kidney function testing per financial year, stratified by gender.



Supplementary Figure 2 - Rates of kidney function testing per financial year, stratified by ethnicity.



Supplementary Figure 3 - Rates of kidney function testing per financial year, stratified by IMD quintile.



Supplementary Figure 4 - Rates of kidney function testing per financial year, stratified by SHA region.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 - 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7

Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) If applicable, explain how loss to follow-up was addressed	5
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8 - 9
		(b) Indicate number of participants with missing data for each variable of interest	8 - 9
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-13 & 23

		(b) Report category boundaries when continuous variables were categorized	6 - 7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13 - 14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14 - 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14 - 16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trends in kidney function testing in UK primary care since the introduction of the Quality and Outcomes Framework: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028062.R1
Article Type:	Research
Date Submitted by the Author:	18-Mar-2019
Complete List of Authors:	Feakins, Benjamin; University of Oxford, Nuffield Department of Primary Care Health Sciences Oke, Jason; University of Oxford, Nuffield Department of Primary Care Health Sciences McFadden, Emily; University of Oxford, Nuffield Department of Primary Care Health Sciences Aronson, Jeffrey; University of Oxford, Nuffield Department of Primary Care Health Sciences Lasserson, Daniel; University of Birmingham, Institute of Applied Health Research; University of Oxford, Nuffield Department of Medicine O'Callaghan, Christopher; University of Oxford, Nuffield Department of Medicine; Oxford Radcliffe Hospitals NHS Trust, John Radcliffe Hospital Taylor, Clare; University of Oxford, Nuffield Department of Primary Care Health Sciences Hill, Nathan; Bristol-Myers Squibb Pharmaceuticals Ltd Stevens, Richard; University of Oxford, Nuffield Department of Primary Care Health Sciences Perera, Rafael; University of Oxford, Nuffield Department of Primary Care Health Sciences
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Health services research, Renal medicine, Medical management
Keywords:	Serum creatinine, Proteinuria, Kidney function, PRIMARY CARE, Monitoring, Chronic Kidney Disease

Trends in kidney function testing in UK primary care since the introduction of the Quality and Outcomes Framework: a retrospective cohort study using CPRD

Benjamin G. Feakins[1] (benjamin.feakins@phc.ox.ac.uk), Jason L. Oke[1] (jason.oke@phc.ox.ac.uk), Emily C. McFadden[1] (emily.mcfadden@phc.ox.ac.uk), Jeffrey K. Aronson[1] (jeffrey.aronson@phc.ox.ac.uk), Daniel S. Lasserson[2,3] (d.s.lasserson@bham.ac.uk), Chris A. O'Callaghan[1,3] (chris.ocallaghan@ndm.ox.ac.uk), Clare J. Taylor[1] (clare.taylor@phc.ox.ac.uk), Nathan R. Hill[4] (nathan.hill@bms.com), Richard J. Stevens[1] (richard.stevens@phc.ox.ac.uk), Rafael Perera[1] (rafael.perera@phc.ox.ac.uk)

[1] Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.

[2] Institute of Applied Health Research, University of Birmingham, Birmingham, UK.

[3] Nuffield Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

[4] Bristol-Meyers Squibb Pharmaceuticals Limited, Uxbridge, UK

Word count:

Abstract: 300

Main text: 4,425

Corresponding author:

Jason Oke, DPhil (jason.oke@phc.ox.ac.uk)
Nuffield Department of Primary Care Health Sciences
Radcliffe Observatory Quarter, Woodstock Road
Oxford
OX2 6GG

Abstract

Objectives: To characterise serum creatinine and urinary protein testing in UK general practices from 2005 to 2013, and to examine how the frequency of testing varies across demographic factors, with the presence of chronic conditions, and with the prescribing of drugs for which kidney function monitoring is recommended.

Design: Retrospective open cohort study.

Setting: Routinely collected data from 630 UK general practices contributing to the Clinical Practice Research Datalink.

Participants: 4,573,275 patients aged over 18 years registered at up-to-standard practices between 1st April 2005 and 31st March 2013. At study entry, no patients were kidney transplant donors or recipients, pregnant, or on dialysis.

Primary outcome measures: The rate of serum creatinine and urinary protein testing per year, and the percentage of patients with isolated and repeated testing per year.

Results: The rate of serum creatinine testing increased linearly across all age groups. The rate of proteinuria testing increased sharply in the 2009-10 financial year, but only for patients aged 60 or over. For patients with established chronic kidney disease (CKD), creatinine testing increased rapidly in 2005-06 and 2006-07, and proteinuria testing in 2009-10, reflecting the introduction of Quality and Outcomes Framework indicators. In adjusted analyses, CKD Read codes were associated with up to a two-fold increase in the rate of serum creatinine testing, while other chronic conditions and potentially nephrotoxic drugs were associated with up to a six-fold increase. Regional variation in serum creatinine testing reflected country boundaries.

Conclusions: Over a nine-year period, there have been increases in the numbers of patients having kidney function tests annually and in the frequency of testing. Changes in the recommended management of CKD in primary care were the primary determinant, and increases persist even after controlling for demographic and patient-level factors. Future studies should address whether increased testing has led to better outcomes.

Keywords: Serum creatinine, proteinuria, kidney function, primary care, monitoring, chronic kidney disease.

Article summary

Strengths and limitations of this study

- To date, this is the largest population study of trends in renal function testing in primary care.
- The data source did not permit us to ascertain why a kidney function test was performed.

- The transitioning of 'high risk' patients from primary to secondary care means the estimates in this study may be liable to underestimate the amount of testing performed in certain patient subgroups.

Introduction

Kidney function testing in primary care is used to diagnose and monitor chronic kidney disease (CKD). Testing is recommended at baseline, and after initiation of some drugs such as antihypertensives [1]. Kidney function is usually tested by measuring serum creatinine, and screening for glomerular disease is undertaken by measuring urine albumin or protein concentrations.

In 2002 the Kidney Disease Outcomes and Quality Initiative (K/DOQI) published clinical guidelines advocating that CKD be categorised into five stages [2]. Two years later, these stages were adopted by the UK Quality and Outcomes Framework (QOF), which is a set of business rules for primary care that include financial incentives to regularly monitor and test certain subsets of patients, and to record their data [3]. The 2006-07 financial year saw an extension to QOF that required general practitioners to maintain a register of patients with CKD stages 3-5 [4]. In 2008, the National Institute for Health and Care Excellence (NICE) recommended monitoring eGFR levels in high risk patients [5]. Then in the 2009-10 financial year a further QOF extension incentivised monitoring urinary markers of kidney disease (such as proteinuria) in patients on the CKD register [6]. Current NICE recommendations on the frequency of testing are based on the underlying cause of CKD, previous test results, comorbidities, and the treatments being used. Monitoring is recommended annually in patients with mild to moderate reductions in kidney function and every three months in patients with more advanced disease [1].

National rates of kidney function testing and potential differences between different populations have not been characterised. In contrast, rates of kidney function testing in patients with diabetes have been well documented. A cohort study of adults with diabetes showed that under 13% had incomplete CKD screening and just 4.4% had no serum creatinine measurement on record in the two and half years before the start of the study, whereas the albumin-creatinine ratio (ACR) was not monitored in 37% during the same period [7]. Similarly, high frequencies of creatinine testing have been observed among patients with diabetes in studies looking at individual health regions, but with more variable levels of recording in patients without diabetes across different ages, genders and ethnic groups [8].

There has been a dramatic increase in the use of laboratory testing over recent decades, particularly repeated testing or monitoring [9,10]. However, it is unclear whether this increase is appropriate and consistent with guideline recommendations or whether it represents over-testing. Appropriate testing of kidney function might be of value in planning management to slow the progression of the disease and, therefore, lead to tangible patient benefit. However, over-use of tests provides little patient benefit and adds to the financial burden of healthcare systems. A recent meta-analysis of the use of laboratory tests during the last 15 years showed that under-use of high-volume tests (such as creatinine) was more likely than over-use [11]. A cross-sectional survey of US physicians' patterns of care in patients with CKD showed that 85% of physicians recommended one additional test, which was not recommended in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [12]. These tests were most likely to be magnetic resonance angiography of renal arteries or serum protein electrophoresis, rather than blood or urinary measurements [13]. It is, of course, possible that over-use and under-use may co-exist, with some patients receiving more tests than indicated and other patients not receiving tests warranted by their clinical history, recent health, and age.

Currently, the UK is the only nationalised and publicly funded health service that has introduced financial incentives to improve the quality of healthcare for patients with CKD. National guidelines in other countries also recommend quality standards for CKD care, including diagnosis, monitoring of renal function, and control of cardiovascular risk factors [14]. However, guideline bodies outside the UK have stopped short of implementing financial incentives for CKD care, and therefore studying the impact of QOF in the UK can inform international efforts to improve outcomes for patients with CKD.

The aim of this study is to describe rates of kidney function testing since the introduction of the QOF in UK general practice. Specifically, we have examined the numbers of serum creatinine and proteinuria tests requested in each financial year during the nine years from 2005 to 2013 by: age category, gender, ethnicity, index of multiple deprivation (IMD), Strategic Health Authority (SHA), CKD stage, the presence or absence of major comorbidities (such as diabetes, hypertension, cardiovascular disease, atrial fibrillation), and the prescription of nephrotoxic drugs.

Methods

Data

We used the Clinical Practice Research Datalink (CPRD) [15] to construct an open cohort study of adults (≥ 18 years of age) registered at UK general practices whose data quality was deemed to be "up-to-standard", i.e. the data committed by general practices has reached a standard suitable for research (based on a CPRD algorithm that primarily focusses on death recording and gaps in the data). The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (protocol number 14_150R) and the approved protocol was made available to the journal and reviewers during peer review. Ethical approval for observational research using the CPRD with approval from ISAC has been granted by a National Research Ethics Service committee (Trent MultiResearch Ethics Committee, REC reference number 05/MRE04/87).

Study period

We selected a start date of 1st April 2005, which post-dated the publication of the K/DOQI guidelines for classification of CKD in 2002 [2], and the introduction of QOF in UK primary care in 2004 [3]. The study end date was 31st March 2013.

Inclusion and exclusion criteria

Eligible patients had to have been registered with their practice for a minimum of 12 months before their study entry to ensure adequate recording of baseline covariates. The study entry date was defined as the latest of either the study start date (1st April 2005) or the date of the patient's current registration date + 12 months. We excluded patients who were living kidney donors, had a renal transplant, ever underwent dialysis, or women who were pregnant in the 12 months prior to study entry. Follow-up ended at the study end date, unless preceded by the patient's death, transfer out of CPRD, the last available linked data, or (where applicable) pregnancy, renal transplantation/donation, or dialysis. For any given financial year, patient records were excluded if their data were incomplete/censored.

Outcomes

A serum creatinine test was deemed to have occurred when a patient test record contained a valid date, an entity type associated with serum creatinine testing or blood/serum biochemistry, and a Read code for serum creatinine testing (Supplementary Table 1).

A proteinuria test was deemed to have occurred when a patient test record contained a valid date, an entity type associated with urine biochemistry tests and a Read code for albuminuria or proteinuria testing (Supplementary Table 2).

Subsequent tests recorded per patient on the same day were discarded, under the assumption that they were data entry errors.

Variables

Nominal CKD stage was identified by Read codes (Supplementary Table 1). Albuminuria status was derived using either ACR or protein: creatinine ratio (PCR). When these were unavailable, raw albumin excretion rate or protein excretion rate were used. Normoalbuminuria (albuminuria stage A1) was defined as <3 mg/mmol, microalbuminuria (albuminuria stage A2) was defined as 3-30 mg/mmol, and macroalbuminuria (albuminuria stage A3) as >30 mg/mmol, in accordance with the 2012 KDIGO guidelines for evaluation and management of CKD [12]. Estimated glomerular filtration rate (eGFR) was calculated using the four-part Modification of Diet in Renal Disease (MDRD) equation based on recorded values of serum creatinine, sex, age at test, and ethnicity [16]. The four-part MDRD equation was used in place of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17], more recently advocated by NICE, as this was the equation that would predominantly have been used to monitor patients during the follow-up period.

Prevalence data for the comorbidities of: atrial fibrillation, cancer, diabetes, heart failure, hypertension, ischaemic heart disease, peripheral vascular disease, stroke or transient ischaemic attack, and thyroid disease, were assessed by the presence of diagnostic Read codes in patient clinical records.

Pharmacotherapies that were either nephrotoxic, excreted by the kidneys or that affected serum potassium were established through consensus between the general practitioners/pharmacologists (JA, CO'C and CT). These consisted of: angiotensin-converting enzyme inhibitors (ACE-is), angiotensin receptor blockers (ARBs), amiodarone/dronedarone, digoxin, diuretics, gold, immunosuppressants, lithium, mesalazine, non-steroidal anti-inflammatory drugs (NSAIDs) and oral-anticoagulants (OACs).

Patient demographic data were also extracted, including, age, gender, ethnicity, deprivation, and region. Within these variables, age was categorised into seven levels (18-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+), ethnicity was divided into six categories ("white", "Asian", "black", "mixed", "other" or "missing"), deprivation was categorised into six levels (representing quintiles of IMD data plus a "missing" level), and region was divided into 13 categories (aligning with the 10 SHAs of England, and the countries of Northern Ireland, Scotland and Wales).

Analyses

Trends across kidney disease categorisations

Adherence to the most current NICE guidelines [1] was evaluated by stratifying crude rates of serum creatinine and proteinuria testing (herein jointly referred to as "kidney function testing") by CKD stage, and eGFR and albuminuria categories. We present these rates as tile and line plots.

Trends over time

We calculated crude rates of kidney function tests, stratified by financial year, and further stratified by CKD stage, demographic factors (such as age, ethnicity and deprivation), the presence of various comorbidities and concurrent prescriptions for nephrotoxic drugs. We present the percentage of patients with 1, 2, 3, 4 and >4 tests per financial year for serum creatinine and urinary albumin/protein as bar plots.

Factors associated with kidney function testing

We examined factors associated with serum creatinine testing in CPRD. We used a negative binomial regression model to assess the relationship between demographic factors, the presence of markers for CKD and other chronic conditions, and indicators of drug therapy. We fitted age and year of entry into the study as categorical factors in order to model non-linear associations. The presence of Read codes for CKD was used as markers of kidney disease. We studied 13 geographic regions corresponding to the SHAs of England, and the countries of Scotland, Northern Ireland and Wales. The model was adjusted for the presence of chronic conditions and medications. These were added to the models as binary covariates if a Read code or Gemscript code was present within the eligible data preceding the study entry date for that patient. The outcome of the model was the number of serum creatinine tests on record following study entry with the log person-years of follow-up used as the offset term. The model, therefore, estimates the natural log rates of serum creatinine testing, and covariate effects are log incidence rate ratios (IRRs). We have presented results from unadjusted, i.e. univariable, minimally adjusted, i.e. adjusted for gender, age, ethnicity, deprivation, region and year of entry, and fully adjusted, i.e. adjusted for all extracted variables, models on a natural scale, as IRRs with 95% confidence intervals.

Statistical software and packages

All analyses were conducted in R (version 3.5.1) [18]. Plots were produced using the *ggplot2* package [19]. Crude rates and their 95% confidence intervals were calculated via the skewness-corrected asymptotic score method [20] implemented in the `scaspci()` function of the *ratesci* package [21]. Negative binomial models were fit using the `glm.nb()` function of the *MASS* package [22].

Patient and public involvement

This project has been reviewed by individuals with long term conditions that require frequent monitoring, as well as nurse practitioners and general practice commissioners. Patient and public involvement members have also been invited to the steering and senior management groups. A patient and public involvement expert was also involved as a strategic consultant in a programme of work including this project.

Results

Baseline Demographics

We identified 4,573,275 patients from 630 practices with 26,496,643 person-years of eligible follow-up data, containing a total of 15,049,063 serum creatinine tests and 995,524 proteinuria tests. The median length of follow up was 6.1 (interquartile range (IQR) 3.5 to 9.0) years. The cohort comprised 49.7% men and 50.3% women. The median (IQR) age was 46 (34 to 61) years (Table 1).

Table 1 - Characteristics of the cohort at study entry. (Note: missing categories omitted).

Characteristic	Female (N = 2,279,097)	Male (N = 2,294,178)	Everyone (N =4,573,275)
Age (years)			
18-39	807,015 (35.4%)	904,018 (39.4%)	1,711,033 (37.4%)
40-49	437,734 (19.2%)	475,130 (20.7%)	912,864 (20.0%)
50-59	370,235 (16.2%)	379,112 (16.5%)	749,347 (16.4%)
60-69	286,951 (12.6%)	278,903 (12.2%)	565,854 (12.4%)
70-79	212,826 (9.3%)	174,193 (7.6%)	387,019 (8.5%)
80-89	132,990 (5.8%)	73,456 (3.2%)	206,446 (4.5%)
≥90	31,346 (1.4%)	9,366 (0.4%)	40,712 (0.9%)
Ethnicity			
White	512,088 (22.5%)	441,467 (19.2%)	953,555 (20.9%)
Asian	42,888 (1.9%)	43,623 (1.9%)	86,511 (1.9%)
Black	19,819 (0.9%)	17,302 (0.8%)	37,121 (0.8%)
Mixed	316,792 (13.9%)	303,891 (13.2%)	620,683 (13.6%)
Other	13,933 (0.6%)	14,310 (0.6%)	28,243 (0.6%)
Index of multiple deprivation			
1 (least deprived)	334,473 (14.7%)	337,305 (14.7%)	671,778 (14.7%)
2	340,977 (15.0%)	337,861 (14.7%)	678,838 (14.8%)
3	293,127 (12.9%)	294,250 (12.8%)	587,377 (12.8%)
4	269,680 (11.8%)	277,279 (12.1%)	546,959 (12.0%)
5 (most deprived)	206,571 (9.1%)	217,148 (9.5%)	423,719 (9.3%)
Chronic kidney disease stage			
1	699 (0.0%)	608 (0.0%)	1,307 (0.0%)
2	2,512 (0.1%)	2,009 (0.1%)	4,521 (0.1%)
3	8,149 (0.4%)	4,760 (0.2%)	12,909 (0.3%)
4	687 (0.0%)	459 (0.0%)	1,146 (0.0%)
5	73 (0.0%)	75 (0.0%)	148 (0.0%)
Estimated glomerular filtration rate (mL/min/1.73m^2)			
≥90	142,918 (6.3%)	154,064 (6.7%)	296,982 (6.5%)
60-89	512,731 (22.5%)	459,469 (20.0%)	972,200 (21.3%)
45-59	188,796 (8.3%)	95,043 (4.1%)	283,839 (6.2%)
30-44	52,765 (2.3%)	23,242 (1.0%)	76,007 (1.7%)
15-29	10,543 (0.5%)	5,782 (0.3%)	16,325 (0.4%)
<15	833 (0.0%)	480 (0.0%)	1,313 (0.0%)
Albuminuria (mg/mmol)			
<3.0	39,442 (1.7%)	42,665 (1.9%)	82,107 (1.8%)
3-30	11,978 (0.5%)	14,489 (0.6%)	26,467 (0.6%)
>30	3,096 (0.1%)	3,757 (0.2%)	6,853 (0.1%)
Comorbidities			
Atrial fibrillation	37,041 (1.6%)	28,662 (1.2%)	65,703 (1.4%)

Cancer	44,136 (1.9%)	52,068 (2.3%)	96,204 (2.1%)
Diabetes	267,791 (11.7%)	238,922 (10.4%)	506,713 (11.1%)
Heart failure	12,692 (0.6%)	12,964 (0.6%)	25,656 (0.6%)
Hypertension	21,381 (0.9%)	21,497 (0.9%)	42,878 (0.9%)
Ischaemic heard disease	49,227 (2.2%)	59,621 (2.6%)	108,848 (2.4%)
Peripheral vascular disease	19,153 (0.8%)	21,166 (0.9%)	40,319 (0.9%)
Stroke/Transient ischaemic attack	21,988 (1.0%)	21,774 (0.9%)	43,762 (1.0%)
Thyroid disease	73,289 (3.2%)	16,009 (0.7%)	89,298 (2.0%)

Trends across kidney disease categorisations

Chronic kidney disease categories

When categorising kidney disease according to CKD stages, the highest rates of kidney function testing were found in patients with CKD stage 4 (Figure 1). The lowest rates of testing were observed in patients without a Read code for CKD, however, such patients were still receiving roughly one serum creatinine test every two years and one proteinuria test every nine years. Rates of serum creatinine testing were roughly in line with NICE guidelines for CKD stages 1-4, but fell below recommendation in stage 5 [1].

Figure 1 - Rates of kidney function testing (per year), stratified by CKD stage.

Estimated glomerular filtration rate and albuminuria categories

The rates of serum creatinine testing observed in the data were higher than those advocated by NICE [1] and KDIGO [23] in all eGFR-albuminuria subcategories (Figure 2). The highest rates of serum creatinine testing were in patients with eGFR stage G5. Patterns of proteinuria testing were less consistent, with patients with eGFR stage G5 or albuminuria stage A3 both exhibiting high rates of proteinuria testing. Rates of kidney function testing were generally higher than expected for individuals with either no eGFR or proteinuria stage assigned. For instance, patients with no assignable eGFR category and normal (A1) albuminuria levels were still receiving 0.84 (95% CI: 0.84, 0.85) tests per year, while patients with no assignable albuminuria level and normal (G1) eGFR levels were still receiving 0.25 (95% CI: 0.25, 0.25) proteinuria tests per year.

Figure 2 - Rates of kidney function testing (per year), stratified by eGFR and albuminuria categories.

Trends over time

Trends across CKD categories

Figure 3 shows trends in serum creatinine (left-panel) and urinary protein testing (right-panel), stratified by stage of CKD for the same period. Rates of kidney function testing increased with CKD stage up to stage 4, though rates in CKD stage 5 were lower or similar to rates in CKD stage 4. For patients in stages 2-5, rapid increases in the number of serum creatinine tests coincided with the inclusion of CKD management in QOF in 2006-07 [4] and then stabilised after 2007-08. Sharp increases in proteinuria testing for patients with CKD stages 2-5 also coincided with the incorporation of proteinuria testing into QOF guidelines for the monitoring of CKD in 2009-10 [6].

Figure 3 - Rates of kidney function testing per financial year, stratified by CKD stage.

General trends in testing

The percentage of patients receiving kidney function tests has been steadily increasing year on year (Figure 4). In the 2005-06 financial year, 27.2% of patients received a serum creatinine test, while 7.5% of patients received a proteinuria test. In the 2012-13 financial year, these figures were 38.1% and 11.8%, respectively. These increases appear to be driven by increases in the number of patients with isolated kidney function testing, i.e. patients receiving one test per year, which for serum creatinine tests increased from 18.5% in 2005-06 to 25.2% in 2012-13. For proteinuria testing isolated testing increased from 5.6% in 2005-06 to 9.1% in 2012-13. In the same time period, the percentage of patients with repeated serum creatinine testing, i.e. two or more tests per year, increased from 8.7% to 12.9%, while the percentage of patients with repeated proteinuria testing increased from 2.0% to 2.7%.

Figure 4 - Percentage of patients that have had 1, 2 ,3, 4, or more than 4 kidney function tests per financial year.

Trends in testing across demographic data

Figure 5 shows the yearly trend in testing for serum creatinine (left panel) stratified by age and the equivalent trends in urinary protein tests (right panel). In general, rates of testing were higher with higher age, up to age 80-89 years, but note that rates in the 90+ years age group are not the highest. Serum creatinine test rates increased approximately linearly over time within each decile of age. In contrast, urinary protein test rates were constant over time in age groups less than 60 years, and increased over time for patients over 60 years of age, with a sharp increase in the year 2009-10.

Figure 5 - Rates of kidney function testing per financial year, stratified by age category.

Differences between the rates of kidney function testing were much lower when stratifying by gender (Supplementary Figure 1), ethnicity (Supplementary Figure 2), IMD quintile (Supplementary Figure 3), and geographic region (Supplementary Figure 4). Testing was marginally higher in women than men for both serum creatinine and proteinuria tests, with rate differences of roughly 0.1 tests per year and 0.02 tests per year, respectively. These differences remained relatively constant throughout the follow-up period. Testing remained higher in patients coded in the CPRD as white or mixed ethnicity, with patients of black or Asian ethnicity having lower rates of testing. A similar pattern was found in proteinuria testing. Rates of kidney function testing were similar when stratifying by IMD quintile, with rates being lowest in the lowest (most affluent) IMD quintile, for both markers of kidney function. Stratification by SHA region resulted in slightly larger differences in testing rates of up to 0.25 tests per year for serum creatinine and 0.14 tests per year for proteinuria. London demonstrated the lowest rates of kidney function testing for the majority of the study observation period. The highest rates of serum creatinine testing were initially seen in North-East England, being surpassed by Northern Ireland in 2007-08. Rates of serum creatinine testing were

initially lowest in Scotland and London, until 2010-11, where rates of testing in Scotland increased. Conversely, the highest rates of proteinuria testing were present in the English East Midlands.

Trends in testing across comorbidities and pharmacotherapies

For all evaluated comorbidities, rates of kidney function testing were elevated when compared to a population for whom these comorbidities were absent (Figure 6). Testing appears to have increased across all comorbidities with time, with the exception of diabetes, where the rate of testing appears to have decreased. The highest rates of serum creatinine testing were present in patients with heart failure and diabetes, however, all comorbidities were associated with at least one serum creatinine test per year by 2007-08. The highest rates of proteinuria testing were present in patients with diabetes.

Figure 6 - Rates of kidney function testing per financial year, stratified by comorbidity. Key: AFib = atrial fibrillation; HF = heart failure; HTN = hypertension; IHD = ischaemic heart disease; PVD = peripheral vascular disease; TIA = transient ischaemic attack; THY = thyroid.

Across all evaluated pharmacotherapies, rates of kidney function testing were higher than in patients for whom prescriptions of these therapies were absent (Figure 7). Rates of kidney function testing were relatively stable across time for most comorbidities with a few notable exceptions. For patients receiving prescriptions for gold, methotrexate or other immunosuppressants, serum creatinine testing appears to have increased with time. Proteinuria testing was elevated in patients prescribed gold but was generally less than 0.5 tests/year for all other pharmacotherapies.

Figure 7 - Rates of kidney function testing per financial year, stratified by concomitant pharmacotherapy. Key: ACE-is = angiotensin-converting-enzyme inhibitors; ARBs = angiotensin II receptor blockers; Darones = amiodarone or dronedarone; OACs = oral anticoagulants; Immuno = other (non-methotrexate) immunosuppressants; NSAIDs = nonsteroidal anti-inflammatory drugs.

Factors associated with serum creatinine testing

The presence of a Read code for CKD was independently associated with more frequent serum creatinine testing in primary care, with stage 4 CKD conferring the highest rates of testing (Table 2). Testing frequency increased with age up to a peak at ages 80-89. Variation in testing between the SHA regions of England was quite low, with the exception of the North-East and the South-West, where the rates of testing were roughly 20% higher than that of London. Rates in Northern Ireland, Scotland and Wales were 21-48% greater than those of London, possibly reflecting differences in clinical guidelines between England and other countries. In our adjusted model of testing frequency, the extent of testing in men and women differed by 14% IRR 1.14, (95% CI: 1.14, 1.14). All assessed comorbidities were significantly associated with elevated rates of serum creatinine testing with the exception of atrial fibrillation. With the exception of ethambutol, for all analysed pharmacotherapies, serum creatinine testing increased independently of other factors and was most marked in patients taking methotrexate, other immunosuppressants, gold and lithium.

Table 2 - Results of regression models describing the demographic characteristics, the presence/absence of chronic conditions and drug prescription, and associations with the frequency of serum creatinine testing in primary care.

Characteristic	Univariable IRR (95%CI)	Minimally Adjusted IRR (95%CI)	Fully Adjusted IRR (95%CI)
Gender			
Female	1.20 (1.20, 1.21)	1.18 (1.18, 1.18)	1.14 (1.14, 1.14)
Age (years)			
40-49	2.09 (2.08, 2.10)	2.10 (2.09, 2.11)	1.92 (1.91, 1.92)
50-59	3.50 (3.49, 3.51)	3.53 (3.52, 3.54)	2.87 (2.86, 2.88)
60-69	5.38 (5.36, 5.40)	5.39 (5.37, 5.41)	3.94 (3.93, 3.96)
70-79	7.25 (7.22, 7.27)	7.23 (7.20, 7.26)	4.83 (4.81, 4.85)
80-89	7.57 (7.53, 7.61)	7.47 (7.43, 7.51)	4.86 (4.83, 4.88)
≥90	6.17 (6.10, 6.25)	5.94 (5.87, 6.01)	4.05 (4.00, 4.10)
Ethnicity			
Asian	0.78 (0.77, 0.79)	1.25 (1.24, 1.27)	1.23 (1.22, 1.24)
Black	0.77 (0.76, 0.78)	1.19 (1.18, 1.21)	1.16 (1.14, 1.17)
Mixed	0.96 (0.96, 0.97)	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)
Other	0.71 (0.69, 0.72)	1.05 (1.03, 1.06)	1.04 (1.02, 1.05)
Not recorded	0.83 (0.83, 0.83)	0.84 (0.84, 0.84)	0.84 (0.84, 0.84)
Index of multiple deprivation			
2	1.07 (1.06, 1.07)	1.04 (1.04, 1.05)	1.03 (1.02, 1.03)
3	1.07 (1.06, 1.07)	1.07 (1.06, 1.07)	1.04 (1.04, 1.04)
4	1.03 (1.03, 1.04)	1.11 (1.11, 1.12)	1.08 (1.07, 1.08)
5 (most deprived)	1.04 (1.03, 1.04)	1.14 (1.13, 1.14)	1.09 (1.08, 1.09)
Not recorded	1.05 (1.05, 1.05)	1.07 (1.07, 1.08)	1.03 (1.03, 1.04)
Year of Study Entry			
2006	0.72 (0.71, 0.72)	0.96 (0.95, 0.96)	1.08 (1.08, 1.09)
2007	0.78 (0.77, 0.78)	0.96 (0.95, 0.96)	1.10 (1.09, 1.10)
2008	0.81 (0.80, 0.81)	0.99 (0.98, 1.00)	1.13 (1.13, 1.14)
2009	0.77 (0.76, 0.78)	1.00 (0.99, 1.01)	1.13 (1.12, 1.14)
2010	0.83 (0.82, 0.83)	1.04 (1.03, 1.04)	1.17 (1.17, 1.18)
2011	0.92 (0.92, 0.93)	1.11 (1.10, 1.12)	1.29 (1.28, 1.30)
2012	0.96 (0.95, 0.97)	1.18 (1.16, 1.19)	1.34 (1.33, 1.35)
Region			
East Midlands	1.29 (1.28, 1.30)	1.18 (1.17, 1.19)	1.07 (1.07, 1.08)
East of England	1.18 (1.17, 1.18)	1.09 (1.09, 1.10)	1.04 (1.04, 1.05)
North-East	1.44 (1.42, 1.45)	1.27 (1.26, 1.28)	1.20 (1.19, 1.21)
North-West	1.30 (1.29, 1.31)	1.18 (1.18, 1.19)	1.10 (1.10, 1.11)
South Central	1.21 (1.20, 1.22)	1.14 (1.13, 1.14)	1.10 (1.09, 1.10)
South-East Coast	1.23 (1.22, 1.24)	1.12 (1.11, 1.12)	1.10 (1.10, 1.11)
South-West	1.43 (1.42, 1.44)	1.22 (1.22, 1.23)	1.17 (1.17, 1.18)
West Midlands	1.24 (1.24, 1.25)	1.14 (1.13, 1.15)	1.08 (1.07, 1.08)
Yorkshire & The Humber	1.24 (1.23, 1.25)	1.08 (1.07, 1.09)	0.97 (0.96, 0.97)
Northern Ireland	1.51 (1.50, 1.53)	1.55 (1.54, 1.57)	1.48 (1.47, 1.49)
Scotland	1.21 (1.20, 1.22)	1.22 (1.21, 1.22)	1.21 (1.20, 1.22)
Wales	1.33 (1.32, 1.34)	1.26 (1.26, 1.27)	1.22 (1.21, 1.22)
Chronic kidney disease stage			
1	1.93 (1.76, 2.11)	2.18 (2.03, 2.35)	2.05 (1.92, 2.19)
2	2.30 (2.21, 2.40)	1.82 (1.76, 1.88)	1.93 (1.87, 1.99)
3	3.32 (3.25, 3.40)	1.67 (1.64, 1.70)	1.48 (1.46, 1.51)
4	4.98 (4.60, 5.39)	2.61 (2.45, 2.77)	2.17 (2.05, 2.30)

5	3.92 (3.05, 5.03)	2.37 (1.94, 2.89)	1.74 (1.45, 2.09)
Comorbidities			
Atrial fibrillation	3.09 (3.04, 3.13)		1.00 (0.99, 1.02)
Cancer	2.14 (2.12, 2.17)		1.15 (1.14, 1.16)
Diabetes	3.48 (3.45, 3.51)		1.98 (1.97, 1.99)
Heart failure	3.89 (3.83, 3.95)		1.07 (1.05, 1.08)
Hypertension	2.37 (2.37, 2.38)		1.28 (1.28, 1.29)
Ischaemic heard disease	2.76 (2.73, 2.78)		1.23 (1.23, 1.24)
Peripheral vascular disease	2.55 (2.52, 2.58)		1.20 (1.19, 1.21)
Stroke/Transient ischaemic attack	2.85 (2.81, 2.88)		1.14 (1.13, 1.15)
Thyroid disease	2.09 (2.07, 2.11)		1.31 (1.30, 1.32)
Pharmacotherapies			
ACE Inhibitors	3.20 (3.18, 3.21)		1.41 (1.41, 1.42)
ARBs	2.98 (2.96, 3.00)		1.25 (1.24, 1.26)
Amiodarone/Dronedarone	3.49 (3.41, 3.56)		1.15 (1.13, 1.17)
Digoxin	3.39 (3.34, 3.44)		1.17 (1.16, 1.19)
Diuretics	3.27 (3.25, 3.28)		1.46 (1.46, 1.47)
Ethambutol	1.37 (1.09, 1.73)		1.16 (0.97, 1.40)
Gold	11.11 (9.59, 12.88)		5.48 (4.95, 6.07)
Immunosuppressants (Not Inc. Methotrexate)	5.06 (4.97, 5.15)		3.44 (3.40, 3.49)
Lithium	4.14 (4.00, 4.28)		4.42 (4.32, 4.52)
Mesalazine	2.44 (2.37, 2.50)		2.23 (2.19, 2.28)
Methotrexate	9.41 (9.19, 9.64)		6.17 (6.07, 6.28)
NSAIDs	1.55 (1.55, 1.56)		1.25 (1.25, 1.25)
Oral Anticoagulants	2.93 (2.89, 2.96)		1.17 (1.16, 1.18)

Discussion

Key results

This is the first study to evaluate the rates of kidney function testing over a nine-year period following the introduction of the QOF in a large UK primary care database. Over the course of this study, rates of serum creatinine and proteinuria testing increased by 40% and 36%, respectively, and by 2012-13 almost four in every 10 people were receiving at least one serum creatinine test per year and over one in every 10 people were receiving at least one proteinuria test per year.

Across most strata evaluated, rates of kidney function testing appear to have either remained constant or increased with time. One notable exception to this was diabetes, where rates appear to have decreased with time. Women appear to be tested more than men, receiving roughly an extra 0.1 serum creatinine tests per year and an extra 0.02 proteinuria tests per year. This may be because women are more likely to schedule and attend appointments in primary care, as evidenced by a UK national study of patient factors associated with missed appointments [24]. When stratifying by age, rates of kidney function testing increased between successive age categories up to age 80-89, with patients aged ≥90 typically having lower rates of testing than patients aged 70-79. Serum creatinine and urinary protein testing have both increased across all ethnic groups, but patients of white and mixed ethnicities still have higher rates of testing than patients of black and Asian ethnicity. Stratification by IMD quintile demonstrated minimal differences in testing rates. Conversely, stratification by comorbidity revealed the highest rates of both serum creatinine and proteinuria

testing to be present in patients with heart failure or diabetes. Creatinine testing is undertaken in the primary care practice in the UK, rather than in a separate facility, and therefore creatinine testing is sensitive to factors that influence practice attendance. However, some patients with diabetes will be managed by specialists as part of an out-patient hospital service and will have blood tests requested and taken at the hospital. These blood tests will not be sent to primary care electronic health records and will not appear in CPRD. The smaller rate of testing seen in this database for patients with diabetes may therefore not reflect deficiencies in overall care, but simply the fact that care is shared with the hospital for some of those patients. Stratification by concomitant pharmacotherapy, revealed the highest rates of kidney function testing to be present in patients prescribed gold. Serum creatinine testing was also more frequent in patients prescribed immunosuppressants.

The effects of pay-for-performance indicators are visible in most plots present in this paper with noticeable increases in the rates of serum creatinine testing in 2006-07 and of proteinuria testing in 2009-10. The former of these coincided with the requirement that general practices maintain a register of patients with CKD stages 3-5 [4], while the latter coincided with the inclusion of the monitoring of secondary markers of kidney disease via ACR and PCR tests in patients on the CKD register [5]. There was no obvious impact in any of the plots from the 2008-09 NICE guidelines which recommended monitoring eGFR levels in high risk patients [5].

Frequency of serum creatinine testing was strongly associated with increasing age and the presence of a Read code for CKD in adjusted analyses. Testing frequency was also independently associated with chronic conditions and prescription of potentially nephrotoxic drugs but has risen year on year, even after accounting for age, chronic conditions, and prescription of drugs that require monitoring of kidney function.

Strengths and limitations

To date, this is the largest population-based study of trends in renal function testing in primary care. The study population was an unselected sample of over 4.5 million patients from over 600 general practices across the UK included in the CPRD database, which has been shown to be representative of the UK. The scale and design of the study allowed us to test associations adjusted for many important potential explanatory and confounding factors. Our study has limitations, some of which are inherent in the CPRD database. We were not able to ascertain why the tests were performed. Even though the CPRD contains consultation codes, these provide only a very broad classification of the time and type of consultation (e.g. Clinic, Night visit, Home visit). An in-depth analysis of Read codes or mining of the consultation free text would be required to start to explain the reasons for test ordering, which is beyond the scope of this study. Finally, the use of the MDRD equation could be challenged. It was the formula in use during the period of the study but is now considered inferior to the CKD-EPI formula. However, we have used MDRD, because we wanted the analysis to reflect the clinical decision made at the time of the study.

Relationship to the literature

The rise in the number of patients having serum creatinine concentration measurements and the increased frequency of testing for those being tested can be interpreted in two ways. CKD has

gained more attention since the incorporation of CKD into the QOF in 2006-07. The establishment of a register in 2006-07 and its subsequent extension has encouraged renal function testing to identify those with CKD who may benefit from risk factor modification. From the viewpoint of patient safety, our results are encouraging and show that, for all the therapies we examined, the prescription of drugs that are potentially nephrotoxic is associated with more frequent monitoring.

Our results could be interpreted in a different light. There is little direct evidence that extra testing has improved outcomes in the short term or long term [25]. Additional testing has increased the apparent prevalence of CKD from 0.12% to 6.51%, but as yet, there has been no change in long-term outcomes, such as patients requiring renal replacement therapy [26,27]. Increases in consultations with general practitioners or practice nurses for either newly diagnosed disease or monitoring, with associated laboratory tests, place further strain on limited healthcare resources and increase expenditure. The very substantial costs of renal replacement therapy or cardiovascular complications [27] mean that testing might be cost-effective, even if it results in only modest reductions in the number of patients who progress to this stage, but whether this is the case is unclear. In a report from one NHS trust in the period following the introduction of renal QOF there was an abrupt 61% increase in the number of new referrals to nephrology, 54% of which were classified as inappropriate and a further 22% as inadequate [28]. Inappropriate referrals use up resources and may cause unnecessary distress to patients and their carers [29].

Implications for practice

Rates of testing have increased over the observation period in our study. Much of these increases appear to be driven by financial incentivisation schemes, such as the QOF. However, the increases were found to be independent of comorbidities, age and prescriptions for 'high risk' drugs. Much of the increase in testing appears to have occurred in patients with mildly to moderately impaired kidney function (CKD stages 2-3). However, there is limited evidence to suggest any benefit from interventions delivered in the early stages of CKD [30]. Moreover, studies in cholesterol monitoring have shown that more frequent testing can have negative consequences [31] - particularly for biomarkers that have high within-person variability, such as serum creatinine [32], with an increased likelihood of raising false alarms for increased CKD severity. Hence, a more targeted approach could prove beneficial for most patients.

Increases in testing are also likely to have knock-on effects to other aspects of healthcare, including the financial burden on the NHS, the time burden on general practitioners, and laboratory workloads; potentially resulting in delayed or missed diagnosis [33]. Reducing the amount of serum creatinine testing performed as part of kidney function monitoring could ease some of these burdens, although we acknowledge that a reasonable amount of serum creatinine testing is performed as part of test batches not directly related to the assessment of kidney function and including other tests such as full blood counts [34].

Conclusion

The observed increase in kidney function testing could be attributable to any or all of several changes that have occurred over the period of the study. The introduction of pay-for-performance indicators, the establishment of a CKD register, national guidelines promoting monitoring of renal

function in high-risk groups, and linkage of pathology laboratories to practice systems have potentially all raised the profile of CKD in primary care and contributed to the observed increases in testing. While it is clear that these initiatives have changed process measures, it is still not clear whether clinical outcomes have improved as a consequence.

Statements

Funding

This article presents independent research funded by the National Institute for Health Research (NIHR) under the programme grants for applied research programme (RP-PG-1210-12003). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. CT is funded through an NIHR academic clinical lectureship. RP receives funding from the NIHR Oxford Biomedical Research Centre Program, the NIHR Program for Applied Research, the NIHR Health Protection Research Unit (HPRU) Gastrointestinal Infections Group, and the NIHR Diagnostic Evidence Co-operative (DEC).

Competing interests

NH is currently employed by Bristol-Meyers Squibb Limited; a company that manufactures ACE inhibitors, which are drugs indicated in the treatment of CKD, when present in conjunction with other comorbidities such as type 2 diabetes. CT reports speaker fees from Vifor and Novartis and non-financial support from Roche outside of the submitted work. All other authors declare no conflicts of interest.

Author contributions

RP and RS provided substantial contributions to the concept and design of the study. JO, BF, RS, RP and EM provided statistical expertise, while JA, CT, CO'C and DL lent clinical and pharmacological expertise. Any coding work necessary for the project was performed by BF, JO, EM and NH. All authors contributed to the drafting and critical appraisal of the manuscript. Final approval for the version to be published was given by RP.

Patient consent and ethical approval

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (protocol number 14_150R), and the approved protocol was made available to the journal and reviewers during peer review. Ethical approval for observational research using the CPRD with approval from ISAC has been granted by a National Research Ethics Service committee (Trent MultiResearch Ethics Committee, REC reference number 05/MRE04/87).

Data sharing

The data that support the findings of this study are available from the Medicines and Healthcare Products Regulatory Agency, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. Data are, however, available from the Medicines and Healthcare Products Regulatory Agency, subject to approval from ISAC.

Acknowledgements

We would like to thank Alice Fuller and Dr Sarah Lay-Flurrie for their hard work in providing much of the initial data management for this project.

Suggested reviewers

Prof Simon de Lusignan (s.lusignan@surrey.ac.uk)

Professor of Primary Care & Clinical Informatics / Chair in Health Care Management / Head of the Department of Clinical and Experimental Medicine.

Prof Martin Gulliford (martin.gulliford@kcl.ac.uk)

Professor of Public Health

Bibliography

1 National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. Clinical guideline [CG182]. 2014.https://www.nice.org.uk/guidance/cg182

2 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**:S1–266.

3 Department of Health. The National Services Framework for Renal Services. Part One: Dialysis and Transplantation. 2004.

4 British Medical Association. Revisions to the GMS contract 2006/07. 2006.http://www.nhsemployers.org/-/media/Employers/Documents/Primary-care-contracts/QOF/2006-07/Revisions-to-the-GMS-contract-200607---Delivering-investments-in-general-practice.pdf?la=en&hash=C4949A6E6518C75287E55BCB13A8D311AD0DF3E4

5 National Institute for Health and Care Excellence. NICE Clinical Guideline 73: Chronic Kidney Disease: Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care. 2008.https://www.nice.org.uk/guidance/CG73

6 British Medical Association. Quality and Outcomes Framework guidance for GMS contract 2009/10. 2009.http://www.nhsemployers.org/~/media/Employers/Documents/Primary care contracts/QOF/2010-11/Quality and Outcomes Framework guidance for GMS contract 200910 - Delivering investment in general practice.pdf

7 McGovern AP, Rusholme B, Jones S, *et al.* Association of chronic kidney disease (CKD) and failure to monitor renal function with adverse outcomes in people with diabetes: a primary care cohort study. *BMC Nephrol* 2013;**14**:198. doi:10.1186/1471-2369-14-198

8 de Lusignan S, Nitsch D, Belsey J, *et al.* Disparities in testing for renal function in UK primary care: cross-sectional study. *Fam Pract* 2011;**28**:638–46. doi:10.1093/fampra/cmr036

9 Doll H, Shine B, Kay J, *et al.* The rise of cholesterol testing: how much is unnecessary. *Br J Gen Pract* 2011;**61**:e81-8. doi:10.3399/bjgp11X556245

10 Oke J, Shine B, McFadden E, *et al.* Trends in serum creatinine testing in Oxfordshire, UK, 1993-2013: a population-based cohort study. *BMJ Open* 2015;**5**:e009459. doi:10.1136/bmjopen-2015-009459

11 Zhi M, Ding EL, Theisen-Toupal J, *et al.* The landscape of inappropriate laboratory testing: a 15-year meta-analysis. *PLoS One* 2013;**8**:e78962. doi:10.1371/journal.pone.0078962

12 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013;**3**:1–150.

13 Charles RF, Powe NR, Jaar BG, *et al.* Clinical Testing Patterns and Cost Implications of Variation in the Evaluation of CKD Among US Physicians. *Am J Kidney Dis* 2009;**54**:227–37. doi:10.1053/j.ajkd.2008.12.044

14 Choi M, Montgomery E, Saffer T, *et al.* Chronic Kidney Disease Change Package: Population Health Strategies for Cardiovascular and Kidney Disease Risk Reduction. 2018. doi:10.1093/med/9780199651610.003.0003

15 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;**44**:827–36. doi:10.1093/ije/dyv098

16 Levey AS, Bosch JP, Lewis JB, *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461–70. doi:10.7326/0003-4819-130-6-199903160-00002

17 Levey AS, Stevens LA, Schmid CH, *et al.* A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* 2009;**150**:604–12. doi:10.7326/0003-4819-150-9-200905050-00006

18 R Core Team. R: A Language and Environment for Statistical Computing. 2018.https://www.r-project.org

19 Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York: : Springer-Verlag 2016. http://ggplot2.org

20 Laud PJ. Equal-tailed confidence intervals for comparison of rates. *Pharm Stat* 2017;**16**:334–48. doi:10.1002/pst.1813

21 Laud PJ. ratesci: Confidence Intervals for Comparisons of Binomial or Poisson Rates. 2018.

22 Venables WN, Ripley BD. *Modern Applied Statistics with S*. Fourth. New York: : Springer 2002. http://www.stats.ox.ac.uk/pub/MASS4

23 KDIGO. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013;**3**:136–50.

24 Ellis DA, McQueenie R, McConnachie A, *et al.* Demographic and Practice Factors Predicting Repeated Non-Attendance in Primary Care: A National Retrospective Cohort Analysis. *Lancet Public Heal* 2017;**2**:e551–9. doi:10.1016/S2468-2667(17)30217-7

25 Inker LA, Astor BC, Fox CH, *et al.* KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD. *Am J Kidney Dis* 2014;**63**:713–35. doi:10.1053/j.ajkd.2014.01.416

26 Byrne C, Caskey F, Dawnay CC, *et al.* UK Renal Registry UK Renal Registry 19th Annual Report of the Renal Association. *Nephron* 2017;**137**.

27 Kerr M, Bray B, Medcalf J, *et al.* Estimating the Financial Cost of Chronic Kidney Disease to the NHS in England. *Nephrol Dial Transplant* 2012;**27**:iii73-80. doi:10.1093/ndt/gfs269

28 O'Callaghan CA, Shine B, Lasserson DS. Chronic Kidney Disease: A Large-Scale Population-Based Study of the Effects of Introducing the CKD-EPI Formula for eGFR Reporting. *BMJ Open* 2011;**1**:e000308. doi:10.1136/bmjopen-2011-000308

29 Glassock RJ, Winearls C. Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol* 2008;**3**:1563–8. doi:10.2215/CJN.00960208

30 Fink HA, Ishani A, Taylor BC, *et al.* Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: a systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2012;**156**:570–81. doi:10.7326/0003-4819-156-8-201204170-00004

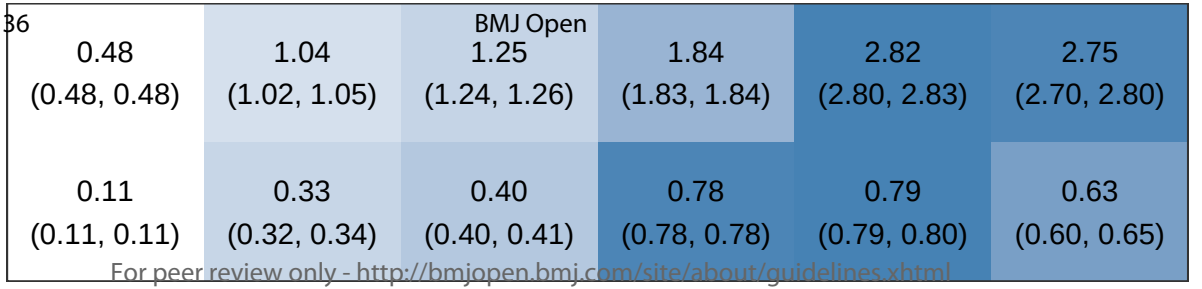
31 Glasziou PP, Irwig L, Heritier S, *et al.* Monitoring Cholesterol Levels: Measurement Error or True Change? *Ann Intern Med* 2008;**148**:656–61.

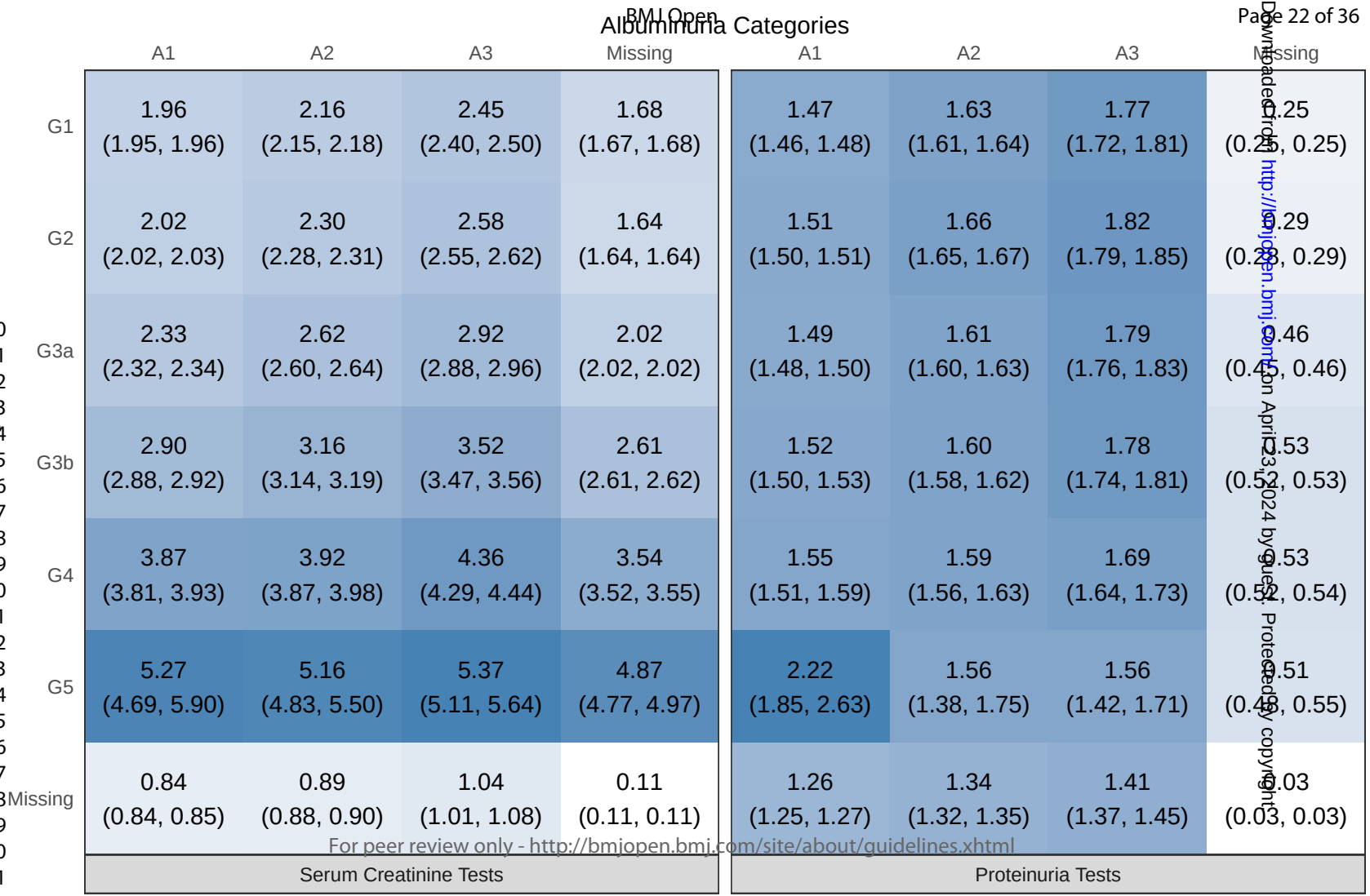
32 Lamb EJ, Brettell EA, Cockwell P, *et al.* The eGFR-C study: Accuracy of Glomerular Filtration Rate (GFR) Estimation Using Creatinine and Cystatin C and Albuminuria for Monitoring Disease Progression in Patients with Stage 3 Chronic Kidney Disease - Prospective

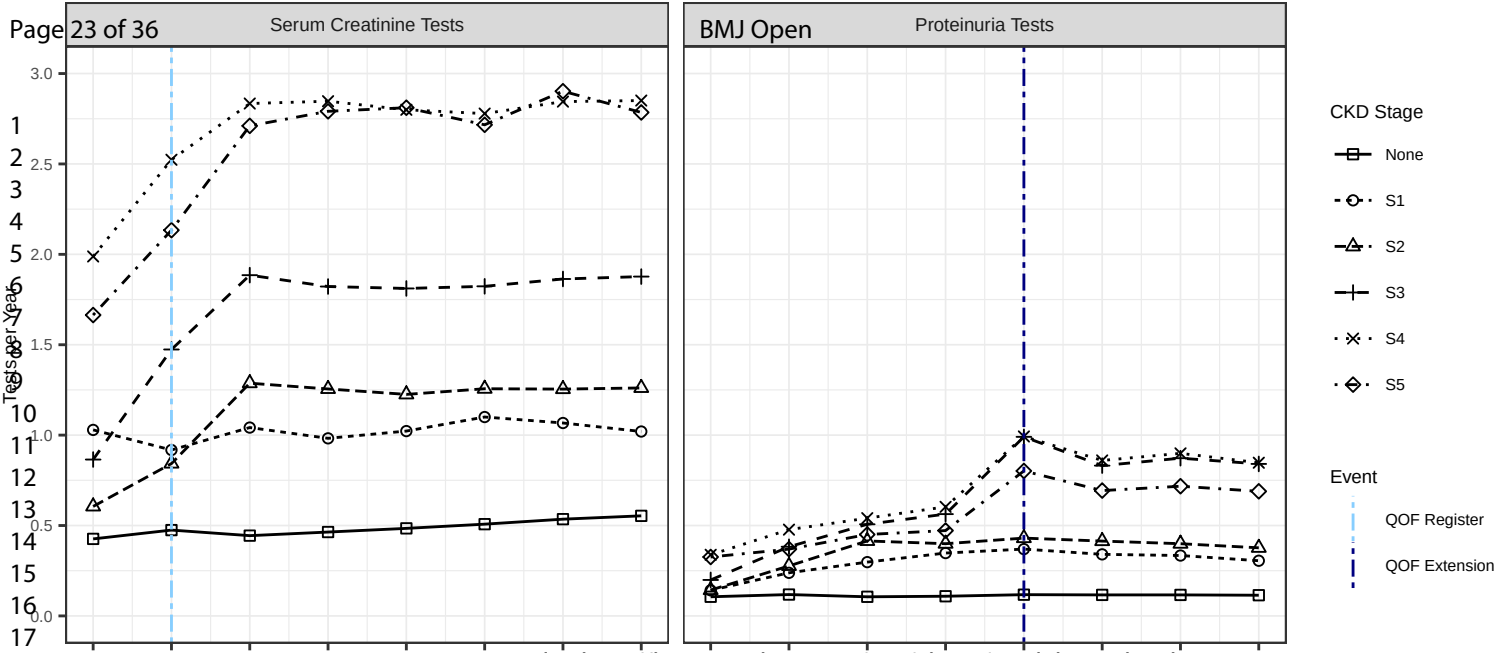
Longitudinal Study in a Multiethnic . *BMC Nephrol* 2014;**15**:13. doi:10.1186/1471-2369-15-13

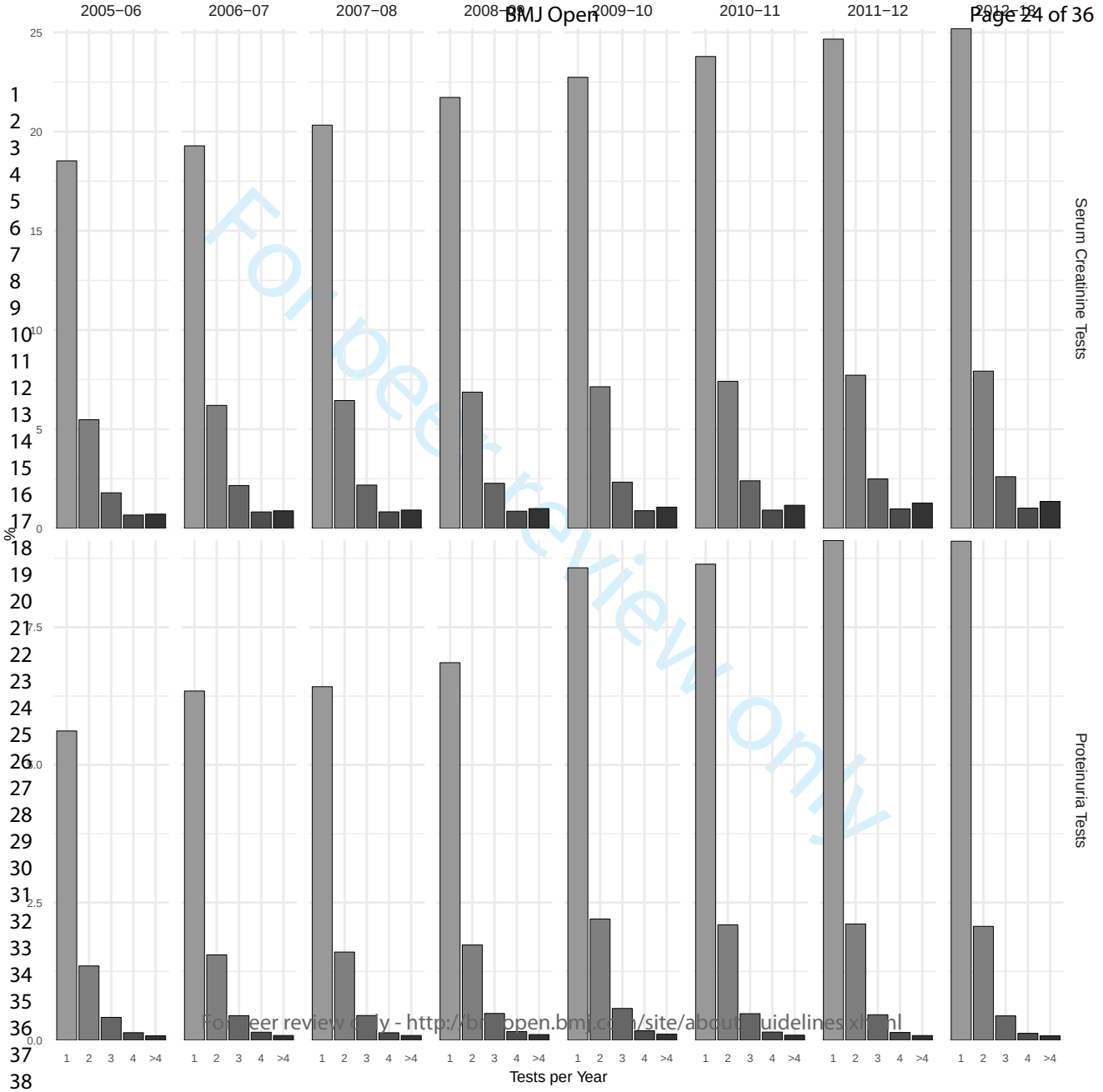
33 Gandhi TK, Kachalia A, Thomas EJ, *et al.* Missed and Delayed Diagnoses in the Ambulatory Setting: A Study of Closed Malpractice Claims. *Ann Intern Med* 2006;**145**:488–96.

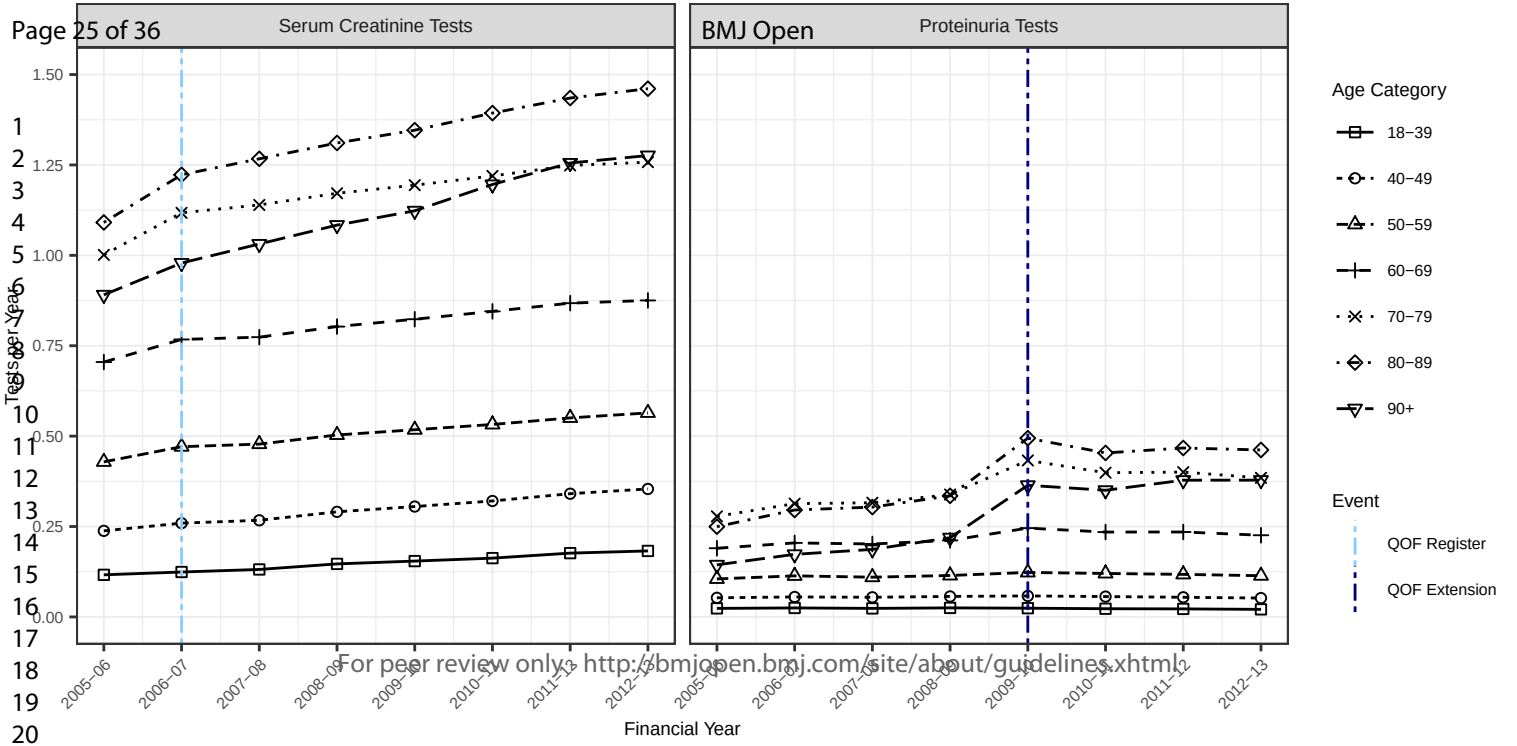
34 Fanshawe TR, Ordóñez-Mena JM, Turner PJ, *et al.* Frequencies and Patterns of Laboratory Test Requests From General Practice: A Service Evaluation to Inform Point-of-Care Testing. *J Clin Pathol* 2018;**0**:1–6. doi:10.1136/jclinpath-2018-205242

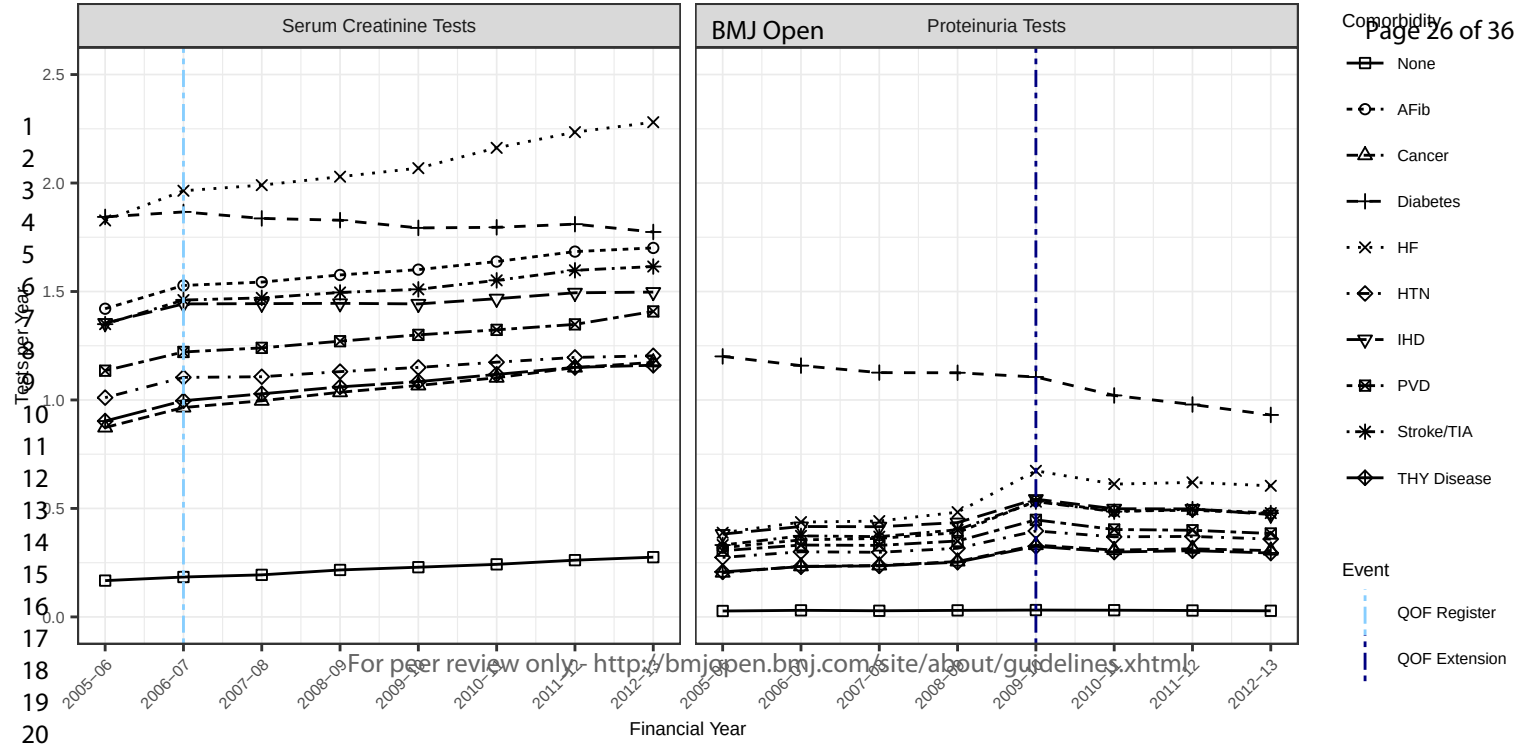


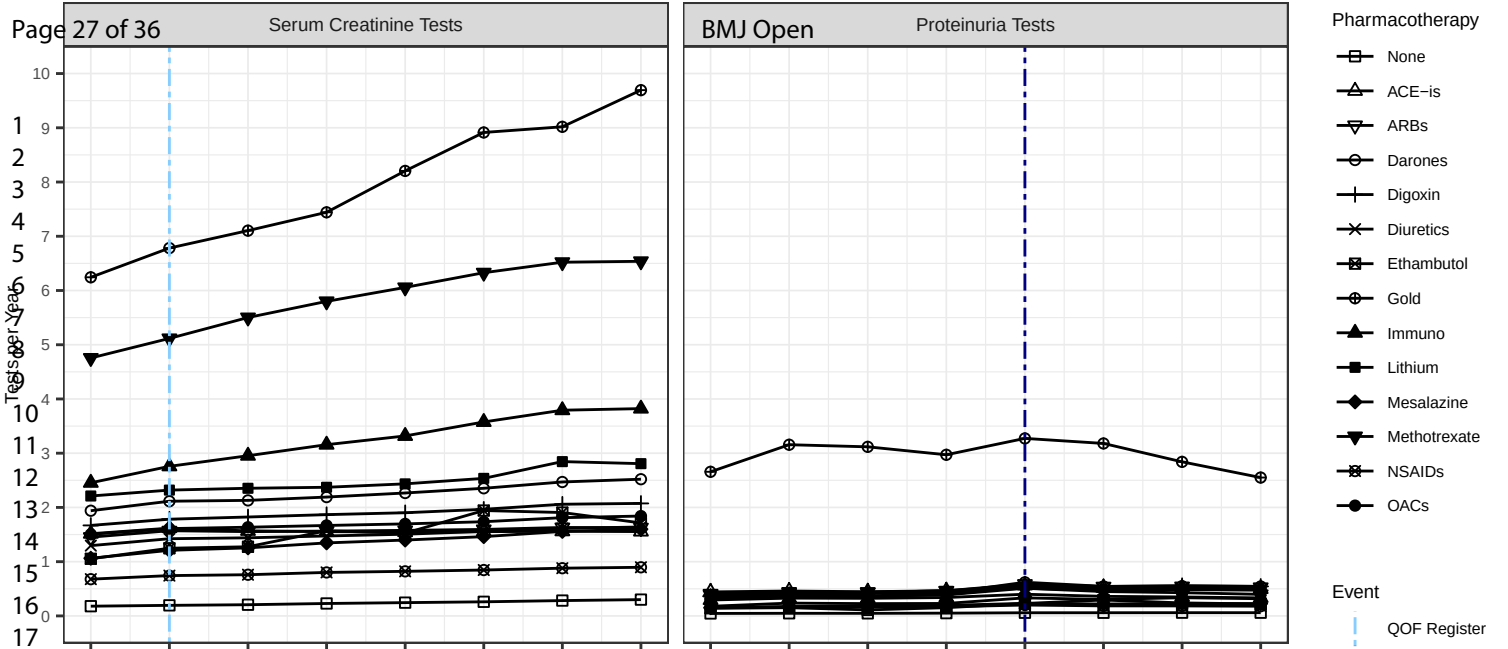












Supplementary material

Serum creatinine test Read codes

Supplementary Table 1 - Serum creatinine testing Read codes.

Medical Code	Read Code	Read Term
5	44J3.00	Serum creatinine
3927	44J3300	Serum creatinine raised
13736	44JF.00	Plasma creatinine level
26903	44J3200	Serum creatinine normal
31277	44J3000	Serum creatinine abnormal
35545	44J3100	Serum creatinine low
42345	44J3z00	Serum creatinine NOS
45096	44JD.00	Corrected serum creatinine level
62062	44JC.00	Corrected plasma creatinine level

Proteinuria test Read codes

Supplementary Table 2 - Proteinuria testing Read codes.

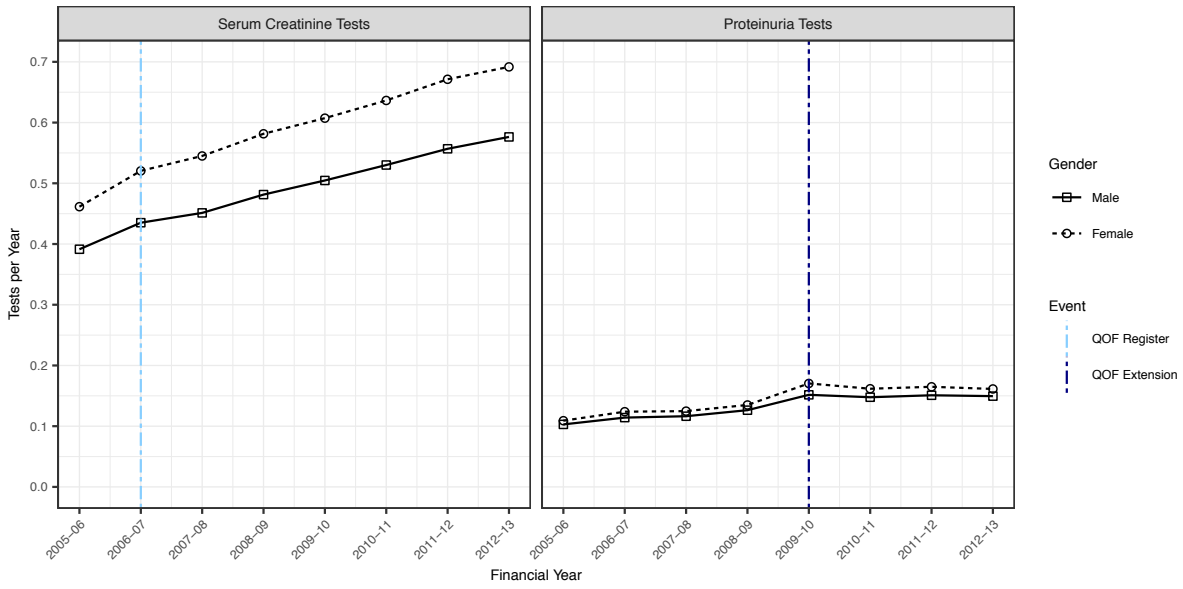
Medical Code	Read Code	Read Term
43	467..00	Urine protein test
1802	4678	Proteinuria
2482	D011100	Vit B12 defic anaemia due to malabsorption with proteinuria
2607	46TC.00	Urine albumin:creatinine ratio
5451	R110000	[D]Albuminuria
8482	467A.00	24 hour urine protein output
9430	4679	Urine dipstick for protein
10924	R110300	[D]Microalbuminuria
11248	R110.00	[D]Proteinuria
13590	4674	Urine protein test = +
13600	4677	Urine protein test = ++++
13611	4675	Urine protein test = ++
13612	4673	Urine protein test = trace
13613	46N2.00	Urine protein abnormal
13621	4676	Urine protein test = +++
14091	4672	Urine protein test negative
14092	4671	Urine protein test not done
14094	467E.00	Urine protein level
14113	44J7.00	Albumin / creatinine ratio
14382	46N1.00	Urine protein normal

Medical Code	Read Code	Read Term
14389	46N5.00	24 hour urine protein excretion test
14391	46TD.00	Urine microalbumin:creatinine ratio
14395	46N..00	Urine protein
14405	46N6.00	24 hour urine albumin output
14410	46N4.00	Urine albumin
14411	46M7.00	Urine creatinine
14429	46N3.00	Urine total protein
14434	46MD.00	24 hour urine creatinine output
14563	46W..00	Urine microalbumin
14564	46W2.00	Microalbumin excretion rate
14901	K136.00	Benign postural proteinuria
16465	K190X00	Persistent proteinuria, unspecified
17106	46W1.00	Urine microalbumin negative
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
23281	44J6.00	Albumin excretion rate
23334	L162.11	Albuminuria in pregnancy without hypertension
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
27059	467Z.00	Urine protein test NOS
27214	46NZ.00	Urine protein NOS
27266	44lD.00	Urine protein/creatinine ratio
28180	46W0.00	Urine microalbumin positive
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
34173	L12B.00	Proteinuric hypertension of pregnancy
34265	L16C000	Gestational proteinuria
34680	R110200	[D]Exercise proteinuria
36243	K136.11	Orthostatic proteinuria
36394	L16C.00	Pregnancy induced oedema+proteinuria without hypertension
37201	L16C100	Gestational oedema with proteinuria
38284	R110z00	[D]Proteinuria NOS
39248	46N8.00	Urine microalbumin profile
43262	467H.00	Random urine protein level
43524	44JG.00	Overnight albumin excretion rate
43611	K0A4.00	Isolated proteinuria with specified morphological lesion
44179	46N7.00	Urine protein/creatinine index
49741	68K2.00	Urine screen for protein
59992	K0A4W00	Isolated proteinuria, with unspecified morpholog changes
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
61470	66Al.00	Diabetic monitoring - higher risk albumin excretion
64030	Kyu5G00	[X]Persistent proteinuria, unspecified

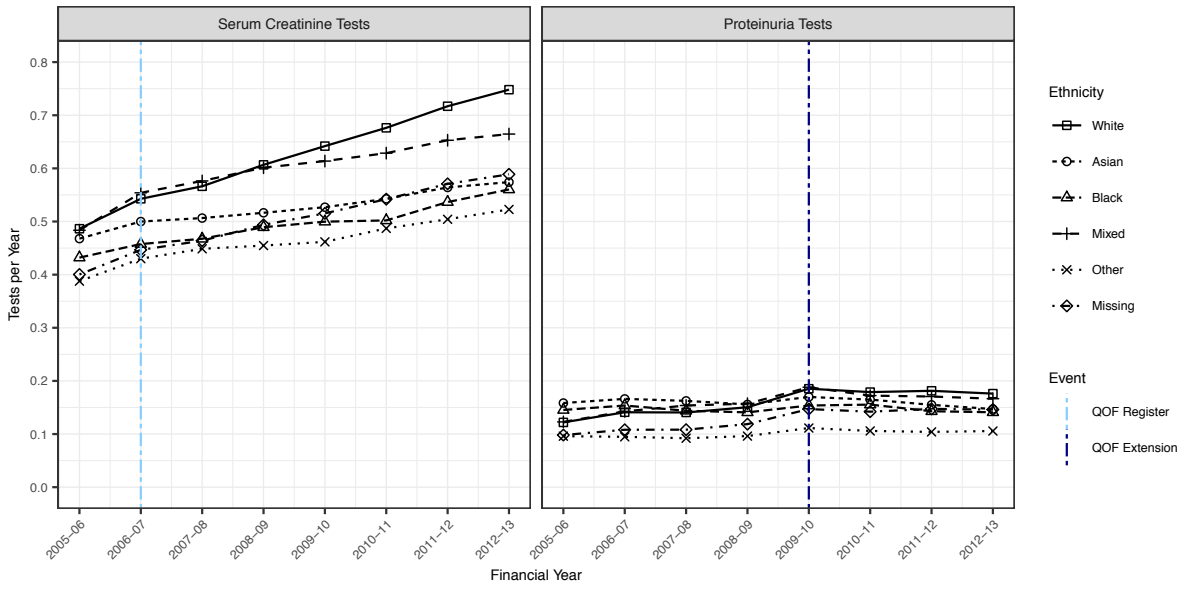
Medical Code	Read Code	Read Term
66475	66Ak.00	Diabetic monitoring - lower risk albumin excretion
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
92998	Lyu1.00	[X]Oedema,proteinuria+hypertens in pregnancy,childbrth,puerp
94789	1Z17.00	Chronic kidney disease stage 1 with proteinuria
94793	1Z1B.00	Chronic kidney disease stage 3 with proteinuria
95121	1Z1A.00	Chronic kidney disease stage 2 without proteinuria
95122	1Z1H.00	Chronic kidney disease stage 4 with proteinuria
95123	1Z1C.00	Chronic kidney disease stage 3 without proteinuria
95145	1Z1B.11	CKD stage 3 with proteinuria
95146	1Z19.00	Chronic kidney disease stage 2 with proteinuria
95175	1Z1E.00	Chronic kidney disease stage 3A without proteinuria
95176	1Z1E.11	CKD stage 3A without proteinuria
95177	1Z1G.00	Chronic kidney disease stage 3B without proteinuria
95178	1Z1F.00	Chronic kidney disease stage 3B with proteinuria
95180	1Z1F.11	CKD stage 3B with proteinuria
95188	1Z1C.11	CKD stage 3 without proteinuria
95405	1Z1L.00	Chronic kidney disease stage 5 without proteinuria
95406	1Z1J.00	Chronic kidney disease stage 4 without proteinuria
95408	1Z1D.00	Chronic kidney disease stage 3A with proteinuria
95508	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
95571	1Z1D.11	CKD stage 3A with proteinuria
95572	1Z18.00	Chronic kidney disease stage 1 without proteinuria
97587	1Z1J.11	CKD stage 4 without proteinuria
97683	1Z1L.11	CKD stage 5 without proteinuria
97978	1Z1A.11	CKD stage 2 without proteinuria
97979	1Z19.11	CKD stage 2 with proteinuria
97980	1Z17.11	CKD stage 1 with proteinuria
99160	1Z1K.11	CKD stage 5 with proteinuria
99312	1Z1H.11	CKD stage 4 with proteinuria
100633	1Z1G.11	CKD stage 3B without proteinuria
101572	K0A4X00	Isolated proteinuria, with oth specif morpholog changes
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria
104677	2126A00	Proteinuria resolved
105302	K08yA00	Proteinuric diabetic nephropathy
108916	44lzX00	Random urine protein:creatinine ratio
109657	1Z1Y.00	CKD with GFR category G3b & albuminuria category A2
109804	1Z1T.00	CKD with GFR category G3a & albuminuria category A1
109805	1Z1V.00	CKD with GFR category G3a & albuminuria category A2
109904	1Z1b.00	CKD with GFR category G4 & albuminuria category A2
109905	1Z1W.00	CKD with GFR category G3a & albuminuria category A3

Medical Code	Read Code	Read Term
109963	1Z1X.00	CKD with GFR category G3b & albuminuria category A1
109980	1Z1a.00	CKD with GFR category G4 & albuminuria category A1
109981	1Z1e.00	CKD with GFR category G5 & albuminuria category A2
109990	1Z1Z.00	CKD with GFR category G3b & albuminuria category A3
110003	1Z1N.00	CKD with GFR category G1 & albuminuria category A2
110033	1Z1M.00	CKD with GFR category G1 & albuminuria category A1
110108	1Z1R.00	CKD with GFR category G2 & albuminuria category A2
110133	1Z1d.00	CKD with GFR category G5 & albuminuria category A1
110251	1Z1S.00	CKD with GFR category G2 & albuminuria category A3
110269	1Z1Q.00	CKD with GFR category G2 & albuminuria category A1
110467	1Z1f.00	CKD with GFR category G5 & albuminuria category A3
110484	1Z1P.00	CKD with GFR category G1 & albuminuria category A3
110626	1Z1c.00	CKD with GFR category G4 & albuminuria category A3
111022	1Z18.11	CKD stage 1 without proteinuria

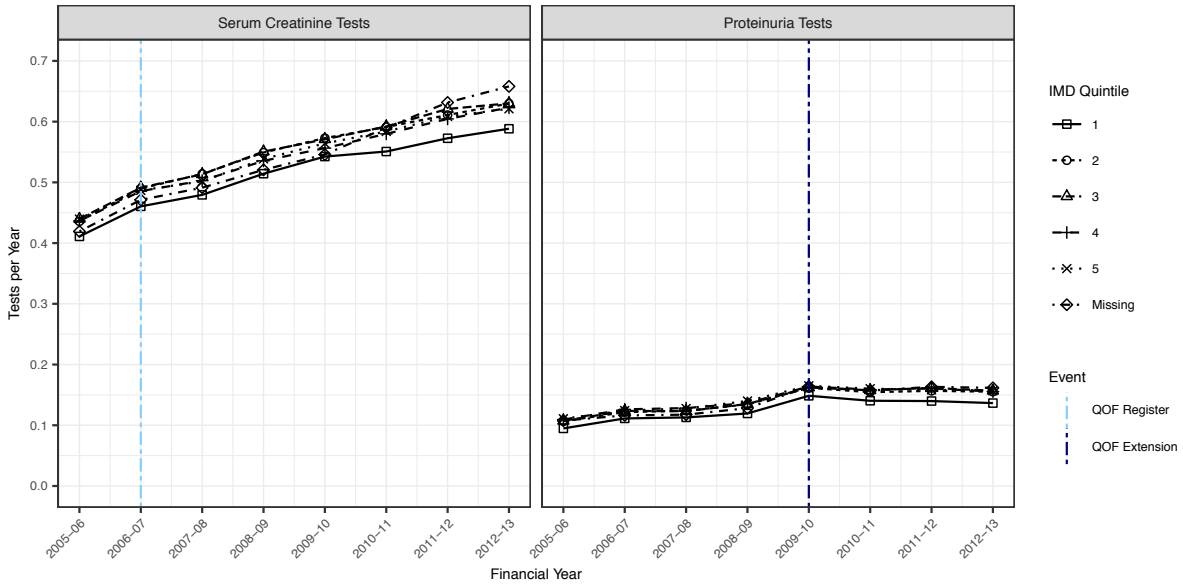
Trends over time



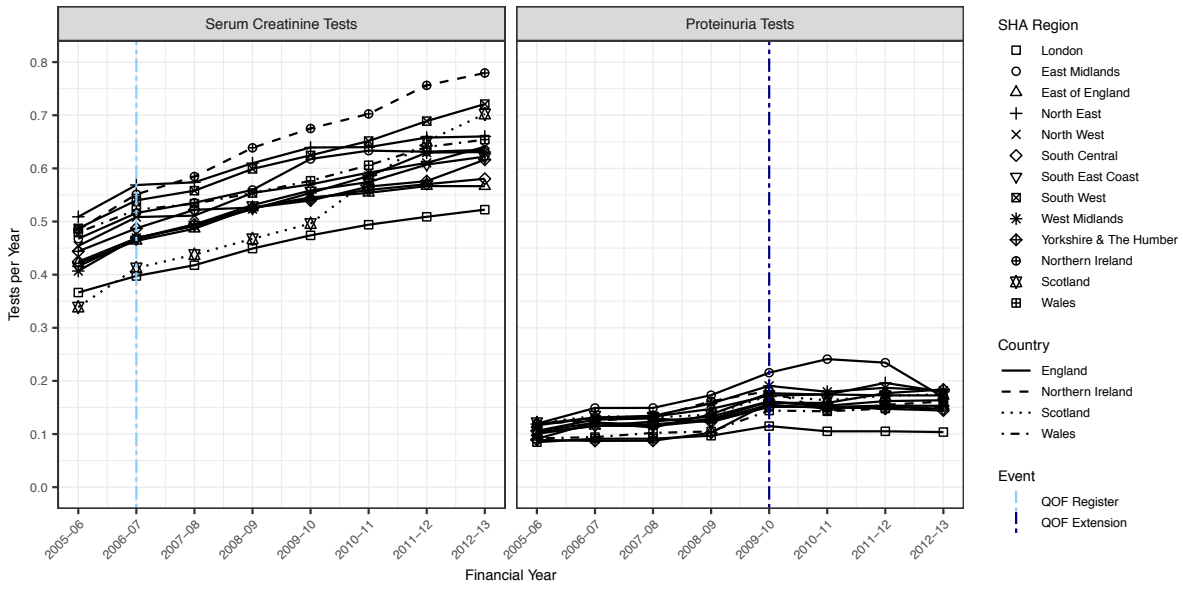
Supplementary Figure 1 - Rates of kidney function testing per financial year, stratified by gender.



Supplementary Figure 2 - Rates of kidney function testing per financial year, stratified by ethnicity.



Supplementary Figure 3 - Rates of kidney function testing per financial year, stratified by IMD quintile.



Supplementary Figure 4 - Rates of kidney function testing per financial year, stratified by SHA region.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 - 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7

Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) If applicable, explain how loss to follow-up was addressed	5
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8 - 9
		(b) Indicate number of participants with missing data for each variable of interest	8 - 9
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-13 & 23

		(b) Report category boundaries when continuous variables were categorized	6 - 7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13 - 14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14 - 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14 - 16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trends in kidney function testing in UK primary care since the introduction of the Quality and Outcomes Framework: a retrospective cohort study using CPRD

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028062.R2
Article Type:	Research
Date Submitted by the Author:	01-May-2019
Complete List of Authors:	Feakins, Benjamin; University of Oxford, Nuffield Department of Primary Care Health Sciences Oke, Jason; University of Oxford, Nuffield Department of Primary Care Health Sciences McFadden, Emily; University of Oxford, Nuffield Department of Primary Care Health Sciences Aronson, Jeffrey; University of Oxford, Nuffield Department of Primary Care Health Sciences Lasserson, Daniel; University of Birmingham, Institute of Applied Health Research; University of Oxford, Nuffield Department of Medicine O'Callaghan, Christopher; University of Oxford, Nuffield Department of Medicine; Oxford Radcliffe Hospitals NHS Trust, John Radcliffe Hospital Taylor, Clare; University of Oxford, Nuffield Department of Primary Care Health Sciences Hill, Nathan; Bristol-Myers Squibb Pharmaceuticals Ltd Stevens, Richard; University of Oxford, Nuffield Department of Primary Care Health Sciences Perera, Rafael; University of Oxford, Nuffield Department of Primary Care Health Sciences
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Health services research, Renal medicine, Medical management
Keywords:	Serum creatinine, Proteinuria, Kidney function, PRIMARY CARE, Monitoring, Chronic Kidney Disease

Trends in kidney function testing in UK primary care since the introduction of the Quality and Outcomes Framework: a retrospective cohort study using CPRD

Benjamin G. Feakins[1] (benjamin.feakins@phc.ox.ac.uk), Jason L. Oke[1] (jason.oke@phc.ox.ac.uk), Emily C. McFadden[1] (emily.mcfadden@phc.ox.ac.uk), Jeffrey K. Aronson[1] (jeffrey.aronson@phc.ox.ac.uk), Daniel S. Lasserson[2,3] (d.s.lasserson@bham.ac.uk), Christopher A. O'Callaghan[1,3] (chris.ocallaghan@ndm.ox.ac.uk), Clare J. Taylor[1] (clare.taylor@phc.ox.ac.uk), Nathan R. Hill[4] (nathan.hill@bms.com), Richard J. Stevens[1] (richard.stevens@phc.ox.ac.uk), Rafael Perera[1] (rafael.perera@phc.ox.ac.uk)

[1] Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.

[2] Institute of Applied Health Research, University of Birmingham, Birmingham, UK.

[3] Nuffield Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

[4] Bristol-Meyers Squibb Pharmaceuticals Limited, Uxbridge, UK

Word count:

Abstract: 300

Main text: 4,425

Corresponding author:

Jason Oke, DPhil (jason.oke@phc.ox.ac.uk)
Nuffield Department of Primary Care Health Sciences
Radcliffe Observatory Quarter, Woodstock Road
Oxford
OX2 6GG

Abstract

Objectives: To characterise serum creatinine and urinary protein testing in UK general practices from 2005 to 2013, and to examine how the frequency of testing varies across demographic factors, with the presence of chronic conditions, and with the prescribing of drugs for which kidney function monitoring is recommended.

Design: Retrospective open cohort study.

Setting: Routinely collected data from 630 UK general practices contributing to the Clinical Practice Research Datalink.

Participants: 4,573,275 patients aged over 18 years registered at up-to-standard practices between 1st April 2005 and 31st March 2013. At study entry, no patients were kidney transplant donors or recipients, pregnant, or on dialysis.

Primary outcome measures: The rate of serum creatinine and urinary protein testing per year, and the percentage of patients with isolated and repeated testing per year.

Results: The rate of serum creatinine testing increased linearly across all age groups. The rate of proteinuria testing increased sharply in the 2009-10 financial year, but only for patients aged 60 or over. For patients with established chronic kidney disease (CKD), creatinine testing increased rapidly in 2005-06 and 2006-07, and proteinuria testing in 2009-10, reflecting the introduction of Quality and Outcomes Framework indicators. In adjusted analyses, CKD Read codes were associated with up to a two-fold increase in the rate of serum creatinine testing, while other chronic conditions and potentially nephrotoxic drugs were associated with up to a six-fold increase. Regional variation in serum creatinine testing reflected country boundaries.

Conclusions: Over a nine-year period, there have been increases in the numbers of patients having kidney function tests annually and in the frequency of testing. Changes in the recommended management of CKD in primary care were the primary determinant, and increases persist even after controlling for demographic and patient-level factors. Future studies should address whether increased testing has led to better outcomes.

Keywords: Serum creatinine, proteinuria, kidney function, primary care, monitoring, chronic kidney disease.

Article summary

Strengths and limitations of this study

- To date, this is the largest population study of trends in renal function testing in primary care.
- The data source did not permit us to ascertain why a kidney function test was performed.

- The transitioning of 'high risk' patients from primary to secondary care means the estimates in this study may be liable to underestimate the amount of testing performed in certain patient subgroups.

Introduction

Kidney function testing in primary care is used to diagnose and monitor chronic kidney disease (CKD). Testing is recommended at baseline, and after initiation of some drugs such as antihypertensives [1]. Kidney function is usually tested by measuring serum creatinine, and screening for glomerular disease is undertaken by measuring urine albumin or protein concentrations.

In 2002 the Kidney Disease Outcomes and Quality Initiative (K/DOQI) published clinical guidelines advocating that CKD be categorised into five stages [2]. Two years later, these stages were adopted by the UK Quality and Outcomes Framework (QOF), which is a set of business rules for primary care that include financial incentives to regularly monitor and test certain subsets of patients, and to record their data [3]. The 2006-07 financial year saw an extension to QOF that required general practitioners to maintain a register of patients with CKD stages 3-5 [4]. In 2008, the National Institute for Health and Care Excellence (NICE) recommended monitoring eGFR levels in high risk patients [5]. Then in the 2009-10 financial year a further QOF extension incentivised monitoring urinary markers of kidney disease (such as proteinuria) in patients on the CKD register [6]. Current NICE recommendations on the frequency of testing are based on the underlying cause of CKD, previous test results, comorbidities, and the treatments being used. Monitoring is recommended annually in patients with mild to moderate reductions in kidney function and every three months in patients with more advanced disease [1].

National rates of kidney function testing and potential differences between different populations have not been characterised. In contrast, rates of kidney function testing in patients with diabetes have been well documented. A cohort study of adults with diabetes showed that under 13% had incomplete CKD screening and just 4.4% had no serum creatinine measurement on record in the two and half years before the start of the study, whereas the albumin-creatinine ratio (ACR) was not monitored in 37% during the same period [7]. Similarly, high frequencies of creatinine testing have been observed among patients with diabetes in studies looking at individual health regions, but with more variable levels of recording in patients without diabetes across different ages, genders and ethnic groups [8].

There has been a dramatic increase in the use of laboratory testing over recent decades, particularly repeated testing or monitoring [9], [10]. However, it is unclear whether this increase is appropriate and consistent with guideline recommendations or whether it represents over-testing. Appropriate testing of kidney function might be of value in planning management to slow the progression of the disease and, therefore, lead to tangible patient benefit. However, over-use of tests provides little patient benefit and adds to the financial burden of healthcare systems. A recent meta-analysis of the use of laboratory tests during the last 15 years showed that under-use of high-volume tests (such as creatinine) was more likely than over-use [11]. A cross-sectional survey of US physicians' patterns of care in patients with CKD showed that 85% of physicians recommended one additional test, which was not recommended in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [12]. These tests were most likely to be magnetic resonance angiography of renal arteries or serum protein electrophoresis, rather than blood or urinary measurements [13]. It is, of course, possible that over-use and under-use may co-exist, with some patients receiving more tests than indicated and other patients not receiving tests warranted by their clinical history, recent health, and age.

Currently, the UK is the only nationalised and publicly funded health service that has introduced financial incentives to improve the quality of healthcare for patients with CKD. National guidelines in other countries also recommend quality standards for CKD care, including diagnosis, monitoring of renal function, and control of cardiovascular risk factors [14]. However, guideline bodies outside the UK have stopped short of implementing financial incentives for CKD care, and therefore studying the impact of QOF in the UK can inform international efforts to improve outcomes for patients with CKD.

The aim of this study is to describe rates of kidney function testing since the introduction of the QOF in UK general practice. Specifically, we have examined the numbers of serum creatinine and proteinuria tests requested in each financial year during the nine years from 2005 to 2013 by: age category, gender, ethnicity, index of multiple deprivation (IMD), Strategic Health Authority (SHA), CKD stage, the presence or absence of major comorbidities (such as diabetes, hypertension, cardiovascular disease, atrial fibrillation), and the prescription of nephrotoxic drugs.

Methods

Data

We used the Clinical Practice Research Datalink (CPRD) [15] to construct an open cohort study of adults (≥ 18 years of age) registered at UK general practices whose data quality was deemed to be "up-to-standard", i.e. the data committed by general practices has reached a standard suitable for research (based on a CPRD algorithm that primarily focusses on death recording and gaps in the data). The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (protocol number 14_150R) and the approved protocol was made available to the journal and reviewers during peer review. Ethical approval for observational research using the CPRD with approval from ISAC has been granted by a National Research Ethics Service committee (Trent MultiResearch Ethics Committee, REC reference number 05/MRE04/87).

Study period

We selected a start date of 1st April 2005, which post-dated the publication of the K/DOQI guidelines for classification of CKD in 2002 [2], and the introduction of QOF in UK primary care in 2004 [3]. The study end date was 31st March 2013.

Inclusion and exclusion criteria

Eligible patients had to have been registered with their practice for a minimum of 12 months before their study entry to ensure adequate recording of baseline covariates. The study entry date was defined as the latest of either the study start date (1st April 2005) or the date of the patient's current registration date + 12 months. We excluded patients who were living kidney donors, had a renal transplant, ever underwent dialysis, or women who were pregnant in the 12 months prior to study entry. Follow-up ended at the study end date, unless preceded by the patient's death, transfer out of CPRD, the last available linked data, or (where applicable) pregnancy, renal transplantation/donation, or dialysis. For any given financial year, patient records were excluded if their data were incomplete/censored.

Outcomes

A serum creatinine test was deemed to have occurred when a patient test record contained a valid date, an entity type associated with serum creatinine testing or blood/serum biochemistry, and a Read code for serum creatinine testing (Supplementary Table 1).

A proteinuria test was deemed to have occurred when a patient test record contained a valid date, an entity type associated with urine biochemistry tests and a Read code for albuminuria or proteinuria testing (Supplementary Table 2).

A protocol-specified additional analysis, of Read codes for kidney function tests that could not be identified as serum creatinine or proteinuria, could not be carried out because use of these codes was highly heterogeneous by practice, with some practices making extensive use and other no use of such codes.

Subsequent tests recorded per patient on the same day were discarded, as these appeared to either be multiple abstractions from the same sample or data entry anomalies.

Variables

Nominal CKD stage was identified by Read codes (Supplementary Table 1). Albuminuria status was derived using either ACR or protein: creatinine ratio (PCR). When these were unavailable, raw albumin excretion rate or protein excretion rate were used. Normoalbuminuria (albuminuria stage A1) was defined as <3 mg/mmol, microalbuminuria (albuminuria stage A2) was defined as 3-30 mg/mmol, and macroalbuminuria (albuminuria stage A3) as >30 mg/mmol, in accordance with the 2012 KDIGO guidelines for evaluation and management of CKD [12]. Estimated glomerular filtration rate (eGFR) was calculated using the four-part Modification of Diet in Renal Disease (MDRD) equation based on recorded values of serum creatinine, sex, age at test, and ethnicity [16]. The four-part MDRD equation was used in place of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17], more recently advocated by NICE, as this was the equation that would predominantly have been used to monitor patients during the follow-up period.

Prevalence data for the comorbidities of: atrial fibrillation, cancer, diabetes, heart failure, hypertension, ischaemic heart disease, peripheral vascular disease, stroke or transient ischaemic attack, and thyroid disease, were assessed by the presence of diagnostic Read codes in patient clinical records.

Pharmacotherapies that were either nephrotoxic, excreted by the kidneys or that affected serum potassium were established through consensus between the general practitioners/pharmacologists (JA, CO'C and CT). These consisted of: angiotensin-converting enzyme inhibitors (ACE-is), angiotensin receptor blockers (ARBs), amiodarone/dronedarone, digoxin, diuretics, gold, immunosuppressants, lithium, mesalazine, non-steroidal anti-inflammatory drugs (NSAIDs) and oral-anticoagulants (OACs).

Patient demographic data were also extracted, including, age, gender, ethnicity, deprivation, and region. Within these variables, age was categorised into seven levels (18-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+), ethnicity was divided into six categories ("white", "Asian", "black", "mixed", "other" or "missing"), deprivation was categorised into six levels (representing quintiles of IMD data plus a

"missing" level), and region was divided into 13 categories (aligning with the 10 SHAs of England, and the countries of Northern Ireland, Scotland and Wales).

Analyses

Trends across kidney disease categorisations

Adherence to the most current NICE guidelines [1] was evaluated by stratifying crude rates of serum creatinine and proteinuria testing (herein jointly referred to as "kidney function testing") by CKD stage, and eGFR and albuminuria categories. We present these rates as tile and line plots.

Trends over time

We calculated crude rates of kidney function tests, stratified by financial year, and further stratified by CKD stage, demographic factors (such as age, ethnicity and deprivation), the presence of various comorbidities and concurrent prescriptions for nephrotoxic drugs. We present the percentage of patients with 1, 2, 3, 4 and >4 tests per financial year for serum creatinine and urinary albumin/protein as bar plots.

Factors associated with kidney function testing

We examined factors associated with serum creatinine testing in CPRD. We used a mixed effects Poisson model implemented as a negative binomial regression model [18] to assess the relationship between demographic factors, the presence of markers for CKD and other chronic conditions, and indicators of drug therapy. We fitted age and year of entry into the study as categorical factors in order to model non-linear associations. The presence of Read codes for CKD was used as markers of kidney disease. We studied 13 geographic regions corresponding to the SHAs of England, and the countries of Scotland, Northern Ireland and Wales. The model was adjusted for the presence of chronic conditions and medications. These were added to the models as binary covariates if a Read code or Gemscript code was present within the eligible data preceding the study entry date for that patient. The outcome of the model was the number of serum creatinine tests on record following study entry with the log person-years of follow-up used as the offset term. The model, therefore, estimates the natural log rates of serum creatinine testing, and covariate effects are log incidence rate ratios (IRRs). We have presented results from unadjusted, i.e. univariable, minimally adjusted, i.e. adjusted for gender, age, ethnicity, deprivation, region and year of entry, and fully adjusted, i.e. adjusted for all extracted variables, models on a natural scale, as IRRs with 95% confidence intervals.

Statistical software and packages

All analyses were conducted in R (version 3.5.1) [19]. Plots were produced using the *ggplot2* package [20]. Crude rates and their 95% confidence intervals were calculated via the skewness-corrected asymptotic score method [21] implemented in the `scaspci()` function of the *ratesci* package [22]. Negative binomial models were fit using the `glm.nb()` function of the *MASS* package [23].

Patient and public involvement

This project has been reviewed by individuals with long term conditions that require frequent monitoring, as well as nurse practitioners and general practice commissioners. Patient and public involvement members have also been invited to the steering and senior management groups. A

patient and public involvement expert was also involved as a strategic consultant in a programme of work including this project.

Results

Baseline Demographics

We identified 4,573,275 patients from 630 practices with 26,496,643 person-years of eligible follow-up data, containing a total of 15,049,063 serum creatinine tests and 995,524 proteinuria tests. The median length of follow up was 6.1 (interquartile range (IQR) 3.5 to 9.0) years. The cohort comprised 49.7% men and 50.3% women. The median (IQR) age was 46 (34 to 61) years (Table 1).

Table 1 - Characteristics of the cohort at study entry. (Note: missing categories omitted).

Characteristic	Female (N = 2,279,097)	Male (N = 2,294,178)	Everyone (N =4,573,275)
Age (years)			
18-39	807,015 (35.4%)	904,018 (39.4%)	1,711,033 (37.4%)
40-49	437,734 (19.2%)	475,130 (20.7%)	912,864 (20.0%)
50-59	370,235 (16.2%)	379,112 (16.5%)	749,347 (16.4%)
60-69	286,951 (12.6%)	278,903 (12.2%)	565,854 (12.4%)
70-79	212,826 (9.3%)	174,193 (7.6%)	387,019 (8.5%)
80-89	132,990 (5.8%)	73,456 (3.2%)	206,446 (4.5%)
≥90	31,346 (1.4%)	9,366 (0.4%)	40,712 (0.9%)
Ethnicity			
White	512,088 (22.5%)	441,467 (19.2%)	953,555 (20.9%)
Asian	42,888 (1.9%)	43,623 (1.9%)	86,511 (1.9%)
Black	19,819 (0.9%)	17,302 (0.8%)	37,121 (0.8%)
Mixed	316,792 (13.9%)	303,891 (13.2%)	620,683 (13.6%)
Other	13,933 (0.6%)	14,310 (0.6%)	28,243 (0.6%)
Index of multiple deprivation			
1 (least deprived)	334,473 (14.7%)	337,305 (14.7%)	671,778 (14.7%)
2	340,977 (15.0%)	337,861 (14.7%)	678,838 (14.8%)
3	293,127 (12.9%)	294,250 (12.8%)	587,377 (12.8%)
4	269,680 (11.8%)	277,279 (12.1%)	546,959 (12.0%)
5 (most deprived)	206,571 (9.1%)	217,148 (9.5%)	423,719 (9.3%)
Chronic kidney disease stage			
1	699 (0.0%)	608 (0.0%)	1,307 (0.0%)
2	2,512 (0.1%)	2,009 (0.1%)	4,521 (0.1%)
3	8,149 (0.4%)	4,760 (0.2%)	12,909 (0.3%)
4	687 (0.0%)	459 (0.0%)	1,146 (0.0%)
5	73 (0.0%)	75 (0.0%)	148 (0.0%)
Estimated glomerular filtration rate (mL/min/1.73m^2)			
≥90	142,918 (6.3%)	154,064 (6.7%)	296,982 (6.5%)
60-89	512,731 (22.5%)	459,469 (20.0%)	972,200 (21.3%)
45-59	188,796 (8.3%)	95,043 (4.1%)	283,839 (6.2%)
30-44	52,765 (2.3%)	23,242 (1.0%)	76,007 (1.7%)
15-29	10,543 (0.5%)	5,782 (0.3%)	16,325 (0.4%)
<15	833 (0.0%)	480 (0.0%)	1,313 (0.0%)
Albuminuria (mg/mmol)			
<3.0	39,442 (1.7%)	42,665 (1.9%)	82,107 (1.8%)

3-30	11,978 (0.5%)	14,489 (0.6%)	26,467 (0.6%)
>30	3,096 (0.1%)	3,757 (0.2%)	6,853 (0.1%)
Comorbidities			
Atrial fibrillation	37,041 (1.6%)	28,662 (1.2%)	65,703 (1.4%)
Cancer	44,136 (1.9%)	52,068 (2.3%)	96,204 (2.1%)
Diabetes	267,791 (11.7%)	238,922 (10.4%)	506,713 (11.1%)
Heart failure	12,692 (0.6%)	12,964 (0.6%)	25,656 (0.6%)
Hypertension	21,381 (0.9%)	21,497 (0.9%)	42,878 (0.9%)
Ischaemic heard disease	49,227 (2.2%)	59,621 (2.6%)	108,848 (2.4%)
Peripheral vascular disease	19,153 (0.8%)	21,166 (0.9%)	40,319 (0.9%)
Stroke/Transient ischaemic attack	21,988 (1.0%)	21,774 (0.9%)	43,762 (1.0%)
Thyroid disease	73,289 (3.2%)	16,009 (0.7%)	89,298 (2.0%)

Trends across kidney disease categorisations

Chronic kidney disease categories

When categorising kidney disease according to CKD stages, the highest rates of kidney function testing were found in patients with CKD stage 4 (Figure 1). The lowest rates of testing were observed in patients without a Read code for CKD, however, such patients were still receiving roughly one serum creatinine test every two years and one proteinuria test every nine years. Rates of serum creatinine testing were roughly in line with NICE guidelines for CKD stages 1-4, but fell below recommendation in stage 5 [1].

Figure 1 - Rates of kidney function testing (per year), stratified by CKD stage.

Estimated glomerular filtration rate and albuminuria categories

The rates of serum creatinine testing observed in the data were higher than those advocated by NICE [1] and KDIGO [24] in all eGFR-albuminuria subcategories (Figure 2). The highest rates of serum creatinine testing were in patients with eGFR stage G5. Patterns of proteinuria testing were less consistent, with patients with eGFR stage G5 or albuminuria stage A3 both exhibiting high rates of proteinuria testing. Rates of kidney function testing were generally higher than expected for individuals with either no eGFR or proteinuria stage assigned. For instance, patients with no assignable eGFR category and normal (A1) albuminuria levels were still receiving 0.84 (95% CI: 0.84, 0.85) tests per year, while patients with no assignable albuminuria level and normal (G1) eGFR levels were still receiving 0.25 (95% CI: 0.25, 0.25) proteinuria tests per year.

Figure 2 - Rates of kidney function testing (per year), stratified by eGFR and albuminuria categories.

Trends over time

Trends across CKD categories

Figure 3 shows trends in serum creatinine (left-panel) and urinary protein testing (right-panel), stratified by stage of CKD for the same period. Rates of kidney function testing increased with CKD stage up to stage 4, though rates in CKD stage 5 were lower or similar to rates in CKD stage 4. For

patients in stages 2-5, rapid increases in the number of serum creatinine tests coincided with the inclusion of CKD management in QOF in 2006-07 [4] and then stabilised after 2007-08. Sharp increases in proteinuria testing for patients with CKD stages 2-5 also coincided with the incorporation of proteinuria testing into QOF guidelines for the monitoring of CKD in 2009-10 [6].

Figure 3 - Rates of kidney function testing per financial year, stratified by CKD stage.

General trends in testing

The percentage of patients receiving kidney function tests has been steadily increasing year on year (Figure 4). In the 2005-06 financial year, 27.2% of patients received a serum creatinine test, while 7.5% of patients received a proteinuria test. In the 2012-13 financial year, these figures were 38.1% and 11.8%, respectively. These increases appear to be driven by increases in the number of patients with isolated kidney function testing, i.e. patients receiving one test per year, which for serum creatinine tests increased from 18.5% in 2005-06 to 25.2% in 2012-13. For proteinuria testing isolated testing increased from 5.6% in 2005-06 to 9.1% in 2012-13. In the same time period, the percentage of patients with repeated serum creatinine testing, i.e. two or more tests per year, increased from 8.7% to 12.9%, while the percentage of patients with repeated proteinuria testing increased from 2.0% to 2.7%.

Figure 4 - Percentage of patients that have had 1, 2, 3, 4, or more than 4 kidney function tests per financial year.

Trends in testing across demographic data

Figure 5 shows the yearly trend in testing for serum creatinine (left panel) stratified by age and the equivalent trends in urinary protein tests (right panel). In general, rates of testing were higher with higher age, up to age 80-89 years, but note that rates in the 90+ years age group are not the highest. Serum creatinine test rates increased approximately linearly over time within each decile of age. In contrast, urinary protein test rates were constant over time in age groups less than 60 years, and increased over time for patients over 60 years of age, with a sharp increase in the year 2009-10.

Figure 5 - Rates of kidney function testing per financial year, stratified by age category.

Differences between the rates of kidney function testing were much lower when stratifying by gender (Supplementary Figure 1), ethnicity (Supplementary Figure 2), IMD quintile (Supplementary Figure 3), and geographic region (Supplementary Figure 4). Testing was marginally higher in women than men for both serum creatinine and proteinuria tests, with rate differences of roughly 0.1 tests per year and 0.02 tests per year, respectively. These differences remained relatively constant throughout the follow-up period. Testing remained higher in patients coded in the CPRD as white or mixed ethnicity, with patients of black or Asian ethnicity having lower rates of testing. A similar pattern was found in proteinuria testing. Rates of kidney function testing were similar when stratifying by IMD quintile, with rates being lowest in the lowest (most affluent) IMD quintile, for both markers of kidney function. Stratification by SHA region resulted in slightly larger differences in

testing rates of up to 0.25 tests per year for serum creatinine and 0.14 tests per year for proteinuria. London demonstrated the lowest rates of kidney function testing for the majority of the study observation period. The highest rates of serum creatinine testing were initially seen in North-East England, being surpassed by Northern Ireland in 2007-08. Rates of serum creatinine testing were initially lowest in Scotland and London, until 2010-11, where rates of testing in Scotland increased. Conversely, the highest rates of proteinuria testing were present in the English East Midlands.

Trends in testing across comorbidities and pharmacotherapies

For all evaluated comorbidities, rates of kidney function testing were elevated when compared to a population for whom these comorbidities were absent (Figure 6). Testing appears to have increased across all comorbidities with time, with the exception of diabetes, where the rate of testing appears to have decreased. The highest rates of serum creatinine testing were present in patients with heart failure and diabetes, however, all comorbidities were associated with at least one serum creatinine test per year by 2007-08. The highest rates of proteinuria testing were present in patients with diabetes.

Figure 6 - Rates of kidney function testing per financial year, stratified by comorbidity. Key: AFib = atrial fibrillation; HF = heart failure; HTN = hypertension; IHD = ischaemic heart disease; PVD = peripheral vascular disease; TIA = transient ischaemic attack; THY = thyroid.

Across all evaluated pharmacotherapies, rates of kidney function testing were higher than in patients for whom prescriptions of these therapies were absent (Figure 7). Rates of kidney function testing were relatively stable across time for most comorbidities with a few notable exceptions. For patients receiving prescriptions for gold, methotrexate or other immunosuppressants, serum creatinine testing appears to have increased with time. Proteinuria testing was elevated in patients prescribed gold but was generally less than 0.5 tests/year for all other pharmacotherapies.

Figure 7 - Rates of kidney function testing per financial year, stratified by concomitant pharmacotherapy. Key: ACE-is = angiotensin-converting-enzyme inhibitors; ARBs = angiotensin II receptor blockers; Darones = amiodarone or dronedarone; OACs = oral anticoagulants; Immuno = other (non-methotrexate) immunosuppressants; NSAIDs = nonsteroidal anti-inflammatory drugs.

Factors associated with serum creatinine testing

The presence of a Read code for CKD was independently associated with more frequent serum creatinine testing in primary care, with stage 4 CKD conferring the highest rates of testing (Table 2). Testing frequency increased with age up to a peak at ages 80-89. Variation in testing between the SHA regions of England was quite low, with the exception of the North-East and the South-West, where the rates of testing were roughly 20% higher than that of London. Rates in Northern Ireland, Scotland and Wales were 21-48% greater than those of London, possibly reflecting differences in clinical guidelines between England and other countries. In our adjusted model of testing frequency, the extent of testing in men and women differed by 14% IRR 1.14, (95% CI: 1.14, 1.14). All assessed comorbidities were significantly associated with elevated rates of serum creatinine testing with the exception of atrial fibrillation. With the exception of ethambutol, for all analysed

pharmacotherapies, serum creatinine testing increased independently of other factors and was most marked in patients taking methotrexate, other immunosuppressants, gold and lithium.

Table 2 - Results of regression models describing the demographic characteristics, the presence/absence of chronic conditions and drug prescription, and associations with the frequency of serum creatinine testing in primary care.

Characteristic	Univariable IRR (95%CI)	Minimally Adjusted IRR (95%CI)	Fully Adjusted IRR (95%CI)
Gender			
Female	1.20 (1.20, 1.21)	1.18 (1.18, 1.18)	1.14 (1.14, 1.14)
Age (years)			
40-49	2.09 (2.08, 2.10)	2.10 (2.09, 2.11)	1.92 (1.91, 1.92)
50-59	3.50 (3.49, 3.51)	3.53 (3.52, 3.54)	2.87 (2.86, 2.88)
60-69	5.38 (5.36, 5.40)	5.39 (5.37, 5.41)	3.94 (3.93, 3.96)
70-79	7.25 (7.22, 7.27)	7.23 (7.20, 7.26)	4.83 (4.81, 4.85)
80-89	7.57 (7.53, 7.61)	7.47 (7.43, 7.51)	4.86 (4.83, 4.88)
≥90	6.17 (6.10, 6.25)	5.94 (5.87, 6.01)	4.05 (4.00, 4.10)
Ethnicity			
Asian	0.78 (0.77, 0.79)	1.25 (1.24, 1.27)	1.23 (1.22, 1.24)
Black	0.77 (0.76, 0.78)	1.19 (1.18, 1.21)	1.16 (1.14, 1.17)
Mixed	0.96 (0.96, 0.97)	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)
Other	0.71 (0.69, 0.72)	1.05 (1.03, 1.06)	1.04 (1.02, 1.05)
Not recorded	0.83 (0.83, 0.83)	0.84 (0.84, 0.84)	0.84 (0.84, 0.84)
Index of multiple deprivation			
2	1.07 (1.06, 1.07)	1.04 (1.04, 1.05)	1.03 (1.02, 1.03)
3	1.07 (1.06, 1.07)	1.07 (1.06, 1.07)	1.04 (1.04, 1.04)
4	1.03 (1.03, 1.04)	1.11 (1.11, 1.12)	1.08 (1.07, 1.08)
5 (most deprived)	1.04 (1.03, 1.04)	1.14 (1.13, 1.14)	1.09 (1.08, 1.09)
Not recorded	1.05 (1.05, 1.05)	1.07 (1.07, 1.08)	1.03 (1.03, 1.04)
Year of Study Entry			
2006	0.72 (0.71, 0.72)	0.96 (0.95, 0.96)	1.08 (1.08, 1.09)
2007	0.78 (0.77, 0.78)	0.96 (0.95, 0.96)	1.10 (1.09, 1.10)
2008	0.81 (0.80, 0.81)	0.99 (0.98, 1.00)	1.13 (1.13, 1.14)
2009	0.77 (0.76, 0.78)	1.00 (0.99, 1.01)	1.13 (1.12, 1.14)
2010	0.83 (0.82, 0.83)	1.04 (1.03, 1.04)	1.17 (1.17, 1.18)
2011	0.92 (0.92, 0.93)	1.11 (1.10, 1.12)	1.29 (1.28, 1.30)
2012	0.96 (0.95, 0.97)	1.18 (1.16, 1.19)	1.34 (1.33, 1.35)
Region			
East Midlands	1.29 (1.28, 1.30)	1.18 (1.17, 1.19)	1.07 (1.07, 1.08)
East of England	1.18 (1.17, 1.18)	1.09 (1.09, 1.10)	1.04 (1.04, 1.05)
North-East	1.44 (1.42, 1.45)	1.27 (1.26, 1.28)	1.20 (1.19, 1.21)
North-West	1.30 (1.29, 1.31)	1.18 (1.18, 1.19)	1.10 (1.10, 1.11)
South Central	1.21 (1.20, 1.22)	1.14 (1.13, 1.14)	1.10 (1.09, 1.10)
South-East Coast	1.23 (1.22, 1.24)	1.12 (1.11, 1.12)	1.10 (1.10, 1.11)
South-West	1.43 (1.42, 1.44)	1.22 (1.22, 1.23)	1.17 (1.17, 1.18)
West Midlands	1.24 (1.24, 1.25)	1.14 (1.13, 1.15)	1.08 (1.07, 1.08)
Yorkshire & The Humber	1.24 (1.23, 1.25)	1.08 (1.07, 1.09)	0.97 (0.96, 0.97)
Northern Ireland	1.51 (1.50, 1.53)	1.55 (1.54, 1.57)	1.48 (1.47, 1.49)
Scotland	1.21 (1.20, 1.22)	1.22 (1.21, 1.22)	1.21 (1.20, 1.22)
Wales	1.33 (1.32, 1.34)	1.26 (1.26, 1.27)	1.22 (1.21, 1.22)
Chronic kidney disease stage			
1	1.93 (1.76, 2.11)	2.18 (2.03, 2.35)	2.05 (1.92, 2.19)

2	2.30 (2.21, 2.40)	1.82 (1.76, 1.88)	1.93 (1.87, 1.99)
3	3.32 (3.25, 3.40)	1.67 (1.64, 1.70)	1.48 (1.46, 1.51)
4	4.98 (4.60, 5.39)	2.61 (2.45, 2.77)	2.17 (2.05, 2.30)
5	3.92 (3.05, 5.03)	2.37 (1.94, 2.89)	1.74 (1.45, 2.09)
Comorbidities			
Atrial fibrillation	3.09 (3.04, 3.13)		1.00 (0.99, 1.02)
Cancer	2.14 (2.12, 2.17)		1.15 (1.14, 1.16)
Diabetes	3.48 (3.45, 3.51)		1.98 (1.97, 1.99)
Heart failure	3.89 (3.83, 3.95)		1.07 (1.05, 1.08)
Hypertension	2.37 (2.37, 2.38)		1.28 (1.28, 1.29)
Ischaemic heard disease	2.76 (2.73, 2.78)		1.23 (1.23, 1.24)
Peripheral vascular disease	2.55 (2.52, 2.58)		1.20 (1.19, 1.21)
Stroke/Transient ischaemic attack	2.85 (2.81, 2.88)		1.14 (1.13, 1.15)
Thyroid disease	2.09 (2.07, 2.11)		1.31 (1.30, 1.32)
Pharmacotherapies			
ACE Inhibitors	3.20 (3.18, 3.21)		1.41 (1.41, 1.42)
ARBs	2.98 (2.96, 3.00)		1.25 (1.24, 1.26)
Amiodarone/Dronedarone	3.49 (3.41, 3.56)		1.15 (1.13, 1.17)
Digoxin	3.39 (3.34, 3.44)		1.17 (1.16, 1.19)
Diuretics	3.27 (3.25, 3.28)		1.46 (1.46, 1.47)
Ethambutol	1.37 (1.09, 1.73)		1.16 (0.97, 1.40)
Gold	11.11 (9.59, 12.88)		5.48 (4.95, 6.07)
Immunosuppressants (Not Inc. Methotrexate)	5.06 (4.97, 5.15)		3.44 (3.40, 3.49)
Lithium	4.14 (4.00, 4.28)		4.42 (4.32, 4.52)
Mesalazine	2.44 (2.37, 2.50)		2.23 (2.19, 2.28)
Methotrexate	9.41 (9.19, 9.64)		6.17 (6.07, 6.28)
NSAIDs	1.55 (1.55, 1.56)		1.25 (1.25, 1.25)
Oral Anticoagulants	2.93 (2.89, 2.96)		1.17 (1.16, 1.18)

Discussion

Key results

This is the first study to evaluate the rates of kidney function testing over a nine-year period following the introduction of the QOF in a large UK primary care database. Over the course of this study, rates of serum creatinine and proteinuria testing increased by 40% and 36%, respectively, and by 2012-13 almost four in every 10 people were receiving at least one serum creatinine test per year and over one in every 10 people were receiving at least one proteinuria test per year.

Across most strata evaluated, rates of kidney function testing appear to have either remained constant or increased with time. One notable exception to this was diabetes, where rates appear to have decreased with time. Women appear to be tested more than men, receiving roughly an extra 0.1 serum creatinine tests per year and an extra 0.02 proteinuria tests per year. This may be because women are more likely to schedule and attend appointments in primary care, as evidenced by a UK national study of patient factors associated with missed appointments [25]. When stratifying by age, rates of kidney function testing increased between successive age categories up to age 80-89, with patients aged ≥90 typically having lower rates of testing than patients aged 70-79. Serum creatinine and urinary protein testing have both increased across all ethnic groups, but patients of white and

mixed ethnicities still have higher rates of testing than patients of black and Asian ethnicity. Stratification by IMD quintile demonstrated minimal differences in testing rates. Conversely, stratification by comorbidity revealed the highest rates of both serum creatinine and proteinuria testing to be present in patients with heart failure or diabetes. Creatinine testing is undertaken in the primary care practice in the UK, rather than in a separate facility, and therefore creatinine testing is sensitive to factors that influence practice attendance. However, some patients with diabetes will be managed by specialists as part of an out-patient hospital service and will have blood tests requested and taken at the hospital. These blood tests will not be sent to primary care electronic health records and will not appear in CPRD. The smaller rate of testing seen in this database for patients with diabetes may therefore not reflect deficiencies in overall care, but simply the fact that care is shared with the hospital for some of those patients. Stratification by concomitant pharmacotherapy, revealed the highest rates of kidney function testing to be present in patients prescribed gold. Serum creatinine testing was also more frequent in patients prescribed immunosuppressants.

The effects of pay-for-performance indicators are visible in most plots present in this paper with noticeable increases in the rates of serum creatinine testing in 2006-07 and of proteinuria testing in 2009-10. The former of these coincided with the requirement that general practices maintain a register of patients with CKD stages 3-5 [4], while the latter coincided with the inclusion of the monitoring of secondary markers of kidney disease via ACR and PCR tests in patients on the CKD register [5]. There was no obvious impact in any of the plots from the 2008-09 NICE guidelines which recommended monitoring eGFR levels in high risk patients [5].

Frequency of serum creatinine testing was strongly associated with increasing age and the presence of a Read code for CKD in adjusted analyses. Testing frequency was also independently associated with chronic conditions and prescription of potentially nephrotoxic drugs but has risen year on year, even after accounting for age, chronic conditions, and prescription of drugs that require monitoring of kidney function.

Strengths and limitations

To date, this is the largest population-based study of trends in renal function testing in primary care. The study population was an unselected sample of over 4.5 million patients from over 600 general practices across the UK included in the CPRD database, which has been shown to be representative of the UK. The scale and design of the study allowed us to test associations adjusted for many important potential explanatory and confounding factors. Our study has limitations, some of which are inherent in the CPRD database. We were not able to ascertain why the tests were performed. Even though the CPRD contains consultation codes, these provide only a very broad classification of the time and type of consultation (e.g. Clinic, Night visit, Home visit). An in-depth analysis of Read codes or mining of the consultation free text would be required to start to explain the reasons for test ordering, which is beyond the scope of this study. Finally, the use of the MDRD equation could be challenged. It was the formula in use during the period of the study but is now considered inferior to the CKD-EPI formula. However, we have used MDRD, because we wanted the analysis to reflect the clinical decision made at the time of the study.

Relationship to the literature

The rise in the number of patients having serum creatinine concentration measurements and the increased frequency of testing for those being tested can be interpreted in two ways. CKD has gained more attention since the incorporation of CKD into the QOF in 2006-07. The establishment of a register in 2006-07 and its subsequent extension has encouraged renal function testing to identify those with CKD who may benefit from risk factor modification. From the viewpoint of patient safety, our results are encouraging and show that, for all the therapies we examined, the prescription of drugs that are potentially nephrotoxic is associated with more frequent monitoring.

Our results could be interpreted in a different light. There is little direct evidence that extra testing has improved outcomes in the short term or long term [26]. Additional testing has increased the apparent prevalence of CKD from 0.12% to 6.51%, but as yet, there has been no change in long-term outcomes, such as patients requiring renal replacement therapy [27], [28]. Increases in consultations with general practitioners or practice nurses for either newly diagnosed disease or monitoring, with associated laboratory tests, place further strain on limited healthcare resources and increase expenditure. The very substantial costs of renal replacement therapy or cardiovascular complications [28] mean that testing might be cost-effective, even if it results in only modest reductions in the number of patients who progress to this stage, but whether this is the case is unclear. In a report from one NHS trust in the period following the introduction of renal QOF there was an abrupt 61% increase in the number of new referrals to nephrology, 54% of which were classified as inappropriate and a further 22% as inadequate [29]. Inappropriate referrals use up resources and may cause unnecessary distress to patients and their carers [30].

Implications for practice

Rates of testing have increased over the observation period in our study. Much of these increases appear to be driven by financial incentivisation schemes, such as the QOF. However, the increases were found to be independent of comorbidities, age and prescriptions for ‘high risk’ drugs. Much of the increase in testing appears to have occurred in patients with mildly to moderately impaired kidney function (CKD stages 2-3). However, there is limited evidence to suggest any benefit from interventions delivered in the early stages of CKD [31]. Moreover, studies in cholesterol monitoring have shown that more frequent testing can have negative consequences [32] - particularly for biomarkers that have high within-person variability, such as serum creatinine [33], with an increased likelihood of raising false alarms for increased CKD severity. Hence, a more targeted approach could prove beneficial for most patients.

Increases in testing are also likely to have knock-on effects to other aspects of healthcare, including the financial burden on the NHS, the time burden on general practitioners, and laboratory workloads; potentially resulting in delayed or missed diagnosis [34]. Reducing the amount of serum creatinine testing performed as part of kidney function monitoring could ease some of these burdens, although we acknowledge that a reasonable amount of serum creatinine testing is performed as part of test batches not directly related to the assessment of kidney function and including other tests such as full blood counts [35].

Conclusion

The observed increase in kidney function testing could be attributable to any or all of several changes that have occurred over the period of the study. The introduction of pay-for-performance indicators, the establishment of a CKD register, national guidelines promoting monitoring of renal function in high-risk groups, and linkage of pathology laboratories to practice systems have potentially all raised the profile of CKD in primary care and contributed to the observed increases in testing. While it is clear that these initiatives have changed process measures, it is still not clear whether clinical outcomes have improved as a consequence.

Statements

Funding

This article presents independent research funded by the National Institute for Health Research (NIHR) under the programme grants for applied research programme (RP-PG-1210-12003). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. CT is funded through an NIHR academic clinical lectureship. RP receives funding from the NIHR Oxford Biomedical Research Centre Program, the NIHR Program for Applied Research, the NIHR Health Protection Research Unit (HPRU) Gastrointestinal Infections Group, and the NIHR Diagnostic Evidence Co-operative (DEC).

Competing interests

NH is currently employed by Bristol-Meyers Squibb Limited; a company that manufactures ACE inhibitors, which are drugs indicated in the treatment of CKD, when present in conjunction with other comorbidities such as type 2 diabetes. CT reports speaker fees from Vifor and Novartis and non-financial support from Roche outside of the submitted work. All other authors declare no conflicts of interest.

Author contributions

RP and RS provided substantial contributions to the concept and design of the study. JO, BF, RS, RP and EM provided statistical expertise, while JA, CT, CO'C and DL lent clinical and pharmacological expertise. Any coding work necessary for the project was performed by BF, JO, EM and NH. All authors contributed to the drafting and critical appraisal of the manuscript. Final approval for the version to be published was given by RP.

Patient consent and ethical approval

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (protocol number 14_150R), and the approved protocol was made available to the journal and reviewers during peer review. Ethical approval for observational research using the CPRD with approval from ISAC has been granted by a National Research Ethics Service committee (Trent MultiResearch Ethics Committee, REC reference number 05/MRE04/87).

Data sharing

The data that support the findings of this study are available from the Medicines and Healthcare Products Regulatory Agency, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. Data are, however, available from the Medicines and Healthcare Products Regulatory Agency, subject to approval from ISAC.

Acknowledgements

We would like to thank Alice Fuller and Dr Sarah Lay-Flurrie for their hard work in providing much of the initial data management for this project.

Bibliography

[1] National Institute for Health and Care Excellence, "Chronic kidney disease in adults: assessment and management. Clinical guideline [CG182]," 2014. [Online]. Available: https://www.nice.org.uk/guidance/cg182.

[2] National Kidney Foundation, "K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification," *Am J Kidney Dis*, vol. 39, no. 2 Suppl 1, pp. S1–S266, Feb. 2002.

[3] Department of Health, "The National Services Framework for Renal Services. Part One: Dialysis and Transplantation." 2004.

[4] British Medical Association, "Revisions to the GMS contract 2006/07," 2006. [Online]. Available: http://www.nhsemployers.org/-/media/Employers/Documents/Primary-care-contracts/QOF/2006-07/Revisions-to-the-GMS-contract-200607---Delivering-investments-in-general-practice.pdf?la=en&hash=C4949A6E6518C75287E55BCB13A8D311AD0DF3E4.

[5] National Institute for Health and Care Excellence, "NICE Clinical Guideline 73: Chronic Kidney Disease: Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care," 2008. [Online]. Available: https://www.nice.org.uk/guidance/CG73.

[6] British Medical Association, "Quality and Outcomes Framework guidance for GMS contract 2009/10," 2009. [Online]. Available: http://www.nhsemployers.org/~/media/Employers/Documents/Primary care contracts/QOF/2010-11/Quality and Outcomes Framework guidance for GMS contract 200910 - Delivering investment in general practice.pdf.

[7] A. P. McGovern *et al.*, "Association of chronic kidney disease (CKD) and failure to monitor renal function with adverse outcomes in people with diabetes: a primary care cohort study," *BMC Nephrol.*, vol. 14, p. 198, Jan. 2013.

[8] S. de Lusignan *et al.*, "Disparities in testing for renal function in UK primary care: cross-sectional study," *Fam. Pract.*, vol. 28, no. 6, pp. 638–646, Dec. 2011.

[9] H. Doll, B. Shine, J. Kay, T. James, and P. Glasziou, "The rise of cholesterol testing: how much is unnecessary," *Br. J. Gen. Pract.*, vol. 61, no. 583, pp. e81-8, 2011.

[10] J. Oke, B. Shine, E. McFadden, R. Stevens, D. Lasserson, and R. Perera, "Trends in serum creatinine testing in Oxfordshire, UK, 1993-2013: a population-based cohort study," *BMJ Open*, vol. 5, no. 12, p. e009459, 2015.

[11] M. Zhi, E. L. Ding, J. Theisen-Toupal, J. Whelan, and R. Arnaout, "The landscape of inappropriate laboratory testing: a 15-year meta-analysis," *PLoS One*, vol. 8, no. 11, p. e78962, 2013.

[12] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, "KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease," *Kidney Int Suppl*, vol. 3, pp. 1–150, 2013.

[13] R. F. Charles, N. R. Powe, B. G. Jaar, M. U. Troll, R. S. Parekh, and L. E. Boulware, "Clinical Testing Patterns and Cost Implications of Variation in the Evaluation of CKD Among US Physicians," *Am. J. Kidney Dis.*, vol. 54, no. 2, pp. 227–237, 2009.

[14] M. Choi, E. Montgomery, T. Saffer, and J. Vassalotti, "Chronic Kidney Disease Change Package: Population Health Strategies for Cardiovascular and Kidney Disease Risk Reduction,"

2018.

[15] E. Herrett *et al.*, "Data Resource Profile: Clinical Practice Research Datalink (CPRD)," *Int J Epidemiol*, vol. 44, no. 3, pp. 827–836, 2015.

[16] A. S. Levey, J. P. Bosch, J. B. Lewis, T. Greene, N. Rogers, and D. Roth, "A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group," *Ann. Intern. Med.*, vol. 130, no. 6, pp. 461–470, 1999.

[17] A. S. Levey *et al.*, "A New Equation to Estimate Glomerular Filtration Rate," *Ann. Intern. Med.*, vol. 150, no. 9, pp. 604–612, 2009.

[18] B. R. Kirkwood and J. A. C. Sterne, "31.4 Random Effects (Multilevel) Models," in *Essential Medical Statistics*, 2nd ed., Malden, Massachusetts, USA: Wiley-Blackwell, 2003, pp. 361–364.

[19] R Core Team, "R: A Language and Environment for Statistical Computing." R Foundation for Statistical Computing, Vienna, Austria, 2018.

[20] H. Wickham, *ggplot2: Elegant Graphics for Data Analysis*. New York: Springer-Verlag, 2016.

[21] P. J. Laud, "Equal-tailed confidence intervals for comparison of rates," *Pharm. Stat.*, vol. 16, no. 5, pp. 334–348, 2017.

[22] P. J. Laud, "ratesci: Confidence Intervals for Comparisons of Binomial or Poisson Rates." 2018.

[23] W. N. Venables and B. D. Ripley, *Modern Applied Statistics with S*, Fourth. New York: Springer, 2002.

[24] KDIGO, "KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease," *Kidney Int Suppl*, vol. 3, no. 1, pp. 136–150, 2013.

[25] D. A. Ellis, R. McQueenie, A. McConnachie, P. Wilson, and A. E. Williamson, "Demographic and Practice Factors Predicting Repeated Non-Attendance in Primary Care: A National Retrospective Cohort Analysis," *Lancet Public Heal.*, vol. 2, no. 12, pp. e551–e559, 2017.

[26] L. A. Inker *et al.*, "KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD," *Am. J. Kidney Dis.*, vol. 63, no. 5, pp. 713–735, 2014.

[27] C. Byrne *et al.*, "UK Renal Registry UK Renal Registry 19th Annual Report of the Renal Association," *Nephron*, vol. 137, no. suppl1, 2017.

[28] M. Kerr, B. Bray, J. Medcalf, D. J. O'Donoghue, and B. Matthews, "Estimating the Financial Cost of Chronic Kidney Disease to the NHS in England," *Nephrol. Dial. Transplant.*, vol. 27, no. Suppl 3, pp. iii73-80, 2012.

[29] C. A. O'Callaghan, B. Shine, and D. S. Lasserson, "Chronic Kidney Disease: A Large-Scale Population-Based Study of the Effects of Introducing the CKD-EPI Formula for eGFR Reporting," *BMJ Open*, vol. 1, no. 2, p. e000308, 2011.

[30] R. J. Glassock and C. Winearls, "Screening for CKD with eGFR: doubts and dangers," *Clin. J. Am. Soc. Nephrol.*, vol. 3, no. 5, pp. 1563–8, Sep. 2008.

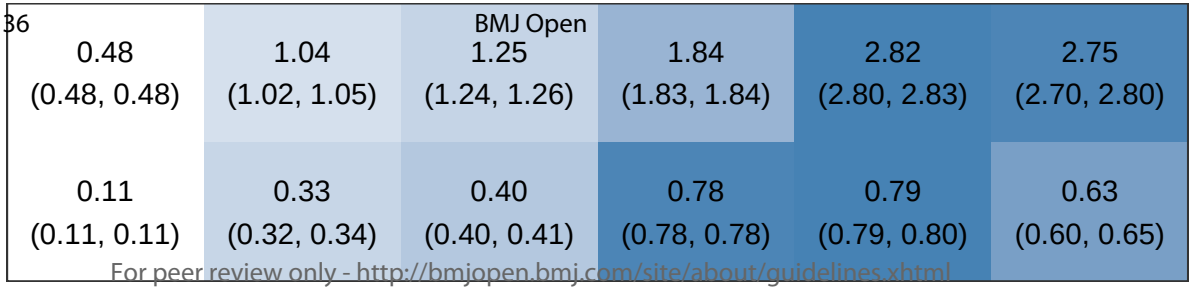
[31] H. A. Fink *et al.*, "Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: a systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline," *Ann. Intern. Med.*, vol. 156, no. 8, pp. 570–581, Apr. 2012.

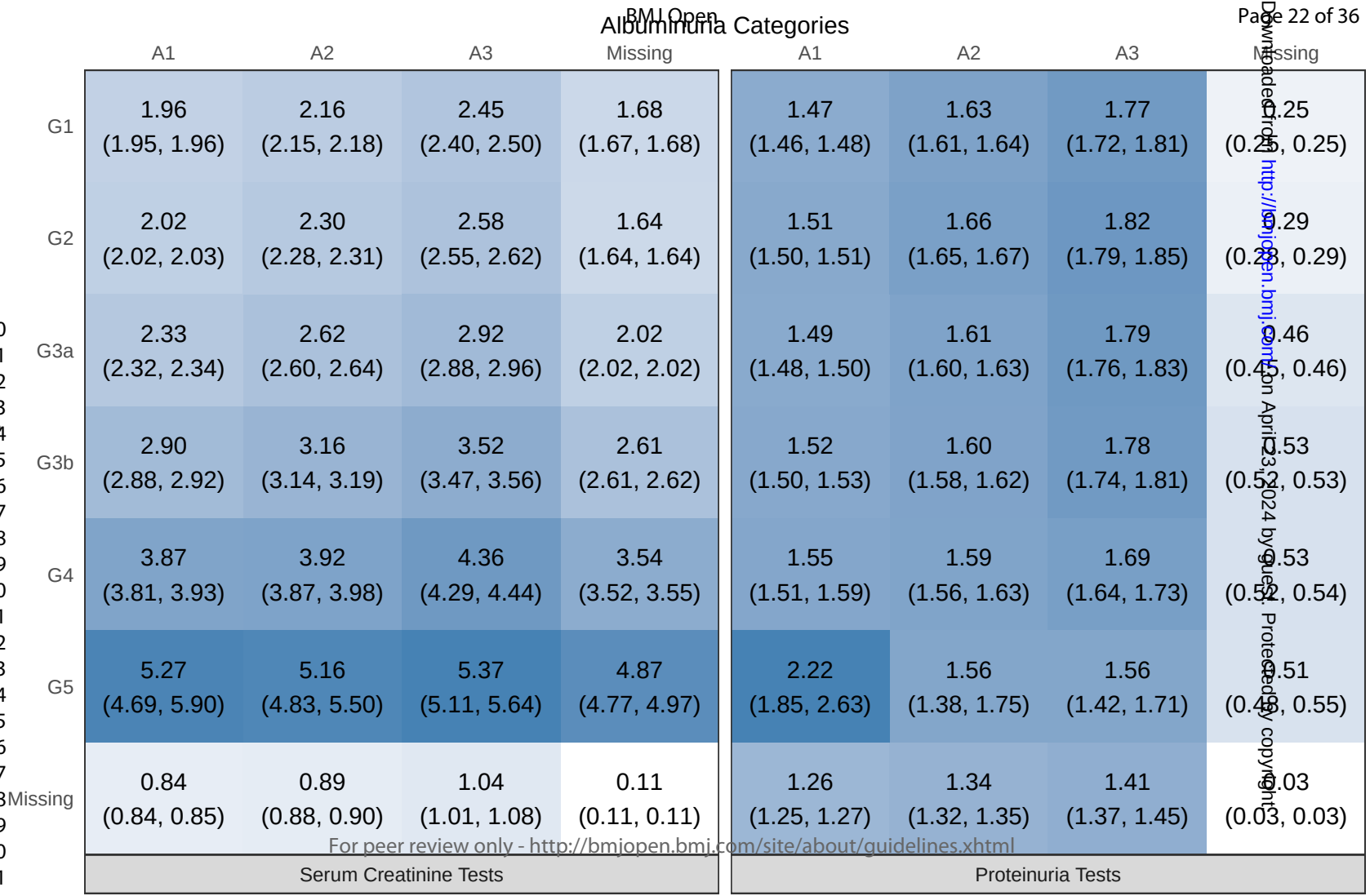
[32] P. P. Glasziou, L. Irwig, S. Heritier, R. J. Simes, and A. Tonkin, “Monitoring Cholesterol Levels: Measurement Error or True Change?,” *Ann. Intern. Med.*, vol. 148, no. 9, pp. 656–661, May 2008.

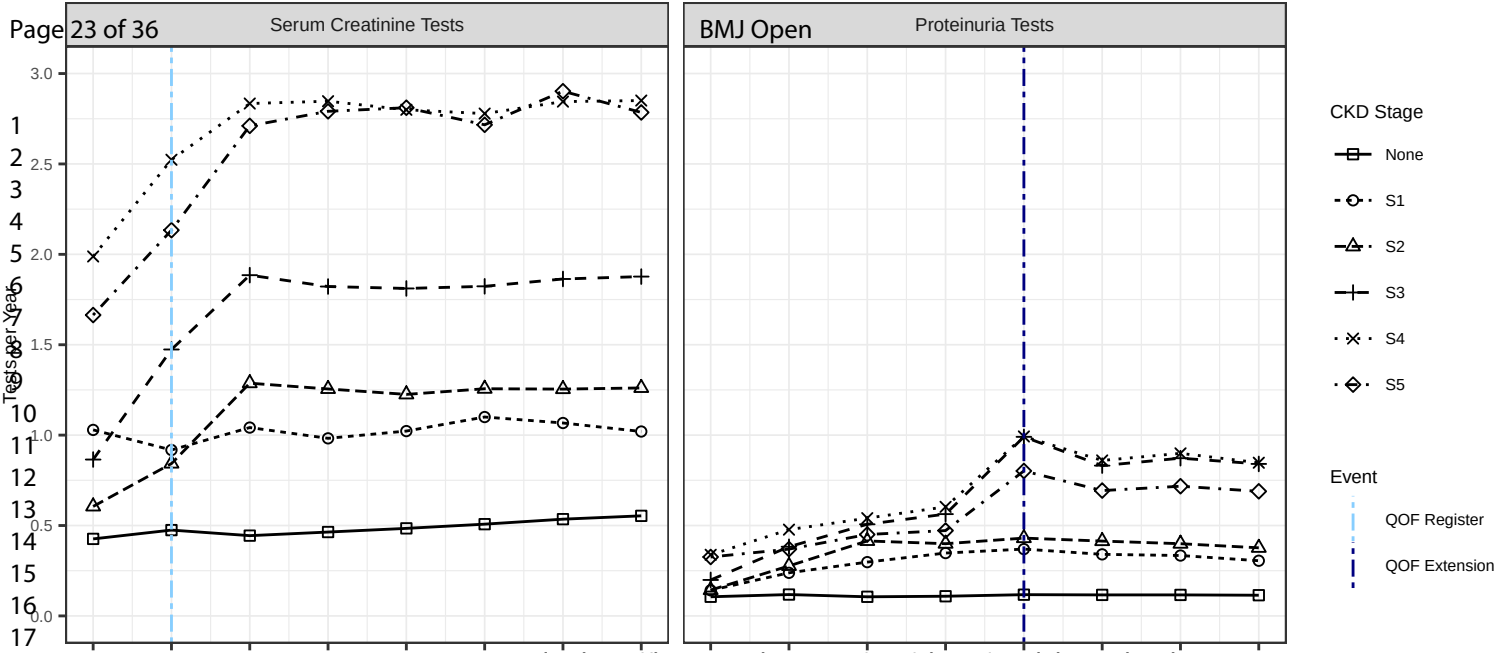
[33] E. J. Lamb *et al.*, “The eGFR-C study: Accuracy of Glomerular Filtration Rate (GFR) Estimation Using Creatinine and Cystatin C and Albuminuria for Monitoring Disease Progression in Patients with Stage 3 Chronic Kidney Disease - Prospective Longitudinal Study in a Multiethnic ,” *BMC Nephrol.*, vol. 15, no. 1, p. 13, 2014.

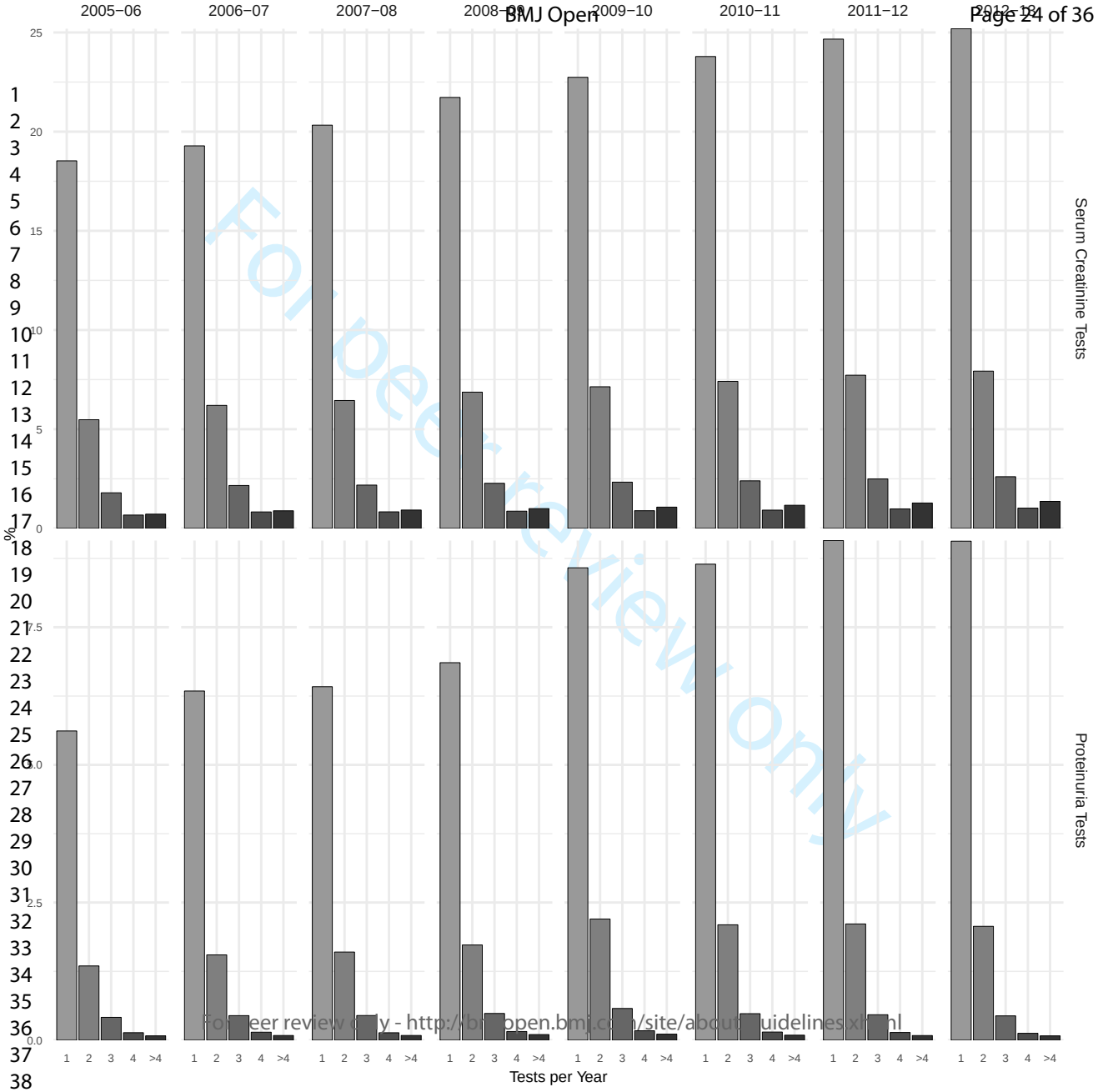
[34] T. K. Gandhi *et al.*, “Missed and Delayed Diagnoses in the Ambulatory Setting: A Study of Closed Malpractice Claims,” *Ann. Intern. Med.*, vol. 145, no. 7, pp. 488–496, Oct. 2006.

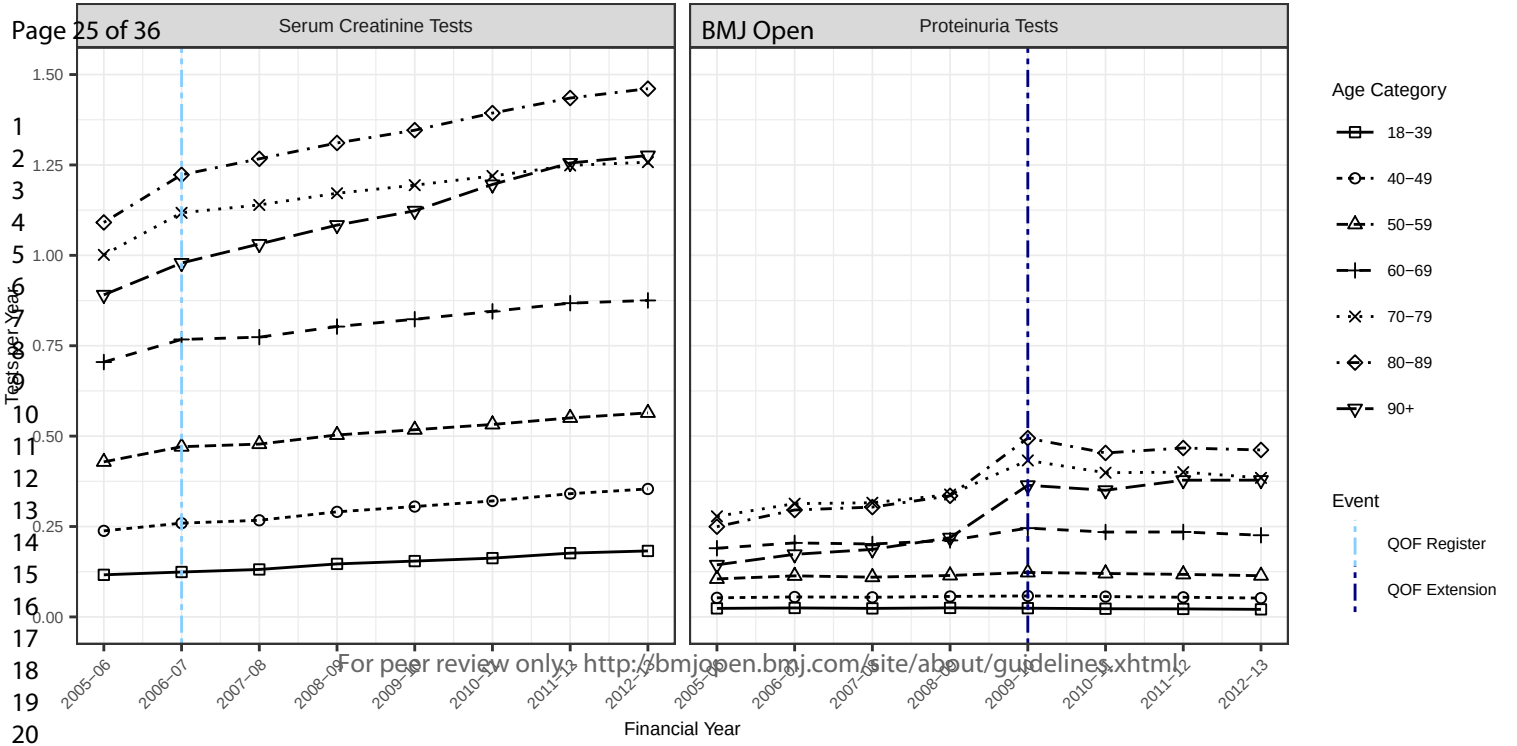
[35] T. R. Fanshawe, J. M. Ordóñez-Mena, P. J. Turner, A. Van den Bruel, B. Shine, and G. N. Hayward, “Frequencies and Patterns of Laboratory Test Requests From General Practice: A Service Evaluation to Inform Point-of-Care Testing,” *J. Clin. Pathol.*, vol. 0, pp. 1–6, 2018.

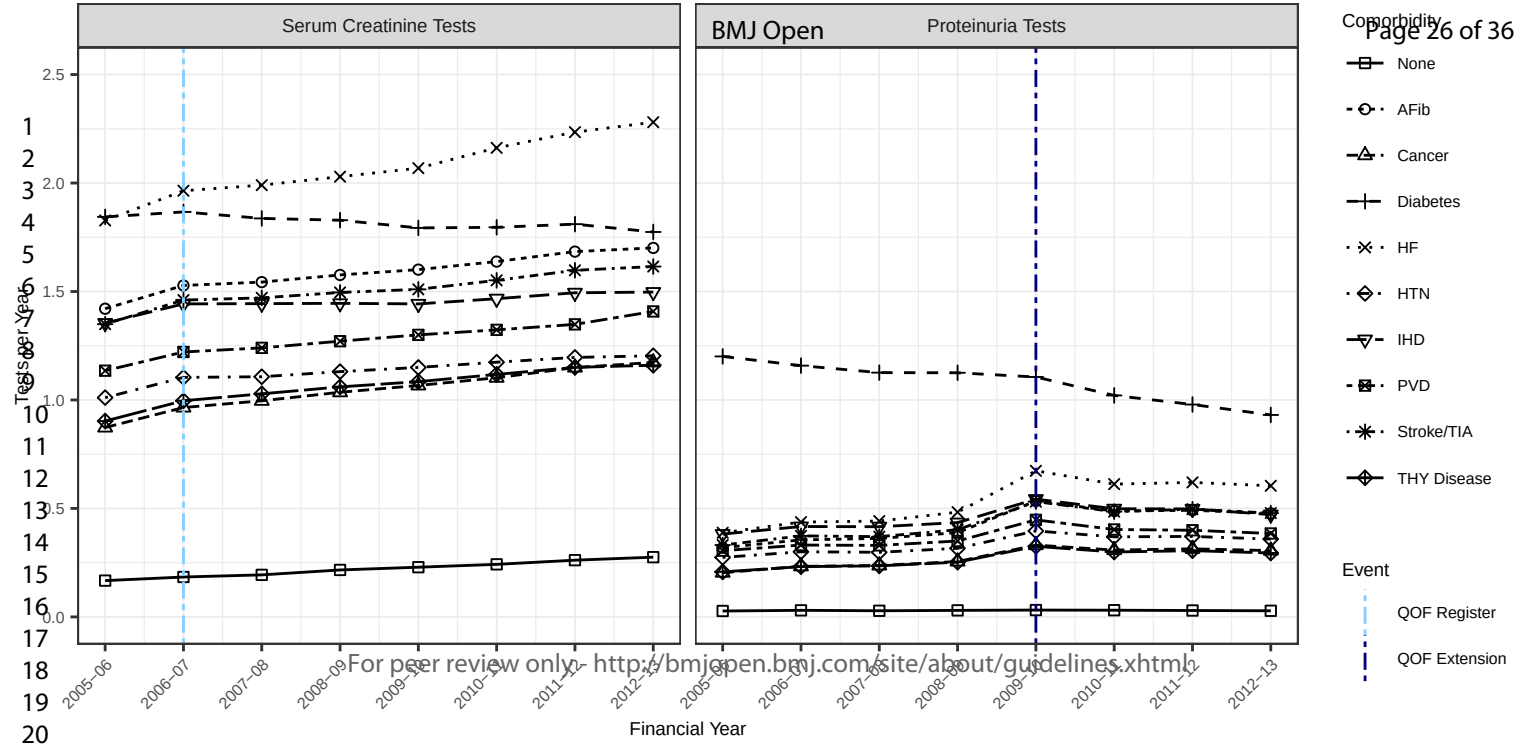


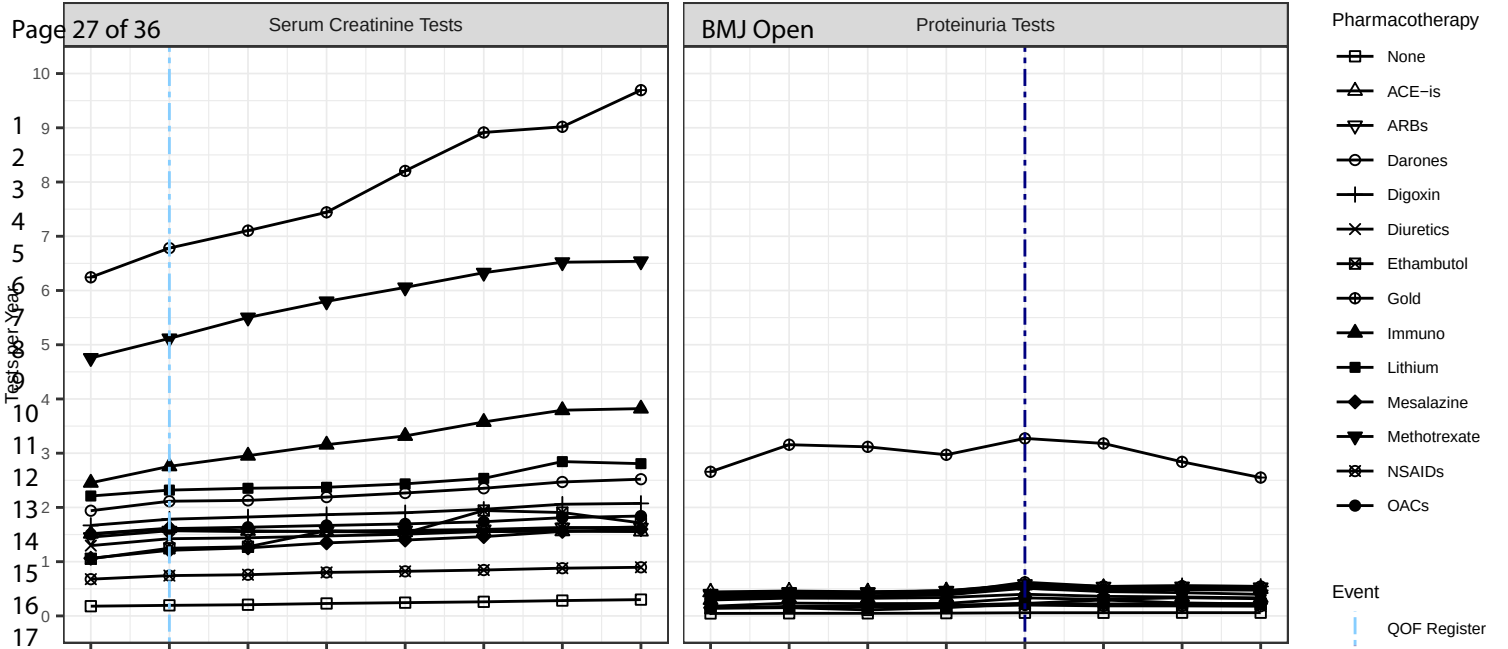












Supplementary material

Serum creatinine test Read codes

Supplementary Table 1 - Serum creatinine testing Read codes.

Medical Code	Read Code	Read Term
5	44J3.00	Serum creatinine
3927	44J3300	Serum creatinine raised
13736	44JF.00	Plasma creatinine level
26903	44J3200	Serum creatinine normal
31277	44J3000	Serum creatinine abnormal
35545	44J3100	Serum creatinine low
42345	44J3z00	Serum creatinine NOS
45096	44JD.00	Corrected serum creatinine level
62062	44JC.00	Corrected plasma creatinine level

Proteinuria test Read codes

Supplementary Table 2 - Proteinuria testing Read codes.

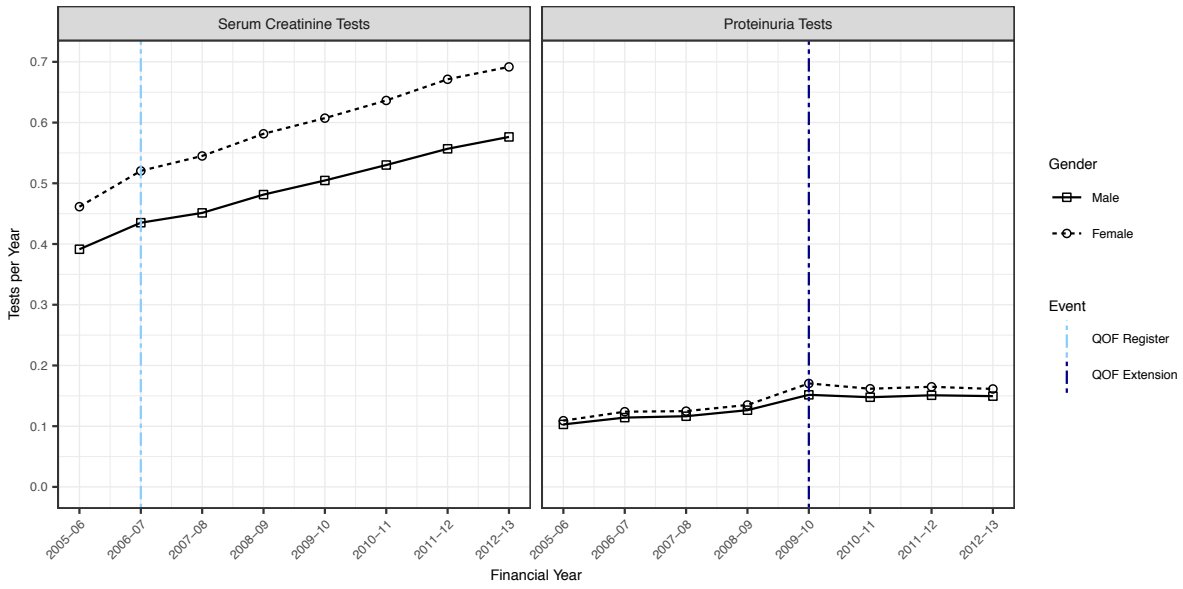
Medical Code	Read Code	Read Term
43	467..00	Urine protein test
1802	4678	Proteinuria
2482	D011100	Vit B12 defic anaemia due to malabsorption with proteinuria
2607	46TC.00	Urine albumin:creatinine ratio
5451	R110000	[D]Albuminuria
8482	467A.00	24 hour urine protein output
9430	4679	Urine dipstick for protein
10924	R110300	[D]Microalbuminuria
11248	R110.00	[D]Proteinuria
13590	4674	Urine protein test = +
13600	4677	Urine protein test = ++++
13611	4675	Urine protein test = ++
13612	4673	Urine protein test = trace
13613	46N2.00	Urine protein abnormal
13621	4676	Urine protein test = +++
14091	4672	Urine protein test negative
14092	4671	Urine protein test not done
14094	467E.00	Urine protein level
14113	44J7.00	Albumin / creatinine ratio
14382	46N1.00	Urine protein normal

Medical Code	Read Code	Read Term
14389	46N5.00	24 hour urine protein excretion test
14391	46TD.00	Urine microalbumin:creatinine ratio
14395	46N..00	Urine protein
14405	46N6.00	24 hour urine albumin output
14410	46N4.00	Urine albumin
14411	46M7.00	Urine creatinine
14429	46N3.00	Urine total protein
14434	46MD.00	24 hour urine creatinine output
14563	46W..00	Urine microalbumin
14564	46W2.00	Microalbumin excretion rate
14901	K136.00	Benign postural proteinuria
16465	K190X00	Persistent proteinuria, unspecified
17106	46W1.00	Urine microalbumin negative
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
23281	44J6.00	Albumin excretion rate
23334	L162.11	Albuminuria in pregnancy without hypertension
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
27059	467Z.00	Urine protein test NOS
27214	46NZ.00	Urine protein NOS
27266	44lD.00	Urine protein/creatinine ratio
28180	46W0.00	Urine microalbumin positive
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
34173	L12B.00	Proteinuric hypertension of pregnancy
34265	L16C000	Gestational proteinuria
34680	R110200	[D]Exercise proteinuria
36243	K136.11	Orthostatic proteinuria
36394	L16C.00	Pregnancy induced oedema+proteinuria without hypertension
37201	L16C100	Gestational oedema with proteinuria
38284	R110z00	[D]Proteinuria NOS
39248	46N8.00	Urine microalbumin profile
43262	467H.00	Random urine protein level
43524	44JG.00	Overnight albumin excretion rate
43611	K0A4.00	Isolated proteinuria with specified morphological lesion
44179	46N7.00	Urine protein/creatinine index
49741	68K2.00	Urine screen for protein
59992	K0A4W00	Isolated proteinuria, with unspecified morpholog changes
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
61470	66Al.00	Diabetic monitoring - higher risk albumin excretion
64030	Kyu5G00	[X]Persistent proteinuria, unspecified

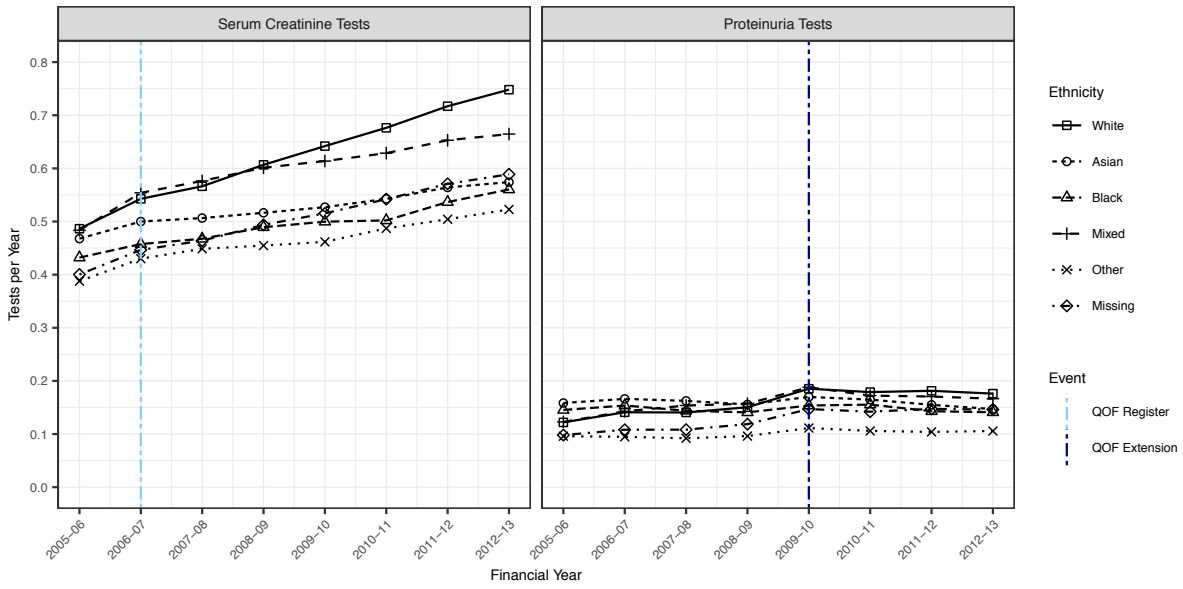
Medical Code	Read Code	Read Term
66475	66Ak.00	Diabetic monitoring - lower risk albumin excretion
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
92998	Lyu1.00	[X]Oedema,proteinuria+hypertens in pregnancy,childbrth,puerp
94789	1Z17.00	Chronic kidney disease stage 1 with proteinuria
94793	1Z1B.00	Chronic kidney disease stage 3 with proteinuria
95121	1Z1A.00	Chronic kidney disease stage 2 without proteinuria
95122	1Z1H.00	Chronic kidney disease stage 4 with proteinuria
95123	1Z1C.00	Chronic kidney disease stage 3 without proteinuria
95145	1Z1B.11	CKD stage 3 with proteinuria
95146	1Z19.00	Chronic kidney disease stage 2 with proteinuria
95175	1Z1E.00	Chronic kidney disease stage 3A without proteinuria
95176	1Z1E.11	CKD stage 3A without proteinuria
95177	1Z1G.00	Chronic kidney disease stage 3B without proteinuria
95178	1Z1F.00	Chronic kidney disease stage 3B with proteinuria
95180	1Z1F.11	CKD stage 3B with proteinuria
95188	1Z1C.11	CKD stage 3 without proteinuria
95405	1Z1L.00	Chronic kidney disease stage 5 without proteinuria
95406	1Z1J.00	Chronic kidney disease stage 4 without proteinuria
95408	1Z1D.00	Chronic kidney disease stage 3A with proteinuria
95508	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
95571	1Z1D.11	CKD stage 3A with proteinuria
95572	1Z18.00	Chronic kidney disease stage 1 without proteinuria
97587	1Z1J.11	CKD stage 4 without proteinuria
97683	1Z1L.11	CKD stage 5 without proteinuria
97978	1Z1A.11	CKD stage 2 without proteinuria
97979	1Z19.11	CKD stage 2 with proteinuria
97980	1Z17.11	CKD stage 1 with proteinuria
99160	1Z1K.11	CKD stage 5 with proteinuria
99312	1Z1H.11	CKD stage 4 with proteinuria
100633	1Z1G.11	CKD stage 3B without proteinuria
101572	K0A4X00	Isolated proteinuria, with oth specif morpholog changes
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria
104677	2126A00	Proteinuria resolved
105302	K08yA00	Proteinuric diabetic nephropathy
108916	44lzX00	Random urine protein:creatinine ratio
109657	1Z1Y.00	CKD with GFR category G3b & albuminuria category A2
109804	1Z1T.00	CKD with GFR category G3a & albuminuria category A1
109805	1Z1V.00	CKD with GFR category G3a & albuminuria category A2
109904	1Z1b.00	CKD with GFR category G4 & albuminuria category A2
109905	1Z1W.00	CKD with GFR category G3a & albuminuria category A3

Medical Code	Read Code	Read Term
109963	1Z1X.00	CKD with GFR category G3b & albuminuria category A1
109980	1Z1a.00	CKD with GFR category G4 & albuminuria category A1
109981	1Z1e.00	CKD with GFR category G5 & albuminuria category A2
109990	1Z1Z.00	CKD with GFR category G3b & albuminuria category A3
110003	1Z1N.00	CKD with GFR category G1 & albuminuria category A2
110033	1Z1M.00	CKD with GFR category G1 & albuminuria category A1
110108	1Z1R.00	CKD with GFR category G2 & albuminuria category A2
110133	1Z1d.00	CKD with GFR category G5 & albuminuria category A1
110251	1Z1S.00	CKD with GFR category G2 & albuminuria category A3
110269	1Z1Q.00	CKD with GFR category G2 & albuminuria category A1
110467	1Z1f.00	CKD with GFR category G5 & albuminuria category A3
110484	1Z1P.00	CKD with GFR category G1 & albuminuria category A3
110626	1Z1c.00	CKD with GFR category G4 & albuminuria category A3
111022	1Z18.11	CKD stage 1 without proteinuria

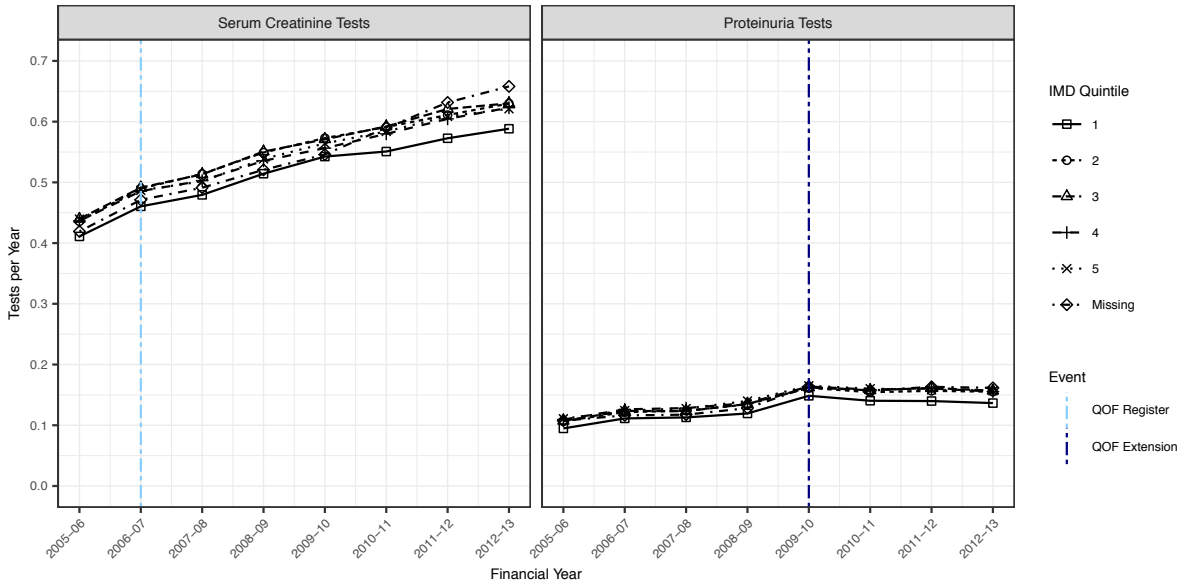
Trends over time



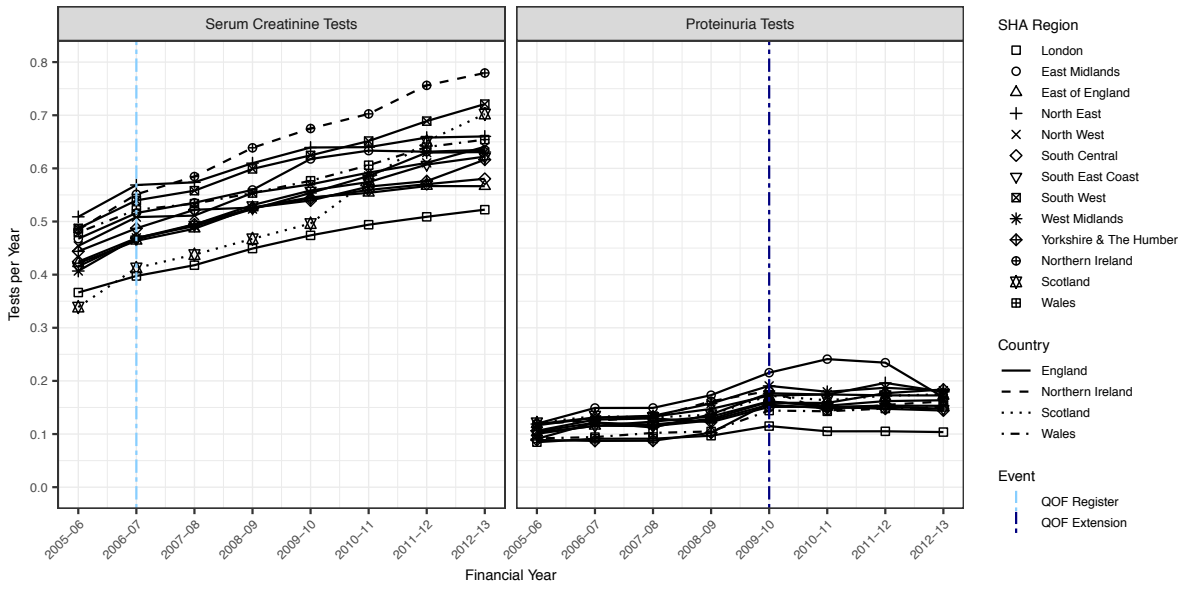
Supplementary Figure 1 - Rates of kidney function testing per financial year, stratified by gender.



Supplementary Figure 2 - Rates of kidney function testing per financial year, stratified by ethnicity.



Supplementary Figure 3 - Rates of kidney function testing per financial year, stratified by IMD quintile.



Supplementary Figure 4 - Rates of kidney function testing per financial year, stratified by SHA region.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 - 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7

Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) If applicable, explain how loss to follow-up was addressed	5
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8 - 9
		(b) Indicate number of participants with missing data for each variable of interest	8 - 9
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-13 & 23

		(b) Report category boundaries when continuous variables were categorized	6 - 7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13 - 14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14 - 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14 - 16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

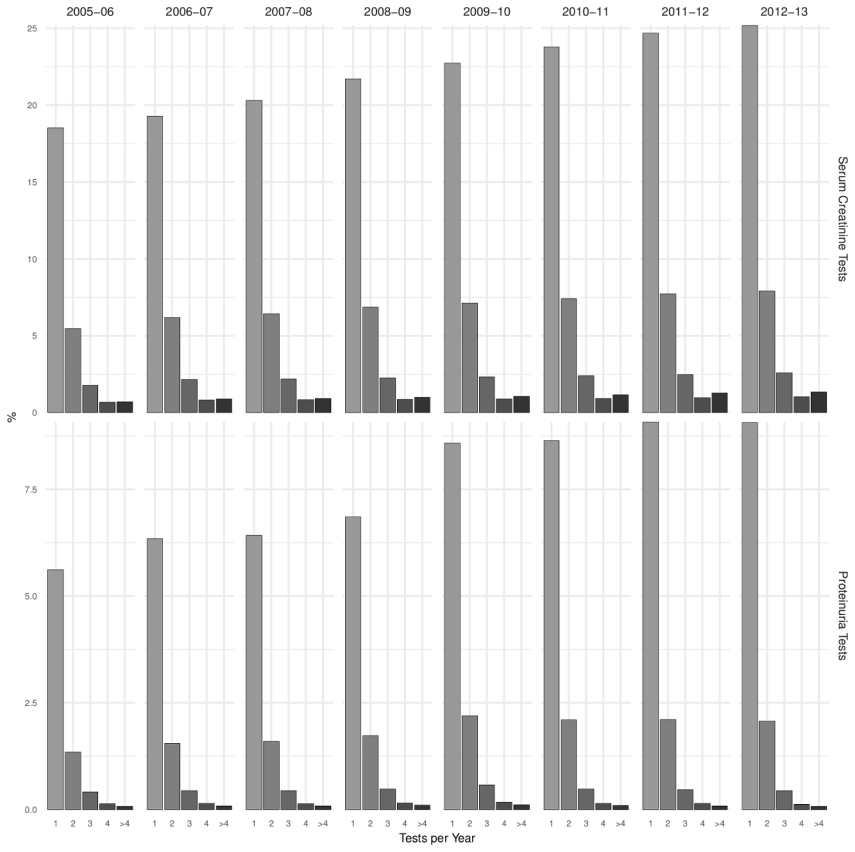
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Correction: *Trends in kidney function testing in UK primary care since the introduction of the quality and outcomes framework: a retrospective cohort study using CPRD*

Feakins B, Oke J, McFadden E, *et al*. Trends in kidney function testing in UK primary care since the introduction of the quality and outcomes framework: a retrospective cohort study using CPRD. *BMJ Open* 2019;9:e028062. doi: 10.1136/bmjopen-2018-028062.

This article was previously published with an error in the figure.

In the publication, Figure 4 is incorrect, and is a duplicate of figure 7. The correct Figure 4 is below:



BMJ Open 2019;**9**:e028062corr1. doi:10.1136/bmjopen-2018-028062corr1