The rise in creatinine testing and link to CKD diagnosis and monitoring: population based study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-009459
Article Type:	Research
Date Submitted by the Author:	22-Jul-2015
Complete List of Authors:	Oke, Jason; University of Oxford, Nuffiled Department of Primary Care Health Sciences Perera, Rafael; University of Oxford, Nuffield Department of Primary Care Health Sciences McFadden, Emily; University of Oxford, Nuffield Department of Primary Care Health Sciences Stevens, Richard; University of Oxford, Nuffield Department Primary Care Health Sciences Lasserson, Daniel; University of Oxford, Nuffield Department of Primary Care Health Sciences Shine, Brian; University of Oxford, Nuffield Department of Clinical Biochemistry
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Renal medicine, Health services research
Keywords:	PRIMARY CARE, EPIDEMIOLOGY, NEPHROLOGY

Title: The rise in creatinine testing and link to CKD diagnosis and monitoring: population based study

Authors: Jason Oke[1], Rafael Perera[1], Emily McFadden[1], Daniel Lasserson[1,2], Richard Stevens[1], Brian Shine[3].

Affiliations :

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

[2]NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU.

[3] Department of Clinical Biochemistry, John Radcliffe Hospital, University of Oxford.

Strengths and Limitations of the Study

- This study uses twenty years of data from a single laboratory that serves a well-defined population, typical of the wider UK population.
- To our knowledge, no other study has looked specifically at changes in serum creatinine test ordering rates, over time, in the UK.
- We did not have access to data on patient history or prescriptions or reasons for test ordering and so cannot comment on whether they were ordered with appropriate frequency.

Jason Oke is the corresponding author.

Correspondence to Dr Jason L Oke; jason.oke@phc.ox.ac.uk

Abstract

Objectives: To determine how many kidney function tests are done, on whom, how frequently they are performed and how they have changed over time.

Design: Retrospective study of all serum creatinine, urine albumin and urine creatinine tests

Setting: Primary and secondary care in Oxfordshire from 1993 to 2013

Participants: Unselected population of 1,220,447 people

Main outcome measures : The total number of creatinine and urinary protein tests ordered from primary and secondary care and the number of tests per year stratified by categories of estimated glomerular filtration rate (eGFR). The frequency of testing in patients having their kidney function monitored.

Results

Creatinine requests from primary care increased steadily from 1997 and exceeded 220,000 requests in 2013. Tests corresponding to normal kidney function (eGFR > $60/ml/min^2$) constituted 59% of all kidney function tests in 1993 and accounted for 83% of all tests in 2013. Test corresponding to CKD stages 3-5 declined after 2007. Reduced kidney function, albuminuria, male gender, diabetes and age were independently associated with more frequent monitoring. For a female patient between 61 and 80 years and with stage 3a CKD, the average number of serum creatinine tests (95% C.I) was 3.23 per year (3.19 to 3.26) and for a similar woman with diabetes, the average number of tests was 5.50 (5.44 to 5.56) tests per year.

Conclusion:

There has been a large increase in the number of kidney function tests over the last two decades. However, we found little evidence that this increase is detecting more CKD. Tests are becoming more frequent in people with and without evidence of renal impairment. Future work using a richer data source could help unravel the underlying reasons for the increased testing and determine how much is necessary and useful.

Trial registration: Not applicable

Keywords: Creatinine, monitoring, primary care, chronic kidney disease, laboratory.

Introduction.

Serum creatinine is widely used to measure renal function in the detection, diagnosis and management of chronic kidney disease (CKD) and other renal disorders such as acute kidney injury (AKI). Urinary albumin and protein are markers of kidney damage but also indicate disease from anywhere within the urinary tract. Renal function monitoring with serum creatinine testing is also critical for the safe administration of a wide range of therapeutic agents including those for bipolar disorder (1), cancer (2) and hypertension (3). In order to take into account factors such as age, gender and ethnic group, serum creatinine can be converted to an estimated glomerular filtration rate (eGFR) through equations such as Modification of Diet in Renal Disease (MDRD) (4) or CKD-EPI (5).

The Kidney Disease Outcomes and Quality Initiative (KDOQI) clinical practice guidelines in early 2002 (6) proposed that stages of CKD be defined primarily according to eGFR. In 2004, the UK Department of Health's National Service Framework for Renal Services (7) adopted the KDOQI staging classification of CKD. In the same year the Quality and Outcomes Framework (QOF), part of the contract for UK general practice (8), introduced incentives for the recording of serum creatinine in people with diabetes or on lithium therapy. The 2006/2007 extension of QOF required general practice (GP) doctors to maintain a register of adults with CKD stages 3-5 (9). In 2008 guidance from the National Institute for Health and Care Excellence (NICE) (10) recommended monitoring of renal function through creatinine testing in high risk groups. The 2009/2010 extension of QOF did not specifically incentivise serum creatinine testing or eGFR calculation, but incentivised the monitoring of urinary markers of kidney disease such as urinary albumin-creatinine ratio (ACR) in patients on the CKD register (8).

Motivated by a previous analysis of lipid testing in the same region (11), we examined serum creatinine tests and urinary albumin and protein tests ordered in Oxfordshire (UK) from 1993 to 2013. Secondly, we describe the distribution of CKD stages among those tested over time. Lastly, we explore how the frequency of monitoring has varied over time and between patients with different characteristics.

Methods

Data included all requests for serum creatinine (SCr), albumin to creatinine ratio (ACR), protein to creatinine (PCR) and glycated haemoglobin (HbA1c) measurements from the Oxford University Hospitals Trust Clinical Biochemistry laboratories for the entire periods covered by the database (May 1969 to November 2014). Recording of creatinine requests prior to 1993 was inconsistent and there were few records of ACR/PCR tests prior to 2006. For each test result, the sex and date of birth of the patient, and the date, location and name of the requesting physician were extracted from the database. A request was coded as coming from either primary care or other non-primary care (secondary or tertiary) care using an amended version of the in-house laboratory coding system. Locales that had requested less than 50 tests over the entire study period were not included in the analysis.

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the MDRD formula (4), chosen to reflect clinical practice in the timeframe of the study. We split eGFR into six categories of renal impairment using thresholds that define CKD. The first two represent normal (> 90 ml/min/m^2) and mildly impaired (60 - 89 ml/min/m^2) kidney function and the remaining four represent moderate to severely impaired kidney function and correspond directly to CKD stages 3a (45 - 59 ml/min/m^2) ,3b (30 - 44 ml/min/m^2) ,4 (15 -29 ml/min/m^2) and 5 (< 15 ml/min/m^2) . The MDRD formula has an adjustment for ethnicity, which raises eGFR for non-white ethnicity. We were unable to obtain this data so made no adjustment and hence our eGFR staging is biased slightly towards more severe renal impairment. HbA1c (expressed in IFCC units) was categorised into four levels: 1) not measured, 2) under the diagnostic thresholds for diabetes (<less than 48 mmol/mol), 3) controlled glycaemia (48 – 58 mmol/mol) and 4) uncontrolled glycaemia (> 58 mmol/mol). Albuminuria was categorised similarly into four levels using diagnostic thresholds for microalbuminuria (> 3 mg/mol) and macroalbuminuria (> 30 mg/mmol) as cut-points.

Number of creatinine and urinary albumin or protein tests over time

The total number of SCr, ACR and PCR tests ordered from primary care and non-primary care locales was calculated separately for each year from 1993 to 2013. Tests requested from primary care were additionally stratified by stages of renal impairment.

Predictors of the intensity of monitoring

We examined factors related to the frequency of monitoring in a sub-cohort of people having kidney function/damage monitored, defined as having at least 2 tests further to the first year's measurement and complete covariate data. Measurements within the first year of follow-up were excluded as they are likely to be for reasons other than monitoring. We used poisson regression to model the frequency of monitoring adjusting for initial level of kidney function, HbA1c testing, evidence of albuminuria or proteinuria, gender and age. All analyses were carried out using R v3.1.2 (12)

Results

Data was obtained on 1,220,447 people, 527,753 of which had only one entry and the remaining 692,694 had median (IQR) follow-up of 7.6 (3.7, 12.5) years.

Number of kidney function tests over time

Figure 1 shows the trend lines for both creatinine and ACR/PCR tests with dates of key publications, guidelines, and changes to the QOF. Between 1993 and 2013, the last full year of follow-up, the number of creatinine requests from primary care locales increased from 3,235 per year to 221,557 per year. Requests from secondary and tertiary care locales rose from 138,519 in 1993 to 431,198 in 2013. Record of requests for ACR/PCR tests began in 2006 and totalled 7,831 in primary care and 4,306 in secondary or tertiary care and in 2013 the respective totals were 26,317 and 17,769.

Figure 1 here:

*Figure 1: Total number of serum creatinine tests ordered from secondary and primary care between 1993 and 2013 and dates of key publications. * indicates enlargement of population denominator.*

Distribution of renal impairment over time in primary care

Figure 2 shows the total number of tests stratified by eGFR categories corresponding to the stages of CKD. Between 1998 and 2013 creatinine testing increased in primary care. The number of tests for normal, mildly reduced and impaired renal function (CKD stages 3-5) showed a marked increase between 1998 and 2005. However after 2005 the number of tests showing impaired function remained stable. Therefore all the increase after 2005 is in tests from patients with normal kidney function. The number of tests corresponding to CKD increased from 1317 tests in 1993 to 54,597 in 2006 but has since fallen back to 38,107 in 2013. Impaired kidney function tests accounted for 41% of all kidney function tests requested in 1993 and only 17% in 2013. A similar pattern was observed for secondary and tertiary care (figure not shown), and when limiting one test per patient.

Figure 2 here

Figure 2: The number of serum creatinine tests between 1993 and 2013 by stages of renal impairment

Frequency of monitoring

There were 167,701 subjects with at least 2 tests further to the first year's measurement and complete covariate data. Table 1 shows the results of the fitted model of monitoring frequency.

Table 1 here.

The average rate (95% C.I.) of monitoring in the reference group (males aged less than 20 with normal renal function, no albuminuria or diabetes) was 1.09 (1.09 to 1.11) tests per year (equivalent to one test every 335 days on average). Relative increases in the frequency of monitoring were found for older people, for people with micro or macro-albuminuria, lower eGFR, those with any HbA1c tests and higher HbA1c. The frequency of monitoring was also shown to increase with time, independently of other associated factors. Female gender was associated with a small but statistically significant relative decrease in the frequency of monitoring. For a female patient aged between 61 and 80 with stage 3a CKD (eGFR 45 – 59 ml/min/m^2) the average rate of monitoring is estimated as 3.23 tests per year with 95% confidence interval (3.19 to 3.26) and for a similar woman with controlled glycaemia, the average number of tests rises to 5.50 tests per year on average with 95% confidence interval (5.44 to 5.56).

Conclusion

Summary

We find that the number of serum creatinine tests has risen dramatically since the late 1990s, especially in primary care, and exceeded 600,000 tests in 2013. Publication of the KDOQI guidelines in 2002 came after the start of a sharp increase in test ordering from secondary or tertiary care doctors and later publications did not seem to influence test ordering rates. There was also little evidence that KDOQI, the introduction of QOF in 2004 and later extensions directly affected creatinine testing rates in primary care. In contrast, a rise in urinary ACR and PCR testing around 2009/10 coincides with the introduction of relevant QOF indicators.

Older people, people with higher HbA1c and people with kidney disease were most frequently tested for serum creatinine. Up until 2005, the increasing volume of testing in primary care was accompanied by increasing numbers with CKD among those tested. After 2005, the volume of creatinine testing continued to increase, but the number of tests with eGFR corresponding to CKD stages 3 - 5 stabilised or decreased while the number of eGFR tests with results in the normal or mildly impaired range (≥60 ml/min per $1.73m^2$) increased. The number of tests with results in the normal range (> 90 ml/min per $1.73m^2$) has risen fastest since 2006/7.

Strengths and Limitations

We had access to data from all requests over twenty years at a single laboratory that serves a well-defined population, typical of the wider UK population. However, we did not have data on patient history or prescriptions. In particular we have no data on the reasons for creatinine or urine testing and therefore cannot comment on whether tests were ordered with appropriate frequency, or to what extent the observed rise in testing reflects the increase in the UK in prescriptions for medicines, many of which require renal function testing (3)(13). Without ethnicity data, we were obliged to approximate eGFR by the MDRD equation without the appropriate adjustment for people of non-white ethnic group, and hence we underestimate eGFR and overestimate the amount CKD. However, this would affect fewer than 5% of people in Oxfordshire, and therefore we expect this would only make minor changes to the stage distributions in this sample (14).

Comparison with existing literature

To our knowledge, no other study has looked specifically at changes in serum creatinine test ordering rates, over time, in the UK. An analysis of primary care computer records in Kent, Manchester and Surrey between 1998 and 2003, and a similar study in south-west London in 2007, reported that 30% of patients had a valid serum creatinine measurement (15) (16). These figures provide context for our analysis but are not directly comparable, since we do not have an equivalent denominator (total number of patients in the region served by the laboratory), and since these studies report number of patients rather than number of tests. A study using Health Survey for England data between 2003 and 2010 found a modest decline in rates of CKD, despite increases in diabetes and obesity (17). We have shown a similar decline in tests reflecting CKD in Oxfordshire in recent years, even after adjusting for risk factors such as age and HbA1c, but we have also shown that the total number of serum creatinine tests ordered has continued to rise, driven by an increase in serum creatinine tests with values above 90 ml/min per $1.73m^2$.

Implications

The increase in the volume of kidney function tests in Oxfordshire, and in particular creatinine testing, is likely to be due to a number of factors. There is a net increase in number of patients being tested year on year and people are being tested more frequently independent of changes in common risk factors for CKD. Since the recent increase in testing is driven by tests on patients with high eGFR, it would be desirable to know how much this reflects appropriate monitoring of patients on medication, and how much reflects unofficial screening or case-finding by GPs for possible cases of early CKD, for which at present there is little evidence for worthwhile interventions (18). Future work using a richer data source with prescription records and GPs' notes could help unravel the underlying reasons for the increased testing and determine how much is necessary and useful.

Ethics: Ethical approval was not required for this study. Clinical databases were only accessed by those with permission to do so. No individual data points were examined manually, and the data were anonymised at all stages of the analysis.

Contributorship statement: RP, BS, DL and RS contributed to the conception and design of the study. JO, EM and RS were responsible for the analysis and interpretation of the data. JO, RP, EM, DL and RS drafted the manuscript. All authors were involved in the final revision of the article. All of the authors approved the final article.

Competing interests: All of the authors have completed the ICMJE form for disclosure of potential conflicts of interest form (available on request from the corresponding author) and declare that (1) they have not received at any time payment or services from a third party for any aspect of the submitted work (2) that they have had no financial relationships with relevant entities outside of the submitted work (3) that they have no patents, planned, pending or issued broadly relevant to the work and (4) that they have no relationships or activities that readers could perceive to have influenced, or give the appearance of potentially influencing what was written in the submitted work.

Funding: This work is supported by funding from the National Institute for Health Research (NIHR) School for Primary Care Research (Project reference number 156) and the programme Grants for Applied Research programme (Ref: RP-PG-1210-12003). DSL is supported by the NIHR Oxford Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health

Data sharing statement: No additional data available.

1. Kirkham E, Skinner J, Anderson T, Bazire S, Twigg MJ, Desborough JA. One lithium level >1.0 mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database. BMJ Open [Internet]. 2014 Jan [cited 2015 Feb 25];4(11):e006020. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4225230&tool=pmcentrez&rendertype=abstract

2. Aapro M, Launay-Vacher V. Importance of monitoring renal function in patients with cancer. Cancer Treat Rev [Internet]. 2012 May [cited 2014 May 22];38(3):235–40. Available from: http://www.sciencedirect.com/science/article/pii/S0305737211000788

3. McDowell SE, Coleman JJ, Evans SJW, Gill PS, Ferner RE. Laboratory monitoring and adverse patient outcomes with antihypertensive therapy in primary care. Pharmacoepidemiol Drug Saf [Internet]. 2010 May [cited 2014 Sep 8];19(5):482–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20306453

4. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. 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 [Internet]. 1999 Mar 16 [cited 2015 Mar 30];130(6):461–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10075613

5. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med [Internet]. 2009 May 5 [cited 2014 Dec 3];150(9):604–12. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2763564&tool=pmcentrez&rendertype=abstract

6. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis [Internet]. 2002 Feb [cited 2014 Dec 10];39(2 Suppl 1):S1–266. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11904577

7. Department of Health Renal NSF Team. The National Service Framework for Renal Services - Part Two: Chronic Kidney Disease, Acute Renal Failure and End of Life Care. London; 2005.

8. British Medical Association. 2014/15 General Medical Services (GMS) Contract Quality and Outcomes Framework (QOF): Guidance for GMS Contract 2014/15. 2014.

9. O'Donoghue DJ. Going upstream: the implication and opportunities of early detection. J Ren Care [Internet]. 2009 Dec [cited 2015 Feb 26];35 Suppl 2:3–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19891679

10. 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.

11. Doll H, Shine B, Kay J, James T, Glasziou P. The rise of cholesterol testing: how much is unnecessary. Br J Gen Pract [Internet]. 2011 Feb [cited 2013 Jun 26];61(583):e81–8. Available from:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3026174&tool=pmcentrez&rendertype=abstract

12. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria; 2012. Available from: http://www.r-project.org/

13. Health and Social Care Information Centre. Prescriptions dispensed in the community: England 2002-2012 [Internet]. 2013. Available from: http://www.hscic.gov.uk/catalogue/PUB11291

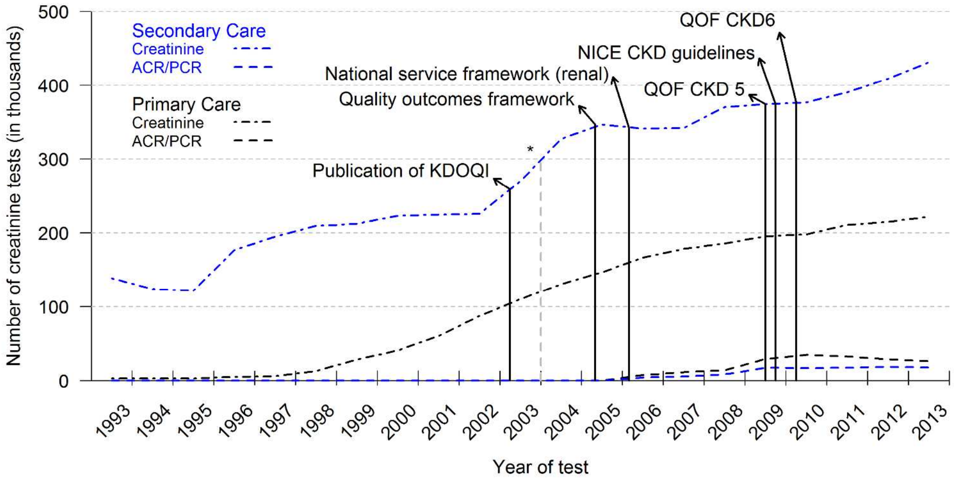
14. O'Callaghan CA, Shine B, Lasserson DS. Chronic kidney disease: a large-scale population-based study of the effects of introducing the CKD-EPI formula for eGFR reporting. BMJ Open [Internet]. 2011 Jan [cited 2014 Jul 10];1(2):e000308. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3244664&tool=pmcentrez&rendertype=abstract

15. Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int [Internet]. 2007 Jul 18 [cited 2015 Jan 13];72(1):92–9. Available from: http://dx.doi.org/10.1038/sj.ki.5002273

16. De Lusignan S, Nitsch D, Belsey J, Kumarapeli P, Vamos EP, Majeed A, et al. Disparities in testing for renal function in UK primary care: cross-sectional study. Fam Pract [Internet]. 2011 Dec 1 [cited 2015 Mar 3];28(6):638–46. Available from: http://fampra.oxfordjournals.org/content/28/6/638.long

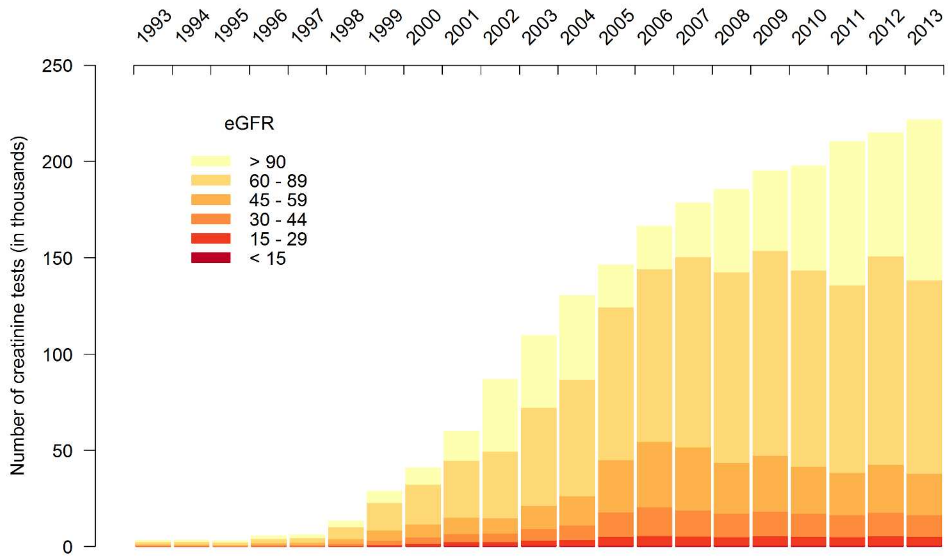
17. Aitken GR, Roderick PJ, Fraser S, Mindell JS, O'Donoghue D, Day J, et al. Change in prevalence of chronic kidney disease in England over time: comparison of nationally representative cross-sectional surveys from 2003 to 2010. BMJ Open [Internet]. 2014 Jan 29 [cited 2015 Jun 22];4(9):e005480. Available from: http://bmjopen.bmj.com/content/4/9/e005480.full

18. Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald R, Rossini D, 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 [Internet]. 2012 Apr 17 [cited 2013 Sep 25];156(8):570–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22508734



No. Individuals with tests (thousands)

SC	41	42	38	48	49	51	54	56	59	61	76	97	102	101	102	109	111	116	120	126	130
PC	2	3	2	4	4	12	24	32	45	61	73	85	93	102	108	114	120	122	130	134	138


1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
250
200
150
100
50
0
Number of creatinine tests (in thousands)
eGFR
> 90
60 - 89
45 - 59
30 - 44
15 - 29
< 15

		n	Rate per year (95% C.I)
Renal function as measured by eGFR (ml/min/1.73^2)	> 60 (Reference)	146604	1.09 (1.09 to 1.11)
	45 - 59 (3a)	16343	1.12 (1.11 to 1.12)
	30 – 44 (3b)	3723	1.26 (1.25 to 1.27)
	15 – 29 (4)	791	1.43 (1.40 to 1.47)
	< 15 (5)	240	1.28 (1.23 to 1.33)
Albuminuria	Not measured	167128	1
	< 3 mg/mmol	430	1.07 (1.03 to 1.12)
	3 - 30 mg/mmol	116	1.06 (0.98 to 1.15)*
	> 30 mg/mmol	27	1.39 (1.19 to 1.60)
Time of initial measurement	pre 1998	38679	1
	1999 - 2003	63530	1.06 (1.05 to 1.06)
	2004 - 2008	51998	1.16 (1.16 to 1.17)
	2009 - 2013	13494	1.88 (1.86 to 1.89)
Age	< 20 years	9398	1
	21-40 years	36838	0.99 (0.98 to 1.00)*
	41 -60 years	61106	1.20 (1.19 to 1.21)
	61 - 80 years	51405	1.45 (1.43 to 1.46)
	81 -100 years	8954	1.51 (1.49 to 1.53)
	Not measured	105770	1
HbA1c	< 48 mmol/mol	49570	1.11 (1.10 to 1.11)
	48 - 58 mmol/mol	5691	1.70 (1.69 to 1.71)
	> 58 mmol/mol	6670	1.77 (1.77 to 1.79)
	Male	74014	1
Sex	Female	93687	0.98 (0.97 to 0.98)

Table 1: Parameter estimates for the intensity of monitoring renal function in primary care (significant at p <0.001 except *)

BMJ Open

The rise in creatinine testing in a UK population

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009459.R1
Article Type:	Research
Date Submitted by the Author:	28-Sep-2015
Complete List of Authors:	Oke, Jason; University of Oxford, Nuffiled Department of Primary Care Health Sciences Perera, Rafael; University of Oxford, Nuffield Department of Primary Care Health Sciences McFadden, Emily; University of Oxford, Nuffield Department of Primary Care Health Sciences Stevens, Richard; University of Oxford, Nuffield Department Primary Care Health Sciences Lasserson, Daniel; University of Oxford, Nuffield Department of Primary Care Health Sciences Shine, Brian; University of Oxford, Nuffield Department of Clinical Biochemistry
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Renal medicine, Health services research
Keywords:	PRIMARY CARE, EPIDEMIOLOGY, Chronic kidney disease, serum creatinine, Biochemistry < TROPICAL MEDICINE

Title: The rise in creatinine testing in a UK population

Authors: Jason Oke[1], Rafael Perera[1], Emily McFadden[1], Richard Stevens[1] ,Daniel Lasserson[1,2], Brian Shine[3].

Affiliations :

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

[2]NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU.

[3] Department of Clinical Biochemistry, John Radcliffe Hospital, University of Oxford.

Strengths and Limitations of the Study

- This study uses twenty years of data from a single laboratory that serves a well-defined population, typical of the wider UK population.
- To our knowledge, no other study has looked specifically at changes in serum creatinine test ordering rates, over time, in the UK.
- We did not have access to data on patient history or prescriptions or reasons for test ordering and so cannot comment on whether they were ordered with appropriate frequency.

Jason Oke is the corresponding author.

Correspondence to Dr Jason L Oke; jason.oke@phc.ox.ac.uk

Abstract

Objectives: To determine how many kidney function tests are done, on whom, how frequently they are performed and how they have changed over time.

Design: Retrospective study of all serum creatinine, urine albumin and urine creatinine tests

Setting: Primary and secondary care in Oxfordshire from 1993 to 2013

Participants: Unselected population of 1,220,447 people

Main outcome measures : The total number of creatinine and urinary protein tests ordered from primary and secondary care and the number of tests per year stratified by categories of estimated glomerular filtration rate (eGFR). The frequency of testing in patients having their kidney function monitored.

Results

Creatinine requests from primary care increased steadily from 1997 and exceeded 220,000 requests in 2013. Tests corresponding to normal kidney function (eGFR > 60/mL/min/1.73m^2) constituted 59% of all kidney function tests in 1993 and accounted for 83% of all tests in 2013. Test corresponding to CKD stages 3-5 declined after 2007. Reduced kidney function, albuminuria, male gender, diabetes and age were independently associated with more frequent monitoring. For a female patient between 61 and 80 years and with stage 3a CKD, the average number of serum creatinine tests (95% C.I) was 3.23 per year (3.19 to 3.26) and for a similar woman with diabetes, the average number of tests was 5.50 (5.44 to 5.56) tests per year.

Conclusion:

There has been a large increase in the number of kidney function tests over the last two decades. However, we found little evidence that this increase is detecting more CKD. Tests are becoming more frequent in people with and without evidence of renal impairment. Future work using a richer data source could help unravel the underlying reasons for the increased testing and determine how much is necessary and useful.

Trial registration: Not applicable

Keywords: Creatinine, monitoring, primary care, chronic kidney disease, laboratory.

Introduction.

Serum creatinine is widely used to measure renal function in the detection, diagnosis and management of chronic kidney disease (CKD) and other renal disorders such as acute kidney injury (AKI). Urinary albumin and protein are markers of kidney damage but also indicate disease from anywhere within the urinary tract. As both reduced renal function and elevated urinary albumin or protein are independently associated with adverse kidney outcomes (end-stage renal disease, acute kidney injury and progression of CKD (1) as well as cardiovascular events in the general population, monitoring may be warranted . Renal function monitoring with serum creatinine testing is also critical for the safe administration of a wide range of therapeutic agents including those for bipolar disorder (2), cancer (3) ,hypertension (4) and diabetes . In order to take into account factors such as age, gender and ethnic group, serum creatinine can be converted to an estimated glomerular filtration rate (eGFR) through equations such as Modification of Diet in Renal Disease (MDRD) (5) or CKD-EPI (6).

The Kidney Disease Outcomes and Quality Initiative (KDOQI) clinical practice guidelines in early 2002 (7) proposed that stages of CKD be defined primarily according to eGFR. In 2004, the Department of Health's National Service Framework for Renal Services (8) adopted the KDOQI staging classification of CKD. In the same year the Quality and Outcomes Framework (QOF), part of the contract for UK general practice (9), introduced incentives for the recording of serum creatinine in people with diabetes or on lithium therapy. The 2006/2007 extension of QOF required general practice (GP) doctors to maintain a register of adults with CKD stages 3-5 (10). In 2008 guidance from the National Institute for Health and Care Excellence (NICE) (11) recommended monitoring of renal function through creatinine testing in high risk groups. The 2009/2010 extension of QOF did not specifically incentivise serum creatinine testing or eGFR calculation, but incentivised the monitoring of urinary markers of kidney disease such as urinary albumin-creatinine ratio (ACR) in patients on the CKD register (9).

Motivated by a previous analysis of lipid testing in the same region (12), we examined serum creatinine tests and urinary albumin and protein tests ordered in Oxfordshire (UK) from 1993 to 2013. Secondly, we describe the distribution of CKD stages among those tested over time. Lastly, we explore how the frequency of monitoring has varied over time and between patients with different characteristics.

Methods

Data included all requests for serum creatinine (SCr), albumin to creatinine ratio (ACR), protein to creatinine (PCR) and glycated haemoglobin (HbA1c) measurements from the Oxford University Hospitals Trust Clinical Biochemistry laboratories for the entire periods covered by the database (May 1969 to November 2014). One of the co-authors (BS) is the custodian of the laboratory information system and all data were anonymised prior to extraction and analysis. We used the NHS number as the primary identifier. Before this was available, patients were linked to their hospital number if they were known. Where neither of these were available, specimens were not extracted. Numerators were based on all tests, whether linked or not.

Recording of creatinine requests prior to 1993 was inconsistent and there were few records of ACR/PCR tests prior to 2006. In September 2009, the reference method for creatinine changed to isotope dilution mass spectrometry (IDMS) and all creatinine measurement have been adjusted to reflect this. For each test result, the sex and date of birth of the patient, and the date, location and name of the requesting physician were extracted from the database. A request was coded as coming from either primary care or other non-primary care (secondary or tertiary) care using an amended version of the in-house laboratory coding system. Locales that had requested less than 50 tests over the entire study period were not included in the analysis.

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the MDRD formula (5), chosen to reflect clinical practice in the timeframe of the study. We split eGFR into six categories of renal impairment using thresholds that define CKD. The first two represent normal (> 90 mL/min/1.73m^2) and mildly impaired (60 - 89 mL/min/1.73m^2) kidney function and the remaining four represent moderate to severely impaired kidney function and correspond directly to CKD stages 3a (45 - 59 mL/min/1.73m^2) ,3b (30 - 44 mL/min/1.73m^2) ,4 (15 -29 mL/min/1.73m^2) and 5 (< 15 mL/min/1.73m^2) . The MDRD formula has an adjustment for ethnicity, which raises eGFR for non-white ethnicity. We were unable to obtain this data so made no adjustment and hence our eGFR staging is biased slightly towards more severe renal impairment. HbA1c (expressed in IFCC units) was categorised into four levels: 1) not measured, 2) under the diagnostic thresholds for diabetes (<less than 48 mmol/mol), 3) controlled glycaemia (48 – 58 mmol/mol) and 4) uncontrolled glycaemia (> 58 mmol/mol). Albuminuria was categorised similarly into four levels using diagnostic thresholds for microalbuminuria (> 3 mg/mol for ACR and 15 mg/mmol for PCR) and macroalbuminuria (> 30 mg/mmol for ACR and 50 mg/mmol units PCR) as cut-points.

Number of creatinine and urinary albumin or protein tests over time

The total number of SCr, ACR and PCR tests ordered from primary care and non-primary care locales was calculated separately for each year from 1993 to 2013. In an additional analysis, we calculated age-adjusted yearly totals of creatinine testing in primary and secondary care by standardising to the age distribution in 1999. For this, we calculated creatinine testing rates per five year age brackets using population pyramid data for England between 1971 and 2011 (13) and estimates of the population of Oxfordshire local authority district (14) as the denominator . These rates were multiplied by the reference age distribution and summed to form age-adjusted totals. Tests requested from primary care were additionally stratified by stages of renal impairment.

Predictors of the frequency of monitoring

We examined factors related to the frequency of monitoring in a sub-cohort of people having kidney function/damage monitored, defined as having at least 2 tests further to the first year's measurement and complete covariate data. Measurements within the first year of follow-up were excluded as they are likely to be for reasons other than monitoring. We used poisson regression to model the frequency of monitoring adjusting for initial level of kidney function, HbA1c testing, evidence of albuminuria or proteinuria, gender and age. All analyses were carried out using R v3.1.2 (15)

Results

Data was obtained on 1,220,447 people, 527,753 of which had only one entry and the remaining 692,694 had median (IQR) follow-up of 7.6 (3.7, 12.5) years. The percentage of specimens that could not be linked to either a hospital or NHS number was 20% in 1993 and dropped steadily to less than 1% in 2013 (see supplementary material figure S.1)

Number of kidney function tests over time

Figure 1 shows the trend lines for both creatinine and ACR/PCR tests with dates of key publications, guidelines, and changes to the QOF. Between 1993 and 2013, the last full year of follow-up, the number of creatinine requests from primary care locales increased from 4,048 per year to 221,557 per year. Requests from secondary and tertiary care locales rose from 173,323 in 1993 to 431,198 in 2013. Record of requests for ACR/PCR tests began in 2006 and totalled 8,125 in primary care and 4,467 in secondary or tertiary care and in 2013 the respective totals were 26,317 and 17,769.

The age distribution of people that have creatinine measured in Oxfordshire changed over the duration of the study. There were more people (as a proportion of the total) being tested in age brackets 85 or older in 2013, compared to 1999, but fewer in the 70-80's age brackets (see supplementary figure S.2). Adjusted creatinine totals were lower than unadjusted totals and suggest that for 2013, 11.9% of the tests in secondary care and 12.6% in primary care can be attributed to shifts in age demographics since 1999 (see supplementary figure S.3)

Figure 1 here:

*Figure 1: Total number of serum creatinine tests ordered from secondary and primary care between 1993 and 2013 and dates of key publications. * indicates enlargement of population denominator.*

Distribution of renal impairment over time in primary care

Figure 2 shows the total number of tests stratified by eGFR categories corresponding to the stages of CKD. Between 1998 and 2013 creatinine testing increased in primary care. The number of tests for normal, mildly reduced and impaired renal function (CKD stages 3-5) showed a marked increase between 1998 and 2005. However after 2005 the number of tests showing impaired function remained stable. Therefore all the increase after 2005 is in tests from patients with normal kidney function. The number of tests corresponding to CKD increased from 1648 tests in 1993 to 55,970 in 2006 but has since fallen back to 38,056 in 2013. Impaired kidney function tests accounted for 41% of all kidney function tests requested in 1993 and only 17% in 2013. A similar pattern was observed for secondary and tertiary care (figure not shown), and when limiting one test per patient (see supplementary figure S.4).

Figure 2 here

Figure 2: The number of serum creatinine tests between 1993 and 2013 by stages of renal impairment

Frequency of monitoring

There were 167,701 subjects with at least 2 tests further to the first year's measurement and complete covariate data. Table 1 shows the results of the fitted model of monitoring frequency.

		n	Rate per year (95% C.I)
Renal function as measured by eGFR (ml/min/1.73^2)	> 60 (Reference)	146604	1.09 (1.09 to 1.11)
	45 - 59 (3a)	16343	1.12 (1.11 to 1.12)
	30 – 44 (3b)	3723	1.26 (1.25 to 1.27)
	15 – 29 (4)	791	1.43 (1.40 to 1.47)
	< 15 (5)	240	1.28 (1.23 to 1.33)
Albuminuria	Not measured	167128	1
	< 3 mg/mmol	430	1.07 (1.03 to 1.12)
	3 - 30 mg/mmol	116	1.06 (0.98 to 1.15)*
	> 30 mg/mmol	27	1.39 (1.19 to 1.60)
Time of initial measurement	pre 1998	38679	1
	1999 - 2003	63530	1.06 (1.05 to 1.06)
	2004 - 2008	51998	1.16 (1.16 to 1.17)
	2009 - 2013	13494	1.88 (1.86 to 1.89)
Age	< 20 years	9398	1
	21-40 years	36838	0.99 (0.98 to 1.00)*
	41 -60 years	61106	1.20 (1.19 to 1.21)
	61 - 80 years	51405	1.45 (1.43 to 1.46)
	81 -100 years	8954	1.51 (1.49 to 1.53)
	Not measured	105770	1
HbA1c	< 48 mmol/mol	49570	1.11 (1.10 to 1.11)
	48 - 58 mmol/mol	5691	1.70 (1.69 to 1.71)
	> 58 mmol/mol	6670	1.77 (1.77 to 1.79)
	Male	74014	1
Sex	Female	93687	0.98 (0.97 to 0.98)

Table 1: Parameter estimates for the intensity of monitoring renal function in primary care (significant at p <0.001 except *)

The average rate (95% C.I.) of monitoring in the reference group (males aged less than 20 with normal renal function, no albuminuria or diabetes) was 1.09 (1.09 to 1.11) tests per year (equivalent to one test every 335 days on average). Relative increases in the frequency of monitoring were found for older people, for people with micro or macro-albuminuria, lower eGFR, those with any HbA1c tests and higher HbA1c. The frequency of monitoring was also shown to increase with time, independently of other associated factors. Female gender was associated with a small but statistically significant relative decrease in the frequency of monitoring. For a female patient aged between 61 and 80 with stage 3a CKD (eGFR 45 – 59 mL/min/1.73m^2) the average rate of monitoring is estimated as 3.23 tests per year with 95% confidence interval (3.19 to 3.26) and for a similar woman with controlled glycaemia, the average number of tests rises to 5.50 tests per year on average with 95% confidence interval (5.44 to 5.56).

Conclusion

Summary

We find that the number of serum creatinine tests has risen dramatically since the late 1990s, especially in primary care, and exceeded 600,000 tests in 2013. Some of this increase can be attributed to a shift in the age-distribution of the population and the expansion of the area that the laboratory serves in 2003. Publication of the KDOQI guidelines in 2002 came after the start of a sharp increase in test ordering from secondary or tertiary care doctors and later publications did not seem to influence test ordering rates. There was also little evidence that KDOQI, the introduction of QOF in 2004 and later extensions directly affected creatinine testing rates in primary care. In contrast, a rise in urinary ACR and PCR testing around 2009/10 coincides with the introduction of relevant QOF indicators.

Older people, people with higher HbA1c and people with kidney disease were most frequently tested for serum creatinine. Up until 2005, the increasing volume of testing in primary care was accompanied by increasing numbers with CKD among those tested. After 2005, the volume of creatinine testing continued to increase, but the number of tests with eGFR corresponding to CKD stages 3 - 5 stabilised or decreased while the number of eGFR tests with results in the normal or mildly impaired range (≥60 mL/min/er1.73m^2) increased. The number of tests with results in the normal range (> 90 mL/min/1.73m^2) has risen fastest since 2006/7.

Strengths and Limitations

We had access to data from all requests over twenty years at a single laboratory that serves a well-defined population, typical of the wider UK population. However, we did not have data on patient history or prescriptions. In particular we have no data on the reasons for why blood samples were taken for renal function testing. Given that the majority of laboratories will analyse sodium, potassium and creatinine as a set, the primary target of monitoring by a GP may be the electrolyte levels rather than the creatinine level. Whilst this makes interpretation of the rise in creatinine testing more complex, if abnormalities are detected in electrolyte levels this prompts an immediate clinical need to determine the creatinine level, and therefore creatinine testing is an important component of monitoring of electrolytes as well as for CKD itself. Furthermore we cannot comment on whether tests were ordered with appropriate frequency, or to what extent the observed rise in testing reflects the increase in the UK in prescriptions for medicines, many of which require renal function testing. (4)(16). Without ethnicity data, we were obliged to approximate eGFR by the MDRD equation without the appropriate adjustment for people of non-white ethnic group, and hence we underestimate eGFR and overestimate the amount CKD. However, this would affect fewer than 5% of people in Oxfordshire, and therefore we expect this would only make minor changes to the stage distributions in this sample (17).

Comparison with existing literature

To our knowledge, no other study has looked specifically at changes in serum creatinine test ordering rates, over time, in the UK, but there are studies looking at CKD prevalence which have data on testing rates. One such study reported similar size increases in both the number of blood samples being taken and the number of people having their creatinine tested between 2004 and 2010 (18) In contrast, an analysis of primary care computer records in Kent, Manchester and Surrey between 1998 and 2003, and a similar study in south-west London in 2007, each reported that 30% of patients had a valid serum creatinine measurement (19) (20). The latter figures provide context for our analysis but are not directly comparable, since we do not have an equivalent denominator (total number of patients in the region served by the laboratory), and since these studies report number of patients rather than number of tests. A study using Health Survey for England data between 2003 and 2010 found a modest decline in rates of CKD, despite increases in diabetes and obesity (21). We have shown a similar decline in tests reflecting CKD in Oxfordshire in recent years, even after adjusting for risk factors such as age and HbA1c, but we have also shown that the total number of serum creatinine tests ordered has continued to rise, driven by an increase in serum creatinine tests with values above 90 mL/min/1.73m^2.

Implications

The increase in the volume of kidney function tests in Oxfordshire, and in particular creatinine testing, is likely to be due to a number of factors. There is a net increase in number of people being tested year on year and people are being tested more frequently independent of changes in common risk factors for CKD. Given the uncertainty around the best methods and intervals for monitoring renal function it is unclear whether more frequent monitoring may lead to a net-benefit, but as eGFR has considerable biological variability (22), more frequent monitoring may lead to many false alarms and over-adjustment of treatment (23). Since most of the recent increase in testing is driven by tests on patients with normal to mildly reduced eGFR and as there is little evidence of benefit from intervening in people with early stage CKD (24), these results are unlikely to influence clinical decisions or contribute to better care. Future work using a richer data source with prescription records and GPs' notes could help unravel the underlying reasons for the increased testing and determine how much is necessary and useful.

Ethics: Ethical approval was not required for this study. Clinical databases were only accessed by those with permission to do so. No individual data points were examined manually, and the data were anonymised at all stages of the analysis.

Contributorship statement: RP, BS, DL and RS contributed to the conception and design of the study. JO, EM and RS were responsible for the analysis and interpretation of the data. JO, RP, EM, DL and RS drafted the manuscript. All authors were involved in the final revision of the article. All of the authors approved the final article.

Competing interests: All of the authors have completed the ICMJE form for disclosure of potential conflicts of interest form (available on request from the corresponding author) and declare that (1) they have not received at any time payment or services from a third party for any aspect of the submitted work (2) that they have had no financial relationships with relevant entities outside of the submitted work (3) that they have no patents, planned, pending or issued broadly relevant to the work and (4) that they have no relationships or activities that readers could perceive to have influenced, or give the appearance of potentially influencing what was written in the submitted work.

Funding: This work is supported by funding from the National Institute for Health Research (NIHR) School for Primary Care Research (Project reference number 156) and the programme Grants for Applied Research programme (Ref: RP-PG-1210-12003). DSL is supported by the NIHR Oxford Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health

Data sharing statement: No additional data available.

1. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int [Internet]. 2011 Jul [cited 2015 Sep 3];80(1):93–104. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3959732&tool=pmcentrez&rendertype=abstract

2. Kirkham E, Skinner J, Anderson T, Bazire S, Twigg MJ, Desborough JA. One lithium level >1.0 mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database. BMJ Open [Internet]. 2014 Jan [cited 2015 Feb 25];4(11):e006020. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4225230&tool=pmcentrez&rendertype=abstract

3. Aapro M, Launay-Vacher V. Importance of monitoring renal function in patients with cancer. Cancer Treat Rev [Internet]. 2012 May [cited 2014 May 22];38(3):235–40. Available from: http://www.sciencedirect.com/science/article/pii/S0305737211000788

4. McDowell SE, Coleman JJ, Evans SJW, Gill PS, Ferner RE. Laboratory monitoring and adverse patient outcomes with antihypertensive therapy in primary care. Pharmacoepidemiol Drug Saf [Internet]. 2010 May [cited 2014 Sep 8];19(5):482–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20306453

5. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. 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 [Internet]. 1999 Mar 16 [cited 2015 Mar 30];130(6):461–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10075613

6. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med [Internet]. 2009 May 5 [cited 2014 Dec 3];150(9):604–12. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2763564&tool=pmcentrez&rendertype=abstract

7. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis [Internet]. 2002 Feb [cited 2014 Dec 10];39(2 Suppl 1):S1–266. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11904577

8. Department of Health Renal NSF Team. The National Service Framework for Renal Services - Part Two: Chronic Kidney Disease, Acute Renal Failure and End of Life Care. London; 2005.

9. British Medical Association. 2014/15 General Medical Services (GMS) Contract Quality and Outcomes Framework (QOF): Guidance for GMS Contract 2014/15. 2014.

10. O'Donoghue DJ. Going upstream: the implication and opportunities of early detection. J Ren Care [Internet]. 2009 Dec [cited 2015 Feb 26];35 Suppl 2:3–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19891679

11. 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.

12. Doll H, Shine B, Kay J, James T, Glasziou P. The rise of cholesterol testing: how much is unnecessary. Br J Gen Pract [Internet]. 2011 Feb [cited 2013 Jun 26];61(583):e81–8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3026174&tool=pmcentrez&rendertype=abstract

13. Office for National Statistics. Population Estimates Total Persons for England and Wales, Mid 2011 (Census Based) [Internet]. 30 Apr. 2013 [cited 2015 Sep 17]. Available from: http://www.ons.gov.uk/ons/datasets-and-tables/index.html?pageSize=50&sortBy=none&sortDirection=none&newquery=population+pyramid&content-type=Reference+table&content-type=Dataset

14. Fransham M. Population estimates and forecasts, 2001 to 2026. Oxford; 2013.

15. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria; 2012. Available from: http://www.r-project.org/

16. Health and Social Care Information Centre. Prescriptions dispensed in the community: England 2002-2012 [Internet]. 2013. Available from: http://www.hscic.gov.uk/catalogue/PUB11291

17. 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 [Internet]. 2011 Jan [cited 2014 Jul 10];1(2):e000308. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3244664&tool=pmcentrez&rendertype=abstract

18. Gifford FJ, Methven S, Boag DE, Spalding EM, Macgregor MS. Chronic kidney disease prevalence and secular trends in a UK population: the impact of MDRD and CKD-EPI formulae. QJM [Internet]. 2011 Dec [cited 2015 Sep 14];104(12):1045–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21821654

19. Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int [Internet]. 2007 Jul 18 [cited 2015 Jan 13];72(1):92–9. Available from: http://dx.doi.org/10.1038/sj.ki.5002273

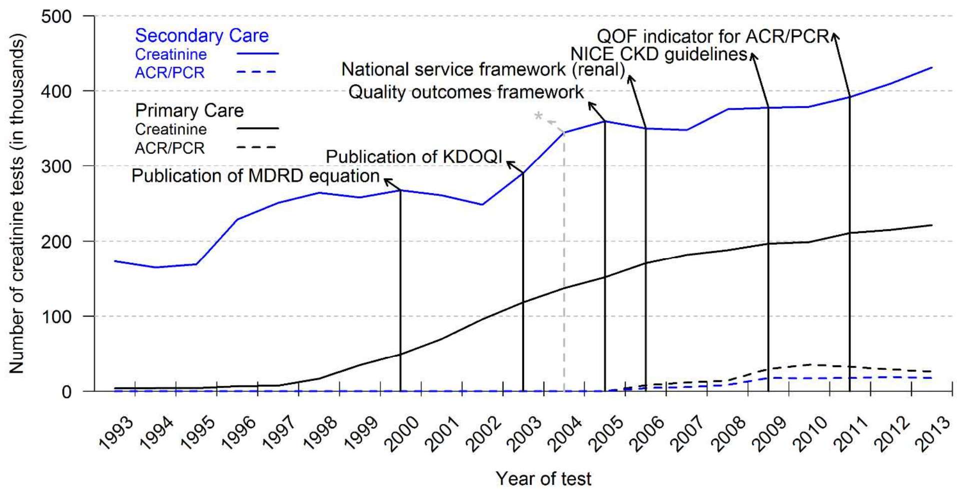
20. De Lusignan S, Nitsch D, Belsey J, Kumarapeli P, Vamos EP, Majeed A, et al. Disparities in testing for renal function in UK primary care: cross-sectional study. Fam Pract [Internet]. 2011 Dec 1 [cited 2015 Mar 3];28(6):638–46. Available from: http://fampra.oxfordjournals.org/content/28/6/638.long

21. Aitken GR, Roderick PJ, Fraser S, Mindell JS, O'Donoghue D, Day J, et al. Change in prevalence of chronic kidney disease in England over time: comparison of nationally representative cross-sectional surveys from 2003 to 2010. BMJ Open [Internet]. 2014 Jan 29 [cited 2015 Jun 22];4(9):e005480. Available from: http://bmjopen.bmj.com/content/4/9/e005480.full

22. Lamb EJ, Brettell EA, Cockwell P, Dalton N, Deeks JJ, Harris K, 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 p. BMC Nephrol [Internet]. 2014 Jan [cited 2014 Aug 28];15(1):13. Available from: http://www.biomedcentral.com/1471-2369/15/13

23. Glasziou, Paul, Irwig L, Aronson J. Evidence-Based Medical Monitoring. First Edit. Blackwell Publishing; 2008. 362 p.

24. Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald R, Rossini D, 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 [Internet]. 2012 Apr 17 [cited 2013 Sep 25];156(8):570–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22508734



No. Individuals with tests (thousands)

SC	50	55	52	61	63	64	65	67	67	65	81	101	105	103	104	110	112	116	120	125	129
PC	3	4	3	5	6	14	28	37	51	67	78	89	95	104	110	115	120	123	129	131	134
All	52	58	54	65	67	74	87	96	108	119	143	171	180	184	190	200	206	211	221	228	234

Figure 1: Total number of serum creatinine tests ordered from secondary and primary care between 1993 and 2013 and dates of key publications. * indicates enlargement of population denominator.

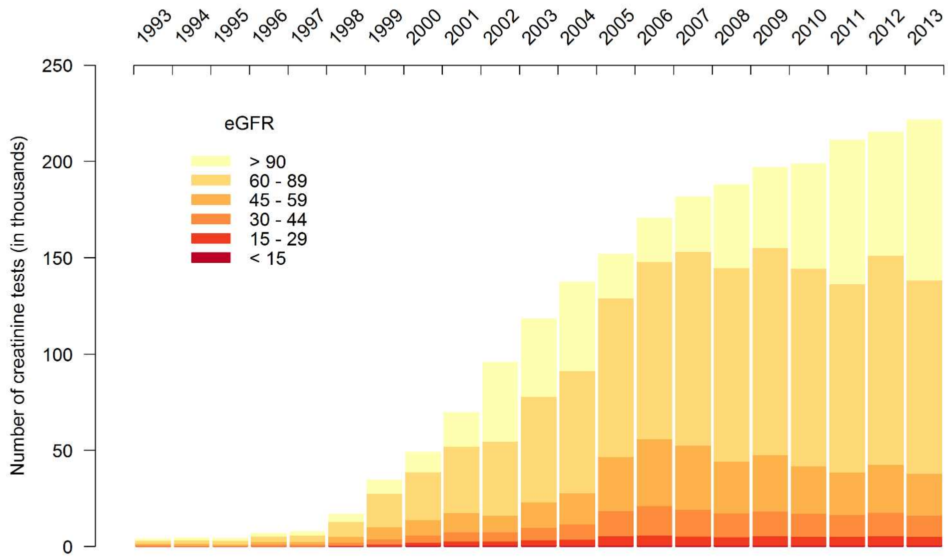


Figure 2: The number of serum creatinine tests between 1993 and 2013 by stages of renal impairment

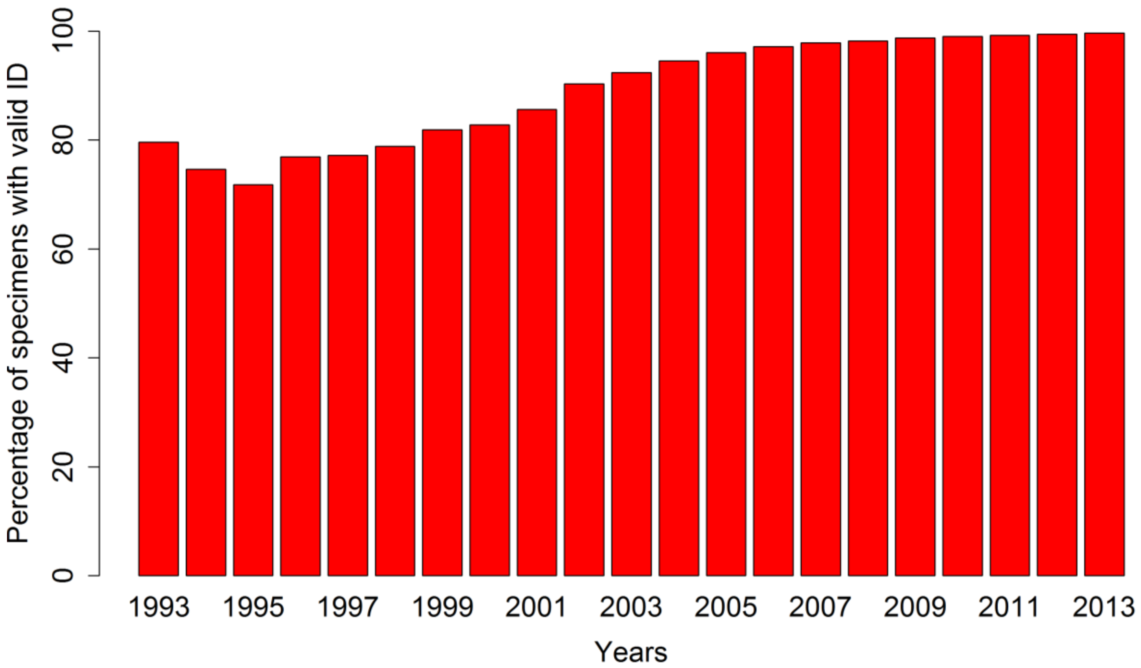


Figure S.1: Proportions of specimens that could be linked to a valid Id (NHS or Hospital number)

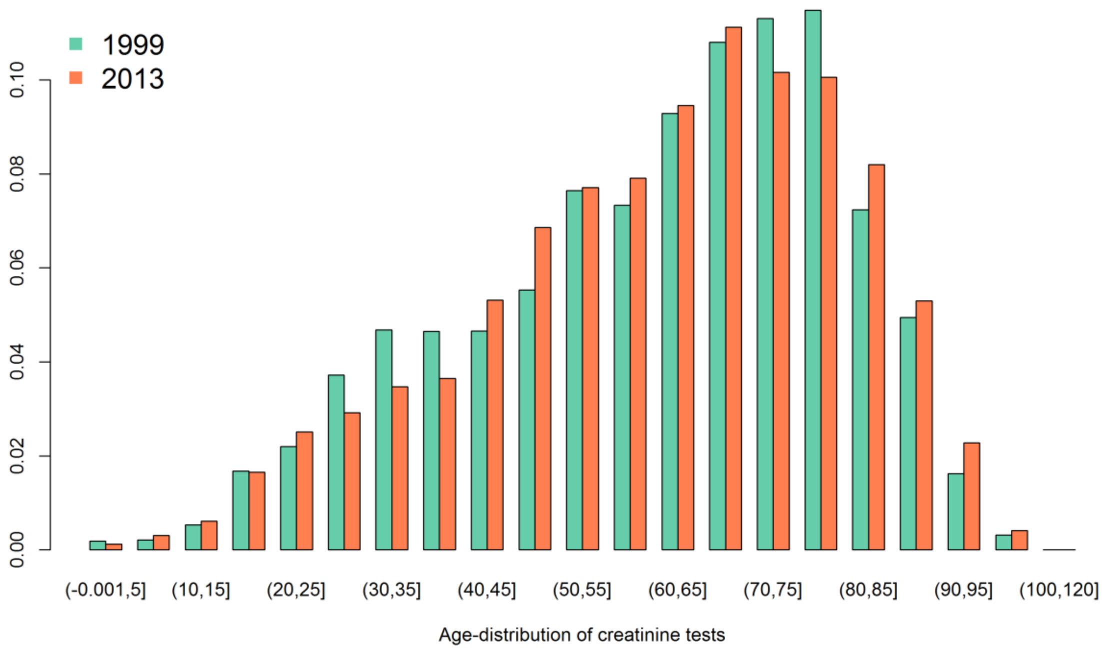


Figure S.2 Barplot showing normalised age-distribution in 1999 and 2013

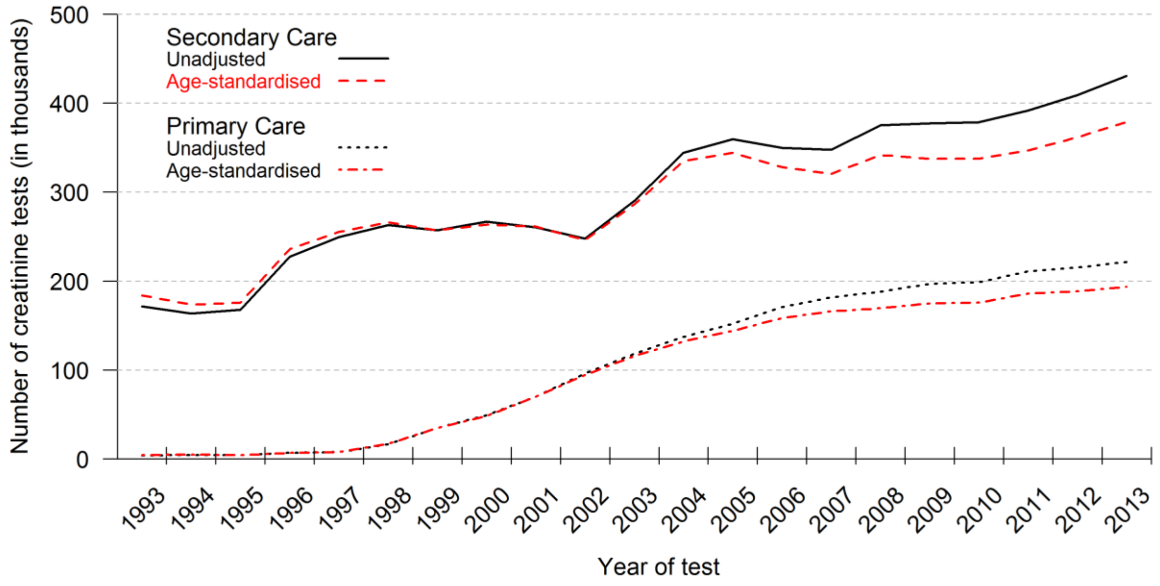


Figure S.3 Unadjusted and age-standardised total number of serum creatinine tests ordered from secondary and primary care between 1993 and 2013.

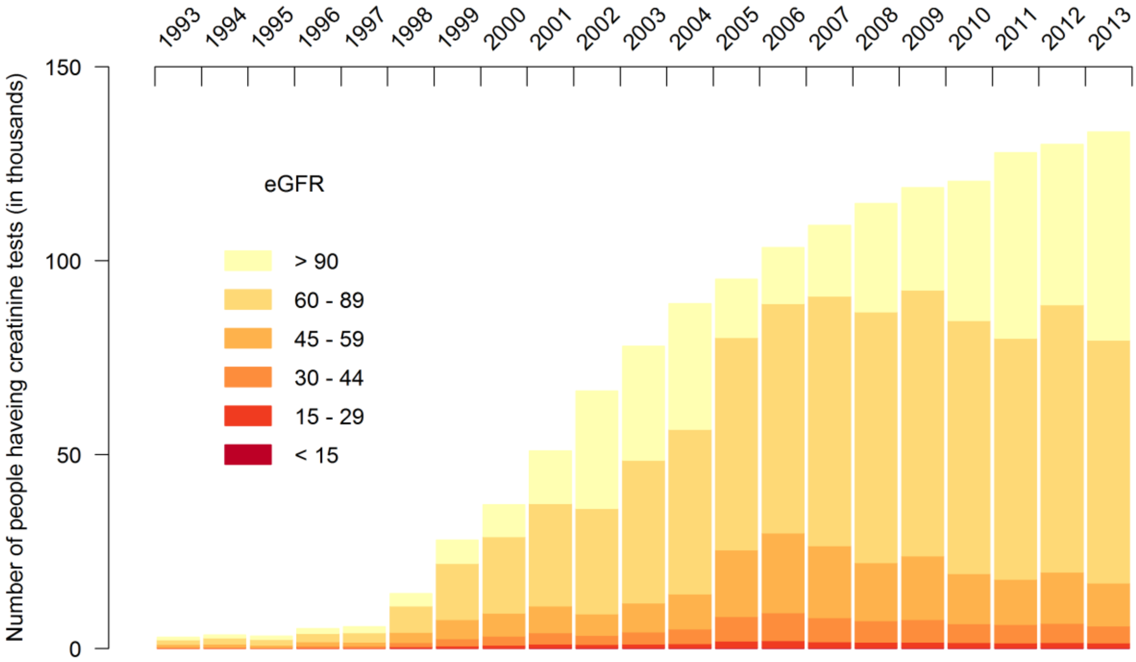


Figure S.4: The number of people who had at least one serum creatinine tests between 1993 and 2013 by stages of renal impairment

BMJ Open

Trends in serum creatinine testing in Oxfordshire, UK 1993-2013: A population based cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009459.R2
Article Type:	Research
Date Submitted by the Author:	06-Nov-2015
Complete List of Authors:	Oke, Jason; University of Oxford, Nuffiled Department of Primary Care Health Sciences Perera, Rafael; University of Oxford, Nuffield Department of Primary Care Health Sciences McFadden, Emily; University of Oxford, Nuffield Department of Primary Care Health Sciences Stevens, Richard; University of Oxford, Nuffield Department Primary Care Health Sciences Lasserson, Daniel; University of Oxford, Nuffield Department of Primary Care Health Sciences Shine, Brian; University of Oxford, Nuffield Department of Clinical Biochemistry
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Renal medicine, Health services research
Keywords:	PRIMARY CARE, EPIDEMIOLOGY, Chronic kidney disease, serum creatinine, Biochemistry < TROPICAL MEDICINE

Title: Trends in serum creatinine testing in Oxfordshire, UK 1993-2013: A population based cohort study

Authors: Jason Oke[1], Rafael Perera[1], Emily McFadden[1], Richard Stevens[1] ,Daniel Lasserson[1,2], Brian Shine[3].

Affiliations :

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

[2]NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU.

[3] Department of Clinical Biochemistry, John Radcliffe Hospital, University of Oxford.

Strengths and Limitations of the Study

- This study uses twenty years of data from a single laboratory that serves a well-defined population, typical of the wider UK population.
- To our knowledge, no other study has looked specifically at changes in serum creatinine test ordering rates, over time, in the UK.
- We did not have access to data on patient history or prescriptions or reasons for test ordering and so cannot comment on whether they were ordered with appropriate frequency.

Jason Oke is the corresponding author.

Correspondence to Dr Jason L Oke; jason.oke@phc.ox.ac.uk

Abstract

Objectives: To determine how many kidney function tests are done, on whom, how frequently they are performed and how they have changed over time.

Design: Retrospective study of all serum creatinine, urine albumin and urine creatinine tests

Setting: Primary and secondary care in Oxfordshire from 1993 to 2013

Participants: Unselected population of 1,220,447 people

Main outcome measures : The total number of creatinine and urinary protein tests ordered from primary and secondary care and the number of tests per year stratified by categories of estimated glomerular filtration rate (eGFR). The frequency of testing in patients having their kidney function monitored.

Results

Creatinine requests from primary care increased steadily from 1997 and exceeded 220,000 requests in 2013. Tests corresponding to normal kidney function (eGFR > 60/mL/min/1.73m^2) constituted 59% of all kidney function tests in 1993 and accounted for 83% of all tests in 2013. Test corresponding to CKD stages 3-5 declined after 2007. Reduced kidney function, albuminuria, male gender, diabetes and age were independently associated with more frequent monitoring. For a female patient between 61 and 80 years and with stage 3a CKD, the average number of serum creatinine tests (95% C.I) was 3.23 per year (3.19 to 3.26) and for a similar woman with diabetes, the average number of tests was 5.50 (5.44 to 5.56) tests per year.

Conclusion:

There has been a large increase in the number of kidney function tests over the last two decades. However, we found little evidence that this increase is detecting more CKD. Tests are becoming more frequent in people with and without evidence of renal impairment. Future work using a richer data source could help unravel the underlying reasons for the increased testing and determine how much is necessary and useful.

Trial registration: Not applicable

Keywords: Creatinine, monitoring, primary care, chronic kidney disease, laboratory.

Introduction.

Serum creatinine is widely used to measure renal function in the detection, diagnosis and management of chronic kidney disease (CKD) and other renal disorders such as acute kidney injury (AKI). Urinary albumin and protein are markers of kidney damage but also indicate disease from anywhere within the urinary tract. As both reduced renal function and elevated urinary albumin or protein are independently associated with adverse kidney outcomes (end-stage renal disease, acute kidney injury and progression of CKD (1) as well as cardiovascular events in the general population, monitoring may be warranted . Renal function monitoring with serum creatinine testing is also critical for the safe administration of a wide range of therapeutic agents including those for bipolar disorder (2), cancer (3) ,hypertension (4) and diabetes . In order to take into account factors such as age, gender and ethnic group, serum creatinine can be converted to an estimated glomerular filtration rate (eGFR) through equations such as Modification of Diet in Renal Disease (MDRD) (5) or CKD-EPI (6).

The Kidney Disease Outcomes and Quality Initiative (KDOQI) clinical practice guidelines in early 2002 (7) proposed that stages of CKD be defined primarily according to eGFR. In 2004, the Department of Health's National Service Framework for Renal Services (8) adopted the KDOQI staging classification of CKD. In the same year the Quality and Outcomes Framework (QOF), part of the contract for UK general practice (9), introduced incentives for the recording of serum creatinine in people with diabetes or on lithium therapy. The 2006/2007 extension of QOF required general practice (GP) doctors to maintain a register of adults with CKD stages 3-5 (10). In 2008 guidance from the National Institute for Health and Care Excellence (NICE) (11) recommended monitoring of renal function through creatinine testing in high risk groups. The 2009/2010 extension of QOF did not specifically incentivise serum creatinine testing or eGFR calculation, but incentivised the monitoring of urinary markers of kidney disease such as urinary albumin-creatinine ratio (ACR) in patients on the CKD register (9).

Motivated by a previous analysis of lipid testing in the same region (12), we examined serum creatinine tests and urinary albumin and protein tests ordered in Oxfordshire (UK) from 1993 to 2013. Secondly, we describe the distribution of CKD stages among those tested over time. Lastly, we explore how the frequency of monitoring has varied over time and between patients with different characteristics.

Methods

Data included all requests for serum creatinine (SCr), albumin to creatinine ratio (ACR), protein to creatinine (PCR) and glycated haemoglobin (HbA1c) measurements from the Oxford University Hospitals Trust Clinical Biochemistry laboratories for the entire periods covered by the database (May 1969 to November 2014). One of the co-authors (BS) is the custodian of the laboratory information system and all data were anonymised prior to extraction and analysis. We used the NHS number as the primary identifier. Before this was available, patients were linked to their hospital number if they were known. Where neither of these were available, specimens were not extracted. Numerators were based on all tests, whether linked or not.

Recording of creatinine requests prior to 1993 was inconsistent and there were few records of ACR/PCR tests prior to 2006. In September 2009, the reference method for creatinine changed to isotope dilution mass spectrometry (IDMS) and all creatinine measurement have been adjusted to reflect this. For each test result, the sex and date of birth of the patient, and the date, location and name of the requesting physician were extracted from the database. A request was coded as coming from either primary care or other non-primary care (secondary or tertiary) care using an amended version of the in-house laboratory coding system. Locales that had requested less than 50 tests over the entire study period were not included in the analysis.

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the MDRD formula (5), chosen to reflect clinical practice in the timeframe of the study. We split eGFR into six categories of renal impairment using thresholds that define CKD. The first two represent normal (> 90 mL/min/1.73m^2) and mildly impaired (60 - 89 mL/min/1.73m^2) kidney function and the remaining four represent moderate to severely impaired kidney function and correspond directly to CKD stages 3a (45 - 59 mL/min/1.73m^2) ,3b (30 - 44 mL/min/1.73m^2) ,4 (15 -29 mL/min/1.73m^2) and 5 (< 15 mL/min/1.73m^2) . The MDRD formula has an adjustment for ethnicity, which raises eGFR for non-white ethnicity. We were unable to obtain this data so made no adjustment and hence our eGFR staging is biased slightly towards more severe renal impairment. HbA1c (expressed in IFCC units) was categorised into four levels: 1) not measured, 2) under the diagnostic thresholds for diabetes (<less than 48 mmol/mol), 3) controlled glycaemia (48 – 58 mmol/mol) and 4) uncontrolled glycaemia (> 58 mmol/mol). Albuminuria was categorised similarly using diagnostic thresholds as; 1) not measured, 2) measured but less than 3 mg/mol for ACR or less than 15 mg/mmol for PCR , 3) microalbuminuria (> 3 mg/mol (ACR) and >15 mg/mmol (PCR)) and 4) macroalbuminuria (> 30 mg/mmol (ACR) or >50 mg/mmol (PCR)).

Number of creatinine and urinary albumin or protein tests over time

The total number of SCr, ACR and PCR tests ordered from primary care and non-primary care locales was calculated separately for each year from 1993 to 2013. In an additional analysis, we calculated age-adjusted yearly totals of creatinine testing in primary and secondary care by standardising to the age distribution in 1999. For this, we calculated creatinine testing rates per five year age brackets using population pyramid data for England between 1971 and 2011 (13) and estimates of the population of Oxfordshire local authority district (14) as the denominator . These rates were multiplied by the reference age distribution and summed to form age-adjusted totals. Tests requested from primary care were additionally stratified by stages of renal impairment.

Predictors of the frequency of monitoring

We examined factors related to the frequency of monitoring in a sub-cohort of people having kidney function/damage monitored, defined as having at least 2 tests further to the first year's measurement and complete covariate data. Measurements within the first year of follow-up were excluded as they are likely to be for reasons other than monitoring. We used poisson regression to model the frequency of monitoring adjusting for initial level of kidney function, HbA1c testing, evidence of albuminuria or proteinuria, gender and age. All analyses were carried out using R v3.1.2 (15)

Results

Data was obtained on 1,220,447 people, 527,753 of which had only one entry and the remaining 692,694 had median (IQR) follow-up of 7.6 (3.7, 12.5) years. The percentage of specimens that could not be linked to either a hospital or NHS number was 20% in 1993 and dropped steadily to less than 1% in 2013 (see supplementary material figure S.1)

Number of kidney function tests over time

Figure 1 shows the trend lines for both creatinine and ACR/PCR tests with dates of key publications, guidelines, and changes to the QOF. Between 1993 and 2013, the last full year of follow-up, the number of creatinine requests from primary care locales increased from 4,048 per year to 221,557 per year. Requests from secondary and tertiary care locales rose from 173,323 in 1993 to 431,198 in 2013. Record of requests for ACR/PCR tests began in 2006 and totalled 8,125 in primary care and 4,467 in secondary or tertiary care and in 2013 the respective totals were 26,317 and 17,769.

The age distribution of people that have creatinine measured in Oxfordshire changed over the duration of the study. There were more people (as a proportion of the total) being tested in age brackets 85 or older in 2013, compared to 1999, but fewer in the 70-80's age brackets (see supplementary figure S.2). Adjusted creatinine totals were lower than unadjusted totals and suggest that for 2013, 11.9% of the tests in secondary care and 12.6% in primary care can be attributed to shifts in age demographics since 1999 (see supplementary figure S.3)

Figure 1 here:

*Figure 1: Total number of serum creatinine tests ordered from secondary and primary care between 1993 and 2013 and dates of key publications. * indicates enlargement of population denominator.*

Distribution of renal impairment over time in primary care

Figure 2 shows the total number of tests stratified by eGFR categories corresponding to the stages of CKD. Between 1998 and 2013 creatinine testing increased in primary care. The number of tests for normal, mildly reduced and impaired renal function (CKD stages 3-5) showed a marked increase between 1998 and 2005. However after 2005 the number of tests showing impaired function remained stable. Therefore all the increase after 2005 is in tests from patients with normal kidney function. The number of tests corresponding to CKD increased from 1648 tests in 1993 to 55,970 in 2006 but has since fallen back to 38,056 in 2013. Impaired kidney function tests accounted for 41% of all kidney function tests requested in 1993 and only 17% in 2013. A similar pattern was observed for secondary and tertiary care (figure not shown), and when limiting one test per patient (see supplementary figure S.4).

Figure 2 here

Figure 2: The number of serum creatinine tests between 1993 and 2013 by stages of renal impairment

Frequency of monitoring

There were 167,701 subjects with at least 2 tests further to the first year's measurement and complete covariate data. Table 1 shows the results of the fitted model of monitoring frequency.

		n	Rate per year (95% C.I)
Renal function as measured by eGFR (ml/min/1.73^2)	> 60 (Reference)	146604	1.09 (1.09 to 1.11)
	45 - 59 (3a)	16343	1.12 (1.11 to 1.12)
	30 – 44 (3b)	3723	1.26 (1.25 to 1.27)
	15 – 29 (4)	791	1.43 (1.40 to 1.47)
	< 15 (5)	240	1.28 (1.23 to 1.33)
Albuminuria	Not measured	167128	1
	< 3 mg/mmol	430	1.07 (1.03 to 1.12)
	3 - 30 mg/mmol	116	1.06 (0.98 to 1.15)*
	> 30 mg/mmol	27	1.39 (1.19 to 1.60)
Time of initial measurement	pre 1998	38679	1
	1999 - 2003	63530	1.06 (1.05 to 1.06)
	2004 - 2008	51998	1.16 (1.16 to 1.17)
	2009 - 2013	13494	1.88 (1.86 to 1.89)
Age	< 20 years	9398	1
	21-40 years	36838	0.99 (0.98 to 1.00)*
	41 -60 years	61106	1.20 (1.19 to 1.21)
	61 - 80 years	51405	1.45 (1.43 to 1.46)
	81 -100 years	8954	1.51 (1.49 to 1.53)
	Not measured	105770	1
HbA1c	< 48 mmol/mol	49570	1.11 (1.10 to 1.11)
	48 - 58 mmol/mol	5691	1.70 (1.69 to 1.71)
	> 58 mmol/mol	6670	1.77 (1.77 to 1.79)
	Male	74014	1
Sex	Female	93687	0.98 (0.97 to 0.98)

Table 1: Parameter estimates for the intensity of monitoring renal function in primary care (significant at p <0.001 except *)

The average rate (95% C.I.) of monitoring in the reference group (males aged less than 20 with normal renal function, no albuminuria or diabetes) was 1.09 (1.09 to 1.11) tests per year (equivalent to one test every 335 days on average). Relative increases in the frequency of monitoring were found for older people, for people with micro or macro-albuminuria, lower eGFR, those with any HbA1c tests and higher HbA1c. The frequency of monitoring was also shown to increase with time, independently of other associated factors. Female gender was associated with a small but statistically significant relative decrease in the frequency of monitoring. For a female patient aged between 61 and 80 with stage 3a CKD (eGFR 45 – 59 mL/min/1.73m^2) the average rate of monitoring is estimated as 3.23 tests per year with 95% confidence interval (3.19 to 3.26) and for a similar woman with controlled glycaemia, the average number of tests rises to 5.50 tests per year on average with 95% confidence interval (5.44 to 5.56).

Conclusion

Summary

We find that the number of serum creatinine tests has risen dramatically since the late 1990s, especially in primary care, and exceeded 600,000 tests in 2013. Some of this increase can be attributed to a shift in the age-distribution of the population and the expansion of the area that the laboratory serves in 2003. Publication of the KDOQI guidelines in 2002 came after the start of a sharp increase in test ordering from secondary or tertiary care doctors and later publications did not seem to influence test ordering rates. There was also little evidence that KDOQI, the introduction of QOF in 2004 and later extensions directly affected creatinine testing rates in primary care. In contrast, a rise in urinary ACR and PCR testing around 2009/10 coincides with the introduction of relevant QOF indicators.

Older people, people with higher HbA1c and people with kidney disease were most frequently tested for serum creatinine. Up until 2005, the increasing volume of testing in primary care was accompanied by increasing numbers with CKD among those tested. After 2005, the volume of creatinine testing continued to increase, but the number of tests with eGFR corresponding to CKD stages 3 - 5 stabilised or decreased while the number of eGFR tests with results in the normal or mildly impaired range (≥60 mL/min/1.73m^2) increased. The number of tests with results in the normal range (> 90 mL/min/1.73m^2) has risen fastest since 2006/7.

Strengths and Limitations

We had access to data from all requests over twenty years at a single laboratory that serves a well-defined population, typical of the wider UK population. However, we did not have data on patient history or prescriptions. In particular we have no data on the reasons for why blood samples were taken for renal function testing. Given that the majority of laboratories will analyse sodium, potassium and creatinine as a set, the primary target of monitoring by a GP may be the electrolyte levels rather than the creatinine level. Whilst this makes interpretation of the rise in creatinine testing more complex, if abnormalities are detected in electrolyte levels this prompts an immediate clinical need to determine the creatinine level, and therefore creatinine testing is an important component of monitoring of electrolytes as well as for CKD itself. Furthermore we cannot comment on whether tests were ordered with appropriate frequency, or to what extent the observed rise in testing reflects the increase in the UK in prescriptions for medicines, many of which require renal function testing. (4)(16). Without ethnicity data, we were obliged to approximate eGFR by the MDRD equation without the appropriate adjustment for people of non-white ethnic group, and hence we underestimate eGFR and overestimate the amount CKD. However, this would affect fewer than 5% of people in Oxfordshire, and therefore we expect this would only make minor changes to the stage distributions in this sample (17).

Comparison with existing literature

To our knowledge, no other study has looked specifically at changes in serum creatinine test ordering rates, over time, in the UK, but there are studies looking at CKD prevalence which have data on testing rates. One such study reported similar size increases in both the number of blood samples being taken and the number of people having their creatinine tested between 2004 and 2010 (18) In contrast, an analysis of primary care computer records in Kent, Manchester and Surrey between

1998 and 2003, and a similar study in south-west London in 2007, each reported that 30% of patients had a valid serum creatinine measurement (19) (20). The latter figures provide context for our analysis but are not directly comparable, since we do not have an equivalent denominator (total number of patients in the region served by the laboratory), and since these studies report number of patients rather than number of tests. A study using Health Survey for England data between 2003 and 2010 found a modest decline in rates of CKD, despite increases in diabetes and obesity (21). We have shown a similar decline in tests reflecting CKD in Oxfordshire in recent years, even after adjusting for risk factors such as age and HbA1c, but we have also shown that the total number of serum creatinine tests ordered has continued to rise, driven by an increase in serum creatinine tests with values above 90 mL/min/1.73m^2.

Implications

The increase in the volume of kidney function tests in Oxfordshire, and in particular creatinine testing, is likely to be due to a number of factors. There is a net increase in number of people being tested year on year and people are being tested more frequently independent of changes in common risk factors for CKD. Given the uncertainty around the best methods and intervals for monitoring renal function it is unclear whether more frequent monitoring may lead to a net-benefit, but as eGFR has considerable biological variability (22), more frequent monitoring may lead to many false alarms and over-adjustment of treatment (23). Conversely, increased laboratory workloads and the subsequent strain on limited resources may contribute to an increase in missed or delayed diagnoses (24). If resources allowed, electronic health records could be used to identify abnormal creatinine tests for further investigation, potentially reducing delays (25). However it is not currently clear whether increased test ordering in the UK contributes to errors in the management of CKD, or leads to clinically relevant delays in diagnosis. Since most of the recent increase in testing is driven by tests on patients with normal to mildly reduced eGFR and as there is little evidence of benefit from intervening in people with early stage CKD (26), these results are unlikely to influence clinical decisions or contribute to better care. Future work using a richer data source with prescription records and GPs' notes could help unravel the underlying reasons for the increased testing and determine how much is necessary and useful.

Ethics: Ethical approval was not required for this study. Clinical databases were only accessed by those with permission to do so. No individual data points were examined manually, and the data were anonymised at all stages of the analysis.

Contributorship statement: RP, BS, DL and RS contributed to the conception and design of the study. JO, EM and RS were responsible for the analysis and interpretation of the data. JO, RP, EM, DL and RS drafted the manuscript. All authors were involved in the final revision of the article. All of the authors approved the final article.

Competing interests: All of the authors have completed the ICMJE form for disclosure of potential conflicts of interest form (available on request from the corresponding author) and declare that (1) they have not received at any time payment or services from a third party for any aspect of the submitted work (2) that they have had no financial relationships with relevant entities outside of the submitted work (3) that they have no patents, planned, pending or issued broadly relevant to the work and (4) that they have no relationships or activities that readers could perceive to have influenced, or give the appearance of potentially influencing what was written in the submitted work.

Funding: This work is supported by funding from the National Institute for Health Research (NIHR) School for Primary Care Research (Project reference number 156) and the programme Grants for Applied Research programme (Ref: RP-PG-1210-12003). DSL is supported by the NIHR Oxford Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health

Data sharing statement: No additional data available.

1. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int [Internet]. 2011 Jul [cited 2015 Sep 3];80(1):93–104. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3959732&tool=pmcentrez&rendertype=abstract

2. Kirkham E, Skinner J, Anderson T, Bazire S, Twigg MJ, Desborough JA. One lithium level >1.0 mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database. BMJ Open [Internet]. 2014 Jan [cited 2015 Feb 25];4(11):e006020. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4225230&tool=pmcentrez&rendertype=abstract

3. Aapro M, Launay-Vacher V. Importance of monitoring renal function in patients with cancer. Cancer Treat Rev [Internet]. 2012 May [cited 2014 May 22];38(3):235–40. Available from: http://www.sciencedirect.com/science/article/pii/S0305737211000788

4. McDowell SE, Coleman JJ, Evans SJW, Gill PS, Ferner RE. Laboratory monitoring and adverse patient outcomes with antihypertensive therapy in primary care. Pharmacoepidemiol Drug Saf [Internet]. 2010 May [cited 2014 Sep 8];19(5):482–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20306453

5. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. 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 [Internet]. 1999 Mar 16 [cited 2015 Mar 30];130(6):461–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10075613

6. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med [Internet]. 2009 May 5 [cited 2014 Dec 3];150(9):604–12. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2763564&tool=pmcentrez&rendertype=abstract

7. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis [Internet]. 2002 Feb [cited 2014 Dec 10];39(2 Suppl 1):S1–266. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11904577

8. Department of Health Renal NSF Team. The National Service Framework for Renal Services - Part Two: Chronic Kidney Disease, Acute Renal Failure and End of Life Care. London; 2005.

9. British Medical Association. 2014/15 General Medical Services (GMS) Contract Quality and

Outcomes Framework (QOF): Guidance for GMS Contract 2014/15. 2014.

10. O'Donoghue DJ. Going upstream: the implication and opportunities of early detection. J Ren Care [Internet]. 2009 Dec [cited 2015 Feb 26];35 Suppl 2:3–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19891679

11. 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.

12. Doll H, Shine B, Kay J, James T, Glasziou P. The rise of cholesterol testing: how much is unnecessary. Br J Gen Pract [Internet]. 2011 Feb [cited 2013 Jun 26];61(583):e81–8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3026174&tool=pmcentrez&rendertype=abstract

13. Office for National Statistics. Population Estimates Total Persons for England and Wales, Mid 2011 (Census Based) [Internet]. 30 Apr. 2013 [cited 2015 Sep 17]. Available from: http://www.ons.gov.uk/ons/datasets-and-tables/index.html?pageSize=50&sortBy=none&sortDirection=none&newquery=population+pyramid&content-type=Reference+table&content-type=Dataset

14. Fransham M. Population estimates and forecasts, 2001 to 2026. Oxford; 2013.

15. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria; 2012. Available from: http://www.r-project.org/

16. Health and Social Care Information Centre. Prescriptions dispensed in the community: England 2002-2012 [Internet]. 2013. Available from: http://www.hscic.gov.uk/catalogue/PUB11291

17. 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 [Internet]. 2011 Jan [cited 2014 Jul 10];1(2):e000308. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3244664&tool=pmcentrez&rendertype=abstract

18. Gifford FJ, Methven S, Boag DE, Spalding EM, Macgregor MS. Chronic kidney disease prevalence and secular trends in a UK population: the impact of MDRD and CKD-EPI formulae. QJM [Internet]. 2011 Dec [cited 2015 Sep 14];104(12):1045–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21821654

19. Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int

[Internet]. 2007 Jul 18 [cited 2015 Jan 13];72(1):92–9. Available from: http://dx.doi.org/10.1038/sj.ki.5002273

20. de Lusignan S, Nitsch D, Belsey J, Kumarapeli P, Vamos EP, Majeed A, et al. Disparities in testing for renal function in UK primary care: cross-sectional study. Fam Pract [Internet]. 2011 Dec 1 [cited 2015 Mar 3];28(6):638–46. Available from: http://fampra.oxfordjournals.org/content/28/6/638.long

21. Aitken GR, Roderick PJ, Fraser S, Mindell JS, O'Donoghue D, Day J, et al. Change in prevalence of chronic kidney disease in England over time: comparison of nationally representative cross-sectional surveys from 2003 to 2010. BMJ Open [Internet]. 2014 Jan 29 [cited 2015 Jun 22];4(9):e005480. Available from: http://bmjopen.bmj.com/content/4/9/e005480.full

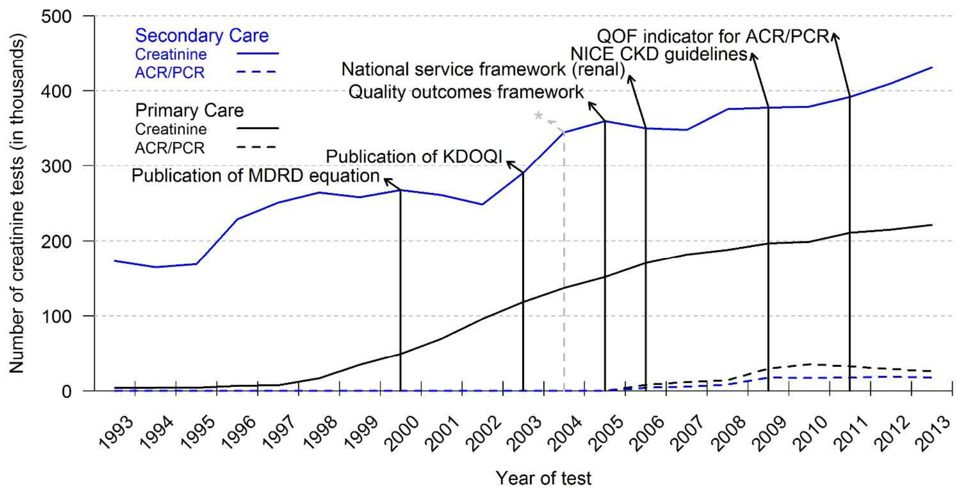
22. Lamb EJ, Brettell EA, Cockwell P, Dalton N, Deeks JJ, Harris K, et al. The eGFR-C study: accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease--prospective longitudinal study in a multiethnic p. BMC Nephrol [Internet]. 2014 Jan [cited 2014 Aug 28];15(1):13. Available from: http://www.biomedcentral.com/1471-2369/15/13

23. Glasziou, Paul, Irwig L, Aronson J. Evidence-Based Medical Monitoring. First Edit. Blackwell Publishing; 2008. 362 p.

24. Gandhi TK, Kachalia A, Thomas EJ, Puopolo AL, Yoon C, Brennan TA, et al. Missed and delayed diagnoses in the ambulatory setting: a study of closed malpractice claims. Ann Intern Med [Internet]. 2006 Oct 3 [cited 2015 Jul 20];145(7):488–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17015866

25. Sim JJ, Rutkowski MP, Selevan DC, Batech M, Timmins R, Slezak JM, et al. Kaiser Permanente Creatinine Safety Program: A Mechanism to Ensure Widespread Detection and Care for Chronic Kidney Disease. Am J Med [Internet]. 2015 Jun 16 [cited 2015 Sep 14]; Available from: http://www.sciencedirect.com/science/article/pii/S0002934315005367

26. Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald R, Rossini D, 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 [Internet]. 2012 Apr 17 [cited 2013 Sep 25];156(8):570–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22508734



No. Individuals with tests (thousands)

SC	50	55	52	61	63	64	65	67	67	65	81	101	105	103	104	110	112	116	120	125	129
PC	3	4	3	5	6	14	28	37	51	67	78	89	95	104	110	115	120	123	129	131	134
All	52	58	54	65	67	74	87	96	108	119	143	171	180	184	190	200	206	211	221	228	234

Figure 1: Total number of serum creatinine tests ordered from secondary and primary care between 1993 and 2013 and dates of key publications. * indicates enlargement of population denominator.
270x186mm (300 x 300 DPI)

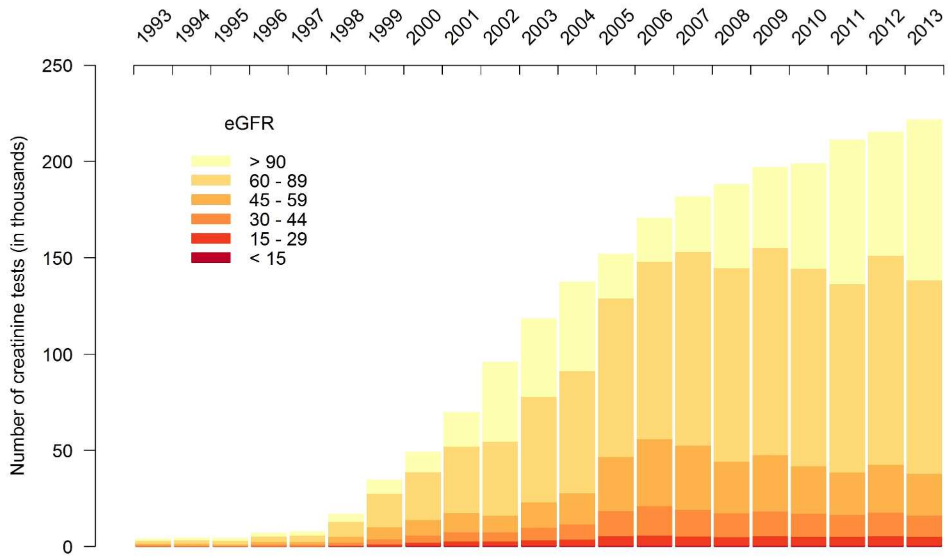


Figure 2: The number of serum creatinine tests between 1993 and 2013 by stages of renal impairment
270x169mm (300 x 300 DPI)

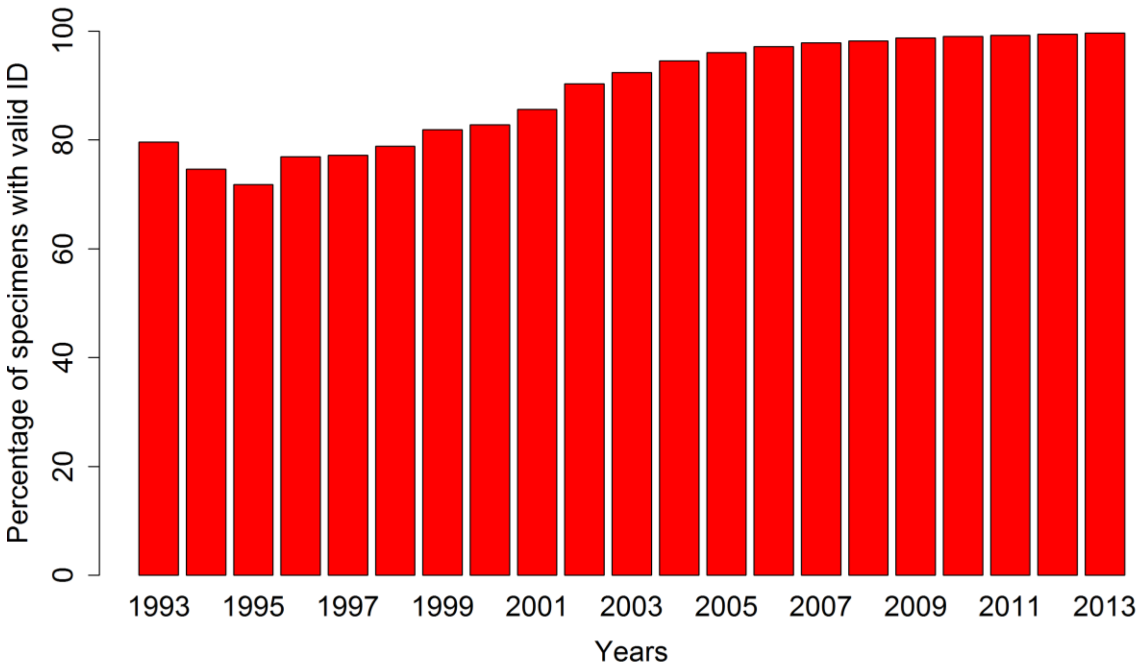


Figure S.1: Proportions of specimens that could be linked to a valid Id (NHS or Hospital number)

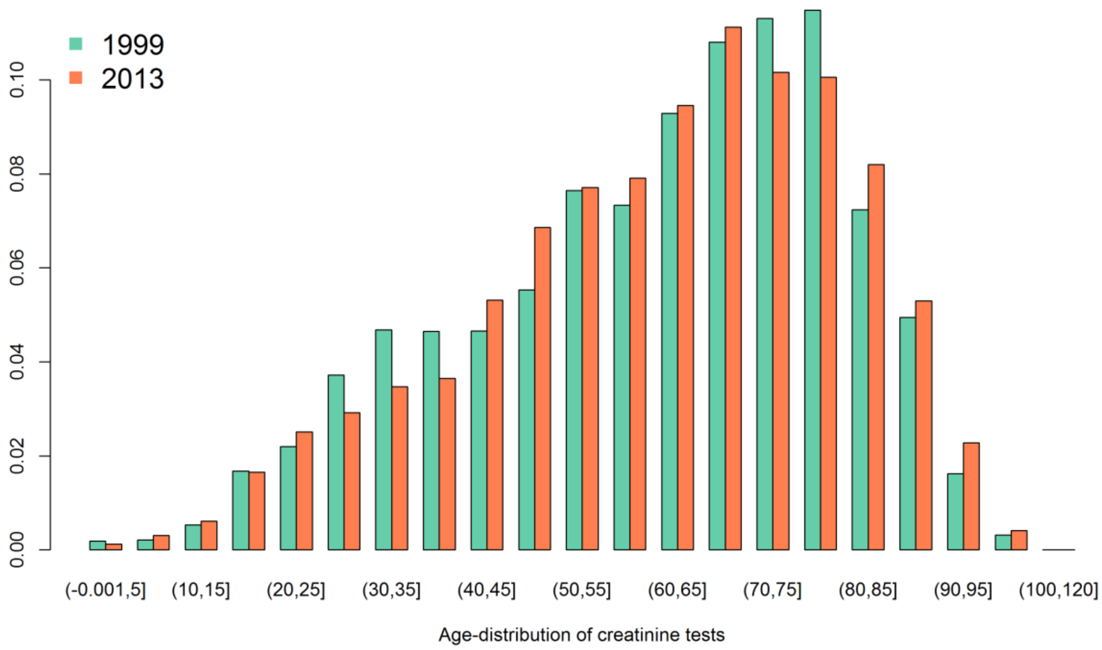


Figure S.2 Barplot showing normalised age-distribution in 1999 and 2013

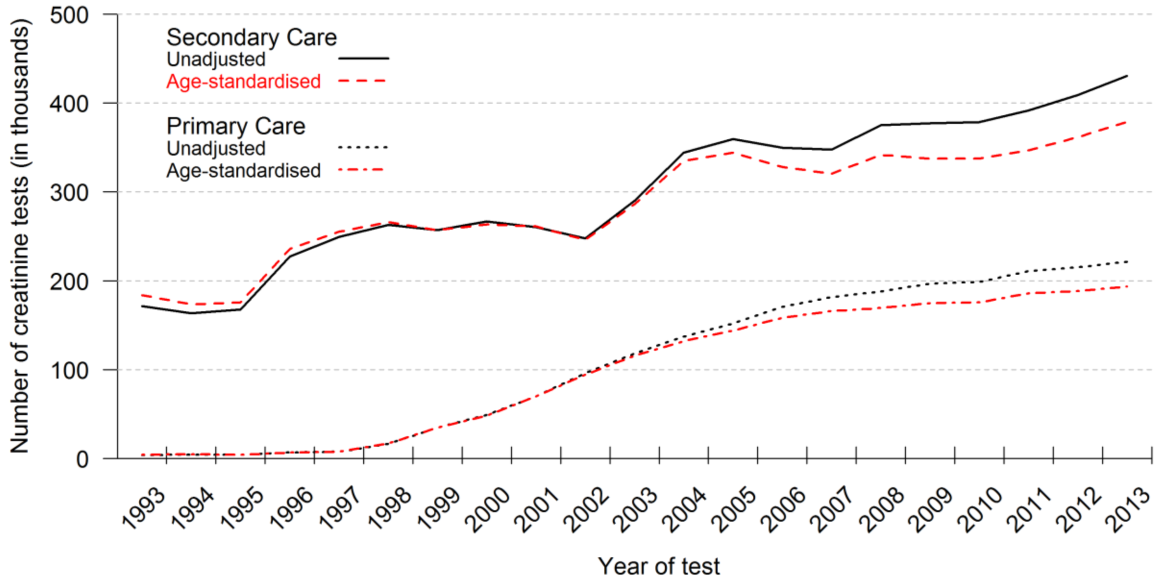


Figure S.3 Unadjusted and age-standardised total number of serum creatinine tests ordered from secondary and primary care between 1993 and 2013.

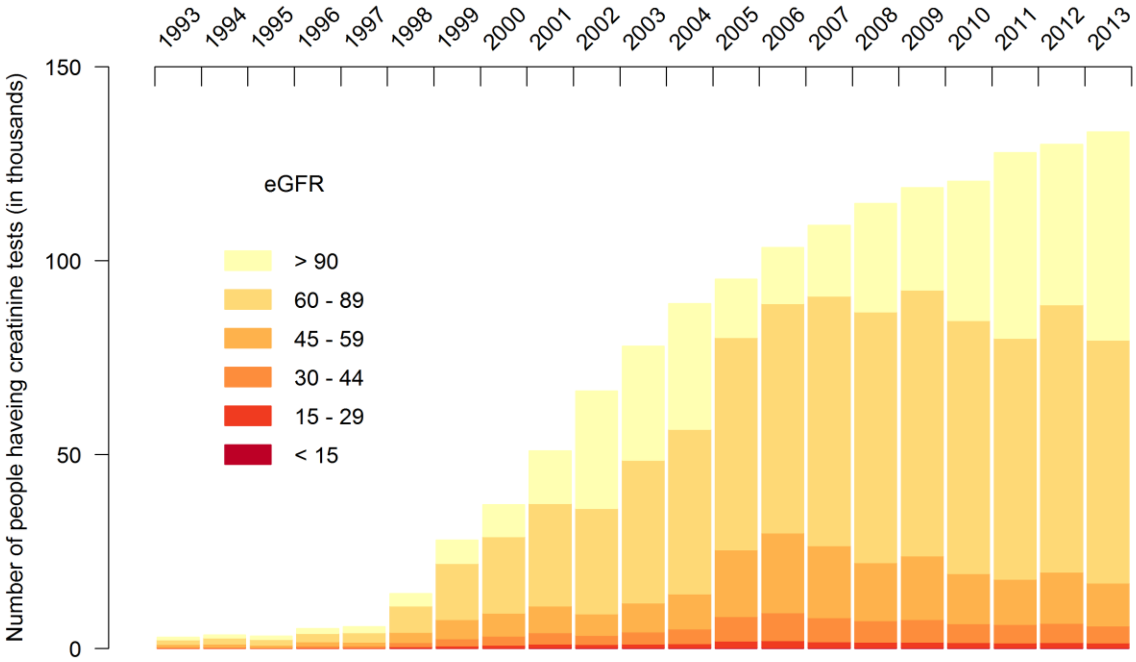
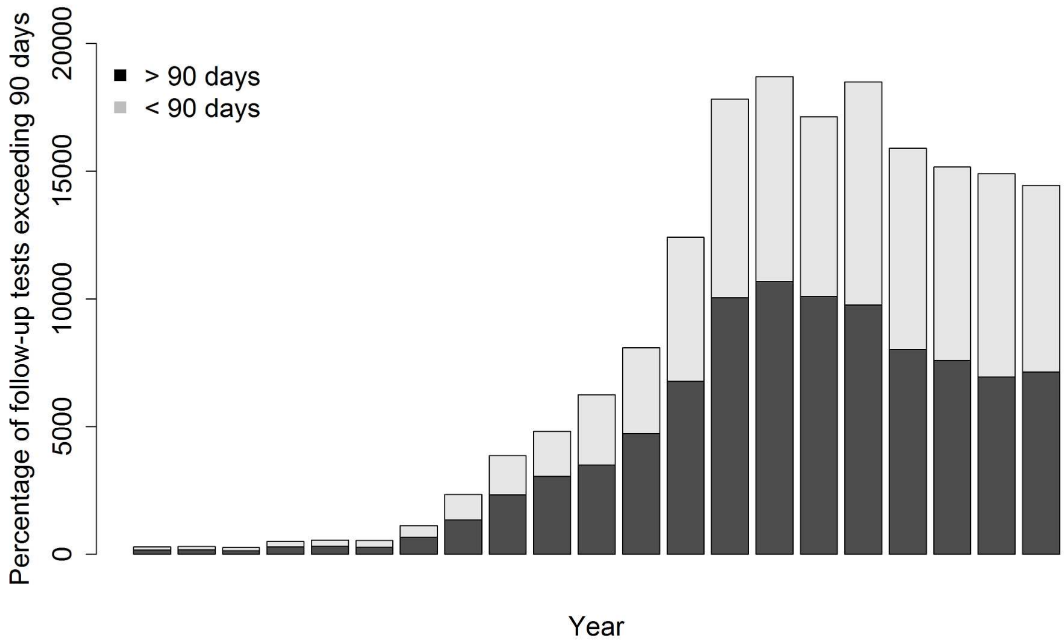


Figure S.4: The number of people who had at least one serum creatinine tests between 1993 and 2013 by stages of renal impairment



Barplot showing number of follow-up tests that were either longer than 90 days or less than 90 days since an abnormal eGFR (< 60ml/min/1.73m^2)