Health Survey for England 2016
Kidney and liver disease

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This report examines the prevalence of chronic kidney disease and of markers of chronic liver disease among adults in England in 2016, using self-report and biological measures.

Key findings

Chronic Kidney Disease

- Among all adults, 2% reported having a chronic kidney disease as diagnosed by a doctor.
- Using eGFR levels and urinary albumin, 15% of adults aged 35 and over had any chronic kidney disease stage (stage 1 to 5), and 7% had the most severe stages (stage 3 to 5).
- The prevalence and severity of abnormal kidney function and disease increased among older adults. Among adults aged 75 and over:
    - Two in five (39%) had abnormal kidney function (an $eGFR_{creat}$ level <60ml/min/1.73m^2).
    - One in four (25%) had abnormal albuminuria levels.
    - 34% had chronic kidney disease (levels 3 to 5).

Liver Disease

- Among all adults, 1% reported having doctor-diagnosed chronic liver disease. The prevalence was highest among those aged 55 to 64 (3%) and in the most deprived areas (2%).
- Raised levels of AST or ALT (more than 1.5 times the upper limit of normal) may be an indicator of liver damage. 1% of adults had raised levels of AST, and 3% had raised ALT. A raised level of ALT was more prevalent among men (4%) than women (2%).

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Contents

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This report may be of interest to policy officials, people working in public health and to commissioners of health and care services to see the prevalence of Kidney and Liver disease among adults in England.

Introduction

Contents

This report gives details of the prevalence of chronic kidney disease (CKD) and liver disease in the adult population, across different social and demographic groups, using self-report and biological measurements. From blood samples, serum creatinine and cystatin C are used to estimate the glomerular filtration rate (eGFR), and from urine, albumin and creatinine are used to calculate an albumin:creatinine ratio, key markers of renal damage. For the first time in HSE, levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in blood samples have been measured. Raised levels of AST or ALT are markers of potential liver damage.

Background

Chronic Kidney Disease

Chronic kidney disease is recognised as a global public health problem.[1] Chronic kidney disease is defined and staged using two measures. The estimated glomerular filtration rate (eGFR), a measure of how efficiently the waste product creatinine is filtered from the blood, reflects kidney function. Albuminuria, the presence of albumin (a protein) in the urine, is a marker of kidney damage.[2] Both eGFR and albuminuria are strong independent risk factors for progression to end-stage renal disease and acute kidney injury, but also all-cause and cardiovascular disease mortality.[3,4] Chronic kidney disease is classified into stages based on eGFR and albuminuria levels. No symptoms are found with chronic kidney disease in its early stages (1, 2, 3a), but appropriate medication can reduce the risk of progression. Symptoms are more likely as severity increases and stage 5 (end-stage renal disease) may require renal replacement therapy (dialysis or transplantation). Kidney disease may be detected by routine testing in people with diabetes or hypertension.

In 2015 in England, the prevalence of renal replacement therapy was 913 per million population. The National Health Service (NHS) costs of renal replacement therapy were estimated at £780 million for 2009/2010, and the total cost of chronic kidney disease at more than £1.4 billion, a nearly threefold increase on estimated costs for 2002.[5,6] Alongside population ageing, causal factors for chronic kidney disease such as obesity and Type 2 diabetes are increasing in the population and will increase the

[1] Couser, WG, Remuzzi G, Mendis S, et al. *The contribution of chronic kidney disease to the global burden of major noncommunicable disease.* Kidney Int. 2011;**80:**1258-70.

[2] Kidney Disease Improving Global Outcomes (KDIGO). *Clinical Practice Guideline for the evaluation and management of chronic kidney disease.* Kidney Int Suppl 2013;**3**:1-150. www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf

[3] Matsushita K, van der Velde M, Astor BC, et al. *Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis.* Lancet 2010;**375**:2073-81.

[4] Gansevoort Rt, Matshushita K, van der Velde M, et al. *Lower estimate GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts.* Kidney Int. 2011;**80**:93-104.

[5] MacNeil SJ, Casula A, Shaw C, et al. *UK Renal Registry 18th Annual Report: Chapter 2 UK RRT Prevalence in 2014: national and centre-specific analyses.* UK Renal Registry, 2015. https://www.renalreg.org/reports/2015-eighteenth-annual-report/

[6] Kerr, M, Bray B, Medcalf J, et al. *Estimating the financial costs of chronic kidney disease in the NHS in England.* Nephrol Dial Transplant 2012;**27**(suppl 3):iii73-80.

frequency of chronic kidney disease.[7,8] Conversely there is evidence from the HSE of some improvement in population blood pressure, another causal factor, and in blood pressure control in patients with hypertension.[9,10]

Several policy initiatives were introduced in England that may have had an impact on the prevention, detection and management of chronic kidney disease. The National Service Framework for Renal Services 2004/2005 led to the national reporting of eGFR by clinical biochemistry laboratories from 2006.[11] The General Practice Pay for Performance Quality Outcomes Framework (QOF) has included targets for hypertension and diabetes management and, from 2006/2007, chronic kidney disease. Chronic kidney disease indicators have more recently been reduced to only chronic kidney disease prevalence from GP register data, which was last presented in 2016/2017.[12] The NHS Vascular Checks Programme, introduced in 2009, includes screening for chronic kidney disease (Stages 3 to 5) in people aged 35 to 74 with newly identified type 2 diabetes or hypertension.[13]

The population prevalence of chronic kidney disease in England was reported for the first time using data on serum creatinine-based eGFR ($eGFR_{creat}$) and albuminuria in HSE 2009 and 2010.[14] Although there had previously been estimates based on routine testing using primary care data, these were based on people who visit their GP, rather than the general population.[15] HSE 2009 and 2010 used two different equations for calculating $eGFR_{creat}$, which produced slightly different estimates. In the combined 2009/2010 HSE, 5% had an $eGFR_{creat}$ <60 ml/min/1.73 m^2 (equivalent to chronic kidney disease stage 3 to 5 if chronic), using the CKD-EPI equation, and 6% using the MDRD equation, with a very strong age gradient. (For more information on $eGFR_{creat}$, CKD-EPI and MDRD equations, see the Methods report.[16])

[7] Wang YC, McPherson K, Marsh T et al. *Health and economic burden of the projected obesity trends in the USA and the UK.* Lancet. 2011;**27**;378(9793):815-25.

[8] González EL, Johansson S, Wallander M-A, et al. *Trends in the prevalence and incidence of diabetes in the UK: 1996-2005.* J Epidemiol Community Health. 2009**;63**:332-6.

[9] Falaschetti E, Mindell JS, Knott C, et al. *Major Improvements in hypertension management in England. Serial Cross-Sectional Data from 1994 to 2011.* Lancet 2014;**383**:1912-9.

[10] See HSE 2016 Adult Health Trends, available on the HSE 2016 report website https://digital.nhs.uk/pubs/hse2016.

[11] *The National Service Framework for Renal Services. Part two: chronic kidney disease, acute renal failure and end of life care.* London. Department of Health, 2005. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/199002/National_Service_Framework_for_Renal_Services_Part_Two_-_Chronic_Kidney_Disease__Acute_Renal_Failure_and_End_of_Life_Care.pdf .

[12] NHS Digital *Quality and Outcomes Framework – Prevalence, Achievements and Exceptions Report England 2016-17.* http://digital.nhs.uk/catalogue/PUB30124

[13] *NHS Health Check programme best practice guidance.* London: Department of Health, 2013. www.healthcheck.nhs.uk

[14] Roth M, Roderick P, Mindell J. *Kidney disease and renal function.* Chapter 8 in Craig R, Mindell J (eds). *Health Survey for England 2010.* Health and Social Care Information Centre, Leeds, 2011. https://digital.nhs.uk/catalogue/PUB03023

[15] De Lusignan S, Chan T, Stevens P, et al. *Identifying patients with chronic kidney disease from general practice computer records.* Fam Pract. 2005;**22**:234-41.

[16] HSE 2016 Methods, available on the HSE 2016 report website https://digital.nhs.uk/pubs/hse2016.

This report extends the findings from HSE 2009/2010 and takes account of evidence-based recommendations of kidney function assessment, as in recent NICE guidelines.[17,18,19]

Chronic Liver Disease

Chronic liver disease causes 2% of deaths in the UK[20] but is the fifth commonest cause of death in the UK in people aged under 65, and is the only major cause of mortality that is increasing.[21] Liver disease mortality rates have increased fourfold in the past few decades, largely due to alcoholic liver disease.[22] Hospital admission rates due to liver disease have been increasing year on year, as have admissions from alcoholic liver disease specifically.[23] Management of liver-related hospital admissions is costly.[24] There are also increasing levels of non-alcoholic fatty liver disease due to metabolic determinants such as obesity and diabetes; obesity and alcohol may interact synergistically on the risk of liver damage.[25,26]

Chronic liver disease develops with few, if any, signs or symptoms until significant scarring (cirrhosis) occurs.[27,28,29] The early identification of developing liver disease is therefore paramount. In 2014, the Lancet Commission on Liver Disease identified the need to 'strengthen detection of early liver disease and its treatment by improving the level of expertise and facilities in primary care'.[30]

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[17] Matushita K, Mahmoodi BK, Woodward M, et al. *Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate.* JAMA 2012;**307:**1941-51.

[18] Shlipak MG, Matsushita K, Arnlov J, et al*. Cystatin C versus creatinine in determining risk based on kidney function*. NEJM 2013;**369:**932-43.

[19] Coresh J, Selvin E, Stevens LA, et al. *Prevalence of chronic kidney disease in the United States.* JAMA 2007;**298:**2038-47.

[20] National End of Life Care Intelligence Network. *Deaths from liver disease. Implications for end of life care in England.* London, NHS, 2012. www.endoflifecare-intelligence.org.uk/resources/publications/deaths_from_liver_disease

[21] Bhala N, Aithal G, Ferguson J. *How to tackle rising rates of liver disease in the UK.* BMJ 2013;346:f807.

[22] Office for National Statistics. *Alcohol-specific deaths in the UK: registered in 2016*. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/alcoholrelateddeathsintheunitedkingdom/registeredin2016 .

[23] NHS Digital. *Statistics on alcohol, England, 2017.* https://digital.nhs.uk/catalogue/PUB23940

[24] Bouttell J, Lewsey J, Geue C, et al. *The Scottish Alcoholic Liver disease Evaluation: A population-level matched cohort study of hospital-based costs,* 1991-2011. PLoS One. 2016;**11**:e0162980.

[25] Hart CL, Morrison DS, Batty GB, *Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies.* BMJ 2010;340.

[26] Trembling, P, Apostoildou, S, Gentry-Maharaj A. *Risk of chronic liver disease in post-menopausal women due to body mass index, alcohol and their interaction: a prospective nested cohort study within the United Kingdom Collaborative Kingdom Collborative Trial of Ovarian Cancer Screening (UKCTOCS).* BMC Public Health. 2017;**17:**603

[27] Stal P. *Liver fibrosis in non-alcoholic fatty liver disease - diagnostic challenge with prognostic significance.* World J Gastroenterol. 2015;21(39):11077-87.

[28] Shah VH*. Managing alcoholic liver disease*. Clin Mol Hepatol. 2015;**21**:212-9.

[29] Dugum M, McCullough A. *Diagnosis and management of alcoholic liver disease*. J Clin Transl Hepatol. 2015**;3:**109-16.

[30] Williams R, Aspinall R, Bellis M, et al. *Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis*. Lancet. 2014;**384**:1953-97.

A key difficulty lies in the accurate diagnosis of liver damage (fibrosis). The gold-standard test for many years was liver biopsy, but this is costly and invasive.[31] Primary care has relied on standard routine liver function tests, especially alanine transaminase (ALT), as markers of liver damage. These tests lack specificity and sensitivity for severe liver disease and have limited prognostic value in identifying individuals at an earlier stage of fibrosis who will go on to develop cirrhosis.[32,33,34] However, they give some indication of liver health at a population level: they have been used in national surveys,[35] and they are used to calculate some diagnostic indices of liver disease (e.g. Fib-4[36]).

Methods and definitions

Methods

Self-reported data

Questions on kidney and liver disease were asked during the nurse interview to all adults aged 16 and over. These consisted of the following questions:

- Have you ever been told by a doctor that you had chronic kidney disease?
- Have you ever been told you were being tested for kidney disease?
- Have you ever been told by a doctor or health professional that you are at risk of kidney disease?

The same questions were asked about chronic liver disease.

Measurement of biological markers for renal function

Non-fasting blood samples and mid-flow urine samples were obtained from adults who gave written consent at the nurse visit. These were posted to the Blood Sciences Department at the Royal Victoria Infirmary (RVI), Newcastle-upon Tyne.

For non-fasting blood, samples in a plain (no anti-coagulant) tube were used for analyses. These were spun, separated and creatinine and cystatin C were measured in the serum, using internationally standardised enzymatic methods.

Albumin and creatinine concentrations were measured from spot urine samples.

[31] Kobyliak N, Dynnyk O, Abenavoli L. *The role of liver biopsy to assess alcoholic liver disease.* Rev Recent Clin Trials. 2016;**11**:175-9.

[32] Sheron N, Moore M, Ansett S, et al. *Developing a 'traffic light' test with potential for rational early diagnosis of liver fibrosis and cirrhosis in the community.* Br J Gen Pract. 2012;**62**:e616-24.

[33] McLernon DJ, Donnan PT, Sullivan FM, et al. *Prediction of liver disease in patients whose liver function tests have been checked in primary care: model development and validation using population-based observational cohorts.* BMJ Open. 2014;**4**:e004837.

[34] Lurie Y, Webb M, Cytter-Kuint R, et al. *Non-invasive diagnosis of liver fibrosis and cirrhosis.* World J Gastroenterol. 2015;**21**:11567-83.

[35] Clark JM, Brancati FL, Diehl AM *The prevalence and etiology of elevated aminotransferase levels in the United States.* Am Journal of Gastroenterol 2003 **98;**960–67.

[36] Li, Y, Chen Y. *The diagnostic value of the FIB-4 Index for staging hepatitis B-related fibrosis: A meta-analysis.* PLoS One. 2014 **9**:e105728.

Measurement of biological markers for liver disease

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured in the Blood Sciences Department at the RVI, using an optimised International Federation of Clinical Chemistry (IFCC) method, on a Roche Cobas 702 analyser.

Details of laboratory analysis, internal quality control, and external quality assurance for all these analytes are provided in the Methods report.[37] Responses to urine and blood samples can also be found in that report.

Definitions

Doctor-diagnosed kidney disease

Participants who answered 'yes' to the question 'Have you ever been told by a doctor that you had chronic kidney disease?' were defined as having doctor-diagnosed kidney disease.

Renal function

Two methods were used to assess renal function; through the estimated glomerular filtration rate (eGFR), a measure of how efficiently the waste product creatinine is filtered from the blood, and albuminuria, which is the presence of albumin (a protein) in the urine.

The estimated glomerular filtration rate (eGFR)
An eGFR can be calculated using either serum creatinine or cystatin C (referred to as $eGFR_{creat}$ and $eGFR_{cys}$ respectively). $eGFR_{creat}$ is generally used as the measure to assess renal function, however under certain conditions, it is recommended to use $eGFR_{cys}$ (see definition of 'chronic kidney disease' below for more information). The eGFR is a better estimate of kidney function than serum creatinine on its own, as eGFR takes into account factors that will influence higher levels of creatinine such as older age, sex, muscle mass, and ethnicity.

In this report, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate the eGFR.[38,39] This equation is considered more

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[37] HSE 2016 Methods, available on the HSE 2016 report website https://digital.nhs.uk/pubs/hse2016.

[38] A correction factor is applied to the CKD-EPI equation for $eGFR_{creat}$, for people of African-Caribbean or African family origin, consisting of a multiplication of 1.159.

The CKD-EPI equation for $eGFR_{creat}$ is as follows:

$\mathbf{eGFR_{creat}} = 141 * \min(S_{cr}/\kappa,1)^{\alpha} * \max(S_{cr}/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if Black]

S_{cr}: Serum creatinine (mg/dL)

κ is 0.7 for females, and 0.9 for males

α = -0.329 if female

α = -0.411 if male

The CKD-EPI equation used to calculate eGFRcys is as follows:

$\mathbf{eGFR_{cys}} = 133 \times \min(S_{cys}/0.8, 1)^{-0.499} \times \max(S_{cys}/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932$ [if female]

S_{cys}: Cystatin C

min = The minimum of $S_{cys}/0.8$ or 1

max=The maximum of $S_{cys}/0.8$ or 1

[39] Björk, J, Grubb, A, Larsson, A et al. *Accuracy of GFR estimating equations combining standardized cystatin C and creatinine assays: a cross-sectional study in Sweden.* Clin Chem Lab Med 2015;**53**:403-14.

accurate than the Modification of Diet in Renal Diseases (MDRD) equation, which may over-diagnose chronic kidney disease.[40] The MDRD equation was used in the previous kidney disease and renal function chapters using HSE 2009/10 data, as it was being used widely at the time. The results for HSE 2016 are therefore not directly comparable with those in the HSE 2009 or 2010 reports.[41]

The eGFR was categorised into 90+ ml/min/1.73m^2, which is considered normal, and 60-89 ml/min/1.73m^2, 30-59 ml/min/1.73m^2 and less than 30 ml/min/1.73m^2. The eGFR decreases with increasing severity of kidney damage; anything below 60 ml/min/1.73m^2 was considered abnormal. Abnormal levels indicate kidney disease or acute kidney injury.

Albuminuria

Kidney disease is associated with higher levels of albumin in the urine. The presence of albumin in the urine was assessed using the albumin:creatinine ratio (ACR), which correlates well with 24 hour urinary albumin excretion. Non-sex-specific thresholds were used, in accordance with NICE guidelines.[40] Up to 3mg/mmol is considered normal. Abnormal levels are split into two groups. Micro-albuminuria is defined as small, though raised, excretion of albumin (3mg/mmol to 30mg/mmol). Macro-albuminuria is defined as more than 30mg/mmol. This differs from the previous HSE report in 2010, when sex-specific references were used to define normal and micro-albuminuria.[41]

Chronic Kidney Disease

Chronic kidney disease stage was assessed using combinations of the eGFR and the albumin:creatinine ratio (ACR), in accordance with NICE guidelines.[40] Serum creatinine is used to calculate an eGFR, however for participants with both an $eGFR_{creat}$ of 45-59ml/min/1.73m^2 and an ACR below 3mg/mmol (chronic kidney disease category G3a A1), cystatin C was used to calculate the eGFR, as recommended in NICE guidelines as it may prevent over classifying people as having chronic kidney disease. Among these participants, an $eGFR_{cys}$ of 60ml/min/1.73m^2 or above was considered normal.[42]

Due to small numbers, the four more severe stages of chronic kidney disease were combined into two groups: 3a/3b and 4/5. The stages of kidney failure and how they have been defined are outlined in Table A below, using 2002[43] and 2012[44] KDOQI definitions:

[40] NICE Clinical Guidance [CG182]. *Chronic kidney disease in adults: assessment and management.* Nice, 2015 https://www.nice.org.uk/guidance/cg182/chapter/1-recommendations

[41] Roth M, Roderick P, Mindell J. *Kidney disease and renal function.* Chapter 8 in Craig R, Mindell J (eds). *Health Survey for England 2010.* Health and Social Care Information Centre, Leeds, 2011. https://digital.nhs.uk/catalogue/PUB03023

[42] 6% of adults (n=198) had an $eGFR_{creat}$ of 45-59ml/min/1.73m^2 and normal albuminuria (chronic kidney disease category G3aA1) and so were reclassified using $eGFR_{cys}$. 39% of this group were reclassified as normal according to their $eGFR_{cys}$ level (n=78). One case only (1%) was reclassified into the more advanced stage 4/5, based on their $eGFR_{cys}$ level.

[43] KDOQI. *KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation Classification, and Stratification.* KDOQ1, 2002. http://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_ckd/index.htm

[44] Kidney Disease Improving Global Outcomes (KDIGO), see note 2.

Table A: Stages of kidney failure used in analysis

Stage[a]	Chronic kidney disease category[b]		Description
	eGFR	ACR[c]	
Normal/Low risk/No Chronic kidney disease	G1, G2	A1	eGFR 60ml/min/1.73m^2 or more and normal albuminuria
1	G1	A2, A3	eGFR 90ml/min/1.73m^2 or more and micro- or macro-albuminuria
2	G2	A2, A3	eGFR 60-89 ml/min/1.73m^2 and micro- or macro-albuminuria
3a/3b	G3a, G3b	A1, A2, A3	eGFR 30-59 ml/min/1.73m^2, regardless of albuminuria
4/5	G4, G5	A1, A2, A3	eGFR less than 30 ml/min/1.73m^2, regardless of albuminuria

a According to KDOQI 2002 classifications
b According to KDOQI 2012 classifications
c A1: Normal albuminuria; A2: Micro-albuminuria; A3: Macro-albuminuria

Doctor-diagnosed liver disease

Participants who answered 'yes' to the question 'Have you ever been told by a doctor that you had chronic liver disease?' were defined as having doctor-diagnosed liver disease.

Markers of liver damage

Raised levels of AST or ALT can be an indicator of liver damage. The reference range for normal from the RVI laboratory was 0-40 IU/L for men and women for both ALT and AST (as had been agreed with other laboratories in the North East). Raised levels were defined for this report as more than 1.5 times the upper limit of normal. Hence levels of AST or ALT over 60 IU/L (1.5 x 40 IU/L) were considered abnormal. As mentioned in the introduction, these tests lack specificity and sensitivity for liver disease, and are more effective as a diagnostic tool when used in combination with other factors,[45] however aminotransferase levels may give some indication of liver health, as has been used in other national surveys.[46]

Age-standardisation

Age-standardised data are presented in this report for some analyses shown in the text, tables and charts. Age-standardisation allows comparisons between groups after adjusting for the effects of any differences in their age distributions.

For regions, both observed and age-standardised data are provided. Those wishing to ascertain the actual levels of chronic kidney disease, for example, in each region should use the observed data, while those making comparisons between regions should use the age-standardised data. The comments on region in this report are based on age-standardised results.

[45] Giboney, P. *Mildly elevated liver transaminase levels in the asymptomatic patient.* Am Fam Physician. 2005;**71**(6):1105-10.

[46] Clark et al, see note 35.

Index of Multiple Deprivation

The English Indices of Deprivation 2015, which measure and rank local levels of deprivation, are calculated by the Department for Communities and Local Government. The indices are based on 37 indicators, across seven domains of deprivation.[47] The Index of Multiple Deprivation (IMD) is a measure of the overall deprivation experienced by people living in a neighbourhood.[48]

In this publication IMD rankings have been split into quintiles. The lowest quintile indicates the lowest levels of deprivation; the highest quintile indicates that the neighbourhood experiences the highest levels of deprivation. Not everyone who lives in a deprived neighbourhood will be deprived themselves.

About the survey estimates

The Health Survey for England, in common with other surveys, collects information from a sample of the population. The sample is designed to represent the whole population as accurately as possible within practical constraints, such as time and cost. Consequently, statistics based on the survey are estimates, rather than precise figures, and are subject to a margin of error, also known as a 95% confidence interval. For example the survey estimate might be 24% with a 95% confidence interval of 22% to 26%. A different sample might have given a different estimate, but we expect that the true value of the statistic in the population would be within the range given by the 95% confidence interval in 95 cases out of 100.

Where differences are commented on in this report, these reflect the same degree of certainty that these differences are real, and not just within the margins of sampling error. These differences can be described as statistically significant.[49]

Confidence intervals are quoted for key statistics within this report and are also shown in more detail in the Excel tables accompanying the Methods report. Confidence intervals are affected by the size of the sample on which the estimate is based. Generally, the larger the sample, the smaller the confidence interval, and hence the more precise the estimate.

[47] The seven domains used to calculate IMD are: income deprivation; employment deprivation; health deprivation and disability; education; skills and training deprivation; crime; barriers to housing and services; and living environment deprivation.

[48] Department for Communities and Local Government. *The English Indices of Deprivation 2015,* London, 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/465791/English_Indices_of_Deprivation_2015_-_Statistical_Release.pdf

[49] Statistical significance does not imply substantive importance; differences that are statistically significant are not necessarily meaningful or relevant.

Doctor-diagnosed chronic kidney disease

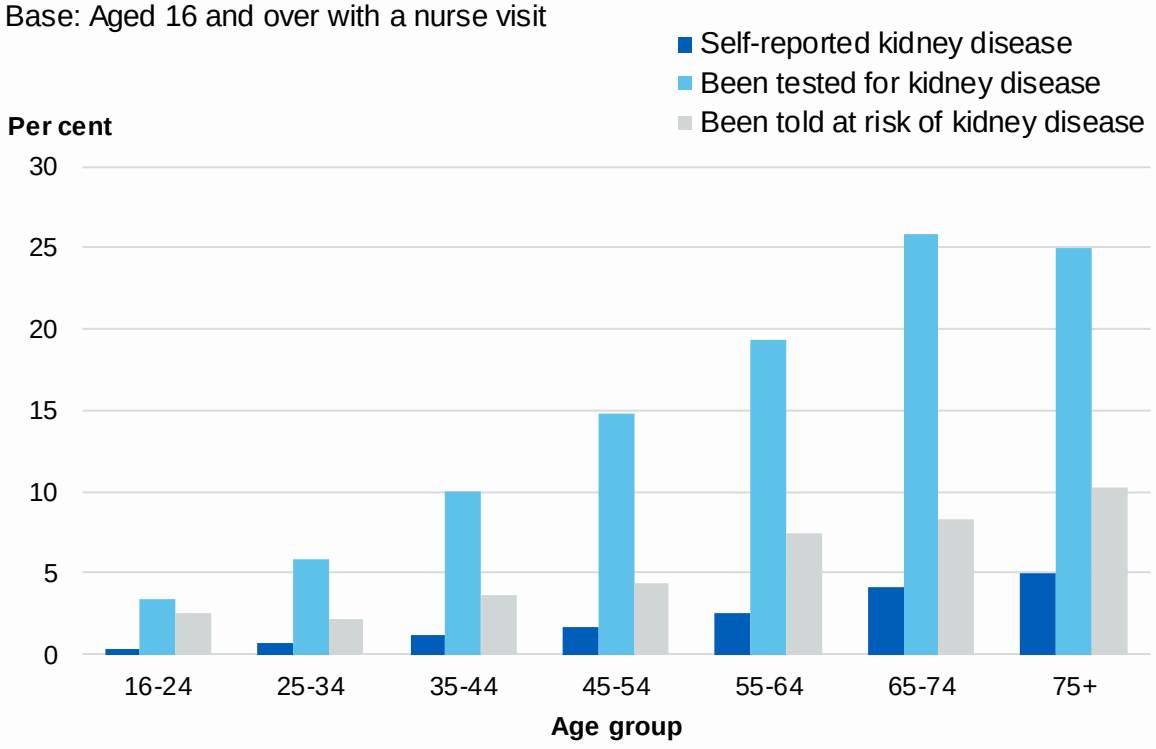
Testing for and diagnosis of chronic kidney disease, by age and sex

The prevalence of self-reported doctor-diagnosed chronic kidney disease was around 2% in both men and women. The prevalence was higher among older people, increasing from less than 0.5% among those aged 16 to 24 years to 5% in those aged 75 and over. The proportions who had been tested for kidney disease, or had been identified as being at risk of kidney disease also increased markedly with older age. 14% of adults reported having been tested for kidney disease, and 5% had been told they were at risk. Among adults aged 75 and over, these proportions were 25% and 10% respectively.

Figure 1, Table 1

Figure 1: Prevalence of self-reported doctor-diagnosed chronic kidney disease, having been tested for, and at risk, by age

Base: Aged 16 and over with a nurse visit



Source: NHS Digital

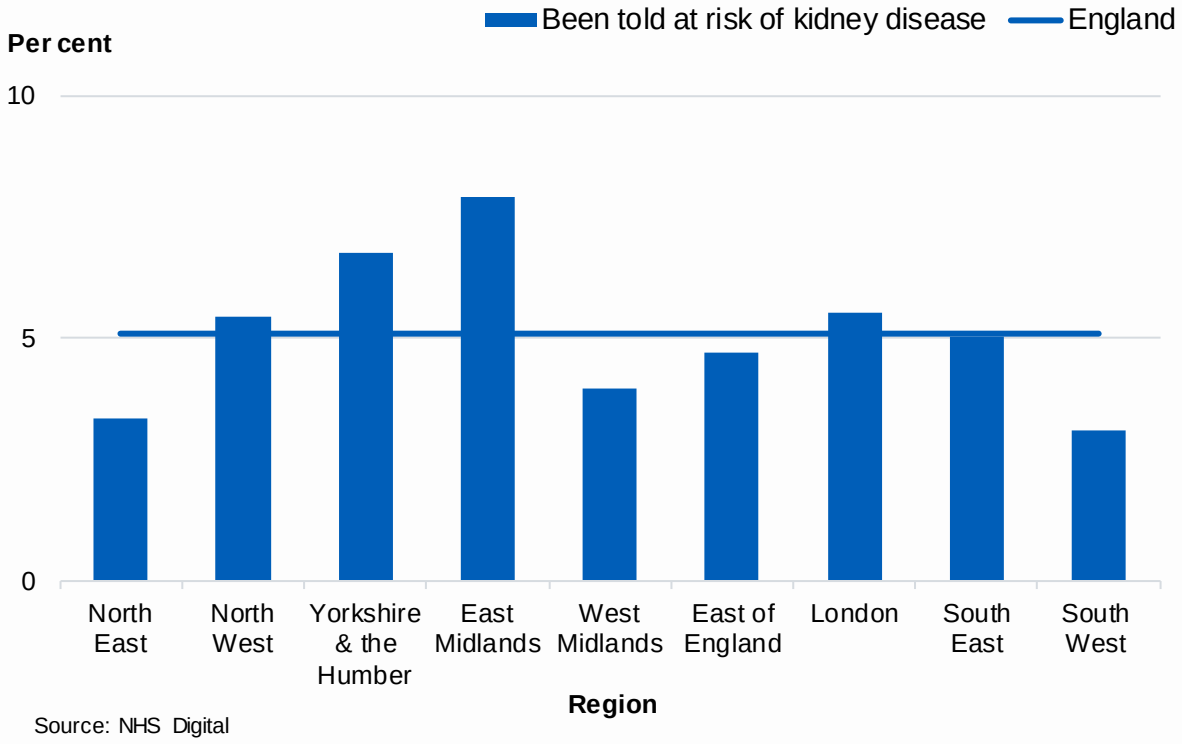
Testing for and diagnosis of chronic kidney disease, by region

The (age-standardised) proportion of participants that had been told they were at risk of kidney disease varied by region, being highest in the East Midlands (8%) and Yorkshire and the Humber (7%), and lowest in the North East and South West (3%). There were no statistically significant differences between regions in the proportions with doctor-diagnosed kidney disease or who had been tested for kidney disease: the apparent differences are within the margins of error which apply to this survey sample.

Figure 2, Table 2

Figure 2: Age-standardised prevalence of ever have been told at risk of kidney disease, by region

Base: Aged 16 and over with a nurse visit



Source: NHS Digital

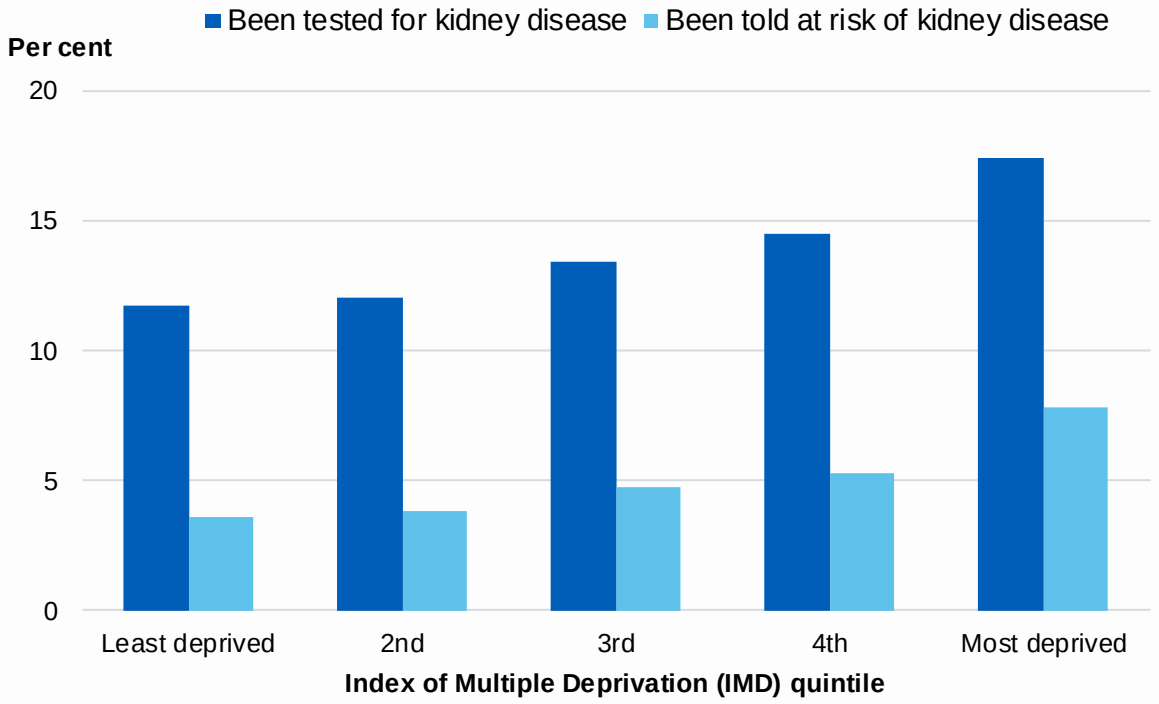
Testing for and diagnosis of chronic kidney disease, by Index of Multiple Deprivation (IMD)

The proportion of adults in the most deprived IMD quintile reporting that they had ever been told they were at risk of kidney disease was double the proportion in the least deprived IMD quintile (8% and 4% respectively). Having ever been tested for kidney disease was also higher in the most deprived compared with the least deprived quintile (17% and 12% respectively). The proportion with doctor-diagnosed chronic kidney disease was similar across IMD quintiles.

Figure 3, Table 3

Figure 3: Age-standardised prevalence of having been tested for, and ever been told at risk of kidney disease, by IMD

Base: Aged 16 and over with a nurse visit



Source: NHS Digital

Renal function and chronic kidney disease stage based on eGFR and urine albumin

Serum creatinine, $eGFR_{creat}$ and $eGFR_{cys}$ levels, by age and sex

Renal function, or how well the kidneys function, can be measured with various analytes. For an explanation of these survey analytes see the Methods and definitions section of this report.

As expected, mean serum creatinine was higher among men than women (91.2mmol/L and 71.6mmol/L respectively). Also as expected, mean serum creatinine increased with age, ranging from 76.5mmol/L in adults aged 16 to 24 years to 90.7mmol/L in those aged 75 years and over. Mean serum creatinine levels are known to be influenced by factors such as age, sex, muscle mass and ethnicity therefore the

eGFR, which takes account of these factors, is considered a more precise measurement of renal function than creatinine levels on their own.

Using $eGFR_{creat}$, 50% of adults had a normal eGFR (90ml/min/1.73m^2 or above) while 7% had an abnormal $eGFR_{creat}$ (less than 60ml/min/1.73m^2). The prevalence and severity of abnormal eGFR increased with age. Almost two in five adults (39%) aged 75 and over had an $eGFR_{creat}$ less than 60ml/min/1.73m^2, compared with none among adults aged 16 to 24. Survey estimates are subject to a margin of error. It is likely that the proportion of adults with an abnormal $eGFR_{creat}$ is between 6% and 8%, and the proportion among adults aged 75 and over is between 34% and 44%.

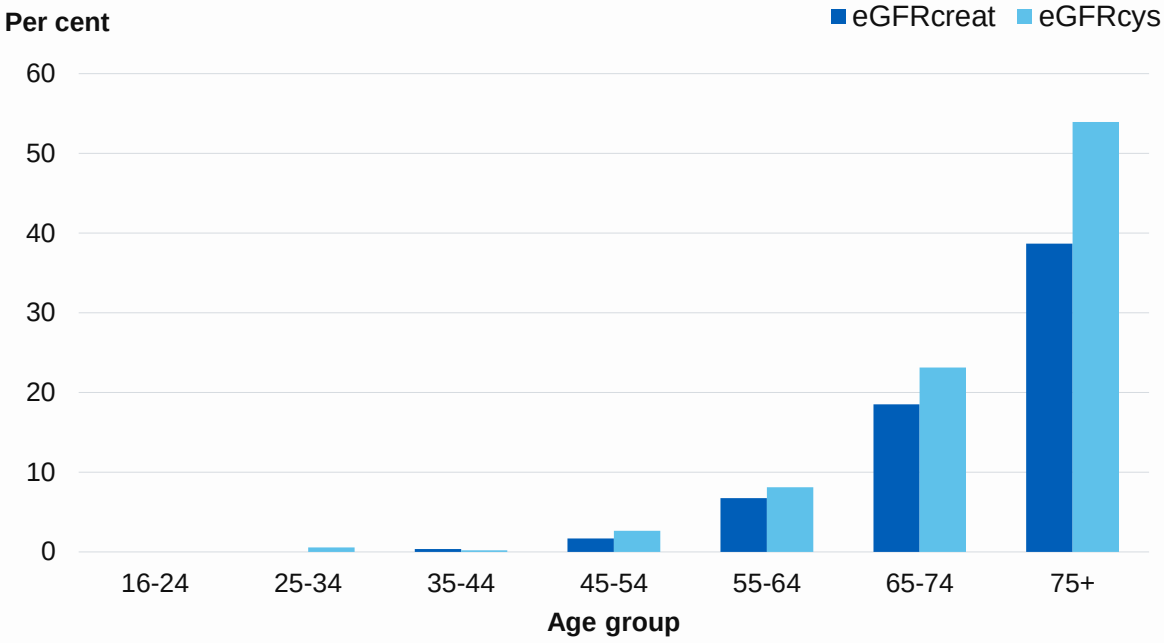
The $eGFR_{cys}$ categorised 8 percentage points more adults than did $eGFR_{creat}$ as having normal eGFR (90+ ml/min/1.73m^2): 58% compared with 50% respectively. However $eGFR_{cys}$ also categorised more adults as having an eGFR less than 60ml/min/1.73m^2, compared with $eGFR_{creat}$ (10% and 7% respectively).

The proportion with an $eGFR_{cys}$ less than 60ml/min/1.73m^2 was highest among those aged 75 and over (54%); this was higher than for $eGFR_{creat}$ (39%). There were no statistically significant differences by sex for either $eGFR_{creat}$ or $eGFR_{cys}$.

Figure 4, Table 4

Figure 4: Prevalence of abnormal eGFR levels (<60ml/min/1.73m^2), by age and eGFR analyte

Base: Aged 16 and over with a valid blood sample



Source: NHS Digital

Urine albumin excretion, by age and sex

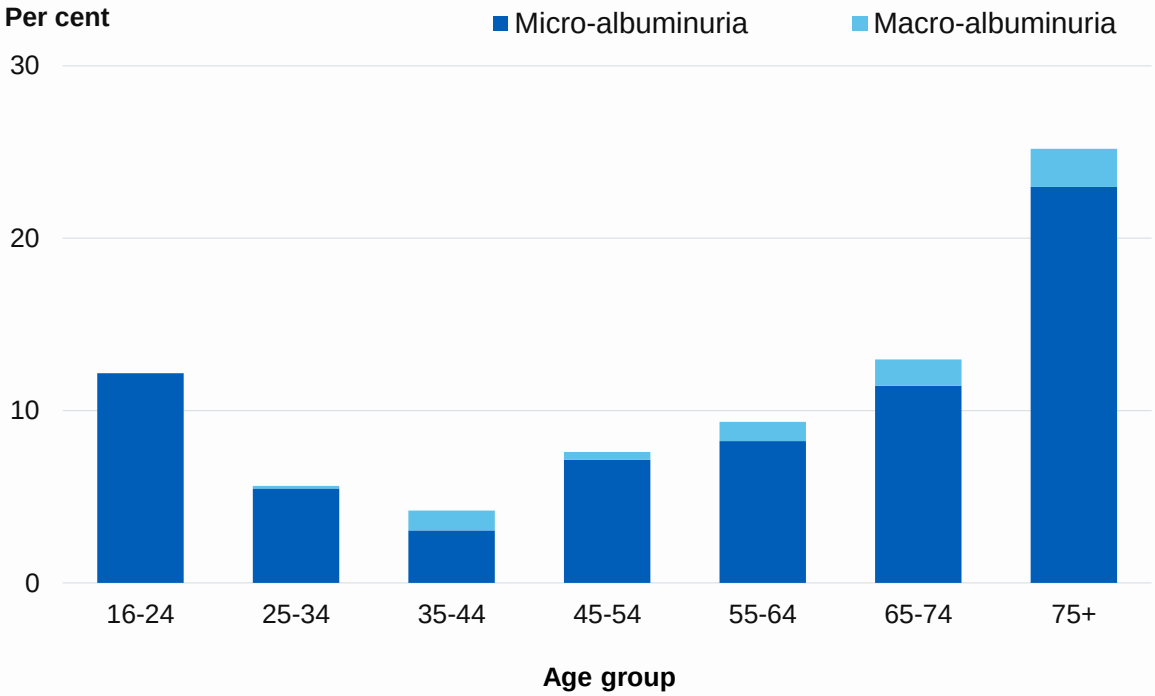
Excretion of abnormal quantities of albumin was found in 10% of adults, with this predominately being micro-albuminuria (9%) rather than macro-albuminuria (1%).

Abnormal levels of albumin were anomalously high among the youngest age groups, with 13% of men and 11% of women aged 16 to 24 having micro-albuminuria. Among young adults, and particularly in men, this may be due to orthostatic proteinuria (an increased excretion of urinary protein occurring when standing up, generally a benign condition, which is rare among those aged 30 and over), rather than renal disease.[50] Among younger women, the detected micro-albuminuria may also be due to contamination from menstruation. Abnormal levels of albumin otherwise increased with age and were highest among the oldest age group. Among those aged 75 and over, 23% had micro-albuminuria, and 2% had macro-albuminuria.

Figure 5, Table 5

Figure 5: Prevalence of abnormal urinary albumin excretion, by age

Base: Adults aged 16 and over with a valid urine sample



Source: NHS Digital

[50] UK Renal Association. *Clinical practice guidelines for the Detection, Monitoring and Care of Patients with Chronic Kidney disease.* 2011. https://renal.org/wp-content/uploads/2017/06/detection-monitoring-care-of-patients-with-ckd-5th-edition-1.pdf

Chronic kidney disease stage based on eGFR and urine albumin, by age and sex

A combination of eGFR levels and urinary albumin excretion status was used to calculate chronic kidney disease stage in accordance with NICE definitions (see Methods and Definitions section of the report). This analysis is restricted to adults aged 35 and over, because the estimated proportion with kidney disease stage 1 to 2 among younger adults (8%) is likely to be affected by high albuminuria in the youngest age group (16 to 24) due to reasons other than renal disease; see the previous section of this report for a discussion of this.

Among all adults aged 35 and over, 85% had normal kidney function and 15% had chronic kidney disease (stages 1 to 5);[51] 7% had the more severe chronic kidney disease stages 3 to 5. More women than men had kidney disease (stages 1 to 5) (17% and 12% respectively).

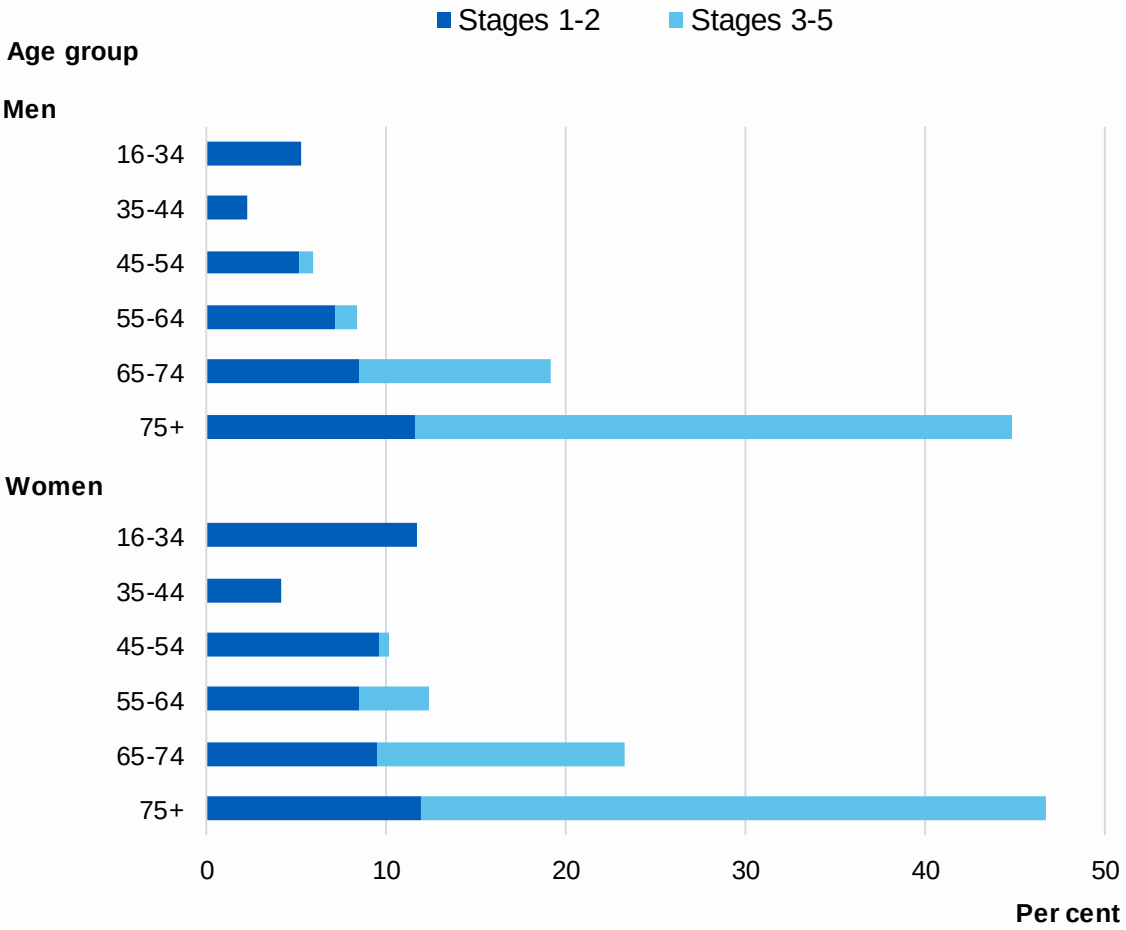
Prevalence and severity of chronic kidney disease stage increased with age. The proportion with chronic kidney disease stage 3 to 5 ranged from no measured cases among those aged under 44 to 12% in those aged 65 to 74 and 34% in those aged 75+. Among those aged 75 and over, 46% had any stage of kidney disease.

Figure 6, Table 6

[51] The relatively high proportion with kidney disease stage 1 to 2 in the young age group 16 to 34 (8%) is most likely due to high albuminuria in the youngest 16 to 24 age group due to reasons other than renal disease as detailed in section ‘Urine albumin excretion, by age and sex’ (Table 5).

Figure 6: Chronic kidney disease stage based on eGFR and urine albumin, by age and sex

Base: Adults aged 16 and over with valid blood and urine samples



Source: NHS Digital

Chronic kidney disease stage based on eGFR and urine albumin, by region and Index of Multiple Deprivation (IMD)

The prevalence of chronic kidney disease was similar across regions and IMD quintiles. The apparent differences are within the margins of error which apply to this survey sample.

Tables 7 and 8

Chronic kidney disease stage (based on eGFR and urine albumin), by doctor-diagnosed chronic kidney disease

Among adults aged 35 and over with no self-reported doctor-diagnosed kidney disease, 14% had chronic kidney disease (any kidney disease stage 1 to 5), and 6% the more severe chronic kidney disease stages 3 to 5, based on their eGFR and

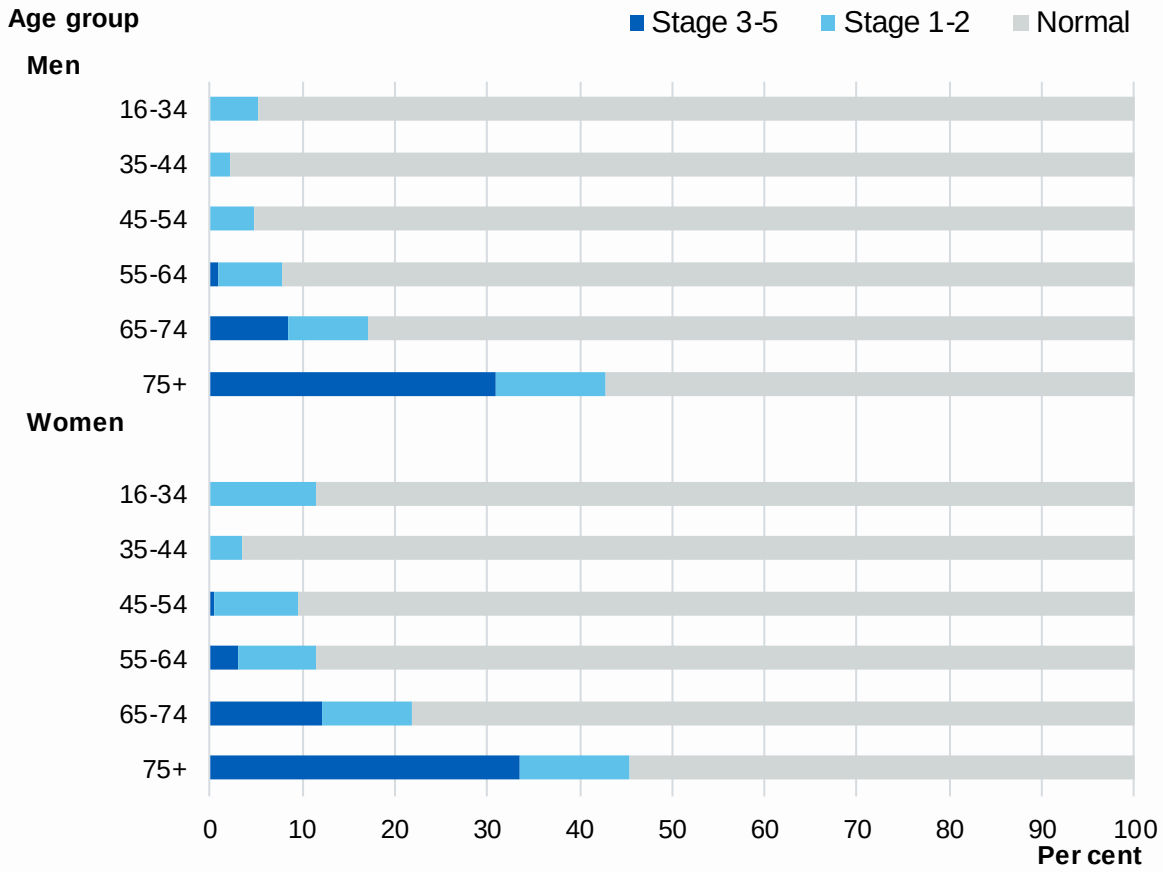
urinary albumin levels. [52,53] Among those aged 35 and over with no doctor diagnosis, the proportion with chronic kidney disease stage 3 to 5 was higher among women (7%) than men (5%), and increased with age.

Among adults aged 65 to 74 who did not report a doctor diagnosis, 20% had chronic kidney disease stages 1 to 5, rising to 44% among adults aged 75 and over. The severity of the disease was also higher among older age groups; 32% of those aged 75 and over had chronic kidney disease stages 3 to 5 despite reporting no doctor diagnosis, compared with none among those aged 16 to 44.

Figure 7, Table 9

Figure 7: Chronic kidney disease (CKD) stage based on eGFR and urine albumin, among those with no reported doctor diagnosis, by sex and age

Base: Adults aged 16 and over with no doctor-diagnosed CKD and valid blood and urine samples



Source: NHS Digital

[52] There are two definitions of being undiagnosed. The standard definition is 'of those with disease according to objective data, what percentage do not report diagnosed disease'. These results are presented in Table 10.

There is an alternative definition (given by Chatterji et al.), which is 'of those who do not report diagnosed disease, what proportion have the disease according to objective criteria'. Table 9 presents results using this alternative definition.

Chatterji P, Joo H, Lahiri K. *Examining the education gradient in chronic illness*. Education Economics. 2015;**23**:735-750.

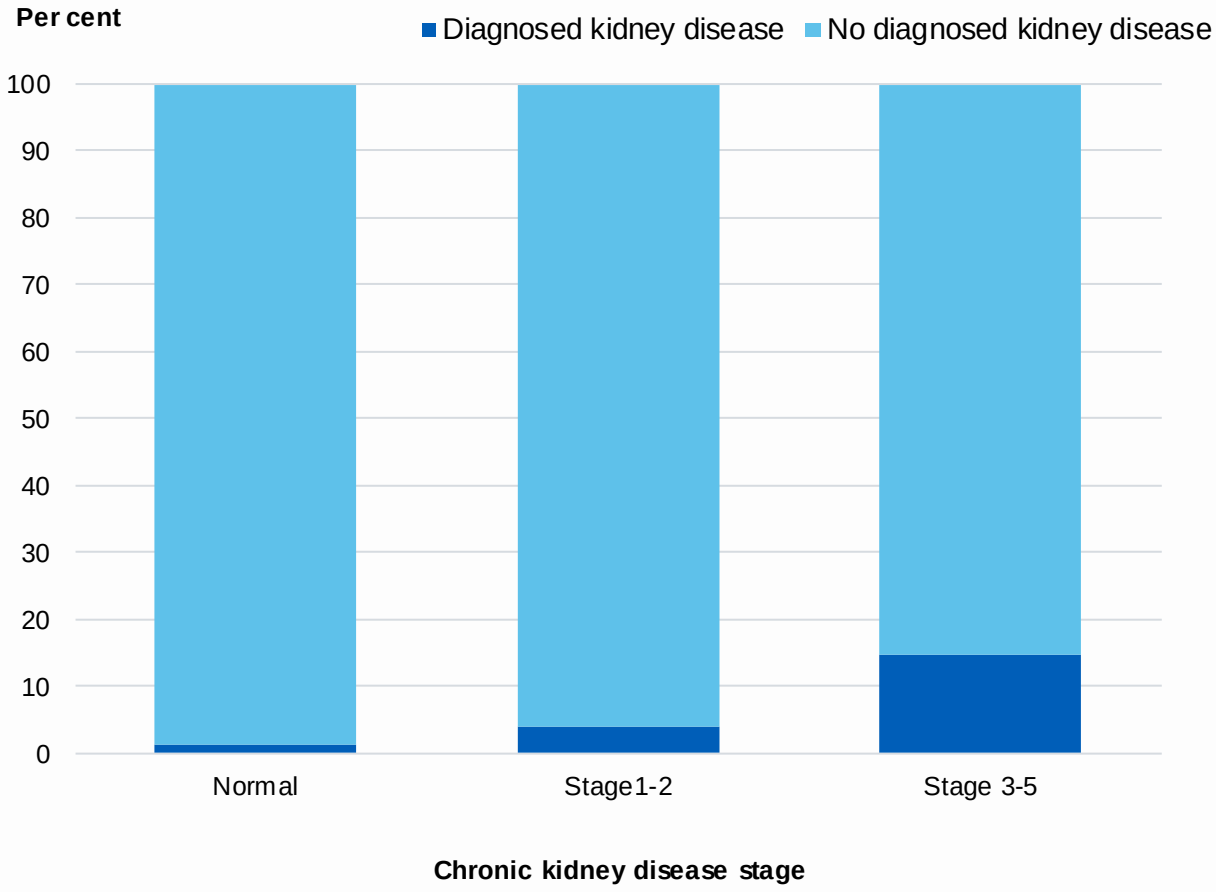
[53] Chronic kidney disease stages 1 to 2 among those aged 16 to 34 who did not report a doctor diagnosis was relatively high due to high prevalence of albuminuria in those aged 16 to 34, as detailed in section 'Urine albumin excretion, by age and sex' (Table 5), rather than probable renal disease.

Among adults aged 35 years and over, only 4% with chronic kidney disease stages 1 to 2 and 15% in stages 3 to 5, based on eGFR and urine albumin levels, reported being diagnosed. 11% of adults with chronic kidney disease stage 1 to 2 and 23% in stages 3 to 5 had been told they were at risk of kidney disease.

Figure 8, Table 10

Figure 8: Prevalence of self-reported doctor-diagnosed kidney disease, by chronic kidney disease stage based on eGFR and urine albumin

Base: Adults aged 35 and over with valid blood and urine samples



Source: NHS Digital

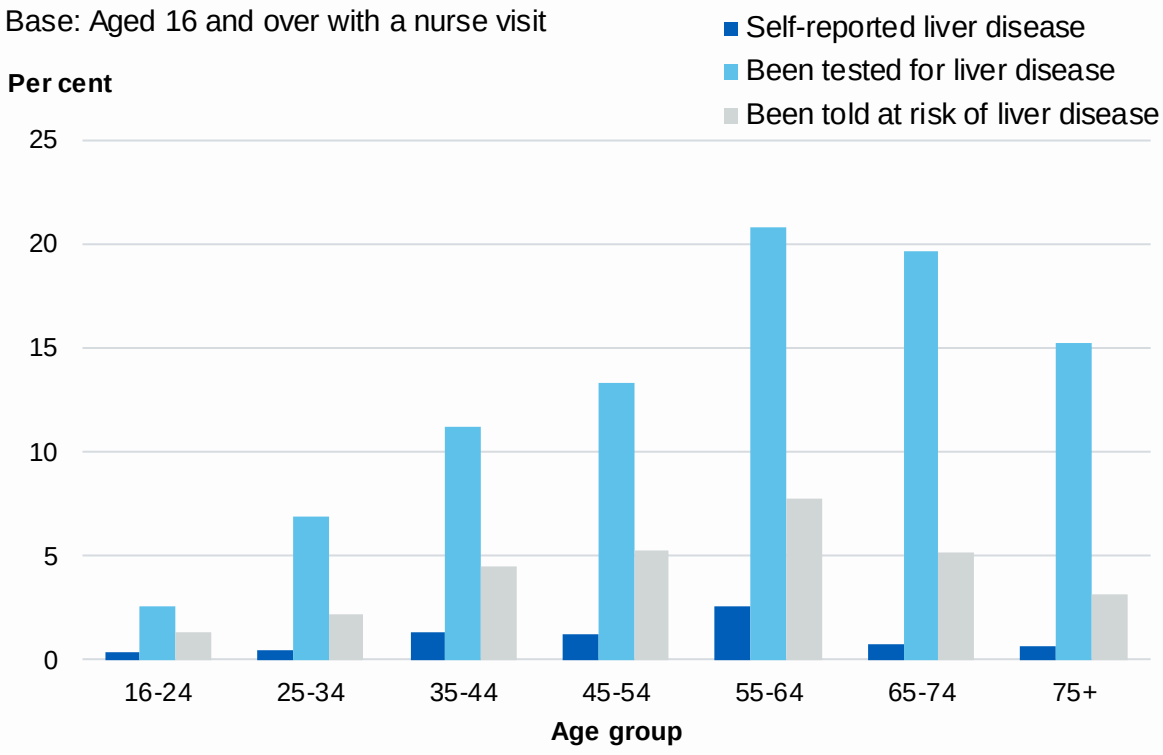
Liver disease

Testing for and diagnosis of liver disease, by age and sex

Among adults, 1% reported having doctor-diagnosed liver disease. This varied by age, peaking in the 55 to 64 age group where it was 3%, levelling off at 1% for older age groups. Having been tested for liver disease and ever been identified as at risk of liver disease followed a similar pattern by age, also peaking in the 55 to 64 age group. Among all adults, 12% reported being tested for liver disease, and 4% reported ever having been told they were at risk; among adults aged 55 to 64 these proportions were 21% and 8% respectively.

Figure 9, Table 11

Figure 9: Prevalence of self-reported doctor-diagnosed chronic liver disease, having been tested for, and at risk, by age



Source: NHS Digital

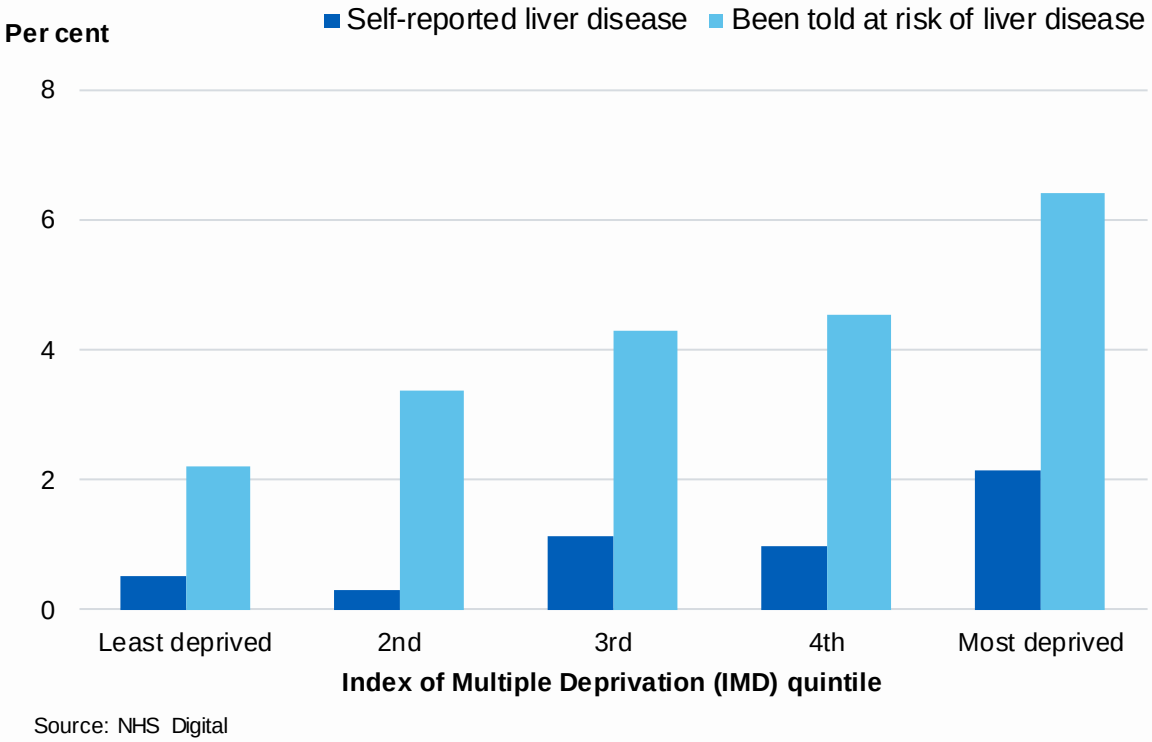
Testing for and diagnosis of liver disease, by Index of Multiple Deprivation (IMD)

The proportion of adults with doctor-diagnosed liver disease in the most deprived quintile (2%) was higher than in the two least deprived quintiles (less than 1%). Being told they were at risk of liver disease was also higher in the most deprived quintile (6% of adults) compared with the least deprived quintile (2%). The proportions who had been tested for liver disease were similar across IMD quintiles.

Figure 10, Table 12

Figure 10: Prevalence of self-reported doctor-diagnosed chronic liver disease, and at-risk of liver disease, by IMD

Base: Aged 16 and over with a nurse visit



Source: NHS Digital

Prevalence of abnormal aspartate transaminase (AST), alanine transaminase (ALT), by age and sex

For an explanation of the survey analytes and their relationship to liver disease see the Methods and definitions section of this report.

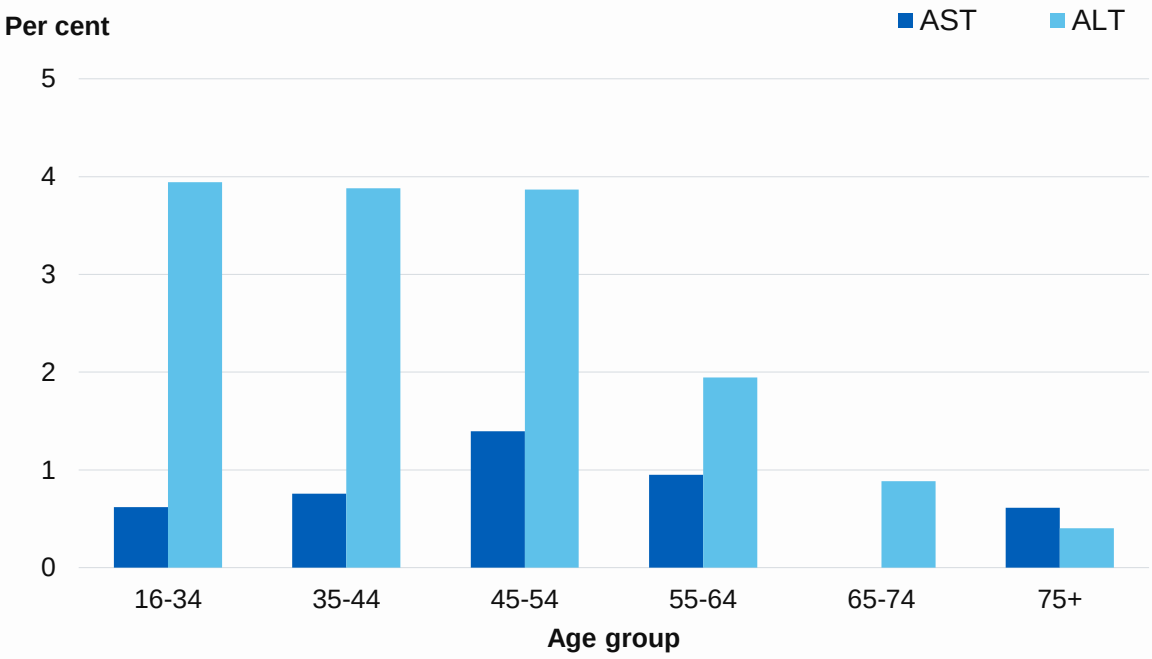
Among all adults, less than 1% had an AST>60 U/L (above 1.5 times the upper limit of normal). As explained in the Introduction to this report, survey estimates are subject to a margin of error. It is likely that the proportion of adults in the population whose AST was greater than 60 U/L is between 0.5% and 1.1%. The proportion with AST>60 U/L varied with age, and was at similar levels for men and women.

A higher proportion of adults (3%) had an ALT>60 U/L (above 1.5 times the upper limit of normal). It is likely that the proportion of adults in the population whose ALT was greater than 60 U/L is between 2% and 4%. This proportion was higher among men (4%) than women (2%). The proportion for men is likely to be between 3% and 6%, and for women 1% to 2%. The prevalence was highest amongst those aged under 55, declining with age thereafter.

Figure 11, Table 13

Figure 11: Prevalence of AST> 60U/L and ALT >60U/L (1.5 x the upper limit of normal), by age

Base: Aged 16 and over with a valid blood sample



Source: NHS Digital

Discussion

Kidney disease

Prevalence and severity of chronic kidney disease

Using participants' eGFR levels and urinary albumin to define chronic kidney disease stage, 13% of adults had any chronic kidney disease (Stages 1 to 5), similar to the global prevalence of 13.4% for any chronic kidney disease stage, according to a systematic review and meta-analysis.[54] In HSE 2016, 5% had chronic kidney disease stages 3 to 5 but the estimated global prevalence of chronic kidney disease in stages 3 to 5 was 10.6%, a value considered surprisingly high by many experts. A factor influencing this difference in the prevalence of more severe disease may be the use of a general sample of adults aged 16 and over within HSE, as well as other potential differences in the population representativeness of studies, standardisation for age and sex, and underlying risks including ethnic mix and levels of diabetes, as well as potential variations in assays used. Among older people in England, prevalence of chronic kidney disease stages 3 to 5 was much higher than in younger people; for example, 34% of those aged 75 and over had chronic kidney disease stages 3 to 5, compared with none among those aged 16 to 44. However, Hill et al[54] found that samples limited to older populations did not significantly change pooled estimates in sensitivity analyses in their international meta-analysis.

Data from the General Practice Pay for Performance Quality Outcomes Framework (QOF), which is based on patients at GP practices in England, estimated the prevalence of chronic kidney disease (eGFR<60ml/min/1.73m^2, equivalent to chronic kidney disease stage 3 to 5) to be 4.1%.[55] This was near to the prevalence of self-reported doctor-diagnosed kidney disease (no specified stage) in HSE at 2% when taking into account that the HSE estimate is subject to a margin of error due to sampling and definitional differences. The QOF estimate is based on GP practice registers of patients aged 18 and over,[55] whereas HSE data are based on the general population aged 16 and over. There may also be low level of awareness of diagnosis in the population. A study in the US found that awareness among patients of having the disease was below 40%, even among those with CKD stage 4.[56]

A strength of these HSE analyses is the ability to use $eGFR_{cys}$, in accord with NICE guidance. 6% of the population with a valid blood and urine sample had an $eGFR_{creat}$ of 45-59ml/min/1.73m^2 and normal albuminuria (chronic kidney disease category G3a A1): among these, 39% were reclassified as 'normal' following the use of $eGFR_{cys}$. This would reaffirm the benefit of using cystatin C in these cases, preventing over-diagnosis and hence reducing disease management costs. One case only (1%) was reclassified into the more advanced stages 4 to 5; the proportion reclassified from stage 3a to 3b is not presented here due to these groups being aggregated. In a different study, the use of $eGFR_{cys}$ resulted in over-classification of people in more advanced stages, which would require more frequent monitoring, outweighing a

[54] Hill, N, Fatoba, S, Oke, J L et al. *Global prevalence of chronic kidney disease – a systematic review and Meta-Analysis.* PLoS One 2016 **11**:e0158765.

[55] NHS Digital *Quality and Outcomes Framework – Prevalence, Achievements and Exceptions Report England 2016-17.* http://digital.nhs.uk/catalogue/PUB30124

[56] Platinga L, Delphine, S, Neil R. Powe. *Awareness of chronic kidney disease among patients and providers.* Adv Chronic Kidney Dis. 2010:03:002.

potential benefit.[57] While $eGFR_{cys}$ categorised more adults as normal than $eGFR_{creat}$ in this report, it also categorised a higher proportion of those with <60ml/min/1.73m^2 particularly in the oldest age group (54% among adults aged over 75 using $eGFR_{cys}$ compared with 39% using $eGFR_{creat}$). Therefore the use of cystatin C may not be straightforward.

Sex and socio-economic variations in chronic kidney disease

HSE 2016 survey measurements found that in England, more women (15%) than men (10%) had any chronic kidney disease stage. This is consistent with findings elsewhere.[58] This difference existed, despite applying a correction factor for women in the eGFR equations, as in general women have lower muscle mass than men, which contributes to lower serum creatinine concentrations. Differences between men and women are also somewhat inconsistent. Data from the UK Renal Registry has consistently found substantially more men than women starting renal replacement therapy in every age group,[59] but there were no differences in reporting a doctor diagnosis of chronic kidney disease by sex (2%) in HSE 2016, while another study found similar risk levels for men and women of end stage renal disease for any given GFR and ACR level.[60] The reasons for sex differences in chronic kidney disease, including the more advanced stages, are not fully understood and require further research.

Across IMD quintiles, the prevalence of self-reported doctor-diagnosed chronic kidney disease and of chronic kidney disease stage based on eGFR and urine albumin levels were similar and apparent differences were within margins of error for this sample (not statistically significant). However, other studies have demonstrated an association between low socioeconomic position and chronic kidney disease, including higher renal replacement therapy rates.[61,62] This could be due to using area (IMD) rather than individual characteristics, such as income or education, or because of the smaller numbers tested in HSE 2016.[63]

However, having been tested or ever been told they were at risk of kidney disease did vary by deprivation. Twice as many HSE participants in the most deprived quintile reported having been told by a doctor or a health physician that they were at risk of kidney disease than in the least deprived quintile. This is likely to be due to risk factors such as diabetes and hypertension being more prevalent in more deprived areas. Due to small numbers in the sample, the relationship between ethnicity and chronic kidney

[57] Roderick, P et al. *The clinical utility and cost impact of cystatin C measurement in the diagnosis and management of chronic kidney disease: A primary care cohort study.* PLoS Med. 2017 Oct 10;14(10):e1002400. doi: 10.1371 https://www.ncbi.nlm.nih.gov/pubmed/29016597

[58] Hill et al, see note 54.

[59] Casjet F, Castledine C, Dawnay A et al. *UK Renal Registry – 18th Annual Report.* The Renal Association, 2015. www.renalreg.org/wp-content/uploads/2015/01/web_book_07-04-16.pdf

[60] Nitsch, D Grams, D, Sang Y et al. *Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis.* BMJ. 2013;346:f234.

[61] Roderick, P, Hollinshead, J, O'Donoghue D et al. *Health inequalities and chronic kidney disease in adults.* NHS. 2011. http://webarchive.nationalarchives.gov.uk/20111108145535/http://www.kidneycare.nhs.uk/Library/CKD_Inequalities_Report_web.pdf

[62] Shoham, DA, Vupputuri, S, Diez Roux, A et al. *Kidney disease in life-course socioeconomic context: the Antheroscelrosis Risk in Communities (ARIC) Study.* Am J Kidney Dis. 2007;**49**:217-46.

[63] Fraser, S, Aitken, G, Maarten W, T et al. *Exploration of Chronic Kidney Disease prevalence estimates using new measures of kidney function in the Health Survey for England.* 2015 PLoS One. **10**:e0118676.

disease was not explored, although the incidence rate of starting renal replacement therapy for end-stage renal disease is higher among ethnic minorities.[64]

Methodological considerations

NICE guidance defines chronic kidney disease as 'abnormalities of kidney function or structure present for more than 3 months', and an eGFR less than 60ml/min/1.73m^2 on at least two occasions spread over at least 90 days.[65] However in HSE 2016, as with all health surveys, only a single sample was tested, therefore the persistence and extent of reduced eGFR levels cannot be assessed. Similarly, only a single sample of urine was tested; about two thirds of people with a single raised albumin:creatinine ratio (ACR) will have persistently raised ACR. Retesting would be particularly helpful in young people, given the high proportion with microalbuminuria. Taking this into account and that repeated testing may result in extreme values being averaged out (regression to the mean), this may result in HSE data yielding a slight overestimate of chronic kidney disease. Nonetheless, the use of a large, nationally representative sample of individuals living in private households provides a good approximation to levels of chronic kidney disease in the general population. Conversely, severe levels of chronic kidney disease (stages 4 and 5) may be underestimated due to non-response to the survey, particularly from those with kidney disease who were unable to provide blood and urine samples due to poor health or hospitalisation, or those in residential care who are not included in the HSE sample.

Awareness of having chronic kidney disease

In HSE 2016, 2% of men and women aged 16 and over reported a doctor diagnosis of chronic kidney disease, which is slightly higher than in in the 2009/2010 report (1%).[66] However, the proportion of adults with an abnormal eGFR less than 60ml/min/1.73m^2 was also higher in HSE 2016 than HSE 2009/2010[67] (7% compared with 5% using $eGFR_{creat}$), therefore it is difficult to assess whether diagnosis and awareness of a diagnosis have increased in line with increasing prevalence of kidney disease. As in HSE2009/2010, a high proportion of chronic kidney disease was not reported as being diagnosed, with 85% of adults aged 35 and over with chronic kidney disease stage 3 to 5 based on eGFR and urine albumin levels not reporting a doctor diagnosis. This was predominately people with chronic kidney disease stage 3, with the initial stage 3a presenting no symptoms, which may be a factor in influencing low awareness. Low level of diagnosis is a known area of concern, prompting Kidney Research UK's 'Missing Millions' campaign, referring to the millions of people with undiagnosed kidney disease.[68]

Given the public health importance of chronic kidney disease, robust surveillance data are needed to assess the impact of policy and practice initiatives; to inform the planning of health care services; and to highlight the case, and generate hypotheses, for further research. The HSE series provide a robust method of achieving this. The data reported here enable assessment of patterns in chronic kidney disease

[64] Casjet F, et al, See note 59.

[65] NICE Clinical Guidance [CG182]. *Chronic kidney disease in adults: assessment and management.* Nice, 2015 https://www.nice.org.uk/guidance/cg182/chapter/1-recommendations

[66] Roth M, Roderick P, Mindell J. *Kidney disease and renal function.* Chapter 8 in Craig R, Mindell J (eds). *Health Survey for England 2010.* Health and Social Care Information Centre, Leeds, 2011. https://digital.nhs.uk/catalogue/PUB03023

[67] Fraser et al, see note 63.

[68] Kidney Research UK. https://www.kidneyresearchuk.org

prevalence over time to monitor the impact of trends in both underlying causal factors and policy initiatives. There are international efforts to monitor, prevent and treat non-communicable diseases; these HSE findings can contribute to European and global surveillance of chronic kidney disease.

Liver disease

This is the first time that there has been a nationally-representative survey of liver disease. The proportion with doctor-diagnosed liver disease in the population was low, at 1%. There are no robust markers of population prevalence of chronic liver disease so it is difficult to assess how well this survey reflects true prevalence. The low value may be due both to under-presentation to health care and to under-diagnosis, possibly due to stigma associated with alcohol misuse (and under-representation of such individuals in HSE) and uncertainty of the significance of labelling abnormal routine liver function test results in those with metabolic risk factors such as obesity. Using AST and ALT, the proportions with raised levels (more than 1.5 times the upper limit of normal) were 1% and 3% respectively. This largely comprised adults without a doctor diagnosis.[69] Whilst this may suggest that a substantial proportion of liver damage in the population is undiagnosed, raised AST and ALT may not be useful indicators of liver damage on their own in a mostly healthy population.[70] The age profile of abnormal tests showed highest levels in a younger age group than the pattern of severe liver disease in the population. To understand more about chronic liver disease prevalence in England, further studies are needed with more robust non-invasive indices (e.g. Fib-4)[71] and markers of liver fibrosis (e.g. Enhanced Liver Fibrosis score, ELF),[72] and their relationship to liver risk factors such as obesity, diabetes, alcohol consumption and socioeconomic status.

[69] 29 out of 30 adults with AST>60U/L did not report a doctor-diagnosed chronic liver disease. 86 out of 87 adults with ALT>60U/L did not report a doctor-diagnosed chronic liver disease. Data not presented in tables due to small base sizes.

[70] Giboney, P. *Mildly elevated liver transaminase levels in the asymptomatic patient.* Am Fam Physician. 2005;**71**(6):1105-10.

[71] Li, Y, Chen Y. *The diagnostic value of the FIB-4 Index for staging hepatitis B-related fibrosis: A meta-analysis.* PLoS One. 2014 **9**:e105728.

[72] Lichtinghagen R1, Pietsch D, Bantel H, et al. *The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values.* J Hepatol. 2013;**59**:236-42.

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