13. De Smet R, Van Kaer J, Van Vlem B *et al*. Toxicity of free p-cresol: a prospective and cross-sectional analysis. *Clin Chem* 2003; 49: 470–478
14. Meijers BK, Bammens B, De Moor B *et al*. Free p-cresol is associated with cardiovascular disease in hemodialysis patients. *Kidney Int* 2008; 73: 1174–1180
15. Bammens B, Evenepoel P, Keuleers H *et al*. Free serum concentrations of the protein-bound retention solute p-cresol predict mortality in hemodialysis patients. *Kidney Int* 2006; 69: 1081–1087
16. de Loor H, Bammens B, Evenepoel P *et al*. Gas chromatographic-mass spectrometric analysis for measurement of p-cresol and its conjugated metabolites in uraemic and normal serum. *Clin Chem* 2005; 51: 1535–1538
17. Schepers E, Meert N, Glorieux G *et al*. P-cresylsulphate, the main in vivo metabolite of p-cresol, activates leucocyte free radical production. *Nephrol Dial Transplant* 2007; 22: 592–596
18. Meijers BK, Van Kerckhoven S, Verbeke K *et al*. The uraemic retention solute p-cresyl sulfate and markers of endothelial damage. *Am J Kidney Dis* 2009; 54: 891–901
19. Meert N, Eloot S, Waterloos MA *et al*. Effective removal of protein-bound uraemic solutes by different convective strategies: a prospective trial. *Nephrol Dial Transplant* 2009; 24: 562–570
20. Stevens LA, Coresh J, Schmid CH *et al*. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 2008; 51: 395–406
21. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39: S1–S266
22. Zureik M, Temmar M, Adamopoulos C *et al*. Carotid plaques, but not common carotid intima-media thickness, are independently associated with aortic stiffness. *J Hypertens* 2002; 20: 85–93
23. Asmar R, Benetos A, Topouchian J *et al*. Assessment of arterial distensibility by automatic pulse wave velocity measurement. *Validation and clinical application studies. Hypertension* 1995; 26: 485–490
24. Kauppila LI, Polak JF, Cupples LA *et al*. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. *Atherosclerosis* 1997; 132: 245–250
25. Fitzmaurice G. Confounding: propensity score adjustment. *Nutrition* 2006; 22: 1214–1216
26. Cerini C, Dou L, Anfosso F *et al*. P-cresol, a uraemic retention solute, alters the endothelial barrier function in vitro. *Thromb Haemost* 2004; 92: 140–150
27. Dou L, Bertrand E, Cerini C *et al*. The uraemic solutes p-cresol and indoxyl sulfate inhibit endothelial proliferation and wound repair. *Kidney Int* 2004; 65: 442–451
28. Evenepoel P, Bammens B, Verbeke K *et al*. Acarbose treatment lowers generation and serum concentrations of the protein-bound solute p-cresol: a pilot study. *Kidney Int* 2006; 70: 192–198
29. Schulman G, Agarwal R, Acharya M *et al*. A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of AST-120 (Kremezin) in patients with moderate to severe CKD. *Am J Kidney Dis* 2006; 47: 565–577
30. Niwa T, Ise M, Miyazaki T *et al*. Suppressive effect of an oral sorbent on the accumulation of p-cresol in the serum of experimental uraemic rats. *Nephron* 1993; 65: 82–87
31. Ueda H, Shibahara N, Takagi S *et al*. AST-120, an oral adsorbent, delays the initiation of dialysis in patients with chronic kidney diseases. *Ther Apher Dial* 2007; 11: 189–195
32. Ueda H, Shibahara N, Takagi S *et al*. AST-120 treatment in pre-dialysis period affects the prognosis in patients on hemodialysis. *Ren Fail* 2008; 30: 856–860
33. Meijers BK, De Preter V, Verbeke K *et al*. p-Cresyl sulfate serum concentrations in haemodialysis patients are reduced by the prebiotic oligofructose-enriched inulin. 2009 Aug 19. [Epub ahead of print]
34. Manolio T. Novel risk markers and clinical practice. *N Engl J Med* 2003; 349: 1587–1589

Received for publication: 17.7.09; Accepted in revised form: 14.10.09

Nephrol Dial Transplant (2010) 25: 1191–1199
doi: 10.1093/ndt/gfp607
Advance Access publication 30 November 2009

The association of renal impairment with all-cause and cardiovascular disease mortality

Dorothea Nitsch[1], Debbie A. Lawlor[2], Rita Patel[2], Claire Carson[1] and Shah Ebrahim[1]

[1]Non-Communicable Disease Epidemiology Unit, Department of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK and [2]Department of Social Medicine, University of Bristol, Bristol, UK

Correspondence and offprint requests to: Dorothea Nitsch; E-mail: dorothea.nitsch@lshtm.ac.uk

Abstract

Background. The prognostic value of reduced glomerular filtration rate (GFR) was examined in a community-based cohort of British women.

Methods. Serum creatinine measurements were available for 90% (n = 3851) of a representative random sample of 4286 women aged 60–79 years. GFR was estimated using the Modification of Diet in Renal Disease equation. Hazard ratios (HR) were calculated using Cox regression with outcomes of all-cause and cardiovascular disease (CVD) mortality.

Results. Eight hundred and thirty-two women (21.6%) had a GFR <60 ml/min/1.73 m^2. Over a median follow-up of 5.6 years, there were 318 deaths (100 CVD deaths). Women with GFR <60 ml/min/1.73 m^2 compared to all others showed only a borderline increased risk of all-cause mortality [HR 1.35 (95% confidence intervals: 0.99, 1.85)] and CVD mortality [1.34 (0.97, 1.85)]. Adjustment for

conventional CVD risk factors had little impact. The association with CVD mortality was attenuated in women with pre-existing CVD [adjusted HR: 0.51 (0.24, 1.04)]. Only the subset of women without CVD at baseline were at risk for later CVD death [adjusted HR: 1.80 (1.13, 2.88)].

Conclusions. A substantial proportion of older British women have GFR <60 ml/min/1.73 m^2 without strong evidence for statistical association with all-cause mortality. The effect on CVD mortality is partly explained by existing CVD and its risk factors. GFR measurement appears only to play a useful role in the subset of older women without pre-existing CVD who are at higher risk of premature CVD death.

Keywords: all-cause mortality; cardiovascular mortality; chronic kidney disease; general population; women

Introduction

Chronic kidney disease (CKD) is an important public health threat, with an estimated 8 million adults in the US suffering from moderate or severe kidney disease, which has been found to be associated with increased risk of cardiovascular and all-cause mortality [1–3]. Most data in a meta-analysis of the effects of CKD on all-cause mortality were from the US and in particular from clinical populations with existing cardiovascular disease (CVD) [3]. European representative data on the prevalence of early CKD and its implications for the community are more limited, but findings suggest that CKD is associated with all-cause mortality and future CVD risk in those without disease at baseline [4]. Incident rates of chronic renal replacement therapy (RRT) within the UK are about 3-fold lower than the US suggesting possible substantive differences in the profile of CKD between the US and UK population [5]. However, incident RRT rates are a poor measure of the population burden of moderate CKD as ethnic mix, diabetes and blood pressure control and the ability to survive up to onset of dialysis may influence dialysis use [5,6].

The presence of moderate to severe CKD is defined as reduced glomerular filtration rate (GFR). In routine clinical practice and large epidemiological studies, GFR is estimated using the four-variable (serum creatinine measurements, gender, ethnicity and age) Modification of Diet in Renal Disease (MDRD) equation which provides a reasonable estimate of GFR at values <60 ml/min/1.73 m^2 [7,8]. However, there is evidence that MDRD underestimates renal function in women [9–13]. Heterogeneity between studies due to gender [3] points towards potential problems of the MDRD-GFR prediction formula for women and possible sex differences in underlying pathophysiology [14–16]. Current guidelines for screening advocate the systematic use of MDRD-GFR in general practice using identical cut-offs for both sexes [16–19], although a new formula may perform better [20,21].

Whilst also advocating the same MDRD-GFR approach in both sexes, current UK National Institute for Clinical Excellence guidelines acknowledge the need for more research to examine the association of CKD with CVD risk and best methods for evaluating GFR [18]. The aim of this study was to assess the effects of MDRD-GFR on all-cause and CVD mortality in a nationally representative community cohort of women.

Methods

Study population and follow-up

Between 1999 and 2001, 4286 women (99% white) aged 60–79 years (60% of those who were invited) were randomly selected from 23 British towns, interviewed and examined. The interviews and examinations were standardised and more details of the study are reported elsewhere [22,23]. The women completed medical questionnaires and had detailed reviews of their medical records [22,23]. These women have been followed up over a median of 5.6 years by flagging with the National Health Service central register for mortality data and two-yearly reviews of their medical records. CVD deaths were defined as either death with an underlying or contributing cause of coronary heart disease (CHD) or stroke (ICD10 codes I20–I25, I51.6, I60–69, G45). The censoring date for events was 31 December 2005. The study was approved by local research ethics committees, and women gave informed consent for participation in the study.

Estimation of renal function

Blood samples were taken after a minimum 6-h fast. The samples were used for assessment of serum lipids, plasma glucose and serum creatinine using standard procedures in a single central biochemistry laboratory [22,23]. C-reactive protein (CRP) was assayed by a high-sensitivity immunonephelometric assay on a ProSpec protein analyser (Dade-Behring) [22,23]. Glycated haemoglobin (HbA1c) and full blood count were measured on fresh whole blood. The assay measurements for serum creatinine used a Roche modular system with a modified Jaffe creatinine method (O'Leary modification) with the Roche CFAS used as a calibrator. A UK-wide study found that this calibration method did not substantially improve the overestimation bias for GFR using the isotope dilution mass spectrometry (IDMS)-corrected MDRD formula [8,24]. According to current clinical GFR reporting in the respective central laboratory, we used the original abbreviated MDRD-GFR formula [7] as our *a priori* preferential approach:

$$\begin{aligned}&\text{GFR [ml/min/1.73 m}^2\text{]} = 186\\ &\times(\text{correction factor for female gender : } 0.742)\\ &\times(\text{serum creatinine in mg/dl})^{-1.154}\times(\text{age in years})^{-0.203}\end{aligned}$$

GFR was analysed as continuous measure and in quartiles. The robustness of the findings were assessed in sensitivity analyses in which we only compared women with a GFR <60 ml/min/1.73 m^2 to those above because values below this threshold are less likely to be affected by creatinine calibration [8,12,24] and correspond to moderate to severe renal impairment [17]. Analyses were repeated in a further sensitivity analysis using the original serum creatinine measurements in the IDMS-MDRD formula [8].

Other risk factors

Information on smoking was obtained from interview and/or postal questionnaire. A Dinamap 1846SX vital sign monitor (GE Healthcare, Chalfont St. Giles, UK) was used to measure blood pressure. We corrected for the systematic overestimate of systolic blood pressure with this instrument [25]. Right-arm measurements were taken twice in succession, with a 1-min interval in between. The participant was seated, and the arm was supported on a cushion at chest level. Arm circumference was measured, and the appropriate cuff size was used. The mean of the two measurements was used for all analyses. Standing and seated height were measured, without shoes, using a Harpenden stadiometer (Holtain, Crymych, UK), recording to the nearest millimetre. Weight was measured in light clothing without shoes to the nearest 0.1 kg with Soehnle portable scales (Soehnle, Murrhardt, Germany) [22,23].

Prevalent CHD at baseline was defined as a woman having either of the following: a medical record of a myocardial infarction, angina, coronary artery bypass or angioplasty or a self-report of a doctor diagnosis of a heart attack or angina. Prevalent stroke and diabetes were similarly defined as any woman with a medical record of a diagnosis or a self-report of a doctor diagnosis. Including both self-reported and those from medical records provides greater assurance that all women with baseline disease have been excluded in the prospective analysis of CVD disease-free women. In the questionnaire, participants were asked to report their father's occupation when they were children, their own occupation and, where appropriate, the occupation of their spouse. These items were used to derive childhood and adulthood occupational social class. Participants were also asked whether the house they lived in as a child had a bathroom, whether it had a hot water supply and whether the family had access to a car. Childhood social class of the women was based on their fathers' longest held occupation and adult social class was based on the head of household's longest held occupation. Adult and childhood social classes were defined according to the registrar general's classification (I, II, III non-manual, III manual, IV, V—with I being professional occupations and V being manual unskilled occupations).

Statistical methods

Data were adjusted using robust standard errors for clustering in towns. Simple tabulations of means and proportions of age, co-morbidities and other characteristics according to category of MDRD-GFR were performed. For initial baseline analyses, Kruskal–Wallis tests, *F* tests, chi-square tests or Fisher's exact tests were carried out as appropriate. Checking for the assumption of proportionality needed for subsequent Cox regression was carried out graphically (using Nelson Aalen plots) as well as using Schoenfeld residuals in the final Cox models. Martingale residuals were used to investigate the linearity of effects. Based on these residuals both in crude and adjusted models, we found that a quadratic effect of GFR was the most appropriate transformation in the Cox model with the best fit for the continuous GFR measurements. To ensure robustness of our findings, we also used the cut-offs as advocated by existing literature (>=60 ml/min/1.73 m^2 and those <60 ml/min/1.73 m^2 into categories <45 and 45–59 ml/min/1.73 m^2). Uni- and multivariable Cox proportional hazard regression analyses with adjustment for age at entry in all models were run on the follow-up time scale. To evaluate the effects of sequential adjustments, analyses were carried out in the complete case dataset which omitted observations for women with missing measurements. Estimates for a given shift of continuous GFR were calculated hazard ratios for a woman with a GFR of 50 ml/min/1.73 m^2 compared to a woman with a GFR of 60 ml/min/1.73 m^2 (a 10 ml/min/1.73 m^2 GFR reduction) as well as for a woman of GFR of 30 ml/min/1.73 m^2 relative to a woman with GFR of 60 ml/min/1.73 m^2 (a 30 ml/min/1.73 m^2 GFR reduction).

We investigated the robustness of our results to selection bias by using multiple imputation of missing data using switching regression [26]. All variables in the analysis, log of the survival times of CVD, CVD event and death indicators, were used in the imputation model, including all subsequently tested interaction terms. After imputation, analyses were carried out on 25 imputed datasets and combined using Rubin's rules [26]. Analyses were carried out with Stata version 9.2.

Results

Baseline characteristics

At recruitment into the study, approximately a fifth (832) of the 3851 women included in the study, were classified according to MDRD as having moderate to severe renal impairment (GFR <60 ml/min/1.73 m^2; Table 1). Women with GFR <60 ml/min/1.73 m^2 (i.e. those described in the first column of Table 1) were ~2–3 years older than other women within the cohort. Mean systolic blood pressure was higher for those with lower GFR and 42% of the women with GFR <60 ml/min/1.73 m^2 reported using blood pressure medication, most commonly angiotensin-converting enzyme (ACE) inhibitors, thiazides and beta-blockers (Table 1). Women with GFR <60 ml/min/1.73 m^2 had lower HDL, higher LDL and substantially higher triglyceride subfractions. There were more women who reported using statins in the lower GFR categories. Women with GFR <60 ml/min/1.73 m^2 had higher CRP levels, lower socio-economic position and adverse levels of other conventional cardiovascular risk factors when compared to women in higher GFR categories (Table 1). Approximately a quarter of women with GFR <60 ml/min/1.73 m^2 (27%, $n = 224$) had co-existing CVD; 93% of these ($n = 208$) had documented CHD. Amongst women with GFR <60 ml/min/1.73 m^2, there were only 76 women with an eGFR <45 ml/min/1.73 m^2, and 35 of these had documented CVD at baseline.

MDRD-GFR and all-cause mortality

Over a median follow-up of 5.6 years, 318 deaths occurred, with 100 of these due to CVD. Crude mortality rates were significantly higher for women with moderate to severe renal impairment, especially among women with pre-existing CVD (Table 2). Table 3 shows the multivariable association of GFR with all-cause mortality in women in the cohort with complete data and stratified by baseline CVD status. All analyses were adjusted for age at baseline. Focusing on the top row of Table 3, women with a GFR <60 ml/min/1.73 m^2 compared to all others (age adjusted) had a borderline increased risk of all-cause mortality [hazard ratio (HR) 1.35 (95% confidence intervals, CI: 0.99, 1.85)] which did not reach conventional levels of statistical significance. The HR for a GFR <60 ml/min/1.73 m^2 changed little after adjustment for (i) blood pressure and antihypertensive drug treatment, (ii) addition of diabetes, (iii) addition of conventional cardiovascular risk factors, (iv) addition of social class and CRP and (v) further addition of anaemia, and did not reach statistical significance.

The analyses then proceeded by separating the group of women with GFR <60 ml/min/1.73 m^2 into those with GFR <45 ml/min/1.73 m^2 and above, and this improved the significance of prediction of all-cause mortality. In age-adjusted analyses, when compared to women with GFR of 60 ml/min/1.73 m^2 or more, women with GFR <45 ml/min/1.73 m^2 had a more pronounced increase in hazard [1.76 (1.03, 2.99)] than those with GFR 45–59 ml/min/1.73 m^2 [1.32 (1.03, 1.70)], both reaching conventional levels of statistical significance. However, in the large subset of women without pre-existing CVD, this association was much weaker with no clear evidence for an effect on all-cause mortality: for women with GFR <45, the HR was 1.31 (0.56, 3.03) and for GFR 45–59 ml/min/1.73 m^2 the HR was 1.19 (0.87, 1.62), respectively, when compared to GFR values ≥60.

To investigate this further, we decided to use GFR as continuous variable to retain power for further sequentially adjusted analyses. In all models, there appeared to be a curvilinear (threshold) relationship with a marked increased risk for those with a GFR <60 ml/min/1.73 m^2 compared to all other groups and a ~20% relative increase in hazard per 10 ml/min/1.73 m^2 GFR reduction <60 ml/

Table 1. Baseline characteristics by approximate quartiles of the estimated glomerular filtration rate (GFR) [abbreviated Modification of Diet in Renal Disease (MDRD) formula]

(min–max) [ml/min/1.73 m^2]	GFR category (16.2, 59.9)	(60.0, 67.5)	(67.5, 74.0)	(75.0, 171.8)	Total			*n* missing of total 4286 women	*P* value trend for imputed data
(*n*)	(832)	(1046)	(1035)	(938)	(3851)	*P* value[a]	*P* value trend[a]	435	
Creatinine, mmol/l Median (IQR)	93 (89, 99)	82 (80, 84)	75 (73, 76)	67 (64, 69)	78 (72, 85)	n.a.	n.a.	435	
Age in years, mean (SD)	71.1 (5.2)	69.1 (5.4)	68.2 (5.4)	67.3 (5.1)	68.8 (5.5)	n.a.	n.a.	1	
Adult manual social class, *n* (%)	333 (40.0)	412 (39.4)	364 (35.2)	318 (33.9)	1,427 (37.1)	0.037	0.015	0	0.02
Childhood manual social class, *n* (%)	696 (83.7)	829 (79.3)	809 (78.2)	739 (78.8)	3,073 (79.8)	0.024	0.026	0	0.03
BMI in kg/m^2, mean (SD)	28.4 (5.4)	27.9 (5.0)	27.3 (4.6)	26.7 (4.8)	27.6 (5.0)	<0.001	<0.001	329	<0.001
Waist-to-hip ratio, mean (SD)	0.83 (0.07)	0.82 (0.07)	0.81 (0.07)	0.82 (0.07)	0.82 (0.07)	0.005	0.006	340	0.01
Cholesterol, mean (SD)	6.7 (1.3)	6.7 (1.2)	6.6 (1.2)	6.6 (1.2)	6.6 (1.2)	0.027	0.021	435	0.02
HDL, mean (SD)	1.59 (0.44)	1.65 (0.44)	1.67 (0.43)	1.70 (0.50)	1.66 (0.45)	0.013	0.002	441	0.53
LDL, mean (SD)	4.21 (1.6)	4.16 (1.1)	4.14 (1.1)	4.08 (1.1)	4.14 (1.1)	0.022	0.004	524	0.83
TG, mean (SD)	2.00 (0.95)	1.89 (1.08)	1.76 (0.89)	1.85 (1.68)	1.87 (1.19)	<0.001	0.003	435	0.003
Statins, *n* (%)	89 (10.7)	73 (7.0)	66 (6.4)	57 (6.1)	285 (7.4)	<0.001	<0.001	374	<0.001
CRP, median (IQR)	2.14 (1.08, 4.65)	1.97 (0.91, 4.25)	1.59 (0.74, 3.65)	1.56 (0.72, 3.62)	1.82 (0.84, 4.03)	<0.001	<0.001	452	<0.001
Documented CHD, *n* (%)	208 (25.0)	172 (16.4)	124 (12.0)	119 (12.7)	623 (16.2)	<0.001	<0.001	0	<0.001
Documented CVD, *n* (%)	224 (26.9)	192 (18.4)	138 (13.3)	130 (13.9)	684 (17.8)	<0.001	<0.001	0	<0.001
Diabetes[b], *n* (%)	108 (13.0)	94 (9.1)	90 (8.8)	85 (9.1)	377 (9.9)	0.008	0.025	457	0.02
HbA1c, median (IQR)	5 (4.6, 6)	4.9 (4.5, 5)	4.8 (4.5, 5)	4.8 (4.4, 5)	4.9 (4.5, 5)	0.010	0.003	532	0
Homa score, median (IQR)	1.9 (1.2, 2.9)	1.6 (1.1, 2.6)	1.6 (1.1, 2.3)	1.5 (1.0, 2.3)	1.6 (1.1, 2.5)	0.001	<0.001	914	<0.001
Ex smokers, *n* (%)	295 (35.5)	320 (30.6)	327 (31.6)	322 (34.3)	1264 (32.8)	0.056	0.096	19	0.67
Current smokers, *n* (%)	85 (10.2)	99 (9.5)	119 (11.5)	122 (13.0)	425 (11.0)				0.04
Systolic blood pressure, mean (SD)	149.8 (25.1)	147.2 (24.7)	145.5 (25.4)	146.4 (25.6)	147.1 (25.2)	0.002	0.005	320	0.01
Diastolic blood pressure, mean (SD)	80.0 (12.0)	79.6 (11.5)	78.9 (11.9)	79.4 (11.7)	79.4 (11.8)	0.196	0.140	320	0.14
Blood pressure medication, *n* (%)	346 (41.6)	341 (32.7)	261 (25.3)	214 (22.9)	1162 (30.2)	<0.001	<0.001	300	<0.001
On ACE inhibitors, *n* (%)	132 (15.9)	103 (9.9)	78 (7.5)	56 (6.0)	369 (9.6)	<0.001	<0.001	300	<0.001
On beta-blockers, *n* (%)	179 (21.5)	166 (15.9)	118 (11.4)	101 (10.8)	564 (14.7)	<0.001	<0.001	300	<0.001
On thiazides, *n* (%)	159 (19.1)	166 (15.9)	139 (13.5)	122 (13.0)	586 (15.3)	0.025	0.003	300	0.002
Haemoglobin levels, mean (SD)	13.4 (1.2)	13.6 (1.0)	13.6 (0.9)	13.5 (1.0)	13.5 (1.1)	<0.001	0.039	534	0.04

Women in the first column have GFR <60 ml/min/1.73 m^2, possibly indicative of chronic renal failure.
[a]Adjusted for clustering in town.
[b]Clinically diagnosed diabetes or fasting glucose >7 mmol/l; n.a., not applicable (test meaningless because of variable derivation).

Table 2. All-cause and cardiovascular disease (CVD) mortality rates by quartiles of estimated glomerular filtration rate (GFR, in ml/min/1.73 m^2), stratified by CVD at baseline

Quartile of GFR (ml/min/1.73 m^2)	*n*	Deaths	Mortality (per 100 py[a])	(95% CI)	CVD deaths	CVD death rate (per 100 py[a])	(95% CI)
All women							
<60	832	107	2.35	(1.94, 2.84)	38	0.83	(0.61, 1.15)
60–67.4	1046	79	1.36	(1.09, 1.70)	23	0.40	(0.26, 0.60)
67.5–74.9	1035	63	1.10	(0.86, 1.41)	20	0.35	(0.22, 0.54)
75+	938	69	1.36	(1.08, 1.73)	19	0.38	(0.24, 0.59)
Women without baseline CVD							
<60	608	62	1.85	(1.44, 2.37)	19	0.57	(0.36, 0.89)
60–67.4	854	58	1.22	(0.94, 1.58)	12	0.25	(0.14, 0.44)
67.5–74.9	897	48	0.96	(0.73, 1.28)	10	0.20	(0.11, 0.37)
75+	808	57	1.31	(1.01, 1.70)	14	0.32	(0.19, 0.54)
Women with baseline CVD							
<60	224	45	3.74	(2.79, 5.01)	19	1.58	(1.01, 2.48)
60–67.4	192	21	2.01	(1.31, 3.08)	11	1.05	(0.58, 1.90)
67.5–74.9	138	15	2.00	(1.20, 3.31)	10	1.33	(0.72, 2.48)
75+	130	12	1.70	(0.97, 2.99)	5	0.71	(0.29, 1.70)

[a]py, person-years.

min/1.73 m^2 (Figure 1), and a steeper increase the more GFR decreases. Stratification on baseline CVD showed a much steeper increase of risk per 10 ml/min/1.73 m^2 reduction of GFR for women with CVD at baseline when compared to women without CVD in all models (lower panel of Figure 1, *P* values for interaction in crude and fully adjusted analyses: 0.007 and 0.02, respectively). Therefore, the numbers for the continuous data analysis in Table 3 display two HR depending on how far left a woman shifts on Figure 1, i.e. a comparison of hazards between a woman with GFR of 60 ml/min/1.73 m^2 to a woman with GFR of 50 ml/min/1.75 m^2 (a 10 ml/min/1.73 m^2 GFR reduction) and the comparison between a woman with GFR of 60 ml/min/1.73 m^2 to a woman with GFR of 30 ml/min/1.75 m^2 (a 30 ml/min/1.73 m^2 GFR reduction). In women without CVD, the association of continuous GFR with all-cause mortality is flat.

MDRD-GFR and CVD mortality

The crude rates of CVD-related mortality showed higher rates for women in the lowest quartile of GFR and this was so for all women (first set of results in Table 2), as well as when results were presented separately for those with no evidence of baseline CVD (second set of results in Table 2) and those with baseline CVD (third set of results in Table 2). Table 2 also shows, as expected, that mortality rates are higher in women with baseline CVD compared to those who had no evidence of baseline CVD. Women with a GFR <60 ml/min/1.73 m^2 compared to all others had a borderline increased HR for CVD mortality [1.34 (0.97, 1.85)] in unadjusted models, which attenuated to 1.24 (0.82, 1.87) with adjustment for conventional risk factors, with little change with further adjustment for CRP, social class and anaemia (online Table I).

In the total cohort, women with GFR <45 ml/min/1.75 m^2 may have a steeper increase in hazard [age-adjusted HR 2.12 (0.99, 4.57)] than those with GFR 45–59 [1.59 (1.06, 2.39)] when compared with those GFR 60 ml/min/1.73 m^2 or more. In women without CVD, the increase in CVD mortality risk started at eGFR <60 ml/min/1.73 m^2; for GFR 45–59, the age-adjusted HR was 1.75 (1.02, 2.99) when compared to higher GFR values; and for GFR <45, the HR was 1.72 (0.51, 5.78; note the wide confidence interval due to small numbers). For women with CVD, a GFR <45 may be worse [HR 2.14 (0.78, 5.85)] than having a GFR 45–59 ml/min/1.73 m^2 [HR 1.10 (0.59, 2.07)], but there were wide confidence intervals which included 1 for no effect. However, in all adjusted analyses of women without CVD, a GFR <60 ml/min/1.73 m^2 was a strong independent predictor of CVD mortality [fully adjusted HR: 1.80 (1.13, 2.88); online table I].

In continuous analyses of GFR, there was a curvilinear increase in risk with decreasing GFR as suggested by categorical analyses and as observed for all-cause mortality (see also Figure 2). The effect of GFR on CVD mortality appeared weaker in women with CVD at baseline compared to those without CVD [adjusted HR: 0.51 (0.25, 1.04), *P* value for interaction in the complete case dataset 0.01]. However, in this subset of women with baseline CVD, there were only 45 CVD deaths. The *P* value of interaction of GFR and baseline CVD in the imputed dataset was 0.04. Examining the effects of sequential adjustment of GFR in the imputed data showed that the effect of GFR on CVD mortality in those without CVD was partially explained by CVD risk factors, and in those with CVD it disappeared after adjustment for cholesterol, smoking and obesity (online table III).

There was no statistical evidence to support an interaction between the association of anaemia depending on GFR or baseline CVD when analysing all-cause mortality and/or CVD mortality. The IDMS formula shifted the whole GFR distribution to the left (lower values), with 1298 women (33%) classified as having a GFR <60 ml/min/1.73 m^2 by this formula. The sensitivity analyses using IDMS-GFR on outcomes were similar throughout, but had higher standard errors, possibly due to the decreased specificity of the IDMS formula for the creatinine calibration that was used (data not

Table 3. Crude and adjusted effects (hazard ratios, HR) of GFR on all-cause mortality with their 95% confidence intervals (95% CI), calculated for the total cohort as well as stratified by CVD at baseline

				Adjusted for									
				Blood pressure		Diabetes		Smoking, overweight, cholesterol		Social class, CRPHaemoglobin		Haemoglobin	
Effect of GFR	Unit	HR[a]	(95% CI)	HR[b]	(95% CI)	HR[c]	(95% CI)	HR[d]	(95% CI)	HR[d]	(95% CI)	HR[d]	(95% CI)
All (n = 3077)	<60 ml/min/1.73 m^2 vs above	1.35	(0.99, 1.84)	1.31	(0.95, 1.82)	1.32	(0.96, 1.82)	1.30	(0.92, 1.80)	1.29	(0.93, 1.79)	1.27	(0.92, 1.78)
	Per 10 ml/min/1.73 m^2 decrease from 60	1.19	(1.01, 1.41)	1.19	(1.01, 1.40)	1.19	(1.01, 1.40)	1.14	(0.96, 1.35)	1.14	(0.97, 1.35)	1.14	(0.96, 1.34)
	Per 30 ml/min/1.73 m^2 decrease from 60	2.07	(1.16, 3.69)	2.06	(1.17, 3.63)	2.06	(1.18, 3.62)	1.68	(0.94, 2.98)	1.69	(0.96, 2.97)	1.65	(0.94, 2.91)
Without CVD	<60 ml/min/1.73 m^2 vs above	1.32	(0.98, 1.76)	1.31	(0.97, 1.77)	1.31	(0.97, 1.77)	1.29	(0.94, 1.78)	1.27	(0.92, 1.75)	1.27	(0.93, 1.75)
(n = 2555)	Per 10 ml/min/1.73 m^2 decrease from 60	1.12	(0.92, 1.36)	1.12	(0.92, 1.37)	1.12	(0.92, 1.37)	1.11	(0.90, 1.37)	1.05	(0.86, 1.26)	1.05	(0.87, 1.27)
	Per 30 ml/min/1.73 m^2 decrease from 60	1.62	(0.79, 3.31)	1.62	(0.79, 3.35)	1.62	(0.79, 3.35)	1.53	(0.72, 3.24)	1.18	(0.60, 2.34)	1.21	(0.61, 2.40)
With CVD	<60 ml/min/1.73 m^2 vs above	1.21	(0.61, 2.40)	1.12	(0.56, 2.26)	1.12	(0.56, 2.26)	1.20	(0.57, 2.52)	1.20	(0.56, 2.56)	1.17	(0.57, 2.38)
(n = 522)	Per 10 ml/min/1.73 m^2 decrease from 60	1.36	(1.16, 1.60)	1.34	(1.12, 1.59)	1.34	(1.12, 1.60)	1.41	(1.13, 1.78)	1.44	(1.14, 1.81)	1.40	(1.16, 1.68)
	Per 30 ml/min/1.73 m^2 decrease from 60	5.57	(2.50, 12.44)	5.57	(2.37, 13.10)	5.63	(2.38, 13.29)	6.08	(1.96, 18.18)	6.34	(1.94, 20.79)	5.62	(2.06, 15.26)

All models are adjusted for age at entry into the study.
[a]Adjusted for age.
[b]Adjusted for age, systolic and diastolic blood pressure and blood pressure medication.
[c]Adjusted for age, systolic and diastolic blood pressure, blood pressure medication and diagnosis of diabetes.
[d]Adjusted for age, systolic and diastolic blood pressure, blood pressure medication, diagnosis of diabetes and homa score, smoking status, BMI, waist-to-hip ratio and absolute serum cholesterol measurements, HDL, LDL, triglycerides and statin prescription, as indicated in the table.

shown). Findings for raw untransformed serum creatinine were comparable.

Imputed data gave similar results in all analyses (online tables II and III in web appendix). The crude effects of GFR appeared stronger throughout but adjustments for CVD risk factors rendered effects of identical size as found in the complete case dataset. This suggests that missing values are unlikely to have influenced the main findings.

Discussion

This study showed that at least 20% of older British women from the general population have GFR <60 ml/min/1.73 m^2 according to a single assessment of MDRD-GFR. Women with an MDRD-GFR <60 ml/min/1.73 m^2 compared to all other women had more adverse cardiovascular disease risk factors. There appeared to be a threshold effect of GFR on both all-cause and CVD mortality, with a curvilinear association of increasing risk with each 10 ml/min/1.73 m^2 starting below the threshold of 60. Our results suggest that in women without pre-existing CVD, the use of a value of <60 ml/min/1.73 m^2 (i.e. same as that currently recommended for both sexes but based on more robust evidence for men) to define at risk is likely to identify women at risk for CVD mortality. In women with existing CVD, there was an association of GFR with all-cause mortality which was not affected by adjustment for conventional cardiovascular risk factors, but the association with CVD mortality appeared to be explained by cardiovascular risk factors.

A strength of this study is that it uses data from a representative general population sample of women, unlike a number of other studies that rely on databases of unsystematic recordings of serum creatinine measurements. By using GFR as a continuous variable with parametric assumption on the form of relation with mortality, we had more power to examine the effect of sequential adjustments. We used multiple imputation to exclude the presence of biases that may occur with selectively missing data. A further strength of this study is the ability to rigorously adjust for a number of important confounders including social class and CRP.

Limitations of this study are the lack of urine protein measurements and direct measures of renal function. Albuminuria appears to be a marker of early endothelial dysfunction associated with a strong cardiovascular risk in all populations examined [2,27,28]. Direct measures of renal function are impractical for large-scale epidemiological studies or as initial screening tools in clinical practice; indeed, all epidemiological studies reviewed by Tonelli and colleagues [3] had only single measurements. The MDRD-GFR has been shown to be a reasonably accurate assessment of GFR in men [8,9] with only 4% of intra-personal daily variation on an average mixed diet [28]. It is unlikely that women who were participating in our study were categorised as GFR <60 ml/min/1.73 m^2 as a result of cooked meat intake [29] because blood samples for the present study were taken after a minimum 6-h fast. A possible limitation of this study is that we have estimated GFR based on a single measure of serum creatinine. Current

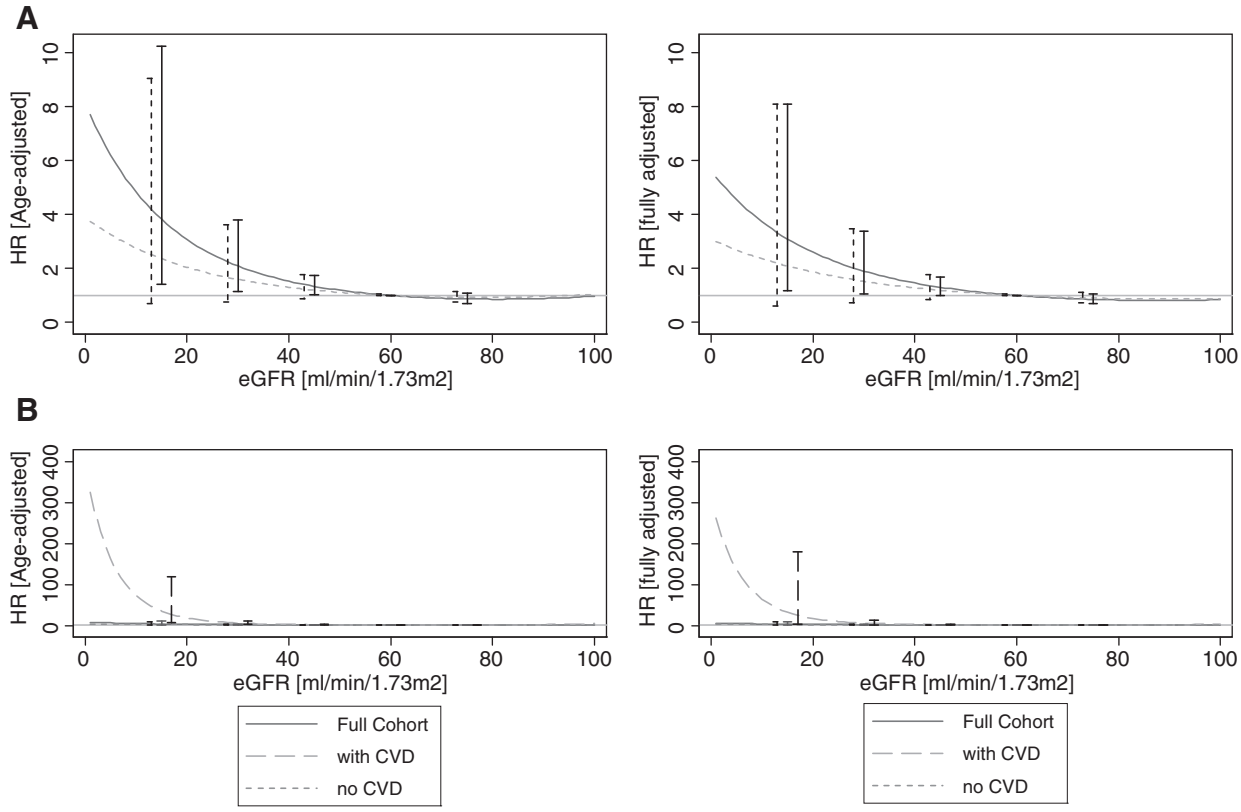

Fig. 1. Associations of eGFR with all-cause mortality in the British Regional Heart Study. $N = 3851$ women aged 60–79 years at baseline.
(**A**) The top two figures show age-adjusted (left hand panel) and multivariable-adjusted (right hand panel) hazard ratios (HR) for all-cause mortality (*Y*-axis) by GFR (*X*-axis) in the whole cohort and in the women who had no evidence of CVD at baseline.
(**B**) The bottom two figures show age-adjusted (left hand panel) and multivariable-adjusted (right hand panel) HR for all-cause mortality (*Y*-axis) by eGFR (*X*-axis) in women who had evidence of CVD at baseline compared to the others. There is a considerable change in scale for the HR (*Y*-axis) in comparison to the above figure. In all panels, vertical lines indicate 95% confidence intervals at that point; the horizontal grey line indicates the HR of 1 for no effect.

guidelines define CKD as kidney damage or a GFR <60 ml/min/1.73 m^2 for at least 3 months, regardless of cause [17], and it is possible that some of the women with low rates in this study would not fulfil this criterion. However, given that eGFR changes <1 ml/min/1.73 m^2 over 3 months in women of the general population of this age [30], the current estimates from the present study are likely to be reliable with regards to the predictive power of MDRD eGFR on outcome in women. The majority of existing large-scale epidemiological studies, including the National Health and Nutrition Examination Survey III, derived their estimates of the prevalence of CKD in the general population similarly from single measurements of MDRD-GFR [1–4]. With respect to the associations examined here, having GFR measured at just one time point may mean that these are slightly underestimated because of an inability to take into account the regression to the mean. Some studies suggest that cystatin C may be a better marker of underlying renal function in the elderly and those with low creatinine generation [31], but this measure is not available for this cohort and is currently not readily available in clinical practice in the UK. Our study is of older women, the vast majority of whom were described as white at the baseline examination. Thus, we were unable to compare associations by gender, age and ethnicity, and our findings are not necessarily generalisable to these other groups.

Estimated effects of MDRD-GFR on all-cause mortality in women with CVD were of comparable size to those described previously for pooled samples of women and men [1–5]. The effects of MDRD-GFR on CVD mortality in the total cohort of women were consistent with associations reported separately for women in some, but not all, community-based studies [3]. The association with CVD mortality in women with CVD at baseline was in this study much weaker [3]. This is a new finding, but due to small numbers for this analysis, further confirmation in larger studies is required.

The pathways by which renal impairment lead to higher all-cause and CVD mortality are unclear. An explanation might be that metabolic changes resulting from more severe renal impairment are by themselves associated with poorer survival and increased cardiovascular risk. Such metabolic changes include decreased clearance of the endogenous NOS inhibitor ADMA, anaemia, decreased control of calcium–phosphate metabolism, metabolic acidosis, malnutrition, difficulties of blood pressure control and possibly a more inflammatory state [32]. Two studies reported that traditional cardiovascular disease risk factors

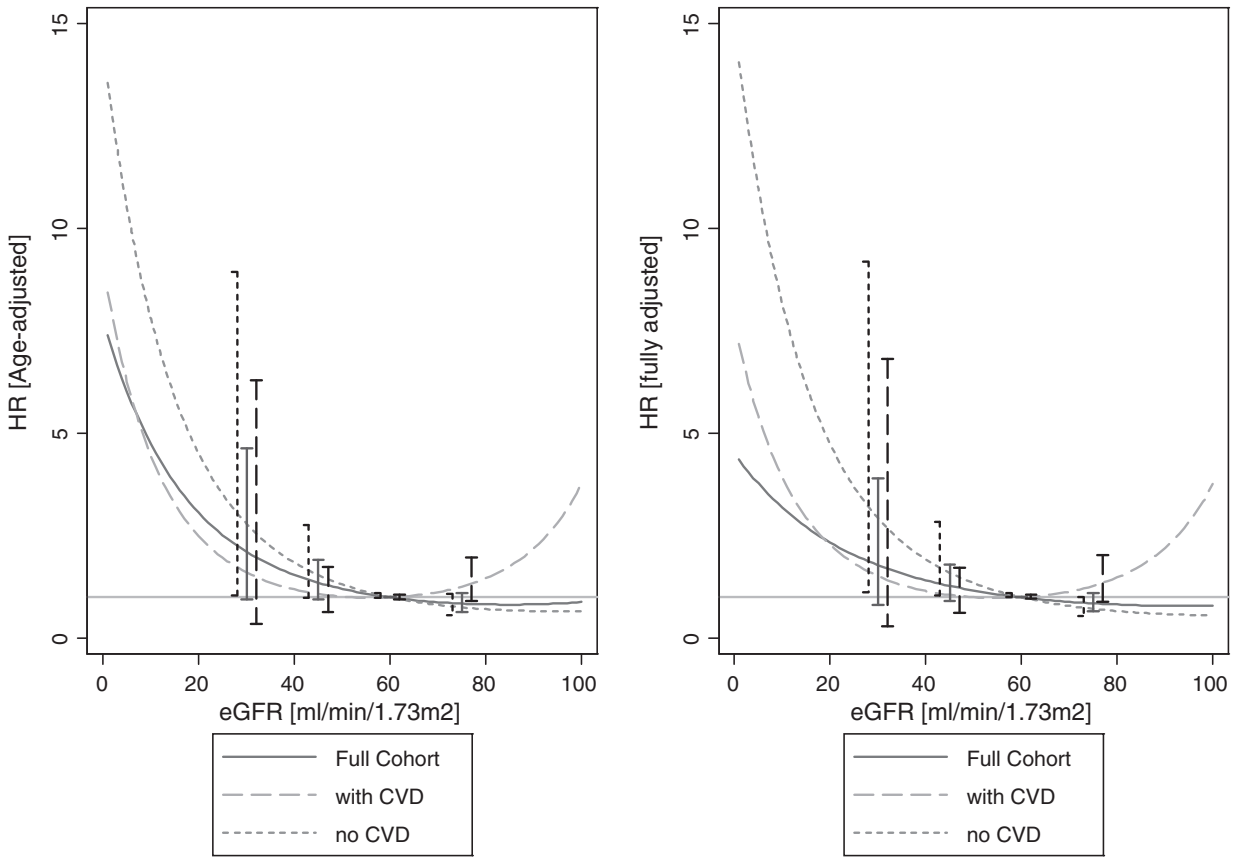

Fig. 2. Associations of eGFR with CVD mortality in the British Regional Heart Study. $N = 3851$ women aged 60–79 years at baseline. The figures show age-adjusted (left hand panel) and multivariable-adjusted (right hand panel) hazard ratios (HR) for CVD mortality (*Y*-axis) by eGFR (*X*-axis) in the whole cohort and in the women who had evidence of CVD at baseline and those who had not. In all panels, vertical lines indicate 95% confidence intervals at that point; the horizontal grey line indicates the HR of 1 for no effect.

(smoking, left ventricular hypertrophy, systolic blood pressure, diabetes and physical inactivity) had stronger associations with CVD mortality than novel risk factors, such as CRP, interleukin 6 and homocysteine, in patients with CKD [33–35]. Our findings were consistent with these in that we found a marked attenuation of the association between GFR with CVD mortality upon adjustment for conventional risk factors and less attenuation when further adjusting for lifetime social circumstances, CRP and anaemia. The increased risk of all-cause mortality amongst women with CVD and GFR <60 ml/min/1.73 m^2 was however not explained by any of these CVD risk factors.

Our results suggest that a fifth of post-menopausal women have a GFR <60 ml/min/1.73 m^2 and that these women have a more adverse cardiovascular risk profile and, depending on the presence of underlying CVD, a greater risk of all-cause and CVD mortality. Evaluation of renal function may play a useful role in identifying older women at risk of premature death.

Acknowledgements. The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The British Women's Heart and Health Study is co-directed by Professor Shah Ebrahim, Professor Debbie Lawlor, Professor Peter Whincup and Dr Goya Wannamethee. We thank Carol Bedford, Alison Emerton, Nicola Frecknall, Karen Jones, Mark Taylor and Katherine Wornell for collecting and entering data, all of the general practitioners and their staff who have supported data collection and the women who have participated in the study. The British Women's Heart and Health Study was funded by the UK Department of Health Policy Research Programme and British Heart Foundation. D.A.L. was funded by a UK Department of Health Career Scientist Award when working on this study. The views expressed in this publication are those of the authors and not necessarily any funding body.

Conflict of interest statement. None declared.

References

1. Coresh J, Astor BC, Greene T *et al*. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003; 41: 1–12
2. Astor BC, Hallan SI, Miller ER 3rd *et al*. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. *Am J Epidemiol* 2008; 167: 1226–1234
3. Tonelli M, Wiebe N, Culleton B *et al*. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006; 17: 2034–2047
4. Hallan SI, Dahl K, Oien CM *et al*. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. *BMJ* 2006; 333: 1047
5. UK Renal Registry Report 2004. *Chapter 17: International Comparisons: Incidence, Prevalence, Markers of Quality of Care and Survival* Available from http://www.renalreg.com/Report%202004/Cover_Frame.htm, accessed 8 August 2006

6. Hallan SI, Coresh J, Astor BC *et al*. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 2006; 17: 2275–2284
7. Levey AS, Bosch JP, Lewis JB *et al*. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470
8. Levey AS, Coresh J, Greene T *et al*. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; 145: 247–254
9. Froissart M, Rossert J, Jacquot C *et al*. Predictive performance of the modification of diet in renal disease and Cockcroft–Gault equations for estimating renal function. *J Am Soc Nephrol* 2005; 16: 763–773
10. Nitsch D, Dietrich DF, Eckardstein AV *et al*. Prevalence of renal impairment and its association with cardiovascular risk factors in a general population: results of the Swiss SAPALDIA study. *Nephrol Dial Transplant* 2006; 21: 935–944
11. Stevens PE, O'donoghue DJ, de Lusignan S *et al*. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney Int* 2007; 72: 92–99
12. Lamb E, Tomson CV, Roderick PJ. Estimating kidney function in adults using formulae. *Ann Clin Biochem* 2005; 42: 321–345
13. Cirillo M, Anastasio P, DeSanto NG. Relationship of gender, age, and body mass index to errors in predicted kidney function. *Nephrol Dial Transplant* 2005; 20: 1791–1798
14. Pechère-Bertschi A, Burnier M. Female sex hormones, salt, and blood pressure regulation. *Am J Hypertens* 2004; 17: 994–1001
15. Neugarten J. Gender and the progression of renal disease. *J Am Soc Nephrol* 2002; 13: 2807–2809
16. Poggio ED, Rule AD. Can we do better than a single estimated GFR threshold when screening for chronic kidney disease?. *Kidney Int* 2007; 72: 534–536
17. Levey AS, Coresh J, Balk E *et al*. National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; 139: 137–147
18. *CG73 Chronic kidney disease: NICE guideline* 24 September 2008 http://www.nice.org.uk/Guidance/CG73/NiceGuidance/doc/English, last accessed 20.03.2009
19. Brosius FC 3rd, Hostetter TH, Kelepouris E *et al*. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney And Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. *Circulation* 2006; 114: 1083–1087
20. Björk J, Bäck SE, Sterner G *et al*. Prediction of relative glomerular filtration rate in adults: new improved equations based on Swedish Caucasians and standardized plasma-creatinine assays. *Scand J Clin Lab Invest* 2007; 1–18
21. Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
22. Lawlor DA, Davey SG, Ebrahim S. Life course influences on insulin resistance: findings from the British Women's Heart and Health Study. *Diabetes Care* 2003; 26: 97–103
23. Lawlor DA, Bedford C, Taylor M *et al*. Geographical variation in cardiovascular disease, risk factors, and their control in older women: British Women's Heart and Health Study. *J Epidemiol Community Health* 2003; 57: 134–140
24. Vickery S, Stevens PE, Dalton RN *et al*. Does the ID-MS traceable MDRD equation work and is it suitable for use with compensated Jaffe and enzymatic creatinine assays?. *Nephrol Dial Transplant* 2006; 21: 2439–2445
25. Whincup P, Bruce N, Cook D *et al*. The Dinamap 1846SX automated blood pressure recorder: comparison with the Hawksley random zero sphygmomanometer under field conditions. *J Epidemiol Community Health* 1992; 46: 164–169
26. Royston P. Multiple imputation of missing values. *Stata Journal* 2004; 4: 227–241
27. Hillege HL, Fidler V, Diercks GF *et al*. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; 106: 1777–1782
28. Yuyun MF, Khaw KT, Luben R *et al*. Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *Int J Epidemiol* 2004; 33: 189–198
29. Larsson A, Akerstedt T, Hansson LO *et al*. Circadian variability of cystatin C, creatinine, and glomerular filtration rate (GFR) in healthy men during normal sleep and after an acute shift of sleep. *Chronobiol Int* 2008; 25: 1047–1061
30. Preiss DJ, Godber IM, Lamb EJ *et al*. The influence of cooked meat on glomerular filtration rate. *Ann Clin Biochem* 2007; 44: 35–42
31. Kronborg J, Solbu M, Njølstad I *et al*. Predictors of change in estimated GFR: a population-based 7-year follow-up from the Tromso study. *Nephrol Dial Transplant* 2008; 232818–2826
32. Seliger SL, Longstreth WT Jr, Katz R *et al*. Cystatin C and subclinical brain infarction. *J Am Soc Nephrol* 2005; 16: 3721–3727
33. Zoccali C. Traditional and emerging cardiovascular and renal risk factors: an epidemiologic perspective. *Kidney Int* 2006; 70: 26–33
34. Shlipak MG, Fried LF, Cushman M *et al*. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 2005; 293: 1737–1745
35. Muntner P, He J, Astor BC *et al*. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol* 2005; 16: 529–538

Received for publication: 4.12.08; Accepted in revised form: 20.10.09