European Heart Journal (2007) **28**, 478–483
doi:10.1093/eurheartj/ehl455

The glomerular filtration rate in an apparently healthy population and its relation with cardiovascular mortality during 10 years

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Received 20 June 2006; revised 1 December 2006; accepted 7 December 2006; online publish-ahead-of-print 12 January 2007

KEYWORDS
Epidemiology;
Chronic kidney disease;
Cardiovascular risk factor;
Glomerular filtration rate

Aims Moderate-to-severe chronic renal failure is an established risk factor for cardiovascular disease and mortality. However, most studies have been performed in selected populations and the impact of very small decrements of renal function on long-term cardiac morbidity and mortality has not yet been established. Also, the cut-off level of glomerular filtration rate (GFR) from which cardiovascular risk increases has not exactly been established. This study wants to address these questions.
Methods and results Ten year follow-up of a representative population-based cohort comprised 8913 randomly selected, apparently healthy participants. Participants were randomly drawn from Belgian voting lists. Cardiovascular risk factors were noted. Serum creatinine values were corrected to isotope dilution mass spectrometry standard, and GFR was calculated using the recently modified 'modification of diet in renal disease' equation. Participants were followed for 10 years, and cause-specific death was registered by analysis of death certificates. The probability to die from all causes or from cardiovascular causes during the 10 year follow-up period increased in each quartile of GFR, even after correction for different other comorbid conditions.
Conclusion Even mild renal failure is an independent risk factor for cardiovascular mortality within 10 years in an apparently healthy unselected population. This detrimental effect starts already at a relatively high GFR of 90 mL/min/1.73 m^2 and remains present after correction for other established cardiovascular risk factors.

Introduction

Chronic kidney disease (CKD) is related with cardiovascular risk.[1,2] The exact glomerular filtration rate (GFR) below which this risk starts to increase is however not yet established, since most, if not all, studies dealing with this issue compare only a few broad strata of kidney dysfunction (e.g. GFR $>$ 60, vs. between 60 and 30, vs. $<$30 mL/min/1.73 m^2),[2] although most of them concentrate on the more severe degrees of kidney dysfunction. In addition, most studies have been performed in selected patient groups,[3–5] or have only a short-term follow up.[2] Most of these studies[6,7] rely upon serum creatinine to determine GFR, which is also a potential source of bias, especially in the near-normal range.[8] Meanwhile, several authors[9–11] have demonstrated that the new modification of diet in renal disease (MDRD) formula as defined by Levey *et al.*,[10] using isotope dilution mass spectrometry (IDMS)-calibrated creatinine values, is more accurate, especially in the near-normal range, and can thus be used in large studies of an apparently healthy population.

The correct understanding of the relationship between mild renal impairment and cardiovascular disease (CVD) is vital to guide preventive strategies for screening and treatment. Such preventive strategies may have a substantial impact on the health care budget because some efficient treatments offer possibilities to tackle the negative evolution related to these problems.[12]

In this study, the impact of even mild stages of CKD on CVD in a large, apparently healthy and unselected population was explored. More specifically, we wanted to determine the level of GFR below which cardiovascular risk starts to increase.

Patients and methods

The Belgian Interuniversity Research on Nutrition and Health population sample was composed at random from voting lists in Belgium[13] during the period 1980–84.

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Initially, a random sample of 30 000 persons was established. Participation rate was 36%. A 10% random sample of non-participants was asked to complete a questionnaire related to cardiovascular lifestyle aspects. From the answers to this survey, it was concluded that no differences between participants and non-participants were present.

Lifestyle parameters and medical history were collected by experienced technicians, using pre-defined standardized questionnaires.

Data presented in this paper are from the 8913 patients who were free from prevalent coronary heart disease, defined as being free from angina pectoris, having no history of myocardial infarction according to the Rose questionnaire[14] and having no evidence of an old myocardial infarction on their resting ECG. Patients with pre-existing cardiac disease were excluded from further analysis, as we wanted to estimate the risk for *de novo* cardiac disease.

Diabetes was defined as the patient-reported need for insulin or oral anti-diabetics or the application of specific dietary measures because of insulin resistance. Also, these patients were excluded from further analysis, as we wanted to analyse an apparently healthy population.

Blood pressure was measured by experienced technicians after 5 min of rest in a sitting position. Mean arterial pressure (MAP) was defined as the sum of the systolic and two times the diastolic blood pressure, divided by 3, and expressed in mmHg. Body mass index (BMI) was defined as the weight of the patient (kilograms) divided by the square of height (metres).

Blood was sampled from the antecubital vein. Serum was separated by centrifugation and stored at -80°C. All analyses were performed by a single centralized laboratory.

Serum creatinine (Screa) was measured according to the Jaffé methodology, using the SMAC Technicon technology. In line with the new recommendations,[15] these creatinine values were calibrated to IDMS standard[16] according to the following equation:

$\text{Screa}_{\text{IDMS}} = -0.31 + (1.11 * \text{Screa}_{\text{SMAC}})$, with Screa values expressed in mg/dL. Different authors[9–11] found that this equation gave very reliable results under different conditions, especially in the near-normal range of serum creatinine values. Vickery *et al.*[17] found that using this equation provided better results than calibrating the creatinines to the Cleveland standard and using the old MDRD formula.[16] These 'calibrated' serum creatinines were then introduced in the new abbreviated MDRD equation to estimate the GFR (new abbreviated MDRD: $\text{GFR} = 175 * \text{Screa}^{-1.154} * \text{age}^{-0.203}$ for males, and $\text{GFR} = 175 * \text{Screa}^{-1.154} * \text{age}^{-0.203} * 0.742$ for females). All participants were Caucasian.

Serum cholesterol was measured using the SMAC Technicon analyser according to the methodology of Abell *et al.*[18]

The few subjects with an estimated GFR < 20 mL/min were considered as a pre-dialysis population and were not considered for further analysis.

The global sample was followed for cause-specific mortality for at least 10 years or until death. Follow-up was complete in 99% of the sample. Vital status was checked through local community registers and causes of death were ascertained from the family doctor and/or the physician who completed the death certificate. Where appropriate, more information on the exact cause of death was collected from hospital or medical records. According to the ninth revision of the International Classification of Disease,[19] we considered all codes ranging from 390 to 459 as cause of death from CVD.

Statistical methods

Comparisons between two groups were performed using the Mann–Whitney *U* test for continuous variables and using Fisher's exact test for categorical variables.

Statistical analysis of the association between GFR and subsequent mortality was performed by fitting Cox proportional hazards models[20] with additional covariates of age (in years), gender, BMI (kg/m^2), current smoking (yes/no), mean arterial blood pressure (mmHg), total cholesterol (mmol/L), and serum uric acid level (μmol/L). The statistical significance of a variable in the model was determined according to the Wald χ^2 statistic, and the strength of the association is given by the adjusted hazard ratios (HR), which are given with their 95% confidence intervals (CI). In order to test whether the prognostic value of GFR was similar for men and women, a formal interaction test was performed between GFR and sex. The significance of the interaction was evaluated by comparing the log likelihood functions of the fitted models with and without the multiplicative effect. Under the null hypothesis of no interaction, minus double this difference, follows a χ^2 distribution with 1 degree of freedom. All models were checked on the assumption of proportionality of hazards. The global level for significance was taken as $\alpha < 0.05$ and all analyses were performed using SAS software (SAS for Windows, release 6.11, SAS Institute Inc., Cary, NC, USA).

Results

In total, after exclusion of diabetics and participants with pre-existing CVD, 4708 males and 4205 females were included in the study. Results for the demographic and laboratory data are given in *Table 1*.

After 10 years, 559 men and 224 women had died. Of these, deaths of 166 men and 73 women were classified as CVD deaths.

Individuals who died during follow-up were older (63 ± 9 vs. 47 ± 13 years, $P < 0.0001$), had a higher MAP (103.7 ± 14.7 vs. 98.1 ± 13.1 mmHg, $P < 0.001$), serum cholesterol level of 6.28 ± 1.27 vs. 6.02 ± 1.19 mmol/L, $P < 0.001$, and a lower GFR (66 ± 13 vs. 71.9 ± 13.4, $P < 0.0001$). Death was more likely in smokers (12.0 vs. 7.4%, $P < 0.0001$).

Individuals who died from a cardiovascular cause were older (64.7 ± 8.7 vs. 47.8 ± 12.9, $P < 0.0001$) and had a lower GFR (63.6 ± 12.5 vs. 71.9 ± 13.4 mL/min/1.73 m^2, $P < 0.0001$).

Distribution of GFR in males and females is given in *Table 2* and *Figure 1*. According to the stages proposed by K/DOQI,[21] 50.0 and 7.4% of participants had a GFR < 90 (CKD stage 2) and 60 mL/min/1.73 m^2 (CKD stage 3), respectively.

HR for cardiovascular mortality in the different quartiles of GFR are given in *Table 3* and *Figure 2*. Results are given as the

Table 1 Demographic variables of participants

	Males	Females
Age (years)	48.4 ± 13.3	47.8 ± 12.8
Systolic blood pressure (mmHg)	135.5 ± 17.4	130.7 ± 20.4
Diastolic blood pressure (mmHg)	81.7 ± 11.9	79.4 ± 12.1
MAP (mmHg)	99.6 ± 12.5	96.5 ± 13.8
Body weight (kg)	76.8 ± 11.5	65.8 ± 11.2
Cholesterol (mmol/L)	6.01 ± 1.13	6.05 ± 1.12
BMI	25.8 ± 3.5	25.7 ± 4.4
Corrected serum creatinine (mg/dL)	0.94 ± 0.22	0.73 ± 0.19
GFR (mL/min/1.73 m^2)	91.1 ± 22.2	123.9 ± 35.8
Uric acid (μmol/L)	370.56 ± 76.73	285.40 ± 67.81
Current smoking (%)	50.0	17.1
Total 10 year mortality (*n*)	559	224
Cardiovascular 10 year mortality (*n*)	166	73

Mortality was registered during the 10 year follow-up.

Table 2 Distribution of GFR by sex

	Men	Women
Mean ± SD	91.2 ± 22.1	92.0 ± 26.5
Median	89.4	89.3
P25–P75	75.6–104.3	74.1–106.9
P10–P90	65.3–119.2	61.2–126.4

P25, P75, P10, P90: values indicating the 25th, 75th, 10th, 90th percentile of GFR in the observed population, expressed in mL/min/1.73 m^2.

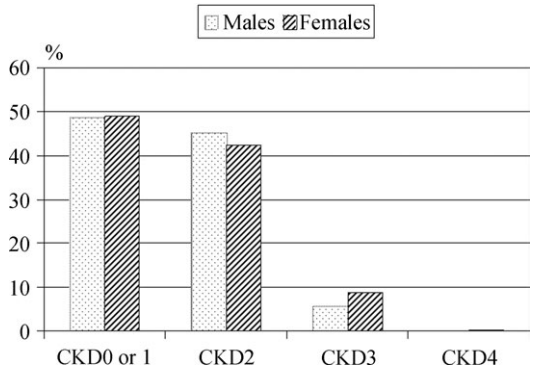

Figure 1 Distribution of CKD classification in males and females.

absolute number of CVD deaths/total number at baseline and expressed as rate per 1000 person-years (standardized for age with total population as reference). HR for cardiovascular mortality were adjusted for age and gender and, additionally, for BMI, current smoking, MAP, total cholesterol, and uric acid. The upper quartile (GFR > 105 mL/min/1.73 m^2) was taken as the reference group. Cardiovascular risk increased substantially, but not significantly in the third quartile (89.4–105 mL/min/1.73 m^2, HR = 1.9, 95% CI: 0.93–3.86) and increased further to a plateau in the second and first quartiles (<89.4 mL/min/1.73 m^2, HR = 2.62, 95% CI 1.34–5.14). Correcting for traditional cardiovascular risk factors did not alter the HR substantially, pointing to the independent impact of GFR.

In a multivariable Cox model including an interaction term between gender and GFR, the effect of GFR on CVD mortality proved to be homogeneous in men and women (interaction test: $\chi^2 = 0.16$, $P = 0.69$).

The results for cardiovascular mortality risk for GFR, expressed as a continuous variable, are given in *Table 4*. After correction for the different confounders, the cardiovascular risk decreased by 8% (RR 0.92, CI 0.85–0.99) per 10 mL/min/1.73 m^2.

Discussion

Main findings of this study

This publication is the first report on the impact of mild chronic renal impairment on cardiovascular morbidity and mortality in a large random sample of an apparently healthy general population, with a 10 year follow-up of outcome and with possibility to correct for traditional cardiovascular risk factors. It appears that mild CKD is a frequent condition in the general population. Most important, however, is the finding that the impact of CKD on the cardiovascular mortality risk starts already at near-normal levels of GFR (<90 mL/min/1.73 m^2).

This observation of the impact on cardiovascular mortality of the non-traditional risk factor 'chronic renal impairment' can be important for the further exploration of underlying mechanisms and the treatment of CVD in patients with impaired kidney function, as it relates retention of uremic waste products with CVD.[22]

Clinical impact of the results of this study

Both the NKF K-DOQI (National Kidney Foundation Dialysis Outcome Quality Initiative)[21] and the KDIGO (Kidney Disease: Improving Global Outcomes)[23] accept a GFR of 60 mL/min/1.73 m^2 as a cut-off to accept an increased risk for secondary complications of CKD. On the basis of the analysis of data compiled from 24 reported studies, Vanholder *et al.*[1] predicted a cut-off of GFR of 75 mL/min/1.73 m^2 for an increased cardiovascular risk. This meta-analysis was based on piecewise linear regression analysis of relative risks for CVD in 24 studies, including also studies with selected populations or studies applying the Cockcroft and Gault formula or uncorrected serum creatinines for estimation of glomerular filtration. Despite these drawbacks, the predicted cut-off of 75 mL/min/1.73 m^2 in that study corresponds quite well with the results of the present analysis, from which it appears that cardiovascular risk starts to increase even at higher levels of GFR, i.e. at 90 mL/min/1.73 m^2. It therefore seems advisable to advocate an enhanced vigilance for secondary cardiovascular complications in all patients in CKD class 2 or higher and to accept a GFR < 90 mL/min/1.73 m^2 as a new cardiovascular risk factor.

Our data imply that, if cost-effective, measures to prevent further progression of renal and CVD should start already very early in CKD patients and that active screening for mild renal impairment in the global population might be warranted,[15] especially when also other risk factors for CVD are present.

Comparison with the existing literature

To the best of our knowledge, there are no large-scale studies evaluating a potential cut-off of GFR as a risk factor for long-term cardiovascular risk in a large, unselected population, using proper estimates of GFR. The Hoorn study is a prospective population study with a 10 year follow-up, with a study sample of 631. In contrast with our study, the Hoorn study included also patients with pre-existing CVD and diabetes, and they used a selected population between 50 and 75 years of age. This probably explains the higher cardiovascular death rate ($n = 50$ out of 631 vs. 239 out of 8913 in our study) and the higher HR for cardiovascular mortality (1.26 per 5 mL/min/1.73 m^2 decrease of GFR vs. 0.92 per 10 mL/min/1.73 m^2 increase in GFR) in the Hoorn population.

Previous studies concentrating on the problem of glomerular filtration and CVD evaluated selected patient populations,[3–5,24,25] and/or only evaluated more severe renal dysfunction (GFR < 60 mL/min/1.73 m^2),[2,26] or introduced serum creatinine only as a continuous variable,[25] so that the upper threshold from which decreased GFR started to be negatively related to cardiovascular risk could not be

Table 3 CVD mortality rates according to quartiles of GFR

	CVD deaths[a]	CVD mortality rate[b]	HR (95% CI)[c]	HR (95% CI)[d]
Q1 (<75.6 mL/min/1.73 m^2)	95/2228	2.57	2.46 (1.27–4.78)	2.21 (1.13–4.32)
Q2 (75.6–89.4 mL/min/1.73 m^2)	60/2228	2.61	2.62 (1.34–5.14)	2.48 (1.26–4.87)
Q3 (89.4–104.3 mL/min/1.73 m^2)	32/2229	1.9	1.90 (0.93–3.86)	1.84 (0.90–3.71)
Q4 (>104.3 mL/min/1.73 m^2)	10/2228	0.99	1	1

Q1: lowest quartile, thus participants with a GFR < 75.6 mL/min/1.73 m^2; Q2: second lower quartile, thus participants with a GFR between 75.6 and 89.4 mL/min:1.73 m^2; Q3: second highest quartile, thus participants with a GFR between 89.4 and 104.3 mL/min/1.73 m^2; Q4: highest quartile, thus participants with a GFR > 104.3 mL/min/1.73 m^2. HR indicate the risk of dying expressed relatively, compared with the reference population with a GFR > 104.3 mL/min/1.73 m^2.

[a]Number of CVD deaths/total number at baseline.

[b]Per 1000 person-years (standardized for age with total population as reference).

[c]Adjusted for age and sex.

[d]Adjusted for age, sex, BMI, current smoking, MAP, total cholesterol, and uric acid.

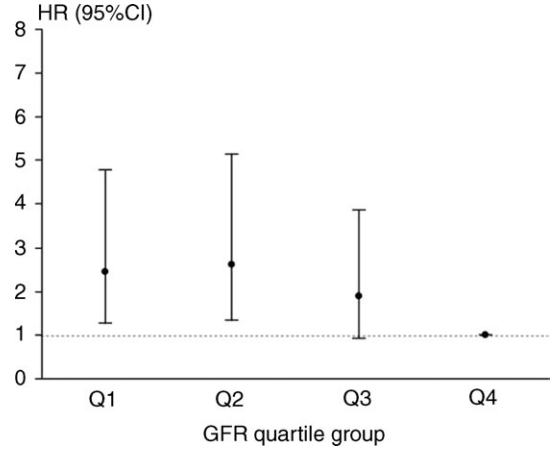

Figure 2 Age and sex-adjusted HR for CVD mortality according to quartile groups of GFR.

evaluated. Go *et al.*[2] found a dose-dependent relation between cardiovascular risk and GFR in a population of a large, integrated system of health care insurance (Kaiser Permanente), but they only evaluated cohorts with a GFR < 60 mL/min/1.73 m^2, with those having a GFR higher than 60 mL/min/1.73 m^2 as a reference. In addition, their mean follow-up was only 2.8 years, whereas our study allowed a 10 year follow-up. Shlipak *et al.*[27] analysed cardiovascular mortality in elderly patients with an estimated GFR > 60 mL/min/1.73 m^2, using Cystatin C levels to quantify glomerular filtration. They found a four-fold increase in cardiovascular risk in patients with increased Cystatin C levels.

Our study evaluated an unselected cohort, representative of the adult population in Belgium, with a follow-up of 10 years. We measured serum creatinine with the Jaffé technique using the SMAC-Technicon technology, which allowed us to recalibrate our serum creatinines to the IDMS standard, using the calibration formula as proposed by Hallan *et al.*[28] It has been shown that using this methodology allows making accurate estimations of GFR even in the near-normal range.[9] We compared subgroups on the basis of quartiles of GFR, which allowed us to indicate a more precise cut-off point of GFR level beneath which the cardiovascular risk started to increase. Using this methodology, it became apparent that even near-normal levels of GFR (<90 mL/min/1.73 m^2) were associated with an increased risk of cardiovascular death.

There is an increased risk for cardiovascular mortality in males compared with females.[29] There is also some evidence for a higher prevalence of end stage renal disease (ESRD) in males.[30,31] It is thus tempting to hypothesize that the cardiovascular risk of GFR is different in males and females. However, the interaction term for gender and GFR and cardiovascular death was not significant, pointing that the effect of GFR on cardiovascular mortality is not different in males and females.

Potential drawbacks of this study

A potential drawback of this study is that no data on proteinuria are available. It is well established that proteinuria as such is related to CVD.[32] However, proteinuria is considered to be a marker of endothelial dysfunction and colliding causes of cardiovascular and renal disease,[33] whereas GFR can rather be seen as a marker of filtration, and thus of retention of toxic waste products. The relationship between CVD and renal failure is potentially a reciprocal one, whereby evolving vascular damage, e.g. endothelial dysfunction,[34] might lead to chronic renal impairment, and, vice versa, accumulation of toxic retention solutes by renal failure might lead to enhanced vascular damage.[35–38] Our data are compatible with the hypothesis that renal dysfunction adds to the cardiovascular risk by accumulation of uremic substances, as frequency of CVD increases with declining renal function. Further exploration of this hypothesis is certainly warranted.

We have no data on incidence of cardiovascular morbidity, as we only have data on cardiovascular death. Most likely, the relation between cardiovascular morbidity and GFR is even stronger, as shown in other studies,[35] since cardiovascular mortality only reveals the most serious cases of CVD.

Conclusion

This study underscores the high prevalence of mild chronic renal failure in the general population. Even mild impairment of renal function (GFR < 90 mL/min/1.73 m^2) is a cardiovascular risk factor when correction is made for other traditional cardiovascular risk factors. Screening for mild renal impairment can thus be of importance to decrease the burden of CVD.

Table 4 Results of multivariable Cox analysis

	HR (95% CI)	χ^2	*P*-value
GFR (per 10 mL/min/1.73 m^2)	0.92 (0.85–0.99)	4.99	0.02
Sex (female)	0.59 (0.41–0.86)	7.57	0.006
Age (per 5 years)	1.79 (1.64–1.95)	173.93	<0.0001
BMI (per 5 kg/m^2)	1.03 (0.85–1.25)	0.11	0.74
Smoking (current)	1.55 (1.13–2.15)	7.17	0.007
MAP (per 10 mmHg)	1.32 (1.19–1.48)	26.08	<0.0001
Total cholesterol (per mmol/L)	1.01 (0.86–1.20)	0.03	0.87
Uric acid (per μmol/L)	1.002 (1.0002–1.003)	3.9	0.04

Acknowledgement

The BIRNH study was supported by the National Fund for Scientific Research grant no. 3.9002.79 and the Algemene Spaar-en Lijfrente Kas (semi-governmental insurance company), Brussels, Belgium. D.D. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: none declared.

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