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Original article

Renal hyperfiltration revisited—Role of the individual body surface area on mortality

Päivi E. Korhonen [a,*], Mikael O. Ekblad [a], Hannu Kautiainen [b,c], Satu Mäkelä [d]

[a] Department of General Practice, Turku University and Turku University Hospital, 20014 Turku, Finland
[b] Folkhälsan Research Center, 00250 Helsinki, Finland
[c] Unit of Primary Health Care, Kuopio University Hospital, 70210 Kuopio, Finland
[d] Department of Internal Medicine, Tampere University Hospital, 33520 Tampere, Finland

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ABSTRACT

Background: Higher than normal estimated glomerular filtration rate (eGFR), i.e. renal hyperfiltration (RHF), has been associated with mortality.
Methods: A population-based screening program in Finland identified 1747 apparently healthy middle-aged cardiovascular risk subjects in 2005–2007. GFR was estimated with the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation indexed for 1.73 m^2 and for the actual body surface area (BSA) of the subjects. This individually corrected eGFR was calculated as eGFR (ml/min/BSA m^2) = eGFR (ml/min/1.73 m^2) x (BSA/1.73). BSA was calculated by the Mosteller formula. RHF was defined as eGFR of more than 1.96 SD above the mean eGFR of healthy individuals. All-cause mortality was obtained from the national registry.
Results: The higher the eGFR, the greater was the discrepancy between the two GFR estimating equations. During the 14 years of follow-up, 230 subjects died. There were no differences in mortality rates between the categories of individually corrected eGFR (p = 0.86) when adjusted for age, sex, body mass index, systolic BP, total cholesterol, new diabetes, current smoking, and alcohol use. The highest eGFR category was associated with increased standardized mortality rate (SMR) when CKD-EPI formula indexed for 1.73 m^2 was used, but SMR was at the population level when individually corrected eGFR was applied.
Conclusions: Higher than normal eGFR calculated by the creatinine-based CKD-EPI equation is associated with all-cause mortality when indexed to 1.73 m^2, but not when indexed to actual BSA of a person. This challenges the current perception of the harmfulness of RHF in apparently healthy individuals.

1. Introduction

Renal hyperfiltration (RHF) has been associated with mortality in several studies which have estimated glomerular filtration rate (eGFR) with the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [1–9]. However, this relationship remains controversial since the pathophysiological mechanisms responsible for the association are not known. Moreover, the definition of RHF has varied between the studies, most of them using an eGFR threshold between 90 and 125 ml/min per 1.73 m^2. Also the methods to assess eGFR seem to have an impact on the association of RHF and mortality. In the meta-analyses of 11 general-population studies with over 90,000 participants, increased mortality was observed among those with eGFR ≥105 ml/min/1.73 m^2 calculated by the creatinine-based CKD-EPI equation, but the increased mortality risk was diminished when using the cystatin C-based eGFR, and eGFR based on combined measurements of creatinine and cystatin C [10].

The CKD-EPI equations index eGFR for body surface area (BSA) since GFR is proportional to kidney size. The index value of 1.73 m^2 has been chosen because it was the average calculated BSA of 25-year-old Americans in 1920s [11]. However, since then height and weight of individuals have grown substantially. For example, in Finland the average height and weight of adult males was 177 cm and 87 kg, respectively, in 2017 [12]. This corresponds a BSA of 2.07 m^2 calculated

* Corresponding author.
E-mail addresses: paivi.korhonen@utu.fi (P.E. Korhonen), moekbl@utu.fi (M.O. Ekblad), hannu.kautiainen@medcare.fi (H. Kautiainen), satu.makela@pirha.fi (S. Mäkelä).

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by the commonly used Mosteller formula [13].

In relatively large individuals, indexing eGFR for BSA of 1.73 m^2 may lead to underestimation of GFR when comparing a patient's eGFR to normal values. This is problematic when prescribing drugs with narrow therapeutic indices. Accordingly, the US National Institutes of Health (NIH) states that in very large or very small patients, eGFR should be multiplied by the BSA of a person and divided by 1.73 m^2 to obtain eGFR in units of ml/min for drug dosing [14].

Our study group has previously reported that among apparently healthy cardiovascular risk subjects, those with eGFR ≥105 ml/min/1.73 m^2 at baseline had a two-fold risk for all-cause mortality when compared to eGFR category 90–104 ml/min and to the Finnish general population when eGFR was calculated with the creatinine-based CKD-EPI equation [15]. This prompted us to investigate if the results of the 14-year study period would be different when adjusting eGFR to the actual BSA of the study subjects, that is individually corrected eGFR. We hypothesize that all-cause mortality risk associated with RHF among relatively larger subjects is lower when eGFR is indexed to the actual BSA of a person rather than to traditionally used 1.73 m^2.

2. Materials and methods

We examined 1747 white subjects drawn from the participants of the population survey carried out in southwestern Finland from autumn 2005 to autumn 2007. Inclusion criteria were age 45–70 years, hypertension, history of gestational diabetes or hypertension, family history of cardiovascular disease or at least 12 points in Finnish Diabetes Risk Score[z] (available from www.diabetes.fi/english). Exclusion criteria were established cardiovascular or renal disease or previously known diabetes. A detailed description of the enrolment and examination methods has been published earlier [15].

Clinical measurements were performed by trained study nurses: height, weight, blood pressure (BP), waist circumference. Pulse pressure was calculated as systolic BP – diastolic BP, and mean arterial pressure (MAP) as diastolic BP + 1/3 x (systolic BP – diastolic BP). Body mass index (BMI) was calculated as weight (kg) over height squared (m^2), and BSA with the Mosteller formula (weight (kg) x height (cm)/3600)^{½} [13].

Laboratory tests were performed after at least 12 h fasting. GFR was estimated from plasma creatinine values using the CKD-EPI equation for white men and women [16]. Individually corrected eGFR was calculated using the formula eGFR (ml/min/BSA m^2) = eGFR (ml/min/1.73 m^2) x (BSA/1.73) [14]. Individually corrected eGFR values were divided into five categories: ≤65, 66–84, 85–113, 114–131, and ≥132 ml/min/BSA m^2 corresponding to grades containing 5%, 20%, 50%, 20%, and 5% of the total distribution.

The test method of plasma creatinine (enzymatic method, Olympus® AU640, Japan) is calibrated to be traceable to isotope dilution mass spectrometry.

Two-hour oral glucose tolerance test (OGTT) was performed using HemoCue® Glucose 201+ system (Ängelholm, Sweden) which converts the results of capillary whole blood glucose values to plasma glucose values. Plasma total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically (Olympus AU604, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula [17].

Self-administrated questionnaires were used to assess smoking, alcohol consumption (Alcohol Use Disorders Identification Test, AUDIT), leisure-time physical activity (LTPA), education, and health-related quality of life (EuroQol instrument, EQ-5D) [18,19].

Personal lifestyle counselling was offered at the appointments of the study nurse and the study physician. Preventive antilipid and/or antihypertensive medication and low-dose aspirin was prescribed if the ten-year risk for a fatal cardiovascular event currently, or extrapolated to the age of 60 years, was ≥5% estimated by the Systematic Coronary Risk Evaluation (SCORE) system [20]. According to Finnish national guidelines at the time, antihypertensive medication was initiated if systolic BP was ≥160 mmHg or diastolic BP ≥100 mmHg (in patients with hypertensive target organ damage or diabetes ≥140/90 mmHg).

2.1. Definitions

RHF was defined as eGFR of more than 1.96 standard deviations (SDs) above the mean eGFR of healthy individuals as recommended by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [21].

Type 2 diabetes was diagnosed with fasting glucose ≥7.0 mmol/l or 2-hour postload glucose ≥12.2 mmol/l [22].

Metabolic syndrome was diagnosed according to the criteria of the International Diabetes Federation (IDF) 2005 definition [23].

Leisure-time physical activity (LTPA) was classified into three categories: high (LTPA for at least 30 min at a time for six or more times a week), moderate (LTPA for at least 30 min at a time for four to five times a week), and low (LTPA for at least 30 min at a time for a maximum of three times a week).

The Pharmacological Risk Assessment Online system (Pharao®) was used to identify the number of potentially nephrotoxic drugs [24].

2.2. Mortality data

Data on all-cause mortality was obtained from Statistics Finland. For each person, the date of the invitation to the Harmonica project was the start date of the observational period. Follow-up time ended on December 31st, 2019.

2.3. Ethical approval

The study protocol and consent forms were approved by the ethics committee of Satakunta hospital district on October 3rd 2005. All participants provided written consent for the project and subsequent medical research. All tests were complimentary and voluntary for the participants.

2.4. Statistical analysis

Descriptive statistics are presented as means with SD, as medians with interquartile range (IQR) or as counts with percentages. The hypothesis of linearity was tested using the Cochran–Armitage test, linear-by-linear, analysis of variance or logistic models with an appropriate contrast. Concordance correlation coefficient (CCC) for agreement was used for the assessment of the reproducibility of the two eGFR equations, including 95% bias-corrected accelerated bootstrap confidence intervals [25]. CCC 0.00–0.20 represents slight; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 substantial; and 0.81–1.00 almost perfect concordance [26]. Adjusted all-cause mortality based on covariate-adjusted stratified cumulative hazard function, Cox regression model; age, sex, BMI, systolic BP, total cholesterol, new diabetes, current smoking, and AUDIT score at baseline were used as covariates in these models.

Cox proportional hazards regression was used to estimate the adjusted hazard ratios (HR) and their 95% confidence intervals (CIs). The proportional-hazards assumption was evaluated by Schoenfeld residuals and log–log plots. A possible nonlinear relationship between mortality and two equations of eGFR were assessed by using 4-knot restricted cubic spline Cox regression models. The length of the distribution of knots were located at the 5th, 35th, 65th and 95th percentiles, using Harrell's recommended percentiles. The ratio of observed to expected number of deaths, the standardized mortality ratio (SMR) for all-cause deaths, was calculated using subject-years methods with 95% CIs. The expected number of deaths was calculated on the basis of sex-, age- and calendar-period-specific mortality rates in the Finnish population (Official Statistics of Finland). The normality of variables was evaluated graphically and by using the Shapiro–Wilk W test. Stata 17.0 (StataCorp LP, College Station, TX, USA) was used for the statistical analyses.

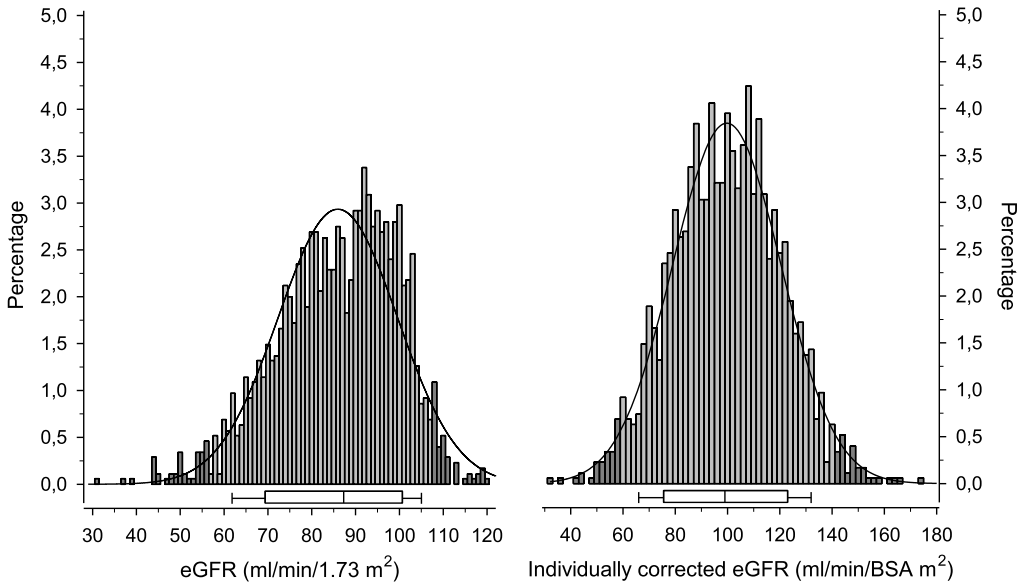

Fig. 1. Distributions of estimated glomerular filtration rate (eGFR) and individually corrected eGFR with normal curve overlay in the study population at baseline. The darkened areas denote the smallest 2.5% and the highest 2.5% of the eGFR values in the standard normal distribution. Box and whiskers plots show median and interquartile range (25th, 75th percentiles), whiskers indicate 5th and 95th percentiles.

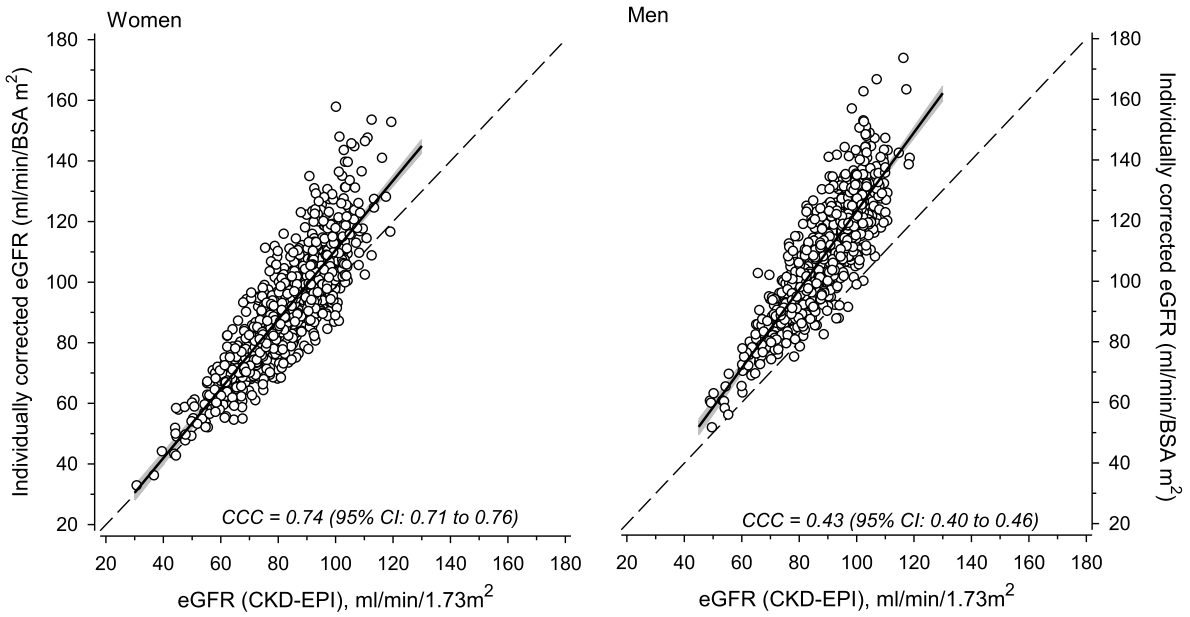

Fig. 2. Concordance between individually corrected and creatinine-based estimated glomerular filtration rates (eGFR) in women and men at baseline. Solid lines are the regression lines and gray areas show 95% confidence intervals. Dashed lines indicate complete concordance. CCC denotes concordance correlation coefficient.

3. Results

We examined 1747 home-dwelling, 45–70-years old cardiovascular risk subjects who had no previously diagnosed cardiovascular disease, diabetes or kidney disease at baseline. Their mean eGFR was 85.9 (SD 13.6) ml/min/1.73 m^2, and the mean individually corrected eGFR 99.7 (SD 20.8) ml/min/BSA m^2 (Fig. 1).

Fig. 2 illustrates the relationship between eGFR and individually corrected eGFR. In women, the concordance between the two measures was quite good at values <100 ml/min/1.73 m^2 of eGFR but decreased thereafter at higher levels. In men, individually corrected eGFR values were constantly higher than eGFR values. The higher the eGFR, the greater was the discrepancy between the two measures in both sexes.

Table 1 shows the characteristics of the subjects according to the levels of individually corrected eGFR at baseline. RHF was present in 93/1747 (5.3%) subjects. The proportion of male subjects, education years, waist circumference, smoking, alcohol use, diastolic BP, triglyceride and fasting glucose concentrations, and presence of metabolic syndrome increased linearly with increasing individually corrected eGFR. Age and LTPA level of the subjects, systolic BP and pulse pressure, total cholesterol and HDL-C levels, and 2-h glucose concentration decreased with increasing individually corrected eGFR. Regular use of antilipid, antihypertensive, and nephrotoxic drugs was more common in lower individually corrected eGFR levels.

Table 1
Baseline characteristics of the 1747 subjects according to percentile categories of estimated glomerular filtration rate. Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; EQ-5D, EuroQol Instrument; LTPA, leisure-time physical activity; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

	Individually corrected eGFR (ml/min/BSA m^2) at baseline					*P*-value for trend
	≤65 *N* = 84	66–84 *N* = 345	85–113 *N* = 880	114–131 *N* = 345	≥132 *N* = 93	
eGFRcr, ml/min/1.73 m^2, mean (SD)	57 (8)	73 (8)	87 (9)	98 (6)	104 (7)	…
Women, n (%)	73 (87)	277 (80)	463 (53)	86 (25)	17 (18)	<0.001
Height, cm, mean (SD)						
Women	159 (6)	161 (6)	163 (6)	165 (5)	168 (8)	<0.001
Men	175 (8)	172 (6)	175 (7)	178 (6)	182 (6)	<0.001
Weight, kg, mean (SD)						
Women	71 (13)	74 (12)	82 (14)	96 (14)	119 (15)	<0.001
Men	79 (9)	81 (10)	87 (12)	96 (12)	112 (17)	<0.001
BSA, m^2, mean (SD)						
Women	1.76 (0.17)	1.82 (0.16)	1.92 (0.17)	2.09 (0.16)	2.35 (0.15)	<0.001
Men	1.95 (0.15)	1.97 (0.14)	2.06 (0.15)	2.18 (0.15)	2.37 (0.19)	<0.001
Age, years, mean (SD)	64 (5)	62 (6)	59 (6)	56 (6)	52 (6)	<0.001
Education years, mean (SD)	9.7 (3.0)	9.9 (2.7)	10.2 (2.7)	10.5 (2.6)	11.2 (2.7)	<0.001
Body mass index, kg/m^2, mean (SD)	27.7 (4.6)	28.5 (4.6)	29.6 (4.6)	31.5 (4.7)	35.5 (6.4)	<0.001
Waist circumference, cm, mean (SD)						
Women	89 (13)	91 (11)	96 (12)	107 (12)	121 (11)	<0.001
Men	97 (9)	97 (8)	100 (9)	106 (10)	116 (12)	<0.001
Current smoking, n (%)	12 (14)	38 (11)	150 (17)	83 (24)	25 (27)	<0.001
AUDIT score, mean (SD)	2.5 (3.5)	3.2 (3.5)	4.8 (4.9)	6.6 (6.0)	8.2 (5.5)	<0.001
LTPA level, n (%)						<0.001
Low	13 (16)	41 (12)	160 (19)	98 (29)	38 (42)	
Moderate	37 (45)	160 (48)	422 (50)	175 (52)	38 (42)	
High	32 (39)	130 (39)	264 (31)	63 (19)	15 (16)	
Blood pressure, mmHg, mean (SD)						
Systolic	147 (19)	146 (18)	144 (18)	142 (19)	143 (22)	0.010
Diastolic	83 (10)	84 (9)	86 (10)	89 (10)	91 (11)	<0.001
Pulse pressure	65 (17)	63 (15)	60 (13)	57 (13)	54 (14)	<0.001
Mean arterial pressure	108 (10)	108 (10)	107 (10)	108 (11)	108 (11)	0.62
Plasma creatinine, μmol/l, mean (SD)	97 (17)	81 (12)	74 (13)	70 (11)	66 (10)	<0.001
Plasma lipids, mmol/l, mean (SD)						
Total cholesterol	5.49 (0.94)	5.36 (1.03)	5.27 (0.98)	5.19 (0.95)	5.18 (0.98)	0.002
HDL cholesterol	1.62 (0.45)	1.56 (0.44)	1.49 (0.45)	1.38 (0.40)	1.23 (0.28)	<0.001
LDL cholesterol	3.27 (0.86)	3.22 (0.86)	3.20 (0.87)	3.18 (0.81)	3.26 (0.88)	0.48
Triglycerides	1.36 (0.64)	1.41 (1.27)	1.37 (0.67)	1.49 (0.82)	1.56 (0.82)	0.048
Plasma glucose, mmol/l, mean (SD)						
Fasting	5.55 (0.88)	5.57 (0.77)	5.71 (1.23)	5.73 (0.91)	6.03 (1.66)	0.003
2-hour glucose	8.32 (2.58)	8.06 (2.19)	7.74 (2.42)	7.38 (2.59)	7.84 (2.55)	<0.001
New diabetes mellitus, n (%)	12 (14)	27(8)	83 (9)	33 (10)	18 (19)	0.54
Metabolic syndrome, n (%)	51 (61)	196 (57)	517 (59)	244 (71)	76 (82)	<0.001
EQ-5D score, mean (SD)	0.80 (0.21)	0.83 (0.18)	0.81 (0.17)	0.82 (0.18)	0.79 (0.19)	0.96
Regular medication, n (%)						
Antilipid	19 (23)	68 (20)	153 (17)	42 (12)	8 (9)	<0.001
Antihypertensive	48 (57)	166 (49)	408 (47)	128 (37)	42 (46)	<0.001
Nephrotoxic drugs	8 (10)	19 (6)	43(5)	16 (5)	1 (1)	0.022

3.1. All-cause mortality

For mortality, a total of 22,347 person-years (women 11,874, men 10,474) was followed up, and 230 deaths (women 94, men 136) occurred. There were no differences in mortality rates between the categories of individually corrected eGFR ($p = 0.86$) when adjusted for age, sex, BMI, systolic BP, total cholesterol, new diabetes, current smoking, and AUDIT score (Fig. 3).

Compared to the individually corrected eGFR category of 85–113 ml/min/BSA m^2, the adjusted hazard ratio (HR) for all-cause mortality was 1.18 (95% CI: 0.66 to 2.13) in category ≤65 ml/min, 0.89 (95% CI: 0.61 to 1.31) in 66–84 ml/min, 1.12 (95% CI: 0.77 to 1.62) in 114–131 ml/min, and 0.98 (95% CI: 0.49 to 1.96) in ≥132 ml/min.

Fig. 4 illustrates the adjusted HRs for all-cause mortality when eGFR and individually corrected eGFR were handled as continuous variables with eGFR 95 ml/min set as the reference.

The curve relating the categories of eGFR and SMR was U-shaped ($p < 0.001$, quadratic contrast). The highest eGFR category was associated with increased SMR. Regarding individually corrected eGFR, the highest values were not associated with increased SMR (Fig. 5).

4. Discussion

Among 45–70 years old apparently healthy cardiovascular risk subjects, RHF was associated with all-cause mortality when GFR was estimated with creatinine-based CKD-EPI equation and indexed to 1.73 m^2. However, the increased mortality risk was fully attenuated when the formula for individually corrected eGFR was used. In this observational screening and intervention program, eGFR <60 ml/min/1.73 m^2 at baseline was not associated with elevated risk for all-cause mortality during the 14-year follow up.

The creatinine-based CKD-EPI equation is the most widely used

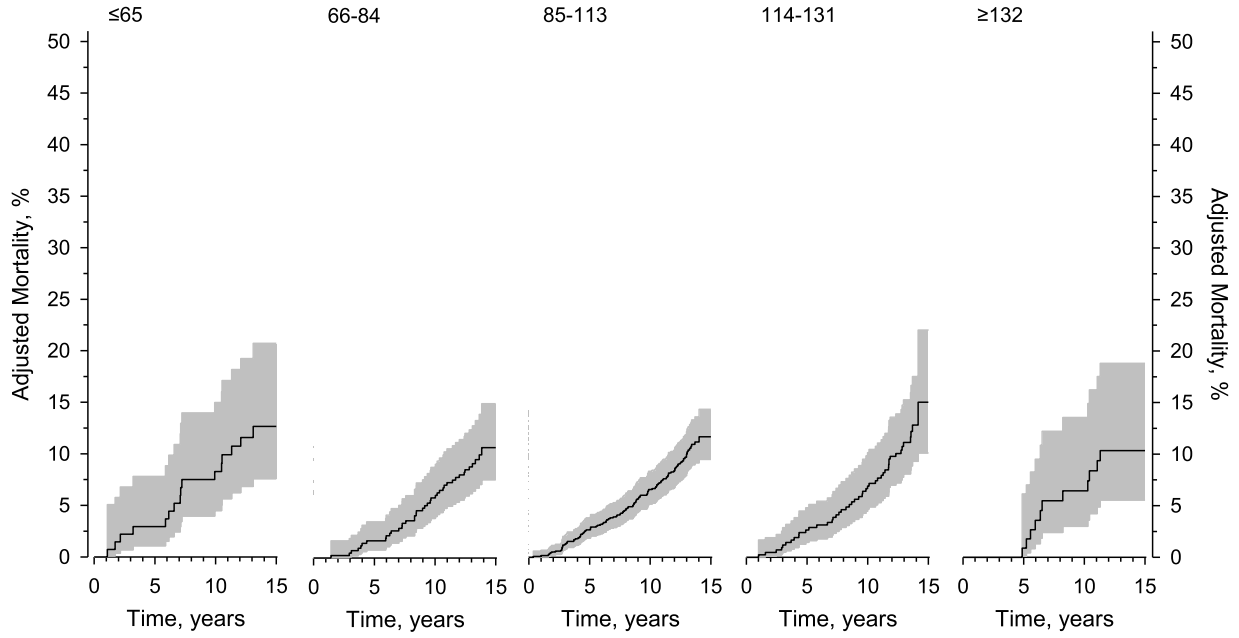

Fig. 3. Adjusted cumulative all-cause mortality in the categories individually corrected estimated glomerular filtration rate (eGFR) at baseline. Gray areas show the 95% confidence intervals. Adjustments were made for age, sex, body mass index, systolic blood pressure, total cholesterol, new diabetes, current smoking, and AUDIT score.

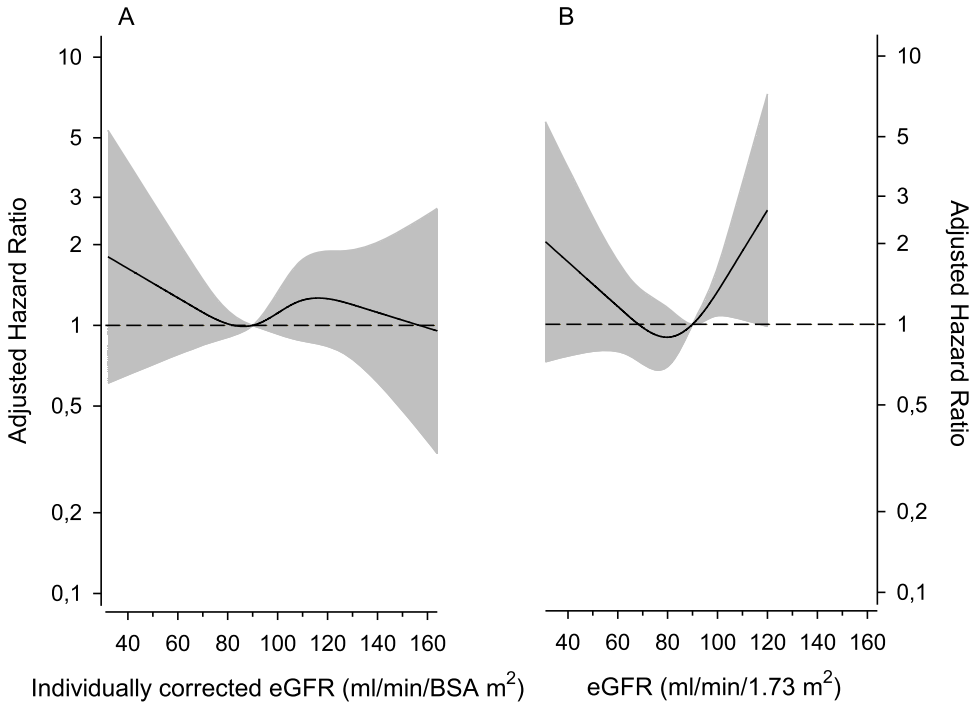

Fig. 4. Adjusted hazard ratios for all-cause mortality as a function of the continuous estimated glomerular filtration rate (eGFR) values calculated by individually corrected (Panel A) and creatine-based (Panel B) models derived from a 4-knot restricted cubic spline Cox proportional hazards regression models. The eGFR 95 ml/min was set as the reference in both models. Whiskers and the gray area represent the 95% confidence intervals. Adjustments were made for age, sex, body mass index, systolic blood pressure, total cholesterol, new diabetes, current smoking, and AUDIT score at baseline.

formula in clinical practice. In the CKD-EPI method, the effect of body size is removed by normalization and eGFR is reported in ml/min per 1.73 m^2 . As for individually corrected eGFR, the formula reports results in ml/min per BSA of a person, i.e. the actual volume of fluid passing through the glomeruli per unit of time. Previously, the increased mortality risk associated with RHF defined by eGFR ≥105 ml/min/1.73 m^2 was shown to diminish when using the cystatin C-based eGFR, and eGFR based on combined measurements of creatinine and cystatin C [10]. This difference was speculated to reflect confounding by non-GFR determinants of creatinine (muscle mass, diet, physical activity) and cystatin C (obesity, inflammation, diabetes) [10,27-30]. The results of the present study suggest that the same phenomenon can be detected by using the actual BSA of a subject in estimating GFR without measuring cystatin C. This raises the possibility that RHF may not be a pathological entity *per se*.

BSA may be regarded as the framework of the human body in which the kidneys function. It is reasonable to assume that the larger the framework, the larger the internal organs. Indeed, normal kidney size in adults has a direct positive correlation with body height and weight [31]. BSA is an absolute measure of total surface area of the human

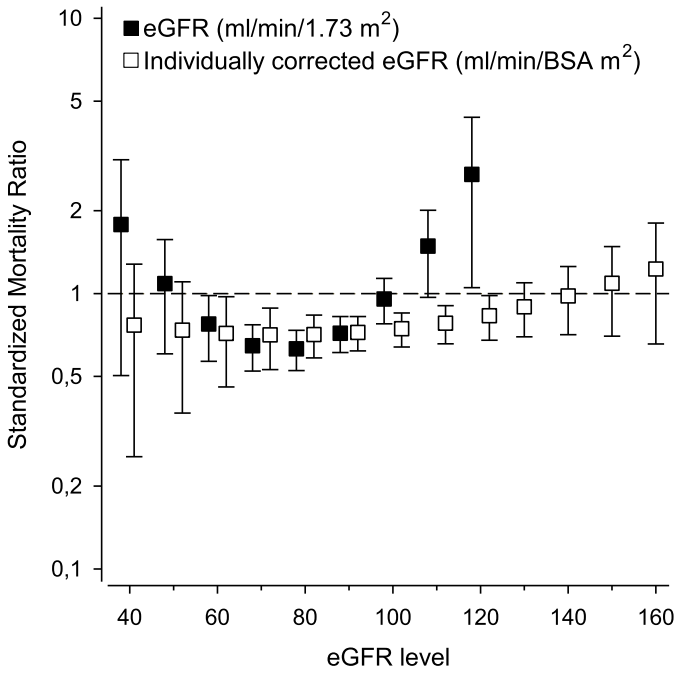

Fig. 5. Standardized mortality ratio over the 14-year follow-up according to the categories of individually corrected and creatinine-based estimated glomerular filtration rate (eGFR) at baseline.

body, whereas BMI is a ratio of weight and the square of height. Thus, the effect of height on BSA is more pronounced than that of BMI [32]. Moreover, a larger BSA has been shown to predict higher infrarenal aortic diameter [33].

Our results also imply that comparing eGFR values between different ethnic groups might benefit from using individually corrected eGFR formula. For example, an increased risk for mortality with RHF defined at cut-off values starting from 84 to 97 ml/min/1.73 m^2 in a Korean and a Finnish cohort of middle-aged men, respectively, has recently been reported [4,9]. The results may have been different if individuals' actual BSAs had been taken into account. In large international datasets, combining eGFR results from different populations and ethnic groups without acknowledging differences in mean population body size may be an obstacle.

We acknowledge limitations in our study. Despite a long follow-up period the number of deaths was quite small which may lower the power of the study. We do not have information on the study subjects' compliance to medical treatment affecting eGFR such as diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Nor do we have knowledge of any new drugs prescribed since the baseline of the Harmonica project. Our study population is a representative sample of 45–70 years old patients typically treated in primary care, but all of them are of European origin and our results may not be generalized to other age groups or ethnic groups. The baseline clinical measurements were made by trained study nurses, and data on mortality were obtained from a national register with high validity [34].

In conclusion, higher than normal eGFR calculated by the creatinine-based CKD-EPI equation is associated with all-cause mortality when indexed to 1.73 m^2, but not when indexed to actual BSA of a person. Our findings challenge the current perception of the harmfulness of RHF or at least the use of GFR estimating equations to assess RHF. To our knowledge, there are no studies regarding the association of mortality and RHF defined with measured GFR. This would be an interesting topic for future research.

4.1. Role of the funding source

This work was supported by the Finnish Cultural Foundation, Satakunta Regional Fund. The funding source had no role in the design of the study, the collection, analysis, and interpretation of the data, and the decision to approve publication of the finished manuscript.

Declaration of Competing Interest

None.

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