

Original Article

Body mass index modifies the risk of cardiovascular death in proteinuric chronic kidney disease

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Abstract

Background. In subjects with end-stage renal disease, a high body mass index (BMI) is inversely related to overall mortality, which has been coined reverse epidemiology phenomenon. This study sought to investigate this paradox as well as a possible risk modification by proteinuria on the relationship of BMI with earlier stages of chronic kidney disease (CKD) concerning cardiovascular mortality.

Methods. We used the Vienna Health Screening Initiative, a longitudinal cohort study from 1990 to 2006, including 49 398 volunteers (49.9% women, age 20–89 years): $n = 2487$ showed mild CKD (proteinuria and $\text{GFR} > 60$ ml/min/1.73 m²) and $n = 392$ showed moderate CKD ($\text{GFR} = 30\text{--}59$ ml/min/1.73 m²). The follow-up period was 5.5 ± 4.2 years; $n = 148$ cardiovascular deaths occurred. Exposure variables were BMI, glomerular filtration rate (GFR) and proteinuria. Cox regression models on cardiovascular mortality with adjustment for age, sex, log(cholesterol/HDL), uric acid, smoking, glucose, diabetes, mean blood pressure, hypertension and antihypertensive drug use were fitted.

Results. The risk factor paradox is shown in moderate CKD ($\text{GFR} = 45$ ml/min/1.73 m²): hazard ratios (HR) of BMI contrasts decreased consistently from 1.28 (95% CI 0.33–5.82) at BMI 20 kg/m² versus 25 kg/m² to 0.76 (95% CI 0.38–1.50) at BMI 30 kg/m² versus 25 kg/m² and to 0.58 (95% CI 0.13–2.64) at BMI 35 kg/m² versus 25 kg/m², thus showing an inverse relationship compared to mild CKD/healthy participants. Examining proteinuria as an effect modifier in this context showed that in moderate CKD (contrast: proteinuria versus no proteinuria) HR decreased more profoundly from 9.43 (95% CI 2.66–27.40) at BMI 25 kg/m² to 3.74 (95% CI 0.93–15.70) at BMI 30 kg/m² and to 1.95 (95% CI 0.37–22.30) at BMI 35 kg/m²,

and conversely in non-proteinuric subjects, hazards for cardiovascular mortality increased in underweight as well as in overweight/obese subjects in a U-shaped manner.

Conclusions. Our results suggest that obese subjects with proteinuric CKD may not be counselled for weight reduction since a higher BMI was associated with a remarkably reduced risk of death.

Keywords: body mass index; cardiovascular death; chronic kidney disease; proteinuria; reverse epidemiology phenomenon

Introduction

Subjects with chronic kidney disease (CKD) or end-stage renal disease (ESRD) have a dramatically increased risk of cardiovascular and overall mortality [1–3]. Interestingly, traditional key risk factors for cardiovascular disease in the general population such as obesity, hypercholesterolaemia and hypertension are inversely related to mortality in haemodialysis patients [4]. This paradox has been coined ‘risk factor reversal’ or ‘reverse epidemiology phenomenon’ [5].

In fact, it has been shown in the largest international prospective cohort study of 16 720 haemodialysis patients followed up for 5 years that irrespective of race, gender, severity of comorbidities, age, smoking and diabetic status, obesity is associated with a reduced risk of death [6].

Moreover, mild to moderate renal insufficiency was shown to be associated with elevated long-term risk of cardiovascular and overall death adjusted for several covariables [1,3,7]. The question of effect modification by body mass index (BMI) in earlier stages of CKD has been investigated in several studies: a higher BMI was associated with a higher prevalence of the metabolic syndrome, but even when adjusted for the factors of the metabolic syndrome, cardiovascular comorbidities and inflammation parameters a higher BMI was associated with a better

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overall survival in moderate CKD [8]. Another study revealed that after adjustment for case mix and surrogate parameters of the malnutrition–inflammation–cachexia syndrome this inverse association was still present in patients with CKD not yet on dialysis [9]. These findings are supported by a study where a low BMI was related to a greater mortality rate in the same context [10].

Other studies could not boundlessly confirm these findings: higher BMI and waist circumference were associated with a higher incidence of coronary heart disease among people with CKD [11]. In a cohort including rather young subjects with nondiabetic CKD, BMI did not appear to be an independent predictor of cardiovascular and overall mortality [12].

Apart from these studies, waist–hip ratio was shown to be associated with incident CKD and mortality, whereas a higher BMI appeared protective for this outcome [13].

In advanced CKD, protein–energy wasting that appears in ~20–50% of these patients is an important comorbid condition that predicts a poor clinical outcome [14]. It appears that the common pathway for several metabolic derangements is related to exaggerated protein degradation relative to protein synthesis [14].

Concerning markers of body composition, a higher BMI rather reflects both higher fat and higher muscle mass, whereas an elevated waist–hip ratio better represents the amount of visceral body fat [13,15]. Keeping in mind the high prevalence of the protein–energy wasting that is strongly associated with poor clinical outcomes in CKD [16], this study sought to elucidate whether proteinuria might be an effect modifier of the relationship between BMI and cardiovascular mortality in CKD. Additional protein loss due to proteinuria might be tolerated better in patients with a higher BMI, because a higher protein reserve might lead to a more favourable outcome in this context.

Therefore, we analysed the effects of BMI, GFR and proteinuria as well as their interactive effects on cardiovascular mortality in earlier stages of CKD, and we selected patients with mild to moderate CKD using the database of the Vienna Health Screening Initiative [17,18].

Subjects and methods

Study sample

The Vienna Health Screening Initiative is an ongoing prospective cohort study that began in 1990. Since then, preventive health examinations free of charge were regularly organized by the community of Vienna within a total of five health care centres. The study sample, recruitment of participants (volunteers) and assessment of risk factors are described in detail elsewhere [17,18].

In order to investigate volunteers at an earlier stage of kidney disease, participants with a baseline GFR <30 ml/min/1.73 m² [calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) equation] were excluded. Within the Vienna Health Study Initiative (VHSI) until 31 December 2006, 49 398 apparently healthy volunteers (49.9% women, age range 20–84 years; 50.1% men 20–89 years) performed a baseline examination at any time

within the study period. The overall attendance rate was 65%. Causes of death occurring before 31 December 2006 were assessed via record linkage with the Austrian Death Registry of the governmental Statistics Austria. Since Austrian laws regulate all deaths to be recorded in the central death registry, this approach allows an almost complete follow-up of all patients. Moreover, autopsy is required by law if a plausible cause of death is missing. This results in a high frequency of autopsy in Austria (28%), and we assume that causes of death are recorded correctly in the vast majority of patients. The study was approved by the institutional review board of the Department of Health Prevention. Informed consent was given according to the Helsinki declaration.

Ascertainment of risk factors

Assessment of medical history, habits in daily living and physical examination were performed by specially trained general practitioners and study nurses with respect to the study protocol, and chemical laboratory analyses are described in detail elsewhere [17,18].

BMI was defined as weight in kilograms divided by the square of height in metres.

The mean arterial blood pressure (MAP, mmHg) was calculated by the generally used empiric equation: MAP (mmHg) = diastolic blood pressure + (systolic blood pressure – diastolic blood pressure)/3.

CKD was classified using the National Kidney Foundation chronic kidney disease (NKF-CKD) classification [19].

Ascertainment of kidney function: creatinine was measured by means of a kinetic Jaffé method on the Hitachi 917[®] clinical chemistry analyser [17,18]. Measurements, calibration, standardization and validation were performed in a single laboratory throughout the whole study period. Kidney function was estimated by GFR [20,21], which was calculated by the abbreviated MDRD equation [22]: $GFR (ml/min/1.73 m^2) = 186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female})$. Since the MDRD formula is sensitive to the creatinine assay methodology, the following correction formula was necessary (due to our creatinine assay methodology used) to convert measured creatinine to ‘MDRD creatinine’ [23,24]: $\text{MDRD creatinine (mg/dl)} = -0.215 + 1.08 \times \text{measured creatinine}$.

Ascertainment of proteinuria: dipstick proteinuria was measured semi-quantitatively by a Combur Test[®] (Roche Inc., Vienna, Austria) using automated devices; the lowest urinary-protein detection limit was 50 mg/dl.

Determination of outcome variables: cardiovascular mortality was considered present in the case of ICD9 codes 390–459 and ICD10 codes I00–I99, respectively.

Ascertainment of confounders: baseline variables were selected as confounders if they were significantly associated with the exposure variable at baseline, as well as causally related to death from cardiovascular disease [25].

Statistical methods

Stratified baseline characteristics were summarized by mean and standard deviation for quantitative variables, and by absolute and relative group sizes for qualitative variables.

We fitted the Cox proportional hazard regression models on cardiovascular mortality with the main risk factors, i.e. the exposure variables GFR, BMI and proteinuria. Restricted cubic splines with three knots for GFR (first model) and BMI (second model) were used. Proteinuria was examined in a third model. Adjustment for the following detected confounders was done: age, sex, log(cholesterol/HDL), uric acid, smoking, fasting serum glucose, diabetes, MAP, hypertension, antihypertensive drug use, as well as for BMI, GFR and proteinuria when appropriate, i.e. depending on the exposure variable. Furthermore, a two-way interaction

term BMI*GFR (first interaction model) and finally a three-way interaction term BMI*GFR*proteinuria (second interaction model) were introduced.

The results of these first and second models (nonlinear spline effect prediction) were summarized by predefined BMI and GFR levels. In addition to calculated contrasts, estimated effects of increasing BMI and GFR were plotted. The results of the third model (exposure variable proteinuria) were only calculated. In order to investigate the ‘risk factor paradox’, the estimated effects (first interaction model; nonlinear spline effect prediction) of increasing

Table 1. Baseline characteristics: (a) quantitative parameters, (b) qualitative parameters

	SFKD	Mild CKD	Moderate CKD
(a) Quantitative parameters			
Sample size (<i>n</i>)	<i>n</i> = 46 519	<i>n</i> = 2487	<i>n</i> = 392
Age (years)	43 ± 12	40 ± 12	62 ± 15
GFR (ml/min/1.73 m ²)	100 ± 19	98 ± 21	53 ± 11
Total cholesterol (mg/dl)	217 ± 41	212 ± 42	231 ± 41
LDL cholesterol (mg/dl)	133 ± 37	126 ± 38	146 ± 43
HDL cholesterol (mg/dl)	61 ± 16	63 ± 16	60 ± 17
Triglycerides (mg/dl)	119 ± 75	126 ± 74	139 ± 86
Cholesterol/HDL	3.8 ± 1.3	3.6 ± 1.2	4.2 ± 1.5
Uric acid (mg/dl)	5.2 ± 1.3	5.1 ± 1.3	6.0 ± 1.6
Fasting serum glucose (mg/dl)	87 ± 12	84 ± 14	93 ± 21
BMI (kg/m ²)	24.1 ± 3.4	24.0 ± 3.8	26.1 ± 3.4
Systolic blood pressure (mmHg)	127 ± 15	124 ± 15	135 ± 18
Diastolic blood pressure (mmHg)	80 ± 9	79 ± 9	82 ± 9
MAP (mmHg)	95 ± 10	94 ± 10	99 ± 11
(b) Qualitative parameters			
Sample size (<i>n</i> , %)	<i>n</i> = 46 519	<i>n</i> = 2487	<i>n</i> = 392
Cardiovascular death	<i>n</i> = 89	<i>n</i> = 19	<i>n</i> = 40
Men	23 504 (51%)	995 (40%)	102 (26%)
Women	23 015 (49%)	1492 (60%)	290 (74%)
BMI groups			
Underweight	831 (2%)	106 (4%)	5 (1%)
Normal range	27 445 (59%)	1518 (61%)	172 (44%)
Overweight	15 201 (33%)	683 (28%)	180 (46%)
Obesity	3042 (6%)	180 (7%)	35 (9%)
Blood pressure groups			
Normal range	13 983 (30%)	902 (36%)	68 (17%)
Prehypertension	22 316 (48%)	1129 (45%)	162 (41%)
Hypertension stage 1	8626 (19%)	384 (16%)	119 (31%)
Hypertension stage 2	1594 (3%)	72 (3%)	43 (11%)
Antihypertensive drug use			
ACE inhibitors	498 (1.1%)	32 (1.3%)	27 (6.9%)
Calcium antagonists	142 (0.3%)	7 (0.3%)	8 (2.0%)
Diuretics	63 (0.1%)	1 (0.0%)	9 (2.3%)
Beta blockers	770 (1.7%)	55 (2.2%)	34 (8.7%)
Blood glucose groups			
Normal	42 379 (91.1%)	2328 (93.6%)	309 (78.8%)
Impaired fasting glucose	3907 (8.4%)	137 (5.5%)	76 (19.4%)
Diabetes mellitus	230 (0.5%)	22 (0.9%)	7 (1.8%)
Smoking status			
Non-smoker	25 578 (55%)	1175 (47%)	273 (70%)
Ex-smoker	7157 (15%)	325 (13%)	57 (14%)
Current smoker	13784 (30%)	987 (40%)	62 (16%)
Alcohol consumption			
<3 drinks/week	41 402 (89%)	2239 (90%)	353 (90%)
≥3 drinks/week	5117 (11%)	248 (10%)	39 (10%)
Physical exercise			
No	39 799 (86%)	2182 (88%)	355 (91%)
Yes	6720 (14%)	305 (12%)	37 (9%)

SFKD, seemingly free of kidney disease (GFR >60 ml/min/1.73 m², no proteinuria); mild CKD (GFR >60 ml/min/1.73 m² and proteinuria); moderate CKD (GFR = 30–59 ml/min/1.73 m²) [11]; GFR, glomerular filtration rate; BMI, body mass index; MAP, mean arterial blood pressure. Data are means (standard deviations) or percentages, respectively.

BMI and GFR were plotted, and in addition contrasts were calculated. Finally, in order to investigate a possible effect modification by proteinuria on the ‘risk factor paradox’, the estimated effects (second interaction model; nonlinear spline effect prediction) of increasing BMI and GFR stratified by the presence of proteinuria were plotted, and in addition contrasts were calculated.

All data analysis was done in the R environment for statistical computing, version 2.6.1, using Frank Harrell’s Design Library, version 2.1 [26,27].

Results

Overall, 49 398 seemingly healthy volunteers at baseline were included in the study. The mean observation period (time span between the baseline examination and death) was 5.5 ± 4.2 years. A total of 513 participants died: 148 participants died from cardiovascular disease, and 365 from other causes. At baseline 2487 participants had a GFR >60 ml/min/1.73 m² and proteinuria, i.e. mild-CKD group (CKD stages 1 and 2), and 392 participants were classified into the moderate-CKD group, i.e. GFR = 30–59

Table 2. Glomerular filtration rate (ml/min/1.73 m²) stratified by weight groups and CKD stages

Weight groups	SFKD	Mild CKD	Moderate CKD
Underweight	107 ± 21	80 ± 8	47 ± 24
Normal	101 ± 20	81 ± 7	52 ± 13
Overweight	98 ± 19	80 ± 7	53 ± 9
Obesity	99 ± 19	80 ± 8	52 ± 11

SFKD, seemingly free of kidney disease (GFR >60 ml/min/1.73 m², no-proteinuria); mild chronic kidney disease CKD (GFR >60 ml/min/1.73 m² and proteinuria); moderate CKD (GFR = 30–59 ml/min/1.73 m²).

The NHLBI classification defines body mass index (BMI) <18.5 kg/m² as underweight, BMI = 18.5–24.9 kg/m² as normal, BMI = 25.0–29.9 kg/m² as overweight and BMI ≥ 30 kg/m² as obesity [11,13].

ml/min/1.73 m² (CKD stage 3) [19]. Nineteen cardiovascular deaths were observed in the mild CKD group, and 40 cardiovascular deaths in the moderate CKD group.

Quantitative baseline characteristics stratified by the predefined CKD groups, i.e. seemingly free of kidney disease (SFKD), mild CKD (CKD stages 1 and 2) and moderate CKD (CKD stage 3), are shown in Table 1a; with increasing severity of CKD we observed higher age, slightly higher cholesterol/HDL, higher uric acid, higher fasting serum glucose, higher BMI and higher MAP.

Regarding qualitative baseline characteristics (Table 1b), we observed with increasing severity of CKD a much higher proportion of women versus men, increasing BMI, increasing blood pressure/hypertension, increasing antihypertensive drug use, a higher proportion of impaired fasting glucose/diabetes mellitus despite a very low prevalence, lower current smokers, similar alcohol consumption and lower physical exercise.

Different GFR levels stratified by weight groups and CKD stages are shown in Table 2: with increasing severity of CKD, GFR decreases, but remains very similar in the different weight groups [19,28].

Estimated effects of BMI and GFR on cardiovascular mortality in a fully adjusted model are shown in Figure 1A and B, respectively. Concerning BMI, hazards increased in underweight as well as in overweight/obese compared to normal weight subjects: contrast 20 versus 25 kg/m², hazard ratios (HR) 1.35 (95% CI 0.82–2.20); contrast 30 versus 25 kg/m², HR 1.37 (95% CI 1.07–1.75); contrast 35 versus 25 kg/m², HR 2.05 (95% CI 1.19–3.55). Concerning GFR, hazards increased with decreasing GFR: contrast 45 versus 75 ml/min/1.73 m², HR 1.72 (95% CI 1.17–2.52); contrast 75 versus 105 ml/min/1.73 m², HR 1.41 (95% CI 1.08–1.85). The HR of proteinuria versus no proteinuria in the fully adjusted model was 3.35 (95% CI 1.67–6.71).

The ‘risk factor paradox’ is demonstrated in Figure 2 and Table 3. In moderate CKD (GFR = 45 ml/min/m²), HR decreased consistently from 3.1 to 1.3 compared to

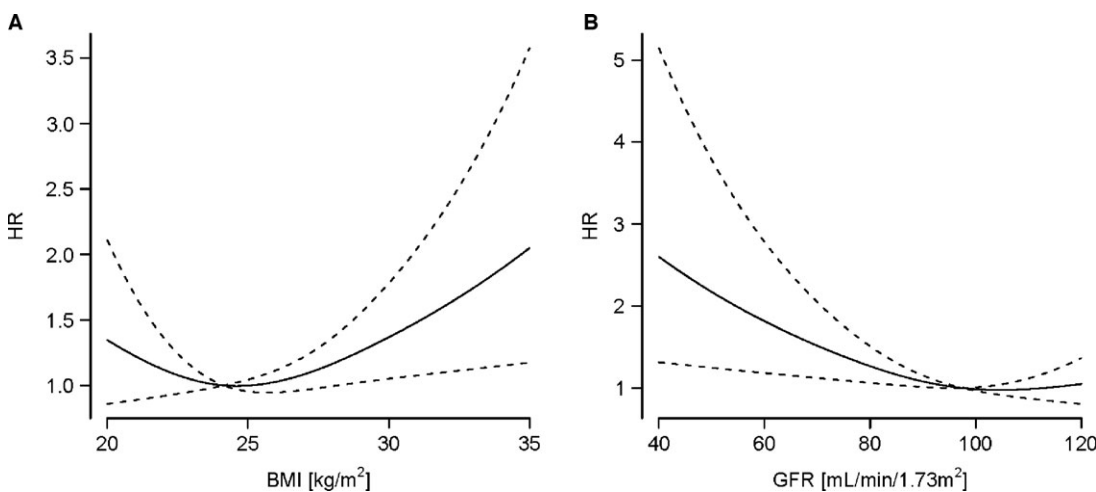


Fig. 1. (A) Effect of BMI on cardiovascular mortality. Predicted hazard ratios (95% CI) of cardiovascular death depending on BMI adjusted for age, sex, log(cholesterol/HDL), uric acid, smoking, fasting serum glucose, diabetes, MAP, hypertension, antihypertensive drug use, proteinuria and GFR. (B) Effect of GFR on cardiovascular mortality. Predicted hazard ratios (95% CI) of cardiovascular death depending on GFR adjusted for age, sex, log(cholesterol/HDL), uric acid, smoking, fasting serum glucose, diabetes, MAP, hypertension, antihypertensive drug use, proteinuria and BMI.

overall hazards when BMI increased from 20 to 35 kg/m², showing an inverse relationship compared to mild CKD as well as seemingly healthy participants. Respective effect contrasts of BMI depending on GFR concerning cardiovascular mortality are shown in Table 3.

Investigating a possible effect modification by the presence of proteinuria in this context revealed opposite findings: in non-proteinuric subjects, hazards for cardiovascu-

lar mortality increased in underweight as well as in overweight/obese subjects depending on GFR, i.e. showing a U-shaped curve (Figure 3A). In contrast, the ‘risk factor paradox’ is observed only in proteinuric participants. In moderate CKD, effect modification by proteinuria showed that a remarkably elevated HR decreased rapidly from 7.0 to 1.3 compared to overall hazards when BMI increased from 20 to 35 kg/m². In mild CKD, this paradox was still present, but considerably attenuated (Figure 3B). Respective effect contrasts of proteinuric versus non-proteinuric CKD depending on BMI and GFR concerning cardiovascular mortality are shown in Table 4.

It is noteworthy that the prevalence of proteinuria is increasing rapidly with decreasing GFR up to 40% in moderate CKD as shown in Figure 4A, whereas it is widely constant at ~6–7% in a broad BMI range and slowly increasing up to ~8% at a BMI of 35 kg/m² (Figure 4B).

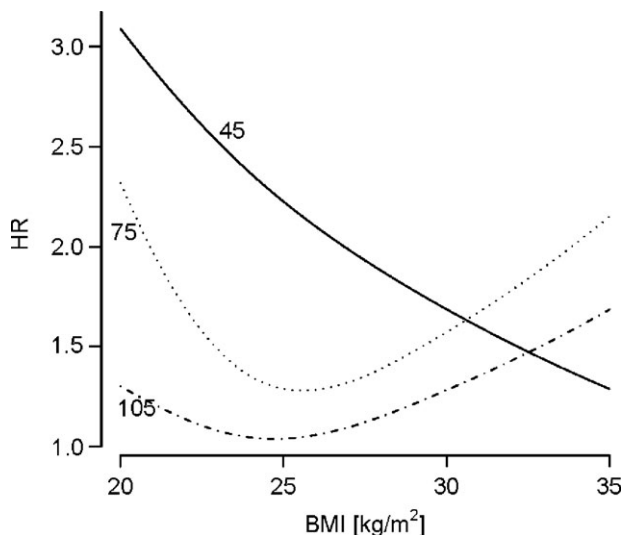


Fig. 2. Effect of BMI and GFR on cardiovascular mortality. Predicted hazard ratios (y-axis) of cardiovascular death depending on BMI (x-axis) and GFR (denoted by dashed line for GFR = 105 ml/min/1.73 m², dotted line for GFR = 75 ml/min/1.73 m², solid line for GFR = 45 ml/min/1.73 m²), compared to overall hazards adjusted for age, sex, log(cholesterol/HDL), uric acid, smoking, fasting serum glucose, diabetes, MAP, hypertension and antihypertensive drug use. Calculated contrasts are shown in Table 3.

Table 3. Effect contrasts of BMI depending on GFR on cardiovascular mortality

GFR (ml/min/1.73 m ²)	BMI (kg/m ²) contrasts	Predicted effect
45	20 versus 25	1.28 (0.33–5.82)
	30 versus 25	0.76 (0.38–1.50)
	35 versus 25	0.58 (0.13–2.64)
75	20 versus 25	1.80 (1.05–3.06)
	30 versus 25	1.18 (0.93–1.60)
	35 versus 25	1.67 (0.91–3.05)
105	20 versus 25	1.25 (0.50–3.13)
	30 versus 25	1.23 (0.78–1.94)
	35 versus 25	1.62 (0.59–4.43)

Estimated hazard ratios (95% confidence intervals) depending on GFR and BMI adjusted for age, sex, log(cholesterol/HDL), uric acid, smoking, fasting serum glucose, diabetes, MAP, hypertension and antihypertensive drug use.

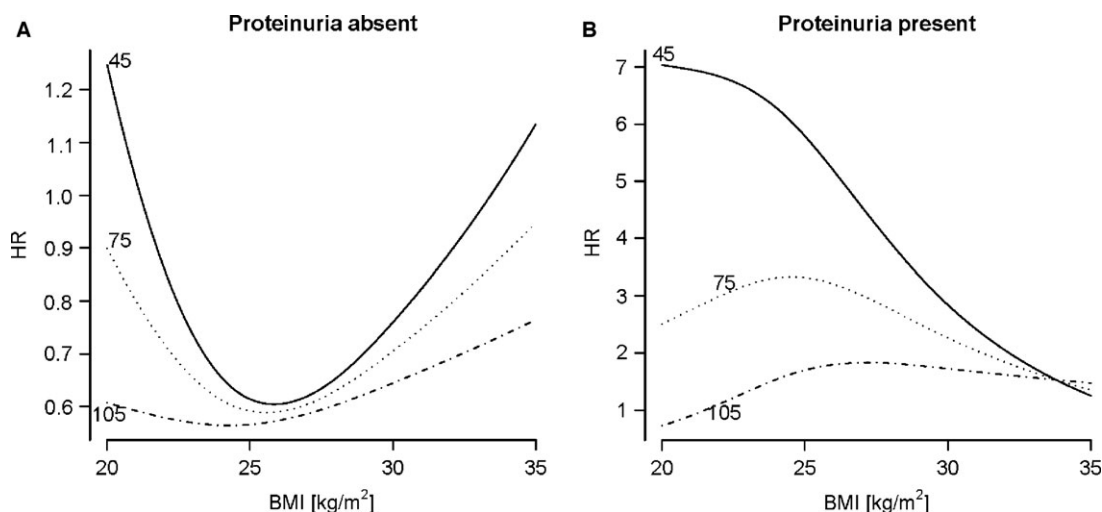


Fig. 3. (A) Effect of BMI and GFR in non-proteinuric subjects on cardiovascular mortality. Predicted hazard ratios (y-axis) of cardiovascular death depending on BMI (x-axis) and GFR in non-proteinuric subjects (denoted by dashed line for GFR = 105 ml/min/1.73 m², dotted line for GFR = 75 ml/min/1.73 m², solid line for GFR = 45 ml/min/1.73 m²), compared to overall hazards adjusted for age, sex, log(cholesterol/HDL), uric acid, smoking, fasting serum glucose, diabetes, MAP, hypertension and antihypertensive drug use. (B) Effect of BMI, GFR and proteinuria on cardiovascular mortality. Predicted hazard ratios (y-axis) of cardiovascular death depending on BMI (x-axis) and GFR stratified for proteinuria (denoted by dashed line for GFR = 105 ml/min/1.73 m², dotted line for GFR = 75 ml/min/1.73 m², solid line for GFR = 45 ml/min/1.73 m²), compared to overall hazards adjusted for age, sex, log(cholesterol/HDL), uric acid, smoking, fasting serum glucose, diabetes, MAP, hypertension and antihypertensive drug use.

Discussion

Our data support the hypothesis that highly elevated BMI may reduce the risk of cardiovascular death only in subjects having proteinuric CKD, whereas opposite effects appear in non-proteinuric CKD.

Regarding our stepwise examination of the ‘risk factor paradox’, we first separately investigated the impact of BMI, GFR and proteinuria on cardiovascular mortality in fully adjusted models. As expected, BMI increased risk of cardiovascular death in underweight as well as overweight/obese subjects [29]. With decreasing GFR as well as the presence of proteinuria, the risk of cardiovascular death continuously increased [30,31].

When examining the ‘risk factor paradox’ in earlier stages of CKD, our results generally support this phenomenon. In moderate CKD, hazards decreased with increasing BMI, showing an inverse relationship compared to mild CKD as well as seemingly healthy participants.

This finding is supported by many of the studies using BMI as the parameter for evaluation of body composition [8–10,13].

Table 4. Effect contrasts of proteinuria versus no proteinuria depending on BMI and GFR concerning cardiovascular mortality

GFR (ml/min/1.73 m ²)	BMI (kg/m ²) contrasts	Proteinuria versus no proteinuria predicted effect
45	25	9.43 (2.66–27.4)
	30	3.74 (0.93–15.7)
	35	1.95 (0.37–22.3)
75	25	5.61 (2.37–13.3)
	30	3.22 (1.19–8.72)
	35	1.43 (0.17–12.1)
105	25	3.01 (0.66–13.6)
	30	2.68 (0.55–13.2)
	35	1.93 (0.14–32.9)

Estimated hazard ratios (95% confidence intervals) depending on GFR, BMI and the presence of proteinuria adjusted for age, sex, log(cholesterol/HDL), uric acid, smoking, fasting serum glucose, diabetes, MAP, hypertension and antihypertensive drug use.

Concerning this paradox some controversy exists, and a plausible hypothesis is not yet proposed. Our observational study cannot answer this question either. However, keeping in mind the protein–energy wasting in CKD patients due to the high prevalence of the malnutrition–inflammation–cachexia syndrome in up to 50% of participants, it appears plausible that additional protein loss due to proteinuria might be better tolerated in subjects with a higher BMI due to a higher protein reserve.

Indeed, our results suggest that proteinuria may be an effect modifier of the relationship between BMI and cardiovascular mortality in CKD: in this study the ‘risk factor paradox’ was observed only in proteinuric participants and this paradox was most of all present in moderate CKD, whereas in mild CKD it was still present, but considerably attenuated.

In our study cohort, the prevalence of proteinuria is increasing rapidly to 40% of participants with decreasing GFR, whereas it is widely constant at ~6–8% in a broad BMI range. This appears as a plausible explanation why proteinuric participants with moderate CKD having an elevated BMI are more likely to benefit concerning the outcome, compared to normal weight subjects, who might become malnourished.

It is noteworthy that in this study cohort, even subjects with a BMI of 35 kg/m² having proteinuric moderate CKD showed a 20–30% elevated HR for cardiovascular death, which is very similar to subsets of participants that were nonproteinuric. Maybe a BMI >35 kg/m² represents the changing point, where a continuously increasing BMI becomes protective concerning the outcome only in the subset of patients having proteinuric moderate CKD, but this could not be examined in this study due to the very low prevalence of severely obese subjects. This assumption is supported by another study where a higher BMI was shown to be associated with a higher prevalence of the metabolic syndrome, but even when adjusted for the factors of the metabolic syndrome, cardiovascular comorbidities and inflammation parameters a higher BMI was associated with a better overall survival in moderate CKD [8]. Apart from this, a higher

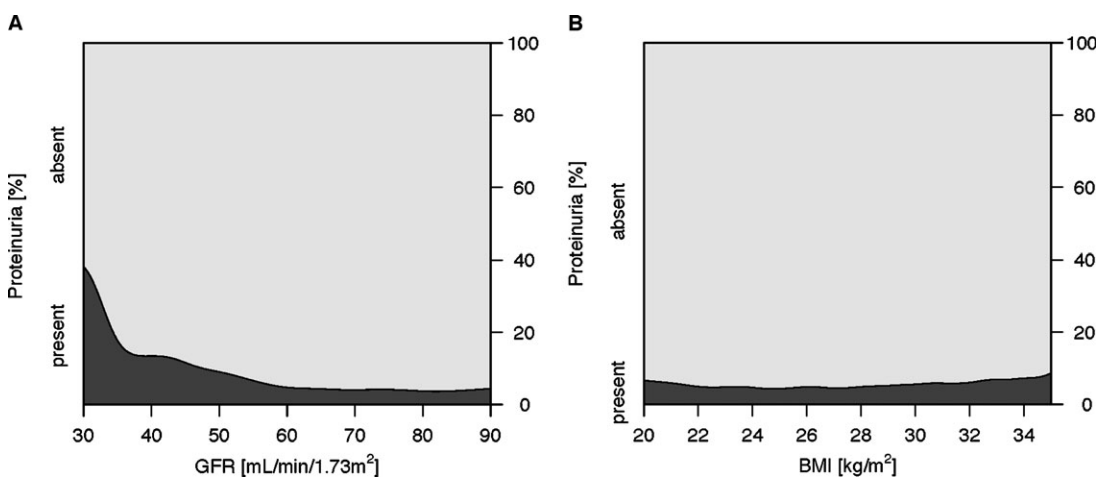


Fig. 4. (A) Prevalence of proteinuria depending on GFR. Black area indicates percentages of proteinuria for varying GFR levels. (B) Prevalence of proteinuria depending on BMI. Black area indicates percentages of proteinuria for varying GFR levels.

waist–hip ratio was shown to be associated with incident CKD and increased overall mortality, whereas a higher BMI appeared protective for this outcome [13].

This raises the question of an ideal parameter for evaluation of body composition in this context: the waist–hip ratio is much more strongly associated with the metabolic syndrome and all its unfavourable consequences compared to BMI, which reflects the individual amount of muscle mass, fat mass and bone mass. But in our rather young cohort, BMI would better reflect the amount of muscle mass, and thus nutritional status, compared to e.g. waist–hip ratio, because ageing body composition generally changes and muscle mass shifts to fat mass accompanied by a lower bone mass [15,32].

Therefore, effect modification by proteinuria may close the gap between the conflicting findings from some other studies examining the ‘risk factor paradox’ where BMI is widely used as marker of body composition. BMI and mean age as well as the prevalence and amount of proteinuria vary considerably in different study cohorts thus inevitably leading to different findings concerning the suggested benefit of a higher BMI when investigating the relationship between CKD and cardiovascular mortality [32,33].

It is noteworthy that the current analysis cannot test causal inference. Furthermore, participants of a voluntary health screening were analysed; thus, the death rates were low. This remarkably reduces statistical power, and therefore, interpretation of HR is a more accurate reflection of the relationships than an actual *P*-value. The complexity of the statistical models, i.e. the number of covariables and the number of tested hypotheses, had to be *a priori* restricted in order to avoid overfitting as well as the multiple hypotheses testing problem. Although the analysis was adjusted for potential confounders of the association between elevated BMI, GFR and proteinuria, non-measured variables could not be included into the analysis, e.g. inflammatory parameters such as ultrasensitive C-reactive protein or serum albumin. Apart from this, the results are not generalizable to a community-based population due to the recruitment of seemingly healthy participants, e.g. the prevalence of diabetes is really low in this cohort. Moreover, using estimated GFR calculated by the MDRD formula to represent the severity of kidney disease is not a gold standard method and correction of routine measured creatinine to ‘MDRD creatinine’ is mandatory [23]. Nevertheless imprecision and bias are greater at a higher GFR, limiting the accuracy of classification in the mildly decreased GFR group [34]. This may have led to an underestimation of GFR. Moreover, the MDRD formula is less precise in the obese, but it must be considered as the second best choice compared to a gold standard method when performing epidemiologic studies [35]. Dipstick proteinuria measurement is only able to pick up proteinuria with a lowest detection limit of 50 mg/dl. Therefore, some subjects with CKD stages 1 and 2 are likely misclassified as being normal. However, dipstick tests are cheap, widely used in health screening projects as well as in large epidemiologic studies and its sensitivity and specificity were 81% and 77%, respectively, when compared with the true quantitative evaluation of proteinuria either by time urine collection or by the ratio of protein to creatinine in a spot urine sample [36,37,38]. Due to our

study hypothesis, i.e. testing the association of a high BMI with GFR in proteinuric patients, this should be considered as a minor limitation. From a pathophysiologic viewpoint, subjects having higher amounts of proteinuria should more likely benefit from a higher BMI.

Despite these limitations, the present analysis may have important implications for the clinical practice. In individual patients with normal renal function, obesity is a key risk factor for long-term mortality. Weight reduction, although not analysed in this observational study, is likely to be of major benefit in the general population [38,39]. It is noteworthy that in middle-aged people, maintaining a stable BMI seemed to be protective for maintaining kidney function in CKD even in obese subjects [40].

Improving nutritional status in mild to moderate CKD accompanied by the hope of a survival benefit in this subset of patients needs to be investigated in interventional studies using a series of parameters for evaluation of body composition other than BMI [16]. Furthermore, patient-specific measures such as quantitative proteinuria, and moreover, parameters of the metabolic syndrome as well as of the malnutrition–cachexia syndrome, need to be taken into account. The different subsets of subjects with mild to moderate renal failure may benefit from individually adapted preventive measures.

Our results suggest that obese subjects with proteinuric kidney disease may not be counselled for weight reduction since a higher BMI was associated with a reduced risk of death. However, the clinical significance is yet to be investigated.

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References

1. Weiner DE, Tighiouart H, Amin MG *et al.* Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004; 15: 1307–1315
2. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32: S112–119
3. Cullerton BF, Larson MG, Wilson PWF *et al.* Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999; 56: 2214–2219
4. Goodkin DA, Bragg-Gresham JL, Koenig KG *et al.* Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; 14: 3270–3277
5. Kalantar-Zadeh K, Block G, Humphreys MH *et al.* Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003; 63: 793–808
6. Leavey SF, McCullough K, Hecking E *et al.* Body mass index and mortality in ‘healthier’ as compared with ‘sicker’ haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2001; 16: 2386–2394
7. Muntner P, He J, Hamm L *et al.* Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 2002; 13: 745–753

8. Kwan BCH, Murtaugh MA, Beddhu S. Associations of body size with metabolic syndrome and mortality in moderate chronic kidney disease. *Clin J Am Soc Nephrol* 2007; 2: 992–998
9. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Paradoxical association between body mass index and mortality in men with CKD not yet on dialysis. *Am J Kidney Dis* 2007; 49: 581–591
10. Evans M, Fryzek JP, Elinder C-G *et al.* The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. *Am J Kidney Dis* 2005; 46: 863–870
11. 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
12. Madero M, Sarnak MJ, Wang X *et al.* Body mass index and mortality in CKD. *Am J Kidney Dis* 2007; 50: 404–411
13. Elsayed EF, Sarnak MJ, Tighiouart H *et al.* Waist–hip ratio, body mass index, and subsequent kidney disease and death. *Am J Kidney Dis* 2008; 52: 29–38
14. Ikitzler TA. Nutrition, inflammation and chronic kidney disease. *Curr Opin Nephrol Hypertens* 2008; 17: 162–167
15. Baumgartner RN, Heymsfield SB, Roche AF. Human body composition and the epidemiology of chronic disease. *Obes Res* 1995; 3: 73–95
16. Kovesdy CP, Kalantar-Zadeh K. Why is protein-energy wasting associated with mortality in chronic kidney disease? *Semin Nephrol* 2009; 29: 3–14
17. Obermayr RP, Temml C, Knechtelsdorfer M *et al.* Predictors of new-onset decline in kidney function in a general middle-European population. *Nephrol Dial Transplant* 2008; 2: 1265–1273
18. Obermayr RP, Temml C, Gutjahr G *et al.* Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol* 2008; 19: 2407–2413
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39(Suppl 1): S1–S266
20. Stevens LA, Coresh J, Greene T *et al.* Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 354: 2473–2483
21. Coresh J, Stevens LA. Kidney function estimation equations: where do we stand? *Curr Opin Nephrol Hypertens* 2006; 15: 276–284
22. Levey AS, Bosch JP, Lewis JB *et al.* Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; 130: 461–470
23. Van Biesen W, Vanholder R, Veys N *et al.* The importance of standardization of creatinine in the implementation of guidelines and recommendations for CKD: implications for CKD management programs. *Nephrol Dial Transplant* 2006; 21: 77–83
24. Hallan S, Asberg A, Lindberg M *et al.* Validation of the modification of diet in renal disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. *Am J Kid Dis* 2004; 44: 84–93
25. Szklo M, Nieto FJ. *Epidemiology Beyond the Basics*, 2nd edn. Boston, MA: Jones and Bartlett Publishers, 2007, 154–187
26. Harrell EF. *Regression Modelling Strategies*. New York: Springer, 2001
27. R Development Core Team. 2008. R: a language environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at <http://www.R-project.org>. Last accessed 2008-11-12
28. National Heart, Lung and Blood Institute, National Institutes of Health. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report*. Bethesda, MD: National Institutes of Health, 1998
29. McGee DL, Diverse Populations Collaboration. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol* 2005; 15: 87–97
30. De Zeeuw D. Renal disease: a common silent killer. *Nat Clin Pract Cardiovasc Med* 2008; 5(Suppl 1): S27–S35
31. Schiffrin EL, Lipman ML, Mann JFE. Chronic kidney disease: effects on the cardiovascular system. *Circulation* 2007; 116: 85–97
32. Janssen I, Kazmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 2004; 79: 379–384
33. 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
34. Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007; 298: 2038–2047
35. Bird NJ, Peters C, Michell AR *et al.* Reliability of the MDRD method for estimating glomerular filtration rate in relation to gender, body mass index and extracellular fluid volume. *Eur J Clin Invest* 2008; 38: 486–493
36. De Jong PE, Van Der Velde M, Gansevoort RT *et al.* Screening for chronic kidney disease. Where does Europe go? *Clin J Am Soc Nephrol* 2008; 3: 616–623
37. Abebe J, Eigbefoh J, Isabu P *et al.* Accuracy of urine dipsticks, 2-h and 24-h urine collections for protein measurement as compared with the 24-h collection. *J Obstet Gynaecol* 2008; 28: 469–500
38. Nilsson PM. Is weight loss beneficial for reduction of morbidity and mortality? What is the controversy about? *Diabetes Care* 2008; 31(Suppl 2): S278–S283
39. Andres R, Muller DC, Sorkin JD. Long-term effects of change in body weight on all-cause mortality: a review. *Ann Intern Med* 1993; 119: 737–743
40. Tokashiki K, Tozawa M, Iseki C *et al.* Decreased body mass index as an independent risk factor for developing chronic kidney disease. *Clin Exp Nephrol* 2008; 13: 55–60

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