

Original Paper

Regional Variation of Chronic Kidney Disease in Germany: Results From Two Population-Based Surveys

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Key Words

Albuminuria • Chronic kidney disease • Cohort study • Creatinine • Cystatin C • eGFR • Prevalence

Abstract

Background/Aims: Due to the increasing prevalence of risk factors for chronic kidney disease (CKD), kidney dysfunction becomes a major public health problem. We investigated the CKD prevalence and determined to what extent the variation of risk factors explains the different CKD prevalence in Germany. **Methods:** We analyzed data from 6,054 participants, aged 31 to 82 years, from the Study of Health in Pomerania (SHIP-1) in Northeast Germany and the Cooperative Health Research in the Region of Augsburg (KORA F4) Study in Southern Germany. Regional differences in selected percentiles corresponding to the cutpoints for estimated glomerular filtration rate (eGFR, <60 ml/min per 1.73 m²) and albumin-to-creatinine ratio (ACR, ≥30 mg/g) were tested using quantile regression models that adjusted for CKD risk factors. **Results:** The prevalence of decreased eGFR_{creatinine-cystatinC} (5.9 vs. 3.1 %, p <0.001) and albuminuria (20.2 vs. 8.8 %, p <0.001) were higher in SHIP-1 than in KORA F4. The differential distribution of risk factors explained 18-21% of the regional differences of decreased eGFR_{creatinine-cystatinC} and high ACR. **Conclusions:** The CKD prevalence is higher in Northeast than in Southern Germany. Differences in the prevalence of risk factors partly explain the higher disease burden of CKD in Northeast than in Southern Germany.

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Introduction

Kidney dysfunction confers an increased risk of all-cause mortality and cardiovascular disease and has, due to its increasing prevalence, become a major public health problem worldwide [1-3]. Obesity, type 2 diabetes mellitus, and hypertension are major risk factors for chronic kidney disease (CKD) [4-6]. Previous studies demonstrated regional differences in the prevalence of such risk factors within Germany, with higher levels in East than in West Germany [7-10]. Along with demographic changes related to the ageing societies in European countries, the rising prevalence of kidney dysfunction and its risk factors underline the role of CKD as a major public health problem in Germany.

Traditionally, CKD has been assessed using markers such as estimated glomerular filtration rate (eGFR) based on creatinine (eGFR_{creatinine} <60 ml/min per 1.73 m²) and/or albuminuria [albumin-to-creatinine ratio (ACR) ≥30 mg/g] [11]. A potential alternative for creatinine as an endogenous glomerular filtration marker is the circulating protein cystatin C [12]. In fact, some studies have shown that the serum cystatin C concentration is a more sensitive and accurate indicator of early kidney dysfunction than either the serum creatinine concentration, eGFR_{creatinine} or creatinine clearance [13, 14]. According to the newest recommendation of the Kidney Disease Improving Global Outcome (KDIGO) 2012 guideline [15], the use of the 2009 CKD-EPI creatinine equation, the 2012 CKD-EPI cystatin C, or the 2012 CKD-EPI creatinine-cystatin C equation, an equation for eGFR based on both creatinine and cystatin C, will improve accuracy of eGFR compared to the alternative eGFR equations [16-20]. The newer equations represent an advance over currently available equations across the range of eGFR and have greater accuracy in subjects with mildly impaired kidney function [17]. A recent study showed that the performance of the combined equation for creatinine and cystatin C to determine the prevalence of CKD in epidemiological studies is better than the eGFR equations based on either of these markers of kidney function alone [17]. However, most studies [21-25] assessing the prevalence of kidney dysfunction in different populations used only traditional markers and equations to estimate kidney function.

In the present analyses, we investigated possible regional disparities in the prevalence of CKD within Germany using the newest equations to estimate kidney function [15]. We used data from two population-based studies: the Study of Health in Pomerania (SHIP) in Northeast Germany and the Cooperative Health Research in the Region of Augsburg (KORA) in Southern Germany. Moreover, we analyzed to what extent regional differences in risk factor burden explain the difference in CKD prevalence in the two study regions. We selected these two regions because they have been shown to differ markedly in the distribution of major CKD risk factors as well as in the rates for all-cause mortality and cardiovascular events [8, 9, 26, 27].

Materials and Methods

Study populations

Data from two population-based studies were used. Both studies conformed to the principles of the Declaration of Helsinki. All investigations were approved by the local ethics committees and public data protection agencies.

SHIP-1 is the first follow-up examination of the SHIP-0 study, a cross-sectional population-based survey conducted in Northeast Germany in the cities of Greifswald and Stralsund as well as in surrounding communities between 1997 and 2001 [28]. Out of 4,308 subjects who participated in the SHIP-0 baseline study, 3,300 also took part in the 5-year follow-up SHIP-1 examination (2002-2006, follow-up response 83.6%) [29].

The KORA F4 study is the first follow-up of the KORA S4 study, a cross-sectional population-based survey conducted in Southern Germany in the city of Augsburg and in two surrounding counties between

1999 and 2001 [30]. Out of 4,261 subjects who participated in the S4 baseline study, 3,080 also took part in the 7-year follow-up KORA F4 examination (2006-2008, follow-up response 79.6%).

In order to create a comparable age range between studies, we excluded 258 SHIP-1 participants who were outside the age range of 31 to 82 years. We also excluded subjects with missing data on serum creatinine (SHIP-1, n = 14; KORA F4, n = 5), serum cystatin C (SHIP-1, n = 14; KORA F4, n = 22), urinary albumin or creatinine (SHIP-1, n = 14; KORA F4, n = 29), and with eGFR <15 ml/min per 1.73 m² (SHIP-1, n = 3; KORA F4, n = 2). Thus, the final study sample comprised 3,014 participants in SHIP-1 and 3,040 participants in KORA F4.

Data collection

In both studies, information on socio-demographic variables, smoking habits, alcohol consumption, physical activity level, medical history, and medication use was collected by trained and certificated medical staff during a standardized personal interview. Educational level was defined as the self-reported highest level of school education (<10 years of school, 10 years of school, >10 years of school based on the East German three-level school system). Assessment of alcohol intake (in grams per day) was derived from a beverage-specific quantity-frequency index that used self-reported data regarding weekday and weekend consumption of beer, wine, and spirits [31]. Study participants provided information on whether they had ever smoked cigarettes regularly (never, past only, current) [32]. Individuals who participated in leisure time physical training during summer or winter for less than one hour per week were classified as being physically inactive [33]. Diabetes mellitus was defined as self-report based on the question whether a physician had ever diagnosed type 2 diabetes mellitus or whether the subjects took antidiabetic medication (Anatomic Therapeutic Chemical {ATC} Classification System code: A10) [28].

In both studies, all participants underwent an extensive standardized physical examination. Based on recommendations of the WHO [34], we measured height, body weight, and waist circumference. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of body height in meters [35]. Waist circumference was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane in subjects standing comfortably with weight distributed evenly on both feet [36]. Further, waist-to-height ratio was calculated as waist circumference divided by height in centimeters. Systolic and diastolic blood pressures were measured three times after an initial five-minute rest period on the right arm of seated subjects using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan). Measurements were separated by three-minute intervals. The mean of the second and third measurements was calculated and used for the present analyses. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication defined by the ATC code (C02L, C03A/B/C/D/E, C07B/C/D, C08G, C09BA, C09DA) [37].

Laboratory procedures

In SHIP-1, blood samples were taken from the cubital vein of non-fasting participants in the supine position between 07:00 a.m. and 04:00 p.m. Blood collection and processing was conducted using a standardized protocol. Serum aliquots were prepared for immediate analysis in a central laboratory. Serum creatinine concentrations were determined with the Jaffé method (Siemens Dimension RxL; Siemens Healthcare Medical Diagnostics, Eschborn, Germany). Serum cystatin C concentrations were measured by the particle-enhanced immunonephelometry (N Latex Cystatin C kit, Siemens Healthcare Diagnostics, Eschborn, Germany) on the Behring BN Prospec nephelometer (Dade Behring, Liederbach, Germany). A single spot urine sample was collected from each subject and stored for a maximum duration of two days at 6° C. The urinary creatinine concentration (Jaffé-method) was determined on a Hitachi 717 (Roche Diagnostics, Mannheim, Germany). The urinary albumin concentration was determined on a Behring Nephelometer (Siemens BN albumin; Siemens Healthcare, Marburg, Germany).

In KORA F4, blood samples were taken from the cubital vein of seated, overnight fasting participants in the morning. Internal and external quality controls were performed according to the WHO MONICA Manual [38]. Serum creatinine concentrations were determined using an automated Jaffé method (Technicon, SMAC autoanalyzer; Tarrytown, New York, USA). Serum cystatin C concentrations were measured by the particle-enhanced immunonephelometry (N Latex Cystatin C kit, Dade Behring, Marburg, Germany) on the Behring

Nephelometer II analyzer (Dade Behring, Marburg, Germany). A single spot urine sample was collected from each subject and stored at -80°C until measurement. The urinary creatinine concentration (Jaffé-method) was determined on a Cobas Mira (Greiner, Bahlingen, Germany). The urinary albumin concentration was measured quantitatively with an immunoturbidimetric test (Tina-quant_ Albumin in urine, Boehringer Mannheim, Germany).

Definition of CKD

According to the recommendation of the KDIGO 2012 guideline [15], CKD was defined as $\text{eGFR} < 60$ ml/min per 1.73 m^2 and/or albuminuria ($\text{ACR} \geq 30$ mg/g). The eGFR was determined from serum creatinine and cystatin C using three different established equations. We estimated the $\text{eGFR}_{\text{creatinine}}$ (ml/min per 1.73 m^2) using the 2009 CKD-EPI creatinine equation:

$$141 \times \min(\text{SCr}/\kappa, 1)^{\alpha} \times \max(\text{SCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \left[\times 1.018 \text{ if female} \right] \left[\times 1.159 \text{ if black} \right],$$

where SCr is serum creatinine measured in mg/dl, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, \min is the minimum of SCr/κ or 1, and \max is the maximum of SCr/κ or 1 [15]. Before entering serum creatinine concentrations into the eGFR equation, we calibrated the data to the National Health and Nutrition Examination Survey III within age – sex groups to obtain values close to Cleveland Clinic creatinine [39, 40]. The $\text{eGFR}_{\text{cystatinC}}$ (ml/min per 1.73 m^2) was estimated using the 2012 CKD-EPI cystatin C equation:

$$133 \times \min(\text{SCysC}/0.8, 1)^{-0.499} \times \max(\text{SCysC}/0.8, 1)^{-1.328} \times 0.996^{\text{Age}} \left[\times 0.932 \text{ if female} \right],$$

where SCysC is serum cystatin C measured in mg/l, \min indicates the minimum of $\text{SCysC}/0.8$ or 1, and \max indicates the maximum of $\text{SCysC}/0.8$ or 1 [15]. We estimated the $\text{eGFR}_{\text{creatinine-cystatinC}}$ (ml/min per 1.73 m^2) using the 2012 CKD-EPI creatinine-cystatin C equation:

$$135 \times \min(\text{SCr}/\kappa, 1)^{\alpha} \times \max(\text{SCr}/\kappa, 1)^{-0.601} \times \min(\text{SCysC}/0.8, 1)^{-0.375} \times \max(\text{SCysC}/0.8, 1)^{-0.711} \\ \times 0.995^{\text{Age}} \left[\times 0.969 \text{ if female} \right] \left[\times 1.08 \text{ if black} \right],$$

where SCr is serum creatinine measured in mg/dl, SCysC is serum cystatin C measured in mg/l, κ is 0.7 for females and 0.9 for males, α is -0.248 for females and -0.207 for males, $\min(\text{SCr}/\kappa, 1)$ indicates the minimum of SCr/κ or 1, and $\max(\text{SCr}/\kappa, 1)$ indicates the maximum of SCr/κ or 1; $\min(\text{SCysC}/0.8, 1)$ indicates the minimum of $\text{SCysC}/0.8$ or 1 and $\max(\text{SCysC}/0.8, 1)$ indicates the maximum of $\text{SCysC}/0.8$ or 1 [15]. Since all study participants were of European Caucasian descent, the race variable was omitted from eGFR equations.

Statistical analyses

Data are reported as medians (25th and 75th percentile) or means (standard deviation) for continuous variables and as percentages for categorical variables. Group comparisons were performed using t-test (mean) or Kruskal-Wallis test (median) for continuous variables and Pearson χ^2 tests for categorical variables. Tests were considered statistically significant at a two-sided p-value < 0.05 . Correlation coefficients between $\text{eGFR}_{\text{creatinine}}$, $\text{eGFR}_{\text{cystatinC}}$, and ACR were calculated in SHIP-1 and KORA F4. Differences in the age and sex structure between the study regions were accounted for by direct standardization to the German standard population (date 31/12/2007). Age- and sex-specific prevalence estimates for CKD were calculated, and results for each age stratum were expressed as percentages with a 95% confidence interval (95% CI). Age was stratified into the categories 31–82, 31–44, 45–64, and 65–82 years. Additionally, we performed sensitivity analyses by excluding participants in SHIP-1 which reported intake of food during the last 5 hours.

Factors explaining differences in selected percentiles corresponding to the cut-points of decreased $\text{eGFR}_{\text{creatinine-cystatinC}}$ (5th percentile, corresponding to 60 ml/min per 1.73 m^2) [15] and high ACR (85th percentile, corresponding to 30 mg/g) [15] between the study regions were tested using quantile regression models. In these regression models, we adjusted for covariables that might explain regional differences in CKD prevalence. The first model included age, sex and a variable indicating the study sample (SHIP or KORA). The second model added BMI, waist circumference, or waist-to-height ratio. The third model additionally included type 2 diabetes mellitus and the fourth model added hypertension. The final model included all

covariables of the previous models as well as physical inactivity, education, alcohol intake, and smoking status. We calculated the ratio of unadjusted and adjusted quantile regression coefficients:

$$\left[(\beta_{unadjusted} - \beta_{adjusted}) / \beta_{unadjusted} \right]$$

[41]. Analyses were performed using Stata 11.2 (Stata Corporation, College Station, TX, USA).

Results

Socio-demographic characteristics and CKD risk factors for individuals living in Northeast (SHIP-1) and Southern Germany (KORA F4) are displayed in Table 1. BMI, waist circumference, and waist-to-height ratio were similar in both populations. The prevalence of hypertension and type 2 diabetes mellitus was higher in SHIP-1 than in KORA F4. Figure 1 shows moderate correlations between $eGFR_{creatinine}$ and $eGFR_{cystatinC}$ in SHIP-1 and KORA F4. The correlation coefficient between $eGFR_{creatinine-cystatinC}$ and ACR in SHIP-1 and KORA F4 was 0.023.

Table 1. Baseline characteristics of the SHIP-1 and KORA F4 study populations

Characteristics	SHIP-1	KORA F4	p value
Sex (%), female	51.8	51.8	0.970
Age (years), range 31-82	56.0 (44.0, 66.0)	56.0 (45.0, 67.0)	0.043
Age (%)			
31-44 years	26.6	25.0	0.164
45-64 years	44.2	43.8	
65-82 years	29.2	31.2	
School education (%)			
<10 years	41.7	51.8	<0.001
10-12 years	45.0	24.7	
>12 years	13.3	23.6	
Smoking status (%)			
Never smoker	41.7	44.1	<0.001
Former smoker	31.0	37.9	
Current smoker	27.3	18.0	
Alcohol intake (g/day)*	8.5 (13.2)	14.3 (19.6)	<0.001
Physical inactivity (%)	64.7	45.6	<0.001
BMI (kg/m ²)	27.6 (24.6, 31.0)	27.0 (24.3, 30.3)	<0.001
Waist circumference (cm)	93.0 (83.3, 102.3)	93.2 (84.2, 102.8)	0.147
Waist-to-height ratio	0.6 (0.5, 0.6)	0.6 (0.5, 0.6)	0.137
Hypertension (%)	59.3	38.1	<0.001
Type 2 diabetes mellitus (%)	10.6	7.0	<0.001
Measures of kidney function			
Serum creatinine (mg/dl ^a)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.075
Serum cystatin C (mg/l)	90.9 (76.0, 107.3)	106.4 (90.5, 121.2)	<0.001
ACR (mg/g)	59.4 (305.1)	24.5 (194.1)	<0.001

Entries are medians (25th, 75th percentile), *means (standard deviation), or %. ACR, albumin-to-creatinine ratio; BMI, body mass index; KORA, Cooperative Health Research in the Region of Augsburg; SHIP, Study of Health in Pomerania. ^aTo convert to $\mu\text{mol/l}$, multiply by 88.4.

Continuous traits of kidney function in SHIP-1 and KORA F4

In both samples, all four indices of kidney function ($eGFR_{creatinine}$, $eGFR_{cystatinC}$, $eGFR_{creatinine-cystatinC}$, and ACR) decreased with increasing age (Table 2). Median values of $eGFR_{creatinine}$ were

similar in SHIP-1 and KORA F4, whereas the two populations differed from each other with respect to median values of $eGFR_{cystatinC}$ combined $eGFR_{creatinine-cystatinC}$ and ACR, which provides some evidence of lower kidney function in SHIP-1. Specifically, the age-standardized median values of $eGFR_{cystatinC}$ were lower in SHIP-1 [104.7 (84.6; 116.5) ml/min per 1.73 m²] than in KORA F4 [114.2 (102.5; 123.0)

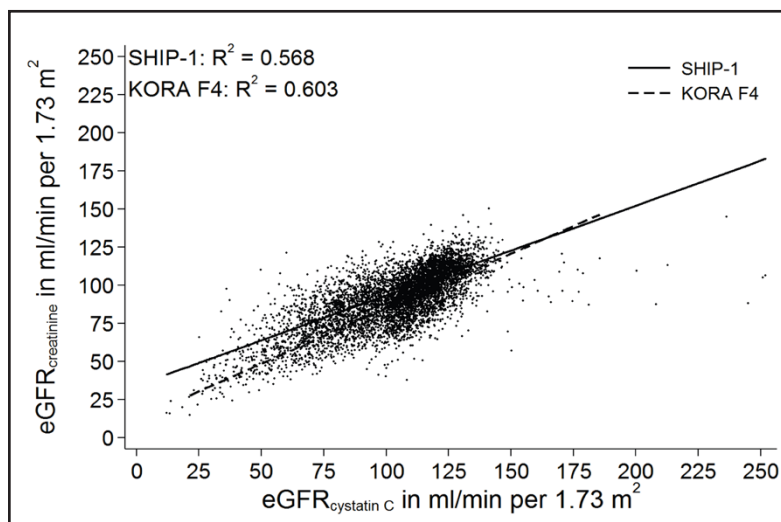


Fig. 1. Correlation between $eGFR_{creatinine}$ and $eGFR_{cystatinC}$ in SHIP-1 and KORA F4.

ml/min per 1.73 m²] in the overall sample. Additionally, the age-standardized median values of $eGFR_{creatinine-cystatinC}$ were also lower in SHIP-1 [99.5 (84.7; 111.1) ml/min per 1.73 m²] than in KORA F4 [105.3 (91.6; 116.4) ml/min per 1.73 m²] in the overall sample. The differences in $eGFR$ between SHIP-1 and KORA F4 were consistently present in each age group. In line with the observation related to $eGFR_{cystatinC}$ and $eGFR_{creatinine-cystatinC}$ the age-standardized median of ACR was higher in SHIP-1 than in KORA F4 in the overall sample and in each age group.

Prevalence of decreased eGFR and albuminuria in SHIP-1 and KORA F4

Table 3 provides the prevalence of the binary trait decreased eGFR, based on a combination of creatinine and cystatin C, and albuminuria in SHIP-1 and KORA F4. Consistent with the continuous trait analyses mentioned above, the prevalence of decreased $eGFR_{creatinine-cystatinC}$ and the prevalence of albuminuria as well as the prevalence of the combination of both endpoints were significantly higher in SHIP-1 than in KORA F4. Sensitivity analyses after excluding subjects in SHIP-1 with food during the last 5 hours showed almost identical estimates of renal function (data not shown). Thus, we can exclude the possibility that regional differences of decreased $eGFR_{creatinine-cystatinC}$ and high ACR might result from differences in fasting status at the time of blood withdrawal for laboratory measurements.

Adjustment for covariables to explain regional differences in $eGFR_{cystatinC}$ and ACR

Differences in decreased $eGFR_{creatinine-cystatinC}$ values (5th percentile, corresponding to 60 ml/min per 1.73 m²) and in high ACR (85th percentile, corresponding to 30 mg/g) between SHIP-1 and KORA F4 are displayed in Table 4. Age, sex, BMI (or waist circumference, or waist-to-height ratio), type 2 diabetes mellitus, and hypertension cumulatively explained 5.6%, and the fully adjusted model cumulatively explained 18.0% of the difference in decreased $eGFR_{creatinine-cystatinC}$ values between SHIP-1 and KORA F4. With respect to high ACR, the above mentioned risk factors cumulatively explained 20.6% of the difference between SHIP-1 and KORA F4.

Discussion

In the present study, we observed a higher prevalence of CKD in Northeast than in South Germany. The difference in decreased $eGFR_{creatinine-cystatinC}$ values and high ACR is in part

Table 2. Kidney function in the SHIP-1 and KORA F4 surveys by age-group

	31 – 82 [§]		31 – 44		45 – 64		65 – 82	
	SHIP-1 n=3,014	KORA F4 n=3,040	SHIP-1 n=801	KORA F4 n=759	SHIP-1 n=1,332	KORA F4 n=1,331	SHIP-1 n=881	KORA F4 n=950
eGFR _{creatinine} (ml/min per 1.73 m ²)	96.1 (83.3; 107.3)	95.0* (81.8; 106.8)	110.6 (103.0; 116.0)	109.3* (100.8; 114.9)	95.6 (85.7; 103.2)	95.6 (85.3; 102.8)	77.6 (66.1; 87.8)	76.6 (65.4; 87.0)
eGFR _{cystatinC} (ml/min per 1.73 m ²)	104.7 (84.6; 116.5)	114.2* (102.5; 123.0)	119.1 (112.8; 125.5)	125.3* (120.7; 130.3)	103.9 (89.9; 112.6)	113.4* (107.4; 119.5)	76.9 (63.0; 90.3)	94.9* (79.2; 104.1)
eGFR _{creatinine-cystatinC} (ml/min per 1.73 m ²)	99.5 (84.7; 111.1)	105.3* (91.6; 116.4)	113.1 (106.1; 120.0)	118.1* (111.0; 123.4)	97.4 (87.9; 106.3)	104.2* (95.6; 111.7)	76.6 (64.2; 86.5)	84.3* (72.1; 94.4)
ACR (mg/g)	9.3 (5.0, 23.1)	5.4* (3.4, 10.6)	8.0 (4.4, 18.1)	4.6* (3.1, 8.0)	9.7 (5.4, 22.1)	5.3* (3.5, 9.6)	14.3 (7.4, 42.3)	9.1* (5.2, 19.9)

Entries are median (25th, 75th percentile). ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; eGFR_{creatinine}, estimated GFR using the CKD-EPI creatinine equation; eGFR_{cystatinC}, estimated GFR using the CKD-EPI cystatin C equation; eGFR_{creatinine-cystatinC}, estimated GFR using the CKD-EPI creatinine-cystatin C equation; KORA, Cooperative Health Research in the Region of Augsburg; SHIP, Study of Health in Pomerania. §Age- and sex-standardized according to the age distribution of the German standard population (31.12.2007). *p<0.05 for comparison between SHIP and KORA values in the respective age group.

(to about 18% to 21%) explained by regional disparities in the prevalence of major CKD risk factors.

Table 3. Prevalence of decreased eGFR and albuminuria in SHIP-1 and KORA F4

	SHIP-1		KORA F4		p value
	n	% (95% CI)*	n	% (95% CI)*	
eGFR _{creatinine-cystatinC} <60 ml/min per 1.73 m ²	205	5.9 (5.1-6.8)	106	3.1 (2.5-3.7)	<0.001
Albuminuria (ACR >30 mg/g)	668	20.2 (18.8-21.8)	285	8.8 (7.9-9.9)	<0.001
eGFR _{creatinine-cystatinC} <60 ml/min per 1.73 m ² and albuminuria	99	3.0 (2.5-3.7)	45	1.4 (1.0-1.9)	<0.001

ACR, albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; eGFR_{creatinine}, estimated GFR using the CKD-EPI creatinine equation; eGFR_{cystatinC}, estimated GFR using the CKD-EPI cystatin C equation; eGFR_{creatinine-cystatinC}, estimated GFR using the CKD-EPI creatinine-cystatin C equation; KORA, Cooperative Health Research in the Region of Augsburg; SHIP, Study of Health in Pomerania. *Age- and sex-standardized according to the age distribution of the German population (31.12.2007).

Table 4. Effects of covariables to explain differences in decreased eGFR_{creatinine-cystatinC} and high ACR in SHIP-1 and KORA F4

SHIP-1 vs. KORA F4	Coef.	(95% CI)	p value	%*
eGFR_{creatinine-cystatinC} (5th percentile)				
Adjusted for age and sex	-4.6	(-5.3 – -3.9)	<0.001	
+ body mass index	-4.3	(-5.0 – -3.6)	<0.001	7.5
or waist circumference	-4.7	(-5.4 – -3.9)	<0.001	-1.1
or waist-to-height ratio	-4.6	(-5.3 – -3.8)	<0.001	0.4
+ Type 2 diabetes mellitus	-4.4	(-5.1 – -3.6)	<0.001	5.6
+ Hypertension	-4.0	(-4.8 – -3.3)	<0.001	13.9
+ Physical activity, smoking, education, alcohol	-3.9	(-4.7 – -3.1)	<0.001	18.0
ACR (85th percentile)				
Adjusted for age and sex	24.3	(22.4 – 26.2)	<0.001	
+ BMI	23.9	(22.1 – 25.8)	<0.001	1.4
or waist circumference	24.0	(22.1 – 25.9)	<0.001	1.3
or waist-to-height ratio	23.7	(21.8 – 25.7)	<0.001	2.3
+ Type 2 diabetes mellitus	22.3	(20.6 – 23.9)	<0.001	8.4
+ Hypertension	19.5	(17.7 – 21.3)	<0.001	19.8
+ Physical activity, smoking, education, alcohol	19.3	(17.7 – 20.9)	<0.001	20.6

β, quantile regression coefficient; ACR, albumin-to-creatinine ratio (85th percentile corresponding to 30 mg/g); BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; eGFR_{creatinine-cystatinC}, estimated GFR using the CKD-EPI creatinine-cystatin C equation (5th percentile corresponding to 60 ml/min per 1.73 m²); KORA, Cooperative Health Research in the Region of Augsburg; SHIP, Study of Health in Pomerania; * % change due to confounder.

In recent years the prevalence of CKD and the number of patients with kidney failure treated by dialysis and transplantation increased dramatically worldwide [2, 3]. It is well established that CKD is strongly associated with an increased risk of cardiovascular morbidity and mortality [1, 2]. In individuals with early stages of CKD, the risk of cardiovascular morbidity and mortality is higher than the risk of progression to kidney failure. Therefore, cardiovascular risk factor management is critical in this group [42].

The increase in the prevalence of CKD worldwide might be partly explained by the increase in the prevalence of major risk factors for CKD including obesity, type 2 diabetes mellitus, and hypertension [5, 6, 22]. Ageing of societies is likewise a contributing factor to increasing CKD prevalence. In the United States, approximately 17% of persons older than 60 years of age have a eGFR_{creatinine} of less than 60 ml/min per 1.73 m² and the prevalence of low eGFR_{creatinine} increases from 2.9% among adults with an ideal weight (BMI 18.5–24.9 kg/m²) to 4.5% among obese adults (BMI ≥30 kg/m²) [5].

The increase in the proportion of individuals with obesity, type 2 diabetes mellitus, and hypertension and the association of kidney dysfunction with cardiovascular disease lead to a large public health problem regarding CKD in Germany [1, 2]. Previous studies demonstrate regional disparities in the prevalence of established CKD risk factors including obesity, type 2 diabetes mellitus, and hypertension with higher levels in East compared to West Germany [7–10]. In the present analysis, we demonstrate that the higher prevalence of CKD in Northeast Germany is partially explained by the above mentioned differences in major risk factors for CKD including hypertension and type 2 diabetes mellitus. Specifically, adjustment for all major risk factors explained 21% of the regional variation in high ACR, but only 18% of the regional variation in decreased eGFR_{creatinine-cystatinC} values (Table 4). The difference in the predictive value of major CKD risk factors for the two endpoints decreased eGFR_{creatinine-cystatinC} values and high ACR, is partly explained by the stronger association of

type 2 diabetes mellitus with albuminuria than with low eGFR [22]. Additionally, obesity may cause glomerular hyperfiltration, increased urinary albumin excretion and progressive loss of kidney function [43, 44]. Despite its increasing prevalence, obesity may be the most important potentially preventable risk factor for CKD due to its strong link with type 2 diabetes mellitus and hypertension, the two major causes of CKD [5]. Furthermore, our data are consistent with the notion that life style risk factors including smoking, alcohol consumption, and physical inactivity increase the prevalence of CKD, albeit the effects of these factors on kidney function are less important than those of hypertension or type 2 diabetes mellitus [45-47]. However, adjustment for all risk factors explained only a fraction (by up to 21%) of the regional variation in decreased eGFR_{creatinine-cystatinC} values and high ACR. A possible explanation could be that CKD and complications of decreased kidney function may be associated with other CKD related risk factors including a family history of kidney disease, cardiovascular disease, hemodynamic and metabolic abnormalities that were not taken into consideration in this study [48-50].

CKD has been estimated based on a decreased eGFR_{creatinine} and/or albuminuria [11]. However, the serum creatinine concentration is not only determined by the tubular secretion of creatinine, but also by the production of creatinine in muscular tissue, which depends on age, weight, gender, and muscle mass [51]. The large variety of non-renal influences leads to a wide reference range for the serum creatinine concentration [52]. Therefore, we calibrated our serum creatinine data to the National Health and Nutrition Examination Survey III within age – sex groups to obtain values close to Cleveland Clinic creatinine [39, 53]. Then, we used the CKD-EPI creatinine equation that more precisely estimates the eGFR in the range of 60 – 90 ml/min per 1.73 m² than other eGFR equations, such as the widely used Modification of Diet in Renal Disease (MDRD) formula [19]. By achieving a greater accuracy in subjects with mildly impaired kidney function, the CKD-EPI equation also reduces the rate of false positive diagnoses of CKD by GFR category G3a (defined as eGFR <60 ml/min per 1.73 m²) [19]. However, there are several limitations to the use of eGFR equations based on serum creatinine. There are reasons to believe that both equations overestimate the prevalence of CKD because they underestimate the GFR [16]. In contrast to serum creatinine, serum cystatin C concentration is less influenced by age, race, and muscle mass [14, 20]. The eGFR_{cystatinC} might therefore be a more sensitive and accurate indicator of early kidney dysfunction than eGFR_{creatinine} [14, 20, 54]. Yet, BMI, diabetes, and inflammation may affect serum cystatin C concentration independent of kidney function [55]. However, the combined equation for creatinine and cystatin C provides more precise GFR estimates than equations based on either of these markers alone [17, 20].

Strengths and limitations

Strengths of the present analyses include the large sample size, the population-based approach, and the comparable study design of KORA and SHIP, including the high degree of standardization in measuring covariates and markers of kidney function. On the other hand, several limitations should be considered. In the present study we cannot exclude the possibility of bias produced by acute kidney injury because we did not measure acute kidney injury. Further, albuminuria was measured using the urinary albumin-to-creatinine ratio from a spot urine sample and not by obtaining 24-h urine collections, which are time consuming and hard to perform in a population-based study. Several studies reported good correlations between the ACR measured in 24-h urine collections and the ACR measured in spot urine samples [56, 57]. Another limitation is that different assays were used for measurements of urinary albumin in both studies. In SHIP-1, the urinary albumin concentration was determined with a nephelometric assay, whereas in KORA F4 it was measured quantitatively with an immunoturbidimetric test. Yet, both immunological methods have been developed to detect minimal amounts of albumin. In a comparative study, Kleine and Merten obtained similar results with both techniques [58]. Further, cystatin C was measured on the Behring

Nephelometer II (Dade Behring) in KORA F4 and the BN Prospec Nephelometer (Siemens Healthcare Diagnostics) in SHIP-1. The BN Prospec Nephelometer is the successor model of the Nephelometer II. As the reagents used for the cystatin C measurement are similar, it is reasonable to assume that the measurements are comparable. However, a direct comparison between the two analyzers was not available, thus, we are not able to fully exclude or correct for possible small measurement differences. Our study is further limited by the lack of direct measurements of kidney function such as inulin clearance. For obvious reasons, such invasive measurements are not suitable in a population-based study. No “gold standard” diagnosis of kidney dysfunction was available, but we calibrated serum creatinine data to the National Health and Nutrition Examination Survey III within age – sex groups to obtain values close to Cleveland Clinic creatinine [39, 53]. In addition, food intake could bias measurements of renal function, especially intake of cooked meat may affect serum creatinine concentration and eGFR [59, 60]. Sensitivity analyses after excluding subjects in SHIP-1 with food during the last 5 hours (data not shown) exclude the possibility that regional differences of decreased eGFR_{creatinine-cystatinC} and high ACR might result from differences in fasting status between the two study populations during blood withdrawal for laboratory measurements.

Conclusion

In conclusion, the differences in the local prevalence of relevant risk factors for kidney dysfunction can partly explain the higher disease burden of CKD in Northeast Germany compared to Southern Germany. Further studies are needed to investigate the influence of other CKD related risk factors. Strong and effective prevention, detection, and treatment of risk factors for kidney dysfunction may reduce the risk for development of CKD.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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