ORIGINAL RESEARCH

Differential Prognostic Utility of Adiposity Measures in Chronic Kidney Disease

Vladimir Cejka,[*] Stefan Störk,[,†] Jennifer Nadal,[‡] Matthias Schmid,[‡] Claudia Sommerer,[§] Thomas Sitter,[¶] Heike Meiselbach,[**] Martin Busch,[††] Markus P. Schneider,[**] Turgay Saritas,[‡‡] Ulla T. Schultheiss,[§§,¶¶] Fruzsina Kotsis,[§§,¶¶] Christoph Wanner,[*,***] and Kai-Uwe Eckardt,[**,†††] Vera Krane,[*,***] GCKD Study Investigators[‡‡‡]*

Abstract: Objective: Adipose tissue contributes to adverse outcomes in chronic kidney disease (CKD), but there is uncertainty regarding the prognostic relevance of different adiposity measures. We analyzed the associations of neck circumference (NC), waist circumference (WC), and body mass index (BMI) with clinical outcomes in patients with mild to severe CKD.

Methods: The German Chronic Kidney Disease study is a prospective cohort study, which enrolled Caucasian adults with mild to severe CKD, defined as estimated glomerular filtration rate : 30-60 mL/min/1.73 m^2, or >60 mL/min/1.73 m^2 in the presence of overt proteinuria. Associations of NC, WC, and BMI with all-cause death, major adverse cardiovascular events (MACE: a composite of nonfatal stroke, nonfatal myocardial infarction, peripheral artery disease intervention, and cardiovascular death), and kidney failure (a composite of dialysis or transplantation) were analyzed using multivariable Cox proportional hazards regression models adjusted for confounders and the Akaike information criteria were calculated. Models included sex interactions with adiposity measures.

Results: A total of 4537 participants (59% male) were included in the analysis. During a 6.5-year follow-up, 339 participants died, 510 experienced MACE, and 341 developed kidney failure. In fully adjusted models, NC was associated with all-cause death in women (hazard ratio 1.080 per cm; 95% CI 1.009-1.155) but not in men. Irrespective of sex, WC was associated with all-cause death (hazard ratio 1.014 per cm; 95% CI 1.005-1.038). NC and WC showed no association with MACE or kidney failure. BMI was not associated with any of the analyzed outcomes. Models of all-cause death, including WC offered the best (lowest) Akaike information criteria.

[*]*Department Clinical Research and Epidemiology, Comprehensive Heart Failure Center, University Hospital Würzburg, Würzburg, Germany.*

[†]*Department of Medicine I – Cardiology, University Hospital of Würzburg, Würzburg, Germany.*

[‡]*Institute for Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany.*

[§]*Department of Nephrology, University of Heidelberg, Heidelberg, Germany.*

[¶]*Department of Medicine, Ludwig-Maximilians-University Hospital, Munich, Germany.*

[**]*Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.*

[††]*Department of Internal Medicine III, University Hospital Jena, Jena, Germany.*

[‡‡]*Division of Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany.*

[§§]*Department of Medicine IV – Nephrology and Primary Care, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany.*

[¶¶]*Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany.*

[***]*Department of Internal Medicine I – Division of Nephrology, University Hospital of Würzburg, Würzburg, Germany.*

[†††]*Department of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany.*

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[‡‡‡]*a list of the GCKD Investigators is included Current GCKD investigators and collaborators with the GCKD study: University of Erlangen-Nürnberg: Kai-Uwe Eckardt, Heike Meiselbach, Markus P. Schneider, Mario Schiffer, Hans-Ulrich Prokosch, Barbara Bärthlein, Andreas Beck, André Reis, Arif B. Ekici, Susanne Becker, Dinah Becker-Grosspitsch, Ulrike Alberth-Schmidt, Birgit Hausknecht, Anke Weigel University of Freiburg: Gerd Walz, Anna Köttgen, Ulla T. Schultheiß, Fruzsina Kotsis, Simone Meder, Erna Mitsch, Ursula Reinhard RWTH Aachen University: Jürgen Floege, Turgay Saritas; Charité, University Medicine Berlin: Elke Schaeffner, Seema Baid-Agrawal, Kerstin Theisen Hannover Medical School: Hermann Haller, University Hospital, Renal Center, Heidelberg: Martin Zeier, Claudia Sommerer, Johanna Theilinger University Hospital Jena: Gunter Wolf, Martin Busch, Rainer Paul Ludwig-Maximilians University of München: Thomas Sitter University of Würzburg: Christoph Wanner, Vera Krane, Antje Börner-Klein, Britta Bauer; Medical University of Innsbruck, Division of Genetic Epidemiology: Florian Kronenberg, Julia Raschenberger, Barbara Kollerits, Lukas Forer, Sebastian Schönherr, Hansi Weissensteiner University of Regensburg, Institute of Functional Genomics: Peter Oefner, Wolfram Gronwald Department of Medical Biometry, Informatics and Epidemiology (IMBIE), University Hospital of Bonn: Matthias Schmid, Jennifer Nadal*

Address correspondence to Vladimir Cejka, University Hospital Würzburg, Comprehensive Heart Failure Center (CHFC), Am Schwarzenberg 15, Haus A15, 97078, Würzburg, Germany. E-mail: Cejka_V@ukw.de

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Conclusion: In Caucasian patients with mild to severe CKD, higher NC (in women) and WC were significantly associated with increased risk of death from any cause but BMI was not.

Keywords: chronic kidney disease; neck circumference; waist circumference; body Mass Index; mortality; adiposity

Introduction

CHRONIC KIDNEY DISEASE (CKD) affects >10% of the general population globally and has major implications for health care systems.[1,2] Patients with CKD share increased risks of cardiovascular disease, kidney failure, and overall mortality.[3-6] Prognosis generally worsens with decreasing glomerular filtration rate and increasing proteinuria.[7]

Body composition affects the course of CKD,[8] and distinct compartments within the adipose tissue can be differentiated. Women tend to accumulate subcutaneous fat in the lower body, whereas men tend to accumulate mainly visceral and upper body (abdominal) subcutaneous fat.[9] In clinical research and practice, whole body adiposity is usually assessed by body mass index (BMI). Obesity, i.e. BMI >30 kg/m^2, is associated with a higher risk for incident CKD, cardiovascular events, and overall mortality,[10-12] but its impact on cardiovascular events and mortality weakens in individuals with CKD.[13] In fact, this association reverts in the advanced stages of CKD (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) and in dialysis patients.[11,14,15] In these populations, obesity is linked to better survival, a phenomenon referred to as the "obesity paradox."

The main mediator of adverse prognosis in overweight people is considered to be visceral fat, comprising mainly abdominal cavity adipose tissue. As such, visceral fat correlates more strongly with waist circumference (WC) than does BMI[16] and is a determinant of the metabolic syndrome. It is a source of inflammatory cytokines (e.g., interleukin-6 and tumor necrosis factor), adipokines (e.g., adiponectin), and hormones (leptin) and is involved in insulin resistance, atherosclerosis, and lipid metabolism.[17,18] Obesity guidelines recommend the broad use of WC for the assessment of visceral adiposity.[19,20] Increasing risk of death with higher WC seems to persist in CKD, unlike with BMI.[21-23] Some authors have thus hypothesized that in CKD, WC is a better predictor of adverse outcomes than BMI.[22] Upper body subcutaneous fat is also independently associated with hypertension, dyslipidemia, and diabetes mellitus and can be reliably approximated by neck circumference (NC).[5,24] Higher NC values are a marker of obesity and the metabolic syndrome.[25,26] NC correlates with the 10-year Framingham risk score for coronary artery disease.[27] Asian cohort studies indicate, that NC might be related to kidney function.[28-30] However, the association between NC and health-relevant outcomes in CKD has not been prospectively evaluated so far.

We investigated the prognostic utility of NC, WC, and BMI in the German Chronic Kidney Disease (GCKD) study, the largest cohort worldwide of Caucasian patients with mild to severe CKD during a follow-up period of 6.5 years.

Methods

The GCKD study is an ongoing, prospective, observational, national cohort study among patients with mild to severe CKD.[31] Details of the study enrollment and follow-up procedures have been described previously.[31,32] Briefly, 5217 adult CKD patients under routine nephrological care were enrolled between March 2010 and March 2012 across nine regional study centers, including 159 study sites throughout Germany. Inclusion criteria were estimated glomerular filtration rate (eGFR) 30-60 mL/min/1.73 m^2, or >60 mL/min/1.73 m^2 in the presence of overt albuminuria/proteinuria. Major exclusion criteria were non-Caucasian ancestry, previous solid organ or bone marrow transplantation, active malignancy within the last 24 months, or New York Heart Association class IV heart failure. All participants provided written informed consent before study entry. The study was approved by the appropriate ethics committees.

At baseline and follow-up study visits, trained and certified personnel used standardized questionnaires to obtain information about each patient's medical history, sociodemographic and lifestyle factors, and medication intake. Further information about medical history and additional medical records were obtained from the treating nephrologists. All clinical measurements were performed according to predefined standard operating procedures.

NC was measured with a measuring tape. Patients were asked to stand upright with their head positioned in the Frankfort horizontal plane. The circumference was measured perpendicular to the long axis of the neck just below the laryngeal prominence.[24]

WC was measured as the lowest abdominal circumference while standing. If determination of the lowest circumference was not possible, WC was measured in the middle of the distance between the *spina iliaca anterior superior* and the lowest point of the costal arch.[33] WC was measured with the patient in the supine position for those who could not stand.

BMI was calculated as weight in kilograms divided by the height in meters squared. In patients with amputated lower extremities, the following correction of weight to calculate BMI was applied: weight (kg) × 100/100–correction. Corrections were as follows: 18 for a foot amputation, 7.1 for an amputation below the knee, and 18.7 for an amputation above the knee.

Blood pressure was measured consecutively three times, and the mean values of the systolic (SBP) and diastolic (DBP) blood pressure were used for analysis. Blood pressure measurements were performed with the patient in a sitting position after 5 minutes of rest. Measurements were made at least 1 minute apart. Pulse pressure was calculated as the difference between SBP and DBP. Mean arterial pressure was calculated as 1/3 SBP +2/3 DBP. Hypertension was defined as either SBP ≥140 mmHg or DBP ≥90 mmHg or use of antihypertensive medication. Diabetes mellitus was defined as HbA1c ≥ 6.5% or use of antidiabetic medication. Ever-smoker was defined as currently smoking or having smoked in the past.

At baseline and follow-up visits, biomaterials, including serum, plasma, and urine, were collected and transported frozen to a central biobank following standard operating procedures for future analyses.[12] Blood and urine specimens were analyzed in a central certified laboratory. Serum creatinine was analyzed using an IDMS-traceable methodology [Creatinine Plus, Roche]. Measures of kidney function included eGFR estimated with the CKD-EPI formula[34] and urinary albumin/creatinine ratio (UACR). Commercially available kits were used to analyze: cystatin C [ADVIA Chemistry Systems, Siemens], creatinine, urea [Harnstoff-N kinetischer UV-test, Cobas], albumin [Tina-quant Albumin, Cobas], total cholesterol [CHOD-PAP, Cobas], low-density lipoprotein (LDL) [LDL_C, Cobas] and high-density lipoprotein [high-density lipoprotein -cholesterol plus 3rd generation, Cobas] cholesterol, triglycerides [Triglyceride GPO_PAP, Cobas], HbA1c [Cobas Integra Tina-quant Hemoglobin A1c gen. 2], and C-reactive protein (CRP) [Tina-quant cardiac CRP(Latex) high sensitive, Cobas].

Endpoints were continuously recorded based on hospital discharge letters and death certificates and were centrally adjudicated by experienced physicians. For this project, we included endpoints occurring over the first 6.5 years of follow-up. The endpoints of interest were all-cause mortality; major adverse cardiovascular events (MACE) (4-point MACE), defined as a composite of nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, and a peripheral artery disease event (revascularization or amputation); and kidney failure, defined as a composite of initiation of maintenance dialysis therapy or kidney transplantation.

Systematic NC measurements were performed annually from the 2-year follow-up visit onwards. On average, measurements did not show any significant change over time. The mean of repeated NC measurements was calculated to substitute for lack of baseline values (see supplementary material Table 1 and Figure 1 for further detail). All other characteristics, measurements, and laboratory parameters were drawn from the baseline study visit. We describe the population overall and stratified by sex and use mean values and standard deviations for normally distributed variables and medians with interquartile ranges for non-normally distributed variables. Values of categorical variables are presented as frequency distributions with percentages.

Multivariable Cox proportional hazards regression models were used to examine the associations of mean NC, WC, and BMI at baseline with all-cause death, MACE, and kidney failure. We created base models including age, sex, and one of the adiposity measures with its respective interaction with sex to assess sex-dependent effects. These models were then fully adjusted for the following additional confounders: ever-smoker, diabetes mellitus, hypertension, LDL cholesterol, eGFR, UACR, and CRP. The confounders were chosen with respect to the clinical judgment and experience of the authors. Models were compared using the Akaike information criterion (AIC).[35] As a sensitivity analysis of visceral fat, fully adjusted models with waist-hip ratio (WHR) and conicity index were calculated.[36] Estimates obtained from Cox models are presented in terms of hazard ratios (HRs) with 95% confidence intervals (CIs). All P values were two-sided, and $P < .05$ was considered significant. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC). Analyzed outcomes correspond to the central database export as of December 2018.

Results

4537 out of the 5217 patients enrolled in the GCKD study were analyzed. Fully adjusted models included 4280 cases with complete data. The mean age was 59.9 years (11.8), 59.4% were men, 34.5% had diabetes mellitus, 15.3% were ever-smoked, mean eGFR was 49.9 (18.0) mL/min/1.73 m^2, and median UACR 49 (10-374) mg/g. The mean NC was 42.7 (3.6) cm in men and 37.2 (3.7) cm in women, mean WC was 108 (14) cm in men and 97 (16) cm in women, and mean BMI was 29.9 (5.3) kg/m^2 in men and 29.6 (6.7) kg/m^2 in women. Baseline patient characteristics are summarized in Table 1. A comprehensive list of NC correlations is provided in the supplementary material Table 2. During 6.5 years of follow-up, 341 patients died, 510 patients experienced MACE, and 339 patients developed kidney failure.

Base Models

NC was associated with all-cause death (per cm increase: HR 1.042; 95% CI 1.006-1.079) and MACE (HR 1.040; 95% CI 1.010-1.070). Higher NC in women further increased the risk of death (interaction HR 1.090; 95% CI 1.021-1.164). NC did not predict kidney failure.

Table 1. Descriptive Statistics of the Study Participants

Variable	All participants N = 4573	Male n = 2693	Female n = 1844
Age [years]	59.9 (11.8)	60.7 (11.2)	58.7 (12.5)
Male sex (%)	2693 (59.4)	—	—
NC [cm]	40.4 (4.5)	42.7 (3.6)	37.2 (3.7)
WC [cm]	103 (16)	108 (14)	97 (16)
HC [cm]	110 (12)	109 (10)	111 (14)
WHR [cm]	0.94 (0.09)	0.98 (0.07)	0.87 (0.07)
BMI [kg/m^2]	29.7 (5.9)	29.9 (5.3)	29.6 (6.7)
Hypertension [n, % yes]	4361 (96.2)	2368 (98.0)	1732 (93.5)
SBP [mmHg]	139 (20)	142 (20)	136 (20)
DBP [mmHg]	79 (12)	80 (12)	79 (11)
MAP [mmHg]	99 (13)	100 (13)	98 (13)
PP [mmHg]	60 (17)	62 (17)	57 (17)
eGFR [mL/min/1.73 m^2]	50 (18)	49 (17)	51 (19)
Creatinine [mg/dL]	1.4 (1.2-1.7)	1.6(1.3-1.9)	1.2 (1.0-1.5)
Cystatin C [mg/dL]	1.4 (1.2-1.7)	1.4 (1.2-1.8)	1.4 (1.1-1.6)
Urea [mg/dL]	55 (43-71)	58 (45-7)	51 (40-66)
Albumin [g/L]	39 (36-41)	39 (38-41)	38 (36-40)
UACR [mg/g]	49 (10-374)	76 (11-493)	27 (8-223)
Diabetes mellitus, [n, % yes]	1563 (34.5)	1031 (38.3)	532 (28.9)
HbA1c [mmol/mol]	42 (39-48)	43 (39-50)	42 (39-47)
HbA1c [%]	6.3 (1.0)	6.4 (1.0)	6.2 (1.0)
Total cholesterol [mg/dL]	208 (177-240)	200 (169-231)	219 (190-251)
HDL-cholesterol [mg/dL]	49.0 (39.761.8)	44.2 (36.8-53.9)	57.8 (47.1-70.4)
LDL-cholesterol [mg/dL]	115 (90-143)	110 (86-138)	122 (96-151)
Triglycerides [mg/dL]	168 (118-238)	181 (125-259)	153 (108-215)
CRP [mg/dL]	2.2 (1.0-4.9)	2.1 (1.0-4.6)	2.3 (1.0-5.4)
Ever-smoker, [n, % yes]	693 (15.3)	426 (15.8)	267 (14.5)

BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (CKD-EPI formula); HbA1c, glycated hemoglobin A1c; HC, hip circumference; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; MAP, mean arterial blood pressure; NC, neck circumference; PP, pulse pressure; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio; WC, waist circumference; WHR, waist–hip circumference ratio.

Variables are presented as mean (SD), median (quartiles), or n (%), as appropriate.

WC was a predictor of all outcomes studied. The HR for all-cause death with each centimeter increase in WC was 1.025 (95% CI 1.016-1.034), and for MACE it was 1.012 (95% CI 1.004-1.019). For kidney failure, the HR per centimeter increase was 1.014 (95% CI 1.005-1.023), but this effect weakened in women (interaction HR 0.984; 95% CI 0.969-0.999).

BMI predicted both all-cause death (HR per kg/m^2 increase: 1.041; 95% CI 1.019-1.063) and MACE (HR per kg/m^2 increase: 1.027; 95% CI 1.008-1.046) but not

Table 2. Base models of Adiposity measures and Clinical Outcomes

		NC	WC	BMI
Death n = 339	HR (95% CI)*	**1.042 (1.006-1.079)**	**1.025 (1.016-1.034)**	**1.041 (1.019-1.063)**
	HR (95% CI)† (interaction with sex)	**1.090 (1.021-1.164)**	0.998 (0.982-1.014)	0.995 (0.957-1.034)
	AIC	5293	5277	5299
MACE n = 510	HR (95% CI)*	**1.040 (1.010-1.070)**	**1.012 (1.004-1.019)**	**1.027 (1.008-1.046)**
	HR (95% CI)† (interaction with sex)	0.992 (0.937-1.050)	0.996 (0.982-1.009)	0.979 (0.948-1.012)
	AIC	8106	8104	8107
Kidney failure n = 341	HR (95% CI)*	0.993 (0.957-1.031)	**1.014 (1.005-1.023)**	1.018 (0.995-1.041)
	HR (95% CI)† (interaction with sex)	0.993 (0.928-1.063)	**0.984 (0.969-0.999)**	0.963 (0.927-1.001)
	AIC	5436	5427	5433

Bold for significant effects (95% CI not including 1.0).

AIC, Akaike information criterion; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MACE, 4-point major adverse cardiovascular events; NC, neck circumference; WC, waist circumference.

*Adjusted for age, sex and interaction of adiposity measure with sex.

†HR of the interaction term for women.

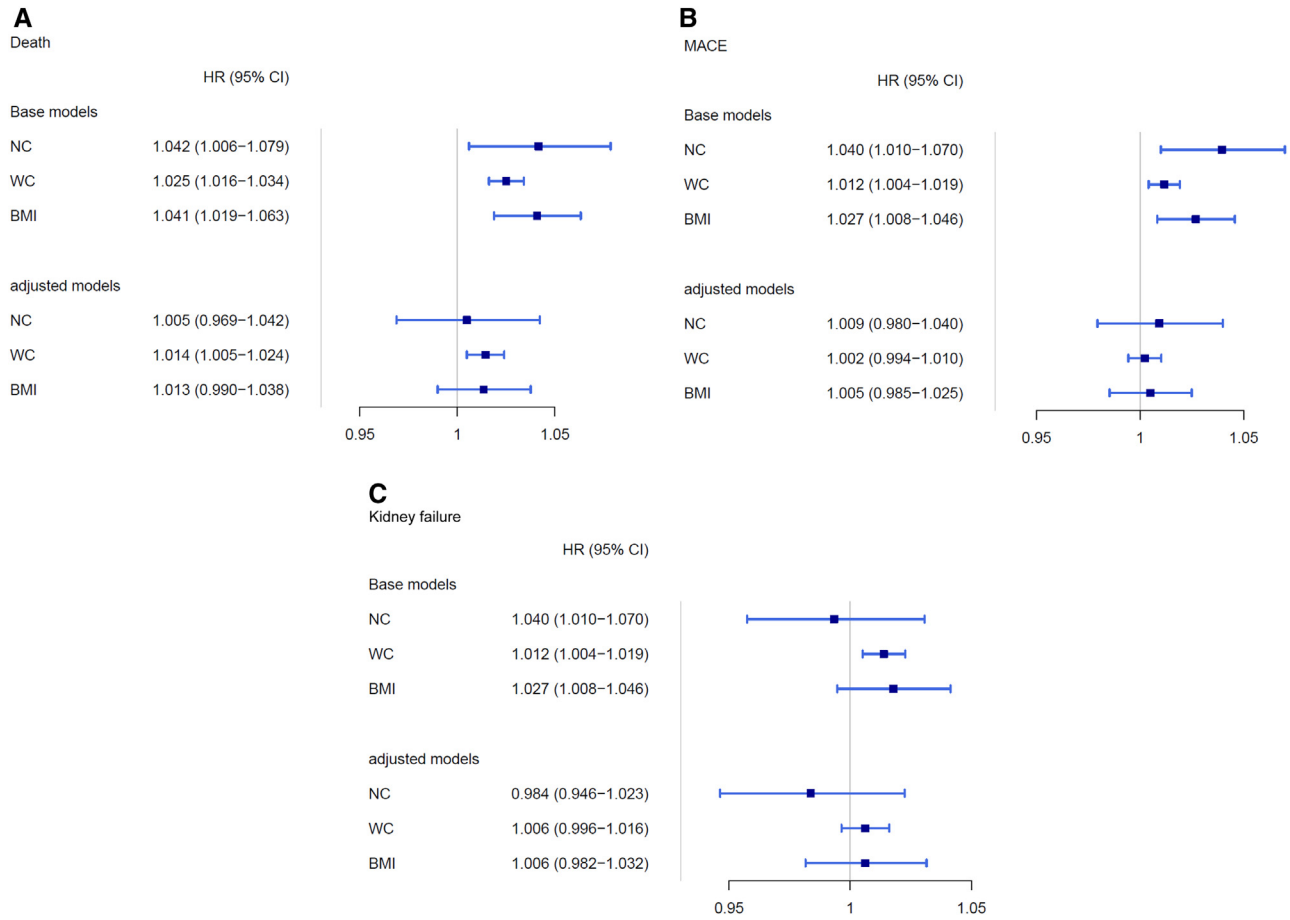

Figure 1. (A). Forest plots of proportional hazard ratios of all-cause death in base and fully adjusted Cox regression models. Figure legend: Depicted are Forest plots of proportional hazard ratios of death in base and fully adjusted Cox regression models. Hazard ratios shown are per centimeter (NC and WC) or per kg/m^2 (BMI). Base models adjusted for age, sex, and interaction adiposity measure with sex. Adjusted models are adjusted for age, sex, ever-smoker, diabetes mellitus, hypertension, LDL cholesterol, eGFR, UACR, CRP, sex, and interaction adiposity measure with sex. NC, neck circumference; BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval. (B). Forest plots of proportional hazard ratios of major adverse cardiovascular outcomes in base and fully adjusted Cox regression models. Figure legend: Depicted are Forest plots of proportional hazard ratios of major adverse cardiovascular events in base and fully adjusted Cox regression models. Hazard ratios shown are per centimeter (NC and WC) or per kg/m^2 (BMI). Base models are adjusted for age, sex, and interaction adiposity measure with sex. Adjusted models are adjusted for age, sex, ever-smoker, diabetes mellitus, hypertension, LDL cholesterol, eGFR, UACR, CRP, sex, and interaction adiposity measure with sex. MACE, major adverse cardiovascular events; NC, neck circumference; BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval. (C). Forest plots of proportional hazard ratios of kidney failure in base and fully adjusted Cox regression models. Figure legend: Depicted are Forest plots of proportional hazard ratios of kidney failure in base and fully adjusted Cox regression models. Hazard ratios shown are per centimeter (NC and WC) or per kg/m^2 (BMI). Base models are adjusted for age, sex, and interaction adiposity measure with sex. Adjusted models are adjusted for age, sex, ever-smoker, diabetes mellitus, hypertension, LDL cholesterol, eGFR, UACR, CRP, sex, and interaction adiposity measure with sex. NC, neck circumference; BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval.

kidney failure. Interaction of BMI with sex was statistically not significant for all analyzed outcomes.

Base models with WC yielded the lowest AIC for all three outcomes studied. Results of the base models are shown in Table 2 and Figure 1A-C.

Fully Adjusted Models

After further adjustment for potential confounders, most associations of adiposity measures with clinical outcomes were attenuated. In fully adjusted models, NC (per cm increase) no longer predicted death in the whole study group (HR 1.005; 95% CI 0.969-1.042). However, in women, this association was maintained (interaction HR 1.080 per cm; 95% CI 1.009-1.155). Associations of NC with the remaining outcomes were not statistically significant.

WC (per cm) predicted all-cause death (HR 1.014; 95% CI 1.005-1.024) in both sexes but not MACE or kidney

Table 3. Fully adjusted models of Adiposity measures and Clinical Outcomes

		NC	WC	BMI
Death n = 327	HR (95% CI)*	1.005 (0.969-1.042)	**1.014 (1.005-1.024)**	1.013 (0.990-1.038)
	HR (95% CI)† (interaction with sex)	**1.080 (1.009-1.155)**	0.998 (0.981-1.015)	1.000 (0.959-1.041)
	AIC	4971	4968	4977
MACE n = 495	HR (95% CI)*	1.009 (0.980-1.040)	1.002 (0.994-1.010)	1.005 (0.985-1.025)
	HR (95% CI)† (interaction with sex)	0.975 (0.921-1.033)	0.995 (0.981-1.008)	0.981 (0.948-1.014)
	AIC	7702	7702	7701
Kidney failure n = 335	HR (95% CI)*	0.984 (0.946-1.023)	1.006 (0.996-1.016)	1.006 (0.982-1.032)
	HR (95% CI)† (interaction with sex)	1.001 (0.936-1.071)	0.988 (0.973-1.004)	0.972 (0.934-1.012)
	AIC	4788	4786	4786

Bold for significant effects (95% CI not including 1.0).

AIC, Akaike information criterion; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MACE, 4-point major adverse cardiovascular events; NC, neck circumference; WC, waist circumference sex for woman.

*Adjusted for age, sex, ever-smoker, diabetes mellitus, hypertension, LDL cholesterol, eGFR, UACR, CRP, and interaction of the adiposity measure with sex.

†HR of the interaction term for women.

failure. There were no longer significant associations of BMI or its interaction with any of the analyzed outcomes.

Our fully adjusted models showed a significant impact of adiposity measures (NC and WC) only on all-cause death. When we compared the fit of our fully adjusted all-cause death models, we found that the data favored WC (AIC 4968), followed by NC (AIC 4971) and finally BMI (AIC 4977). Table 3 and Figure 1A-C summarize the fully adjusted models. In the sensitivity analyses of visceral fat, conicity index yielded coherent results with WC. WHR was a significant predictor of 4P-MACE only (supplemental material Table 3).

Discussion

In this study we compared the prognostic impact of NC, WC, and BMI on outcomes in a large-scale prospective observational cohort study in Caucasian patients with mild to severe CKD during 6.5 years of follow-up. Higher NC and WC predicted an increased risk for all-cause death. We found an association of WC with mortality regardless of sex, but the association of NC with mortality was found in women only. Fully adjusted models failed to indicate any prognostic utility of BMI.

Neck Circumference

To our knowledge, this study is the first to demonstrate an increased risk of all-cause death with increasing NC in female Caucasian patients with mild to severe CKD. To date, several studies have demonstrated an association of NC with obesity, insulin resistance, and dyslipidemia.[24,37-40] Similar associations were also found in patients on dialysis.[41] Although these data implicate an increased risk for cardiovascular events and mortality, we found no significant impact of NC on cardiovascular events using the composite outcome of 4-point MACE. The increased mortality risk in women seen in our study is probably attributable to other factors than cardiovascular causes of death, like infection or cancer. A possible pathogenetic link to multiple diseases might be elevated levels of plasma free fatty acids (FFA), which mediate endothelial injury, insulin resistance, immune cell activation, and even kidney disease.[42-45] Upper body subcutaneous fat is a major source of systemic FFA and women tend to accumulate FFA in this region more than men.[44,45] Lipotoxicity could be further amplified by CKD, which has been associated with impaired beta-oxidation and elevation of pathogenic FFA.[42] Earlier data suggest a possible link between NC to kidney function and outcomes.[28,30] Yoon et al. investigated the effect of higher NC on the incidence of newly diagnosed CKD in a prospective Korean cohort study of 2268 people with overweight. They also reported sex-specific differences, with the relative risk of developing either eGFR <60 mL/min/1.73 m^2 or proteinuria increasing by 15.9% per cm NC in women but not in men.[29] However, no group has investigated the respective association with endpoints such as initiation of kidney replacement therapy. In our study, NC did not affect the composite kidney outcome, i.e., initiation of maintenance dialysis therapy or kidney transplantation. Further research is needed to confirm the sex-specific prognostic relevance of NC.

Waist Circumference

In this study, a 10 cm increase in WC was associated with a 13.7% increase in all-cause mortality risk. These data are supported by similar findings in a subgroup analysis of the REGARDS study investigating 5805 adults with stage 1-4 CKD, in which the highest WC category ($\geq$108 cm for women; $\geq$122 cm for men) predicted death (HR 1.57; 95% CI 1.12-2.21) in comparison to the reference category ($<$80 cm for women; $<$94 cm for men).[33] Their results cannot be completely superimposed on ours, however. We analyzed WC as a continuous variable because categorization of variables can distort statistical findings.[46] Moreover, in the former analysis, 45% of participants were of African ancestry, and study participants had a different range of kidney function than the participants in our study.

In contrast to the subgroup analysis of the REGARDS study, Navaneethan et al. found no significant impact of WC on mortality risk in 2153 participants with CKD in the U.S. National Health and Nutrition Examination Survey, 1999-2004. This divergence might result from the smaller sample size investigated in that study. As in the REGARDS study, this U.S. study included multiple ethnicities and a broader eGFR spectrum than our analysis. The mean baseline eGFR of 73 mL/min/1.73 m^2 was much higher than in our cohort (50 mL/min/1.73 m^2), indicating an overall lower risk of death at baseline.[47]

Higher WC implies increased visceral fat and elevated cardiometabolic risk.[16] Associations of visceral fat with cardiovascular risk factors in CKD have been reported even for subcompartments, such as epicardial fat.[48] Nevertheless, a prospective study among 1669 patients with eGFR 15-60 mL/min/1.73 m^2 did not show a significant association of WC with cardiovascular events.[49] In line with that result, we found no significant association either.

We also found no significant impact of WC on kidney outcomes. Although some evidence suggests that WC might predict incident CKD and kidney function decline in prospectively followed cohorts,[12,50] our data support the findings from Davis et al., who also reported no significant impact of WC on kidney disease progression in 903 patients with CKD.[51]

There are many visceral adiposity measures described in scientific literature.[52] Our sensitivity analysis showed coherent effects of WC and conicity index as predictors of death, whereas WHR was significantly associated only with 4-point MACE. Whether different visceral adiposity measures express disparate associations with cause-specific clinical outcomes is beyond the scope of this investigation and remains to be shown elsewhere.

Body Mass Index

Fully adjusted models showed no impact of BMI on prognosis in our study, which is in line with previous findings in CKD cohorts.[13] In the general population, BMI is significantly associated with mortality, cardiovascular events, and even incident CKD,[11,53] but in already established CKD, these associations weaken or even vanish, depending on the cohort studied. For example, Madero et al. analyzed BMI in 1772 patients with CKD from the MDRD study and found no significant association of BMI with all-cause or cardiovascular mortality risk.[13] In the subgroup analysis of the REGARDS study, only the highest BMI category of ≥40 kg/m^2 was associated with an increased risk of all-cause death when compared to the 25-30 kg/m^2 category in multivariable models, a finding not applicable to most of the CKD population. Of note, after the authors further adjusted the BMI model for WC, the significance vanished.[33] Besides body fat, BMI incorporates muscle mass, which could be why BMI is not a good prognosticator in CKD, as higher muscle mass predicts more favorable clinical outcomes.[47] BMI also incorporates total adipose tissue rather than a distinct compartment. For a given value of BMI, the proportion of any fat compartment might vary among individuals. Higher BMI values thus do not necessarily imply higher amounts of fat compartments, such as visceral fat, associated with adverse outcomes. Thus, our study adds to the evidence that BMI may not be a reliable indicator of adverse outcomes in moderate CKD and that related results should be interpreted with caution.

Limitations

Our study has limitations. The generalizability of our findings is limited, since we investigated a homogenous sample of a Caucasian CKD population under nephrological care in Germany.

Missing baseline NC values were substituted by the mean of repeated measurements from second year follow-up onward, given that NC was on average stable over time. Accordingly, the mean NC value qualifies as a time-independent variable with the advantage of reduced measurement error (see supplementary Table and Figure 1). Analyzing NC as a time-dependent covariate or investigating the cohort from the 2-year follow-up visit onward has also been considered. However, each prospectively followed cohort changes after baseline, and participants develop diseases that would have originally disqualified them from participation. Thus, new confounders of prognosis can arise, and endpoint events that occurred before the 2-year follow-up would have been excluded from analysis, reducing statistical power. Furthermore, the comparison with baseline WC and BMI would have been compromised. Accordingly, the most suitable statistical procedure was substitution of baseline NC measurements.

We did not integrate the effects of NC, WC, and BMI at once, i.e., in one model. We avoided this step to preclude collinearity and enable a basic comparison of analyzed adiposity measures.

A potential source of bias might be missing systematic information about goiter, neck deformities, and hypercortisolism in our cohort, which we were not able to take into account and which might have influenced NC measurements in certain cases.

Conclusion

Our study provides evidence that NC in women and WC in both sexes are independent predictors of all-cause death in Caucasian patients with mild to severe CKD. We did not find a relevant impact of BMI on death, cardiovascular events, or kidney failure. Further research is needed to elucidate the underlying mechanisms of these findings.

Practical Application

In adults with mild to severe CKD, measuring WC and maybe NC in women to assess adiposity might provide valuable information about mortality risk. In contrast,

BMI does not seem to be of prognostic relevance in these patients.

Data Availability Statements

Public posting of individual level participant data is not covered by the informed patient consent form. As stated in the patient consent form and approved by the Ethics Committees, a dataset containing pseudonyms can be obtained by collaborating scientists upon approval of a scientific project proposal by the steering committee of the GCKD study: https://www.gckd.org.

CRediT authorship contribution statement

Vladimir Cejka: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Stefan Störk:** Conceptualization, Supervision, Writing – review & editing. **Jennifer Nadal:** Visualization, Formal analysis, Methodology, Writing – review & editing. **Matthias Schmid:** Visualization, Methodology, Writing – review & editing, Supervision. **Claudia Sommerer:** Project administration, Writing – review & editing, Investigation. **Thomas Sitter:** Project administration, Writing – review & editing, Investigation. **Heike Meiselbach:** Data curation, Project administration. **Martin Busch:** Project administration, Writing – review & editing, Investigation. **Markus P. Schneider:** Project administration, Writing – review & editing, Investigation. **Turgay Saritas:** Writing – review & editing, Investigation. **Ulla T. Schultheiss:** Writing – review & editing, Investigation, Data curation, Funding acquisition. **Fruzsina Kotsis:** Writing – review & editing, Investigation. **Christoph Wanner:** Supervision, Writing – review & editing, Project administration. **Kai-Uwe Eckardt:** Project administration, Funding acquisition, Writing – original draft, Writing – review & editing, Investigation. **Vera Krane:** Supervision, Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Project administration.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2023.04.006.

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