Health-Related Quality of Life according to Renal Function: Results from a Nationwide Health Interview and Examination Survey

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Keywords

Health-related quality of life · Short form health Survey-36 · Chronic kidney disease · Glomerular filtration rate

Abstract

Background: Most studies on health-related quality of life (HRQoL) in chronic kidney disease (CKD) focus on patients with end-stage kidney disease although they represent a small proportion of patients with CKD. We aimed to analyze HRQoL according to glomerular filtration rate (GFR) categories in a population-based sample of adults living in Germany. **Methods:** Data from the German health interview and examination survey conducted from 2008 to 2011 were used. Participants with valid interview and examination data aged 40–79 years were included ($n = 5,159$). Serum creatinine levels were used to calculate estimated GFR via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. We classified kidney function in GFR categories according to the Kidney Disease Improving Global Outcomes Initiative (KDIGO) guidelines on CKD: G1 (high): ≥ 90 mL/min/1.73 m², G2 (normal): 60–89 mL/min/1.73 m², G3a (mildly decreased): 45–59 mL/min/1.73 m², G3b (moderately decreased): 30–44 mL/min/1.73 m², G4/5 (severely decreased/end-stage kidney disease): <30 mL/min/1.73 m². HRQoL was evaluated with the Short Form Health Survey (SF-36). Different multivariate linear and logistic regression

models were used to analyze the association of HRQoL with GFR categories. **Results:** Overall, 5.9% had a GFR <60 mL/min/1.73 m² (corresponding to categories G3a, G3b, and G4/5). Compared to category G2 linear regression showed a decline in physical HRQoL in categories G3a (-2.34 , $p = 0.004$), G3b (-5.37 , $p = 0.009$), and G4/5 (-4.82 , $p = 0.117$). No decline in mental HRQoL was detected with increasing GFR categories. Categories G3a to G4/5 were significantly associated with a low perceived general state of health (G3a: odds ratio [OR] = 2.03, $p = 0.001$; G3b: OR = 3.01, $p = 0.009$; G4/5: OR = 8.70, $p = 0.016$) when compared to category G2. **Conclusion:** In a representative sample of adults living in Germany, both physical HRQoL and the perceived general state of health are already significantly reduced in category G3a.

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Introduction

Chronic kidney disease (CKD) is a heterogeneous condition defined as either kidney dysfunction or signs of kidney damage [1, 2]. The frequency of CKD is increasing [3] and associated with a substantial morbidity and mortality [4]. Hence, the Kidney Disease Improving Global Outcomes Initiative (KDIGO) describes CKD as a “worldwide public health problem” [5]. CKD affects approxi-

mately 752.7 million individuals worldwide [6] and circa 2 to 2.5 million in Germany [7]. In a cohort representative of the adult population living in Germany aged 18–79 years, the prevalence of CKD is estimated at 2.3% [7]. However, the prevalence drastically increases with age. There exists evidence that 46.6% of the German population aged 80 or older are affected by CKD [7]. In industrialized countries, diabetes and hypertension are the leading causes of CKD [2].

Especially higher stages of CKD are frequently linked to comorbidities, like cardiovascular diseases, anemia, malnutrition, polypharmacy, or sleep disturbance [8–11]. In addition, patients with CKD often display depressive symptoms [12, 13] or anxiety [14]. Higher levels of CKD are associated with higher chances of suffering from depression [12].

Health-related quality of life (HRQoL) is a subjective measurement that reflects the impact of disease and its therapy regime on patients [15]. The final stages of CKD are associated with a reduced HRQoL [16, 17]. However, end-stage kidney disease (ESKD) represents merely a small proportion of the population with CKD [4]. The association of the less severe stages of CKD with HRQoL remains largely unclear as the majority of studies are not population-based and have not classified renal function according to KDIGO guidelines into 5 categories (G1–G5) [3, 18–24]. Some studies could detect impairment in HRQoL in the early stages of CKD [3, 11, 18, 25, 26]. Other studies could not confirm this finding [27] or results were not significant after adjusting for confounders [11, 19, 20, 27]. A small German study analyzing patients with CKD stage 3–5 ($n = 119$) was able to detect an impairment of merely the physical but not the mental dimension of HRQoL [28]. Panuccio et al. [29] showed that merely the general state of health decreases as CKD progresses whereas mental or physical HRQoL are not affected by a declining kidney function. Only few studies assessed all these measures of HRQoL in a population-based sample [26, 30]. Hence, the objective of our study was to analyze both mental and physical HRQoL and perceived general state of health according to glomerular filtration rate (GFR) categories in a large and representative sample of adults aged 40–79 years living in Germany.

Materials and Methods

Study Design

We used data from the German health interview and examination survey (DEGS1) which was conducted from November 2008 to December 2011 by the Robert Koch Institute (RKI) as part of

continuous health monitoring [31]. The DEGS1 study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved on 1 October 2008, by the Ethics Committee 2, Campus Virchow-Klinikum, Charité (No. EA2/047/08). Subjects have given their written informed consent.

To ensure that the study population was representative of the adult population in Germany, data from 180 primary sampling units (PSUs) from different regions in Germany were collected. Participants were randomly allocated to PSUs by the local residence registration offices. A total of 17,410 adults were invited to participate and interview and clinical examination data were collected from 7,115 participants. We further excluded participants <40 years of age as the prevalence of cardiovascular diseases (myocardial infarction and stroke) was not assessed in this cohort. Therefore, our final study population consisted of 5,203 participants (Fig. 1 [31]). The process of excluding participants of the DEGS1 study for various reasons from our study population is shown in Figure 1 [31].

Two teams of health professionals conducted examinations and visited all PSUs in random order to eliminate bias. Urine and blood samples were collected. Blood pressure, body weight, and height were recorded. Participants completed a self-filled questionnaire (SFQ), the Short Form Health Survey (SF-36) version 2, and the Patient Health Questionnaire (PHQ). A detailed anamnesis was obtained by a standardized physician-administered computer-assisted personal interview (CAPI) [32].

Evaluation of Kidney Function

Serum creatinine (IDMS traceable creatinine assay; Abbott Diagnostics, Wiesbaden, Germany) was measured in all participants and used to calculate estimated GFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. In this equation, serum creatinine, sex, age, and ethnicity are taken into account [33]. We assumed that all participants were Caucasians, and the appropriate equation was used. Due to the cross-sectional design of the DEGS1 study, we could detect renal dysfunction but not CKD. We classified kidney function in GFR categories according to the KDIGO guidelines on CKD: G1 (high): ≥ 90 mL/min/1.73 m², G2 (normal): 60–89 mL/min/1.73 m², G3a (mildly decreased): 45–59 mL/min/1.73 m², G3b (moderately decreased): 30–44 mL/min/1.73 m², G4 (severely decreased): 15–29 mL/min/1.73 m², G5 (ESKD): <15 mL/min/1.73 m² [34]. However, we do not have proof of neither kidney damage nor albuminuria. Therefore, categories G1 and G2 are not pathological. This is in accordance with the KDIGO guidelines [34]. Moreover, we have defined category G2 as “normal” as the KDIGO guidelines refer to young adult level, and our study population is ≥ 40 years.

HRQoL was measured by means of the generic SF-36 instrument version 2, which is a validated, reliable, and recommended tool in patients with CKD [4, 10, 35]. It reflects HRQoL over the last 4 weeks as reported by the patient. The questionnaire consists of 36 questions covering 8 dimensions (physical functioning [PF], role-physical [RP], bodily pain [BP], general health [GH], vitality [VT], social functioning [SF], role-emotional [RE], and mental health [MH] [36]). Hence, the questionnaire is in line with the World Health Organization's (WHO) definition of health comprising the dimensions “physical, mental and social well-being” [37]. Scores for each of these dimensions are directly transformed to a scale ranging from 0 to 100. A higher score indicates a better HRQoL. Physical component summary (PCS) and mental compo-

Fig. 1. The process of excluding participants of DEGS1 (German health interview and examination survey) for various reasons from our study population is shown in Figure 1 - based on data from Kamtsiuris and Dolle [31].

nent summary (MCS) are generated by summing up the weighted scores of the original SF-36 scores. PCS includes the dimensions PF, RP, BP, GH, and MCS includes VT, SF, RE, and MH [36]. These summary scores are generated by standardized calculations resulting in a mean score of 50 and a standard deviation of 10 when applied to the general population. Consequently, scores >50 are above and scores <50 are below the mean [4, 36].

Moreover, we evaluated one of the 5 questions included in the dimension GH as an overall measure of self-reported health. The evaluation of self-reported health is widely spread in literature [38, 39]. The 5 response items to the question how participants perceive their state of health in general were dichotomized. Excellent, very good and good were combined to high perceived general state of health; less well and bad were classified as low perceived general state of health.

Covariates

All diseases were self-reported, and participants were asked whether a certain disease had ever been diagnosed by a physician. This included hypertension, diabetes, dyslipidemia, heart failure, myocardial infarction, stroke, and rheumatoid arthritis (RA). Smoking status was also assessed.

Socioeconomic status (SES) was assessed using the index developed by the RKI, including level of education, profession, and income. The index converts these dimensions into a metric system ranging from 3 to 21 points which are divided into 3 groups: “low SES” (1st quintile = 20% of population), “medium SES” (2nd–4th quintile = 60% of population), and “high SES” (5th quintile = 20% of population) [40].

Depressive symptoms were obtained via the German version of the Patient Health Questionnaire-9 (PHQ-9). The frequency of 9 different depressive symptoms over the last 2 weeks according to the Diagnostic and Statistical Manual of Mental Disorders IV

(DSM IV) was assessed. The response items comprised “not at all” (0 points), “on several days” (1 point), “more than half the days” (2 points) to “nearly every day” (3 points). A sum was calculated; 0–4 points indicating no depressive symptoms, 5–9 points indicating slight depressive symptoms, and 10 or more points indicating severe depressive symptoms [41].

Statistical Analysis

Firstly, sociodemographic characteristics were descriptively analyzed according to GFR categories. Significant differences were assessed using Rao-Scott χ^2 tests. Throughout this study, categories G4 and G5 were combined due to their small numbers. Secondly, mean scores and 95% confidence intervals for the different dimensions of the SF-36 (PF, RP, BP, GH, VT, SF, RE, and MH) and for the adjusted component summary scores (PCS and MCS) were analyzed according to GFR categories.

Thirdly, multivariate linear regression was carried out to determine whether the PCS and MCS scores of the SF-36 were associated with different GFR categories. In this model, we adjusted for different sociodemographic variables (sex, age, marital status, and SES), comorbidities (hypertension, diabetes, dyslipidemia, heart failure, myocardial infarction, stroke, and RA), lifestyle factors (smoking, body weight as determined by body mass index [BMI]), and psychological well-being (depressive symptoms as recorded by PHQ).

Fourthly, in a multivariate logistic regression model, we assessed the association of a low perceived general state health with the different GFR categories and adjusted for the abovementioned variables. Odds ratios were estimated.

For analysis, the weighting factors as suggested by RKI were applied. Hence, deviations from the basic population in Germany (December 31, 2010) were corrected for age, sex, region, citizenship, size of hometown, and level of education. Descriptive analy-

Table 1. Sociodemographic characteristics and comorbidities according to GFR categories in %

Characteristics*	GFR categories					p value
	G1 (n = 2,249), %	G2 (n = 2,568), %	G3a (n = 257), %	G3b (n = 69), %	G4/5 (n = 16), %	
Sex (female) (n = 5,159)	46.4	55.4	51.6	53.3	77.7	<0.0001
Age (n = 5,159)						
Mean years	51.2	61.6	70.1	70.4	66.5	<0.0001
40–64 years	92.0	54.6	19.9	13.6	16.1	
65–79 years	8.0	45.4	80.1	86.4	83.9	
Marital status (n = 5,117)						
Married	74.5	74.5	68.4	67.3	69.0	<0.0001
Unmarried/separated	21.7	16.1	10.9	10.2	2.1	
Widowed	3.8	9.4	20.7	22.5	28.9	
SES (n = 5,126)						
Low	20.5	19.0	19.8	28.6	26.1	0.0454
Medium	59.1	59.3	67.6	58.8	73.9	
High	20.4	21.7	12.6	12.5	0.0	
Lifestyle factors						
BMI, kg/m ² (n = 5,123)						
Mean	27.3	28.0	29.9	31.2	31.9	<0.0001
<25	35.5	26.6	14.8	11.7	2.1	
25–<30	38.7	44.5	43.2	35.2	26.6	
≥30	25.9	28.9	42.0	53.0	71.2	
Smoking (currently) (n = 5,128)	32.6	17.0	7.0	11.5	0	<0.0001
Comorbidities						
Hypertension (n = 4,798)	33.3	51.9	83.1	84.9	82.6	<0.0001
Diabetes (n = 4,798)	5.2	11.2	30.2	44.5	57.5	<0.0001
Dyslipidemia (n = 4,797)	31.7	42.3	61.6	58.6	38.4	<0.0001
Heart failure (n = 4,795)	2.2	6.9	21.0	29.1	27.2	<0.0001
Myocardial infarction (n = 4,794)	2.1	5.0	17.1	15.8	14.7	<0.0001
Stroke (n = 4,795)	1.8	3.1	9.0	10.5	26.6	<0.0001
RA (n = 4,793)	2.9	3.9	2.1	4.4	5.9	0.3142
Psychological well-being						
Depressive symptoms (n = 4,841)						
No (0–4 points)	66.1	67.5	70.1	77.3	41.1	0.5363
Slight (5–9 points)	26.8	25.2	23.3	18.3	51.2	
Moderate/severe (10–27 points)	7.1	7.3	6.6	4.4	7.6	
Perceived general state of health (n = 5,028)						
High	82.3	80.4	59.8	50.6	38.3	<0.0001
Low	17.7	19.6	40.2	49.4	61.7	

GFR, glomerular filtration rate; BMI, body mass index; SES, socioeconomic status; RA, rheumatoid arthritis. * Figures differ due to missing values, sample sizes given are unweighted.

ses were conducted with SPSS IBM® version 25 (IBM, Armonk, NY, USA), and all other analyses were performed with SAS® for Windows version 9.4 (SAS Institute INC, Cary, NC, USA) using procedures for complex survey designs.

Results

Baseline Characteristics

The total analyzed population consisted of 5,159 adults as the serum creatinine measurements were not available

for 44 participants (weighted $n = 4,699$). 48.8% and 45.3% of the participants had a kidney function classified as G1 and G2, respectively. 4.3% of all participants belonged to category G3a, 1.2% to category G3b, and 0.3% to category G4/5. At 16.3%, the prevalence of a GFR <60 mL/min/1.73 m² was higher in those aged 65–79 years (compared to 1.5% in those aged 40–64 years) with only minor differences between males and females.

Baseline characteristics are presented in Table 1 according to GFR categories. The mean age of participants

Table 2. Mean values of SF-36 dimensions according to GFR categories

Characteristics*	GFR categories				
	G1 mean (95%CI)	G2 mean (95%CI)	G3a mean (95%CI)	G3b mean (95%CI)	G4/5 mean (95%CI)
PF (n = 4,962)	86.1 (85.0–87.1)	81.7 (80.6–82.8)	69.0 (65.0–73.0)	58.2 (49.0–67.3)	49.0 (37.4–60.7)
RP (n = 4,947)	81.4 (80.2–82.7)	77.1 (75.8–78.5)	62.3 (57.9–66.7)	55.4 (46.1–64.6)	54.1 (40.5–67.6)
BP (n = 5,020)	72.5 (71.0–73.9)	70.5 (69.2–71.9)	62.8 (58.6–66.9)	54.1 (46.7–61.5)	67.5 (49.2–85.7)
GH (n = 4,976)	68.0 (67.0–69.0)	67.8 (66.8–68.8)	60.3 (57.4–63.2)	58.1 (53.1–63.1)	49.5 (40.8–58.2)
PCS (n = 4,857)	50.8 (50.3–51.3)	49.0 (48.5–49.6)	43.2 (41.6–44.8)	38.4 (34.6–42.2)	38.8 (33.8–43.8)
VT (n = 4,987)	62.1 (61.0–63.1)	63.3 (62.3–64.3)	61.5 (58.5–64.6)	60.2 (56.1–64.4)	59.5 (49.0–69.9)
SF (n = 5,028)	85.6 (84.5–86.7)	86.7 (85.7–87.6)	84.1 (80.5–87.7)	82.9 (76.1–89.6)	88.8 (80.0–97.5)
RE (n = 4,944)	85.8 (84.5–86.9)	84.6 (83.4–85.9)	78.4 (73.8–82.9)	82.8 (76.5–89.0)	73.9 (50.9–96.9)
MH (n = 4,982)	72.4 (71.5–73.3)	74.3 (73.3–75.2)	74.5 (71.6–77.4)	75.1 (71.5–78.8)	73.5 (62.9–84.2)
MCS (n = 4,857)	49.3 (48.8–49.9)	50.6 (50.0–51.1)	51.1 (49.3–53.0)	53.6 (51.4–55.9)	52.1 (47.8–56.4)

PF, physical functioning; RP, physical role functioning; BP, bodily pain; GH, general health; PCS, physical component summary; VT, vitality; SF, social functioning; RE, emotional role functioning; MH, mental health; MCS, mental component summary; GFR, glomerular filtration rate. * Figures differ due to missing values.

in categories G1 and G2 was 51–62 years compared to a mean age of 67–70 years in categories G3a, G3b, and G4/5. In categories G4/5, 77.7% of the participants were females. Mean BMI increased with decreasing kidney function. The percentage of participants with hypertension and diabetes increased most substantially with decreasing kidney function. 33.3% of all participants in category G1 suffered from hypertension compared to 84.9% in category G3b and 82.6% in category G4/5. The percentage of patients with diabetes increased from 5.2% in category G1 to 44.5% in category G3b and to 57.5% in category G4/5. For heart failure, myocardial infarction, stroke, and RA the same trend could be detected, however less pronounced. More than half (51.2%) of the participants in category G4/5 experienced slight depressive symptoms over the last 2 weeks compared to 26.8% in category G1.

Physical HRQoL

With decreasing kidney function HRQoL declined in all dimensions categorized as physical HRQoL (PF, RP, and GH) except for BP. In those dimensions, a significant and sudden decline in HRQoL was found when comparing categories G2 and G3a. The sharpest decline could be detected in the dimension RP (from 77.1 points in category G2 to 62.3 points in category G3a). Consequently, PCS scores showed the same trend, a significant reduction in HRQoL was detected when comparing categories G2 (49.0 points) and G3a (43.2 points) (Table 2).

Multivariate linear regression showed that categories G3a and G3b had a significant negative effect on the PCS

score compared to category G2. In comparison to category G2, categories G3a and G3b scored on average 2.34 and 5.37 points less, respectively. Category G4/5 scored 4.82 points less than category G2. However, this was not significant. Moreover, female sex, increasing age, low or medium SES, and different comorbidities (apart from dyslipidemia) were also associated with a significant decrease in physical HRQoL (Table 3).

Mental HRQoL

For the different mental HRQoL dimensions (VT, SF, RE, and MH) and for MCS scores, no definite association of the different GFR categories with HRQoL could be detected (Table 2). In multivariate linear regression, no significant association of categories G3a or G3b with MCS scores could be detected. Female sex, being unmarried/separated, heart failure, and depressive symptoms were associated with a significant decrease in mental HRQoL. Increasing age and a BMI ≥ 25 kg/m² were associated with a slight but significant increase in mental HRQoL (Table 3).

Perceived General State of Health

The percentage of participants perceiving their general state of health as low increased progressively with decreasing kidney function. The sharpest increase in the number of participants perceiving their general state of health as low could be detected when comparing categories G2 (19.6%) and G3a (40.2%) (Table 1).

In our multivariate model, all GFR categories were significantly associated with a low perceived general state of

Table 3. Multivariate linear regression for variables associated with the physical and mental SF-36 component summary scores ($n = 4,334$, unweighted)

	PCS			MCS		
	β	95% CI	p value	β	95% CI	p value
GFR categories						
G1	−0.21	(−0.97 to 0.56)	0.591	−0.71	(−1.33 to −0.09)	0.024
G2	Ref			Ref		
G3a	−2.34	(−3.94 to −0.75)	0.004	0.24	(−1.36 to 1.83)	0.772
G3b	−5.37	(−9.41 to −1.34)	0.009	1.62	(−1.23 to 4.46)	0.264
G4/5	−4.82	(−10.84 to 1.21)	0.117	3.75	(1.30 to 6.21)	0.003
Sex (female)	−1.04	(−1.72 to −0.37)	0.003	−0.90	(−1.47 to −0.33)	0.002
Age						
40–64 years	Ref		0.001	Ref		0.011
65–79 years	−3.03	(−3.91 to −2.14)		1.01	(0.24 to 1.78)	
Marital status						
Married	Ref			Ref		
Unmarried/separated	−0.28	(−1.25 to 0.69)	0.57	−1.54	(−2.38 to −0.69)	≤0.001
Widowed	0.34	(−0.93 to 1.60)	0.60	−0.29	(−1.42 to 0.84)	0.062
SES						
Low	−4.70	(−5.93 to −3.47)	<0.001	−0.39	(−1.45 to 0.67)	0.468
Medium	−1.82	(−2.42 to −1.23)	<0.001	−0.23	(−0.78 to 0.33)	0.426
High	Ref			Ref		
Lifestyle factors						
BMI, kg/m ²						
<25	Ref			Ref		
25– <30	−1.11	(−1.77 to −0.45)	0.001	0.64	(−0.04 to 1.32)	0.064
≥30	−3.72	(−4.60 to −2.83)	<0.001	1.04	(0.19 to 1.89)	0.017
Smoking (currently)	−0.96	(−1.87 to −0.06)	0.037	−0.08	(−0.79 to 0.63)	0.825
Comorbidities						
Hypertension	−1.50	(−2.20 to −0.80)	<0.001	−0.15	(−0.77 to 0.48)	0.646
Diabetes	−2.04	(−3.31 to −0.78)	0.002	−0.51	(−1.59 to 0.58)	0.356
Dyslipidemia	−0.35	(−1.01 to 0.31)	0.298	0.24	(−0.36 to 0.84)	0.433
Heart failure	−4.00	(−5.43 to −2.57)	<0.001	−1.39	(−2.71 to −0.07)	0.039
Myocardial infarction	−2.69	(−4.76 to −0.63)	0.011	−0.38	(−2.20 to 1.45)	0.686
Stroke	−3.85	(−6.48 to −1.22)	0.004	−1.03	(−3.39 to 1.33)	0.390
RA	−4.74	(−6.68 to −2.81)	<0.001	1.16	(−0.28 to 2.62)	0.113
Psychological well-being						
Depressive symptoms						
No (0–4 p.)	Ref			Ref		
Slight (5–9 p.)	−3.29	(−4.10 to −2.49)	<0.001	−9.05	(−9.75 to −8.36)	<0.001
Moderate/severe (10–27 points)	−5.61	(−7.21 to −4.01)	<0.001	−22.17	(−23.64 to −20.70)	<0.001

PCS, physical component summary; MCS, mental component summary; SES, socioeconomic status; BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; RA, rheumatoid arthritis.

health. With decreasing kidney function, the odds ratio for a low perceived general state of health increased from 2.03 in category G3a to 8.70 in category G4/5 compared to category G2. Furthermore, age, a low or medium SES, a BMI ≥ 30 , hypertension, heart failure, and depressive symptoms were also significantly associated with an increased likelihood for a low perceived general state of health (Table 4).

Discussion

This study explored HRQoL according to GFR categories in a representative sample of adults living in Germany. Our results can be summarized as follows: first, already categories G3a and G3b led to a significant decline in physical HRQoL. Second, categories from G3a to G4/5

Table 4. Multivariate logistic regression for variables associated with a low perceived general state of health ($n = 4,442$, unweighted)

	OR	95% CI	<i>p</i> values
GFR categories			
G1	1.23	(0.94–1.61)	0.128
G2	Ref		
G3a	2.03	(1.33–3.08)	0.001
G3b	3.01	(1.32–6.87)	0.009
G4/5	8.70	(1.51–50.03)	0.016
Sex (female)	0.95	(0.74–1.21)	0.649
Age			
40–64 years	Ref		0.048
65–79 years	1.40	(1.00–1.97)	
Marital status			
Married	Ref		
Unmarried/separated	1.06	(0.75–1.49)	0.756
Widowed	0.79	(0.53–1.19)	0.259
SES			
Low	2.40	(1.62–3.55)	<0.001
Medium	1.48	(1.10–2.00)	0.01
High	Ref		
Lifestyle factors			
BMI, kg/m ²			
<25	Ref		
25–<30	1.11	(0.82–1.50)	0.486
≥30	1.75	(1.30–2.36)	0.000
Smoking (currently)	1.29	(0.91–1.84)	0.156
Comorbidities			
Hypertension	1.56	(1.23–1.97)	0.000
Diabetes	1.65	(1.16–2.37)	0.006
Dyslipidemia	1.02	(0.82–1.27)	0.879
Heart failure	2.69	(1.72–4.19)	<0.001
Myocardial infarction	1.50	(0.85–2.65)	0.1575
Stroke	2.40	(1.25–4.61)	0.009
RA	3.38	(1.96–5.84)	<0.001
Psychological well-being			
Depressive symptoms			
No (0–4 points)	Ref		
Slight (5–9 points)	3.44	(2.67–4.41)	<0.001
Moderate/severe (10–27 points)	17.10	(11.78–24.83)	<0.001

SES, socioeconomic status; BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; OR, odds ratio; RA, rheumatoid arthritis.

significantly increased the likelihood for a low perceived general state of health. Third, no significant effect of the different GFR categories on mental HRQoL has been detected.

So far, only few studies on HRQoL have included categories from G1 to G5 [3, 21, 24, 42]. Other studies have not classified the GFR categories according to KDIGO guidelines [18, 19, 21, 22] or have not distinguished between the different categories [20, 22, 23]. However, we have shown that the distinction between categories G3a and G3b might be important as already in category G3a

both physical HRQoL and the perceived general state of health are reduced significantly. In accordance with “the screening for CKD among older people across Europe” (SCOPE) study, we were able to prove that already in category G3a HRQoL is impaired significantly [26]. However, in contrast to the SCOPE Study which analyzed a geriatric cohort (>75 years), we could also detect the negative effect on HRQoL in a population aged 40–79 years. Thus, we have been able to debunk the hypothesis that a slight decrease in kidney function is not linked independently to HRQoL as it is often asymptomatic [4]. More-

over, our findings were corroborated by the Chinese Cohort Study of Chronic Kidney Disease (C-Stride study) which showed a significant reduction in PCS scores in categories G3a and G3b. Similar to our assumption, the authors also concluded that the differentiation between categories G3a and G3b is very important [30]. In contrast, the findings of the Irish Longitudinal Study on Aging (TILDA), a cluster-sampled cohort of Irish community-dwelling adults ≥ 50 years similar to our study set-up, differed markedly from ours. Canney et al. [27] concluded that a slightly impaired kidney function did not have an effect on HRQoL. In contrast, our results suggest that already a mild GFR reduction < 60 mL/min/1.73 m² significantly reduces physical HRQoL. Hence, we also cannot corroborate the 2 previously reported GFR dividing lines for a reduction in HRQoL of < 45 mL/min/1.73 m² and of < 30 mL/min/1.73 m² [10, 18]. Yet, all findings mentioned should be interpreted in the context of the setting and the population included in the studies. Chin et al. [18] have analyzed the effect of CKD on HRQoL; in a cohort of elderly Koreans, Pagels et al. [10] have studied a cohort consisting predominantly of participants with ESKD and Aggarwal et al. [24] have examined a small cohort of Indian patients.

However, our findings are corroborated by several studies: a small German study has detected a significant impairment in physical HRQoL in patients with CKD stages 3–5; unfortunately, no distinction between G3a and G3b has been made [28]. Similarly, a significant increase in the risk of experiencing an impaired HRQoL has been reported for participants with a GFR of 30–59 mL/min/1.73 m² in a large Korean population-based study. However, Lee et al. [21] have not differentiated between G3a and G3b. Moreover, the African American Study of Disease and Hypertension (AASK Trial) has reported a significant reduction in physical HRQoL in a cohort with a mean GFR of 45.7 mL/min/1.73 m², concluding that early CKD stages reduce HRQoL [22]. In addition, Odden et al. [20] have shown that a GFR < 60 mL/min/1.73 m² leads to an impaired overall health; however, CKD has not been classified in stages.

Furthermore, HRQoL might even be affected in CKD stages 1 and 2. A small Brazilian study with a predominance of participants with ESKD has reported that physical HRQoL is reduced in all stages of CKD [3]. However, findings have to be interpreted with caution due to small case numbers in CKD stages 1 and 2 ($n = 18$) [3]. Yet, a British population-based study has also described that HRQoL is significantly affected in CKD stages 2, 4, 5 and stage 3 with albuminuria. However, Nguyen et al. [42] have measured

HRQoL with a health utility index which differs from the SF-36 used in our study. Moreover, Nguyen et al. [42] have not distinguished between GFR categories 3a and 3b but instead divide GFR category 3 into G3 with and G3 without albuminuria. Hence, comparability is limited.

On top of that, we have been able to show that the perceived general state of health decreases progressively with decreasing kidney function. The Heart and Soul Study has also detected impairment in the self-assessed overall health in patients with mild or moderate CKD [20]. Moreover, Panuccio et al. [29] have shown that as CKD progresses the SF-36 dimension of GH decreases whereas mental and physical HRQoL remain stable.

In addition, our study has shown that categories G2, G3a, and G3b have no significant effect on mental HRQoL. This is in line with numerous international studies [3, 4, 20, 28, 43]. The AASK Trial has even detected slightly higher MCS scores in the population with CKD compared to the control group [22].

Strengths and Limitations

The major strength of DEGS1 is the large sample size and the fact that the data are representative of the adult population aged 40–79 years living in Germany. Moreover, this study has not relied on self-reported diagnosis of CKD. In all participants, standardized serum creatinine levels have been measured to calculate estimated GFR using the CKD-EPI-equation. Although the CKD-EPI-equation may overestimate GFR in some participants, this equation is the most accurate and validated option to analyze GFR in a population that includes participants with a high and low GFR [44].

As the generic SF-36 was used to measure HRQoL a comparison to different populations is possible. A strength is the fact that the questionnaire is recommended by the National Kidney Foundation (NKF) [10].

Cognitive impairment is an important factor in patients with renal insufficiency as described in literature [45]. Unfortunately, data concerning cognitive impairment were not included in the DEGS study. However, as we focused on analyzing the association of HRQoL and GFR categories this shortcoming should not have a large impact on our findings.

Due to the low number of participants in category G4/5, the results in this subgroup must be interpreted with caution. Thus, categories G4 and G5 were combined. Consequently, differences between these 2 categories could not be studied.

As all comorbidities have been self-reported, they might be subject to recall or reporting bias. However,

there exists evidence that self-reported diagnosis of cardiovascular diseases (hypertension and myocardial infarction) and well-defined chronic diseases (diabetes) have a high validity [46, 47].

Conclusion

We demonstrated a significant reduction in physical HRQoL already in category G3a in a population-based sample in Germany. The chance of a low perceived general state of health increases progressively with decreasing kidney function. As expected, the negative effect was most pronounced in category G4/5. Therefore, assessing HRQoL already in patients with a kidney function classified as G3a might be an important tool in the physician's box and could become an integral part of patient-centered care.

Statement of Ethics

The DEGS1 study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved on 1 October 2008 by the Ethics Committee 2, Campus Virchow-Klinikum, Charité (No. EA2/047/08). Subjects have given their written informed consent.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Liv Faulhaber, Stefan Herget-Rosenthal, and Falk Hoffmann conceptualized the study. Liv Faulhaber, Falk Hoffmann, and Hannes Jacobs conducted the analysis. Liv Faulhaber wrote the first draft of the article. All authors interpreted the data, critically revised the manuscript, read, and approved the final version.

Data Availability Statement

The dataset analyzed for this study is available as a public use file and can be requested upon application from the Research Data Centre of the Robert Koch-Institute (https://www.rki.de/EN/Content/Health_Monitoring/Public_Use_Files/application/application_node.html).

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