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Mild-to-Moderate Chronic Kidney Disease and Geriatric Outcomes: Analysis of Cross-Sectional Data from the Berlin Aging Study II

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Chronic kidney disease · Assessment · Physical function · Cognition · Mobility · Nutrition

Abstract
Background: Mild-to-moderate chronic kidney disease (CKD G3a) is prevalent in older adults. Substantial evidence suggests that individuals with advanced CKD face a high risk for common geriatric conditions, like functional impairment and cognitive decline, whereas the relationships between mild-to-moderate CKD and functional impairment and cognitive decline, but also poor nutritional status and mood disorders, are still unclear. ***Objective:*** The aim of this study was to explore associations between mild-to-moderate CKD and impairments in the core domains of geriatric assessment (GA) in a large cohort of community-dwelling older adults. ***Methods:*** This was a cross-sectional analysis of 1,476 participants of the Berlin Aging Study II. Study participants were stratified as to presence or absence of CKD G3a (estimated glomerular filtration rate [eGFR] 45–59 mL/min/1.73 m^2 vs. eGFR ≥60 mL/min/1.73 m^2). GA comprised the following instruments: the Activities of Daily Living Scale (ADL), the Timed up and Go (TUG), the Tinetti test (Tinetti), the Mini-Mental-State Examination (MMSE), the Geriatric Depression Scale (GDS), and the Mini Nutritional Assessment (MNA). We used logistic regression models to estimate multivariable-adjusted associations between CKD G3a and impairments in the respective domains. ***Results:*** A total of 282 subjects with mild-to-moderate CKD (CKD G3a) were identified (19.1%). Overall, the prevalence of impairments identified was higher among subjects with compared to without CKD G3a (21 vs. 15.9%, $p = 0.043$). In multivariable-adjusted models, CKD G3a was consistently associated with increased odds of an impaired gait performance as to the TUG (adjusted odds ratio 2.06, 95% CI 1.04–4.09). In contrast, on average, individuals with and without CKD G3a did not differ as to their results in the MMSE, the ADL, the MNA, and the GDS. ***Conclusion:*** GA

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identified impairments in 21 versus 15.9% of older adults with and without mild-to-moderate CKD, respectively. However, except for an increased likelihood of impaired gait performance (TUG) with mild-to-moderate CKD, we did not find independent associations between mild-to-moderate CKD and geriatric conditions.

Introduction

Chronic kidney disease (CKD) affects large proportions of older adults. Reduced kidney function is associated with an increased risk of unsuccessful aging and adverse clinical outcomes, e.g. cardiovascular events, hospitalizations, and death [1–6]. Moreover, substantial evidence suggests that individuals with CKD face a high risk for common geriatric conditions, like functional impairment and cognitive decline [3].

The vast majority of individuals with CKD only show mild-to-moderately decreased glomerular filtration rate (GFR 45–59 mL/min/1.73 m^2) [5]. There is an ongoing debate about the clinical significance of early-stage CKD among older adults, and whether the universal GFR threshold for the definition of CKD (< 60 mL/min/1.73 m^2), as proposed by the KDIGO (Kidney Disease/Improving Global Outcomes), is applicable in older adults, or should be lower (e.g., <45 mL/min/1.73 m^2) in view of the age-related decline in renal function [3, 7, 8].

In this context, it is not only important to consider the implications of mild-to-moderately decreased GFR for cardiovascular risk and renal disease progression, but also to consider functional status, mental health, nutritional status, and cognition.

In fact, previous studies have mainly shown a high prevalence and incidence of functional impairment and cognitive decline in older adults with *advanced* CKD (estimated GFR [eGFR] <45 mL/min/1.73 m^2) and dialysis patients, but to date only few studies have examined functional and cognitive impairments in older adults with only *mild-to-moderate* CKD (GFR 45–59 mL/min/1.73 m^2, CKD G3a) [3, 9–11].

Geriatric conditions, including medical, psychosocial, and functional limitations, can best be identified by a geriatric assessment (GA). GA uses established diagnostic tools to identify geriatric conditions otherwise often not identified in routine history or physical examination. In addition to its routine use in clinical geriatrics, following calls for a widespread use, GAs have also been incorporated step by step into the practice of various medical subspecialties, such as oncology, surgery, and nephrology [3, 12–14]. Common and established tests of the GA are the Activities of Daily Living Scale (ADL), the Timed Up and Go (TUG) and the Tinetti test, both testing gait performance and mobility, the Mini-Mental State Examination (MMSE) as a screening test for cognitive impairments, the Geriatric Depression Scale (GDS), and the Mini Nutritional Assessment (MNA) [15, 16].

The aim of the present study was to explore associations between mild-to-moderate CKD (G3a) and prevalent impairments, identified by GA in cross-sectional data of a large cohort of community-dwelling older adults. We hypothesized that GA would identify significantly more impairments in subjects with CKD G3a compared to subjects with preserved kidney function (eGFR ≥60 mL/min/1.73 m^2). This, in turn, would support the clinical relevance of mild-to-moderate CKD.

Methods

Study Sample

Altogether 1,476 participants (mean age: 68.6 ± 3.6 years) from the Berlin Aging Study II (BASE-II) were included in this cross-sectional analysis. BASE-II was launched to investigate factors associated with "healthy" and "unhealthy" aging. The study has been described previously in detail [17, 18]. Briefly, the BASE-II sample was recruited as a convenience sample from the greater Berlin metropolitan area. In 2009–2014, 2,172 participants (~75% aged 60–84 years and ~25% aged 20–35 years) were enrolled in the medical part of the study. All participants gave written informed consent and the study was approved by Ethics Committee at Charité-Universitätsmedizin Berlin (EA2/029/09). Data sets including all relevant variables for the present analysis were available from 1,498 participants of the older group of BASE-II (aged 60 years and older). We a priori excluded participants with eGFR <45 mL/min/1.73 m^2 (n = 22), as we intended to study mild-to-moderate CKD (eGFR 45–59 mL/min/1.73 m^2). Thus, analyses were limited to 1,476 subjects.

Geriatric Assessment

GA comprised the following instruments (see also Table 1).

Tinetti Test

The Tinetti test, also known as Performance Oriented Mobility Assessment (POMA), is the most widely used clinical test for assessing a person's static balance abilities and gait. The maximum achievable score is 28. A score of ≤23 was rated as an impairment in this test [19].

Timed Up and Go

The TUG is a commonly used screening tool for mobility and falls. A faster time indicates a better gait performance (stand up, walk, turn, sit down). In accordance with the previous literature [20] a time of >12 s was rated as impairment, indicating impaired gait performance.

Table 1. Overview of instruments, domains, scoring and cutoffs used

Instrument	Domain	Scoring	Cutoff for impairment	Ref.
TUG	gait, mobility	time (s)	>12 s	[20]
Tinetti	balance and gait	0–28 points	≤23 points	[19]
ADL (Barthel index)	functioning	0–100 points	<95 points	[21]
MNA	nutrition	0–30 points	≤23.5 points	[16, 22]
GDS	depression	0–15 points	>5 points	[23, 24]
MMSE	cognition	0–30 points	≤24 points	[25]

TUG, Timed Up and Go; ADL, Activities of Daily Living Scale; MNA, Mini Nutritional Assessment; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination;

Activities of Daily Living

The ADL, also known as Barthel index, is used to measure a person's ability to perform basic daily self-care tasks. A higher score (max. 100) is associated with a greater likelihood of being able to live at home without problems [21]. A score of <95 was rated as impairment, indicating difficulty in one or more ADL tasks.

Mini Nutritional Assessment

The MNA is a validated nutrition screening and assessment tool (maximum achievable score 30). It comprises 18 questions from four categories: anthropometric assessment, general state, dietary assessment and self-assessment. It identifies geriatric patients who are malnourished (score <17) or at risk of malnutrition (score ≤23.5) [16, 22]. We used ≤/>23.5 as cutoff for classification into poor and normal nutritional status, respectively.

Geriatric Depression Scale

The GDS is a simple, 15-item, self-report instrument used to identify clinical depression among elderly people. In BASE-II, a physician read the items of the questionnaire to the participants during a structured interview. Higher scores indicate more symptoms of depression. In line with previous studies, we rated scores >5 as impairment [23, 24].

Mini-Mental State Examination

The MMSE measures global cognitive function. The total score for the MMSE ranges from 0 to 30. Scores >24 indicate basically no cognitive impairment, whereas scores ≤24 may indicate cognitive impairment [25]. In BASE-II, a trained physician administered the MMSE, and scores ≤24 were rated as cognitive impairment.

Kidney Function

Serum creatinine levels were measured in a certified central laboratory by a compensated Jaffe assay, traceable to IDMS (Roche Diagnostics, Mannheim, Germany). eGFR was calculated according to the FAS (Full Age Spectrum) equation based on serum creatinine, age, and weight [26]. Urinary albumin and creatinine excretion were quantified from spot urine samples, and albumin/creatinine ratio (ACR) was calculated. Albuminuria was defined as an ACR ≥30 mg/g. Subjects were classified into GFR stages (G1–G5) and albuminuria categories (A1–A3) according to the KDIGO (Kidney disease improving global outcomes) guidelines [3]. Stage G3a indicates mild-to-moderate CKD (GFR 45–59 mL/min/1.73 m^2).

Other Study Variables

We computed a morbidity index (MI), largely based on the categories of the Charlson index, which is a weighted sum of moderate to severe, mostly chronic physical illnesses, including cancer, cardiovascular, and metabolic diseases [27]. Diagnoses were obtained by integration of information from medical examination, medical history, and further diagnostics such as laboratory tests (for details, see Bertram et al. [17]). The MI had a range of 0–10.

All blood and urine parameters were measured in a central certified laboratory using standardized protocols, as previously described [4]. Vitamin D deficiency was defined as a 25(OH)D concentration of <50 nmol/L. Anemia was defined according to the WHO criteria [28] as a hemoglobin concentration lower than 12 g/dL in women and 13 g/dL in men. Handgrip strength was measured with a Smedley Dynamometer (Scandidact, Denmark), and reduced hand grip was defined according to the cutoffs proposed by Fried et al. [29]. Subjects were considered physically inactive if they had affirmed the statement "I rarely or never do any physical activities."

Statistics

Performance in the GA was compared between subjects with eGFR 45–59 mL/min/1.73 m^2 (CKD G3a, mild-to-moderate CKD) and those with eGFR ≥60 mL/min/1.73 m^2 (preserved kidney function). Values are expressed as counts and percentages or mean ± standard deviation or median and 10–90 percentiles, respectively.

Multiple logistic regression models were computed to estimate multivariable-adjusted associations of CKD G3a (eGFR 45–59 mL/min/1.73 m^2 vs. eGFR ≥60 mL/min/1.73 m^2 as reference group) with the performances in the various tests. Test outcomes were dichotomized according to validated thresholds, defining impairment (see above). Those covariates were included in the final model, which showed significant differences in univariate analyses (Table 2): age, sex, BMI, MI count, vitamin D deficiency, and current smoking. We performed additional regression analyses with albuminuria (ACR ≥30 mg/g) as another covariate, and we tested an alternative definition of CKD, including GFR and albuminuria (GFR 45–59 mL/min/1.73 m^2 or GFR ≥60 mL/min/1.73 m^2 and ACR ≥30 mg/g), respectively.

Likewise, effect modification by sex was assessed by including an interaction term for CKD G3a and sex. Statistical significance was evaluated at $p < 0.05$. We used IBM SPSS Statistics version 23.

Table 2. Characteristics of the study sample by CKD status

	Total sample (n = 1,476)	GFR ≥60 mL/min/1.73 m^2 (n = 1,194)	GFR 45–59 mL/min/1.73 m^2 (n = 282)	p
Females	757 (51.3)	595 (49.8)	162 (57.4)	0.024
Age, years	68.6±3.6	68.1±3.5	70.5±3.7	<0.001
Body mass index	26.7±4.2	26.6±4.1	27.2±4.2	0.048
eGFR, mL/min/1.73 m^2	69.4±10.7	72.9±8.7	54.8.±3.9	<0.001
ACR >30 mg/g	113 (8)	83 (11.2)	30 (7.2)	0.033
HbA1c, %	5.59±0.55	5.58±0.54	5.65±0.59	0.080
HDL cholesterol, mg/dL	62.6±17.0	62.8±17.0	61.9±17.1	0.400
Morbidity index	1 (0–3)	1 (0–3)	1 (0–3)	0.015
Morbidity index >3	82 (5.6)	58 (4.7)	26 (9.2)	0.003
Physical inactivity	130 (9.2)	103 (8.9)	27 (10.2)	0.479
Hypertension[a]	1,043 (76.6)	839 (81.3)	204 (75.5)	0.098
Diabetes[a]	178 (12.4)	143 (12.2)	35 (13.2)	0.680
Heart failure	25 (1.8)	20 (1.8)	5 (2.0)	0.796
History of malignancy	180 (12.2)	136 (11.4)	44 (15.6)	0.068
Current smoking	138 (9.4)	124 (10.4)	14 (5.0)	0.004
Reduced handgrip	100 (7.3)	79 (7.1)	21 (8.4)	0.503
Vitamin D deficiency[a]	621 (43.5)	530 (46.1)	91 (33.0)	<0.001
Anemia[a]	87 (6.0)	65 (5.5)	22 (8.0)	0.685

Data are presented as n (%), mean ± SD, or median (10–90 percentiles). Differences in proportions between GFR 45-59 mL/min/1.73 m^2 and GFR ≥60 vs. mL/min/1.73 m^2 were assessed using χ^2 or Fisher's exact test. t test or Mann-Whitney U test were used to assess statistical difference between continuous variables. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; CKD, chronic kidney disease; HbA1c, glycated hemoglobin; ACR, albumin/creatinine ratio. [a] Confirmed diagnoses, otherwise self-reported.

Results

Table 2 shows the participant characteristics (n = 1,476). The mean age was 68.6 ± 3.6 years, 51.3% were female. The mean eGFR was 69.4 ± 10.7 mL/min/1.73 m^2 (range 45.2–104.6 mL/min/1.73 m^2). 282 subjects (19.1%) had CKD stage 3a (eGFR of 45–59 mL/min/1.73 m^2).

Subjects with CKD G3a were slightly older (70.5 ± 3.7 vs. 68.1 ± 3.5 years, p < 0.001) compared to participants with preserved kidney function (eGFR ≥60 mL/min/1.73 m^2). The average eGFR was 54.8 ± 3.9 and 72.9 ± 8.7 mL/min/1.73 m^2, respectively. More people with CKD G3a likewise had albuminuria (11.2 vs. 7.2%, p = 0.033).

On average, participants with CKD G3a had a higher MI score, and were more likely to have a MI of >3, indicating multiple comorbidities, compared to those with preserved kidney function (9.2 vs. 4.7%, p = 0.003). Likewise, the average BMI was higher among participants with CKD G3a. Remarkably, vitamin D deficiency was significantly more prevalent among subjects without CKD. Moreover, those without CKD G3a reported more often current smoking. To note, we did not find any significant differences in the prevalence of hypertension, type 2 diabetes, and anemia between participants with and without CKD G3a, as defined by an eGFR of 45–59 versus ≥60 mL/min/1.73 m^2 (Table 2).

Association of CKD G3a and GA Outcomes

As shown in Table 3, participants with CKD G3a (eGFR 45–59 mL/min/1.73 m^2) performed significantly worse in the TUG, compared to those with eGFR ≥60 mL/min/1.73 m^2. On average, time to complete the TUG (stand up, walk, turn, sit down) differed by 0.41 s. Likewise, in the Tinetti, there were small but significant differences between the two groups. In contrast, participants with and without CKD G3a did not differ as to the results of the GDS, the MMSE, the ADLs, and the MNA (Table 3).

We applied validated cutoffs (see Methods and Tables 1 and 4) to the test results in order to define clinically relevant impairments for each instrument. In the TUG (6.8 vs. 2.5%, p < 0.001) as well as in the Tinetti (3.2 vs. 1.3%, p = 0.032), participants with CKD G3a were more likely to show impairments, compared to subjects with eGFR ≥60 mL/min/1.73 m^2. Proportions of participants with

Table 3. Results of the geriatric assessment in the total sample and according to CKD status (GFR ≥60 vs. GFR 45–59 mL/min/1.73 m^2)

	Total sample (n = 1,476)	GFR ≥60 mL/min/1.73 m^2 (n = 1,194)	GFR 45–59 mL/min/1.73 m^2 (n = 282)	p
ADL score	100 (95–100)	100 (95–100)	100 (95–100)	0.078
Tinetti score	28 (27–28)	28 (27–28)	28 (26–28)	<0.001
TUG, s	7.90±1.90	7.82±1.88	8.23±1.96	0.002
MNA score	27.5 (25–29.5)	27.5 (25–29,5)	27.5 (25.5–29.5)	0.812
GDS score	1 (0–4)	1 (0–4)	1 (0–4)	0.705
MMSE score	29 (28–30)	29 (28–30)	29 (28–30)	0.937

Data are presented as mean ± SD or median (10–90 percentiles). Differences in mean ± SD or median (10–90 percentiles) between the two groups GFR 45–59 mL/min/1.73 m^2 vs. GFR ≥60 vs. mL/min/1.73 m^2 were assessed using t test (TUG) or Mann-Whitney U test (ADL, Tinetti, MNA, GDS, MMSE), respectively. GFR, glomerular filtration rate; ADL, Activities of Daily Living Scale; TUG, Timed Up and Go test; MNA, Mini Nutritional Assessment; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; CKD, chronic kidney disease.

impairments in the other tests (MMSE, GDS, MNA, ADLs) were similar in both groups. In sum, in about one-fifth (21%) of participants with CKD G3a, compared to only 15.9% of participants without CKD, one or more impairments were identified. The difference was statistically significant (p = 0.043).

As shown in Table 2, in addition to differences in kidney function measures, the two groups differed significantly in terms of age, sex, BMI, vitamin D deficiency and current smoking status, rendering further adjusted analyses necessary.

We used logistic regression analyses to estimate adjusted associations of CKD G3a with impairments in the examined domains (Table 5). Compared to the reference category (GFR ≥60 mL/min/1.73 m^2), CKD G3a significantly raised the odds of showing impairments in the TUG. This association remained statistically significant after we adjusted for all the above-mentioned covariates (adjusted odds ratio = 2.06, 95% CI 1.04–4.09). There was no evidence of effect modification by sex in the association of CKD G3a and TUG impairments (p for interaction = 0.279). By contrast, the association between CKD G3a and presence of impairments in the Tinetti was attenuated and did not remain statistically significant when controlling for confounding factors. Evidence of impairments in the MMSE, the MNA, the GDS, and the ADL scale was consistently not statistically associated with mild-to-moderate CKD in unadjusted and adjusted analyses.

Presence of albuminuria (ACR ≥30 mg/g) is another diagnostic criterion of CKD, independent of the evidence of a decreased GFR [3]. We also considered this in our analyses. Admittedly, including microalbuminuria as another covariate did not alter the results of the multiple regression analyses. Likewise, the magnitude of the association between CKD G3a and impaired gait performance (TUG) was not changed when albuminuria was added to the definition of mild-to-moderate CKD (adjusted odds ratio: 2.2, 95% CI 1.1–4.4, p = 0.02).

Table 4. Distribution of impairments in 6 different assessment instruments by CKD status

Test	GFR ≥60 mL/min/1.73 m^2	GFR 45–59 mL/min/1.73 m^2	p
MNA	3.7 (44/1,192)	2.5 (7/281)	0.322
GDS	5.6 (65/1,157)	5.6 (15/267)	1.000
TUG	2.5 (30/1,194)	6.8 (19/281)	**0.001**
Tinetti	1.3 (15/1,179)	3.2 (9/282)	**0.032**
MMSE	0.8 (10/1,194)	2.1 (6/282)	0.100
ADL	2.6 (31/1,193)	3.9 (11/282)	0.237
Any test	15.9 (189/1,186)	21.0 (58/276)	**0.043**

Data are presented as % (n/N). χ^2 or Fisher's exact test were used to assess differences between the two groups GFR 45–59 mL/min/1.73 m^2 vs. GFR ≥60 mL/min/1.73 m^2. GFR, glomerular filtration rate; MNA, Mini Nutritional Assessment; GDS, Geriatric Depression Scale; TUG, Timed Up and Go; MMSE, Mini-Mental State Examination; ADL, Activities of Daily Living Scale; any test, impairment in at least one test; CKD, chronic kidney disease. Test results were dichotomized, for cutoffs see Methods and Table 1.

Table 5. Logistic regression results for mild-to-moderate CKD (reference category: eGFR ≥60 mL/min/1.73 m^2) as predictor of impairments in different assessment instruments

Test	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)[a]	Adjusted odds ratio (95% CI)[b]
MNA	0.67 (0.30–1.50)	0.71 (0.31–1.64)	0.70 (0.29–1.65)
GDS	1.0 (0.56–1.78)	1.09 (0.60–1.99)	1.02 (0.54–1.91)
TUG	**2.81 (1.56–5.08)**	**1.99 (1.07–3.71)**	**2.06 (1.04–4.09)**
Tinetti	**2.59 (1.12–5.98)**	2.26 (0.93–5.48)	1.86 (0.68–5.07)
MMSE	2.58 (0.93–7.14)	2.02 (0.69–5.92)	2.30 (0.74–7.20)
ADL	1.52 (0.76–3.07)	1.08 (0.51–2.27)	0.84 (0.38–1.86)
Any test	**1.4 (1.01–1.95)**	1.23 (0.87–1.74)	1.17 (0.81–1.68)

MNA, Mini Nutritional Assessment; GDS, Geriatric Depression Scale; TUG, Timed Up and Go; MMSE, Mini-Mental State Examination; ADL, Activities of Daily Living Scale; any test, impairment in at least one test; CKD, chronic kidney disease; CI, confidence interval. [a] Adjusted for sex and age. [b] Adjusted for sex, age, BMI, morbidity index, vitamin D deficiency and current smoking status. Statistically significant results ($p < 0.05$) were highlighted (boldface).

Discussion

In this study, we investigated whether mild-to-moderate CKD (CKD G3a) was associated with an increased prevalence of impairments in the core domains of GA, with consideration of gait performance (TUG/Tinetti), nutrition (MNA), cognition (MMSE), mood disorders (GDS), and independence in activities of daily living (ADL).

As a result, we indeed found that the odds of showing impaired gait performance (TUG) were significantly raised for participants with CKD G3a, compared to participants with preserved kidney function; but altogether, mild-to-moderate CKD was not associated with a markedly increased burden of impairments. In fact, we did not find relevant associations between CKD G3a and restrictions in ADL, cognitive impairments (MMSE), depression (GDS), or abnormalities in the MNA.

Remarkably, although in 21% of participants with CKD G3a GA revealed impairments in one or more domains, compared to 15.9% of participants without CKD, prevalence of impairments in the respective domains was altogether rather low (<10%, respectively) in the control group as well as in the CKD G3a group. This is probably owing to the fact that the BASE-II cohort on average was rather young (68.6 ± 3.6 years), and participants were predominantly well functioning, as was reported before [17]. Therefore, also the prevalence of kidney disease was rather on the lower bound of what can normally be expected in the general population [4]. In contrast, studies in older patients and with more advanced CKD found much higher prevalence rates of deficits [13].

Our results support and extend beyond the findings of prior studies on early-stage CKD and functional status, cognitive impairment, mood disorders, and nutritional risk in older adults. As to functional status, results from previous studies have been inconsistent, yet altogether, the available evidence suggests that even early stages of CKD are linked with increased functional impairment. For example, Smyth et al. [30] could show in 3,499 older adults (66.0 ± 10.3 years) that mild-to-moderate CKD (mean $eGFR_{crea}$ 50.2 mL/min/1.73 m^2, GFR range 30–59 mL/min/1.73 m^2) was positively associated with self-reported functional impairment (ADLs), independent of age, gender, comorbidities, and cardiovascular risk factors. In the present study, we could not establish any association between CKD G3a and limitations in ADLs. However, one must acknowledge that renal impairment was significantly less pronounced in our sample (mean eGFR 54.8 mL/min/1.73 m^2, GFR range 45–59 mL/min/1.73 m^2).

Indeed, our results suggest, that CKD G3a is associated with increased odds of impaired gait performance, as assessed by the TUG. Correspondingly, Liu et al. [31] could show that mild CKD was associated with increased odds of incident self-reported mobility impairment and greater decline in gait speed (Framingham Offspring Study). However, this was only evident when eGFR was estimated from cystatin C instead of creatinine. This finding has been confirmed by a recent study by Canney et al. [32]. In contrast, in the Health ABC study a positive relationship between mild reductions in kidney function and physical performance was consistently found using cystatin C or creatinine, respectively [33]. Apparently, cystatin C seems

to hold advantages as a biomarker for geriatric outcomes like impaired gait performance and physical impairment, and also frailty [34, 35], whereas, when creatinine is used to estimate GFR, findings are more inconsistent.

A comprehensive review of mechanisms linking GFR decline to physical impairment, and gait performance in particular, is beyond the scope of this paper; anyway, there is growing evidence that muscle impairment (impaired muscle metabolism, sarcopenia) represents an important intermediate step in the causal chain [36].

Furthermore, we could not show a significant association of CKD G3a with cognitive impairment, as assessed by the MMSE. It should be noted, however, that the MMSE lacks sensitivity to detect mild cognitive impairment, particularly among those with higher educational attainment as in this study [17, 37]. Accordingly, the number of participants with cognitive impairment (MMSE ≤24/30) was particularly small in the BASE-II cohort (Table 4). Moreover, previous studies have likewise provided conflicting results as to the relationship between cognitive impairment and early-stage CKD. Some studies have indeed reported positive associations between mild-to-moderately reduced levels of kidney function and cognitive impairment [11, 38, 39], whereas others have not [40, 41]. For example, Kurella et al. [42] demonstrated a significant positive association between impaired cognition and severe CKD, but not mild-to-moderate CKD.

Regarding depression, it has been repeatedly shown that depression is common and underrecognized in patients with advanced CKD or end-stage-renal disease [43]. Whether or not less severe forms of impaired kidney function (eGFR ≥30 or even ≥45 mL/min/1.73 m^2) are associated with more depressive symptoms compared to preserved kidney function (eGFR ≥60 mL/min/1.73 m^2) is still unclear. In line with our results, Ricardo et al. [41, 44] could not establish an association of early-stage CKD with depression. In contrast, Heeres et al. [45] recently showed that an increase in depressive symptoms was already present in patients with eGFR <60 mL/min/1.73 m^2, compared to those with a better eGFR [45]. Whereas the implications of marginal uremia at a GFR of 45–59 mL/min/1.73 m^2 are unclear anyway, it appears plausible, that, given individuals affected by mild-to-moderate CKD do not even notice or know they have a kidney problem, and that functional status and cognition are also largely preserved, this may not pose a challenge for mental health.

At last, it is well known that advanced CKD leads to a state of metabolic and nutritional derangements, referred to as protein energy wasting or anorexia in CKD, and attributed to the retention of uremic toxins, intercurrent illness, inflammation, and comorbid diseases [46]. However, there are currently no data linking mild-to-moderate CKD and nutrition. Likewise, our results do not suggest an increased nutritional risk with CKD G3a.

In view of the ongoing debate, whether older adults with an eGFR of 45–59 mL/min/1.73 m^2 should be labeled with "CKD," or rather manifest physiological age-related GFR decline [3, 7, 8], our results and the above-mentioned findings of others are valuable, although they do not allow for a clear position yet. Admittedly, in the present study the relative differences in geriatric conditions comparing individuals with CKD G3a and individuals with preserved kidney function were rather marginal. Anyway, in about one-fifth of individuals (21 and 15.9%, with and without CKD G3a, respectively), we identified one or more geriatric conditions by performing a GA. Identifying these conditions is essential to prevent or delay their complications, and may lead to better health outcomes.

The strengths of our study include the comprehensive characterization of the BASE-II cohort. To our knowledge, this is the first study investigating the relationship between mild-to-moderately decreased GFR (CKD G3a) and the outcomes of a broad GA in large a cohort of community-dwelling older adults. Whereas most previous studies often have only examined one domain in relation to kidney function, we were able to consider a set of 6 commonly used instruments previously recommended to be used in older adults with CKD [15].

Since cystatin C was not available in BASE-II, which is a limitation, we chose to use the novel FAS equation to estimate kidney function, which has been demonstrated to be very sensitive and accurate in the elderly with the extra advantage of being applicable across the whole age spectrum [26], as the otherwise recommended CKD-EPI equation has been consistently shown to overestimate GFR in older adults [4]. Moreover, in contrast to other studies, we excluded subjects with eGFR <45 mL/min/1.73 m^2 from our analyses. Accordingly, our CKD group had effectively "mild-to-moderate" CKD. Furthermore, it has to be pointed out that extra-trained physicians surveyed the complete GA implemented in this study, whereas most previous studies used, for example, questionnaires or telephone interviews for data acquisition.

Some limitations of the present study have to be addressed. First, diagnosis of CKD was based on single time point measurements of creatinine and albuminuria. Due to the cross-sectional design, conclusions regarding cau-

sality and direction of causality are limited. Moreover, since BASE-II participants were well functioning, educated above average and had a relatively small disease burden [17, 18], our results should be interpreted with caution with respect to their validity for the general population. Also, our results may not be generalized to non-Caucasian populations.

Conclusion

To conclude, altogether, our GA identified one or more impairments in the domains functional status, gait, cognition, mood, and nutrition, in 21% of participants with mild-to-moderate CKD, and 15.9% of participants with preserved kidney function. After adjusting for covariates, only a positive association between mild-to-moderate CKD and impaired gait performance (TUG) remained statistically significant. Given the high prevalence of early-stage CKD in older adults, improved understanding of the associated implications on geriatric conditions is essential to improve health outcomes. Therefore, further studies are warranted to clarify the value of GA in the management of early-stage CKD.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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