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The relationship between kidney function and quality of life among community-dwelling adults varies by age and filtration marker

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Abstract

Background: The impact of a diminished level of kidney function on the well-being of an older individual is poorly understood. We sought to determine the association between estimated glomerular filtration rate (eGFR) and overall quality of life (QoL) among older adults.

Methods: Cross-sectional analysis of 4293 participants from the Irish Longitudinal Study on Ageing, a population-based study of community-dwelling adults ≥ 50 years of age. We used multivariable negative binomial regression to model the relationship between categories of cystatin C eGFR (eGFR_{cys}) or creatinine eGFR (eGFR_{cr}) and the number of QoL deficits from the Control, Autonomy, Self-realization and Pleasure (CASP-19) scale, a holistic measure of QoL among older adults (range 0–57). We further explored this relationship across age strata.

Results: Median age was 61 [interquartile range (IQR) 55–68] years, 53% were female, mean (SD) CASP-19 score was 44.8 (7.4) and median eGFR_{cys} was 81 (IQR 68–93) mL/min/1.73 m². After multivariable adjustment, participants with eGFR_{cys} < 45 mL/min/1.73 m² had 14% greater QoL deficits [incidence rate ratio 1.14 (95% confidence interval 1.03–1.25)] relative to the reference group (eGFR_{cys} ≥ 90 mL/min/1.73 m²). This relationship appeared linear across eGFR_{cys} categories and was more pronounced in younger (50–64 years) compared with older participants (65–74 or ≥ 75 years). There was no substantive relationship between eGFR_{cr} and CASP-19.

Conclusions: Cystatin C but not creatinine eGFR was associated with clinically modest declines in QoL among a large sample of community-dwelling older adults. This relationship varied by age, suggesting that a diminished eGFR contributes little to overall QoL beyond middle age in this population.

Key words: age, chronic kidney disease, creatinine, cystatin c, epidemiology, quality of life

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Introduction

To date, studies examining the relationship between kidney disease and quality of life (QoL) have mainly been restricted to end-stage kidney disease and referred chronic kidney disease (CKD) populations. Individuals with advanced CKD have markedly lower QoL scores than the general population, and poorer QoL is a predictor of mortality in this group [1, 2]. The burden of CKD is highest among the general population of older adults [3], yet few population studies have assessed the potential impact of a reduced level of kidney function on the QoL of an older person or where along the range of kidney function one might expect to see changes in QoL. Prior studies [4–6] have defined CKD using creatinine, the generation of which can be unstable with increasing age due to changing muscle mass. Cystatin C, produced by all nucleated cells in the body, has been proposed as an alternative filtration marker in this population, as it is less influenced by muscle mass [7] and is a stronger predictor of clinical outcomes [8].

Many of the instruments used to quantify health-related QoL tend to emphasize physical determinants, such that a high QoL is characterized by the lack of functional impairments to fulfilling a ‘normal’ life [9]. This represents a somewhat narrow view of QoL, especially among older individuals who may have excellent QoL despite the presence of physical limitations. The Control, Autonomy, Self-realization and Pleasure (CASP-19) scale was developed in a general population sample 65–75 years of age with the aim of providing a broader conceptualization of QoL, encompassing both positive and negative influences of QoL in early old age [10]. By focusing on a ‘needs satisfaction’ approach, the CASP-19 can distinguish between physical limitations or perceived health status and overall QoL. It has been argued that a QoL instrument that measures overall satisfaction with life is superior to those that conflate health status and QoL [9]. The CASP-19 instrument has been validated across several different cohorts around the world, including longitudinal ageing studies [11]. A number of health conditions have been associated with reductions in CASP-19, including decreased lung function [12] and central obesity [13]. Data from older Irish adults have demonstrated that the mean CASP-19 score is curvilinear with age, increasing from age 50 to a peak at age 67 years, before falling gradually thereafter [14].

We sought to examine the relationship between kidney function and CASP-19 in community-dwelling older adults, compare cystatin C and creatinine as predictors of CASP-19 and explore whether the association between kidney function and CASP-19 varies by age.

Materials and methods

Participants

This was a cross-sectional analysis from Wave 1 (June 2009–June 2011) of the Irish Longitudinal Study on Ageing (TILDA), a cluster-sampled cohort of Irish community-dwelling adults ≥ 50 years of age. Details of the study design have been described elsewhere [15, 16]. Participants were interviewed in their homes by way of a computer-assisted personal interview. Separately they were asked to fill out and return a self-completion questionnaire (SCQ) that included the CASP-19. All participants were subsequently invited to take part in a health assessment, either in their home or at a dedicated health centre. The present study includes 4293 participants who completed the CASP-19 and had a blood sample taken at the health assessment (Figure 1). All participants

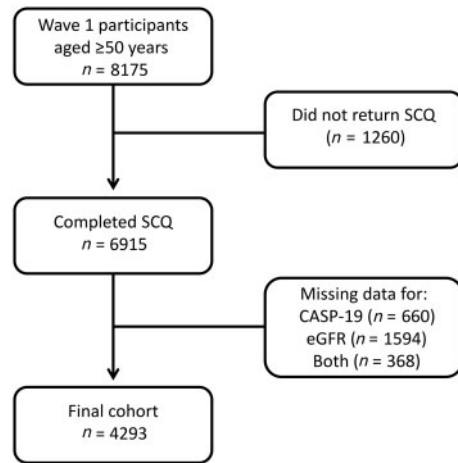


Fig. 1. Flowchart of case ascertainment.

provided informed signed consent. Ethical approval for TILDA was granted by the Research Ethics Committee of Trinity College, Dublin. All experimental procedures adhered to the Declaration of Helsinki.

Outcome

The CASP-19 consists of 19 Likert-scale items capturing four domains of QoL: control, autonomy, self-realization and pleasure [10]. A full description is provided in a supplementary data file. Respondents are shown a statement and are asked to rate how often they feel a particular way about that aspect of their life (often, 3; not often, 2; sometimes, 1; never, 0). An example of a positive statement is ‘I can do the things that I want to do.’ Negative items (e.g. ‘I feel that what happens to me is out of my control’) are reverse coded, such that higher scores represent higher QoL. The total score can range from 0 to 57.

Exposure

We categorized estimated glomerular filtration rate from either cystatin C (eGFR_{cys}) or creatinine (eGFR_{cr}) as follows (mL/min/1.73 m²): ≥ 90 (reference), 75–89, 60–74, 45–59 and < 45 . Due to relatively small numbers of participants with eGFR < 30 mL/min/1.73 m², we created a single category for participants with eGFR < 45 mL/min/1.73 m².

Covariates

Covariates were chosen based on their association with both the exposure of interest (eGFR) and outcome (CASP-19). Demographic variables included age, sex and educational attainment (primary/none, secondary, tertiary/higher). We included a quadratic age term to account for non-linear relationships between age and both CASP-19 [14] and eGFR [3]. Medication use was recorded during the interview and cross-checked with medication labels. All medications were coded according to the World Health Organization Anatomical Therapeutic Chemical Classification [17]. We defined the presence of diabetes as a self-reported physician’s diagnosis and/or receiving insulin or oral hypoglycaemics. We defined the presence of hypertension as a self-reported physician’s diagnosis and/or receiving antihypertensives. We defined the presence of cardiovascular disease as the number (0, 1, 2 or more) of the following self-reported physician-diagnosed conditions: angina, myocardial infarction, percutaneous coronary intervention, coronary

artery bypass graft, heart failure, stroke and transient ischaemic attack. Smoking status was coded as current, former or never. Waist circumference was measured at the health assessment. Comorbidity variables included polypharmacy (use of five or more medications, excluding supplements) and the number (0, 1, 2 or more) of the following self-reported physician-diagnosed conditions: chronic lung disease, asthma, arthritis, osteoporosis, malignancy, stomach ulcers and varicose ulcers, cirrhosis/severe liver damage.

Measurement of renal biomarkers

At Wave 1, a venous blood sample (25 mL) was collected from each participant who provided consent. Samples were transported to a central laboratory in temperature-controlled shipping boxes where they were centrifuged, aliquoted into cryovials and stored at -80°C . Cystatin C and creatinine were measured simultaneously from frozen plasma. Cystatin C was measured using a second-generation particle-enhanced immunoturbidimetric assay (Roche Tina-quant) on a Roche Cobas 701 analyser. The assay has a measuring range of 0.40–6.80 mg/L and is traceable to the European reference standard material (ERM-DA471/IFCC) for cystatin C. Creatinine was measured on the same analyser using an enzymatic method traceable to isotope-dilution mass spectrometry. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equations for cystatin C [18] or creatinine [19].

Statistical analysis

All analyses were performed using Stata version 14 (StataCorp, College Station, TX, USA).

Continuous variables are reported as mean (SD) or median [interquartile range (IQR)] as appropriate. Categorical variables are reported as number (percentage). As CASP-19 demonstrated a ceiling effect, we created a 'QoL deficits' count variable by subtracting each participant's score from 57, the maximum score obtainable. This QoL deficits variable is therefore a count of impairments in the CASP-19 score. Due to evidence of overdispersion in the QoL deficits variable, we used negative binomial regression to quantify the relationship between eGFR categories and QoL deficits. Model coefficients are expressed as incident rate ratios (IRRs). For example, an IRR of 1.20 represents a 20% increase in the severity of the outcome for a given factor relative to the reference group. Analyses incorporated a survey weight to account for cluster sampling at the household level [16]. Two models were generated: Model 1—adjusted for age, age², sex and educational attainment; Model 2—further adjusted for smoking status, waist circumference, diabetes, hypertension, number of cardiovascular conditions, polypharmacy and number of chronic health conditions. We explored the association between eGFR_{cys} categories and QoL deficits within age strata (50–64, 65–74, ≥ 75 years) in a secondary analysis.

Results

Participant characteristics

A description of the characteristics of the cohort, stratified by eGFR_{cys} categories, is provided in Table 1. The median age was 61 (IQR 55–68) years, 52.5% were female, median eGFR_{cys} was 81 (IQR 68–93) mL/min/1.73 m² and mean CASP-19 score was 44.8 (SD 7.4). Individuals with diminished eGFR_{cys} (<45 mL/min/1.73 m²) tended to be older, have lower educational attainment and have a higher prevalence of cardiovascular and non-

cardiovascular conditions. A description of participants who did not complete the SCQ and participants who completed the SCQ but had missing data for CASP-19 or eGFR is provided in Supplementary data, Table S1. Compared with the final study population, participants with missing data tended to be older, female and have lower educational attainment. They also tended to have a higher burden of diabetes, hypertension, cardiovascular disease and polypharmacy.

eGFR and QoL scores

eGFR_{cys}

After adjusting for age, age², sex and educational attainment, participants with eGFR_{cys} <45 mL/min/1.73 m² had 28% greater QoL deficits [incidence rate ratio [IRR] 1.28 [95% confidence interval (CI) 1.16–1.40]] relative to the reference group (Table 2). This corresponds to an absolute increase in QoL deficit count of 3.2 (95% CI 1.8–4.5). The relationship appeared linear across eGFR_{cys} categories (Supplementary data, Figure S1). After further adjustment for cardiovascular risk factors and comorbidities, participants with eGFR_{cys} <45 mL/min/1.73 m² had 14% greater QoL deficits [IRR 1.14 (95% CI 1.03–1.25)] versus the reference group. This corresponds to an absolute increase in QoL deficit count of 1.6 (95% CI 0.4–2.8).

eGFR_{cr}

In the base model, only individuals with eGFR_{cr} <45 mL/min/1.73 m² had any evidence of an increase in QoL deficit count compared with the reference group [IRR 1.12 (95% CI 1.00–1.24)]. We found no statistically significant association between eGFR_{cr} categories and QoL deficits in the extended model (Table 2).

Age strata

The relationship between eGFR_{cys} and QoL deficits was strongest among participants 50–64 years of age (Table 3). We did not observe any substantive associations between eGFR_{cys} and CASP-19 among participants 65–74 years of age or among participants ≥ 75 years of age. It should be acknowledged that this analysis was exploratory and these estimates may have been underpowered by comparatively reduced sample sizes at the extremes of age and eGFR, that is, younger participants with severe reductions in eGFR and older participants with preserved eGFR (Table 1). This is reflected in the weak evidence we observed for the full 3 \times 5 interaction between age strata and eGFR categories in Model 1 ($P = 0.15$) and Model 2 ($P = 0.23$).

Discussion

In this study of community-dwelling older adults, we observed a relationship between declines in kidney function and poorer QoL using the CASP-19 score, a holistic measure of QoL in older individuals. eGFR_{cys} was linearly related to QoL after adjustment for demographics, cardiovascular risk factors and comorbidities. The relationship between eGFR_{cys} and QoL was strongest in middle-aged participants, whereas there was little evidence of an association among older participants. We found no substantive association between eGFR_{cr} and QoL.

Although we detected a statistically significant signal for eGFR_{cys}, this should be interpreted in the context of what constitutes a clinically meaningful difference in QoL score. Two approaches have been advocated in the literature: distribution-based and anchor-based [20]. As neither strategy is unequivocally superior to the other [21], we discuss both approaches

Table 1. Participant characteristics according to category of cystatin C estimated glomerular filtration rate (eGFR in mL/min/1.73 m²)

Variable	eGFR ≥90 (n = 1380)	eGFR 75–89 (n = 1328)	eGFR 60–74 (n = 976)	eGFR 45–59 (n = 418)	eGFR <45 (n = 191)
Age (years)					
Median (IQR)	56 (52–61)	60 (55–65)	66 (59–71)	72 (66–78)	77 (71–83)
50–64	1194 (86.5)	935 (70.4)	443 (45.4)	89 (21.3)	22 (11.5)
65–74	169 (12.3)	348 (26.2)	383 (39.2)	165 (39.5)	57 (29.8)
≥75	17 (1.2)	45 (3.4)	150 (15.4)	164 (39.2)	112 (58.6)
Female sex	698 (50.6)	687 (51.7)	526 (53.9)	243 (58.1)	98 (51.3)
Education					
Primary/none	185 (13.4)	260 (19.6)	263 (27.0)	151 (36.1)	83 (43.7)
Secondary	634 (45.9)	527 (39.7)	388 (39.8)	157 (37.6)	75 (39.5)
Tertiary/higher	561 (40.7)	541 (40.7)	324 (33.2)	110 (26.3)	32 (16.8)
Smoking					
Never	678 (49.1)	622 (46.8)	424 (43.4)	166 (39.7)	85 (44.5)
Former	556 (40.3)	506 (38.1)	367 (37.6)	173 (41.4)	90 (47.1)
Current	146 (10.6)	200 (15.1)	185 (19.0)	79 (18.9)	16 (8.4)
Waist (cm), mean (SD)	92.1 (13.0)	94.3 (12.8)	97.6 (13.8)	99.1 (14.6)	102.1 (15.8)
Diabetes	70 (5.1)	73 (5.5)	78 (8.0)	54 (12.9)	32 (16.8)
Hypertension	392 (28.4)	443 (33.4)	472 (48.4)	287 (68.7)	158 (82.7)
CV conditions					
None	1308 (94.8)	1228 (92.5)	859 (88.0)	336 (80.4)	133 (69.6)
One	58 (4.2)	76 (5.7)	80 (8.2)	63 (15.1)	32 (16.8)
Two or more	14 (1.0)	24 (1.8)	37 (3.8)	19 (4.6)	26 (13.6)
Polypharmacy	96 (7.0)	137 (10.4)	191 (19.6)	140 (33.9)	103 (54.8)
Comorbidities					
None	829 (60.1)	706 (53.2)	465 (47.6)	151 (36.1)	72 (37.7)
One	418 (30.3)	452 (34.0)	352 (36.1)	180 (43.1)	67 (35.1)
Two or more	133 (9.6)	170 (12.8)	159 (16.3)	87 (20.8)	52 (27.2)
CASP-19 Mean (SD)	45.1 (7.2)	45.2 (7.3)	44.7 (7.4)	43.7 (7.6)	42.6 (7.6)

Data presented as number (%) unless stated otherwise.

Data missing for education (n = 2), waist circumference (n = 15) and polypharmacy (n = 23).

CV, cardiovascular.

Table 2. Association between categories of estimated glomerular filtration rate (eGFR in mL/min/1.73 m²) and QoL deficits

eGFR category	Model 1	P-value	Model 2	P-value
eGFR _{cys}				
≥90	Reference		Reference	
75–89	1.04 (1.00–1.09)	0.08	1.03 (0.98–1.08)	0.21
60–74	1.11 (1.05–1.17)	<0.001	1.07 (1.01–1.12)	0.02
45–59	1.21 (1.13–1.31)	<0.001	1.11 (1.03–1.20)	0.004
<45	1.28 (1.16–1.40)	<0.001	1.14 (1.03–1.25)	0.008
eGFR _{cr}				
≥90	Reference		Reference	
75–89	0.98 (0.94–1.03)	0.42	1.00 (0.95–1.04)	0.86
60–74	1.00 (0.94–1.05)	0.89	1.00 (0.95–1.06)	0.99
45–59	0.99 (0.91–1.07)	0.80	0.98 (0.91–1.06)	0.66
<45	1.12 (1.00–1.24)	0.04	1.04 (0.94–1.16)	0.42

Estimates are expressed as IRR (95% CI).

Model 1 (n = 4291) adjusted for age, age², sex and education.

Model 2 (n = 4253) adjusted for Model 1 covariates plus waist circumference, smoking, diabetes, hypertension, cardiovascular disease, polypharmacy and chronic health conditions.

in an effort to enhance interpretation of our findings. The distribution-based approach expresses a change relative to the within-population SD. An effect size of 0.2 SD is considered 'small', 0.5 is considered 'moderate' and ≥0.8 is considered 'large' [22]. For example, in our base model adjusting for age,

sex and educational attainment, participants with eGFR_{cys} <45 mL/min/1.73 m² had 3.2 more QoL deficits compared with the reference group. This represents an effect size of 0.43 (3.2/7.4), between small and moderate on the suggested scale. The corresponding score in the extended model was 0.22 (1.6/7.4), a small effect size. The distribution approach is based on statistical criteria that are dependent on the magnitude of variability in the particular sample studied, potentially limiting the generalizability of results [20]. The alternative anchor-based approach provides a context in which to interpret a difference in QoL score, by examining the association between the QoL instrument and an independent measure. An analysis from the English Longitudinal Study of Ageing (ELSA), a similar cohort to TILDA, examined the cross-sectional and longitudinal relationships between CASP-19 and eight readily interpretable independent variables that one would expect to correlate with QoL, such as health status and socio-economic position [23]. The CASP-19 discriminated well between these anchor variables and was shown to be responsive to change in most variables over time. These models were adjusted for age, age², sex and education, thus facilitating a comparison with our Model 1 estimates. The effect size for eGFR_{cys} <45 mL/min/1.73 m² in our analysis corresponds to less than half the effect size for CASP-19 and any of the following anchor variables in ELSA: having difficulty walking one quarter of a mile, having a limiting chronic illness or the presence of depression.

Previous studies in CKD patients have observed an association between CKD severity and diminished QoL [24–26].

Table 3. Age stratum-specific estimates of the relationship between categories of cystatin C estimated glomerular filtration rate (eGFR in mL/min/1.73 m²) and QoL deficits

eGFR category	Model 1	P-value	Model 2	P-value
50–64 years (n = 2683)				
≥90	Reference		Reference	
75–89	1.06 (1.00–1.11)	0.04	1.04 (0.99–1.10)	0.10
60–74	1.17 (1.09–1.25)	<0.001	1.11 (1.04–1.19)	0.002
45–59	1.29 (1.14–1.46)	<0.001	1.16 (1.02–1.32)	0.02
<45	1.51 (1.26–1.81)	<0.001	1.39 (1.16–1.67)	<0.001
65–74 years (n = 1122)				
≥90	Reference		Reference	
75–89	0.93 (0.84–1.04)	0.19	0.92 (0.83–1.02)	0.13
60–74	0.94 (0.85–1.05)	0.28	0.92 (0.83–1.02)	0.10
45–59	1.09 (0.96–1.25)	0.17	1.02 (0.90–1.15)	0.79
<45	1.21 (1.03–1.42)	0.02	1.07 (0.92–1.24)	0.39
≥75 years (n = 488)				
≥90	Reference		Reference	
75–89	1.22 (0.97–1.55)	0.09	1.19 (0.94–1.51)	0.15
60–74	1.17 (0.93–1.48)	0.18	1.13 (0.91–1.42)	0.27
45–59	1.20 (0.96–1.50)	0.10	1.10 (0.88–1.38)	0.38
<45	1.21 (0.96–1.53)	0.11	1.10 (0.87–1.40)	0.42

Estimates are expressed as IRR (95% CI).

Model 1 adjusted for age, sex and education.

Model 2 adjusted for Model 1 covariates plus waist circumference, smoking, diabetes, hypertension, cardiovascular disease, polypharmacy and chronic health conditions.

Referred CKD populations are likely to have a different perception of their QoL compared with the general population. The mean eGFR in these studies was generally <30 mL/min/1.73 m², a level of kidney function at which complications such as anaemia and mineral bone disease are encountered. The prospect of the future need for renal replacement therapy could also contribute to an individual's QoL. Population studies offer key advantages over referred CKD samples, including a broader range of kidney function and the availability of an internal comparator group. The link between kidney function and QoL in population studies has not been consistent however. A study of older diabetic individuals found no association between kidney function, measured by 24-h creatinine clearance, and QoL after adjustment for cardiovascular disease [27]. A regional cohort of older Korean adults observed trends for poorer physical components of QoL with diminishing eGFR, but these were only statistically significant at an eGFR <45 mL/min/1.73 m² [6]. A similar trend for worsening physical, but not mental, components of QoL was found among a large US population sample [4]. A population study of Australian adults demonstrated clear reductions in both physical and mental components of QoL among those with CKD (eGFR_{cr} <60 mL/min/1.73 m²) compared with those without CKD [5]. In contrast to most of these studies, we examined QoL across the spectrum of eGFR from creatinine and cystatin C in a national cohort of community-dwelling older adults. We measured overall QoL using an instrument that does not emphasize physical ailments but rather encompasses both positive and negative aspects of life in older adults.

The incongruous findings for cystatin C and creatinine raise important questions about these biomarkers. Cystatin C has a stronger correlation with directly measured GFR than creatinine [28], and it is generally assumed that the stronger associations with clinical outcomes observed for cystatin C [29] reflect more accurate estimation of GFR. The differential profile for cystatin C and creatinine in our study may well be explained by more

accurate estimation of GFR by cystatin C compared to creatinine. However, the median eGFR_{cys} in our cohort was 81 mL/min/1.73 m², whereas symptoms of kidney disease are classically reported at very low levels of GFR. The differences between the biomarkers were so marked that other explanations should be considered. An increasing body of literature has identified correlations between cystatin C and so-called non-GFR determinants, such as obesity and inflammation [30–32]. Rather than solely measuring kidney function, cystatin C may be a surrogate marker of other biological determinants of ill health, which culminate in a phenotype of accelerated ageing [33] and contribute to lower QoL.

Analysis of the relationship between eGFR_{cys} and CASP-19 within age strata suggested greater differences among middle-aged compared with older participants. Among the AusDiab cohort, the effect of CKD was greater among younger individuals for mental components of QoL and greater among older individuals for physical components [5]. This is consistent with our findings, in that CASP-19 places less emphasis on physical determinants of QoL compared with instruments such as the Short Form-36 questionnaire. CKD has consistently been shown to predict hard outcomes such as mortality [34], yet it is largely unknown what impact a diminished level of kidney function has on the well-being of an older individual. Our data suggest little or no association between mild to moderate reductions in eGFR and overall QoL beyond middle age in community-dwelling adults. For these individuals, a diminished eGFR could be one of a number of chronic health conditions that accumulate with age and contribute to their QoL. Given the high prevalence of 'mild' CKD (eGFR 45–59 mL/min/1.73 m²) in the general population of older adults, the identification of meaningful connected outcomes such as reduced QoL would strengthen the case for detecting modest reductions in kidney function in this demographic.

Our findings should be interpreted in the context of the study's potential limitations. We measured kidney biomarkers at a single time point and urinary protein was not measured. The cross-sectional design of the study limits our ability to infer causality in the relationship between kidney function and QoL. There may have been residual observed or unobserved confounding in this relationship. There were missing data for both eGFR and CASP-19, which may have introduced a selection bias into our results. The TILDA sample is a relatively robust cohort of middle-aged and older community-dwelling Caucasian adults, thus limiting the generalizability of our results. Although CASP-19 has been shown to be a valid and reliable tool, relatively few studies have investigated objective health measures as predictors of CASP-19 [11]. These limitations are balanced by several strengths. The sample size is large with a broad range of age and eGFR. The TILDA data set is rich with respect to relevant covariates, including comorbidities and medications. Both cystatin C and creatinine were measured simultaneously using standardized assays, facilitating a comparison of both biomarkers as predictors of QoL.

In conclusion, we have demonstrated a statistically significant, but clinically modest, relationship between diminished eGFR and poorer QoL among community-dwelling older adults. This association was only evident using cystatin C to calculate eGFR and was more pronounced in middle-aged participants. Our findings suggest that eGFR is not a clinically significant predictor of overall QoL among the general population of older adults. The discordant findings for cystatin C and creatinine, at levels of eGFR where symptoms of CKD are not typically encountered, suggest that the relationship between eGFR_{cys} and QoL could be confounded by non-GFR determinants of cystatin C.

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Conflict of interest statement

None declared.

Supplementary data

Supplementary data are available online at <http://ckj.oxfordjournals.org>.

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