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ORIGINAL ARTICLE

Association of renal impairment with cognitive dysfunction in the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA)

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ABSTRACT

Introduction. Chronic kidney disease (CKD) is a recognized risk factor for cognitive impairment. Identification of those at greatest risk of cognitive impairment may facilitate earlier therapeutic intervention. This study evaluated associations between estimated glomerular filtration rate (eGFR) and cognitive function in the Northern Ireland Cohort for the Longitudinal Study of Ageing.

Methods. Data were available for 3412 participants ≥50 years of age living in non-institutionalized settings who attended a health assessment between February 2014 and March 2016. Measures of serum creatinine (SCr) and cystatin C (cys-C) were used for eGFR. Cognitive function was measured using the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE).

Results. Following adjustment for potential confounders, a single unit decrease in eGFR was significantly associated with reduced cognitive function defined by an MMSE ≤24/30 {eGFR calculated using serum cys-C [eGFRcys]: β = −0.01 [95% confidence interval (CI) −0.001 to −0.01], P = 0.01} and MoCA <26/30 [β = −0.01 (95% CI −0.002 to −0.02), P = 0.02]. Similarly, CKD Stages 3–5 were also associated with a moderate increase in the odds of cognitive impairment (MMSE ≤24) following adjustment for confounders [eGFRcys: odds ratio 2.73 (95% CI 1.38–5.42), P = 0.004].

Conclusions. Decreased eGFRcys was associated with a significantly increased risk of cognitive impairment in a population-based cohort of older adults. However, there was no evidence of an association between cognitive impairment and the more commonly used eGFR calculated using SCr. eGFRcys may offer improved sensitivity over eGFRcr in the determination of renal function and associated risk of cognitive impairment.

Keywords: biomarkers, CKD-EPI, creatinine, cystatin C, GFR

INTRODUCTION

Improvements in healthcare have resulted in longer lifespans, leading to a greater prevalence of cognitive impairment [1]. Mild cognitive impairment (MCI) is a transitional stage between normal age-related decline and dementia and is characterized by problems with memory, language, thinking or judgement while the individual is able to function independently. MCI prevalence has been reported to be as high as 21% in individuals >60 years of age [2], with ∼6% of individuals having dementia [3]. Dementia prevalence is ∼20–25% among those in the UK who survive beyond their ninth decade of life [3].

Chronic kidney disease (CKD) is characterized by impaired renal function and may represent a significant independent risk factor for cognitive decline, although the basis for this association is not well understood. Pathological cerebral changes characteristic of dementia exacerbated by reduced renal function have also been reported in those with cognitive impairment in the absence of overt dementia [4–6]. CKD may contribute to the pathoaetiology of vascular dementia (VaD) via traditional

KEY LEARNING POINTS

What is already known about this subject?

- Chronic kidney disease (CKD) is associated with an increased risk of cognitive impairment.
- Identification of those at greatest risk of cognitive impairment may facilitate earlier therapeutic intervention.
- Comparison of serum creatinine (SCr)- and/or cystatin C (cys-C)-based estimated glomerular filtration rate (eGFR) with robust markers of cognitive function may identify improved sensitivity to differentiate those at increased risk.

What this study adds?

- Decreased eGFR calculated using serum cys-C (eGFRcys) is associated with a significantly increased risk of cognitive impairment in our population-based cohort of older adults.
- There was no evidence of an association between cognitive impairment and the more commonly used eGFR calculated using SCr (eGFRcr).
- eGFRcys may offer improved sensitivity over eGFRcr in the determination of renal risk associated with cognitive impairment.

What impact this may have on practice or policy?

- Measurement of serum cys-C and use of the eGFRcys equation for CKD diagnosis may be more sensitive in characterizing renal function in those groups at risk of cognitive impairment, such as the elderly.

cardiovascular disease risk factors, including diabetes, hypertension, dyslipidaemia, smoking and family history [7], as well as the non-traditional cardiovascular risk factors, including endothelial dysfunction, uraemic neurotoxins and calcification. Impaired flow-mediated dilatation and arterial stiffness have been reported in small [8] and large [9, 10] arterial vessels in those with CKD, where homocysteine clearance is diminished [11] and reduced erythropoietin production results in lower oxygen-carrying capacity [12]. Moreover, variations in mineral metabolite concentration that result in calcification of soft tissues and bone remodelling is another recognized feature of CKD [13]. Although vascular calcification is more prominent in later-stage CKD [14, 15], it may result as a consequence of only moderate renal impairment with perturbed mineral metabolism contributing to neuronal cell death [13, 16].

In addition to VaD, CKD may also contribute to Alzheimer's disease (AD)-related pathology [characterized by an accumulation of cerebral extracellular amyloid-β (Aβ) plaques and neurofibrillary tangles caused by intracellular hyperphosphorylated tau protein [17] via impaired Aβ clearance]. Many molecular mediators of cognitive decline remain in the circulation as a consequence of renal impairment in CKD, leading to complex changes in blood composition. CKD patients undergoing dialysis have been reported to have serum Aβ levels similar to cognitively intact controls, while those with CKD not receiving dialysis had relatively higher serum Aβ levels that negatively correlated with estimated glomerular filtration rate (eGFR) [18]. Systemic reduction in serum Aβ following haemodialysis has also been demonstrated [19], with associated improvements in cognitive function [20]. In addition, murine studies have shown renal clearance of peripheral Aβ leading to reduced cerebral levels in APPswe/PS1dE9 mice that spontaneously produced amyloid plaques by 6 months [21]. Furthermore, structural cerebral changes associated with AD and VaD, such as Aβ deposition and white matter lesion formation, are also commonly found in individuals with MCI, suggestive of an overlapping pathophysiology across a disease continuum [4].

As such, individuals with CKD may be at increased risk of cognitive impairment, and impaired renal function is a recognized risk factor associated with cognitive decline. Moreover, reductions in renal function correlate strongly with older age [22], increasing the risk of cognitive impairment, although potentially confounding the associations observed. Cognitive decline has been reported in association with the presence and magnitude of albuminuria [23–25] and the duration of kidney disease following adjustment for the confounding influence of age [26]. Early identification of those at increased risk of cognitive impairment may enable earlier therapeutic intervention. Estimates suggest that between 22% and 46% of those with MCI progress to dementia, representing a significant risk of progression to advanced neurodegenerative disease [2, 27, 28]. Dementia is a significant contributor to global mortality [29] and carries a high burden of morbidity, affecting memory, reasoning, physical functioning and emotional regulation associated with greater socio-economic burden [30, 31].

Current treatment options for cognitive impairment are limited to targeting a range of lifestyle and other risk factors to slow progression of cognitive decline [32, 33]. Therefore identification of at-risk individuals would be advantageous. However, the relationship between the stage of CKD (based on eGFR) and the severity of cognitive function is unclear. Serum creatinine (SCr) is the most commonly used metabolite for eGFR and renal function estimates, but its utility is limited by the influences of sex, age, diet and muscle mass (recognized risk factors for cognitive impairment) on Cr clearance by the kidney. As such, other biomarkers not influenced by age, sex, muscle mass or dietary intake, such as cystatin C (cys-C), might better reflect the early diminished GFR of renal impairment. The aim of this study was to determine the value of serum cys-C and SCr as

estimates of renal function (eGFR) to quantify associations with cognitive function in an older population using data collected by the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA).

MATERIALS AND METHODS

NICOLA is a longitudinal cohort study of 8478 community-dwelling men and women ≥50 years of age, resident in Northern Ireland (individuals in care homes or other residential institutions were excluded at baseline) [34]. The study was established in 2013 with three main components: a computer-aided personal interview (CAPI), a self-completion questionnaire and a health assessment. The CAPI was extensive in scope and included assessment of demographic, social and health-related factors. Measures of cardiovascular, physical, cognitive and visual function were determined during the health assessment and biological samples were collected. Ethical approval was obtained from the School of Medicine, Dentistry and Biomedical Sciences Ethics Committee, Queen's University Belfast (SREC 12/23) and written informed consent was obtained prior to participation in accordance with the Helsinki Declaration.

Measurement of renal function and classification of CKD

SCr (mg/dL) standardized to isotope dilution mass spectrometry–calibrated techniques and cys-C (mg/L) were assayed on an ARCHITECT c8000 system (Abbott, Abbott PArk, IL, USA) using kinetic alkaline picrate and turbidimetric/immunoturbidimetric methods, respectively. The coefficient of variation for SCr and cys-C was <4.68 and <1.80%, respectively. eGFR [eGFR calculated using SCr (eGFRcr) and eGFR calculated using serum cys-C (eGFRcys)] was based on a single serum sample using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2009 equation for Cr and 2012 equation for cys-C) [22]. CKD Stages 3–5 were defined as eGFR <60 mL/min/1.73 m^2 and CKD Stages 1–2 as eGFR ≥60 mL/min/1.73 m^2.

Measurement of cognitive function

Cognitive function was evaluated in the participants who attended a health assessment that included a Mini-Mental State Examination (MMSE) and a Montreal Cognitive Assessment (MoCA) of short-term memory recall tasks, visuospatial abilities and executive function, phonemic fluency and two-item verbal abstraction tasks. Attention, concentration, language orientation to time and working memory were also assessed. An extra point was added to the MoCA test score for participants with <12 years of formal education. Cognitive impairment thresholds included an MoCA score <26 or an MMSE score ≤24.

Other variables

Measures of obesity included percentage body fat, waist circumference and body mass index (BMI). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were the average of two independent readings. Diabetic status was defined using a combination of participant percentage haemoglobin A1c (>6.5%), diabetic medication use or self-reported diabetes. Self-reported medication use was defined according to the Anatomical Therapeutic Chemical Classification System based on the active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Educational attainment was classified as completing primary, secondary or tertiary-level education. Smoking status was characterized as current, past or non-smoker. Alcohol consumption was categorized into three groups: non-drinker, drinker and ex-drinker.

Statistical methods

Only cross-sectional baseline data from Wave 1 was available. Continuous variables were summarized using mean [standard deviation (SD)] and categorical variables by frequencies and percentages. Between-group differences were assessed using *t*-tests and chi-squared tests. Multivariate linear regression tested associations between eGFR and cognitive function, with eGFR as the independent variable and MoCA and MMSE scores as the dependent variables. The primary analyses used multivariate linear regression to test associations between a single-unit reduction in renal function (eGFR) and cognition assessed by MoCA. Secondary analyses tested for associations between eGFR and cognitive impairment by MMSE. Logistic regression tested associations between CKD Stages 3–5 (eGFR <60 ml/min/1.73 m^2) as the independent variable and cognitive impairment (as the dependent variables).

Regression models were unadjusted or adjusted in a stepwise manner for age, sex, waist circumference, BP, diabetes status, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, education level, smoking, alcohol intake and deprivation score (overall income domain score) and self-reported use of lipid-modifying agents, antihypertensive drugs and drugs used for the treatment of diabetes.

RESULTS

Baseline characteristics for the 3412 NICOLA participants who attended for health assessment and for whom data were available are shown in Table 1. The mean age of the sample was 64 years (SD 9). Participants had a mean waist circumference of 96 cm (SD 14), indicating a high prevalence of unhealthy adiposity in the sample, and those characterized with impaired cognition were more likely to have significantly higher mean percentage body fat (45% versus 43%) and mean BMI (29.2versus 28.7 kg/m^2). The mean SBP and DBP were 133 and 81 mmHg, respectively, with 2% of participants reporting the use of antihypertensive medication. The mean LDL cholesterol was 3.4 mmol/L (SD 1.11), indicating a high prevalence of unhealthy LDL and the use of lipid-modifying agents was reported by 33% of participants. The mean HDL cholesterol was 1.61 mmol/L (SD 0.44).

The mean MoCA score was 25.4 (SD 3.3), a value below the threshold for cognitive impairment of 26/30. In contrast, the mean MMSE score was 28.5 (SD 1.8), exceeding the normal cognition threshold of 24/30. The mean eGFRcr was 80.2 mL/

Table 1. Population characteristics

Variable	All participants ($N = 3412$), mean (SD)	Cognitively normal ($n = 1941$), mean (SD)	Impaired cognition ($n = 1471$), mean (SD)	P-value
Age (years)	64 (9)	62 (8)	67 (9)	<0.001
Body fat (%)	44 (7)	43 (7)	45 (6)	<0.001
Waist circumference (cm)	96 (14)	94 (14)	98 (14)	<0.001
BMI (kg/m^2)	28.9 (5.2)	28.7 (5.2)	29.2 (5.3)	0.003
<25	751 (22)	459 (24)	292 (20)	0.003
25–30	1445 (42)	833 (43)	612 (42)	–
>30	1216 (36)	649 (33)	567 (38)	–
SBP (mmHg)	133 (19)	132 (19)	134 (19)	0.001
DBP (mmHg)	81 (11)	82 (11)	81 (11)	0.003
Overall income domain score	0.23 (0.14)	0.19 (0.12)	0.22 (0.13)	<0.001
LDL (mmol/L)	3.34 (1.11)	3.46 (1.07)	3.20 (1.13)	<0.001
HDL (mmol/L)	1.61 (0.44)	1.66 (0.45)	1.56 (0.42)	<0.001
MMSE score	28.5 (1.8)	29.2 (1.0)	27.7 (2.0)	<0.001
MoCA score	25.4 (3.3)	27.7 (1.3)	22.5 (2.6)	<0.001
eGFRcr (mL/min/1.73 m^2)	80.2 (16.0)	81.9 (14.8)	78.4 (16.7)	<0.001
CKD stages (Cr)				<0.001
CKD Stages 1–2	2627 (90)	1550 (92)	1077 (87)	–
CKD Stage 3	214 (7)	109 (6)	105 (9)	–
CKD Stages 4–5	84 (3)	32 (2)	52 (4)	–
eGFRcys (mL/min/1.73 m^2)	67.2 (18.3)	70.7 (17.5)	63.5 (18.1)	<0.001
CKD stages cys-C				<0.001
CKD Stages 1–2	1952 (67)	1236 (75)	716 (58)	–
CKD Stage 3	637 (22)	305 (18)	332 (27)	–
CKD Stages 4 and 5	291 (11)	115 (7)	176 (15)	–
Male, *n* (%)	1604 (47)	838 (43)	766 (52)	<0.001
DM, *n* (%)	307 (9)	134 (7)	173 (12)	<0.001
Using lipid-modifying agents, *n* (%)	1132 (33)	541 (28)	591 (40)	<0.001
Using antihypertensive drugs, *n* (%)	79 (2)	34 (2)	45 (3)	<0.001
Using drugs for diabetes, *n* (%)	212 (6)	93 (5)	119 (8)	<0.001
Education level, *n* (%)				<0.001
Primary or less	479 (14)	113 (6)	366 (25)	–
Secondary	1509 (44)	789 (41)	720 (49)	–
Tertiary	1483 (44)	1038 (54)	383 (26)	–
Smoking status, *n* (%)				0.05
Never	1779 (52)	1043 (54)	741 (50)	–
Ex	1272 (37)	689 (36)	582 (40)	–
Current	353 (11)	207 (11)	146 (10)	–
Alcohol consumption, *n* (%)				<0.001
Current	2362 (69)	1440 (74)	922 (63)	–
Ex	495 (15)	239 (12)	256 (17)	–
Never	553 (16)	261 (14)	292 (20)	–

Medication use was defined according to the Anatomical Therapeutic Chemical Classification System that classifies the active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Secondary education includes the following categories: GCSE, A level: advanced level. Tertiary education includes the following categories: diploma/certificate, primary degree, post-graduate degree. Ex-smoker includes the following categories: stopped >10 years ago, between 10 years and 12 months ago and within the last 12 months. P-values show the significance for the comparison between those who are cognitively normal versus those with impaired cognition, based on MoCA scores >26 and <26.

Table 2. Linear regression models for associations between eGFR and cognitive function scores

Outcome	Model 1 β (95% CI), P-value	Model 2 β (95% CI), P-value
MoCA (mL/min/1.73 m^2)		
eGFRcr	−0.03 (−0.02 to −0.04), <0.001	0.002 (0.01 to −0.01), 0.53
eGFRcys	−0.05 (−0.04 to −0.05), <0.001	−0.01 (−0.002 to −0.02), 0.02
MMSE (mL/min/1.73 m^2)		
eGFRcr	−0.02 (−0.01 to −0.02), <0.001	−0.002 (0.002 to −0.01), 0.24
eGFRcys	−0.02 (−0.02 to −0.03), <0.001	−0.01 (−0.001 to −0.01), 0.01

Model 1: unadjusted model. Model 2: adjusted model including age, sex, waist circumference, SBP, diabetes status, LDL and HDL cholesterol, education level, smoking, drinking and deprivation score and self-reported use of lipid-modifying agents, antihypertensive drugs and drugs used for the treatment of diabetes.

Table 3. Binary logistic regression models for associations between estimated CKD Stages 3–5 (eGFR <60 mL/min/1/73 m^2) and cognitive impairment

Outcome	Model 1 OR (95% CI), P-value	Model 2 OR (95% CI), P-value
MoCA <26		
CKD Stages 3–5 cr	1.61 (1.28–2.03), <0.001	0.78 (0.59–1.03), 0.08
CKD Stages 3–5 cys	1.97 (1.69–2.30), <0.001	0.98 (0.80–1.19), 0.83
MMSE ≤24		
CKD Stages 3–5 cr	3.31 (1.89–5.81), <0.001	1.75 (0.90–3.38), 0.10
CKD Stages 3–5 cys	4.90 (2.82–8.53), <0.001	2.70 (1.37–5.33), 0.004

Model 1: unadjusted model. Model 2: adjusted model including age, sex, waist circumference, SBP, diabetes status, LDL and HDL cholesterol, education level, smoking, drinking and deprivation score and self-reported use of lipid-modifying agents, antihypertensive drugs and drugs used for the treatment of diabetes.

min/1.73 m^2 (SD 16.0) and the mean eGFRcys was 67.2 mL/min/1.73 m^2 (SD 18.3); 47% of participants were male, 9% had diabetes, 6% reported using diabetes medication, 86% were educated to the General Certificate of Secondary Education (GCSE) level or higher, 48% had previously or were current smokers and 69% were classified as current alcohol drinkers.

In an unadjusted regression to test associations between eGFR and MoCA (Table 2), a single-unit decrease in eGFR was associated with lower cognitive function {eGFRcr: $\beta = -0.03$ [95% confidence interval (CI) −0.02 to −0.04], $P < 0.001$; eGFRcys: $\beta = -0.05$ [95% CI −0.04 to −0.05], $P < 0.001$}. Following adjustment for confounders, only eGFRcys remained significantly associated with lower cognitive function [$\beta = -0.01$ (95% CI: −0.002 to −0.02), $P = 0.02$].

In a secondary analysis where cognitive impairment was characterized by MMSE ≤24, a single-unit decrease in eGFR was significantly associated with a lower MMSE score [eGFRcr: $\beta = -0.02$ (95% CI −0.01 to −0.02), $P < 0.001$; eGFRcys: $\beta = -0.02$ (95% CI −0.02 to −0.03), $P < 0.001$]. Following adjustment for confounders, only eGFRcys remained significant [$\beta = -0.01$ (95% CI −0.001 to −0.01), $P = 0.01$].

Using a MoCA score <26 to characterize cognitive impairment, CKD Stages 3–5 (eGFR <60 mL/min/1.73 m^2) were associated with a moderate increase in the odds of cognitive impairment in unadjusted analyses [eGFRcr: odds ratio (OR) 1.61 (95% CI 1.28–2.03), $P < 0.001$; eGFRcys: OR 1.97 (95% CI 1.69–2.30), $P < 0.001$], although neither remained significant following adjustment for confounding variables (Table 3).

CKD Stages 3–5 were also associated with a moderate increase in the odds of cognitive impairment in unadjusted analyses [eGFRcr: OR 3.31 (95% CI 1.89–5.81), $P < 0.001$; eGFRcys: OR 4.90 (95% CI 2.82–8.53), $P < 0.001$]. Following adjustment for potential confounders, only eGFRcys remained significant [OR 2.73 (95% CI 1.38–5.42), $P = 0.004$].

DISCUSSION

In this population-based cohort of older adults, lower eGFRcys was independently associated with cognitive impairment following adjustment for potential confounding variables. Similarly, CKD Stages 3–5, characterized by eGFRcys <60 mL/min/1.73 m^2, were associated with increased odds of MMSE ≤24 (OR 2.73). However, there was no evidence of an association between renal function characterized by eGFRcr and cognitive function, independent of potential confounders.

Several studies have previously reported associations between CKD and cognitive function [35, 36]. AD and VaD possess similar aetiological origins, despite variable pathologies, and share several important risk factors. The risk of onset of AD is increased by diabetes mellitus (DM), hypertension and obesity (particularly in midlife), physical inactivity, smoking, lower educational attainment and depression [37], risk factors commonly shared with VaD [38–44]. Likewise, CKD also shares several of these risk factors (obesity, diabetes, hypertension, smoking, education and physical activity) [45, 46] and may influence cognitive decline as a result of effects associated with vascular remodelling and Aβ clearance. Similarly, individuals with end-stage renal disease (ESRD) are more susceptible to atherosclerotic changes [47] and ischaemic and haemorrhagic stroke, which may be as much as 4–10 times more common [48]. The systemic vascular effects of CKD begin early in the disease process, long before symptoms of ESRD are observed [13, 16]. Impaired clearance of uraemic metabolites has also been suggested as a contributory factor to cognitive decline in patients with CKD as an explanation for the limited efficacy of treatments targeting traditional cardiovascular risk factors to ameliorate cognitive impairment in CKD patients [49, 50]. In a meta-analysis, individuals with CKD tended to have poorer memory, executive function, language, concept formation, attention orientation, reasoning domains and global cognition [51]. In addition, cognitive function improved following renal transplant in those with ESRD [52].

This study provides evidence that characterization of CKD using cys-C-based estimates was associated with a moderately greater risk of cognitive impairment. Given that cognitive impairment is commonly underdetected and associated with poor adherence to treatment [53], cognitive assessment in CKD populations may be of value. Indeed, recent findings suggest that those with CKD Stages 4 and 5 and cognitive impairment have a far greater mortality rate than those with either condition alone [49]. Renal function estimates using the more common eGFRcr biomarker were less sensitive, suggesting eGFRcys may offer improved sensitivity and characterization of renal function for the detection of subtle associations between eGFR and cognitive outcomes, especially in those with reduced cognitive function. These findings support similar previously reported associations between eGFRcys independent of confounding factors in older individuals, particularly in populations with more comorbid conditions [54].

This study had several strengths. The present analyses made use of a large, population-based cohort that allowed for a

well-powered, analysis generalizable to the wider population of older adults. The NICOLA dataset included measures on a wide variety of lifestyle and health outcomes, which allowed for adjustment of important potential confounding factors. Prevalence of CKD and cognitive risk factors vary widely by geographic region [55, 56], and this study provided those relative to the Northern Irish population. The primary predictor and outcome variables were quantified using clinically relevant measures (MoCA and MMSE for cognitive function and eGFR using CKD-EPI equations for two independent biomarkers of renal function), thus providing clinical relevance to the analyses. Associations between renal function and cognitive impairment were evaluated using commonly used instruments such as MMSE and the more sensitive MoCA, with the latter proving sufficiently informative alone for associations with eGFRcys [57]. Furthermore, eGFRcys has been reported to be less affected by variations in muscle mass and diet and a better predictor of CKD-associated mortality and morbidity compared with eGFRcr [58–60]. In general, eGFRcys was lower than eGFRcr in the NICOLA study participants. Nevertheless, the use of both Cr and cys-C in eGFR equations in people with unusual muscle mass or high levels of obesity is complex and has been reported to be less accurate [61, 62]. The mean difference between eGFRcr and eGFRcys for NICOLA study participants was lowest in those with a BMI $<25\,kg/m^2$ (9.7 mL/min/1.73 m^2; SD 13.0) in contrast to those who were most obese with a BMI $>30\,kg/m^2$ [16.5 mL/min/1.73 m^2 (SD 13.2)].

There were several limitations to the design of our study. NICOLA included adults >50 years of age and excluded individuals with dementia and institutionalized adults. Therefore, by design, and as a result of selection bias, the findings likely reflect associations with cognitive impairment in older adults and not clinical dementia. Moreover, the study sample was biased towards healthy individuals who may represent the 'worried well'. As a result, individuals with renal dysfunction and cognitive impairment are likely to be underrepresented compared with the population at large.

Although NICOLA is a longitudinal cohort study, at the time of analysis only cross-sectional data were available. This precluded examination of cause-and-effect relationships in the dataset and increased the likelihood of survival bias. Renal function was assessed using a clinically relevant estimation of GFR; however, direct measurement of GFR would have provided an assessment of renal function with smaller inherent error [63]. Moreover, to account for diurnal and acute variations in renal function, kidney disease is clinically assessed using two measures of serum cr and cys-C taken at least 3 months apart [22]. The use of a single measure in this study to estimate renal function is likely to increase the variability of the data and increase the probability of false null findings, although this was reduced in part by the large number of participants. Albuminuria is an early marker of endothelial damage within the renal glomeruli and another important measure of renal health used in the diagnosis and management of CKD that identifies a disease population with only partial overlap to those identified using eGFR alone [64]. Generalized endothelial dysfunction has been hypothesized to lead to neuronal damage and neurotoxin accumulation that may reflect the disease processes of cognitive decline and explain previous associations between albuminuria and reduced cognitive performance [23–25]. In common with many population-based studies, measures of albuminuria were not available for NICOLA study participants. In addition, potential explanatory covariates, such as anaemia, depression, poor sleep quality and polypharmacy, have been linked to CKD-related cognitive dysfunction [65] and were not considered in the present analyses. Furthermore, some of the variables included self-reported data, such as medication use, which may be prone to recall bias. Finally, although we adjusted for major potential confounders, the possibility of residual confounding by variables that were not included in the analyses remains.

To conclude, eGFR and CKD Stages 3–5 were associated with cognitive impairment in a Northern Irish population-based cohort, indicating that patients with reduced eGFR or CKD Stages 3–5 are at increased risk of cognitive impairment. However, associations between cognition and the more commonly used but less sensitive eGFRcr-based measures of renal function could largely be explained by known covariates such as age, diabetes and hypertension. In contrast, renal function based on the more sensitive, but less commonly used, eGFRcys identified associations with cognitive impairment with moderately increased odds (2.73-fold). The sensitivity to evaluate eGFR as a risk factor for cognitive impairment may be limited when using the more traditional renal function biomarker of SCr due to the confounding effects of other factors. Nevertheless, associations of increased risk are explained using the more sensitive cys-C estimate of renal function, which is less susceptible to potential confounding factors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the School of Medicine, Dentistry and Biomedical Sciences Ethics Committee, Queen's University Belfast (SREC 12/23) and written informed consent was obtained prior to participation, in accordance with the Helsinki Declaration.

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AUTHORS' CONTRIBUTIONS

E.P. undertook data analysis. G.M.K., E.P. and A.P.M. proposed the research hypothesis and were major contributors to the writing of the manuscript. F.K. and I.Y. conceived and designed NICOLA. B.M.G. and S.C. acquired and interpreted NICOLA health assessment data. All authors revised the manuscript critically for important intellectual content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Finally, all authors read and approved the final manuscript before submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the NICOLA but restrictions apply to the availability of these data. Data access is available by request through the NICOLA Data Access Committee.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part. The authors declare that they have no conflicts of interest

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