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Mild chronic kidney disease and functional impairment in community-dwelling older adults

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Abstract

Background: chronic kidney disease (CKD) has been associated with an increased risk of death and cardiovascular events, but its relationship with non-vascular outcomes, including functional impairment (FI), is less well understood.

Objective: in this study, we review the association between CKD and FI, adjusting for potential confounders and risk factors, with a primary outcome of impairment in any instrumental ADL (IADL) or basic ADL (BADL). 

Design: the Cardiovascular Multimorbidity in Primary Care Study (CLARITY) is a cross-sectional study of community-dwelling adults.
Introduction

Chronic kidney disease (CKD) has a prevalence of 13% [1] in the general population, is associated with a significantly increased risk of mortality [2] and >1.8 million people worldwide receive renal replacement therapy for end-stage kidney disease (ESKD). A large body of epidemiological studies has reported the association between reduced glomerular filtration rate (GFR) and an increased risk of death and cardiovascular events [3]. However, the association between GFR and non-cardiovascular outcomes has been poorly studied, especially in community-based populations with moderate CKD.

Preservation of functional independence is a key determinant of ‘successful ageing’ and in subjective surveys of older adults, functional independence is reported to be more important than the absence of disease [4]. Subclinical cardiovascular and cerebrovascular disease, especially covert stroke, has been associated with functional decline, the loss of independence and the ability to perform routine activities of daily living [5]. Although the association between ESKD and functional impairment (FI) is established [6], the relationship between earlier stages of CKD and FI has been understudied in community-dwelling adults. Such information would inform the epidemiology of CKD and the conduct of future clinical research on potential interventions for CKD prevention.

In our study, we determined the association between moderate CKD and FI in a representative sample of community-dwelling older adults in the West of Ireland.

Methods

The Cardiovascular Multimorbidity in Primary Care (CLARITY) study is a cross-sectional study of people in the West of Ireland. Patients were recruited from primary care centres included in the Western Research and Education Network (WREN), a University-affiliated primary care research network, previously reported to be representative of the Irish national general practice profile [7]. A geographical balance of primary care centres was identified and practices that used the same practice software program were invited to take part in CLARITY. From a total of 71 practices, 17 were invited and 65% (n = 11) took part in the study. Within each primary care centre, all patients of age ≥50 years that had two or more consultations in the previous 24 months were considered eligible. This approach was used to include only active patients and to ensure one-off visitors and patients who had moved away from the primary care centre were not included.

The following data were collected in all patients: demographics (age, gender and race), place of residence (including nursing home), hospital medical care (outpatient attendance and inpatient admissions in the previous 2 years), smoking status, past medical history (including medication use) and results of laboratory investigations including blood glucose, glycosylated haemoglobin, serum creatinine, estimated glomerular filtration rate (eGFR), cholesterol and triglyceride levels.

Smoking status was defined as current, former or non-smoker. Hypertension was defined as either documented hypertension in medical records or a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. A prior history of coronary artery disease was defined as a history of angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft. CKD was defined as either documented CKD in medical records or eGFR ≤60 ml/min/1.73 m², calculated using the Modification of Diet in Renal Disease (MDRD) formula.

A subset of patients received a postal, standardised, self-reported health questionnaire to measure additional demographics, perceived health, well-being and functional status. Of the 9,698 patients recruited, 2,212 were excluded; this included patients who had died since study initiation, had moved away from the area and those deemed unsuitable (due to dementia or terminal illness) by their primary care physician. A final total of 7,486 participants received the questionnaire that was completed by 47% (n = 3,499). We included only those who completed the questionnaire in
this study. Compared with the overall CLARITY cohort, patients who responded to the questionnaire were older (mean age 66.3 ± 10.3 versus 65.2 ± 10.6, \( P < 0.001 \)) and more likely to be female (36.1% of females responded compared with 34.2% of males, \( P = 0.045 \)), but were as likely to have serum creatinine measured as non-responders (\( P = 0.734 \)).

Instrumental activities of daily living (IADL) and basic activities of daily living (BADL) were measured using modified items from the Lawton and Barthel scales, respectively \([8, 9]\). Patients were asked about difficulty (including the need for assistance and/or dependence on another person) with mobility, self-care (washing and dressing) and usual activities (work, housework and leisure activities). They were also asked to report pain, discomfort, anxiety, depression, measures of well-being, smoking status, age on leaving formal education, marital status, employment status, alcohol use and if they had a fall within the preceding year.

The primary outcome measure was a composite of any impairment in IADL or BADL, with BADL defined as self-care tasks including washing, dressing and mobility and IADL as activities including work, housework and leisure activities. Secondary outcomes included impairment in BADL, IADL or fall requiring hospital admission within the preceding year.

### Statistical analysis

Continuous variables are expressed as mean (SD) and compared using the \( t \)-test or the Mann–Whitney test, where appropriate. Categorical variables are expressed as a proportion and compared using the Chi-square test.

Binary logistic regression analyses were used to determine the independent association between CKD and impairment in activities of daily living. A multivariable model was developed \( a \) priori including variables that may confound eGFR (age and gender) and FI (including age, vascular risk factors, previous vascular events and prescribed treatments). The final model included the following predictor variables: CKD, age, gender, age at leaving formal education, hypertension, history of coronary artery disease, congestive cardiac failure, stroke or transient ischaemic attack, peripheral vascular disease, diabetes mellitus and hypertension (Table 1).

### Chronic kidney disease and activities of daily living

Functional impairment was reported by 40.4\% (\( n = 1,413 \)) of included patients, with a higher proportion of impairment reported by patients with CKD than those without (\( P < 0.001 \)). There was no difference in the proportion of patients reporting FI between patients with an eGFR of <30 ml/min/1.73 m\(^2\) (54.5\%, 12/22) and patients with an eGFR of 30–60 ml/min/1.73 m\(^2\) (55.6\%, 338/608) (\( P = 0.895 \)). Dependence on a person for any ADL was reported by 17.3\% (\( n = 607 \)), including 21.9\% (\( n = 138 \)) of patients with CKD and 16.3\% (\( n = 469 \)) of patients without CKD (\( P = 0.001 \)).

On univariate analysis, CKD was associated with an increased risk of any FI (OR: 2.12, 1.78–2.53), impairment in IADL (OR: 2.02, 1.70–2.41) and BADL (OR: 2.25, 1.88–2.68) compared with those without CKD. CKD was also associated with an increased risk of fall requiring hospital admission (OR: 1.77, 1.12–2.81).

On multivariable logistic regression, the presence of CKD was independently associated with an increased risk of any FI (OR: 1.43, 1.15–1.78), impairment in IADL (OR: 1.43, 1.15–1.78) and impairment in BADL (OR: 1.39, 1.11–1.75). The association between CKD and falls requiring hospital admission was no longer significant (Table 2).

On subgroup analyses, age, sex and previous history of cardiovascular disease did not modify the association between CKD and FI, showing no evidence of interaction (Table 3).

### Discussion

We found that CKD was associated with an increased risk of FI, independent of age, gender, co-morbidities, traditional vascular risk factors and cardiovascular events. Although the association with FI is established in patients with ESKD \([6]\) and those with moderate-severe CKD (mean GFR 25 ml/min/1.73 m\(^2\) \([10]\) and 37 ml/min/1.73 m\(^2\) \([11]\), respectively), our study shows that this association...
extends to patients with milder CKD, with a mean GFR of 50 ml/min/1.73 m². Our study also highlights the burden of FI in patients with mild-moderate CKD, reported in one-fifth of participants.

A number of observational studies have reported the relationship between CKD and FI. These include a small cross-sectional study of 50 patients with advancing CKD that were expected to require dialysis [11], cross-sectional analyses of the MDRD clinical trial which included 900 patients with CKD [12] and cross-sectional analysis of the Heart and Estrogen/Progestin Replacement Study (HERS) of 2,761 menopausal women, half of whom had CKD [13]. Other observational studies have focused on an exclusively elderly population including a prospective cohort study of patients without CKD at baseline [14] and a cross-sectional study of 2,431 patients from NHANES [15].

### Table 1. Parameters by CKD status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n = 3,499)</th>
<th>CKD (n = 630)</th>
<th>No CKD (n = 2,869)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>66.2 (10.3)</td>
<td>74.0 (9.9)</td>
<td>64.4 (9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1,546/3,390 (45.6%)</td>
<td>253/630 (40.2%)</td>
<td>1,293/2,760 (46.8%)</td>
<td>0.002</td>
</tr>
<tr>
<td>White race</td>
<td>3,387/3,390 (99.9%)</td>
<td>629/630 (99.8%)</td>
<td>2,758/2,760 (99.9%)</td>
<td>0.465</td>
</tr>
<tr>
<td>Mean age on leaving education (SD)</td>
<td>17.3 (4.6)</td>
<td>16.2 (3.2)</td>
<td>17.5 (4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Coronary artery disease</td>
<td>398/3,392 (11.7%)</td>
<td>124/630 (19.7%)</td>
<td>274/2,762 (9.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>84/3,390 (2.5%)</td>
<td>50/630 (7.9%)</td>
<td>34/2,760 (1.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>163/3,392 (4.8%)</td>
<td>61/630 (9.7%)</td>
<td>102/2,762 (3.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>104/3,385 (3.1%)</td>
<td>25/629 (4.0%)</td>
<td>79/2,756 (2.9%)</td>
<td>0.146</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>413/3,382 (12.2%)</td>
<td>117/629 (18.7%)</td>
<td>296/2,755 (10.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking status</td>
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<tr>
<td>Current smoker</td>
<td>473/3,479 (13.6%)</td>
<td>56/629 (8.9%)</td>
<td>417/2,850 (14.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1,406/3,479 (40.4%)</td>
<td>263/629 (42.0%)</td>
<td>1,143/2,850 (40.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1,600/3,479 (46.0%)</td>
<td>308/629 (49.1%)</td>
<td>1,292/2,850 (45.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>712/3,389 (21.3%)</td>
<td>404/630 (64.1%)</td>
<td>308/2,760 (10.7%)</td>
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<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2. Risk of functional impairment by CKD status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n = 3,499) (%)</th>
<th>CKD (n = 630) (%)</th>
<th>No CKD (n = 2,869) (%)</th>
<th>P-value CKD unadjusted</th>
<th>CKD adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite any functional impairment</td>
<td>1,413/3,499 (40.4%)</td>
<td>350/630 (55.6%)</td>
<td>1,063/2,869 (37.1%)</td>
<td>&lt;0.001</td>
<td>2.12 (1.78, 2.53)</td>
</tr>
<tr>
<td>Impairment in IADL</td>
<td>1,240/3,499 (35.4%)</td>
<td>310/630 (49.2%)</td>
<td>930/2,869 (32.4%)</td>
<td>&lt;0.001</td>
<td>2.02 (1.70, 2.41)</td>
</tr>
<tr>
<td>Impairment in BADL</td>
<td>1,029/3,499 (29.4%)</td>
<td>279/630 (44.3%)</td>
<td>750/2,869 (26.1%)</td>
<td>&lt;0.001</td>
<td>2.23 (1.88, 2.66)</td>
</tr>
<tr>
<td>Impaired mobility</td>
<td>1,004/3,499 (28.7%)</td>
<td>272/630 (41.9%)</td>
<td>732/2,869 (25.5%)</td>
<td>&lt;0.001</td>
<td>2.22 (1.86, 2.65)</td>
</tr>
<tr>
<td>Impaired ability to provide self-care</td>
<td>344/3,499 (9.8%)</td>
<td>107/630 (17.0%)</td>
<td>237/2,869 (8.3%)</td>
<td>&lt;0.001</td>
<td>2.27 (1.78, 2.91)</td>
</tr>
<tr>
<td>Fall requiring admission</td>
<td>94/3,499 (2.7%)</td>
<td>26/630 (4.1%)</td>
<td>68/2,869 (2.4%)</td>
<td>0.014</td>
<td>1.77 (1.12, 2.81)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Model adjusted for age, gender, age left education, hypertension, coronary artery disease, congestive cardiac failure, stroke or transient ischaemic attack, peripheral vascular disease, diabetes mellitus, smoking status, andanthrombotic therapy and tertile of LDL:HDL ratio.

CKD and functional impairment

Table 1. Parameters by CKD status

Table 2. Risk of functional impairment by CKD status

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Australian population-based self-administered questionnaire of 10,525 adults aged ≥25 years, 11.2% of which had CKD, reported CKD to be associated with FI after multivariable adjustment [16]. However, our sample is representative of the community-dwelling population with a prevalence of CKD closer to the 15.1% recently reported by the United States Renal Data System (USRDS) [17].

In line with previous reports, our study highlights a substantial under recognition of CKD in primary care [18], as only 21.9% of patients who fulfilled diagnostic criteria for CKD had a documented diagnosis in the medical notes. Although one would expect patients with established CKD to be prescribed more medication than those without CKD, our study reports the opposite. We suspect that this finding is due to the high proportion of patients with unrecognised CKD in this study, and therefore, not prescribed medications to reduce progression of renal disease and complications. We chose a definition of CKD as an eGFR of ≤60 ml/min/1.73 m², in line with the National Kidney Foundation definition, and measurements at below this level of eGFR are considered reliable. However, measurements of eGFR at higher levels of renal function are less reliable that those for lower eGFR levels [19].

A higher proportion of women completed the questionnaire, and there was a higher proportion of women in the CKD group. Although patients with CKD were younger on leaving formal education than patients without CKD, there was no evidence of interaction between gender and age leaving formal education (P = 0.408). Although responders to the questionnaire are reported to be significantly older than non-responders, the mean difference in age is only 1.1 years and not likely to represent a clinically meaningful difference. In addition, patients with CKD were, on average, almost 10 years older than those without CKD. This finding is not surprising as age is a recognised risk factor for decline in renal function and age is required to calculate eGFR using the MDRD formula from serum creatinine measurement. Despite this difference, and after adjusting for age in the multivariable model, CKD remains a significant risk factor for FI.

Impaired renal function is associated with accelerated atherosclerosis and endothelial dysfunction, which may lead to vascular disease and/or progressive renal disease [20]. In addition, traditional vascular risk factors may be more prevalent in patients with CKD, which may increase the risk of both clinical and subclinical vascular disease, especially covert stroke, which may result in FI [21]. Even after controlling for previous cardiovascular disease and vascular risk factors, CKD remained significantly associated with FI and suggests that abnormal renal function may contribute to covert cardiovascular disease. This finding is in line with previous studies that report a high incidence of subclinical cerebrovascular disease in patients with CKD [22].

Mechanisms potentially contributing to FI in patients with CKD include anaemia [23], hyperphosphataemia [24], secondary hyperparathyroidism [25], acidosis [26] and protein-energy malnutrition [27]. Vitamin D deficiency, common in CKD patients, is associated with lower muscle strength, increased body sway, falls, sarcopenia and disability in older men and women [28]. The metabolic disturbance associated with CKD may cause myopathy and neuropathy [29], resulting in reductions exercise tolerance, independence and the ability to perform ADL. However, the patients included in our study, on average, have milder CKD where these metabolic derangements are less likely, and if they occur, will be milder compared with patients with more advanced CKD. In our study, these parameters were not measured. In addition, we did not capture the use of non-steroidal anti-inflammatory drugs (NSAID), which may have contributed to reverse causality, in that patients with FI are expected to use more NSAIDs, which are associated with CKD [30].

Sarcopenia, the loss of muscle strength and muscle mass with ageing, is reported to increase the risk for functional limitation [31]. While studies have reported the association between renal impairment and frailty [32] and quality of life, no study has included a detailed assessment of function that includes IADL and BADL in community-dwelling patients with moderate CKD. In addition, a better understanding of the underlying mechanisms contributing to FI in patients with CKD is needed to identify potential therapeutic targets to prevent functional decline.

Similar to other studies addressing this research question, the main limitation of this study is that it is observational in nature. However, clinical trials, that include interventions to improve the functional status of patients with CKD, should be informed by observational studies. Secondly, only 47% of patients who received the questionnaire completed it, potentially introducing responder bias. Similarly, women were more likely to respond to the questionnaire, which may have contributed to the bigger proportion of women with CKD, unlike previous studies. Thirdly, primary care physicians determined the suitability of sending participants the questionnaire, which may have

### Table 3. Subgroup analyses of multivariable regression between CKD and composite for any functional impairment by age, gender and cardiovascular disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.43 (1.02, 2.02)</td>
<td>0.911</td>
</tr>
<tr>
<td>Female</td>
<td>1.43 (1.07, 1.91)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>1.32 (0.906, 1.761)</td>
<td>0.716</td>
</tr>
<tr>
<td>≥75 years</td>
<td>1.52 (1.06, 2.20)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseasea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.37 (0.84, 2.25)</td>
<td>0.860</td>
</tr>
<tr>
<td>No</td>
<td>1.47 (1.15, 1.89)</td>
<td></td>
</tr>
</tbody>
</table>

*Defined as the presence of coronary artery disease or congestive cardiac failure or stroke.

*The Wald test for interaction.
introduced selection bias. Although there were slight age and gender differences between responders and non-responders, there was no significant difference in the rate of measurement of serum creatinine and calculation of eGFR, used to diagnose CKD. The main strength of our study is the high proportion of subjects with measured eGFR (90.5%). Secondly, unlike the majority of previous studies, our sample is representative of a community-based population.

In conclusion, our study reports that CKD is significantly underdiagnosed and is significantly associated with FI in community-dwelling adults. The association remained significant after adjustment for age, gender, vascular risk factors and previous cardiovascular events. In this population, CKD is significantly underdiagnosed and future studies examining if these patients develop progressive renal impairment over time are required, to inform further study of targeted interventions to reduce the burden of CKD.

Key points

- CKD is a predictor of FI.
- This effect is independent of vascular events, comorbidities or previous vascular events.
- CKD is significantly under-recognised in community-dwelling older adults.

Conflicts of interest

None declared.

Ethical approval

Ethical approval was successfully obtained from the Irish College of General Practitioners (ICGP).

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References


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Time trends of incidence of age-associated diseases in the US elderly population: medicare-based analysis

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Abstract

Objectives: time trends of age-adjusted incidence rates of 19 ageing-related diseases were evaluated for 1992–2005 period with the National Long Term Care Survey and the Surveillance, Epidemiology and End Results Registry data both linked to Medicare data (NLTCS-Medicare and SEER-Medicare, respectively).

Methods: the rates were calculated using individual medical histories (34,077 individuals from NLTCS-Medicare and 199,418 from SEER-Medicare) reconstructed using information on diagnoses coded in Medicare data, dates of medical services/procedures and Medicare enrolment/disenrolment.

Results: increases of incidence rates were dramatic for renal disease [the average annual percent change (APC) is 8.56%, 95% CI = 7.62, 9.50%], goiter (APC = 6.67%, 95% CI = 5, 90, 7, 44%), melanoma (APC = 6.15%, 95% CI = 4.31, 8.02%), and Alzheimer's disease (APC = 3.96%, 95% CI = 2.67, 5.26%), and less prominent for diabetes and lung cancer. Decreases of incidence rates were remarkable for angina pectoris (APC = −6.17%, 95% CI = −6.96, −5.38%); chronic obstructive pulmonary disease (APC = −5.14%, 95% CI = −6.78, −3.47%), and ulcer (APC = −5.82%, 95% CI = −6.77, −4.86%) and less dramatic for carcinomas of colon and prostate, stroke, hip fracture and asthma. Incidence rates of female