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Mild to moderate chronic kidney disease and functional disability in community-dwelling older adults. The Cardiovascular risk profile in Renal patients of the Italian Health Examination Survey (CARHES) study

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ABSTRACT

Objectives: Chronic kidney disease (CKD) negatively impacts aging success. This study evaluates the association between CKD and functional disability, defined as limitations in performing mobility tasks, basic (ADLs) and instrumental activities of daily living (IADLs), in a population-based sample of older adults. In particular, we examined whether such a relationship extended to mild-moderate CKD stages (G1-G3ab).

Methods: Data from the Cardiovascular risk profile in Renal patients of the Italian Health Examination Survey (CARHES) study were used.Prevalence of CKD was estimated by means of urinary albumin to creatinine ratio (ACR) and eGFR (CKD-EPI equation-enzymatic assay of serum creatinine). A validated questionnaire was used to assess functional limitations. Potentially confounding variables, e.g. socio-demographic features, lifestyles, cardiovascular (CV) risk factors and prevalent CV diseases, were considered.

Results: 1309 participants, age 71.4 ± 4.3 years, 53.8% men, were studied. 15.2% of participants were identified as having CKD. Of these, 11.5% were aware of the condition. Prevalence of CKD increased with age, and was similar between men and women. Mild-moderate CKD was found to be significantly associated with disability in mobility (OR = 1.05, 95%CI = 1.01–1.09, p = .014) and ADLs/IADLs (OR = 1.06, 95%CI = 1.02–1.12, p = .011) after multiple simultaneous adjustment including socio-demographic variables, CV risk profile, ACR, cognitive impairment and self-rated health.

Conclusions: Mild-moderate CKD independently associated with functional disability in a population-based sample of older adults. Evidence-based recommendations for disability prevention in CKD are needed.

1. Introduction

Chronic kidney disease (CKD) is a prevalent condition in the older population, and a public health concern worldwide (Jha et al., 2013). Systematic screening for CKD in at-risk individuals, e.g. older adults and those with cardiovascular (CV) risk factorfs, is of eminent importance, as even moderate reductions in estimated glomerular filtration rate (eGFR), such as a 30% drop over 2 years, and albuminuria, heralds end-stage kidney disease (ESKD) and all-cause and CV mortality (Fox et al., 2012; Jha et al., 2013). Recent research has focused on non-CV outcomes of CKD. Evidence suggests reduced kidney function negatively impacts aging success (Chowdhury, Peel, Krosch, & Hubbard, 2017; Etgen, Chonchol, Förstl, & Sander, 2012; Gopinath, Harris, Burlutsky, & Mitchell, 2013; Nordberg et al., 2007; Thai, Barnhart, Cagle, & Smith, 2013). Population-based studies have indicated that older CKD patients have greater risk of cognitive impairment (Etgen et al., 2012), physical frailty (Chowdhury et al., 2017), and are more likely to use formal home care services (Gopinath et al., 2013), a proxy measure of functional disability. A link between end-stage kidney disease (ESKD) and disability is established (Kurella Tamura et al., 2009). Population-based studies assessing the relationship between earlier stages of CKD with functional disability in older adults have consistently reported a link between CKD and mobility limitations, e.g. reduced gait speed and fear of falling (Fried et al., 2006; Gopinath et al., 2013; Kurella Tamura et al., 2009; Walker et al., 2013; Wolfgram et al., 2017). However, epidemiological data on the relationship with

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impairment in the other fundamental domains of function, that are basic (ADLs) and instrumental (IADLs) activities of daily living, are limited (Bowling, Sawyer, Campbell, Ahmed, & Allman, 2011; Cavanaugh, LaCroix, Kritz-Silverstein, Rillamas-Sun, & Rifkin, 2017; Feng, Yap, Yeoh, & Ng, 2012; König et al., 2018; Smyth et al., 2013), with some author reporting no association (Cavanaugh et al., 2017; König et al., 2018). Prevention of late-life disability is a global public health priority. Loss of independence in ADLs and IADLs has been reported to be more informative than assessment of prevalent comorbidities to predict risk of adverse outcomes in older adults (Nordberg et al., 2007; Thai et al., 2013). Disabled individuals place considerable stress on public health spending, since they have higher rates of hospitalizations and long-term care facility admissions (Nordberg et al., 2007; Thai et al., 2013). In this context, population-based data on the association between potentially preventable conditions, e.g. CKD, and disability, are essential to guide healthcare systems to implement proper actions for screening and prevention of late-life disability. The present study is therefore aimed at evaluating the association between CKD and functional disability in a representative sample of community-dwelling older adults in Italy, using data from the Cardiovascular risk profile in Renal patients of the Italian Health Examination Survey (CARHES) study (De Nicola et al., 2015).

2. Methods

2.1. Study population

The CARHES study is a sub-project of the Health Examination Survey 2008–2012, whose details have been previously described (De Nicola et al., 2015; Giampaoli, Vanuzzo, & Gruppo di ricerca del Progetto Osservatorio Epidemiologico Cardiovascolare/Health Examination Survey, 2014; Giampaoli et al., 2015). The HES 2008–2012 was launched by the Italian Ministry of Health and performed by the National Institute of Health (ISS) and the National Association of Hospital Cardiologists/ Heart Care Foundation to provide a comprehensive picture of the Italian adult population's health, with the goal to facilitate implementation of preventive programs (Giampaoli & Vanuzzo, 2014; Giampaoli et al., 2015). The survey lasted from April 2008 to July 2012. The Italian HES was recognized as part of the Joint Action of the European Health Examination Survey (EHES) projects, a pilot study for a surveillance system at the European level. Procedures and methods used for data collection and measurements followed EHES guidelines (Tolonen, 2013, 2018; Tunstall-Pedoe, 2003). The study was approved by the ethics committee of ISS. Written informed consent was obtained from all participants. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Participants with age ≥ 65 years and assessment of kidney function and functional disability were considered for the present analysis. Subjects were extracted from residence lists and invited to the survey by letter and phone contacts. Subjects were stratified by age and gender, with planned inclusion of 25 subjects for gender in each year of age in the range 65–74 years, and 20 subjects for gender in each year of age in the range 75–79 years. Overall, participation rate of older adults was 48.4%. Rates were higher in men than in women (51.7% vs 45.2%, $p = .001$) and lower in southern when compared to northern and central regions (43.6% vs 51.1%, $p < .001$). Participants were invited to public hospitals, one in each of the 20 Italian regions. Interviews and clinical examinations were performed by trained staff. All procedures were standardized and kept under quality control by ISS staff throughout the survey (De Nicola et al., 2015; Giampaoli & Vanuzzo, 2014; Giampaoli et al., 2015). Trained staff administered a questionnaire assessing personal and medical history, measured anthropometric features and blood pressure (BP), and collected blood and 24-h urine samples.

2.2. Covariates

Comorbidities were ascertained using data from personal and medical history, medications, and objective evidence. CV comorbidity was also assessed by measured CV risk factors, i.e. BP, body mass index (BMI), lipids and glycemia. Hypertension was defined by BP levels ≥140/90 mmHg or use of antihypertensive medications; diabetes mellitus by fasting glycemia ≥126 mg/dl or diagnosis or treatment; obesity by body mass index (BMI) values ≥30 Kg/m^2; prevalence of a previous myocardial infarction was evaluated by the London School of Hygiene and Tropical Medicine (LSHTM) questionnaire (Rose & Blackburn, 1968), including symptoms, hospital records and the presence of specific ECG items according to the Minnesota Code; the presence of angina pectoris by the LSHTM questionnaire (Rose & Blackburn, 1968); the prevalence of revascularization procedures, percutaneous transluminal coronary angioplasty (PTCA) and coronary artery by-pass graft (CABG) by self-reported or documented diagnosis; cerebrovascular events and chronic obstructive pulmonary disease (COPD) by self-reported or documented diagnosis or treatment. Anemia was defined by hemoglobin levels < 13 g/dL in men and < 12 g/dL in women. Information on smoking habits (current), education level (defined as low for < 8 years of formal education and high for ≥ 8 years) and marital status were also collected.

2.3. Laboratory analyses

Isotope dilution mass spectrometry (IDMS)-traceable creatinine measurement (enzymatic assay) was used to estimate glomerular filtration rate (eGFR) by means of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009). 24-hours urine samples were stored at −80 °C and used to assess albumin to creatinine ratio (ACR). Albuminuria was measured by immunoturbidimetry and urine creatinine by enzymatic assay. All biochemical tests were performed using reagents and automatic analyzers (MODULAR Analytic, ROCHE Diagnostics, Monza, Italy). Lipids and glucose were measured in serum samples using commercially-available enzyme colorimetric kits (Instrumentation Laboratory, Milan, Italy) and an automatic analyzer (IL 350).

2.4. Assessment of chronic kidney disease

CKD was classified in 6 stages, following the KDIGO 2012 guidelines (KDIGO, 2013). The first 2 stages were defined by ACR ≥ 30 mg/g and either eGFR ≥ 90 mL/min/1.73 m^2 (Stage G1 A2-3) or eGFR 89–60 mL/min/1.73 m^2 (Stage G2 A2-3). More advanced stages were only defined by eGFR values: 59–45 mL/min/1.73 m^2 (Stage G3a); 44–30 mL/min/1.73 m^2 (Stage G3b); 29–15 mL/min/1.73 m^2 (Stage G4); < 15 mL/min/1.73 m^2 (Stage G5). A2 identified subjects with ACR 30–299 mg/g, A3 those with ACR ≥ 300 mg/g. Participants without CKD were those with ACR < 30 mg/g and eGFR ≥ 90 mL/min/1.73 m^2. Awareness of CKD was assessed by administration of a specific questionnaire.

2.5. Geriatric assessment

Cognitive function was assessed by administration of the Folstein's Mini Mental State Examination (MMSE) test, a measure of global cognitive function (Folstein, Folstein, & McHugh, 1975; Magni, Binetti, Bianchetti, Rozzini, & Trabucchi, 1996). The questionnaire was administered in electronic format except for the tasks "write a sentence" and "copy the figure". Results were adjusted for age and education level using Italian normative procedures (Magni et al., 1996). Comprehensive scores ranged from 0 to 30, with higher scores indicating better cognition. Cognitive impairment was defined by MMSE score < 24. Functional disability in performing basic and instrumental activities of daily living (ADLs and IADLs) and mobility limitations was determined by administration of a standardized questionnaire (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963). ADLs disability was defined as self-reported inability or limitation to perform one or more of the following tasks: dress and undress, take a bath or shower, go to the toilette; IADLs disability was defined as self-reported inability or limitation to perform one or more of the following tasks: use of telephone; shopping; light housework. Mobility disability was defined as self-reported inability or limitation to walk 500 m or climb a flight of stairs. Self-rated general health status was assessed by the question “In general, how would you say your health is today?”. Participants were asked to rate their health status on a 0 to 10 scale, with 0 indicating the poorest and 10 the best health status. Self-rated health status was categorized as: excellent (score 8–10), good (score 6–7), poor (score 4–5) and very poor (score ≤ 3).

2.6. Statistical analysis

All analyses were done via Statistical Package for Social Sciences (SPSS) version 22.0 for Windows (SPSS Inc. Chicago, Il, USA). Prevalence and 95% confidence intervals (95% CI) of CKD were calculated in the total sample, by gender, by age and disease stages. Socio-demographic and clinical characteristics of participants are presented by CKD status (yes/no). The Student’s unpaired *t*-test and the χ^2-test were used for comparison of continuous and categorical variables respectively. Bivariate regression analyses were performed to identify age-adjusted associations of socio-demographic and clinical variables with disability. The associations between CKD and domain-specific disability were further analyzed using multivariable logistic regression analyses. Associations were expressed as odds ratios (OR) and 95% CI. Two models were constructed for each independent variable examined. Model 1 was minimally adjusted for age, gender and education. Model 2 also included potentially-confounding clinical variables. Multivariable regression analyses were also performed after exclusion of participants with advanced CKD stages (G4 and G5) to assess whether the association between CKD and disability fully extended to mild-moderate CKD. For all analyses statistical significance was set at two-sided p values at < 0.05.

3. Results

Out of 2622 adults ages ≥ 65 years who participated to the OEC/HES 2008–2012, 2289 underwent evaluation of kidney function. These subjects had comparable age (71.4 ± 4.2 vs 71.3 ± 4.0) and prevalence of CV disease (6.8% vs 6.5%) compared to those for whom evaluation of kidney function was not available (n = 333). 980 subjects were further excluded because they gave no information on functional disability. Thus, the study sample consisted of 1309 participants, age 71.4 ± 4.3 years, 53.8% men. 199 participants were identified as having CKD (15.2%). As shown by Fig. 1, a linear increase of prevalence with age was observed, either for CKD overall and disease stages. Overall CKD prevalence was similar between men and women, whereas a higher prevalence of the first two stages (G1 and G2) was observed in men and a higher prevalence of G3 (A and B) stages was observed in women. Awareness of CKD was poor, with only 11.5% of persons with CKD being aware of the condition. None of CKD participants was on renal replacement treatment, that is dialysis or kidney transplantation. As shown by Table 1, participants with CKD were on average 1.5 years older than those without and, as expected, they had less favorable CV risk profile. Disability in all three functional domains, that is ADLs (8.1% vs 2.1%, p < .001), IADLs (14.6% vs 3.9%) and mobility (17.2% vs 6.5%), and cognitive impairment were significantly more prevalent in CKD participants. Those with CKD were less likely to perceive their health status as satisfactory. As all participants with disability in ADLs were also disabled in ≥ 1 IADLs, disability in ADLs/IADLs was considered as a unique variable. 38.7% of those with mobility limitations were also disabled in ≥ 1 ADLs or IADLs. Table 2 shows variables associated with disability in functional domains by age-adjusted bivariate

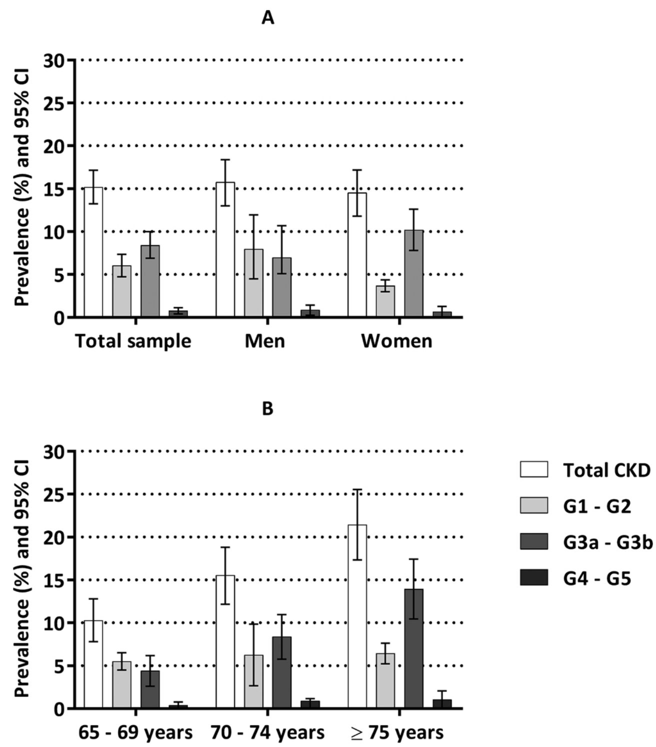

Fig. 1. Crude prevalence estimates and 95% confidence intervals of chronic kidney disease (CKD) by disease stage, gender and age.

regression. Such analysis allowed to identify variables that could potentially affect the association of CKD with disability. Table 3 shows multivariable regression models testing CKD as determinant of disability. After minimal adjustment for age, gender and education, robust associations between CKD and disability in either ADLs/IADLs and mobility were observed. CKD persisted as significant correlate of ADLs/IADLs and mobility disability after further adjustment for ACR ratio ≥ 30 mg/g, CV risk factors and other clinical covariates. Results persisted virtually unchanged when analyses were done after exclusion of participants with CKD stages G4 and G5 (n = 10) (OR for mobility disability = 1.05, 95%CI = 1.01–1.09, p = .014; OR for ADLs/IADLs disability = 1.06, 95%CI = 1.02–1.12, p = .011). Due to co-linearity between prevalent CV disease and statin use, statin use was not considered as covariate.

4. Discussion

Population aging is expected to influence CKD epidemiology, as old age is itself associated with reduced eGFR and with increased prevalence of CV risk factors and established CV diseases, which are known determinants of CKD (Jha et al., 2013). Previous results of CARHES reported a CKD prevalence of 7% in the age range 35–79 years without gender differences, and predominance of early stages (De Nicola et al., 2015). Such prevalence is relatively lower than that reported by other surveys in North Europe, USA, Canada, China and Australia, despite older age and unfavorable CV risk profile of the Italian population (De Nicola et al., 2015). This present study shows a CKD overall prevalence of 15.2%, confirming a predominance of early stages, with men being more likely to exhibit albuminuria. Overall CKD prevalence linearly increased with age, varying from 10.29% at age 65–69 to 21.44% at age ≥ 75 years. Of note, only 11.5% of individuals identified as having CKD were aware of the condition and/or had a documented diagnosis of CKD, strengthening the idea that CKD awareness remains disturbingly low in the general population and in the medical community as well (Jha et al., 2013; Minutolo et al., 2008). Maintaining functional independence is a fundamental aspect of healthy aging (Gopinath et al.,

Table 1
Characteristics of participants by chronic kidney disease status.

	All	CKD	No CKD	
N	1309	199	1110	p
Age (years)	71.4 ± 4.3	72.6 ± 4.2	71.1 ± 4.2	< .001
Men (%)	53.8	55.8	53.4	.592
Education (%)				
< 8 years	25.5	25.1	25.6	.961
≥ 8 years	74.5	74.9	74.4	
Marital status (%)				
Married	81.1	81.0	81.2	.303
Widowed	16.4	18.0	16.1	
Albuminuria (mg/24 h)	24.0 [0 – 2901.4]	135.6 [0-2901.4]	6.0 [0-29.0]	< .001
ACR ≥ 30 mg/g (%)	6.5	42.7	–	
Hypertension (%)	77.4	85.0	76.0	.008
Systolic BP (mmHg)	141.8 ± 18.3	142.7 ± 21.0	141.7 ± 17.8	.478
Diastolic BP (mmHg)	80.6 ± 10.2	80.0 ± 11.4	80.7 ± 10.0	.374
Total cholesterol (mg/dl)	197.3 ± 41.7	190.0 ± 45.1	198.7 ± 41.0	.007
HDL cholesterol (mg/dl)	55.6 ± 14.7	51.3 ± 14.1	56.4 ± 14.7	< .001
Triglycerides (mg/dl)	121.1 ± 58.7	134.7 ± 57.3	118.7 ± 58.6	< .001
Statins use (%)	26.9	37.7	25.0	< .001
Body mass index (Kg/m^2)	28.6 ± 4.7	29.2 ± 5.5	28.5 ± 4.6	.05
Body mass index ≥ 30 (%)	33.4	39.7	32.3	.05
Diabetes (%)	21.3	31.1	19.5	< .001
Current smoking (%)	10.0	11.0	9.8	.684
Anemia (%)	8.7	17.6	7.1	< .001
Prevalent CV disease (%)	6.9	13.0	5.7	< .001
Coronary heart disease	4.7	9.5	3.8	.001
Cerebrovascular disease	2.2	3.5	1.9	.274
COPD (%)	25.4	34.2	23.8	.003
Functional disability (%)				
ADLs	3.0	8.1	2.1	< .001
IADLs	5.6	14.6	3.9	< .001
Mobility	8.2	17.0	6.5	< .001
MMSE (score)[a]	25.2 ± 3.1	24.8 ± 3.5	25.2 ± 3.1	.102
MMSE score < 24 (%)[a]	24.6	32.8	23.1	.005
Self-rated health status (%)				
Excellent	49.3	41.7	49.0	.008
Good	39.3	41.2	39.0	
Poor / very poor	11.4	17.1	12.0	

CKD: chronic kidney disease; ACR: albumin to creatinine ratio; BP: blood pressure; HDL: high density lipoprotein; CV: cardiovascular; COPD: chronic obstructive pulmonary disease; ADLs: basic activities of daily living; IADLs: instrumental activities of daily living; MMSE: Mini-mental State Examination.
[a] MMSE was administered to 1300 participants, 198 with CKD and 1102 without.

2013; Nordberg et al., 2007; Thai et al., 2013). Thus, identification of potentially-modifiable conditions contributing to disability in old age is of eminent importance. The association of ESKD with functional decline is established (Kallenberg et al., 2016; Kurella Tamura et al., 2009), with influential evidence indicating that only one of eight older ESKD patients maintain previous level of function 1-year after initiation of dialysis (Kurella Tamura et al., 2009). Some population-based studies have addressed the relationship between mild-to-moderate CKD and disability in old age (Cavanaugh et al., 2017; Chowdhury et al., 2017; Feng et al., 2012; Fried et al., 2006; Gopinath et al., 2013; König et al., 2018; Smyth et al., 2013; Walker et al., 2013; Wolfgram et al., 2017). Most of authors support an association with physical frailty and diminished mobility (Bowling et al., 2014; Chowdhury et al., 2017; Fried et al., 2006; König et al., 2018; Kurella Tamura et al., 2009; Roshanravan et al., 2015; Walker et al., 2013; Wolfgram et al., 2017), whereas less studied and defined is the relationship with impairment in ADLs and IADLs (Bowling et al., 2011; Cavanaugh et al., 2017; Chowdhury et al., 2017; Feng et al., 2012; König et al., 2018; Smyth et al., 2013; Wolfgram et al., 2017). The Blue Mountains Eye Study (BMES) on a sample of 1952 adults with baseline age ≥ 50 years reported that CKD was cross-sectionally and prospectively associated with greater utilization of community support services, e.g. help from “Meals on Wheels” or home visits from a community nurse. In addition, baseline CKD predicted 10-year incident disability in both ADLs and IADLs (Gopinath et al., 2013). Results from the Health, Aging and Body Composition Study reported a prospective association of CKD to decline in mobility, defined as difficulty in walking one-quarter of a mile or climbing 10 steps, in 2135 community-dwelling older individuals without mobility limitations at baseline (Fried et al., 2006). A recent analysis from the Systolic Blood Pressure Intervention Trial (SPRINT) showed that in a cohort of 2620 hypertensive individuals ages ≥75 years, ACR but not eGFR was associated with functional limitation and reduced gait speed after adjustment for potentially confounding variables, suggesting that albuminuria might represent the underlying mechanism driving the association between CKD and disability in either mobility and usual daily activities (Wolfgram et al., 2017). A relationship between CKD and mobility limitations, i.e. impairments in gait speed and Timed up and Go test, was found in the Berlin Aging Study II, but not with impairment in ADLs (König et al., 2018). An analysis on 357 older subjects who participated to the University of Alabama at Birmingham Study of Aging indicated significantly greater 2-year risk of functional decline in both ADLs and IADLs, with most of decline observed in those with baseline CKD stage ≥ 3B (Bowling et al., 2011). Among 7178 post-menopausal women from the Women's Health Initiative, better kidney function was prospectively associated with survival to age 85, but no effect on disability-free survival, defined as limitations in mobility and ADLs, was observed (Cavanaugh et al., 2017). An analysis on 3499 older subjects in the Cardiovascular Multimorbidity in Primary Care Study (CLARITY) found that even mild reductions in eGFR associate with ADLs and IADLs disability after

Table 2
Age-adjusted associations of socio-demographic and clinical variables with disability. Bivariate regression analysis.

	Mobility disability	ADLs/IADLs disability
	OR 95%CI	OR 95%CI
Age (years, continuous)	**1.06 1.02-1.09*****	**1.08 1.02-1.13*****
Male gender (yes/no)	**0.91 0.88-0.94*****	**1.18 1.09-1.28*****
Married (yes vs no)	0.98 0.94-1.02	0.98 0.92-1.04
Low education (yes/no)	**1.06 1.03-1.09*****	**1.09 1.06-1.13*****
BMI ≥ 30 Kg/m^2 (yes/no)	**1.11 1.08-1.15*****	**1.09 1.04-1.15*****
Current smoking (yes/no)	0.95 0.91-1.00	0.98 0.90-1.06
Total cholesterol (mg/dl, continuous)	1.00 1.00-1.00	1.00 1.00-1.00
HDL cholesterol (mg/dl, continuous)	1.00 0.99-1.01	1.00 0.99-1.00
Triglycerides (mg/dl, continuous)	1.00 1.00-1.00	1.00 1.00-1.00
Systolic BP (mmHg, continuous)	0.99 0.99-1.00	1.00 0.99-1.00
Diastolic BP (mmHg, continuous)	**0.99 0.98-1.00***	**0.99 0.99-1.00***
Hypertension (yes/no)	1.01 0.98-1.05	1.04 0.98-1.10
Diabetes (yes/no)	**1.05 1.01-1.09****	**1.05 1.01-1.10****
Statin use (yes/no)	**1.04 1.00-1.07***	1.01 0.95-1.06
Anemia (yes/no)	**1.05 1.02-1.09***	1.02 0.99-1.06
CV disease (yes/no)	**1.10 1.01-1.20***	**1.08 1.01-1.16***
COPD (yes/no)	**1.06 1.02-1.09***	1.02 0.97-1.08
CKD (yes/no)	**1.10 1.06-1.15*****	**1.09 1.02-1.16****
ACR ≥ 30 mg/g (yes/no)	**1.06 1.02-1.11****	**1.08 1.03-1.14****
Mobility disability (yes/no)	–	**1.18 1.09-1.29*****
ADLs/IADLs disability (yes/no)	**2.07 1.92-2.24*****	–
Cognitive impairment (yes/no)	**1.07 1.03-1.10*****	**1.11 1.07-1.16*****
Poor/very poor self-rated health (yes/no)	**1.31 1.28-1.40*****	**1.22 1.14-1.32*****

OR: odds ratio; CI: confidence intervals; BMI: body mass index; HDL: high density lipoprotein; BP: blood pressure; CV: cardiovascular; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; ACR: albumin to creatinine ratio; ADLs: basic activities of daily living; IADLs: instrumental activities of daily living.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 3
Association between chronic kidney disease and disability. Multiple regression models.

Mobility disability (yes/no)	Model 1		Model 2	
	OR 95%CI	p	OR 95%CI	p
N = 1309	1.10 1.06-1.15	< .001	1.04 1.01-1.08	.016
N = 1299[a]	1.10 1.05-1.17	< .001	1.05 1.01-1.09	.014
ADLs/IADLs disability (yes/no)				
N = 1309	1.06 1.04-1.12	.008	1.05 1.03-1.12	.01
N = 1299[a]	1.06 1.03.1.14	.01	1.06 1.02-1.12	.011

Model 1: adjusted for age (years, continuous), male gender (yes/no) and low education (yes/no).
Model 2: adjusted as in Model 1 + body mass index ≥30 Kg/m^2 (yes/no), diastolic blood pressure (mmHg, continuous), diabetes (yes/no), anemia (yes/no), cardiovascular disease (yes/no), albumin to creatinine ratio ≥ 30 mg/g (yes/no), chronic obstructive pulmonary disease (yes/no), cognitive impairment (yes/no) and poor/very poor self-rated health (yes/no).
[a] Excluded participants with CKD stages G4 and G5 (n = 10).

multiple adjustment for CV and non-CV comorbidities (Smyth et al., 2013). The Singapore Longitudinal Aging Study found decreased levels of eGFR and CKD to be prospectively associated with 4-year decline in IADLs score, whereas ADLs and mobility were not assessed (Feng et al., 2012). Such existing literature is characterized by methodological differences in CKD assessment. In most of studies CKD was only identified by eGFR values (Bowling et al., 2014; Chowdhury et al., 2017; Fried et al., 2006; König et al., 2018; Kurella Tamura et al., 2009; Roshanravan et al., 2015; Walker et al., 2013; Wolfgram et al., 2017), estimated by Modification of Diet in Renal Disease Study (MDRD) equation (Bowling et al., 2011; Chowdhury et al., 2017; Kurella Tamura et al., 2009; Smyth et al., 2013; Wolfgram et al., 2017), or CKD-EPI equation (Cavanaugh et al., 2017), with only one study reporting information on ACR (Wolfgram et al., 2017). One study also assessed kidney function using cystatin C concentrations (Fried et al., 2006). Lack of ACR assessment might lead to under-diagnosis of early forms of CKD (De Nicola et al., 2015; KDIGO, 2013). Furthermore, the KDIGO 2012 guidelines recommend that $eGFR_{creat}$ should be calculated using the 2009 CKD-EPI creatinine equation (KDIGO, 2013). The CKD-EPI equation has been reported to have less bias than the MDRD Study equation, especially at GFR ≥ 60 ml/min/1.73 m^2 (Levey et al., 2009; KDIGO, 2013). A further limitation is that not all studies assessed disability in all of the major domains of function (Bowling et al., 2011; Cavanaugh et al., 2017; Feng et al., 2012; Fried et al., 2006; König et al., 2018). The major finding of our study are the following: 1) CKD significantly correlated with disability in all major domains of function, i.e. ADLs, IADLs and mobility, in a representative population-based sample of older Italian adults; 2) such relationships fully extended to mild-moderate CKD stages; 3) the observed relationships were not completely attributable to prevalent CV risk factors, established CV diseases, pathological ACR, and other potentially confounding variables, e.g. anemia, suggesting that there must be other mechanisms through which CKD may relate to functional impairment in older individuals. Although the cross-sectional design of the present study does not allow to imply causality, an etiological contribution of CKD to functional disability appears biologically plausible for several reasons. Even though we have found that the relationship between CKD and disability might occur independently of CV risk factors and diseases, certainly the greater CV burden of CKD represents an important contributor to disability in such population. CKD is associated with accelerated atherosclerosis and greater occurrence of CV events (De Nicola et al., 2015; Major et al., 2016). The greater prevalence of both clinical and covert cerebrovascular disease and coronary heart disease is expected to lead to greater impairment in everyday functions (Major et al., 2016). Further underlying mechanisms might account for such relationship. Altered homeostasis of phosphate and calcium and secondary hyperparathyroidism have been reported to be associated with fatigability (Karakan, Sezer, & Ozdemir, 2011), and such disorders also play an important role in determining muscle wasting and bone fragility (Molina et al., 2017). Vitamin D deficiency, a common and early finding in CKD, is particularly associated with detrimental effects on muscle quality and function, as well as with reduced bone mineral density (Molina et al., 2017). The central role in determining physical frailty is supported by observation that in CKD patients 25-hydroxyvitamin D levels are reduced in parallel with the severity of muscle symptoms (Molina et al., 2017). An interventional study including both non-dialysis and peritoneal dialysis CKD patients with severe vitamin D deficiency reported significant improvement in physical performance tests by vitamin D supplementation (Taskapan et al., 2011). Other important contributors to muscle impairment are protein-energy malnutrition and protein-energy wasting, that are common in CKD, especially in more advanced stages (Molina et al., 2017; Roshanravan, Gamboa, & Wilund, 2017). Other mechanisms contributing to fatigue and physical frailty in CKD patients are acidosis, chronic low-grade systemic inflammation, uremic toxins accumulation, and muscle resistance to anabolic hormones, e.g. insulin and testosterone (Karakan et al., 2011; Molina et al., 2017; Roshanravan et al., 2017; Taskapan et al., 2011). It is reasonable to assume a causal relationship between all of such aforementioned mechanisms and physical frailty and mobility limitations. Such mechanisms may also exert detrimental effects in time on independence in performing more complex tasks, that are ADLs and IADLs. However, efficiency in performing ADLs and IADLs also requires that the subjects have sufficiently high cognitive performance (Overdorp, Kessels, Claassen, & Oosterman, 2016), because integrity in specific cognitive domains, e.g. problem solving, planning, recall memory, semantic memory, is necessary to independently perform actions such as taking a bath, shopping, or using the telephone. CKD patients have greater the risk of cognitive impairment than non-CKD age-matched controls (Etgen et al., 2012). Although in this study the relationship between CKD and disability was not significantly affected by adjustment for impaired cognitive function (i.e. MMSE < 24), we hypothesize that greater cognitive impairment might be a strong contributor of disability in CKD patients. In particular, we hypothesize that the interplay between impaired physical performance and diminished cognitive function might be greater than the sum of its parts in determining the burden of functional impairment in either mobility, ADLs and IADLs in CKD. Our study has major limitations that are shared with other population-based surveys. We have a single measurement of creatinine and ACR. Correct identification of CKD requires confirmation over at least a 3-month period (KDIGO, 2013). In addition, response rate of 48.4% of those ages ≥ 65 years might introduce a bias, as these subjects might be healthier or sicker than the rest of the population. Furthermore, response rate was lower in southern regions, which might be compatible with the lower educational and economic level of this area. Strengths of the study include its population-based sample of relatively large size, availability of rich confounder information, and a comprehensive assessment of functional limitations. In addition, we believe that assessment of albuminuria, which allowed to identify early stages of disease, is of great epidemiological and practical interest. In fact, albuminuria is an independent predictor of ex novo development of renal function impairment, ESKD, and all-cause and CV mortality (De Nicola et al., 2015; Fox et al., 2012). In conclusion, we report that CKD is significantly associated with functional disability in community-dwelling older adults. The association is independent of CV burden, albuminuria, cognitive impairment and other relevant variables. Importantly, such association fully extends to mild to moderate CKD. Loss of functional independence is among the strongest predictors of adverse health outcomes and mortality in older individuals. In light of mounting evidence suggesting a link between CKD and accelerated functional impairment, nephrologists and CKD guidelines are demanded to make the effort to address the goal of preventing or postponing functional decline in CKD patients. Future research is needed to provide evidence-based recommendations for disability prevention in CKD.

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Conflict of interest

The authors declare that no conflict of interest exists in relation to the present paper.

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