Estimated glomerular filtration rate and functional status among older people: A systematic review


a Italian National Research Center on Aging (INRCA), Ancona, Fermo and Cosenza, Italy
b Department of Internal Medicine, Medical University of Graz, Austria
c Department of Geriatrics, Healthy Ageing Research Centre, Medical University of Lodz, Poland
d Section of Geriatric Medicine, Department of Internal Medicine, Erasmus University Medical Center Rotterdam, The Netherlands
e Department of Geriatric Medicine, Hospital Clinico San Carlos, Madrid, Spain
f The Recanati School for Community Health Professions, Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel
g Maccabi Healthcare Services Southern Region, Israel
h Geriatric Unit, Internal Medicine Department and Nephrology Department, Bellvitge University Hospital – IDIBELL - L'Hospitalet de Llobregat, Barcelona, Spain
i School of Health and Social Studies, Dalarna University, Falun, Sweden
j Department of Medical Sciences, Uppsala University, Sweden
k Division of Family Medicine, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden

ARTICLE INFO

Keywords:
Estimated glomerular filtration rate (eGFR)
Creatinine
Cystatin C
Frailty
Disability

ABSTRACT

Background: The association between chronic kidney disease (CKD) and functional status may change as a function of the equation used to estimate glomerular filtration rate (eGFR). We reviewed the predictive value of different eGFR equations in regard to frailty and disability outcomes.

Methods: We searched Pubmed from inception to March 2018 for studies investigating the association between eGFR and self-reported and/or objective measures of frailty or disability. Cross-sectional and longitudinal studies were separately analysed.

Results: We included 16 studies, one of which reporting both cross-sectional and longitudinal data. Three out of 7 cross-sectional studies compared different eGFR equations in regard to their association with functional status: two studies showed that cystatin C-based, but not creatinine-based eGFR may be associated with hand-grip strength or frailty; another study showed that two different creatinine-based eGFR equations may be similarly associated with disability. Four out of 10 longitudinal studies provided comparative data: two studies reported similar association with disability for different creatinine-based eGFR equations; one study showed that creatinine-based eGFR was not associated with frailty, but a not significant trend for association was observed with cystatin C-based eGFR; one study showed that cystatin C-based but not creatinine-based eGFR may predict incident mobility disability, while both methods may predict gait speed decline. High heterogeneity was observed in regard to confounders included in reviewed studies. None of them included the most recently published equations.

Conclusion: Available data do not support the superiority of one of the eGFR equations in terms of measuring or predicting functional decline.

⁎ Corresponding author.
E-mail addresses: andrea_corsonello@tin.it, a.corsonello@inrca.it (A. Corsonello).
https://doi.org/10.1016/j.ejim.2018.05.030

Received 18 April 2018; Received in revised form 23 May 2018; Accepted 23 May 2018
Available online 21 June 2018

0953-6205/ © 2018 The Authors. Published by Elsevier B.V. on behalf of European Federation of Internal Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).
1. Introduction

Progressive aging of the population in industrialized countries is accompanied by an increase in the prevalence of chronic kidney disease (CKD) [1]. Recently, it has been estimated that the residual lifetime incidence of CKD among US people aged 65 or more is 42%, while the prevalence of CKD among older adults is projected to increase from 13.2% currently to 14.4% in 2020 and 16.7% in 2030 [2]. Thus, CKD has a relevant public health burden in the older population, resulting in an increased risk of end-stage renal disease (ESRD), morbidity and mortality [3].

Besides carrying negative prognostic implications in general and selected diseased populations, including older ones [4–8], CKD also has negative implications in terms of functional limitation and disability, including impaired physical function [9, 10], frailty [11, 12], and sarcopenia [13, 14]. Thus, early identification and management of CKD patients are paramount for planning interventions aimed at slowing the progression of kidney disease and associated comorbidities, but also to delay the onset of its functional complications.

Currently available creatinine-based measures of kidney function are plagued by some degree of inaccuracy and may provide discrepant estimates [15, 16]. Indeed, several studies showed the existence of a U-shaped relationship between creatinine-based eGFR and mortality in frail and older people [17–20]. Additionally, creatinine-based eGFR may systematically underestimate measured GFR at higher levels of kidney function [21], leading to systematic over-diagnosis of CKD in clinically healthy older people.

Efforts have been made to improve the estimating equations, especially in older patients. The Berlin Initiative Study (BIS) equations have been developed and tested in older people and have been proved to be accurate and precise in this population [22]. Nevertheless, the creatinine-based CKD-EPI (CKD-EPIcre) remains the recommended equation also for older people [23], as the role and practical place of BIS equations have not been conclusively defined. Additionally, the potential usefulness of cystatin C-based equations is still to be clarified. Finally, given the mounting evidence about the disabling potential of CKD, individual equations should be tested not only as for their accuracy in predicting measured GFR as reference standard or traditional endpoints (e.g. mortality and end-stage renal disease (ESRD)), but also for their ability in predicting functional outcomes.

Therefore, greater focus should be on the comparison between the recommended CKD-EPIcre and other eGFR equations in predicting functional status. Improving knowledge on this issue may assist in designing CKD-related disability risk assessments and in tailoring interventions for older people. Thus, the purpose of this systematic literature review was to (i) identify all studies reporting on the relationship between eGFR and self-reported or objectively measured functional status among older people, and (ii) describe findings with regard to the difference between data obtained with CKD-EPIcre compared to other eGFR equations.

2. Methods

2.1. Data Sources and Searching

We conducted a systematic literature review in MEDLINE (via PubMed) from inception to March 2018, using the following syntax:

- Reference assessment of kidney function: Creatinine-based CKD-EPI equation
- Participants: studies not including people older than 65 years were excluded, while studies including also people younger than 65 were included for further evaluation.
- Comparator: CKD-EPI to other equations in regards to their association with functional status. However, in order to obtain a comprehensive review, we also included papers investigating only one eGFR equation.
- Outcomes: physical functional status outcomes were considered. Studies including self-reported and/or objectively measured functional status were gathered and analysed.
- Measures for cross-sectional studies: β coefficients for continuous outcomes and ORs for binary outcomes. Measures for longitudinal studies: HRs for survival analyses, β coefficients for continuous outcomes and ORs for binary outcomes. Relative risk for eGFR value < 60 ml/min/1.73 m² was also extracted or calculated from data reported in retrieved longitudinal studies.

The full-text of the articles selected by at least one of the assessors was further evaluated. The same assessors extracted independently information from the selected studies, including study aims, population, eGFR equation(s) used, specification of outcomes and main findings. The list of confounders included in each study was also gathered. Additional details were collected as deemed necessary. Any disagreement was resolved through consensus building in the focus group. Data were grouped according to study design (cross-sectional and cohort studies).

Quality assessment was carried out by the same assessors using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [24], a 14-item tool designed to aid appraisal of internal validity (potential risk of selection, information, or measurement bias, or confounding). Any disagreement in quality assessment was resolved through consensus.

3. Results

Fig. 1 shows information about the process of literature review and the reasons for inclusion and exclusion of identified citations. The electronic search strategy identified a total number of 5796 citations. Of these, 55 were considered as potentially eligible during title/abstract evaluation and included in full-text assessment. Fourteen primary studies [9, 11, 12, 25–35] and one systematic review/meta-analysis [36] were selected. The five studies included in the systematic review by Shen et al. [36] were analysed: one study was excluded because it did not include older people, while two other studies were excluded because kidney function was not estimated by eGFR. The remaining two studies [37, 38] were retrieved, leading to a total of 16 studies included in the analysis. One of the included studies reported both cross-sectional and prospective data [38]. The overall number of subjects included in reviewed studies was 45,381.

The equations used to calculate eGFR mentioned in this systematic
Eligibility

n o i t a c i f i t n e d I

Table 1

In Table 1, the equations for estimating GFR used in reviewed studies are reported. CKD-EPI SCys is given by:

- **MDRD**: 
  \[
  \text{MDRD} = \frac{186.3 \times (\text{Scr})^{1.154} \times \text{(age)}^{-0.203}}{\text{BUN}^{0.742} \times \text{weight}^{0.411} \times \text{(0.993)}^{0.176} \times \text{sex}^{0.041} \times \text{race}^{0.012}}
  \]
  where **sex** = 0 for male, **race** = 0 for black.

- **MDRDcys**: 
  \[
  \text{MDRDcys} = \frac{186.3 \times (\text{Scys})^{1.154} \times \text{(age)}^{-0.203}}{\text{BUN}^{0.742} \times \text{weight}^{0.411} \times \text{(0.993)}^{0.176} \times \text{sex}^{0.041} \times \text{race}^{0.012}}
  \]
  where **sex** = 0 for male, **race** = 0 for black.

- **CKD-EPIcre**: 
  \[
  \text{CKD-EPIcre} = \frac{140 - \text{age} - 0.999 \times \text{Scr} - 0.178 \times \text{BUN} - 0.170 \times \text{serum albumin} + 0.997 \times \text{sex}}{0.762 \times \text{in females}}
  \]
  where **sex** = 0 for male.

- **CRIC**: 
  \[
  \text{CRIC} = \frac{767 \times \text{cystatin C}^{0.61} \times \text{creatinine}^{0.46} \times \text{age}^{0.57}}{0.87 \times \text{if female}}
  \]

- **FAS**: 
  \[
  \text{FAS} = 107.3 \times \text{Scr/0.7} \times \text{age} \times \text{for age} < 20 \text{ years} \times \text{and 20 years} \times \text{for age} \geq 20 \text{ years}
  \]

Studies included in qualitative synthesis (n = 16)

Studies included in qualitative synthesis (meta-analysis) (n = 0)

Studies included in qualitative synthesis (n = 16)

Studies included in qualitative synthesis (n = 0)

Additional records identified through other sources (n = 2)

Records excluded based on title/abstract assessment (n = 5,654)

Fig. 1. PRISMA diagram.

Table 1

Equations for estimating GFR used in reviewed studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Equation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD (40)</td>
<td>[186.3 \times (\text{Scr})^{1.154} \times (\text{age})^{-0.203} \times (\text{BUN})^{0.742} \times (\text{weight})^{0.411} \times (\text{sex})^{0.041} \times (\text{race})^{0.012}]</td>
<td>[29, 31]</td>
</tr>
<tr>
<td>CKD-EPIcre</td>
<td>[140 - \text{age} - 0.999 \times \text{Scr} - 0.178 \times \text{BUN} - 0.170 \times \text{serum albumin} + 0.997 \times \text{sex}]</td>
<td>[32]</td>
</tr>
<tr>
<td>CKD-EPIcys</td>
<td>[144 \times (\text{Scr}^{0.7})^{0.129} \times (0.993)^{0.097}]</td>
<td>[33]</td>
</tr>
<tr>
<td>MDRDcys</td>
<td>[141 \times (\text{Scr}^{0.9})^{0.411} \times (0.993)^{0.097}]</td>
<td>[34]</td>
</tr>
<tr>
<td>CRIC</td>
<td>[133 \times (\text{Scys}/0.8)^{0.499} \times (0.996^{0.097})]</td>
<td>[35]</td>
</tr>
<tr>
<td>FAS</td>
<td>[107.3 \times (\text{Scr/0.7})^{2.40} \times (\text{age})^{0.53}]</td>
<td>[36]</td>
</tr>
</tbody>
</table>

Scr: serum creatinine; BUN: blood urea nitrogen; Scys: serum cystatin C; CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiological Collaboration; CRIC, Chronic Renal Insufficiency Cohort; BIS: Berlin Initiative Study; FAS: Full Age Spectrum.

3.1. Overview of Included cross-sectional studies

Among the 7 cross-sectional studies retrieved (Table 3), only three studies provided a comparison between different eGFR equations in regards to their association with functional status: Plantinga et al. [32] compared CKD-EPIcre and MDRD, while Tufan et al. [33] compared CKD-EPIcre, CKD-EPIcys, and MDRD, and Dalrymple et al. [38] compared CKD-EPIcre and CKD-EPIcys. Other cross-sectional studies used only MDRD [29, 31], CKD-EPIcre [9], or CRIC [37] equations. Six studies involved community-dwelling individuals [29, 31, 33, 37], while only one study included hospitalized patients [9]. The study by Plantinga et al. [32] also included people aged 18–65 years, but only results for subjects aged > 65 were included in the present analysis. The outcomes were self-reported in two out of six studies [29, 32], while one or more objective measures of functional status were used in the remaining five studies [9, 31, 33, 37, 38].

Among comparative studies, Plantinga et al. [32] showed that MDRD-based stage 3–4 CKD is associated with higher prevalence of disability in ability to work, type or amount of work performed, walking or difficulties in basic activity of daily living (BADL), instrumental activities of living (IADL), leisure and social activities, lower extremity mobility, and general physical activity. However, after adjusting for potential confounders most of these associations were no longer significant, so that only disability in type or amount of work and leisure-time activities resulted to be more prevalent in CKD compared to no-CKD subjects. Similarly, a significantly increased adjusted prevalence of disability in leisure-time activities among patients with stage 3–4 CKD was observed when using CKD-EPIcre equation [32]. On the other hand, Tufan et al. showed that CKD-EPIcre was significantly correlated to reduced hand grip strength, while MDRD and CKD-EPIcys were not [33]. Finally, Dalrymple et al. [38] showed that CKD-EPIcys < 45 ml/min/1.73 m² was significantly associated with frailty, while CKD-EPIcre was not.

Non comparative cross-sectional studies provided consistent results across different outcome measures [9, 29, 31, 37]: MDRD was found...
A. Corsonello et al.  


MDRD [11, 28], one used the 6-variables MDRD [25], and three used predicting incident frailty and mobility disability or change in gait regarding their association with functional status. Dalrymple et al. [38].

3.2. Overview of included cohort studies

Among the 10 cohort studies (Table 4), only one study was retrospective, while the remaining nine had a prospective design. Pedone et al. [12] provided a comparison between Cockcroft-Gault (CG) and MDRD, while Bowling et al. [26] compared MDRD and CKD-EPIcre in regard to their association with functional status. Dalrymple et al. [38] and Liu et al. [30] compared the ability of CKD-EPIcre and CKD-EPIcys in predicting incident frailty and mobility disability or change in gait speed, respectively. Among the remaining cohort studies, two used MDRD [11, 28], one used the 6-variables MDRD [25], and three used CKD-EPIcre [27, 34, 35]. Seven out of ten studies involved community-dwelling individuals [11, 12, 26–28, 30, 38], while the remaining three were carried out in the hospital setting [25, 34, 35]. The outcomes were self-reported in five studies [12, 26–28, 30] and objectively measured or rated by study researchers in the remaining ones [11, 25, 34, 35, 38]. The comparative study by Pedone et al. [12] showed that both CG and MDRD equations were able to predict the loss of at least 1 BADI during a 6-years follow-up period among community-dwelling older people. Bowling et al. [26] showed that both CKD-EPIcre and MDRD were similarly associated with incident BADI and IADL dependency during a 2-year follow-up period. At variance, despite the observed increased relative risk for CKD-EPIcys < 60 ml/min/1.73 m², creatinine-based eGFR did not predict incident frailty after adjusting for potential confounders in the study by Dalrymple et al., while a not significant trend for increased risk was observed with CKD-EPIcre [38]. Finally, Liu et al. showed that CKD-EPIcys but not CKD-EPIcre may predict incident mobility disability, while both equations may predict gait speed decline [30].

Non comparative studies showed that MDRD equation could predict IADL and BADI decline, as well as difficulty in walking or climbing stairs [11, 28]. The 6-variable MDRD equation could predict motor, but not total Functional Impairment Measurement (FIM) score at discharge among older patients with hip fracture in the only study with retrospective design [25]. CKD-EPIcre was found associated with IADL and BADI decline, self-reported difficulty in walking or climbing stairs, and gait speed decline in community-dwelling individuals [27, 30]. The relative risk for incident stroke disability was also increased among hospitalized patients with CKD-EPIcre eGFR < 60 ml/min/1.73 m², but such an association was no longer significant in multivariable analysis [34, 35] (Table 4).

None of the cohort studies reported sample size justification. The exposure variable was assessed more than once over time only in the studies by Adusnky et al. [25] and Dalrymple et al. [38]. Relative risk or data for its calculation were available for eight out of ten cohort studies reviewed. Subjects lost to follow up were not reported in five out of eight studies [12, 25, 30, 34, 35] (Table S1). Age, gender, cardiovascular comorbidities and diabetes were the most frequently included

Table 2
Summary of outcomes reported in reviewed studies.

<table>
<thead>
<tr>
<th>Outcome(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported</td>
<td>Self-reported limitation in listed tasks</td>
</tr>
<tr>
<td>Leisure and social activities</td>
<td>Self-reported limitation in listed tasks</td>
</tr>
<tr>
<td>Lower extremity mobility</td>
<td>Self-reported limitation in listed tasks</td>
</tr>
<tr>
<td>General physical activity</td>
<td>Self-reported limitation in listed tasks</td>
</tr>
<tr>
<td>Walking or climbing stairs</td>
<td>Self-reported limitation in listed tasks</td>
</tr>
<tr>
<td>Basic activities of daily living (BADL)</td>
<td>Rating dependency in bathing, dressing, toileting, transferring, continent, eating</td>
</tr>
<tr>
<td>Instrumental activities of daily living (IADL)</td>
<td>Rating dependency in ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, managing medications, managing money</td>
</tr>
<tr>
<td>Short Form-36 (SF36) physical function scale (PFS)</td>
<td>SF36 is a 36-item questionnaire which measures Quality of Life across eight domains, including: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain; general health. The Physical function scale is calculated as average score of items 3 to 12.</td>
</tr>
<tr>
<td>Functional Independence Measurement (FIM)</td>
<td>The FIM is an 18-item, 7-level functional assessment designed to evaluate the amount of assistance required by a person with a disability to perform basic life activities safely and effectively.</td>
</tr>
</tbody>
</table>

Objectively measured or mixed

- **400-m walk time**: Time taken to walk a distance of 400 m
- **Lower extremity performance score**: Modified version of the lower extremity performance test used in the Established Populations for Epidemiologic Studies of the Elderly (EPSESE), including five repeated chair stands, semi-tandem, full tandem, and single-leg standing balance tests, a 6-min walking test to determine usual gait speed, and a narrow walk test of balance.
- **Hand grip strength**: Isokinetic dynamometer
- **Knee extension strength**: Isokinetic dynamometer
- **Walking (gait) speed**: Gait speed in m/s measured on a 4- or 6-m path at usual pace.
- **SPPP [45]**: The short physical performance battery (SPPB) is a group of measures that combines the results of walking speed, chair stand and balance tests.
- **Frailty [47]**: Frailty defined as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss, weakness (handgrip strength), self-reported exhaustion or poor endurance, slowness (walking speed), and low physical activity (kilocalories expended per week).
- **Rankin scale [48]**: Measures the degree of disability or dependence in the daily activities of people with stroke or other neurological disabilities. The 6 levels of rating are: no symptoms; no significant disability despite symptoms; slight disability; moderate disability; moderately severe disability; severe disability; dead.

Associated with 400-m walk time, lower extremity performance, grip strength, knee extension [31]; eGFR decline ≥25% (based on MDRD equation) during the 10 years preceding functional assessment was found associated with impaired SF36™ physical performance scale [29]; CKD-EPIcre was found associated with Short Physical Performance Battery (SPPB) total score, balance and muscle strength sub-scores, but not walking speed [9]; Chronic Renal Insufficiency Cohort (CRIC) equation was found associated with SPPB total score and frailty [37] (Table 3).

Overall, the quality of cross-sectional studies was fair (Table S1). Sample size justification was reported by Lin et al. [29], while Lattanzio et al. [9] and Plantinga et al. [32] reported different levels of kidney function as related to the outcomes. Confounders included age, gender and comorbidities (especially cardiovascular disease, diabetes, cancer, and anemia) in the majority of studies [9, 29, 32, 37]. Results obtained by Odden et al. [31] and Tufto et al. [33] were not adjusted for comorbidity, while the study by Lattanzio et al. [9] also included cognitive status and cumulative comorbidity as potential confounders. Selected studies also adjusted their analysis by serum albumin [9, 33].
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Design and setting</th>
<th>Outcome(s)</th>
<th>eGFR method</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Odden [31]    | 3043| 74  | Cross-sectional    | 400-m walk time Lower extremity performance score Knee extension strength     | MDRD        | Among patients with eGFR < 60 ml/min/1.73 m²:  
- 400-m walking time: $\beta = 19.7$, 95% CI = 9.2–30.1  
- Lower extremity performance: $\beta = -0.26$ to -0.10  
- Knee extension: $\beta = -10.2$, 95% CI = -14.7 to -5.6  
Among patients with eGFR ≥ 60 ml/min/1.73 m²:  
- 400-m walking time: $\beta = -3.5$, 95% CI = -7.0 to 0.0  
- Lower extremity performance: $\beta = 0.04$, 95% CI = 0.02 to 0.07  
- Knee extension: $\beta = 3.8$, 95% CI = 2.2 to 5.5 |
| Lin [29]      | 2544| 67  | Cross-sectional    | SF36 physical function scale (PFS)                                          | MDRD        | Association between former eGFR decline ≥ 25% and actual PFS  
- Linear analysis: $\beta = -3.5$, 95% CI = -5.4, -1.5  
- Logistic regression analysis considering PFS ≤ 65 as outcome variable: OR = 1.37, 95% CI = 1.04 to 1.81 (not significant after adjusting for BMI: OR 1.15; 95% CI 0.90 to 1.47) |
| Plantinga [32]| 16,011| ≥ 65 | Cross-sectional   | Self-reported limitations in: Working, walking, and cognition; BADL; IADL; Leisure and social activities; Lower extremity mobility; General physical activity | MDRD        | Stage 3–4 CKD compared to no CKD Using MDRD:  
- Adjusted prevalence of disability in type or amount of work performed (43.7% (95% CI = 39.0–48.4) vs 39.0% (95% CI = 35.5–42.4), p < .05)  
- Adjusted prevalence of disability in leisure time activities (21.5% (95% CI = 18.5–24.6) vs 17.4% (95% CI = 15.5–19.3), p < .05)  
Using CKD-EPIcre:  
- Adjusted prevalence of disability in leisure time activities (21.7% (95% CI = 18.5–24.9) vs 17.4% (95% CI = 15.5–19.2), p < .05) |
| Lattanzio [9] | 486 | 80.1| Cross-sectional    | SPPB, either global score or its individual components (muscle strength, balance, and walking speed) | CKD-EPIcre  | Linear association between eGFR and:  
- SPPB total score (B = 0.49, 95% CI = 0.18–0.66)  
- Balance (B = 0.30, 95% CI = 0.10–0.49)  
- Muscle strength (B = 0.06, 95% CI = 0.01–0.10)  
- Walking speed (B = -0.04, 95% CI = -0.09–0.11)  
Compared to patients with eGFR > 60:  
- eGFR = 30.0–44.9, adjusted mean difference = 1.28 (95% CI = 2.37–0.18) for SPPB total score, and −0.63 (95% CI = −1.12 to −0.14) for balance score;  
- eGFR ≤ 30, adjusted mean difference = 2.26 (95% CI = −3.66 to −0.93) for total SPPB score, 0.76 (95% CI = 3.80–0.22) for muscle strength score, and −1.03 (95% CI = −1.63 to −0.43) |
| Dalrymple [38]| 4150| ≥ 65| Cross-sectional    | Frailty (slow gait speed, muscle weakness, low physical activity, exhaustion and unintentional weight loss) | CKD-EPIcre  | CKD-EPIcre > 90: reference  
- 76–89 OR = 0.48 (95% CI 0.42–0.73)  
- 60–75 OR = 0.59 (95% CI 0.39–0.89)  
- 45–59 OR = 0.69 (95% CI 0.45–1.07)  
- 15–44 OR = 0.83 (95% CI 0.49–1.41)  
CKD-EPIcre ≤ 90: reference  
- 76–89 OR = 0.77 (95% CI 0.48–1.31)  
- 60–75 OR = 1.05 (95% CI 0.64–1.72)  
- 45–59 OR = 1.47 (95% CI 0.89–2.43)  
- 15–44 OR = 2.44 (95% CI 1.43–4.19)  
For SPPB:  
- eGFR 30–59: $\beta = -0.43$, 95% CI = −0.80 to 0.22  
- eGFR 15–29: $\beta = -0.61$, 95% CI = −1.03 to −0.19  
- eGFR < 15: $\beta = -1.75$, 95% CI = −2.33 to −1.16  
For frailty:  
- eGFR 30–59: OR = 1.45, 95% CI = 1.05–1.99  
- eGFR 15–29: OR = 2.02, 95% CI = 1.29–3.16  
- eGFR < 15: OR = 4.83, 95% CI = 2.60–8.98.  
(continued on next page) |
confounders in cohort studies [11, 12, 28, 30, 34, 35, 38]. Other potential confounders considered in cohort studies were serum albumin [25, 27, 28, 38], hemoglobin [25, 27, 28, 38], lipids [27, 38], smoking habits and alcohol consumption [27, 30, 34, 35]. Few studies also included cognitive status [25, 26, 28], depression [28] and physical activity [28, 30] among potential confounders.

4. Discussion

Our systematic review shows that eGFR is associated with different phenotypes of functional impairment in most of the studies included in the analysis. However, selected differences among studies deserve mention. Indeed, two comparative cross-sectional studies showed that CKD-EPIcre, but not MDRD and/or CKD-EPIcys was associated with hand grip strength or frailty [33, 38]. Additionally, one comparative cohort study showed CKD-EPIcre may not predict incident frailty, while a not significant trend for increased risk could be observed with CKD-EPIcys [38]. Finally, CKD-EPIcre was not associated with incident stroke disability [34, 35]. Thus there is consistent uncertainty, if changes in kidney function estimated with different equations may predict phenotypes of functional decline with different accuracy.

While the potential superiority of cystatin C-based equations in predicting functional status needs to be further investigated in comparative studies, the small evidence currently available suggests that sarcopenia may represent an important confounder in the association between eGFR and functional phenotypes. Indeed, normal or even high eGFR based on a calculation using serum creatinine may at least partly reflect inflammation, frailty and/or muscle loss with consequent reduced creatinine production rather than normal kidney function [53, 54]. This incongruence affirms the need for new approaches to estimate kidney function in elderly individuals. Ideally, a new formula should not only extrapolate age-associated declining muscle mass but also reflect functional decline.

eGFR has been considered a key prognostic and classificatory indicator in public health campaigns, whereas serum creatinine is an unreliable marker of renal function [55]. Equations have been developed by incorporating demographic and clinical variables as surrogates for unmeasured physiological factors, such as creatine generation and tubular secretion, that contribute – apart from filtration function – to serum creatinine concentration [22, 40–42]. Estimating equations seems to be reasonably accurate in detecting changes in kidney function over time [56]. However, the distinctive lack of data comparing the predictive value of different eGFR equation in regard to functional status observed in the present study is a relevant issue because the accuracy in predicting outcomes may change as a function of the equation used. Indeed, disagreement between eGFR equations has been consistently reported [15, 16, 57–60], with age, gender, weight, and study setting representing important sources of discrepancy between equations [15]. Thus, results obtained with different equations may be difficult to interpret. As an example, a U-shaped relationship between eGFR and mortality has been observed by using MDRD [17], CKD-EPIcre [18, 20], and BIScre [61], but not with cystatin C-based CKD-EPI equation [20]. This evidence further suggests that eGFR may not only reflect kidney function, but rather muscle loss, which may contribute to a low serum creatinine concentration [61]. Such hypothesis is also sustained by the observation that both low serum creatinine and low 24 h urine creatinine are associated with adverse outcomes [62], while cystatin C is less influenced by body composition [63]. Nevertheless, only two longitudinal study [30, 38] and two cross-sectional studies [33, 38] compared the predictive value of creatinine- and cystatin C-based eGFR in regard to functional status.

Current evidence suggests that filtration markers other than serum creatinine and not affected by muscle loss (i.e. cystatin C, beta-trace protein and beta2-microglobulin) [64] may better predict negative outcomes, but their usefulness in predicting functional decline is still to be investigated. Despite CKD-EPIcre remains recommended as a reference equation [23], it may not perform better than other equations in predicting outcomes in older populations [58, 65]. The cross-sectional association between MDRD or CKD-EPIcre, and disabilities was no longer significant after adjusting for potential confounders [32]. On the other hand, CKD-EPIcys but not CKD-EPIcre was found cross-sectionally associated with frailty [38]. In cohort studies, CG, MDRD and CKD-EPIcre showed similar associations with incident disability [12, 26]. However, when comparing CKD-EPIcre and CKD-EPIcys in regard to their ability to predict incident frailty or mobility disability, only the latter equation showed a near significant trend for increased risk [30, 38]. Thus, available studies are not sufficient to build a meta-analysis of comparative studies. Additionally, it is worth noting that we could not find any study including the most recent equations addressing the issue of estimating kidney function among older people. The BIS equations have been specifically developed in an older population and published in 2012 [22]. It showed a reduced rate of misclassification of CKD stages [22, 56], which was confirmed in two external validation studies in older patients [66, 67]. In our review, three cross-sectional studies and five longitudinal studies were published after 2012, but none of them included BIS equation for kidney function assessment. Furthermore, the Full Age Spectrum (FAS) equation has been published in 2016, and it has been mathematically obtained by requiring continuity during the pediatric–adult and adult–old age transition to improve validity across the full age spectrum [68]. Thus, it seems sensible to suggest for including BIS and FAS equations in future studies investigating the relationship between kidney function and functional impairment.

The major strengths of the present study are the careful study selection and the assessment of their quality, both of which contribute to provide a reliable overview of the evidence in this research field. Additionally, most of the retrieved studies involve community-dwelling older people, which likely enhance the generalizability of our results. As for limitations, more than one-third of reviewed studies are cross-sectional, which limits the exploration of the causal relationship between eGFR and functional status. Another important limitation is the frequent use of self-reported outcome measures. Indeed, the outcome was self-reported in two out of seven cross-sectional studies, and in five out of ten cohort studies. Finally, a high heterogeneity was observed in confounding variables included in retrieved studies. Future studies are expected to bridge these gaps by using both objective and subjective outcome measures in order to increase the strength of evidence. From this point of view, the Screening for Chronic Kidney Disease among Older People across Europe (SCOPE) project, a large prospective multicenter cohort study, represents an important ongoing effort towards
Table 4
Summary of findings from retrieved cohort studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Design and setting</th>
<th>Outcome(s)</th>
<th>eGFR method</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fried [11]</td>
<td>2135</td>
<td>73.5</td>
<td>Prospective F.U.: Up to 54 months</td>
<td>Difficulty in walking 1/4 mile or</td>
<td>MDRD</td>
<td>Relative risk not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Community-dwelling</td>
<td>climbing 10 steps on two consecutive reports</td>
<td></td>
<td>eGFR &lt; 60: HR = 1.30 (95%CI = 1.08–1.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months apart.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowling [26]</td>
<td>357</td>
<td>77.4</td>
<td>Prospective F.U.: 2 yrs.</td>
<td>BADL decline</td>
<td>MDRD</td>
<td>Using MDRD equation -</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Community-dwelling</td>
<td></td>
<td>CKD-EPIcre</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Using CKD-EPIcre equation -</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adunsky [25]</td>
<td>499</td>
<td>83.6</td>
<td>Retrospective cohort Hospital Hip</td>
<td>FIM at discharge after hospital</td>
<td>6-variables</td>
<td>Relative risk not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fracture patients</td>
<td>rehabilitation</td>
<td>MDRD</td>
<td>eGFR was significantly associated with motor FIM (β = 0.028, p = 0.022) but</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not total FIM (β = 0.072, p = .101).</td>
</tr>
<tr>
<td>Feng [28]</td>
<td>1186</td>
<td>65.6</td>
<td>Prospective F.U.: 4 yrs.</td>
<td>IADL decline (total and cognitive)</td>
<td>MDRD</td>
<td>Relative risk for eGFR &lt; 60 = 2.91, 95%CI = 2.60–3.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Community-dwelling</td>
<td></td>
<td></td>
<td>OR = 1.99, 95%CI = 1.16–3.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IADL cognitive decline</td>
</tr>
<tr>
<td>Pedone [12]</td>
<td>666</td>
<td>73.1</td>
<td>Prospective F.U.: 6 yrs.</td>
<td>Loss of independency in ≥ 1 BADL</td>
<td>CG</td>
<td>Relative risk for CG &lt; 60 = 1.98 (95%CI = 1.11–3.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Community-dwelling</td>
<td></td>
<td>MDRD</td>
<td>HR = 4.40 (95%CI = 2.80–6.94) for CG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relative risk for MDRD &lt; 60 = 1.72 (95%CI = 1.09–2.70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR = 3.19 (95%CI = 2.12–4.79) for MDRD</td>
</tr>
<tr>
<td>Dalrymple [38]</td>
<td>4150</td>
<td>≥65</td>
<td>Prospective Community-dwelling</td>
<td>Frailty (slow gait speed, muscle</td>
<td>CKD-EPIcre</td>
<td>Relative risk for eGFRcre &lt; 60 = 1.30, 95%CI = 1.07–1.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>weakness, low physical activity, exhaustion</td>
<td>CKD-EPIcys</td>
<td>76–89 IRR = 0.60 (95%CI 0.37–0.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>and unintentional weight loss)</td>
<td>≥90: reference</td>
<td>60–75 IRR = 0.86 (95%CI 0.54–1.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45–59 IRR = 0.67 (95%CI 0.40–1.12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15–44 IRR = 1.08 (95%CI 0.58–2.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CKD-EPIcre ≥90: reference</td>
<td>Relative risk for eGFRcre &lt; 60 = 1.55, 95%CI = 1.39–1.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76–89 IRR = 1.51 (95%CI 0.80–2.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60–75 IRR = 1.62 (95%CI 0.88–2.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45–59 IRR = 1.77 (95%CI 0.89–3.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15–44 IRR = 1.87 (95%CI 0.95–3.69)</td>
</tr>
<tr>
<td>Chin [27]</td>
<td>984</td>
<td>≥65</td>
<td>Prospective F.U.: 59.4 ± 6.9 months</td>
<td>IADL decline</td>
<td>CKD-EPIcre</td>
<td>eGFR ≥ 60: reference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Community-dwelling</td>
<td>BADL decline</td>
<td></td>
<td>For IADL decline –</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relative risk for eGFR &lt; 60 = 2.36, 95%CI = 1.63–3.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eGFR 45–59: OR = 1.41, 95%CI = 0.82–2.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eGFR &lt; 45: OR = 3.0, 95%CI = 1.57–5.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For BADL decline –</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relative risk for eGFR &lt; 60 = 2.24, 95%CI = 1.81–2.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eGFR 45–59: OR = 0.64, 95%CI = 0.20–2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eGFR &lt; 45: OR = 2.94, 95%CI = 0.99–8.73</td>
</tr>
</tbody>
</table>

(continued on next page)
Conclusions

Low eGFR is significantly associated with impaired functional status among older people. However, our findings do not allow to draw a definitive conclusion on which eGFR equation may better predict self-reported and/or objectively measured functional decline. Further studies based on longitudinal design and including both self-reported and objective outcome measures, as well as eGFR assessment by equations specifically developed in older people, and cystatin-based ones may be very informative and helpful to define CKD-related disability risk assessment among older people.

Acknowledgments

The Authors are grateful to Drs Antonio Cherubini, Iosief Abraha and Carlos Chiatti for their skillful support.

Declarations of Interest

None.

Competing Interests

All Authors declare to have no competing interests with this manuscript.

Funding

The work reported in this publication was granted by the European Union Horizon 2020 program (Grant Agreement no 634869). Funder had no role in the systematic review.

Authors’ contributions

Andrea Corsonello, Regina Roller-Wirnsberger and Fabrizia Lattanzio conceived the study and participated in manuscript writing and revising.

Andrea Corsonello, Mirko Di Rosa and Paolo Fabbietti carried out literature search.

Gerhard Wirnsberger, Tomasz Kostka, Agnieszka Guligowska, Francesco Mattace-Raso, Lisanne Tap, Pedro Gil, Lara Guardado Fuentes, Ithshak Meltzer, Ilan Yehoshua, Francesc Formiga-Perez, Rafael Moreno-González, Christian Weingart, Ellen Freiberger, Johan Ärnlöv and Axel C. Carlsson participated in manuscript revision and approval.

Appendix A. SCOPE study Investigators

A.1. Coordinating Center

Fabrizia Lattanzio, Italian National Research Center on Aging (INRCA), Ancona, Italy – Principal Investigator.

Andrea Corsonello, Silvia Bustacchini, Silvia Bolognini, Paola D’Ascoli, Raffaella Moresi, Giuseppina Di Stefano, Laura Cassetta, Anna Rita Bonfigli, Roberta Galeazzi, Federica Lenci, Stefano Della Bella, Enrico Bordoni, Mauro Provinciali, Robertina Gigli, Cinzia Giuli, Demetrio Postacchini, Sabrina Garasto, Annalisa Cozza – Italian National Research Center on Aging (INRCA), Ancona, Fermo and Cosenza, Italy – Coordinating staff.

Romano Firmani, Moreno Nacciariiti, Mirko Di Rosa, Paolo Fabbietti – Technical and statistical support.

A.2. Participating Centers

- Department of Internal Medicine, Medical University of Graz, Austria: Gerhard Hubert Wirnsberger, Regina Elisabeth Roller-Wirnsberger.
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.05.030.

References


