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The Modified CKiD Study Estimated GFR Equations for Children and Young Adults Under 25 Years of Age: Performance in a European Multicenter Cohort

To the Editor:

The CKiD creatinine- and cystatin C–based glomerular filtration rate (GFR) estimating equations have recently been modified by incorporation of continuous age- and sex-dependent *k* values to yield less biased internal validation results in chronic kidney disease (CKD) patients aged under 25 years.[1] Here we report an external validation of these CKiDU25 equations in the European Kidney

Table 1. Patient Characteristics of the Cohorts

		Young Adults (N = 1,816)	
	Children With Creatinine and Cystatin C Measured (N = 2,293)	With Creatinine Measured (n = 1,816)	With Cystatin C Measured (n = 348)
Age, y	11.9 (2.3-17.8)	20.0 (18.0-24.6)	18.9 (18.0-24.1)
Female sex	949 (41%)	846 (47%)	144 (41%)
Body mass index, kg/m^2	18 (14-29)	21 (16-31)	22 (15-35)
Body surface area, m^2	1.29 (0.54-2.05)	1.68 (1.29-2.14)	1.73 (1.33-2.36)
Plasma/serum creatinine, μmol/L	52 (19-155)	75 (41-191)	78 (38-196)
Plasma/serum cystatin, mg/L	0.96 (0.61-2.72)	–	0.96 (0.62-2.39)
mGFR, mL/min/1.73 m^2	97 (28-169)	92 (31-141)	91 (30-134)
mGFR <75 mL/min/1.73 m^2	503 (22%)	543 (30%)	95 (27%)

Children defined as aged 2.0-17.9 years; young adults as 18.0-24.9 years. Continuous variables given as median (2.5 and 97.5 percentiles).

Table 2. Bias, Precision, and Accuracy of eGFR Equations in Children and Young Adults

	Creatinine Equations				Cystatin C Equations			
	CKiDU25	CKD-EPI40	EKFC	LMR18	CKiDU25	CAPA	CKD-EPI$_{cys}$	FAS
Children (n = 2,293 for creatinine equations and for cystatin C equations)								
Bias, median	1.3 (0.6; 2.2)	−5.3 (−6.1; −4.5)	−1.6 (−2.4; −0.4)	−4.5 (−5.3; −3.7)	−12.8 (−13.8; −11.8)	−0.6 (−1.7; 0.3)	−2.5 (−3.3; −1.3)	−4.2 (−4.8; −3.4)
Precision, IQR	23.6	23.9	23.4	23.0	24.2	26.9	24.5	23.9
Accuracy, P_{30}	83.8 (82.3; 85.3)	83.9 (82.4; 85.4)	85.2 (83.8; 86.7)	86.3 (84.9; 87.8)	82.6 (81.0; 84.1)	82.0 (80.4; 83.6)	84.3 (82.9; 85.8)	85.9 (84.5; 87.3)
P_{30} difference	Reference	0.1 (−1.4; 1.6)	1.4 (0.1; 2.7)	2.5 (1.1; 3.8)	Reference	−0.6 (−2.4; 1.2)	1.8 (0.1; 3.4)	3.4 (1.9; 4.8)
Young adults (n = 1,816 for creatinine equations and n = 348 for cystatin C equations)								
Bias, median	2.1 (1.3; 2.9)	−1.7 (−2.8; −1.1)	2.5 (1.8; 3.1)	−2.6 (−3.5; −1.5)	−11.5 (−13.6; −8.6)	−0.2 (−1.9; 1.4)	2.0 (−0.6; 4.3)	3.7 (1.7; 5.3)
Precision, IQR	22.3	21.8	21.3	21.5	22.3	23.5	22.2	23.4
Accuracy, P_{30}	82.8 (81.0; 84.5)	85.4 (83.7; 87.0)	84.0 (82.3; 85.7)	86.1 (84.5; 87.7)	83.9 (80.0; 87.8)	84.8 (81.0; 88.5)	83.3 (79.4;87.2)	84.2 (80.4; 88.0)
P_{30} difference	Reference	2.6 (1.2; 4.0)	1.3 (−0.2; 2.7)	3.4 (1.9; 4.8)	Reference	0.9 (−3.6; 5.3)	−0.6 (−5.3; 4.1)	0.3 (−4.5; 5.0)

Differences in P_{30} were evaluated statistically using 95% CIs for paired proportions. Abbreviations and definitions: bias, median error eGFR – mGFR (given with 95% CI); precision, IQR of eGFR – mGFR, expressed in mL/min/1.73 m^2; P_{30}, accuracy expressed in percentage of GFR estimates within ±30% of mGFR (given with 95% CI).; IQR, interquartile range; CKiDU25, Chronic Kidney Disease in Children equation for individuals under 25 years; CKD-EPI40, Chronic Kidney Disease Epidemiology equation based on creatinine values adjusted for individuals under 40 years[3]; EKFC, European Kidney Function Consortium equation[7]; LMR18, Lund-Malmö revised equation based on creatinine values adjusted for individuals under 18 years[6]; CAPA, Caucasian, Asian, Paediatric and Adult equation[4]; CKD-EPIcys, CKD-EPI cystatin C equation; FAS, Full Age Spectrum equation.[5]

Function Consortium (EKFC) multicenter cohort (Table 1, Item S1).[2,3] In this cohort of children and young adults, the vast majority have a measured GFR (mGFR) ≥75 mL/min/1.73 m^2, thus resembling a setting where CKD is screened for. Comparisons were made with 3 creatinine and 3 cystatin C GFR equations (Items S2 and S3) applicable for the entire lifespan starting from 2 years of age,[3-7] including the adult cystatin C–based CKD-EPI equation,[8] shown to have an acceptable performance in children.[2] Plasma and renal clearance methods for mGFR were used as the reference test and plasma/serum creatinine and cystatin C assays were traceable to international standards (Item S1). Comparisons focused on bias, precision, and accuracy, with P_{30} accuracy as the main performance metric.

For creatinine-based equations, the overall distribution of CKiDU25 eGFR followed mGFR more closely at higher levels of kidney function than did eGFRs calculated with CKD-EPI40, EKFC, or LMR18 (Fig S1). On the other hand, $CKiDU25_{cr}$ yielded overestimations exceeding 50 mL/min/1.73 m^2 more often than the other creatinine-based equations (Fig S2). Overall, P_{30} for $CKiDU25_{cr}$ exceeded 80% in both children and young adults. In children, it was not different from CKD-EPI40, but was lower than for EKFC and LMR18 (Table 2). In young adults, it was not different from EKFC but was lower than for CKD-EPI40 and LMR18. In both age groups, the accuracy for $CKiDU25_{cr}$ was lower in male than female patients (Table S1).

For cystatin C–based equations, CKiDU25 exhibited marked underestimation in both children and young adults, and in both male and female patients; the overall distribution of $CKiDU25_{cys}$ eGFR thus deviated markedly from the mGFR distribution (Table S1, Figs S3 and S4). Overall, P_{30} for $CKiDU25_{cys}$ exceeded 80% in children and young adults. In children, it was not different from CAPA, but was lower than for CKD-EPI and FAS (Table 2). In young adults, P_{30} was not different from the other cystatin C equations but results were hampered by statistical imprecision, as reflected by the wide confidence intervals.

For simplicity and to limit the number of comparisons, stratification by the eGFR threshold[9] 75 mL/min/1.73 m^2 was limited to the best-performing equations (Table S2). $CKiDU25_{cr}$ was more accurate than EKFC in patients with lower eGFR, whereas EKFC was more accurate in those with higher eGFR. These findings were consistent irrespective of whether eGFR based on $CKiDU25_{cr}$ or EKFC was used for stratifying. $CKiDU25_{cys}$ was less accurate than FAS, and was negatively biased both below and above the eGFR threshold of 75 mL/min/1.73 m^2.

A study limitation was that 44% and 68% of the children and young adults, respectively, were included in the development cohort for the EKFC equation, and 20% and 4.5% of the children and young adults, respectively, were included in the development cohort for the CAPA equation (see Item S1 for more details). This means that the performance estimates for these equations may be somewhat upwardly biased. Also, it was not possible to stratify results by ethnic origin, as such data were not available; thus, the generalizability of the results to specific population groups is uncertain.

$CKiDU25_{cr}$ is less suitable for automatic laboratory reporting than the height-independent lifespan equations, since height is often missing at the time of analysis. Another drawback is the potential for implausible changes in eGFR at the transition from $CKiDU25_{cr}$ to an adult equation at age 25, which is avoided by using lifespan equations. For $CKiDU25_{cys}$ a particular concern is the observed underestimation in both children and young adults, which may lead to inflation of false-positives when screening for CKD.

In conclusion, if the focus is on overall estimation accuracy in children and young adults in settings where the vast majority can be expected to have near-normal or normal GFR, then our results do not provide strong arguments for using any of the two CKiDU25 equations instead of lifespan equations. However, if the aim is to screen for and detect CKD, then including patient's height and using $CKiDU25_{cr}$ may be advantageous.

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Supplementary Material

Supplementary File (PDF)

Figures S1-S4; Items S1-S3; Tables S1-S2.

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Effect of Aspirin on CKD Progression in Older Adults: Secondary Analysis From the ASPREE Randomized Clinical Trial

To the Editor:

Aspirin is a commonly prescribed and "over-the-counter" therapy in older persons. While its use in the secondary prevention of cardiovascular disease (CVD) events is well established,[1] aspirin is not recommended for primary CVD prevention in adults aged 60 years or older.[2] Low-dose aspirin increases the risk of bleeding in older persons,[3] but whether it has any effect on kidney function is not clear.[4,5]

We sought to investigate the effect of low-dose aspirin on kidney function in healthy older persons enrolled in the Aspirin in Reducing Events in the Elderly (ASPREE) trial (Clinicaltrials.gov identifier, NCT01038583).[6] ASPREE was a large double-blind, randomized, placebo-controlled trial designed to assess whether daily treatment with 100 mg of enteric-coated aspirin could extend the duration of life free of dementia and persistent physical disability.

The aim of the present study was to compare the trajectory of kidney measures, namely estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR), in participants randomized to aspirin treatment or placebo from the trial's commencement until its cessation.

In brief, 19,114 healthy community-dwelling individuals aged ≥70 years (aged ≥65 years for African American and Hispanic participants in the United States) were recruited in Australia and in the United States. Recruitment took place from March 2010 through December 2014, with annual assessments conducted from randomization until the intervention period ended in June 2017 (median follow-up, 4.7 years). Participants were randomly assigned to receive a 100 mg tablet of enteric-coated aspirin or matching placebo daily in double-blind fashion. For this analysis, 7 participants with stage G5 chronic kidney disease[7] were omitted, as were 1,349 participants missing baseline kidney measures. Full details, including the ASPREE trial protocol and main results, are reported in detail elsewhere and in Item S1.[6,8,9]