Research Article

Estimation of Glomerular Filtration Rate Based on Serum Cystatin C versus Creatinine in a Uruguayan Population

Inés Lujambio,1,2 Mariana Sottolano,1,2,3 Leonella Luzardo,1,2,3 Sebastián Robaina,1,2 Nadia Krul,4 Lutgarde Thijs,5 Florencia Carusso,1 Alicia da Rosa,1,2 Ana Carina Ríos,4 Alicia Olascoaga,4 Mariela Garau,6 Liliana Gadola,2,3 Oscar Noboa,1,3 Jan A. Staessen,5,7 and José Boggia1,2,3

1 Unidad de Hipertensión Arterial, Hospital de Clínicas Dr. Manuel Quintela, Universidad de la República, Avenida Italia 2870, 11600 Montevideo, Uruguay
2 Departamento de Fisiopatología, Universidad de la República, Montevideo, Uruguay
3 Centro de Nefrología, Universidad de la República, Montevideo, Uruguay
4 Departamento Laboratorio de Patología Clínica at Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay
5 Department of Cardiovascular Sciences, Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, University of Leuven (KU Leuven), Leuven, Belgium
6 Departamento de Métodos Cuantitativos, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay
7 Department of Epidemiology, Maastricht University, Maastricht, The Netherlands

Correspondence should be addressed to José Boggia; jboggia@hc.edu.uy

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Background. Estimation of glomerular filtration rate (eGFR) from biomarkers has evolved and multiple equations are available to estimate renal function at bedside. Methods. In a random sample of 119 Uruguays (54.5% women; 56.2 years (mean)), we used Bland and Altman’s method and Cohen’s kappa statistic to assess concordance on a continuous or categorical (eGFR < 60 mL/min/1.73 m²) scale between eGFR_{cys} (reference) and eGFR derived from serum creatinine according to the Modification of Diet in Renal Disease (eGFR_{mdrd}) or the Chronic Kidney Disease Epidemiology Collaboration equations (eGFR_{epi}) or from both serum cystatin C and creatinine (eGFR_{mix}). Results. In all participants, eGFR_{mdrd}, eGFR_{epi}, and eGFR_{mix} were, respectively, 9.7, 11.5, and 5.6 mL/min/1.73 m² higher (P < 0.0001) than eGFR_{cys}. The prevalence of eGFR < 60 mL/min/1.73 m² was the highest for eGFR_{cys} (21.8%), intermediate for eGFR_{mix} (11.8%), and the lowest for eGFR_{mdrd} (5.9%) and eGFR_{epi} (3.4%). Using eGFR_{cys} as reference, we found only fair agreement with the equations based on creatinine (Cohen’s kappa statistic 0.15 to 0.23). Conclusion. Using different equations we reached clinically significant differences in the estimation of renal function. eGFR_{cys} provides lower estimates, resulting in higher prevalence of eGFR < 60 mL/min/1.73 m².

1. Introduction

The glomerular filtration rate (GFR) is the most widely used indicator of overall renal function. The GFR can be measured by clearance of an ideal, usually exogenous, filtration marker such as inulin, iothalamate, EDTA, diethylene triamine pentaacetic acid, or iohexol. The clearance of endogenous markers such as creatinine or blood urea nitrogen can overestimate or underestimate the GFR. All these methods have the drawback to be complex and require 24-hour urine collection, which is not always practicable in day-to-day clinical practice. A more pragmatic approach is to estimate GFR from equations based on serum creatinine [1, 2].

More recently, experts proposed cystatin C as an alternative to creatinine [3]. Cystatin C is a nonglycosylated protein with low molecular mass (13.3 kDa) generated by all nucleated cells of the body at a constant rate, is freely filtered by the glomerulus, and is not secreted by renal tubules.
2. Materials and Methods

2.1. Study Population. GEnotipo Fenotipo y Ambiente de la HiperTension en Uruguay (GEFA-HT-UY) is a prospective cohort study started in April 2012 conducted by the Unidad de Hipertensión Arterial, Hospital de Clínicas Dr. Manuel Quintela, Universidad de la República, Montevideo, Uruguay [8]. The Ethics Committee of the University Hospital approved the study protocol and all participants gave informed written consent. The aim of the study is to explore the relation of blood pressure with genetic and environmental factors in a representative Uruguayan population sample. Nuclear families were randomly recruited from the inhabitants of a geographically defined area, the Juana de América housing project, located about 10 km from downtown Montevideo. A nuclear family had to include at least one parent and two siblings. The minimum age was 18, without upper age limit. Family members living at the same address or within a distance of no more than 10 km were eligible. We invited participants by telephone. The participation rate among eligible subjects was 72.7%. In November 2013, 149 people had participated, of whom we excluded 30 from the present analysis, because either cystatin C or creatinine had not been measured \( n = 22 \) or because they had not yet completed the physical examination \( n = 8 \). Thus, the number of participants analysed statistically totalled 119.

2.2. Field Work. The examinations took place at a field centre located within the neighbourhood. Trained observers administered a standardised questionnaire inquiring into each participant’s medical history, smoking and drinking habits, and intake of medications. They measured blood pressure according to the European guidelines. After participants had rested for 5 minutes in the sitting position, the observers obtained five consecutive blood pressure readings (phase V diastolic pressure) to the nearest 2 mm Hg, using mercury sphygmomanometers. Standard cuffs had a 12 × 24 cm inflatable portion, but if upper arm girth exceeded 31 cm, larger cuffs with 15 × 35 cm bladders were used. Pulse pressure is the difference of systolic minus diastolic blood pressure. Mean arterial pressure is diastolic pressure plus one-third of pulse pressure. For analysis, the five blood pressure readings were averaged. Hypertension was an office blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive drugs. The observers measured body height to the nearest 0.5 cm with a pliable measurer and the participant standing against the wall. Participants wore light indoor clothing without shoes for body weight measurements. Body mass index was weight in kilograms divided by square of height in meters. Venous blood samples were obtained after at least 12 hours fasting and were kept at 4 °C and within 2 hours period were analysed for serum levels of cystatin C, creatinine, cholesterol, and glucose. Diabetes mellitus was the use of anti-diabetic drugs or a fasting glucose ≥ 126 mg/dL (7 mmol/L).

2.3. Arterial Phenotypes. After the participants had rested 15 min in the supine position, we recorded during an 8 s period the radial waveforms at the right side by applanation tonometry. We used a high-fidelity SPC-301 micromanometer (Millar Instruments, Houston, TX) interfaced with a computer running SphygmoCor software, version 8.2 (AtCor Medical, West Ryde, New South Wales, Australia). We discarded recordings when the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV. We calibrated the radial pulse wave on the brachial blood pressure [9]. From the radial signal, the SphygmoCor software calculates the aortic pulse wave by means of a validated generalised transfer function [10, 11]. The augmentation index was the ratio of the second to the first peak of the pressure wave expressed as a percentage.

Aortic pulse wave velocity was measured by sequential ECG-gated recordings of the arterial pressure waveform at the carotid and femoral arteries [12]. We measured the distances from the suprasternal notch to the carotid sampling site (distance \( A \)) and from the suprasternal notch to the femoral sampling site (distance \( B \)). Pulse wave travel distance was calculated as distance \( B \) minus distance \( A \). Pulse transit time was the average of 10 consecutive beats. Pulse wave velocity was the distance in meters divided by the transit time in seconds [12].

2.4. Laboratory Methods. Serum cystatin C was measured by a particle-enhanced turbidimetric immunoassay (PETIA), (COBAS, Roche diagnostics, Germany). The latex enhanced particles coated with anticystatin C antibodies in the reagent agglutinate with the human cystatin C in the sample. The degree of the turbidity caused by the aggregate was determined turbidimetrically at 546 nm. This assay has a detection limit of 0.4 mg/L and a coefficient of variation of 1.3%. Serum creatinine was measured by modified kinetic Jaffé methods with the modifications described elsewhere [13, 14]. The detection limit is 0.17 mg/dL and the coefficient of variation was 1.6%. We use a creatinine method that has calibration traceable to an IDMS reference measurement procedure according to present recommendations [15, 16].
2.5. Estimated Glomerular Filtration Rate. We estimated GFR using four equations. First, we computed eGFR from serum cystatin C (eGFR\textsubscript{cys}), as described by Inker and colleagues [3]. Next, we calculated eGFR from serum creatinine according to the IDMS-traceable MDRD Study Equation (MDRD) [17, 18] formula (eGFR\textsubscript{mdrd}) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [2] equation (eGFR\textsubscript{epi}). Finally, as proposed by Inker and colleagues, [3] we also derived eGFR from both serum cystatin C and serum creatinine (eGFR\textsubscript{mix}). All aforementioned estimates [1–3] account for sex and age and with the exception of eGFR\textsubscript{cys}, also consider ethnicity (black versus nonblack). This particular characteristic was irrelevant for our current study as our participants only included Whites mainly of European descent. Table SI in the online data supplement provides detailed information on each formula (see Table SI in Supplementary Material available online at http://dx.doi.org/10.1155/2014/837106). In our current analyses, we compared findings based on the various methods to estimate GFR against eGFR\textsubscript{cys} as the referent method. Low glomerular filtration rate (L-GFR) was an eGFR < 60 mL/min/1.73 m\(^2\) based on a single determination of each biomarker.

2.6. Statistical Analysis. For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute, Cary, NC). First, in exploratory analyses, we assessed the characteristics of participants by fourths of the distribution of eGFR\textsubscript{cys}. For comparison of means and proportions, we applied Student’s 𝑡-test (or ANOVA) and the \(\chi^2\) statistic, respectively. We assessed agreement between paired measurements on a continuous scale by Bland and Altman’s method [19]. To allow comparison with literature data, we also computed correlation coefficients. The National Kidney Foundation KDOQI guideline proposes a threshold of 60 mL/min/1.73 m\(^2\) to diagnose chronic kidney disease [20]. In categorial analyses, we, therefore, also assessed the agreement between equations to dichotomize subjects in L-GFR or not-L-GFR using Cohen’s kappa statistic [21]. A kappa value of 0.20 or less indicates slight agreement, 0.20 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.81 to 1.00 almost perfect agreement. We studied the association between the four definitions of eGFR dichotomized at 60 mL/min/1.73 m\(^2\) in hypertensive and diabetic subjects by McNemar’s test for paired comparisons of proportions. Because of the low frequencies in some cells, we applied exact statistics in two-by-two tables. Finally, we assessed the added capacity of eGFR\textsubscript{cys} to differentiate between normotension versus hypertension or between people with or without diabetes mellitus, using the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) [22, 23]. Statistical significance was an \(\alpha\) level of 0.05.

3. Results

3.1. Characteristics of Participants. The 119 participants included 68 women (57.1%) and 53 (44.5%) hypertensive patients, of whom 35 (66.0%) were on antihypertensive drug treatment. Among 68 women and 51 men, 11 (16.2%) and 5 (9.8%) were smokers; 21 women (30.1%) and 32 men (62.7%) reported intake of alcohol. In smokers, median tobacco use was 10 cigarettes per day (interquartile range, 6–15). In drinkers, the median alcohol consumption was 8 g per day (interquartile range, 4–54). In the whole study population, age (SD) averaged was 56.5 (17.3) years and systolic and diastolic blood pressure 126.5 (19.6) mmHg and 79.6 (11.7) mmHg, respectively. Based on a self-report of the main maternal and paternal background, 37 participants (31.1%) reported a mixture of Caucasian, African, or Native-American, while 82 participants (68.9%) reported coincident Caucasian background.

Among all participants, serum cystatin C and serum creatinine averaged from 0.99 (0.22) mg/L to 0.81 (0.21) mg/dL with no difference between women and men for cystatin C (0.99 versus 1.00 mg/L; \(P = 0.77\)), whereas women had lower serum creatinine than men had (0.72 versus 0.93 mg/dL; \(P < 0.0001\)). In all participants, mean values were 80.0 (23.8) mL/min/1.73 m\(^2\) for eGFR\textsubscript{cys}, 89.7 (22.5) mL/min/1.73 m\(^2\) for eGFR\textsubscript{mdrd}, 91.5 (19.0) mL/min/1.73 m\(^2\) for eGFR\textsubscript{epi}, and 85.6 (20.2) mL/min/1.73 m\(^2\) for eGFR\textsubscript{mix}, with no sex differences (\(P \geq 0.23\)).

Table 1 provides the characteristics of participants by fourths of the distribution of eGFR\textsubscript{cys}, which was used as reference. The prevalence of hypertension (\(P = 0.027\)), age (\(P < 0.0001\)), and systolic blood pressure (\(P = 0.0097\)), but not diastolic blood pressure (\(P = 0.79\)) or mean arterial pressure (\(P = 0.18\)) increased (\(P = 0.027\)) with lower eGFR\textsubscript{cys} category. The central systolic augmentation index and aortic pulse wave velocity also rose (\(P < 0.0001\)) across decreasing fourths of the eGFR\textsubscript{cys} distribution. Trends in eGFR\textsubscript{mdrd}, eGFR\textsubscript{epi}, and eGFR\textsubscript{mix} ran in parallel with the distribution of eGFR\textsubscript{cys}.

3.2. Concordance between Estimates of GFR on a Continuous Scale. Figure 1 shows the Bland and Altman plots comparing eGFR\textsubscript{mdrd}, eGFR\textsubscript{epi}, and eGFR\textsubscript{mix} with eGFR\textsubscript{cys} as the referent method. Table 2 shows the mean deviations of eGFR\textsubscript{mdrd}, eGFR\textsubscript{epi}, and eGFR\textsubscript{mix} from eGFR\textsubscript{cys}. In all participants, eGFR\textsubscript{mdrd}, eGFR\textsubscript{epi}, and eGFR\textsubscript{mix} were, respectively, 9.7, 11.5, and 5.6 mL/min/1.73 m\(^2\) higher than eGFR\textsubscript{cys}. The corresponding ±2 SD intervals expressed in mL/min/1.73 m\(^2\) (Figure 1) ranged from −38.5 to +57.9 for eGFR\textsubscript{mdrd}, −25.5 to +48.5 for eGFR\textsubscript{epi}, and −10.2 to +21.4 for eGFR\textsubscript{mix}, and the corresponding correlation coefficients were −0.04 (\(P = 0.69\)), −0.26 (\(P = 0.0046\)), and −0.40 (\(P < 0.0001\)), respectively. Analyses stratified according to sex, age, normotension versus hypertension, and absence versus presence of diabetes mellitus were consistent with those in all participants (Table 2). Figure 2 shows that across fourths of the distribution of eGFR\textsubscript{cys}, eGFR\textsubscript{mdrd}, eGFR\textsubscript{epi}, and eGFR\textsubscript{mix} were consistently higher (\(P < 0.002\)) than eGFR\textsubscript{cys} except in the highest category of eGFR\textsubscript{cys} (\(P = 0.25\)).

3.3. Concordance between Estimates of GFR on a Categorical Scale. The prevalence of L-GFR was the highest for eGFR\textsubscript{cys},
intermediate for eGFR\textsubscript{mix}, and the lowest for eGFR\textsubscript{mdrd} and eGFR\textsubscript{epi} (Table 3). Using eGFR\textsubscript{cys} as reference, Cohen’s kappa statistic was 0.230 (95% confidence interval [CI], 0.036 to 0.427; \( P = 0.0005 \)) for eGFR\textsubscript{mdrd}, 0.151 (CI, −0.021 to 0.322; \( P = 0.032 \)) for eGFR\textsubscript{epi}, and 0.587 (CI, 0.399 to 0.775; \( P < 0.0001 \)) for eGFR\textsubscript{mix}.

### 3.4. Association between Chronic Kidney Disease and Response Variables

Among 53 hypertensive patients, the prevalence of L-GFR was higher (\( P < 0.0001 \)) if patients were categorized based on eGFR\textsubscript{cys} (17 patients, 32.1%) compared with eGFR\textsubscript{mdrd} (4 patients, 7.5%), eGFR\textsubscript{epi} (3 patients, 5.7%), or eGFR\textsubscript{mix} (8 patients, 15.1%). Among 20 diabetic patients, we observed a similar trend. The prevalence of L-GFR was 8 patients (40.0%) based on eGFR\textsubscript{cys}, 2 patients (10.0%) based on eGFR\textsubscript{mdrd}, 2 patients (10.0%) based on eGFR\textsubscript{epi}, and 3 patients (15%) based on eGFR\textsubscript{mix}. However, the differences with eGFR\textsubscript{cys} did not reach formal statistical significance (\( P \geq 0.075 \)).

Finally, we explored whether an eGFR\textsubscript{cys} below 60 mL/min/1.73 m\(^2\) improved the differentiation between normotension \textit{versus} hypertension or between people without or with diabetes mellitus based on the other estimates of GFR. However, the classification based on eGFR\textsubscript{cys} did not improve IDI (\( P \geq 0.53 \)) or NRI (\( P \geq 0.24 \)) for hypertension or IDI (\( P \geq 0.37 \)) or NRI (\( P \geq 0.24 \)) for diabetes mellitus.

### 4. Discussion

In our current analysis, we compared the performance of the equations based on cystatin C and creatinine to estimate GFR in a Uruguayan population sample. The Uruguayan population has been considered as mainly European descent, with a negligible Native American or African contributions.
However, based on serological and molecular markers, recent studies demonstrate that Native American and African had an important influence in the conformation of the present one [24–26]. The key finding was that eGFR<sub>cys</sub> provides lower estimates in comparison with creatinine based equations (eGFR<sub>mdrd</sub> and eGFR<sub>epi</sub>). Mean eGFR was 80.0, 89.7, 91.5, and 85.6 mL/min/1.73 m<sup>2</sup> for eGFR<sub>cys</sub>, eGFR<sub>mdrd</sub>, eGFR<sub>epi</sub>, and eGFR<sub>mix</sub>, respectively. Thus, the prevalence of L-GFR, was higher when derived from equations involving cystatin C (eGFR<sub>cys</sub> and eGFR<sub>mix</sub>) than when derived from creatinine based equations. The prevalence of L-GFR using eGFR<sub>cys</sub>, eGFR<sub>mdrd</sub>, eGFR<sub>epi</sub>, and eGFR<sub>mix</sub> was 21.8%, 5.9%, 3.4%, and 11.8%, respectively. In categorical analysis, the agreement between cystatin-based (eGFR<sub>cys</sub>) equations and creatinine-based equations (eGFR<sub>mdrd</sub> and eGFR<sub>epi</sub>) to detect eGFR under 60 mL/min/1.73 m<sup>2</sup> was low.

Over the past, many reports highlighted the ability of cystatin C to detect renal disease early in different settings [27–31]. Several researchers reported cystatin C outperforms...
Table 2: Differences between various estimates of GFR with eGFR derived from serum cystatin C as referent method.

| Group              | N   | eGFR_mdrd (mL/min/1.73 m²) | eGFR_epi (mL/min/1.73 m²) | eGFR_mix (mL/min/1.73 m²) |
|--------------------|-----|--------------------------|---------------------------|--------------------------|
| All participants   | 119 | 9.7 (5.3–14.0)           | 11.5 (8.2–14.9)           | 5.6 (4.1–7.0)            |
| Women              | 68  | 11.3 (4.7–17.9)          | 13.7 (8.7–18.6)           | 6.4 (4.3–8.5)            |
| Men                | 51  | 7.5 (2.1–12.9)           | 8.7 (4.3–12.9)            | 4.5 (2.6–6.3)            |
| <60 years          | 57  | 3.2 (−4.1–10.4)          | 9.6 (3.9–15.3)            | 4.5 (2.1–6.8)            |
| ≥60 years          | 62  | 15.6 (10.8–20.5)         | 13.3 (9.4–17.2)           | 6.6 (4.9–8.3)            |
| Hypertension       | 53  | 11.6 (7.3–15.9)          | 12.9 (9.5–16.4)           | 6.3 (4.8–7.7)            |
| No diabetes        | 99  | 9.5 (4.7–14.4)           | 11.9 (8.3–15.7)           | 5.7 (4.1–7.3)            |
| Diabetes           | 20  | 10.3 (−0.7–21.3)         | 9.4 (0.7–18.1)            | 4.9 (1.4–8.4)            |

eGFR_mdrd, eGFR_epi, and eGFR_mix indicate estimated glomerular filtration rate from serum creatinine according to the Modification of Diet in Renal Disease or the Chronic Kidney Disease Epidemiology Collaboration equations, or from both serum cystatin C and creatinine. Differences were computed as eGFR_mdrd, eGFR_epi, or eGFR_mix minus GFR estimated from serum cystatin C (eGFR_cys). The values between brackets were the 95% confidence intervals (mean ± 1.96 standard errors). N indicates the number of participants. Significance of the difference with eGFR_cys: *P ≤ 0.05; †P ≤ 0.01; ‡P ≤ 0.001; §P ≤ 0.0001.

![Figure 2](image-url)  

**Figure 2:** Mean and mean ±1 standard deviation interval of eGFR_cys (●), eGFR_mdrd (■), eGFR_epi (▲), and eGFR_mix (●) across fourths of the distribution of eGFR_cys. The abbreviations eGFR_cys, eGFR_mdrd, eGFR_epi, and eGFR_mix indicate estimated glomerular filtration rate derived from serum cystatin C, from serum creatinine according to the Modification of Diet in Renal Disease or the Chronic Kidney Disease Epidemiology Collaboration equations, or from both serum cystatin C and creatinine. eGFR_mdrd, eGFR_epi, and eGFR_mix were consistently higher (P < 0.0001) than eGFR_cys except in the highest category of eGFR_cys (P = 0.25).

Serum cystatin C was measured using a turbidimetric assay (PETIA). Furthermore, our samples were analysed within one year after blood collection and were processed with calibration each time. We used a validated method [40, 41] and reagents (Tina-quant Cystatin C Gen. 2) standardized to the international reference material ERM-DA471/IFCC, as currently recommended for the use of CKD-EPI equations [3, 7]. Studies of bias (mean difference from reference method) usually overestimated GFR compared to cystatin C.

How to explain the discrepancies between cystatin C and creatinine based equations? We first discarded all potential sources of preanalytical and analytical errors. We analysed creatinine in fresh serum samples and cystatin C in samples that were kept frozen at −80°C. Over a period of 10 years, a decay in cystatin C levels occurs using a particle-enhanced nephelometric assay (PENIA) [40]. Such decay is not observed if one uses the more robust particle-enhanced turbidimetric assay (PETIA). Furthermore, our samples were analysed within one year after blood collection and were processed with calibration each time. We used a validated method [40, 41] and reagents (Tina-quant Cystatin C Gen. 2) standardized to the international reference material ERM-DA471/IFCC, as currently recommended for the use of CKD-EPI equations [3, 7]. Studies of bias (mean difference from reference method) usually overestimated GFR compared to cystatin C.
with the reference when using MDRD (range –1.0 to +3.5) or CKD-EPI (range –0.23 to +4.4) and underestimated when using cystatin C based equations (range –5.7 to –1.2) [38, 42–44]. Fewer studies showed a lower positive bias of cystatin C than CKD-EPI based equations [7, 45].

Several epidemiological studies showed that cystatin C is a better predictor of outcomes in coronary heart disease, acute coronary syndrome, and heart failure, independently of serum creatinine and GFR estimation [6, 46–49]. Furthermore, Peralta et al. demonstrated in a large and ethnically diverse population that subjects with decreased eGFRcys had elevated risk of death, cardiovascular disease, and heart failure and had an elevated risk of kidney failure [50, 51]. In keeping with these studies, our population sample had a high cardiovascular risk profile. We found a higher prevalence of L-GFR among hypertensive subjects (P < 0.001) if they were categorized based on eGFRcys (32.1%) than on eGFRepi (5.7%) with a similar but not significant trend among the few diabetics patients. However, when computing IDI and NRI we did not observe significant differences between the various estimates of eGFR for hypertension or diabetes (P > 0.24). In accordance with previous reports [48, 52–54], the prevalence of hypertension (P = 0.27) and age (P < 0.0001), systolic blood pressure (P < 0.01), cholesterol (P = 0.004), aortic pulse wave velocity (P < 0.0001), and the central augmentation index (P < 0.0001) increased with lower categories of eGFRcys (Table 1).

Our results should be interpreted within the limitation of the study. First, we did not have a reliable “gold standard” due to the variability in 24 h urine collections. Performing inulin or iothalamate clearance implies invasive and tedious procedures that are not suitable for our population study. Second, participants of the study may not be representative of the Uruguayan population, because we randomly sampled a neighbourhood and our participants had a higher cardiovascular risk profile than the general population of Uruguay [55]. Finally, the small sample size of our population is a limiting factor to analyse specific subgroups of participants. However, the number of participants is large enough to describe the difference between eGFR estimating equations.

In conclusion, to our knowledge, this is the first report based on a population from South America comparing to the performance of eGFR equations based on cystatin C and creatinine. We confirm discrepancies in eGFR using equation based on different biomarkers, particularly in the range of GFR under 60 mL/min/1.73 m². Generally, the equation based on cystatin C, compared with creatinine, results in lower eGFR values and, therefore, higher estimates of the prevalence of eGFR below 60 mL/min/1.73 m².

Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

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