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Comparison of the Modification of Diet in Renal Disease Study and Chronic Kidney Disease Epidemiology Collaboration Equations for Detection of Cardiovascular Risk: Tehran Lipid and Glucose Study

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Abstract

Objectives: The study aimed to compare the Modification of Diet in Renal Disease Study (MDRD) and the Epidemiology Collaboration (CKD-EPI) equations for the detection of cardiovascular risk.

Methods: Data of 9,970 Tehranian participants aged $\geq$ 20 years were analyzed. The prevalence of cardiovascular disease (CVD), its risk factors, and 10-year atherosclerotic cardiovascular disease (ASCVD) risk were compared across the categories of glomerular filtration rate based on the MDRD and CKD-EPI equations. Chronic kidney disease (CKD) was defined as the estimated Glomerular Filtration Rate (eGFR) $<$ 60 mL/min/1.73 m^2 according to each equation.

Results: The prevalence of CKD weighted to the 2016 Tehranian urban population was 11.0% (95% confidence interval: 10.3 - 11.6) and 9.7% (9.1 - 10.2) according to the MDRD and CKD-EPI equations, respectively. Besides, 8.3% and 1.5% of the participants with CKD_{MDRD} and non-CKD_{MDRD} were reclassified to non-$CKD_{CKD-EPI}$ and $CKD_{CKD-EPI}$ categories, respectively. Participants with $CKD_{CKD-EPI}$ but without CKD_{MDRD} were more likely to be male and older, and more frequently had diabetes, hypertension, dyslipidemia, and CVD, when compared to those without CKD according to both equations; they were also more likely to be male, older, and smokers, and had less dyslipidemia and more CVD, when compared to those with CKD by using both equations. In multivariate logistic regression analysis, compared to CKD_{MDRD}, the odds of $CKD_{CKD-EPI}$ were significantly higher for older age and lower for the female gender.

Conclusions: Compared to MDRD, the CKD-EPI equation provides more appropriate detection of cardiovascular risk, which is caused by the reclassification of older individuals and fewer females into lower eGFR categories.

Keywords: Chronic Kidney Disease, Glomerular Filtration Rate, MDRD Equation, CKD-EPI Equation, Cardiovascular Cardiovascular Disease

1. Background

Serum creatinine (Cr) is most commonly used to quantify the glomerular filtration rate (GFR) and is considered a classic kidney function indicator (1). Decreased GFR has been regarded as an independent risk factor for cardiovascular disease (CVD) morbidity and mortality (2). In 2013, a GFR of $<$ 60 ml/min/1.73 m^2 contributed to nearly 4% of all deaths and 18.7 million cardiovascular DALYs worldwide (3). Moreover, the presence of cardiovascular risk factors confers higher CVD mortality and morbidity in patients with decreased GFR (4, 5).

The Modification of Diet in Renal Disease Study (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are widely used in clinical laboratories for the estimation of GFR and reporting the prevalence of chronic kidney disease (CKD) based on serum Cr concentrations. The MDRD equation was developed in patients with CKD, and its use in clinical and public health practice is limited by the systematic underestimation of GFR in populations with normal or near-normal kidney function and overestimation of CKD prevalence. The CKD-EPI equation has been developed to provide more reliable GFR estimations and improve the precision and bias of the MDRD equation, especially in individuals with higher levels of measured GFR; thus, it can have important implications for clinical decision-making in patients with de-

creased kidney function (6, 7).

The burden of CVD, as the leading cause of premature mortality in Iran and the Middle East, is high and still increasing, with larger trends than those in America, Europe, and Eastern Asia (8). A meta-analysis of studies mainly conducted in western and eastern Asian countries has indicated that the CKD-EPI equation predicts all-cause and cardiovascular mortality and end-stage renal disease (ESRD), more accurately than the MDRD equation (9). However, since both of these equations were derived from large North American populations and comprise coefficients adjusted for the African American ethnicity (7, 10), there are still concerns that they may not perform similarly in different ethnicities. This is while experimental evidence to support these results being applicable across the middle eastern populations is lacking.

2. Objectives

The purpose of this study was to compare the MDRD and CKD-EPI equations for the detection of CVD and cardiovascular risk factors in a large sample of the general Tehranian adult population.

3. Methods

3.1. Study Population

The Tehran Lipid and Glucose Study (TLGS) is an observational population-based cohort study being launched since 1999 to evaluate the incidence of cardiovascular outcomes and their risk factors among a representative sample of the general Tehranian population. The aims and designs of TLGS have been described previously (11). The participants were recruited by a multistage cluster random sampling technique from the urban district 13 of Tehran in the first phase (1999 - 2001) and the second phase (2002 - 2005). The follow-up assessments were performed in subsequent surveys at approximately 3.6-year intervals. For the current study, from a total of 11,420 participants in the sixth (2016 - 2018) TLGS phase, 10,092 adults aged $\geq$ 20 years were initially selected, and 122 were excluded due to missing data. All procedures performed in studies involving human participants followed the ethical standards of the Human Research Review Committee of the Endocrine Research Center, Shahid Beheshti University, Tehran, Iran, and the 1964 Helsinki declaration and its later amendments, with approval from the National Research Council of the Islamic Republic of Iran (No. 121).

3.2. Clinical and Laboratory Measurements

Data on age, gender, medical history, medication (antihypertensive, lipid-lowering, and antidiabetic agents), and smoking status were collected by trained interviewers using a pretested questionnaire. The protocol for the CVD outcome data collection has been described in detail elsewhere (12). Height was measured barefoot using a stadiometer. Waist circumference (WC) was measured at the level of umbilicus with minimal clothing, using a tape with an accuracy of 1 mm. Weight was measured using digital scales and recorded to the nearest 100 g. Two measurements of systolic and diastolic blood pressures were done from the right arms of participants after 15 minutes of resting in the supine position. The laboratory methods of TLGS have been described in detail elsewhere (11). Laboratory measurements were done at the TLGS research laboratory on the same day of sampling. Plasma Cr concentrations were assessed by the standard colorimetric Jaffe_Kinetic reaction method (Pars Azmon Inc., Iran; with intra- and inter-assay coefficients of variation of 2.5% and 1.9%, respectively, and sensitivity of 0.2 mg/dL). The assay range was between 18 and 1330 μmol/L (0.2 - 15 mg/dL). The reference intervals according to the manufacturer's recommendations were 80 - 115 μmol (0.9 - 1.3 mg/dL) and 53 - 97 μmol (0.6 - 1.1 mg/dL) in men and women, respectively.

3.3. Definitions

We calculated the estimated GFR (eGFR) in ml/min/1.73 m^2 using the four-variable MDRD equation (13) and the CKD-EPI equation (7), as follows:

$$MDRD\,eGFR = 186.3 \times (serum\,Cr)^{-1.154} \times age^{-0.203} \times (0.742\,if\ female) \times (1.212\,if\ African-American)$$

$$CKD-EPI\,eGFR = 141 \times min\left(serum\frac{Cr}{k}or\,1\right)^{\alpha} \times max\left(serum\frac{Cr}{k}or\,1\right)^{-1.209} \times 0.993^{age} \times (1.018\,if\ female)$$

in which *k* is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of serum Cr/k or 1, and max indicates the maximum of serum Cr/k or 1.

Besides, CKD was defined as eGFR < 60 mL/min/1.73 m^2 according to each equation. The body mass index (BMI) was classified into three categories of < 25, 25 - 29.9, and $\geq$ 30 kg/m^2. Diabetes mellitus (DM) was defined based on the 2016 guideline of the American Diabetes Association

as fasting plasma glucose $\geq$ 126 mg/dL, 2-h post-challenge plasma glucose $\geq$ 200 mg/dL, or the use of any anti-hyperglycemic medications (14). Hypertension was defined as blood pressure of $\geq$ 140/90 mmHg, a self-reported history of hypertension, or usage of anti-hypertensive agents (15). Dyslipidemia was defined as serum triglyceride of $\geq$ 200 mg/dL, TC of $\geq$ 240 mg/dL, or taking any lipid-lowering medications (16). Regarding smoking status, participants were placed into two groups of 1) current smokers, referring to those with a daily or occasional use of any tobacco products at the time of examination, and 2) non-smokers, including quitters and those who have never smoked. Moreover, CVD was defined as any coronary heart disease (CHD) or stroke (a new neurological deficit that lasted $\geq$ 24 h), where CHD was regarded as present if cases had definite myocardial infarction according to diagnostic electrocardiographic results and biomarkers; probable myocardial infarction, positive electrocardiographic findings plus cardiac symptoms or signs plus missing biomarkers or positive electrocardiographic findings plus equivocal biomarkers; or proven CHD by angiography. The 10-year risk of atherosclerotic cardiovascular disease (ASCVD) was defined according to the guidelines of the American College of Cardiology/American Heart Association and estimated in subjects aged 40 to 79 years (17).

3.4. Statistical Methods

Continuous variables, all with normal distribution, were expressed as mean $\pm$ standard deviation (SD), and categorical variables were expressed as percentages. To reduce selection bias, the prevalence of CKD was weighted directly to the characteristics of the urban population of Tehran (18) based on the 2016 national Iranian census. For this, a propensity score, the estimated probability of a participant being followed in the study, was computed for each participant using maximum likelihood logistic regression analysis based on all baseline measures including age, sex, education level, systolic and diastolic blood pressure, FPG, TG, HDL, WC, BMI, intervention, family history of diabetes, and CVD as exposures in a logistic model, with participation in the follow-up as the outcome. The characteristics of the study participants were compared between those with and without CKD, using Student's t-test or chi-square test for continuous and categorical variables, respectively. All the participants were then categorized into four subgroups of CKD, according to each, both, or neither of the MDRD and the CKD-EPI equations, using the 2 $\times$ 2 cross-tabulation. Comparisons across the subgroups were performed using the one-way analysis of variance with the post hoc Bonferroni multiple-comparison test for continuous variables. The chi-square tests were used for the comparison of categorical variables. Multivariate logistic regression models, expressed as odds ratios (OR) and 95% confidence intervals (CIs), were used to explore the association of clinical characteristics with CKD_{MDRD} and $CKD_{CKD\text{-}EPI}$, separately. SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA) was used to conduct the analysis. A two-tailed p-value of $\leq$ 0.05 was considered significant in conjunction with all statistical tests.

4. Results

A total of 9,970 participants were enrolled in this study, of whom 4,399 (44.1%) were males. The mean age was 48.8 $\pm$ 16.6 years. The mean serum creatinine was 1.1 $\pm$ 0.2 mg/dl. The mean $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI}$ values were 76.3 $\pm$ 13.8 and 80.5 $\pm$ 16.1 mL/min/1.73 m^2, respectively. The weighted prevalence (95% CI) of CKD_{MDRD} and $CKD_{CKD\text{-}EPI}$ was 11.0% (10.3 - 11.6) and 9.7% (9.1 - 10.2), respectively. The prevalence of DM, hypertension, and dyslipidemia was 18.4%, 26.7%, and 47.0%, respectively; and CVD was detected in 711 (7.1%) of the total study population. The mean ACC/AHA 10-year ASCVD risk score among participants aged 40 - 79 years was 5.4 $\pm$ 7.3.

Table 1 shows the eGFR classification of study participants based on the MDRD and CKD-EPI equations. From the classification of the MDRD equation, 830 (8.3%) subjects were reclassified into a higher eGFR category and 182 (1.8%) subjects into a lower eGFR category by the CKD-EPI equation; 152 (1.5%) of the study participants had $CKD_{CKD\text{-}EPI}$ but not CKD_{MDRD}, and 347 (3.5%) had CKD_{MDRD} but not $CKD_{CKD\text{-}EPI}$.

In bivariate analysis, older age, female gender, higher WC and BMI, having DM, hypertension, dyslipidemia, and CVD, and not being currently a smoker were significantly associated with CKD according to both equations. Besides, CVD associated with CKD was 16.3% and 18.6% using the MDRD and CKD-EPI equations, respectively. Among participants aged 40 to 79 years, subjects with CKD, according to both equations, had significantly higher mean ACC/AHA 10-year ASCVD risk scores than those without CKD (Table 2).

According to Table 3, participants with $CKD_{CKD\text{-}EPI}$ but without CKD_{MDRD} tended to be male and older, and more frequently had diabetes, hypertension, dyslipidemia, and CVD when compared to those without CKD based on either equation; and were more likely to be male, older, and current smokers and have more CVD but less dyslipidemia when compared to those with CKD_{MDRD} and

Table 1. Distribution of eGFR Categories Defined by the MDRD and CKD-EPI Equations [a]

MDRD eGFR, mL/min/1.73 m^2	CKD-EPI eGFR, mL/min/1.73 m^2				Total
	< 30	30 - 59	60 - 89	≥ 90	
< 30	29 (0.3)	0 (0)	0 (0)	0 (0)	29 (0.3)
30 - 59	26 (0.3)	2,268 (22.7)	347 (3.5)	0 (0)	2,641 (26.5)
60 - 89	0 (0)	152 (1.5)	6,340 (63.6)	483 (4.8)	6,975 (70.0)
≥ 90	0 (0)	0 (0)	5 (0)	320 (3.2)	325 (3.3)
Total	55 (0.5)	2,420 (24.3)	6,692 (67.1)	803 (8.0)	9,970 (100.0)

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration.
[a] Values are presented as No. (%).

Table 2. Characteristics of Study Participants with and without Chronic Kidney Disease Defined Using MDRD and CKD-EPI Equations

	Total	$eGFR_{MDRD}$, mL/min/1.73 m^2		P Value	$eGFR_{CKD-EPI}$, mL/min/1.73 m^2		P Value
		Non-CKD	CKD		Non-CKD	CKD	
Total, No. (%)	9970	7300 (73.2)	2670 (26.8)	< 0.001	7495 (75.2)	2475 (24.8)	< 0.001
Females, No. (%)	5571 (55.9)	3711 (50.8)	1860 (69.7)	< 0.001	3995 (53.3)	1576 (63.7)	< 0.001
Mean age, y	48.8 ± 16.6	43.8 ± 14.7	62.6 ± 13.4	<0.001	43.2 ± 13.8	65.9 ± 11.9	< 0.001
Age categories, No. (%)				<0.001			< 0.001
20 - 39 years	3366 (33.8)	3227 (44.2)	139 (5.2)		3325 (44.4)	41 (1.7)	
40 - 59 years	3866 (38.8)	3020 (41.4)	846 (31.7)		3180 (42.4)	686 (27.7)	
60 - 69 years	1461 (14.7)	624 (8.5)	837 (31.3)		695 (9.3)	766 (30.9)	
≥ 70 years	1277 (12.8)	429 (5.9)	848 (31.8)		295 (3.9)	982 (39.7)	
Mean WC, cm	94.3 ± 12.3	93.1 ± 12.3	98.0 ± 11.2	< 0.001	93.1 ± 12.3	98.4 ± 11.0	< 0.001
Mean BMI, kg/m^2	28.0 ± 5.1	27.5 ± 5.0	29.3 ± 5.0	< 0.001	27.6 ± 5.0	29.1 ± 4.9	< 0.001
BMI categories, No. (%)				< 0.001			< 0.001
< 25 kg/m2	2740 (28.6)	2301 (32.4)	439 (17.9)		2321 (31.7)	419 (18.7)	
25 - 29.9 kg/m^2	3920 (41.0)	2878 (40.5)	1042 (42.5)		2965 (40.5)	955 (42.6)	
≥ 30 kg/m^2	2906 (30.4)	1933 (27.2)	973 (39.6)		2040 (27.8)	866 (38.7)	
DM, No. (%)	1587 (18.4)	834 (13.2)	753 (32.9)	< 0.001	831 (12.7)	756 (36.0)	< 0.001
Hypertension, No. (%)	2644 (26.7)	1327 (18.3)	1317 (49.6)	< 0.001	1308 (17.6)	1336 (54.3)	< 0.001
Dyslipidemia, No. (%)	4677 (47.0)	3068 (42.1)	1609 (60.4)	< 0.001	3136 (41.9)	1541 (62.5)	< 0.001
Currently smoking, No. (%)	1282 (13.0)	1123 (15.5)	159 (6.0)	< 0.001	1133 (15.2)	149 (6.1)	< 0.001
CVD, No. (%)	711 (7.1)	276 (3.8)	435 (16.3)	< 0.001	250 (3.3)	461 (18.6)	< 0.001
10-year ASCVD risk, %	5.4 ± 7.3	4.2 ± 5.9	7.7 ± 9.0	< 0.001	3.7 ± 5.2	8.9 ± 9.5	< 0.001
Serum Cr, mg/dL	1.10 ± 0.22	1.05 ± 0.15	1.25 ± 0.31	< 0.001	1.05 ± 0.15	1.26 ± 0.32	< 0.001
Mean MDRD eGFR	67.03 12.25	72.35 ± 9.01	52.49 ± 7.04	< 0.001	71.92 ± 9.26	52.24 ± 7.35	< 0.001
Mean CKD-EPI eGFR	69.65 14.75	76.07 ± 10.87	52.10 ± 8.32	< 0.001	75.77 ± 10.85	51.11 ± 7.92	< 0.001

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; BMI, body mass index; WC, waist circumference; DM, diabetes mellitus; CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; Cr, creatinine.

$CKD_{CKD\text{-}EPI}$. On the other side, 347 (3.5%) subjects with CKD_{MDRD} but without $CKD_{CKD\text{-}EPI}$ were more likely to be female and younger and had a lower prevalence of diabetes, hypertension, dyslipidemia, and CVD when compared to those with CKD according to both equations, and more likely to be female and current smokers when compared to those without CKD based on either equation. Participants with $CKD_{CKD\text{-}EPI}$ but without CKD_{MDRD} and those with CKD_{MDRD} but without $CKD_{CKD\text{-}EPI}$ presented the highest and the lowest 10-year ASCVD risks across the study subgroups, respectively.

In multivariate logistic regression analysis, ORs of CKD_{MDRD} and $CKD_{CKD\text{-}EPI}$ were statistically significant for older age, female gender, higher BMI, hypertension, dyslipidemia, and CVD. Older age and female gender were the only factors with significantly different odds between the MDRD and CKD-EPI equations (Table 4).

5. Discussion

The primary findings of this study were that among the general Tehranian adult population, older individuals, males, and those with higher rates of CVD and cardiovascular risk factors were more frequently classified to have CKD based on the CKD-EPI equation compared to the MDRD equation. These findings were in line with those observed in a multi-ethnic meta-analysis of populations from America, Europe, and Eastern Asia. In the mentioned studies, subjects reclassified to non-$CKD_{CKD\text{-}EPI}$ were younger, more likely to be female, and had lower rates of DM and hypertension, while subjects who were reclassified to $CKD_{CKD\text{-}EPI}$ were much older as compared to those who remained in the same eGFR categories according to both equations. Moreover, the reclassification of individuals to $CKD_{CKD\text{-}EPI}$ categories from the MDRD equation provided a more accurate prediction of cardiovascular mortality, even after adjustment for multiple potential confounders (9).

While CVD is preventable and treatable in patients with CKD, these patients are more likely to die from CVD than to develop ESRD (19). Both CVD and CKD have become important health problems in Iran, associated with alarming decreases in longevity and quality of life over the previous decades (20, 21). In 2015, Iran was among the countries with the greatest burden of CVD in the world, with an overall prevalence of 9% and one million DALYs, accounting for 46% of all deaths (21). Likewise, in 2017, the prevalence of CKD was estimated to be 8.6% and 5.8% among Iranian males and females, respectively, which were higher than the global averages (22). Together, these data imply the importance of identifying CKD patients and appropriate allocation of health-care resources.

In this study, we observed that the CKD-EPI equation categorized participants more appropriately respecting their 10-year risk of developing ASCVD events than did the MDRD equation. In Italy, using the UK Prospective Diabetes Study 10-year CHD risk score among patients with type 2 DM and without a previous CVD event, subjects with $CKD_{CKD\text{-}EPI}$ had significantly higher 10-year CHD risks when compared to those with CKD by only the MDRD and both of the equations (23). Likewise, in a general Korean population with a rather high average eGFR of 96.8 ml/min/1.73 m^2, with only 2.6% of the participants having CKD, reclassification by the CKD-EPI equation improved the 10-year Framingham CVD risk prediction in all GFR categories (24).

The presence of CKD is associated with the increased risk of CVD in community-based populations with and without preexisting CVD. Moreover, the level of kidney function is now recognized as an independent risk factor for the development of non-fatal and fatal CVD events in the general population (25-27). The increased risk of CVD in patients with CKD is not only due to the high prevalence of traditional risk factors, including obesity, DM, and hypertension but also independently because of atherogenic lipid profile and low-grade inflammation, attributed to excessive oxidative stress and accumulation of toxins due to impaired kidney function; moreover, increased activity of the renin-angiotensin system, and decreased bioavailability of nitric oxide, which suggests a possible mechanism for coronary endothelial dysfunction in early stages of CKD (28).

We demonstrated by multivariate logistic analysis that the better performance of the CKD-EPI equation was independently and substantially caused by the reclassification of older individuals and fewer females into $CKD_{CKD\text{-}EPI}$. The GFR decreases with aging, and decreased GFR is an independent risk factor for CVD morbidity and mortality in older adults (29). In addition, in the general population, the female gender is associated with a lower cardiovascular risk across all GFR levels (30, 31). Hence, this finding would be another endorsement of the superior performance of CKD-EPI over the MDRD equation. Similarly, in a representative sample of 11,247 Australians, the reclassification of subjects with CKD_{MDRD} into the category of non-$CKD_{CKD\text{-}EPI}$ was associated with a significant improvement in 10-year Framingham CVD risk score, only for those aged over 65 years, but with no improvement in younger age groups (32). In a study of 9,308 adults aged $\geq$ 50 years, 0% and 77.7% of their population reclassified

Table 3. Characteristics of Study Participants with Chronic Kidney Disease Based on Each, Neither, or Both of MDRD and CKD-EPI Equations [a]

Variables	$CKD_{CKD\text{-}EPI}$ and CKD_{MDRD}	Non-$CKD_{CKD\text{-}EPI}$ and non-CKD_{MDRD}	Non-$CKD_{CKD\text{-}EPI}$ and CKD_{MDRD}	$CKD_{CKD\text{-}EPI}$ and non-CKD_{MDRD}
No. (%)	2323 (23.3)	7148 (71.7)	347 (3.5)	152 (1.5)
Females	67.3	51.7	85.6 [b, c]	8.6 [b,c]
Age, y	65.2 ± 11.8	43.1 ± 14.0	44.8 ± 9.5 [b]	77.0 ± 8.1 [b,c]
Age categories				
20 - 39 years	1.8	45.1	28.2 [b,c]	0.0 [b,c]
40 - 59 years	28.8	42.0	51.3 [b,c]	11.8 [b,c]
60 - 69 years	33.0	8.7	20.5 [b,c]	0.0 [b,c]
≥ 70 years	36.5	4.1	0.0 [b,c]	88.2 [b,c]
BMI, kg/m²	29.3 ± 4.9	27.5 ± 5.0	29.3 ± 5.1 [c]	26.5 ± 4.1 [b]
WC, cm	98.6 ± 11.0	93.0 ± 12.4	94.6 ± 11.6 [b]	96.0 ± 10.4 [c]
DM	36.0	12.7	12.9 [b]	36.1 [c]
Hypertension	54.1	17.4	19.9 [b]	57.9 [c]
Dyslipidemia	63.2	41.9	42.4 [b]	52.0 [b,c]
Currently smoking	5.7	15.6	8.1 [b,c]	12.1 [b,c]
CVD	18.2	3.3	3.7 a	25.7 [b,c]
10-year ASCVD risk score	8.4 ± 9.2	3.9 ± 5.3	1.6 ± 2.2 [b,c]	18.9 ± 10.0 [b,c]
Serum Cr, mg/dL	1.3 ± 0.3	1.0 ± 0.1	1.1 ± 0.1 [b]	1.2 ± 0.1 [b,c]
Mean $eGFR_{MDRD}$	51.6 ± 7.1	72.6 ± 9.0	58.5 ± 1.1 [b]	62.2 ± 1.3 [b,c]
Mean $eGFR_{CKD\text{-}EPI}$	50.7 ± 8.0	76.5 ± 10.6	61.7 ± 1.4 [b]	57.8 ± 1.8 [b,c]

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; BMI, body mass index; WC, waist circumference; DM, diabetes mellitus; CVD, cardiovascular disease; Cr, creatinine; ASCVD, atherosclerotic cardiovascular disease.
[a] Values are expressed as percentages or mean ± SD.
[b] Significantly different compared to $CKD_{CKD\text{-}EPI}$ and CKD_{MDRD}.
[c] Significantly different compared to non-$CKD_{CKD\text{-}EPI}$ and non-CKD_{MDRD}.

to $CKD_{CKD\text{-}EPI}$ were aged 50 - 64 and ≥ 75 years, respectively, while these rates were 76.7% and 1.8%, respectively, among those who were reclassified to non-$CKD_{CKD\text{-}EPI}$. Subjects reclassified to non-$CKD_{CKD\text{-}EPI}$ and $CKD_{CKD\text{-}EPI}$ from the MDRD categories had respectively lower and higher 10-year Framingham CVD risk scores when compared to those who were not reclassified (33). In a 16.9-year cohort of 131,905 U.S. adults aged 45 to 64 years, the better performance of the CKD-EPI equation over the MDRD equation for the prediction of CHD, stroke, and all-cause mortality was explained by more frequent classification of younger participants and females to higher CKD-EPI eGFR categories (34).

The present study is the first of its kind that provides evidence on the superiority of the CKD-EPI equation over the MDRD equation for the detection of cardiovascular risk in a large Middle Eastern population. However, several limitations should be noted. First, we calculated eGFR based on single-time Cr measurement and could not validate it as persistent CKD. Second, we used the traditional MDRD equation because the serum Cr assay was not traceable to isotope dilution mass spectroscopy. Third, since we included participants from the 2016 - 2018 TLGS survey, the representativeness of the data was a major concern; accordingly, we weighted our population characteristics to the 2016 Tehranian urban population. Finally, due to the cross-sectional design of the study, it was impossible to infer a causal relationship between eGFR decline and cardiovascular events.

5.1. Conclusions

As in other ethnicities, in a large sample of the general Tehranian adult population, the CKD-EPI equation provided more appropriate detection of cardiovascular risk than did the MDRD equation, which is caused by the reclassification of older individuals and fewer females into lower eGFR categories. Our findings imply the potential benefits of replacing MDRD with the CKD-EPI equation in clinical and public health practice across the Middle Eastern countries.

Table 4. Multivariate Logistic Regression for CVD and its Risk Factors in Association with Chronic Kidney Disease Based on MDRD and CKD-EPI Equations

Variables	CKD_{MDRD}, Odds Ratio (95% CI)	$CKD_{CKD-EPI}$, Odds Ratio (95% CI)
Gender		
Male	Reference	Reference
Female	3.1 (2.7 - 3.6)	2.2 (1.9 - 2.5)
Age		
20 - 39 years	Reference	Reference
40 - 59 years	5.3 (4.3 - 6.6)	14.3 (10.1 - 20.4)
60 - 69 years	25.0 (19.8 - 31.5)	65.2 (45.2 - 93.9)
$\geq$ 70 years	37.2 (28.8 - 48.2)	193.4 (131.4 - 284.8)
BMI		
< 25 kg/m^2	Reference	Reference
25 - 29.9 kg/m^2	1.3 (1.1 - 1.6)	1.3 (1.1 - 1.5)
$\geq$ 30 kg/m^2	1.3 (1.1 - 1.6)	1.2 (1.0 - 1.5)
DM	1.0 (0.9 - 1.2)	1.1 (0.9 - 1.3)
Hypertension	1.3 (1.1 - 1.5)	1.4 (1.2 - 1.6)
Dyslipidemia	1.3 (1.1 - 1.4)	1.3 (1.1 - 1.5)
Currently smoking	0.9 (0.7 - 1.4)	0.8 (0.6 - 1.0)
CVD	1.4 (1.2 - 1.8)	1.4 (1.1 - 1.7)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; BMI, body mass index; DM, diabetes mellitus.

Footnotes

Authors' Contribution: Study conception and design: Farhad Hosseinpanah. Literature search, interpretation, and manuscript preparation: Pouria Mousapour. Data collection and analysis: Maryam Barzin and Maryam Mahdavi. Manuscript review, critical appraisal, and specialist advice: Majid Valizadeh, Fereidoun Azizi, and Farhad Hosseinpanah. All authors have revised and approved the submitted manuscript.

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References

1. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet*. 2017;**389**(10075):1238–52. doi: 10.1016/s0140-6736(16)32064-5.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;**351**(13):1296–305. doi: 10.1056/NEJMoa041031. [PubMed: 15385656].
3. Thomas B, Matsushita K, Abate KH, Al-Aly Z, Arnlov J, Asayama K, et al. Global cardiovascular and renal outcomes of reduced GFR. *J Am Soc Nephrol*. 2017;**28**(7):2167–79. doi: 10.1681/ASN.2016050562. [PubMed: 28408440]. [PubMed Central: PMC5491277].
4. Whaley-Connell A, Pavey BS, McCullough PA, Saab G, Li S, McFarlane SI, et al. Dysglycemia predicts cardiovascular and kidney disease in the Kidney Early Evaluation Program. *J Clin Hypertens (Greenwich)*. 2010;**12**(1):51–8. doi: 10.1111/j.1751-7176.2009.00190.x. [PubMed: 20047632].
5. Zhang R, Zheng L, Sun Z, Zhang X, Li J, Hu D, et al. Decreased glomerular filtration rate is associated with mortality and cardiovascular events in patients with hypertension: a prospective study. *PLoS One*. 2011;**6**(11). e27359. doi: 10.1371/journal.pone.0027359. [PubMed: 22096561]. [PubMed Central: PMC3214042].
6. McFadden EC, Hirst JA, Verbakel JY, McLellan JH, Hobbs FDR, Stevens RJ, et al. Systematic review and metaanalysis comparing the bias and accuracy of the modification of diet in renal disease and chronic kidney disease epidemiology collaboration equations in

community-based populations. *Clin Chem*. 2018;**64**(3):475–85. doi: 10.1373/clinchem.2017.276683. [PubMed: 29046330].
7. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;**150**(9):604–12. doi: 10.7326/0003-4819-150-9-200905050-00006. [PubMed: 19414839]. [PubMed Central: PMC2763564].
8. Turk-Adawi K, Sarrafzadegan N, Fadhil I, Taubert K, Sadeghi M, Wenger NK, et al. Cardiovascular disease in the Eastern Mediterranean region: epidemiology and risk factor burden. *Nat Rev Cardiol*. 2018;**15**(2):106–19. doi: 10.1038/nrcardio.2017.138. [PubMed: 28933782].
9. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA*. 2012;**307**(18):1941–51. doi: 10.1001/jama.2012.3954. [PubMed: 22570462]. [PubMed Central: PMC3837430].
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;**130**(6):461–70. doi: 10.7326/0003-4819-130-6-199903160-00002. [PubMed: 10075613].
11. Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, et al. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. *Trials*. 2009;**10**:5. doi: 10.1186/1745-6215-10-5. [PubMed: 19166627]. [PubMed Central: PMC2656492].
12. Hadaegh F, Harati H, Ghanbarian A, Azizi F. Association of total cholesterol versus other serum lipid parameters with the short-term prediction of cardiovascular outcomes: Tehran Lipid and Glucose Study. *Eur J Cardiovasc Prev Rehabil*. 2006;**13**(4):571–7. doi: 10.1097/01.hjr.0000216552.81882.ca. [PubMed: 16874147].
13. Levey A. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol*. 2000;**11**.
14. American Diabetes Association. Standards of medical care in diabetes-2015 abridged for primary care providers. *Clin Diabetes*. 2015;**33**(2):97–111. doi: 10.2337/diaclin.33.2.97. [PubMed: 25897193]. [PubMed Central: PMC4398006].
15. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JJ, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;**42**(6):1206–52. doi: 10.1161/01.HYP.0000107251.49515.c2. [PubMed: 14656957].
16. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*. 2001;**285**(19):2486–97. doi: 10.1001/jama.285.19.2486. [PubMed: 11368702].
17. Goff DJ, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RS, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;**63**(25 Pt B):2935–59. doi: 10.1016/j.jacc.2013.11.005. [PubMed: 24239921]. [PubMed Central: PMC4700825].
18. Iran SCO. *Population and housing censuses*. 2016. Available from: https://www.amar.org.ir/english/Population-and-Housing-Censuses.
19. Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension*. 1989;**13**(5 Suppl):I80–93. doi: 10.1161/01.hyp.13.5_suppl.i80. [PubMed: 2490833].
20. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;**395**(10225):709–33. doi: 10.1016/s0140-6736(20)30045-3.
21. Sarrafzadegan N, Mohammmadifard N. Cardiovascular disease in Iran in the last 40 years: Prevalence, mortality, morbidity, challenges and strategies for cardiovascular prevention. *Arch Iran Med*. 2019;**22**(4):204–10. [PubMed: 31126179].
22. Azizi F, Hadaegh F, Hosseinpanah F, Mirmiran P, Amouzegar A, Abdi H, et al. Metabolic health in the Middle East and north Africa. *Lancet Diabetes Endocrinol*. 2019;**7**(11):866–79. doi: 10.1016/S2213-8587(19)30179-2. [PubMed: 31422063].
23. Pugliese G, Solini A, Bonora E, Orsi E, Zerbini G, Giorgino F, et al. The chronic kidney disease epidemiology collaboration (CKD-EPI) equation provides a better definition of cardiovascular burden associated with CKD than the modification of diet in renal disease (MDRD) study formula in subjects with type 2 diabetes. *Atherosclerosis*. 2011;**218**(1):194–9. doi: 10.1016/j.atherosclerosis.2011.04.035. [PubMed: 21612781].
24. Hong N, Oh J, Lee YH, Youn JC, Park S, Lee SH, et al. Comparison of association of glomerular filtration rate with metabolic syndrome in a community-based population using the CKD-EPI and MDRD study equations. *Clin Chim Acta*. 2014;**429**:157–62. doi: 10.1016/j.cca.2013.12.008. [PubMed: 24360849].
25. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol*. 2003;**41**(1):47–55. doi: 10.1016/s0735-1097(02)02663-3. [PubMed: 12570944].
26. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol*. 2004;**15**(5):1307–15. doi: 10.1097/01.asn.0000123691.46138.e2. [PubMed: 15100371].
27. Weiner DE, Tighiouart H, Stark PC, Amin MG, MacLeod B, Griffith JL, et al. Kidney disease as a risk factor for recurrent cardiovascular disease and mortality. *Am J Kidney Dis*. 2004;**44**(2):198–206. doi: 10.1053/j.ajkd.2004.04.024. [PubMed: 15264177].
28. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*. 2013;**382**(9889):339–52. doi: 10.1016/S0140-6736(13)60595-4. [PubMed: 23727170].
29. Fried LF, Shlipak MG, Crump C, Bleyer AJ, Gottdiener JS, Kronmal RA, et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol*. 2003;**41**(8):1364–72. doi: 10.1016/s0735-1097(03)00163-3. [PubMed: 12706933].
30. Carrero JJ, de Jager DJ, Verduijn M, Ravani P, De Meester J, Heaf JG, et al. Cardiovascular and noncardiovascular mortality among men and women starting dialysis. *Clin J Am Soc Nephrol*. 2011;**6**(7):1722–30. doi: 10.2215/CJN.11331210. [PubMed: 21734088].
31. Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, et al. Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. *Kidney Int*. 2005;**68**(1):228–36. doi: 10.1111/j.1523-1755.2005.00397.x. [PubMed: 15954912].
32. White SL, Polkinghorne KR, Atkins RC, Chadban SJ. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis*. 2010;**55**(4):660–70. doi: 10.1053/j.ajkd.2009.12.011. [PubMed: 20138414].
33. Rocco MV, Chapman A, Chertow GM, Cohen D, Chen J, Cutler JA, et al. Chronic kidney disease classification in systolic blood pres-

sure intervention trial: Comparison using modification of diet in renal disease and CKD-epidemiology collaboration definitions. *Am J Nephrol*. 2016;**44**(2):130–40. doi: 10.1159/000448722. [PubMed: 27513312]. [PubMed Central: PMC5096787].

34. Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis*. 2010;**55**(4):648–59. doi: 10.1053/j.ajkd.2009.12.016. [PubMed: 20189275]. [PubMed Central: PMC2858455].