Research Square

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Mean Corpuscular Volume and Renal Markers in Non-anemic Adults

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Research Article

Keywords: mean corpuscular volume, erythrocyte indices, albuminuria, hyperfiltration, estimated glomerular filtration rate, sex factors

Posted Date: July 30th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10062430/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Mean corpuscular volume (MCV) has been linked to cardiovascular disease and mortality, but its relationship with renal function is not well established. We examined the association of MCV quintiles with albuminuria and hyperfiltration in non-anemic Korean adults.

Methods

This cross-sectional study analyzed 57,908 non-anemic adults aged 19 years or older who underwent health screening from 2005 to 2025 at Seoul National University Hospital. Subjects were divided into age- and sex-specific MCV quintiles. Multivariable logistic regression evaluated the association of MCV quintile with albuminuria (urine dipstick ≥ 1+) and hyperfiltration (estimated glomerular filtration rate [eGFR] above the age- and sex-specific 97.5th percentile), and a generalized linear model evaluated its association with eGFR. All models were adjusted for age, body mass index, hypertension, diabetes, red cell distribution width (RDW), hemoglobin, and lifestyle factors; the albuminuria model was additionally adjusted for eGFR. Missing covariates were imputed using chained equations.

Results

In women, the lowest MCV quintile showed higher odds ratios of albuminuria (OR 1.21, 95% CI 1.06–1.38) and hyperfiltration (OR 1.54, 95% CI 1.24–1.92) versus the third quintile. When stratified by age, the albuminuria association was prominent in elderly women, while hyperfiltration was seen in both age groups. Similar trends were not observed in men. After adjustment for age and metabolic risk factors, a negative MCV-eGFR association was observed in all subgroups of both sexes.

Conclusion

In non-anemic adults, low MCV was associated with albuminuria and hyperfiltration, particularly in women, whereas higher MCV was associated with lower eGFR. These findings suggest that MCV reflects the systemic metabolic stress and biological aging underlying early kidney damage.

Background

Mean corpuscular volume (MCV), one of the indices reported on a complete blood count (CBC), has traditionally been used in the differential diagnosis of anemia. MCV is known to vary with nutritional status, age, alcohol intake, and smoking [1]. More recently, it has also been reported that MCV predicts survival and coronary events in patients with chronic kidney disease [2, 3], influences prognosis after percutaneous coronary intervention [4], and is related to outcomes in several malignancies [5–8]. Even in the general population, MCV has been linked to cardiovascular disease [9, 10], all-cause mortality, and liver cancer mortality [11]. These findings suggest that MCV may reflect aspects of systemic health more than just the hematological parameters.

Chronic kidney disease (CKD) places a heavy burden on health care because of its high prevalence and its strong association with cardiovascular events and premature death [12]. Albuminuria is an early sign of microvascular injury, and a decreased estimated glomerular filtration rate (eGFR) reflects loss of renal function. Both are well known as the predictors of cardiovascular disease and mortality and widely used for CKD screening and prognosis [13, 14]. Glomerular hyperfiltration is another early marker of kidney damage, defined as an abnormally elevated glomerular filtration rate. It is known to result from metabolic burden such as metabolic syndrome, insulin resistance, and obesity [15], and it has been reported to be associated with albuminuria in the general population [16]. Furthermore, hyperfiltration has been reported as an independent precursor of subsequent proteinuria in a large longitudinal study [17], and it is considered to reflect an early stage of renal injury that progresses from glomerular hemodynamic overload to structural damage.

Given the observed links between MCV and cardiovascular outcomes in diverse populations, and the role of albuminuria and eGFR as core markers of cardiovascular risk, it is reasonable to ask whether MCV is also associated to renal indices. However, the independent relationship of MCV with eGFR and albuminuria has not yet been examined. The present study was therefore designed to evaluate the association of MCV with eGFR and albuminuria in non-anemic adults aged 19 years or older.

Methods

Participants

From January 1, 2005 to May 22, 2025, 161,293 health check-ups were performed at the Seoul National University Health Promotion Center. After keeping only the first visit for each individual, we identified 67,728 participants for initial inclusion. Then we applied the following exclusion criteria in order. 6,428 subjects with missing values for any of the key analytic variables—MCV, urine albumin, blood urea nitrogen (BUN), or creatinine—were excluded. Next, 72 subjects younger than 19 years were excluded and to avoid confounding from anemia-related MCV changes, 3,320 subjects with hemoglobin (Hb) below 13 g/dL in men or 12 g/dL in women were excluded. A total of 57,908 participants (29,279 men and 28,629 women) were included in the final analysis (Fig. 1).

Covariates

Information on comorbidities such as hypertension, diabetes mellitus, and dyslipidemia, as well as medication use, smoking history, alcohol intake, and exercise habits, was collected through a self-completed questionnaire and trained nurses reviewed it. Smoking status was classified as current, former, or never smoker. Subjects who consumed at least one drink per week were categorized as regular drinkers. Regular exercise was defined as at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity per week.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or self-report of a physician diagnosis or current use of antihypertensive medication. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL or HbA1c ≥ 6.5%, or self-report of a physician diagnosis or current use of antidiabetic medication.

Height, weight, blood pressure, and all blood and urine tests were obtained after an overnight fasting of at least 12 hours.

Exposure variable

MCV was calculated automatically by the analyzer using the formula Hematocrit (%) / red blood cell(RBC) count (10^6/μL). Subjects were divided into quintiles of MCV within each sex- and age-specific subgroup (younger or older than the median age of 53 years for men and 54 years for women). The quintile cutoffs (20th, 40th, 60th, and 80th percentiles in fL) were 88.5, 90.6, 92.5, and 94.9 in young men; 90.2, 92.4, 94.3, and 96.7 in elderly men; 88.9, 91.2, 93.1, and 95.3 in young women; and 90.0, 92.0, 93.8, and 96.0 in elderly women.

Outcome

A first morning urine sample collected after 12 hours of fasting underwent dipstick analysis, which was graded as negative, trace, 1+, 2+, 3+, or 4+. According to previous literature, 1 + or higher indicated albuminuria [18]. Renal function was estimated by eGFR calculated with the Modification of Diet in Renal Disease (MDRD) equation [19]. For sensitivity analysis, eGFR was additionally calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [20].

Because there is no universally accepted definition of glomerular hyperfiltration, we defined it here as an eGFR above the age- and sex-specific 97.5th percentile. Subjects were classified as younger or elderly using the median age in each sex, which was 53 years for men and 54 years for women. (Young Men ≤ 53 years: 116.85 mL/min/1.73 m^2; Elderly Men > 53 years: 108.63 mL/min/1.73 m^2; Young Women ≤ 54 years: 123.02 mL/min/1.73 m^2; Elderly Women > 54 years: 109.92 mL/min/1.73 m^2.)

Statistical analysis

Participants were assigned to one of four sex- and age-specific subgroups and then distributed into quintiles according to their MCV. For continuous variables, a linear trend across MCV quintiles was tested using linear regression with the quintile as an ordinal predictor (P for trend). For categorical variables, differences in distribution across MCV quintiles were tested using Pearson's chi-squared test. The effect of MCV quintile on albuminuria and hyperfiltration was examined by multivariable logistic regression. For albuminuria, the model was adjusted for age, BMI, eGFR, hypertension, diabetes mellitus, RDW, hemoglobin, smoking status, alcohol use, and exercise. For hyperfiltration, the same set of covariates was used except for eGFR, since hyperfiltration was defined based on eGFR. The effect of MCV quintile on eGFR was evaluated using a generalized linear model with the same set of covariates (excluding eGFR itself).

To improve statistical efficiency, we applied multiple imputation to handle missing data. Missingness in the covariates (BMI, RDW, hypertension, diabetes mellitus, smoking status, alcohol use, and exercise) was assumed to be missing at random, and imputation was performed using multivariate imputation by chained equations. The imputation model included all variables without missing values that were used in the main analysis (age, sex, hemoglobin, MCV quintile, eGFR, albuminuria, and hyperfiltration). Fifty complete datasets were generated. Each dataset was analyzed separately, and the 50 sets of results were then pooled to produce the final estimates and standard errors. All analyses were performed using STATA MP 18.0 (StataCorp, College Station, TX, USA) and a two-sided $P < 0.05$ was considered statistically significant.

Results

The distribution of clinical variables across MCV quintiles is summarized in Table 1 and Supplementary Table S1. Mean MCV was higher in men than women, and the overall quintile cut-off values were also higher in men. Most variables differed significantly across the quintiles. In both sexes, mean age rose with increasing MCV. BMI, systolic blood pressure (SBP), fasting glucose, and HbA1c moved in the opposite direction, and the prevalence of hypertension (HTN) and diabetes mellitus (DM) followed the negative trend. The proportion of current smokers and regular drinkers was higher in the higher MCV quintiles in both sexes, but so was the proportion of those who exercised regularly.

Table 1
Baseline characteristics according to MCV quintiles in men and women.

	Baseline Characteristics (Men)							Baseline Characteristics (Women)					
	MCV_quintile							MCV_quintile					
	1	2	3	4	5	Total	P	1	2	3	4	5	Total
N	5,959 (20.4%)	5,908 (20.2%)	5,768 (19.7%)	5,934 (20.3%)	5,710 (19.5%)	29,279 (100%)		5,846 (20.4%)	5,771 (20.2%)	5,740 (20.0%)	5,663 (19.8%)	5,609 (19.6%)	28,629 (100%)
Age	49.5 (13.6)	50.7 (13.3)	51.4 (13.1)	52.0 (12.6)	53.4 (12.1)	51.4 (13.0)	< 0.001	51.8 (12.7)	51.8 (12.7)	52.1 (12.7)	53.1 (12.5)	53.7 (13.1)	52.5 (12.8)
BMI	25.3 (3.4)	24.8 (3.2)	24.5 (3.1)	24.4 (3.1)	24.0 (3.0)	24.6 (3.2)	< 0.001	23.5 (3.7)	23.1 (3.4)	22.8 (3.4)	22.6 (3.2)	22.2 (3.2)	22.9 (3.4)
Hb	15.6 (1.1)	15.6 (1.0)	15.5 (1.0)	15.5 (1.0)	15.5 (1.1)	15.5 (1.1)	< 0.001	13.5 (0.9)	13.6 (0.8)	13.6 (0.8)	13.5 (0.8)	13.5 (0.8)	13.5 (0.8)
RDW	12.8 (0.8)	12.7 (0.6)	12.7 (0.6)	12.7 (0.6)	12.7 (0.8)	12.7 (0.7)	< 0.001	13.0 (1.0)	12.7 (0.7)	12.6 (0.7)	12.6 (0.7)	12.6 (0.7)	12.7 (0.8)
HTN(yes)[a]	1,076 (18.2)	1,011 (17.2)	922 (16.1)	842 (14.2)	732 (12.9)	4,583 (15.7)	< 0.001	786 (13.6)	686 (12.0)	633 (11.2)	591 (10.6)	581 (10.5)	3,277 (11.6)
DM(yes)[b]	572 (9.6)	462 (7.8)	415 (7.2)	374 (6.3)	315 (5.5)	2,138 (7.3)	< 0.001	352 (6.0)	247 (4.3)	250 (4.4)	209 (3.7)	213 (3.8)	1,271 (4.4)
Smoking (never)	1,239 (34.4)	1,038 (30.9)	813 (26.3)	755 (25.4)	455 (19.4)	4,300 (28.0)		2,761 (92.8)	2,776 (92.3)	2,778 (90.9)	2,676 (91.3)	2,535 (88.0)	13,526 (91.1)
Smoking (Ex-)	1,622 (45.1)	1,503 (44.7)	1,401 (45.4)	1,257 (42.2)	946 (40.2)	6,729 (43.8)	< 0.001	137 (4.6)	154 (5.1)	159 (5.2)	140 (4.8)	164 (5.7)	754 (5.1)
Smoking (Current)	736 (20.5)	821 (24.4)	872 (28.3)	964 (32.4)	950 (40.4)	4,343 (28.3)		77 (2.6)	78 (2.6)	119 (3.9)	114 (3.9)	181 (6.3)	569 (3.8)
Alcohol[c](yes)	2,339 (65.6)	2,324 (69.6)	2,195 (71.6)	2,243 (75.4)	1,833 (79.0)	10,934 (71.6)	< 0.001	1,049 (34.9)	1,148 (38.0)	1,242 (40.4)	1,166 (39.6)	1,234 (42.6)	5,839 (39.1)
Exercise[d](yes)	1,561 (44.0)	1,533 (45.9)	1,496 (48.5)	1,549 (51.7)	1,209 (51.4)	7,348 (48.0)	< 0.001	1,100 (35.8)	1,109 (36.0)	1,248 (39.5)	1,236 (40.5)	1,249 (41.6)	5,942 (38.7)
eGFR-MDRD	83.6 (15.6)	82.4 (14.9)	82.0 (15.2)	81.5 (14.4)	80.4 (14.9)	82.0 (15.1)	< 0.001	84.8 (16.8)	83.6 (16.2)	83.5 (15.7)	81.9 (15.5)	80.8 (15.5)	82.9 (16.0)
Albuminuria[e]	748 (12.6)	703 (11.9)	687 (11.9)	660 (11.1)	689 (12.1)	3,487 (11.9)	0.2	570 (9.8)	521 (9.0)	454 (7.9)	421 (7.4)	460 (8.2)	2,426 (8.5)
Hyperfiltration[f]	171 (2.9)	134 (2.3)	149 (2.6)	138 (2.3)	140 (2.5)	732 (2.5)	0.231	222 (3.8)	143 (2.5)	139 (2.4)	112 (2.0)	97 (1.7)	713 (2.5)

Values are presented as mean (standard deviation) or number (%). P for trend was calculated by linear regression for continuous variables and Pearson's ch test for categorical variables, with MCV quintile as an ordinal variable.

Abbreviations: MCV, mean corpuscular volume; BMI, body mass index; eGFR-MDRD, estimated glomerular filtration rate by Modification of Diet in Renal Dise equation; Hb, hemoglobin; RDW, red cell distribution width; HTN, hypertension; DM, diabetes mellitus.

[a] Hypertension, blood pressure ≥ 140/90 mmHg or on antihypertensive medication. [b] Diabetes, fasting glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, or on antidiabeti medication. [c] Regular drinker, ≥ 1 drink/week. [d] Regular exercise, ≥ 150 min moderate or ≥ 75 min vigorous aerobic activity/week. [e] Albuminuria, urine dipstic Hyperfiltration, eGFR above the age- and sex-specific 97.5th percentile. Full definitions are provided in the Methods.

For the main renal endpoints, the prevalence of albuminuria did not differ across MCV quintiles in men, but in women it tended to fall as MCV rose (total cases: 3,487 men, 2,426 women). eGFR declined with rising MCV in both sexes; mean eGFR was 82.0 ± 15.1 mL/min/1.73 m² in men and 82.9 ± 16.0 mL/min/1.73 m² in women. Hyperfiltration was identified in 732 men and 713 women.

After adjusting for age, BMI, hypertension, diabetes mellitus, RDW, Hb, smoking status, alcohol use, and exercise, the estimated mean eGFR had negative relationships with MCV quintile in all subgroups, and this trend was more prominent in young men, young women, and elderly women (Fig. 2).

Compared with the third MCV quintile, the adjusted odds ratio (OR) for albuminuria was significantly higher in the first MCV quintile among women (OR 1.21, 95% CI 1.06–1.38; P-trend = 0.004). On age-stratified analysis, this association was significant only in elderly women in the first quintile (OR 1.37, 95% CI 1.10–1.70; P-trend = 0.034) (Table 2). A reduced odds ratio of albuminuria was seen in the fourth quintile of elderly men, but this was not kept in the fifth quintile, and no consistent pattern was found.

Table 2

The association between albuminuria and quintiles of mean corpuscular volume(MCV)[a,b,c]

	Men			Women		
	Young[e]	**Elderly[e]**	**Total**	**Young[e]**	**Elderly[e]**	**Total**
P_{trend}[d]	0.541	0.102	0.206	0.018	0.034	0.004
MCV						
1st Quintile	1.06 (0.90–1.24)	1.04 (0.88–1.23)	1.04 (0.93–1.17)	1.13 (0.95–1.34)	1.37 (1.10–1.70)	1.21 (1.06–1.38)
2nd Quintile	1.02 (0.87–1.19)	0.98 (0.83–1.16)	1.00 (0.89–1.12)	1.11 (0.94–1.31)	1.18 (0.94–1.47)	1.12 (0.99–1.29)
3rd Quintile	-	-	-	-	-	-
4th Quintile	1.00 (0.86–1.17)	0.83 (0.70–0.99)	0.92 (0.82–1.03)	0.93 (0.78–1.11)	0.97 (0.77–1.23)	0.95 (0.82–1.09)
5th Quintile	1.01 (0.86–1.18)	0.96 (0.80–1.14)	0.99 (0.88–1.12)	0.96 (0.81–1.15)	1.17 (0.93–1.47)	1.05 (0.92–1.21)

[a] Analyzed by multivariate logistic regression, adjusted for age, body mass index (BMI), estimated glomerular filtration rate (eGFR), hypertension, diabetes, red cell distribution width (RDW), hemoglobin, smoking status, alcohol intake, and regular exercise.

[b] Missing data for covariates (BMI, RDW, hypertension, diabetes, smoking status, alcohol intake, and regular exercise) were handled using multiple imputation by chained equations.

[c] Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs) compared with the 3rd quintile of mean corpuscular volume (MCV) as the reference group.

[d] P_{trend} was calculated by treating the mean corpuscular volume(MCV) quintiles as a continuous variable in the model to evaluate linear trends.

[e] Young group was defined as younger than or equal to the median age (53 year for men and 54 year for women) and the elderly group was defined as older than the median age in each sex.

For hyperfiltration, again with the third MCV quintile as reference, the OR was significantly higher in the first MCV quintile among women (OR 1.54, 95% CI 1.24–1.92; P-trend < 0.001). The result was also significant in the first quintile of both young women (OR 1.52, 95% CI 1.13–2.06; P-trend < 0.001) and elderly women (OR 1.50, 95% CI 1.08–2.09; P-trend < 0.001). A reduced risk was also observed in the highest quintile of total women (OR 0.73, 95% CI 0.56–0.95), in line with the negative association between MCV and eGFR (Table 3). No significant association was found in men.

Table 3

The risk of hyperfiltration[e] according to the quintiles of mean corpuscular volume(MCV)[a,b,c]

	Men			Women		
	Young[f]	**Elderly[f]**	**Total**	**Young[f]**	**Elderly[f]**	**Total**
P_{trend}[d]	0.737	0.062	0.848	< 0.001	< 0.001	< 0.001
MCV						
1st Quintile	0.97 (0.71–1.32)	0.94 (0.67–1.34)	1.06 (0.84–1.33)	1.52 (1.13–2.06)	1.50 (1.08–2.09)	1.54 (1.24–1.92)
2nd Quintile	0.84 (0.61–1.16)	0.80 (0.56–1.15)	0.86 (0.68–1.10)	0.74 (0.52–1.04)	1.35 (0.96–1.89)	1.01 (0.80–1.28)
3rd Quintile	-	-	-	-	-	-
4th Quintile	0.89 (0.63–1.25)	1.09 (0.78–1.52)	0.93 (0.73–1.18)	0.83 (0.58–1.18)	0.90 (0.62–1.30)	0.83 (0.65–1.07)
5th Quintile	1.04 (0.72–1.48)	1.18 (0.85–1.64)	1.01 (0.79–1.28)	0.72 (0.50–1.05)	0.78 (0.53–1.15)	0.73 (0.56–0.95)

[a] Analyzed by multivariate logistic regression, adjusted for age, body mass index (BMI), hypertension, diabetes mellitus, red cell distribution width (RDW), hemoglobin, smoking status, alcohol intake, and regular exercise.

[b] Missing data for covariates (BMI, RDW, hypertension, diabetes mellitus, smoking status, alcohol intake, and regular exercise) were handled using multiple imputation by chained equations.

c Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs) compared with the 3rd quintile of mean corpuscular volume (MCV) as the reference group.

[d] P_{trend} was calculated by treating the MCV quintiles as a continuous variable in the model to evaluate linear trends.

[e] Hyperfiltration was defined as an eGFR above the age- and sex-specific 97.5th percentile (> 116.85 mL/min/1.73m² for young men, > 108.63 mL/min/1.73m² for elderly men, > 123.02 mL/min/1.73m² for young women, and > 109.92 mL/min/1.73m² for elderly women).

[f] The young group was defined as younger than or equal to the median age (53 year for men and 54 year for women), and the elderly group was defined as older than the median age in each sex.

In the sensitivity analysis using eGFR calculated by the 2021 CKD-EPI equation, the overall direction of the associations was consistent with the main results. The increased odds ratio of albuminuria in the lowest MCV quintile among women remained significant, especially in elderly women (Supplementary Table S2). For hyperfiltration, the significant association in women persisted in the overall analysis (OR 1.38, 95% CI 1.10–1.72) and the reduced odds ratio in the highest quintile was further strengthened (OR 0.60, 95% CI 0.46–0.80) (Supplementary Table S3). A borderline significant association in total men also emerged (OR 1.26, 95% CI 1.00–1.58; P-trend < 0.001), which was not observed in the main analysis. The negative association between MCV quintile and adjusted eGFR was observed across all sex and age subgroups in the sensitivity analysis as well (Supplementary Figure S1).

Discussion

In this study of non-anemic adults, MCV was independently associated with albuminuria and hyperfiltration, which are both early markers of kidney damage. These associations were kept significant after adjustment for conventional metabolic risk factors, and they differed by sex. In women, low MCV was related to higher risk of both hyperfiltration and albuminuria, but such pattern was not observed in men. In addition, a higher MCV was associated with a lower eGFR, and this inverse association was consistent across all sex and age subgroups.

Baseline characteristics of study participants (Table 1) showed that the low-MCV group in both sexes had significantly higher BMI, SBP, fasting glucose, HbA1c, triglycerides, and prevalence of hypertension and diabetes mellitus, as well as higher hs-CRP, a marker of systemic inflammation, than the high-MCV group. This suggests that low MCV is more than a hematologic finding—it reflects a metabolically unhealthy state regardless of sex. This result is consistent with the previous study showing that lower MCV is associated with higher prevalence of metabolic syndrome in both men and women [21]. Tanaka et al. suggested that both insulin resistance and metabolic syndrome are accompanied by increased inflammation and oxidative stress, which can reduce RBC volume—oxidative stress promotes erythrocyte shrinkage, and chronic inflammation is itself a known cause of microcytosis [21]. The higher high-sensitivity C-reactive protein (hs-CRP) in our low-MCV group supports this inflammatory pathway.

Hyperfiltration is considered as a key hemodynamic step that links metabolic stress to albuminuria. Insulin resistance and low-grade inflammation caused by metabolic overload induce abnormal dilatation of the afferent arteriole and raise intraglomerular pressure [22]. Large cohort studies have shown that hyperfiltration is a strong and independent predictor of subsequent proteinuria [17]. The concept that this kind of hemodynamic overload from metabolic stress is the starting point of renal dysfunction is well established [23]. Albuminuria is not only a sign of kidney injury but also reflects systemic vascular health [24]. Under metabolic stress, systemic inflammation and insulin resistance damage the glycocalyx of glomerular endothelial cells and increase the permeability of filtration barrier, which results in true vascular injury [25]. A large meta-analysis already established the link between systemic metabolic abnormalities and albuminuria [26].

The finding that low MCV was independently associated with both albuminuria and hyperfiltration in women after adjustment for multiple confounders suggests that MCV seems to capture the underlying systemic metabolic stress which drives functional and structural injury of the kidney.

The lack of similar pattern in men is interesting. Men in this cohort had much higher proportion of current smokers (28.3%) and regular drinkers (71.6%) than women (Table 1). Both behaviors were most common in the highest MCV quintile. Alcohol and tobacco are strong risk factors for renal endothelial dysfunction through cytotoxic and oxidative stress pathways, and they are also well-known causes of macrocytosis [27–29]. Therefore, in men, the high frequency of drinking and smoking may raise the risk of kidney damage in the high-MCV group, and this could offset or mask the metabolic-injury signal carried by low MCV. In women, who are less exposed to these behaviors, the relationship between metabolic factors and renal markers may appear more clearly.

In the stratified analysis, the association with albuminuria was most clear in elderly women. This is likely due to the combined effects of hormonal change and shifts in body composition with aging. Before menopause, estrogen suppresses the renin-angiotensin-aldosterone system and protects glomerular endothelial cells and podocytes from oxidative stress [30, 31]. After menopause, estrogen falls, and inherently lower skeletal muscle mass and slower metabolic rate make older women especially prone to sarcopenic obesity and visceral fat accumulation [32]. Once visceral fat exceeds a certain threshold, adipocyte hypertrophy and local hypoxia develop, and adipose tissue acts as an endocrine organ that releases pro-inflammatory cytokines such as TNF-α and IL-6 [33]. The resulting systemic inflammation and worsening insulin resistance then act directly on the glomerular filtration barrier, which already lost its post-menopausal protection. This sequence helps to explain why the cumulative metabolic stress—reflected in low MCV—appears as structural injury in the form of albuminuria in elderly women.

Another interesting observation in this study was that a rise in MCV was independently associated with a fall in eGFR. Two main mechanisms may explain this inverse relationship.

First, from the standpoint of microcirculatory hemodynamics, higher MCV may physically reduce glomerular filtration pressure. Glomerular capillaries are extremely narrow, so red blood cells must deform to pass through them. As MCV increases and the cell volume grows, the surface-area-to-volume ratio shifts, and red blood cell deformability declines [34]. These enlarged cells raise flow resistance within the glomerular capillaries and slow microvascular flow, which in turn lowers the effective filtration pressure and eGFR [35]. Since the kidney is highly sensitive to small changes in microcirculation, higher MCV may serve as an indicator of hemodynamic dysfunction in the renal microvasculature.

Second, the association between high MCV and lower eGFR can also be considered as a marker of biological aging. In our multivariable analysis, the link between the two was kept after adjustment for chronological age. With aging, the hematopoietic system gradually produces larger red cells, and the kidney undergoes structural aging with a fall in eGFR [36, 37]. Therefore, a rising MCV is considered as a sign of biological aging. Even within the same chronological age, individuals can differ in how fast they age biologically, and this difference cannot be fully captured by statistical models. The persistent inverse relationship between higher MCV and lower eGFR after age adjustment is likely to reflect this acceleration of biological aging.

However, in our study, the high-MCV group had lower prevalence of obesity, hypertension, diabetes mellitus, and dyslipidemia than the low-MCV group. This suggests that pathophysiologic mechanisms other than insulin resistance and obesity-related inflammation may be involved in the link between high MCV and decreased eGFR.

A related point is that the relationship between MCV and eGFR was less clear in the elderly men subgroup. This may be because age-related structural changes in the kidney are already widespread in older adults, so the additional sensitivity of a single variable like MCV to changes in eGFR becomes statistically underestimated.

These findings were robust in the sensitivity analysis using the 2021 CKD-EPI equation, in which the main associations in women remained significant (Supplementary Tables S2 and S3, Supplementary Figure S1).

Several limitations of this study should be acknowledged. First, the cross-sectional design with single MCV measurement does not allow firm conclusion about causality between changes in MCV and development of renal injury markers. Second, since participants came from the health screening center of a single university hospital, they may have higher level of health awareness and socioeconomic status than the general population, so the findings should be generalized with caution. Third, although subjects with anemia were excluded, detailed iron-metabolism markers such as serum ferritin and transferrin saturation as well as detailed nutritional status were not available in our database, so we could not clearly distinguish whether low MCV reflected true iron deficiency or functional iron sequestration due to chronic inflammation. Fourth, renal function was based on a single time point, so acute kidney injury and transient fluctuations cannot be entirely ruled out. Prospective longitudinal studies including direct iron-metabolism markers and long-term follow-up will be needed to address these issues.

Conclusion

Low MCV, as a downstream effect of metabolic syndrome and systemic inflammation, was particularly sensitive in women in capturing the continuum from glomerular hemodynamic overload (hyperfiltration) to structural injury (albuminuria). Even a rise in MCV within normal range was associated with lower eGFR, which likely reflects reduced red cell deformability, impaired microcirculation, and biological aging. These findings suggest that MCV, which can be obtained from a routine and widely accessible CBC test, reflects the underlying systemic metabolic stress and biological aging that drive early kidney damage in non-anemic adults.

Abbreviations

BMI
Body mass index
BUN
Blood urea nitrogen
CBC
Complete blood count
CI
Confidence interval
CKD
Chronic kidney disease
CKD-EPI
Chronic Kidney Disease Epidemiology Collaboration
DM
Diabetes mellitus
eGFR
Estimated glomerular filtration rate
Hb
Hemoglobin
HbA1c
Glycated hemoglobin
hs-CRP
High-sensitivity C-reactive protein
HTN
Hypertension
IL-6
Interleukin-6
IRB
Institutional Review Board
MCV
Mean corpuscular volume
MDRD
Modification of Diet in Renal Disease

OR
Odds ratio
RBC
Red blood cell
RDW
Red cell distribution width
SBP
Systolic blood pressure
TNF-α
Tumor necrosis factor-alpha

Declarations

Ethics approval and consent to participate

This study followed the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2505-126-1641). Informed consent was waived because of the retrospective study design.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contribution

Junhyeok Byun: Conceptualization, Investigation, Writing – original draft, Writing – review and editing.Sinyoung Cho: Writing – review & editing.Seoeun Hwang: Data curation, Resources.Minseon Park: Supervision, Writing – review & editing.All authors read and approved the final manuscript.

Acknowledgement

The authors used a large language model (Claude, Anthropic) for language editing of the manuscript. No content was generated by the model, and the authors take full responsibility for the entire content of the manuscript.

Availability of data and materials

The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants and are subject to the data-protection policies of Seoul National University Hospital. De-identified data may be available from the corresponding author upon reasonable request, subject to institutional review board approval.

References

1. Kaferle J, Strzoda CE. Evaluation of macrocytosis. Am Fam Physician. 2009;79:203–8.
2. Hsieh Y-P, Chang C-C, Kor C-T, Yang Y, Wen Y-K, Chiu P-F. Mean Corpuscular Volume and Mortality in Patients with CKD. Clin J Am Soc Nephrol CJASN. 2017;12:237–44. https://doi.org/10.2215/CJN.00970116.
3. Solak Y, Yilmaz MI, Saglam M, Demirbas S, Verim S, Unal HU, et al. Mean corpuscular volume is associated with endothelial dysfunction and predicts composite cardiovascular events in patients with chronic kidney disease. Nephrology. 2013;18:728–35. https://doi.org/10.1111/nep.12130.
4. Sun L, Zhang C, Ju Y, Tang B, Gu M, Pan B, et al. Mean Corpuscular Volume Predicts In-Stent Restenosis Risk for Stable Coronary Artery Disease Patients Receiving Elective Percutaneous Coronary Intervention. Med Sci Monit Int Med J Exp Clin Res. 2019;25:3976–82. https://doi.org/10.12659/MSM.914654.
5. Sato R, Oikawa M, Kakita T, Okada T, Abe T, Yazawa T, et al. Prognostic significance of the mean corpuscular volume (MCV) and red cell distribution width (RDW) in obstructive colorectal cancer patients with a stent inserted as a bridge to curative surgery. Surg Today. 2022;52:1699–710. https://doi.org/10.1007/s00595-022-02504-9.

6. Zheng Y-Z, Dai S-Q, Li W, Cao X, Li Y, Zhang L-J, et al. Prognostic value of preoperative mean corpuscular volume in esophageal squamous cell carcinoma. World J Gastroenterol. 2013;19:2811–7. https://doi.org/10.3748/wjg.v19.i18.2811.
7. Cui M-T, Liang Z-W, Sun Y-Z, Wu J, Lu H, Wang W-J, et al. The prognostic roles of red blood cell-associated indicators in patients with resectable gastric cancers. Transl Cancer Res. 2020;9:2300–11. https://doi.org/10.21037/tcr.2020.03.46.
8. Jomrich G, Hollenstein M, John M, Ristl R, Paireder M, Kristo I, et al. High Mean Corpuscular Volume Predicts Poor Outcome for Patients With Gastroesophageal Adenocarcinoma. Ann Surg Oncol. 2019;26:976–85. https://doi.org/10.1245/s10434-019-07186-1.
9. Wu T-H, Fann JC-Y, Chen SL-S, Yen AM-F, Wen C-J, Lu Y-R, et al. Gradient Relationship between Increased Mean Corpuscular Volume and Mortality Associated with Cerebral Ischemic Stroke and Ischemic Heart Disease: A Longitudinal Study on 66,294 Taiwanese. Sci Rep. 2018;8:16517. https://doi.org/10.1038/s41598-018-34403-w.
10. Li D, Wang A, Li Y, Ruan Z, Zhao H, Li J, et al. Nonlinear relationship of red blood cell indices (MCH, MCHC, and MCV) with all-cause and cardiovascular mortality: A cohort study in U.S. adults. PLoS ONE. 2024;19:e0307609. https://doi.org/10.1371/journal.pone.0307609.
11. Yoon H-J, Kim K, Nam Y-S, Yun J-M, Park M. Mean corpuscular volume levels and all-cause and liver cancer mortality. Clin Chem Lab Med. 2016;54:1247–57. https://doi.org/10.1515/cclm-2015-0786.
12. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305. https://doi.org/10.1056/NEJMoa041031.
13. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–81. https://doi.org/10.1016/S0140-6736(10)60674-5.
14. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3:514–25. https://doi.org/10.1016/S2213-8587(15)00040-6.
15. Bystad EW, Stefansson VTN, Eriksen BO, Melsom T. The Association Between Metabolic Syndrome, Hyperfiltration, and Long-Term GFR Decline in the General Population. Kidney Int Rep. 2023;8:1831–40. https://doi.org/10.1016/j.ekir.2023.06.022.
16. Hong S, Choi YM, Ihm S-H, Kim D, Choi M-G, Yu JM, et al. Association between metabolic parameters and glomerular hyperfiltration in a representative Korean population without chronic kidney disease. PLoS ONE. 2018;13:e0207843. https://doi.org/10.1371/journal.pone.0207843.
17. Lee SM, Park J-Y, Park M-S, Park JH, Park M, Yoon H-J. Association of renal hyperfiltration with incident proteinuria - A nationwide registry study. PLoS ONE. 2018;13:e0195784. https://doi.org/10.1371/journal.pone.0195784.
18. White SL, Yu R, Craig JC, Polkinghorne KR, Atkins RC, Chadban SJ. Diagnostic accuracy of urine dipsticks for detection of albuminuria in the general community. Am J Kidney Dis Off J Natl Kidney Found. 2011;58:19–28. https://doi.org/10.1053/j.ajkd.2010.12.026.
19. Steffl JL, Bennett W, Olyaei AJ. The old and new methods of assessing kidney function. J Clin Pharmacol. 2012;52(1 Suppl). https://doi.org/10.1177/0091270011420260. :63S-71S.
20. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385:1737–49. https://doi.org/10.1056/NEJMoa2102953.
21. Tanaka M, Okada H, Hashimoto Y, Kumagai M, Nishimura H, Fukui M. Combined effect of hemoglobin and mean corpuscular volume levels on incident metabolic syndrome: A population-based cohort study. Clin Nutr ESPEN. 2020;40:314–9. https://doi.org/10.1016/j.clnesp.2020.08.010.
22. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. Am J Med. 1982;72:375–80. https://doi.org/10.1016/0002-9343(82)90490-9.
23. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. Am J Physiol Ren Physiol. 2000;278:F817–822. https://doi.org/10.1152/ajprenal.2000.278.5.F817.
24. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. Steno hypothesis Diabetologia. 1989;32:219–26. https://doi.org/10.1007/BF00285287.
25. Satchell SC, Tooke JE. What is the mechanism of microalbuminuria in diabetes: a role for the glomerular endothelium? Diabetologia. 2008;51:714–25. https://doi.org/10.1007/s00125-008-0961-8.
26. Rashidbeygi E, Safabakhsh M, Delshad Aghdam S, Mohammed SH, Alizadeh S. Metabolic syndrome and its components are related to a higher risk for albuminuria and proteinuria: Evidence from a meta-analysis on 10,603,067 subjects from 57 studies. Diabetes Metab Syndr. 2019;13:830–43. https://doi.org/10.1016/j.dsx.2018.12.006.
27. Eisenga MF, Wouters HJCM, Kieneker LM, van der Klauw MM, van der Meer P, Wolffenbuttel BHR, et al. Active smoking and macrocytosis in the general population: Two population-based cohort studies. Am J Hematol. 2019;94:E45–8. https://doi.org/10.1002/ajh.25346.
28. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol. 2014;34:509–15. https://doi.org/10.1161/ATVBAHA.113.300156.
29. Das Kumar S, Vasudevan DM. Alcohol induced effects on kidney. Indian J Clin Biochem IJCB. 2008;23:4–9. https://doi.org/10.1007/s12291-008-0003-9.
30. Valdivielso JM, Jacobs-Cachá C, Soler MJ. Sex hormones and their influence on chronic kidney disease. Curr Opin Nephrol Hypertens. 2019;28:1–9. https://doi.org/10.1097/MNH.0000000000000463.
31. O'Donnell E, Floras JS, Harvey PJ. Estrogen status and the renin angiotensin aldosterone system. Am J Physiol Regul Integr Comp Physiol. 2014;307:R498–500. https://doi.org/10.1152/ajpregu.00182.2014.

32. Park JY, Chung Y-J, Song J-Y, Kil KC, Lee HY, Chae J, et al. Sarcopenic Obesity: A Comprehensive Approach for Postmenopausal Women. J Menopausal Med. 2024;30:143–51. https://doi.org/10.6118/jmm.24004.
33. Czaja-Stolc S, Potrykus M, Stankiewicz M, Kaska Ł, Małgorzewicz S. Pro-Inflammatory Profile of Adipokines in Obesity Contributes to Pathogenesis, Nutritional Disorders, and Cardiovascular Risk in Chronic Kidney Disease. Nutrients. 2022;14:1457. https://doi.org/10.3390/nu14071457.
34. Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. Semin Thromb Hemost. 2003;29:435–50. https://doi.org/10.1055/s-2003-44551.
35. Barshtein G, Gural A, Arbell D, Barkan R, Livshits L, Pajic-Lijakovic I, et al. Red Blood Cell Deformability Is Expressed by a Set of Interrelated Membrane Proteins. Int J Mol Sci. 2023;24:12755. https://doi.org/10.3390/ijms241612755.
36. Kyriacou RP, Shibeeb S. Red Blood Cells and Human Aging: Exploring Their Biomarker Potential. Diagnostics. 2025;15:1993. https://doi.org/10.3390/diagnostics15161993.
37. Denic A, Glassock RJ, Rule AD. Structural and Functional Changes With the Aging Kidney. Adv Chronic Kidney Dis. 2016;23:19–28. https://doi.org/10.1053/j.ackd.2015.08.004.

Figures

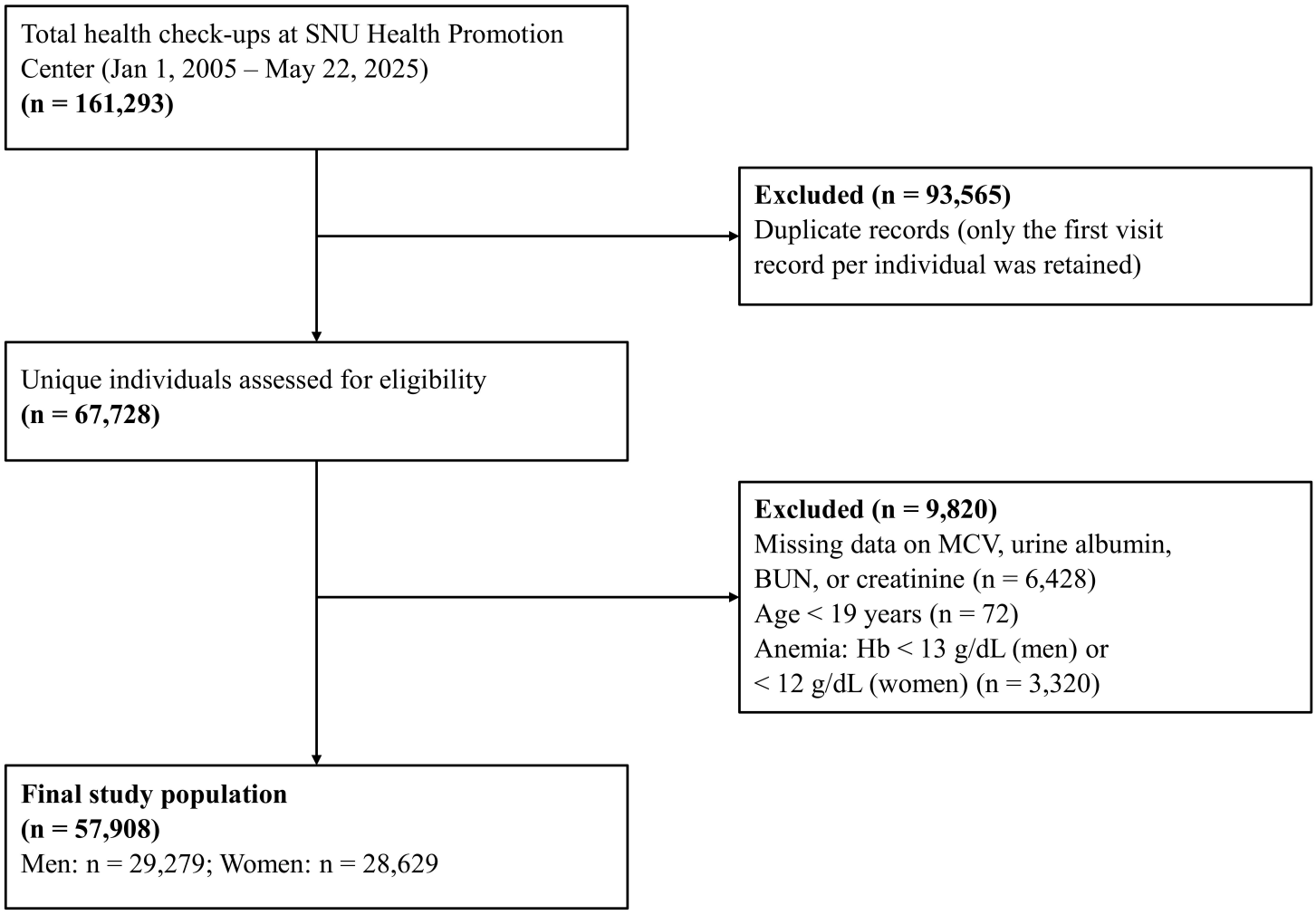


Figure 1

Flow diagram of the study population. SNU, Seoul National University; MCV, mean corpuscular volume; BUN, blood urea nitrogen; Hb, hemoglobin.

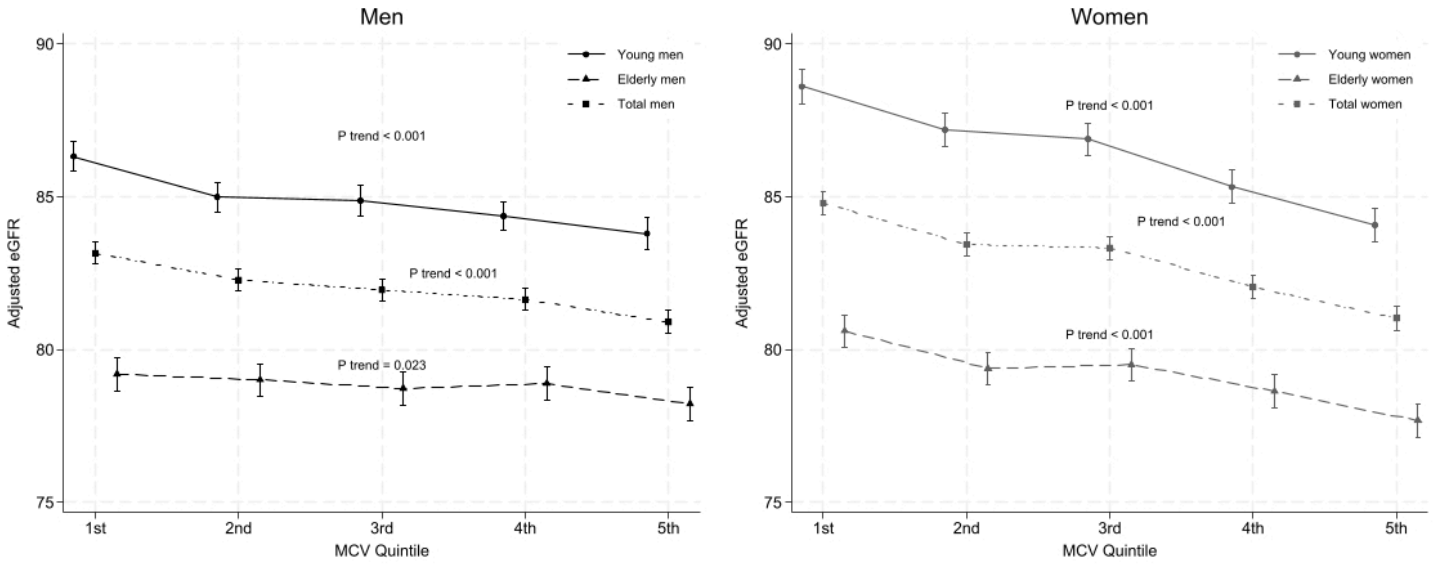


Figure 2

Adjusted mean estimated glomerular filtration rate (eGFR) according to MCV quintile, adjusted for age, body mass index, hypertension, diabetes mellitus, red cell distribution width, hemoglobin, smoking status, alcohol intake, and exercise. Data are presented as estimated mean eGFR and standard error of the mean, with the P for trend provided for each group. Adjusted eGFR values were estimated from imputed datasets.

Supplementary Files

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