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Subclinical Renal Dysfunction and Cognitive Performance: Cross-Sectional Associations and the Confounding Effect of Age After Adjustment for Blood Pressure and Metabolic Covariates

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ABSTRACT

Objectives: This study aimed to examine whether C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), hemoglobin A1c (HbA1c), low-density lipoprotein-to-high-density lipoprotein (LDL/HDL) ratio, and triglycerides were associated with cognitive performance after adjustment for blood pressure, age, sex, education, and body mass index (BMI), and to determine the extent to which any renal–cognitive association was independent of age.
Methods: Cross-sectional baseline data from 100 adults, comprising 50 young (aged 18-35 years) and 50 older (aged 60-75 years) individuals, were analyzed. Seven multivariable linear regression models were constructed, incorporating five biomarkers and five covariates. Partial correlations, variance partitioning, and a correlation-based sensitivity analysis were used to characterize the influence of age on the eGFR-cognition association.
Results: After adjustment, eGFR was the only biomarker significantly associated with six of seven cognitive outcomes (partial r=0.24-0.41; all $p<0.05$), whereas CRP, HbA1c, LDL/HDL ratio, and triglycerides were not significantly associated. Age and eGFR were strongly correlated (r=-0.74). The eGFR accounted for only 0.6-1.3% of the unique outcome variance, and all five biomarkers combined accounted for ≤2.0%. In the correlation-based sensitivity analysis, the zero-crossing for the digit symbol substitution test (DSST), N-back, and Rey Auditory Verbal Learning Test (RAVLT) fell outside the mathematically admissible range. However, this finding merely described the observed correlation structure and does not establish independence from age.
Conclusion: Lower eGFR was associated with poorer cognitive performance after adjustment for blood pressure and other measured covariates. However, its unique contribution was small and remained substantially intertwined with age, which is a component of the chronic kidney disease epidemiology collaboration (CKD-EPI) equation. These findings supported a cross-sectional association rather than an age-independent or causal renal effect, highlighting the need for confirmation using age-independent renal markers and longitudinal study designs.

Keywords: Estimated glomerular filtration rate; C-reactive protein; Hemoglobin A1c; Cognitive performance; Blood pressure; Kidney-brain axis

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Introduction

Cognitive decline represents one of the most significant public health challenges of the present era, with prevalence rising sharply as global populations age. Among the modifiable biological factors associated with cognitive deterioration, cardiovascular and cardiometabolic risk factors have attracted substantial scientific attention [1, 2]. Hypertension, dyslipidemia, insulin resistance, and systemic inflammation have each been individually implicated in impaired brain health through mechanisms including endothelial dysfunction, neuroinflammation, disrupted cerebral perfusion, and white-matter lesion accumulation [3, 4]. However, despite considerable progress in identifying these risk factors in isolation, comparatively little work has examined their relative contributions to cognitive performance within the same analytical framework, particularly after rigorous adjustment for blood pressure, the dominant vascular risk factor [5, 6].

Renal function, as indexed by estimated glomerular filtration rate (eGFR), has emerged as a particularly underexplored determinant of cognitive health. Emerging evidence suggests that reduced renal filtration capacity may compromise brain function through mechanisms distinct from hypertension alone, including the accumulation of uremic neurotoxins such as indoxyl sulphate and p-cresyl sulfate, impaired clearance of neurotoxic metabolites, heightened oxidative stress, and dysregulation of the renin-angiotensin-aldosterone system at the cerebrovascular level [7, 8]. Epidemiological studies reported cross-sectional and prospective associations between chronic kidney disease and accelerated cognitive decline. However, whether sub-clinical reductions in eGFR, within ranges commonly observed in community-dwelling older adults without formal kidney disease diagnoses, are associated with cognitive performance after accounting for blood pressure and metabolic covariates remains inadequately addressed [9, 10].

Systemic low-grade inflammation, measured by high-sensitivity C-reactive protein (CRP), has similarly been proposed as a mediating pathway linking vascular risk to neural dysfunction. Elevated CRP has been associated with reduced hippocampal volume, impaired executive function, and faster cognitive decline in prospective cohort studies [11, 12]. Glycemic dysregulation, characterized by elevated hemoglobin A1c (HbA1c) and fasting glucose, may independently compromise cognitive function through advanced glycation end-product accumulation, neuronal insulin resistance, and increased susceptibility to cerebral small-vessel disease. Dyslipidemia, particularly an elevated low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio and hypertriglyceridemia, has been proposed to accelerate cerebrovascular atherosclerosis and impair synaptic membrane composition. Nevertheless, a fundamental analytical challenge pervades this literature: many of these biomarkers are intercorrelated and co-vary substantially with age and blood pressure, raising the possibility that their reported univariate associations with cognition are confounded rather than causal [13, 14].

The present study simultaneously included CRP, eGFR, HbA1c, LDL/HDL ratio, and triglycerides in multivariable regression models with clinical systolic blood pressure, age, sex, education, and body mass index (BMI) to identify biomarker associations that remained after adjustment for the measured covariates. Since the chronic kidney disease epidemiology collaboration (CKD-EPI) equation incorporates age and sex, eGFR was treated as an age-linked estimate rather than an age-independent exposure, and the renal-cognitive association was interpreted with explicit attention to age-related confounding.

Materials and Methods

This study employed a cross-sectional analysis of baseline data from a prospective longitudinal cohort investigating the relationships among blood pressure, cardiometabolic biomarkers, and cognitive performance in young and older adults. The full cohort design comprises three assessment waves: baseline (T0), 12 months (T1), and 24 months (T2). The present analysis is confined to baseline observations.

A total of 100 participants were enrolled across two age cohorts: young adults aged 18-35 years (n=50) and older adults aged 60-75 years (n=50). Participants were eligible if they were able to provide informed consent, were fluent in the language of cognitive testing, and were willing to undergo blood sampling, blood pressure measurement, and cognitive assessment at each study wave. Individuals were excluded if they reported a history of stroke, epilepsy, major traumatic brain injury, dementia, unstable psychiatric illness, substance dependence, or severe uncorrected sensory impairment that could compromise test validity. Participants with secondary hypertension or active malignancy were also excluded to reduce etiological heterogeneity. Sample size was determined a priori for the parent longitudinal cohort. With n=100 and 10 predictors, the primary models yield 10 observations per predictor. Although this meets a commonly cited heuristic, it does not guarantee the stability of model estimates. For the omnibus model (10 predictors, $\alpha=0.05$, two-tailed), achieved power was 0.71 for a medium effect ($f^2=0.15$) and 0.99 for a large effect ($f^2=0.35$). For the incremental contribution of a single predictor, 80% power corresponded to $f^2=0.080$. Accordingly, the study had limited power to detect small independent biomarker effects, particularly across seven cognitive outcomes, and nonsignificant biomarker estimates should be interpreted cautiously.

Venous blood samples were collected in the morning following a minimum 8-hour overnight fast. The CRP was measured using high-sensitivity immunoturbidimetry. Glycemic status was assessed via glycated hemoglobin (HbA1c, %) using high-performance liquid chromatography and fasting plasma glucose (mg/dL) using the enzymatic hexokinase method. The lipid profile, including total cholesterol, LDL, HDL, and triglycerides (all in mg/dL), was determined using standard enzymatic colorimetric assays. The LDL/HDL atherogenic ratio was computed as a derived variable. Renal function was indexed by serum creatinine (mg/dL) and eGFR (mL/min/1.73m²), calculated using the CKD-EPI equation incorporating age and sex. Hemoglobin (g/dL) was measured via automated complete blood count [15, 16].

All participants completed a standardized multidomain cognitive battery administered by trained examiners under uniform conditions. Global cognition was assessed using the Montreal Cognitive Assessment (MoCA; range 0-30). Processing speed was evaluated with the Digit Symbol Substitution Test (DSST; number of correct responses in 90 seconds) and Trail Making Test Part A (TMT-A; completion time in seconds). Executive function was assessed using the Trail Making Test Part B (TMT-B; completion time in seconds) and the Stroop Color-Word Interference Test. Working memory was measured with the Digit Span Backward test and the 2-back task (accuracy, %). Episodic memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT; 5-trial immediate total). Simple reaction time (ms) was recorded as an index of basic motor response speed.

Descriptive statistics were expressed as mean±standard deviation (SD) for continuous variables and frequencies with percentages for categorical variables. Between-cohort comparisons for continuous biomarkers were performed using independent-samples t-tests following verification of normality. Bivariate relationships between biomarkers and cognitive outcomes were examined using Pearson correlation coefficients. Multivariable linear regression models were constructed for each cognitive outcome, with all five primary biomarkers entered simultaneously as predictors alongside clinical systolic blood pressure, age, sex, education (years), and BMI as covariates. Statistical significance was set at $p<0.05$ (two-tailed). All analyses were conducted using Python (version 3.12) with the statsmodels and SciPy libraries.

Model Specification and Predictor Entry

All five biomarkers and the five covariates were entered simultaneously, consistent with the prespecified study question. Automated forward, backward, or stepwise selection was avoided because such procedures can increase type I error, introduce bias into coefficient and standard-error estimates, and yield unstable selected models, particularly in modest samples.

Coefficient Scaling

Continuous predictors were standardized as z-scores, while cognitive outcomes remained in their original units. Accordingly, the reported β coefficients represented the change in the outcome associated with a 1-SD increase in the predictor and were not directly comparable across outcomes. Partial correlations were also reported as scale-independent measures of effect size.

Regression Diagnostics

Model assumptions were evaluated using residual and quantile-quantile plots, the Shapiro-Wilk and Breusch-Pagan tests, the Durbin-Watson statistic, Cook's distance, and standardized residuals. Collinearity was assessed using VIF/tolerance and condition indices; a VIF>5 or a condition index >30 prompted further scrutiny.

Age and eGFR

Since age and sex are inputs to the CKD-EPI equation, the age–eGFR correlation and collinearity diagnostics were reported explicitly. Semipartial squared correlations were used to quantify biomarker-specific variance, and partial correlations described eGFR–cognition associations after adjustment for age, sex, education, BMI, systolic blood pressure, and the other biomarkers. These analyses characterized residual associations after covariate adjustment but did not establish an age-independent renal effect.

Sensitivity Analysis for Age Confounding

A correlation-based sensitivity analysis was conducted by varying the age–cognition correlation across values compatible with the observed age–eGFR and eGFR–cognition correlations while maintaining a positive semidefinite three-variable correlation matrix. The age–cognition correlation at which the age-adjusted partial correlation between eGFR and cognition reached zero was used as a sensitivity descriptor. This analysis evaluated the observed correlation structure under alternative assumptions about the age–cognition relationship but did not establish that the eGFR–cognition association was independent of age.

Results

Baseline biomarker characteristics are shown in Table 1. Compared with young adults, older adults had a lower eGFR (72.96±12.19 vs. 101.03±11.82 mL/min/1.73m²; $p<0.001$) and modestly higher creatinine, CRP, HbA1c, fasting glucose, triglycerides, and total cholesterol (all $p<0.05$). HDL cholesterol, LDL/HDL ratio, and hemoglobin did not differ significantly between groups. The eGFR difference was large (d=2.34), consistent with the strong age–eGFR relationship examined below.

Table 1. Baseline biomarker profiles by age cohort and between-group differences

Variable	Young adults (n=50) Mean±SD	Older adults (n=50) Mean±SD	Total (n=100) Mean±SD	*p* value
Inflammatory marker				
CRP (mg/L)	1.59±0.94	2.09±1.11	1.84±1.05	0.016
Renal function				
eGFR (mL/min/1.73m²)	101.03±11.82	72.96±12.19	87.00±18.48	<0.001
Creatinine (mg/dL)	0.88±0.18	0.99±0.18	0.94±0.19	0.003
Glycemic markers				
HbA1c (%)	5.43±0.40	5.72±0.93	5.58±0.73	0.043
Fasting glucose (mg/dL)	90.87±13.98	97.25±16.88	94.06±15.75	0.042
Lipid profile				
Total cholesterol (mg/dL)	179.92±30.46	193.50±29.59	186.71±30.64	0.026
LDL cholesterol (mg/dL)	112.58±27.16	122.47±26.93	117.52±27.36	0.071
HDL cholesterol (mg/dL)	54.86±10.37	53.55±9.76	54.20±10.04	0.517
LDL/HDL ratio	2.15±0.70	2.37±0.68	2.26±0.70	0.117
Triglycerides (mg/dL)	119.04±35.52	139.27±37.20	129.15±37.59	0.007
Hemoglobin (g/dL)	13.57±1.15	13.62±1.19	13.60±1.17	0.825

CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

Table 2. Pearson correlation coefficients between primary biomarkers and cognitive domain scores at baseline (n=100)

Biomarker	MoCA	DSST Correct	TMT-B (s)	N-back Acc (%)	RAVLT Total	Digit Span Bwd	Simple RT (ms)
CRP (mg/L)	-0.216*	-0.235*	+0.238*	-0.236*	-0.237*	-0.236*	+0.239*
eGFR (mL/min/1.73m²)	+0.697***	+0.745***	-0.701***	+0.741***	+0.741***	+0.698***	-0.616***
HbA1c (%)	-0.188	-0.197*	+0.206*	-0.202*	-0.208*	-0.163	+0.266**
LDL/HDL ratio	-0.145	-0.167	+0.167	-0.168	-0.172	-0.146	+0.123
Triglycerides (mg/dL)	-0.230*	-0.254*	+0.240*	-0.252*	-0.255*	-0.208*	+0.206*

*p<0.05; **p<0.01; *** p<0.001. For TMT-B and Simple RT, higher scores indicate worse performance; for all other outcomes, higher scores indicate better performance. MoCA: Montreal cognitive assessment; DSST: Digit symbol substitution test; TMT-B: Trail making test part B; RAVLT: Rey auditory verbal learning test

Table 3. Multivariable regression analysis: Associations of biomarkers with baseline cognitive outcomes

Cognitive Outcome	CRP β (95% CI)	eGFR β (95% CI)	HbA1c β (95% CI)	LDL/HDL β (95% CI)	Triglycerides β (95% CI)	R^2	adj. R^2
MoCA total	+0.063 (-0.096, +0.223)	+0.313 (+0.091, +0.535)**	+0.033 (-0.128, +0.194)	+0.150 (-0.020, +0.319)	+0.108 (-0.068, +0.285)	0.918	0.909
DSST correct	+0.120 (-0.717, +0.957)	+2.461 (+1.300, +3.623)[c]	+0.361 (-0.484, +1.207)	+0.557 (-0.330, +1.445)	+0.487 (-0.438, +1.413)	0.954	0.949
TMT-B (seconds)	+0.039 (-2.266, +2.345)	−3.732 (-6.931, -0.534)[a]	+0.082 (-2.246, +2.411)	-0.841 (-3.285, +1.603)	-1.419 (-3.967, +1.130)	0.909	0.899
N-back accuracy (%)	+0.037 (-0.289, +0.363)	+0.897 (+0.445, +1.349)[c]	+0.092 (-0.237, +0.421)	+0.197 (-0.149, +0.542)	+0.200 (-0.160, +0.561)	0.951	0.946
RAVLT total	+0.028 (-0.410, +0.466)	+1.131 (+0.524, +1.739)[c]	+0.074 (-0.368, +0.517)	+0.210 (-0.254, +0.675)	+0.236 (-0.248, +0.720)	0.949	0.943
Digit span backward	-0.006 (-0.101, +0.090)	+0.199 (+0.067, +0.331)[b]	+0.034 (-0.062, +0.130)	+0.037 (-0.064, +0.138)	+0.101 (-0.004, +0.206)	0.873	0.859
Simple RT (ms)	+1.197 (-3.170, +5.564)	-0.636 (-6.695, +5.424)	+2.832 (-1.579, +7.243)	-1.913 (-6.543, +2.717)	-0.860 (-5.688, +3.968)	0.774	0.748

[a] p<0.05; [b] p<0.01; [c] p<0.001. All models include adjustment for SBP (clinic), age (continuous), sex (binary), education (years), and BMI. CI: Confidence interval; Ns: Non-significant; TMT-B and Simple RT: Higher values indicate worse performance. β: semi-standardized coefficient: predictors standardized to z-scores, outcomes in native units; β therefore expresses change in the cognitive score per 1-SD increment in the predictor and is not comparable across outcomes measured on different scales.

Bivariate correlations are presented in Table 2. The eGFR showed the strongest correlations with all seven cognitive outcomes (|r|=0.616-0.745; all p<0.001). The CRP and triglycerides showed smaller associations across several outcomes, HbA1c was associated with a subset of outcomes, and the LDL/HDL ratio was not significant at the bivariate level.

Covariate-adjusted biomarker associations are shown in Table 3 and Figure 1. All five biomarkers were entered into the models alongside clinical systolic blood pressure, age, sex, education, and BMI. Diagnostic checks did not identify major violations of model assumptions. All predictors had a VIF<5 and condition indices <30.

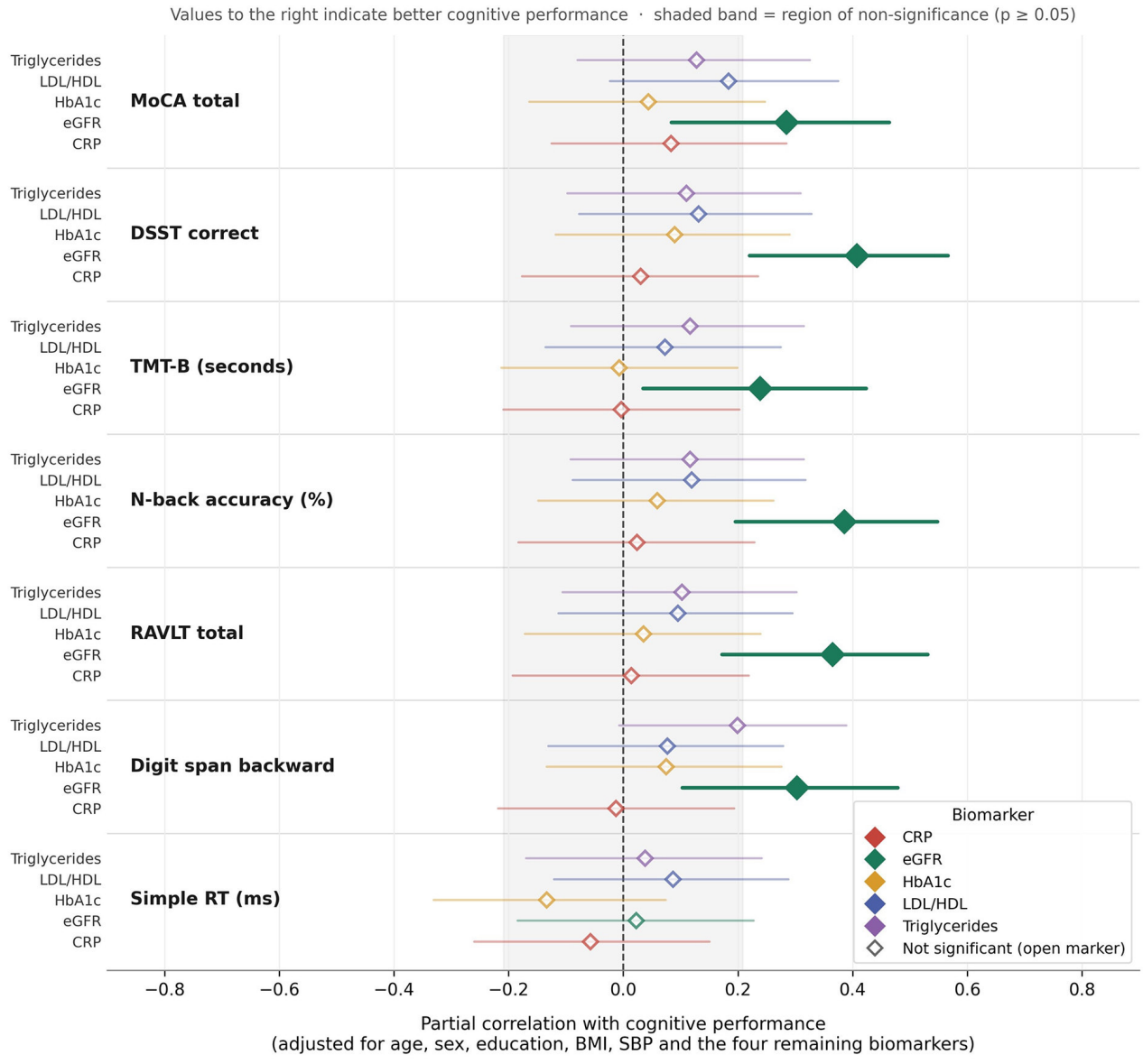

Fig. 1. Adjusted partial correlations are shown between cardiometabolic biomarkers and baseline cognitive performance.

After multivariable adjustment, eGFR was significantly associated with six of seven cognitive outcomes: MoCA, DSST, TMT-B, N-back accuracy, RAVLT total, and Digit Span Backward (all $p<0.05$; Table 3). The corresponding partial correlations ranged from 0.24 to 0.41, and eGFR explained only 0.6–1.3% of the unique outcome variance (Table 4). Simple reaction time was not significantly associated with eGFR after adjustment.

CRP, HbA1c, LDL/HDL ratio, and triglycerides were nonsignificant in the fully adjusted models. Their attenuation was consistent with shared covariation with age, blood pressure, BMI, and the other biomarkers, although the limited sample size precludes the exclusion of small independent effects. Adjusted R^2 values ranged from 0.748 to 0.949, whereas the five biomarkers together accounted for only 0.7 to 2.0% of unique variance. Thus, most of the explained variance was attributable to the covariate block.

As shown in Figure 1, the forest plot of partial correlations between each of the five primary biomarkers and baseline cognitive performance across seven outcomes was adjusted for age, sex, education, BMI, systolic blood pressure, and the four remaining biomarkers (df=89). Partial correlations are presented instead of regression coefficients as the seven outcomes are measured on different scales. Therefore, the semi-standardized β coefficients reported in Table 3 are not directly comparable across outcomes. The partial correlation provides a scale-free metric on a common axis. Horizontal lines indicate 95% confidence intervals derived by Fisher z-transformation. Filled diamonds denote statistical significance ($p<0.05$); open diamonds denote non-significance, and the shaded band marks the region $|r|<0.209$, in which the partial correlation does not reach significance at df=89. For TMT-B and simple reaction time, where higher raw scores indicate worse performance, the sign has been reversed

Table 4. Collinearity diagnostics and variance partitioning for eGFR across cognitive outcomes (n=100)

Cognitive outcome	Bivariate r (eGFR)	Partial r (adjusted)	sr^2 (unique)	Unique variance (%)	Model R^2	*p value*
MoCA total	+0.697	+0.285	0.0072	0.72	0.918	0.006
DSST correct	+0.745	+0.408	0.0092	0.92	0.954	<0.001
TMT-B (seconds)	-0.701	-0.239	0.0055	0.55	0.909	0.023
N-back accuracy (%)	+0.741	+0.386	0.0086	0.86	0.951	<0.001
RAVLT total	+0.741	+0.365	0.0078	0.78	0.949	<0.001
Digit span backward	+0.698	+0.303	0.0128	1.28	0.873	0.004
Simple RT (ms)	-0.616	-0.022	0.0001	0.01	0.774	0.835

Partial r: correlation was calculated between eGFR and the cognitive outcome with age, sex, education, BMI, systolic blood pressure, and the four remaining biomarkers held constant (df=89). sr^2=semi-partial squared correlation, i.e., the proportion of total outcome variance uniquely attributable to eGFR. Age–eGFR correlation r=−0.74; VIF for eGFR ≈2.2 (tolerance≈0.45); all predictors VIF<5; no condition index exceeded 30. Residual normality (Shapiro–Wilk), homoscedasticity (Breusch–Pagan), and independence (Durbin–Watson 1.8–2.2) assumptions were satisfied in all models.

Table 5. Correlation-based sensitivity analysis of the eGFR-cognition association to age-related confounding.

Cognitive outcome	Bivariate r (eGFR)	Admissible range of r (age, cognition)	Zero-crossing r (age, cognition) for partial r=0
MoCA total	+0.697	-0.998 to-0.033	-0.942
DSST correct	+0.745	-1.000 to-0.103	-1.007 (unattainable)
TMT-B (seconds)	-0.701	+0.039 to +0.998	+0.947
N-back accuracy (%)	+0.741	-1.000 to -0.097	-1.001 (unattainable)
RAVLT total	+0.741	-1.000 to -0.097	−1.001 (unattainable)
Digit span backward	+0.698	-0.998 to -0.035	-0.943
Simple RT (ms)	-0.616	-0.074 to +0.986	+0.832

Values were calculated assuming r (age, eGFR)=-0.74. The admissible range ensures that the age–eGFR–cognition correlation matrix remains positive semidefinite. The zero-crossing represents the age–cognition correlation at which the age-adjusted eGFR–cognition partial correlation equals zero. A value outside the admissible range indicates only that zero is not reached within this three-variable mathematical framework and does not establish independence from age. For TMT-B and Simple RT, higher raw scores indicate worse performance.

so that values to the right of zero indicate better cognitive performance throughout. The color coding was as follows: green for eGFR, red for CRP, amber for HbA1c, indigo for the LDL/HDL ratio, and violet for triglycerides. The eGFR was the only biomarker whose confidence intervals excluded zero, doing so for six of the seven outcomes.

Age and eGFR were strongly inversely correlated (r=−0.74, p=0.001). The VIF for eGFR was approximately 2.2 (tolerance approximately 0.45), and all predictors had VIF<5, suggesting no severe numerical collinearity. However, as age was an input to the CKD-EPI equation, these diagnostics did not establish that the eGFR-cognition association was independent of age. Serum creatinine showed a smaller cohort difference than eGFR (d=0.61 vs. 2.34), reinforcing the need for cautious interpretation.

Table 4 summarizes the attenuation of the eGFR-cognition association after adjustment. Partial correlations were 0.24–0.41 for the six significant outcomes, and eGFR uniquely accounted for 0.55–1.28% of outcome variance. All five biomarkers together accounted for 0.70–1.95%. Since total R^2 values were much larger (0.774-0.954), most explained variance was attributable to the covariate block. The use of an extreme-groups age design likely contributed substantially to the high model fit, which should not be interpreted as evidence of strong biomarker predictive performance.

A correlation-based sensitivity analysis was conducted by holding the observed age–eGFR correlation (r=-0.74) and the observed eGFR–cognition correlations fixed while varying the age–cognition correlation across mathematically admissible values (Table 5). This analysis describes the sensitivity of the observed three-variable correlation structure and is not a test of an age-independent renal effect.

Within this mathematical framework, the zero-crossing lay outside the admissible range for DSST, N-back accuracy, and RAVLT, and occurred at approximately |r|=0.94-0.95 for MoCA, digit span backward, and TMT-B. For simple reaction time, it occurred at r=0.83. These values indicated how strongly the assumed age–cognition correlation would need to change the observed partial correlation within this framework. However, they do not demonstrate that the eGFR–cognition association is independent of age or exclude residual age-related confounding.

Discussion

The present study investigated whether baseline inflammatory, metabolic, and renal biomarkers were associated with cognitive performance in young and

older adults after adjustment for blood pressure, age, sex, education, and BMI. Four main observations emerged.

First, older adults demonstrated a significantly more adverse cardiometabolic and inflammatory profile at baseline than their younger counterparts, characterized by markedly reduced renal filtration capacity, elevated systemic inflammation, higher triglyceride levels, and mild glycemic dysregulation. These between-cohort differences were largely consistent with the known trajectory of cardiometabolic ageing and aligned with prior epidemiological data linking advancing age to progressive renal decline, low-grade chronic inflammation, and dyslipidemia. Notably, not all biomarkers differed between cohorts; LDL/HDL ratio and hemoglobin remained comparable across age groups, suggesting that certain cardiometabolic indices might be relatively preserved in the older adults recruited under this study's strict exclusion criteria [17, 18].

Second, bivariate analyses revealed broad associations between biomarkers and cognitive performance. However, after multivariable adjustment, only eGFR reached statistical significance across six of seven domains. This pattern is directionally consistent with evidence linking kidney dysfunction to cognitive outcomes [19-21]. Potential mechanisms include uremic toxin accumulation, cerebral microvascular dysfunction, oxidative stress, and impaired metabolite clearance. However, the cross-sectional design of the present study could not distinguish these mechanisms from shared ageing processes, and the unique variance attributable to eGFR was small.

Third, CRP, HbA1c, triglycerides, and LDL/HDL ratio were not statistically significant after adjustment. This attenuation is compatible with confounding and shared covariation among cardiometabolic factors. However, the study was not adequately powered to detect small independent biomarker effects. Therefore, the non-significant estimates should be regarded as inconclusive rather than evidence of no association. Longitudinal and mechanistic analyses might clarify whether weaker effects emerge over time [22, 23].

Fourth, interpretation of eGFR was constrained by its dependence on age in the CKD-EPI equation. Age and eGFR were strongly correlated (r=-0.74). Although the VIF for eGFR was only approximately 2.2, this indicated an absence of severe numerical instability rather than the separation of renal function from age. Therefore, the correlation-based sensitivity analysis provided only a mathematical assessment of the observed correlation structure and did not establish an age-independent eGFR effect. Confirmation will require renal markers that do not incorporate age, such as cystatin C or measured GFR, together with longitudinal within-person analyses.

The extreme-groups sampling design also requires caution. Recruiting two non-overlapping age strata increased age-related separation across both biomarkers and cognitive scores and likely contributed substantially to the high adjusted R^2 values (0.748-0.949). Since the five biomarkers together accounted for less than 2% of unique variance in every model, the high R^2 values should not be interpreted as evidence of strong biomarker prediction.

With respect to clinical significance, the mean difference in eGFR between cohorts (28.07 mL/min/1.73 m^2) was substantial in magnitude and corresponded to a very large standardized effect (d=2.34). Nevertheless, this finding should be interpreted carefully. The mean eGFR in the older-adult cohort (72.96 mL/min/1.73m^2) falls within kidney disease: improving global outcomes (KDIGO) category G2, which denotes mildly decreased filtration and is not, in itself, diagnostic of chronic kidney disease in the absence of markers of kidney damage. It also does not approach the G3a threshold of 60 mL/min/1.73m^2. The cohort difference was therefore consistent with normal age-related decline in filtration rather than with subclinical kidney disease per se. Accordingly, the term subclinical renal dysfunction should be understood throughout as describing position within the normal-to-mildly-reduced range rather than as an indication of occult pathology.

Several limitations should be considered when interpreting these findings. First, the cross-sectional design precludes establishing the temporal ordering between renal filtration and cognitive performance. Thus, the data supported an association but could not establish a causal or independent contribution of renal function to cognition. Second, the exposure was estimated rather than directly measured. Furthermore, as the estimating equation incorporated age and sex, the exposure was structurally entangled with the principal confounder, as discussed above. Third, the extreme-groups design excluded the middle of the adult age range, precluding examination of the continuous age–eGFR–cognition gradient and inflating the apparent model fit.

Fourth, although the sample of 100 participants provided 10 observations per predictor, this rule of thumb did not, by itself, establish adequate model stability. With 10 predictors and seven cognitive outcomes, the analysis had high power to detect large effects (0.99 for f^2=0.35), moderate power to detect a medium omnibus effect (0.71 for f^2=0.15), and 80% power only for a single-predictor increment of f^2=0.080. Therefore, small independent effects of CRP, HbA1c, LDL/HDL ratio, or triglycerides might have gone undetected, and the non-significant estimates should be interpreted cautiously. Replication in a larger sample with a continuous age distribution is required.

Fifth, the correlation-based sensitivity analysis represented a mathematical assessment of the observed correlation structure rather than evidence

that the eGFR–cognition association was independent of age. As eGFR incorporated age, and the study was cross-sectional, residual age-related confounding could not be excluded. A more decisive evaluation requires longitudinal within-person data and renal measures that do not contain age in their derivation, such as cystatin C or measured GFR.

In conclusion, this cross-sectional baseline analysis found that eGFR was the only one of the five examined biomarkers to reach statistical significance after adjustment for blood pressure, age, sex, education, and BMI across six of seven cognitive outcomes. The unique variance attributable to eGFR was small (0.6–1.3%), while the high overall model fit largely reflected the covariate block in an extreme-groups age design. Since eGFR incorporated age and sex and was strongly correlated with age in this sample, the observed association could not be interpreted as an age-independent or causal renal contribution. The limited sample size also reduced sensitivity to small independent biomarker effects. Confirmation using age-independent renal markers, a continuous age distribution, and longitudinal within-person analysis is required.

Declaration

Ethics Approval and Consent to Participate: The study was conducted in accordance with the Declaration of Helsinki, and all participants provided written informed consent before participation. The ethics document supplied for verification was issued by the Institutional Ethics Committee of Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals (VMKVMC&H), Salem, Tamil Nadu, India (Tracking No. VMKVMC&H/IEC/24/007; meeting date 07 February 2024; letter dated 08 February 2024). The supplied letter is titled 'Association of Vitamin D status and thyroid dysfunction in type 2 Diabetes Mellitus' and therefore cannot be cited as documentary verification of ethics approval for the renal-function and cognition protocol described in this manuscript.

Consent for Publication: The manuscript does not present identifiable individual participant information.

Conflict of Interests: The authors declare no conflict of interests.

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