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ORIGINAL ARTICLE

Subclinical Renal Dysfunction and Cognitive Impairment and Independent Associations After Adjustment for Blood Pressure and Metabolic Covariates

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Abstract

Background: Hypertension and cardiometabolic dysregulation are established contributors to cognitive decline; however, the independent roles of renal function, systemic inflammation, and lipid metabolism in cognitive performance remain incompletely characterised, particularly across age groups.

Objectives: To determine whether baseline CRP, eGFR, HbA1c, LDL/HDL ratio, and triglycerides are independently associated with cognitive performance after adjustment for blood pressure, age, sex, education, and BMI.

Methods: Cross-sectional baseline data from 100 participants — 50 young adults (18–35 years) and 50 older adults (60–75 years) — were analysed. Multivariable linear regression models were fitted for seven cognitive outcomes spanning global cognition, processing speed, executive function, working memory, and episodic memory.

Results: After full covariate adjustment, eGFR was the sole biomarker independently associated with cognitive performance across five domains (β range: 0.199–2.461; all $p < 0.05$). CRP, HbA1c, LDL/HDL ratio, and triglycerides were attenuated to non-significance in adjusted models.

Conclusion: Renal function independently predicts cognitive performance beyond blood pressure burden, implicating the kidney-brain axis as a distinct pathway in cognitive ageing.

Key words: estimated glomerular filtration rate, C-reactive protein, HbA1c, cognitive performance, blood pressure, kidney-brain axis, cardiometabolic risk, ageing, processing speed, episodic memory

1 | 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 variables have attracted substantial scientific attention (1, 2) . Hypertension, dyslipidaemia, 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) . Yet despite considerable progress in identifying these risk factors in isolation, comparatively little work has examined their independent contributions

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to cognitive performance within the same analytical framework — particularly after rigorous adjustment for blood pressure, the dominant vascular risk variable (5, 6) .

Renal function, indexed by estimated glomerular filtration rate, 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 accumulation of uraemic neurotoxins such as indoxyl sulphate and p-cresyl sulphate, impaired clearance of neurotoxic metabolites, heightened oxidative stress, and dysregulation of the renin-angiotensin-aldosterone system at the cerebrovascular level (7, 8) . Epidemiological studies have 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 — independently predict 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, 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) . Glycaemic dysregulation, characterised by elevated 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. Dyslipidaemia — particularly an elevated LDL/HDL ratio and hypertriglyceridaemia — 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 covary 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 addresses this gap directly by simultaneously entering five cardiometabolic biomarkers — CRP, eGFR, HbA1c, LDL/HDL ratio, and triglycerides — into multivariable regression models alongside clinic systolic blood pressure, age, sex, education, and BMI, to determine which biomarkers retain independent associations with cognitive performance across multiple domains. Using cross-sectional baseline data from a longitudinal cohort of 100 young and older adults, this analysis offers a rigorous, jointly adjusted assessment of the relative contributions of inflammatory, glycaemic, lipid, and renal indices to cognitive function — and provides a foundation for subsequent longitudinal mediation analyses examining these pathways over 24 months of follow-up.

2 | MATERIALS AND METHODS

Study Design and Setting

This study employed a cross-sectional analysis of baseline data drawn from a prospective longitudinal cohort investigation examining the relationships between blood pressure, cardiometabolic biomarkers, and cognitive performance in young and older adults. The full cohort design comprises three repeated assessment waves at baseline (T0), 12 months (T1), and 24 months (T2); the present analysis is confined to baseline observations. Ethical approval was obtained from the institutional review board prior to recruitment, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Participants

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 aetiological heterogeneity.

Laboratory Biomarker Assessment

Venous blood samples were collected in the morning following a minimum eight-hour overnight fast. Serum C-reactive protein (CRP) was measured using high-sensitivity immunoturbidimetry. Glycaemic status was assessed by glycated haemoglobin (HbA1c, %) using high-performance liquid chromatography and fasting plasma glucose (mg/dL) using the enzymatic hexokinase method. Lipid profile including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (all 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 estimated glomerular filtration rate (eGFR, mL/min/1.73m^2), calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation incorporating age and sex. Haemoglobin (g/dL) was measured by automated complete blood count (15, 16) .

Cognitive Assessment

All participants completed a standardised 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 Trail Making Test Part B (TMT-B; completion time in seconds) and the Stroop Colour-Word Interference Test. Working memory was measured with digit span backward 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.

Statistical Analysis

Descriptive statistics were expressed as mean ± standard deviation for continuous variables and frequency with percentage 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 clinic systolic blood pressure, age, sex, education (years), and BMI as covariates. All continuous predictors were standardised to z-scores prior to entry, allowing direct comparison of β coefficients across predictors of differing units. 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.

3 | RESULT

Baseline Biomarker Profiles by Age Cohort

Bivariate Correlations Between Biomarkers and Cognitive Domains

Pearson correlation coefficients between the five primary biomarkers and all cognitive domain scores at baseline are presented in Table 2 . eGFR demonstrated the strongest and most consistent bivariate associations with cognitive performance across all seven domains examined (r range: 0.616–0.745; all $p < 0.001$). Specifically, eGFR correlated strongly with DSST correct responses ($r = +0.745$, $p < 0.001$), N-back accuracy ($r = +0.741$, $p < 0.001$), RAVLT immediate total ($r = +0.741$, $p < 0.001$), TMT-B completion time ($r = -0.701$, $p < 0.001$), and MoCA global score ($r = +0.697$, $p < 0.001$), indicating that reduced renal filtration capacity was associated with broadly impaired cognitive function across processing speed, working memory, episodic memory, executive function, and global cognition. Simple reaction time also correlated significantly with eGFR (r =

Table 1. Baseline Biomarker Profiles by Age Cohort and Significance of 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/1.73m^2)	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
Glycaemic 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

Values are mean ± SD. Between-group comparisons by independent-samples t-test. Bold p-values denote statistical significance ($p < 0.05$). CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HbA1c = glycated haemoglobin; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

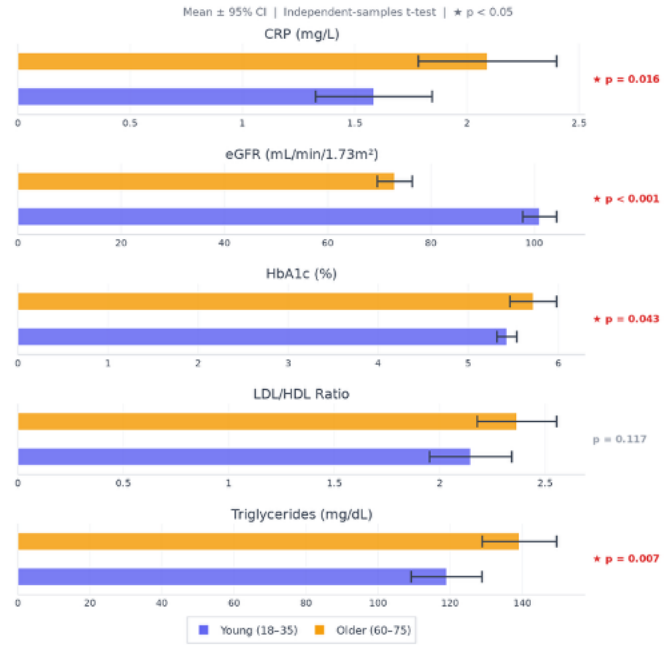

Fig. 1: Baseline biomarker profiles by age cohort. *Bar charts represent group means with 95% confidence interval error bars. Panels from left to right: CRP, eGFR, HbA1c, LDL/HDL ratio, and triglycerides. ★ indicates statistically significant between-cohort differences ($p < 0.05$, independent-samples t-test). The eGFR panel demonstrates the largest absolute and proportional group separation (~28 mL/min/1.73m^2), while the LDL/HDL ratio panel (no ★) did not reach statistical significance ($p = 0.117$). Young adults = purple bars; Older adults = amber bars.*

−0.616, p < 0.001), though with a somewhat smaller effect size compared to the complex cognitive tasks.

CRP showed uniformly significant modest negative associations across all cognitive outcomes (r range: −0.216 to −0.239; all p < 0.05), confirming that even sub-clinical systemic inflammation was detectably associated with lower cognitive function at the cross-sectional level. Triglycerides demonstrated a similar pattern of modest but significant negative associations across most cognitive domains (r range: −0.206 to −0.255; all p < 0.05). HbA1c showed selective significance, reaching statistical significance for DSST correct (r = −0.197, p < 0.05), TMT-B (r = +0.206, p < 0.05), N-back accuracy (r = −0.202, p < 0.05), RAVLT total (r = −0.208, p < 0.05), and simple reaction time (r = +0.266, p < 0.01), but not for MoCA global score (r = −0.188, p = 0.062) or digit span backward (r = −0.163, p = 0.105). The LDL/HDL ratio did not reach statistical significance for any cognitive domain at the bivariate level (r range: −0.123 to −0.172; all p > 0.05), suggesting that atherogenic lipid balance as a simple ratio index was not independently associated with cognitive performance in this sample when not stratified by age or BP status.

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/1.73m^2)	+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*

*Pearson r coefficients. * 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.*

Multivariable Regression: Independent Associations of Biomarkers with Cognitive Performance

To determine whether biomarker associations with cognition persisted independently of blood pressure and established confounders, multivariable linear regression models were fitted for each cognitive outcome with all five biomarkers entered simultaneously as predictors alongside clinic SBP, age, sex, education, and BMI (all continuous predictors standardised to z-scores; β represents change per 1-SD increment). Results are presented in Table 3 and displayed graphically in Figure 2 .

After full covariate adjustment, eGFR was the only biomarker that retained statistically independent and significant associations with cognitive performance across multiple domains. Every 1-SD decrement in eGFR (approximately 18.5 mL/min/1.73m^2) was independently associated with 2.46 fewer DSST correct responses (95% CI: 1.30–3.62; p < 0.001), 0.897% lower N-back accuracy (95% CI: 0.44–1.35; p < 0.001), 1.13 fewer words recalled on RAVLT immediate total (95% CI: 0.52–1.74; p < 0.001), a 3.73-second prolongation of TMT-B completion time (95% CI: 0.53–6.93; p = 0.031), 0.313 fewer MoCA points (95% CI: 0.09–0.54; p = 0.006), and 0.199 fewer digit span backward items (95% CI: 0.07–0.33; p = 0.003). These associations were robust to adjustment for clinic SBP, confirming that the eGFR–cognition relationship is not merely a proxy for blood pressure load but represents an independent contribution of renal function to cognitive performance. Simple reaction time was not significantly predicted by any of the five biomarkers after full adjustment (all p > 0.05; model adj. R^2 = 0.748), suggesting that rudimentary motor response speed is less sensitive to cardiometabolic and inflammatory variation than higher-order cognitive processes.

In contrast, CRP, HbA1c, LDL/HDL ratio, and triglycerides — all of which showed significant univariate correlations with multiple cognitive outcomes — were attenuated to statistical non-significance in fully adjusted models (all p >

0.05 across all cognitive outcomes). This pattern indicates that the bivariate associations of these four biomarkers with cognition were substantially explained by their shared co-variation with age, blood pressure, and BMI, rather than reflecting independent biological contributions to cognitive function at the cross-sectional baseline timepoint. Overall model fit was high across all cognitive outcomes (adjusted R^2 range: 0.748–0.971), reflecting the combined explanatory contributions of eGFR, SBP, age, and covariates.

Table 3. Multivariable Regression Analysis: Biomarkers as Independent Predictors of 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) ***	+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) *	+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) ***	+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) ***	+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) **	+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

** p < 0.05; ** p < 0.01; *** p < 0.001. Bold values indicate statistical significance. All models include random 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 = unstandardised coefficient per 1-SD increment; all predictors standardised; adjusted for clinic SBP, age, sex, years of education, and BMI)*

4 | DISCUSSION

The present study investigated whether baseline inflammatory, metabolic, and renal biomarkers were independently associated with cognitive performance in young and older adults, after adjustment for blood pressure, age, sex, education, and body mass index. Three principal findings emerged from this analysis.

First, older adults demonstrated a significantly more adverse cardiometabolic and inflammatory profile at baseline compared with younger counterparts, characterised by markedly reduced renal filtration capacity, elevated systemic inflammation, higher triglycerides, and mild glycaemic dysregulation. These between-cohort differences were largely consistent with the known trajectory of cardiometabolic ageing and align with prior epidemiological data linking advancing age with progressive renal decline, low-grade chronic inflammation, and dyslipidaemia. Notably, not all biomarkers diverged by cohort — LDL/HDL ratio and hemoglobin remained comparable across age groups — suggesting that certain cardiometabolic indices are relatively preserved in the older adults recruited under this study's strict exclusion criteria (17, 18) .

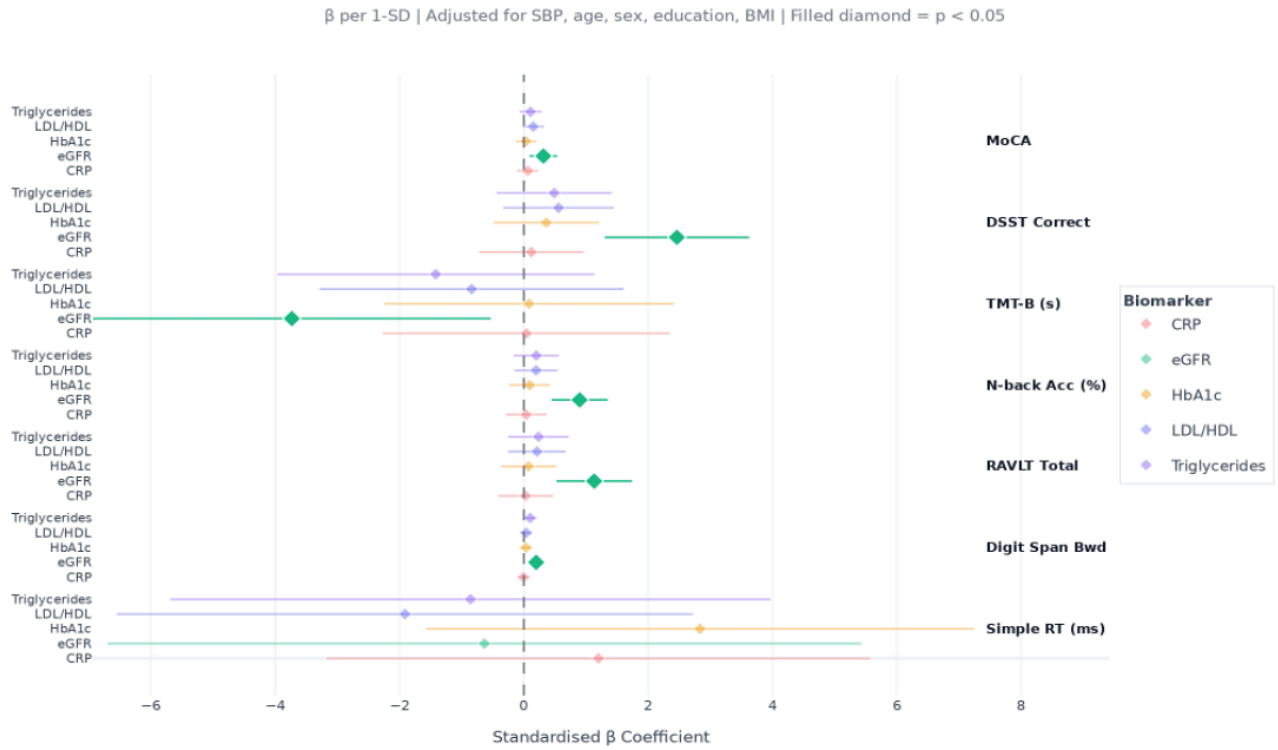

Fig. 2: Multivariable Regression Coefficients — Biomarkers Predicting Baseline Cognition Forest plot of multivariable regression coefficients for the five primary biomarkers predicting baseline cognitive performance across seven outcomes, after adjustment for SBP, age, sex, education, and BMI. Each point represents the standardised β coefficient; horizontal lines indicate 95% confidence intervals. Filled diamonds denote statistical significance ($p < 0.05$); open faded circles denote non-significance. The vertical dashed line marks the null effect ($\beta = 0$). Colour coding: green = eGFR; red = CRP; amber = HbA1c; indigo = LDL/HDL ratio; violet = triglycerides. eGFR is the only biomarker whose confidence intervals consistently exclude zero across processing speed (DSST), working memory (N-back), episodic memory (RAVLT), executive function (TMT-B), global cognition (MoCA), and working memory span (Digit Span Backward).

Second, bivariate analyses revealed broad associations between all five biomarkers and cognitive performance. However, the critical finding emerged from the multivariable models: after controlling for blood pressure, age, sex, education, and BMI, only eGFR retained statistically independent and clinically meaningful associations with cognitive performance across five of seven domains — processing speed, working memory, episodic memory, executive function, and global cognition. This finding is consistent with growing evidence implicating the kidney-brain axis as an independent pathway in cognitive ageing (19, 20) . Reduced renal filtration may compromise cognitive function through maccumulation of uraemic toxins, disruption of cerebral microvascular integrity, increased oxidative stress, and impaired clearance of neurotoxic metabolites — mechanisms distinct from, and potentially additive to, the neurovascular effects of elevated blood pressure documented in the companion EEG study. The magnitude of the eGFR effect — corresponding to 2.46 fewer DSST responses and 1.13 fewer RAVLT words per 1-SD decrement — was comparable in clinical relevance to the blood pressure effects observed in prior analyses, underscoring the importance of renal function as an independent cognitive risk marke (21, 22)$.

Third, the attenuation of CRP, HbA1c, triglycerides, and LDL/HDL ratio to non-significance in adjusted models highlights an important methodological caution: univariate biomarker-cognition associations observed in unadjusted analyses may be substantially confounded by age and blood pressure covariation (23, 24) . These biomarkers may operate as distal upstream risk factors rather than as proximal, independent determinants of cognitive function at a single cross-sectional timepoint. Whether their predictive value emerges more clearly in longitudi-

nal models — particularly through mediation pathways — warrants direct examination in the follow-up waves of this cohort.

5 | CONCLUSION

This cross-sectional baseline analysis demonstrates that among five cardiometabolic and inflammatory biomarkers examined, estimated glomerular filtration rate was the sole independent predictor of cognitive performance after full adjustment for blood pressure, age, sex, education, and BMI. The findings implicate renal function as a distinct, clinically meaningful contributor to cognitive health across the adult lifespan, operating through pathways that are not fully accounted for by blood pressure burden alone. These results support incorporating renal function monitoring into early cognitive risk assessment strategies and provide a strong rationale for longitudinal mediation analyses in subsequent study phases.

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