

# Associations of cognitive performance with cardiovascular magnetic resonance phenotypes in the UK Biobank

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## Aims

Existing evidence suggests links between brain and cardiovascular health. We investigated associations between cognitive performance and cardiovascular magnetic resonance (CMR) phenotypes in the UK Biobank, considering a range of potential confounders.

## Methods and results

We studied 29763 participants with CMR and cognitive testing, specifically, fluid intelligence (FI, 13 verbal-numeric reasoning questions), and reaction time (RT, a timed pairs matching exercise); both were considered continuous variables for modelling. We included the following CMR metrics: left and right ventricular (LV and RV) volumes in end-diastole and end-systole, LV/RV ejection fractions, LV/RV stroke volumes, LV mass, and aortic distensibility. Multivariable linear regression models were used to estimate the association of each CMR measure with FI and RT, adjusting for age, sex, smoking, education, deprivation, diabetes, hypertension, high cholesterol, prior myocardial infarction, alcohol intake, and exercise level. We report standardized beta-coefficients, 95% confidence intervals, and *P*-values adjusted for multiple testing. In this predominantly healthy cohort (average age 63.0 ± 7.5 years), better cognitive performance (higher FI, lower RT) was associated with larger LV/RV volumes, higher LV/RV stroke volumes, greater LV mass, and greater aortic distensibility in fully adjusted models. There was some evidence of non-linearity in the relationship between FI and LV end-systolic volume, with reversal of the direction of association at very high volumes. Associations were consistent for men and women and in different ages.

## Conclusion

Better cognitive performance is associated with CMR measures likely representing a healthier cardiovascular phenotype. These relationships remained significant after adjustment for a range of cardio-metabolic, lifestyle, and demographic factors, suggesting possible involvement of alternative disease mechanisms.

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**Table 1** Baseline population characteristics

	Whole cohort (n = 29 763)	Men (n = 14 379; 48.3%)	Women (n = 15 384; 51.7%)
Age at imaging	63.0 (±7.5)	63.7 (±7.6)	62.4 (±7.3)
Current smoker	1851 (6.2%)	1066 (7.4%)	785 (5.1%)
Education			
Left school age ≤14 years without qualifications	75 (0.3%)	42 (0.3%)	33 (0.2%)
Left school at age ≥15 without qualifications	1981 (6.7%)	954 (6.6%)	1027 (6.7%)
High school diploma or equivalent	3900 (13.1%)	1500 (10.4%)	2400 (15.6%)
Sixth form qualification or equivalent	1691 (5.7%)	751 (5.2%)	940 (6.1%)
Professional qualification (e.g. teaching, nursing)	8283 (27.8%)	4198 (29.2%)	4085 (26.6%)
Higher education university degree	13 526 (45.4%)	6782 (47.2%)	6744 (43.8%)
Townsend score	-2.7 (-3.9, -0.7)	-2.7 (-4.0, -0.7)	-2.6 (-3.9, -0.6)
IPAQ (MET minutes/week)	1530 (671, 3016)	1590 (693, 3111)	1464 (642, 2933)
Alcohol intake			
Daily or almost daily	6554 (22.0%)	3832 (26.6%)	2722 (17.7%)
Three or four times a week	8426 (28.3%)	4388 (30.5%)	4038 (26.2%)
Once or twice a week	7731 (26.0%)	3632 (25.3%)	4099 (26.6%)
One to three times a month	3223 (10.8%)	1227 (8.5%)	1996 (13.0%)
Special occasions only	2423 (8.1%)	717 (5.0%)	1706 (11.1%)
Never	1390 (4.7%)	574 (4.0%)	816 (5.3%)
Diabetes	893 (3.0%)	581 (4.0%)	312 (2.0%)
Hypertension	4016 (13.5%)	2417 (16.8%)	1599 (10.4%)
High cholesterol	6640 (22.3%)	3616 (25.1%)	3024 (19.7%)
Prior MI	590 (2.0%)	494 (3.4%)	96 (0.6%)
Fluid intelligence (items)	6.7 (±2.1)	6.8 (±2.1)	6.5 (±2.0)
Reaction time (ms)	573 (518, 644)	565 (510, 636)	581 (526, 655)
LVEDVi (mL/m <sup>2</sup> )	78.8 (±13.9)	83.8 (±14.7)	74.1 (±11.1)
LVESVi (mL/m <sup>2</sup> )	31.1 (26.3, 36.7)	34.5 (29.5, 40.3)	28.3 (24.5, 32.7)
LVEF (%)	59.5 (±6.1)	57.8 (±6.2)	61.0 (±5.6)
LVSVi (mL/m <sup>2</sup> )	46.6 (±8.3)	48.2 (±9.0)	45.1 (±7.4)
LVMi (g/m <sup>2</sup> )	45.7 (±8.7)	51.1 (±7.9)	40.6 (±5.9)
RVEDVi (mL/m <sup>2</sup> )	83.2 (±15.2)	90.0 (±15.3)	76.9 (±12.1)
RVESVi (mL/m <sup>2</sup> )	35.9 (±9.4)	40.5 (±9.3)	31.5 (±7.1)
RVEF (%)	57.2 (±6.1)	55.1 (±5.9)	59.1 (±5.6)
RVSVi (mL/m <sup>2</sup> )	47.4 (±8.7)	49.5 (±9.3)	45.4 (±7.7)
PDA AoD (10 <sup>-3</sup> /mmHg)	2.3 (1.6, 3.1)	2.3 (1.7, 3.1)	2.2 (1.5, 3.0)

Mean (standard deviation) for continuous data, number (percentage) for categorical data. Median (interquartile range) where absolute skew is ≥0.9.

IPAQ, International Physical Activity Questionnaire; i, indexation to body surface area; LVEDVi, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVESVi, left ventricular end-systolic volume; LVSVi, left ventricular stroke volume; MET, metabolic equivalents; MI, myocardial infarction; PDA AoD, aortic distensibility at the proximal descending aorta; RVEDVi, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume; RVSVi, right ventricular stroke volume.

statistically significant. Overall, associations were consistent for both men and women (Table 2). There was no evidence of interaction effect with sex or age in relationships with the LV or RV measures (Supplementary data online, Table S3).

## Non-linearity of relationships

All models were screened for non-linearity with cubic and squared polynomials. For both FI and RT, in fully adjusted models, there was a trend towards attenuation of associations at the high extremes of the distribution for LV volumes and mass (very high volumes and mass). This appeared most convincing for the relationship between FI and LV end-systolic volume, where there was suggestion of attenuation

and possible reversal of the direction of association at the very high extremes of the distribution (Supplementary data online, Figure S2). However, nested model testing indicated that none of the non-linear models showed a statistically significant improvement over linear model fits (Supplementary data online, Table S4).

## Discussion

### Summary of findings

In this predominantly healthy cohort of 15 384 women and 14 379 men from the UK Biobank, we demonstrated association of better

**Table 2** Multivariable linear regression models representing standard deviation change in fluid intelligence and reaction time per one standard deviation increase in CMR measures

		Whole cohort	Men	Women
LVEDVi (mL/m <sup>2</sup> )	FI	0.043 <sup>a</sup> (0.031, 0.056) 1.45 × 10 <sup>-11</sup>	0.046 <sup>a</sup> (0.030, 0.062) 3.06 × 10 <sup>-8</sup>	0.040 <sup>a</sup> (0.020, 0.060) 9.31 × 10 <sup>-5</sup>
	RT	-0.028 <sup>a</sup> (-0.040, -0.015) 1.24 × 10 <sup>-5</sup>	-0.031 <sup>a</sup> (-0.047, -0.015) 1.64 × 10 <sup>-4</sup>	-0.024 <sup>a</sup> (-0.044, -0.004) 0.018
LVESVi (mL/m <sup>2</sup> )	FI	0.040 <sup>a</sup> (0.028, 0.053) 2.76 × 10 <sup>-10</sup>	0.044 <sup>a</sup> (0.028, 0.059) 6.28 × 10 <sup>-8</sup>	0.035 <sup>a</sup> (0.014, 0.055) 0.001
	RT	-0.019 <sup>a</sup> (-0.031, -0.006) 0.003	-0.020 <sup>a</sup> (-0.036, -0.005) 0.011	-0.017 (-0.038, 0.004) 0.104
LVEF (%)	FI	-0.018 <sup>a</sup> (-0.030, -0.006) 0.003	-0.026 <sup>a</sup> (-0.043, -0.010) 0.002	-0.009 (-0.026, 0.008) 0.303
	RT	0.002 (-0.010, 0.014) 0.725	0.002 (-0.014, 0.018) 0.831	0.002 (-0.015, 0.019) 0.792
LVSVi (mL/m <sup>2</sup> )	FI	0.026 <sup>a</sup> (0.015, 0.038) 1.17 × 10 <sup>-5</sup>	0.027 <sup>a</sup> (0.011, 0.043) 7.70 × 10 <sup>-4</sup>	0.026 <sup>a</sup> (0.008, 0.044) 0.004
	RT	-0.024 <sup>a</sup> (-0.035, -0.012) 7.81 × 10 <sup>-5</sup>	-0.028 <sup>a</sup> (-0.043, -0.012) 5.03 × 10 <sup>-4</sup>	-0.019 (-0.037, -0.001) 0.039
LVMi (g/m <sup>2</sup> )	FI	0.048 <sup>a</sup> (0.034, 0.063) 3.50 × 10 <sup>-11</sup>	0.042 <sup>a</sup> (0.023, 0.060) 1.09 × 10 <sup>-5</sup>	0.058 <sup>a</sup> (0.035, 0.081) 6.87 × 10 <sup>-7</sup>
	RT	-0.039 <sup>a</sup> (-0.053, -0.025) 8.25 × 10 <sup>-8</sup>	-0.045 <sup>a</sup> (-0.063, -0.027) 1.26 × 10 <sup>-6</sup>	-0.032 <sup>a</sup> (-0.055, -0.010) 0.005
PDA AoD (×10 <sup>-3</sup> /mmHg)	FI	0.030 <sup>a</sup> (0.014, 0.045) 2.02 × 10 <sup>-4</sup>	0.033 <sup>a</sup> (0.010, 0.057) 0.006	0.032 <sup>a</sup> (0.010, 0.053) 0.003
	RT	-0.017 (-0.032, -0.001) 0.036	-0.016 (-0.039, 0.006) 0.159	-0.015 (-0.036, 0.006) 0.171

Results are standardized beta coefficients followed by 95% confidence interval in brackets and corresponding *P*-value displayed below. Each cell represents results from an individual linear regression model. Models are adjusted for: age, sex (whole cohort only), education, deprivation, diabetes, hypertension, high cholesterol, prior myocardial infarction, smoking, alcohol, and exercise. PDA AoD has been scaled to remove skew.

CMR, cardiovascular magnetic resonance; FI, fluid intelligence; i, indexation to body surface area; LVEDVi, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume; LVSVi, left ventricular stroke volume; PDA AoD, aortic distensibility at the proximal descending aorta. RT, reaction time.

<sup>a</sup>*P*-value is significant using a false discovery rate of 5%.

cognitive performance with CMR measures likely representing a healthier cardiovascular phenotype, independent of a range of life-style, demographic, and vascular risk factors. Specifically, better cognitive performance (higher FI and lower RT) was associated with larger LV and RV volumes, greater LV and RV stroke volumes, higher LV mass, and greater aortic distensibility. There was some evidence of non-linearity for the relationship between FI and LV end-systolic volume, with a trend towards reversal of the direction of association at the high extremes of the distribution (very high volumes). Associations appeared consistent for men and women and with age. For the relationship with FI, there was significant interaction between aortic distensibility and age, with participants with higher aortic distensibility showing less rapid age-related decline in FI.

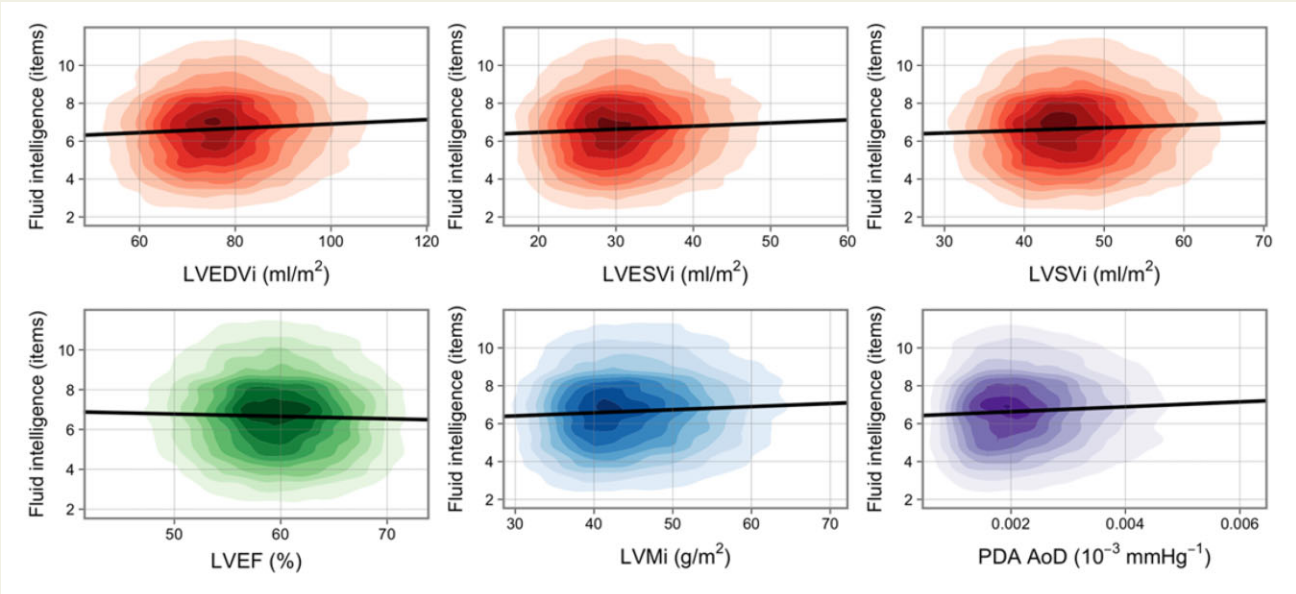
## Interpretation of cardiovascular phenotypes

Although there was no prerequisite for healthy status for recruitment into UK Biobank, there is a significant healthy participant effect, as such, our results reflect trends within a spectrum of normality. This means that in this analysis, for the most part, we do not report

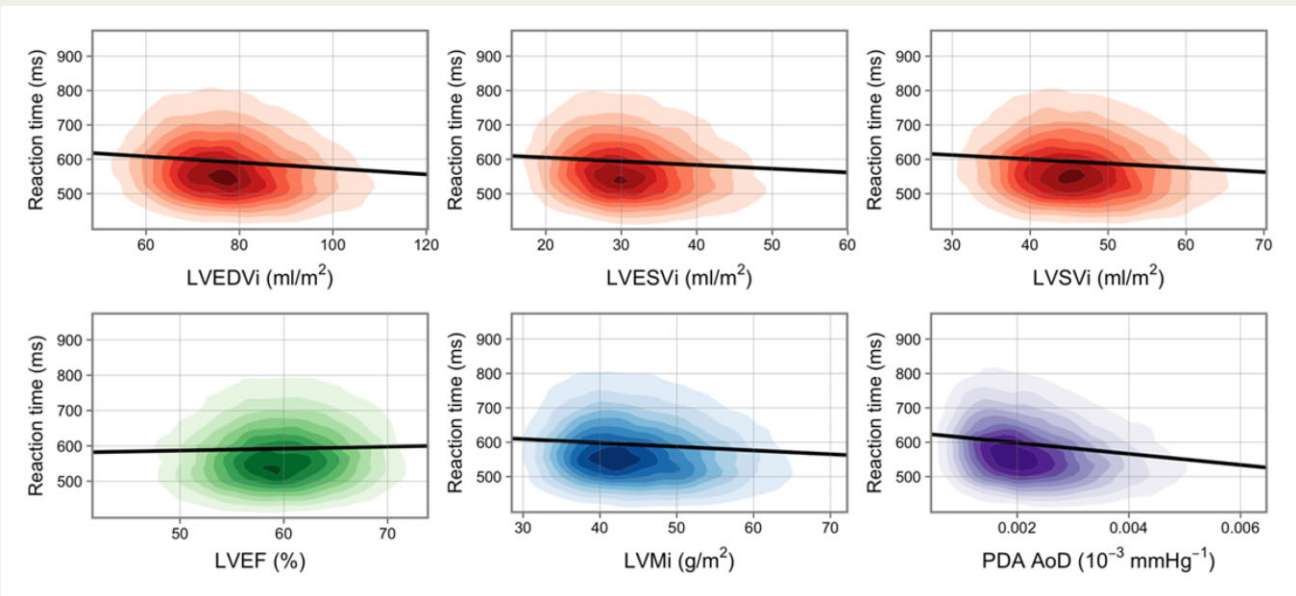
transitions from health to 'disease', but rather trends within a predominantly healthy sample. It is also essential that interpretation of the nature of cardiac phenotypes considers the overall pattern of associations as interpretation of single CMR metrics in isolation, outside the context of the other metrics, may be misleading.

Our findings demonstrate association of better cognitive performance with larger ventricular cavity volumes, larger LV and RV stroke volumes, and higher LV mass. This pattern of associations is indicative of better right and left ventricular contractile function (higher stroke volumes) and a pattern of ventricular remodelling, interpreted within the spectrum of normality, akin to decelerated heart ageing (reverse of alterations seen in healthy ageing). There was some evidence of reversal of the direction of associations between FI and LV end-systolic volume at the high extremes of the distribution (very high volumes), suggesting that LV volumes larger than the normal range are linked with poorer cognition. However, within our analysis sample, the non-linear models did not show a statistically significant improvement over linear model fits. This may be because there were few participants with extreme values in our sample. Better cognitive performance was also linked to greater aortic distensibility (statistically





**Figure 2** Univariate linear regression models of the association between fluid intelligence and CMR measures. Each graph displays a kernel density plot of one CMR variable against one cognition variable. The nine coloured rings each represent a decile of the data, while the remaining 10% lies in the uncoloured area. Univariate linear regression is shown by black line. All plot areas are trimmed at the 1st and 99th percentile in both x and y directions. Fluid intelligence has had uniform random jitter/noise (-0.5, 0.5) added for visual smoothing. CMR, cardiovascular magnetic resonance; i, indexation to body surface area; LVEDVi, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume; LVSVi, left ventricular stroke volume; PDA AoD, Aortic distensibility at the proximal descending aorta.



**Figure 3** Univariate linear regression models of the association between reaction time and CMR measures. Each graph displays a kernel density plot of one CMR variable against one cognition variable. The nine coloured rings each represent a decile of the data, while the remaining 10% lies in the uncoloured area. Univariate linear regression is shown by black line. All plot areas are trimmed at the 1st and 99th percentile in both x and y directions. CMR, cardiovascular magnetic resonance; i, indexation to body surface area; LVEDVi, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume; LVSVi, left ventricular stroke volume; PDA AoD, Aortic distensibility at the proximal descending aorta.

significant for FI). Aortic distensibility is a measure of local aortic compliance and a maker of aortic bioelastic function, with higher distensibility values indicating better vascular health. Conversely, poorer cognitive function was associated with smaller ventricular volumes and lower LV mass, together with smaller LV and RV stroke volumes, and lower aortic compliance. Overall, this presents a picture of a cardiac phenotype with poorer myocardial function, small, perhaps stiff, ventricles, and higher aortic stiffness. This suggests that poorer cognition is associated with adverse cardiovascular phenotypes, perhaps resembling a heart failure preserved ejection fraction (HFpEF) phenotype.

## Comparison with existing literature

Existing evidence is limited to small cohorts of select populations with highly variable study designs. Several studies report poorer cognitive function indices in small heart failure cohorts. Zuccalà *et al.*<sup>28</sup> report an independent association between poorer LV function on echocardiography and worse performance in a number of cognitive tests (mini mental state examination, Raven score) in 57 patients with heart failure. In a study of structural brain abnormalities in heart failure patients, Vogels *et al.*<sup>29</sup> report greater periventricular and white matter hyperintensities, lacunar and cortical infarcts, and global and medial temporal lobe atrophy in 58 patients with heart failure compared with controls.<sup>30</sup> Similarly, studies in dementia cohorts demonstrate links with adverse cardiovascular phenotypes. Oh *et al.*<sup>31</sup> describe a correlation between greater left atrial enlargement on echocardiography (an early indicator of raised filling pressures and diastolic dysfunction) and adverse white matter changes on brain magnetic resonance imaging in 93 patients with dementia. Two other cohort studies demonstrate greater prevalence of diastolic dysfunction (assessed by echocardiography) in individuals with Alzheimer's disease compared with controls.<sup>32,33</sup> Limited studies have examined associations with other cardiovascular phenotypes. In a cohort of 303 participants, Manolio *et al.*<sup>34</sup> report association of greater cerebral atrophy on brain MRI with greater internal carotid artery thickness on ultrasound (a marker of atherosclerosis risk).

Whilst direct comparisons with our study are not possible, in general, existing work supports associations between adverse cardiovascular phenotypes and poorer cognitive function metrics. In particular, there is evidence to support association of poorer cognitive function indices with heart failure, which is perhaps more pronounced in those with diastolic heart failure.<sup>35</sup> This is consistent with our findings demonstrating association of poorer cognitive function with smaller LV/RV cavities and lower LV/RV stroke volumes. Overall, this pattern of associations is suggestive of an adverse remodelling phenotype most in keeping with an HFpEF pattern of dysfunction, in which diastolic impairment is a prominent feature.

## Potential underlying mechanisms

Numerous studies highlight links between individual cardiovascular risk factors (diabetes, high cholesterol, smoking, hypertension, and obesity) and worse cognitive performance.<sup>36–40</sup> Furthermore, association of cardiovascular risk factors and subclinical cardiovascular disease with worse cognition and dementia has been demonstrated in multiple large epidemiological studies.<sup>9,41,42</sup> More specific associations between cardiac risk factors and both vascular and Alzheimer's disease have also been demonstrated in large cohorts.<sup>7,43,44</sup> The

systemic atherosclerotic arterial disease that occurs as a consequence of these vascular risk factors may have direct adverse impact on both cardiovascular and brain health through local hypoperfusion and systemic embolic phenomena (Figure 4).

Associations between cognitive function and cardiovascular phenotypes in the present study were not attenuated by adjustment for a wide range of vascular risk factors. This raises the possibility of alternative disease mechanisms contributing to heart–brain associations. For instance, limited studies propose that A $\beta$  deposition, which is hallmark of Alzheimer's disease, may also be pathologically deposited in the myocardium<sup>33</sup> producing electrographic and echocardiographic manifestations typical of cardiac amyloid. Cardiac amyloid is characteristically associated with a HFpEF pattern of dysfunction. This is consistent with the cardiac phenotype most consistently linked with cognitive impairment and in keeping also with observations in the present study. However, these phenotypes are not specific to cardiac amyloid and may be seen with a wide range of other exposures. Another possibility is that poorer brain and cardiovascular health may both be a consequence of accelerated multisystem ageing. For instance, persistently elevated inflammatory cytokines, which is a proposed driver of accelerated ageing, has been linked to both cardiovascular disease and Alzheimer's disease.<sup>45,46</sup> Regardless of the underlying cause, it seems likely that these pathways initiate a positive feedback cycle of adverse heart–brain interactions with cardiac dysfunction resulting in chronic systemic hypoperfusion, disruptions to cerebral perfusion, and further exacerbation of brain injuries (Figure 4).

Whatever the underlying mechanisms, our findings suggest links between cardiovascular and cognitive health which might, with further investigation and validation, underpin novel clinical approaches to risk assessment for associated outcomes such as myocardial infarction and dementia.

## Strengths and limitations

In this study, we made use of the large and standardized UK Biobank dataset to describe novel associations between cognitive function and CMR phenotypes. The extensive algorithm-coded morbidity, demographic, and lifestyle data available permitted adjustment for a wide range of covariates. However, inherent to the observational cross-sectional study design, the possibility of residual confounding cannot be excluded, and it is not possible to establish a strict causal relationship from the results. Further, the large sample size in this study may reveal statistically but not clinically relevant associations. With this in mind, we have taken a strict hypothesis based approach to the analysis, applied conservative correction of *P*-value thresholds, and consider biological (rather than clinical) interpretation of the findings. Common to all research in the field of cognitive performance and dementia, the questionnaires and scoring systems used to quantify cognitive performance may not accurately reflect global cognitive ability and may be subject to bias depending on underlying educational status and other factors. In addition, there is, as is expected with such cohorts, evidence of healthy selection in UK Biobank,<sup>47</sup> thus the associations observed in this study describe, predominantly, relationships within the limits of healthy populations. Therefore, the pattern of associations observed may not be directly applicable to disease cohorts. Another limitation of our work is that despite considering the potential confounding effect of an extensive range of





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**Conflict of interest:** none declared.

## Data availability statement

This research was conducted using the UKB resource under access application 2964. UK Biobank will make the data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: <http://www.ukbiobank.ac.uk/register-apply/>.

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