

Associations of cardiorespiratory fitness with structural brain networks in ageing: Insights from The Maastricht Study

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Background

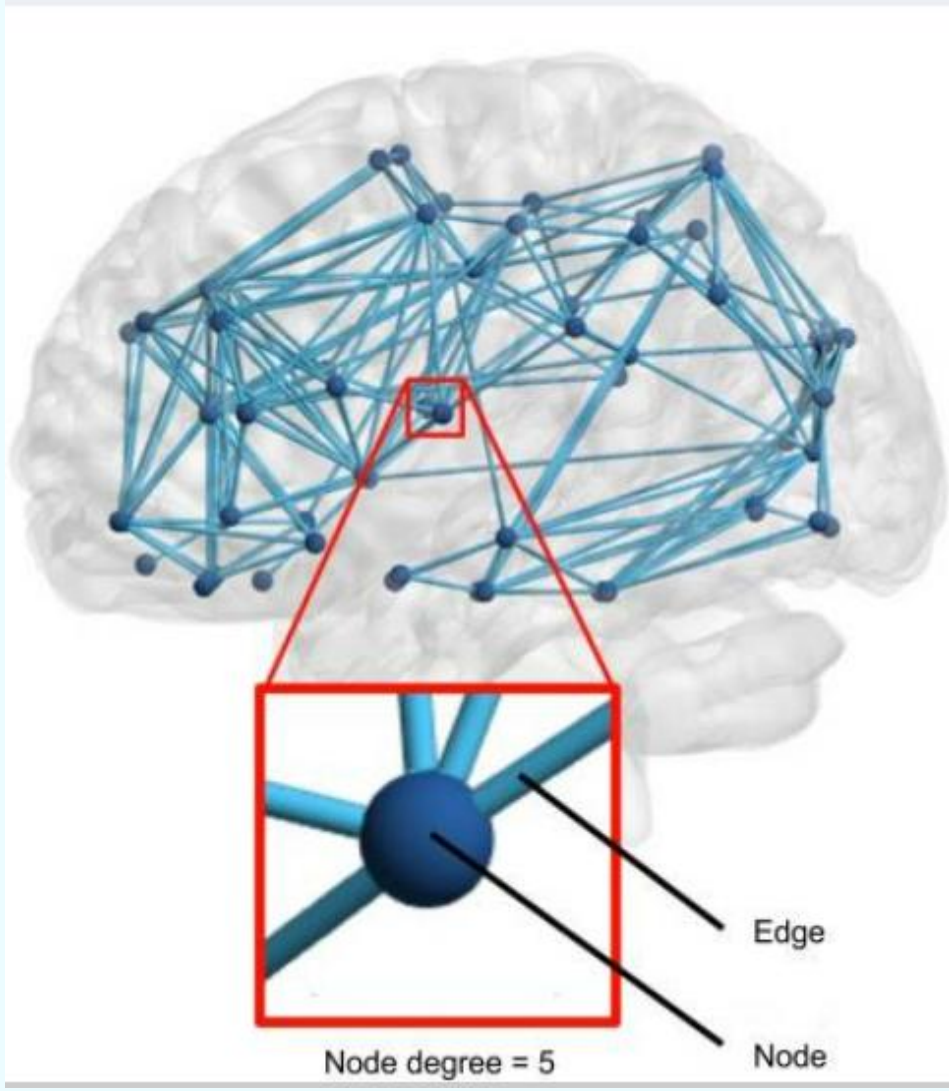
- Higher **cardiorespiratory fitness (CRF)**, improved and maintained through regular physical activity, has been linked to better cognition and preserved brain structure in ageing
- This includes greater **white matter (WM)** volume and microstructural integrity in specific tracts (1, 2).
- However, **whether CRF relates to the organization of whole-brain WM networks remains unclear.**

Objectives

- To examine associations of CRF with WM network metrics:
 - Efficiency: global, local
 - Node degree (i.e., WM connection count): whole-brain (average WM connection count per brain region), PFC (connection count within the prefrontal cortex).
- To explore whether these associations vary by age.

Methods

- 4,432 adults (mean age 59.2 ± 8.7 years, range 40–79, 51% female) with cross-sectional data from **The Maastricht Study** (3)
- CRF (VO_2 -max) was estimated from submaximal ergometry (4)
- Structural brain networks were derived from 3T diffusion MRI images using Brain Connectivity Toolbox (MATLAB; 94 brain regions = nodes) (5)
- Analyses were performed using linear regression models adjusted for age, sex, education, smoking, alcohol intake, and technical MRI covariates (model 1); and additionally for cardiometabolic health* (model 2)



Results

- Higher CRF was associated with greater whole-brain node degree and PFC node degree; both associations were attenuated after adjusting for cardiometabolic factors in model 2 (Table 1)**
- No significant associations of CRF with local or global efficiency
- CRF $\times$ age interactions indicated stronger associations of CRF with whole-brain node degree and with local efficiency at older ages; models with additional CRF $\times$ age² terms improved fit but attenuated all CRF-by-age interaction effects (Figure 1)**

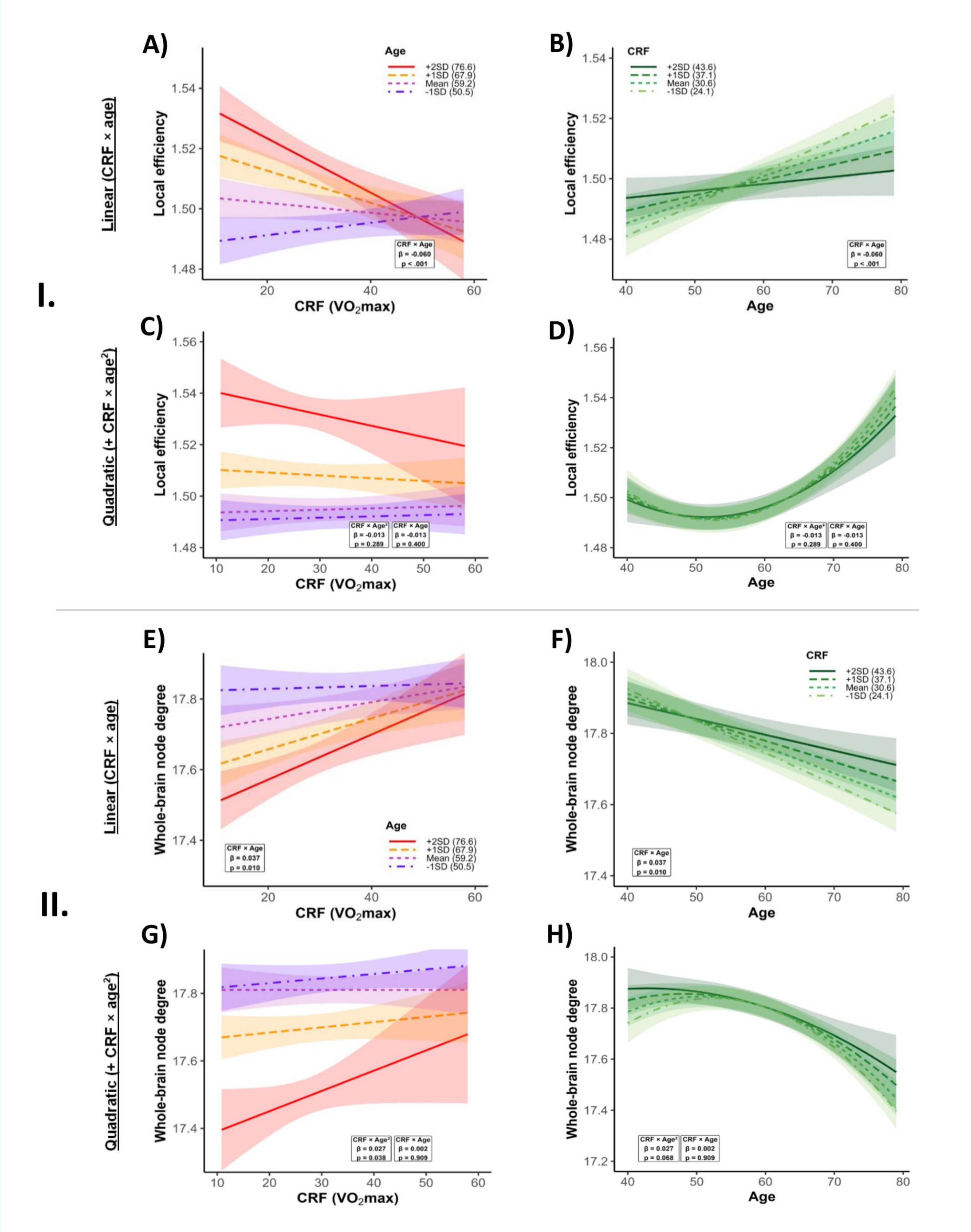
Results – continued

Table 1: Associations of CRF with WM network metrics

Global efficiency		Local efficiency		Whole-brain node degree		PFC node degree	
β	P	β	P	β	P	β	P
(95% CIs)	P_{FDR}	(95% CIs)	P_{FDR}	(95% CIs)	P_{FDR}	(95% CIs)	P_{FDR}
Linear age covariate (age)							
Model 1							
CRF	0.018	0.293	−0.011	0.494	0.053	0.001	0.042
	(−0.016, 0.052)	0.361	(−0.043, 0.021)	0.565	(0.022, 0.085)	0.013	(0.010, 0.075)
Model 2							
CRF	0.023	0.256	−0.021	0.253	0.041	0.031	0.034
	(−0.017, 0.062)	0.361	(−0.058, 0.015)	0.361	(0.004, 0.078)	0.096	(−0.004, 0.073)
Additional quadratic age covariate (age + age²)							
Model 1							
CRF	0.019	0.272	0.003	0.831	0.042	0.010	0.037
	(−0.015, 0.053)	0.361	(−0.028, 0.035)	0.883	(0.010, 0.073)	0.061	(0.004, 0.069)
Model 2							
CRF	0.024	0.233	−0.003	0.883	0.026	0.172	0.027
	(−0.015, 0.063)	0.361	(−0.039, 0.034)	0.883	(−0.011, 0.063)	0.344	(−0.011, 0.066)

Note: Model 1: adjusted for age, sex, education, smoking, alcohol, MRI covariates. Model 2: additionally adjusted for cardiometabolic health* (type 2 diabetes status, body mass index, history of cardiovascular disease, office systolic blood pressure, ratio of total-to-high-density lipoprotein, anti-hypertensive and lipid-lowering medication use). Bold = $p < 0.05$. β = standardized coefficient.

Figure 1: CRF-by-age interactions on WM network metrics (model 2)



Note: Left: age-stratified associations of CRF with WM network metrics. Right: CRF-stratified associations of age with WM network metrics. A–D, E–F: linear interaction terms; G–H: additional quadratic interaction terms. Lines represent values relative to sample means (age = 59.2 years; CRF = 30.6 mL/kg/min).

Discussion

- Associations of CRF with greater WM connection count (node degree) – aligned with previous CRF–WM integrity findings (6, 7).**
- Attenuation of CRF–node degree associations by cardiometabolic factors (especially type 2 diabetes status) suggests possible mediating role of cardiometabolic health (CRF $\rightarrow$ cardiometabolic health $\rightarrow$ WM connectivity). However, the reverse cannot be excluded (e.g., higher cardiometabolic health causing both higher CRF and better WM connectivity).**
- Age-dependent patterns aligns with the hypothesis of putative CRF benefits for brain health strengthening with age (1, 6, 7).** This could be because age-related declines in WM health renders the brain more responsive to CRF-related neuroprotective processes.
- No associations of CRF with network efficiency contrasts with a previous study reporting CRF–efficiency associations (8), likely reflecting differences in efficiency metric definitions and calculations.

Conclusion

- Our findings hint that **CRF may help preserve WM connection count**, especially in older age (approx. >70 years), possibly in part via cardiometabolic pathways.
- Findings broadly align with previous research linking CRF to brain health in older age.
- Longitudinal and intervention studies are needed to confirm and further explore these patterns.**

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