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Body mass index is associated with functional brain network efficiency in midlife world trade center responders with cognitive impairment

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Abstract

Background Higher body mass index (BMI) is associated with lowered risk of dementia in aging populations, possibly because it improves cognitive reserve in old age. Little is known about mechanisms implicated in reductions in vulnerability and less is known about implications of BMI in cognitively impaired (CI) individuals at midlife. Here, we examined whether BMI relates to functional brain network efficiency and cognition in a physically active cohort of midlife World Trade Center (WTC) responders with documented 9/11-related exposures, testing how systemic inflammatory burden and body composition jointly shape brain networks.

Methods Resting-state fMRI data from 99 WTC responders and 10 matched controls were analyzed. Functional cerebral network efficiency metrics included characteristic path length (CPL), clustering coefficients (CC), global efficiency (GE), and small-worldness (SWN), and were derived across proportional sparsity thresholds to enhance robustness. Multivariate models tested the effects of BMI, CI, and their interaction on network efficiency.

Results Higher BMI and CI were independently associated with cerebral network efficiency. A significant BMI × CI interaction was identified (CPL: p=0.024; SWN: p=0.010; GE: p=0.034), indicating that the positive association between BMI and network efficiency was strongest among cognitively impaired responders. Specifically, elevated BMI correlated with more integrated and efficient networks (e.g., shorter CPL and greater CC, GE, and SWN). Functional network efficiency metrics were modestly associated with attention and processing speed, but not with memory or visuospatial performance, suggesting selective relevance to cognitive domains vulnerable to early disruption.

Conclusions Consistent with hypotheses of cognitive reserve, this study provides novel evidence that functional brain network topology is influenced by BMI among cognitively impaired WTC responders. Findings highlight a complex interplay among systemic health, brain organization, and cognitive function at midlife.

Keywords Functional connectivity, Graph theory, Cognitive impairment, World trade center responders

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1 Introduction

Obesity in youth and during adulthood is a risk factor for many chronic conditions including cardiometabolic risk and disability [28]. However, the Obesity Paradox at midlife and in old age refers to the tendency for old age studies to report that a higher body mass index (BMI) can be a source of cognitive reserve in the contexts of mild cognitive impairment and dementia with results noting that cognitive decline may be slowed in those who are overweight or who maintain higher weight in old age [9, 10, 25].

Beyond its established role in cardiometabolic risk, BMI is increasingly recognized as relevant to brain health. Cross-sectional and longitudinal investigations have associated elevated BMI with structural and functional brain alterations, including reductions in gray matter volume and diminished white-matter integrity, which in turn are linked to poorer cognitive performance [14, 32]. Evidence from prospective cohorts further suggests that overweight and obesity in midlife are associated with an increased risk of dementia in late life, highlighting BMI as a brain-relevant exposure well before the onset of clinical symptoms [37, 39]. Importantly, the physiological implications of elevated BMI vary across the lifespan: in late life, higher BMI often reflects visceral adiposity and metabolic dysfunction, whereas in midlife it may also capture aspects of preserved lean mass and energy availability ("metabolic reserve"). Consistent with this view, body-composition studies demonstrate distinct contributions of lean and fat mass to health outcomes [26, 27].

Cognitive reserve refers to the brain's ability to sustain cognitive performance despite aging or pathology and is commonly indexed by educational attainment or engagement in cognitively stimulating activities [33]. Extending this concept, body-composition–related "metabolic reserve" (e.g., BMI when reflecting adequate muscle mass or energy availability) may also support neural efficiency under disease stress; however, any protective association is context-dependent and likely varies with age, cardiorespiratory fitness, and metabolic health [27, 30]. One explanation for improved cognitive reserve in old age may be that higher BMI may help to maintain cerebral network structure and neural efficiency among individuals whose brains are aging.

Neural network organization can be characterized with graph-theory analysis of resting-state fMRI, which quantifies core topological properties of functional brain connectivity. Characteristic path length (CPL) reflects the average number of steps linking any two regions, with shorter CPL indicating more integrated communication. The clustering coefficient (CC) measures the density of local connections, such that higher CC denotes stronger regional cohesion. Global efficiency (GE), defined as the average inverse shortest path length, indexes the brain's capacity for parallel information transfer, with higher GE reflecting greater global integration. Small-worldness (SWN) captures the balance between segregation and integration by comparing CC and CPL to degree-matched random networks [4, 11, 19, 29, 36]. In midlife populations, obesity has been linked to reduced efficiency, disrupted small-world organization, and diminished default-mode connectivity associated with executive deficits [1, 2]. Thus, examining whether midlife BMI relates to network-efficiency metrics (CPL, CC, GE, SWN) can clarify whether body composition functions serve as a marker of resilience or a risk factor for prodromal cognitive decline and early-onset dementia.

World Trade Center (WTC) responders including police, firefighters, and paramedics, were occupationally fit yet sustained well-documented 9/11-related exposures,

providing a natural experiment to test how body composition (e.g., BMI) and systemic inflammation jointly shape large-scale brain networks. Studying early-onset dementia (< 65 years) in this group minimizes late-life confounds and targets early mechanisms; because BMI's biological meaning shifts across the lifespan, a midlife focus is critical to distinguish metabolic reserve from cardiometabolic burden. Thus, this study examined whether BMI and cognitive status are associated with functional network efficiency, as measured by resting-state fMRI and graph-theoretic metrics (CPL, CC, GE, SWN), and how these measures relate to domain-specific cognitive performance. Midlife WTC responders with cognitive impairment represent a particularly informative population in which to test whether BMI modulates functional brain network efficiency under conditions of neurodegenerative stress.

2 Methods

2.1 Setting

This study is a secondary analysis of a cohort of 99 eligible WTC responders and 10 unexposed healthy controls, recruited from an academic monitoring program. On 9/11/2001 and in the months that followed, WTC responders were exposed to intense physical, chemical, and emotional stress during rescue, recovery, and cleanup operations [18, 38]. Mounting evidence links WTC exposure to a range of aging-related cognitive dysfunction [5, 7, 17], with several studies reporting that a subset of WTC responders have elevated risk of deficits in memory and executive functioning [5, 6]. Brain imaging studies in this population have reported structural and functional changes potentially reflecting accelerated brain aging or early neurodegenerative processes [16]. Eligibility criteria for participation in this study included documentation required to be recognized as an eligible WTC responder including documented involvement of at least 4 h of on-site activities at the WTC site, alongside research inclusion/exclusion criteria including age 44–65 years, English fluency, meeting MRI safety guidelines, no history of traumatic brain injury, and BMI ≤ 40 kg/m^2 (to ensure the responders can comfortably fit inside of the MRI scanner). The 10 controls were drawn from available healthy responders who underwent identical imaging protocols, representing the entire pool of eligible participants without cognitive complaints.

2.2 Measures

Cognitive evaluations were conducted by licensed neuropsychologists as part of the WTC Health Program's standardized neurocognitive protocol. Classification into cognitively impaired (CI) or cognitively unimpaired (CU) was determined by a clinical consensus panel that considered performance on the full neuropsychological battery, Montreal Cognitive Assessment (MoCA) screening scores, and informant or self-reported functional decline. While MoCA provided an initial screen, the final determination was not based on MoCA alone. Functional decline was assessed via structured questionnaires or informant reports of changes in daily living tasks. Our approach aligns with methods used in prior WTC neuroimaging and biomarker studies that have employed similar consensus-based classification within this cohort [5, 7].

Global cognition was assessed with the MoCA as part of the ongoing longitudinal WTC cohort protocol. MRI and cognitive testing were scheduled on separate study visits but were completed within three months of each other due to scanner scheduling

and participant availability. Only individuals without intervening medical or neurological events were included, and cognitive status remained stable during this period [24]. All WTC responders fit standard criteria for the diagnosis of mild to moderate early-onset dementia [22], evidence of severe multi-domain CI that was validated at screening alongside functional limitations that lacked an alternative medical or pharmacological explanation. We use the label CI here because the nature of early-onset dementia may be exposure-related. Additionally, eligible participants could not have evidence of neurological, pharmaceutical, or medical explanations for CI. At screening, individuals with CI also had to have MoCA scores that were consistent with their status. To be considered cognitively unimpaired (CU), participants had to have MoCA scores ≥ 26 for all prior recorded visits and be able to score ≥ 26 at the screening interview. All unexposed healthy controls met the criteria for CU. Finally, among the 99 WTC responders, 48 were classified as CI and 51 as CU. The 10 controls were cognitively unimpaired and were grouped with WTC CU for the primary CI versus CU analyses.

Domain-specific cognitive performance was evaluated with the Cogstate computerized battery, a validated tool designed to assess multiple aspects of cognitive functioning. The following five tasks were retrieved: throughput (one-card learning accuracy divided by testing speed), visual memory (one-card learning), episodic memory (continuous paired associate learning), visuospatial learning (Groton maze learning test), visuospatial recall (Groton maze learning test delayed recall), intra-individual item-response variability (detection response variability), reaction speed (detection responses per second), and processing speed (identification responses per second).

Environmental exposure was assessed based on the cumulative duration of on-site work at the WTC recovery area, specifically high-risk zones such as the pit or pile, exposure to fine particulate dust and potentially neurotoxic debris, duration of work, and the use of personal protective equipment. It was designed to capture the cumulative neurotoxic exposure. Exposure data were collected through a structured interviewer-administered questionnaire at the time of enrollment in the parent study. Consistent with previous studies [7, 42], exposure severity was categorized into five levels ranging from minimal to severe. Importantly, this was determined using standardized indices maintained by the WTC Health Program instead of relying on the report of the participants. Variables include arrival time at site, duration of work, tasks performed, and use of personal protective equipment. These measures are recorded in the WTC monitoring protocol and have been validated and used in prior WTC cognitive, imaging, and dementia research.

2.3 Structural MRI and fMRI data acquisition and preprocessing

Participants were scanned using a 3-Tesla Siemens mMR Biograph scanner with a 20-channel head and neck coil. T1-weighted structural images were acquired with a volumetric three-dimensional magnetization prepared rapid gradient echo (MPRAGE) sequence with the following parameters: repetition/echo/inversion time = 1900/2.49/900 ms, flip angle = 9°, matrix size = 256 × 256, voxel size = 0.89 × 0.89 × 0.89 mm^3. Subsequently, resting state fMRI was conducted with a gradient-echo echo-planar imaging sequence (repetition/echo time = 1500/27ms, flip angle = 80°, matrix size = 74 × 74, voxel size = 2.9 × 2.9 × 2.5 mm^3). Each volume comprised 50 axial slices, and each functional

run contained 400 image volumes after the first 20 images were discarded to allow the magnetization to reach equilibrium.

Preprocessing was performed with fMRIPrep (v20.2.7), ICA-AROMA, and in-house scripts in MATLAB and Python. Functional data were slice-time corrected, co-registered to T1w images, normalized to MNI152NLin6Asym space, smoothed, and denoised with ICA-AROMA. Additional nuisance regressors included white matter, cerebrospinal fluid, and motion parameters. Data were bandpass filtered (0.01–0.1 Hz), detrended, and scrubbed at framewise displacement > 0.5 mm.

Cortical parcellation was performed with FreeSurfer's recon-all pipeline to generate individualized Desikan–Killiany–Tourville (DKT) atlases, registered to MNI space. Sixty-two cortical regions (31 per hemisphere) were defined as nodes. Functional network efficiency matrices were created using Pearson correlations between mean fMRI time series for each pair of regions, thus forming 62×62 weighted undirected graphs.

2.4 Graph-theory based metrics

As shown in Fig. 1, we computed CPL, CC, GE, and SWN using the Brain Connectivity Toolbox, summarizing each metric as the area under the curve (AUC) across sparsity thresholds (0.10–0.34, step 0.01) per established methods [20, 34]. AUC-derived metrics minimize the bias introduced by single-threshold selection.

2.5 Statistical analysis

Analyses were conducted in Python (v3.13.1) and SPSS (v29.0.2.0), with the threshold for statistical significance set at two-tailed $p < 0.05$. Group differences in demographics and clinical variables were tested with independent-samples t-tests or Mann–Whitney U tests for continuous variables, and chi-square tests for categorical variables. Normality was assessed with the Shapiro–Wilk test. A MANCOVA was conducted with CPL, CC, GE, and SWN as dependent variables; cognitive status (CI vs. CU) and BMI as independent variables; and age, sex, and race as covariates. Significant multivariate findings were followed by ANCOVAs. Partial eta squared (η^2_p) was determined to estimate effect sizes. Two models were tested, baseline model:

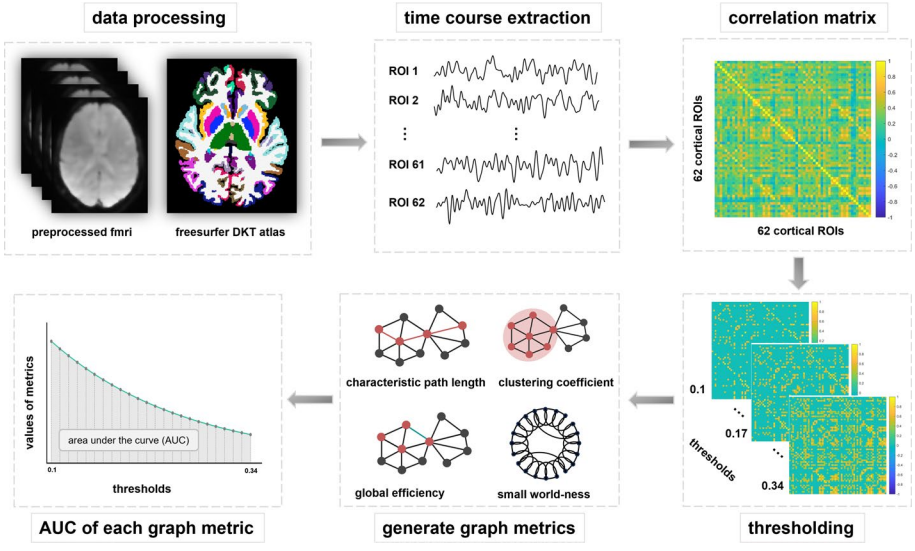

Fig. 1 Schematic plot of the derivation of the graph-theory based functional network efficiency metrics

$$y \sim CI + BMI + age + sex + race \quad (1)$$

, which examined the main effects of cognitive status (CI vs. CU) and BMI on brain network measures while adjusting for demographic covariates (age, sex, and race); and Interaction model:

$$y \sim CI + BMI + age + sex + race + BMI \times CI \quad (2)$$

which additionally tested whether the association between BMI and network topology differed by cognitive status.

To examine the relationship between brain network topology and cognitive function, we conducted partial correlation analyses (Spearman/Pearson, as appropriate) between graph-theory metrics and Cogstate test performance, controlling for age, sex, BMI, and race. Sensitivity analyses included Apolipoprotein E (APOE) genotyping, and dust exposure as additional covariates in the MANCOVA to assess robustness.

To explore BMI–network efficiency associations, we computed partial correlations, adjusting for age, sex, and race. Subgroup analyses stratified by cognitive status (CI vs. CU) were performed to examine differential effects.

3 Results

3.1 Primary analyses

Participants were in their mid-fifties, and groups were comparable in terms of age, sex, BMI, educational level, APOE genotype, and neurotoxic exposure severity (Table 1). As expected, a significant difference in MoCA scores was observed between groups ($p < 0.001$).

Here we analyzed CI ($n = 48$) versus CU ($n = 61$; 51 WTC CU plus 10 controls). MANCOVA revealed statistically significant associations between BMI and functional brain network efficiency metrics (Wilks' $\lambda = 0.879$, $p = 0.012$, $\eta^2_p = 0.121$), whereas CI was not associated (Wilks' $\lambda = 0.941$, $p = 0.196$, $\eta^2_p = 0.059$) (Table 2). Post hoc ANCOVAs (Table 3) indicated that BMI was associated with all four graph-theory metrics ($p = 0.003$ for CPL, $p = 0.009$ for CC, $p = 0.001$ for GE, $p = 0.004$ for SWN).

To further investigate whether this association varied by cognitive status, we extended the model by including the interaction term (BMI × CI). A significant interaction was observed between BMI and cognitive status on global network efficiency (Wilks' $\lambda = 0.884$, $p = 0.017$, $\eta^2_p = 0.116$) (Table 2). *Post hoc* ANCOVAs (Table 3) also indicated that BMI was associated with all four graph-theory metrics ($p = 0.001$ for CPL, $p = 0.002$ for CC, $p < 0.001$ for GE, $p = 0.001$ for SWN).

Partial correlation analyses (Fig. 2), controlling for age, sex, and race, revealed significant associations between BMI and global fMRI-derived network measures. Higher BMI was associated with lower CPL ($\rho = -0.307$, $p = 0.001$), indicative of shorter average paths between brain regions. In contrast, BMI was positively correlated with CC ($r = 0.251$, $p = 0.009$), GE ($\rho = 0.336$, $p < 0.001$), and SWN ($\rho = 0.283$, $p = 0.003$).

Table 1 Characteristics of world trade center responders

Characteristics	CU (*n* = 61)	CI (*n* = 48)	*p*
Age, years (mean ± SD)	55.3 ± 4.5	55.8 ± 5.9	0.552[a]
Sex (n, %)			
Male	46 (75%)	37 (77%)	0.839[c]
Female	15 (25%)	11 (23%)	
Body Mass, kg/m^2 (mean ± SD)	28.7 ± 4.7	29.7 ± 4.1	0.210[a]
Race/Ethnicity (n, %)			
White	53 (86%)	31 (65%)	**0.021**[c]
Black	4 (7%)	7 (15%)	
Others	4 (7%)	10 (20%)	
Education attainment (n, %)			
High school or less	8 (13%)	14 (29%)	0.058[c]
Some college	29 (48%)	23 (48%)	
Bachelor's degree	24 (39%)	11 (23%)	
MoCA scores (median [Q1, Q3])	27 [27, 29]	19 [17, 20]	**< 0.001**[b]
APOE gene (n, %)			
Positive	10 (16%)	11 (23%)	0.404[c]
Negative	38 (63%)	31 (64%)	
Unknown	13 (21%)	6 (13%)	
Dust exposure degree (n, %)			
0 Unexposed	11 (18%)	1 (2%)	0.070[c]
1 Minimal	31 (51%)	24 (50%)	
2 Mild	13 (22%)	14 (29%)	
3 Moderate	2 (3%)	6 (13%)	
4 High	2 (3%)	1 (2%)	
5 Severe	2 (3%)	2 (4%)	

Data are presented as median [Q1, Q3] for non-normally distributed variables and mean ± SD for normally distributed variables

CI cognitively impaired, *CU* cognitively unimpaired,*MoCA* Montreal Cognitive Assessment, *APOE* Apolipoprotein E

[a]t-test;[b]Mann–Whitney U test;[c]chi-square test

Table 2 MANCOVA results demonstrating the association between the graph-theory based functional network efficiency metrics and BMI, CI, and the interaction of these two

MANCOVA						
Factors	Baseline model[a]			Interaction model[b]		
	Wilks' λ	p	η^2_p	Wilks' λ	p	η^2_p
BMI	0.879	**0.012**	0.121	0.863	**0.006**	0.137
CI	0.941	0.196	0.059	0.898	**0.033**	0.102
BMI × CI	–	–	–	0.884	**0.017**	0.116

BMI body mass index, *CI* cognitive impairment status

[a] y ~ CI + BMI + age + sex + race

[b] y ~ CI + BMI + age + sex + race + BMI × CI

η^2_p indicates partial eta squared effect size (small = 0.01, medium = 0.06, large = 0.14) [8]

3.2 Subgroup analyses: CI and CU groups

To further understand the interaction between CI and BMI, we conducted partial correlation analyses in the CI and CU groups separately, adjusting for age, sex, and race (Fig. 3). In the CI group ($n = 48$), BMI was negatively associated with CPL (r = -0.474, $p < 0.001$), but positively associated with CC ($r = 0.436$, $p = 0.002$), GE ($r = 0.474$, $p < 0.001$),

Table 3 Post hoc ANCOVA results showing the association between in the individual graph theory based functional network efficiency metrics and BMI, CI, and the interaction of these two

Post hoc ANCOVA									
Metrics	**Factors**	**Baseline model[a]**				**Interaction model[b]**			
		F	***p***	**η^2_p**	**Model adjusted R^2**	**F**	***p***	**η^2_p**	**Model adjusted R^2**
CPL	BMI	9.064	**0.003**	0.082	0.061	12.581	**0.001**	0.112	0.099
	CI	0.116	0.734	0.001		5.368	**0.023**	0.051	
	BMI × CI	–	–	–		5.247	**0.024**	0.05	
CC	BMI	7.166	**0.009**	0.066	0.041	10.068	**0.002**	0.091	0.074
	CI	0.385	0.537	0.001		4.909	**0.029**	0.047	
	BMI × CI	–	–	–		4.605	**0.034**	0.044	
GE	BMI	12.512	**0.00**1	0.11	0.087	14.962	**< 0.001**	0.13	0.103
	CI	0.435	0.511	0.004		3.018	0.085	0.029	
	BMI × CI	–	–	–		2.747	0.101	0.027	
SWN	BMI	8.508	**0.004**	0.078	0.060	12.702	**0.001**	0.113	0.112
	CI	0.004	0.949	0		6.856	**0.010**	0.064	
	BMI × CI	–	–	–		6.957	**0.010**	0.065	

BMI body mass index, *CI* cognitive impairment status, *CPL* characteristic path length, *CC* clustering coefficient, *GE* global efficiency, *SWN* small-worldness

[a] y ~ CI + BMI + age + sex + race.

[b] y ~ CI + BMI + age + sex + race + BMI × CI

η^2_p indicates partial eta squared effect size (small = 0.01, medium = 0.06, large = 0.14) [8]

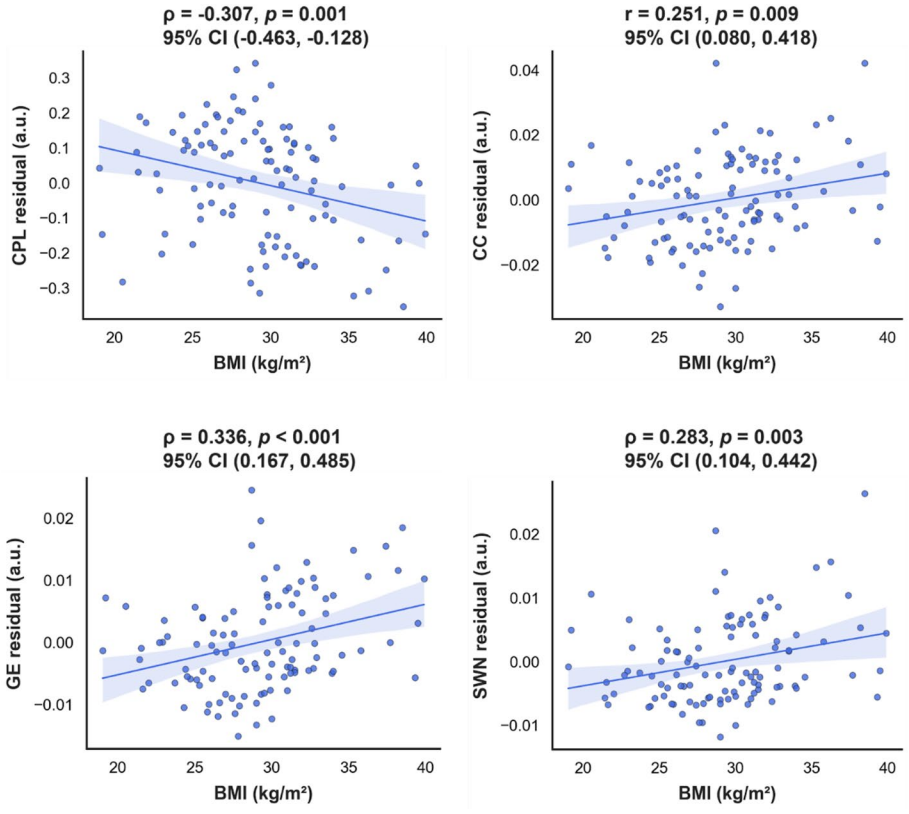

Fig. 2 Scatter plots of BMI and the residuals of the graph theory metrics after controlling for age, sex, and race. The partial Pearson / Spearman correlation coefficients are shown as appropriate (r, ρ, respectively) along with the corresponding *p* value. *CPL* characteristic path length, *CC* clustering coefficient, *GE* global efficiency, *SWN* small-worldness, *BMI* body mass index, *95% CI* 95% confidence interval

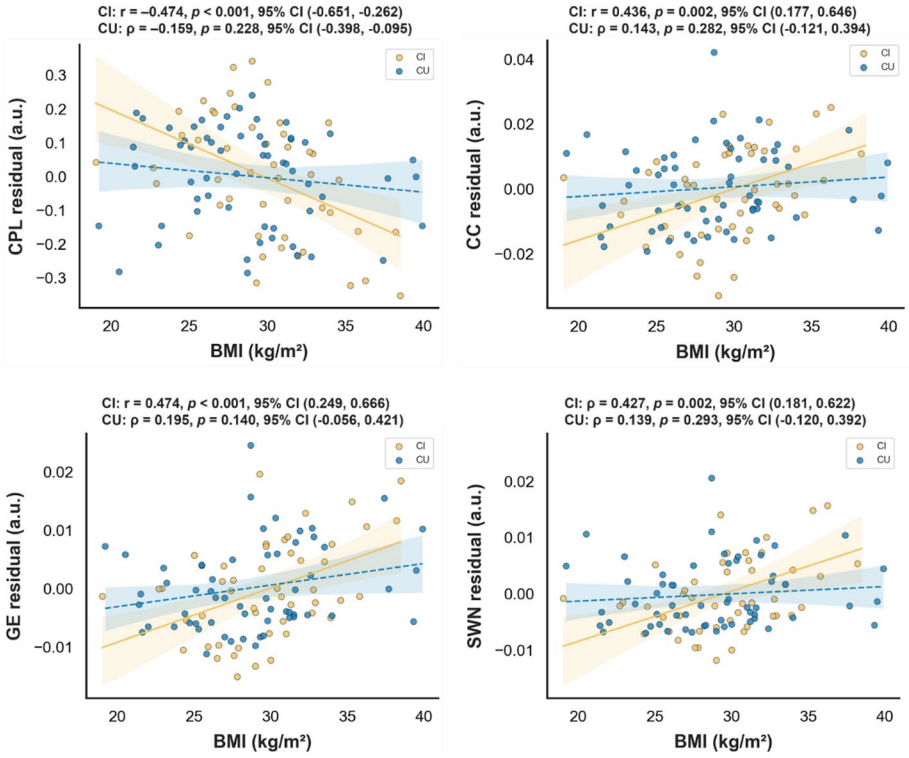

Fig. 3 Scatter plot of BMI and the residuals of the graph-theory metrics after correction for age, sex, and race. The partial Pearson / Spearman correlation coefficients are shown as appropriate (r, ρ, respectively) along with the corresponding *p* value. *CPL* characteristic path length, *CC* clustering coefficient, *GE* global efficiency, *SWN* small-worldness, *BMI* body mass index, *CI* cognitively impaired, *CU* cognitively unimpaired, *95% CI* 95% confidence interval

and SWN ($r = 0.427$, $p = 0.002$). In contrast, despite a larger sample size in the CU group ($n = 61$) we found no correlations between BMI and graph-theory metrics. These findings indicate that higher BMI was linked to more efficient network organization only among individuals with CI, suggesting that the influence of BMI on brain connectivity may become more pronounced under conditions of cognitive vulnerability.

Table 4 shows the results of the associations between graph-theory metrics and cognitive performance. Attention was associated with multiple graph-theory parameters, including a negative partial correlation with CPL (ρ = -0.226, $p = 0.028$), and positive correlations with CC (ρ = 0.288, $p = 0.005$), GE (ρ = 0.292, $p = 0.004$) and SWN (ρ = 0.264, $p = 0.010$). We found a statistically significant partial correlation of reaction variability with both CPL (ρ = -0.234, $p = 0.023$) and GE (ρ = 0.216, $p = 0.036$).

Marginal associations (ρ = 0.204, $p = 0.049$) were observed between SWN and reaction speed. Choice reaction time also showed a marginal correlation with SWN (ρ = 0.203, $p = 0.050$). Collectively, these findings suggest that shorter paths, higher integration, and more small-world-like structure may be modestly linked to faster and more consistent performance in speeded response tasks. No significant relationships were found between CPL, CC, GE, or SWN and performance on tasks assessing episodic memory accuracy, visuospatial learning errors, visuospatial recall errors, visual working memory, or throughput.

Table 4 Partial correlation analysis results between graph-theory metrics and cognitive performance, controlling for age, sex, BMI, and race

	CPL		CC		GE		SWN	
	r/ρ	*p*	*r*/ρ	*p*	*r*/ρ	*p*	*r*/ρ	*p*
Episodic Memory, accuracy	**– 0.044**	0.673	**0.090**	0.389	**0.096**	0.356	**0.085**	0.414
Reaction Spead	**– 0.164**	0.113	**0.199**	0.055	**0.111**	0.288	**0.204**	**0.049**
Intraindividual Reaction Variability	**– 0.234**	**0.023**	**0.172**	0.098	**0.216**	**0.036**	**0.193**	0.062
Visuospatial Learning	**– 0.073**	0.486	**– 0.002**	0.981	**– 0.004**	0.969	**0.028**	0.789
Visuospatial Recall	**– 0.070**	0.503	**0.014**	0.890	**– 0.007**	0.945	**0.043**	0.681
Attention	**– 0.226**	**0.028**	**0.288**	**0.005**	**0.292**	**0.004**	**0.264**	**0.010**
Processing Speed	**– 0.175**	0.092	**0.197**	0.057	**0.136**	0.192	**0.203**	**0.050**
Visual Working Memory	**– 0.021**	0.841	**– 0.029**[a]	0.783	**0.022**	0.834	**0.025**	0.809
Throughput	**0.031**	0.764	**– 0.088**[a]	0.401	**– 0.003**	0.980	**– 0.029**	0.782

[a] Pearson correlation

All other used Spearman correlation

CPL: characteristic path length; CC: clustering coefficient; GE: global efficiency; SWN: small-worldness.

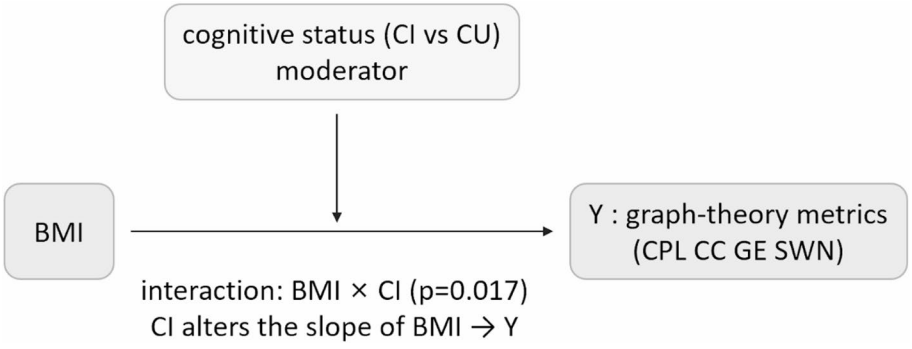

Fig. 4 Conceptual moderation diagram. Cognitive status (CI vs. CU) moderates the association between BMI and graph-theory network metrics. The interaction term (BMI × CI) was significant ($p = 0.017$). After adjusting for age, sex, and race, higher BMI was associated with greater network efficiency in the CI group, whereas no association was observed in the CU group. *CPL* characteristic path length, *CC* clustering coefficient, *GE* global efficiency, *SWN* small-worldness, *BMI* body mass index, *CI* cognitively impaired, *CU* cognitively unimpaired

3.3 Sensitivity analyses

We conducted sensitivity analyses by including APOE genotype, dust exposure severity, post-traumatic stress disorder (PTSD), and major depressive disorder (MDD) as additional covariates. The inclusion of these covariates did not identify any new statistically significant associations with any of the outcomes and did not alter the main results.

4 Discussion

4.1 Summary

This study examined how CI and BMI relate to brain network organization at midlife in a population characterized by both severe environmental exposure and above-average occupational fitness. Resting-state fMRI graph-theory analysis showed that both BMI and CI status independently affected global network efficiency, with a stronger association between BMI and network metrics in responders with CI. Notably, network efficiency correlated with processing speed and attention. This is among the first studies to characterize functional brain organization in a cohort with combined occupational and environmental exposures (Fig. 4).

In most midlife community samples, higher BMI—particularly when associated with excess adiposity—is associated with lower GE and disrupted small-world organization, probably through vascular, metabolic, and inflammatory mechanisms [1, 21]. However, in older adults, some studies have reported a paradoxical or attenuated relationship, in which higher BMI is associated with preserved cognition or slower rates of cognitive decline potentially reflecting maintained cognitive reserve. In this midlife WTC cohort, we found higher BMI predicted better network efficiency. Two features of this WTC cohort might account for this paradoxical finding: (1) occupational fitness, given that police officers and firefighters often have higher BMI because of greater lean mass rather than excess fat [3, 23], and (2) stringent inclusion criteria (BMI ≤ 40 kg/m^2), which truncated the upper adiposity range.

Consistent with literature in prodromal Alzheimer's disease suggesting that higher CPL and lower SWN signal early disconnection [12, 40], WTC responders with CI had longer paths, less clustering, and lower small-world structure than unimpaired responders. These alterations at mid-life may underscore accelerated neurobiological aging previously reported in this cohort.

An interaction reported a steeper BMI–network metric slope among impaired responders, may imply that BMI plays a role in brain maintenance or cognitive reserve in the presence of environmental exposures. This finding aligns with findings of an "obesity paradox" in late-life dementia, wherein preserved body weight is associated with slower cognitive decline [15, 25]. In WTC responders, higher BMI might have helped sustain functional network integrity among those individuals with CI. In contrast, it is likely that cognitively unimpaired responders already are operating near peak efficiency, thereby limiting the observable effects of BMI.

While higher SWN and GE in CI individuals with elevated BMI might reflect neural resilience, such patterns could also represent compensatory hyper-integration—a phenomenon reported in early Alzheimer's disease and traumatic brain injury [13, 35]. This alternative interpretation suggests that network over-engagement may precede eventual functional breakdown.

4.2 Interpretation: BMI may act as a marker of systemic reserve

Elevated BMI in non-WTC-exposed firefighters has been associated with muscle mass and anaerobic capacity rather than excess fat [3], and similar results may be evident for WTC responders. This distinction is critical in the interpretation of results, given that the observed association between higher BMI and more efficient brain network properties could reflect physiological resilience. In the context of environmental exposure-related CI, cognitive reserve might help preserve functional network integration and mitigate the effects of neurotoxic stressors. Future studies should incorporate direct measures of body composition to help differentiate between fat and muscle mass.

Associations observed between brain network efficiency and cognitive performance underscored the relevance of imaging-based graph theory metrics. Notably, shorter CPL and higher GE were significantly associated with better performance in processing speed and attention tasks, as measured with the Cogstate battery, while a marginally significant association between SWN and choice reaction time (p = 0.049) further supported the link between efficient brain network properties and attentional processing. Findings link global network efficiency to faster processing and attention, but not

memory or visuospatial performance, indicating selectivity for domains sensitive to early cognitive change. Indeed, some studies suggest that higher-order cognitive tasks (e.g., memory, spatial recall) may rely more on regional or modular brain dynamics (e.g., hippocampal–prefrontal interactions), which may not be reflected in global metrics like GE or SWN [31]. In the context of WTC responders, who have elevated risk of environmentally linked CI, graph-theory metrics might serve as noninvasive biomarkers for identifying functional disruptions.

Whereas the current study focused on functional brain network organization using fMRI, prior work [17] has used DTI-based graph analysis to reveal that structural connectivity was associated primarily with PTSD symptoms. Although both studies employed graph-theoretical approaches, the metrics capture distinct phenomena across modalities. For example, while fMRI measures reflect the degree of temporal coordination, DTI measures the absence of physical white matter connections. In general, the DTI-based CPL is not correlated with the functional network efficiency metrics studied here, and PTSD and MDD status were not associated with these network metrics. Our current fMRI-based results expand this narrative by demonstrating that functional network properties are modulated by systemic health (as indicated by BMI) in participants with CI, potentially reflecting a broader interplay between cognitive reserve, functional resilience, and cognitive functioning. Multimodal findings underscore the complementary value of structural and functional graph-theory metrics in characterizing latent brain network disruptions in this population.

Sensitivity analyses revealed that neither the APOE genotype nor cumulative dust exposure had strong or consistent effects on graph-theory network metrics. These null findings might be partially explained by the limited variability in APOE status and the relatively small proportion of ε4 carriers within the sample. In addition, the reliance on duration-based exposure metrics might not have fully captured the complexity of individual toxicant burden or biological susceptibility, particularly in a population with heterogeneous exposures and resilience profiles. Future work incorporating more granular exposure indices (e.g., specific toxin levels, respiratory burden, and systemic inflammatory markers), as well as larger samples with adequate representation of genetic subgroups, might help clarify these relationships.

5 Limitations

Several limitations warrant consideration when interpreting results from this study. First, the cross-sectional design precluded causal inference from being drawn and limited our ability to determine temporal relationships among BMI, cognitive decline, and brain network changes. Second, direct measures of body composition or muscle mass were not available, limiting interpretation of BMI as a proxy for metabolic reserve. Third, the sample size was modest for certain subgroup comparisons, such as those involving the APOE genotype and consequently might have limited the statistical power. Finally, the predominantly male cohort, though reflecting the demographic makeup of the WTC responder population, constrains generalizability of findings to females and non-responders.

6 Clinical implications

Graph-theory based metrics derived from resting-state fMRI might serve as sensitive and noninvasive biomarkers for the early detection of network-level disruptions associated with cognitive decline. Associations with cognitive performance support the utility for identifying vulnerable individuals before severe limitations emerge. Results further suggest that higher BMI might have value as an indirect marker of systemic reserve in aging or cognitively impaired adults, and in physically trained populations. Rather than serving solely as a metabolic risk factor, higher BMI might reflect an underlying physiological capacity that supports brain network resilience under stress.

7 Future directions

Our findings indicate the need for longitudinal follow-up studies to determine whether these brain network properties can predict future cognitive decline and to assess how changes in systemic health indicators, such as BMI or body composition, relate to neural aging trajectories in this high-risk cohort.

Author contributions
XZ, JY, and TZ contributed to data analysis. CH and XZ drafted the manuscript. SC and CH provided scientific direction and critically edited the manuscript. SC managed the data collation and BJL and SC provided funding for this study. All authors had access to the data throughout the analysis period.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability
Not applicable.

Declarations

Ethics approval
All study procedures adhered to the 1964 Declaration of Helsinki and its later amendments. Study procedures were reviewed and approved by the Institutional Review Board (CORIHS-A) at Stony Brook University.

Consent to participate
Informed written consent was obtained from all participants after a comprehensive explanation of the study procedures.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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