

A Network Analysis Of Cardiometabolic Disease, Cerebral Small Vessel Disease, And Alzheimer’s Disease Biomarkers Across Clinical Stages

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Background

Previous research found independent associations between individual cardiometabolic disease (CMD), cerebral small vessel disease (CSVD), and Alzheimer’s disease (AD) biomarkers.

Objective

We aim to assess how CMDs, CSVD, and AD biomarkers are interrelated across AD clinical stages through network models.

Methods

Harmonisation of European cohorts:

- European Prevention of Alzheimer’s Dementia (EPAD)
- Amsterdam Dementia Cohort (ADC)
- European Medical Information Framework (EMIF-AD) Multimodal Biomarker Study & PreclinAD

Variables

- **AD biomarker abnormality**
 - CSF amyloid-β42 (using local cutoffs)
 - CSF p-tau181 (using local cutoffs)
 - Scheltens medial temporal atrophy (MTA) ≥2
- **Presence of cerebral small vessel disease (CSVD)**
 - White matter hyperintensities (WMH) by Fazekas score ≥2
 - Number of microbleeds ≥1
 - Number of lacunes ≥1
- **Presence of cardiometabolic disease (CMD)**
 - Diabetes Mellitus (DM)
 - Hypercholesterolemia
 - Hypertension
 - Obesity

Analysis

Mixed graphical models (R package *mgm*) estimating regression-based coefficients across cognitively normal, MCI and dementia groups. All networks were adjusted for age and sex.

Results

Demographics are shown in **Table 1**.

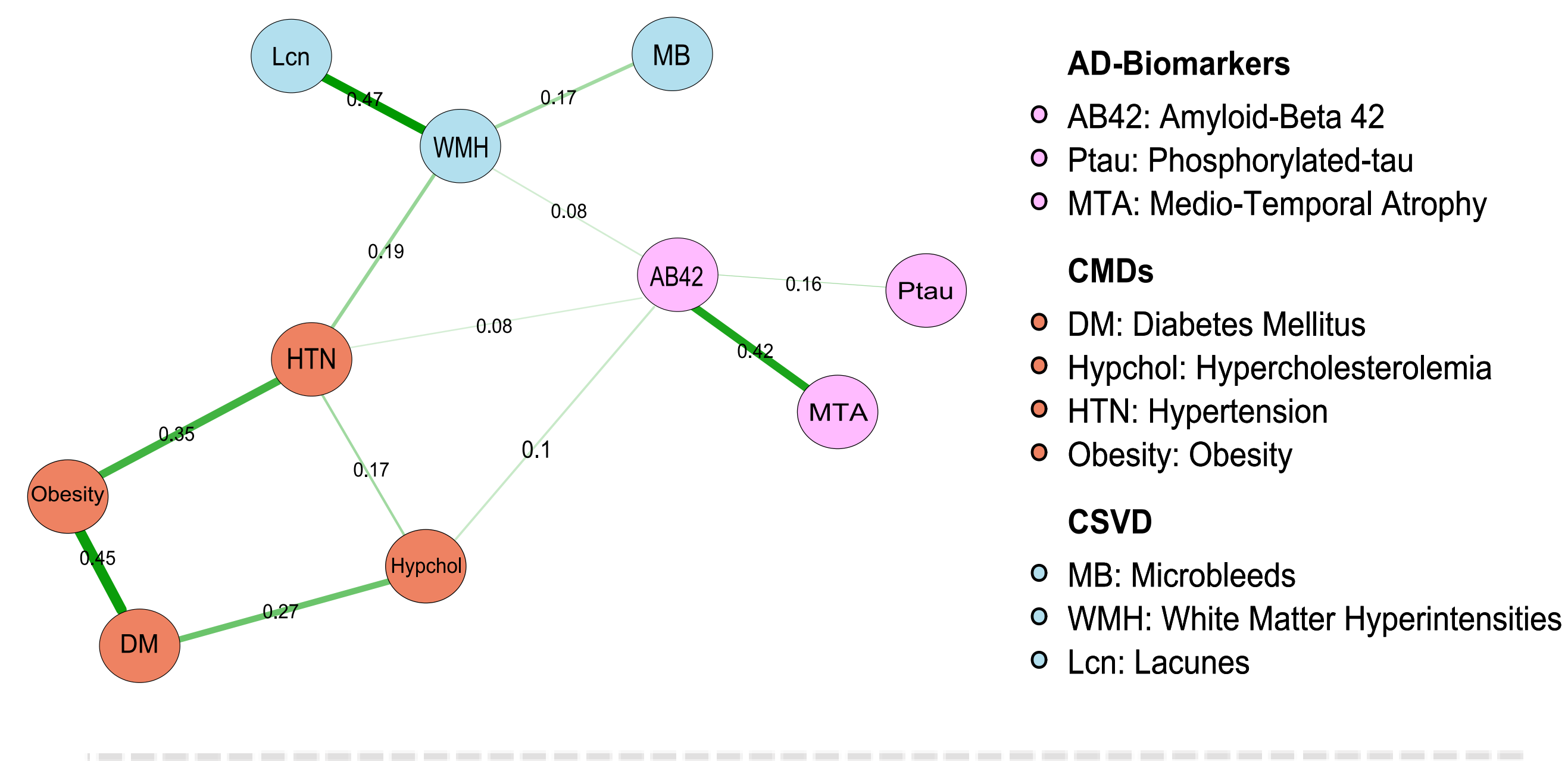
Networks stratified for cognitive stage are shown in **Figure 1**.

- Networks primarily showed within-category associations
 - CMDs primarily show associations in CN
 - CSVD and AD biomarkers show strongest associations in MCI and dementia
- Across categories, CN participants showed associations of
 - Hypertension and hypercholesterolemia with amyloid-β42
 - Hypertension <> WMH <> amyloid-β42
- In more advanced stages, only associations between DM and lacunes (MCI) + WMH and MTA (dementia) were shown.

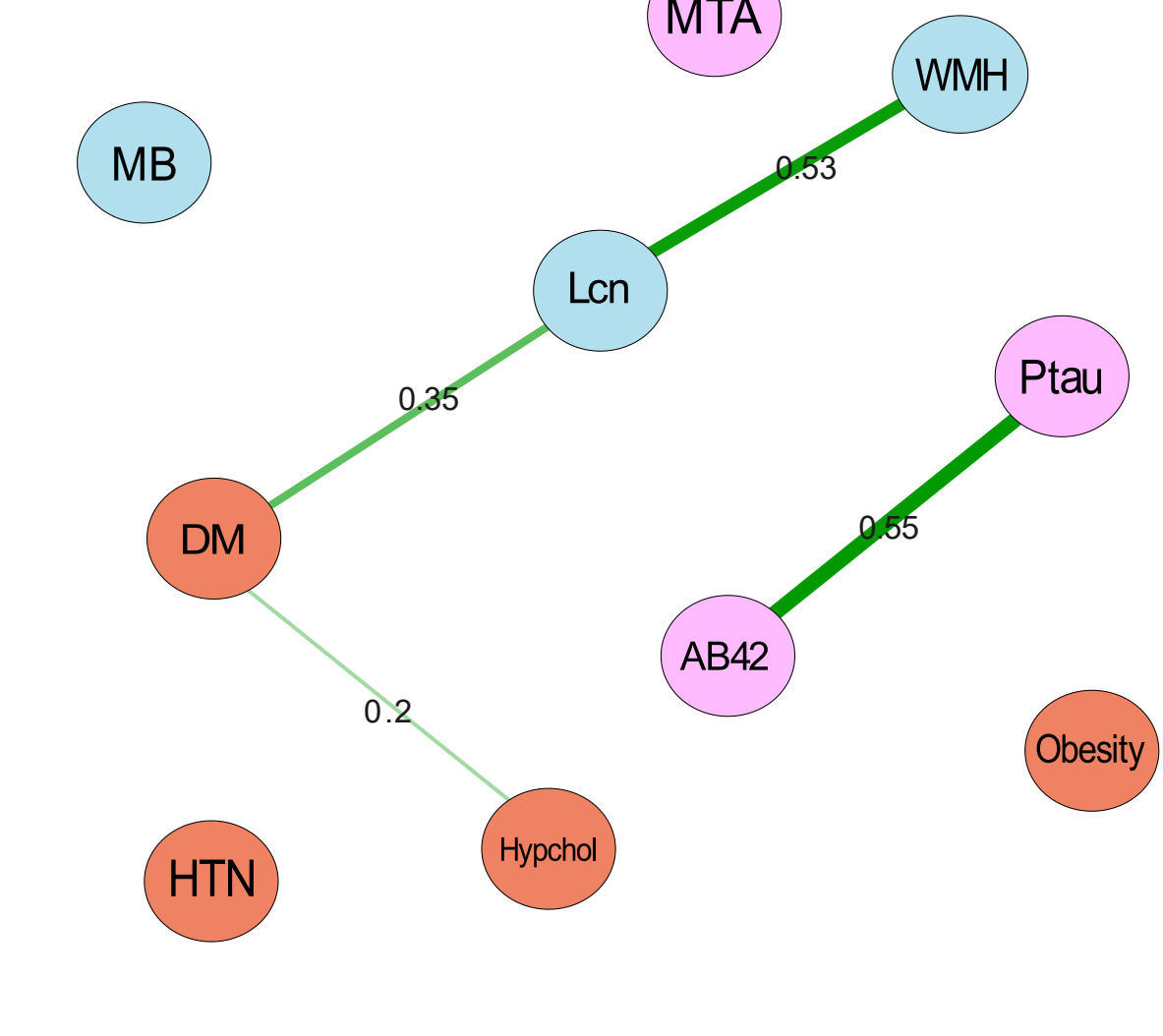
Table 1. General characteristics.

Characteristic Mean (SD) or N(%)	Cognitively normal N=1,930	MCI N=908	Dementia N=732
Age (Years)	63.9 (7.2)	67.4 (7.5)	65.6 (7.1)
Aβ-42 positivity	552 (29%)	485 (53%)	693 (95%)
P-tau181 positivity	393 (20%)	423 (47%)	611 (83%)
MTA	57 (3%)	162 (18%)	328 (45%)
WMH	275 (14%)	210 (23%)	170 (23%)
Microbleeds	292 (15%)	194 (21%)	158 (22%)
Lacunes	126 (7%)	123 (14%)	58 (8%)
Obesity	308 (16%)	93 (10%)	60 (8%)
Hypertension	1,492 (77%)	707 (78%)	609 (83%)
Hypercholesterolemia	436 (23%)	251 (28%)	87 (12%)
Diabetes Mellitus	145 (8%)	103 (11%)	45 (6%)

Cognitively normal



MCI



Dementia

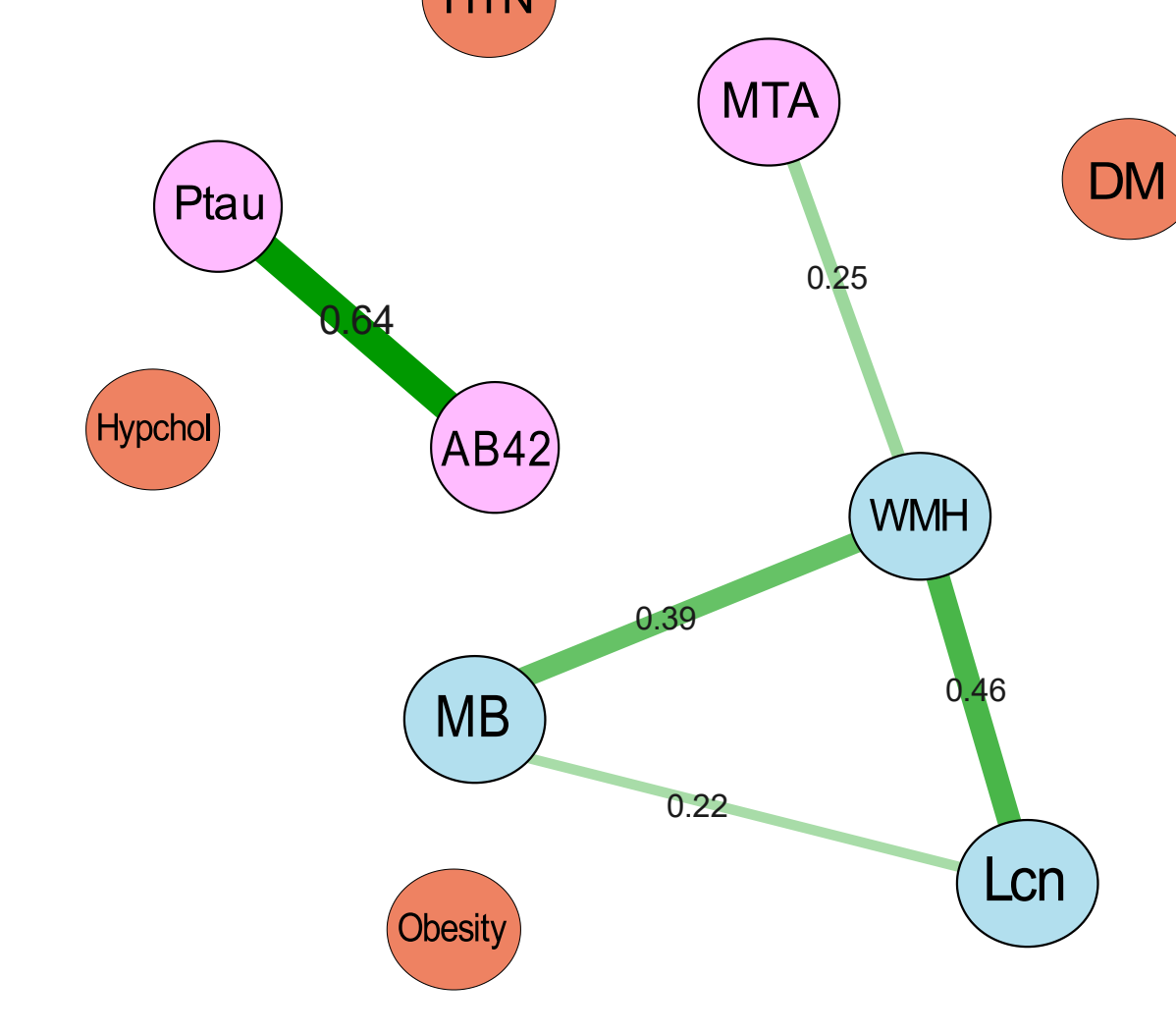


Figure 1. Network models across CN, MCI and dementia stages.

Significant associations in a network model are indicated by the presence of a line (an “edge”) connecting variables (the “nodes”). Green edges indicate positive relationships between two nodes when controlled for all other variables, and red edges indicate negative. The numbers on every edge indicate the regression-based edge weights. MCI = Mild cognitive impairment.

Node strenghts are shown in Figure 2.

- Strenghts varied per cognitive stage. Overall, age and WMH showed greatest strength centrality across all cognitive stages.

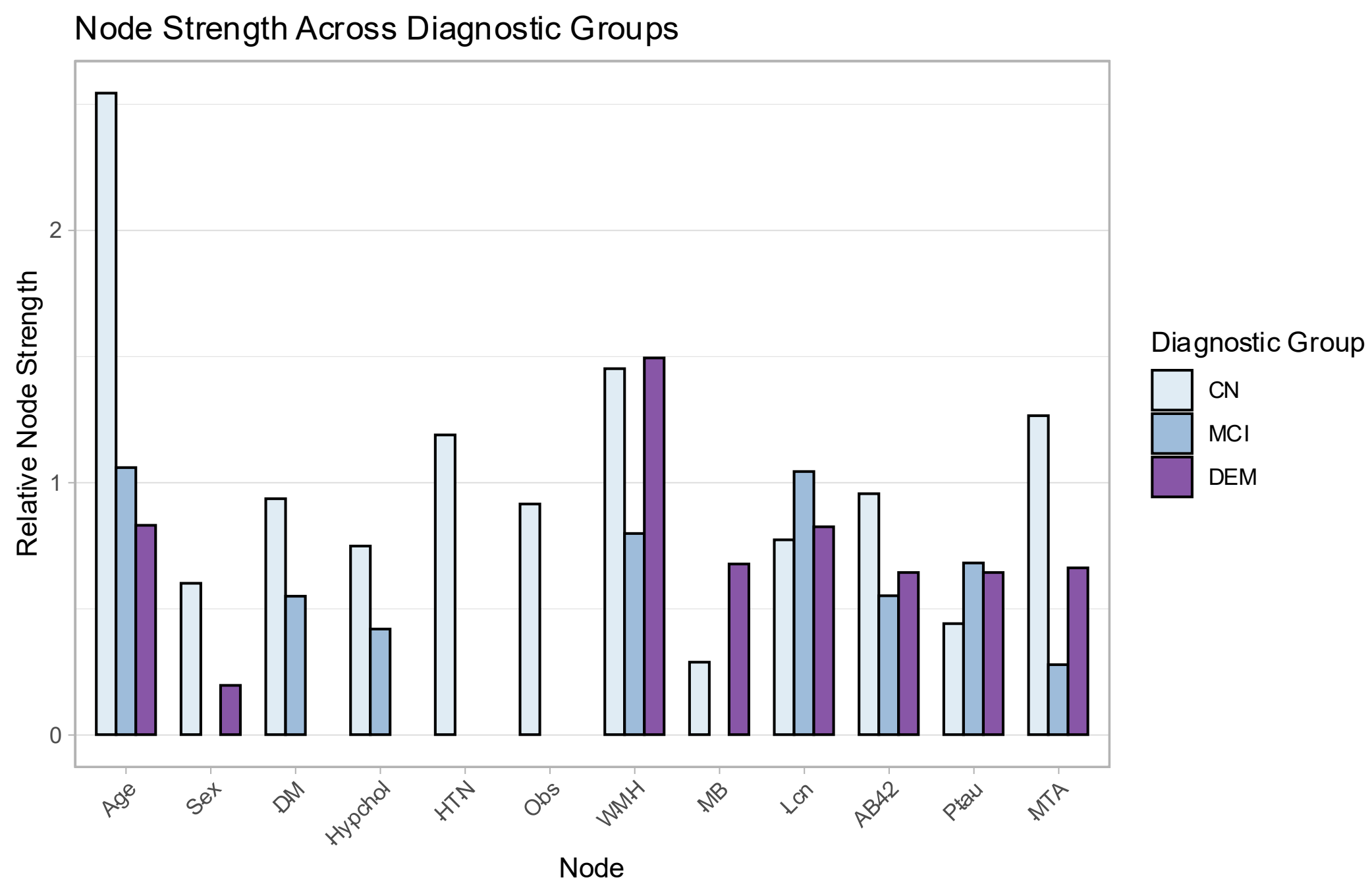


Figure 2. Node strength across cognitive stages.

Strength centrality scores describe the strength of a node in comparison to others within the network. A score of zero indicates that the node is not connected to other nodes within the network. CN = Cognitively normal, MCI = Mild Cognitive Impairment, DEM = Dementia; DM = diabetes mellitus, Hypchol = Hypercholesterolemia, HTN = Hypertension, Obs = obesity, WMH = White Matter Hyperintensities, MB = Microbleeds, Lcn = Lacunes, AB42 = Amyloid-Beta 42, P-tau = Phosphorylated-tau181, MTA = medial temporal atrophy.

Conclusions

- **CSVD and AD biomarkers are predominantly independent pathologies and more strongly co-present in advanced AD clinical stages.**
- **In CN persons, hypercholesterolemia and hypertension were associated with amyloid; the latter potentially through WMH.**

These findings add relevant knowledge for improving diagnostic procedures and defining effective time windows for preventive treatment.



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