

White matter microstructural damage mediates sex-specific cognitive decline in overt metabolic syndrome in late life

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KEY MESSAGE

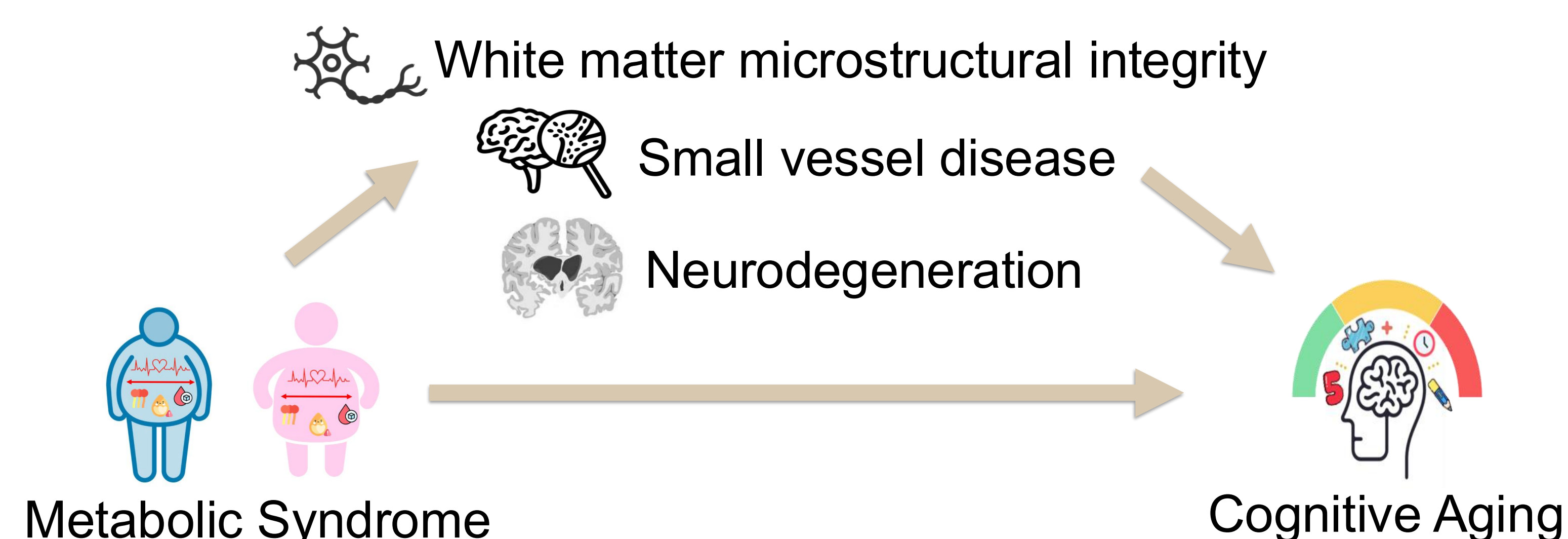
Overt metabolic syndrome is associated with distinct patterns of cognitive decline in men and women through different white matter microstructural pathways. In women, overt metabolic syndrome is associated with reduced global and executive function, mediated by axonal injury (AxD) and reduced tract coherences (FA). In men, overt metabolic syndrome is associated with faster visuospatial decline, mediated by microstructural deterioration (MD) and demyelination (RD).

BACKGROUND

- Metabolic syndrome is a well-known factor associated with increased risk of cerebrovascular disease and cognitive impairment, yet the underlying mechanisms - particularly potential sex differences - remain poorly understood.
- Translating metabolic syndrome into prevention is not straightforward because these factors are already highly prevalent from midlife (33% of older adults in Sweden)
- Yet it remains unclear whether different clinical manifestations, specifically overt and non-overt forms, differentially influence cognitive decline and brain pathology.

AIMS

To investigate specific associations of non-overt and overt metabolic syndrome with cognitive trajectories, and to evaluate which brain vulnerability mediates these associations.



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Our team's research focuses on understanding vascular contributions to cognitive disorders, particularly linked to cerebral small vessel disease, as well as mechanisms of cognitive resilience and sex-related differences.

METHODS

Study population. 582 participants aged 70 years old without dementia at baseline from the Gothenburg H70-1944 Birth Cohort study. Follow-up assessment was conducted at age 75.

Non-overt metabolic syndrome. ≥ 3 of 5 according to the Joint Criteria but not meeting clinical cutoffs (except waist circumference)

Overt metabolic syndrome. meeting clinical cutoff for ≥ 3 of: reduced HDL cholesterol, elevated triglyceride, blood pressure, fasting glucose

Cognition. Global, memory, executive function, verbal fluency, attention, and visuospatial (all standardized to baseline)

Statistical analysis. Sex-specific linear mixed effect models adjusted for age, sex to estimate association between metabolic syndrome and cognitive decline. Mediation analysis to identify the role of SVD and white matter integrity alterations.

Table 1. Sex-specific association of overt syndrome with 5-year cognitive decline

WOMEN		β	(95% CI)	p
	Global	-0.27	(-0.5, -0.04)	0.024
	Executive function	-0.6	(-1.1, -0.11)	0.017
	Visuospatial	-0.11	(-0.46, 0.24)	0.526

MEN		β	(95% CI)	p
	Global	0.07	(-0.13, 0.26)	0.494
	Executive function	0.27	(-0.12, 0.66)	0.181
	Visuospatial	-0.3	(-0.59, -0.01)	0.041

Reference. No metabolic syndrome

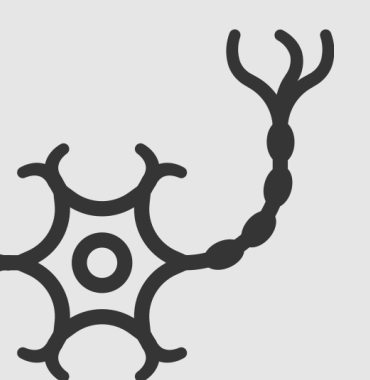
FDR-adjusted p-values are shown

β represents mean difference in cognitive decline compared to no metabolic syndrome

Non-overt metabolic syndrome showed no association with cognitive decline

White matter microstructural integrity. 4 DTI measures:

- Fractional anisotropy (FA) – tract coherence
- Mean diffusivity (MD) – microstructural integrity
- Axial diffusivity (AxD) – axonal integrity
- Radial diffusivity (RD) – myelin damage

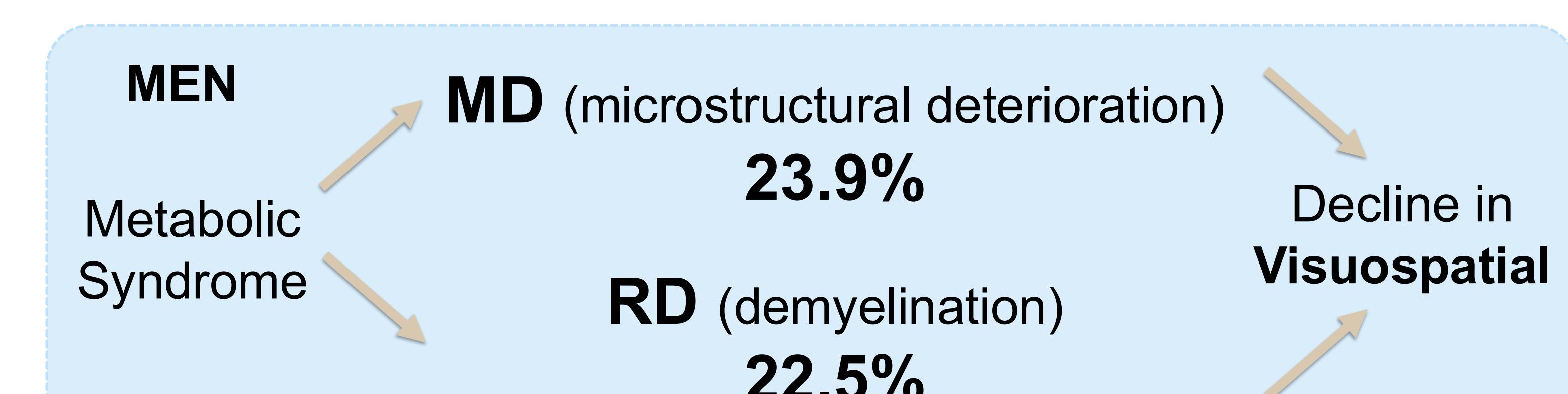
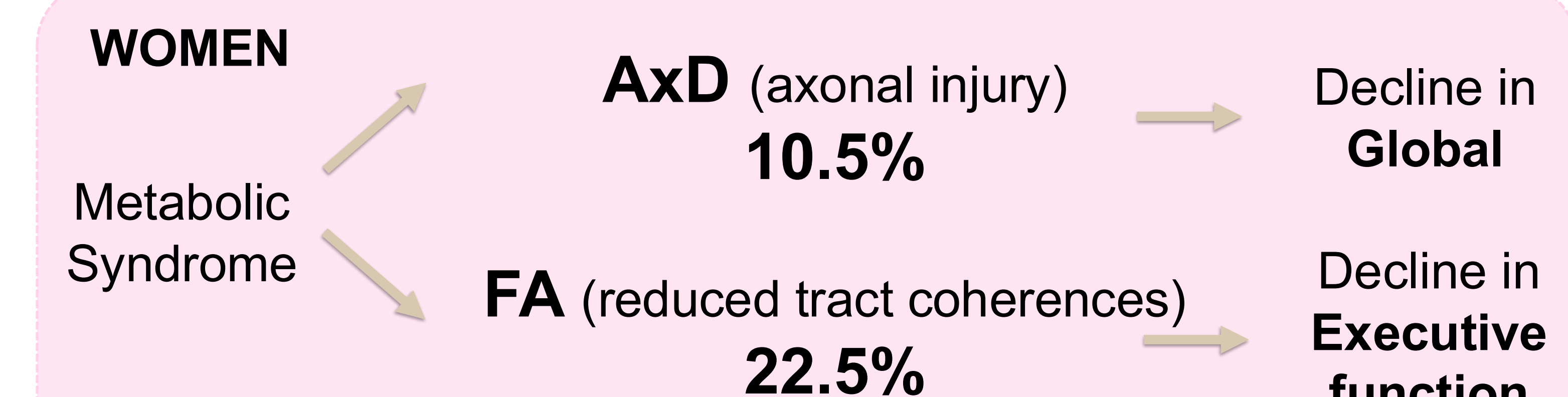


Neurodegeneration. Overall & Alzheimer's related cortical thickness

Small vessel disease (SVD). SVD burden score (0, 1, 2-4) from WMHs burden (Fazekas's score 2-3), ≥ 1 lacunes, ≥ 1 cerebral microbleeds, PVS score in basal ganglia ≥ 2

Statistical analysis. Sex-specific linear mixed effect models adjusted for age, sex to estimate association between metabolic syndrome and cognitive decline. Mediation analysis to identify the role of SVD and white matter integrity alterations.

Figure 1. Proportion of the total association mediated



No mediation by SVD and neurodegeneration markers