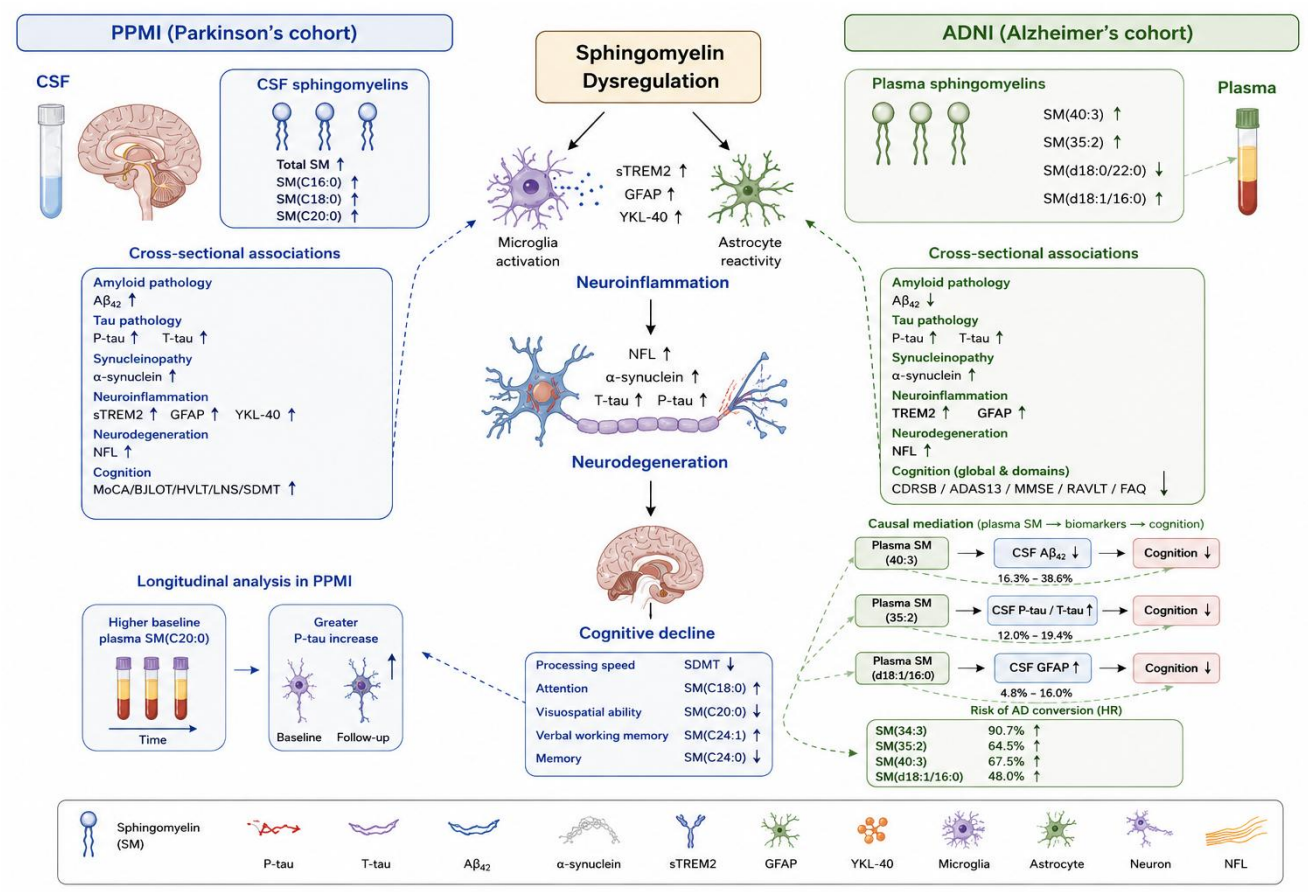


Sphingomyelin affects cognitive function in neurodegenerative diseases through neuroinflammation

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Sphingomyelin; Alzheimer's disease; Parkinson's disease; Neurodegeneration; Neuroinflammation				
INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
With the rapid aging of the global population, neurodegenerative diseases (NDs) have become a major public health burden [1]. Emerging evidence suggests that sphingomyelin (SM), a major structural and signaling lipid, plays a critical role in neurodegeneration and cognitive impairment [2,3]. However, the relationships between SM species, neuroinflammatory processes, and cognitive decline in neurodegenerative diseases remain unclear.	Using two independent longitudinal cohorts, the Parkinson's Progression Markers Initiative (PPMI) and the Alzheimer's Disease Neuroimaging Initiative (ADNI), we employed multivariable regression, linear mixed-effects, mediation, and Cox proportional hazards models to examine both cross-sectional and longitudinal associations of cerebrospinal fluid (CSF) and plasma sphingomyelins with neurodegenerative and neuroinflammatory biomarkers, cognition, and incident AD risk.	In PPMI, higher CSF total SM and multiple SM species were associated with CSF Aβ42, P-tau, T-tau, α-synuclein, NfL, sTREM2, GFAP, and YKL-40. Higher CSF sphingomyelin levels, particularly SM(C18:0), were associated with longitudinal changes in CSF Aβ42 and cognition. Neuroinflammatory markers partly mediated associations between CSF sphingomyelins and neurodegenerative biomarkers. In ADNI, higher plasma SM(34:3), SM(35:2)B, SM(40:3)B, and SM(d18:1/16:0) were associated with lower CSF Aβ42 levels, faster cognitive decline, and increased AD risk.CSF Aβ42 partially mediated associations between plasma sphingomyelin species and cognition.	CSF sphingomyelins may reflect early PD changes, whereas plasma sphingomyelins reflect amyloid pathology, cognitive decline, and AD progression, supporting sphingomyelin metabolism as a potential biomarker and mechanistic link in neurodegeneration.	[1] GBD 2016 Neurology Collaborators (2019) Lancet Neurol 18, 459–480. [2] Czubowicz K (2019) Mol Neurobiol 56, 5436–5455. [3] Zhang J (2026) Ageing Res Rev 119, 103159.
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