Relationship Between White Matter Lesions and Gray Matter Atrophy in Multiple Sclerosis
A Systematic Review

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Study Question
Are white matter (WM) lesions associated with global and regional gray matter (GM) atrophy in patients with multiple sclerosis (MS), and does the association differ between the different disease phenotypes?

What Is Known and What This Paper Adds
There is currently no consensus about the extent of GM atrophy that can be attributed to secondary changes after WM lesions or the temporal and spatial relationships between the 2 phenomena. The results of this study show that WM lesion volumes are inversely associated with global, cortical, and deep GM volumes, particularly in early (relapsing) disease, and less so in progressive MS. The findings suggest that GM neurodegeneration is mostly secondary to damage in the WM during early disease stages and due to other, likely primary neurodegenerative disease mechanisms, in progressive MS.

Methods
In this systematic review, we searched PubMed and Embase for reports evaluating direct associations between brain GM and WM lesion measures obtained by conventional MRI sequences in patients with clinically isolated syndrome and MS. No restriction was applied for publication date. We included a total of 90 studies, of which 57 and 25 were observational case-control and cohort studies, respectively, and 8 were clinical trials. The quality and risk of bias were evaluated with the Quality Assessment Tool for observational cohort and cross-sectional studies (NIH, Bethesda, MA). Qualitative and descriptive analyses were performed.

Results and Study Limitations
WM lesion volumes were related to global GM volume in the majority of studies, but for cortical and deep GM, associations were less consistent. The reviewed literature suggests that the mechanisms of neurodegeneration in MS are not static through the disease course, i.e., GM neurodegeneration is mostly secondary to damage in the WM during early disease stages, while more detached and dominated by other, possibly primary neurodegenerative disease mechanisms in progressive MS. Hence, therapeutic targets will most likely differ for the various patient groups. Important limitations of this review are the statistical rather than causal relationships investigated, the interstudy methodologic variability, and the relatively small number of longitudinal studies and studies focused on progressive disease types.

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