Original Article

White Matter Lesions in the Brain Tissue of Patients with Multiple Sclerosis: A Systematic Review and Network-Meta-Analysis of Diffusion Kurtosis Imaging Studies

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Abstract

Introduction: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Magnetic resonance imaging (MRI) is used to improve MS diagnosis and evaluation in clinical practice. However, conventional MRI cannot capture microstructural damage information. Diffusion tensor imaging (DTI) is widely used in clinical practice and research to evaluate microstructural patterns in white matter lesions (WMLs) and normal-appearing white matter (NAWM), which provides more sensitive measurement for clinically relevant brain pathology. However, the diffusion of water molecules in brain tissue follows a non-Gaussian distribution, which DTI does not fully characterise. Diffusion kurtosis imaging (DKI) is an extension of DTI that can quantify the non-Gaussian diffusion properties of water molecules in tissues and delivers more accurate tissue microstructure details than DTI.

Objectives: The primary objective is to assess the primary DKI parameter known as Mean Kurtosis (MK) that has been used to quantify microstructural abnormalities in neuroaxonal pathology in WMLs and NAWM in MS subjects compared with the healthy WM in controls. It was measured as standardised mean difference (SMD), where MK's lower values will equal more advanced axonal pathology.

Materials and methods: Three reviewers conducted the literature search of four electronic databases (Medline, Embase, Scopus, and PubMed) according to the updated PRISMA guidelines. We performed a random-effect network meta-analysis. Pairwise comparison estimates for each category were in tabular format, and rankings represented the probability of each node producing the best outcome. The rankings were presented with mean ranks, 95% confidence intervals, and the surface under the cumulative ranking curve. Analyses were conducted using MetaInsight Software and an open-source web interface to perform analysis in an intuitive 'point and click' manner.

Result: We included 6 studies and a total of 239 participants with three comparison groups in our network meta-analysis. 3 studies compared MK in NAWM and WM among MS subjects; 4 studies compared MK in WM among control subjects and patients with MS, 5 studies compared MK in WM and NAWM among control and MS subjects. We identified more reduced MK values in MS WMLs compared to NAWM and healthy WM. Also, less reduced MK values were seen in NAWM compared with MS WMLs. There was a statistically significant difference in standardised mean difference among groups.

Conclusion: This network meta-analysis concluded that the MK is decreased in MS WMLs and NAWM from healthy WM in participants, which may correspond to axonal loss or myelin sheath damage.

Keywords: Multiple Sclerosis, White Matter, Diffusion Kurtosis Imaging, Neuroaxonal Pathology, Magnetic Resonance Imaging

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1 INTRODUCTION

Multiple Sclerosis (MS) is one of the most common chronic inflammatory disorders, characterised by oedema, demyelination, inflammation, and loss of axons in the central nervous system[1,2]. Magnetic resonance imaging (MRI) is a sensitive diagnostic technique that can offer information and track disease progression, improving MS diagnosis and evaluation in clinical practice[3]. On MRI T2-weighted (T2WI) or fluid-attenuated inversion recovery (FLAIR) images, white matter lesions WMLs appear as regions of hyperintensity. These T2-hyperintense lesions (T2Ls) relate to various pathological alterations, including remyelination, oedema, demyelination, inflammation, gliosis, liquid necrosis, and axonal loss[4]. Non-enhancing T1-hypointense lesions (T1Ls) show more damage than T2Ls, showing demyelination, gliosis, and loss of axons that are likely to demonstrate a complete explanation of the microstructural change in MS patients[5,6]. As a result, the differences in intensity of WMLs on T1WI and T2WI/FLAIR images may demonstrate different pathogenic alterations in WM that contribute to disease progression differently.

Conventional MRI can be utilised to assess the number, volume, and location of pathology in MS patients; however, microstructural damage information is not captured. Diffusion tensor imaging (DTI) is widely utilised in clinical practice and research to detect microstructural alterations in white matter lesions (WMLs) and normal-NAWM, which gives sensitive parameters for clinically relevant brain microstructural alteration. Diffusion of water molecules in brain tissue frequently follows a non-Gaussian distribution, which is not completely defined by DTI[7].

Diffusion kurtosis imaging (DKI) is an advanced form of diffusion tensor imaging (DTI) that measures the movement of water molecules in tissues by accounting for non-Gaussian diffusion, providing more precise information about tissue microstructure compared to DTI[8]. DKI provides parameters to estimate the diffusivity and kurtosis of water molecules. WM integrity is evaluated using diffusivity parameters, such as fractional anisotropy (FA), mean diffusivity (MD), and kurtosis metrics, such as kurtosis fractional anisotropy (KFA) and mean kurtosis (MK). The KFA value quantifies the directional shift of kurtosis, reflecting the anisotropy of kurtosis that can be utilised to characterise the brain tissue's more complex environment[8]. The MK values represent the microstructural complexity and density of both axons and myelin, offering enhanced sensitivity for detecting changes in tissue microstructure associated with neurological disorders[9]. Decreased MK values were detected in chronic demyelinated lesions, which are thought to be associated with a loss of microstructure[10]. However, higher MK values were observed during the early acute inflammatory demyelinating phase of the lesions, which were linked to microgliosis[11]. Therefore, DKI can potentially reflect microstructural or pathological alterations in WM tissues (WMLs or NAWM). Also, it helps in a better understanding of the mechanisms that underlie pathology[11].

Summarising the literature in this subject, a systematic review and network meta-analysis of studies was conducted using the DKI-MK metric to quantify brain microstructural changes and neuroaxonal pathology in WMLs and NAWM in people with MS.

2 Materials and Methods

Study Registration

This review was conducted following PRISMA guidelines[12] and was prospectively registered in the PROSPERO database (CRD42022364173) in October 2022.

Study Selection

Eligibility criteria:

Studies were considered eligible if they employed cross-sectional or cohort designs, were peer-reviewed articles published in English, and reported diffusion kurtosis imaging (DKI) metrics—specifically mean kurtosis—for normal-appearing white matter (NAWM) and white matter lesions (WML) in individuals with multiple sclerosis (MS), compared with healthy white matter, using 3.0 T magnetic resonance imaging (MRI). Additional inclusion criteria required that participants were aged between 18 and 75 years and comprised healthy controls without neurological disorders alongside patients with any MS subtype. Eligible studies also needed to investigate brain microstructural alterations within WM lesions and NAWM.

Studies were excluded if they were reviews, qualitative analyses, editorials, technical or validation reports, non–full-text publications; involved non-MS conditions; or included animal or in-vitro experiments or MS-only cohorts. All eligibility criteria were verified prior to registration by a board-certified neurologist (C.S.C.) and a neuroradiologist (R.A.D.).

Sources, Search Strategy, and Screening

A number of four specialised reviewers, namely A.A., A.T., M.A., and H.A., performed the searching strategy, the selections of databases, the screening/identification of the studies, the study eligibility/inclusion, and the quality assessment independently and blindly. The reviewers carried out citation chaining from reviews and other papers discovered, and the searches were re-run before the final analysis in November 2024. Mutual discussions solved disagreements between reviewers A systematic literature search was

conducted across Medline (Northfield, IL, USA), Embase (Amsterdam, Netherlands), Scopus (Amsterdam, Netherlands), and PubMed (Bethesda, Maryland, USA). The search strategy utilized the following keywords: "Diffusion Kurtosis Imaging" or "DKI", "Gaussian Diffusion", and "Multiple Sclerosis" or "MS". Boolean operators and database-specific filters were applied to refine the results. Three subspecialized reviewers (A.A., A.T., and M.A.) independently and blindly conducted all review stages, including database selection, study screening, eligibility assessment, and quality appraisal. To ensure a comprehensive search, citation chaining was performed using relevant articles identified during initial screening, and all searches were updated prior to final analysis in November 2024. Discrepancies regarding study inclusion or exclusion were resolved through discussion until consensus was achieved.

Data Extraction and Collection

Data extraction was carried out by reviewer A.A. using Microsoft Excel in November 2022. For each eligible study, demographic and clinical characteristics of both MS and control groups were recorded, including age, sex, disease duration, Expanded Disability Status Scale (EDSS) scores, population characteristics, and sample size. In addition, clinical findings derived from region-of-interest (ROI) analyses were collected and organized for synthesis. Specifically, the mean and standard deviation (SD) of mean kurtosis (MK) values were extracted for white matter (WM) lesions, normal-appearing white matter (NAWM), and healthy WM.

To ensure completeness of data for meta-analysis, corresponding authors of included studies were contacted via email up to three attempts spaced seven days apart to request raw data. The requested information included the mean and SD of MK values for MS lesions and NAWM, along with associated EDSS scores and disease duration.

Outcome Measures

The primary outcome measure is assessing the Mean Kurtosis (MK) used to quantify microstructural neuroaxonal pathology in WMLs and NAWM in MS subjects compared with the WM in healthy controls. It will be measured as standardised mean difference (SMD), where the lower number of MK equals more advanced axonal pathology.

Statistical Analysis and Data Visualisation

Network meta-analysis (NMA) aims to evaluate multiple (n>2) interventions or measurements. They may or may not have been directly compared in the studies. This approach combines studies making different intervention or measurement comparisons to form a connected network of evidence to obtain relative treatment to diagnostic effects for all interventions or measurements compared to one another. Analyses were conducted using MetaInsight Software V3.1.13 (including Bayesian estimates)[13] and an open-source web interface to perform analysis in an intuitive 'point and click' manner.

Random-effects Analysis

Random-effects network meta-analyses were conducted. Pairwise comparison estimates for each category were in tabular format, and rankings represented the probability of each node producing the best outcome. The rankings were reported as mean ranks with corresponding 95% confidence intervals and summarized using the surface under the cumulative ranking curve [14].

Network Analysis Diagram

We used a network diagram to depict the structure of a network of interventions graphically. This network diagram consisted of nodes representing the interventions in the network and lines showing the available direct comparisons between pairs of interventions[15]. A network plot was generated to illustrate treatment nodes, with node size reflecting the number of included articles. The numbers displayed on connecting lines represent the number of trials contributing to each comparison.[14]. To identify and exclude outliers, a sensitivity meta-analysis was performed.

Evaluating the Global Inconsistency

Incoherence (also called inconsistency) occurs when different sources of information (e.g. direct and indirect) about a particular intervention comparison disagree[15]. We evaluated the global inconsistency in the network by analysing the difference between the direct diagnostic effect estimates from head-to-head comparisons and effect estimates obtained from indirect information on the treatments analysed. For comparisons within closed evidence loops (where both direct and indirect data were available), the difference between estimates was calculated along with 95% confidence intervals. These discrepancies were further assessed using p-values, indicating the probability that any observed inconsistency was due to chance[16].

3 Results

Studies Included and Sample Characteristics

The electronic search across three databases initially identified 910 records. After removing duplicates and screening titles and abstracts, 200 studies remained, of which 121 were excluded for not meeting eligibility criteria. Seventy-nine studies were retrieved for full-text review, and 43 were excluded. Of the 36 studies assessed for eligibility, 30 were excluded for reasons detailed in the PRISMA diagram (Fig. 1). Ultimately, six studies investigating brain microstructure in MS patients using DKI met all inclusion criteria and were included in this network meta-analysis.[17 18 19 20 21 22].

A total of 151 patients with MS (mean age of 39.1 years) and 88 healthy controls (mean age of 39.4 years) were included. The mean MS duration of patients included in all studies was 11 years, and there was no significant difference in the age and sex distribution between healthy controls and MS patients. Additional clinical and technical characteristics are summarised in Tables 1 and 2.

The Network Meta-Analysis Result

We included 6 studies and a total of 239 participants with three comparison groups in our network meta-analysis. 3 studies compared MK in NAWM and WM lesions among MS subjects; 4 studies compared MK in WM and WM lesions among control subjects and patients with MS, 5 studies compared MK in WM and NAWM among control and MS subjects (Fig.2 & 3).

MK in MS-WM lesions, MS-NAWM and Healthy WM

This network meta-analysis identified more reduced MK values in MS-WM lesions compared to NAWM and healthy WM. Also, less reduced MK values were seen in NAWM compared with MS-WM lesions. There is a statistically significant difference in standardised mean difference among groups, and the between-study standard deviation was 1.45. Using the random effects mode and compared to the SMDs in WM of healthy participants, the SMDs of MK in MS NAWM and MS-WM lesions were -2.39 (95%CI -2.76 to -1.01) and -3.39 (95%CI -4.83 to -1.95), respectively. More details are presented in Table 3 and Fig.4.

4 Discussions

This systematic review of published DKI studies comparing mean kurtosis (MK) values in white matter (WM) lesions and normal-appearing white matter (NAWM) in MS versus healthy WM identified a sufficient number of studies to enable a network meta-analysis. The key findings of this network meta-analysis are that the lowest MK values can be seen in WM focal lesions, followed by NAWM, as compared to WM in healthy controls. These findings are in line with a previous study that investigated the WM microstructural change in MS lesions, NAWM, compared with healthy WM[23]. In MS patients, the most severe microstructural damage was observed in WM lesions, which revealed a different pathological state than NAWM. NAWM microstructure differed considerably from WM in healthy subjects, although having less histological damage than focal lesions. Therefore, the microstructural damage detected by MK in WM lesions could be distinguished from the damage in NAWM and WM in healthy controls. The reduced MK values indicated a shift in the diffusion kurtosis toward free water, along with a reduction in microstructure complexity[24], which could be the result of axonal loss, myelin sheath degradation, and cellular component destruction[25]. Therefore, the lowest MK values in WM lesions revealed the most severe WM damage location. These findings demonstrated that MK values were closely associated with structural abnormalities observed on conventional MRI, and they were able to detect abnormalities in NAWM that conventional MRI and DTI could not identify in MS patients (Fig.5). When using DKI to assess the heterogeneity of MS lesions, Thaler et al. found that MK values had a stronger discriminative power than MD values and could serve as an imaging biomarker for differentiating MS lesion types. The MK values differed significantly between each MS WMLs, including T1Ls and pure-T2Ls, as well as NAWM and WM in healthy controls. However, they did not find a significant difference between NAWM and WM in healthy controls, which contradicts our findings[26]. The MD values did not perform well in discriminating between the two WML types or in identifying NAWM and WM in healthy controls. MK, as the name implies, is the average kurtosis value in all directions, which might reflect the complexity and integrity of the microstructure[27].

This systematic review has several limitations. First, MK data from ultra-high-field MRI could not be pooled due to insufficient studies. Second, information on the impact of disease-modifying therapies on MK measurements was unavailable. Third, our analysis focused exclusively on MK as the quantitative parameter for assessing white matter microstructural damage in MS. Lastly, this network meta-analysis did not include the relationship between neurocognition and WM damage revealed by MK in MS patients.

Conclusion

This network meta-analysis demonstrates that mean kurtosis (MK) is significantly lower in MS lesions and NAWM compared to healthy white matter, reflecting underlying axonal loss, myelin degeneration, and cellular disruption. These findings suggest that diffusion kurtosis imaging (DKI), particularly the MK parameter, holds promise as a biomarker for assessing white matter integrity, disease severity, and progression in MS.

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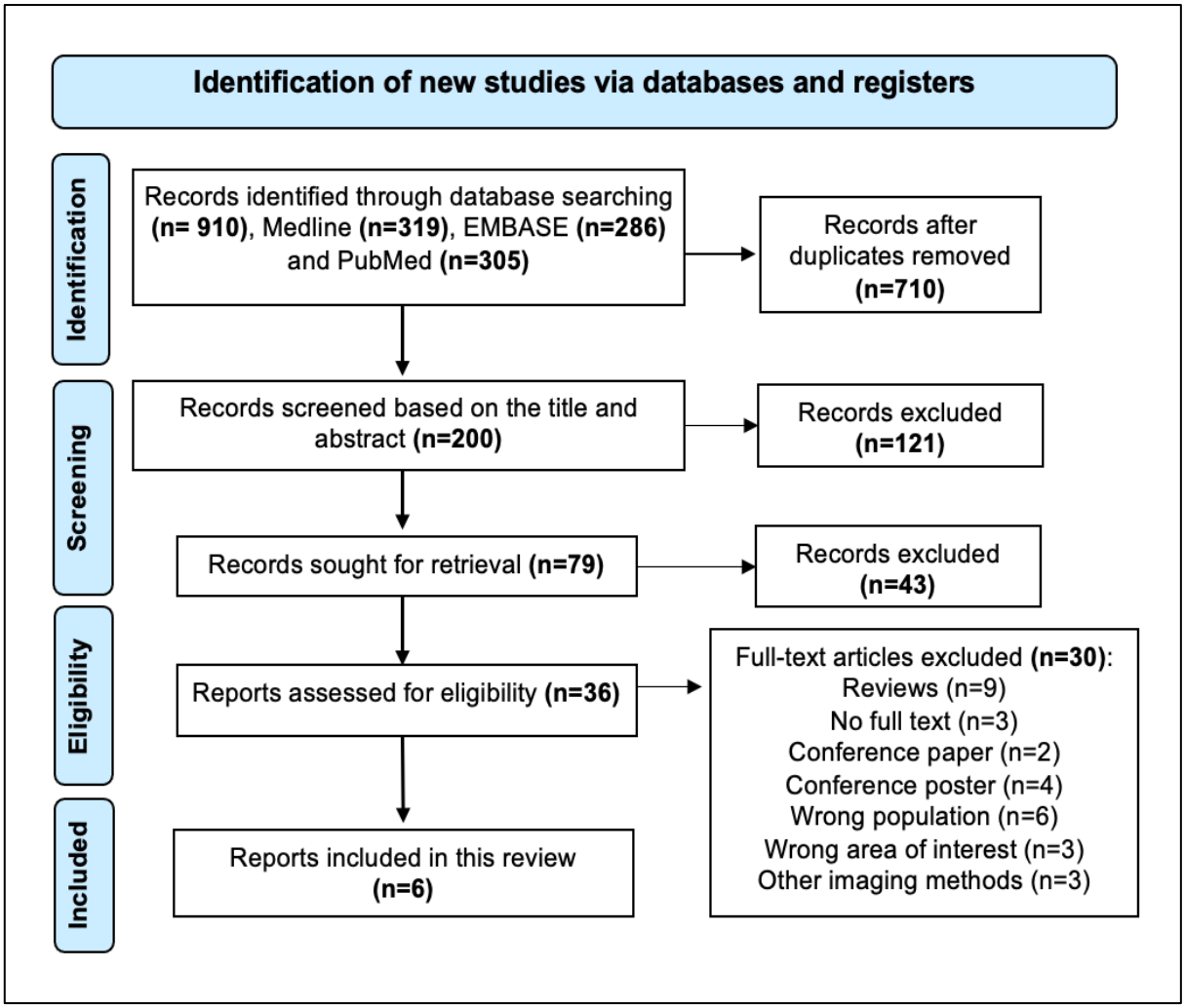

Figure 1. PRISMA flow diagram showing how studies were systematically searched, identified, screened, checked for eligibility, and included.

Demographic and Clinical Characteristics of MS Patients and Healthy Individuals														
		Group size		Gender (# of Females)		Age				Disease Duration		EDSS		
Study	Author	MS	HC	MS	HC	MS - Mean	MS - SD	HC - Mean	HC - SD	Mean	SD	Median/Mean	Minimum/SD	Maximum/SD
1	Thaler, 2021	37	11	24	9	41	32.52	41	25.4	13	12.7	2.75	3.8	5.5
2	Qiyuan Zhu, 2022	48	26	31	17	33.1	9.2	37	8.3	5.4	5.2	2.2	1.3	--
3	De Santis, 2019	7	6	4	3	42	15	42	15	21	11	--	1	3
4	Yoshida, 2013	11	6	7	3	38.4	8.5	35.3	5.9	9.76	7.71	1.77	0	6
5	Wenshu Qian, 2015	17	18	12	9	41.1	9.4	43.3	12.4	8.2	8	2.6	1.4	--
6	Sevim Sahin, 2019	31	21	16	12	39.32	9.9	38.29	10.92	9.5	7.03	2.8	1.5	--

Table 1. Demographics and clinical characteristics of the included DKI studies on MS. Abbreviations: HC = healthy controls; -- = not available; SD = standard deviation.

Technical characteristics of the included studies						
Study	Author	Field Strength	RF coil	b-values (s/mm2)	Fitting Software	Method of Analysis/Regions
1	Thaler, 2021	3.0T	32	1000-2500	Fast DKI	ROI Analysis
2	Qiyuan Zhu, 2022	3.0T	32	1000-2000	DKE	VBM and ROI Analysis
3	Silvia De Santis, 2019	3.0T	--	700-2000	FDT	ROI Analysis
4	Mariko Yoshida, 2013	3.0T	32	500-1000-1500-2000-2500	dTV II FZR	ROI Analysis
5	Wenshu Qian, 2015	3.0T	32	1000-2000	DKE	ROI Analysis
6	Sevim Sahin, 2019	3.0T	16	500-1000-1500-2000	DKE	ROI Analysis

Table 2. Technical characteristics of included studies. Abbreviations: -- = not available; T = tesla; ROI = region of interest; RF = radiofrequency; and s·mm−2 = second per millimetre

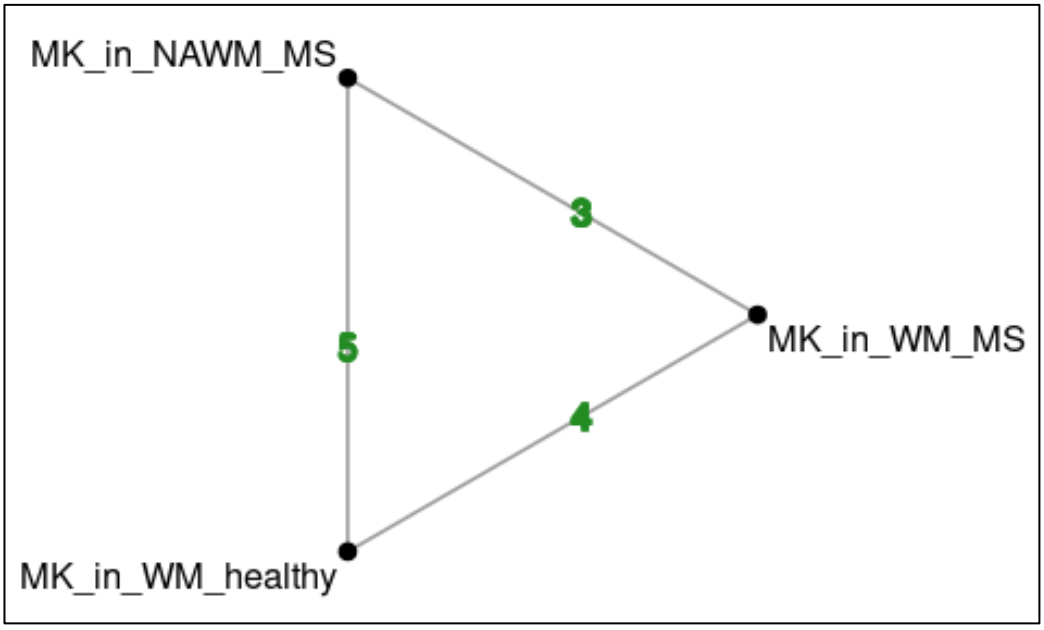

Figure 2. The network plot illustrates the three-way comparisons and the included studies.

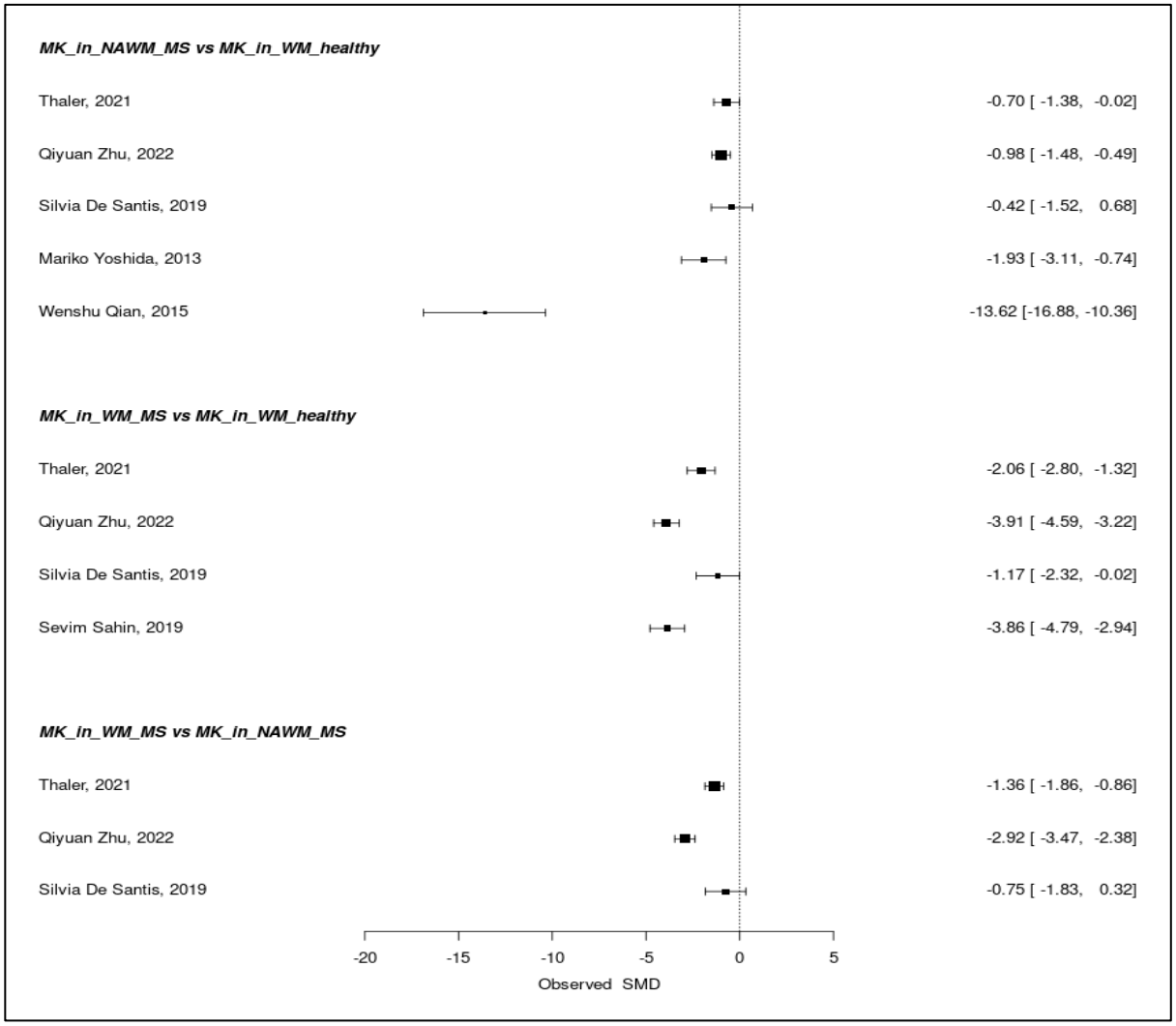

Figure 3. A forest plot of the individual study results included in the network meta-analysis was grouped by each pairwise treatment comparison. This forest plot does not display any pooled results. It only provides a visualization of the individual study results based on the uploaded data.

MK in WM MS	-1.71 [-3.40; -0.02]	-2.78 [-4.26; -1.29]
-1.00 [-2.55; 0.55]	MK in NAWM MS	-2.33 [-3.74; -0.93]
-3.39 [-4.83; -1.95]	-2.39 [-3.76; -1.01]	MK in WM healthy

Table 3. A matrix of all the comparisons in a network meta-analysis and the relative effects in ranked order for all studies.

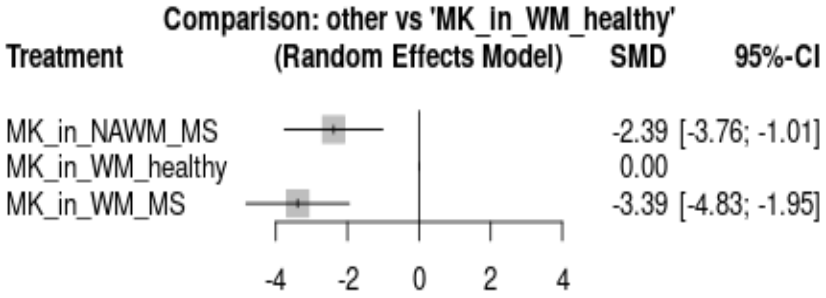

Figure 4. The forest plot displays the pooled effect estimates and their associated uncertainty (95% confidence intervals) for all interventions compared to the reference treatment: MK in WM healthy.

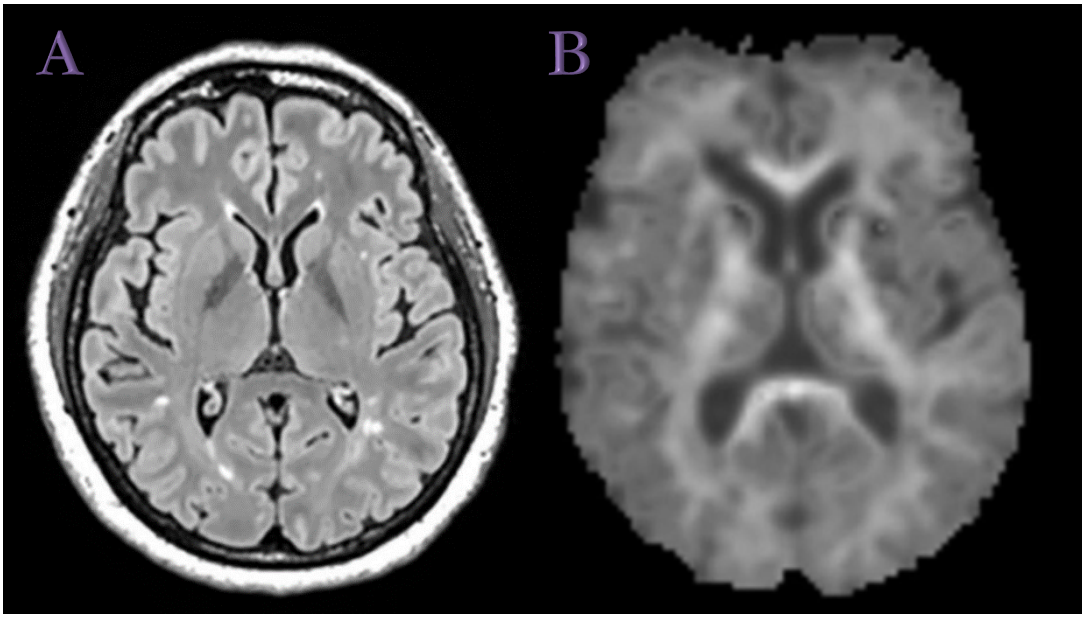

Figure 5. MR scans and lesion masks from a 53-year-old patient with relapsing-remitting multiple sclerosis. (A) Axial FLAIR image showing hyperintense lesions. (B) Mean kurtosis (MK) parametric map obtained using a DKI sequence.