Systematic Reviews

PROTOCOL

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Risk of cancer development associated with disease-modifying therapies for multiple sclerosis: study protocol for a systematic review and meta-analysis of randomised and non-randomised studies

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Abstract

Background The association between cancer and multiple sclerosis has long been investigated. Several studies and reviews have examined the risk of cancer among patients with multiple sclerosis treated with disease-modifying therapies (DMTs) but with conflicting results. This study will aim to investigate the association between DMTs for multiple sclerosis and subsequent cancer risk using research synthesis methods.

Methods/design We designed and registered a study protocol for a systematic review and meta-analysis. We will include randomised and non-randomised trials, prospective or retrospective cohort studies, and case–control studies of treatment with DMTs compared with placebo, no treatment, or another active agent. The primary outcome will be the risk of cancer (all-malignant neoplasms) in association with the exposure of DMTs. Secondary outcomes will include site-specific cancers (e.g. breast cancer). Literature searches will be conducted in multiple electronic databases (from their inception onwards), including the following: PubMed/MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL). Two researchers will screen all citations, full-text articles, and abstract data independently. The risk of bias (quality) of individual studies will be appraised using an appropriate tool. If feasible, we will use a two-stage approach to evidence synthesis: (1) Peto's method for meta-analysis of data from randomised trials alone; and (2) Random-effects model for meta-analysis adding data from non-randomised studies. We will calculate odds ratios and their associated 95% confidence intervals. Potential sources of heterogeneity will be explored in additional analyses (e.g. subgroups considering different DMTs individually, mechanism of action, type of control, length of follow-up, mode of treatment).

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Discussion This systematic review and meta-analysis of randomised and non-randomised studies will provide an updated synthesis of the risk of cancer associated with DMTs for adult patients with multiple sclerosis. This study will also examine some factors that may explain potential variations across studies. The findings will be published in a peer-reviewed journal.

Systematic review registration Open Science Framework (https://osf.io/v4sez).

Keywords Cancer, Disease-modifying therapy, Meta-analysis, Multiple sclerosis, Systematic review

Background

Multiple sclerosis is a chronic inflammatory disease of the central nervous system that causes demyelination and neuronal injury [1, 2]. Multiple sclerosis typically presents in young adults (aged 20–30 years), with an average life expectancy around 5 to 10 lower than in general population [2]. It affects approximately 1.9 million people worldwide (based on the latest Global Burden of Disease Study) [3], and represents one of the most common causes of disability in young adults aged 18–40 years [3, 4].

Clinical practice guidelines for multiple sclerosis [5–7] recommend initiating disease-modifying therapy (DMT) in people with confirmed multiple sclerosis, given that a large body of evidence supports their efficacy for reducing disease activity. Most DMTs have primarily anti-inflammatory effects, showing a decrease in clinical relapse rate, MRI-based activity, and short-term disability worsening, especially when administered during the relapsing phase of the disease (clinically isolated syndrome, relapsing–remitting multiple sclerosis, and active secondary progressive multiple sclerosis) [1]. In July 2023, the World Health Organization announced its decision to include, for the first time, DMTs for multiple sclerosis in their Essential Medicine List (e.g. cladribine, glatiramer acetate, and rituximab) [8] filling a critical gap to address the global burden of multiple sclerosis [3, 4, 8, 9].

The association between cancer and multiple sclerosis has long been investigated [10–17]. Several studies [18–22] and reviews [23–25] have examined the risk of cancer after exposure to DMT in patients with multiple sclerosis, but with conflicting (or inconclusive) results. A 2023 Cochrane review with network meta-analysis [25] of exclusively randomised controlled trials examined the adverse effects of DMTs for adults with multiple sclerosis. Regarding the risk of cancer (67 trials, 42,700 participants, and 449 events), the authors observed there was uncertainty for all DMT, with estimates including no difference and upper 95% confidence interval of the risk ratio vs placebo ranging from 1.08 to 243.64. Specifically, the Cochrane review [25] argued future systematic reviews and meta-analyses of DMTs addressing adverse effects (such as malignant neoplasms) should include non-randomised studies, 'because the(se) effects are unlikely to be seen in randomised trials due to their small size, short duration and selected eligibility criteria'. Given that patients with multiple sclerosis are exposed to DMTs for long periods, it is of utmost importance to evaluate potential risks (such as cancer) associated with these treatments [2, 23–25].

Several case reports have suggested a potential risk of cancer among people with multiple sclerosis treated with DMTs, particularly for immunosuppressant drugs [26]. Because of their action on the immune system, and due to a lack of available long-term data, several warnings on the potential risk of cancer and/or contraindications of their use were added to the product labelling of some DMTs (e.g. cladribine [27], fingolimod [28], natalizumab [29], alemtuzumab [30], ocrelizumab [31]), and regulatory agencies (such as the European Medicines Agency [EMA]) recommend using risk management plans and risk minimization measures [26–31]. By contrast, considering inflammation is a major driver of cancer [32], and that evidence suggests that anti-inflammatory drugs (such as NSAIDS and aspirin) may prevent or delay cancer onset [33–35], an alternative hypothesis to explore might be that DMTs could potentially decrease the risk of some cancers.

The main objective of this study will be to investigate the risk of cancer associated with the treatment of DMTs in adult patients with multiple sclerosis, using available evidence from both randomised and non-randomised studies.

Methods

Protocol registration and reporting

The present study protocol has been registered within the Open Science Framework (registration number: https://osf.io/v4sez) and is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [36, 37] (see checklist in Additional file 1) and the PRISMA statement extension for systematic reviews including harm outcomes [38].

Information sources and search strategy

The primary source of literature will be a structured search of major electronic databases (from their inception onwards), including MEDLINE through PubMed (National Library of Medicine, Bethesda, Maryland, USA), EMBASE through the Elsevier platform (Elsevier B.V., Amsterdam, The Netherlands), and the Cochrane Central Register of Controlled Trials (CENTRAL) though the Cochrane Library. The initial literature searches in MEDLINE, EMBASE, and CENTRAL will start in February 2025.

We will hand-search the reference lists of included studies, relevant reviews, clinical practice guidelines, and other relevant documents for additional studies. We will also scan the reference lists of related systematic reviews and meta-analyses identified through the search, as well as the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group's specialised register (https://ms.cochrane.org/our-review). In addition, citation searches (e.g. Science Citation Index Expanded via the Web of Science) will be carried out for studies selected for inclusion in the systematic review. Content experts and authors who are prolific in the field will be contacted.

The literature searches will be designed and conducted by the review team, including an experienced health information specialist (AA-A). Our main literature search will be peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist [39]. The search strategy will include a broad range of terms and keywords related to 'multiple sclerosis', 'names of DMTs', 'randomised and non-randomised studies', and 'cancer'. To identify randomised controlled clinical trials in the databases, we will use the Cochrane Highly Sensitive Search strategy for identifying randomised trials in MEDLINE [40], and the Cochrane EMBASE randomised controlled trial filter for EMBASE [40, 41]. Draft search strategies for MEDLINE are provided in Additional file 2.

Eligibility criteria

Studies will be selected according to the following criteria: participants, study design, interventions being evaluated, outcomes of interest, and language of publication.

- *Participants:* We will include studies that enrolled participants ≥ 18 years of age with a diagnosis of multiple sclerosis according to any accepted diagnostic criteria. We will include all study participants regardless of sex/gender, ethnicity, type of multiple sclerosis, disease duration, or degree of disability.
- *Study design*: We will include randomised and non-randomised controlled clinical trials, prospective or retrospective cohort studies, and case–control studies of treatment with DMTs compared with placebo, no treatment or another active agent. We will exclude studies in which the drug regimen was compared with a different regimen of the same drug without a placebo, no treatment or another active agent as a control group. We will exclude studies that compared treatment-switch strategies versus continuing treatment.
- *Interventions being evaluated:* We will include all DMTs that are used as monotherapies, whether approved by the EMA, the Food and Drug Administration (FDA), or off-label, for the treatment of multiple sclerosis [1, 25]. To be classified as an unconfounded comparison, we will require that planned interventions are identical between treatment and comparison groups except for the DMTs under consideration. We will consider treatment regimens as defined in the primary studies, irrespective of their dose and duration. The complete list of currently available DMTs, up to January 2024, includes the following:
- Injections-based medications (approved by the EMA and/or the FDA): beta interferon (Betaferon®, Extavia®, Rebif®, Avonex®), peginterferon beta-1a (Plegridy®), glatiramer acetate (Copaxone®, Brabio®, or generic equivalent medications), and ofatumumab (Kesimpta®).
- Oral medications (approved by the EMA and/or the FDA): fingolimod (Gilenya®), teriflunomide (Aubagio®), dimethyl fumarate (Tecfidera®), cladribine (Mavenclad® or Movectro®), siponimod (Mayzent®), diroximel fumarate (Vumerity®), monomethyl fumarate (Bafiertam®), ozanimod (Zeposia®), and ponesimod (Ponvory®).
- Intravenous medications (approved by the EMA and/or the FDA): mitoxantrone (Novantrone®), natalizumab (Tysabri®, Tyruko®), alemtuzumab (Lemtrada®), ocrelizumab (Ocrevus®), ublituximab (Briumvi®) and daclizumab (Zenapax®, Zinbryta®; marketing authorisation withdrawn in 2018).
- Other medications (used off-label): azathioprine (Imurel®, Jayempi®), rituximab (MabThera®, Truxima®), methotrexate (Bertanel®, Glofer®, Imeth®, Methofill®, Metoject®, Quinux®, generic equivalent medications), laquinimod (Nerventra®), cyclophosphamide (Genoxal®), intravenous immunoglobulins, and long-term corticosteroids (e.g., methylprednisolone, prednisolone).
- *Outcomes of interest:* The primary outcome will be the risk of cancer development (all malignant neoplasms; ICD-11: 2A00 – 2F9Z) associated with the exposure of DMTs at the longest follow-up. Secondary outcomes will include site-specific cancers

(e.g. breast cancer, melanoma, lymphomas). Studies should explicitly report the numbers of cancer events in all treatment groups under consideration. Studies that do not present quantitative data on the associations between evaluated interventions and cancer events (e.g. relative risks (RR) with 95% CIs, numbers of cancer events per intervention group) or sufficient data for an association to be calculated will be excluded.

- *Language of publication:* Publications of studies will be limited to peer-reviewed journal articles written in English, Spanish, German, French, Italian, and/or Portuguese.

Screening and selection procedure

All articles identified from the literature searches will be screened by at least two researchers independently using the software Rayyan (Rayyan Systems, Cambridge, Massachusetts, USA) [42]. First, titles and abstracts of articles returned from initial searches will be screened based on the eligibility criteria outlined earlier. Second, full texts will be examined in detail and screened for eligibility. A form for screening full-text articles will be designed in Microsoft Excel (Microsoft, Seattle, Washington, USA) and pilot tested on a random sample of 5 articles. Third, references of all considered articles will be handsearched to identify any relevant report missed in the search strategy. Any discrepancies here and throughout will be resolved through discussions, if necessary. A flow chart showing details of studies included and excluded at each stage of the selection process will be provided.

Data collection

Data for each included study will be abstracted independently by at least two researchers, and potential conflicts will be resolved through discussion. We will use predesigned forms that will be piloted initially on a small number (e.g. 5–10) of included articles. The data extracted from each article will be comprehensive in scope as we address multiple characteristics of the included studies. Full articles and supplementary materials with data and analyses will be examined for general and methodological characteristics and study results. We will collate all data into a single study for multiple reports of the same trial. We will review the final versions of the articles available online. All data will be extracted into Microsoft Excel spreadsheets (Microsoft, Seattle, Washington, USA).

The standardised data extraction form will include the following information of interest:

- General characteristics: first author or acronym, year of publication, countries involved, study design (e.g. randomised controlled clinical trial, non-randomised controlled clinical trial, retrospective cohort study, prospective cohort study, case–control study), international study (yes/no), number of countries involved, number of participants (sample size), number of treatment groups, length of follow-up (e.g. months), characteristics of participants (e.g. age, sex, disease duration, baseline Expanded Disability Status Scale [EDSS] score) and type of multiple sclerosis (e.g. relapsing, primary progressive or secondary progressive). For observational studies (e.g. cohort and case–control studies), we will also collect information on sources of data (such as claims data), methods of ascertaining multiple sclerosis (such as ICD code), exposures (such as DMT as a therapeutic class or individual agent), methods for confounding adjustment (e.g. crude/unadjusted analysis, multivariable analysis, propensity scores, matching, instrumental variables, other), and variables used for these techniques.
- Details on interventions: drugs commonly used across all groups (baseline treatment), DMTs (including dose, frequency, or duration of treatment), and control group.
- Details on outcomes: cancer events (e.g. all-cancer, site-specific cancers) in each treatment group and the number of participants included for analyses in each of treatment group (that is, considered a safety dataset). If cancer outcome data are reported at multiple follow-up points, we will use data from the longest follow-up. For observational studies, we will document unadjusted and adjusted results (e.g. RR with 95% CIs), in addition to raw event and exposure time.

Risk of bias (quality) in individual studies

At least two researchers will independently assess the risk of bias (quality) of each study, and any disagreements will be resolved by discussion. For randomised controlled clinical trials, we will determine the risk of bias (quality) of each included study by using the Cochrane Risk of Bias 2.0 [43], which considers random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias. We will judge the risk of bias in each study based on each criterion and classify the study as having a'low',high', or'unclear' risk of bias. The Newcastle Ottawa Scale (NOS) will be used to assess the risk of bias (quality) in observational studies [44]. For cohort studies, this scale assigns points for representativeness of the exposed and control groups, adequate ascertainment

of exposure, clarity of the absence of outcomes at study start, comparability of groups based on study design and analysis, blinded assessment or record linkage to confirm study outcomes, the sufficiency of follow-up duration to observe the outcomes of interest, and reporting of a sufficiently low withdrawal rate that would not threaten a great risk of bias to the study. For case–control studies, this scale assigns points for adequate case definition, representativeness of the cases, adequate selection and definition of controls, comparability of cases and controls based on the design or analysis, adequate ascertainment of exposure, same method of ascertainment for cases and controls, and same (non-response) rate for both groups. A maximum of nine points can be assigned. Discrepant scores will be resolved by discussion and consensus. We will provide a narrative summary of the risk of bias (quality) of the included studies, which will be supported by a table showing the results of the critical appraisal results.

Methods for evidence synthesis

The data from each article (e.g. participants, study design, interventions being evaluated, outcomes of interest, and findings) will be used to build a summary of evidence tables, including an overall description of the studies. We will use a two-stage approach to evidence synthesis of randomised and non-randomised studies. In the first stage, we will use data from randomised controlled clinical trials alone. In the second stage, we will add data from non-randomised 'adjusted (for confounding factors)' studies, allowing for the assessment of the additional contribution from observational studies. We will pool randomised controlled clinical trials using the method for meta-analysis by Yusuf et al. (the so-called, Peto's method) [45] and will report pooled Peto odds ratios (ORs) and their associated 95% confidence intervals (CI). Peto´s method performs well when events are infrequent [40, 46]. We will pool both randomised and non-randomised studies using the inverse variance method based on the DerSimonian and Laird random-effects model [47] and report pooled ORs and their associated 95% CI. P values < 0.05 will be considered significant.

We will quantify statistical heterogeneity by estimating the variance between studies using I^2 statistic. The I^2 statistic is the proportion of variation in prevalence estimates that is due to genuine variation in prevalence rather than sampling (random) error [48]. I^2 statistic ranges between 0 and 100% (with values of 0–25% and 75–100% taken to indicate low and considerable heterogeneity, respectively) [40]. We will also report Tau^2, and Cochran Q test [49] with P values of < 0.05 considered statistically significant (heterogeneity).

We will use the GRADE methodology [50] to evaluate the certainty (or confidence) in the body of evidence for each outcome assessed (e.g. high, moderate, low, or very low confidence). We will provide an explanation of reasons for rating down (or rating up) the certainty of evidence (such as in footnotes to an evidence summary table). Explanations for each judgment will be concise, informative, relevant to the target audience, and accurate (that is, addressing criteria specified in the GRADE methods guidance [50–52]).

Additional analyses

If sufficient studies are identified and data points are available, potential sources of heterogeneity will be investigated further by subgroup analyses according to clinical and methodological covariates [25, 26]. We plan to explore sources of heterogeneity with a priori subgroup hypotheses:

- Different DMTs individually (e.g. beta interferon *vs* control, glatiramer acetate *vs* control, fingolimod *vs* control).
- Type of DMT based on their mechanism of action: immunomodulating therapy vs control (e.g. beta interferon, peginterferon beta-1a, glatiramer acetate, immunoglobulins, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, laquinimod, teriflunomide), systemic immunosuppression, inducing a reduction in the activation or efficacy of the immune system through cytostatic or cytotoxic effects (e.g., mitoxantrone, methotrexate, cyclophosphamide, long-term corticosteroids, cladribine, azathioprine) and selective immunosuppression, as with monoclonal antibodies or biological agents directed towards specific antigenic targets (e.g., natalizumab, fingolimod, siponimod, ozanimod, ponesimod, alemtuzumab, ofatumumab, daclizumab, rituximab and ocrelizumab).
- Type of control (e.g. DMTs *vs* placebo/no treatment, DMTs *vs* active treatment).
- Length of follow-up (e.g. DMTs *vs* control by subgroup of ≤ 26 weeks, 26–52 weeks, > 52 weeks).
- Mode of treatment (DMT monotherapy vs control, DMT add-on/combination treatment vs control).

In addition, we will explore potential effect modification by age (with baseline age as the explanatory variable) using random effects meta-regression models [53], considering cancer risk increases with age and age-related cancers are likely more strongly driven by inflammation [32, 54].

We will undertake sensitivity analyses by using alternative effect measures (OR vs RR), pooling methods (Peto's method vs Mantel–Haenszel method), and consideration on heterogeneity (random vs fixed effect). In addition,

sensitivity analyses will be carried out wherein removal of randomised controlled clinical trials from the analyses that were not scored as having both adequate allocation concealment and double blinding.

Small study effects (or 'publication bias' across studies) will be assessed by inspection of the funnel plots for asymmetry and with Egger's test [55] and Begg's test [56], with the results considered to indicate potential small study effects when P values < 0.10.

Software considerations

All analyses will be conducted in Stata version 18 or higher (StataCorp LP, College Station, Texas, USA) [57, 58].

Discussion

In this paper, we have presented a study protocol for a systematic review with updated meta-analysis of randomised and non-randomised studies evaluating the risk of cancer associated with DMTs for adult patients with multiple sclerosis. This protocol updates and expands methods for a new systematic review that will supersede previous meta-analyses on this topic [23–25]. The improved approaches to the methods and analyses (e.g. revisions and updates, exploration of the extent of bias, heterogeneity), as well as the widening the scope by considering the current body of evidence with the addition of non-randomised studies, but also the consideration of different DMTs individually, type of DMT based on their mechanism of action, type of control (e.g. placebo/no treatment, or active treatment), or length of follow-up, are all relevant to this study.

A key challenge is that based on knowledge from previous systematic reviews and meta-analyses on cancer and multiple sclerosis [15–17], and DMTs for multiple sclerosis [23–25, 59, 60], we anticipate identifying studies with different features, populations, contexts, co-interventions, and with variable quality of reporting methods and results.

No ethical approval is required for the performance of this study. The proposed systematic review and meta-analysis of randomised and non-randomised studies will be reported by the guidance provided in the PRISMA 2020 statement [61, 62] and their extension incorporating harm outcomes [38]. The final manuscript will outline and report any amendments to this protocol when conducting the study. Results will be disseminated through presentations in scientific conferences and publication in a peer-reviewed journal. All data underlying the findings reported in the final manuscript will be deposited in the Open Science Framework (https://osf.io/), a cross-disciplinary public repository.

Finally, this study will identify knowledge gaps that new research in the field will fill. We anticipate implications for future studies will be discussed in the final manuscript.

Abbreviations

DMT	Disease-modifying therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02677-z.

Additional file 1.

Additional file 2.

Authors' contributions

The study protocol was conceived by FC-L, with critical input from LT-R, JAD, BH, JVS-0, MR, AA-A, PC-G, JF-M, VB-M, AV, IC, and RT-S. FC-L registered the protocol with the Open Science Framework and wrote the first draft of the protocol. LT-R, JAD, BH, MR, IC, and RT-S provided input into the design and edited the draft protocol. All authors commented on the paper for important intellectual content. All authors read and approved the final paper. FC-L accepts full responsibility for the finished paper and controlled the publication decision.

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FC-L is a PhD (Public Health and Preventive Medicine) and MPH. LT-R is a MD (Public Health and Preventive Medicine) and MPH. JAD is a MD (Oncology and Geriatrics) and MPH. BH is a PhD (Epidemiology and Biostatistics) and MSc. JVS-O is a BSc (Hons) Psychology. MR is a PhD (Medicine) and MSc (Economics). AA-A is a PhD (Information and Documentation) and MA. PC-G is a PhD (Psychology). JF-M is a PhD (Biology) and MSc. VB-M is a MD (Psychiatry) and PhD. AV is a PhD (Molecular Biology) and MSc. IC is a MD (Pathology) and PhD. RT-S is a MD (Psychiatry) and PhD.

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Data availability

Not applicable.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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