Predictors of Relapsing MOGAD: A Scoping Review

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Abbreviations

Acute disseminated encephalomyelitis (ADEM); cerebrospinal fluid (CSF); myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD); myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG); optic neuritis (ON); people with myelin oligodendrocyte glycoprotein antibody associated disease (pwMOGAD); relapsing myelin oligodendrocyte glycoprotein antibody associated disease (R-MOGAD); transverse myelitis (TM)

1. Introduction

Approximately 40-50% of people with myelin oligodendrocyte glycoprotein antibody associated disease (pwMOGAD) will experience relapsing disease after the inaugural clinical attack [1][2]. Neurological deterioration is only seen in clinical attacks, which can be severe and debilitating and often leads to disability accrual [1]. This forms the rationale for chronic steroid-sparing immunotherapy as preventative treatment, but this should only be reserved for patients predicted to relapse due to its significant adverse effect burden. However, there are currently no widely accepted predictors of relapsing MOGAD (R-MOGAD) and the evidence on such predictors is heterogenous [1].

The aims of this scoping review were to summarise the findings of the current literature on predictors of R-MOGAD and to provide guidance on which predictors future research should investigate further. The findings of this review informed the selection of variables in the pre-planned analysis of a model testing clinical predictors of R-MOGAD (DOI:10.17639/nott.7368).

2. Methods

The Pubmed National Library of Medicine database was searched with the following query on 12th October 2023:

- ((MOGAD OR myelin oligodendrocyte glycoprotein associated disease OR MOG-antibody disease OR MOG IgG associated disorders OR MOG antibody associated OR MOG antibody associated demyelination OR myelin oligodendrocyte glycoprotein immunoglobulin G associated disorder OR anti MOG associated acquired demyelinating syndromes) AND (predictor OR factor OR cause OR correlate)) AND (relapse OR relapsing OR recurrence OR monophasic OR severity OR prognosis OR course).

The search query was based on the PEO (patient, exposure, and outcome) framework, for which the population was people with MOGAD (pwMOGAD), exposure the predictor and outcome R-MOGAD. Due to the rarity of the disease the population was not restricted to only adult patients to ensure a wide enough scope of literature to review. Exclusion criteria were studies published before 2007 since MOGAD was only discovered in 2007 [4], not having a full text available, animal studies, and languages other than English due to lack of translation resources. Case reports and studies with a sample size below ten were also excluded. Studies comparing preventative steroid-sparing immunotherapies, for example Chen *et al.* [5], were not considered to be useful in this review either.

The initial literature search returned 1089 results and was refined to 534 once search filters were applied. After screening and eligibility assessments 33 studies met the correct criteria, and 12 additional studies were identified from citations of these 33 papers. Seven more resources were added from additional literature searches, resulting in a total of 52 studies. A flowchart summarising the screening process for the review is detailed in Figure 1, and references for the studies identified from the literature search, citations from papers from the literature search and additional searches can be found in the Supplemental Material.

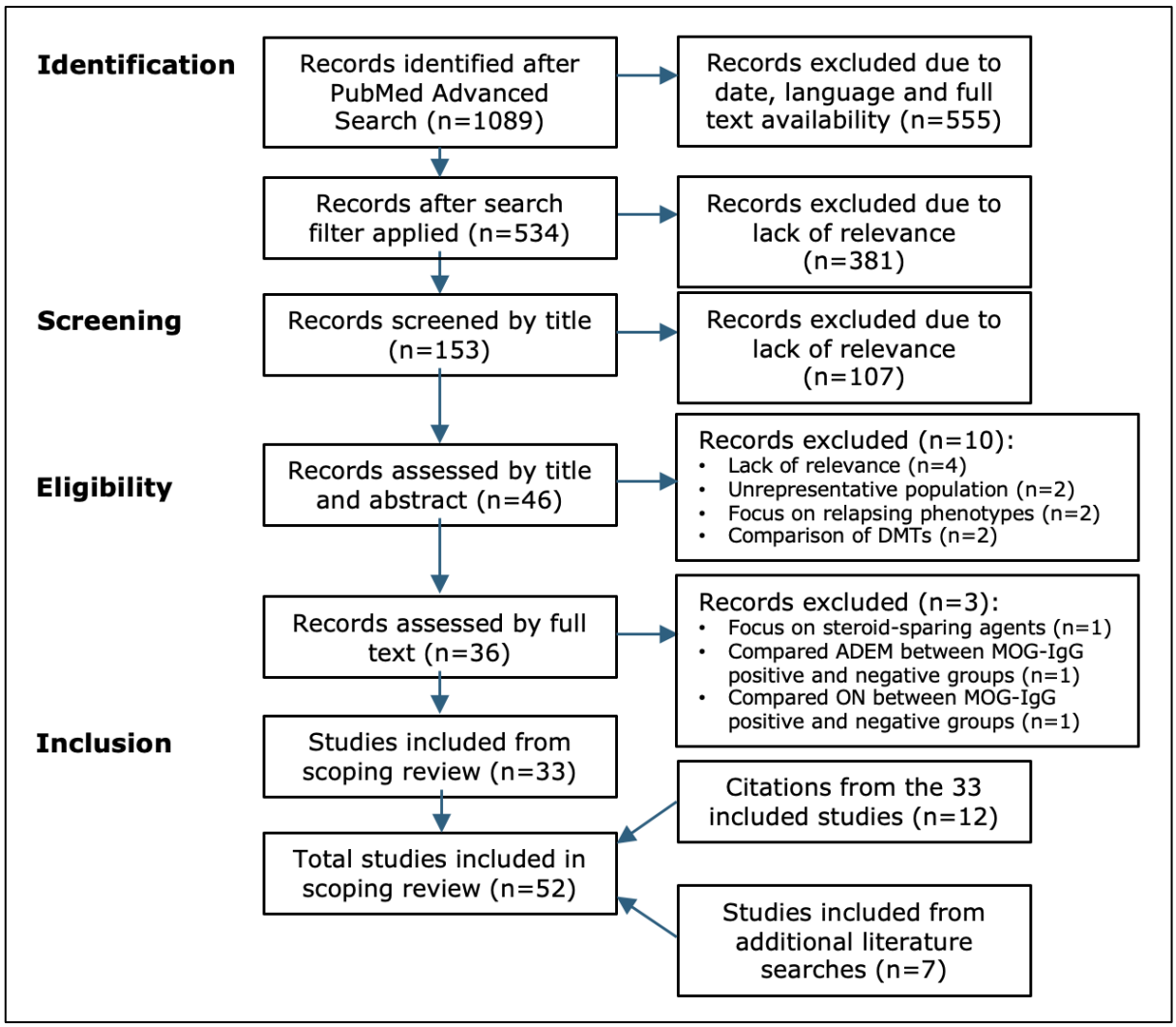

Figure 1. Flowchart showing the literature search screening process.

The evidence from these studies was then mapped in a table with columns for and against each factor being a predictor of R-MOGAD. The against column included any studies finding the predictor in question to have no predictive value or contradicting the general consensus of other studies. Studies were ranked in the table of evidence in ascending order of evidence level using the classification system stated in Table 1 [6].

Level of Evidence	Type of Study
1a	Systematic review of (homogeneous) randomized controlled trials
1b	Individual randomized controlled trials (with narrow confidence intervals)
2a	Systematic review of (homogeneous) cohort studies
2b	Individual cohort study / low-quality randomized control studies
3a	Systematic review of (homogeneous) case-control studies
3b	Individual case-control studies
4	Case series, low-quality cohort, or case-control studies
5	Expert opinions based on non-systematic reviews of results or mechanistic studies

Table 1. Evidence classification system [6].

3. Results

3.1. Description of Literature

Amongst the 52 papers included in this review, 42 were population studies, 9 were literature reviews and one was an online database [7] (see Figure 2). For the 42 population studies, 26 included patients of all ages, 11 were restricted to a paediatric population and five an adult population (see Figure 3). The largest sample size of studies included in the scoping review consisted of 366 pwMOGAD [8] and the smallest 13 patients [9]. Follow-up duration for the whole cohort in the population studies was only clearly reported in 33 of the 42 studies. Waters *et al.* [10] had the longest follow-up duration with a median of 81 months and Sutton *et al.* [11] the shortest with a median of 12 months (see Figure 4). The number of studies using different statistical analyses in the 42 population studies is also shown in Figure 5, with the Mann-Whitney U test being the most frequently utilised.

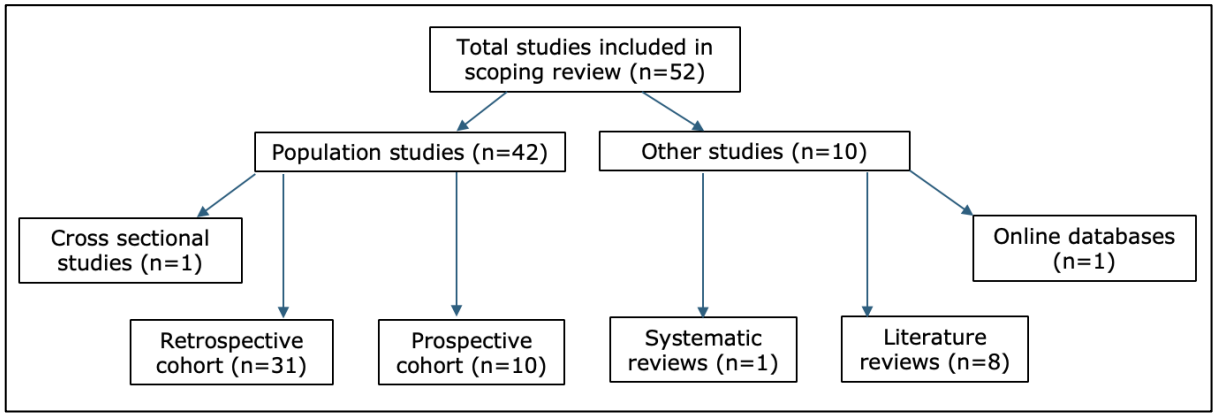

Figure 2. Flowchart describing the types of studies included in the scoping review.

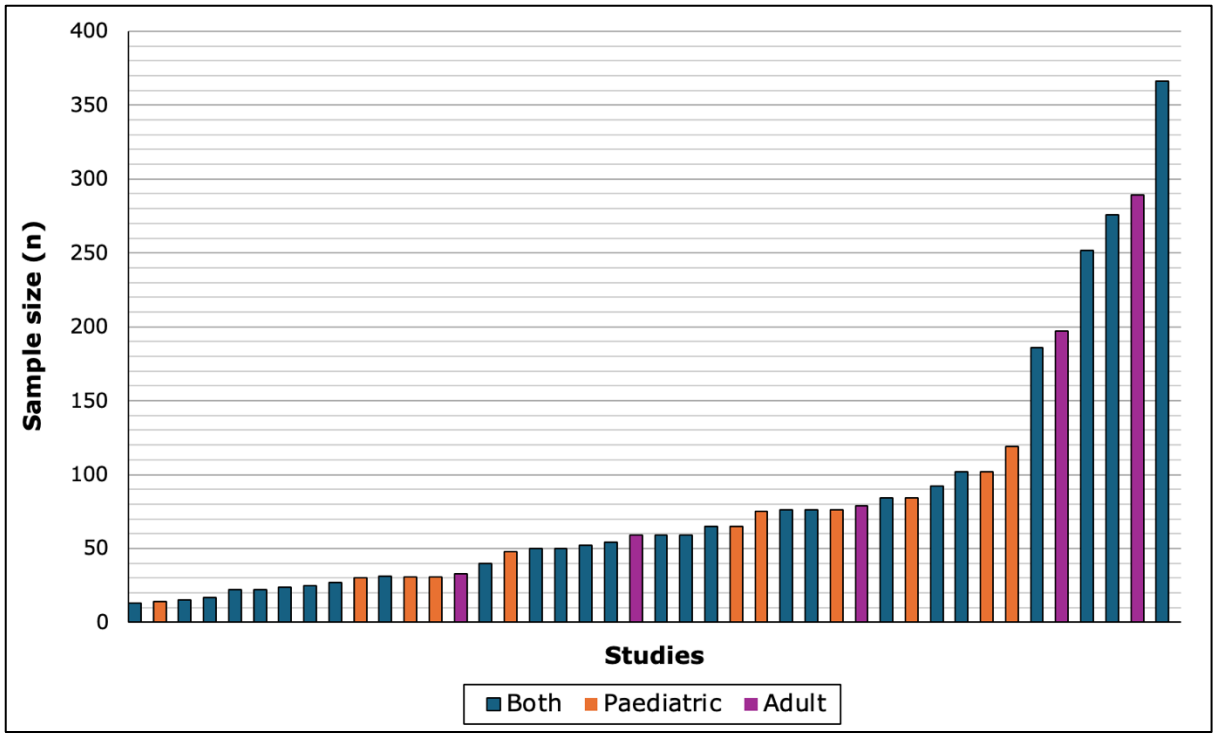

Figure 3. Graph showing the sample sizes of pwMOGAD in each of the 42 population studies included in the scoping review. Dark blue bars show studies that included a population of all ages, orange bars show studies restricted to a paediatric population and purple bars show studies restricted to an adult population.

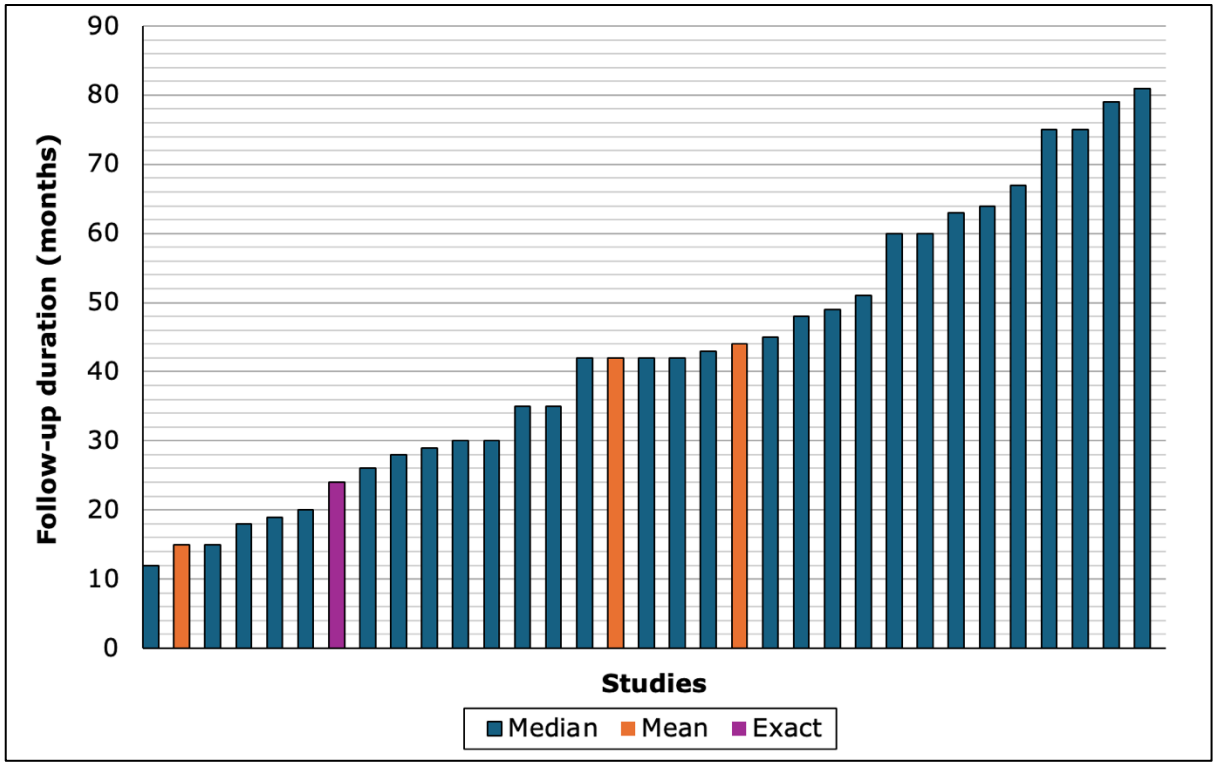

Figure 4. Graph showing the 33 population studies that reported the follow-up duration for their whole cohort included in the scoping review. Dark blue bars show studies that reported follow-up duration as a median, orange bars show studies that reported follow-up duration as a mean and the purple bar a prospective study that followed up all patients for the same duration [12].

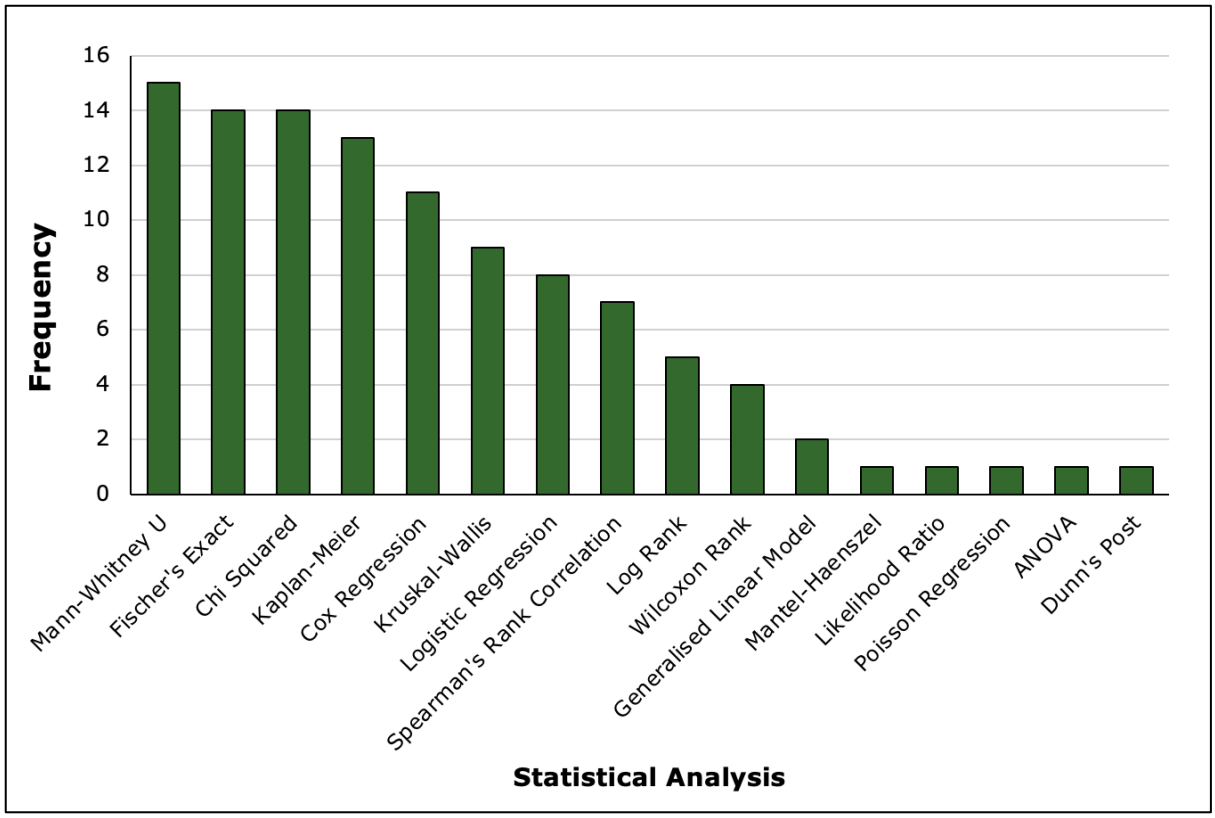

Figure 5. Graph showing the frequency of different types of statistical analysis used in each of the 42 population studies included in the scoping review.

3.2. Findings of Literature

The most frequently investigated predictors of R-MOGAD in descending order were myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) titres, steroids, age, acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), ethnicity, elevated cerebrospinal fluid (CSF) leukocytes and/or protein, sex, and transverse myelitis (TM). Early relapses, grey matter volume, history of immune disease, leukodystrophy, limbic encephalitis, meningoencephalitis and viral infection/vaccine were each cited once. Four studies [9][11][12] and one literature review [15] found no significant predictors of relapsing disease. Figure 2 shows the number of studies for and against each factor predicting a relapsing prognosis.

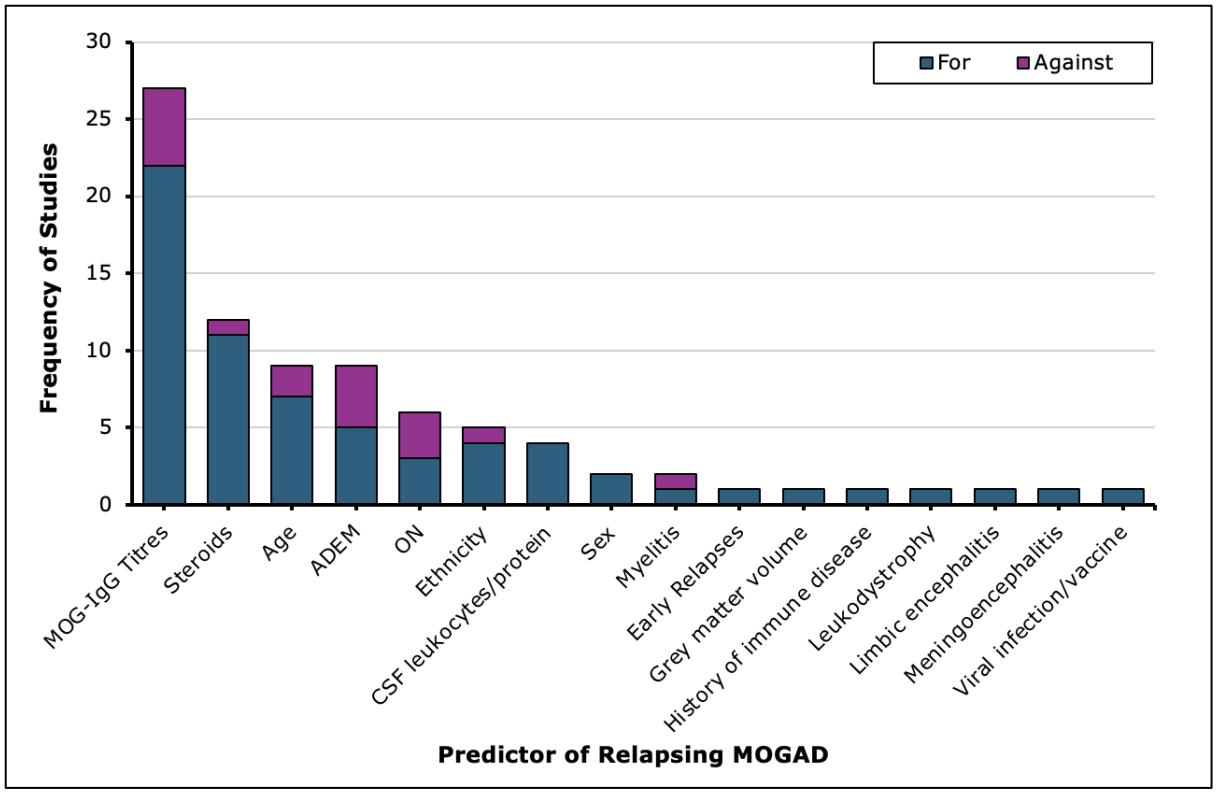

Figure 6. Graph showing the number of studies investigating each potential predictor of R-MOGAD. The dark blue bars show the number of studies in favour of the predictor investigated having predictive value for R-MOGAD. The purple bars show the number of studies that found the predictor to have no predictive value or went against the general consensus of the other studies.

For MOG-IgG titres, persistent positivity compared to negative seroconversion was the most common significant predictor of a relapsing prognosis [7][10][14][15][16][17][18][19][20][21]. ZhangBao *et al.* [24] found this in particular when persistence was ≥ one year and in their discussion acknowledged three studies that did not find this association [22][23][24]. One of these was a case study [26] which did not meet the criteria of the scoping review. Another had a small sample size of 17 patients positive for MOG-IgG [27] and the other, Cobo-Calvo *et al.* [25], only observed MOG-IgG titres within three months of MOGAD onset, perhaps indicating persistence of ≥ one year rather than three months is required to be predictive. However, de Mol *et al.* [28] found that seropositivity can be maintained for years without clinical activity, although patients with negative seroconversion generally had no relapses.

Waters *et al.* [10] argued that MOG-IgG testing 12 months following disease onset will identify more than half of patients and most patients with ADEM destined to become seronegative. This could be explained by the fact that serum MOG-IgG titres were shown to be higher during clinical attacks than remission [11][19][20][21][22][23] and decline at follow-up treatment [19][21][23]. It is also worth noting that high serum levels were found to increase risk of relapsing disease [24][25][27][28] and transiently low titres the

reverse [25]. Gastaldi *et al.* [17] also found that high remission titres ≥31 days after an attack was predictive of R-MOGAD. Viral infection/vaccine trigger was associated with negative seroconversion [38], meaning it could also be associated with a decreased risk of relapsing disease. To summarise, MOG-IgG titres were shown to be a significant predictor of R-MOGAD, and this may only be the case with persistence of ≥ one year.

Steroid treatment after a clinical attack was the second most commonly investigated predictor. Oral tapering of corticosteroid therapy for ≥ three months has been recommended to decrease risk of relapsing disease [2][30][31], especially as premature withdrawal can lead to rapid development of disability and flare-ups [9][23]. To ensure its anti-inflammatory properties a steroid taper was defined as a minimum dosage of 10 mg by Ramanathan *et al.* [39]. The second and third largest studies to date finding steroids to decrease risk of R-MOGAD were Satukijchai *et al.* [40] and Jurynczyk *et al.* [35] with 276 and 252 participants respectively. Whilst the former did not define a minimum treatment duration, Jurynczyk *et al.* [35] concluded a duration of ≥ three months to be statistically significant. Huda *et al.* [38] shared the same findings with ≥ one month of steroids in a dataset of 76 patients and Nosadini *et al.* [41] ≥ five weeks with 75 patients. A systematic review on long term immunotherapies in MOGAD validated maintenance of oral steroids as preventative of relapses [42].

The only study that did not find steroids to be a significant predictor was Chen *et al.* [43], the largest study to date investigating steroids with 289 patients. However, they acknowledged that the majority of participants (217/289, 75.1%) did not receive steroids and that their study was not powered to analyse different dosages and durations. Perhaps a significant result would have been more likely if participants with early relapses had received a slow steroid taper ≥10mg instead to suppress early inflammatory activity, although this is purely speculative. In conclusion, treatment after the onset attack with steroids ≥ three months may reduce the risk of R-MOGAD but more research is required to determine whether this duration is optimal.

Age has also been shown to predict R-MOGAD. A review, published by Al-Ani *et al.* [44] in 2023, found that adults tend to have more relapsing episodes and poorer functional recovery than children [33][39][44]. On the contrary, Jurynczyk *et al.* [35] found a tendency for younger patients to relapse in their sample of 252 pwMOGAD. Furthermore, Rempe *et al.* [34] presented in October 2023 that 12/13 of their patients under nine years of age were relapsing. This predictor is complicated by its confounding relationship with disease phenotype. On the one hand, ADEM presentation tends to occur in younger patients [33][34][38][40][45][46][47], and ON in older patients with relapsing disease

more common in the latter group [33][36][38]. On the other hand, ADEM has been shown to increase risk of relapsing disease when co-presenting with ON [50] and has been associated with higher MOG-IgG titres , which may be a predictor of R-MOGAD in itself. Future research should investigate whether ADEM when adjusted for confounders is a predictor of R-MOGAD.

ON is the most common phenotype in MOGAD and presents in up to 90% of adult patients [16]. Therefore its frequency may diminish its value as a predictor and explain some of the heterogeneity in the literature. Wang *et al.* [36] found it to be associated with relapsing disease, Nosadini *et al.* [41] the reverse and Cobo-Calvo *et al.* [8] no association. ON was also less likely to be associated with high CSF leukocytes [48], which itself was associated with a relapsing prognosis when above 50/mm^3 [36] and 150/mm^3 [34]. Future research should compare risk of relapsing disease in equal sample sizes of patients with and without ON.

Early relapse is a novel potential predictor of long-term relapsing disease and has only been investigated by Chen *et al.* [43], published in May 2023. They found early relapses (< 12 months of MOGAD onset) to be predictive of subsequent relapses, especially when very early (> 30 days and < three months of onset). However, in children < 12 years only relapses ≥ three and < 12 months from onset and were predictive of R-MOGAD. Consequently, they rejected their initial hypothesis that early inflammatory activity is not a risk for long-term activity. This theory is in agreement with other literature suggesting treatment after the onset attack with steroids reduces the risk of relapsing disease [2][25][29][30][31][32][33] as they inherently suppress early inflammatory activity. They also supported the use of a 30-day cut-off for relapse as defined by the International MOGAD Panel Proposed Diagnostic Criteria [1], suggesting that early relapse in itself is a characterisation of R-MOGAD rather than a predictor in its own right.

Non-White ethnicity was also linked to a relapsing prognosis [24][41]. Satukijchai *et al.* [40] found race to have no association with relapse risk, although Cobo-Calvo *et al.* [25] found Caucasians to have higher MOG-IgG titres than those of other ethnicities. Nevertheless, race as a predictor may be worth investigating further. With regards to sex, Huda *et al.* [38] and Cobo-Calvo *et al.* [8] found that males were less likely to have R-MOGAD compared to females. Zhou *et al.* [52] found patients with TM to have a higher relapse frequency, whereas Huda *et al.* [38] found patients with spinal cord involvement to be at lower risk of relapsing disease.

Other predictors that had a positive predictive value of R-MOAGD were high baseline CSF protein > 450mg/L [24], decreased grey matter volume [53], history of immune disease [36], leukodystrophy [54] and meningoencephalitis [34]. Limbic encephalitis had a negative predictive value of R-MOGAD [55]. Minimum follow-up duration varied between studies with some using six months [3][6][17][21][31][49] and others one year [38], [40]. A longer duration is preferable to prevent the mislabelling of future relapsing patients as monophasic, such as a minimum of two years in Chen *et al.* [43], and is a strength of studies investigating predictors of relapse in MOGAD.

4. Conclusion

In conclusion, the primary outcome of identifying the most likely predictors of R-MOGAD were MOG-IgG titres, with persistence of at least 1 year. Steroids after the onset attack were the next most investigated, with a taper of at least 3 months reducing risk of R-MOGAD. This suggests that suppression of early inflammatory activity may prevent relapses in the long term. The literature on age, ADEM, ON and ethnicity as predictors is more heterogenous and is complicated by their confounding relationships. The relationships between these variables and the others identified in the review are displayed in Figure 7, a directed acyclic graph [57].

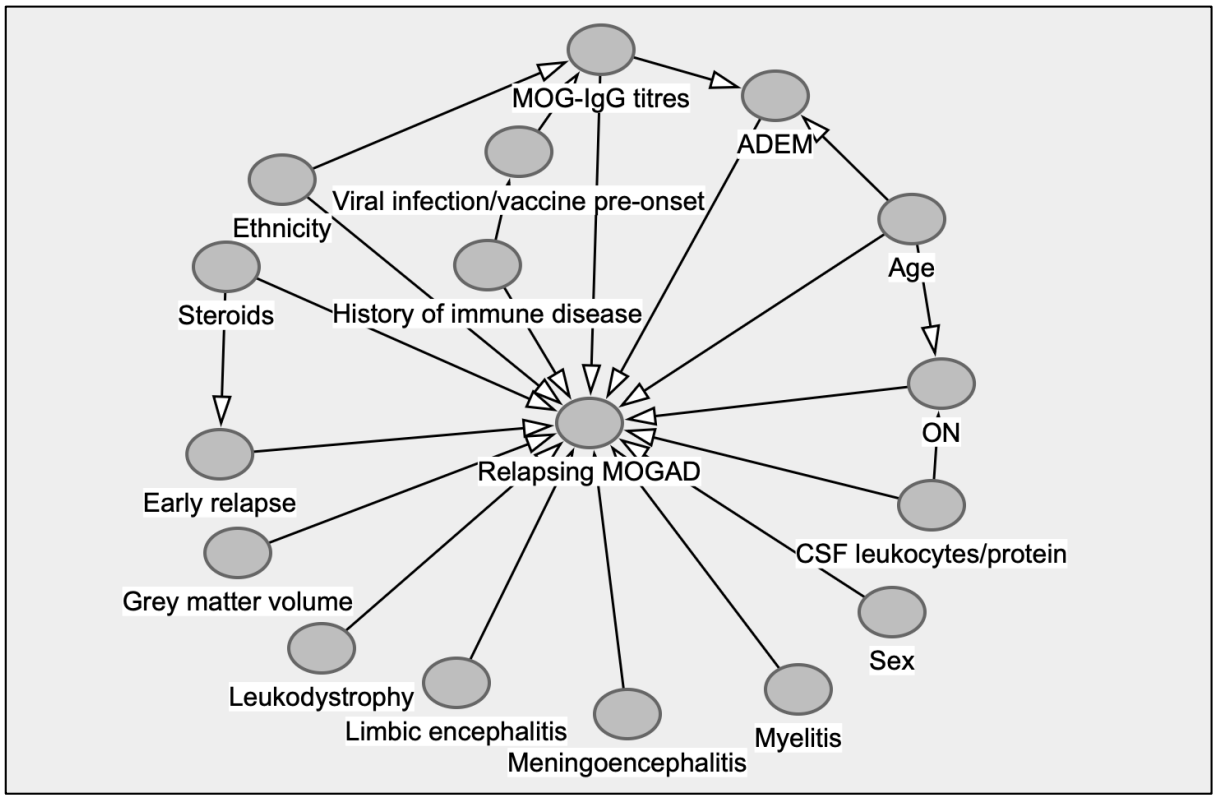

Figure 7. Directed acyclic graph showing the relationships between the potential variables impacting risk of R-MOGAD identified in the scoping review [57].

The findings of Chen *et al.* [43] on early relapses supported a relapse definition in MOGAD to have a 30 day cut-off, meaning that early relapses can be thought of as features of R-MOGAD rather than a predictor itself. The secondary outcome of finding alternative, less investigated potential predictors were CSF leukocytes and/or protein, sex, myelitis, grey matter volume, history of immune disease, leukodystrophy, limbic encephalitis, meningoencephalitis, and viral infection/vaccine pre-onset.

The strengths of this scoping review were the use of a thorough search query, citations from the included studies and additional literature searches. The limitations were the literature search not being performed in duplicate, the search query only being used on one database (Pubmed) and restriction to the English language.

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Conflict of interests: the authors declare no conflict of interest in relation to this study.

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