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MOGAD in South Wales: Diagnostic Evolution and Disease Epidemiology

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ABSTRACT

Background: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a rare antibody-mediated inflammatory demyelinating disorder. In 2023, new international consensus diagnostic criteria were agreed. This study uses these criteria to describe epidemiological features of MOGAD in a population-based cohort of patients from south Wales, UK.

Methods: Retrospective review of case notes on all positive MOG-IgG results in South Wales between 01 January 2011 and 30 June 2024 was undertaken, 2023 diagnostic criteria applied and standardised clinical features recorded. Paediatric MOGAD was defined as age at onset < 16 years and adult MOGAD ≥ 16 years. The incidence period was between 01 January 2015 and 31 December 2023.

Results: Seventy-six prevalent cases were identified: 53 adults and 23 children. Minimum estimated prevalence of MOGAD in south Wales on 30 June 2024 was 76/1,974,110 population (3.85/100,000 population; 95% CI 3.03–4.82). Paediatric prevalence was 6.59/100,000 population (95% CI 4.18–9.89) and adult prevalence 3.26/100,000 population (95% CI 2.44–4.27). Sex ratio was almost equal in males and females. The most frequent presentations were optic neuritis in adults (62.3%) and ADEM in children (34.8%); 64.5% had a monophasic disease course over a median follow-up of 38 months (IQR 13–63). Mean annual incidence was 3.39 (95% CI 2.58–4.39) per million population.

Conclusions: This regional study provides updated prevalence and incidence rates for MOGAD since the introduction of 2023 diagnostic criteria in a stable south Wales, UK population.

1 | Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a rare antibody-mediated inflammatory demyelinating disorder with a broad and expanding clinical spectrum. Whilst anti-MOG antibodies (MOG-IgG) were first recognised in animal models in the 1970s, their pathological association with demyelinating presentations in humans was not well understood until more recently [1–3]. MOGAD is now known to have clinical and pathological features which make it distinct from other demyelinating diseases, including multiple sclerosis (MS) and aquaporin-4-antibody positive neuromyelitis optica spectrum disorders (AQP4-NMOSD) [3–5].

However, research into this rare disease has previously been limited by a lack of consensus diagnostic criteria, making direct

comparison of case series and epidemiological studies problematic. In 2023, international consensus diagnostic criteria were introduced which promise to overcome some of these difficulties [6]. Several groups have now retrospectively validated these diagnostic criteria within existing cohorts reporting high sensitivity and specificity (96.5%–100% and 98.9%–100%, respectively) [7–9]. Whilst future work should aim to validate these criteria prospectively, widespread introduction of the new diagnostic criteria is likely to improve the reliability and validity of comparisons between cohorts [6].

Although there have been some population-based studies over the past decade, often based on immunological services test results, there remains a relative lack of robust epidemiological data on the prevalence and incidence of MOGAD together with a lack of clarity on regional variation of disease phenotype and frequency [10]. In addition, significant changes are also likely to occur over time with increasing recognition of the disorder by relevant clinical specialities, expansion of the clinical phenotype and availability of robust, standardised MOG-IgG testing methodologies. Epidemiological studies to date employing historic diagnostic criteria have estimated prevalence at 0.51–3.70 per 100,000 population and annual incidence of 1.18–4.8 per million population, although confidence limits for individual studies remain wide and many areas of the world remain unstudied [11–18].

In south Wales, all diagnostic MOG-IgG testing is carried out at a single external laboratory, and all demyelinating diseases are referred to one of three networked, specialist centres in a standardised national health care system. This background provides an opportunity to provide further insights into population-based epidemiology of MOGAD and builds on a well-established framework of epidemiological studies of demyelinating disorders, which has been previously described [19–21]. This study aimed to define the clinical characteristics of a cohort of people living with MOGAD in south Wales using the new 2023 diagnostic criteria and to provide contemporary population-based prevalence and incidence data for this area of the United Kingdom.

2 | Methods

2.1 | Study Area

South Wales comprises a geographical area which includes Aneurin Bevan University Health Board (ABUHB), Cardiff and Vale University Health Board (CAVUHB), Cwm Taf Morgannwg University Health Board (CTMUHB) and Swansea Bay University Health Board (SBUHB), serving an estimated population of 1,974,110 (Figure 1). South Wales consists of a semi-rural population which encompasses the major urban centres of Cardiff, Newport and Swansea. The region was a key location for the industrial revolution in the late 18th century and has a legacy of industry, including steel and coal work. Neurological care in this region is delivered by three specialist neurological centres and five general hospitals, which host satellite neurology outpatient and liaison services. All demyelinating disease is referred to one of three specialist neuroinflammatory centres at the University Hospital of Wales, Royal Gwent Hospital or Morriston Hospital. A regional database and clinical tool (PatientCare) for patients with demyelinating disease has been maintained since 1999 and is accessible by all sites. Patients are reviewed annually, where possible and standardised information collected on disease phenotype, relapses and drug interventions.

All MOG-IgG testing was carried out at a reference laboratory (Oxford Autoimmune Neurology Diagnostic Laboratory, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, United Kingdom). IgG1 antibodies that bind human MOG are detected by live cell-based assay. Briefly, serum diluted 1:20 is incubated with HEK293T cells transiently transfected with the alpha1 isoform of human MOG. An anti-human IgG1 specific secondary antibody detects the presence of surface-bound MOG specific patient antibody. Positive test results are repeated, and specificity is confirmed by a lack of binding on a control antigen, often AQP4-M23 expressing cells [3].

2.2 | Case Ascertainment

An initial register was created from five different sources to encompass adults (≥16 years) and children (<16 years) with MOGAD across south Wales. Firstly, the regional neuroinflammatory database (PatientCare) was examined for people seen within the regional neuroinflammatory service who had a diagnosis of MOGAD and/or were registered to the neuromyelitis optica spectrum disorders (NMOSD) clinical service. Secondly, results from all serum MOG-IgG tests sent via the CAVUHB immunology laboratory between 1 January 2015 and 30 June 2024 were obtained, and detailed clinical records of relevant individuals reviewed. Before this date, samples were sent directly to the reference laboratory and not logged separately in the CAVUHB laboratory. Clinicians working within the relevant regional specialist services at CAVUHB, ABUHB and SBUHB were also contacted to review existing case lists and to contribute and/or notify any additional patients. This methodology, when previously applied to epidemiological studies in this region, has resulted in a case capture rate of approximately 95% [20]. Finally, results of all patients with positive MOG-IgG results tested at the reference laboratory between 1 January 2011 and 30 June 2024 were obtained. A period of 6 months continued observation after 30 June 2024 allowed for any delay in notifications to ensure a more complete case capture.

Inclusion criteria were as follows:

1. Positive MOG-IgG test reported by reference laboratory.
2. Fulfilling MOGAD 2023 diagnostic criteria (Figure 2).
3. Living within a defined geographical area as determined by address on electronic health records (Welsh Demographic Database) on 30 June 2024.

Individuals who had moved out of area, those seen as tertiary service referrals from other health boards or had died before the prevalence date were excluded (Table 1).

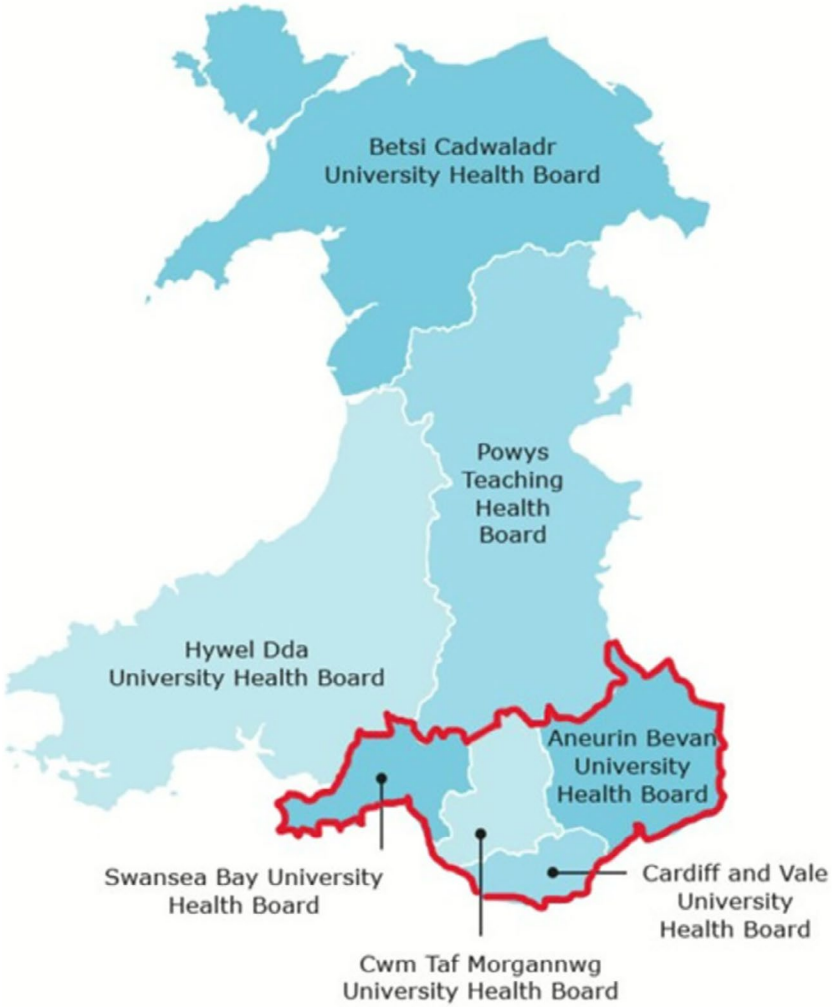

FIGURE 1 | Structure of NHS Wales by health board. The outlined area contains the four health boards included in the study (ABUHB, CAVUHB, CTMUHB, SBUHB). Neuroinflammatory services in south Wales are delivered by one of three specialist neuroinflammatory centres at University Hospital of Wales (CAVUHB), Royal Gwent Hospital (ABUHB) or Morriston Hospital (SBUHB) [22].

Retrospective case review was performed using electronic health records and/or direct review by a specialist neuroinflammatory clinician with disease-specific data recorded on PatientCare. The 2023 diagnostic criteria were applied to all cases (Figure 2) [6]. Patients who failed to meet diagnostic criteria were excluded from further analyses. Expanded Disability Status Scale (EDSS) score was used to characterise disability at onset and at 6-month follow-up [23]. Relapse was defined as new or worsening neurological symptoms occurring at least 30 days from onset of the previous clinical episode [6].

2.3 | Ethics

The majority of participants were identified from an existing long-term study of demyelinating disease for which informed consent was available (SNOWDONIA, Wales Ethics committee 19/WA/0289). However, since the study was undertaken with retrospective analysis of routinely collected clinical data, an independent formal Research Ethics Committee approval was not required. This was confirmed by the NHS Health Research Authority, and local approval was obtained via a regional audit approval (SE/2023–24/04).

2.4 | Statistical Analysis

Population estimates were obtained from UK government figures, broken down by Health Board, and an average percentage change was calculated to estimate the population in each area by mid-year 2024 [24]. Paediatric MOGAD was defined as <16 years of age and adult MOGAD ≥ 16 years of age, as data was captured in these groupings by the Welsh Government [24]. Age and sex-specific prevalence rates were calculated for all prevalent cases (i.e., those fulfilling 2023 diagnostic criteria, alive and living within the area on 30 June 2024). Cases were incident if they had an index event with a positive MOG-IgG between 1 January 2015 and 30 June 2024. Incidence rates were calculated

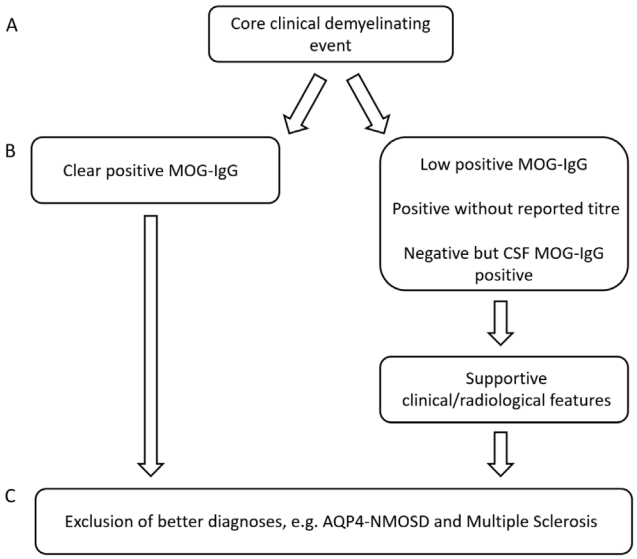

FIGURE 2 | Flow diagram demonstrating the three steps (A–C) which must be fulfilled to diagnose MOGAD according to the 2023 criteria [6]. The first (A) is a core clinical demyelinating event, for example, optic neuritis or ADEM. The second (B) is a positive MOG-IgG test on the cell-based assay (serum). If this is a clear positive (titre ≥ 1:100), then a diagnosis can be made if the third step (C) exclusion of better diagnoses, is met. If the cell-based assay is a low positive, or has an unreported titre, then the individual must be AQP4-IgG seronegative and ≥ 1 additional supportive clinical/radiological feature(s) must be met, as well as step C. These include an optic neuritis with bilateral simultaneous involvement, or other features such as optic disc oedema. If an individual is seronegative for MOG-IgG, they can still fulfil the diagnostic criteria if they have a positive CSF result with a fixed or live cell-based assay with supportive clinical/radiological features and fulfilment of step C.

TABLE 1 | Ascertainment sources for prevalent patients.

Recruitment source	Preliminary register ($n = 109$)		Prevalent register ($n = 83$)		Prevalent and 2023 diagnostic criteria met ($n = 76$)	
	n	%	*n*	%	*n*	%
CAVUHB database	32	29.4	29	34.9	28	36.8
CAVUHB Immunology	11	10.1	11	13.3	11	14.5
ABUHB database	4	3.7	4	4.8	4	5.3
SBUHB database	21	19.3	16	19.3	16	21.1
John Radcliffe Immunology	41	37.6	23	27.7	17	22.4

for all cases with a symptom onset between 1 January 2015 and 31 December 2023. A Poisson distribution was assumed to calculate 95% confidence intervals using R.

TABLE 2 | Prevalence of MOGAD in south Wales.

	Estimated population in South Wales	Prevalent cases June 2024	Rate per 100,000 (95% CI)
Total	1,974,110	76	3.85 (3.03–4.82)
Male	972,142	37	3.81 (2.68–5.25)
Female	1,001,982	39	3.89 (2.77–5.32)
< 16	349,025	23	6.59 (4.18–9.89)
≥ 16	1,625,157	53	3.26 (2.44–4.27)

3 | Results

3.1 | Case Ascertainment

The preliminary register contained 109 patients with a positive MOG-IgG from all sources (Table 1), with sources listed in the order in which they were obtained. Any duplicate referrals were excluded prior to entry on the register. Twenty-six patients (23.9%) on the preliminary register had either died (6), moved away from the area (3), were tertiary referrals from outside the defined geographical area (14), or no relevant clinical records of the individual could be identified (3). This left 83 suspected cases and following review of electronic patient records, 76 (91.6%) fulfilled 2023 diagnostic criteria whilst 7 (8.4%) did not; five had an alternative diagnosis and two had a low-positive test without evidence of relevant supportive radiological or clinical criteria.

3.2 | Prevalence

Seventy-six prevalent patients meeting 2023 diagnostic criteria were identified: 53 adult (≥ 16 years) and 23 paediatric cases (< 16 years) (Table 3). The minimum estimated prevalence of MOGAD in south Wales on 30 June 2024 was 76/1,974,110 population (3.85/100,000 population; 95% CI 3.03–4.82) (Table 2). Paediatric prevalence was 6.59/100,000 population (95% CI 4.18–9.89) and adult prevalence 3.26/100,000 population (95% CI 2.44–4.27). Overall, prevalence was similar in males and females (3.81/100,000 (95% CI 2.68–5.25) versus 3.89/100,000 (95% CI 2.77–5.32)). Median age at first positive MOG-IgG was 33 years (IQR 12–47.5); median age in children was 7 years (IQR 3–10) and 42 years (IQR 32–54) in adults. No overall sex preponderance was identified. However, there was a lower proportion of females with paediatric MOGAD (8/23, 34.8%), compared to adults (31/53, 58.5%).

The most common initial presentation was optic neuritis in adults (33/53, 62.3%) and ADEM in children (8/23, 34.8%) (Table 3, Table S2). Median period of observation was 38 months (IQR 13–63). During follow-up, most individuals followed a monophasic course (49/76, 64.5%); the proportion of adults

TABLE 3 | Demographics of prevalent south Wales MOGAD population.

		Children ($n = 23$)	Adult ($n = 53$)	All ($n = 76$)
Age at diagnosis, median (IQR), years		7 (3–10)	42 (32–54)	33 (12–47.5)
Female, *n* (%)		8 (34.8)	31 (58.5)	39 (51.3)
Follow-up, median (IQR), months		34 (19–52)	39 (8–77.5)	38 (13–63)
Monophasic, *n* (%)		17 (73.9)	32 (60.4)	49 (64.5)
Relapse, *n* (%)		6 (26.1)	21 (39.6)	27 (35.5)
Time to first relapse, median (IQR), months		2 (1–9.75)	65 (10–80)	19 (6–73)
Initial presentation, *n* (%)	Optic neuritis	6 (26.1)	33 (62.3)	39 (51.3)
	Transverse myelitis	3 (13.0)	10 (18.9)	13 (17.1)
	ADEM	8 (34.8)	2 (3.8)	10 (13.2)
	Brainstem/cerebellar	2 (8.7)	1 (1.9)	3 (3.9)
	Other	4 (17.4)	7 (13.2)	11 (14.5)
EDSS at onset, *n* (%)	<4	5 (21.7)	14 (26.4)	19 (25.0)
	≥ 4	17 (73.9)	35 (66.0)	52 (68.4)
	Unknown	1 (4.3)	4 (7.5)	5 (6.6)
EDSS at 6 months, *n* (%)	<4	19 (82.6)	40 (75.5)	59 (77.6)
	≥ 4	2 (8.7)	6 (11.3)	8 (10.5)
	Unknown	2 (8.7)	7 (13.2)	9 (11.8)
CSF oligoclonal bands tested, *n* (%)		21 (91.3)	35 (66.0)	56 (73.7)
CSF positive for oligoclonal bands, *n* (%)		1 (4.8)	7 (20.0)	8 (14.3)
Incident (01 January 2015 to 30 June 2024), *n* (%)		21 (91.3)	39 (73.6)	60 (78.9)
Age at symptom onset (incident cases $n = 60$), median (IQR), years		7 (3–10)	40 (29.3–49.3)	29 (10–43)

experiencing a relapse (39.6%, median follow-up 39 months (IQR 8–77.5)) was higher than paediatric cases (26.1%, median follow-up 34 months (IQR 19–52)). Relapse was more common in children presenting with ADEM (3/8, 37.5%) than adults (0/2). There were no relapses in children presenting with optic neuritis (0/6), whereas 45.5% of adults presenting with optic neuritis experienced one or more relapses (15/33). For those with complete electronic records, EDSS was ≥4 in 73.9% (17/23) of children at presentation compared to 66.0% of adults (35/53). At 6-month follow-up, 8.7% (2/23) of children had an EDSS ≥4 compared to 11.3% of adults (6/53) (Table 3).

3.3 | Incidence

1 January 2015 was chosen as the start of the incidence period, coinciding with widespread regional availability of MOG-IgG testing. There were 60 incident cases between 1 January 2015 and 30 June 2024. The incidence period was set at 1 January 2015 to 31 December 2023 to allow for the capture of full years. Fifty-eight individuals were diagnosed with MOGAD according to the 2023 diagnostic criteria during this period (Figure 3, Table S1). Overall annual incidence rate varied between 2.13 (95% CI 0.58–5.45) and 5.30 (95% CI 2.54–9.74) cases per million. Annual incidence of paediatric MOGAD varied between 2.89 cases per million (95% CI 0.07–16.1) to 8.70 (95% CI 1.79–25.4). The lowest incidence of paediatric MOGAD in children in south Wales was in 2016 and 2017 (one case per year), whilst the highest was in 2021 and 2022 (three cases per year). In adults, the incidence rate varied between 1.27 (95% CI 0.15–4.58) and 4.55 (95% CI 1.83–9.37) cases per million per year. The highest incidence of MOGAD in adults in south Wales was in 2018 (seven new cases), whereas the lowest incidence was in 2015 and 2022 (two new cases). Peaks of incidence in 2017 and 2018 are likely to reflect increased awareness of the disease, whilst the trough in 2020 and subsequent peak in 2021, may reflect the effect of the COVID-19 pandemic and delay in diagnosis. The peak in 2023 may reflect the release of the new diagnostic criteria. The mean annual incidence of MOGAD between 2015 and 2023 was 3.39 (95% CI 2.58–4.39) per million.

4 | Literature Review

Prior to this study, there have been eight population-based studies examining the prevalence and/or incidence of MOGAD [11–18] (Table 4). The size of the epidemiological area varies greatly from a population of 150,000 to around 126 million. They all predate the introduction of the 2023 diagnostic criteria, apart from that of Cacciaguerra et al. *2025* and this study [18].

5 | Discussion

This study represents the first large-scale, population-based epidemiological study of MOGAD in the UK. It has focused on a well-surveyed, stable population in south Wales and provides a contemporary estimate of prevalence and incidence rates following the introduction of the 2023 consensus diagnostic criteria. Since all MOG-IgG tests in south Wales are processed via a central laboratory and the study builds on a longstanding established structure for epidemiological studies of demyelinating diseases, case capture rates are likely to be high and estimates provided reliable. Previous studies have used a variety of techniques to capture prevalence and incidence rates from centralised laboratory results to questionnaires sent to neurology centres and vary considerably in methodology [11–18]. Healthcare in the UK is largely standardised via a National Health Service, and review of electronic patient records was achieved through a centralised all-Wales system, allowing a degree of standardisation. These systems also enabled capture of dynamic demographic data, as well as imaging and clinical data, to ensure that all included cases met 2023 diagnostic criteria. Of 83 prevalent cases on a preliminary register, only seven (8.4%) failed to meet diagnostic criteria, with the majority having a better diagnosis (5), and MS being the most common (3/5). A further two had a low-positive MOG-IgG but no additional supportive clinical or radiological criteria. The first presented with a unilateral optic neuritis, without MRI changes or optic disc oedema. The second did not have a clear, core clinical demyelinating event (recurrent episodes of transient dysarthria, facial weakness, or altered sensation lasting minutes to hours before fully resolving), and

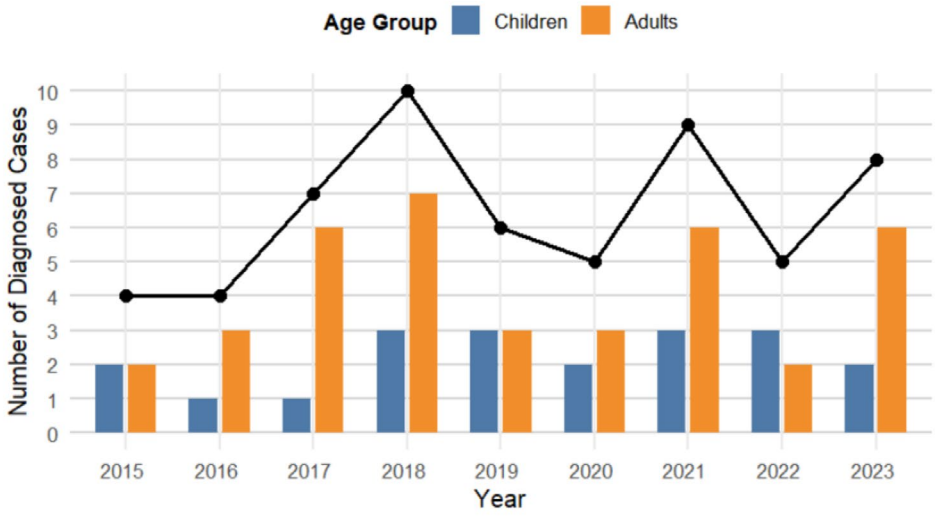

FIGURE 3 | Number of new MOGAD diagnoses by year and group with overall trend of total cases per year.

TABLE 4 | Summary of epidemiological studies of MOGAD to date.

Geographical location (authors)	Category	Population	Prevalence date	Incidence period	Number of prevalent cases Total (adult: paediatric)	Prevalence per 100,000 population (95% CI)	Annual incidence rate per million population (95% CI)
Oxfordshire, UK (O'Connell et al. [15])	Regional	687,500	1 July 2018	2015–2018	14 (12: 2)	2.0 (1.1–3.4)	3.4 (1.4–6.9)
The Netherlands (de Mol et al. [14])	Nationwide	16,987,117	—	2015–2017	—	—	1.6 (1.1–2.3)
Singapore (Tan et al. [12])	Nationwide	~4 million	End June 2020	—	51 (41: 10)	1.26 (0.91–1.61)	—
Verona, Italy (Orlandi et al. [16])	Regional	922,291	1 January 2021	2016–2020	23 (21: 2)	2.5 (1.7–3.7)	4.8 (3.1–7.2)
Chumphon, Thailand (Tisavipat et al. [11])	Regional	509,479	31 December 2021	2016–2021	2 (2: 0)	0.51 (0.14–1.87)	0
Japan (Nakamura et al. [13])	Nationwide	126,167,000	March 2021	2020–2021	1695[a]	1.34 (1.18–1.51)	3.9 (3.2–4.4)
São Paulo, Brazil (Silva et al. [17])	City	12,396,372	May 2021	—	28 (28:0)	0.4[d]	—
Olmsted County, USA and Martinique (Cacciaguerra et al. [18])	Regional and nationwide comparison	159,127[a] 374,892[b]	31 December 2018	2003–2018	6 (4: 2)[b] 9 (9: 0)[c]	3.70 (0.74–6.66)[a] 2.61 (0.85–4.37)[b]	3.00 (0.78–5.22)[a] 1.18 (0.30–2.07)[b]
South Wales, UK (this study)	Regional	1,974,110	30 June 2024	2015–2023	76 (53: 23)	3.85 (3.03–4.82)	3.39 (2.58–4.39)

[a]Estimated cases based on survey responses.
[b]Olmsted Country, Minnesota, USA.
[c]Martinique, Caribbean.
[d]Confidence intervals not reported.

there were no MRI findings in keeping with MOGAD. Both were tested during or close to these events. Long-term follow-up of these low-positive cases and other similar cohorts to explore subsequent rates of conversion to MOGAD is of interest.

We identified 76 individuals with MOGAD in a population of 1,974,110 (53 adults and 23 children) in south Wales. Overall prevalence rate on 30 June 2024 was 3.85/100,000 population (95% CI 3.03–4.82), but prevalence was higher in children than in adults 6.59/100000 population (95% CI 4.18–9.89) versus 3.26/100,000 population (95% CI 2.44–4.27). Given that MOGAD is a lifelong illness, this suggests that further increases in prevalence are likely over time, together with other factors including improved disease recognition, testing availability and longevity. To date, there have been eight other epidemiological studies reporting prevalence and/or incidence of MOGAD (Table 4) [11–18]. Our overall prevalence rate is comparable to another epidemiological study, from the USA and Martinique, which reported similar prevalence rates using the 2023 diagnostic criteria [18]. The overall prevalence figure in our study is higher than an earlier UK Oxfordshire study, which reported an overall prevalence rate of 2.0/100,000 (95% CI 1.1–3.4) [15]. However, the Oxford cohort was considerably smaller, containing only 14 prevalent patients, and predated the 2023 diagnostic criteria [15].

The cohort reported in this study is the second largest population-based study reporting prevalence rates, with the largest being a Japanese cohort which reported an estimated nationwide prevalence of 1.34 per 100,000 (95% CI: 1.18–1.51) [13]. However, that study estimated prevalence based on responses to questionnaires sent to neurology centres without direct review of patients with low response rate (36%), and responses more likely to have come from specialist centres. In addition, the study assumed a rate of MOGAD cases diagnosed in non-specialist centres, potentially introducing further inaccuracies [13]. The higher prevalence rate observed in our cohort is likely to reflect a more detailed approach to case ascertainment in closely engaging the three networked specialist south Wales neurology centres and cross-referencing against the central laboratories to ensure more complete case capture. A Singaporean MOGAD study identified 51 adult and paediatric cases [12]. The authors of this study reported an overall prevalence rate of 1.26/100,000 (95% CI 0.91–1.61) and noted a variable prevalence according to ethnicity, with the highest prevalence rate in people of Indian ethnicity (2.48 per 100,000 (95% CI 0.86–4.11)) and the lowest in people of Chinese ethnicity (1.03 per 100,000 (95% CI 0.57–1.39)) [12]. The MOGAD cohort in this study was overwhelmingly of White, northern European ethnic origin, and therefore, we cannot comment on whether the differing prevalence rates are secondary to the methodology of case ascertainment or ethnicity.

Fifty-eight incident cases were recorded between 1 January 2015 and 31 December 2023 in the south Wales region. Mean annual incidence per million population over the 9 years was 3.39 (95% CI 2.58–4.39) (Table S1). This is comparable to the overall incidence per million population from the Oxfordshire, Verona and Japanese cohorts (Table 4) [13, 15, 16]. In children, the mean incidence rate was 6.41 per million (95% CI 3.92–9.90), and in adults it was 2.72 (95% CI 1.92–3.73). The overall mean incidence rate in south Wales was higher than that of the Dutch cohort, which reported a mean nationwide MOG-positivity of 1.6 per million (95% CI 1.1–2.3) [14]. As in the south Wales cohort, they found a higher incidence in children (3.1 per million; 95% CI 1.7–5.1) than in adults (1.3 per million; 95% CI 0.80–1.9). As the incidence period for the Dutch cohort was between 2015 and 2017, the higher incidence rate in our group could be due to increased testing with increased disease awareness of MOGAD. Whilst the incidence period for the Oxfordshire cohort was similar to the Dutch cohort (2015–2018), the case ascertainment differed [14, 15]. The Dutch cohort was a nationwide audit of all positive MOG-IgG tests, whereas the Oxfordshire cohort represented a regional cohort from the site of the UK specialised national NMOSD service [14, 15]. Therefore, this higher rate between 2015 and 2018 from the Oxfordshire cohort compared to that of the Dutch may reflect increased awareness of MOG-IgG and referral/test bias from a specialist NMOSD centre.

A recent epidemiological study of MS in Wales in 2020 identified a prevalence rate of 221.65/100,000 (95% CI 216.17 to 227.24) [25]. Whilst exact comparison of MS and MOGAD disease frequency is not possible due to methodological differences, we estimate the ratio of MOGAD: MS in Wales at 1:57.6. Three other groups have reported MOGAD:MS disease ratios of 1:1.5, 1:5.2 and 1:37.5 within Thai, Singaporean and Brazilian populations respectively [11, 12, 17]. This variability is likely to reflect ethnicity-based disease susceptibility [26, 27].

No overall gender bias was observed in our study (39/76 female, 51.3%), in keeping with other studies [12, 14]. Median age at diagnosis was 33 years, consistent with other studies [13, 16, 18]. The most common presentation in the south Wales cohort at onset in children was ADEM (34.8%) and optic neuritis in adults (62.3%), which is also in line with other reports [14, 28, 29]. CSF oligoclonal bands were tested in 56/76 (73.7%), of whom 8/56 (14.3%) were positive; none underwent CSF MOG-IgG testing. More children had CSF testing than adults (21/23, 91.3% versus 35/53, 66.0%); only one (4.8%) child had positive oligoclonal bands compared to 7/35 adults (20.0%). Other groups have found positive oligoclonal bands in 13%–52% of MOGAD patients [30–33]. However, direct comparison of studies is problematic because of variability in the timing of CSF analysis, cohort demographics and diagnostic test used [30–33]. Further studies exploring the relationship between CSF oligoclonal bands, MOG-IgG, CSF white cell count, disease presentation and outcome would be of value.

Since the development of the cell-based assay, it has been easier and more reliable to test for MOG-IgG, resulting in an expansion of the clinical spectrum of MOGAD. As a result, the 2023 diagnostic criteria laid out strict laboratory, clinical and radiological features required to diagnose MOGAD to minimise misdiagnosis [6]. These criteria, combined with the expanding clinical spectrum of MOGAD presentations, may account for some variation in clinical phenotype over time and future work should look to prospectively evaluate incident presentations of MOGAD using these criteria.

Whilst 68.4% had an EDSS of ≥4 at onset, only 10.5% (two children and six adults) had an EDSS of ≥4 at six-month follow-up. This

supports recent observations that most individuals with MOGAD have a favourable long-term outcome in comparison to those with NMOSD or MS [34, 35]. However, a small proportion were left with long-term disability; out of eight people with an EDSS of ≥4, five had an index presentation of transverse myelitis (one child and four adults). Understanding the reasons behind poor recovery in these cases should also be a focus for future research.

The south Wales cohort benefitted from a prolonged follow-up period; median follow-up was 38 months (IQR 13–63), during which six children (26.1%) and 21 adults (39.6%) had one or more relapses, and overall relapse rate was 35.5%. This is comparable to that of the Dutch cohort (33%), but lower than reported in the Japanese cohort (53.5%) [13, 14]. Median time to relapse was 19 months (IQR 6–73), which was longer than that reported by the Dutch and Japanese groups (a median of 8 and 7 months to first relapse, respectively) [13, 14]. This longer time to relapse may be explained by the retrospective nature of this study; several people were under prolonged follow-up for presumed seronegative NMOSD and were diagnosed with MOGAD following antibody testing in subsequent relapse. Relapses within our cohort tended to occur either within 2 months of onset or much later, as reported elsewhere [6]. Children were more likely to relapse than adults within 2 months of symptom onset (3/6 (50%) vs. 2/21 (9.5%)).

The increasing incidence of MOGAD from 2017 is likely to reflect increasing awareness of MOGAD-related clinical syndrome and increased availability of testing via cell-based assays, and it seems likely that recorded disease frequency will continue to increase over time. Earlier estimates of disease frequency are likely to be less accurate for the same reasons and do not have the benefit of standardised diagnostic criteria. In contrast, indiscriminate use of MOG-IgG testing, especially if applied in the absence of relevant clinical syndromes or better diagnosis, that is, MS, may result in a higher rate of false diagnosis. This may also delay diagnosis and appropriate treatment. Judicious use of MOG-IgG testing and careful application of the consensus diagnostic criteria should minimise this risk.

We recognise that this study has a few limitations. Firstly, not all patients had complete electronic records, and therefore, we were unable to obtain information on disability in all cases, or acute/long-term treatments, due to the absence of detailed electronic prescribing in all patients. Furthermore, to calculate prevalence, some assumptions were required, including that electronic records were promptly updated when patients moved to or from the prevalence region, or if deaths occurred. However, a strength of this study region is that the population is considered relatively stable, with limited migration, which is likely to minimise this risk.

In conclusion, this regional study provides updated prevalence and incidence rates for MOGAD since the introduction of the 2023 diagnostic criteria in a stable south Wales, UK population. Future work should utilise standardised diagnostic criteria to continue to define geographically distinct cohorts and allow for effective comparison between regions and ethnicities. Given the rarity of MOGAD, these epidemiological studies are likely to be important in ensuring validity in multicentre cohorts, which would likely be required for any future randomised clinical trials.

Author Contributions

Sophie Voase: conceptualization, investigation, methodology, writing – original draft, writing – review and editing, visualization, formal analysis, project administration, data curation. **Patrick Waters:** methodology, data curation, writing – review and editing. **Stephen Jolles:** data curation, resources. **Gillian Ingram:** data curation, resources. **Owen Pearson:** data curation, resources. **Johann te Water Naudé:** data curation, resources. **Katharine Harding:** data curation, resources. **Mark Woodhall:** data curation, resources. **Ray Wynford-Thomas:** data curation, resources. **Callum Wood:** data curation, investigation. **Emma Tallantyre:** data curation, supervision, resources, writing – review and editing. **Neil P. Robertson:** conceptualisation, methodology, data curation, investigation, validation, supervision, visualisation, project administration, resources, writing – review and editing.

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The authors have nothing to report.

Conflicts of Interest

S.V. and C.W. have received travel expenses from Merck to attend an educational meeting. P.W. is a named inventor on patents for antibody assays (WO/2010/046716) with royalties paid by Euroimmun AG and disease biomarker patents (WO2019211633A1, WO2022189788A1). He has received honoraria from Biogen Idec, Mereo Biopharma, Retrogenix, UBC, Euroimmun AG, UCB, F. Hoffmann La-Roche, Forum for Indian Neurology Education (FINE) and Alexion; travel grants from the Guthy-Jackson Charitable Foundation; and research funding from Euroimmun AG and the Guthy-Jackson Charitable Foundation. His work in the Oxford Autoimmune Neurology Diagnostic Laboratory is partly supported by the NHS Commissioning service for NMOSD. He serves on the editorial boards of Neurology, Neuroimmunology & Neuroinflammation and the Journal of Clinical Neurology. MOG-IgG testing is performed in the Oxford Autoimmune Neurology Diagnostic Laboratory. S.J. has received support from CSL Behring, Pharming, Octapharma, Kedrion, UCB Pharma, LFB, Biocryst, Grifols, The Binding Site, Capitainer, Epimune, ADARx Pharmaceuticals and HCRW for projects, meetings, speaker, advisory boards, drug safety monitoring boards and clinical trials. G.I. has accepted speaking fees and travel expenses from Biogen, Merck, Novartis, Roche and Jazz Pharmaceuticals. O.P. has received honoraria and travel expenses from Biogen, Bayer, Genzyme, Merck, Novartis, Roche, Sanofi and Teva and served on advisory boards/acted as a speaker for Biogen, Celgene, Janssen, Merck, Neuraxpharm, Novartis, Roche and Sanofi. K.H. has received speaker and personal fees from Roche, Merck and Biogen and travel grants to attend educational meetings from Roche, Novartis, Merck, Biogen and Sanofi. E.T. has received honorarium for consulting work from Biogen, Janssen, Merck, Novartis and Roche. She has received travel grants to attend or speak at educational meetings from Biogen, Merck, Neuraxpharm, Novartis and Roche. JtWN, MW, RW-T and NR have no COI to declare.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** ene70502-sup-0001-TablesS1,S2.docx.