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Worldwide Incidence and Prevalence of Neuromyelitis Optica

A Systematic Review

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Abstract

Objective

Since the last epidemiologic review of neuromyelitis optica/neuromyelitis optica spectrum disorder (NMO/NMOSD), 22 additional studies have been conducted. We systematically review the worldwide prevalence, incidence, and basic demographic characteristics of NMOSD and provide a critical overview of studies.

Methods

PubMed, Ovid MEDLINE, and Embase using Medical Subject Headings and keyword search terms and reference lists of retrieved articles were searched from 1999 until August 2019. We collected data on the country; region; methods of case assessment and aquaporin-4 antibody (AQP4-Ab) test; study period; limitations; incidence (per 100,000 person-years); prevalence (per 100,000 persons); and age-, sex-, and ethnic group–specific incidence or prevalence.

Results

We identified 33 relevant articles. The results indicated the highest estimates of incidence and prevalence of NMOSD in Afro-Caribbean region (0.73/100 000 person-years [95% CI: 0.45–1.01] and 10/100 000 persons [95% CI: 6.8–13.2]). The lowest incidence and prevalence of NMOSD were found in Australia and New Zealand (0.037/100 000 person-years [95% CI: 0.036–0.038] and 0.7/100,000 persons [95% CI: 0.66–0.74]). There was prominent female predominance in adults and the AQP4-Ab–seropositive subpopulation. The incidence and prevalence peaked in middle-aged adults. African ethnicity had the highest incidence and prevalence of NMOSD, whereas White ethnicity had the lowest. No remarkable trend of incidence was described over time.

Conclusion

NMOSD is a rare disease worldwide. Variations in prevalence and incidence have been described among different geographic areas and ethnicities. These are only partially explained by different study methods and NMO/NMOSD definitions, highlighting the need for specifically designed epidemiologic studies to identify genetic effects and etiologic factors.

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Glossary

AQP4-Ab = aquaporin-4 antibody; **CBA** = cell-based assay; **IPND** = International Panel for NMO Diagnosis; **NMO** = neuromyelitis optica; **NMOSD** = neuromyelitis optica spectrum disorder; **MOG** = myelin oligodendrocyte glycoprotein; **ON** = optic neuritis; **TM** = transverse myelitis.

Neuromyelitis optica (NMO) is an antibody-mediated inflammatory disease of the CNS. The understanding of the disease has evolved extensively through the last 100–125 years.[1] In 2005, the discovery of specific antibodies against the aquaporin-4 (AQP4) water channel in patients with NMO enabled the distinction of NMO from MS and resulted in the 2006 Wingerchuk criteria.[2,3] The introduction of the cell-based assay (CBA) to search for AQP4 antibody (AQP4-Ab) and improvements of test sensitivity allowed the recognition of additional syndromes associated with AQP4-Ab named as neuromyelitis optica spectrum disorders (NMOSDs).[4] The 2015 International Panel for NMO Diagnosis (IPND) criteria united the NMO and NMOSD definitions, proposed a categorization by stratifying for AQP4-Ab serostatus, and recommend the use of CBA owing to highest sensitivity (76.7%) and specificity (99.8%).[1]

The cause of the disease is not fully understood.[5,6] Well-established epidemiologic studies can generate hypotheses and thereby contribute to the identification of potential risk factors and essential features of disease etiology.

The last review of the incidence and prevalence of NMO/NMOSD was published in 2015, when 7 population-based studies were available.[7] Since then, 22 additional epidemiologic studies have been published using also the 2015 criteria, and these may improve our understanding of the NMOSD epidemiology. Here, we provide a critical overview of studies reporting the incidence and prevalence of NMO/NMOSD from around the world and discuss the challenges of such epidemiologic studies.

Methods

We performed a systematic search in PubMed, Ovid MEDLINE, and Embase databases for epidemiologic studies in NMO/NMOSD published from 1999 to August 2019 (figure, supplementary file, doi.org/10.5061/dryad.prr4xgxh9). Two authors (V.P. and Z.I.) independently assessed whether the identified abstracts met the inclusion criteria: (1) NMO/NMOSD; (2) original data; (3) incidence or prevalence of NMO/NMOSD; and (4) available English abstract. Furthermore, we searched the reference lists of review articles and the relevant publications for additional studies. If either reviewer selected an abstract, it underwent independent full-text review by the 2 reviewers. Disagreements were resolved by consensus. We excluded review articles, conference proceedings, and abstracts due to limited data on study design for critical review.

We collected data on the country, region, size of source population, case ascertainment, applied diagnostic criteria and antibody test method, observation period of incidence, definition of incident event, limitations, incidence (100,000 person-years), prevalence (100,000 persons) and age-, sex-, or ethnic group–specific incidence or prevalence, and basic demographic data (tables 1–6, supplementary tables 1–3, doi.org/10.5061/dryad.prr4xgxh9). The review follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Results

Search Strategy

From PubMed, Ovid MEDLINE, and Embase, we identified 664 unique references (figure). We selected 51 articles for full-text review based on relevant abstracts. Of these, we excluded 1 for not including original data and 17 for not providing the incidence and/or prevalence estimates of NMO/NMOSD. Ultimately, 33 articles met the inclusion criteria.

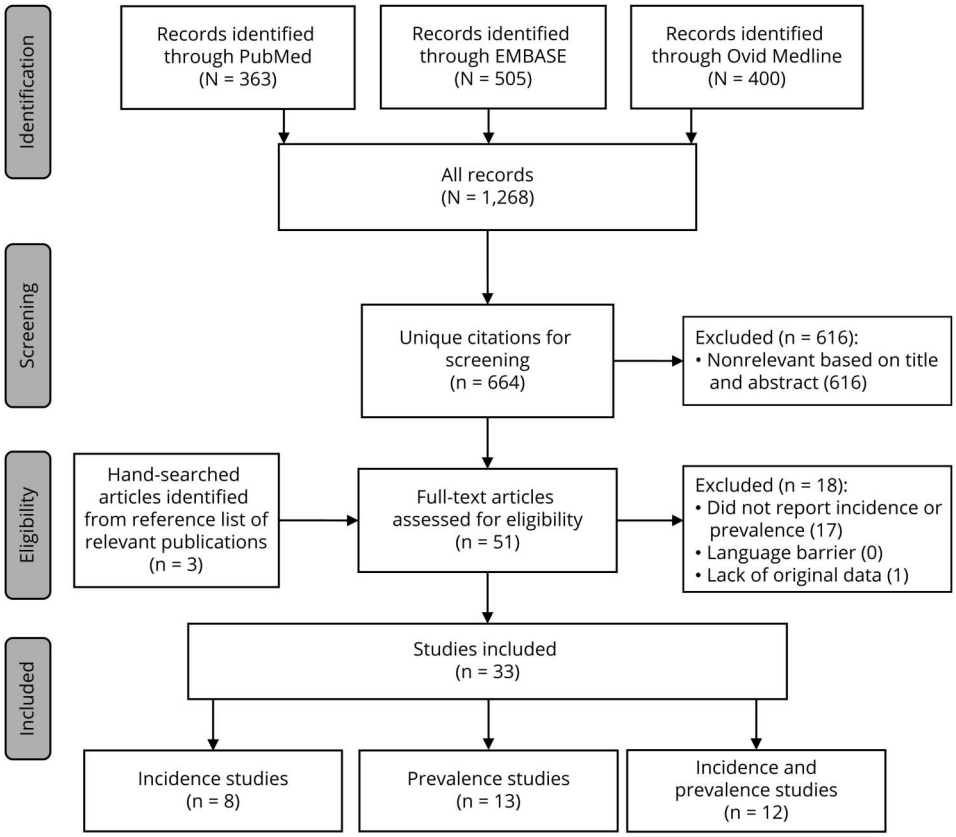
Study Characteristics

The number of epidemiologic data of NMO/NMOSD has remained low. All studies are retrospective (tables 1, 2, and 4). The timing of the study may influence the prevalence and incidence estimates due to several changes in the definition of NMO and NMOSD diagnostic criteria and antibody test method in the last decades.[1,3,4,8,9] Diversity can also be seen in population sample size (varying from 145,979[10] to 130 million[11]), study design (cohort study[10,12–31] or cross-sectional study[11,32–41]; clinical-based[10,12–16,18,19,31,32,37–39,42] or survey study[11,17,22,35,41]), case ascertainment (accepting the reported cases[20,27,34] or validating each NMO/NMOSD case[10,12–17,19,21,23,24,26,28–33,35–38,40,42]), final number of cases calculate by statistical analysis,[11,18,22,41] and AQP4-Ab test (IF-tissue assay, immunoprecipitation, ELISA, and CBA (tables 1, 2, and 4). The overall number of samples tested for AQP4-Ab was reported in 5 studies (supplementary table 3, doi.org/10.5061/dryad.prr4xgxh9).

Four nationwide studies involved solely pediatric populations,[28–30,41] and 3 of these investigated the epidemiology of acquired demyelinating syndromes, not specifically NMO/NMOSD.[28,29,41] Three studies applied the 2006 criteria to calculate the prevalence[41] or incidence[28,29] of NMO, and 1 used the 2015 IPND criteria for incidence assessment.[30] Five studies selectively evaluated the adult population.[12,15,17,22,23,31] The majority of the reports encompassed all ages,[10,11,13,14,16,18–21,24,26,27,32,33,35–38,40] but some did not recognize any patients with pediatric disease onset (tables 1–4).[19,33,37]

Thirteen of the 33 included studies provided inadequate descriptions of study design, case assessment, or type of

Figure The Flowchart Demonstrates the Steps of the Literature Search



AQP4-Ab test.[7,11,20–22,27–29,32,34–36,41] Many studies used multiple sources for case detection (clinical departments, registries, and/or laboratory databases),[10,12–18,24,26,29–32] whereas others used data directly from clinical departments, physicians,[11,19,21–23,27,28,33–42] or laboratory units.[20] Confidence intervals were not always presented.[11,19–21,28,33,42] Standardized estimates are essential when comparing findings in populations with different age and sex distributions, but these were rarely provided. One study applied the US standard population,[10] 1 used the Japanese standard population,[38] and 4 others the WHO standard population.[14,16,18,31]

Some prevalence and incidence estimates were obtained before the discovery of the AQP4-Ab and were solely based on the diagnostic criteria from 1999 restricted to optic neuritis (ON) and transverse myelitis (TM).[26,40] Two other studies applied the 1999 criteria if the AQP4-Ab test was not available, but the 2006 criteria when the AQP4-Ab test was performed.[24,25] Eleven studies purely used the 2006 criteria,[14,15,19,23,27–29,34,38,39,41] 8 other studies reported estimates based on the 2006 criteria combined with other AQP4-Ab–seropositive (AQP4-Ab+) cases,[10–12,16,17,32,33,36] and 10 other studies calculated estimates by applying the 2015 IPND criteria.[14,15,18,19,21,22,30,31,35,37,38] Two studies included only AQP4-Ab+ patients with NMO/NMOSD.[13,20] Another used the 2015 IPND criteria for unknown or AQP4-Ab–seronegative (AQP4-Ab–) NMOSD due to lack of access to AQP4-Ab test.[42]

Incidence

Considerable variation was observed in the definition of the incident event and the duration of the observation period for incidence. Most studies considered incident cases based on the disease onset,[10,13–16,18,19,28,30,31] but a few calculated incidence by the diagnosis date,[17,27,43] date of AQP4-Ab test,[20] or calculated by using the point prevalence and the average disease duration to prevalence day.[26] Other studies did not define incident event.[21–24,29,41] We identified 20 reports regarding the incidence of NMO/NMOSD (tables 1–4, supplementary tables 1 and 2, doi.org/10.5061/dryad.prr4xgxh9). The observation period for the incidence rate ranged from 2 to 27 years.[16,19] These may lead to remarkable differences in the incidence estimates. Incidence rates were reported between 0.039 and 0.73/100,000 person-years for adults[10,18] and between 0.01 and 0.06/100,000 person-years for children[21,28,29] (age <18 years).

Geography and Ethnicity: Incidence

The geographic distribution of the studies is demonstrated in tables 1–4. Most studies were conducted in Europe with predominantly White populations.

Table 1 Study Design and Completeness of the Epidemiologic Studies Including Adults in Predominantly White Populations

Country—study area (year)	No. of cases cohort/ prevalent/ incident	Source	Source population	Incident cases	Criteria	Included as NMO/NMOSD	AQP4-Ab test	Validated patient
Austria—nationwide (2011)[13]	71/62/17	Neurology departments; all registered neurologists; laboratory	Reported by clinicians and laboratory	Disease onset	Only AQP4-Ab+ NMO/ NMOSD	Only AQP4-Ab+ NMO/NMOSD	CBA	NS
United Kingdom—South East Wales (2012)[32]	14/14/-	Registry; laboratory; neurologists; neurology department	Screened a broad population	—	2006, AQP4-Ab+ ON/LETM	NMO, AQP4-Ab+ ON or LETM	NS	Yes
United Kingdom—Northwest England (2013)[12]	13/8/7	WCNN records; regional hospitals; laboratory; BNSU	Screened a broad population	NS	2006, AQP4-Ab+ ON/LETM	NMO, AQP4-Ab+ ON or LETM	CBA	Yes
Netherlands—nationwide (2016)[20]	94/-/89	Laboratory	Reported by the laboratory	NS	NS	AQP4-Ab+ NMOSD	CBA	No
Spain—Catalonia (2018)[14]	74/67/47	Neurology departments with MS unit; NPR (NMO diagnosis); laboratory	Only NMO diagnosis and AQP4-Ab+ from the laboratory, reported by clinicians	Disease onset	2006, 2015	2015	CBA (96%), IHC (3%), ELISA (1%)	Yes
Denmark—Southern Denmark (2011)[17]	42/NS/NS	Natalizumab registry; DNPR (ON, TM, and MS; NMO); regional neurology and ophthalmology departments	Screened a broad population	Date of diagnosis	2006, AQP4-Ab+ ON/LETM	NMO, AQP4-Ab+ ON, LETM, autoimmune diseases related to NMOSD	CBA, IP	Yes
Denmark—Central Denmark (2018)[19]	5/-/3	Neurology departments (IDD) data set	Screened a broad population	Disease onset	2006, 2015	2015	ELISA, CBA	Yes
Denmark—nationwide (2018)[15]	56/50/27	NPR; MS Registry; neurology departments; laboratories	Screened a broad population	Disease onset	2006, 2015	2015	79.5% CBA, 13.7% IP, 6.8% ELISA	Yes
Sweden—nationwide (2019)[16]	92/89/82	NPR and laboratory	Only NMO diagnosis and AQP4-Ab+ from the laboratory	Disease onset	2006, AQP4-Ab+ ON/LETM	NMO, AQP4-Ab+ NMOSD	Before 2012 IB, later CBA	Yes
Hungary (2/3) (2020)[31]	154/123/101	NPR; neurology departments; laboratories	Screened a broad population	Disease onset	2015	2015	100% CBA	Yes
Australia and New Zealand—nationwide (2017)[18]	149/147/27	Adult and pediatric neurology departments; laboratory	Reported by clinicians and seropositive from the laboratory	Disease onset	2015	2015	CBA (46%), IF-tissue (100%)	Yes
United States—Olmsted County (2016)[10]	6/6/1	Registries; neurology department; neurologists (all patients with IDD)	Screened a broad population	Disease onset	2006, AQP4-Ab+ NMOSD	NMO; AQP4-Ab+ NMOSD with single or recurrent TM, single or recurrent ON, brainstem or cerebral attack	CBA	Yes

Abbreviations: AQP4-Ab+ = AQP4 antibody positive; BNSU = British Neurologic Surveillance Unit, BS = brainstem; CBA = cell-based assay; CIS = clinically isolated syndrome; IB = immunoblot; IDD = idiopathic demyelinating disease; IP = immunoprecipitation; LETM = longitudinally extensive; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; NPR = National Patient Registry; NS = not specified; ON = optic neuritis; TM = transverse myelitis.

Table 2 Study Design and Completeness of the Epidemiologic Studies Including Adults in Predominantly Non-White Populations

Country—study area (year)	No. of cases cohort/ prevalent/ incident	Source	Source population	Incident cases	Criteria	Included as NMO/ NMOSD	AQP4-Ab test	Validated patient
Canada—British Columbia (2015)[27]	31/-/31	Hospital data set	Only NMO	Date of diagnosis	2006	NS	NS	No
India—Mangalore (2014)[33]	11/-/11	Different specialists; department	Reported by clinician	—	2006, AQP4-Ab+ ON/ LETM	ON, ADEM, CIS, TM, spastic paraplegia, and myelopathy	NS	Yes
Japan—Tokachi (2012)[39]	3/3/-	Single: 14 MS- and NMOSD-related institutions inside and outside this area	Reported by clinicians	—	2006	NMO 2006	CBA	No
Japan—Tokachi (2017)[38]	14/14/-	Single: 14 MS- and NMOSD-related institutions inside and outside this area	Reported by clinicians	—	2006, 2015	2015	CBA	Yes
Japan—nationwide (2018)[11]	4,377 (1,042)	Departments based on random selection using a stratified sampling method	Reported by clinicians	—	2006, AQP4-Ab+ NMOSD	NMO, AQP4-Ab+ NMOSD	NS	No
Malaysia—Penang Island (2018)[37]	28/14/-	Hospital databases; private neurologists	Reported by clinicians	—	2015	2015	CBA	Yes
Malaysia—nationwide (2019)[22]	580/580/NS	Hospitals	Reported by clinicians	NS	2015	2015	NS	Yes
UAE—Abu Dhabi (2018)[21]	10/10/8	Department databases	Screened a broad population	NS	2015	2015	NS	Yes
Iran—Isfahan (2014)[34]	95/95/-	Hospital database	Only NMO reported in the database	—	2006	NS	NS	NS
Iran—Southwest (2015)[36]	51/51/-	Neurology departments; MS clinic; neurologists	Screened a broad population	—	2006, NMOSD	NMO/NMOSDs: ≥1: ON; LETM; rec. BS; rec. hypothalamus attack; rec. cerebral attack; plus ≥1: AQP4-Ab+; MRI typical of NMO	NS	Yes
Iran—Tehran (2017)[35]	103/103/-	Department	Reported by clinicians	—	2015	NS	ELISA (9 patients unreported)	Yes
Kazakhstan—Semej town (2019)[42]	10	Department	Reported by clinicians	—	2015	Criteria for the unknown/negative status of AQP4-Ab	Not tested	Yes
Mexico—Mexico City (2008)[40]	34/NS/-	Hospital case records	Suspected MS and NMO	—	1999	According to 1999	Not tested	Yes
Cuba—nationwide (2009)[26]	58/58/NS	All neurologic, rehabilitation, pediatric, ophthalmologic department; neurologists; GP; National Clinical Trial of Interferon-2b in RRMS (1993–2003); Cuban Record of MS; Cuban MS Society and the National Association of Persons with MS	Screened a broad population	Prevalence rates and the disease durations to prevalence day	1999	According to 1999 and spectrum disorders of NMO: those with rec. LETM and severe rec. ON	Not tested	Yes

Continued

Table 2 Study Design and Completeness of the Epidemiologic Studies Including Adults in Predominantly Non-White Populations *(continued)*

Country—study area (year)	No. of cases cohort/ prevalent/ incident	Source	Source population	Incident cases	Criteria	Included as NMO/ NMOSD	AQP4-Ab test	Validated patient
France—Martinique and Guadeloupe (2009) [24,25]	48/48/20	Hospital-based, clinic-based neurology, ophthalmology, rehabilitation services; departmental health insurance data, MS patient associations	Reported by the clinicians	NS	1999 or 2006	In the absence of AQP4-Ab assay: 1999 criteria or Wingerchuk 2006 for the patients who were tested for AQP4	Not tested	Yes
France—Martinique (2016) [10]	39/39/27	Hospital-based, clinic-based neurology, ophthalmology, rehabilitation services; departmental health insurance; MS patient associations	Screened a broad population	Disease onset	2006, AQP4-Ab+ NMOSD	NMO, NMOSD (AQP4-Ab+ and single or rec. TM, single or rec. ON, BS, or cerebral attack)	CBA	Yes
Costa Rica (2018) [23]	40	Hospitals	Screened a broad population	NS	2006	2006	ELISA (17 not tested)	Yes

Abbreviations: ADEM = acute disseminated encephalomyelitis; AQP4-Ab+ = AQP4 antibody positive; BS = brainstem; CBA = cell-based assay; CIS = clinically isolated syndrome; FP = full population; IB = immunoblot; IDD = idiopathic demyelinating disease; IP = immunoprecipitation; LETM = longitudinally extensive; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; NPR = National Patient Registry; NS = not specified; ON = optic neuritis; rec = recurrent; TM = transverse myelitis; UAE = United Arab Emirates.

In smaller, predominantly White cohorts, the incidence of NMO/NMOSD was between 0.07 and 0.4/100,000 person-years.[10,12,17,19] In larger White studies applying the 2006 criteria, the incidence was between 0.029 and 0.04/100,000 person-years.[14,15] When including only AQP4-Ab+ NMOSD, the incidence ranged from 0.054 to 0.08/100,000 person-years.[13,20] NMO and AQP4-Ab+ NMOSD together gave an incidence of 0.079/100,000 person-years,[16] whereas based on the last NMOSD 2015 criteria, it ranged from 0.037 to 0.132/100,000 person-years.[14,15,18,31]

Only a few incidence estimates are available from other ethnicities: in Caribbean-African 0.22–0.4/100,000 person-years (1999/2006 criteria)[24] and 0.7/100,000 person-years (2006 criteria plus AQP4-Ab+ NMOSD),[10] in selected Asian populations 0.39–0.6/100,000 person-years (2015 IPND criteria),[22,27] and in Arab populations 0.17/100,000 person-years (2015 IPND criteria).[21] The Dutch study described a higher incidence among non-White compared with White populations living in the same geographic area.[20]

Four studies from White[14,28–30] (0.01–0.06/100,000 person-years) pediatric populations and 1 from an Arab[21] (0.06/100,000 person-years) pediatric population reported incidence estimates of NMO/NMOSD. Three of these were based on a single incident case observed in a period of 7–19 years (table 4).[21,28,29]

Sex- and Age-Related Incidence

The sex-specified incidence rates were higher in females than in males, although the difference was less remarkable or disappeared at extremes of age (supplementary tables 1 and 2, doi.org/10.5061/dryad.prr4xgxh9).[10,14,15,24,28–31] Of interest, in Sweden, over the period 1987–2006, the incidence of NMOSD in males (0.151/100,000 person-years [95% CI: 0.085–0.261]) was more than 2 times higher compared with females (0.067/100,000 person-years [95% CI: 0.044–0.098]), whereas between 2007 and 2013, the incidence of NMOSD in females (0.150/100,000 person-years [95% CI: 0.108–0.203]) was more than 2 times greater compared with males (0.066/100,000 person-years [95% CI: 0.032–0.123]).[16] The highest incidence rates in both sexes were found in the 40–59 year age group.[14,31] Incidence studies showed that 20%–28% of the incidence cohorts had a late-onset NMOSD (age ≥ 60 years).[14,31]

The pediatric cohort of Iceland[28] and Denmark[29] (age ≤18 years) identified a single male case in each country, whereas the very recent Danish study[30] (age ≤18 years) found 2 male and 2 female cases. The Catalonia study[14] reported 3 female and 2 male pediatric patients.

Serostatus and Incidence

Only 4 publications described the serostatus-specific incidence.[10,14,15,31] These found a higher incidence of AQP4-Ab+ NMOSD compared with AQP4-Ab− patients. In the United States, the incidence of AQP4-Ab+ NMOSD was 0.07/100,000 person-years (95% CI: 0.0–0.21) based on a single case, whereas no AQP4-Ab− incident cases were identified. The same study

Table 3 The Incidence and Prevalence of NMO/NMOSD in Epidemiology Studies (Incidence:/100,000 Person-Years, Prevalence:/100,000 Persons)

Country	Population (million)	Period of incidence (Prevalence day)	Incidence (CI)	Prevalence (CI)	Prevalence according to ethnicity (CI)	Sex-specific prevalence (CI)	Sex-specific incidence (CI)
Austria[13]	8.4 (FP)	March 2008–December 2011 (Dec 2011)	0.054 (0.01–0.31)	0.7 (0.17–0.96)	ND	ND	ND
United Kingdom—South East Wales[32]	0.713 (FP)	(May 1, 2010)	ND	1.96 (1.22–2.97)	ND	ND	ND
United Kingdom—Northwest England[12]	1.14 (age >16 y)	2003–2010 (December 30, 2010)	0.08 (0.03–0.16)	0.72 (0.31–1.42)	White: 0.66 (0.27–1.37); Non-White: 1.8 (0.05–10.04)	ND	ND
Netherlands[20]	16.6 (FP)	May 2009–April 2015	0.09 (NS); White: 0.08; Non-White: 0.19	ND	ND	ND	ND
Spain—Catalonia[14]	7.52 (FP)	2006–2015 (January 1, 2016)	2006: 0.040 (0.026–0.055); 2015: 0.063 (0.045–0.081)	2006: 0.58 (0.57–0.60); 2015: 0.89 (0.87–0.91)	ND	F: 1.31 (1.27–0.34); M: 0.46 (0.44–0.48)	F: 0.09 (0.060–0.121); M: 0.035 (0.016–0.054)
Denmark—Southern Denmark[17]	0.952 (age ≥15 y)	1998–2008 (NS)	0.4 (0.3–0.54)	4.4 (3.1–5.7)	ND	ND	ND
Denmark—Central Denmark[19]	1.27 (FP)	2012–2013	2006: 0.08 (NS); 2015: 0.12 (NS)	ND	ND	ND	ND
Denmark—nationwide[15]	4.6 (age ≥16 y)	2007–2013 (January 1, 2014)	2006: 0.029 (0.014–0.051); 2015: 0.070 (0.046–0.102)	2006: 0.566 (0.370–0.830); 2015: 1.09 (0.81–1.44)	White 1.007 (0.732–1.35); Asian: 2.47 (0.674–6.33)	F: 1.76 (1.26–2.39); M: 0.40 (0.18–0.76)	F: 0.104 (0.063–0.16); M: 0.037 (0.015–0.075)
Sweden[16]	9.6 (FP)	2007–2013 (December 31, 2013)	0.079 (0.055–0.103)	1.04 (0.85–1.26)	ND	ND	Extensive data are reported
Hungary (2/3)[31]	6.4 (age ≥16 y)	2006–2015 (January 1, 2016)	0.132 (0.108–0.161)	1.91 (1.52–2.28)	ND	F: 3.22 (2.65–3.89); M: 0.47 (0.25–0.78)	F: 0.22 (0.178–0.27); M: 0.04 (0.02–0.06)
Australia and New Zealand[18]	27.67 (FP)	2009–2012 (July 1, 2013)	0.037 (0.036–0.038)	0.7 (0.66–0.74)	Asian: 1.57 (1.15–1.98); Other: 0.57 (0.50–0.65)	ND	ND
United States—Olmsted County[10]	0.146 (FP)	2003–2011 (December 31, 2011)	0.07 (0.00–0.21)[a]	3.9 (0.8–7.1)[a]	White (5): 4.0 (0.5–7.5); Black (1): 13.0 (0.0–38.4)	F: 6.5 (0.8–12.1); M: 1.4 (0.0–4.1)	F: 0.14 (0.0–0.43); M: 0
Canada—British Columbia[27]	Only Asian: 0.54	1986–2010	0.39 to 0.6	ND	—	Extensive data are reported	ND
India—Mangalore[33]	0.419 (FP)	(2013)	ND	2.6 (NS)	ND	ND	ND
Japan—Tokachi[39]	0.352 (FP)	(March 31, 2011)	ND	0.9 (0.2–2.5)	ND	ND	ND

Continued

Table 3 The Incidence and Prevalence of NMO/NMOSD in Epidemiology Studies (Incidence:/100,000 Person-Years, Prevalence:/100,000 Persons) *(continued)*

Country	Population (million)	Period of incidence (Prevalence day)	Incidence (CI)	Prevalence (CI)	Prevalence according to ethnicity (CI)	Sex-specific prevalence (CI)	Sex-specific incidence (CI)
Japan—Tokachi[38]	0.344 (FP)	(March 31, 2016)	ND	2006: 2.1 (NS); 2015: 4.1 (2.2–6.9)	ND	ND	ND
Japan—nationwide[11]	130 (FP)	(2011)	ND	NMO: 1.64 (NS); NMO/NMOSD: 3.42 (NS)	ND	ND	ND
Malaysia—Penang Island[37]	0.702 (FP)	(July 1, 2017)	ND	1.99 (1.09–3.35)	Chinese: 3.31 (1.76–5.67); Malays: 0.43 (0.01–2.38)	ND	ND
Malaysia—nationwide[22]	28.7 (age >12 y)	2013–2017 (December 29, 2017)	0.39 (0.35–0.47)	1.94 (1.77–2.10)	Wrong denominators were applied!	ND	ND
UAE—Abu Dhabi[21]	2.9 (FP); UAE: 0.55 adult UAE (>20): 0.26	2010–2016 *(NS)*	FP: 0.05 (NS); UAE adult (>20): 0.17 (NS)	FP: 0.34 (NS)	UAE adult (>20): 1.76 (NS)	ND	ND
Iran—Isfahan[34]	NS	(October 10, 2013)	ND	1.9 (1.6–2.3)	ND	F: 2.7 (2–3.3); M: 1.2 (0.8–1.6)	ND
Iran—Southwest Iran[36]	4.5 (FP)	(November 2013)	ND	1.1 (1.04–1.16)	ND	F: 2.00 (1.92–2.09); M: 0.26 (0.23–0.29)	ND
Iran—Tehran[35]	11.9 (FP)	(NS)	ND	0.86 (0.76–0.91)	ND	F: 1.35 (NS); M: 0.26 (NS)	ND
Kazakhstan—Semej town[42]	0.35	(NS)	ND	4.9 (NS)	ND	ND	ND
Mexico—Mexico City[40]	18.4 (FP)	(NS)	ND	1.3 (0.9–1.8)	ND	ND	ND
Cuba[26]	11.18 (FP)	2003–2004 (November 30, 2004)	0.053 (0.040–0.068)	0.52 (0.39–0.67)	White: 0.43 (0.29–0.61); Non-White: 0.69 (0.46–1.01)	F: 0.91 (0.68–1.20); M: 0.12 (0.05–0.25)	ND
France—Martinique and Guadeloupe[24,25]	0.705 (FP)	1992–2007 (June 30, 2007)	0.19 (0.15–0.23)	4.2 (3.7–5.7)	ND	F: 7.14 (4.45–9.83)	F: 1992–97: 0.42 (0.11–0.73); 1997-2002: 0.28 (0.03–0.53); 2002-07: 0.32 (0.06–0.58)
France—Martinique[10]	0.392 (FP)	2003–2011 (December 31, 2011)	0.73 (0.45–1.01)[a]	10 (6.8–13.2)[a]	White: 6.1 (0.0–18.1); Black: 11.5 (7.8–15.2)	F: 17.4 (11.6–23.3); M: 2.5 (0.0–4.9)	F: 1.31 (0.79–1.83); M: 0.12 (0.00–0.30)
Costa Rica[23]	3.88 (age>13 y)	August 2011–December 2015	0.13–0.44 (NS)	ND	ND	ND	ND

Abbreviations: F = Female; FP = full population; M = male; NS = not specified; ND = not done; UAE = The United Arab Emirates.
[a] Only age-standardized estimates were reported.

determined the estimates in Martinique and showed a 5 times higher incidence of AQP4-Ab+NMOSD (0.65/100,000 person-years [95% CI: 0.39–0.92]) in comparison with AQP4-Ab-NMOSD.[10] In Catalonia, AQP4-Ab+ incidence increased from 0.015/100,000 person-years (95% CI: −0.002 to 0.004) in the pediatric population to 0.062/100,000 person-years (95% CI: 0.028–0.096) in adults, whereas the incidence of AQP4-Ab-NMOSD was low in all age groups (ranging from 0.006 to 0.029/100,000 person-years) but similar to seropositive incidence in children.[14] In Denmark, the incidence of AQP4-Ab+ patients was 2-fold higher compared with AQP4-Ab− NMOSD,[15] whereas the Hungarian study revealed 5-fold greater incidence estimates of the AQP4-Ab+ NMOSD.[31]

Temporal Changes in Incidence

Some studies reported the annualized incident rate over longer time periods, where temporal changes could be evaluated (supplementary table 1, doi.org/10.5061/dryad.prr4xgxh9). Studies from the French West Indies covering time periods 1992–1997, 1997–2002, and 2002–2007 and from British Columbia covering the period 1986–2010 showed stable incidence.[25,27] Studies with shorter observational periods published from the Netherlands (6 years),[20] Abu Dhabi (7 years),[21] Denmark (7 years; not published data),[15] Catalonia (10 years),[14] and Hungary (10 years; not published data)[31] revealed no temporal changes in the annualized incidence rates. In contrast to this, the Swedish study found an increasing incidence in females from 0.07/100,000 person-years (95% CI: 0.04–0.09) between 1987 and 2006 to 0.15/100,000 person-years (95% CI: 0.11–0.20) between 2007 and 2013.[16] In Costa Rica, an increase from 0.13 to 0.44 was reported between 2011 and 2015.[23]

Prevalence

We recognized 25 articles presenting prevalence estimates ranging from 0.34 to 10/100,000 in adults and from 0.06 to 0.22/100,000 in children (tables 1–3, supplementary tables 1 and 2, doi.org/10.5061/dryad.prr4xgxh9). The number of prevalent cases ranged from 6 to 4,377 in adults[10,11] and from 3 to 11 in children.[14,41] The census date for prevalence was not reported in 7 publications.[11,17,21,33,35,40,42]

Geography and Ethnicity: Prevalence

The geographic distribution of prevalent studies is presented in tables 1–4. In smaller studies with predominantly White populations, the prevalence varied from 0.72 to 4.4 to/100,000, including patients with NMO based on the 2006 criteria and AQP4-Ab–positive NMOSD.[10,12,17,32] In larger populations, it spanned from 0.57 to 0.58/100,000 based on the 2006 criteria[14,15]; 1.04/100,000 counting NMO and AQP4-Ab+ cases[16]; 0.7/100,000 involving only AQP4-Ab+ patients[13]; and from 0.7 to 1.91 using the 2015 IPND criteria.[14,15,18,31,34–36]

Seven reports from predominantly Asian populations revealed a prevalence between 1.57 and 4.9/100,000.[22,33,37–39,41,42] Similar to incidence data, the highest prevalence was found in African populations: 10/100,000[10] and 4.2/100,000[24] before the era of AQP4-Ab detection. The prevalence estimate of a single study from Arab countries demonstrated a prevalence of 1.76/100,000 in adults.[21]

A few studies provided head-to-head comparison of the prevalence of NMOSD in different ethnicities living in the same geographic area under similar environmental White ancestry.[10,12,15,18,22,26,37] They found that Asian and African ancestries have a higher risk to develop NMO/NMOSD than White ancestry.[10,12,15,18] Furthermore, within Asian ethnicities, a higher prevalence was found among Chinese compared with Malays.[37] When recalculating the prevalence rates of the nationwide Malaysian study based on their presented row data, similar difference can be seen between Chinese and Malay ethnicities.[22]

Sex- and Age-Related Prevalence

All studies that calculated the sex-specific estimates found the highest prevalence among females, which was 2.3–7.6-times greater than for males, both in Whites and Africans (table 3).[10,14,15,26,31,34–36] Prevalence curves by age had a peak from 30 to 39 in India and between 40 and 59 years for both sexes in Catalonia and Hungary.[14,31] For females in Australia and New Zealand,[18] in Tehran and Cuba,[26,35] the peak prevalence age was between 40 and 49 years and between 45 and 55 years in the French Indies (supplementary table 1, doi.org/10.5061/dryad.prr4xgxh9).[24]

Data are scarce in pediatric populations (table 4). The only 2 studies providing sex-specific prevalence in children reported 1.5 to 2 times higher prevalence for females.[14,35]

Serostatus and Prevalence

The prevalence of AQP4-Ab+ NMOSD was greater in the 5 studies reporting serostatus-specific data and indicated a seropositive to seronegative ratio of 2.3:1 in Denmark,[15] 3.4:1 in Japan,[38] 3.8:1 in Martinique,[10] 5:1 in the United States,[10] and 5.2:1 in Hungary.[31] However, this ratio depends also on applied criteria and definition of AQP4-Ab− cases. The serostatus-specific prevalence by age showed higher frequency of AQP4-Ab− NMOSD in children.[14]

Temporal Changes in Prevalence

Two studies from Japan evaluated the same geographic area of Tokachi province over approximately 5-year intervals and showed an increasing prevalence, but different methodological approaches and NMO/NMOSD criteria may also account for this change.[38,39] In 2011, the research group primarily aimed to evaluate MS epidemiology, but also identified patients with NMO using 2006 criteria and calculated NMO prevalence showing 0.9/100,000 (95% CI: 0.2–2.5).[39] In contrast, the surveillance in 2016 was dedicated to NMO/NMOSD and used both 2006 and 2015 criteria: a considerably higher prevalence was found (2006 criteria: 2.1/100,000; 2015 IPND criteria: 4.1/100,000 [95% CI: 2.2–6.9]).[38] An increased prevalence was observed in the French Indies from 1.88/100,000 (95% CI: 0.82–2.94) in 1992 to 4.20/100,000 (95% CI: 2.70–5.70) in 2007, but this was explained by a decrease in mortality.[24] To date, no study evaluated at the population level over a long period of time mortality in NMOSD.

Table 4 Studies Reporting on the Epidemiology of NMO/NMOSD in Pediatric Populations

Country	Japan[41]	Iceland[28]	Denmark[29]	Denmark[30]	Spain[14]	Iran[35]	The United Arab Emirates[21]
Published (year)	2016	2015	2018	2019	2018	2017	2018
Study area	Nationwide	Nationwide	Nationwide	Nationwide	Catalonia	Tehran	Abu Dhabi
Population (million)	17.5	NS	1.8	1.8	NS	3.02	NS
Age group (y)	≤15	≤18	<18	<18	0–17	0–19	<20
NMOSD cases/ prevalent/incident	14/11/-	1/-/1	1/-/1	4/-/4	NS/3/5	NS/5/-	NS/-/1
Source	Pediatric departments of hospitals (randomly selected hospitals according to stratification)	Hospital	NPR, MS, and hospital	Register, laboratory, and hospital	Members of organizations, neurology department with MS unit, national patient registry (NMO diagnosis), and laboratory	Reported by clinician	Department
Source population	Screened a bigger population	Screened a bigger population	Screened a bigger population	Screened a bigger population	Only NMO diagnosis and seropositive cases from the laboratory or reported by clinicians	NS	Screened a bigger population
Definition of incident cases	—	Disease onset	Disease onset	Disease onset	Disease onset	—	NS
Criteria	2006	2006	2006	2015	2015	2015	2015
Included as NMO/ NMOSD	According to 2006	According to 2006	According to 2006	According to 2015	According to 2015	NS	According to 2015
AQP4-Ab test	NS	NS	NS	CBA/ELISA	CBA	ELISA (not all tested)	NS
Incidence/100,000	ND	0.06 (NS)	0.01 (0.015–0.074)	0.031 (0.011–0.082)	0.037 (0.005–0.070)	ND	UAE (<19): 0.06 (NS)
Period of incidence rate	—	1990–2009	2008–2015	2008–2018	2006–2016	—	2010–2016
Prevalence/100,000	0.06 (0.04–0.08)	ND	ND	ND	0.22 (0.19–0.24)	0.16 (NS)	ND
Prevalence day	December 31, 2007	—	—	—	2016	NS	—
Prevalence according to ethnicity	NS	—	—	—	NS	NS	—
Age at onset (mean)	10.3	15–17 y	13.3	11.4	NS	NS	NS
Female	80%	0%	0%	NS	prev: 66%, inc: 60%	60%	100%
AQP4-Ab positive	NS	NS	NS	75%	prev: 33%, inc: 40%	NS	0%
Annual incidence rate/100,000	—	NS	NS	NS	NS	—	NS

Continued

Table 4 Studies Reporting on the Epidemiology of NMO/NMOSD in Pediatric Populations *(continued)*

Country	Japan[41]	Iceland[28]	Denmark[29]	Denmark[30]	Spain[14]	Iran[35]	The United Arab Emirates[21]
Sex-specific incidence/100,000	—	NS	Male: 0.020 (0.0029–0.145); Female: 0	Male: 0.030 (0.0075–0.12); Female: 0.031 (0.0078–0.13)	Male: 0.29 (−0.11 to 0.69); Female: 0.46 (−0.06 to 0.98)	—	NS
Sex-specific prevalence/100,000	NS	—	—	—	Male: 0.14 (0.11–0.17); Female: 0.30 (0.26–0.34)	Male: 0.12 (NS); Female: 0.20 (NS)	—
Serostatus-specific estimates/100,000	NS	NS	NS	NS	AQP4-IgG+: 0.15 (−0.06 to 0.36); AQP4-IgG−: 0.22 (−0.03 to 0.48)	NS	NS
Incidence tendency	—	NS	NS	NS	NS	—	NS

Abbreviations: AQP4-IgG+ = AQP4 antibody positive; AQP4-IgG− = AQP4 antibody negative; CBA = cell-based assay; inc = incidence; ND = not done; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; NPR = National Patient Registry; NS = not specified; MS = multiple sclerosis; prev = prevalence.

Demographic Data

The basic demographic data are summarized in table 4 and supplementary table 2, doi.org/10.5061/dryad.prr4xgxh9. The mean age at onset varied from 29.2[36] to 45.7 years,[13] whereas the median was between 30.5[21] and 43[11,26] years. The youngest age at onset was reported from Iran (mean age: 29.2–31.54 years).[34–36] The percentage of females in different epidemiologic cohorts ranged from 55% to 100%.[33,37,39] However, highest percentages of females ranging from 86% to 100% have been consistently found in populations from West Indies and Far East.[11,24,26,37–39,44] The percentage of AQP4-Ab seropositivity was between 27% and 100% (excluding studies only on AQP4-Ab+ cases and where AQP4-Ab was not tested).[33,37,39] The lowest percentage of AQP4-Ab seropositivity was reported in India,[33] followed by the 3 Iranian studies,[34–36] and the study from Southern Denmark.[17]

The mean follow-up was between 5.85 and 9.9 years,[26,40] and the median from 3.5 to 12.5 years.[10,32] The duration of follow-up was not mentioned in 11 publications.[12,13,17–21,23,24,27,37,39]

The majority of the patients had recurrent disease (71%–97.5%); only 1 study in Iran described monophasic disease in 60% of the cases, but they did not provide data about serostatus of these patients.[34] Progressive disease course was reported in 2 studies and was found between 0.2% and 0.6%.[22,31] The frequency of patients with NMO/NMOSD, who did not survive until the census day, ranged between 0% and 38.5% when reported.[10,12]

Discussion

This systematic review provides several observations: (1) NMO/NMOSD is a rare disease; (2) is reported worldwide in a variety of ethnic ancestry populations; (3) studies investigating the incidence and prevalence of NMOSD are diverse; (4) the number of well-designed epidemiologic studies of NMOSD is increasing; (5) there is a female and AQP4-Ab+ predominance; (6) incidence and prevalence estimates show a peak age in middle-aged adults; however, these are often distorted by incomplete capture (possibly premature death) of older cohorts, and (7) late-onset NMOSD (age ≥60 years) is responsible for one-fourth of the incidence cases. (8) Most of the results suggest that African ethnicity is associated with the highest incidence and prevalence, and White ethnicity may have the lowest. It seems that there has been no definite change in the incidence of NMO/NMOSD over time. Rare head-to-head comparative studies suggest a role of genetic factors in developing NMOSD. However, there is need for more well-designed (large source population with long observation period) studies to identify potentially concealed features of NMOSD epidemiology.

One factor that can contribute to the noticed variation could be the genetic mixture of the observed populations. This is supported by studies involving different ethnic groups living in the same geographic region, where environmental factors are considered comparable.[10,12,15,18,20,37,45] Epidemiologic

Table 5 Reported Limitations and Observed Considerations of the Epidemiologic Studies of NMO/NMOSD in Predominantly White Populations

Country	Limitations reported by the authors	Further potential limitation
Austria[13]	Only seropositive cases. Not checked for overlooked cases (previously not tested patients, severe case).	No further comment.
United Kingdom—South East Wales[32]	Not reported.	Short follow-up. Small population size.
United Kingdom—Northwest England[12]	Small sample size. Only adult, selection bias (ON might be underrepresented).	No further comment.
Netherlands[20]	"Mild cases and rare phenotypes could have been missed. Have not had clinical and imaging data of all included patients."	It was restricted to AQP4-Ab+ cases. Only a single source. CIs were not calculated. Prevalence was not calculated. Clinical and imaging data: not for all patients—no case validation.
Spain—Catalonia[14]	"CHSS registries started in 2011 the inclusion of primary care and specialized outpatients visits, and only those patients coded as NMO and Devic disease were revised.…could not rule out underrepresentation of cases prior to 2005 when AQP4-IgG testing was available and a selection bias toward more recently active cases. Not all IDD were reevaluated."	Narrow CIs.
Denmark—Southern Denmark[17,43]	"Lower number of MS from the departments than expected. Misclassification of cases the database, treatment influence, timing of the MRI." Asgari et al. 2019.: "Incidence rate was based on the diagnosis of NMOSD and not based on the disease onset."	Missing data were not described (17%); questionnaire was applied (recall bias). Different AQP4-IgG assays and 38% of seronegative cases.
Denmark—Central Denmark[19]	"There was insufficient information in medical records or incomplete diagnostic assessment in 50 cases. 36 cases of these patients had not been tested previously via their local departments. Two-year time span was relatively short."	CIs were not reported.
Denmark—nationwide[15]	"Did not review patients with area postrema syndrome, encephalitis, or unspecified demyelinating CNS disease. Patients in whom a severe first relapse led to death may have been lost if AQP4 measurement was not conducted at the onset. Different AQP4 test methods might influence our results."	No further comment.
Sweden[16]	"Retrospective design. The dependency on clinicians' diagnosis or suspicion of NMO/NMOSD. Did not have access to records from outpatient care that was not hospital-based. Some milder cases of NMOSD may have been missed."	Validated only on patients registered with NMO in the national patient registry (*ICD-10*: 36.0 or *ICD-9*: 9.34A) and patients with known AQP4 antibody seropositivity from a central laboratory—potential misclassification bias. The number of patients before the available AQP4 antibody test could be underestimated. Serostatus was not published. CBA available only since 2012.
Hungary (2/3)[31]	"We may have missed cases with severe onset, who died before the AQP4-antibody test could have been performed. We did not screen for all types of demyelinating disorder. Due to missing crucial data, we excluded 86 patients with a single episode of ON or TM, but none were reported as possible NMOSD. Missing cases with pediatric onset may slightly decrease."	No further comment.
Australia and New Zealand[18]	"Only a proportion of our suspected cases had testing for AQP4 antibodies with a cell-based assay. We have not tested every patient with demyelinating disease of the CNS for AQP4 antibodies. These limitations are, however, only likely to have a relatively small impact on the overall prevalence. Only currently or recently active cases who have been seen in clinics or undergone AQP4 antibody testing will have been identified."	Short period for incidence estimate.
United States—Olmsted County[10]	"Serum was not obtained from all potential cases. Underrepresentation of patients with area postrema and brainstem symptoms."	Very small sample size (2 patients died between the census date and subsequent follow-up).

Continued

Table 5 Reported Limitations and Observed Considerations of the Epidemiologic Studies of NMO/NMOSD in Predominantly White Populations *(continued)*

Country	Limitations reported by the authors	Further potential limitation
Pediatric studies		
Iceland[28]	Not reported.	Small sample size. No data on serostatus. No CIs were reported.
Denmark[29]	"Children with mild ON may not have been included"	The registry-based study was not focusing only on NMO. No search for overlooked cases. No data on AQP4-Ab test.
Denmark[30]	"(1) Children with incident NMOSD or anti-MOG-associated disease during 2016–18 not tested for AQP4 or MOG Abs and children tested for MOG or AQP4 Abs only at SSI during the first four months of 2018 were not included in the study. (2) We undertook blinded MRI review only in children with ADEM and not in children with other ADS phenotypes. (3) We validated the final ADS diagnoses using health records and radiological reports which were heterogeneous. (4) Serologic follow-up was not available from most children with ADS. (5) The use of different AQP4/MOG Ab testing methods may have influenced our results."	No further comment.

Abbreviations: ADS = Acquired demyelinating syndrome; ADEM = acute disseminated encephalomyelitis; AQP4-Ab = aquaporin-4 antibody; CBA = cell-based assay; CHSS = The Catalan Health Surveillance System; NMOSD = neuromyelitis optica spectrum disorder; MOG = myelin oligodendrocyte glycoprotein; ON = optic neuritis, SSI = Statens Serum Institute; TM: transverse myelitis.

studies and large case series have reached the same conclusion that individuals from Asian[15,18,33,37–39] and African[10,12,46] ancestries have a disproportionately greater risk to develop NMOSD compared with White ethnic groups. This suggests that genetic factors may be important in disease susceptibility. This hypothesis is also supported by familial clustering recognized in approximately 3% of the cases[47] and by the results of a whole-genome association study.[6] Of interest, genetic susceptibility alleles for NMOSD were more closely linked to those of systemic lupus erythematosus than MS.[6]

Besides these population-based studies, several research groups explored the frequency of NMOSD among patients with idiopathic inflammatory diseases. These works found increased susceptibility for NMOSD in populations with Asian, African, Arab, and Latin American background paralleled with a lower frequency of MS.[48–51]

As an environmental trigger factor, latitudinal gradient was considered in a survey across Australia and New Zealand, where a slightly higher prevalence of NMOSD was noted at lower latitudes.[18] The nationwide Japanese survey also found a greater prevalence of NMO/NMOSD in the Southern part of Japan.[11] A review found no correlation between latitude and prevalence; however, the compared prevalences were calculated based on different diagnostic criteria, i.e., both NMO and NMOSD.[52] The comparison of large population-based studies in Europe involving White populations in neighboring countries in Northern and Central Europe (Denmark, Sweden, Austria, and Hungary) suggests that genetic factors may be responsible for some of these latitudinal differences.[13,15,16,31]

Different results among the studies could also reflect variations in the study design; the size of the study population; the timing and length of the study; the applied diagnostic criteria; access to health care and antibody tests; the type of antibody assays used; whether the estimates were age standardized; the underlying population's structure (age and sex); and ethnic mixture. These factors may remarkably limit the generalizability and reliability of the results. Estimates can be affected by multiple biases and random errors, which could even mask the potential differences among the geographic areas, ethnicities, and environmental factors.

The variable performance of AQP4-Ab assays could lead to misdiagnosis of patients due to false-positive or false-negative results.[53,54] CBA uses transfected live or fixed cells and either semiquantitative immunofluorescence microscopy or fluorescence-activated cell sorting to detect AQP4-Ab. By using a semiquantitative method, the results are dependent on the experience of the person assessing the staining pattern. Further methods such as ELISA, tissue-based immunofluorescence, and immunoprecipitation have particularly shown a tendency to false-positive detection.[55,56]

The recent studies from Catalonia, Sweden, Denmark, Australia/New Zealand, and Hungary showed similarities in study design:

Table 6 Reported Limitations and Observed Considerations of the Epidemiologic Studies of NMO/NMOSD in Predominantly Non-White Populations

Country	Limitations reported by the authors	Further potential limitation
India—Mangalore[33]	"Registry method may have led to underdetection of the cases."	Unknown how many were tested for AQP4-Ab; definition of NMOSD is unsure. Small sample size. 95% CIs were not provided. Access to health care in India can differ remarkably from Europe.
Japan—Tokachi[39]	Not focused on NMO.	Single source. Small sample size. Only prevalence was investigated.
Japan—Tokachi[38]	Not reported.	Survey-based study where they have not searched for overlooked cases.
Japan—nationwide[11]	Not reported.	Estimates were derived with a statistical method. No case reviews. CIs, demographic/clinical data not provided.
Malaysia—Penang Island[37]	Not reported.	Single source. Small sample size. Only prevalence was investigated.
Malaysia—nationwide[22]	"Hospital referral bias. The small sample size and the lack of disease awareness/participation by patients and physicians. The registry-based method of capturing hospital data resulting in underestimated figures and the role of traditional taboos/beliefs and faith healers."	The authors stated that the size of the population was 28.7 m and citizens by the ethnic groups were the following: 68.8% Malay (NMOSD cases: 275—prevalence: 0.98), 23.4% Chinese (NMOSD cases: 271—prevalence: 0.96) and 7% Indian (NMOSD cases: 24—prevalence: 0.08), and 1% others. The size of the Chinese population should be 6.72 million (23.4% of 28.7 million) counting with the 271 identified NMOSD cases results in a prevalence of about 4.04/100,000. For the Malay ethnic group of 19.75 million (68.8% of 18.7 million—275 NMOSD cases), the prevalence of NMOSD is 1.39/100,000. When the authors report on the prevalence according to ethnicity, they applied wrongly the whole population (28.7 m) as denominator instead of the population's number of each ethnic groups. The capture-recapture method was applied, which requests some conditions such as independent sources, but in this study, the same sources were used to capture and to recapture cases.
The United Arab Emirates—Abu Dhabi[21]	"Small sample size. The method of retrospective chart review limited data gathering. 44% of patients in the database were not tested for AQP4-IgG. Many patients did not have a complete work-up for possible seronegative NMOSD. Emirati nationals may also receive their care internationally therefore data may have been missing."	Single source. CIs were not given. Sex- and age-standardized rates would be interesting because only 1/3 of the population is female, and the majority of the population is under 20 years.
Iran—Isfahan[34]	Not reported.	No detailed description of the study design (inclusion, AQP4 antibody test). No detailed results.
Iran—Southwest[36]	"No exact population number for ethnicity was available. Some patients may have been referred to larger city for treatment, so they did not have the exact number of patients."	Used a special interpretation of NMOSD. Only 35 patients were tested for AQP4-Ab. No control for double counting. Population structure is different from Europe (younger). Their oldest NMO/NMOSD patients were 58 years old at the disease onset. Therefore, age-standardized estimates would be helpful. Short follow-up.
Iran—Tehran[35]	"The prevalence of NMOSD might be underestimated because some of the NMOSD cases might not refer to the center studied."	Recall bias may have occurred. Potential selection bias due to single-source approach. ELISA AQP4 antibody test may be false positive and false negative (9 results were not reported).
Canada—British Columbia[27]	Not reported.	Unknown AQP4-Ab test. NMO incidence for 1986 cannot be complete, only incidence calculation.
Mexico—Mexico City[40]	No AQP4 antibody test. Clinical based (not population based). Risk for input bias.	Cases with only ON or TM (confusing how the monophasic disease was interpreted because all patients with monophasic type with initial event of TM had also impaired vision. So they were either not monophasic or the initial event was NMO).
Cuba[26]	Not reported.	Old criteria before AQP4-Ab test. Incidence was calculated based on prevalence and disease duration.
France—Martinique and Guadeloupe[25]	Not reported.	Old criteria before AQP4-Ab test. Small sample size.

Continued

Table 6 Reported Limitations and Observed Considerations of the Epidemiologic Studies of NMO/NMOSD in Predominantly Non-White Populations *(continued)*

Country	Limitations reported by the authors	Further potential limitation
France—Martinique and Guadeloupe[24]	Not reported.	Old criteria before AQP4-Ab test. Small sample size.
France—Martinique[10]	"Serum was not obtained from all potential cases. Underrepresentation of patients with area postrema and brainstem symptoms."	Small sample size.
Costa Rica[23]	Pediatric patients and private hospitals were not included. 85.5% of the Costa Rican population were included. The AQP4-IgG test was not available in all cases.	Single source.
Kazakhstan—Semej town[42]	Not reported.	Small sample size. Single source. No AQP4-Ab test. No CIs were presented. No data on source population.
Pediatric studies		
Japan[41]	"Not all medical facilities responded to our survey. The collected patient data in the present study were based on questionnaire responses, so the reliability could be uneven. Not investigate pediatric patients with solitary optic neuritis who visited only ophthalmologists."	No information on AQP4-Ab test. Low rate of AQP4-Ab test in pediatric ADS.

Abbreviations: ADS = Acquired demyelinating syndrome; AQP4-Ab = aquaporin-4 antibody; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis, TM: transverse myelitis.

large White populations, multiple sources, large proportion tested with CBA, and access to free health care. The results from Catalonia, Denmark, Sweden, and Australia/New Zealand showed similar incidence (0.039–0.063/100,000 person-years) and prevalence (0.7–1.09/100,000), but the Danish nationwide study only investigated the adult population with regard to prevalence.[15] The Hungarian crude and age-standardized prevalence and incidence were higher than the Catalonian, Danish, Australian/New Zealand, and Swedish estimates both according to the 2015 NMOSD and 2006 NMO criteria.[14,18] The 2006 criteria for NMO are more strict because they do not allow NMO diagnosis with a single ON or LETM attack despite the presence of AQP4-Ab. Therefore, it is unlikely that the difference observed between the Hungarian and the other 4 studies would be caused by a difference in the threshold of AQP4-Ab assays. In addition, the population-based Hungarian and Danish studies were designed by overlapping research groups and used similar designs. The major laboratory for the Hungarian study participated in an international validation of CBA.[53]

There have been 4 studies conducted in Scandinavian adults, including 2 nationwide studies[15,16] and 2 smaller regional Danish studies.[17,19] The results of 3 of the 4 reports seem to be consistent with each other and with other large White population studies, but are contrary to the data published from the small study in Southern Denmark delineating the highest prevalence (4.4/100,000) and incidence (4.0/1,000,000 person-year) so far in preponderantly White ancestry.[17] According to the estimates from the Southern Denmark, the nationwide Danish study should have recognized 202 prevalent Danish NMOSD cases, but only 50 prevalent cases were identified. It is unlikely that such an inconsistency would be caused by different study methods. More likely, the higher rates may be due to less strict adherence to criteria or alternative diagnoses in AQP4-Ab– patients and patients with low and transient AQP4-Ab seropositivity.[15] The final estimates of the nationwide Danish study were similar to the nationwide study in Sweden[16] and to another regional study in Denmark.[19]

The Swedish study showed that the incidence was higher in males in the period of 1987–2006. Because of the low number of NMO cases during that time and the overlapping confidence intervals, these estimates should be interpreted with caution. Overall, 74% of all diagnosed patients with NMO in Sweden were women.[16]

Another smaller study of White ethnicity[10] in Olmsted County also revealed a higher prevalence than the larger studies. However, the incidence estimate was comparable with those of the larger studies. The comprehensive approach of the study from Olmsted County is a strong advantage, such as each individual with suspected demyelinating disease in the county's population was tested for AQP4 antibody with CBA providing a probably higher recognition rate of cases. However, this study investigated a small population of 145,979 residents, and there were only 6 prevalent cases (prevalence: 3.9/100,000 (95% CI: 0.8–7.1)) and a single incident case between 2003 and

2011 (incidence: 0.07/100,000 person-years (95% CI: 0.00–0.21)).[10] They also reported that 2 prevalent patients died in the following year after the census date, which would have reduced the prevalence rate to 2.7/100,000, assuming that there were no additional new cases in the following year. Furthermore, because of the small population and few NMOSD cases, even missing or adding 1 or 2 cases might have a considerable impact on the estimates; the lower precision of the estimates is indicated by the broad confidence intervals. Considering these, interpreting the differences between the large studies and the Olmsted County study is difficult.

The recent Dutch study solely estimated the incidence of AQP4-Ab+ NMOSD to be 0.09 presumably based on the 2015 IPND AQP4-Ab+ criteria, but confidence intervals are not reported, and clinical and radiologic information were available only in 38% of the incident cases.[20] The ethnicity of the cases may have influenced the results, as the incidence was 0.08/100,000 for Whites and 0.19/100,000 for non-Whites. It is not clear whether disease onset was defined by the onset of the clinical symptoms or the date of the positive AQP4-Ab. Altogether, the incidence of the Dutch AQP4-Ab+ White NMOSD population seems to be more similar to other White population reports.[12–16,19]

Two works from the United Kingdom used a combination of 2006 criteria[3] and the 2007 NMOSD definition.[4] These publications described the epidemiology of NMO/NMOSD in a small area of Wales and England.[12,32] In Wales, a prevalence of 1.96/100,000 (95% CI: 1.22–2.97) was observed derived from a background population of 712,572 inhabitants.[32] Surprisingly, 21% of the reported prevalent cases were under age 20 years, resulting in a higher prevalence in the age group from 0 to 19 years than in the age group from 20 to 49 years. No other epidemiologic study has shown similar findings. This may be an anomaly of the relatively small study population or some hidden capture bias. Opposite to this, the prevalence of NMO/NMOSD was 0.72/100,000 (95% CI: 0.31–1.42) among the 1.14 million adult residents of England, and the incidence was 0.08/100,000 (95% CI: 0.03–0.16) similar to the other large White population studies.

Three separate investigations were published from different regions of Iran.[34–36] The demographic and clinical data were different from other studies around the world, especially in Isfahan.[38] All 3 Iranian studies found a lower percentage of AQP4-Ab–positive cases (46.8%–66.3%), lower mean age at onset (29.2–31.5 years), and lower last Expanded Disability Status Scale score compared with most of the other studies. This inconsistency may be due to different ethnicities or population structure, but limitations should be also considered (tables 5 and 6).

The first recent study from an Arab region, Abu Dhabi, showed a greater prevalence and incidence of NMOSD compared with larger White populations.[21] The authors provided subgroup analysis for Arab residents and the adult population, but no sex-adjusted and sex- and age-standardized calculations. These would have given more informative estimates, as the percentage of women was only 30% among the residents, and half of the Emirati citizens in Abu Dhabi were younger than 19 years.[21]

According to the latest studies conducted in Asian populations (Japanese,[11,38] Indian,[33] Malaysian-Chinese,[22,27,37] and Kazakhstan[42]), the prevalence ranged from 2.6 to 4.9/100,000, and the incidence was between 0.39 and 0.6/100,000 person-years, which are remarkably higher than in Whites. However, only 2 studies computed the incidence in Asian ancestries.[22,27] The results from India and Kazakhstan may be an underestimation of the true prevalence due to differently organized health care systems and limited or no access to AQP4-Ab assays.[33] It should be noted that there is a lack of prevalence and incidence data from continental China.

APQ4-Ab was found in a high proportion of the patients with NMOSD with a few exceptions from India and Iran,[33,35,36] where low sensitivity assays or other autoantibodies may be suspected. Whereas AQP4-Ab+ patients are likely to be a more consistent cohort to cross compare, AQP4-Ab– cohorts will vary depending on criteria used, access to supportive investigations, and even on the clinician's subjective evaluation.[57] In addition, antibody against myelin oligodendrocyte glycoprotein (MOG) has been recognized in the AQP4-Ab– NMOSD subgroup. Since the increasing knowledge about MOG-Ab and related diseases, there has been increasing concern to separate MOG-Ab–positive patients with NMOSD phenotype from the AQP4-Ab+ and double-seronegative NMOSD.[58] Only epidemiologic studies from Catalonia and Japan had the possibility to test all included AQP4-Ab– patients for anti-MOG.[14,38] They showed that 0% (0/3) of the AQP4-Ab– prevalent NMOSD cases in the Asian population[38] vs 47% (9/19)[14] in the White population were positive for MOG-Ab. More studies are needed to confirm such population differences, especially in cases with low or borderline/uncertain AQP4-Ab positivity. Less standardized methods for MOG-Ab may also contribute to differences.

Epidemiologic studies were conducted in Martinique and Guadeloupe before the era of the AQP4-Ab test and again in Martinique a few years ago.[10,24,25] Both population-based evaluations presented a high prevalence and incidence in African ancestry regardless of diagnostic criteria. The results without AQP4-Ab measurement were 4.2/100,000 (95% CI: 3.7–5.7) for crude prevalence and 0.19/100,000 person-years (95% CI: 0.15–0.23) for crude incidence, whereas the recent study including AQP4-Ab–positive patients based on the 2006 criteria gave a prevalence of 10/100,000 (95% CI: 6.8–13.2) and incidence of 0.73/100,000 person-years (95% CI: 0.45–1.01).

Further epidemiologic studies from Cuba, Mexico, and French West Indies showed lower estimates, which can be expected since the 1999 criteria were applied and access to

AQP4-Ab testing was not available.[26,40,59] Overall, studies reported relatively stable annualized incidence without any trend for significant changes over 10–25 years.[14,15,20,24,27] Only 2 studies showed increasing incidence,[16,23] whereas a single study showed an increasing prevalence over time that could be explained by reduced mortality.[24] The increasing awareness of the disease and easier access to AQP4-Ab CBA may explain the rise of incidence.[16] This together with the earlier introduction of adequate treatments and promising new therapies may result in longer survival and slight increase in the prevalence of NMOSD.

Data regarding pediatric populations are sparse, but indicate that NMOSD rarely develops in childhood.[14,21,28–30,35,41] In Australia/New Zealand, onset before age 20 years was seen in 12% (Prof. Simon Broadley, MD, PhD, written personal communication, December 12, 2019).

In common with other systemic autoimmune diseases, studies universally demonstrated a female predominance. This may relate to female sex hormones and hormonal changes. Female genetic susceptibility to autoimmune disorders due to silenced X chromosome via epigenetic mechanisms has also been suggested.[60–62] A recent multicenter study found potential association between exogenous hormonal exposure and NMOSD onset, whereas it was not associated with endogenous hormonal exposure.[44] The average and/or median age at disease onset were similar in the majority of the studies, but all 3 studies from Iran[34–36] and the studies from the Caribbeans[10,24–26] reported a younger age at onset, which could be caused by environmental factors, ethnic influence, or study design. Finally, highest incidence rates reported in West Indians could be due to accumulation of genes of susceptibility coming from White, Indian, and African ancestry in this population.

Limitation

The major limitation of this work is that we did not use inclusion criteria for study design and quality. Therefore, the included studies have variable study designs that may affect the quality of their results and influence our conclusions. However, we critically reviewed all studies as shown in tables 5 and 6 and report the limitations and point out crucial weaknesses in each publication.

Conclusion

The incidence and prevalence of NMOSD vary among the studies; this could be due to the effects of genetic and environmental factors, but may also be related to differences in study design, study population, and quality of data. NMOSD has been described worldwide, but it seems to be less frequent in White populations compared with Asian and African ones.

Future studies should be carefully planned to obtain reliable results considering the rarity of the disease and to address epidemiology in more specifically designed settings: (1) by systematic methods of ascertainment with AQP4-Ab testing in all suspected demyelinating disease cases in a given population as gold standard or targeting of high-risk cases as secondary standard; (2) use of CBA for AQP4-Ab testing as recommended; (3) strict adherence to clinical and paraclinical criteria for AQP4-Ab− cases, as epidemiology data within specific serologic groups may be useful in identifying genetic effects and etiologic factors; (4) exclusion of MOG-Ab–positive cases; (5) if (1) is not possible, multiple sources and capture/recapture methodology should be used to minimize risks of missed cases; (6) prolonged period of case ascertainment should be considered to avoid missing inactive disease; and (7) inclusion of pediatric sources of cases.

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V. Papp has received honoraria for lecturing from Alexion and support for congress participation from Merck. M. Magyari has served on scientific advisory boards for Biogen, Sanofi, Teva, Roche, Novartis, and Merck and has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, and Genzyme and support for congress participation from Biogen, Genzyme, Teva, and Roche. O. Aktas has received fees from Almirall, Bayer HealthCare, Biogen, MedImmune, Merck, Roche, Sanofi Genzyme, and Teva for speaker services and advisory boards and research grants from Biogen, Merck, and Sanofi Genzyme. T. Berger has participated in the last 2 years in meetings sponsored by and received honoraria (lectures, advisory boards, and consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Almirall, Biogen, Biologix, Bionorica, Celgene, MedDay, Merck, Novartis, Roche, Sanofi Aventis/Genzyme, TG Therapeutics, and Teva. His institution has received financial support in the last 2 years by unrestricted research grants (Biogen, Novartis, Sanofi Aventis/Genzyme, Roche, and Teva) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Bayer, Biogen, Merck, Novartis, Roche, Sanofi Aventis/Genzyme, and Teva. S.A. Broadley has been a

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Melinda Magyari, MD, PhD	Copenhagen University Hospital, Rigshospitalet, Denmark	Study concept and design and revised the manuscript for intellectual content
Orhan Aktas, MD	Heinrich-Heine University, Düsseldorf, Germany	Acquisition of data; analyzed the data; and revised the manuscript for intellectual content
Thomas Berger, MD	Medical University of Vienna, Austria	Providing updates to data; interpretation of data; and revised the manuscript for intellectual content
Simon A. Broadley, MD, PhD	Griffith University, Gold Coast, Gold Coast University Hospital, Australia	Providing updates to data; interpretation of data; and revised the manuscript for intellectual content
Philippe Cabre, MD	Fort-de-France University Hospital Center, Pierre Zobda Quitman Hospital, Fort-de-France, Martinique, France	Interpretation of data and revised the manuscript for intellectual content
Anu Jacob, MD	Cleveland Clinic Abu Dhabi, United Arab Emirates, The Walton Centre, Liverpool, UK	Interpretation of data and revised the manuscript for intellectual content
Jun-ichi Kira, MD, PhD	Kyushu University, Fukuoka, Japan	Interpretation of data and revised the manuscript for intellectual content
M. Isabel Leite, MD, DPhil	John Radcliffe Hospital, University of Oxford, UK	Interpretation of data and revised the manuscript for intellectual content
Romain Marignier, MD, PhD	Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Bron, France	Analyzed the data and revised the manuscript for intellectual content
Katsuichi Miyamoto, MD, PhD	Kindai University Graduate School of Medicine, Osaka, Japan	Providing updates to data; interpretation of data; and revised the manuscript for intellectual content
Jacqueline Palace, MD	John Radcliffe Hospital, University of Oxford, UK	Interpretation of data and revised the manuscript for intellectual content
Albert Saiz, MD, PhD	Hospital Clínic, Barcelona, Spain	Interpretation of data and revised the manuscript for intellectual content
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Olafur Sveinsson, MD, PhD	Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden	Interpretation of data and revised the manuscript for intellectual content
Zsolt Illes, MD, PhD	Odense University Hospital, Denmark	Designed and conceptualized the study; acquisition and interpretation of data; and revised the manuscript for intellectual content

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