**Supplementary File 1**

**Search Strategy**

Database: Pubmed <1999 to August 31, 2019>

1, ALL FIELDS (NMO OR NMOSD OR “neuromyelitis optic\*” OR OSMS OR “optico-spinal MS” OR “Devic´s disease” OR “AQP4” OR “aquaporin-4”) / 5359

2, ALL FIELDS (epidemiolog\* OR prevalence OR incidence) / 2,333,534

3, ALL FIELDS (case OR cases OR cohort\* OR "follow up" OR observational OR retrospective OR "cross sectional" OR population\* OR multicenter) / 5,458,380

4, 1 AND 2 AND 3/ 363

Search Strategy:

Database: EMBASE <1999 to August 31, 2019>

1, (NMO OR NMOSD OR “neuromyelitis optic\*” OR OSMS OR “optico-spinal MS” OR “Devic´s” OR “AQP4” OR “aquaporin-4”)/ 15,214

2, (epidemiolog\* OR prevalence OR incidence)/ 2,657,365

3, (case OR cases OR cohort\* OR "follow up" OR observational OR retrospective OR "cross sectional" OR population\* OR multicentre OR nationwide)/ 7,636,415

4, 1 AND 2 AND 3/ 1020

5, 4 AND ([article]/lim OR [article in press]/lim OR [data papers]/lim OR [editorial]/lim OR [letter]/lim OR [review]/lim OR [short survey]/lim)/ 505

Search Strategy:

Database: MedlineOvid <1999 to August 31, 2019>

1, (NMO OR NMOSD OR “neuromyelitis optic\*” OR OSMS OR optico-spinal OR Devic´s OR AQP4 OR aquaporin-4).mp/ 6,381

2, (epidemiolog\* OR prevalence OR incidence).mp/ 1,883,249

3, (case OR cases OR cohort\* OR "follow up" OR observational OR retrospective OR "cross sectional" OR population\* OR multicenter).mp/ 5,395,681

4, 1 AND 2 AND 3 / 400

mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms

**Supplementary Table 1.** The stratified incidence and prevalence of NMO/NMOSDa (incidence:/100,000 person-years, prevalence:/100,000 persons)

The following studies have not reported any of these data therefore are not included in the table: UK- South East Wales32, UK-North West England12, Denmark- Southern Denmark28, Denmark-Central Denmark30, Malaysia-Nationwide14, Iran-Isfahan35, Iran-Southwest37, Kazakhstan-Semej town42, Mexico-Mexico City41

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Country** | **Age-standardized rates** | **Annual incidence rate** | **Peak age group of incidence** | **Peak age group of prevalence** | **Incidence tendency** | **Reported on the serostatus specific estimates** | **Latitude variation on the prevalence** |
| ***Austria23*** | NS | NS | NS | NS | NS | All were AQP4-Ab+ | NS |
| ***Netherlands31*** | - | 0.07-0.11 | NS | - | no tendency | NS | NS |
| ***Spain-Catalonia25*** | WHO  incidence: 0.064 (0.45–0.82); prevalence: 0.95 (0.76–1.14) | 0.01-0.14 | both sexes:  40-59 | both sexes:  40-59 | no tendency | yes | NS |
| ***Denmark-National26*** | NS | 0.04-0.13 | NS | NS | no tendency | yes | NS |
| ***Sweden27*** | WHO prevalence:  F: 0.99 (0.777-1.26);  M: 1.03 (0.66-1.55) | extensive data are reported | NS | NS | increasing incidence for female | NS | NS |
| ***Hungary (2/3)24*** | WHO  incidence: 0.12 (0.10-0.15); prevalence: 1.87 (1.56–2.23) | 0.07-0.25 | both sexes:  40-59 | both sexes:  40-59 | no tendency | yes | NS |
| ***Australia and New Zealand29*** | WHO prevalence:  0.44 (0.36-0.52) | NS | 40-59 | F: 40-59,  M: 60–69 | no tendency | NS | prevalence increasing at lower latitudes |
| ***USA-Olmsted County10*** | according to the USA population | NS | NS | NS | NS | only the AQP4-Ab+ cohort is reported | NS |
| ***Canada-British Columbia19*** | NS | NS | NS | - | no tendency | NS | NS |
| ***India-Mangalore34*** | NS | - | - | 30-39 | - | NS | NS |
| ***Japan-Tokachi40*** | NS | - | - | NS | - | all patients were  AQP4-Ab+ | NS |
| ***Japan-Tokachi39*** | according to the Japanese population: 4.1 | - | - | NS | - | AQP4-Ab+  prevalence: 3.2 (NS);  AQP4-Ab-prevalence: 0.9 (NS) | NS |
| ***Japan-Nationwide11*** | NS | - | - | NS | - | NS | prevalence increasing at lower latitudes |
| ***Malaysia-Penang Island38*** | NS | - | - | NS | - | all patients were  AQP4-Ab+ | NS |
| ***The United Arab Emirates-Abu Dhabi13*** | NS | 0.00-0.93 | NS | NS | no tendency | NS | NS |
| ***Iran-Tehran36*** | NS | - | - | both sexes:  40–49 | - | NS | NS |
| ***Cuba18*** | NS | NS | NS | whole cohort:  40–49 | NS | NS | NS |
| ***France-Martinique and Guadeloupe16*** | NS | NS | NS | F:  45-55 | no tendency | NS | NS |
| ***France-Martinique10*** | according to the USA population | NS | NS | NS | NS | AQP4-Ab+  prevalence: 7.9  (5.0–12.6); incidence: 0.65  (0.39–0.92) | NS |
| ***Costa Rica15*** | NS | 0.12-0.44 | NS | - | increasing incidence for female | NS | NS |

F: female, FP: full population; M: male, NS: not specified; ND: not done; UAE: The United Arab Emirates, AQP4-Ab+: AQP4-antibody seropositive, AQP4-Ab-: AQP4-antibody seronegative. *aSee also Table 3*

**Supplementary Table 2. Basic demographic features of the NMO/NMOSD**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Country** | **Wingerchuk 2006 fulfilled** | **AQP4-Ab**  **seropositive (%)** | **Female (%)** | **Follow-up in years, median (mean)** | **Age at onset median (mean)** | **Disease course (%)** | **Ethnicity (patients)** | **Death** | **Pediatric onset cases** | |
| ***Austria23*** | 51% | 100% | 87% | NS | (45.7) | RR: 87%, MPH: 13% | Predominantly Caucasian  (100% Caucasian) | 4 (5.6%) prevalent cases | NS | |
| ***UK- South East Wales32*** | 78% | 77%  (1 was not tested) | 85% | 3.5 (9) | 39.5 | RR: 79%, MPH: 21% | 95.6% White (100% Caucasian) | 0 | 4 (28%) below the age of 16 years (prevalent cohort) | |
| ***UK-*** ***Northwest England12*** | 69% | 85% | 75% | NS | NS | NS | 95.1 % White (88% White) | 5 (38.5%) prevalent cases | | NR |
| ***Netherlands31*** | NS | 100% | 83% | NS | NS | NS | 88.1% Caucasian,  11.9% non-Caucasian (75% Caucasian, 25% non-Caucasian) | NS | | 8 (8.5%) below the age of 18 years (incident cohort) |
| ***Spain-Catalonia25*** | 70% | 73% | 76% | (9.7) | 42 | RR: 87% | 82.81% Spain, 4.43% rest of Europe, 6.73% Latin America, 3.87% Africa, 2.00% Asia (81% White, 11 % Hispanic) | 4 prevalent cases | | 5 (10%) below the age of 18 years (incidence cohort) |
| ***Denmark-*** ***Southern28*** | 86% | 62% | 73% | NS | (35.6) | RR:90% MPH:10% | 94.1% Danish  (97.6% Danish, 2.4% African) | 3 (7.1%) | | 3 |
| ***Denmark-*** ***Central30*** | 40% | NS | NS | NS | NS | NS | NS | NS | | 0 |
| ***Denmark-Nationwide26*** | 53.6% | 70% | 82% | 8.00 | 35.5 | NS | 95.2% European, 3.5% Asian, 0.8% African, 0.5% other (89.3% Caucasian, 7.1% Asian, 1.8% Arab, 1.8% African) | 5 (8.9%)  prevalent cases | | 7 (12.5%) age<16 years |
| ***Sweden27*** | 55% | NS | 73.9% | 6.2 (8.0) | (41.5) | NS | (92.3% Caucasian,  9.7% non-Caucasian) | 2 (2.2%)  prevalent cases | | NS |
| ***Hungary (2/3)24*** | 56.5% | 83% | 87.7% | 9 (7.4) | 39.5 | 15.6% | 96.5% Caucasian, 3% Roma, 0.23% Asian, 0.12% Arab  (86.4% Caucasian, 5.2% Roma, 8.4% Uncertain (Caucasian or Roma)) | 26 (16.9%) prevalent cases | | 10 (6.5%) age<16 years |
| ***Australia and New Zealand29*** | NS | 90% | 86% | NS | NS | NS | NS | 2 | | NS |
| ***USA-Olmsted county10*** | 67% | 83% | 83% | 12.5 | 37 | NS | 82% White, 13% Other, 5% Black  (83% White, 17% Black) | 0 prevalent case | | NS |
| ***Canada-British Columbia19*** | NS | NS | 90% | NS | (35.2) | NS | (100% Asian) | NS | | NS |
| ***India-Mangalore34*** | 18% | 27% | 55% | NMO: 6.3, NMOSD: 3 | NMO: (40), NMOSD: (40.4) | NS | NS | NS | | 0 |
| ***Japan-*** ***Tokachi40*** | 100% | 100% | 100% | NS | (34) | NS | 100% Asian (100% Asian) | NS | | 1 |
| ***Japan-*** ***Tokachi39*** | 50% | 79% | 86% | 4.5 (9.5) | 41 (45.2) | RR: 71%, MPH: 29% | 100% Asian (100% Asian) | NS | | 1 (7.1%) age<20 years |
| ***Japan-Nationwide11*** | 50% | NS | 86.5% | (9.8) | 43 (42.2) | NS | not specified | NS | | NS |
| ***Malaysia-*** ***Penang Island38*** | 71% | 100% | 100% | NS | (43.1) | NS | 55.9% Chinese, 33.3% Malays, 10% Indians  (93% Chinese, 7% Malay) | 0 | | 0 (under 18) |
| ***Malaysia-Nationwide14*** | 2015 | 83.2% | 91% | (6.39) | (33.4) | RR: 97.6%, MPH:2.2%  Prog: 0.2% | 68.8% Malays and indigenous groups, 23.4% Chinese, 7% Indians, and 1% others.  (275 Malay, 271 Chinese, 24 Indian, 10 others) | NS | | NS |
| ***The United Arab Emirates-Abu Dhabi13*** | NS | 80% | 70% (UAE: 100%) | NS | 43 (43) | NS | (6 UAE, 1 Indian, 1 Pakistanis, 1 Syrian, 1 Yemen) | 0 | | 1 (10%) |
| ***Iran-*** ***Isfahan35*** | NS | 66.3% | 69% | (6.3) | (30) | RR:40%, MPH:60% | NS | 0 | | NS |
| ***Iran-*** ***Southwest37*** | 71% | 54% | 86% | (6) | (29.2) | RR: 72.5%, MPH: 27.5% | (58.8% Lors, 25.5% Arabs, 11.8% Persians, 2% Kurd/Turk) | 1 | | 10 (19%) below the age of 20 years |
| ***Iran-Tehran36*** | NS | 46.8% | 83.5% | NS | (31.54) | NS | NS | 0 | | 19 (18.4%) below the age of 19 years |
| ***Kazakhstan-*** ***Semej town42*** | 100% | NR | 90% | 6 (7) | 42 (41.4) | RR: 90% MPH:10% | 71.18% Kazakhs, 24.54% Russians, 2.54% Tatars, 0.61% Germans, 0.19% - Ukrainians, 0.05% Belarusians, 0.09% Uighurs, 0.11% Koreans, 0.12% Uzbeks, 0.57% others. (100% Asian) | NS | | NS |
| ***Mexico-Mexico City41*** | NR | NR | 71% | (5.85) | (34) | RR: 32% MPH: 68% | 79% Mestizo, 21% Others  (100% Mestizo) | 1 (3%) | | NS |
| ***Cuba18*** | NR | NR | 88% | 7 (9.9) | 30.5 (31.8) | NS | 65% White, 35% non-White  (53% White, 47% non-White) | NS | | 2 (3.4%) under 20 |
| ***France-Martinique and Guadeloupe16,17*** | NR | NR | 90% | NS | (31.9) | NS | Martinique: 92% African-Caribbean; Guadeloupe: 78% African-Caribbean | NS | | NS |
| ***France-Martinique10*** | 77% | 79% | 90% | 7 | 35 | NS | 90% Black, 5% White, 5% Other (97% Black, 3% White) | 0 prevalent case | | NS |
| ***Costa Rica15*** | 100% | 65% (15/23) | 62% | NS | 35.5 | RR: 97.5% | 45.6% of European ancestry, 33.5% Native American, 11.7% African and 9.2% Chinese | NR | | 0 case < 16 years (excluded <13 years) |

AQP4-Ab: aquaporin 4-antibody, NS: not specified, NR: not relevant, RR: recurrent, MPH: monophasic; Prog: progressive, UAE: The United Arab Emirates

**Supplementary Table 3. The number of patients tested for AQP4-antibodies in the population-based studies**

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| --- | --- | --- | --- | --- |
| **Country, year** | **Number of samples** | **Period (year)** | **Population** | **Number of samples/million/year** |
| Catalonia (Spain), 201825 | 2968 | 10 | 7.5 | 40 |
| Denmark, 201826 | 4067 | 8 | 4.6 | 111 |
| The Netherlands, 201631 | 2795 | 6 | 16.6 | 28 |
| Austria, 201123 | 1957 | 3.8 | 8.4 | 61 |
| Hungary, 201924 | 1844 | 10 | 6.4 | 29 |