

# Incidence and Prevalence of NMOSD in Australia and New Zealand

The Australian and New Zealand NMO Collaboration\*

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## ABSTRACT

**Objectives** We have undertaken a clinic-based survey of neuromyelitis optica spectrum disorders (NMOSD) in Australia and New Zealand in order to establish incidence and prevalence across the region and in populations of differing ancestry.

**Background** NMOSD is a recently defined demyelinating disease of the central nervous system. The incidence and prevalence of NMOSD in Australia and New Zealand has not been established.

**Methods** Centres managing patients with demyelinating disease of the CNS across Australia and New Zealand reported patients with clinical and laboratory features that were suspicious for NMOSD. Testing for AQP4 antibodies was undertaken in all suspected cases. From this group, cases were identified who fulfilled the 2015 Wingerchuk diagnostic criteria for NMOSD. A capture-recapture methodology was used to estimate incidence and prevalence, based on additional laboratory identified cases.

**Results** NMOSD was confirmed in 81/170 (48%) cases referred. Capture-recapture analysis gave an adjusted incidence estimate of 0.37 (95% CI 0.35 – 0.39) per million per year and a prevalence estimate for NMOSD of 0.70 (95% CI 0.61 – 0.78) per 100,000. NMOSD was 3-times more common in the Asian population (1.57 [95% CI 1.15 – 1.98] per 100,000) compared with the remainder of the population (0.57 [95% CI 0.50 – 0.65] per 100,000). The latitudinal gradient evident in multiple sclerosis was not seen in NMOSD.

**Conclusions** NMOSD incidence and prevalence in Australia and New Zealand are comparable with figures from other populations of largely

European ancestry. We found NMOSD to be more common in the population with Asian ancestry.

## INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) are an antibody-mediated autoimmune disease of the central nervous system (CNS) in which the primary target is aquaporin 4 (AQP4), a water channel found in high density on the end-feet of astrocytes, particularly those in close proximity to the blood brain barrier.<sup>1</sup> Difficulties in identifying NMOSD and distinguishing it from multiple sclerosis were dramatically reduced by the discovery of AQP4 antibodies in 2004.<sup>2</sup> Since the identification of these seemingly specific and pathogenic antibodies,<sup>3</sup> the phenotype of this autoimmune astrocytopathy has broadened.<sup>4</sup> It has been noted that the relative frequency of NMOSD is higher in populations of Asian ancestry (50% of CNS demyelinating disease)<sup>5</sup> compared with in populations of predominantly European ancestry (1% of CNS demyelinating disease).<sup>6</sup>

A number of studies have attempted to estimate the population prevalence and incidence of NMOSD in various parts of the world. However, many of these studies have been based on AQP4 antibody positivity from laboratory testing. As a result few population-based clinical surveys of the frequency of NMOSD exist.<sup>7</sup> Australia and New Zealand have a population of 27 – 28 million people with predominantly European ancestry. Both have comprehensive healthcare systems, with a network of adult and paediatric neurologists who have a subspecialty interest in CNS demyelinating disease. We have undertaken a clinic-based survey of NMOSD, using a clinical method of case ascertainment with the aim of estimating the

population incidence and prevalence of NMOSD. As secondary aims we wished to explore the geographical and ethnic distribution of NMOSD.

## **METHODS**

### **Case Ascertainment**

Possible cases of NMOSD were identified using a network of 36 adult and paediatric neurologists at 23 clinics specialising in demyelinating diseases of the central nervous system (ICD-10 G35-G37) across Australia and New Zealand. These centres covered every capital and major city of each state or region, as well as several smaller urban centres. Australia and New Zealand have comprehensive state health care systems in which most patients with demyelinating diseases of the central nervous system are cared for in specialist clinics. Participating neurologists and paediatric neurologists were requested to notify the coordinating centre in Queensland of patients with features identified in earlier diagnostic criteria<sup>8</sup> that are highly suggestive of NMOSD. To be included as a suspected NMOSD case one of the following 'high risk' clinical and laboratory features had to be met 1) optic neuritis that was either severe with poor recovery (residual visual acuity in better eye worse or equal to 6/36), bilateral (simultaneous or sequential within 3 months) or recurrent (more than 2 attacks) as the sole clinical manifestation of demyelinating disease, 2) severe transverse myelitis with a central cord syndrome (symmetrical, motor, sensory and bladder involvement) and poor recovery (residual EDSS greater than 5.0) or a longitudinally extensive lesion of the spinal cord spanning 3 or more

vertebral segments on magnetic resonance imaging (MRI) or 3) demyelinating disease clinically confined to the optic nerve and spinal cord with at least one of the following: normal or atypical MRI of the brain (fewer than 2 periventricular lesions<sup>9</sup>), negative oligoclonal bands in cerebrospinal fluid, raised CSF protein or a CSF pleocytosis (more than 10 cells per  $\mu$ l). Cases were excluded if no serum sample was supplied and clinical criteria for NMOSD were not met, insufficient clinical data were supplied, inclusion criteria for suspected NMOSD were not met, an alternate diagnosis became apparent or subject declined to provide written informed consent. The period of data collection was from 1 January 2011 to 31 December 2013. Informed, written consent was obtained for all cases and institutional human research ethics committee approval was obtained for all participating sites.

To facilitate a capture-recapture methodology, the four laboratories in Australia that offer routine AQP4-Ab testing provided details of positive cases detected in their laboratories for the same time period. Details on these cases included date of birth, initials, age, gender, state/country and ethnicity [Asian or Other]) thereby ensuring the avoidance of double counting and facilitating a whole of population analysis by age, gender, region and ethnicity.

### **Case Definition**

Demographic details (age, gender and ethnicity), relapse history, findings on clinical examination and results of CSF analysis and any prior AQP4-Ab testing were collected using a standard questionnaire in all cases. Serum

samples were obtained and tested for AQP4-Ab using immunofluorescence staining techniques on mouse, rat or monkey brain tissue and rat or mouse kidney sections. A subset of samples was also tested using an ELISA kit, as well as M23 AQP4 transfected HEK cells in a fixed cell assay (Euroimmun™, Germany) and a live cell based assay.<sup>10</sup> MRI of brain, orbits and spinal cord were obtained where available. Cases were defined as having NMOSD (ICD-10 G36) and included in the analysis if they met the 2015 Wingerchuk criteria.<sup>11</sup>

### **Estimation of incidence and prevalence**

Crude incidence rates with 95% confidence intervals were calculated, using the normal approximation to the binomial distribution, from the mean number of cases with disease onset (date of first symptoms) occurring from 2009 to 2012 inclusive. The inevitable lag between symptom onset and clinical assessment means that new cases would typically be identified and referred to the study sometime after the onset of their symptoms. Therefore incident cases for the collection year 2013 were not included. Crude point prevalence rates were calculated for the prevalence date of 1 July 2013. To be included in the prevalence estimate cases were required to have disease onset on or before 1 July 2013 and be alive on this date. Gender and age-adjustment was performed using the WHO Standard World Population Distribution for 2005 to 2025.<sup>12</sup>

The Lincoln-Peterson capture-recapture method<sup>13</sup> was used to adjust prevalence and incidence rates in light of laboratory identified cases that



had been missed in the clinical survey. Standard methods were used to estimate a 95% confidence interval for this adjusted prevalence rate.<sup>14</sup> All analyses were conducted on a state and country basis, to allow for regional variations in referral practice, before being combined. Prevalence rates were also estimated for cases with Asian ancestry separately using the same capture-recapture methodology. The definition of Asian ancestry was self-determined but indicated to include those whose genealogical ancestry arose in the continent of Asia.

Population estimates for Australian states and New Zealand were obtained from the Australian Bureau of Statistics and Statistics New Zealand websites.<sup>15 16</sup> For incidence, population estimates for 2011 were used (the mid-point of the study years). For prevalence, population estimates for 2013 were used (the year of the prevalence date). Latitudinal variation in prevalence was analysed using the latitude of the centre of population for each region.<sup>15-17</sup> The relationship between latitude and prevalence was explored using a regression analysis weighted by the reciprocal variance using Stata<sup>®</sup> v14.0 software (StataCorp, Texas, USA).

## **RESULTS**

### **Incidence and prevalence of NMOSD**

A total of 177 cases of suspected NMOSD were referred to the study centre. Of these 7/177 (4%) were excluded (no serum sample received in 1, inclusion criteria not met in 2, incomplete clinical data in 3 and alternative

diagnosis in 1). The one case excluded because of no serum sample being supplied did not meet the clinical criteria for NMOSD. Clinical information, results of testing for AQP4 antibodies and MR imaging results were available for all of the remaining 170 suspected cases of NMOSD permitting application of the 2015 Wingerchuk criteria. A cell-based assay was used in 79/177 (46%) of suspected cases, immunofluorescence tissue assay was performed in all. NMOSD was confirmed in 81/170 (48%) cases and 73/81 (90%) were seropositive for AQP4 antibodies. The laboratory survey identified 117 AQP4 antibody positive cases of which 70 were not identified in the clinical survey, giving a total of 151 cases of NMOSD. There were 34 incident cases over the period 2010 to 2012, giving a crude incidence of 0.33 (95% CI 0.11 – 0.55) per million per year. Two cases died prior to the prevalence date and 2 cases had disease onset after the prevalence date leaving 147 prevalent cases and giving a crude point prevalence of 0.53 (95% CI 0.45 – 0.62) per 100,000. Standardising to the World Health Organisation 2005-2025 world population gave a gender and age-adjusted prevalence figure of 0.44 (95% CI 0.36 – 0.52) per 100,000. There were 126/147 (86%) female cases, giving a female to male ratio of 6:1. The frequency distribution by age is shown in Figure 1. The peak prevalence age range for women was 40 – 59 years and for men was 60 – 69 years.

### **Capture-recapture analysis and lifetime risk of NMOSD**

There were 47/73 (64%) cases from the clinical survey that were recaptured in the laboratory survey. For the capture-recapture analysis we have extrapolated the total number of seronegative cases assuming the same

proportion of missed cases as seen with the seropositive cases. An additional 8 'seronegative' cases were added according to the observed regional distribution. Capture-recapture gave an adjusted incidence estimate of 0.37 (95% CI 0.35 – 0.39) per million per year and gave an estimated total number of NMOSD cases of 193 and prevalence of 0.70 (95% CI 0.66 – 0.74) per 100,000. The results for prevalence estimates by state, ancestry and overall are shown in Table 1. The prevalence of NMOSD in the population of Australia and New Zealand with Asian ancestry was 1.57 (95% CI 1.15 – 1.98) per 100,000 compared with 0.57 (95% CI 0.50 – 0.65) per 100,000 in the remainder of the population. The lifetime risk of developing NMOSD was calculated using the cumulative age of onset for

**Table 1. Crude and adjusted NMOSD prevalence estimates by region, ancestry and overall**

Subpopulation	NMOSD Cases				Population	Latitude (° South)	Crude Prevalence <sup>b</sup> (per 100,000)	Adj Prevalence <sup>c</sup> (per 100,000)
	Clinical Only	Clinical & Laboratory	Laboratory Only <sup>a</sup>	Total				
Region								
QLD/NT	2	12	26 (2)	40	4,898,100	25.0954	0.82 (0.56 – 1.08)	0.95 (0.78 – 1.12)
WA	1	1	4	6	2,517,200	31.5906	0.24 (0.05 – 0.43)	0.40 (0.00 – 0.89)
NSW/ACT	11	17	27 (2)	55	7,791,100	33.5302	0.68 (0.50 – 0.86)	0.93 (0.71 – 1.15)
SA	2	3	2	7	1,670,800	34.8474	0.37 (0.09 – 0.64)	0.44 (0.24 – 0.63)
VIC/TAS	3	10	13 (2)	26	6,250,600	38.0848	0.43 (0.24 – 0.62)	0.56 (0.42 – 0.71)
NZ	6	9	6 (2)	21	4,442,100	38.1507	0.38 (0.23 – 0.53)	0.47 (0.37 – 0.58)
Ancestry								
Asian	6	12	22	40	3,259,047		1.23 (0.85 – 1.61)	1.57 (1.15 – 1.98)
Other	18	41	56 (8)	115	24,410,853		0.44 (0.36 – 0.52)	0.57 (0.50 – 0.65)
Total	25	52	78	155	27,669,900		0.65 (0.58 – 0.73)	0.70 (0.61 – 0.78)

QLD = Queensland; NT = Northern Territory; WA = Western Australia; NSW = New South Wales; ACT = Australian Capital Territory;

SA = South Australia; VIC = Victoria; TAS = Tasmania; NZ = New Zealand; Adj = Adjusted

<sup>a</sup> Figures in parentheses indicate estimated numbers of missed seronegative cases added to the estimate

<sup>b</sup> Excludes estimated numbers of missed seronegative cases, figures in parentheses indicate 95% confidence interval

<sup>c</sup> Adjusted using Lincoln-Peterson capture-recapture methodology, figures in parentheses indicate 95% confidence interval

the clinical survey cases (data not shown) as 1.26 (95% CI 1.13 – 1.39) per 100,000.

### **Latitudinal variation in NMOSD prevalence**

The prevalence estimates by region are illustrated in Figure 2 and show no increase in prevalence with increasing latitude. In fact there is a reverse relationship which is statistically significant ( $p=0.044$ ). Exclusion of cases and state populations with Asian ancestry did not significantly alter this finding.

## **DISCUSSION**

This is the first incidence and prevalence survey of NMOSD in the Oceania region. We have utilised a clinical survey method combined with a laboratory-based capture-recapture methodology to estimate the incidence and prevalence of NMOSD in Australia and New Zealand and have results that are similar to those previously recorded for both European and Asian populations. The estimates of incidence and prevalence reported here are at the lower end of previous study results (Table 2). There are two studies with significantly higher estimates of prevalence<sup>18 19</sup> and one of these also has a significantly higher estimate of incidence.<sup>19</sup> These studies included methodologies likely to have a high pick up rate for cases of NMOSD through multiple healthcare sources and national databases<sup>19</sup> or systematic serological testing of all possible cases.<sup>18</sup> Relatively small sample sizes

**Table 2. Incidence and prevalence of NMOSD in populations of Caucasian ancestry**

Study <sup>ref</sup>	Population	Incidence (95% CI) (per million per year)	Prevalence (95% CI) (per 100,000)
Cabrera-Gomez et al 2009 <sup>20</sup>	Cuba	0.44 (0.3 – 0.62)	0.43 (0.29 – 0.61)
Asgari et al 2011 <sup>19</sup>	Denmark	4 (3 – 5.4)	4.41 (3.1 – 5.7)
Cosburn et al 2012 <sup>21</sup>	Wales		1.96 (1.22 – 2.97)
Jacob et al 2013 <sup>22</sup>	Merseyside	0.8 (0.3 – 1.6)	0.72 (0.31 – 1.42)
Etemadifar et al 2014 <sup>23</sup>	Iran		1.95 (1.62 – 2.23)
Kashopazha et al 2015 <sup>24</sup>	Iran		0.8 (0.54 – 1.06)
Flanagan et al 2016 <sup>18a</sup>	Olmstead	0.7 (0 – 2.1)	3.9 (0.8 – 7.1)
Present Study	ANZ	0.37 (0.36 – 0.38)	0.7 (0.66 – 0.74)

Results are as presented in original papers

ANZ = Australia and New Zealand

<sup>a</sup> Age and gender-adjusted figures

means that these higher prevalence figures could represent statistical random variation (the number of affected cases in the recent USA study was only 6).<sup>18</sup> Conversely, it is likely the results presented here are an underestimate. There are a number of limitations with the present study. Firstly, only a proportion of our suspected cases had testing for AQP4 antibodies with a cell-based assay. Secondly, we have not tested every patient with demyelinating disease of the central nervous system for AQP4 antibodies. These limitations are however, only likely to have a relatively small impact on the overall prevalence. A third and more significant limitation is that only currently or recently active cases who have been seen in clinics or undergone AQP4 antibody testing will have been identified. Against this is the fact that the age-specific rates of NMOSD in the present series was very consistent for the higher age groups. Finally, we have used the 2015 Wingerchuk criteria,<sup>11</sup> which are more stringent with regards to seronegative NMOSD. Confirmation of seronegative cases was also constrained by the availability of relevant MR imaging having ever been performed. There is certainly also a potential for the referral of these cases to have been reduced compared to seropositive cases, despite the clinically-based mechanism of referral for the initial capture.

The overall estimated number of cases of NMOSD (193) represents less than 1% of the 26,600 people with multiple sclerosis estimated to be living in Australia<sup>25</sup> and New Zealand.<sup>26</sup> This is a similar proportion to that seen in other European populations. The increased frequency of NMOSD in women is consistent with previous studies. In a survey using the same methodology across a defined geographical region we have demonstrated a higher



prevalence of NMOSD in people with Asian ancestry (3-fold increase compared with the remaining population of predominantly European ancestry).

The present data do not support a latitudinal gradient in NMOSD as compared with MS for this region.<sup>27 28</sup> In fact the data suggest a possible weak inverse relationship, with prevalence increasing at lower latitudes. This does not appear to be explained by regional variations in the proportion with Asian ancestry in each region as the trend remained when these populations were removed. Another possible explanation could be ease of access to serological testing, as the two states with the highest prevalence of NMOSD have the two laboratories with the highest throughput of AQP4 antibody testing. The proportions of new cases identified through the laboratory survey certainly suggest that this may have been a factor with the two most distant regions (South Australia/Northern Territory) and New Zealand having the lowest proportions of cases detected through the laboratory survey. We have demonstrated an increased frequency of NMOSD in women compared to men consistent with previous studies (Table 3).

In conclusion, the Australia and New Zealand region has incidence and prevalence estimates for NMOSD which are within the ranges seen in other populations around the world, with the possible exception of populations with African ancestry.<sup>18</sup> The prevalence of NMOSD is higher in people with Asian ancestry compared with the remaining predominantly European ancestry population of Australia and New Zealand and NMOSD does not

share the latitudinal gradient seen with MS across this region. It therefore seems likely that the epidemiology of NMOSD is different to MS and that susceptibility factors thought to be important in MS (e.g. vitamin D and sunlight) may not play a significant role in NMOSD.

**Table 3. Female:Male ratios in NMOSD cohorts**

Author <sup>ref</sup>	Population	Inclusion Criteria	N	Female (%)	Male (%)	Ratio (F:M)
<b>Asian</b>						
Nagaishi et al 2011 <sup>29</sup>	Japan	AQP4-Ab positive	583	533 (91)	50 (9)	10.7:1
Barhate et al 2014 <sup>30</sup>	India	2006 Wingerchuk	44	39 (89)	5 (11)	7.8:1
Pandit & Kundapur 2014 <sup>31</sup>	India	2006/2007 Wingerchuk	11	6 (55)	5 (45)	1.2:1
Yin et al 2015 <sup>32</sup>	China	2006 Wingerchuk plus <sup>a</sup>	108	92 (85)	16 (15)	5.8:1
<b>Black</b>						
Flanagan et al 2016 <sup>18</sup>	US/Martinique	AQP4-Ab positive	45	40 (89)	5 (11)	8:1
Daoudi & Bouzar 2016 <sup>33</sup>	Algeria	2015 Wingerchuk	8	6 (75)	2 (25)	3:1
<b>Caucasian</b>						
Rivera et al 2008 <sup>34</sup>	Mexico	1999 Wingerchuk	34	24 (71)	10 (29)	2.4:1
Cabrera-Gomez et al 2009 <sup>20</sup>	Cuba	1999 Wingerchuk	58	51 (88)	7 (12)	7.3:1
Asgari et al 2011 <sup>19</sup>	Denmark	2006 Wingerchuk	42	31 (74)	11 (26)	2.8:1
Collongues et al 2011 <sup>35</sup>	France	2006 Wingerchuk	155	108 (70)	47 (30)	2.3:1
Cosburn et al 2012 <sup>21</sup>	Wales	2007 Wingerchuk	14	12 (86)	2 (14)	6:1
Aboul-Enein et al 2013 <sup>36</sup>	Austria	AQP4-Ab positive	71	62 (87)	9 (13)	6.9:1
Jacob et al 2013 <sup>22</sup>	England	2006 Wingerchuk	8	7 (88)	1 (13)	7:1
Etemadifar et al 2014 <sup>23</sup>	Iran	2006 Wingerchuk	95	66 (69)	29 (31)	2.3:1
Kashipazha et al 2015 <sup>24</sup>	Iran	2006 Wingerchuk plus <sup>b</sup>	36	30 (83)	6 (17)	5:1
Chitnis et al 2016 <sup>37</sup>	US <sup>c</sup>	2006 Wingerchuk plus <sup>d</sup>	38	26 (68)	12 (32)	2.2:1
Sepulveda et al 2016 <sup>38</sup>	Spain	2006 Wingerchuk	181	157 (87)	24 (13)	6.5:1
Kleiter et al 2016 <sup>39</sup>	Germany	2006 Wingerchuk plus <sup>a</sup>	186	152 (82)	34 (18)	4.5:1
Present Study	ANZ	2015 Wingerchuk	147	126 (86)	21 (14)	6:1
<b>Combined</b>			<b>1864</b>	<b>1568 (84)</b>	<b>296 (16)</b>	<b>5.3:1</b>

<sup>a</sup> additional criteria included AQP4-Ab positive high risk syndromes

## **FIGURE LEGENDS**

### **Figure 1**

Gender and age distribution of NMOSD in Australia and New Zealand.

### **Figure 2**

Latitudinal variation in prevalence of NMOSD across Australia and New Zealand.

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