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Short report

# Socioeconomic burden of AQP4-antibody seropositive NMOSD: a nationwide registry-based study

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## ABSTRACT

**Background** AQP4-antibody seropositive (AQP4-Ab+) neuromyelitis optica spectrum disorder (NMOSD) may cause reduced work capability due to disability. Here, we evaluated the socioeconomic status of patients with AQP4-Ab+NMOSD in off-label therapy era compared with the general population.

**Methods** A longitudinal nationwide population-based study including all Danish patients with AQP4-Ab+NMOSD and matched controls from the general population. The cohort was linked to other Danish nationwide population-based databases. The study period was from 1992 to 2021. The main outcomes were loss of income from salary, limited work capability, disability pension and civil status. The longitudinal risks of outcomes were presented in cumulative incidence curves. Fisher's exact test, $\chi^2$ test or Wilcoxon test were applied for comparison.

**Results** We included 65 patients with a median follow-up of 8.6 years. Annual income declined significantly after disease onset (index year) compared with the general population. One year after the index year, the median annual income in 2015-indexed Euro for patients averaged 13 285 (IQR: 139 to 36 336) versus controls 33 035 (IQR: 6870 to 45 978); p=0.04. Five years postindex year, the average income for patients further dropped to 276 (IQR: 0 to 23 691) versus controls 22 141 (IQR: 0 to 42 986); p=0.03. At the end of follow-up, significantly higher proportion of patients were either in 'flexjob' (36.9% patients vs 14% controls, p<0.00) or receiving disability pension (16.9% patients vs 4.3% controls, p<0.00).

**Conclusions** The socioeconomic status of patients with AQP4-Ab+NMOSD deteriorates rapidly following disease onset. A substantial proportion of these patients lose their work capacity leading to increased financial burden on both their families and society.

## INTRODUCTION

AQP4-antibody seropositive neuromyelitis optica spectrum disorder (AQP4-Ab+NMOSD) is a severe, chronic, relapsing inflammatory disease affecting the optic nerve, spinal cord and brain, which develops most often in adults of working age.[1] Without prompt adequate treatment of relapses and maintenance therapy, patients have a high risk of being left with permanent blindness, paralysis or other neurological disabilities and increased mortality.[2 3] Moreover, patients are at risk of further relapses. The poor or incomplete recovery from relapses causes disability accumulations and limits work capability.[4] There are few studies on the economic burden of NMOSD treatment and management on the healthcare system, and data are scarce on the socioeconomic impact of AQP4-Ab+NMOSD from the patient's perspective.[5–7] This study was conducted to explore the burden of AQP4-Ab+NMOSD on patients' work capability and civil status. These outcomes are important when calculating the global economic burden of NMOSD on society and can improve cost-effectiveness estimations of established and new evidence-based treatments for NMOSD.

## METHODS

This longitudinal nationwide population-based study includes all AQP4-Ab+ patients identified from the 9932 patients tested for AQP4-Ab (January 2007–January 2021) and from the Danish Multiple Sclerosis Registry for those fulfilling the 2015 International Panel for NMO Diagnosis criteria.[8 9] Testing serum for AQP4-Ab was performed with either the commercial cell-based assay (CBA) in Denmark (Euroimmun AG, Lubeck, Germany) or with live CBA at John Radcliffe Hospital, Oxford, UK. Patients were matched 1:10 to individuals from the general population based on sex, education level and birth year. The unique Danish personal identification number linked patients and controls to data from registries hosted by Statistics Denmark: (1) the Income Statistics Register encompassing detailed annual information on citizens submitting a tax return to the Danish Tax Administration since 1970, (2) the Danish Rational Economic Agents Model (DREAM) database containing weekly data since 1991 on social transfer payments inclusively disability pension and 'flexjob' and (3) the Population Statistics Register providing annual information on marriage, partnership and divorce, and so on.[10–12] 'Flexjob' was introduced in 1998 as a special social welfare job offering reduced and flexible working hours adjusted to the permanently reduced working capability. Data were pseudonymised by Statistics Denmark and analysed on their server. The outcomes compared with the general population were (1) loss of regular income from salary for a full calendar year and (2) annual median income expressed in 2015-indexed Euro, (3) disability pension and (4) 'flexjob' defined as the first transfer payment labelled as such. Moreover, we explored (5) civil status.

The study period from 1 January 1992 to 1 January 2021, was chosen based on outcomes

available from the registries. Data analyses on income, disability pension and 'flexjob' included patients between the ages of 18 and 65 years, while data on civil status included patients aged 18 years and above. Above the age of 65, citizens are eligible for state pension. Patients with disease onset before the age of 18 years entered the analyses when they turned 18 years. Index year was considered as the calendar year of disease start and baseline was the calendar year before the first clinical symptom.

Clinical and demographic features are given as median (IQR), mean (SD) or percentage as appropriate. Cumulative incidence curves are plotted to visually represent loss of income from salary, reaching 'flexjob', and disability pension. The annual median income is computed as 2015-indexed Euros providing a standardised financial measure accounting for inflation. A graph presenting its changes during follow-up illustrates the economic impact on patients compared with controls. Fisher's exact test, $\chi^2$ test or Wilcoxon test were applied when comparing patients to the matched controls. All analyses were performed using STATA V.14 (StataCorp) and statistical significance was $p<0.05$.

## RESULTS

Data on matching characteristics of patients, controls and main outcomes are summarised in table 1.

The median follow-up of patients was 8.6 years (IQR: 3.7–17.7). The annual median income of patients with AQP4-Ab+NMOSD did not differ from matched controls at baseline, whereafter it dropped significantly from 22 631 2015 indexed-Euro to 13 285 2015-indexed Euro (figure 1A) after 1 year, a reduction of 41%. Similarly, the cumulative incidence curve (figure 1B) shows that 69.3% (95% CI: 41.4% to 92.7%) of the patients with AQP4-Ab+NMOSD at risk had lost their income from salaries 2 years after disease onset, while it was only 24.2% (95% CI: 16.3% to 35.0%) among matched

**Table 1** Summary of the matching features and the main outcomes

| | Patients | Matched controls | P value |
|---|---|---|---|
| At disease start | | | |
| Total, n | 65 | 650 | |
| Mean age at disease start (years, (SD)) | 45.3 (19.0) | 45.3 (18.9) | |
| Female, n (%) | 58 (89.2) | 580 (89.2) | |
| Education, n (%) | | | |
| Lower secondary | 22 (33.8) | 230 (35.4) | |
| Upper secondary | 22 (33.8) | 217 (33.4) | |
| Post secondary | 15 (23.1) | 132 (20.3) | |
| Socioeconomic status at disease start, n (%) | | | |
| Own business | <3 | 15 (2.3) | |
| Employee | 24 (36.9) | 297 (45.7) | |
| Unemployed or welfare benefit | <3 | 46 (7.1) | |
| Leave of absence (sick leave or parental leave) | 5 (7.7) | 6 (0.9) | |
| Educational support | 0 (0.0) | 49 (7.5) | |
| Other | 25 (38.5) | 222 (34.2) | |
| Outcomes | | | |
| Annual median income | | | |
| Total, n | 35 | 402 | |
| 1-year before index year in 2015-indexed Euro (median, IQR) | 32 928 (10 222 to 42 521) | 32 970 (9256 to 46 721) | 0.38 |
| At index year in 2015-indexed Euro (median, IQR) | 22 631 (4492 to 44 201) | 34 627 (10 963 to 47 497) | 0.14 |
| At 1 year after index year in 2015-indexed Euro (median, IQR) | 13 285 (139 to 36 336) | 33 035 (6870 to 45 978) | 0.04 |
| At 5 years after index year in 2015-indexed Euro (median, IQR) | 276 (0 to 23 691) | 22 141 (0 to 42 986) | 0.03 |
| Disability pension | | | |
| Total, n | 65 | 650 | |
| At baseline, n (%) | 6 (9.2) | 47 (7.2) | 0.56 |
| At follow-up, n (%) | 24 (36.9) | 91 (14.0) | 0.00 |
| 'Flexjob' | | | |
| Total, n | 65 | 650 | |
| At baseline, n (%) | 0 (0.0) | 13 (2.0) | 0.25 |
| At follow-up, n (%) | 11 (16.9) | 28 (4.3) | 0.00 |
| Civil status | | | |
| Total, n | | | |
| Married/regular partnership | 65 | 650 | |
| At baseline, n (%) | 32 (49.2) | 343 (52.8) | 0.59 |
| At follow-up, n (%) | 34 (52.3) | 342 (52.6) | 0.96 |
| Single, divorced or widow | | | |
| At baseline, n (%) | 33 (50.8) | 307 (47.2) | 0.59 |
| Single or widow at follow-up, n (%) | 19 (29.2) | 203 (31.2) | 0.74 |
| Divorced at follow-up, n (%) | 11 (16.9) | 104 (16.0) | 0.84 |

<3: due to the General Data Protection Regulation, extracting precise microdata when the number of cases is below three are not allowed.

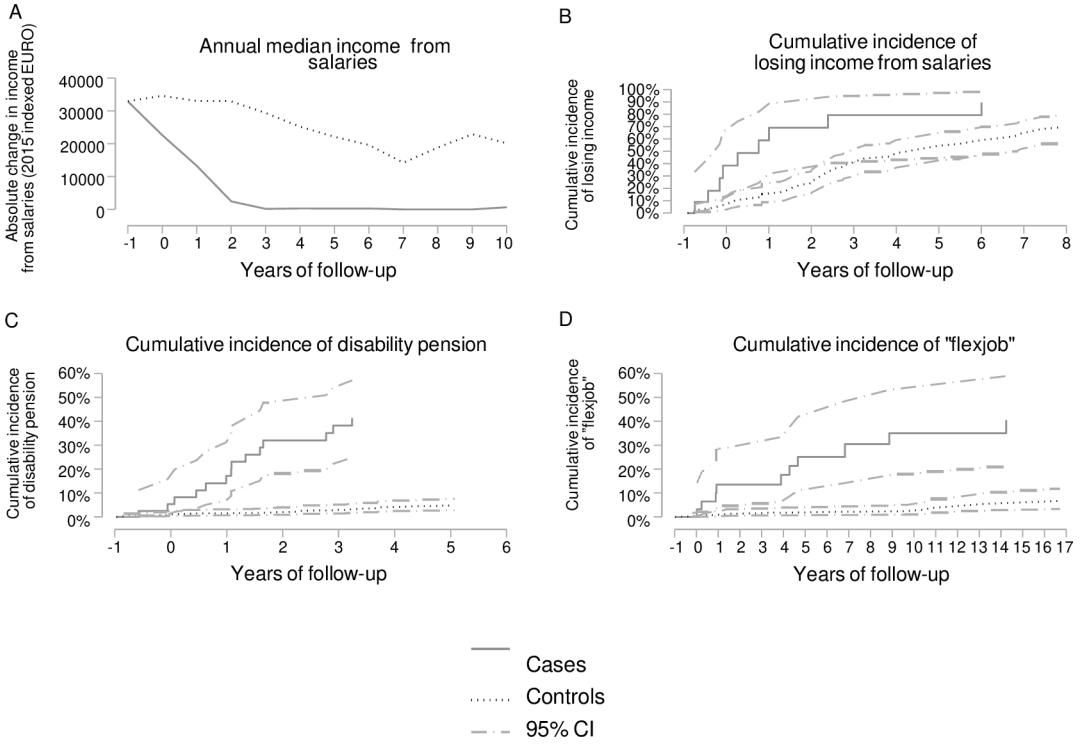


**Figure 1** Median annual income from salaries during follow-up (A); cumulative incidence curves of losing income from salaries (B), disability pension (C), and 'flexjob' (D). Curves are adjusted for competing risks. Bold line: AQP4-Ab+NMOSD cases; dotted line: matched controls from the general population; dash-dotted line: 95% CI. AQP4-Ab+, AQP4-antibody seropositive; NMOSD, neuromyelitis optica spectrum disorder.

controls. A significantly higher proportion of patients with AQP4-Ab+NMOSD were granted disability pensions (37% vs 14%, p<0.00) or 'flexjob' (17% vs 4%, p<0.00) compared with controls at the end of follow-up, while at baseline the proportions were comparable. The cumulative incidence curves accounting for competing risks illustrate differences in the risk of disability pension (figure 1C) and 'flexjob' (figure 1D) occurring shortly after disease onset. Two years after disease onset, 32.9% (95% CI: 19.7% to 51.5%) of patients reached disability pension and 15.5% (95% CI: 6.1% to 36.4%) reached 'flexjob', whereas the proportion of controls reaching the outcome was 2.1% (95% CI: 0.9% to 4.1%) for disability pension and 1.3% (95% CI: 0.5% to 3.5%) for 'flexjob'.

We compared clinical characteristics between patients with disability pension and those without disability pension during the follow-up. We found that 17% of patients on disability pension experienced a multifocal relapse as the first disease manifestation in contrast with the other subgroup (17.4% vs 0%, p=0.02). Rituximab as treatment at last follow-up tended to be slightly more frequent among patients not on disability pension (<3 vs 5, p=0.09). We found no differences in the other evaluated features (online supplemental table 1).

The civil status of patients did not differ from matched controls at baseline or follow-up.

## DISCUSSION

The key findings of this nationwide population-based cohort study are that AQP4-Ab+NMOSD is strongly associated with an increased risk of losing income, being on 'flexjob', or on disability pension compared with the general population. This risk increases drastically immediately after disease onset. The civil status of patients is not affected by AQP4-Ab+NMOSD in this cohort. This study was performed in the off-label therapy era of AQP4-Ab+NMOSD management. No patient was treated with satralizumab, and two patients received eculizumab in later stage of the disease in a period.

Previous studies on the economic burden of NMOSD are heterogeneous in several aspects: patient identification, data sources, serology status and the main outcomes of interest. Cross-country comparisons are difficult given the differences in healthcare and social benefit systems among countries. A study focusing on the healthcare utilisation and expenditure linked to NMOSD in the USA found that the total annualised cost of healthcare utilisation was almost seven times higher for patients with NMOSD than the control patient population without NMOSD.[5] In the UK, patients and carers reported data revealing high costs in healthcare, social care and private expenses, and only 13 (11%) out of 117 patients with NMOSD with a mean follow-up time of 12 years (range: 1–45) were in paid employment. The follow-up time of these 13 patients was not reported.[7] Our data showed that the cumulative incidence of loss of income from salary was 90% at the follow-up time of 6 years. Studies from the UK and Germany found correlation between higher costs and more severe disease disability evaluated with the Expanded Disability Status Scale (EDSS).[6 7] In the present study, we observed that multifocal relapse was more common among patients with disability pension, which may be explained by poorer recovery. The number of relapses and EDSS was not increased among patients reaching disability pension during follow-up, but the small sample size may hinder the detection of such differences.

Comparing the Danish population-based NMOSD and multiple sclerosis (MS) cohorts, 38.0% of MS versus 18.9% of healthy controls lost income, and 30.5% of patients with MS versus 7.7% of healthy controls were granted disability pension with a median MS duration of 13 years (IQR: 13.5).[13] Thus,

patients with AQP4-Ab+NMOSD under the same regulations for income and disability pension reached these outcomes earlier in the disease course and at a higher rate than patients with MS in Denmark. Relationship status estimated in the Danish population showed a high risk of cessation of partnership in MS compared with the background population, which we did not see in the patients with AQP4-Ab+NMOSD population.[14] This difference could be caused by the fact that NMOSD manifests later in life, when couples may already have children and stronger family relationships.

The strengths of our study are that data originate from a previously validated nationwide population-based patient cohort consisting exclusively of AQP4-Ab+NMOSD and the socioeconomic data were derived from well-established national registries and databases.[10–12 15]

The rarity of the disease caused limitations as the relatively small number of patients, and further subgroup and multivariate analyses were not possible.[1]

Our results show a dramatic change in socioeconomic status of patients with NMOSD occurring within a few years after the disease onset. Therefore, it is important to emphasise the potential impact and the need for prompt and highly effective treatment from disease onset along with aggressive relapse treatment to provide the highest probability of complete recovery from relapse and to prevent disability accumulation to protect ability to remain fully employed.

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**Contributors** All authors fulfil the authorship criteria. VP: study concept and design, analysis and interpretation of data, drafting/revising the manuscript and acts as guarantor. MM and ZI: study concept and design, acquisition of data, analysis or interpretation of data and revising the manuscript. MW-H, KBS, JF, FS: acquisition of data and revising the manuscript. ZI and MM are joint last authors.

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**Competing interests** VP received travel grants from Merck and Sanofi and received research support from Roche. MW-H is currently employed by Novo Nordisk. He has served on the scientific advisory board for Sanofi and has received honoraria for lecturing for Novartis and Sanofi. Novo Nordisk is not active in the field of multiple sclerosis, and the author does not consider this employment a conflict of interest regarding his contributions to research in this area. KBS has served as a consultant for Takeda Pharma A/S and received travel grants from TEVA, Biogen, Merck and Novartis. JF has received no funding to support the presented work. She has served on scientific advisory boards for and received funding for travel related to these activities and honoraria from Merck Serono, Sanofi-Aventis, Roche, Novartis and Chiesi. FS has served on scientific advisory boards for, served as consultant for, received support for congress participation or received speaker honoraria from Alexion, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche and Sanofi Genzyme. His laboratory has received research support from Biogen, Merck, Novartis, Roche and Sanofi Genzyme. ZI has received speakers' honoraria and/or research grants from Biogen, Roche, Sanofi, Novartis, Merck, Alexion, Bristol Myers Squibb, Lundbeckfonden and Jascha Fonden, has been member of advisory boards at Alexion, Biogen, Sanofi, Merck, Roche and Novartis, was member of the adjudication relapse committee in phase 3 trials and has been principal investigator in studies sponsored by Biogen, Merck, Roche and Sanofi. MM has served in scientific advisory board for Sanofi, Novartis, Merck, and has received honoraria for lecturing from Biogen, Merck, Novartis, Roche, Genzyme, Bristol Myers Squibb.

**Patient consent for publication** Not applicable.

**Ethics approval** The Danish Data Protection Agency in the Region of Southern Denmark (file no.: 20/27251) and the Regional Ethical Committee (file no.: S-20200178) approved the study. The Danish Health and Medicines Authority waived the requirement for patient informed consent (file no.: 21/8187).

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