Trends in optic neuritis incidence and prevalence in the UK and association with systemic and neurologic disease

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The Epidemiology of Optic Neuritis in the United Kingdom over 22 years

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Ethics

Use of IQVIA Medical Research Data* is approved by the UK Research Ethics Committee (reference number: 18/LO/0441). In accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (SRC) (reference number: 19THIN086).

36 *IQVIA Medical Research Data (IMRD) incorporates data from THIN, A Cegedim Database.
37 Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA.
38 This work used de-identified data provided by patients as a part of their routine primary care.

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3 Key Points

- Question: What are trends in optic neuritis (ON) incidence and prevalence, and associations with systemic and neurological disease?
- Findings: This cohort study of >11 million patients reports ON incidence of 3.7 per 100,000 person-years, affecting 114 per 100,000 population in 2018 (76,279 people in UK). Case-control and matched cohort analyses identify strong association with multiple sclerosis (MS), and weaker associations with Behçet's disease, sarcoidosis and Sjögren's syndrome.
- Meaning: ON incidence is stable, and predominantly associated with MS. Numerous other disease associations, individually rare, indicate a significant burden of non-MS ON patients requiring urgent management to preserve sight.

Abstract

Importance: Epidemiological data on optic neuritis (ON) incidence, and associations with immune-mediated inflammatory diseases (IMIDs), is sparse.

Objective: Estimate 22-year trends in ON prevalence and incidence, and association with IMIDs in the UK.

Study design: Cross-sectional (prevalence), population cohort (incidence and risk factors) (1997-2018); matched case-control and matched cohort (associations with IMIDs at baseline and during follow-up, respectively) (1995-2020).

Setting: The Health Improvement Network, a nationally-representative primary care database.

Participants: Cross-sectional and cohort (n=11,089,365 aged ≥ 1 year); matched case-control and cohort (matched on age, sex, region and Townsend Deprivation Index).

Exposure: ON

Main Outcomes: ON annual point prevalence and incidence rate; adjusted incident rate ratio (IRR, 95%CI) for risk factors; adjusted odds ratio (OR, 95%CI) and adjusted hazard ratio (HR, 95%CI) for 66 IMIDs.

Results: Incident ON patients were 69.5% (n=2011/2894) female, 92.5% (n=1227/1326) white, with mean age 41.6 (SD 15.6, range 2.4-94.2) years. Overall incidence across 22-years was stable at 3.7 (95%CI 3.6-3.9) per 100,000 person-years. Annual point prevalence (per 100,000) increased with database maturity, from 69.3 (95%CI 57.2-81.3) in 1997 to 114.8 (95%CI 111.0-118.6) in 2018. Highest risk of incident ON was associated with female sex, obesity, reproductive age, smoking and residence at higher latitude, with significantly lower risk in South Asian or mixed race compared to white. ON cases had significantly higher odds of prior multiple sclerosis (MS) (OR=98.2, 65.40-147.52), syphilis (OR=5.76, 1.39-23.96), mycoplasma (OR=3.90, 1.09-13.93), vasculitis (OR=3.70, 1.68-8.15), sarcoidosis (OR=2.50, 1.21-5.18), Epstein Barr virus (OR=2.29, 1.80-2.92), Crohn's disease (OR=1.97, 1.13-3.43) and psoriasis (OR=1.28, 1.03-1.58). ON patients had significantly higher hazard of incident MS (HR=284.97, 167.85-483.81), Behçet's disease (HR=17.39, 1.55-195.53), sarcoidosis (HR=14.80, 4.86-45.08), vasculitis (HR=4.89, 1.82-

13.10), Sjögren's syndrome (HR=3.48,1.38-8.76), and herpetic infection (HR=1.68,1.24-2.28).

Conclusions and Relevance: The UK incidence of ON is stable. Whilst predominantly associated with MS we identify numerous other ON associations with IMIDs in a more robust and definitive way than prior studies. Whilst individually rare, together these outnumber MS ON and typically require urgent management to preserve sight.

Introduction

Epidemiological data on optic neuritis (ON) and ON-associated diseases are sparse. Incidence rates (per 100,000 person-years) vary more than 5-fold, between 0.83 (Singapore, 2009)¹ and 5.36 (Barcelona, 2008-2012).² One possible explanation is variation in prevalence of multiple sclerosis (MS) and other immune-mediated inflammatory disease (IMID). Here, we consider IMID as a final common pathway for inciting infectious and non-infectious (autoimmune and autoinflammatory) pathology. Delayed diagnosis and initiation of high dose glucocorticoid therapy in non-MSON ('atypical') cases may result in irreversible sight loss.³⁻⁴ Population-level data on the prior probability of associated IMIDs would inform cross-specialty awareness of ON, and support workforce planning, better-informed investigation, and demand modelling for high-cost immunosuppressive therapy.

A National Health Service primary care electronic patient record database, The Health Improvement Network (THIN), provides opportunity to interrogate the epidemiology of ON and its associated IMIDs. The most frequent associations are with autoimmune disease, extending from MS and neuromyelitis optica (NMO) to include anti-myelin oligodendrocyte glycoprotein (MOG) ON, and many rarer associations.⁵ ON also develops in the context of reactive, primary and secondary vasculitides, infection, post-infectious autoimmune reactions, including with human coronavirus,⁶ recent vaccination, and medication (e.g. anti-TNF α therapy).⁵ ON also develops in conjunction with other ocular presentations, including uveitis,^{7,8} and scleritis.⁹

This study had two aims. Firstly, to ascertain 22-year trends in the incidence and prevalence of ON in the general UK population, and risk factors for incident ON. Secondly, to explore the strength of association between ON and 66 IMIDs.⁵

Methods

Data Source

We analysed THIN data from 01/01/1995 to 01/03/2020. THIN is a UK national population-representative database of electronic primary care records.^{10,11} It contains anonymised, coded information for over 15 million patients from 808 primary care general practices (GP), including patient demographics, diagnoses, drug prescriptions, and laboratory test results.

Design

We estimated annual ON incidence rates through yearly (1st January to 31st December) cohort studies, from 1997 to 2018, inclusive. We estimated annual ON prevalence by performing sequential cross-sectional studies on data collected on January 1st each year for the same period. Data for 1995, 1996, 2019 and 2020 were excluded as incomplete. Risk factors for ON were explored in a cohort analysis from 1997 to 2018. We performed case-control and retrospective cohort studies using data from 01/01/1995 to 01/03/2020, to explore odds of antecedent diagnosis, and hazard of incident diagnosis of 66 IMIDs in ON patients compared to controls.

Study Population

General practices were eligible for inclusion one year after commencing electronic medical record use, and one year after reporting acceptable mortality rates (a data quality indicator). We included patients aged ≥ 1 year, who were registered with an eligible GP at least one year before cohort entry (to ensure documentation of important baseline covariates).

In the UK, ON is diagnosed exclusively by hospital specialists. Diagnosis is communicated to GPs, who enter the clinical (Read) code into the electronic medical record. Supplementary eTable1 reports the Read codes included in our case definition.

For the matched case-control and cohort studies, we randomly matched patients with incident (newly diagnosed during the study period) ON with four controls, selected from a pool of age-, sex-, region- and Townsend Deprivation Index(TDI)-matched patients without ON.^{12,13} We used an established method for randomization to identify matched controls.¹⁴ ON patient index date was the ON diagnosis date. The same index date was assigned to the corresponding matched controls to avoid immortal time bias.¹⁵ We matched age at index date to within one year. ON patients and controls were followed-up from index date until the earliest of the following events: incident IMID diagnosis, defined using Read codes for each disease; death; patient leaving GP; GP ceasing database contributions; or study end. Where TDI was missing, we matched ON patients with a control in whom it was also missing.

Statistical Analysis

We estimated annual ON incidence rates with 95% confidence intervals [95% CI] by dividing the number of newly diagnosed ON patients by total person-years at risk. Across the whole study period, we estimated overall incidence rates stratified by age and sex. For point

prevalence [95% CI], we calculated proportion of eligible ON patients on 1st January each year.

To explore risk factors for ON, we performed univariable and multivariable Poisson regression analyses to estimate crude and adjusted incidence rate ratios (aIRR), offsetting for person-years of follow-up. The adjustment variables we considered included age category at index date, sex, ethnicity, smoking category, BMI category, nation and TDI.^{12,13} We created a separate category for missing data. We included variables with significance $p < .10$ in single variable analyses in multivariable models. All variables were recorded at cohort entry and summarized using descriptive statistics: mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, and frequency (percentage [%], n) for categorical variables.

We performed a case-control and matched cohort study on patients presenting between 01/01/1995 and 01/03/2020. For patients with ON compared to matched controls, we calculated odds of prior diagnosis, and hazard of incident diagnosis, of each IMID, excluding patients with prior diagnosis at baseline from the latter. We performed logistic regression analysis to obtain crude and adjusted odds ratios (OR [95% CI]) for each IMID at baseline, comparing patients with and without ON. We estimated adjusted hazard ratios (HR [95% CI]) using Cox proportional hazards regression models for each IMID. The adjustment variables were the same as those selected for the multivariable Poisson model. We checked model assumptions using log-log plots and the Schoenfeld residuals test. We used the Nelson-Aalen cumulative hazard function to plot cumulative hazard of these outcomes. Analyses were performed with Stata IC, version 13.1 (StataCorp LLC). We set statistical significance at $p < .05$.

Results

Incidence and prevalence

The cross-sectional and retrospective cohort studies (01/01/1997 to 31/12/2018), included 10,937,511 patients with 75.2 million person-years follow-up.

Annual ON incidence remained stable, with an overall rate across the 22-year period of 3.74 [3.60-3.88]/100,000 person-years (Figure 1A, Supplement eTable2). This combined incidence in children (1-17 years) of 0.77 [0.64-0.9], and adults of 4.46 [4.30-4.63] per 100,000 person-years. Figure 1B illustrates incidence stratified by age at ON onset and sex.

ON prevalence (per 100,000) increased from 69.3 [57.2-81] in 1997 to 114.8 [111.0-118.6] in 2018 (eFigure 1, Supplement eTable 2), with an estimated 76,279 [73,744-78,814] patients in the UK in 2018.¹⁶

Risk factors for incident ON

Table 1 compares characteristics of 2826 incident ON patients and the general population without ON. Incident ON patients were 69.4%(n=1962) female, with mean age at study entry 35.6(SD15.6, range 2-94) years, 92.4%(n=1192/1290) were white, mean BMI at study entry was 26.3(SD 5.9)kgm⁻² (missing n=915), 46.5%(n=1013/2178) were smokers or ex-smokers, 25.4%(n=599/2359) were from TDI category 1 (least deprived) and 68.8%(n=1943) resided in England.

In a multivariable Poisson regression model (Table 1), significant predictors of incident ON included age category at study entry (peak difference in 21-30 years group, of 24.9% versus 18.2%, aIRR=6.80 [5.50-8.40], p<0.001), female sex (69.4% versus 50.9%, aIRR=2.26 [2.08-2.45], p<0.001), residence in Scotland compared to England (aIRR=1.19 [1.08-1.32], p=0.001), obesity (aIRR=1.27 [1.11-1.46], p=0.001) or morbid obesity (aIRR=1.37 [1.15-1.63], p<0.001) compared to normal weight, and ex-(aIRR=1.19 [1.05-1.35], p=0.007) or current smoking (aIRR=1.32 [1.20-1.45], p<0.001), compared to never smoking, with no association with TDI. Compared to white ethnicity, risk of incident ON was lower in patients of mixed race (aIRR=0.52 [0.30-0.92], p=0.025) or South Asian ethnicity (aIRR=0.56 [0.39-0.8], p=0.001).

Matched case-control and matched cohort studies

We included 2,894 incident ON patients (113 with onset age ≤17 years) and 11,576 controls (01/01/1995 to 01/03/2020). At first diagnosis, 67.2%(n=1944) ON was idiopathic, 15.5%(n=449) was associated with a baseline non-MS IMID diagnosis, 14.3%(n=415) with baseline MS, and 3.0%(n=86) with both MS and ≥1 IMID (most frequently EBV, psoriasis and herpetic infection). In addition, associated inflammatory ocular phenotypes were not uncommon: uveitis was diagnosed in 1.9%(n=37) idiopathic ON, 4.5%(n=21) non-MS IMID ON, 2.9%(n=12) MSON, and 9.3%(n=8) with both MS and another IMID ON; scleritis was diagnosed in 0.3%(n=6) idiopathic ON and 2.2%(n=10) with baseline non-MS IMID ON.

In a series of adjusted logistic regression analyses, we compared patients with and without ON, and found that baseline IMID diagnosis was more common in ON (Table 2 and Figure

2). ON patients had significantly higher odds of baseline diagnosis of MS, syphilis, mycoplasma, vasculitis, sarcoidosis, Epstein Barr virus, Crohn's disease, and psoriasis (by decreasing strength of association). In addition, diagnoses of NMO (0.21%, n=6), granulomatosis with polyangiitis ([GPA] 0.17%, n=5), Behçet's disease (0.10%, n=3), and Cogan's syndrome (0.03%, n=1) were observed in patients with ON but not controls.

Median follow-up in the cohort study was 5.27 (IQR 2.29-9.43) years for ON patients, and 4.98 (IQR 2.07-9.16) years for controls. Table 2, Figure 2 and eFigure 3 show that in a series of adjusted Cox proportional hazards regression analyses, in comparison to controls, ON patients had significantly higher hazard of incident MS (Figure 3 and eFigure2), Behçet's disease, sarcoidosis, vasculitis, Sjögren's syndrome, and herpetic infection (herpes zoster or simplex) (by decreasing strength of association). In addition, some ON patients, but not controls, developed NMO (1.18%, n=34), GPA (0.14%, 4 cases), toxoplasmosis (0.10%, n=3), paraneoplastic disorder (0.07%, n=2) and 1 patient was diagnosed with each of Henoch-Schönlein purpura, syphilis, Lyme disease and CREST (calcinosis, Raynaud's, esophageal dysfunction, sclerodactyly, telangiectasia) syndrome. ON patients, but not controls, were also significantly more likely to develop incident uveitis but not scleritis.

ON patients were significantly more likely than controls to have a prior diagnosis of giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) and also greater hazard of developing incident GCA and PMR. The mean age of 130 patients with these diseases was 68.9(SD 12.5) years compared to 40.8(SD 15.4) years amongst 14,340 without these.

Discussion

The UK population aged ≥ 1 years has a stable incidence of ON at 3.74/100,000 person-years over 22 years, combining 0.77/100,000 person-years in children <18 years and 4.46/100,000 person-years in adults. Over the study period the THIN database matured, reaching a UK prevalence of 114/100,000 population in 2018. These UK estimates align in the mid-range of ON epidemiological estimates over eight decades, including from the USA (Minnesota, 1935-1991, 5.1/100,000/year);¹⁷ European Countries, Spain (Barcelona, 2008-2012, 5.36/100,000/year),² Finland (Northern, 1970-1978, 2.5/100,000/year),¹⁸ and Sweden (Stockholm, 1990-1995, 1.46/100,000 person-years)¹⁹; Japan (1992-1993, 1.62/100,000 adults/year);²⁰ South Korea (National, 2010-2016, 1.04/100,000/year aged <14 years and 3.29/100,000/year aged 15-65 years²¹; and Singapore (0.83/100,000/year).¹ Our data reveal independent higher risk of ON in patients residing at higher latitude (Scotland, aIRR 1.19,

271 p=0.001) after adjustment for potential confounders, consistent with the latitude effect
272 reported in MS.²²

273 This study finds elevated ON risk amongst young women, as has been reported previously
274 (female to male ratio between 1.5:1 and 2.5:1).^{18-20,23} This is possibly driven by strong
275 association with MS in the UK population.^{5,21,24,25} A further explanation is that many genes
276 related to immune regulation are located on the X chromosome; whilst lyonization results in
277 a greater pool of genes to respond to infection, it may contribute to increased susceptibility
278 to autoimmunity.²⁶

279 Novel were significant associations between ON and both obesity (aIRR 1.27 for obesity and
280 1.37 for morbid obesity, p=0.001) and smoking (aIRR 1.32 for current smoking and 1.19 for
281 previous smoking, p<0.01). However, these variables were measured only once at cohort
282 entry, with missing data in 32.4% and 22.9%, respectively. No meaningful effect modification
283 was observed by age group or sex amongst those with recorded data. Obesity and
284 metabolic syndrome have been linked to more rapid neurodegeneration in MS, and whilst
285 the pathophysiological basis remains unknown, proinflammatory cytokines are hypothesised
286 to be contributory.²⁷ There is no known direct link between smoking and ON, but meta-
287 analysis identified smoking as a significant predictor of MS onset,²⁸ and smokers were more
288 likely to develop secondary progressive MS.²⁹ These potential risk factors will require further
289 prospective evaluation.

290 This study confirms well-established associations between ON and prevalent (17.3%) and
291 incident MS. Figure 3 illustrates that 28.2% of ON cases, compared to 0.1% controls,
292 developed MS by 10 years follow-up.^{21,23,30} This rose to 33.7% of those aged 18-50 years at
293 ON onset (eFigure2). This was lower than reported in Minnesota, USA (1935-1991), where
294 39% progressed to MS at 10 years, rising to 60% at 40 years.¹⁷

295 To our knowledge, this is the first population-representative national study to systematically
296 explore, and demonstrate strength and significance of association between ON and 43
297 potentially relevant IMIDs.⁵ Significant associations included sarcoidosis, psoriasis, Crohn's
298 disease, Sjögren's syndrome, Behçet's Disease, GPA, GCA, other vasculitides, PMR, and
299 infection with herpes viruses (herpes simplex and varicella zoster, combined), EBV,
300 mycoplasma and syphilis. Autoimmune diseases affect between 7.6 and 9.4% of the
301 population,³¹ with studies indicating rising incidence,³² and associated ON.² Our large
302 dataset does not confirm rising incidence in the UK over the past two decades.

Our findings, of ten-fold higher odds of previous scleritis amongst ON patients than controls, and five-fold higher odds of previous uveitis, and hazard of incident uveitis, are consistent with a USA database study (103,867 uveitis patients, including 974 with ON).⁸ This reported similar ON prevalence in anterior uveitis and the general population (0.6%, 120/100,000 people), but higher ON prevalence in intermediate (280/100,000), posterior (290/100,000) and pan-uveitis (380/100,000). MS cohort studies (France n=4300,³³ Turkey n=1702³⁴) similarly report uveitis, especially intermediate and panuveitis, in between 0.52% and 0.65% patients, preceding MS diagnosis in 46%, simultaneous in 18%, and following diagnosis in 36%.³³

Implications

This study confirms the strength of association of many non-MS IMIDs with ON. Cross-specialty awareness of these is important, to ensure prompt recognition and treatment. When faced with an acute non-MSON, this study provides an epidemiological evidence-base to guide appropriate investigation, and directed questions around diagnostic criteria for associated IMIDs.

Future population-based studies are needed in other geographic locations to explore whether these findings, in a high-income, predominantly white (92.5%) population, are globally generalizable. This analysis could be repeated in five years to explore stability of epidemiological trends, association with additional rare IMIDs, and to investigate the impact of the global coronavirus-19 pandemic on ON incidence.⁶ Further analysis of THIN, to explore risk factors predictive of incident ON amongst patients exposed to each of the identified IMIDs, with adjustment for exposure to different immunosuppressive, immunomodulatory and antimicrobial therapies, smoking status and BMI category, could yield valuable insights into pathogenesis, risk and prognosis, and guide targeted investigation (for example, should baseline investigations for non-MS ON include mycoplasma serology?).

Strengths and Limitations

This study has several strengths. The very large sample size permits evaluation of associations between ON and 43 IMIDs, and trends over a 22-year period. In addition, the THIN database is generalizable to the UK population.^{10,11} However, even with >11 million patients, this database was underpowered to identify rare associations between ON and IMIDs (Table 3), with no data on 15 IMIDs.⁵ Subtypes of ON were not explicitly captured by

the available Read codes in this database, for example, chronic relapsing idiopathic optic neuropathy (CRION), post-infectious ON, and post-vaccination ON (eTable1). There were no THIN Read codes for 8 diseases (e.g. Blau syndrome and cat scratch/Bartonella infection). There was insufficient data in ON patients or controls to quantify hazard of some diseases (e.g. NMO), and too few paediatric patients to permit meaningful subgroup analysis.

Furthermore, retrospective estimates from this database of routinely collected primary care data have potential risks of bias. There was risk of diagnostic error in the hospital or incorrect coding resulting in misclassification bias.³⁵ This may explain the apparently strong association between ON and GCA, a cause of arteritic ischemic optic neuropathy (AION). It is likely that some AION patients were misclassified as ON. There was risk of data entry error in the hospital or general practice; and of missing data on new diagnoses or past history of ON. To mitigate these risks, we conservatively included only patients with ON Read codes, excluding those with other or unspecified optic neuropathy. We did not perform a validation study.^{10,11} However, optic neuritis, and the majority of diseases with which it is associated, are diagnosed exclusively by hospital specialists, and reassuringly the incidence estimates aligned with a priori epidemiological expectations.

The stable incidence of ON, with rising prevalence, indicates evolving maturity of the database and improving disease ascertainment, rather than true change in population disease risk over time, with latest prevalence estimates being the most reliable. We excluded data from 1995 and 1996, but patient data for the next five years was considerably less available than for later years, and should be interpreted cautiously. Reasons for evolving maturity include adults registering with a GP at the time of ON onset, having not previously been known to the database (a small number given high proportion of UK population registered with a GP), or adults with a first recurrence since addition of their GP practice to the database volunteering medical history of previous ON omitted from their earlier record. Over time, electronic data capture improves as systems become more familiar. As more patients are added at birth, diagnosed with ON as young adults, and followed throughout the life course, with resulting stabilisation of database age structure, we expect emergence of more reliable estimates of prevalence and age at onset. Some rise in prevalence over time is expected if demographic shifts towards older age continue, or if age at onset reduces, but there was no evidence for the latter. Between 1997 and 2018, life expectancy at birth in the UK's four nations increased modestly by between 4.1 and 4.8 years for men, and 2.9 and 3.4 years for women.³⁶ The impact of emerging health threats,

including the coronavirus disease (COVID-19) pandemic, on the UK and global population age structure, and risk of post-viral ON, will need consideration.

Conclusions

This study highlights that the current era of Big Data offers unprecedented opportunity to advance understanding of the epidemiology of rarer clinical phenotypes and their systemic associations. Here we report stable incidence of ON in the UK over the past 22 years, and multiple significant associations with prevalent and incident autoimmune and infectious IMIDs. From a direct patient-care perspective, it is important to note that at first presentation, non-MS ON cases outnumber MSON, and this should be recognised when planning the diagnostic work-up and making potentially sight-critical treatment decisions.

References

1. Lim SA, Wong WL, Fu E, et al. The incidence of neuro-ophthalmic diseases in Singapore: a prospective study in public hospitals. *Ophthalmic epidemiology* 2009; **16**(2): 65-73.
2. Martinez-Lapiscina EH, Fraga-Pumar E, Pastor X, et al. Is the incidence of optic neuritis rising? Evidence from an epidemiological study in Barcelona (Spain), 2008-2012. *Journal of neurology* 2014; **261**(4): 759-67.
3. Quartilho A, Simkiss P, Zekite A, Xing W, Wormald R, Bunce C. Leading causes of certifiable visual loss in England and Wales during the year ending 31 March 2013. *Eye (Lond)* 2016; **30**(4): 602-7.
4. Petzold A, Braithwaite T, van Oosten BW, et al. Case for a new corticosteroid treatment trial in optic neuritis: review of updated evidence. *Journal of neurology, neurosurgery, and psychiatry* 2020; **91**(1): 9-14.
5. Petzold A, Wong S, Plant GT, 2016. Chapter 20 Autoimmunity in visual loss, in: Pittock SJ & Vincent A (Ed), *Handbook of Clinical Neurology Vol 133 (3rd series)*: 353-76. Elsevier B.V.
6. Dessau RB, Lisby G, Frederiksen JL. Coronaviruses in spinal fluid of patients with acute monosymptomatic optic neuritis. *Acta neurologica Scandinavica* 1999; **100**(2): 88-91.
7. Coric D, Ometto G, Montesano G, et al. Objective quantification of vitreous haze on optical coherence tomography scans: no evidence for relationship between uveitis and inflammation in multiple sclerosis. *Eur J Neurol* 2020; **27**(1): 144-e3.
8. Guo D, Liu J, Gao R, Tari S, Islam S. Prevalence and Incidence of Optic Neuritis in Patients with Different Types of Uveitis. *Ophthalmic epidemiology* 2018; **25**(1): 39-44.
9. Chaganti S, Welty VF, Taylor W, et al. Discovering novel disease comorbidities using electronic medical records. *PloS one* 2019; **14**(11): e0225495.
10. Hall GC. Validation of death and suicide recording on the THIN UK primary care database. *Pharmacoepidemiology and drug safety* 2009; **18**(2): 120-31.
11. Seminara NM, Abuabara K, Shin DB, et al. Validity of The Health Improvement Network (THIN) for the study of psoriasis. *The British journal of dermatology* 2011; **164**(3): 602-9.
12. ReStore National Centre for Research Methods. Townsend Deprivation Index. <http://www.restore.ac.uk/geo-refer/36229duks00y19810000.php> (accessed 5 April 2020 2020).

13. Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. *J Public Health (Oxf)* 2005; **27**(1): 101-6.
14. Adderley NJ, Subramanian A, Nirantharakumar K, et al. Association Between Idiopathic Intracranial Hypertension and Risk of Cardiovascular Diseases in Women in the United Kingdom. *JAMA Neurol* 2019 [epub 2019/07/10].
15. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ* 2010; **340**: b5087.
16. Office for National Statistics, National Records of Scotland, Northern Ireland Statistics and Research Agency - Population Estimates. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2018. Figure 3: Population pyramid for UK, mid-2018, single year of age 0 to 89 2018. <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2018> (accessed 1 April 2020).
17. Rodriguez M, Siva A, Cross SA, O'Brien PC, Kurland LT. Optic neuritis: a population-based study in Olmsted County, Minnesota. *Neurology* 1995; **45**(2): 244-50.
18. Kinnunen E. The incidence of optic neuritis and its prognosis for multiple sclerosis. *Acta neurologica Scandinavica* 1983; **68**(6): 371-7.
19. Jin YP, de Pedro-Cuesta J, Soderstrom M, Stawiarz L, Link H. Incidence of optic neuritis in Stockholm, Sweden 1990-1995: I. Age, sex, birth and ethnic-group related patterns. *Journal of the neurological sciences* 1998; **159**(1): 107-14.
20. Wakakura M, Ishikawa S, Oono S, et al. [Incidence of acute idiopathic optic neuritis and its therapy in Japan. Optic Neuritis Treatment Trial Multicenter Cooperative Research Group (ONMRG)]. *Nippon Ganka Gakkai Zasshi* 1995; **99**(1): 93-7.
21. Lee JY, Han J, Yang M, Oh SY. Population-based Incidence of Pediatric and Adult Optic Neuritis and the Risk of Multiple Sclerosis. *Ophthalmology* 2020; **127**(3): 417-25.
22. Simpson S, Jr., Blizzard L, Otahal P, Van der Mei I, Taylor B. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *Journal of neurology, neurosurgery, and psychiatry* 2011; **82**(10): 1132-41.
23. Woung LC, Peng PH, Liu CC, et al. A nine-year population-based cohort study on the risk of multiple sclerosis in patients with optic neuritis. *The Tohoku journal of experimental medicine* 2013; **231**(3): 171-7.
24. Persson R, Lee S, Yood MU, et al. Multi-database study of multiple sclerosis: identification, validation and description of MS patients in two countries. *Journal of neurology* 2019; **266**(5): 1095-106.
25. Kurtzke JF. Epidemiology and etiology of multiple sclerosis. *Phys Med Rehabil Clin N Am* 2005; **16**(2): 327-49.
26. Wang J, Syrett CM, Kramer MC, Basu A, Atchison ML, Anguera MC. Unusual maintenance of X chromosome inactivation predisposes female lymphocytes for increased expression from the inactive X. *Proceedings of the National Academy of Sciences of the United States of America* 2016; **113**(14): E2029-38.
27. Costello F, Petzold A. Weighting evidence in MS: Obesity and neurodegeneration. *Mult Scler* 2020. [epub 2020/04/17]
28. Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *The Lancet Neurology* 2015; **14**(3): 263-73.
29. Ramanujam R, Hedstrom AK, Manouchehrinia A, et al. Effect of Smoking Cessation on Multiple Sclerosis Prognosis. *JAMA Neurol* 2015; **72**(10): 1117-23.
30. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *The Lancet Neurology* 2010; **9**(5): 520-32.
31. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. *Journal of autoimmunity* 2009; **33**(3-4): 197-207.

32. Lerner A, Matthias T. Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease. *Autoimmunity reviews* 2015; **14**(6): 479-89.
33. Le Scanff J, Seve P, Renoux C, Broussolle C, Confavreux C, Vukusic S. Uveitis associated with multiple sclerosis. *Mult Scler* 2008; **14**(3): 415-7.
34. Kaya D, Kaya M, Ozakbas S, Idiman E. Uveitis associated with multiple sclerosis: complications and visual prognosis. *International journal of ophthalmology* 2014; **7**(6): 1010-3.
35. Stunkel L, Kung NH, Wilson B, McClelland CM, Van Stavern GP. Incidence and Causes of Overdiagnosis of Optic Neuritis. *JAMA ophthalmology* 2018; **136**(1): 76-81.
36. Office for National Statistics. How has life expectancy changed for the UK constituent countries? 2019.
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2015to2017> (accessed 23 June 2020).

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Conflicts of Interest

SM reports other funding from Roche, other from Chugai pharma UK limited, other from Heidelberg Engineering, other from Allergan, other from Neurodiem, other from Santhera, other from Janssen, and other from Novartis, outside the submitted work.

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FIGURE legends

Figure 1A: Annual incidence of optic neuritis in the UK population (per 100,000 person-years, with 95% confidence intervals) from 1997 to 2018

Figure 1B: Age group and sex-specific incidence of optic neuritis (per 100,000 person-years, with 95% confidence intervals) between 1997 and 2018

Figure 2: Forest plots displaying the adjusted odds ratio (left) of a prevalent diagnosis of an IMID at baseline ON diagnosis, and adjusted hazard ratio (right) of an incident diagnosis of an IMID during follow-up after ON diagnosis

Figure 3: Nelson-Aalen cumulative hazard curves estimating risk of incident multiple sclerosis diagnosis in optic neuritis patients compared to controls during 15 years of follow-up. This illustrates that 28.2% (n=815/2894) ON cases compared to 0.1% (n=13/11576) controls are diagnosed with MS by 10 years follow-up.

535 **Table 1. Comparison of the UK population exposed and not exposed to incident optic neuritis**

	Characteristic at baseline	ON % (n)	No ON % (n)	Single variable IRR (95% CI), p value	Adjusted IRR (95% CI), p value)
	Total, % (n)	2826	10,934,685		
Gender	Female, % (n)	69.4 (1,962)	50.9 (5,569,320)	2.26 (2.09-2.45), p<0.001	2.26 (2.08-2.45), p<0.001
Age group at cohort entry	1-10 years	4.3 (121)	19.9 (2,070,338)	1	1
	11-20 years	10.1 (284)	9.9 (1,081,405)	4.56 (3.69-5.64), p<0.001	4.53 (3.65-5.62), p<0.001
	21-30 years	24.9 (704)	18.2 (1,984,337)	7.81 (6.44-9.47), p<0.001	6.80 (5.50-8.40), p<0.001
	31-40 years	28.2 (796)	16.6 (1,814,484)	6.98 (5.77-8.45), p<0.001	6.04 (4.89-7.46), p<0.001
	41-50 years	16.7 (473)	12.1 (1,324,681)	4.84 (3.97-5.91), p<0.001	4.15 (3.33-5.16), p<0.001
	51-60 years	8.3 (235)	9.6 (1,045,254)	2.92 (2.35-3.64), p<0.001	2.45 (1.93-3.10), p<0.001
	61-70 years	4.4 (125)	7.0 (765,334)	2.21 (1.72-2.83), p<0.001	1.82 (1.39-2.38), p<0.001
	71-80 years	2.4 (67)	4.8 (526,666)	2.08 (1.55-2.81), p<0.001	1.69 (1.24-2.31), p<0.001
	81-90 years	0.7 (21)	2.5 (270,755)	2.11 (1.33-3.36), p=0.002	1.68 (1.05-2.69), p<0.001
	91-100 years	0	0.5 (50,687)		
	101+ years	0	0.0 (744)		
Nation	England	68.8 (1,943)	71.3 (7,790,740)	1	1
	Scotland	16.0 (452)	14.1 (1,538,041)	1.22 (1.10-1.35), p<0.001	1.19 (1.08-1.32), p=0.001
	Wales	10.1 (285)	11.0 (1,203,405)	0.91 (0.81-1.04), p=0.158	0.91 (0.80-1.03), p=0.147
	Northern Ireland	5.2 (146)	3.4 (402,499)	1.07 (0.90-1.26), p=0.437	1.08 (0.91-1.28), p=0.376
Townsend deprivation quintile	1 (least deprived)	21.2 (599)	18.2 (1,984,597)	1	Not included in model
	2	18.1 (511)	16.5 (1,807,282)	0.99 (0.88-1.11), p=0.837	
	3	18.2 (513)	17.5 (1,910,584)	1.01 (0.90-1.14), p=0.869	
	4	15.4 (434)	16.3 (1,783,263)	0.98 (0.87-1.11), p=0.763	
	5 (most deprived)	10.7 (302)	12.0 (1,314,297)	0.95 (0.83-1.10), p=0.507	
	Missing	16.5 (467)	19.5 (2,134,662)	1.03 (0.91-1.16), p=0.648	
Ethnicity	White	42.2 (1192)	39.0 (4,262,489)	1	1
	Black	1.5 (42)	1.6 (177,881)	1.21 (0.89-1.65), p=0.225	1.16 (0.85-1.58), p=0.340
	Mixed	0.4 (12)	1.2 (131,325)	0.58 (0.33-1.03), p=0.061	0.52 (0.30-0.92), p=0.025
	Others	0.5 (13)	0.6 (70,383)	1.05 (0.61-1.81), p=0.862	1.14 (0.66-1.97), p=0.636
	South Asian	1.1 (31)	2.4 (262,376)	0.55 (0.39-0.79), p=0.001	0.56 (0.39-0.80), p=0.001
	Missing	54.4 (1536)	55.2 (6,030,231)	0.87 (0.81-0.94), p<0.001	0.97 (0.89-1.05), p=0.403
BMI (kg/m ²) at cohort entry	Underweight (<18.5)	1.6 (46)	3.0 (182,124)	0.96 (0.71-1.29), p=0.768	0.83 (0.61-1.11), p=0.208
	Normal (18.5-24.9)	32.1 (906)	46.7 (2,795,714)	1	1
	Overweight (25-29.9)	19.4 (549)	32.1 (1,918,201)	0.81 (0.73-0.91), p<0.001	1.04 (0.94-1.16), p=0.443
	Obese (30-34.9)	9.2 (259)	12.3 (733,314)	1.03 (0.90-1.19), p=0.644	1.27 (1.11-1.46), p=0.001
	Morbidly obese (>35)	5.3 (151)	5.9 (355,770)	1.30 (1.10-1.55), p=0.003	1.37 (1.15-1.63), p<0.001
	Missing BMI	32.4 (915)	4,949,562	0.54 (0.49-0.59), p<0.001	0.92 (0.82-1.04), p=0.183
Smoking Status at cohort entry	Never smoker	41.2 (1,165)	38.7 (4,229,870)	1	1
	Ex-smoker	11.0 (312)	10.6 (1,158,945)	1.03 (0.91-1.17), p=0.656	1.19 (1.05-1.35), p=0.007
	Current smoker	24.8 (701)	16.9 (1,852,089)	1.37 (1.25-1.50), p<0.001	1.32 (1.20-1.45), p<0.001
	Missing	22.9 (648)	33.8 (3,693,781)	0.56 (0.51-0.62), p<0.001	1.09 (0.95-1.24), p=0.217

536 **Table 2: Comparison of 2894 ON patients and 11576 matched controls, exploring association**
537 **with 66 immune-mediated inflammatory or infectious diseases, highlighting the adjusted odds**
538 **of baseline (prior) diagnosis and adjusted hazard of incident diagnosis during follow-up, with**
539 **the latter excluding baseline diagnoses of the outcome**
540

	Case-control analysis			Retrospective matched cohort analysis ^a		
Associated condition ^b	Cases n (%)	Controls n(%)	Adjusted Odds Ratio (95%CI)*, p value	Optic neuritis n (%)	Controls n(%)	Adjusted Hazard Ratio (95% CI) ^c , p value
TOTAL	2894	11576		2893	11576	
Associated inflammatory ocular clinical phenotypes						
Scleritis	0.55 (16)	0.06 (7)	10.07 (4.04-25.12), p<0.001	0.07 (2)	0.03 (4)	2.49 (0.44-14.23), p=0.305
Uveitis	2.70 (78)	0.58 (67)	4.79 (3.42-6.72), p<0.001	0.75 (21)	0.19 (22)	5.06 (3.21-7.97), p<0.001
Autoimmune and autoinflammatory immune-mediated inflammatory diseases (IMIDs)						
Antiphospholipid syndrome	0.21 (6)	0.01 (1)	0.70 (0.08-6.04), p=0.742	0.07 (2)	0.03 (4)	2.39 (0.33-17.17), p=0.388
Behçet's Disease	0.10 (3)	0.00 (0)	Not estimable	0.07 (2)	0.01 (1)	17.39 (1.55-195.53), p=0.021
Cogan's syndrome	0.03 (1)	0	Not estimable	0	0	No data
CREST syndrome	0	0	No data	0.03. (1)	0	Not estimable
Crohn's disease	0.69 (20)	0.33 (38)	1.97 (1.13-3.43), p=0.016	0.21 (6)	0.10 (12)	1.39 (0.66-2.90), p=0.387
Dermato- or polymyositis	0.07 (2)	0.03 (3)	2.93 (0.46-18.53), p=0.253	0.03 (1)	0.02 (2)	4.57 (0.25-84.43), p=0.308
Giant cell arteritis	0.90 (26)	0.07 (8)	16.16 (6.92-37.75), p<0.001	0.56 (16)	0.03 (4)	27.04 (10.28-71.09), p<0.001
Granulomatosis with polyangiitis	0.17 (5)	0	Not estimable	0.14 (4)	0	Not estimable
Henoch-Schonlein purpura	0.07 (2)	0.19 (22)	0.31 (0.07-1.33), p=0.114	0.03 (1)	0	Not estimable
Juvenile idiopathic arthritis	0.03 (1)	0.03 (4)	0.74 (0.07-7.38), p=0.796	0	0	No data
Kawasaki syndrome	0	0.02 (2)	Not estimable	0	0	No data
Paraneoplastic	0	0	No data	0.07 (2)	0	Not estimable
Polyarteritis nodosum	0	0.02 (2)	Not estimable	0	0	No data
Polymyalgia rheumatica	0.62 (18)	0.28 (32)	2.14 (1.17-3.92), p=0.013	0.45 (13)	0.25 (29)	2.05 (1.14-3.71), p=0.017
Psoriasis	4.28 (124)	3.08 (357)	1.28 (1.03-1.58), p=0.023	1.16 (32)	0.85 (95)	1.04 (0.77-1.41), p=0.789
Reiter's	0.07 (2)	0.02 (2)	4.68 (0.60-36.41), p=0.141	0	0	No data
Rheumatoid arthritis	0.69 (20)	0.54 (63)	1.13 (0.67-1.88), p=0.646	0.42 (12)	0.35 (40)	0.90 (0.55-1.48), p=0.678
Sarcoidosis	0.45 (13)	0.16 (18)	2.50 (1.21-5.18), p=0.014	0.49 (14)	0.03 (4)	14.80 (4.86-45.08), p<0.001
Sjogren's	0.10 (3)	0.08 (9)	1.22 (0.32-4.62), p=0.765	0.24 (7)	0.07 (8)	3.48 (1.38-8.76), p=0.008
Systemic lupus erythematosus	0.17 (5)	0.27 (31)	0.67 (0.26-1.73), p=0.405	0.24 (7)	0.09 (10)	2.12 (0.87-5.15), p=0.099
Systemic sclerosis	0	0.03 (3)	Not estimable	0	0.01 (1)	Not estimable
Ulcerative colitis	0.41 (12)	0.32 (37)	1.42. (0.73-2.76), p=0.297	0.17 (5)	0.12 (14)	1.08 (0.43-2.69), p=0.876
Vasculitis, other	0.45 (13)	0.11 (13)	3.70 (1.68-8.15), p=0.001	0.28 (8)	0.05 (6)	4.89 (1.82-13.10), p=0.002

Table 2 (continued): Comparison of 2894 ON patients and 11576 matched controls, exploring association with 66 immune-mediated inflammatory or infectious diseases, highlighting the adjusted odds of baseline (prior) diagnosis and adjusted hazard of incident diagnosis during follow-up, with the latter excluding baseline diagnoses of the outcome

Diagnosed IMIDs ^b	Case-control analysis			Retrospective matched cohort analysis ^a		
	Cases n (%)	Controls n(%)	Adjusted Odds Ratio (95%CI) ^c , p value	Optic neuritis n (%)	Controls n(%)	Adjusted Hazard Ratio (95% CI) ^c , p value
Neurological immune-mediated inflammatory diseases (IMIDs)						
Multiple Sclerosis	17.31 (501)	0.22 (25)	98.22 (65.40-147.52), p<0.001	22.36 (535)	0.08 (9)	284.97 (167.85-483.81), p<0.001
Neuromyelitis optica	0.21 (6)	0	Not estimable	1.18 (34)	0	Not estimable
Infections / infectious immune-mediated inflammatory diseases (IMIDs)						
Brucellosis	0.03 (1)	0	Not estimable	0	0	No data
Cytomegalovirus	0.03 (1)	0	Not estimable	0	0	No data
Dengue fever	0.03 (1)	0.01 (1)	16.6 (0.33-746.03), p=0.163	0	0	No data
Epstein Barr virus	3.80 (110)	1.73 (200)	2.29 (1.80-2.92), p<0.001	0.07 (2)	0.10 (11)	0.67 (0.15-3.06), p=0.608
Hepatitis B	0.24 (7)	0.23 (27)	1.05 (0.45-2.45), p=0.913	0.03 (1)	0.04 (5)	1.12 (0.10-12.02), p=0.928
Hepatitis C	0.03 (1)	0.08 (9)	0.41 (0.05-3.26), p=0.396	0	0.03 (3)	Not estimable
Herpetic infection	4.08 (118)	3.19 (369)	1.22 (0.98-1.51), p=0.070	1.80 (50)	1.05 (118)	1.68 (1.24-2.28), p=0.001
HIV	0.07 (2)	0.07 (8)	0.88 (0.17-4.52), p=0.879	0	0.03 (3)	Not estimable
Lyme disease	0.03 (1)	0.01 (1)	75.99 (0.12-48418.89), p=0.189	0.03 (1)	0	Not estimable
Measles	1.21 (35)	1.14 (132)	1.06 (0.72-1.55), p=0.764	0.03 (1)	0.01 (1)	118.41 (0.00-993247), p=0.409
Mumps	1.38 (40)	1.26(146)	1.08 (0.75-1.54), p=0.679	0.07 (2)	0.06 (7)	1.02 (0.20-5.08), p=0.982
Mycoplasma	0.17 (5)	0.04 (5)	3.90 (1.09-13.93), p=0.036	0	0	No data
Rubella	0.73 (21)	0.81 (94)	0.91 (0.56-1.47), p=0.686	0	0.03 (4)	Not estimable
Syphilis	0.21 (6)	0.03 (3)	5.76 (1.39-23.96), p=0.016	0.03 (1)	0	Not estimable
Tick borne fever	0	0.03 (3)	Not estimable	0	0	No data
Tuberculosis	0.31 (9)	0.48 (55)	0.69 (0.33-1.41), p=0.303	0.14 (4)	0.09 (10)	1.44 (0.44-4.66), p=0.544
Toxoplasmosis	0.14 (4)	0.04 (5)	2.63 (0.69-10.02), p=0.156	0.10 (3)	0	Not estimable
Yaws	0	0.01 (1)	Not estimable	0	0	No data

^a Patients with a record of the comorbidity at baseline were excluded for the corresponding follow-up analysis estimating adjusted Incident Rate Ratios.

^b Diseases (15) for which Read code data were available in THIN but no data present in ON patients or controls (and thus excluded from analysis): ankylosing spondylitis, Vogt Koyanagi Harada, Churg-Strauss, chikungunya virus, Coxiella virus, histoplasmosis, leprosy, microscopic polyangiitis, Susac syndrome, Takayasu arteritis, toxocariasis, typhus, West Nile virus, Whipple disease and Zika virus. Diseases for which no Read codes were recorded in the THIN dataset (8): Anti-myelin oligodendrocyte glycoprotein (MOG) associated optic neuritis, Blau syndrome, ehrlichiosis, Inoue-Melnick virus, Bartonella or cat scratch disease, hypertrophic pachymeningitis, human herpes 6 virus and human coronavirus. There was also no specific Read code for c or p ANCA positivity, but these were likely captured under a combination of Read codes, grouped here as 'Vasculitis, other'.

^c All models adjusted for gender, age category, ethnicity, BMI category, smoking category, country and Townsend Deprivation Index

Odds of prior IMID diagnosis
aOR (95% CI)

Immune-mediated inflammatory diseases

Hazard of future IMID diagnosis
aHR (95% CI)

Number at risk

No Optic neuritis	11576	(12)	5766	(1)	2426	(1)	658
Optic neuritis	2894	(729)	1087	(86)	418	(12)	101

Online Supplement

eTable 1: Read codes included in case definition of optic neuritis

Read code	Description	Frequency amongst cases % (n)
F4H3.00	Optic neuritis	76.2 (2206)
F4H3200	Acute retrobulbar neuritis	14.0 (406)
F4H3000	Unspecified optic neuritis	5.49 (159)
F4H3z00	Optic neuritis NOS	2.7 (77)
A36y000	Meningococcal optic neuritis	0.9 (27)
A94y300	Syphilitic optic atrophy	0.4 (12)
A94y400	Syphilitic retrobulbar neuritis	0.2 (5)
FyuJ100	[X]Retrobulbar neuritis in diseases classified elsewhere	0.0 (1)
F4H1200	Postinflammatory optic atrophy	0.0 (1)
FyuJ100	[X]Retrobulbar neuritis in diseases classified elsewhere	0.0 (1)
Total		100.0 (2894)

Online Supplement

eTable 2: Time trend analysis of the point prevalence and annual incidence of optic neuritis (per 100,000 people) in the UK between 1997 and 2018

Year	Prevalent ON	Total patients	Prevalence (95% CI)	Incident ON	Person-years at risk	Incidence (100,000 person-years)
1997	127	183385	69.25 (57.21-81.29)	14	377852	3.71 (1.76-5.65)
1998	485	670096	72.38 (65.94-78.82)	29	824828	3.52 (2.24-4.80)
1999	810	1065766	76.00 (70.77-81.23)	50	1163113	4.30 (3.11-5.49)
2000	1084	1333621	81.28 (76.45-86.12)	66	1499486	4.40 (3.34-5.46)
2001	1705	2040725	83.55 (79.59-87.51)	94	2184168	4.30 (3.43-5.17)
2002	2106	2479272	84.94 (81.32-88.57)	118	2750238	4.29 (3.52-5.06)
2003	2611	3107019	84.04 (80.81-87.26)	149	3306972	4.51 (3.78-5.23)
2004	2959	3471125	85.25 (82.18-88.32)	141	3561914	3.96 (3.31-4.61)
2005	3223	3724667	86.53 (83.55-89.52)	173	3900966	4.43 (3.77-5.10)
2006	3610	4091387	88.23 (85.36-91.11)	171	4129366	4.14 (3.52-4.76)
2007	3890	4258181	91.35 (88.48-94.22)	173	4289268	4.03 (3.43-4.63)
2008	4165	4423710	94.15 (91.29-97.01)	167	4543261	3.68 (3.12-4.23)
2009	4667	4744400	98.37 (95.55-101.19)	162	4770143	3.40 (2.87-3.92)
2010	4825	4813391	100.24 (97.41-103.07)	162	4754025	3.41 (2.88-3.93)
2011	4906	4795047	102.31 (99.45-105.18)	181	4798433	3.77 (3.22-4.32)
2012	5111	4887926	104.56 (101.70-107.43)	202	4960408	4.07 (3.51-4.63)
2013	5385	5008807	107.51 (104.64-110.38)	164	4869128	3.37 (2.85-3.88)
2014	5170	4727089	109.37 (106.39-112.35)	151	4590272	3.29 (2.76-3.81)
2015	4901	4428419	110.67 (107.58-113.77)	139	4092658	3.40 (2.83-3.96)
2016	4165	3738221	111.42 (108.04-114.80)	127	3534502	3.59 (2.97-4.22)
2017	3806	3387683	112.35 (108.78-115.91)	85	3170565	2.68 (2.11-3.25)
2018	3472	3023960	114.82 (111.00-118.63)	103	2937674	3.51 (2.83-4.18)

Online Supplement

eFigure 1: Annual point prevalence of optic neuritis in the UK population (per 100,000 people, with 95% confidence intervals) between 1997 and 2018

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A

B

C

eFigure 2: Nelson-Aalen cumulative hazard curves (with 95% confidence intervals [CI]) for diagnosis of incident multiple sclerosis during 15 years of follow-up, comparing patients diagnosed with incident optic neuritis A) aged <17 years, B) aged 18-50 years and C) aged >50 years. Example interpretation: By 10 years follow-up, an estimated 8.5% (n=8/94) with optic neuritis onset aged 1-17 years, 33.7% (n=623+75/2074) with optic neuritis onset aged 18-50 years and 14.8% (n=88+11/671) with optic neuritis onset aged >50 years were diagnosed with multiple sclerosis

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eFigure 3: Nelson-Aalen cumulative hazard curves (with 95% confidence intervals [CI]) for diagnosis with incident systemic, neurological or infectious IMID in optic neuritis patients compared to controls during 15 years of follow-up. Note differing ranges on y-axes.