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Risk of cataract and glaucoma in patients with multiple sclerosis

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Abstract

Background: The aim of the study was to evaluate whether multiple sclerosis (MS) is associated with risk of cataract or glaucoma.
Methods: We conducted a population-based cohort study utilizing the UK General Practice Research Database (1987–2009) linked to the national hospital registry of England (1997–2008). Incident MS patients (5576 cases) were identified and each was matched to six patients without MS (controls) by age, gender, and practice. Cox proportional hazard models were used to estimate hazard ratios (HRs) of incident cataract and glaucoma in MS. Time-dependent adjustments were made for age, history of diseases and drug use.
Results: MS patients had no overall increased risk of cataract, adjusted (adj.) HR 1.15 (95% CI 0.94–1.41) or glaucoma, adj. HR 1.02 (95% CI 0.78–1.33). Risk of cataract (adj. HR 2.45 (95% CI 1.56–3.86)) and glaucoma (adj. HR 1.70 (95% CI 1.01–2.86)) was significantly greater in patients < 50 years, particularly in men < 50 years: cataract, adj. HR 4.23 (95% CI 2.22–8.05) and glaucoma, adj. HR 2.76 (95% CI 1.28–5.93).
Conclusion: This is the first study which showed that the risk of cataract and glaucoma is elevated in MS patients younger than 50 years, particularly men.

Keywords

cataract, epidemiology, glaucoma, glucocorticoids, multiple sclerosis

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Introduction

Multiple sclerosis (MS) is an inflammatory and demyelinating disease of the central nervous system characterized by gradual accumulation of focal plaques of demyelination in the brain. According to the World Health Organization report (2008), it affects more than 1.3 million people world wide, including 630,000 Europeans, 520,000 Americans and 66,000 Eastern Mediterranean patients.[1] Ophthalmological manifestations of MS such as optic neuritis, anterior and posterior uveitis, nystagmus and ocular motor involvements have been reported in epidemiological studies. Glaucoma (15%) and cataract (30%) were common in MS patients with symptomatic intraocular inflammation.[2] The rate of MS in patients with pars planitis has been reported to be higher (12–33%) than in the general population.[3,4]

Cataract is the leading cause of visual impairment in the world and poses a huge burden on the patient. It is characterized by a partial or total opacity of the crystalline intraocular lens. The risk of cataract or glaucoma may be increased in patients with MS due to shared mechanisms of disease processes, or as a consequence of glucocorticoid (GC) use.[5] Lens membrane functions are altered, resulting in cataract formation.[6,7] Imam et al. measured a significantly increased activity of proteolytic enzymes in patients with MS during a relapse.[8] Other studies showed that cataracts are caused by intraocular inflammation of the uveal tract,[9-11] which can be a complication in patients with MS.[12]

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Glaucoma is a type of neuropathy marked by the loss of retinal nerve fibres resulting in visual field loss. The risk of glaucoma may be increased in patients with MS. Previous research has shown that macular thickness is reduced in patients with MS compared with controls.[13,14] In mice, a loss of retinal ganglion cells during an optic neuritis secondary to the inflammatory process was reported.[15] In addition, it has been hypothesized that glaucoma neuropathy may be related to optic neuropathy, which can have various aetiologies including MS.[16]

Not only MS itself, but also the use of high dosage systemic GCs may increase the risk of cataract.[17,18] Treatment with short courses of intravenous methylprednisolone (500–1000 mg daily for 3–5 days), with or without a short prednisone taper, are commonly used in the treatment of relapses in patients with relapsing–remitting MS.[19,20] Previous studies have shown that (long-term) use of GCs increases the risk of cataract.[17,18] The interaction of the GC with the proteins of the lens results in an accumulation of granular material and vacuoles at the posterior pole of the intraocular lens. The combination of MS disease with cataract or glaucoma might even be of greater impact on these patients compared with those who suffer from one of the diseases, especially as most MS patients are of relatively young age. Because the relative risk of cataract or glaucoma in patients with MS as compared with population-based controls has not been studied,[3,4,21] the objective of our study was to evaluate whether MS increases the risk of cataract or glaucoma.

Methods

Data source

We conducted a population-based cohort study utilizing the United Kingdom (UK) General Practice Research Database (GPRD) that was linked to the national hospital statistics of England (HES). Linkage of GPRD and HES covered approximately 45% of practices between April 1997 and March 2008. The GPRD is a computerized database comprising the medical records of more than 10 million UK patients registered with a primary care physician. Previous epidemiological studies based on GPRD data have shown that it can be used to study patients with MS,[22] cataract,[23] and longitudinal exposure to oral GCs.[24,25] Our study was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Product Regulatory Agency (MHRA) of the United Kingdom, protocol number 09_098.

Study population

Eligible patients were aged 18 years and older and registered in GPRD between January 1987 and August 2009. All incident patients with at least one diagnosis of MS in either GPRD or HES were identified. They were matched with up to six control patients without a diagnosis of MS (convenient sample of large source population) by year of birth, gender and practice. The age-matching criterion was extended stepwise in 1-year increments to a maximum of 5 years when an exact age match was unavailable. The date of first diagnosis of MS in either GPRD or HES (index date) defined the start of follow-up. A control patient was assigned the index date of his matching MS patient. Patients were followed until the end of data collection, transfer out of practice or death, whichever came first. We divided the follow-up time of each individual patient into 30-day intervals until the end of follow-up or the outcome of interest (cataract or glaucoma). At the start of each interval, time-varying characteristics such as age, disease and drug history were determined.

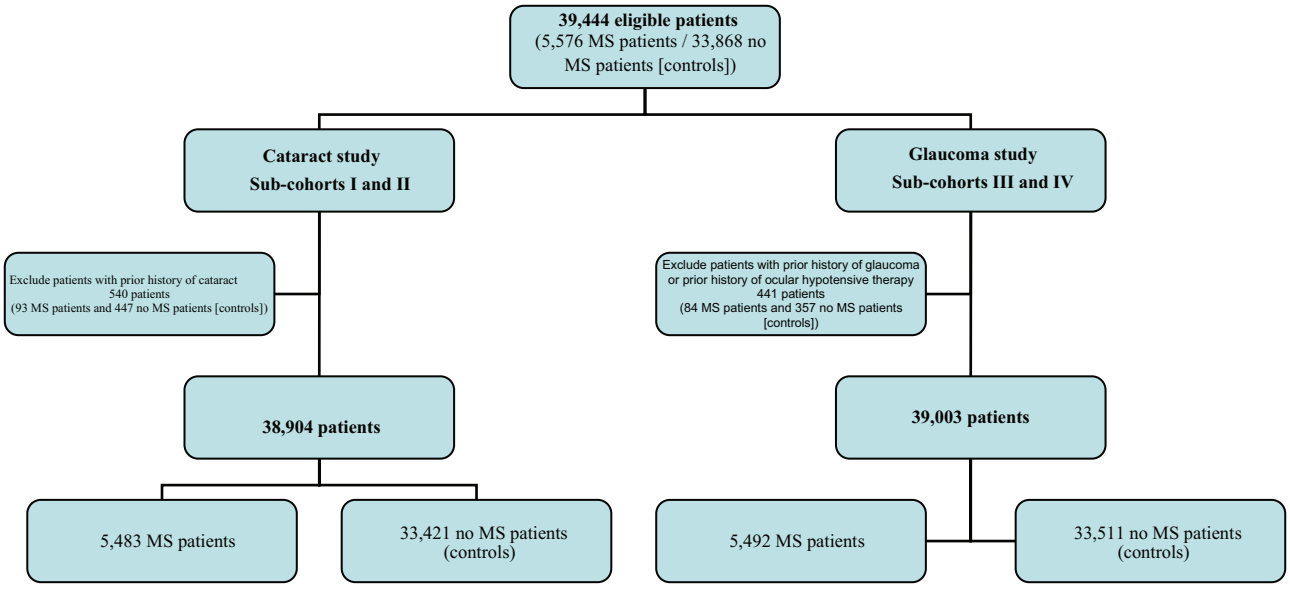

Figure 1. Overview of patient cohorts

Study outcomes

Figure 1 shows that the cohorts of MS patients and controls were slightly modified in the analysis to study cataract (A) and glaucoma (B). In analysis (A), all patients with a history of cataract before or on the start date of follow-up were excluded from MS patients and controls (sub-cohort I and II). In analysis (B), all patients with a history of glaucoma before or on the start date of follow-up were excluded from MS patients and controls (sub-cohorts III and IV).

In sub-cohorts I and II, each patient was then followed for the occurrence of the first record of cataract. Cataract was classified according to the International Classification of Diseases (ICD-10) categories including ICD-10 categories H25.0–H28.8 and cataract extraction status ICD-10 category Z96.1 with the exception of congenital cataract. The corresponding Read codes were selected in GPRD. The first diagnosis of cataract in the computerized medical records in either GPRD or HES was taken as the event date of cataract.

In sub-cohorts III and IV, each patient was then followed for the occurrence of the first record of glaucoma, which was classified according to ICD-10 categories including categories H40.0–H42.8 or the first prescription of intraocular pressure-lowering therapy including topical miotics, beta-blockers, carbonic anhydrase inhibitors, sympathomimetics and prostaglandin analogues. The first diagnosis of glaucoma or initiation of anti-glaucoma therapy in the computerized medical records in either GPRD or HES was taken as the event date of glaucoma.

Statistical analysis

Cox proportional hazard models were used to estimate the hazard ratio (HR) of cataract and glaucoma in MS versus patients without MS. Kaplan–Meier curves were generated. With the exception of body mass index (BMI), smoking status and gender, risk factors were determined in a time-dependent manner. All characteristics, except age, were treated as categorical variables. Each potential confounder was then added individually to the age and gender-adjusted HR. A change of 1% or more from the age and gender-adjusted HR was considered significant and the confounder was added to the model.

In the evaluation of cataract risk in MS (analysis A) we adjusted our analyses for the use of systemic GCs, hypnotics/anxiolytics, anticonvulsants and antidepressants 6 months prior to the start of a period. Furthermore, we adjusted our analyses for age, gender, smoking status, BMI and a history of diseases such as diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, epilepsy, and ocular surgery.

In the analysis of glaucoma risk in MS (analysis B), we adjusted our analyses for the use of systemic GCs, anticonvulsants, serotonin-selective reuptake inhibitors, tricyclic antidepressants and ocular GCs 6 months prior to the start of a period. Furthermore, we adjusted our analyses for age, gender, smoking status, BMI and a history of diseases such as cerebrovascular disease, epilepsy, and uveitis.

Subgroup analysis was performed on age at index date. The age limit was set at 50 years based on the natural risk of cataract and glaucoma. Within these age categories we stratified by gender to detect possible differences.

Average daily dose and cumulative dose of systemic GC use was determined at the start of each period. The pivotal analysis was then stratified by daily and cumulative exposure to GCs. To analyze the use of oral and intravenous GCs during MS relapses, information on steroid exposure during MS relapses was retrieved from anonymized free-text. The Wald statistic was used to test statistical significant difference between all subgroups (and not only the reference group) by using 'test statements' in the PHREG procedure (SAS version 9.1.3). A p-value of 0.05 or smaller was considered statistically significant.

Sensitivity analysis

In order to study the impact of a potential misclassification of incident MS as prevalent cases (due to left censoring of the data) we conducted a sensitivity analysis. We restricted our pivotal analysis to those MS patients who had at least 12 months of valid follow-up time before the index date.

Results

A total number of 5576 incident MS patients and 33,868 matched controls were identified in GPRD and HES. Table 1 shows the baseline characteristics of both sub-cohorts. Exclusion of 540 patients with a history of cataract resulted in sub-cohorts I and II, while exclusion of 441 patients with a history of glaucoma resulted in sub-cohorts III and IV. In all sub-cohorts, the mean age of patients with MS and controls was 45 years and 70% were female. Compared with controls, patients with MS were more likely to smoke and to have a history of exposure to systemic GCs or antidepressants.

Table 2 shows that in sub-cohorts I and II, 861 patients had a recording of cataract during follow-up. The overall risk of cataract in MS patients versus controls was not increased: adjusted (adj.) HR 1.15 (95% CI 0.94–1.41). However, the risk was significantly greater in MS patients who were aged < 50 years: adj. HR 2.45 (95% CI 1.56–3.86). The risk was increased more than four-fold in men < 50 years: adj. HR 4.23 (95% CI 2.22–8.05) as compared with all controls without MS. It was also statistically different from the risk in females with MS who were younger than 50 years of age: adj. HR 1.82 (95% CI 1.00–3.29). In the overall analysis, history of uveitis was not selected as a confounder because the 1% change was not reached. Nevertheless, we considered a history of uveitis as a

Table 1. Baseline characteristics of patients with incident multiple sclerosis and no history of cataract (sub-cohorts I and II) and no history of glaucoma (sub-cohorts III and IV).

	Sub-cohorts I and II (Cataract analysis)		Sub-cohorts III and IV (Glaucoma analysis)	
	MS	No MS (controls)	MS	No MS (controls)
Characteristic	*N* = 5483	*N* = 33,421	*N* = 5492	*N* = 33,511
Mean duration of follow-up (years)	5.7	6.1	5.7	6.1
Age at index date (years)				
Mean	44.5	44.6	44.5	44.7
By category				
18–29	669 (12.2%)	4015 (12.0%)	670 (12.2%)	4017 (12.0%)
30–39	1440 (26.3%)	8720 (26.1%)	1439 (26.2%)	8723 (26.0%)
40–49	1609 (29.3%)	9739 (29.1%)	1607 (29.3%)	9740 (29.1%)
50–59	1045 (19.1%)	6449 (19.3%)	1046 (19.0%)	6441 (19.2%)
60+	720 (13.1%)	4,498 (13.5%)	730 (13.3%)	4590 (13.7%)
Number of females	3843 (70.1%)	23,461 (70.2%)	3839 (69.9%)	23,505 (70.1%)
Smoking status				
Never	2102 (38.3%)	15,148 (45.3%)	2109 (38.4%)	15,202 (45.4%)
Current	1522 (27.8%)	7176 (21.5%)	1527 (27.8%)	7190 (21.5%)
Ex	797 (14.5%)	4268 (12.8%)	798 (14.5%)	4281 (12.8%)
Unknown	1062 (19.4%)	6829 (20.4%)	1058 (19.3%)	6838 (20.4%)
Alcohol consumption				
Never	569 (10.4%)	3,199 (9.6%)	574 (10.5%)	3,231 (9.6%)
Current	3171 (57.8%)	19,536 (58.5%)	3182 (57.9%)	19,582 (58.4%)
Ex	177 (3.2%)	753 (2.3%)	179 (3.3%)	745 (2.2%)
Unknown	1566 (28.6%)	9933 (29.7%)	1557 (28.4%)	9953 (29.7%)
Specialty referral ever before				
Neurology	1480 (27.0%)	432 (1.3%)	1478 (26.9%)	434 (1.3%)
Ophthalmology	383 (7.0%)	794 (2.4%)	383 (7.0%)	805 (2.4%)
History of ocular problems				
Nystagmus	65 (1.2%)	24 (0.1%)	67 (1.2%)	21 (0.1%)
Ocular and head trauma	159 (2.9%)	839 (2.5%)	163 (3.0%)	849 (2.5%)
Optic neuritis	628 (11.5%)	27 (0.1%)	632 (11.5%)	27 (0.1%)
Uveitis	69 (1.3%)	149 (0.4%)	70 (1.3%)	158 (0.5%)
Visual disturbance	1394 (25.4%)	900 (2.7%)	1401 (25.5%)	935 (2.8%)
Diplopia	288 (5.3%)	62 (0.2%)	285 (5.2%)	66 (0.2%)
History of other diseases				
Asthma	572 (10.4%)	3442 (10.3%)	575 (10.5%)	3464 (10.3%)
Cerebrovascular disease	148 (2.7%)	365 (1.1%)	144 (2.6%)	380 (1.1%)
Diabetes mellitus	147 (2.7%)	820 (2.5%)	150 (2.7%)	825 (2.5%)
Epilepsy	131 (2.4%)	439 (1.3%)	129 (2.3%)	443 (1.3%)
Drug use ever before				
Statins	259 (4.7%)	1216 (3.6%)	262 (4.8%)	1241 (3.7%)
Antidepressants	1764 (32.2%)	7044 (21.1%)	1760 (32.0%)	7070 (21.1%)
Systemic glucocorticoids	602 (11.0%)	2076 (6.2%)	608 (11.1%)	2099 (6.3%)
Inhaled glucocorticoids	480 (8.8%)	2775 (8.3%)	487 (8.9%)	2801 (8.4%)
Anti-glaucoma medication	32 (0.6%)	145 (0.4%)	–	–
Ocular glucocorticoids	169 (3.1%)	960 (2.9%)	177 (3.2%)	1022 (3.0%)
Oral oestrogen-containing Contraceptives	1054 (19.2%)	6641 (19.9%)	1054 (19.2%)	6643 (19.8%)

Abbreviations: MS, Multiple Sclerosis; *N*, number

Table 2. Risk of cataract and glaucoma in MS patients compared to patients without MS (controls) according to age and sex.

	Sub-cohorts I and II (Cataract analysis)			Sub-cohorts III and IV (Glaucoma analysis)		
	Number of cases *N* (%)	Age and sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[#]	Number of cases *N* (%)	Age and sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[&]
No MS (controls)	747 (2.2%)	1.00	1.00	479 (1.4%)	1.00	1.00
MS	114 (2.1%)	1.22 (1.00–1.49)	1.15 (0.94–1.41)	69 (1.3%)	1.13 (0.88–1.46)	1.02 (0.78–1.33)
By gender						
Females	73 (64.0%)	1.14 (0.90–1.45)	1.07 (0.84–1.38)	46 (66.7%)	1.11 (0.82–1.45)	0.99 (0.72–1.64)
Males	41 (36.0%)	1.41 (1.03–1.93)	1.29 (0.94–1.12)	23 (33.3%)	1.19 (0.78–1.50)	1.07 (0.70–1.10)
By age category and gender						
18–49	22 (19.3%)	2.67 (1.71–4.18)	2.45 (1.56–3.86)[§]	17 (24.6%)	2.02 (1.21–3.35)	1.70 (1.01–2.86)[§]
Females	12 (10.5%)	2.03 (1.13–3.65)[¥]	1.82 (1.00–3.29)[ξ]	10 (14.5%)	1.63 (0.86–3.11)	1.34 (0.70–2.58)
Males	10 (8.8%)	4.46 (2.35–8.46)	4.23 (2.22–8.05)[π,ξ]	7 (10.1%)	3.05 (1.42–6.52)[π]	2.76 (1.28–5.93)[π]
50+	92 (80.7%)	1.09 (0.88–1.35)	1.03 (0.82–1.29)[§]	52 (75.4%)	1.00 (0.75–1.33)	0.91 (0.67–1.22)[§]
Females	61 (53.5%)	1.05 (0.81–1.37)[¥]	1.01 (0.77–1.31)	36 (52.2%)	1.03 (0.73–1.44)	0.93 (0.66–1.32)
Males	31 (27.2%)	1.16 (0.81–1.67)	1.06 (0.74–1.53)[π]	16 (23.2%)	0.94 (0.57–1.55)[π]	0.85 (0.52–1.41)[π]

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; *N*, number of cataract/glaucoma patients

[#]: referent: patients without multiple sclerosis; adjusted for age and gender (unless stratified), smoking, body mass index, systemic glucocorticoids, hypnotics/anxiolytics, anticonvulsants, antidepressants use 6 months prior, diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, epilepsy and any ocular surgery ever before

[&]: referent: patients without multiple sclerosis; adjusted for age and gender (unless stratified), smoking, body mass index, systemic glucocorticoids, anticonvulsants, serotonin-selective reuptake inhibitors, tricyclic antidepressants, ocular glucocorticoids use 6 months prior, cerebrovascular disease, epilepsy and any uveitis ever before

[§]: Statistically significant difference ($p < 0.05$) of age category < 50 versus age category ≥ 50

[¥]: Statistically significant difference ($p < 0.05$) of females aged 18–49 versus females aged ≥ 50

[π]: Statistically significant difference ($p < 0.05$) of males aged 18–49 versus males aged ≥ 50

[ξ]: Statistically significant difference ($p < 0.05$) of females aged 18–49 versus males aged 18–49

clinically relevant confounder. In a sensitivity analysis, we added history of uveitis to the confounders in the cataract analysis, but there was no substantial change in fully adjusted HR, from HR 1.15 (0.94–1.41) to HR 1.14 (0.93–1.40). In sub-cohorts III and IV 548 patients were diagnosed with glaucoma during follow-up. Overall, there was no increased risk for glaucoma in MS patients compared with controls: adj. HR 1.02 (95% CI 0.78–1.33). Compared with all controls, men aged < 50 years had a 2.8-fold increased risk of glaucoma: adj. HR 2.76 (95% CI 1.28–5.93). This was also statistically different compared with male MS patients aged 50+ whose risk of glaucoma versus controls was 0.85 (95% CI 0.52–1.41). The Kaplan–Meier curves for the overall cataract and glaucoma analysis did diverge slightly (figures not shown). In addition, male MS patients younger than 50 years were compared with male controls younger than 50 years (see Figure 2a), and MS patients exposed to systemic glucocorticoids at baseline were compared with unexposed MS patients (see Figure 2b), for cataract and glaucoma.

Table 3 shows that the risk of cataract was increased in MS patients who were exposed to anticonvulsants, adj. HR 1.68 (95%CI 1.13–2.51), when compared with patients without MS. It was also statistically different from the risk of cataract in MS patients who were not recently exposed to anticonvulsants. Compared with controls, the risk of cataract was increased in MS patients using statins, adj. HR 1.58 (95%CI 1.07–2.32), and systemic GCs, adj. HR 2.95 (95% CI 1.78–4.89), within the preceding 6 months. For both exposures, the risk was statistically different when comparing MS patients recently exposed versus not recently exposed to the medications. The risk of glaucoma was doubled in MS patients who had recently used systemic GCs (adj. HR 2.25 (95% CI 1.15–4.40)).

Table 4 shows that the risk of cataract and glaucoma in MS patients was 2.5–3-fold increased in low-dose users of oral GCs (< 7.5 mg/day) when compared with the healthy control population, yielding adj. HR 3.28 (1.75–6.17) for cataract and adj. HR 2.76 (1.23–6.23) for glaucoma. There were no significant differences for the risk of both outcomes between MS patients who had been exposed to low (< 1 g prednisone equivalent) or high (> 5 g prednisone equivalent) cumulative doses of systemic GCs. MS patients on short-course GC treatment during MS relapse had a 3.5–4.4-fold increased risk of cataract or glaucoma when compared with the healthy control population, yielding adj. HR 3.55 (1.32–9.56) for cataract and adj. HR 4.58 (1.69–12.43) for glaucoma.

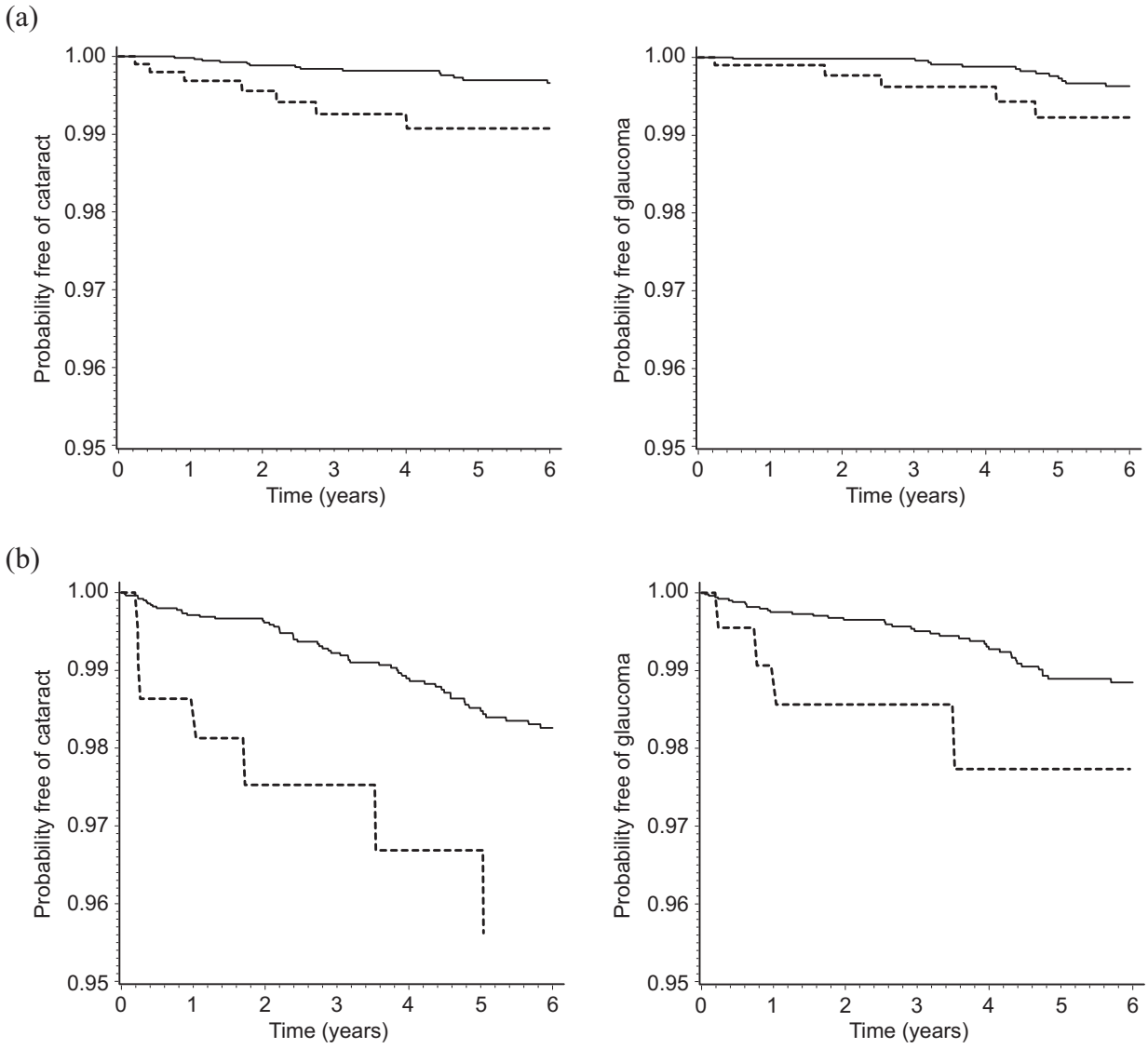

Figure 2. Kaplan–Meier curves for cataract and glaucoma: male MS patients aged < 50 years versus male controls aged < 50 years (a), and MS patients exposed to systemic glucocorticoids at baseline versus unexposed MS patients (b)
(a) Dashed lines: male MS patients aged < 50 years, solid lines: male controls aged < 50 years
(b) Dashed lines: MS patients exposed to systemic glucocorticoids at baseline, solid lines: unexposed MS patients

In order to study the potential impact of misclassification of the diagnosis of MS, we restricted our analysis to patients who had a lead-in time of at least 12 months prior to their MS diagnosis. However, this did not change our results substantially. Taking in account a lead-in time of 12 months, the risk of cataract in MS patients was adj. HR 1.13 (95% CI 0.90–1.42), whereas it was 1.15 (95% CI 0.94–1.41) when no lead-in time was considered. Concerning glaucoma, the risk was adj. HR 1.06 (95% CI 0.79–1.41) with lead-in time considered versus adj. HR 1.02 (95% CI 0.78–1.33) when not accounting for a lead-in time.

Discussion

This study showed that the risk of cataract and glaucoma in MS patients, as compared with healthy controls, was increased in those aged younger than 50 years and in particular in younger men. The risk of cataract and glaucoma was significantly increased in MS patients who had been exposed to systemic GCs during the past 6 months. In contrast, MS patients who were aged 50 or older did not have an increased risk of cataract or glaucoma when compared with a population-based sample without MS.

Table 3. Risk of cataract and glaucoma in MS patients compared with patients without MS (controls) by history of disease and drug use.

	Sub-cohorts I and II (Cataract analysis)			Sub-cohorts III and IV (Glaucoma analysis)		
	Number of cases *N* (%)	Age and sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[#]	Number of cases *N* (%)	Age and sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[&]
No MS (controls)	747 (2.2%)	1.00	1.00	479 (1.4%)	1.00	1.00
MS	114 (2.1%)	1.22 (1.00–1.49)	1.15 (0.94–1.41)	69 (1.3%)	1.13 (0.88–1.46)	1.02 (0.78–1.33)
Duration of MS						
< 1 year	17 (14.9%)	1.50 (0.92–2.43)	1.34 (0.83–2.18)	14 (20.3%)	1.78 (1.05–3.04)	1.59 (0.92–2.72)
1–5 years	42 (36.8%)	1.19 (0.87–1.62)	1.09 (0.80–1.50)	28 (40.6%)	1.16 (0.79–1.70)	1.06 (0.71–1.56)
> 5 year	55 (48.2%)	1.18 (0.90–1.56)	1.14 (0.86–1.52)	27 (39.1%)	0.94 (0.64–1.38)	0.83 (0.56–1.24)
Drug use 6 months before						
Systemic glucocorticoids						
Yes	16 (14.0%)	3.17 (1.93–5.20)[§]	2.95 (1.78–4.89)[§]	11 (15.9%))	2.79 (1.53–5.07)[§]	2.25 (1.15–4.40)[§]
No	98 (86.0%)	1.11 (0.90–1.37)[§]	1.06 (0.85–1.31)[§]	58 (84.1%)	1.02 (0.78–1.34)[§]	0.96 (0.73–1.27)[§]
Inhaled glucocorticoids						
Yes	6 (5.3%)	1.73 (0.78–3.87)	1.22 (0.54–2.75)	3 (4.3%)	1.18 (0.38–3.68)	0.87 (0.28–2.72)
No	108 (94.7%)	1.20 (0.98–1.47)	1.15 (0.93–1.41)	66 (95.7%)	1.13 (0.88–1.47)	1.03 (0.78–1.34)
Ocular glucocorticoids						
Yes	4 (3.5%)	7.20 (2.69–19.25)[§]	5.46 (2.03–14.67)[§]	6 (8.7%)	12.93 (5.78–28.96)[§]	6.75 (2.73–16.68)[§]
No	110 (96.5%)	1.19 (0.97–1.45)[§]	1.12 (0.91–1.38)[§]	63 (91.3%)	1.04 (0.80–1.36)[§]	0.95 (0.73–1.26)[§]
Statins						
Yes	29 (25.4%)	2.25 (1.55–3.27)[§]	1.58 (1.07–2.32)	8 (11.6%)	1.06 (0.53–2.14)	0.88 (0.43–1.79)
No	85 (74.6%)	1.06 (0.84–1.32)[§]	1.05 (0.84–1.33)	61 (88.4%)	1.15 (0.88–1.50)	1.04 (0.79–1.37)
Anticonvulsants						
Yes	27 (23.7%)	1.95 (1.33–2.87)[§]	1.68 (1.13–2.51)[§]	15 (21.7%)	1.66 (0.99–2.78)	1.29 (0.75–2.20)
No	87 (76.3%)	1.10 (0.88–1.37)[§]	1.07 (0.85–1.34)[§]	54 (78.3%)	1.04 (0.79–1.38)	1.01 (0.76–1.34)
History of disease ever before						
Asthma						
Yes	17 (14.9%)	1.82 (1.12–2.94)	1.33 (0.82–2.17)	10 (14.5%)	1.70 (0.91–3.18)	1.30 (0.69–2.46)
No	97 (85.1%)	1.16 (0.94–1.43)	1.12 (0.90–1.40)	59 (85.5%)	1.08 (0.82–1.41)	0.98 (0.74–1.30)
Cerebrovascular disease						
Yes	23 (20.2%)	2.56 (1.69–3.89)[¥]	2.33 (1.53–3.56)[¥]	7 (10.1%)	1.30 (0.62–2.75)	1.12 (0.53–2.39)
No	91 (79.8%)	1.08 (0.87–1.34)[¥]	1.03 (0.82–1.28)[¥]	62 (89.9%)	1.12 (0.86–1.46)	1.01 (0.77–1.33)
Depression						
Yes	41 (36.0%)	1.53 (1.12–2.10)	1.34 (0.97–1.86)	17 (24.6%)	0.97 (0.60–1.57)	0.84 (0.51–1.40)
No	73 (64.0%)	1.10 (0.86–1.40)	1.07 (0.84–1.37)	52 (75.4%)	1.20 (0.90–1.60)	1.08 (0.81–1.45)
Diabetes mellitus						
Yes	19 (16.7%)	2.92 (1.85–4.60)[¥]	2.52 (1.59–4.00)[¥]	4 (5.8%)	0.99 (0.37–2.65)	0.85 (0.32–2.28)
No	95 (83.3%)	1.09 (0.88–1.36)[¥]	1.04 (0.83–1.29)[¥]	65 (94.2%)	1.15 (0.88–1.48)	1.03 (0.78–1.35)

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; *N*, number of cataract/glaucoma patients

[#]: referent: patients without multiple sclerosis; adjusted for age and gender, smoking, body mass index, systemic glucocorticoids (unless stratified), hypnotics/anxiolytics, anticonvulsants (unless stratified), antidepressants use 6 months prior, diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, epilepsy and any ocular surgery ever before

[&]: referent: patients without multiple sclerosis; adjusted for age and gender, smoking, body mass index, systemic glucocorticoids (unless stratified), anticonvulsants (unless stratified), serotonin-selective reuptake inhibitors, tricyclic antidepressants, ocular glucocorticoids (unless stratified) use 6 months prior, cerebrovascular disease, epilepsy and any uveitis ever before

[§]: Statistically significant difference ($p < 0.05$) of the exposure to the medication versus non-exposure to the medication

[¥]: Statistically significant difference ($p < 0.05$) of the exposure to the disease versus non-exposure to the disease

The potential of MS to increase the risk of cataract may be explained by the actions of calpains (proteolytic enzymes) which have been reported to be involved in cellular processes and signal transduction.[26] Iman et al. measured a significantly increased calpain activity and expression in the peripheral blood mononuclear cells of MS patients during a relapse.[8] Calpain 1 (μ-calpain), the lens-specific isoenzyme Lp85, calpain 2 (m-calpain), calpain 3, calpain 10 and the lens-specific

Table 4. Risk of any cataract and glaucoma in MS patients compared with patients without MS (controls) by exposure to systemic glucocorticoids.

	Sub-cohorts I and II (Cataract analysis)			Sub-cohorts III and IV (Glaucoma analysis)		
	Number of cases *N* (%)	Age and sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[#]	Number of cases *N* (%)	Age and sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[&]
No MS (controls)	747 (2.2%)	1.00	1.00	479 (1.4%)	1.00	1.00
MS	114 (2.1%)	1.22 (1.00–1.49)	1.15 (0.94–1.41)	69 (1.3%)	1.13 (0.88–1.46)	1.02 (0.78–1.33)
6 months prior by average daily dose						
No use	98 (86.0%)	1.11 (0.90–1.37)[§]	1.06 (0.85–1.31)[§]	58 (84.1%)	1.02 (0.78–1.34)[§]	0.96 (0.73–1.27)[§]
Any use	16 (14.0%)	3.17 (1.93–5.20)[§]	2.95 (1.78–4.89)[§]	11 (15.9%)	2.79 (1.53–5.07)[§]	2.25 (1.15–4.40)[§]
< 7.5 mg	10 (8.8%)	3.55 (1.90–6.62)	3.28 (1.75–6.17)	6 (8.7%)	3.10 (1.38–6.93)	2.76 (1.23–6.23)
≥ 7.5 mg	6 (5.3%)	2.69 (1.20–6.02)	2.53 (1.13–5.69)	5 (7.2%)	2.49 (1.03–6.01)	1.64 (0.52–5.15)
Ever prior by cumulative dose						
No use	66 (57.9%)	0.95 (0.74–1.22)[¥ξ]	0.92 (0.71–1.19)[¥]	41 (59.4%)	0.92 (0.67–1.26)[¥]	0.87 (0.62–1.20)
Any use	48 (42.1%)	2.03 (1.51–2.72)[¥ξ]	1.83 (1.35–2.48)[¥]	28 (40.6%)	1.74 (1.19–2.55)[¥]	1.31 (0.87–1.98)
< 1 g	20 (17.5%)	1.53 (0.98–2.39)	1.40 (0.89–2.20)	14 (20.3%)	1.59 (0.94–2.71)	1.38 (0.80–2.38)
1–5 g	18 (15.8%)	2.55 (1.59–4.07)	2.19 (1.36–3.52)	10 (14.5%)	2.03 (1.08–3.81)	1.78 (0.94–3.36)
> 5 g	10 (8.8%)	2.86 (1.53–5.34)	2.73 (1.45–5.13)	4 (5.8%)	1.68 (0.63–4.49)	1.37 (0.51–3.69)
Oral and IV exposure 6 months prior by exposure to short-course treatment in the year before[*]						
No use	97 (85.1%)	1.11 (0.90–1.37)	1.05 (0.85–1.31)	58 (84.1%)	1.02 (0.78–1.34)	0.94 (0.71–1.25)
Any use	17 (14.9%)	3.04 (1.88–4.93)[π]	2.83 (1.73–4.62)[π]	11 (15.9%)	2.79 (1.53–5.07)[π]	2.48 (1.34–4.56)[π]
No short-course	13 (11.4%)	2.87 (1.66–4.96)	2.66 (1.53–4.65)	7 (10.1%)	2.22 (1.05–4.68)	1.97 (0.92–4.18)
Short-course	4 (3.5%)	3.83 (1.43–10.25)[ξ]	3.55 (1.32–9.56)[ξ]	4 (5.8%)	5.07 (1.89–13.61)[ξ]	4.58 (1.69–12.43)[ξ]
Oral	1 (0.9%)	1.86 (0.25–13.75)	1.90 (0.26–14.00)	2 (2.9%)	5.60 (1.31–23.97)	5.13 (1.20–22.03)
Intravenous	3 (2.6%)	4.09 (1.28–13.05)[ϕ]	3.73 (1.17–11.85)[ϕ]	2 (2.9%)	2.82 (0.66–12.04)[ϕ]	2.58 (0.60–11.04)[ϕ]

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; *N*, number of cataract/glaucoma patients; IV, intravenous

*analysis includes free-text information on oral and intravenous exposure during MS relapse

#: referent: patients without multiple sclerosis; adjusted for age and gender, smoking, body mass index, hypnotics/anxiolytics, anticonvulsants, antidepressants use 6 months prior, diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, epilepsy and any ocular surgery ever before

&: referent: patients without multiple sclerosis; adjusted for age and gender, smoking, body mass index, anticonvulsants, serotonin-selective reuptake inhibitors, tricyclic antidepressants use 6 months prior, cerebrovascular disease, epilepsy and any uveitis ever before

§: π: Statistically significant difference ($p < 0.05$) of the exposure to oral and intravenous glucocorticoids versus non-exposure to oral and IV glucocorticoids 6 months before

¥: Statistically significant difference ($p < 0.05$) of the exposure to systemic glucocorticoids versus non-exposure to systemic glucocorticoids ever before

π: Statistically significant difference ($p < 0.05$) of the exposure to oral and intravenous glucocorticoids versus non-exposure to oral and IV glucocorticoids 6 months before

ξ: Statistically significant difference ($p < 0.05$) of the short-course exposure to oral and intravenous glucocorticoids versus non-short-.course exposure to oral and IV glucocorticoids in the year before

ϕ: Statistically significant difference ($p < 0.05$) of the short-course exposure to oral glucocorticoids versus intravenous short-course exposure to glucocorticoids in the year before

isoenzyme Lp82 are known to be active in the lens, with calpain 2 being the most prevalent in mammalian cells.[6,26] In the presence of elevated calcium ion (Ca^{2+}) levels, overactivation of calpains is thought to cause the degradation of lens proteins and changes in the cytoskeletal architecture.[6,7,26] These morphological and biological changes then result in the formation of cataract. Lower oestrogen levels in men versus women may explain why the risk in young men is increased compared with young women. In rodent studies, the risk of cataract was doubled in male rates, whereas female rats maintained a clear lens at a similar level of transforming growth factor beta (TGF-beta).[27] The relatively higher oestrogen levels in female rodents are considered to be protective against the cataractogenic influences of TGF-beta.[27,28] Furthermore, hormone replacement therapy in humans has been associated with a protective effect in respect to cataract.[29]

MS and glaucoma have both been associated with retinal nerve fibre layer (NFL) loss. Recent studies on macular region and NFL composition revealed a reduced thickness in both macular area as well as NFL thickness in MS patients compared with controls.[13,14,30] In addition, Bock et al. measured no difference in retinal NFL loss between MS patients and glaucoma patients.[30] However, it is unclear if there is a shared mechanism involved. Male gender is

reported to be predictive for progression of glaucomatous disease.[31] In a population-based study from the Netherlands, it was found that male gender was a risk factor for developing glaucomatous visual field loss.[32] This is in line with our results of an elevated risk of glaucoma in younger males.

The use of GCs has been associated with mainly posterior sub-capsular cataract (PSC) in population-based studies.[17,33] Meanwhile, the exact pathway of GC-induced cataract is still unclear. Several mechanisms for the interaction of GC with lens tissue have been described. They involve activation of GC receptors which change gene transcription, disruption of epithelial cell proliferation and cell differentiation mechanisms.[5,34] A recent study suggested that inadequate concentration of fibroblast growth factor 2 (FGF-2) in the posterior chamber inhibits lens fibre differentiation and causes epithelial cell proliferation and posterior migration instead.[5,34] As a result, granular material and vacuoles accumulate at the posterior pole of the intraocular lens, an irreversible change of lens structure.[34,35] Secondary or GC-induced glaucoma may be the result of altered aqueous outflow, which causes morphological and biological changes at the level of the trabecular meshwork.[36] As a consequence of this imbalance between aqueous production and outflow, intraocular pressure will rise. This may ultimately result in retinal nerve fibre loss. Biological evidence indicates that GC-induced cataract or NFL loss due to secondary glaucoma is irreversible. For this reason, we have evaluated the association between cumulative exposures to GCs in patients with MS. We found a non-significant but positive correlation between ever prior GC use and risk of glaucoma, and a statistically significant correlation between ever prior GC use and risk of cataract in patients with MS. The true relationship may have been stronger because we have not been able to measure patient exposure to GCs before enrolment in GPRD. We were able to evaluate detailed data on GC boosters that can be prescribed to MS patients with the relapsing–remitting type of the disease. There appears to be a trend of dose-dependent risk of cataract with cumulative GC use. However, our results should be evaluated with caution as the number of patients receiving this type of treatment was low.

In this study, we also found an increased risk of cataract in MS patients with recent anticonvulsant use. This is in line with case reports suggesting a link between anticonvulsant use and cataract.[37,38] Punctate lenticular lesions have been reported with carbamazepine use.[37] However, we are not aware of any biological mechanism where anticonvulsants would cause cataract. The link noted may be due to the more frequent use of anticonvulsants in MS patients compared with the general population. In our study, we found an increased risk of cataract in statin users. Compared with controls, MS patients had more often been prescribed statins at baseline. A possible explanation is that during the study period, statins had been suggested to have neuroprotective properties.[39] Epidemiological studies that evaluated statin use and risk of cataract in a general population have shown conflicting results.[39-41] Some studies found either a protective effect[40] or no effect[41,42] after adjustment. Before adjustment, Smeeth et al. did find a slightly increased risk of cataract, which disappeared after adjustment.[42]

An increased risk of cataract and glaucoma in the younger MS population could also indicate a higher activity of the MS. The link may be due either to an intensified treatment regimen, or – if a causal relationship between MS and cataract and glaucoma exists – due to the MS disease. The available data did not allow us to establish the activity of MS disease at any time.

Our study has several strengths, including a reasonable sample size and that it was population based. Previous studies of GPRD data have shown a high level of data validity with respect to the reporting of MS,[22] cataract[43] and glaucoma.[44] Furthermore, we had detailed information on lifestyle parameters such as smoking and BMI, could determine longitudinal drug exposures, and we were able to link our data to the national hospitalization registry of England.

Our study also has several limitations. Diagnostic bias may be an alternative explanation for the 1.7–2.5-fold increased risk of ocular outcomes that we observed in younger patients with MS when compared with healthy controls. As compared with healthy controls, patients with MS are more likely to visit an eye specialist due to frequent ocular symptoms of MS such as double vision, ocular motor dysfunctions and optic neuritis (20%). This difference becomes more pronounced among younger patients. However, this does not explain why, in this study, the risk of cataract and glaucoma in younger men with MS was significantly increased compared with the risk of ocular outcomes in younger women with MS. Another limitation is that the registered date of MS diagnosis may not be the actual date of onset of the disease, as symptoms may arise several years before the ultimate diagnosis is made. For this reason, the early stages of the disease may be insufficiently represented in our study. We performed a sensitivity analysis with respect to the timing of the exposure but the links remained unchanged. Misclassification with regard to the outcome measures may play a role. We may have missed patients with early cataract or early glaucoma and considered them as disease free at the beginning of follow-up, or as disease free during follow-up. We would consider this as a non-differential potential misclassification of the outcome, which could have masked a true overall link between MS and cataract or glaucoma. In this study we had no information on important risk factors for cataract such as UV exposure as this is virtually impossible to measure in a population-based primary care setting. We were also unable to incorporate information on race and family history of glaucoma, known risk factors for the disease.

In conclusion, we found an increased risk of cataract and glaucoma in patients with MS aged younger than 50 years, particularly in men. In addition, we showed that the risk of

cataract and glaucoma was increased in MS patients on systemic GC therapy. Our results suggest that patients with MS on systemic GC therapy, and especially males younger than 50 years, may benefit from ocular screening for cataract and glaucoma. Should further studies confirm our findings, then the financial feasibility of ocular screening should be determined.

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Conflict of interest statement

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References

1. Dua T, Romani P. Atlas Multiple Sclerosis Resources in the World 2008. http://www.who.int/mental_health/neurology/Atlas_MS_WEB.pdf (accessed 24.02.2010): World Health Organization, 2008. pp. 14.
2. Towler HM and Lightman S. Symptomatic intraocular inflammation in multiple sclerosis. *Clin Experiment Ophthalmol* 2000; 28: 97-102.
3. Donaldson MJ, Pulido JS, Herman DC, Diehl N and Hodge D. Pars planitis: a 20-year study of incidence, clinical features, and outcomes. *Am J Ophthalmol* 2007; 144: 812-817.
4. Prieto JF, Dios E, Gutierrez JM, Mayo A, Calonge M and Herreras JM. Pars planitis: epidemiology, treatment, and association with multiple sclerosis. *Ocul Immunol Inflamm* 2001; 9: 93-102.
5. James ER. The etiology of steroid cataract. *J Ocul Pharmacol Ther* 2007; 23: 403-420.
6. De Maria A, Shi Y, Kumar NM, Bassnett S. Calpain expression and activity during lens fiber cell differentiation. *J Biol Chem* 2009; 284: 13542-13550.
7. Shields DC, Schaecher KE, Saido TC and Banik NL. A putative mechanism of demyelination in multiple sclerosis by a proteolytic enzyme, calpain. *Proc Natl Acad Sci U S A* 1999; 96: 11486-11491.
8. Imam SA, Guyton MK, Haque A, Vandenbark A, Tyor WR, Ray SK, et al. Increased calpain correlates with Th1 cytokine profile in PBMCs from MS patients. *J Neuroimmunol* 2007; 190: 139-145.
9. Lowder CY and Char DH. Uveitis. A review. *West J Med* 1984; 140: 421-432.
10. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P and Murray PI. Degree, duration, and causes of visual loss in uveitis. *Br J Ophthalmol* 2004; 88: 1159-1162.
11. Edelsten C, Lee V, Bentley CR, Kanski JJ and Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. *Br J Ophthalmol* 2002; 86: 51-56.
12. Prieto A, Diaz D, Barcenilla H, Castrillo C, Monserrat J, Merino AG, et al. Increased spontaneous ex vivo apoptosis and subset alterations in peripheral blood T cells from patients with multiple sclerosis. *J Clin Immunol* 2006; 26: 101-112.
13. Fisher JB, Jacobs DA, Markowitz CE, Galetta SL, Volpe NJ, Nano-Schiavi ML, et al. Relation of visual function to retinal nerve fiber layer thickness in multiple sclerosis. *Ophthalmology* 2006; 113: 324-332.
14. Gugleta K, Mehling M, Kochkorov A, Grieshaber M, Katamay R, Flammer J, et al. Pattern of macular thickness changes measured by ocular coherence tomography in patients with multiple sclerosis. *Klin Monbl Augenheilkd* 2008; 225: 408-412.
15. Shindler KS, Guan Y, Ventura E, Bennett J and Rostami A. Retinal ganglion cell loss induced by acute optic neuritis in a relapsing model of multiple sclerosis. *Mult Scler* 2006; 12: 526-532.
16. Jankowska-Lech I, Terelak-Borys B, Grabska-Liberek I and Palasik W. [Glaucoma neuropathy and neuropathy in multiple sclerosis--common elements of pathogenesis?]. *Klin Oczna* 2007; 109: 317-320.
17. Chrousos GA, Kattah JC, Beck RW and Cleary PA. Side effects of glucocorticoid treatment. Experience of the Optic Neuritis Treatment Trial. *JAMA* 1993; 269: 2110-2112.
18. Munjal VP, Dhir SP, Jain IS, Gangwar DN and D'Souza M. Topical corticosteroids and cataract. *Ind J Ophthalmol* 1984; 32: 478-480.
19. Kupersmith MJ, Kaufman D, Paty DW, Ebers G, McFarland H, Johnson K, et al. Megadose corticosteroids in multiple sclerosis. *Neurology* 1994; 44: 1-4.
20. Sellebjerg F, Frederiksen JL, Nielsen PM and Olesen J. Double-blind, randomized, placebo-controlled study of oral, high-dose methylprednisolone in attacks of MS. *Neurology* 1998; 51: 529-534.
21. de Seze J, Vukusic S, Viallet-Marcel M, Tilikete C, Zephir H, Delalande S, et al. Unusual ocular motor findings in multiple sclerosis. *J Neurol Sci* 2006; 243: 91-95.
22. Alonso A, Jick SS, Olek MJ and Hernan MA. Incidence of multiple sclerosis in the United Kingdom: findings from a population-based cohort. *J Neurol* 2007; 254: 1736-1741.
23. Ruigomez A, Garcia Rodriguez LA, Dev VJ, Arellano F and Raniwala J. Are schizophrenia or antipsychotic drugs a risk factor for cataracts? *Epidemiology* 2000; 11:620-623.
24. De Vries F, Bracke M, Leufkens HG, Lammers JW, Cooper C and Van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. *Arthritis Rheum* 2007; 56: 208-214.
25. De Vries F, Pouwels S, Lammers JW, Leufkens HG, Bracke M, Cooper C, et al. Use of inhaled and oral glucocorticoids, severity of inflammatory disease and risk of hip/femur fracture:

a population-based case-control study. *J Intern Med* 2007; 261: 170-177.
26. Biswas S, Harris F, Dennison S, Singh J and Phoenix DA. Calpains: targets of cataract prevention? *Trends Mol Med* 2004; 10: 78-84.
27. Hales AM, Chamberlain CG, Murphy CR and McAvoy JW. Estrogen protects lenses against cataract induced by transforming growth factor-beta (TGFbeta). *J Exp Med* 1997; 185: 273-280.
28. Davis VL, Chan CC, Schoen TJ, Couse JF, Chader GJ and Korach KS. An estrogen receptor repressor induces cataract formation in transgenic mice. *Proc Natl Acad Sci U S A* 2002; 99: 9427-9432.
29. Aina FO, Smeeth L, Hubbard R, Hurt LS and Fletcher AE. Hormone replacement therapy and cataract: a population-based case-control study. *Eye (Lond)* 2006; 20: 417-422.
30. Bock M, Brandt AU, Dorr J, Kraft H, Weinges-Evers N, Gaede G, et al. Patterns of retinal nerve fiber layer loss in multiple sclerosis patients with or without optic neuritis and glaucoma patients. *Clin Neurol Neurosurg* 2010; 112: 67-652.
31. AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. *Am J Ophthalmol* 2002; 134: 499-512.
32. Czudowska MA, Ramdas WD, Wolfs RC, Hofman A, De Jong PT, Vingerling JR, et al. Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study. *Ophthalmology* 2010; 117: 1705-1712.
33. Garbe E, LeLorier J, Boivin JF and Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. *Lancet* 1997; 350: 979-982.
34. Jobling AI and Augusteyn RC. What causes steroid cataracts? A review of steroid-induced posterior subcapsular cataracts. *Clin Exp Optom* 2002; 85: 61-75.
35. Pau H. Cortical and subcapsular cataracts: significance of physical forces. *Ophthalmologica* 2006; 220: 1-5.
36. Clark AF and Wordinger RJ. The role of steroids in outflow resistance. *Exp Eye Res* 2009; 88: 752-759.
37. Goldman MJ and Schultz-Ross RA. Adverse ocular effects of anticonvulsants. *Psychosomatics* 1993; 34: 154-158.
38. Kinoshita A, Kitaoka T, Oba K and Amemiya T. Bilateral drug-induced cataract in a patient receiving anticonvulsant therapy. *Jpn J Ophthalmol* 2004; 48: 81-82.
39. Van der Most PJ, Dolga AM, Nijholt IM, Luiten PG and Eisel UL. Statins: mechanisms of neuroprotection. *Prog Neurobiol* 2009; 88: 64-75.
40. Klein BE, Klein R, Lee KE and Grady LM. Statin use and incident nuclear cataract. *JAMA* 2006; 295: 2752-2758.
41. Schlienger RG, Haefeli WE, Jick H and Meier CR. Risk of cataract in patients treated with statins. *Arch Intern Med* 2001; 161: 2021-2026.
42. Smeeth L, Hubbard R and Fletcher AE. Cataract and the use of statins: a case-control study. *QJM* 2003; 96: 337-343.
43. Smeeth L, Boulis M, Hubbard R and Fletcher AE. A population-based case-control study of cataract and inhaled corticosteroids. *Br J Ophthalmol* 2003; 87: 1247-1251.
44. Zhou Z, Althin R, Sforzolini BS and Dhawan R. Persistency and treatment failure in newly diagnosed open angle glaucoma patients in the United Kingdom. *Br J Ophthalmol* 2004; 88: 1391-1394.