Original article

# Myopia in late adolescence and subsequent multiple sclerosis among men

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A B S T R A C T

*Background:* Risk factors such as low vitamin D level has been implicated in the etiology of multiple sclerosis (MS) and may be relevant to myopia, such that there may be an association between myopia and MS.
*Methods:* Using linked Swedish national register data, we conducted a cohort study of men who were born in Sweden between 1950 and 1992, lived in Sweden between 1990 and 2018, and enrolled in military conscription assessment ($n = 1,847,754$). Myopia was defined based on the spherical equivalent refraction measured at conscription assessment, around age 18 years. Multiple sclerosis was identified using the Patient Register. Cox regression produced hazard ratios (HR) with 95% confidence intervals (95% CI), with adjustment for demographic and childhood socioeconomic characteristics and residential region. Due to changes in the assessment of refractive error, the analysis was stratified into two groups by the year of conscription assessment: 1969–1997 and 1997–2010.
*Results:* Among 1,559,859 individuals during a maximum of 48 years of follow-up from age 20 to 68 years (44,715,603 person-years), there were 3,134 MS events, and the incidence rate 7.0 (95% CI [6.8, 7.3] per 100,000 person-years). Among individuals with conscription assessments during 1997–2010, there were 380 MS events. There was no evidence of an association between myopia and MS, with HR 1.09 (95% CI 0.83, 1.43). Among individuals who underwent conscription assessment in 1969–1997, there were 2754 MS events. After adjusting for all covariates, there was no evidence of an association between myopia and MS (HR 0.99 [95% CI 0.91, 1.09]).
*Conclusion:* Myopia in late adolescence is not associated with a subsequent raised risk of MS and thus there does not appear to be important shared risk factors.

## 1. Introduction

Multiple sclerosis (MS) has relatively long subclinical and prodromal phases (Giovannoni, 2016), such that environmental exposures have been linked with raised risk of an MS diagnosis more than 10 or 20 years later. Adolescence appears to be a time of particularly heightened susceptibility to exposures relevant to MS risk (Montgomery et al., 2017; Xu et al., 2021a, 2021b), so some other diagnoses at these ages may be risk factors or markers of shared risk. We hypothesised that myopia in late adolescence would be associated with subsequent raised MS risk as

lower vitamin D levels are implicated in both diseases (Alfredsson and Olsson, 2019; Tideman et al., 2016; Yazar et al., 2014), although findings have been not always consistent (Cuellar-Partida et al., 2017; Chan et al., 2022). Other risk factors such as lower levels of physical fitness or exercise levels have also been linked with both diseases (Gunnarsson et al., 2015; Guggenheim et al., 2012).

There is consistent evidence that lower Vitamin D levels are associated with MS (Alfredsson and Olsson, 2019), including animal models where administration prevents the onset and progression of experimental allergic encephalomyelitis in mice (Lemire and Archer, 1991;

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Cantorna et al., 1996). Vitamin D production results from exposure to UVB radiation and there are gradients in MS risk by latitude of residence (Kurtzke, 1980) and annual mean UVB irradiation (Orton et al., 2011). Vitamin D status was examined in neonates and demonstrated that those with the highest risk of MS were in the lowest quintile of blood vitamin D level. In several case-control studies increased sun exposure in childhood or adolescence or higher vitamin D blood levels were linked to a reduced risk of MS (van der Mei et al., 2003; Bjørnevik et al., 2014; Freedman et al., 2000). A role for vitamin D in MS etiology is also supported by Mendelian randomisation (Mokry et al., 2015). A prospective nested case-control study based on 257 healthy US military personnel at recruitment identified the risk of subsequent MS decreased significantly with higher vitamin D blood levels especially for Whites under the age of 20 years (Munger et al., 2006). This is probably the most convincing trial to validate a link between blood vitamin D level and subsequent MS risk, although the evidence for a causal association remains equivocal.

Myopia is an increasingly common condition worldwide affecting 30–50% of adults in USA and even higher levels (80–90%) in school-leavers in Singapore, South Korea and China (Vitale et al., 2009; Jung et al., 2012; Holden et al., 2016): the change is too rapid for a genetic shift (Mountjoy et al., 2018), although there are genetic risks for myopia indicated by family history (Li and Zhang, 2017) and twin studies (Karlsson, 1974; Lin and Chen, 1987; Teikari et al., 1991). A link between greater sunlight exposure and lower myopia risk has been proposed (Williams et al., 2017) and progression of myopia is more rapid in winter months (Gwiazda et al., 2014) suggesting vitamin D deficiency as a possible causal agent. It has been argued that vitamin D deficiency may change intracellular calcium levels that impairs contraction of the ciliary muscles (Annamaneni et al., 2011) or that vitamin D may be involved in retino-scleral signaling (McBrien and Gentle, 2003). Tideman et al. (2016) studied 2666 Dutch children with measures of visual acuity, eye axial length, serum vitamin D concentration and vitamin D related single-nucleotide polymorphisms (SNPs). After adjustment for covariates, vitamin D level was inversely associated with axial length, and this association remained after further adjustment for time spent outdoors. However, none of the selected vitamin D associated SNPs were linked to axial length or myopia weakening the argument for an important causal role for vitamin D. There is also possible confounding as myopes are more likely to be studious, spend less time outdoors and have higher educational attainment (Williams et al., 2015). If reduced time outdoors is associated with lower levels of physical fitness, then this is another possible link between myopia and MS, given the association of lower fitness levels with these diseases (Gunnarsson et al., 2015; Guggenheim et al., 2012).

Other theories related to myopia emphasize the importance of blue light. Normal eye growth (emmetropization) can respond to wavelength defocus since animals reared in monochromatic light adjust their refractive state relative to that measured in white light. Sunlight consists mainly of blue light and theoretically should protect against myopia. Violet light is claimed to be protective against myopia according to data from a chick myopia model, and experiments on children fitted with violet light blocking or transmitting glasses or contact lenses (Torii et al., 2017). However, the association of blue light with myopia remains equivocal.

This large-scale cohort study examines the association of measured myopia in late adolescence, before age 20 years, with a subsequent diagnosis of MS among men from age 20 years using linked Swedish register data. Those with a diagnosis of MS or other demyelinating diseases before age 20 years were excluded. The assessment of vision was performed as part of a military conscription assessment that was compulsory for part of the study period.

## 2. Material and methods

### 2.1. Study design and population

We conducted a Swedish register-based cohort study that comprised all men who lived in Sweden between 1990 and 2019, aged 25 years and older, born between 1950 and 1992, and participated in a military conscription assessment ($n = 2,021,369$). Data for several Swedish national registers were linked using the unique individual personal identification number. The Total Population Register was used to identify dates of birth, death, and emigration. The Multi-Generation Register was used to identify the cohort members' biological parents and childhood socioeconomic circumstances were identified using the Population and Housing Censuses. The Swedish Military Conscription Register was employed to obtain information on eyesight recorded during the conscription assessment between 1969 and 2010 when these men were mostly aged around 18 years. The information on MS and other relevant diagnoses was supplied from the Patient Register, which was initiated in 1964, achieved full coverage in 1987, and included outpatient diagnoses from 2001.

Ethical approval for this study was granted by the Swedish Ethical Review Authority (reference numbers: 2019–04,755 and 2020–02,406).

### 2.2. Refractive error

The measurement and recording of refractive error in the Swedish Military Conscription Register changed in 1997. Therefore, we separated the data into two cohorts: individuals who underwent conscription assessment from 1969 to 1997, and from 1997 to 2010.

#### 2.2.1. Conscription assessment from 1969 to 1997
The information on visual acuity and spherical equivalent (SE) for each eye was available, with SE recorded as the type of corrective lenses required.

We defined individuals with myopia as those who had negative spherical corrective lenses for both eyes. All others were classified as non-myopic.

#### 2.2.2. Conscription assessment from 1997 to 2010
This cohort had data on full refractive error and SE was calculated in the conventional way (Sphere + Cylinder/2). We defined individuals with myopia as those with a mean SE for both eyes equal to, or more myopic than, $-1.0D$, and non-myopia for all others. Since the SE was measured only for the eyes below 1.0 in visual acuity, a value of 0 was given to the SE for the eyes with visual acuity at least 1.0.

In a sub-analysis, we examined myopia in further detail: moderate and high myopia (mean SE $\leq 3.0D$), low myopia (mean SE $-1D$ to $-2.9D$), emmetropia (mean SE $-0.9D$ to $+ 0.9D$), and hypermetropia (mean SE $\geq 1.0D$).

#### 2.2.3. Conscription assessment 1969-1997 and 1997-2010 combined
Binary measures for both periods, myopia and non-myopia, were combined.

### 2.3. MS diagnosis

Using the Patient Register, individuals with MS were defined as those who had at least two MS diagnoses, separated by a minimum of six months, either as a primary or secondary diagnosis. MS diagnoses were identified using the following codes in the Swedish version of the International Classification of Diseases (ICD): ICD-7 345; ICD-8 and ICD-9 340; and ICD-10 G35. The index date was defined as the date of the first diagnosis.

Any demyelinating diseases in addition to MS that occurred before age 20 years were identified to help exclude those with possible prodromal MS in adolescence. These included ICD-8 and 9 341 (other

demyelinating diseases of the central nervous system) and ICD-10 G36 and G37 (other acute disseminated demyelination and other demyelinating diseases of the central nervous system, respectively).

### 2.4. Covariates

Year of birth was categorised in five-year intervals, as this gave a better model fit than when modelled continuously. We also included birth-year household crowding (person per room ratio) and socioeconomic index (SEI). Region of residence at the year of conscription was included as a further potential confounding factor. Childhood socioeconomic characteristics were defined using the information around the year of birth using censuses from 1960 to 1990. Household crowding was defined as the number of individuals in the dwelling divided by the number of habitable rooms, using prospectively recorded census data or from 1990 onwards, using the Longitudinal Integration Database for Health Insurance and Labour Market Studies (Swedish acronym, *LISA*). Crowding data were selected from the year nearest in time to cohort members' year of birth. The crowding distribution was standardised by year of birth and divided into quarters. SEI was based on the father's SEI, and if the father's information was not available the mother's SEI was substituted. Region of residence was grouped into northern, central, and southern Sweden.

### 2.5. Statistical analysis

Unless otherwise indicated, all analyses were conducted separately for the two conscription assessment periods. In the descriptive statistics, individuals were grouped into ever or never developed MS (based on two separate MS diagnoses). Sample characteristics were summarised using frequencies, percentages and rates with 95% confidence intervals. To assess the association between myopia in late adolescence and a subsequent diagnosis of MS, Cox regression was used to estimate hazard ratios (HR) with 95% confidence intervals. In all Cox regression models, age was used as the underlying timescale for highly effective adjustment (Korn et al., 1997). Follow-up started from age 20 years and ended on the date of first MS diagnosis, emigration, death or 31 December 2018, whichever occurred first. Median follow-up was calculated for all participants. The proportional hazards assumption was assessed through

both Schoenfeld residual tests and graphical assessments of hazard function and log-log survival curves. Two models were fitted: model 1 was adjusted for sex and birth year (and age as it was the underlying timescale), and model 2 was further adjusted for childhood socioeconomic characteristics and residential region. We also conducted analyses combining the two conscription cohorts. In the analysis using the information on the severity of myopia for the cohort with conscription assessment from 1997 to 2010, we conducted two analyses using different reference categories (SE −0.9D to + 0.9D, or SE≥1.0D) to increase the comparability with other studies. Also, we conducted an analysis combining some categories of refractive errors as the number of events were relatively sparce.

### 3. Results

#### 3.1. Analytical samples

Among 2021,369 men identified for this study, the following exclusions were made: potentially unreliable data (*n* = 1266), conscription assessment before 1969 (*n* = 14,760) or after age 20 years (*n* = 42,384), diagnosis of a demyelinating diseases other than MS by age 20 years (*n* = 48), and missing data for socioeconomic variables in childhood (*n* = 115,157) (Fig. 1). After the exclusions, 1847,754 individuals remained. This sample was separated into two cohorts, according to the year of conscription assessment.

#### 3.1.1. Conscription assessment 1997–2010

Among the initial sample, 470,513 individuals underwent conscription assessment from 1997 to 2010. Of these, in total 159,318 individuals were excluded because of missing refraction data (*n* = 152,899) or uncommon combinations of SE values for the two eyes (*n* = 1834): positive SE for one eye and negative for the other, higher than plus or minus 6D for an eye and emmetropic for the other eye (indicating anisometropic amblyopia), or SE ≤ −3 for one eye and the difference of SE between the two eyes was greater than 10 SE. Individuals who had emigrated (*n* = 4573) or diagnosed with MS (*n* = 12) before the start of follow-up were also excluded. The remaining 311,195 individuals were included in the analysis.
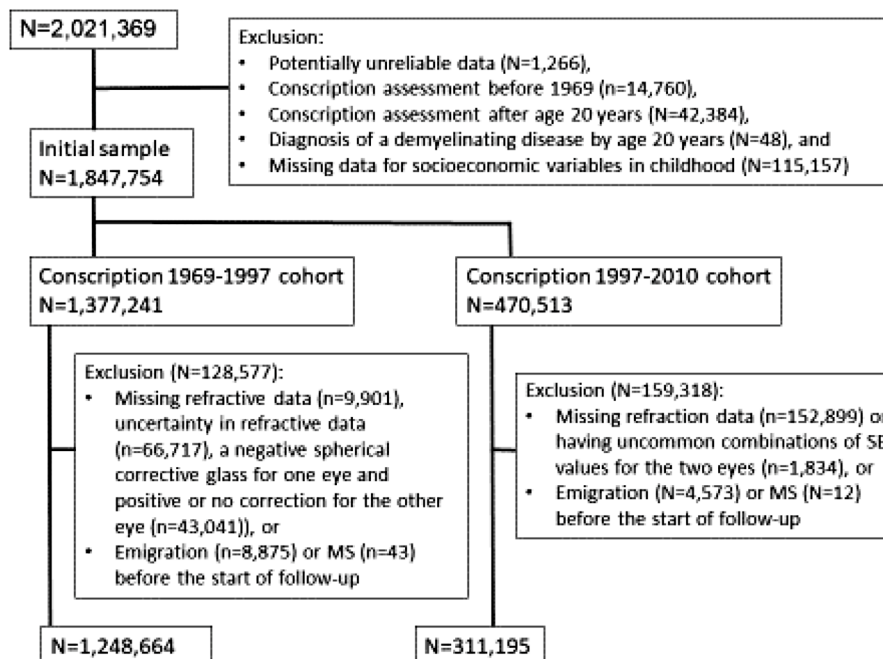


**Fig. 1.** Flowchart for the analytical sample selection.

### 3.1.2. Conscription assessment 1969–1997

Some 1377,241individuals underwent conscription assessment from 1969 to 1997. Of these, in total 128,577 individuals were excluded due to missing refractive data ($n = 9901$), uncertain refractive data ($n = 66,717$), a negative spherical corrective lens for one eye and positive or no correction for the other eye ($n = 43,041$), or emigration ($n = 8875$) or MS diagnosis ($n = 43$) before the start of follow-up. The remaining 1248,664 individuals were included in the analysis.

### 3.2. Descriptive data

Among individuals who attended conscription assessment in 1969–1997, the proportion of individuals with myopia tended to be higher in individuals who had a parent with a more advantageous socioeconomic index and lived in a less crowded household and in the northern or central regions of Sweden (Appendix A, Table A.1). Such differences appeared to be less pronounced in individuals with more recent conscription assessments during 1997 to 2010.

Those diagnosed with multiple sclerosis during the follow-up were more likely with a higher childhood socioeconomic index and less crowded households (Table 1). Among individuals with conscription assessment 1969–1997, the proportion with myopia was similar to those who were ever or never diagnosed with MS, but it was slightly higher for individuals with MS in the cohort with a conscription assessment during 1997–2010.

### 3.3. Myopia and MS risk - 1997–2010

Among individuals who attended conscription assessment during 1997–2010, there were 380 MS events during follow-up from age 20 to a maximum of 41 years, with a median follow-up duration of 15 years. The rate of MS was slightly higher for individuals with myopia than for non-myopia, 9.5 (95% CI 7.5, 12.2) and 8.4 (95% CI 7.5, 9.4) per 100,000 person-years, respectively (Table 2).

Based on Schoenfeld residual tests, there was no evidence of a violation of the proportional hazards assumption, but to fit a model equivalent to the analysis using the 1969–1997 cohort, birth year was included as a stratification variable. During the follow-up from age of 20 to 41 years, the direction of the association between myopia and MS was positive but there was no evidence of higher MS risk associated with myopia: the HR is 0.99 (95% CI 0.91, 1.09) after adjusting for birth year and age, and it was 1.09 (0.83, 1.43) after adjusting further for childhood socioeconomic characteristics and residential region. When we truncated the follow-up to 30 years, the magnitude of association increased slightly, but still, there was no association (HR 1.21 [0.85, 1.72] in the most adjusted model).

When myopia was further categorised by severity, there was no evidence of a dose-dependent association with MS risk (Appendix A, Table A.2).

### 3.4. Myopia and MS risk - 1969–1997

In the 1969–1997 conscription cohort, there were in total of 2754 MS events during a follow-up from age 20 to a maximum of 68 years, with a median follow-up duration of 32 years. The rate of MS was similar for those with and without myopia, 6.9 (95% CI 6.4, 7.5) and 6.8 (95% CI 6.5, 7.1) per 100,000 person-years, respectively (Table 2).

Based on the Schoenfeld residual tests, the proportional hazards assumption was violated for birth year; therefore, the variable was included for stratification to allow baseline hazards to vary by this factor. While there was no evidence of the violation of assumption by myopia, there may be a change of pattern of risk around age of 40 years (Appendix A, Fig A.1–2); therefore we additionally fitted a model truncating the follow- up to this age.

During the follow-up from age 20 to 58 years, there was no association between myopia and MS risk in the model adjusted for birth year

**Table 1**
Distribution of characteristics by ever or never diagnosed with multiple sclerosis.

| | Conscription assessment 1997–2010 | | Conscription assessment 1969–1997 | |
|---|---|---|---|---|
| | Multiple sclerosis | | Multiple sclerosis | |
| | Never | Ever | Never | Ever |
| **Total** | 485,208 | 569 | 1337,120 | 2931 |
| | N (col%) | N (col%) | N (col%) | N (col%) |
| **Myopia based on the mean of spherical equivalent for both eyes** | | | | |
| Non-myopia | | | 276,365 (57.0) | 331 (58.2) |
| Myopia | | | 47,230 (9.7) | 64 (11.3) |
| Missing | | | 161,613 (33.3) | 174 (30.6) |
| **Myopia based on spherical equivalent indicated by lens type** | | | | |
| Non-myopia | | | 1008,975 (75.5) | 2247 (76.7) |
| Myopia | | | 285,412 (21.4) | 612 (20.9) |
| Missing | | | 42,733 (3.2) | 72 (2.5) |
| **Socioeconomic index** | | | | |
| High | 90,178 (18.6) | 119 (20.9) | 156,679 (11.7) | 364 (12.4) |
| Intermediate | 174,243 (35.9) | 197 (34.6) | 430,861 (32.2) | 927 (31.6) |
| Low | 132,804 (27.4) | 155 (27.2) | 502,229 (37.6) | 1102 (37.6) |
| Agricultural work | 9620 (2.0) | 10 (1.8) | 94,673 (7.1) | 236 (8.1) |
| Other | 55,058 (11.4) | 62 (10.9) | 77,273 (5.8) | 164 (5.6) |
| Missing | 23,305 (4.8) | 26 (4.6) | 75,405 (5.6) | 138 (4.7) |
| **Household crowding** | | | | |
| Least crowded | 128,731 (26.5) | 170 (29.9) | 394,202 (29.5) | 907 (31.0) |
| Second least crowded | 205,512 (42.4) | 215 (37.8) | 369,942 (27.7) | 814 (27.8) |
| Second most crowded | 29,335 (6.1) | 41 (7.2) | 248,518 (18.6) | 560 (19.1) |
| Most crowded | 99,727 (20.6) | 117 (20.6) | 248,998 (18.6) | 508 (17.3) |
| Missing | 21,903 (4.5) | 26 (4.6) | 75,460 (5.6) | 142 (4.8) |
| **Region of residence** | | | | |
| Northern | 65,136 (13.4) | 92 (16.2) | 202,300 (15.1) | 413 (14.1) |
| Central | 180,853 (37.3) | 199 (35.0) | 471,046 (35.2) | 987 (33.7) |
| Southern | 239,195 (49.3) | 278 (48.9) | 631,412 (47.2) | 1490 (50.8) |
| Missing | 24 (0.0) | 0 | 32,362 (2.4) | 41 (1.4) |
| **Birth year** | | | | |
| 1950–1954 | | | 202,655 (15.2) | 525 (17.9) |
| 1955–1959 | | | 245,425 (18.4) | 615 (21.0) |
| 1960–1964 | | | 208,463 (15.6) | 459 (15.7) |
| 1965–1969 | | | 254,933 (19.1) | 529 (18.1) |
| 1970–1974 | | | 243,575 (18.2) | 471 (16.1) |
| 1975–1979 | 35,796 (7.4) | 69 (12.1) | 182,069 (13.6) | 332 (11.3) |
| 1980–1984 | 219,707 (45.3) | 333 (58.5) | | |
| 1985–1989 | 183,433 (37.8) | 151 (26.5) | | |
| 1990–1992 | 46,272 (9.5) | 16 (2.8) | | |

N: number of individuals.
Col%: column percentage.
The sample sizes do not agree with Table 2 because individuals with missing data are included in this table.

**Table 2**
Hazard ratios for the association of myopia in late adolescence with a subsequent MS diagnosis.

| | Multiple sclerosis / N | Person-years | Rate (95% CI) | Model 1 | Model 2 |
|---|---|---|---|---|---|
| Conscription years | | | | HR (95% CI) | HR (95% CI) |
| **1997–2010** | | | | | |
| *Follow-up: age 20–41 years* | 380 / 311,195 | 4427,196 | 8.6 (7.8, 9.5) | | |
| Non-myopia | 316 / 266,163 | 3755,107 | 8.4 (7.5, 9.4) | Reference | Reference |
| Myopia | 64 / 45,032 | 672,089 | 9.5 (7.5, 12.2) | 1.10 (0.84, 1.44) | 1.09 (0.83, 1.43) |
| *Follow-up: age 20–30 years* | 221 / 311,195 | 2989,116 | 7.4 (6.5, 8.4) | | |
| Non-myopia | 182 / 266,163 | 2552,459 | 7.1 (6.2, 8.2) | Reference | Reference |
| Myopia | 39 / 45,032 | 436,658 | 8.9 (6.5, 12.2) | 1.23 (0.87, 1.74) | 1.21 (0.85, 1.72) |
| **1969–1997** | | | | | |
| *Follow-up: age 20–68 years* | 2754 / 1248,664 | 40,288,407 | 6.8 (6.6, 7.1) | | |
| Non-myopia | 2162 / 972,749 | 31,712,862 | 6.8 (6.5, 7.1) | Reference | Reference |
| Myopia | 592 / 275,915 | 8575,545 | 6.9 (6.4, 7.5) | 1.00 (0.91, 1.09) | 0.99 (0.91, 1.09) |
| *Follow-up: age 20–40 years* | 1296 / 1248,664 | 24,391,120 | 5.3 (5.0, 5.6) | | |
| Non-myopia | 971 / 972,749 | 19,029,996 | 5.1 (4.8, 5.4) | Reference | Reference |
| Myopia | 325 / 275,915 | 5361,124 | 6.1 (5.4, 6.8) | 1.11 (0.98, 1.26) | 1.11 (0.98, 1.26) |
| **1969–2010 (combined)** | | | | | |
| *Follow-up: age 20–68 years* | 3134 / 1559,859 | 44,715,603 | 7.0 (6.8, 7.3) | | |
| Non-myopia | 2478 / 1238,912 | 35,467,969 | 7.0 (6.7, 7.3) | Reference | Reference |
| Myopia | 656 / 320,947 | 9247,634 | 7.1 (6.6, 7.7) | 1.00 (0.92, 1.09) | 1.00 (0.92, 1.09) |

N: number of individuals.
Rate: per 100,000 person-years.
HR: hazard ratio.
95% CI: 95% confidence interval.
Model 1: adjusted for 5-year interval birth year as a strata variable, and age as the underlying time scale.
Model 2: Model 1 + socioeconomic index, residential region, quartile of household crowding as covariates.

and age (HR 1.00 [95% CI 0.91, 1.09]), and the association hardly changed after further adjusting for childhood socioeconomic characteristics and residential region (HR 0.99 [95% CI 0.91, 1.09]). The direction of association changed to positive when we truncated the follow-up at the age of 40 years, but there was no evidence that myopia is associated with a higher risk of MS (HR 1.11 [0.98, 1.26] in the fully adjusted model).

### 3.5. Both conscription periods combined

When we combined individuals from both of the conscription assessment periods, there was no evidence of an association between myopia and MS, with HR 1.00 (0.92, 1.09) after adjusting for all covariates (Table 2).

## 4. Discussion

This large cohort study of men found that prospectively measured myopia in late adolescence was not associated with a subsequent diagnosis of MS, both before and adjustment for potential confounding factors.

The null nature of the results provides a strong argument that myopia is not associated with subsequent MS risk in men, as military conscription assessments were mostly compulsory in the earlier period of conscription assessments from 1969 to 1997, reducing any potential selection effects. Even if those with extreme myopia were excluded from the assessments, there should be some evidence of an association if one existed: there was no increased risk for those with more severe myopia among those assessed. It is perhaps surprising that an association was not found due to residual confounding alone. Lower levels of physical fitness/activity have been linked with both MS and myopia (Gunnarsson et al., 2015; Guggenheim et al., 2012). Lower-level physical fitness in adolescence associated with subsequent MS risk might reflect prodromal disease-related fatigue or the consequence of exposures relevant to MS risk. Reduced levels of fitness may also signal lower levels of outdoor activity and sunlight exposure. Markers of socioeconomic and material disadvantage, which we adjusted for in the analyses, are associated with reduced risk of both myopia and MS. For myopia, encouragement to study may influence the risk. For MS, factors such as pattern of infection driven by living conditions may modify risk. Some infections in adolescence (particularly infectious mononucleosis), rather than in earlier childhood are strongly associated with increased risk of MS (Xu et al., 2021a, 2021b; Bjornevik et al., 2022). This may happen because infections in earlier childhood result in immunity that protects against the same infection in adolescence which is more likely to trigger the autoimmune processes leading to MS. Those living with relative material disadvantage, such as higher levels of household crowding are likely to experience more frequent and higher dose exposure to infectious agents. Therefore, we included household crowing as a potential confounding factor as lower levels of crowding in childhood have been associated with raised MS risk (Gunnarsson et al., 2015) and as this also signals a more advantaged socioeconomic position, reading and scholastic behavior relevant to myopia risk may be different. Given the direction and magnitude of the associations before and after adjustment, the finding of a null association lends considerable weight to the assertion that no notable relationship exists between myopia and subsequent MS.

If vitamin D deficiency or other exposures were important risks for both myopia and MS, then it would be surprising if we did not find an association. Evidence from some previous studies for the role of vitamin D in the etiology of both diseases may have been subject to various forms of bias, particularly from selective recall of sun exposure and because sun exposure (where measured) is not a direct measure of vitamin D status. At least some confounding is likely due to amount of time spent reading. For example, a study of Alaskan Inuits, where refractive error was measured in multiple families (Young et al., 1969). There was virtually no myopia among grandparents or parents who had not have received a formal education but approximately 58% of children who went to school were myopic.

Strengths of this study include reliable screening for myopia at ages before typical MS onset in a large proportion of the male population in Sweden, with a maximum of 48 years of follow-up from age of 20 years, sufficient to identify MS diagnoses. Use of register data covering hospital health care (both public and private) means that people with MS who

were resident in Sweden are unlikely to have been lost to follow-up. This study has some potential limitations. Use of military conscription assessment data could lead to selection bias as those with a chronic illness, disability or functional limitation are more likely to be excluded. However, as other risk factors in adolescence for MS tend not to be associated with significant levels of contemporaneous chronic illness or disability, this seems unlikely. A more notable potential concern is that females predominate in the MS population and this study is exclusively in male, so the results for the majority of those with MS could potentially be different.

## 5. Conclusions

Despite the burden of other eye diseases associated with MS, it seems unlikely that myopia in late adolescence represents a risk factor or marker of risk for subsequent MS.

## Contributions

AH conducted the analysis and wrote the first draft. AH, CHH, JEN, TO, GG, SM developed the study design and critically edited the manuscript.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.104577.

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