

Lower risk of multiple sclerosis in patients with chronic hepatitis C: a nationwide population-based register study

2001–2013

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BACKGROUND

Multiple sclerosis (MS) is a demyelinating disease of the nerve cells of the central nervous system, which can lead to both physical and mental symptoms in those affected. The etiology of MS is not fully elucidated; however, both genetics and environmental factors have been suggested as the underlying cause (Reich *et al.* 2018). Studies have shown that patients with a previous infection with some neurotropic viruses such as Epstein-Barr, measles, rubella, and varicella zoster, are at higher risk of developing MS (Virtanen and Jacobson 2012). Interestingly, people living with HIV, which is also a neurotropic virus, have a lower risk of developing MS (Gold *et al.* 2015, Nexo *et al.* 2013). The hepatitis C virus is mainly hepatotropic, but has been reported to infect other cells as well (Zignego *et al.* 1992). Patients with chronic hepatitis C (CHC) virus infection are at higher risk of developing peripheral neuropathy, which is another disease affecting the nerves (Santoro *et al.* 2006).

Today, there is no cure for MS, and the goal of the current treatments is to slow down disease progression and alleviate disease symptoms with immunomodulating drugs, including such as interferon- β , steroids, dimethyl fumarate, glatiramer acetate, type II topoisomerase inhibitors, dihydroorotate dehydrogenase inhibitors, or monoclonal antibodies against CD20 (e.g., rituximab), CD25 (daclizumab), CD52 (alemtuzumab), α 4-integrin (natalizumab), or sphingosine-1-phosphate receptor (fingolimod) (Auricchio *et al.* 2017). Autologous hematopoietic stem cell transplantation is under investigation as treatment for aggressive MS by “resetting” the immune system (Muraro *et al.* 2017).

Compared with other countries, the diagnosis rate of CHC in Sweden is estimated to be high (80%) with a low prevalence (0.4%; Cornberg *et al.* 2011), whereas the prevalence of MS is high (Ahlgren *et al.* 2014).

METHODS

Table 1. Description of National Swedish Registers for Patient Visits and Drug Use

Register	Description
National Patient Register	Contains all inpatient and non-primary outpatient care visits, such as treatment visits to an infectious disease specialist or gastroenterologist, but no primary care data. Available register data from: Inpatient care, 1987–2013; Day surgery, 1997–2000; and Non-primary outpatient care, 2001–2013 (including day surgery). It includes information on main and contributory diagnoses based on the <i>International Classification of Diseases</i> (ICD-9, 1987–1996; ICD-10, 1997–2013).
Prescribed Drug Register	Registers all dispensed prescribed drug use in ambulatory care using Anatomical Therapeutic Chemical (ATC) codes. This register retains information on dates, drugs and costs for all pharmacy dispensations of prescriptions in Sweden (July 1, 2005 to December 31, 2013). The coverage is complete for prescriptions in ambulatory care, while in-hospital use of drugs is captured to a lesser extent.

AIM & OBJECTIVE

The aim of the present study was to investigate the risk of MS in patients with CHC compared with a matched comparator cohort using the Swedish patient registry.

METHODS (CONTINUED)

SETTING

In Sweden, universal access to healthcare is provided to the population through a tax-funded system. Patients with CHC patients are typically cared for by specialists in infectious diseases or gastroenterology in hospital-based outpatient clinics or inpatient facilities. They are not managed by general practitioners in primary care (Büsch *et al.* 2017).

DATA SOURCES AND STUDY POPULATIONS

Register sources included are all kept by the Swedish National Board of Health and Welfare (Table 1). The Swedish nationwide National Patient Register was used to identify patients with CHC using the *International Classification of Diseases*, 10th revision (ICD-10) code B18.2. Patients with MS were identified as one listing of G35 (ICD-10). The Prescribed Drug Register was used for information on dispensed drugs. Data on place of residence, vital statistics, and emigration status were retrieved from the Register of the Total Population held by Statistic Sweden (up to December 31, 2013). This register covers the entire Swedish population and includes information on age, sex, and place of residence, as well as dates of birth and emigration status. Information regarding death was retrieved from the Cause of Death registry. The highest attained education was retrieved from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) registry. The Swedish personal identity number (social security number) was used to link individuals between registers.

Up to five general population comparators were matched by age, sex, and county of residence to each patient at time of diagnosis/identification.

The study was approved by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden.

ABBREVIATIONS

ATC – Anatomical Therapeutic Chemical; CI – Confidence Interval; CHC – Chronic Hepatitis C; ICD – International Classification of Diseases; IFN – Interferon; MS – Multiple Sclerosis; SIR – Standardize Incidence Ratio

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METHODS (CONTINUED)

OBSERVATION TIME

The National Patient Registry began to include non-primary outpatient care data in 2001; thus, this date was used as the starting point in the present study. The observation time began for the CHC cohort (n=42,522) at the time of the first physician visit, with an accompanying CHC ICD-10 code from 2001 through 2013. These index dates were also used for each comparator (n=202,694). The observation time ended at the time of death, emigration, or the December 31, 2013, whichever came first.

ASSESSMENTS

The risk for MS diagnosis was expressed using standardized incidence ratios (SIRs) with 95% confidence intervals (CI), where the number of observed events was divided by the number of expected events in the CHC cohort based on the events per person-years in the comparator cohort.

As the comparators were matched by sex, age, and county of residence at inclusion, further subgroup analyses using the whole comparator cohort were not possible. Thus, for the remaining subanalyses, the comparators from other subgroups were excluded (e.g., when comparing the risk in patients with <9 years of education, only the comparators that also had <9 years of education where included in the comparison). Only CHC patients with at least one comparator were included. The number of patients and comparators with ratios for each assessment is indicated within brackets.

STATISTICAL METHODS

Data handling was performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA); data analyses were performed using SPSS (version 24; IBM Corp, Armonk, NY, USA).

DISCLOSURES

ML has consultancies with/for AbbVie, BMS, Gilead, Medivir, and MSD/Merck and is a member of the speakers bureaus for AbbVie, BMS, Gilead, Medivir, and MSD/Merck. MG has received research grants from Gilead Sciences and has received honoraria as a speaker and/or scientific advisor from AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/Viiv, Janssen-Cilag, and MSD. MS is a founder and board member of Svenska Vaccinfabriken. RW has received consultant fees from AbbVie for medical advisory board participation and teaching. AY has received lecture fees from Gilead, Janssen, and AbbVie. JS, JK, AB, and KB are or were employees of AbbVie and may hold AbbVie stocks or stock options.

The design, study conduct, and financial support for the study were provided by AbbVie. AbbVie participated in the study design, data/input analysis, interpretation of results, review, and approval of the publication. The authors determined the final content. No payments were made to the authors for writing this publication.

RESULTS

Lower risk of MS diagnosis

The prevalence of MS diagnoses in the CHC cohort was 0.096% (41/42,522) compared with 0.29% (586/202,694) in the matched comparator cohort. The comparator cohort was followed for 1,504,765 person-years, resulting in 36.2 MS diagnoses per 100,000 person-years. The CHC cohort was followed for 280,123 person-years, and based on the incidence in the comparator cohort, it would be expected that 101 patients with CHC would be diagnosed with MS during the observation time. This suggest that patients with CHC were at a lower risk of being diagnosed with MS (SIR, 0.37; 95% CI, 0.26-0.50; Fig. 1). As a sensitivity analysis, we introduced a requirement of two physician visits with a MS diagnosis. The risk for MS remained lower (SIR, 0.31; 95% CI, 0.21-0.45) with a prevalence of 0.068% in CHC cohort and 0.25% in the comparator cohort.

Different geographies have a different prevalence of MS, with a higher incidence in Sweden compared with other countries (Ahlgren *et al.* 2014). In the present study, around 80% in both the CHC and the comparator cohorts were born in Sweden. The CHC cohort consisted of a higher frequency of patients from northern Europe and Africa, and lower frequency of patients from Asia (Table 2).

Demographics of patients with MS

The mean age of patients at the time of MS diagnosis during the study was 44 years in the CHC cohort and 46 years in the comparator cohort. The proportion of men was 66% in the full CHC cohort were 66% and 65% in the full comparator cohort. The proportion of men with MS was 59% in the CHC cohort and 44% in the comparator cohort. None of the patients with CHC had been treated with either interferon- α or - β after the commencement of the Swedish prescription registry in July 2005. The proportion of patients that received MS-specific treatment was more common in the comparator cohort (7% vs. 11%; Table 3).

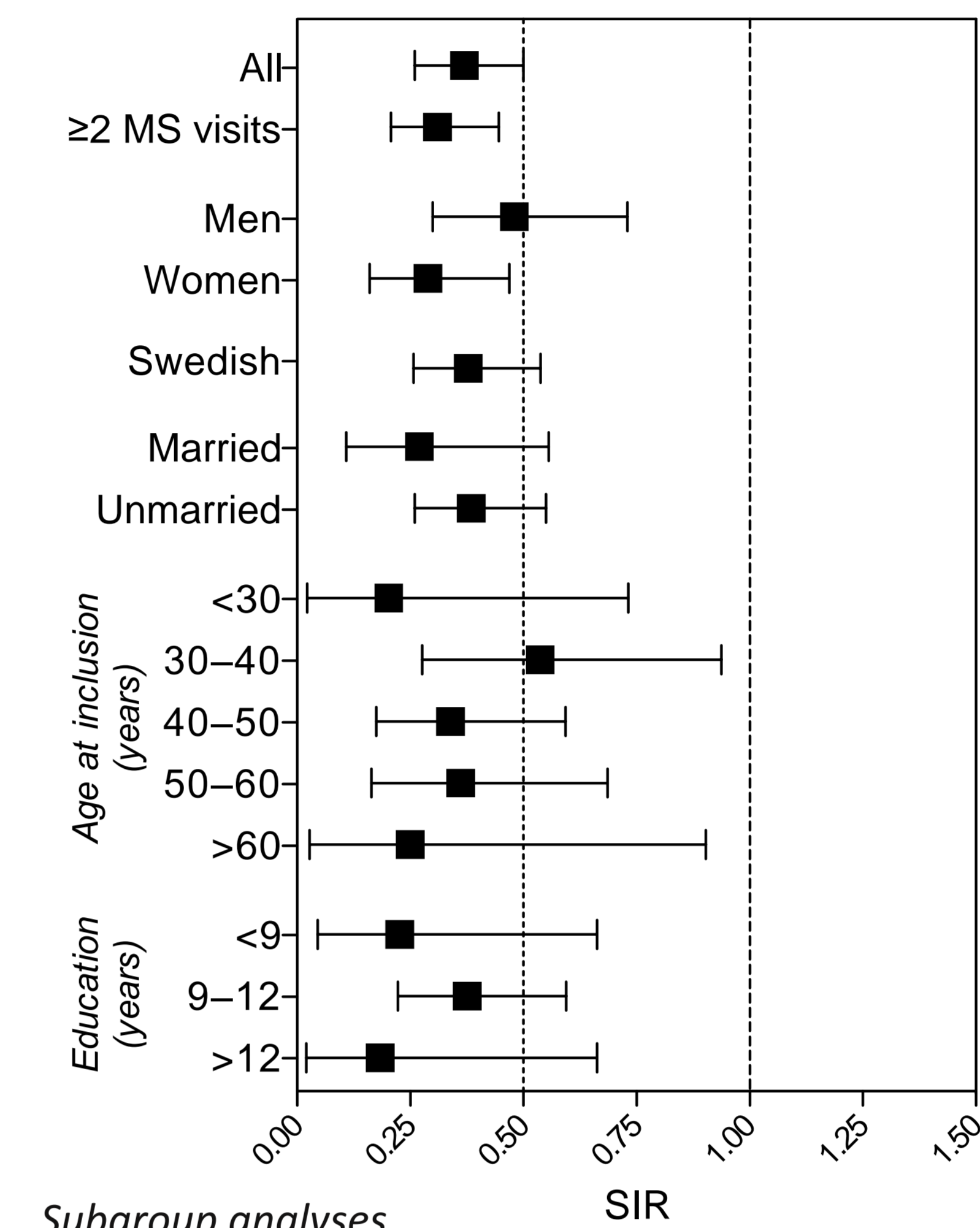
The proportion of Swedish patients with MS was similar among the two cohorts. Northern Europeans were more common in the CHC cohort, whereas Asians were common in the comparator cohort (Table 3).

Table 2. Demographics full cohort

	CHC (n=42,522)	Comparators (n=202,694)
Sex (Male)	28,072 (66%)	132,686 (65%)
Person-years	280,123	1,504,765
Mean observation time (years [95% CI])	6.59 (6.55-6.63)	7.42(7.41-7.44)
MS*	37	544
MS per 100,000 PY	13.2	36.2
Expected MS cases*	101	Not Applicable
MS SIR (95% CI)	0.37 (0.26-0.50)	Not Applicable
Land of origin n (%)		
Sweden	33,970 (79.9%)	162,387 (80.1%)
Northern Europe	2,282 (5.4%)	7,878 (3.9%)
Asia	2,195 (5.2%)	13,250 (6.5%)
Eastern Europe	1,963 (4.6%)	9,599 (4.7%)
Africa	1,000 (2.4%)	3,271 (1.6%)
Western Europe	368 (0.9%)	2,154 (1.1%)
Latin America	320 (0.8%)	2,222 (1.1%)
South Europe	260 (0.6%)	1,098 (0.5%)
North America	140 (0.3%)	713 (0.4%)
Oceania	23 (0.1%)	108 (0.1%)
Information missing	1 (<0.1%)	14 (<0.1%)

*During observation time (Used to estimate SIR).

Fig 1. Standardized incidence ratios (95% CIs) for being diagnosed with MS in patients with CHC, for all patients, as well as different subgroups.



Subgroup analyses

The lower risk for patients with CHC being diagnosed with MS remained significant for both men (SIR, 0.48; 95% CI, 0.30-0.73) and women (SIR, 0.29; 95% CI, 0.16-0.47), as well as the age of inclusion (SIR, 0.21 to 0.54) (Fig. 1). The lower risk was also seen in patients with CHC of Swedish origin (SIR, 0.38; 95% CI 0.26-0.54 [33,970 CHC with 135,255 comparators = ratio 1:3.98]), marital status at inclusion (Married: SIR, 0.27; 95% CI, 0.11-0.56 [8,884 CHC with 22,284 comparators = ratio 1:2.51]; Unmarried: SIR, 0.39; 95% CI, 0.26-0.55 [33,638 CHC with 100,205 comparators = ratio 1:2.98]), as well as for the highest attained education (<9 years: SIR, 0.27; 95 CI, 0.05-0.66 [6,860 CHC with 10,183 comparators = ratio 1:1.48]; 9-12 years: SIR, 0.38; 95% CI, 0.22-0.59 [17,084 CHC with 46,290 comparators = ratio 1:2.71]; >12 years: SIR, 0.18; 95% CI 0.02-0.66 [2,904 CHC with 5,862 comparators = ratio 1:2.02]) (Fig. 1).

Table 3. Demographics patients with MS in each cohort (2001-2013)

	CHC (n=41)	Comparators (n=586)
Dead	7 (17%)	45 (8%)
Interferon- α *	0	0
Sex (Male)	24 (59%)	260 (44%)
MS diagnosis (age) [#]	44.4	46.2
CHC diagnosis (age)	46.1	N/A
CHC to MS (years) [#]	-0.3	N/A
HIV*	2 (5%)	0 (-)
MS treatment*, n (%)	3 (7%)	68 (11%)
Glatiramer	1 (2%)	46 (8%)
Fingolimod	2 (5%)	24 (4%)
Interferon- β	0 (-)	0 (-)
Land of origin, n (%)		
Sweden	35 (86%)	492 (84%)
Northern Europe	3 (7%)	28 (5%)
Western Europe	1 (2%)	5 (<1%)
Eastern Europe	1 (2%)	20 (3%)
Southern Europe	1 (2%)	4 (<1%)
Asia	0 (-)	27 (5%)
Latin America	0 (-)	4 (<1%)
Africa	0 (-)	3 (<1%)
North America	0 (-)	3 (<1%)

*Treatment information was only available from July 2005.

[#]First visit with an MS diagnosis from 2001 through 2013, which may not be the initial MS diagnosis for the patient.

DISCUSSION

Surprisingly, the study showed that patients with CHC had a lower risk of developing MS, with an SIR of 0.37. This lower risk of MS diagnosis would make CHC the largest reported protective factor compared with other previously described factors, including non-smoking, gene markers, HIV infection, non-vitamin D deficiency, and no previous exposure to several other viruses such as Epstein-Barr (Gold *et al.* 2015). MS prevalence is more common in women, but CHC is more common in men. Thus, the prevalence in the present study is not representative of the general population. Nevertheless, the lower risk for MS was significant in both men and women, as well as in subanalyses depending on age, education, marital status, and country of origin.

One possible explanation for the lower risk of MS in patients with CHC could be that patients with MS are less likely to use illicit injectable drugs, which would reduce the likelihood of HCV transmission. However, a previous study suggested that patients with MS to be at a higher risk of using illicit drugs, possibly due to depression (Bombardier *et al.*, 2004).

Historically, patients with MS have been treated using interferon- β . Patients with CHC have increased concentration of systemic type I interferon (Mihm 2015). In contrast, patients with MS have reduced levels of type I interferon (Reder and Feng, 2013). Thus, one hypothesis for the lower incidence of MS in patients with CHC could be the altered immune milieu due to the chronic liver infection, where the elevated systemic type I interferon levels could ameliorate the progression to MS. It would be interesting to investigate this hypothesis in patients with in other chronic liver infections, such as hepatitis B.

Strengths and limitations

The main strength of the study is the large number of patients included, with virtually complete national coverage. While the registry is only as good as the data entered, both MS and CHC are diseases diagnosed by specialists, and a recent study showed that the Swedish National Patient Registry included 99.7% of Swedish patients with MS (Ahlgren *et al.* 2014).

In the general population, the initial MS diagnosis is usually made in patients approximately 30 years of age; however, the initial age at CHC diagnosis for all CHC patients in the present study was 44 years of age old. Therefore, it is possible that some patients in both cohorts were diagnosed with MS ahead of the study but did not have a MS-related visit from 2001 through 2013. In most patients with CHC, the infection occurs during the early twenties; hence, any positive impact by the CHC infection starts around 10 years before the manifestation of MS in the general population.

CONCLUSIONS

- This study suggests that patients with CHC are at a lower risk of developing MS compared with the comparator cohort.
- The lower risk was significant regardless of sex, age, country of origin, and highest attained education.