



**Karolinska  
Institutet**

**Karolinska Institutet**

<http://openarchive.ki.se>

---

**This is a Peer Reviewed Accepted version of the following article, accepted for publication in Multiple Sclerosis.**

2017-03-20

# Similar familial risk in multiple sclerosis subgroup

Song, Jie; Karrenbauer, Virginija; Manouchehrinia, Ali; Almqvist, Catarina; Hillert, Jan; Westerlind, Helga

---

Mult Scler. 2017 Nov;23(13):1782-1785.

<http://doi.org/10.1177/1352458516684214>

<http://hdl.handle.net/10616/45610>

*If not otherwise stated by the Publisher's Terms and conditions, the manuscript is deposited under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.*

## Similar familial risk in multiple sclerosis subgroups

### Introduction

Multiple sclerosis (MS), a chronic autoimmune disease of the central nervous system (CNS), shows great variation in clinical course and severity. This has led to attempts to identify subphenotypes potentially representing independent diseases. One of the hallmarks of MS is the presence of so called oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF). OCBs appear on electrophoretic or isoelectric separation of CSF proteins and consist of clones of immunoglobulin G (IgG) produced by CNS resident plasma cells and plasma blasts<sup>1</sup>. The presence of OCB in CSF indicates intrathecal activity of B-cell believed to contribute to the CNS inflammation,<sup>2</sup> and thus, the bands are relevant as a diagnostic biomarker in MS.

However, a subset of patients diagnosed with MS present with no evidence of OCB in the CSF (i.e., OCB negative (OCB-)). The proportion varies across the world with the lowest figures in Scandinavia (5-10%) and the highest numbers in Asia (50-97%).<sup>3,4</sup> In addition, although OCB positive (OCB+) and OCB- MS share basic clinical characteristics, OCB- patients have been reported to differ significantly also for the other para-clinical tool in MS diagnostics, the MS-typical lesions seen on magnetic resonance imaging (MRI). OCB- MS patients have less white matter lesions and less atrophy in the regional gray matter, basal ganglia and diencephalon<sup>5</sup>, and also differ in the MRI T2 lesion distribution pattern<sup>6</sup>. Different clinical and epidemiological characteristics have also been reported<sup>7</sup>. Maybe more importantly, the strongest genetic association in OCB- MS is not the classical MS risk allele human leukocyte antigen (HLA) DRB1\*15:01, but HLA DRB1\*04:04<sup>3</sup>. Subsequently, whole genome association studies of OCB- patients have revealed partly different genetic associations compared to OCB+ MS<sup>8</sup>. Altogether, MRI lesion distribution and HLA associations may well be interpreted to indicate that the two MS subtypes have different immune specificities and thus may differ in critically important disease mechanisms.

## **Materials and methods**

In a previous study, we reported familial risks for MS patients using nationwide registers from Sweden<sup>9</sup>. By linking these data to the Swedish MS registry (SMSreg; <http://www.neuroreg.se>), we were able to find information on OCB status. To be consistent with the majority who only had one lumbar puncture and to eliminate possible bias due to effect of treatment or physician knowledge, we used the recorded OCB status from the first assessment. Details regarding the registers and patient identification are available in the online supplementary material.

To explore the etiology between OCB- MS and MS, we divided our MS population into four groups based on OCB and MS status (Supplementary Table 2) and estimated the risk for a relative to a patient diagnosed with OCB- MS to be diagnosed with MS. By defining a person diagnosed with OCB-MS as not having MS, we were able to artificially adjust for OCB- MS and to estimate to what extent common causes for OCB- MS and MS exist. Our method is described and motivated in full in the supplementary methods. Further, to investigate the difference in MS risk in OCB- and OCB+ individuals, we applied the same analysis to OCB+ individuals.

Familial risks were measured by odds ratios (ORs) using logistic regression. A robust sandwich estimator of standard errors was used to account for non-independence due to familial clustering.

## **Results**

In the Swedish MS registry, we were able to identify 4,569 MS patients with known OCB status. Among these patients, 525 had ever tested negative for OCB and 37 of these obtained OCB+ results at a later time point(s). Excluding these resulted in a total of 488 OCB- patients. Demographic information is presented in Supplementary Table 1.

Results of familial risks of MS in relatives of patients with OCB+/OCB- status are shown in Table 1. Significant risks for developing MS were observed among several different relationships, such as parents, offspring, and siblings, to OCB- MS patients. The ORs for combined first-degree relatives and second-degree relatives to an OCB- MS patient were 5.22 (95% confidence interval (CI): 3.47-7.87) and 2.59 (95%CI: 1.50-4.45), respectively. The

corresponding estimates for the relatives to the OCB+ individuals were similar (6.23 (95% CI: 5.43-7.14) for first-degree relatives and 2.33 (95% CI: 1.87-2.90) for second-degree relatives).

## **Discussion**

Our findings showed that despite the diverging genetic and imaging associations, a common genetic background seems to be at play in both OCB+ and OCB- MS. To investigate if the association could be due to a common autoimmune genetic background, the familial risks for two autoimmune conditions, rheumatoid arthritis (RA) and type 1 diabetes (T1D), were investigated among relatives to MS patients with different OCB status.<sup>10</sup> The risks for first-degree relatives to OCB- patients to develop RA or T1D were nonsignificant (Supplementary Table 3 and 4), arguing that the familial risk of MS in OCB- MS is unlikely due to a common autoimmune genetic background. Interestingly, a small but increased risk for RA was found in relatives to individuals with OCB+ MS, and amongst all MS patients. The lack of risk in the OCB- group might be due to low numbers, but as the majority of the patients in our sample were OCB+, our unexpected finding is interesting and opens up for further speculations about joint mechanisms in MS and RA. In comparison, though, risks of RA were much smaller than the risks of MS. The risk of T1D was, on the other hand, not significant; however, this was still in line with the systematic review by Dobson and Giovannoni<sup>10</sup> as the registry based studies included in their article showed no familial association with T1D.

One may argue that our sample size of only 488 OCB- MS patients is a limitation of the study. However, the main objective of our study was to investigate whether the underlying genetic backgrounds differ by estimating the familial risks. With such a modest number of individuals, had there been no or very small risks we may not have had sufficient power to detect the risks. The estimates in our study were not only significant but also comparable to our previously published estimates of MS familial risks<sup>9</sup> based on the total Swedish MS population, of which 90% can be assumed to be OCB+.<sup>3</sup> Therefore, we conclude that although the main HLA association differs between OCB+ and OCB- MS, the genetic background for the two groups is indeed shared. In addition to arguing for homogeneity of the MS entity, our findings support

OCB- MS to be a relatively homogeneous group itself; as had there been a significant “contamination” of MS-mimicking conditions in the OCB- group the familial risk would have been affected negatively.

Furthermore, the influence of course type on our results can be speculated upon. Due to the anonymization during the linkage process, it is not possible for us to test this, but looking at unlinked data revealed that close to 90% of both the OCB+ and OCB- patients group had a relapsing remitting onset, numbers that are very unlikely to influence the results of our study.

In summary, we found similar familial risks for these two subgroups of MS, arguing against the heterogeneity between OCB- subtype and “standard” OCB+ MS. Our study shows how familial risks, obtained from population-based data, can have a bearing on problems of taxonomy originating from biomarker studies.

### **Funding**

This study was funded by the Swedish Research Council through the Swedish Council for Working Life and Social Research and the Swedish Initiative for Research on Microdata in the Social and Medical Sciences (SIMSAM) framework grant no. 340-2013-5867.

## References

1. Awad A, Hemmer B, Hartung H-P, *et al.* Analyses of cerebrospinal fluid in the diagnosis and monitoring of multiple sclerosis. *J. Neuroimmunol.* 2010; 219(1–2):1–7.
2. Fujimori J, Nakashima I, Fujihara K, *et al.* Epitope analysis of cerebrospinal fluid IgG in Japanese multiple sclerosis patients using phage display method. *Mult. Scler. Int.* 2011; 2011:353417.
3. Imrell K, Landtblom A-M, Hillert J, Masterman T. Multiple sclerosis with and without CSF bands: clinically indistinguishable but immunogenetically distinct. *Neurology.* 2006; 67(6):1062–4.
4. Kikuchi S, Fukazawa T, Niino M, *et al.* HLA-related subpopulations of MS in Japanese with and without oligoclonal IgG bands. Human leukocyte antigen. *Neurology.* 2003; 60(4):647–51.
5. Ferreira D, Voevodskaya O, Imrell K, *et al.* Multiple sclerosis patients lacking oligoclonal bands in the cerebrospinal fluid have less global and regional brain atrophy. *J. Neuroimmunol.* 2014; 274(1–2):149–54.
6. Huttner HB, Schellinger PD, Struffert T, *et al.* MRI criteria in MS patients with negative and positive oligoclonal bands: equal fulfillment of Barkhof's criteria but different lesion patterns. *J. Neurol.* 2009; 256(7):1121–5.
7. Lechner-Scott J, Spencer B, de Malmanche T, *et al.* The frequency of CSF oligoclonal banding in multiple sclerosis increases with latitude. *Mult. Scler.* 2012; 18(7):974–82.
8. Goris A, Pauwels I, Gustavsen MW, *et al.* Genetic variants are major determinants of CSF antibody levels in multiple sclerosis. *Brain.* 2015; 138(Pt 3):632–43.
9. Westerlind H, Ramanujam R, Uvehag D, *et al.* Modest familial risk for multiple sclerosis - a registry based study of the population of Sweden. *Brain.* 2014; 137(Pt 3):770–8.
10. Dobson R, Giovannoni G. Autoimmune disease in people with multiple sclerosis and their relatives: a systematic review and meta-analysis. *J. Neurol.* 2013; 260(5):1272–85.

**Table 1.** Odds ratios of MS in relatives of patients with OCB- and OCB+ MS <sup>a</sup>

Relationship to proband	Relatives to OCB- patients	Relatives to OCB+	Relatives to controls	OR (95%CI) <sup>b</sup>	<i>p</i> -value <sup>c</sup>	OR (95%CI)	<i>p</i> -value <sup>c</sup>
	(N, %)	patients (N, %)	(N, %)	OCB-	OCB-	OCB+	OCB+
<b>First degree relative</b>	<b>2291 (23, 1.0%)</b>	<b>18486 (218, 1.2%)</b>	<b>45 706 065 (87451, 0.2%)</b>	<b>5.22 (3.47-7.87)</b>	<b>&lt;0.0001</b>	<b>6.23 (5.43-7.14)</b>	<b>&lt;0.001</b>
Parent	847 (11, 1.3%)	7314(106, 1.4%)	16 624 232 (36036, 0.2%)	6.06 (3.34-10.98)	<0.0001	6.77 (5.57-8.23)	<0.001
Offspring	789 (2, 0.3%)	5940(25, 0.4%)	16 618 688 (29150, 0.2%)	1.45 (0.36-5.76)	0.60	2.41 (1.60-3.61)	<0.001
Full sibling	655 (10, 1.5%)	5232(87, 1.7%)	12 463 145 (22265, 0.2%)	8.67 (4.66-16.13)	<0.0001	9.45 (7.61-11.74)	<0.001
<b>Second degree relative</b>	<b>2978 (13, 0.4%)</b>	<b>24162 (79, 0.3%)</b>	<b>67 773 585 (114423, 0.2%)</b>	<b>2.59 (1.50-4.45)</b>	<b>0.001</b>	<b>2.33 (1.87-2.90)<sup>d</sup></b>	<b>&lt;0.001</b>
Grandparent	643 (1, 0.2%)	6428(20, 0.3%)	17 3485 87 (39421, 0.2%)	0.68 (0.10-4.86)	0.70	1.37 (0.87-2.17)	0.18
Grandchild	396 (1, 0.3%)	2820(1, 0.0%)	17 329 180 (16178, 0.1%)	2.71 (0.41-18.06)	0.30	0.38 (0.05-2.69)	0.33
Uncle/aunt	553 (8, 1.4%)	5400(41, 0.8%)	14 791 484 (40112, 0.3%)	5.40 (2.70-10.79)	<0.0001	2.81 (2.05-3.87)	<0.001
Nephew/niece	1159 (1, 0.1%)	7991(11, 0.1%)	14 761 996 (13858, 0.1%)	0.92 (0.13-6.54)	0.93	1.47 (0.82-2.64)	0.20
Paternal half-sibling	144 (1, 0.7%)	919(5, 0.5%)	2 009 079 (2772, 0.1%)	5.06 (0.70-36.59)	0.11	3.96 (1.66-9.44)	0.002
Maternal half-sibling	83 (1, 1.2%)	604(1, 0.2%)	1 533 259 (2082, 0.1%)	8.97 (1.23-65.39)	0.03	1.22 (0.17-8.68)	0.84

Abbreviations: MS: multiple sclerosis; OCB, oligoclonal band; OCB-, oligoclonal band negative; OCB+, oligoclonal band positive; OR, odds ratio; CI, confidence intervals

<sup>a</sup> Affected are the number of relatives diagnosed with MS. Relatives to controls are those relatives to individuals not diagnosed with MS (including OCB-, OCB+ or MS without OCB status).

OR OCB-: the odds of MS in relatives to OCB- patients compared to the odds of MS in relatives to controls;

OR OCB+: the odds of MS in relatives to OCB+ patients compared to the odds of MS in relatives to controls.

<sup>b</sup> A robust (sandwich) estimator of standard errors was used to account for non-independence due to familial clustering. For combined first degree and second degree relatives, the non-independence cannot be fully adjusted, however the 95% CI are assumed not to vary much due to the substantial sample size

<sup>c</sup> Bonferroni correction was applied to adjust for multiple testing (N = 11, significant level set as  $P < 0.005$ )

<sup>d</sup> Estimates of 95% CI were not adjusted for familial clustering due to convergence problems.



## **Online supplementary material**

This document contains support data for Song et al “Similar familial risk in multiple sclerosis subgroups”

Items included:

- \* Supplementary Materials and Methods
- \* Supplementary Table 1
- \* Supplementary Table 2
- \* Supplementary Table 3
- \* Supplementary Figure 1
- \* Supplementary Figure 2

## **Materials and methods**

### *Swedish National Registries and study population*

Several Swedish nationwide registries were used to establish the study population through the linkage of anonymous unique personal identification number. As described in previous studies based on Swedish national registries<sup>1,2</sup>, we obtained data on sex and date of birth from the Total Population Registry (Statistics Sweden), data on immigration and emigration from the Migration Registry (Statistics Sweden) and data on death date from the Cause of Death Registry (National Board of Health and Welfare). The Multi-Generation Registry linked individuals to their biological parents. Using this we identified cohorts of biological relatives with different levels of shared genetic and environment relatedness. The flow chart of data collection is shown in Supplementary Figure 1. All registries were followed from their start to December 31, 2009.

### *Classification of patients*

The identification of multiple sclerosis (MS) was the same as in our previous study<sup>2</sup>. In brief, a person was classified as an MS patient if he/she was either in the Swedish Multiple Sclerosis Registry (SMSreg), had an inpatient admission with MS diagnosis (ICD-10 G35, ICD-9 340 or ICD-8 340), or in the Primary Care Registry for Stockholm with ICD-10 G35.

Patients with oligoclonal band negative and positive MS (OCB- MS and OCB+ MS) were identified through SMSReg. CSF analysis included in this study was done at the neurology clinics at the time of MS diagnostic work-ups. Routine CSF analysis in Sweden typically includes detection of OCBs by isoelectric focusing and immunoblotting, IgG index, CSF/plasma albumin ratio and mononuclear cell count. Patients were considered as OCB + if two or more IgG bands were detected in CSF and not in serum on electrophoresis gels during isoelectric focusing procedure<sup>3</sup>. If an individual had more than one CSF sample registered, the data from the first sample was used.

The identifications of rheumatoid arthritis (RA) and type 1 diabetes were in accordance with previous studies<sup>4,5</sup>. A person was classified as a RA patient if he/she had at least two separate inpatient/outpatient admissions for the following ICD codes: ICD-10 M05, M06.0, M06.2, M06.3, M06.8, M06.9, M12.3; ICD-9 714.0–2, 714.8, 719.3; ICD-8 712.10, 712.20, 712.38, 712.39). The diagnostic validity of RA using the Patient Register has been assessed previously<sup>6</sup>. Type 1 diabetes was defined with the following ICD codes: ICD-10, E10; ICD-9, 250; ICD-8, 250 and ICD-7, 260. Since earlier ICD version do not distinguish between type 1 and type 2 diabetes, only those with hospital discharge dates before the age of 20 years were classified as type 1 diabetes.

### *Statistical analysis*

Due to the lack of information about OCB status in the majority of MS patients, we could not directly estimate the odds ratios (ORs) of being diagnosed with MS in individuals who had relatives with OCB- MS compared with those who did not have relatives diagnosed with OCB- MS. Instead, we selected a clearer sub-population for our estimates.

We divided the MS population into four groups based on OCB and MS status (Supplementary Table 1). In our previous study, we estimated the ORs of being diagnosed with MS in individuals who had relatives with MS (groups 1, 2 and 3) compared to those without relatives diagnosed with MS (group

4), which could be approximately written as follows (under assumption that the prevalence of MS is rare):

$$\begin{aligned} OR_{(MS=1|Relative\ MS)} &= \frac{\Pr (MS = 1|Relative\ MS = 1)/ \Pr(MS = 0 |Relative\ MS = 1)}{\Pr (MS = 1|Relative\ MS = 0)/ \Pr(MS = 0 |Relative\ MS = 0)} \\ &= \frac{\text{odds} ((MS = 1|Relative\ group1,2,3))}{\text{odds} (MS = 1 |Relative\ group4)} \end{aligned}$$

To make the ORs more comparable between OCB- MS, OCB+ MS and general MS, we assigned the same denominator for each analysis. In details, we estimated the ORs of being diagnosed with MS in individuals who had relatives with OCB- MS (group 1) compared with those who did not have relatives diagnosed with MS (group 4).

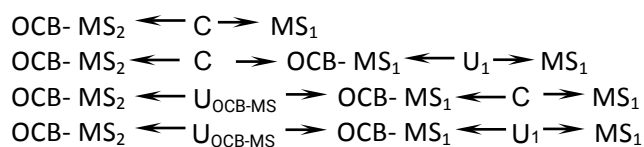
$$\begin{aligned} OR_{(MS=1|Relative\ OCB-MS)} &= \frac{\Pr(MS = 1|Relative\ OCB-MS = 1)/ \Pr(MS = 0 |Relative\ OCB-MS = 1)}{\Pr (MS = 1|Relative\ MS = 0)/ \Pr(MS = 0 |Relative\ MS = 0)} \\ &= \frac{\text{odds} ((MS = 1|Relative\ group1))}{\text{odds} (MS = 1 |Relative\ group4)} \end{aligned}$$

Similarly, we also estimated the ORs of being diagnosed with MS in individuals who had relatives with OCB+ MS (group 2) compared with those who did not have relatives diagnosed with MS (group 4).

$$\begin{aligned} OR_{(MS=1|Relative\ OCB+MS)} &= \frac{\Pr ((MS = 1|Relative\ OCB + MS = 1)/ \Pr(MS = 0 |Relative\ OCB + MS = 1)}{\Pr (MS = 1|Relative\ MS = 0)/ \Pr(MS = 0 |Relative\ MS = 0)} \\ &= \frac{\text{odds} ((MS = 1|Relative\ group2))}{\text{odds} (MS = 1|Relative\ group4)} \end{aligned}$$

Supplementary Figure 2 illustrated the underlying mechanisms between OCB- MS and MS in a Directed Acyclic Graph (DAG)<sup>6</sup>. Here, OCB- MS<sub>1</sub> and MS<sub>1</sub> represent OCB- MS and MS for individual 1 and OCB- MS<sub>2</sub> and MS<sub>2</sub> represent OCB- MS and MS for the individual's relative 2. U<sub>OCB-MS</sub> represents common causes for OCB- MS<sub>1</sub> and OCB- MS<sub>2</sub> and U<sub>MS</sub> represents common causes for MS<sub>1</sub> and MS<sub>2</sub>. U<sub>1</sub> represents common causes for OCB- MS<sub>1</sub> and MS<sub>1</sub> within individual 1 and in the same way, U<sub>2</sub> represents common causes for OCB- MS<sub>2</sub> and MS<sub>2</sub> within relative 2. The set of variable C presents common causes for OCB- MS<sub>1</sub>, OCB- MS<sub>2</sub>, MS<sub>1</sub> and MS<sub>2</sub> that are constant within the relative pair. This can be thought of as representing the familial liability to both OCB- MS and MS. Our aim was to explore to what extent C exists by investigating the association between MS<sub>1</sub> (index individual) and OCB- MS<sub>2</sub> (relative of index individual).

By our definition, a person diagnosed with OCB- MS will be coded as MS = 0, and thereby artificially adjusting for OCB- MS<sub>1</sub>. After this adjustment, the paths that may contribute to a statistical association between OCB- MS<sub>2</sub> and MS<sub>1</sub> are



The first three paths presume the existence of C, whereas the last one does not. Therefore, principally the observed association between OCB- MS<sub>2</sub> and MS<sub>1</sub> may be explained by the 4<sup>th</sup> path. However, by symmetry  $U_{\text{OCB-MS}}$  is more likely to influence OCB- MS<sub>1</sub> and OCB- MS<sub>2</sub> in the same direction. Meanwhile, for  $U_i$ , which varies within individuals, it is easier to think of confounders affecting OCB- MS<sub>1</sub> and MS<sub>1</sub> in the same direction (e.g., genetic or environment “vulnerability”). Under this assumption, adjusting for OCB- MS<sub>1</sub> is likely to induce a negative association between OCB- MS<sub>2</sub> and MS<sub>1</sub>. Hence, the fact that there is a positive association estimated by ORs between OCB- MS<sub>2</sub> and MS<sub>1</sub> after adjustment for OCB- MS<sub>1</sub> would be a strong argument for the existence of C.

A similar magnitude of estimates for ORs between the two groups (Table 2 and Supplementary Table S2) would suggest no difference in familial risks for MS between OCB- and OCB+ MS patients. In addition, we study the association between different types of MS and RA (Table S2).

### *Statistical analysis*

We applied a logistic regression model to estimate the above two ORs. A robust sandwich estimator of standard errors was used to account for non-independence due to familial clustering. Bonferroni correction was applied to adjust for multiple testing (N = 11, significant level set as  $P < 0.005$ ).

Moreover, we performed two additional analyses. First, to investigate if the ORs were strongly confounded by age and sex of individuals, we fitted a conditional logistic regression. We estimated the relative risks for MS for individuals with relatives diagnosed with OCB- MS compared to up to ten randomly selected individuals without relatives affected by MS. Both the individuals and their relatives were matched on sex and year of birth. To ensure equal follow-up time and equal possibility of diagnosis, the matched control was required to be alive, reside in Sweden and, to control for a possible lag for inclusion in the Swedish MS Registry, not diagnosed with MS two years after the cases' diagnosis date of OCB- MS. By this way we avoid the assumed confounding by sex and birth year. The results are shown in Table S4.

Finally, as a sensitivity analysis, we repeated our main models (logistic regression) by defining OCB+ MS as MS (redefinition of Group 2). Since our sample consisted of 90% OCB+ MS cases, the association between OCB-/OCB+ and the full MS sample excluding only the known OCB- patients, did not differ significantly from our main estimates (Data not shown).

The estimated ORs in fact reflect the extent to which shared familial factors, including both genetic background and environmental factors, contribute to the association between OCB- MS and MS. Unfortunately, we are unable to evaluate their contribution separately. On the one hand, rare OCB- MS cases impede adoption studies to explore the extent to which shared environment factors contribute to the association. On the other hand, OCB status is only detectable under primary diagnosis of MS, which hampers the estimates of correlations between OCB- MS and MS in terms of underlying genetic and environmental components.

All analyses were performed in SAS version 9.4<sup>8</sup> (for data management and for conditional logistic regression) and Stata version 13.0<sup>9</sup> (for logistic regression). STROBE Statement was followed ([http://strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE\\_checklist\\_v4\\_case-control.pdf](http://strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_case-control.pdf)).

## References

1. Song, J. *et al.* Bipolar disorder and its relation to major psychiatric disorders: a family-based study in the Swedish population. *Bipolar Disord.* **17**, 184–93 (2015).
2. Westerlind, H. *et al.* Modest familial risk for multiple sclerosis - a registry based study of the population of Sweden. *Brain* **137**, 770–8 (2014).
3. Olsson, T., Kostulas, V. & Link, H. Improved detection of oligoclonal IgG in cerebrospinal fluid by isoelectric focusing in agarose, double-antibody peroxidase labeling, and avidin-biotin amplification. *Clin. Chem.* **30**, 1246–9 (1984).
4. Frisell, T. *et al.* Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. *Arthritis Rheum.* **65**, 2773–82 (2013).
5. Ludvigsson JF, Ludvigsson J, Ekbom A and Montgomery SM. Celiac disease and risk of subsequent type 1 diabetes: a general population cohort study of children and adolescents. *Diabetes care.* 2006; 29: 2483-8.
6. Waldenlind, K., Eriksson, J. K., Grewin, B. & Askling, J. Validation of the rheumatoid arthritis diagnosis in the Swedish National Patient Register: a cohort study from Stockholm County. *BMC Musculoskelet. Disord.* **15**, 432 (2014).
7. Greenland, S., Pearl, J. & Robins, J. M. Causal diagrams for epidemiologic research. *Epidemiology* **10**, 37–48 (1999).
8. SAS Institute Inc. SAS® 9.4 Guide to Software Updates. Cary, NC: SAS Institute Inc. (2013)
9. StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

**Supplementary Table 1.** Demographics and characteristics for the study population of multiple sclerosis patients

Group	Swedish Multiple Sclerosis Registry			National Inpatient Register <sup>a</sup>	Total <sup>a</sup>
	OCB negative	OCB positive <sup>a</sup>	Unknown OCB status		
<b>Number of patients</b>	488	4 081	8 739	27 078	28 161
<b>Mean age at onset, years (SD)<sup>b</sup></b>	34.8 (10.1)	33.2 (10.6)	33.8 (11.0)	47.3 (15.2)	43.8
<b>Mean calendar year of birth</b>	1960	1962	1958	1946	1947
<b>Mean calendar year at onset</b>	1995	1995	1993	1994	1991
<b>Mean calendar year at CSF date</b>	2000	2000	2002	NA	NA
<b>Number of Female (%)</b>	350 (71.7)	2 899 (71.0)	6 208 (71.0)	17 911 (66.1)	18 653 (66.2)
<b>Alive at time of study (%)</b>	465 (95.3)	3 891 (95.3)	8 149 (93.2)	17 801 (65.7)	18 872 (67.0)

a. Figures from Westerlind et al, 2014 [12].

b. The data from the Swedish Multiple Sclerosis Registry reflect the actual age at onset determined by a neurologist, whereas the data from the National Patient Register reflect the first visit to a hospital (or alternatively, to a specialist if after 2001) for multiple sclerosis.

Abbreviations: OCB, oligoclonal band; SD, standard error; CSF, cerebrospinal fluid

**Supplementary Table 2.** Definition of the four groups used to estimate the odds ratios

Group	OCB Negative	OCB Positive	MS
1	Yes	No	No
2	No	Yes	No
3	NA	NA	Yes
4	NA	NA	No

OCB: Oligoclonal band, MS: Multiple Sclerosis, NA: Not Available



**Supplementary Table 3.** Risks of rheumatoid arthritis in individuals with a first degree-relative diagnosed with different types of multiple sclerosis

Diagnosis of the relative of index person	Cases (affected, %)	Controls (affected, %) <sup>a</sup>	Logistic regression <sup>b</sup>		Conditional logistic regression <sup>c</sup>	
			Adjusted OR (95%CI)	P-value <sup>d</sup>	RR (95% CI)	P-value <sup>d</sup>
OCB-	2291(16, 0.7)	45 706 065 (311 278, 0.7)	0.9(0.55-1.48)	0.68	0.81 (0.48-1.37)	0.44
OCB+	18 486 (179, 1.0)	45 706 065 (311 278, 0.7)	<b>1.3(1.12-1.50)</b>	<b>0.0006</b>	<b>1.31(1.12-1.53)</b>	<b>0.001</b>
OCB (OCB+ and OCB-)	20 777 (195, 0.9)	45 706 065 (311 278, 0.7)	<b>1.25(1.09-1.44)</b>	<b>0.002</b>	1.18(1.02-1.37)	0.03
All MS	113 064 (1770, 1.6)	49 872 696 (514 548, 1.0)	<b>1.15(1.10-1.21)</b>	<b>&lt;.0001</b>	1.07(1.00-1.14)	0.06

<sup>a</sup> The difference between first three groups and the fourth group is due to exclusion of the MS patients with missing status on OCB in the controls of the first three groups.

<sup>b</sup> Estimate of odds ratios (ORs) was using ordinary logistic regression with adjustment of relatives' age band. 95% CI were not adjusted for familial clustering due to convergence problems.

<sup>c</sup> Estimate of relative risks (RRs) was using conditional logistic regression which matched cases and controls (1: 10) on age and sex. 95% CI were adjusted for familial clustering by using robust sandwich estimator.

<sup>d</sup> Crude P-values before correction for multiple testing, which corresponds to 95% confidence intervals. Lines in bold indicate the P-values remain significant after Bonferroni correction (N = 2).  
Diagnosis of the relative of index person: OCB-, oligoclonal band negative MS; OCB+, oligoclonal band positive MS; OCB, patients with available information on oligoclonal band; MS: patients diagnosed with multiple sclerosis

**Supplementary Table 4.** Risks of type 1 diabetes in individuals with a first degree-relative diagnosed with different types of multiple sclerosis

Diagnosis of the relative of index person	Cases (affected, %)	Controls (affected, %) <sup>a</sup>	Logistic regression <sup>b</sup>		Conditional logistic regression <sup>c</sup>	
			Adjusted OR (95%CI)	P-value <sup>d</sup>	RR (95% CI)	P-value <sup>d</sup>
<b>OCB-</b>	2291(41, 1.0)	45 706 065 (678 287, 1.5)	0.93 (0.68-1.26)	0.63	0.95 (0.68-1.32)	0.75
<b>OCB+</b>	18 486 (306, 1.7)	45 706 065 (678 287, 1.5)	0.90 (0.80-1.01)	0.08	0.88 (0.78-1.00)	0.04
<b>OCB (OCB+ and OCB-)</b>	20 777 (347, 1.7)	45 706 065 (678 287, 1.5)	0.91 (0.81-1.01)	0.07	0.89 (0.79-1.01)	0.08
<b>All MS</b>	113 064 (1770, 1.6)	45 706 065 (678 287, 1.5)	1.04 (1.00-1.08)	0.07	0.99 (0.94-1.05)	0.82

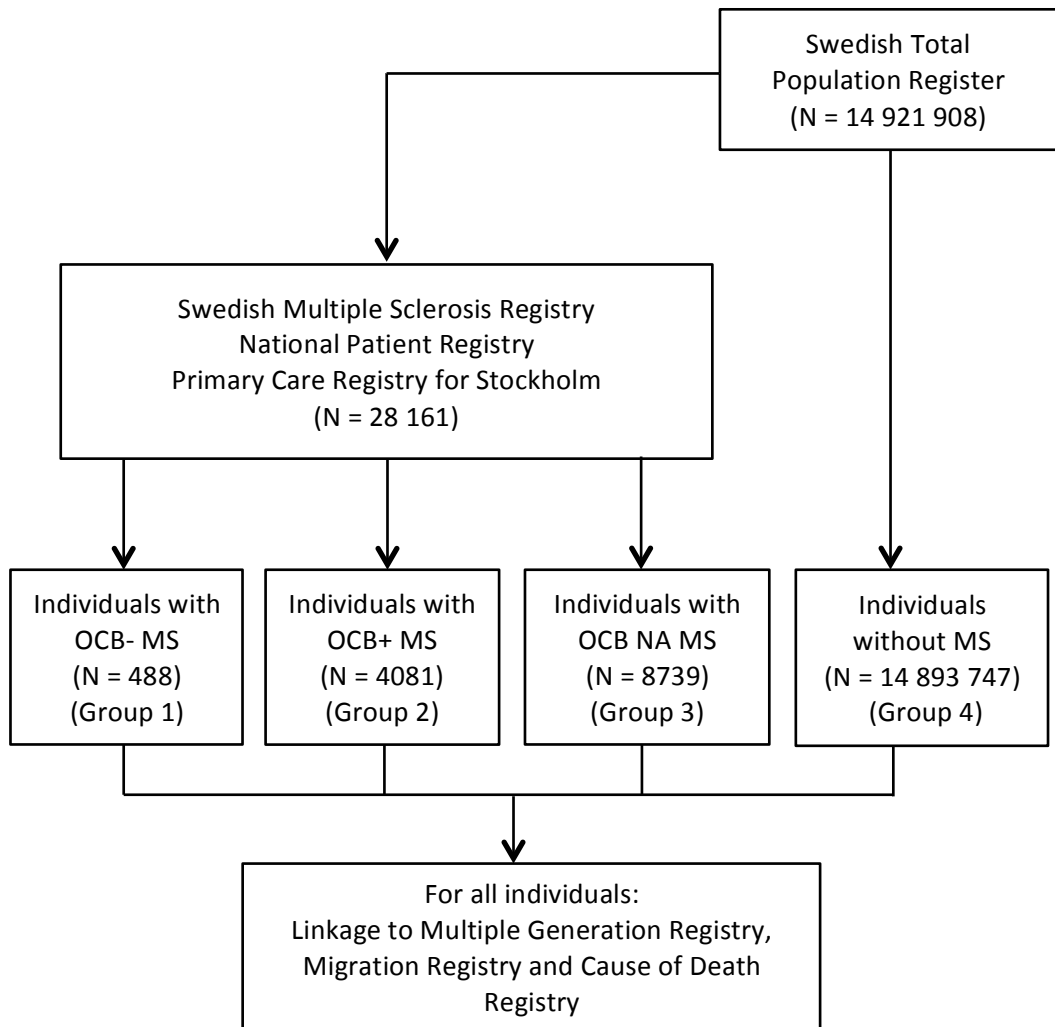
<sup>a</sup> The difference between first three groups and the fourth group is due to exclusion of the MS patients with missing status on OCB in the controls of the first three groups.

<sup>b</sup> Estimate of odds ratios (ORs) was using logistic regression with adjustment of relatives' age band, sex and MS diagnosis. 95% CI were adjusted for familial clustering.

<sup>c</sup> Estimate of relative risks (RRs) was using conditional logistic regression which matched cases and controls (1: 10) on age and sex. 95% CI were adjusted for familial clustering by using robust sandwich estimator.

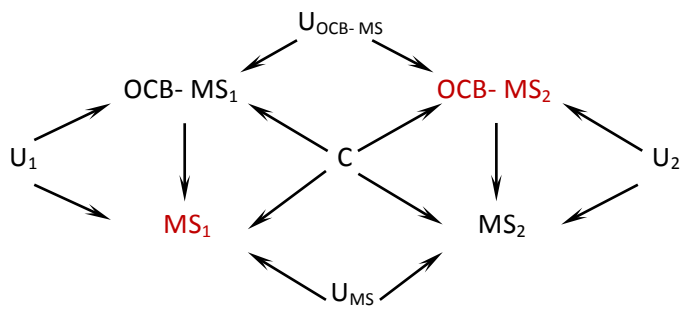
<sup>d</sup> Crude P-values before correction for multiple testing, which corresponds to 95% confidence intervals. Lines in bold indicate the P-values remain significant after Bonferroni correction (N = 2).

Diagnosis of the relative of index person: OCB-, oligoclonal band negative MS; OCB+, oligoclonal band positive MS; OCB, patients with available information on oligoclonal band; MS: patients diagnosed with multiple sclerosis



**Supplementary Figure 1. Flow chart of data collection in Swedish national registries**

Abbreviations: OCB – oligoclonal band; MS – multiple sclerosis



**Supplementary Figure 2.** Directed Acyclic Graph to illustrate if familial factors exist that contributes to OCB- and MS. Abbreviations: OCB- oligoclonal band negative; MS – multiple sclerosis;