Medora

La community dei professionisti della salute By Roche

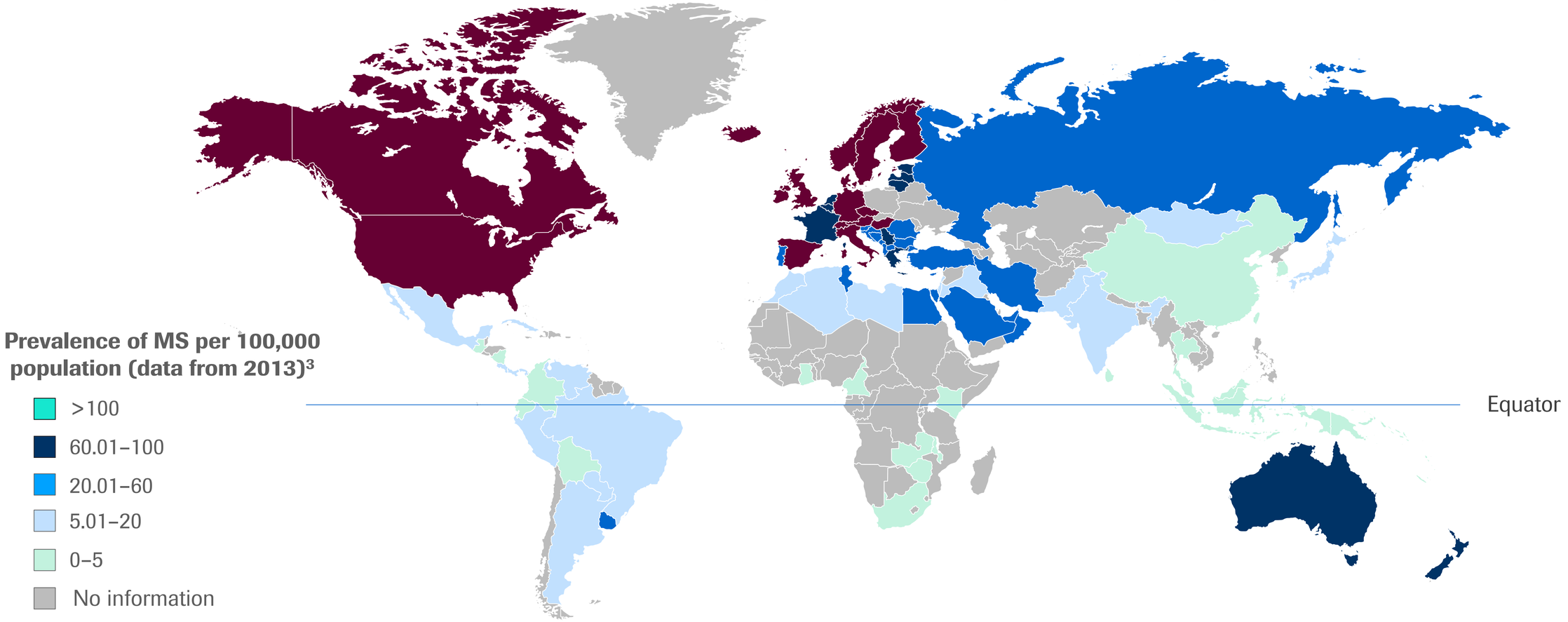
M-IT-00001114

Investigating the patient population

The highest incidence of MS is observed in countries farthest from the equator[1]

More than two million people worldwide are affected by MS[2]

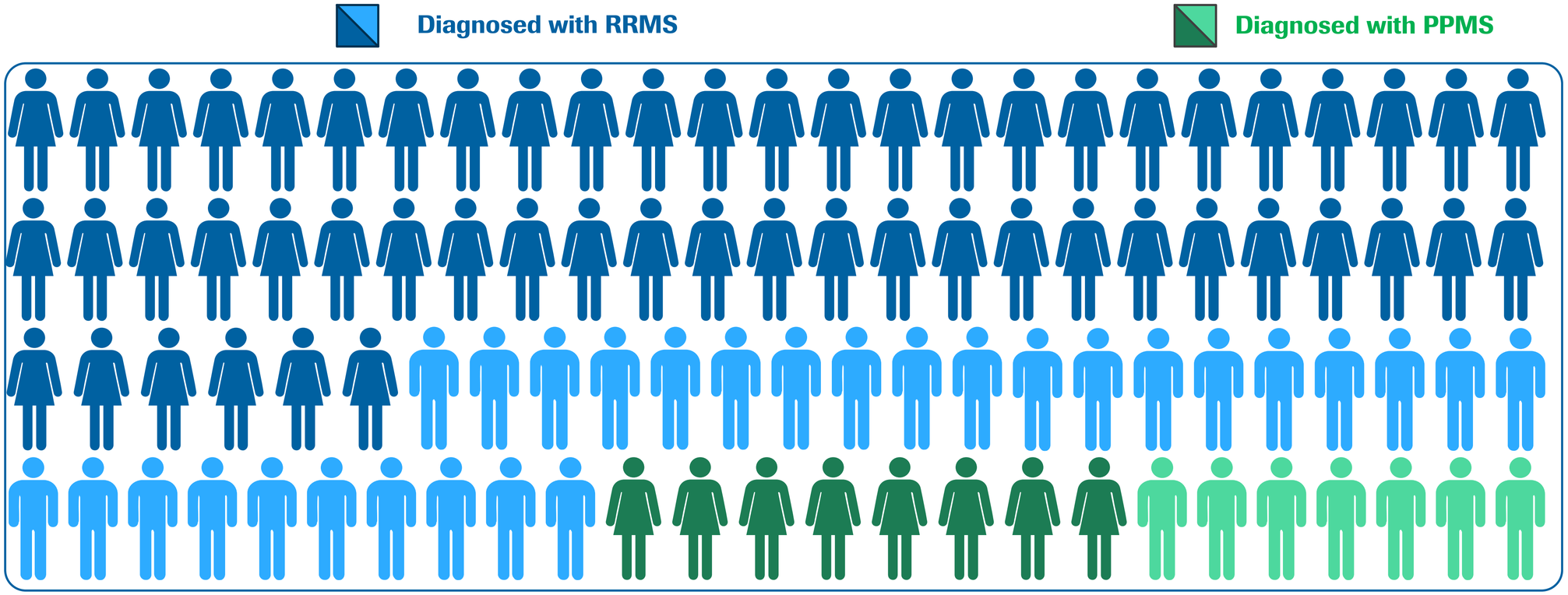
Estimated median worldwide prevalence is 33 per 100,000 population[3]



1. World Health Organization. Atlas multiple sclerosis resources in the world 2008. https://www.who.int/mental_health/neurology/Atlas_MS_WEB.pdf. Accessed January 2020.
2. Reich DS, et al. N Engl J Med 2018;378:169–80;
3. Multiple Sclerosis International Federation. Atlas of MS 2013. https://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf Accessed January 2020.

RRMS is more common in women, whereas PPMS equally common in women and men

Gender distribution and relative incidence of RRMS and PPMS among 100 patients with MS



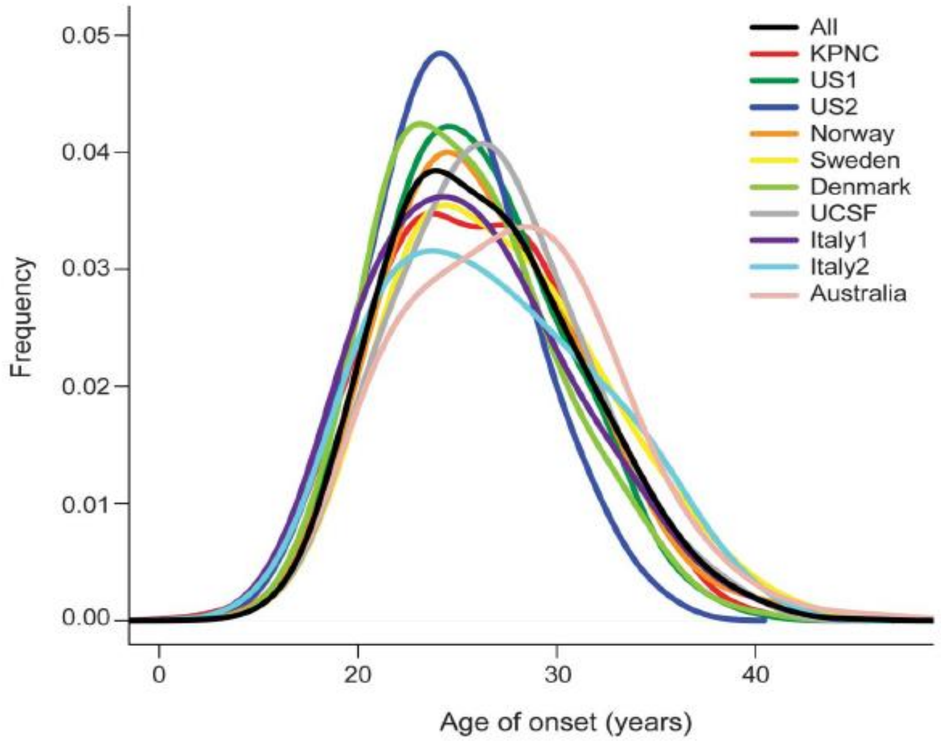
Overall, MS is approximately 2- to 3-fold more common in women than in men and RRMS is more commonly diagnosed than PPMS[1,2]

PPMS, primary progressive MS; RRMS, relapsing-remitting MS.

Multiple Sclerosis International Federation. Atlas of MS 2013. https://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf Accessed January 2020;
2. National Multiple Sclerosis Society. Relapsing-remitting MS. https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS Accessed January 2020.

RMS has an earlier age of onset than PPMS

Age of onset of MS in 10 international MS cohorts[1]



Mean age at onset ranged from 30.1 years to 35.3 years

In a cohort of 1844 patients with MS the median age of onset was:[2]

RRMS (N=1066): 28.7

SPMS (N=496): 29.5

PPMS (N=173): 41.3

KPNC, Kaiser Permanente Medical Care Plan in the Northern California Region; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; UCSF, University of California at San Francisco.

1. George MF, et al. Neurol Genet 2016;2:e87; 2. Confavreux C, Vukusic S. Brain 2006;129:606–16.

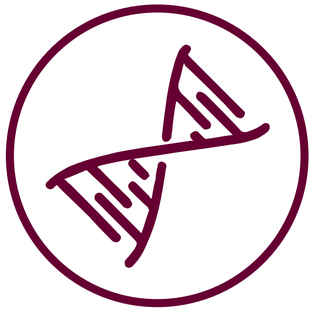
Interplay of multiple factors is thought to give rise to the abnormal immunological response seen in MS

Environmental[1–4]

Smoking
Obesity
Temperate latitude
Low vitamin D

Genetic[5–9]

Female sex
Ethnicity
Family history
Risk-associated genes

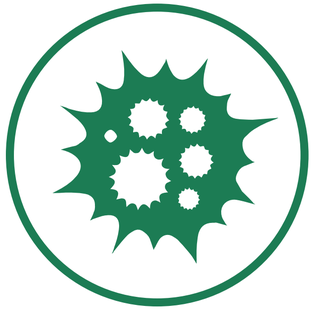


Immunological[10–13]

B cells
T_{reg} cells
$CD8^+$ T cells
Natural killer cells

Infectious[14–17]

Epstein-Barr virus
Fertile field hypothesis
Human herpes virus 6
Hygiene hypothesis



Treg, regulatory T cells.

1. Handel AE, et al. PLoS One 2011;6:e16149; 2. Simpson S, et al. J Neurol Neurosurg Psychiatry. 2011;82:1132–41; 3. Gianfrancesco MA, et al. J Neurol Neuromedicine. 2016;1:1–5;
4. Munger KL, et al. JAMA 2006;296:2832–38; 5. Harbo HF, et al. Ther Adv Neurol Disord. 2013;6:237–48; 6. Xia Z, et al. Ann Neurol. 2016;79:178–89;
7. Wallin MT, et al. Ann Neurol. 2004;55:65–71; 8. Reich D, et al. Nat Genet. 2005;37:1113–8; 9. International Multiple Sclerosis Genetics Consortium. Cell. 2018;175:1679–87 e7;
10. Hauser SL, et al. N Engl J Med. 2017;376:221–34; 11. Mars LT, et al. Biochim Biophys Acta. 2011;1812:151–61; 12. Haas J, et al. EU J Immunol. 2005;35:3343–52;
13. Sospedra M, et al. Semin Neurol. 2016;36:115–27; 14. Guan Y, et al. Neural Regen Res. 2019;14:373–86; 15. Handel AE, et al. PLoS One. 2010;5:e12496;
16. Leibovitch EC, et al. Curr Opin Virol. 2014;9:127–33; 17. Ascherio A, Munger KL. Ann Neurol 2007;61:288–99.

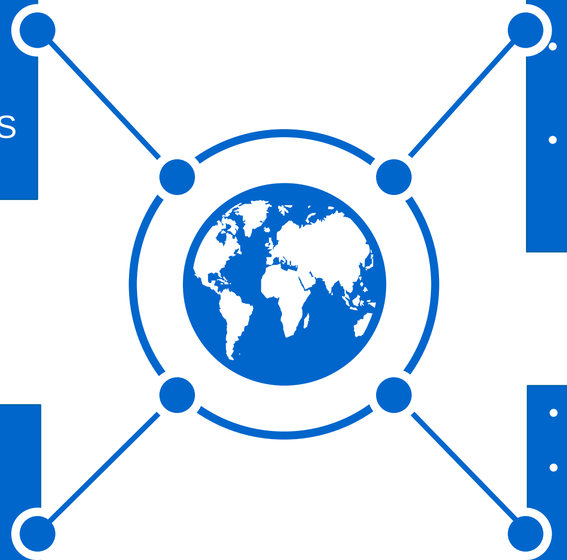
Environmental risk factors for MS

Smoking[1–3]

- Smoking is significantly associated with **MS susceptibility** (RR=1.48; p<0.0001)[1]
- Smoking is associated with a **greater likelihood of an initially primary-progressive disease course** (OR=2.41*; 95% CI 1.09, 5.34)[2,3]
- The effect of smoking risk on secondary progression in MS is **less conclusive** (RR=1.88; p=0.06)[1]

Obesity[4]

- Obesity in young adults, particularly ages 18–25, is associated with **MS susceptibility**
- Association is less clear in children, but it has been estimated that **eliminating childhood obesity could prevent ~ 15% of MS cases**



Latitude[5,6]

- Latitude is significantly associated with **MS prevalence**[5]
- Adjusted prevalence of MS **increases** by 3.3 cases per 100,000 individuals (p<0.001), **for every degree of latitude north** of the mean population line (46.1°)[5]
- MS is **~5x more prevalent in Scandinavia than Latin America**[5]
- The most prominent environmental factors that vary with latitude are **vitamin D and UV radiation** (essential for vitamin D synthesis)[5,6]

Low vitamin D[7]

- Vitamin D may have a **protective** role in MS development
- Risk of developing MS is **reduced** by 41% for every 50 nmol/L **increase** in serum vitamin D in people of Caucasian heritage (p=0.04)
- In contrast, vitamin D levels do not appear to be associated with MS risk in people of afro-Caribbean heritage

*Odds ratio for current smokers versus never smokers.
OR, odds ratio; RR, relative risk.

1. Handel AE, et al. PLoS One 2011;6:e16149; 2. Wingerchuk DM. Ther Adv Neurol Disord. 2012;5:13–22; 3. Healy BC, et al. Arch Neurol. 2009;66:858–64;
4. Gianfrancesco MA, et al. J Neurol Neuromedicine. 2016;1:1–5; 5. Simpson S, et al. J Neurol Neurosurg Psychiatry. 2011;82:1132–41;
6. Mora JR, et al. Nat Rev Immunol 2008;8:685–98; 7. Munger KL, et al. JAMA 2006;296:2832–8.

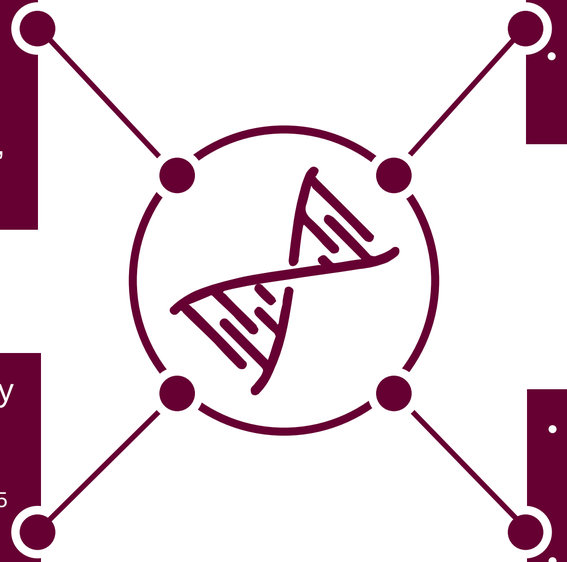
Genetic risk factors for MS

Female sex[1–4]

- Overall, MS is approximately **2- to 3-fold more common in women than in men**[1]
- This gender difference is driven by the greater incidence of RRMS and SPMS in women than men – PPMS occurs in similar proportions of men and women[2]
- There are no MS susceptibility regions on the X chromosome, but symptoms improve during pregnancy, **suggesting a role for sex hormones**[3]

Ethnicity[5–7]

- While MS was historically believed to occur less frequently in African American people compared with Caucasian Americans,[3] more recent data suggest the **risk may be higher** in African Americans, particularly among women[4,5]
- Patients with MS who have African ancestry, such as African Americans, are also at **increased risk of more rapid disease progression** compared with those with European ancestry[6,7]



Family history[8]

- The immediate family of people with MS are **20–40x more likely** to develop MS than the general population
- Furthermore, clinically silent MS-like brain lesions are seen in 4–10% of family members

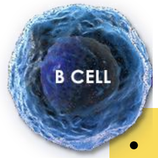
Risk-associated genes[9]

- **~20% of MS risk heritability can be attributed to common genetic variants**, of which over 230 have been identified by GWAS
- These studies have suggested key pathogenic roles for regulatory T-cell homeostasis and regulation, IFNγ biology, and NFkB signaling

GWAS, genome-wide association study; IFNγ; interferon gamma; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells.

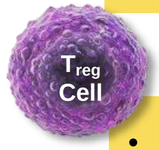
1. Multiple Sclerosis International Federation. Atlas of MS 2013. https://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf. Accessed January 2020; 2. Hawker K. *Neurol Clin* 2011;29(2):423–34;
3. Harbo HF, *et al. Ther Adv Neurol Disord*. 2013;6:237–48; 4. Langer-Gould A, *et al. Neurology*. 2013;80:1734-9; 5. Khan O, *et al. Neurol Clin Pract.* 2015 Apr; 5: 132–42;
6. Howard J, *et al. PLoS One*. 2012;7:e43061; 7. Ferreira Vasconcelos CC, *et al. ISRN Neurol*. 2012:410629; 8. Xia Z, *et al. Ann Neurol*. 2016;79:178–89;
9. International Multiple Sclerosis Genetics Consortium. *Cell*. 2018;175:1679–87 e7.

Immunological risk factors for MS



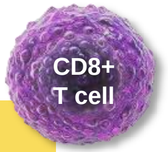
B cells[1]

- B cells are **implicated in the pathogenesis of MS through antigen presentation, autoantibody production, cytokine regulation, and the formation of ectopic lymphoid aggregates** in the meninges, which possibly contribute to cortical demyelination and neurodegeneration



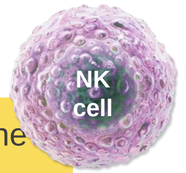
T_{reg} cells[3]

- T_{reg} cells regulate the adaptive immune system, preventing autoreactive responses – suppression of the numbers or activity of T_{reg} cells is associated with various autoimmune conditions
- In patients with MS, **T_{reg} cells have been reported to have an impaired ability to suppress responder T cell proliferation**
- This impaired ability was found regardless of whether the T_{reg} cells were taken from the patient during a relapse or while in remission



CD8+ T cells[2]

- CD8+ T cells are another part of the adaptive immune system
- $CD8^+$ T cells detected within MS lesions demonstrate characteristics of **activated and clonally expanded cells, suggesting that these cells actively contribute to the observed injury**



Natural killer (NK) cells[4]

- NK cells are an important part of the innate immune response, eliminating mutated tumour cells and in defending against viral infections
- Invariant natural killer T cells have been found to be **numerically increased in the CNS in MS**

CNS, central nervous system; NK, natural killer; Treg, regulatory T cells.

1. Hauser SL, et al. N Engl J Med. 2017;376:221–34; 2. Mars LT, et al. Biochim Biophys Acta. 2011;1812:151–61; 3. Haas J, et al. Eur J Immunol. 2005;35:3343–52;
4. Sospedra M, et al. Semin Neurol. 2016;36:115–27.

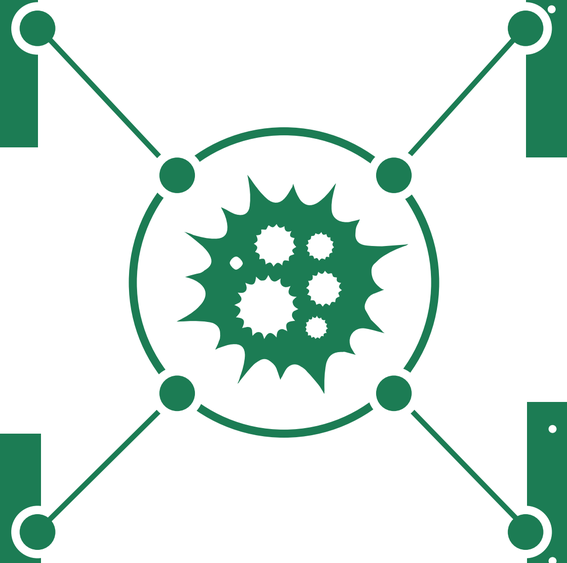
Infection risk factors for MS

Epstein-Barr virus (EBV)[1–3]

- The prevalence of EBV in the general population is ~90%, but **nearly all MS patients are EBV seropositive**[1–3]
- Infectious mononucleosis, caused by delayed primary EBV infection, more than **doubles** the risk of developing MS (RR=2.17; p<0.0001)

Human herpes virus 6 (HHV-6)[4]

- HHV-6 antibodies were first detected in the blood samples of patients with MS over 20 years ago
- **HHV-6 DNA has also been discovered inside MS plaques** – it has been suggested that the amino acids in HHV-6 DNA may mimic those found in human myelin basic protein



Fertile field hypothesis[1]

- “Fertile field hypothesis” posits an **initial viral infection triggers a heightened immune state**
- This could decrease the threshold for activating auto-aggressive T-cells in the presence of later events

Hygiene hypothesis[5]

- An alternative theory is that a **lack of exposure to infectious agents early in life** results in a failure of tolerance in the immune system
- This could explain the apparent protection from MS of individuals born in low-risk areas who migrate to high-risk areas

1. Guan Y, *et al. Neural Regen Res*. 2019;14:373–86; 2. Handel AE, *et al*. *PLoS One*. 2010;5:e12496; 3. Pender MP, Scott RB. *Clin Transl Immunology*. 2014;3:e27;
4. Leibovitch EC, *et al. Curr Opin Virol*. 2014;9:127–33; 5. Ascherio A, Munger KL. *Ann Neurol* 2007;61:288–99.

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Il futuro della medicina, l’avanguardia di noi medici.

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