What If MS Could Be Prevented?

A Look at Risk Factors, Viruses, and Vitamins

Multiple sclerosis (MS) currently affects about 1 million people in the United States (US), with an estimated 15,700 people newly diagnosed each year. If the onset of MS could somehow be stopped, or even slowed, the impact would be profound. Can MS be prevented? If so, how? These are questions that some MS researchers are pursuing. Finding answers would mean getting down the root causes of MS, or the initial triggers that start the disease process.

"It is still not entirely clear what causes some people to develop MS and others to be spared," explains MS expert Alberto Ascherio, MD, PhD, of Harvard University. Dr. Ascherio is an epidemiologist at Harvard's T.H. Chan School of Public Health, where he studies patterns and possible causes of neurologic diseases like MS. "We now know much more about the conditions and factors that increase MS risk," he told *NARCOMS Now*.

MS Risk Factors

In several papers Dr. Ascherio has written on MS prevention, he outlines the key risk factors that occur more often in people with MS (Figure 1). The greatest known risk factor is having a family history of MS. Risk of developing MS is about 30 times higher among siblings of affected individuals than in the general population. Of course, family history and biologic sex are beyond one's control. Other risk factors are considered "modifiable" or *preventable*. These include excess body weight, cigarette smoking, and intake of vitamin D. A key risk factor that may be critical for the development of MS is infection with the Epstein Barr virus (EBV). EBV infection is not currently preventable, but this concept may be an important path toward future MS prevention.

Figure 1. Risk factors for MS include modifiable ones (green circles) like obesity, smoking, and vitamin D levels. Non-modifiable factors are shown in the blue circles. Epstein Barr virus (EBV) is not considered modifiable because most people are exposed at a young age. If some method could be developed to protect against EBV, this could be a potential way to prevent or reduce risk of MS.

About Epstein Barr virus

EBV is a member of the human herpesvirus family, like the viruses that cause chicken pox or shingles. EBV is easily spread through saliva. When the initial infection occurs in young children, it often causes minimal or no symptoms. EBV is the virus that causes infectious mononucleosis, or "mono," which can be a more serious or prolonged illness in adolescents and adults. After the initial infection, EBV takes up permanent residence in the body, usually in a dormant state. It's hard to avoid EBV. Up to 90% of U.S. adults carry the virus in their bodies by the time they are in their mid-thirties.

What does EBV have to do with MS?

Similarities between the epidemiology of MS and that of infectious mononucleosis (mono) are "striking," Dr. Ascherio noted. MS is much more common in people who are positive for EBV and have a history of being sick with mono (**Figure 2**).

- Among all people who carry EBV, the risk of developing MS is 15 times higher in people who have had mono compared with EBV carriers who did not become ill from EBV.
- In people who test negative for EBV, MS is very rare. EBV-negative individuals have a ten-fold lower risk of developing MS versus EBV-positive people of the same age (with no history of mono).

Interestingly, about 90% of children in developing countries have already been exposed to EBV by age 4 years. Infectious mono rates are much lower in these areas

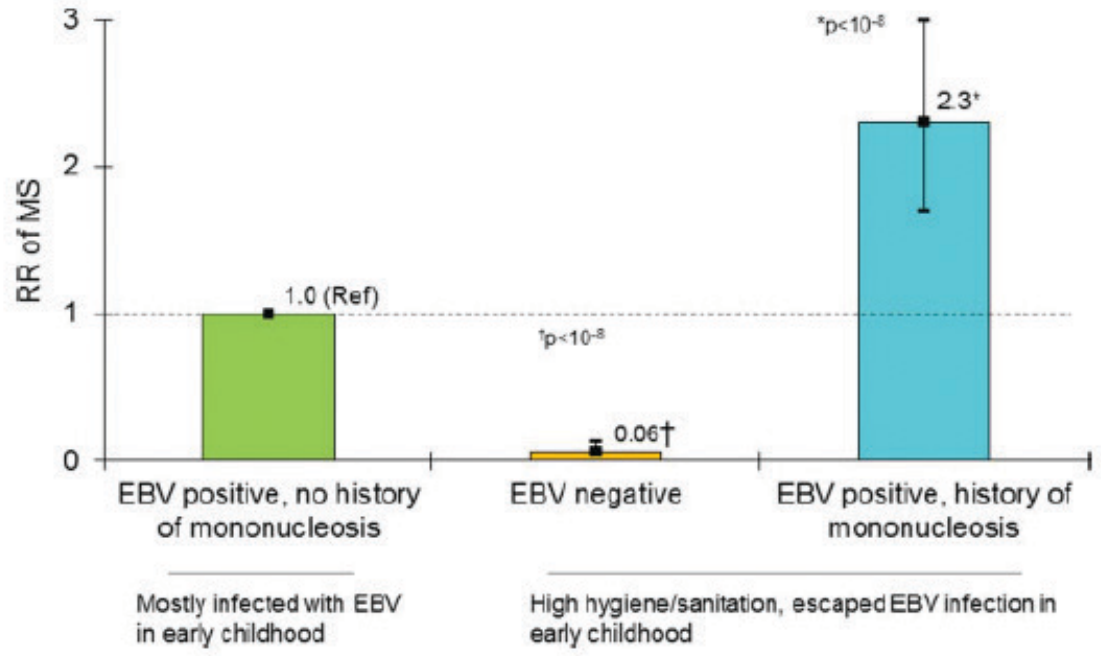


Figure 2. Risk of MS in people with EBV who have never had mono (green bar) was used as a reference point, or value of 1. By comparison, people who were EBV negative (yellow bar) had a very low chance of developing MS. Those with EBV and history of mono (blue bar) had more than double the risk of developing MS. RR = relative risk.

Reprinted with permission from Ascherio A, et al. Epidemiology of multiple sclerosis: from risk factors to prevention—an update. *Semin Neurol.* 2016;36;103-114.

compared to rates in North America and Europe. Likewise, MS prevalence is lowest in developing countries. This observation suggests that the timing of exposure to EBV may trigger a protective process in the immune system that could help to prevent MS later in life. It also suggests that preventing EBV with a vaccine might be helpful in preventing MS (**see Sidebar, page 7**).

Sunlight and vitamin D

Vitamin D behaves like a hormone in the body, regulating the function of many bodily systems. These include bone development, cardiovascular health, and immune system function. We get most of our vitamin D from exposure to sunlight. The rest comes from our diet (oily fish, eggs, vegetables, meat) or supplements. However, in some areas of the world, sunlight is minimal during the cooler months of the year. This provides too little of the ultraviolet B rays needed for our bodies to make enough vitamin D. With more time spent indoors in recent years, much of the population has lower blood levels of vitamin D than in the past.

Vitamin D is thought to play a role in MS development. People with low blood levels of the vitamin have a higher risk of developing MS. A large study of MS risk and vitamin D was based on a database with over 50 million blood samples drawn from U.S. military personnel, some of whom later developed MS. Those with the highest vitamin D levels had a greater than 60% reduced risk of developing MS. The associations between vitamin D and MS risk were stronger for people under age 20 years. In people who already have MS, adequate levels of vitamin D have been associated with lower relapse rates and lower risk of MS progression.

According to Dr. Ascherio, most people can achieve a healthy vitamin D level by taking an oral D3 supplement (suggested 1,000 IU to 2,000 IU per day or as recommended by a healthcare provider). Although the USDA recommended daily dose is currently 600 IU, studies have shown that higher doses are safe and may help to reduce health problems associated with MS and other autoimmune diseases. In fact, vitamin D may help interfere with the effects of EBV. "Awareness of the importance of vitamin D has markedly increased over the past 10 to 15 years," Dr. Ascherio told *NARCOMS Now*. "We have seen higher vitamin D levels across some populations, and I expect there will be a benefit on several conditions related to vitamin D insufficiency."

Body weight and obesity

Obesity is another modifiable condition shown to increase the risk of developing MS. Obesity is associated with low-grade, persistent, systemic (whole-body) inflammation. This inflammatory state can be particularly harmful in women. Fat or "adipose tissue" may attract the inflammatory changes seen in MS. Being overweight could also affect the blood-brain barrier to enhance access of inflammatory cells into the brain.

In a large study following over 200,000 nurses over many years, having a body mass index (BMI) higher than 30 was associated with more than double the risk of having MS. Larger body size during young adulthood is associated with a higher risk of later developing MS, especially for children who are moderately or extremely

obese. A 2019 study from Germany showed that both boys and girls who are overweight or obese have twice the risk of developing MS, compared with non-overweight children or adolescents.

Smoking

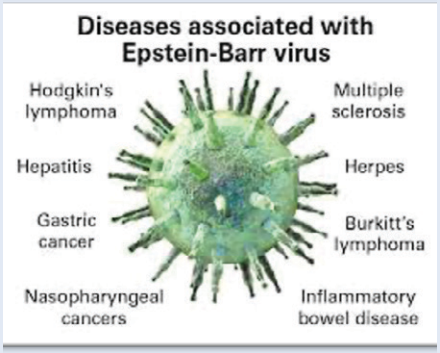
A history of smoking may be another factor that predisposes a person to MS. Several large studies have shown that smokers have a higher risk of developing MS than nonsmokers. One large study in women found that the risk of having MS was 70% higher among those who had smoked 25 or more pack-years, compared with same-aged women who never smoked. (A pack-year refers to smoking 1 pack per day for 1 year). As with obesity, smoking can shift the body's immune system toward a pro-inflammatory state. Nicotine or other components of cigarette smoke may affect the blood-brain barrier as well.

The Importance of Prevention

Why does prevention matter to someone who already has MS? Some feel that preventing the disease may provide some peace of mind for loved ones, along with lifting the burden for society as a whole. "I know that MS has a genetic component. I would love to think that my grandchildren or future great-grandchildren could be spared this disease," said Sandra, a 62-year-old woman who was diagnosed with MS in her early forties. Better understanding of the immune system triggers that "switch on" the disease process may also help on the quest to find novel ways to stop ongoing damage in people who have MS.

Could An Epstein Barr Vaccine Help Prevent MS and Other Diseases?

The Epstein Barr virus (EBV) might remind us of the now-infamous SARS-Cov-2, due to its protruding spikes that enable it to bind to receptors on human cells. Preventing infection with EBV could affect multiple sclerosis (MS), and other conditions associated with chronic EBV infection, as shown in the box below. So far, small trials of vaccines to prevent EBV have yielded disappointing or limited results. However, as we know from the COVID-19 pandemic, vaccine science is evolving very rapidly. Some of this advancement is in genomic vaccines. Genomic vaccines take the form of DNA or RNA that encodes desired proteins. When injected, these genes enter cells and instruct them to make specific proteins that guard against a particular type of viral infection. In addition to vaccines under ongoing study for coronaviruses, genomic vaccines are being studied to prevent hepatitis C and even some cancers.



Can a preventive vaccine be developed to block or prevent EBV infection? If so, would it also succeed in preventing MS? This idea is "appealing, but also fraught with major challenges," said Gavin Giovannoni, MD, an MS expert and researcher based in London, England. Providing immunity against any herpesvirus is "almost an improbable endpoint," he said. However, he suggested that a vaccine to reduce the risk of developing infectious mononucleosis in a person exposed to EBV may be sufficient to have an impact on MS risk. "Challenges exist in development of an EBV vaccine, but efforts have begun and may yield surprising results," Dr. Giovannoni wrote in a recent article on EBV. In addition to vaccines, other treatment approaches being explored to fight the virus include antiviral drugs and cell-based immunotherapies.