

REPORT

MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. The demyelination in the brain and spinal cord is an immune-mediated process (1) possibly triggered by a viral infection (2). Among the putative causal agents, the top candidate is Epstein-Barr virus (EBV) (3). EBV is a human herpesvirus that after infection persists in latent form in B lymphocytes throughout the life of the host (3). A causal role of EBV is supported by the increased MS risk after infectious mononucleosis (4), elevated serum antibody titers against EBV nuclear antigens (EBNAs) (5), and by the presence of EBV in MS demyelinated lesions reported in some (6–8), but not all (9), pathological studies. Evidence of causality, however, remains inconclusive.

Causality implies that some individuals who developed MS after EBV infection would not have developed MS if they had not been infected with EBV. Ruling out a randomized trial, the gold standard to study this counterfactual occurrence is an “experiment of nature,” a longitudinal investigation of MS incidence in a cohort of EBV-negative individuals, some of whom will be infected with EBV during the follow-up and some who will not. The ubiquitous nature of EBV, which infects ~95% of adults, and the fact that MS is a

relatively rare disease, has until now impeded such an investigation. Over the course of a 20-year collaboration with the US military, we have identified cases of MS in a cohort composed of active-duty US military personnel between 1993 and 2013, a racially diverse population of >10 million individuals. Active-duty members are screened for HIV at the start of military service and biennially thereafter, and residual serum from these tests (>62 million serum samples) is archived in the Department of Defense Serum Repository (DoDSR) (10). We used samples stored in the DoDSR to determine EBV status at time of first sample and the relation between EBV infection and MS onset during the period of active duty. In a preliminary study, we found that 5.3% of individuals were EBV-negative at the time of first sample (11), corresponding to hundreds of thousands of EBV-negative young adults at risk of EBV infection and MS.

We documented 955 incident MS cases among active-duty military personnel [including 315 cases from our preliminary study (11)]. For each MS case, we identified up to three serum samples collected before the date of MS onset (the first available, the last collected before disease onset, and one in between). Cases were matched to two randomly selected individuals without MS of the same age, sex,

race/ethnicity, branch of military service, and dates of collection of blood samples who were on active military duty when the case was diagnosed (Fig. 1A and fig. S1). There were 801 MS cases and 1566 controls with samples available to assess EBV infection status. Most of the individuals in our study were <20 years of age at the time of their first blood collection (Fig. 1B), and those who developed MS had symptom onset a median of 10 years after time of first sample (Fig. 1C).

Only one of the 801 MS cases occurred in an individual who was EBV-negative in the last sample, which was collected at a median of 1 year before MS onset [hazard ratio (HR) for MS comparing EBV-positive versus EBV-negative = 26.5; 95% confidence interval (CI): 3.7 to 191.6; $P = 0.001$, conditional logistic regression]. At baseline, 35 MS cases and 107 controls were EBV-negative. All but one of these 35 EBV-negative MS cases became infected with EBV during the follow-up, and all seroconverted before the onset of MS (fig. S3). The median time from the first EBV-positive sample to MS onset was 5 years (range: 0 to 10 years), and the median time from estimated EBV seroconversion, defined as the midpoint between the last seronegative sample and the first seropositive sample, to MS onset was 7.5 years (range: 2 to 15 years). The high seroconversion rate among individuals who developed MS during follow-up (97%) contrasts with the 57% rate of seroconversion observed among individuals who did not develop MS (Fig. 2A), a rate consistent with previous reports among EBV-negative young adults (12). The HR for MS comparing EBV seroconversion versus persistent EBV seronegativity was 32.4 (95% CI: 4.3 to 245.3, $P < 0.001$) (Fig. 2C).

Behavioral, environmental, or personal characteristics may correlate with a predisposition to both infection and MS. To assess this possibility, we measured antibodies against cytomegalovirus (CMV), a herpesvirus that, like EBV, is transmitted through the saliva. CMV displays socioeconomic and racial/ethnic disparities in age at infection in the US population (13) similar to those of EBV (14), thus constituting an ideal negative control (15). Among those who were CMV-negative at baseline, seroconversion for CMV occurred at a similar rate in those who later developed MS and those who did not (Fig. 2B). MS risk was lower among CMV-positive

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than among CMV-negative individuals (Fig. 2D), consistent with a previous report and with suggestions that the immune response to CMV attenuates the adverse effects of EBV (16).

Similar to other neurological diseases, the pathological mechanisms underlying MS likely start several years before the first symptoms appear (17). To further elucidate the temporal relation between EBV infection and MS, we

measured serum concentrations of neurofilament light chain (sNFL), a sensitive, albeit not disease-specific, biomarker of ongoing neuroaxonal degeneration (18), using an ultra-sensitive single-molecule assay (19) in the

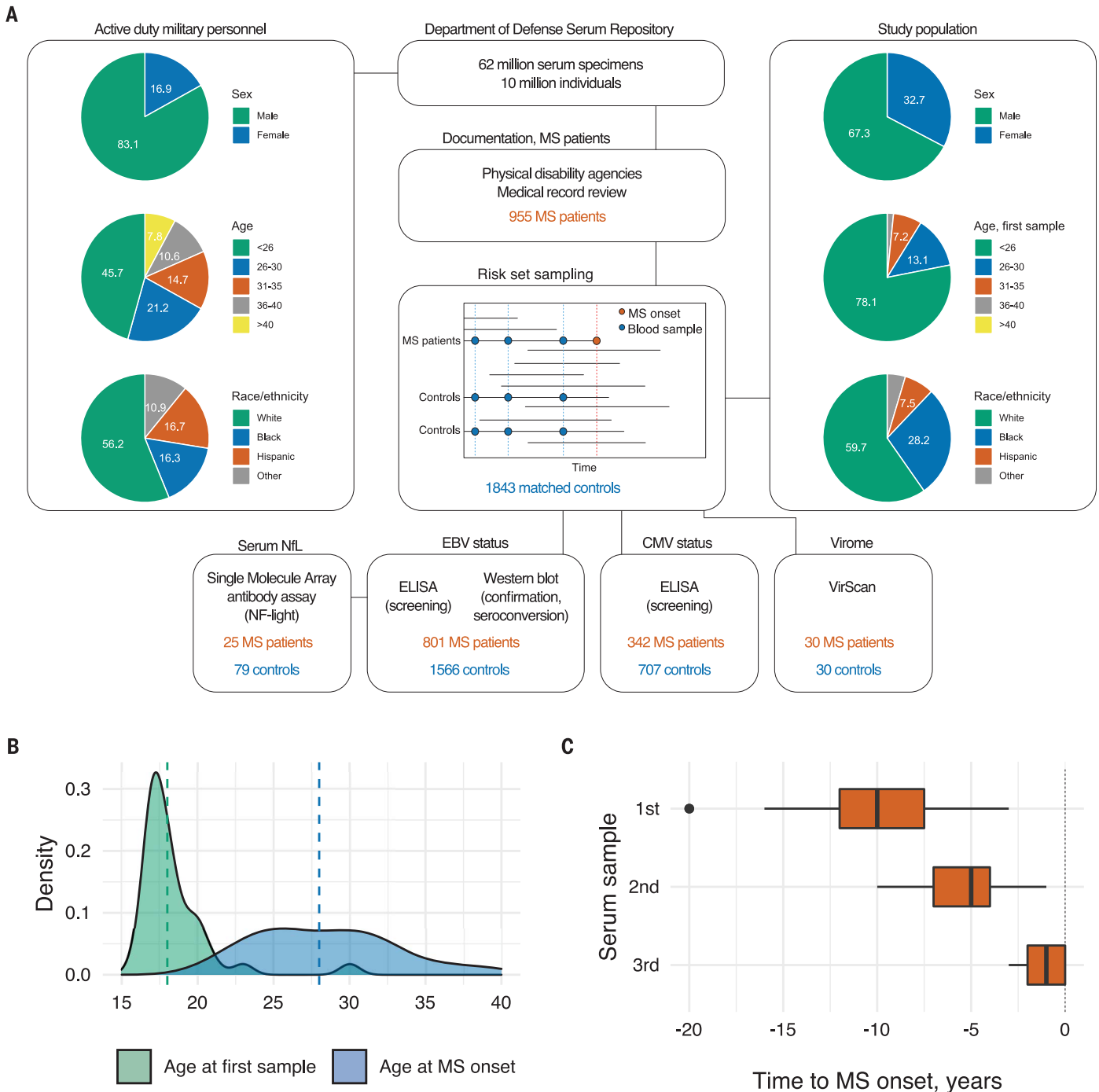
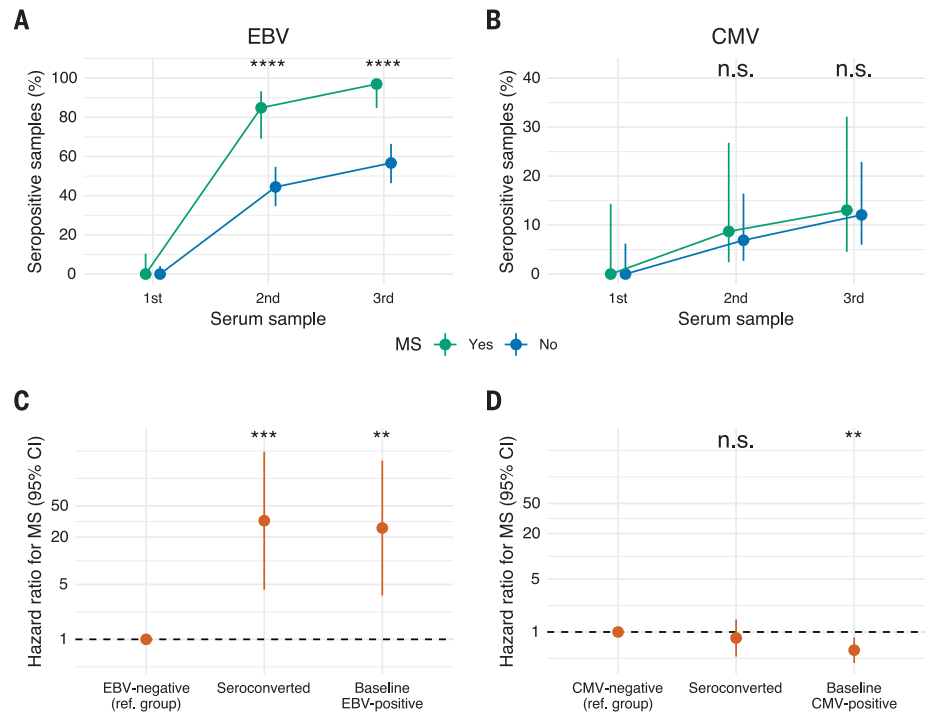


Fig. 1. Study design. (A) Residual serum samples from the DoDSR were obtained from 810 MS patients and 1577 matched controls. We assessed whether individuals were seropositive for EBV and CMV in up to three serum samples per person. We measured sNFL in those who were EBV-negative in the first serum sample. VirScan was used to profile the virome in a subset of MS

cases with serum samples collected shortly before and after symptom onset. (B) Density plot of age at onset among MS patients who were EBV-negative at time of first serum sample. The dashed line marks median age at onset. (C) Box plots of the time to first MS symptoms according to the serum sample.

Fig. 2. EBV infection precedes MS onset and is associated with markedly higher disease risk.

(A) Proportion of individuals who were EBV-positive at the time of the first, second, and third sample. The figure is restricted to those who were EBV-negative at baseline and with EBV measurement in three samples (33 of 35 MS patients and 90 of 107 controls). A significantly higher proportion of individuals who later developed MS were EBV-positive in the second (28 of 33 MS patients) and third (32 of 33 MS patients) sample compared with individuals who did not develop MS (second sample: 40 of 90 controls; third sample: 51 of 90 controls). **** $P < 0.0001$, two-sided Fisher's exact test. **(B)** Proportion of individuals who were CMV-positive at the time of the first, second, and third sample collected in the study. The figure is restricted to those who were CMV- and EBV-negative at baseline. The proportion who were CMV-positive was similar in the second (two of 23 MS patients versus four of 60 controls) and third sample (three of 23 MS patients versus seven of 60 controls). All $P > 0.05$, two-sided Fisher's exact test. **(C)** Risk ratio for MS according to EBV status. EBV seroconversion by the time of the third sample and EBV seropositivity at the time of the first sample were associated with a 32-fold and 26-fold increased risk of developing MS, respectively, in matched analyses. ** $P < 0.01$ and **** $P < 0.001$, two-sided univariable conditional logistic regression model. **(D)** Risk ratio for MS according to CMV status. ** $P < 0.01$, two-sided univariable conditional logistic regression model.



samples from those who were EBV-negative at baseline. We have previously reported that sNfL levels increase as early as 6 years before clinical MS onset and may be a more accurate marker of the time of initiation of the disease process (20). sNfL levels in individuals who were EBV-negative at baseline and went on to develop MS were similar to those of non-MS controls before and around the time of EBV infection but increased after EBV infection (Fig. 3, A to C, and fig. S4). Thus, there were no signs of neuroaxonal degeneration before EBV seroconversion in individuals who later developed MS, indicating that EBV infection preceded not only symptom onset but also the time of the first detectable pathological mechanisms underlying MS.

To further explore whether immune dysregulation during the preclinical phase could increase susceptibility to viral infections more generally, we randomly selected 30 MS cases and 30 matched controls with serum samples collected shortly before (median: 1 year, range: 0 to 3) and soon after symptom onset (median: 1 year, range: 0 to 2) and conducted a comprehensive agnostic search of the antiviral antibody response using VirScan, an assay based on a T7 phage-display immunoprecipitation and sequencing technology (21), which encodes the full proteome of most known human pathogenic viruses (~200 species, ~110,000 peptides) in 56-amino acid peptides with 28-amino acid overlap between

adjacent peptides. VirScan thus enables comprehensive unbiased detection of antibodies raised against all linear peptides encoded in the genomes of viruses known to infect humans. The overall antibody response to viral peptides was similar in cases and controls at both time points, except for EBV (Fig. 4, A to D), arguing that the preclinical and early clinical phases in MS are not associated with immune dysregulation affecting general susceptibility to infections. Using a Z score of >3.5 as an enrichment cutoff for identifying the presence of a peptide-specific antibody (22), the number of antibody-recognized EBV peptides with a nominally significant difference between MS cases and controls clearly stood out, both in the pre-onset (Fig. 4, E and G, and table S1) and post-onset (Fig. 4, F and H, and table S2) samples, which supports the specificity of the association between EBV and MS and argues against a second hit from another virus playing a major role in MS etiology.

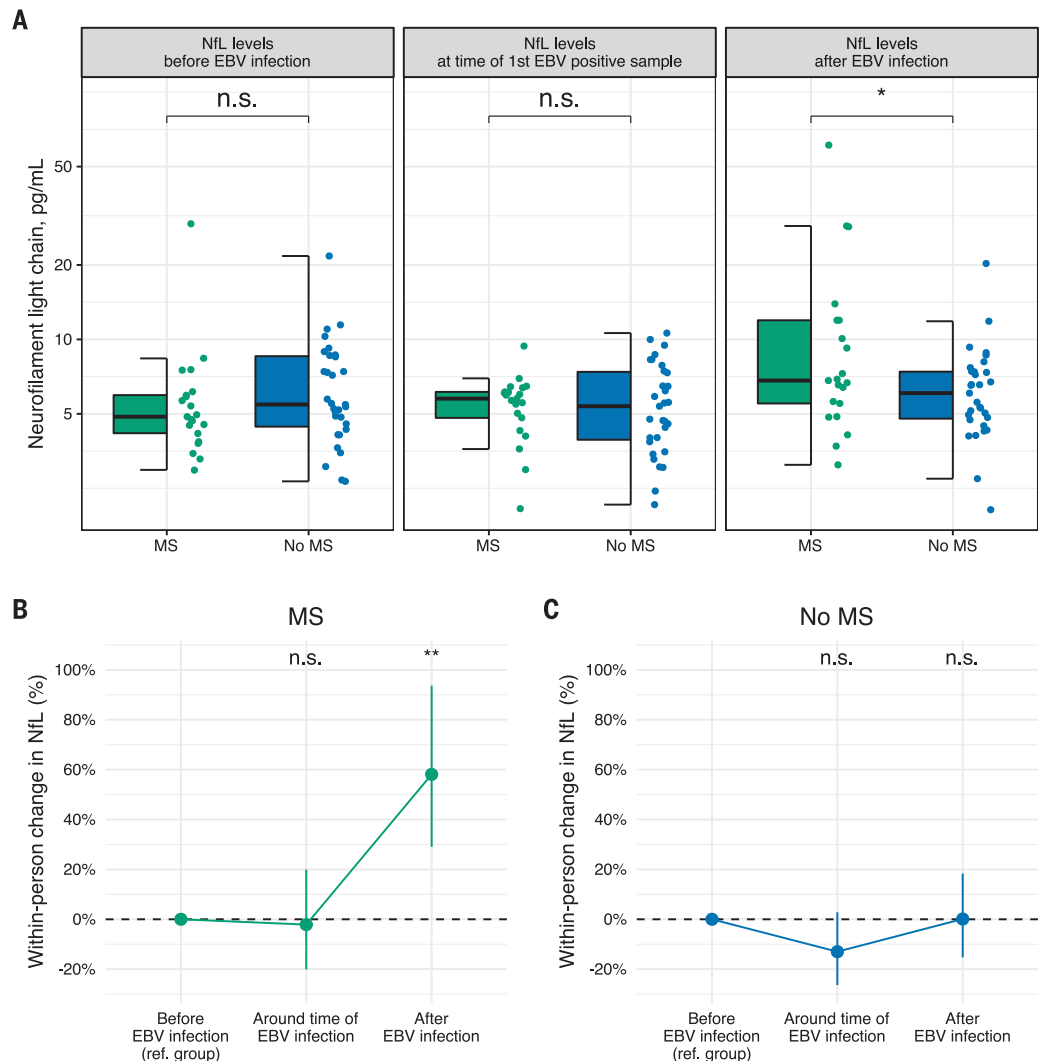
A causal interpretation of our results requires ruling out the possibility that systematic differences between individuals who seroconverted and those who remained EBV-negative explain the results. These differences can be grouped into two categories: (i) confounding by known or unknown factors and (ii) reverse causation.

Confounding by known factors is virtually ruled out by the strength of the association.

To explain a 32-fold increase in MS risk, any confounder would have to confer a >60 -fold increase in risk of EBV seroconversion and a >60 -fold risk of MS (23). None of the known or suspected risk factors for MS has such strong associations. The next strongest known risk factor for MS, homozygosity for the HLA-DR15 allele, which confers a threefold increase in MS risk (24), is not associated with EBV positivity (25) and thus cannot explain the EBV-MS association. Rather, there is epidemiological (26) and experimental (27) evidence that EBV infection and HLA-DR15 may act synergistically in causing MS. Environmental factors are also far too weak to materially confound the EBV-MS association (28). The existence of a still unknown factor that increases the risk of both EBV infection and MS by >60 -fold is rather implausible and there are no good candidates, even hypothetical ones. This conclusion would be robust even in the very unlikely case that EBV seroconversion in one of the MS cases was a false-positive result, in which case EBV infection would confer a 16-fold increase in MS risk.

Reverse causation could occur if the immune dysregulation during the preclinical phase of MS increases the susceptibility to EBV infection. In our agnostic search of the entire human virome during the preclinical phase of MS, we did not find other systematic differences in the antibody response to

Fig. 3. EBV infection precedes elevation of sNFL before the onset of MS. (A) Box plots of sNFL levels before, around, and after the time of EBV infection. * $P < 0.05$, two-sided multivariable linear regression model adjusted for age and sex. (B) Within-person increase in sNFL levels in MS cases around and after time of EBV infection compared with before EBV infection. ** $P < 0.01$, two-sided linear mixed-effects regression model. (C) Within-person increase in sNFL levels in controls around and after time of EBV infection compared with before EBV infection. Error bars in (B) and (C) are 95% CIs. sNFL levels increased significantly more in MS cases than in controls in the sample collected after time of EBV infection compared with before EBV infection ($P < 0.001$, two-sided linear mixed-effects regression model).



any pathogen except EBV that was related to previous infections in MS cases and controls, which makes it unlikely that immune dysregulation during this phase increases susceptibility to infections. This is consistent with previous studies reporting no difference in the frequency of infections in the 5 years preceding MS onset (29) or in individuals with untreated MS (30). Although in one study, hospitalizations for bacterial infections in adolescence were associated with MS risk, this association was modest and therefore cannot explain our study results (31). Additional arguments against reverse causality are that EBV seroconversion occurs before elevation of sNFL levels, which is an early marker of preclinical MS, and the long lag time (median: 7.5 years) between EBV infection and MS clinical onset. The increased MS risk 15 years or longer after infectious mononucleosis (32) and the observation that anti-EBNA antibodies are a strong and consistent predictor of MS risk in EBV-positive indi-

viduals up to 15 to 20 years later (33) provide further and independent evidence against reverse causation. Collectively, these findings strongly suggest that the occurrence of EBV infection, detectable by the elicited immune response, is a cause and not a consequence of MS.

One MS case was EBV-negative in the last sample, obtained 3 months before MS onset, which could suggest that EBV was not the cause of disease in this patient. This individual could have been infected with EBV after the last blood collection, could have failed to seroconvert in response to infection (an uncommon but nevertheless regular phenomenon seen after infections and vaccines), or could have been misdiagnosed. Another explanation is related to etiological diversity, which is common for any clinically defined disease. For example, all cases of paralytic poliomyelitis are by definition caused by poliovirus, but rare cases of acute flaccid paralysis, clinically indistinguishable

from poliomyelitis, can be caused by other enteroviruses (34). The extremely low MS risk in EBV-negative individuals suggests that by far most MS cases are caused by EBV and could thus potentially be prevented by a suitable vaccine. The addition of MS to the list of diseases that an EBV vaccine could target strengthens the rationale to accelerate ongoing research with the primary goal of preventing infectious mononucleosis and posttransplantation lymphoproliferative disease (35).

One of the most effective treatments for MS is anti-CD20 monoclonal antibodies, which deplete circulating memory B cells, the primary site of persistent latent EBV infection (36). This, and preliminary results obtained with EBV-specific T cell therapy (37), suggest that EBV, in addition to causing MS, contributes to MS clinical course, which could thus be potentially modified by antivirals. Directly targeting EBV could have major advantages compared with anti-

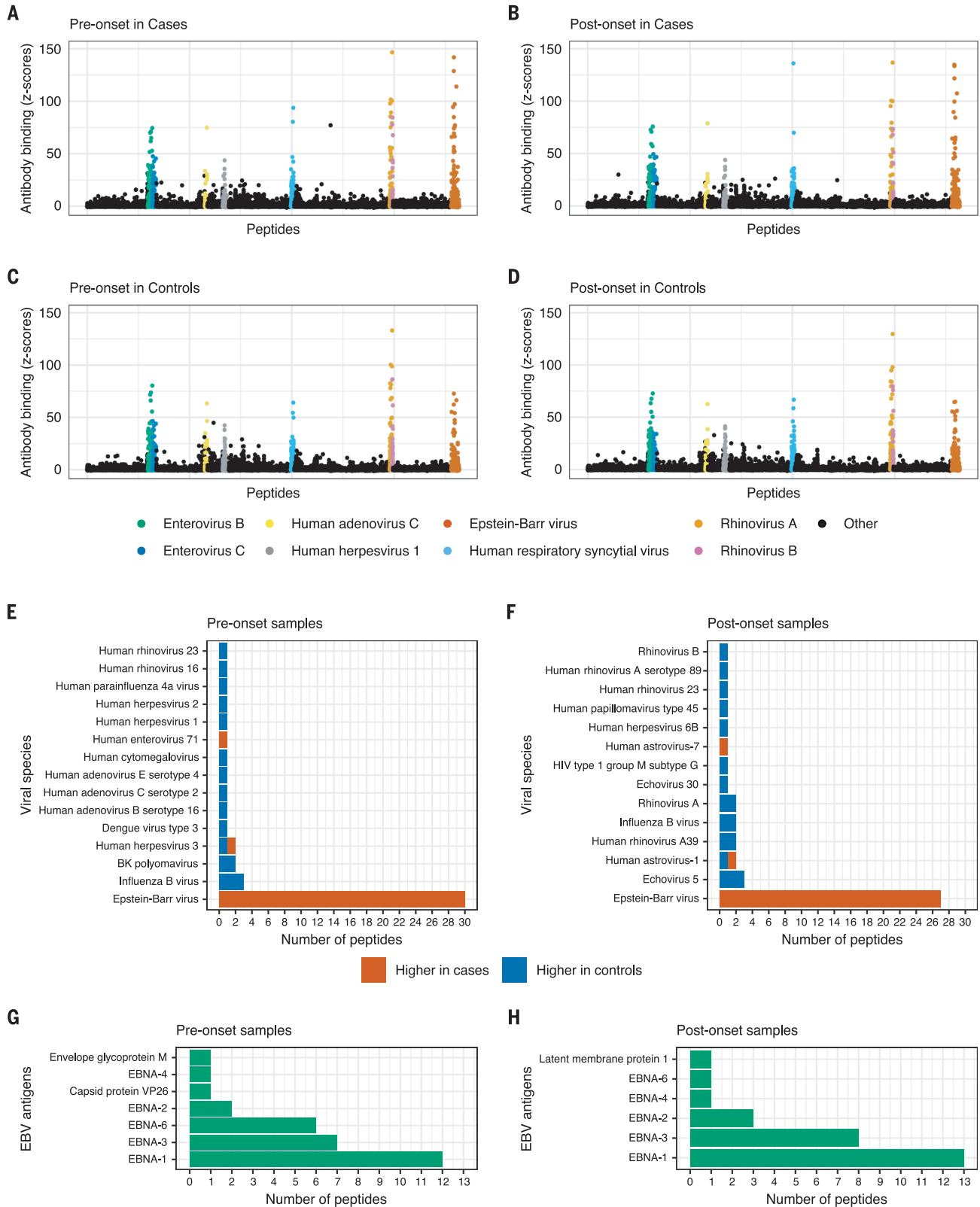


Fig. 4. Antibodies against EBV peptides in MS cases detected using vrome-wide screening. (A to D) Scatter plots showing the mean Z scores of serum antibody enrichment against the entire viral peptidome in cases and controls in the pre- and post-onset samples. Each point represents one peptide. (E and F) Number of viral peptides with nominally significantly different antibody

binding between cases and controls in the pre- and post-onset samples (using a Z score >3.5 as an enrichment cut-off; compared using two-sided Fisher's exact test) and their mapping to viral species. (G and H) Mapping of the statistically significant EBV peptides to EBV antigens (for details, see tables S1 and S2).

CD20-based therapies, which have to be administered by intravenous infusion and may increase the risk of infections (36).

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Figs. S1 to S4

Tables S1 and S2

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Data S1

MDAR Reproducibility Checklist

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Stronger evidence for viral connection

Multiple sclerosis is a chronic demyelinating disease of the central nervous system. The underlying cause of this disease is not known, but Epstein-Barr virus is thought to be a possible culprit. However, most people infected with this common virus do not develop multiple sclerosis, and it is not feasible to directly demonstrate causation of this disease in humans. Using data from millions of US military recruits monitored over a 20-year period, Bjornevik *et al.* determined that Epstein-Barr virus infection greatly increased the risk of subsequent multiple sclerosis and that it preceded the development of disease, supporting its potential role in the pathogenesis of multiple sclerosis (see the Perspective by Robinson and Steinman). —YN

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