

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- ☐ ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☐ ☒ The statistical test(s) used AND whether they are one- or two-sided
Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- ☒ ☐ A description of all covariates tested
- ☐ ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- ☐ ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- ☐ ☒ For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
Give P values as exact values whenever suitable.
- ☒ ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- ☒ ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- ☒ ☐ Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection EXCEL (Version 2021) was used to manage data.

Data analysis All data were analyzed with GraphPad Prism 10.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The anonymized data supporting the findings of this study are available under restricted access due to legal and ethical considerations. Access may be granted to qualified researchers upon request to the corresponding authors and pending approval by the Data-Clearing Committee of the Medical University of Vienna. Source data are provided with this paper. All data generated in this study are included in the Supplementary Information and Source Data files.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	All participants were defined by gender, based on self-reporting of the individuals. Relevant data are available within the manuscript and in the supplementary data.
Reporting on race, ethnicity, or other socially relevant groupings	No information about the race, ethnicity, or other socially relevant grouping were collected.
Population characteristics	There were in total 6085 study participants aged 7.7-70. 704 study participants were MS patients, diagnosed according to the McDonald 2017 criteria between 2001 and 2023. 5381 study participants were healthy controls with no history of any neuro-inflammatory disorder. Healthy controls were recruited between 2000 and 2023. Patients and controls were retrospectively enrolled in the study.
Recruitment	MS patients were part of the Biobanks of the Department of Neurology, Medical University of Vienna, Clinical Department of Neurology, Medical University of Innsbruck, and the Department of Pediatric Neurology, Children's Hospital Datteln, University Witten. All EBV-seropositive patients with complete clinical data and an available plasma sample, which was collected immediately after MS diagnosis (0-14 days) and prior to any MS-specific treatment, were included. No relevant self-selection bias were identified.
Ethics oversight	The study was approved by the Institutional Review Board of the Medical University of Vienna (IRB number: 1339/2022).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	In this pilot study, a maximum of 704 patients was included in the analysis. The number of subjects was chosen in order to obtain insights, adjusted for EBV serostatus, age, and gender of MS patients.
Data exclusions	EBV-seronegative MS patients and controls were excluded from the study, as the analysis focused on assessing EBV-specific immune responses.
Replication	The reported results were consistently replicated using ELISA and SIMOA assays, with two independent replicates producing similar outcomes.
Randomization	Due to the retrospective case-control study design, no randomization occurred during the study.
Blinding	Researchers were blinded in the study. Each MS patient and control was assigned a unique identifier before enrollment, serving as their ID throughout the experiments and data analysis.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Secondary HRP-conjugated goat anti-human IgG ((1:12500 in Blocking Buffer, Host: Goat, Antigen: Human IgG H+L): Thermo Fisher, Waltham, MA, Cat # 31412; RRID:AB_228265.
Validation	To validate the secondary HRP-conjugated goat anti-human IgG, repeated testing of the same EBV-seropositive and EBV-seronegative plasma samples was used. The data are shown in the appendix of the manuscript and revealed a high consistency between the assays.

Plants

Seed stocks	<i>Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.</i>
Novel plant genotypes	<i>Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.</i>
Authentication	<i>Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.</i>