Liu *et al. Epigenetics & Chromatin* (2025) 18:7
https://doi.org/10.1186/s13072-025-00567-9

Epigenetics & Chromatin

RESEARCH Open Access

Assessment of relationships between epigenetic age acceleration and multiple sclerosis: a bidirectional mendelian randomization study

Hongwei Liu[1†], Hanqing Zhang[2†], Zhaoxu Yin[1†] and Miaomiao Hou[3*]

Abstract

Background The DNA methylation-based epigenetic clocks are increasingly recognized for their precision in predicting aging and its health implications. Although prior research has identified connections between accelerated epigenetic aging and multiple sclerosis, the chronological and causative aspects of these relationships are yet to be elucidated. Our research seeks to clarify these potential causal links through a bidirectional Mendelian randomization study.

Methods This analysis employed statistics approaches from genome-wide association studies related to various epigenetic clocks (GrimAge, HannumAge, PhenoAge, and HorvathAge) and multiple sclerosis, utilizing robust instrumental variables from the Edinburgh DataShare ($n = 34,710$) and the International Multiple Sclerosis Genetics Consortium (including 24,091 controls and 14,498 cases). We applied the inverse-variance weighted approach as our main method for Mendelian randomization, with additional sensitivity analyses to explore underlying heterogeneity and pleiotropy.

Results Using summary-based Mendelian randomization, we found that HannumAge was associated with multiple sclerosis (OR = 1.071, 95%CI:1.006–1.140, $p = 0.033$, by inverse-variance weighted). The results suggest that an increase in epigenetic age acceleration of HannumAge promotes the risk of multiple sclerosis. In reverse Mendelian randomization analysis, no evidence of a clear causal association of multiple sclerosis on epigenetic age acceleration was identified.

Conclusions Our Mendelian randomization analysis revealed that epigenetic age acceleration of HannumAge was causally associated with multiple sclerosis, and provided novel insights for further mechanistic and clinical studies of epigenetic age acceleration-mediated multiple sclerosis.

†Hongwei Liu, Hanqing Zhang and Zhaoxu Yin contributed equally to this work and should be considered as co-first authors.

*Correspondence:
Miaomiao Hou
sxmuhmm@163.com

Full list of author information is available at the end of the article

Keywords Multiple sclerosis, Epigenetic age acceleration, Epigenetic clock, Mendelian randomization, Genome-wide association studies

Introduction

Multiple sclerosis (MS) is a common chronic autoimmune disorder that impacts the central nervous system, marked by neurodegeneration, demyelination, and inflammation [1]. It primarily impacts young adults between 20 and 40 years old, with a higher incidence in women, who are twice as likely as men to develop the condition [2]. MS is categorized into four main types: progressive-relapsing MS, relapsing-remitting MS, primary progressive MS, and secondary progressive MS. Clinical manifestations are varied and can include limb weakness, paresthesias, optic neuritis, and ataxia [3]. While the exact cause of MS remains unknown, it is recognized that a combination of environmental and genetic factors increases the susceptibility to the disease [4]. Given that MS is a leading cause of neurological issues in young adults and its incidence is increasing worldwide, it is crucial to identify risk factors accurately.

In recent years, epigenetic age has been established as a benchmark for assessing biological aging [5, 6]. Utilizing DNA methylation profiles from various genomic sites, epigenetic clocks have proven more effective in predicting both chronological age and mortality than traditional markers like telomere length and modern omics-based biomarkers [5]. Epigenetic age acceleration (EAA), the variance between epigenetic and chronological age, is closely associated with a spectrum of age-related diseases and longevity differences among ethnic groups [6, 7]. Several EAA metrics have been devised to capture distinct facets of aging, including intrinsic EAA [8], which indicates aging independent of blood cell composition, HannumAge acceleration [9] associated with extrinsic aging factors, and advanced predictors like PhenoAge acceleration [10] and GrimAge acceleration [11], designed to more accurately forecast age-related health outcomes and mortality. In research by Maltby et al., using DNA methylation data from various studies, MS patients were found to have higher EAA levels compared to controls [12]. Conversely, another study showed lower EAA in MS patients' brain tissue compared to healthy individuals [13]. The links between MS and EAA, however, remain observational and yield conflicting results, complicated by potential confounding factors and reverse causality. This makes it challenging to establish causality through conventional epidemiological methods. Therefore, a dedicated exploration into the causal dynamics between MS and EAA is essential.

Mendelian randomization (MR) employs genetic variations to explore if correlations between risk factors and outcomes suggest a causal relationship. This method capitalizes on the random distribution of genetic variants during meiosis, ensuring that these variations are randomly allocated at birth. MR assesses whether the presence of a risk factor is affected by inherited genetic variations or spontaneous mutations [14]. It utilizes an instrumental variable (IV) to deepen the analysis of causal links between variables [15]. In this study, we conducted a bidirectional two-sample MR analysis to rigorously probe the causal connections between EAA and the risk of developing MS.

Materials and methods

Study design

MR analysis is grounded in three fundamental assumptions: (1) the assumption of correlation, which requires a robust correlation with exposure; (2) the assumption of exclusivity. There is no direct association with the outcome; (3) the assumption of independence. There is no influence on confounding factors [16, 17]. Figure 1 shows a schematic diagram of the MR study of EAA and MS.

Data sources

We acquired genetic instruments for four epigenetic clocks-GrimAge, HannumAge, PhenoAge, and HorvathAge-from a GWAS meta-analysis involving 28 cohorts with 34,710 European ancestry participants [18]. For multiple sclerosis (MS), we used GWAS data from the International Multiple Sclerosis Genetics Consortium (IMSGC), which includes data on 115,803 individuals of European descent, featuring 47,429 MS cases and 68,374 controls [19]. Additionally, the availability of the MS GWAS data was confirmed on the Open GWAS project.

Selection of instrumental variables

For a genetic variation to qualify as an IV in our study, it had to meet the following criteria: (1) The single-nucleotide polymorphisms (SNPs) exhibit a strong association with epigenetic clocks; (2) The SNPs are free from confounders that influence epigenetic age acceleration (EAA) effects on MS; (3) The SNPs do not have a direct association with MS but influence the disease through the EAA pathway. We initially selected SNPs strongly linked to EAA using a significance cutoff of $P < 5 \times 10^{-8}$. To ensure that our IVs were independent, we excluded SNPs in linkage disequilibrium (LD) with others ($r^2 < 0.001$ within a 10,000 kb clumping window). The strength of the IVs was assessed by calculating their F-values [20]. The proportion of trait variance attributable to genetic instruments (R^2) is determined using the formula:

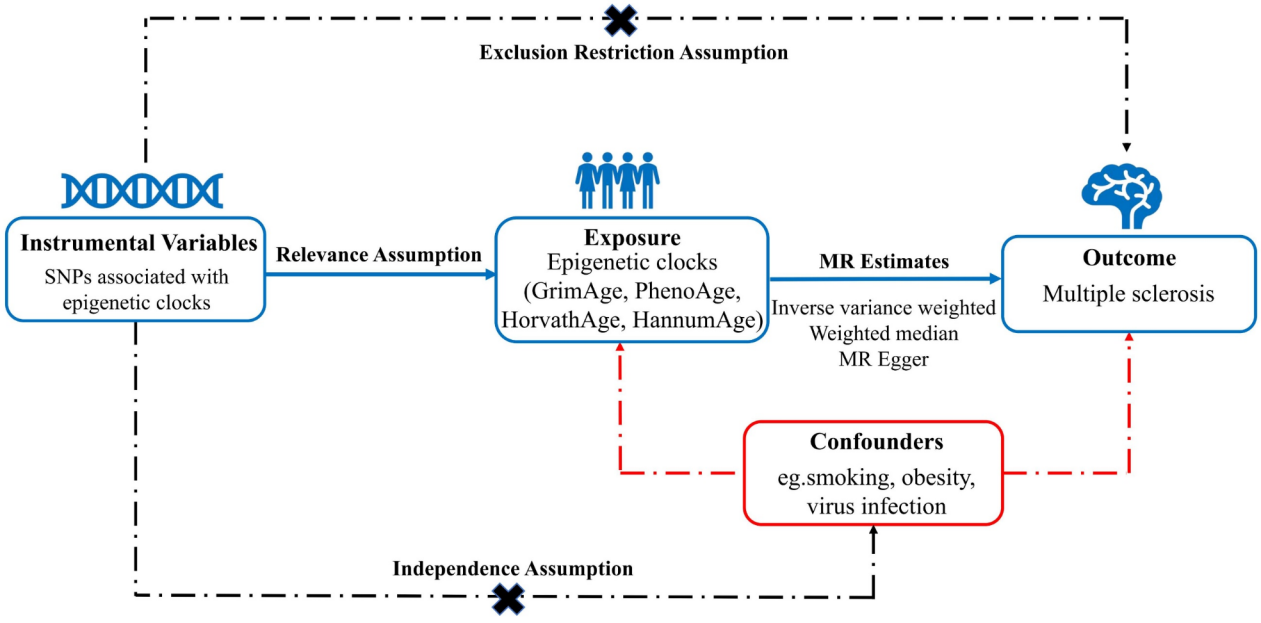

Fig. 1 The process of present Mendelian randomization (MR) analyses is shown in flow chart
Assumption 1: The instrumental variables (IVs) selected for this study should demonstrate a significant association with epigenetic age. Assumption 2: The IVs chosen for present study are required to have no significant associations with other potential confounding factors. Assumption 3: The IVs utilized in present study do not have any independent causal pathways leading to multiple sclerosis other than through epigenetic age acceleration
Abbreviations: IV, instrumental variable; SNPs, single-nucleotide polymorphisms; MR, Mendelian randomization

R^2 = 2×MAF×(1-MAF)×Beta, where MAF is the minor allele frequency, Beta indicates the effect size, SE refers to the standard error, N represents the sample size, and k denotes the number of IVs [21]. The F statistic quantifies the strength of the association between single-nucleotide polymorphisms (SNPs) and EAA. It is computed following the formula F=[(n-k-1)/k]/[R^2/(1-R^2)]. IVs that yield F-values greater than 10 are considered to have strong instrumental strength, which helps reduce potential biases in MR analysis [22]. To confirm that the selected IVs met the independence hypothesis, we used PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) to check if the chosen SNPs were associated with other phenotypes [23]. The analysis revealed that none of the SNPs showed significant associations with any other factors [24, 25].

MR analysis

The two-sample MR approach employed genome-wide significant IVs to ascertain the causal effects of exposures and risk factors on specific outcomes. To achieve robust causal inference, we utilized various analytical methods: Simple Mode (SMod), MR Egger (MRE), inverse-variance weighted (IVW), Weighted Mode (WMod), and Weighted Median (WMed). The IVW method, especially with multiplicative random effects, is considered the most effective for estimating causal effects and allows for the accounting of heterogeneity in these estimates [26]. It is crucial with IVW to verify that the SNPs are free from pleiotropic influences, which could otherwise introduce significant bias. The MRE method, incorporating an intercept term, helps identify potential breaches in IV assumptions, though it may increase type I error rates [27]. Contrary to the IVW method, the MRE approach incorporates an intercept term in its analysis. The Weighted Median method, by analyzing data from potentially invalid IVs, still offers reliable estimates if at least 50% of the genetic information comes from valid instruments [28]. Meanwhile, Weighted Mode methods, although less effective in detecting causal links, tend to introduce less bias into the analysis [29]. Considering the multiple tests in our study, Benjamini-Hochberg method was applied to adjust the p value to reduce the false discovery rate [30].

Heterogeneity, pleiotropy, and sensitivity assessment

Cochran's Q test was used to examine the heterogeneity across individual genetic variants within both MRE and IVW methods [31, 32]. P-value > 0.05 indicated the heterogeneity absence. For assessing directional pleiotropy, we employed the MRE intercept test, considering pleiotropic effects negligible if the intercept did not

significantly differ from zero ($p > 0.05$) [33]. The MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) global test was also applied to detect horizontal pleiotropy and pinpoint outlier variants [34]. To evaluate the robustness of our findings, we conducted leave-one-out analyses using MRE and IVW methods, sequentially removing individual SNPs to see their impact on the overall results. Further sensitivity analyses were performed with both IVW and MR-Egger methods, ensuring the MRE estimate remained unbiased in the absence of pleiotropic effects linked to the genetic instruments.

Statistical analysis

Two-sample MR analysis was carried out using the package 'TwoSampleMR', and the MR-PRESSO test was conducted using the package 'MRPRESSO'. All statistical evaluations were performed in R version 4.3.3. To control for multiple testing, we implemented the false discovery rate (FDR) method. Statistically significant differences were considered when the FDR-adjusted q-value fell below 0.05.

Results

Identification of IVs for MR analysis

We identified 7, 11, 24, and 9 IVs from GWAS data corresponding to GrimAge, PhenoAge, HorvathAge, and HannumAge, respectively. Notably, the F statistics for all selected SNPs exceeded 496, with ranges as follows: GrimAge (977–1836), PhenoAge (859–4527), HorvathAge (579–4610), and HannumAge (496–1561) (Supplementary Table 1). In contrast, 95 IVs were identified from the GWAS data for MS. The selected SNPs exhibited F statistics greater than 25, with a range of 25 to 1269 (Supplementary Table 2). In MR, the F-statistic serves as the criterion for assessing the strength of IVs, with an F value exceeding 10 indicating robust instruments. In our analysis, the strength of the instruments was substantial, with F-statistics in bidirectional MR analyses ranging from 25 to 4610. As a result, we detected no signs of weak IV bias, indicating that these IVs yield dependable estimates of the causal impact of exposure on the outcome.

Bidirectional mendelian randomization results

In the summary-level MR analysis, significant associations were identified between genetically predicted EAA and MS. As depicted in Fig. 2, genetically predicted EAA of HannumAge (OR = 1.071, 95%CI: 1.006–1.140, $p = 0.033$, by IVW) was linked to an increased risk of MS positively. After applying Benjamini-Hochberg false discovery rate correction using the Benjamini-Hochberg procedure, the association remains robust and statistically significant. Conversely, no causal associations were observed between other epigenetic aging-related traits and MS (OR = 0,999, 95%CI: 0.969–1.030, $p = 0.952$, by IVW for GrimAge; OR = 1.000, 95%CI: 0.962–1.040, $p = 0.998$, by IVW for PhenoAge; OR = 1.004, 95%CI: 0.943–1.068, $p = 0.907$, by IVW for HorvathAge). A

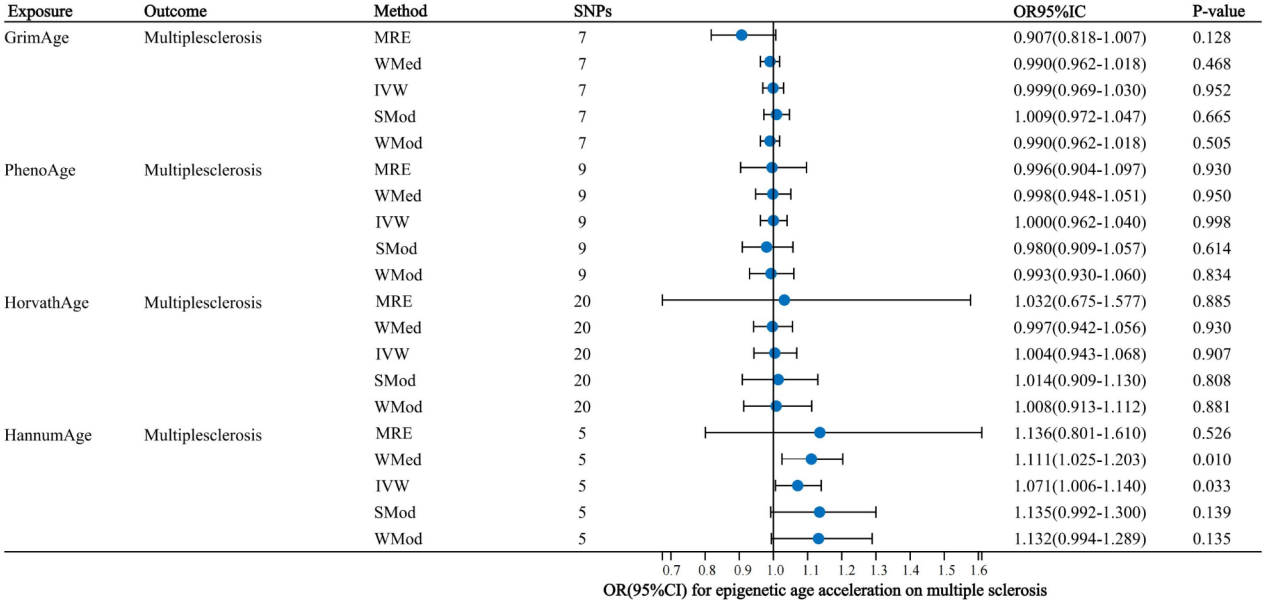

Fig. 2 Forest plot of estimates for effects of epigenetic age acceleration on multiple sclerosis in Mendelian randomization. Estimates were obtained using the IVW, MRE, WMed, WMod and SMod

Abbreviations: IVW, inverse variance weighted. MRE, MR Egger. WMed, Weighted Median. WMod, Weighted Mode. SMod, Simple Mode. CI, confidence interval. OR, odds ratio. SNPs, single-nucleotide polymorphisms

detailed examination of the MR analysis regarding the causal relationship between EAA and MS is shown in Supplementary Table 3. Figure 3 exhibits the scatter plots of the five methods. The trend lines suggested that increases in genetically predicted EAA of HannumAge correlate with a higher risk of MS. Conversely, we conducted an MR analysis with MS as the exposure to investigate potential reverse causality effects on EAA. As depicted in Fig. 4, genetically predicted MS was not associated with any epigenetic aging-related traits (OR = 0.921, 95% CI: 0.805–1.053, $p = 0.226$, by IVW for GrimAge; OR = 1.024, 95% CI: 0.958–1.096, $p = 0.483$, by IVW for PhenoAge; OR = 1.057, 95% CI: 0.998–1.119, $p = 0.058$, by IVW for HorvathAge; OR = 1.054, 95% CI: 0.999–1.113, $p = 0.054$, by IVW for HannumAge). The details of using the MR method analyzing the causal relationship of the MS on EAA are shown in Supplementary Table 4. The scatter plots of the five methods are presented in Fig. 5.

Sensitivity analysis

We conducted sensitivity analyses using Cochran's Q statistics combined with IVW and MRE methods to evaluate heterogeneity. The analyses identified significant heterogeneity between MS and two epigenetic clocks-PhenoAge (Q = 107.422, $P = 0.043$) and HannumAge (Q = 116.593, $P = 0.011$), as detailed in Table 1. Given this heterogeneity, we proceeded with the IVW method using a multiplicative random-effects model for further MR analysis. Additionally, the MRE intercept and the MR-PRESSO global test confirmed that the absence of directional horizontal pleiotropy is statistically significant (Table 1). To further validate our findings, we implemented a "leave-one-out" analysis using the IVW method. In this analysis, each SNP was sequentially

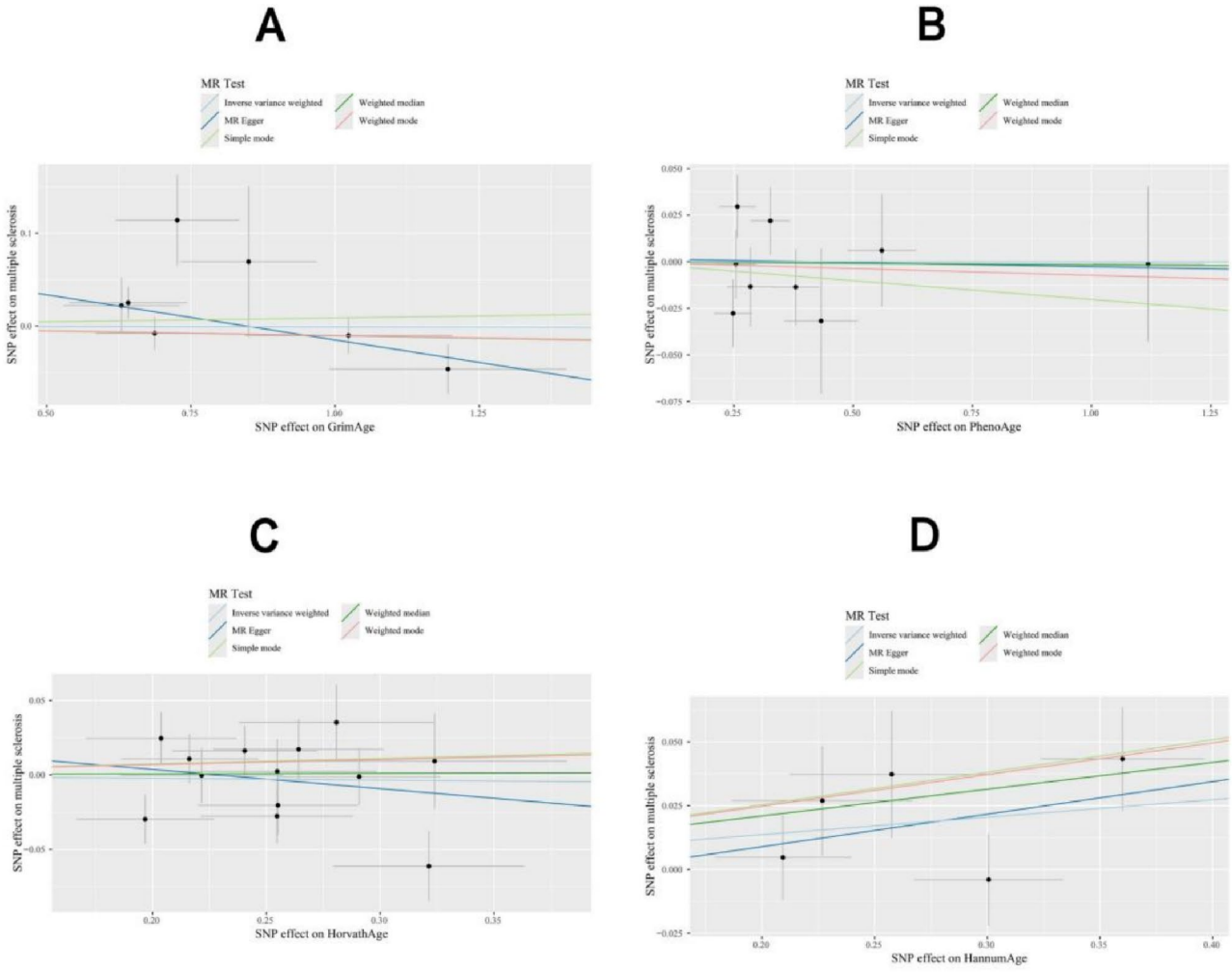

Fig. 3 Scatter plots of epigenetic age acceleration and multiple sclerosis. GrimAge (**A**), PhenoAge (**B**), HorvathAge (**C**) and HannumAge (**D**) as exposure and MS as outcome

Abbreviations: MR, Mendelian randomization; SNP, single-nucleotide polymorphism

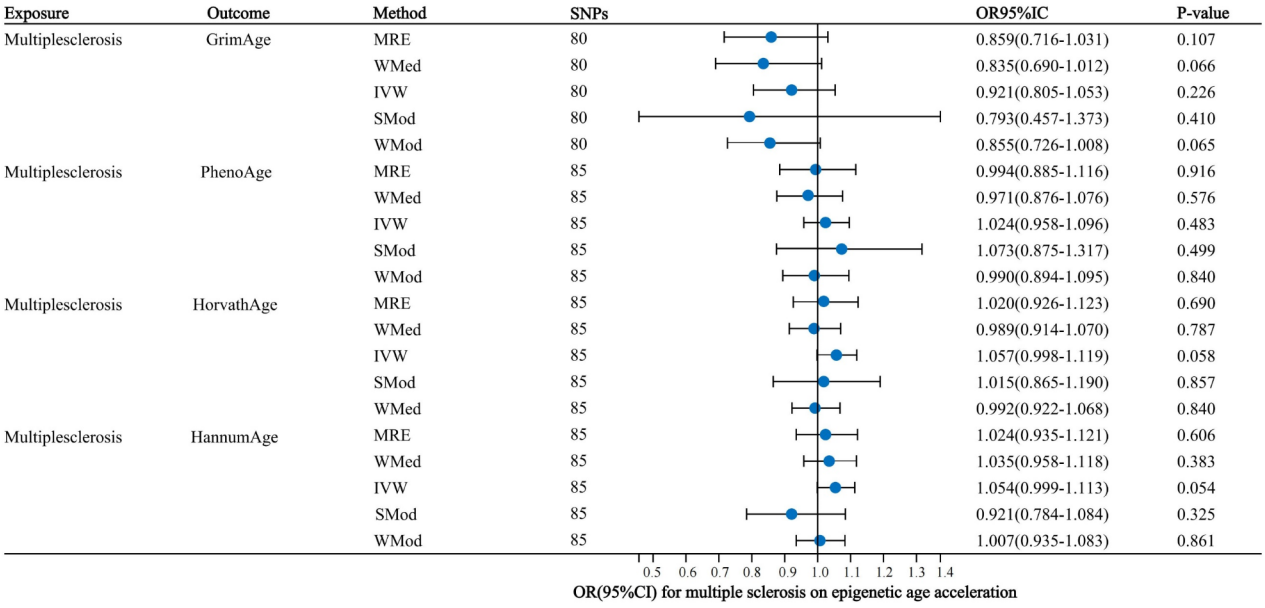

Fig. 4 Forest plot of estimates for effects of multiple sclerosis on epigenetic age acceleration in Mendelian randomization. Estimates were obtained using the IVW, MRE, WMed, WMod and SMod

Abbreviations: IVW, inverse variance weighted. MRE, MR Egger. WMed, Weighted Median. WMod, Weighted Mode. SMod, Simple Mode. CI, confidence interval. OR, odds ratio. SNPs, single-nucleotide polymorphisms

removed, and the impact on the remaining dataset was assessed (as shown in Supplementary Fig. 1 and Fig. 2). This test revealed that no individual SNP significantly altered the outcome, underscoring the robustness and reliability of our results.

Discussion

This is the first bidirectional causal relationship investigation between EAA and MS through a large-scale MR study, to the best of our knowledge. Our research reveals that an increased genetically predicted HannumAge is associated with a higher risk of MS. Conversely, we found no evidence supporting a causal effect of MS on any epigenetic aging-related traits. This suggests that EAA, specifically HannumAge, may be a risk factor for the development of MS.

Chronological age is calculated based on an individual's birthdate, while biological age is assessed through biomarkers that gauge the aging process in various organs and tissues. Research has shown that biological age can diverge significantly among individuals of the same chronological age [35, 36]. DNA methylation at cytosine-phosphate-guanine (CpG) sites is a primary epigenetic marker that changes with age and can be measured in tissues and blood. The methylation percentage at each CpG site helps develop an "epigenetic clock," which closely aligns with chronological age [6, 10]. Different epigenetic clock algorithms can be derived from methylation data across specific cell or tissue types, tailored to detect specific physiological changes or outcomes. The disparity between epigenetic and chronological ages can indicate whether individuals are biologically older or younger than their chronological age. Accelerated epigenetic aging is linked to a higher risk of age-related ailments, including neurodegenerative diseases like Parkinson's and Alzheimer's disease, cardiovascular diseases, and diabetes, as well as increased chances of early death [7, 37].

Previous research has established a link between DNA methylation and MS. Hypomethylation in genes, particularly those related to lymphocyte-mediated leukocyte and immunity pathways, has been shown to contribute to the immune-mediated pathology observed in MS [38]. Additionally, DNA methylation plays a role in modulating the immunogenicity of autoantigens in MS brain [39, 40]. Furthermore, in the peripheral blood mononuclear cells of MS patients, increased PAD2 expression coupled with promoter hypomethylation has been observed, highlighting the epigenetic alterations associated with the disease [41].

EAA may contribute to the development of MS through several interrelated mechanisms, as supported by existing research. 1) Immune dysregulation and "immunosenescence": EAA is closely linked to age-related changes in immune function, collectively termed "immunosenescence;" [42–45] these changes include diminished regulatory T cell efficacy and a shift towards pro-inflammatory immune phenotypes. Aberrant methylation patterns

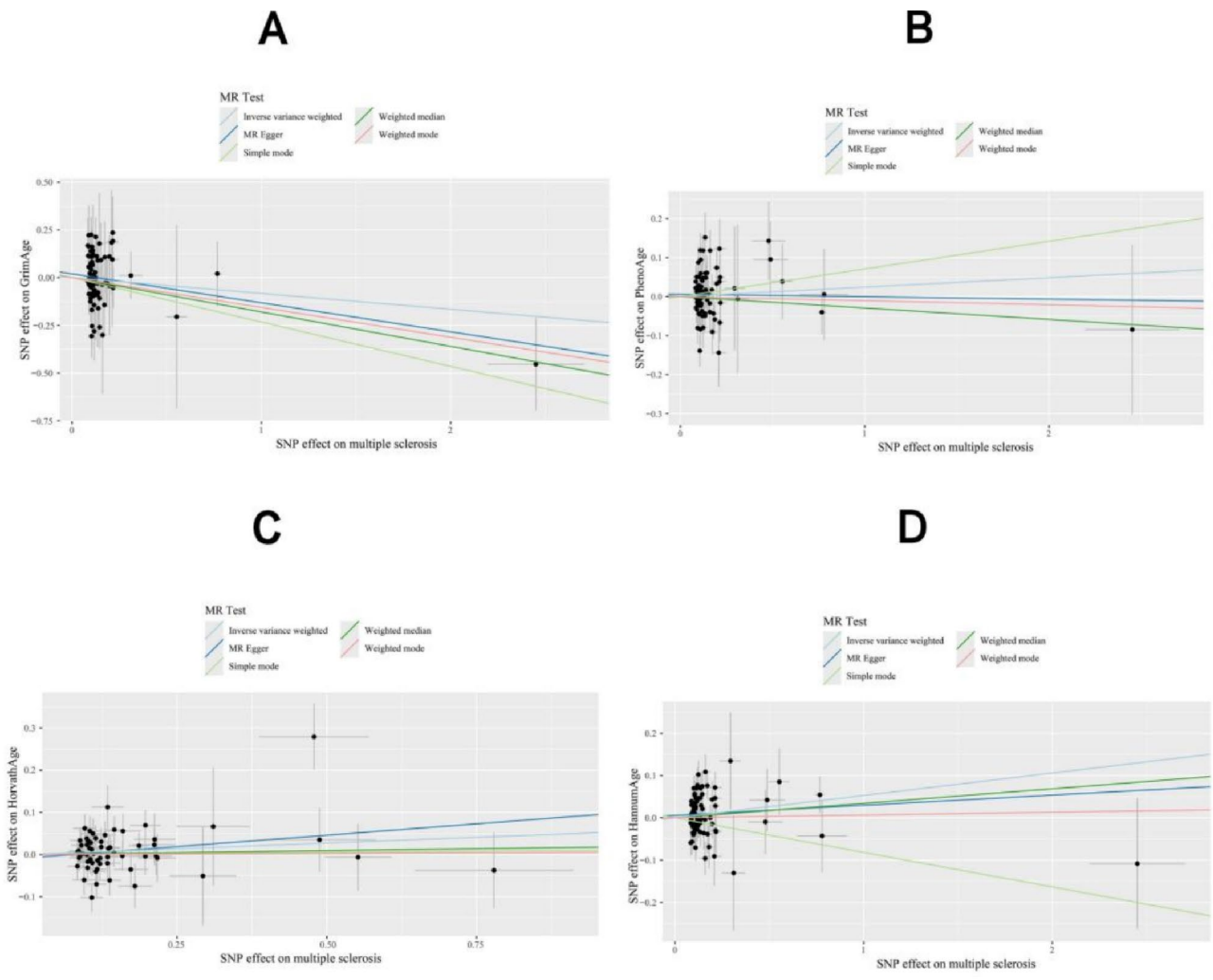

Fig. 5 Scatter plots of multiple sclerosis and epigenetic age acceleration. Multiple sclerosis as exposure, and GrimAge (**A**), PhenoAge (**B**), HorvathAge (**C**) and HannumAge (**D**) as outcome
Abbreviations: MR, Mendelian randomization; SNP, single-nucleotide polymorphism

in genes regulating T cell differentiation and antigen presentation may amplify autoimmune responses, a hallmark of MS pathogenesis [42, 46]. 2) Neuroinflammation amplification: epigenetic modifications associated with EAA may upregulate pro-inflammatory cytokines like IL-6 and TNF-α; [47–49] these changes exacerbate microglial activation, impair the blood-brain barrier, and promote immune cell infiltration into the CNS, driving MS-related neuroinflammation [50, 51]. 3) Cellular senescence in neural and glial cells: accelerated biological aging may induce cellular senescence in key CNS cells, including oligodendrocytes and astrocytes; [42, 52, 53] senescent cells release inflammatory mediators, collectively known as the senescence-associated secretory phenotype, which hampers remyelination and exacerbates neural damage central to MS progression [54]. 4) Oxidative stress and mitochondrial dysfunction: EAA has been associated with oxidative stress and mitochondrial dysfunction, which are pivotal in MS pathology; [42, 55, 56] oxidative damage to myelin-producing cells and neurons drives disease progression, and epigenetic alterations may impair antioxidant defenses, exacerbating these processes [57]. 5) Environmental and Lifestyle Factors as Mediators: EAA serves as a cumulative marker for exposure to environmental and lifestyle factors, including stress, vitamin D deficiency, and poor diet; [58–61] these exposures are independently established as MS risk factors and may synergize with EAA to amplify autoimmune responses and promote disease development [62].

Early research indicates accelerated epigenetic age in individuals with MS. Theodoropoulou E and colleagues observed that the EAA of PhenoAge, which more accurately predicts aging outcomes compared to HorvathAge and HannumAge, was increased in whole blood samples from MS patients relative to healthy controls [63]. Similarly, Maltby et al. found GrimAge in the B cells of MS

Table 1 The heterogeneity and pleiotropy analysis of the MR study on epigenetic age acceleration and multiple sclerosis

Exposure	Outcome	Method	Heterogeneity		Horizontal pleiotropy		MR PRESSO	
			Q	Q_*p*-value	MRE intercept	*p*-value	Qutliers	*p*-value
GrimAge	Multiple sclerosis	MRE	7.378	0.194	0.082	0.121	0	0.051
		IVW	12.509	0.052				
PhenoAge	Multiple sclerosis	MRE	8.406	0.298	0.002	0.924	0	0.530
		IVW	8.418	0.394				
HorvathAge	Multiple sclerosis	MRE	18.689	0.067	0.029	0.555	9	0.150
		IVW	19.319	0.081				
HannumAge	Multiple sclerosis	MRE	3.830	0.280	-0.017	0.757	0	0.235
		IVW	3.977	0.409				
Multiple sclerosis	GrimAge	MRE	76.473	0.528	0.020	0.279	0	0.550
		IVW	77.663	0.521				
Multiple sclerosis	PhenoAge	MRE	106.905	0.040	0.006	0.528	0	0.076
		IVW	107.422	0.043				
Multiple sclerosis	HorvathAge	MRE	73.356	0.153	-0.008	0.462	23	0.084
		IVW	74.003	0.162				
Multiple sclerosis	HannumAge	MRE	115.737	0.010	0.006	0.436	1	0.059
		IVW	116.593	0.011				

Abbreviations: MR, Mendelian randomization; MRE, MR Egger; IVW, Inverse Variance Weighted, Q, Cochran's Q test

participants [12]. In contrast, Kular L and their team reported no significant increase in EAA across HorvathAge, GrimAge, PhenoAge, and HannumAge in the glial cells of MS patients compared to controls [13]. Furthermore, the same set of epigenetic clocks revealed significant disparities related to biological aging in lung immune cells influenced by MS and smoking [64]. These inconsistent findings might be due to the limited number of cases, the absence of longitudinal follow-up, and a lack of comprehensive analysis of MS outcomes. In this study, we investigated the causal link between EAA and MS using MR analyses. To reduce potential bias due to population stratification, we exclusively used GWAS data from individuals of European ancestry. Our data were carefully sourced from the Edinburgh DataShare and the International Multiple Sclerosis Genetics Consortium (IMSGC) Database, ensuring there was no overlap in samples. Quality control measures were implemented to verify the reliability and robustness of our results. This research enhances our understanding of MS risk factors, showing that increased odds of MS are associated with EAA as measured by the HannumAge clock. Epigenetic clocks hold promise as critical tools for clinicians and preventive medicine practitioners in assessing MS risk. Additionally, slowing down biological aging has become a significant area of interest in MS research.

In the context of our analysis, we utilized GrimAge, PhenoAge, HorvathAge, and HannumAge, which are widely recognized first-generation epigenetic clocks. These clocks were chosen for their robustness, extensive validation, and well-established associations with various age-related conditions, including neurodegenerative diseases like MS. Their widespread application highlights their reliability in capturing biological aging processes. Nonetheless, we recognize the potential of advanced epigenetic clocks, such as DamAge and AdaptAge, which represent significant advancements in the field. These newer clocks offer refined granularity and may capture more nuanced biological aging signatures, providing deeper insights into age-related pathologies like MS. Unfortunately, the dataset used in this study lacked the specific methylation markers required to calculate DamAge or AdaptAge scores, precluding their inclusion in the present analysis. Looking ahead, we are eager to incorporate DamAge and AdaptAge in future research. Their application, particularly in conjunction with longitudinal data and larger sample sizes, could greatly enhance our understanding of the intricate interplay between epigenetic age acceleration and MS pathogenesis.

GWAS data we used were drawn exclusively from populations of European ancestry, limiting the generalizability of our findings to other ethnic groups. This necessitates caution when extending these results to racially and ethnically diverse populations. Additionally, we relied on aggregate GWAS data, which prevented a stratified analysis by factors such as age and gender due to the absence of individual-level data. Despite efforts to mitigate confounding, we could not estimate the degree of overlap between exposure and outcome data in the two-sample MR analysis. To minimize bias from sample overlap, we employed robust instruments, ensuring an F statistic substantially greater than 25. Although we reduced confounding bias from SNPs, there remains the possibility that some SNPs could be linked to undetected factors that might affect the association between EAA and MS. The potential pleiotropic effects of these SNPs

cannot be completely ruled out, warranting a cautious interpretation of our MR analysis results. Moreover, the epigenetic GWAS data we utilized are based on blood counts and clinical markers, which could lead to different outcomes as more diverse samples and GWAS data become available in the future.

Conclusion

Our findings indicate a potential causal relationship between EAA and the risk of MS. Specifically, genetically predicted EAA using the HannumAge clock appears to elevate the risk of developing MS. This underscores the significance of targeting biological aging as a novel avenue for MS research and potential intervention. To further substantiate the causal role of EAA in MS, large-scale studies involving diverse populations are essential. These studies will help to clarify the impact of EAA across different genetic backgrounds and improve our understanding of its role in MS pathology.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13072-025-00567-9.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
We extend our gratitude to the International Multiple Sclerosis Genetics Consortium (IMSGC) and Edinburgh DataShare for providing access to the GWAS summary statistics data.

Author contributions
L.H. and Z.H. conceived and designed the study. L.H. and H.M. carried out data analysis and the preparation of visualizations. Z.H. and Y.Z. interpreted the results. L.H. and H.M. wrote the manuscript. Z.H. and Y.Z. provided critical revisions to the manuscript. All authors have read and approved the final manuscript.

Funding
This study was funded by the Shanxi Provincial Science and Technology Department, Basic Research Program (Youth Fund, Free Exploration Category, No. 20210302123415).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Neurology, Taiyuan Central Hospital, Taiyuan, Shanxi Province, China
[2]Department of Neurology, The Fourth Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China
[3]Department of Neurology, Tongji Shanxi Hospital, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Taiyuan, China

Received: 25 July 2024 / Accepted: 2 January 2025
Published online: 30 January 2025

References

1. Trapp BD, et al. Axonal transection in the lesions of multiple sclerosis. N Engl J Med. 1998;338(5):278–85.
2. Amato MP, et al. Environmental modifiable risk factors for multiple sclerosis: report from the 2016 ECTRIMS focused workshop. Mult Scler. 2018;24(5):590–603.
3. Miller D, et al. Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. Lancet Neurol. 2005;4(5):281–8.
4. Jakimovski D, et al. Multiple sclerosis. Lancet. 2024;403(10422):183–202.
5. Jylhävä J, Pedersen NL, Hägg S. Biol Age Predictors EBioMedicine. 2017;21:29–36.
6. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet. 2018;19(6):371–84.
7. Chen BH, et al. DNA methylation-based measures of biological age: meta-analysis predicting time to death. Aging. 2016;8(9):1844–65.
8. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14(10):R115.
9. Hannum G, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol Cell. 2013;49(2):359–67.
10. Levine ME, et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging. 2018;10(4):573–91.
11. Lu AT, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging. 2019;11(2):303–27.
12. Maltby V, et al. Evaluation of cell-specific epigenetic age acceleration in people with multiple sclerosis. Neurology. 2023;101(7):e679–89.
13. Kular L, et al. Epigenetic clock indicates accelerated aging in glial cells of progressive multiple sclerosis patients. Front Aging Neurosci. 2022;14:926468.
14. Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization Jama. 2017;318(19):1925–6.
15. Richmond RC, Davey Smith G. Mendelian randomization: concepts and scope. Cold Spring Harb Perspect Med, 2022. 12(1).
16. Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. Eur J Epidemiol. 2018;33(10):947–52.
17. Botelho J et al. Causal Association between Periodontitis and Parkinson's Disease: A Bidirectional Mendelian Randomization Study. Genes (Basel), 2021. 12(5).
18. McCartney DL, et al. Genome-wide association studies identify 137 genetic loci for DNA methylation biomarkers of aging. Genome Biol. 2021;22(1):194.
19. Multiple sclerosis genomic. Map implicates peripheral immune cells and microglia in susceptibility. Science, 2019. 365(6460).
20. Palmer TM, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. Stat Methods Med Res. 2012;21(3):223–42.
21. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for mendelian randomization studies using multiple genetic variants. Int J Epidemiol. 2011;40(3):740–52.
22. Burgess S, Thompson SG. Avoiding bias from weak instruments in mendelian randomization studies. Int J Epidemiol. 2011;40(3):755–64.
23. Kamat MA, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics. 2019;35(22):4851–3.
24. Zhou J, et al. Effect of basal metabolic rate on osteoporosis: a mendelian randomization study. Front Public Health. 2023;11:1096519.
25. Deng Y, Wong MCS. Association between rheumatoid arthritis and osteoporosis in Japanese populations: a mendelian randomization study. Arthritis Rheumatol. 2023;75(8):1334–43.
26. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37(7):658–65.
27. Burgess S, Thompson SG. Interpreting findings from mendelian randomization using the MR-Egger method. Eur J Epidemiol. 2017;32(5):377–89.
28. Bowden J, et al. Consistent estimation in mendelian randomization with some Invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40(4):304–14.
29. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol. 2017;46(6):1985–98.

30. Yuan S, Larsson SC. An atlas on risk factors for type 2 diabetes: a wide-angled mendelian randomisation study. Diabetologia. 2020;63(11):2359–71.
31. Rees JMB, Wood AM, Burgess S. Extending the MR-Egger method for multivariable mendelian randomization to correct for both measured and unmeasured pleiotropy. Stat Med. 2017;36(29):4705–18.
32. Burgess S, Thompson SG. Multivariable mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. Am J Epidemiol. 2015;181(4):251–60.
33. Zhang Y, et al. Habitual coffee intake and risk for nonalcoholic fatty liver disease: a two-sample mendelian randomization study. Eur J Nutr. 2021;60(4):1761–7.
34. Verbanck M, et al. Detection of widespread horizontal pleiotropy in causal relationships inferred from mendelian randomization between complex traits and diseases. Nat Genet. 2018;50(5):693–8.
35. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? J Gerontol Biol Sci Med Sci. 2013;68(6):667–74.
36. Blackburn EH, Epel ES, Lin J. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. Science. 2015;350(6265):1193–8.
37. Marioni RE, et al. DNA methylation age of blood predicts all-cause mortality in later life. Genome Biol. 2015;16(1):25.
38. Beck H, et al. Cathepsin S and an asparagine-specific endoprotease dominate the proteolytic processing of human myelin basic protein in vitro. Eur J Immunol. 2001;31(12):3726–36.
39. Bradford CM, et al. Localisation of citrullinated proteins in normal appearing white matter and lesions in the central nervous system in multiple sclerosis. J Neuroimmunol. 2014;273(1–2):85–95.
40. Mastronardi FG, et al. Peptidyl argininedeiminase 2 CpG island in multiple sclerosis white matter is hypomethylated. J Neurosci Res. 2007;85(9):2006–16.
41. Calabrese R, et al. Methylation-dependent PAD2 upregulation in multiple sclerosis peripheral blood. Mult Scler. 2012;18(3):299–304.
42. Chan VS. Epigenetics in multiple sclerosis. Adv Exp Med Biol. 2020;1253:309–74.
43. Liotti A, et al. Epigenetics: an opportunity to shape innate and adaptive immune responses. Immunology. 2022;167(4):451–70.
44. Khan Z, et al. Immune System Dysregulation in the progression of multiple sclerosis: Molecular insights and therapeutic implications. Neuroscience. 2024;548:9–26.
45. Liu Z, et al. Immunosenescence: molecular mechanisms and diseases. Signal Transduct Target Ther. 2023;8(1):200.
46. Soto-Heredero G, et al. Extremely differentiated T cell subsets contribute to tissue deterioration during aging. Annu Rev Immunol. 2023;41:181–205.
47. Ghorbani S, Yong VW. The extracellular matrix as modifier of neuroinflammation and remyelination in multiple sclerosis. Brain. 2021;144(7):1958–73.
48. Giallongo S et al. The role of epigenetics in Neuroinflammatory-Driven diseases. Int J Mol Sci, 2022. 23(23).
49. Kular L, Jagodic M. Epigenetic insights into multiple sclerosis disease progression. J Intern Med. 2020;288(1):82–102.
50. Celarain N, Tomas-Roig J. Aberrant DNA methylation profile exacerbates inflammation and neurodegeneration in multiple sclerosis patients. J Neuroinflammation. 2020;17(1):21.
51. Butler CA, et al. Microglial phagocytosis of neurons in neurodegeneration, and its regulation. J Neurochem. 2021;158(3):621–39.
52. Sikora E, et al. Cellular Senescence in Brain Aging. Front Aging Neurosci. 2021;13:646924.
53. Papadopoulos D, et al. Aging, Cellular Senescence, and progressive multiple sclerosis. Front Cell Neurosci. 2020;14:178.
54. Zhu X, et al. Inflammation, epigenetics, and metabolism converge to cell senescence and ageing: the regulation and intervention. Signal Transduct Target Ther. 2021;6(1):245.
55. Tobore TO. Oxidative/Nitroxidative stress and multiple sclerosis. J Mol Neurosci. 2021;71(3):506–14.
56. Blagov AV et al. Significance of mitochondrial dysfunction in the progression of multiple sclerosis. Int J Mol Sci, 2022. 23(21).
57. Ibáñez-Cabellos JS et al. Oxidative stress and epigenetics: miRNA involvement in Rare Autoimmune diseases. Antioxid (Basel), 2023. 12(4).
58. Galkin F, et al. Stress, diet, exercise: common environmental factors and their impact on epigenetic age. Ageing Res Rev. 2023;88:101956.
59. Jamebozorgi K, et al. Epigenetic aspects of multiple sclerosis and future therapeutic options. Int J Neurosci. 2021;131(1):56–64.
60. Scazzone C, et al. Vitamin D and genetic susceptibility to multiple sclerosis. Biochem Genet. 2021;59(1):1–30.
61. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol. 2017;13(1):25–36.
62. Manna I, De Benedittis S, Porro D. A Comprehensive examination of the role of epigenetic factors in multiple sclerosis. Int J Mol Sci, 2024. 25(16).
63. Theodoropoulou E, et al. Different epigenetic clocks reflect distinct pathophysiological features of multiple sclerosis. Epigenomics. 2019;11(12):1429–39.
64. Klose D, et al. Smoking affects epigenetic ageing of lung bronchoalveolar lavage cells in multiple sclerosis. Mult Scler Relat Disord. 2023;79:104991.

Publisher's note