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Co-exposure to PFAS and hydroxylated PCBs is associated with increased odds of multiple sclerosis

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ABSTRACT

Persistent organic pollutants often co-occur in human exposure environments, yet their combined effects on disease risk remain poorly understood. This study examined associations between serum concentrations of 14 per- and polyfluorinated substances (PFAS) and three hydroxylated polychlorinated biphenyls (OH-PCBs) and the onset of multiple sclerosis (MS), utilizing data from the Swedish population-based Epidemiological Investigation of Multiple Sclerosis (EIMS) cohort, comprising 907 MS cases and 907 matched controls. We employed single-substance logistic regression and quantile g-computation to evaluate cumulative and individual compound associations. We considered linear and non-linear risk patterns while adjusting for lifestyle factors and MS-associated HLA alleles.

Our analysis revealed non-linear associations for several individual compounds, particularly perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid, 2,2′,3,4′,5,5′,6-heptachloro-4-biphenylol (4-OH-CB187), and 2,2′,4,4′,5,5′-, Hexachloro-3-biphenylol (3-OH-CB153), with increased odds of MS. Interaction analyses further indicated that the association between PFOS and MS odds was modified by the presence of the *HLA-B*44:02* allele, known for its protective effect on MS risk. Mixture modeling highlighted that combined exposures to PFAS and OH-PCBs significantly increased MS odds, even when associations for individual compounds were weak or absent.

These findings emphasize the complexity of associations between environmental contaminants, lifestyle and genetic risk factors, and the odds of MS. They underscore the importance of addressing co-exposure in environmental health research and call for further studies to elucidate underlying biological mechanisms.

Abbreviations: 4-OH-CB187, 2,2′,3,4′,5,5′,6-heptachloro-4-biphenylol; 3-OH-CB153, 2,2′,4,4′,5,5′-,Hexachloro-3-biphenylol; 4-OH-CB107, 2,3,3′,4′,5-Pentachloro-4-biphenylol; AhR, Aromatic hydrocarbon receptors; BMI, Body mass index (kg/m^2); EAE, Experimental autoimmune encephalomyelitis; EBV, Epstein-Barr virus; EDC, Endocrine-disrupting chemicals; EIMS, Epidemiological Investigation of Multiple Sclerosis; FDR, False discovery rate; MC, Matched controls; HLA, Human leukocyte antigen; MS, Multiple sclerosis; N-EtFOSAA, N-ethylperfluoro-1-octanesulfonamidoacetic acid; N-MeFOSAA, N-methylperfluoro-1-octanesulfonamidoacetic; NF-κB, Nuclear factor kappaB; OH-PCBs, Hydroxylated polychlorinated biphenyls; pwMS, People with multiple sclerosis; PCBs, Polychlorinated biphenyls; PFAS, Per- and polyfluoroalkyl substances; PFDA, Perfluorodecanoic acid; PFDS, Perfluorodecanesulfonic acid; PFDoA, Perfluorododecanoic acid; PFHpS, Perfluoroheptanesulfonic acid; PFHxS, Perfluorohexanesulfonic acid; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFOS, Perfluorooctane sulfonic acid; PPAR, Peroxisome proliferator-activated receptor; RA, Rheumatoid arthritis; Th17, T helper 17 cell; Treg, Regulatory T.

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1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system (Dobson and Giovannoni, 2019; Attfield et al., 2022), with its onset influenced by a complex interplay of genetic and environmental factors. Among the most well-known risk factors, Epstein-Barr virus (EBV) infection stands out as one of the most important, alongside female sex, adolescent obesity, smoking, and specific human leukocyte antigen (HLA)-associated variants (Dobson and Giovannoni, 2019; Attfield et al., 2022; Alfredsson and Olsson, 2019). Moreover, low vitamin D levels have been associated with an increased risk of MS, however, some uncertainty remains (Ascherio et al., 2010; Munger et al., 2006). The HLA complex carries the highest genetic susceptibility to develop MS, with HLA class II alleles driving the disease risk and HLA I alleles acting as protective allele (Attfield et al., 2022; Moutsianas, 2015). Despite these recognized factors, substantial unexplained variance in MS risk remains (van der Mei et al., 2016).

Emerging evidence indicates that chronic exposure to endocrine-disrupting chemicals (EDCs), such as per- and polyfluoroalkyl substances (PFAS), may modulate immune function (Ehrlich et al., 2023; Crawford et al., 2023). Recent studies have associated PFAS exposure with both decreased risk of rheumatoid arthritis (RA) (Qiao et al., 2024) and increased risk of ulcerative colitis (Steenland et al., 2013), yet their impact on MS remains inadequately explored. A previous study has demonstrated decreased perfluorooctane sulfonic acid (PFOS), a common PFAS, concentrations in people with MS (pwMS) compared to controls; however, no risk analysis was performed (Ammitzbøll, 2019). Moreover, a cross-sectional study found no significant association between estimated past exposure to perfluorooctanoic acid (PFOA), a common PFAS, and MS incidence (Steenland et al., 2013). We have recently demonstrated sex-and disease-specific concentration differences in pwMS compared to controls; however, exposure to individual PFAS compounds was not significantly associated with odds of MS (Vaivade et al., 2025). More recently, a Mendelian randomization study using genetically predicted PFOS concentrations suggested a potential causal relationship between PFOS exposure and increased MS risk, identifying genes implicated in immune dysregulation and neuroinflammation. Molecular docking and pathway enrichment analyses further suggest peroxisome proliferator-activated receptor (PPAR) signaling as a possible mechanistic pathway (Liu et al., 2025). These partly conflicting findings between observational and genetic approaches underscore the need for population-based studies that combine measured chemical exposures with genetic data to better clarify the role of PFAS in MS pathogenesis.

Polychlorinated biphenyls (PCBs), another type of endocrine-disrupting substances, have been associated with various harmful human health effects, including developmental toxicity, neurotoxicity, and immunosuppressive effects (Safe, 1994; Tehrani and Van Aken, 2014). PCB exposure has been associated with an increased risk of developing RA, specifically in women (Lee et al., 2007). Moreover, inverse associations between PCB 153 exposure and type 1 diabetes have also been observed (Rignell-Hydbom et al., 2010). However, knowledge regarding PCBs' association with the risk of developing MS is lacking. In a recent study, we demonstrated an association between hydroxylated PCBs (OH-PCBs), specifically 2,2′,3,4′,5,5′,6-heptachloro-4-biphenylol (4-OH-CB187) and 2,2′,4,4′,5,5′-, Hexachloro-3-biphenylol (3-OH-CB153), exposure, and increased odds of MS (Vaivade et al., 2025). PCBs' toxicity has been suggested to partially originate from their hydroxylated metabolites, OH-PCBs, partially. These metabolites also exhibit a range of toxic traits, such as disruption of thyroid hormone and estrogen activity, mitochondrial respiration inhibition, and the generation of reactive oxygen species, not observed in their parent PCBs (Tehrani and Van Aken, 2014).

The PFAS and PCB focus is particularly relevant in Sweden, where long-term environmental contamination has resulted in persistent exposure to PFAS and PCBs. Several regions, including Ronneby in southern Sweden, have experienced PFAS-contaminated drinking water, mainly due to the use of aqueous film-forming foams, leading to elevated PFAS serum levels (Gyllenhammar et al., 2015; Li et al., 2020). Among the health effects reported in the Ronneby population are increased susceptibility to common infectious diseases (Ebel et al., 2025), sex-specific differences in birth weight (Engström et al., 2022), and elevated risk of type 2 diabetes (Xu et al., 2023). Serum PCB levels have also been linked to residential area among elderly Swedish women (Glynn, 2003). Moreover, both PFAS and PCBs have been linked to dietary exposure, particularly through drinking water (Sunderland et al., 2019) and fish consumption, with Baltic Sea fish being a major source of PCBs (Glynn, 2003; Bjermo, 2013). While PCBs accumulate mainly in the liver and adipose tissue, their hydroxylated metabolites are more water-soluble and reversibly bind to serum proteins, resulting in accumulation that is not lipid-dependent (Grimm et al., 2015). OH-PCBs are predominantly detected and appear to be selectively retained in plasma (Purkey et al., 2004; Bergman et al., 1994). Thus, their distribution and protein-binding properties resemble those of PFAS, further supporting the combined investigation of PFAS and OH-PCBs in this study.

The aim of this study was to investigate the association of individual and mixture exposure to PFAS and OH-PCBs with odds of developing MS. We additionally examined potential non-linear exposure–response relationships and evaluated interactions with MS-associated HLA alleles to explore possible gene-environmental interplay.

2. Methods

2.1. Cohort

This study is based on Epidemiological Investigations of Multiple Sclerosis (EIMS), a population-based case-control cohort based in Sweden (Hedström et al., 2009). All MS incident cases fulfilled the McDonald criteria (Polman et al., 2011; Polman et al., 2005) and were recruited from neurological clinics and all university hospitals throughout Sweden between 2005 and 2015. For each case, matched controls (MC) were randomly chosen from the national registry. Controls were matched on age, sex, and residential area. Serum was collected from newly diagnosed pwMS and their MC. Further, all participants completed a detailed questionnaire concerning environmental exposures and lifestyle factors. PwMS and MC were included if questionnaire data were available. In this study, a total of 907 pwMS and 907 MC were analyzed.

2.2. PFAS and OH-PCBs analysis

The method used for PFAS and OH-PCBs analysis has previously been described in detail (Vaivade et al., 2025; Carlsson et al., 2023). A total of 31 compounds were analysed through targeted analysis, including 24 PFAS compounds and seven OH-PCBs. In brief, serum samples (50 μL) were thawed, followed by the addition of internal standards (50 μL) and ice-cold methanol (100 μL) for protein precipitation. The samples were vortexed and centrifuged, and 100 μL of the supernatant was transferred to an LC vial. Calibrators and calibration QC samples were prepared in newborn bovine serum and spiked to seven concentrations within the 0.02–80 ng/mL range for all compounds where native and isotope-labeled standards were available. Where only isotope-labeled standards were available, one-point calibration compared with the corresponding internal standard was performed (Supplementary Table S1). For the sample analysis, a reversed-phase liquid chromatography column (Accucore C18, 100 × 2.1 mm, 2.6 μm, Thermo Scientific) using an Ultimate 3000 liquid chromatography system (Thermo Scientific) connected to a high-resolution hybrid quadrupole Q Exactive Orbitrap mass spectrometer (Thermo Scientific) operating in negative mode was used. All data was processed using TraceFinder 4.1 (Thermo Scientific) and exported for further analysis.

2.3. Definition of sun exposure habit

To assess sun exposure habits, participants answered three questions regarding their sun exposure during the 5-year period prior to study inclusion. Each question was rated on a four-point scale. An index was created by summing the scores, resulting in a range from three (representing the lowest exposure) to 12 (representing the highest exposure). Finally, sun exposure habits were dichotomized using the 25th and 75th percentile in the MC.

2.4. HLA genotyping

The method used for HLA genotyping has previously been described in detail (Tengvall et al., 2019). In brief, HLA-DRB1 and HLA-A were obtained at four-digit resolution by imputing from the Illumina-based MS replication chip using HLA*IMP:02 (Dilthey et al., 2013) with an extended reference panel including Swedish individuals for MHC class II. The MS replication chip (International Multiple Sclerosis Genetics Consortium, 2019) had enriched SNP density in the MHC region. In primary analysis, alleles were coded as carriers vs non-carriers (1/0), and in sensitivity analysis, allele count (0/1/2) was used for *DRB1*15:01* and *A*02:01*.

2.5. Statistical analysis

R version 4.4.0 was used for all computations (R Core Team. R, 2024). Compounds not detected in more than 20 % of the study cohort were excluded. Due to the non-normal distribution of PFAS and OH-PCB concentrations, they were $\log_2$-transformed. Not quantifiable concentrations were imputed with half of the lowest measured concentration for each compound. Due to the short half-lives, below one year, of short-chain PFAS they were excluded from further analysis. Within perfluoroalkyl sulfonic acids, short-chain PFAS contains less than six carbons. While in perfluoroalkyl carboxylic acids, however, short-chain PFAS has less than seven fluorinated carbons (Brendel et al., 2018).

2.5.1. Individual compound analysis

Logistic regression was used to evaluate the association of individual compound concentrations with the odds of MS. Three models were employed: a base model, model 1, and model 2. Covariate selection and model structure were defined by a directed acyclic graph (Supplementary Fig. S1), with the minimal sufficient adjustment set guiding the base model. The base model was adjusted for age, sex, and body mass index (BMI, kg/m^2), as well as residential area. For individuals between the ages 15 and 25, if either their current BMI or the BMI at age 20 was missing, it was assumed that the two BMIs were the same. Further, lifestyle factors were included in the base model, and the likelihood ratio test p-value was assessed. In model 1 lifestyle factors influencing MS risk and PFAS and OH-PCB concentrations were included using the diagnosis date as an index date. For each MC the same index date was set as the matched pwMS. The covariates in model 1 were: age, sex, BMI, BMI at the age of 20, number of childbirths, regular smoking, irregular smoking, history of infectious mononucleosis, sun habits, Swedish-born status, and residential area treated as a random effect. Model 2 adjusted for the same covariates as model 1, as well as six MS-associated HLA alleles of interest: *DRB1*15:01*, *DRB1*13:03*, *DRB1*03:01*, *DRB1*08:01, A*02:01*, and *B*44:02*. Finally, to explore the possibility of an interaction between compound concentrations and the MS-associated HLA allele of interest, an interaction term was introduced in model 2 for each allele.

Further, similar analyses were performed using compound concentration quartiles instead to assess the possibility of a non-linear association between compound exposure and odds of MS. Quartiles were defined based on non-imputed values. Odds ratios for each quartile were calculated with the first quartile (Q1) as a reference. Non-linear associations were illustrated using cubic splines.

Finally, a sensitivity analysis based on model 2 was conducted, further adjusting for genetic ancestry and heritability, via genetic principal components PC1-PC5. Moreover, since the number of alleles play an important role in HLA alleles impact on MS susceptibility, a sensitivity analysis was performed adjusting model 2 for allele count. This was applied to HLA alleles with at least 100 individuals carrying two copies, specifically *DRB1*15:01* and *A*02:01*. Both sensitivity analysis was applied to both $\log_2$-transformed concentration and concentration quartiles. In all analysis, p-values were corrected for multiple testing using the false discovery rate (FDR).

2.5.2. Mixture analysis

Mixture analysis offers insight into partial and cumulative dose–response relationships between chemical exposure and health outcomes. These relationships are often hidden in single compound models. Moreover, this type of analysis takes into account co-exposure. For the mixture analysis, quantile g-computation was applied using quartile-based exposure categorization. ORs with 95 % confidence intervals were estimated using non-parametric bootstrapping, with 2,000 resamples, to quantify the joint effect of increasing all exposures in the mixture by one quartile. The following mixtures were analyzed: PFAS and OH-PCBs, only PFAS, and only OH-PCBs. The following three models were employed: base, model 1, and model 2. The base model was adjusted for age, sex, BMI at study inclusion, and residential area. In addition to the covariates in the base model, model 1 also included the following lifestyle factors: number of childbirths, regular smoking, irregular smoking, history of infectious mononucleosis, sun habits, and Swedish-born status. Finally, model 2 adjusted for the same covariates as model 1, as well as six MS-associated HLA alleles of interest: *DRB1*15:01*, *DRB1*13:03*, *DRB1*03:01*, *DRB1*08:02, A*02:01*, and *B*44:02*. Finally, a sensitivity analysis based on model 2 was conducted, further adjusting for genetic ancestry and heritability via genetic principal components PC1-PC5. Moreover, another sensitivity analysis adjusting model 2 for allele count was also performed for HLA alleles with at least 100 individuals carrying two copies, specifically *DRB1*15:01* and *A*02:01*. P-values were corrected for multiple comparisons using the FDR in all analyses.

2.6. Ethical statement

Recruitment of study participants, sample collection, and data collection complied with local ethical requirements and applicable national laws related to human population genetic studies. The ethical permissions are EPN Stockholm: 04–252/1–4 and 2017/2386–32; from the Swedish Ethical Review Authority 2021–00702. All participants provided informed written consent.

3. Results

This study included 907 pwMS and 907 MC from the Swedish population-based EIMS cohort (2005–2015) (Hedström et al., 2009). The study population's general and clinical characteristics, including lifestyle factors, are presented in Table 1. Using targeted analysis, a total of 31 different compounds were analyzed. These compounds were chosen based on environmental relevance, commercial availability, and detectability in serum using liquid chromatography-mass spectrometry. The 24 targeted PFAS included common compounds from the most commonly studied PFAS classes. The OH-PCBs included predominant congeners in human blood, such as 4-OH-CB187 (Grimm et al., 2015). The compound mean concentration in this cohort has been previously reported in Supplementary Table S1 (Vaivade et al., 2025). Moreover, compound min and max concentrations and the 25-, 50-, and 75-percentile cutoffs are presented in Supplementary Table S1.

Table 1
Descriptive table of the cohort Epidemiological Investigations of Multiple Sclerosis (EIMS) from 2005 to 2015, n = 1,814. The cohort comprises people with multiple sclerosis (pwMS) and matched controls (MC), matched on sex, age, and residential area.

Characteristics	MC	pwMS
Sex (F/M)	678 (74.8 %)/229 (25.2 %)	678 (74.8 %)/229 (25.2 %)
Age (Mean ± SD, F/M)	41.0 ± 11.1/41.3 ± 11.2	39.9 ± 10.8/38.9 ± 10.7
BMI (Mean ± SD, F/M)	24.8 ± 4.6/25.9 ± 3.3	25.2 ± 5.2/25.1 ± 4.0
BMI at age of 20 (Mean ± SD, F/M)	21.7 ± 3.4/23.1 ± 2.9	22.3 ± 4.0/23.3 ± 3.2
Regular smoking (Nr. Yes/No/NA)	49/753/105	84/556/161
Irregular smoking (Nr. Yes/No/NA)	17/821/69	30/693 /78
Childbirths (Nr., Mean ± SD)	486, 1.5 ± 1.4	376, 1.3 ± 1.2
History of infectious mononucleosis (Nr. Yes/No/NA)	198/706/3	188/556/57
Sun exposure (Nr. High/Medium/Low)	288/357/262	187/297/317
Swedish born status (Nr. Yes/No/NA)	760/147/0	720/124/63
HLA-DRB1*15:01 (Nr. Yes/No/NA)	203/514/190	402/324/181
HLA-DRB1*13:03 (Nr. Yes/No/NA)	10/707/190	20/706/181
HLA-DRB*03:01 (Nr. Yes/No/NA)	141/576/190	156/570/181
HLA-DRB*08:01 (Nr. Yes/No/NA)	51/666/190	63/663/181
HLA-A*02:01 (Nr. Yes/No/NA)	425/292/190	289/437/181
HLA-B*44:02 (Nr. Yes/No/NA)	137/580/190	87/639/181

Table 2
Associations between single serum per- and polyfluoroalkyl substances (PFAS) and hydroxylated polychlorinated biphenyls (OH-PCBs) concentrations, and the odds of multiple sclerosis (MS). Odds ratios are calculated per doubling of serum substance concentrations.

Substance (ng/ml)	Continuous concentrations (log_2) OR (95 % CI)	*p-value*	*q-value*
PFHxS	1.011 (0.921–1.109)	0.823	0.933
PFHpS	1.09 (0.996–1.196)	0.064	0.272
PFOA	1.125 (0.988–1.255)	0.082	0.278
PFOS	1.103 (1.007–1.211)	**0.037**	0.209
FOSA	1.085 (0.97–1.212)	0.146	0.414
N-MeFOSAA	1.042 (0.951–1.143)	0.375	0.638
N-EtFOSAA	1.053 (0.965–1.15)	0.246	0.465
PFNA	1.062 (0.96–1.177)	0.246	0.465
PFDA	1.014 (0.919–1.119)	0.778	0.933
PFDS	0.968 (0.894–1.047)	0.419	0.648
PFUnA	1.028 (0.942–1.123)	0.531	0.752
PFDoA	1.007 (0.898–1.129)	0.907	0.964
PFTrDA	0.989 (0.932–1.049)	0.706	0.923
8:2 FTS	1.041 (0.979–1.106)	0.201	0.465
4-OH-CB187	1.085 (1.01–1.168)	**0.026**	0.209
3-OH-CB153	1.081 (1.029–1.137)	**2.26e-3**	**0.038**
4-OH-CB107	0.999 (0.937–1.064)	0.968	0.968

The model was adjusted for age, sex, BMI at sample collection, BMI at the age of 20, number of childbirths, regular smoking, irregular smoking, history of infectious mononucleosis, sun exposure, Swedish-born status, and residential area as well as the six alleles of interest; *DRB1*15:01*, *DRB1*13:03*, *DRB1*03:01*, *DRB1*08:01, A*02:01*, and *B*44:02*.
Statistical significance ($p < 0.05$) is indicated with bold.
q-value: the False Discovery Rate (FDR) correction was used.

3.1. Increased concentrations of two OH-PCBs and PFOS are associated with increased odds of MS

This study investigated the association between individual PFAS and OH-PCBs and the odds of MS, adjusting for lifestyle factors, and established HLA-associated risk and protective variants. Among the compounds analysed, 4-OH-CB187, 3-OH-CB153, and PFOS demonstrated a significant association with higher odds of MS. A doubling of serum 4-OH-CB187 concentrations increased the odds of MS by 8.5 % (OR = 1.085, 95 % CI: 1.01–1.168, p = 0.026), while 3-OH-CB153 increased the odds by 8.1 % (OR = 1.081, 95 % CI: 1.029–1.137, p = 2.26e-3). PFOS was also associated with a 10.3 % increase in MS odds (OR = 1.103, 95 % CI: 1.007–1.211, p = 0.037) (Table 2). After correcting for multiple comparisons, a significant q-value (q < 0.05) remained for 3-OH-CB153. The model estimates and likelihood ratio test p-values are presented in Supplementary Table S2. Similar results were obtained for the two OH-PCBs in the base model, however, the association did not remain significant after adjusting for multiple comparisons (Supplementary Table S3). Detailed model estimates and likelihood ratio test p-values are presented in Supplementary Table S4. Finally, two separate sensitivity analyses were performed: one with additional adjustments for the genetic principal components PC1 to PC5 to account for genetic ancestry and heritability, and another adjusting for allele count for *DRB1*15:01* and *A*02:01*. In both analyses, the associations of 4-OHCB187 and 3-OH-CB153 with increased MS odds remained, with PFOS showing similar trends (Supplementary Table S5-S8).

Moreover, we investigated the possibility of an interaction between PFAS and OH-PCB concentrations and the genes of interest in the context of MS odds. Perfluoroheptanesulfonic acid (PFHpS) and 4-OH-CB187 demonstrated a significant interaction with *DRB1*08:01* (p = 0.002) and *DRB1*03:01* (p = 0.043) status, respectively. However, after correcting for multiple comparisons they did not remain significant (Supplementary Table S9). These compounds association with odds of MS depending on *DRB1*08:01* and *DRB1*03:01* status are presented in Supplementary Table S10.

3.2. A nonlinear relationship between the odds of MS and exposure to PFAS and OH-PCB compounds

Moreover, to further investigate the possibility of a nonlinear relationship between PFAS and OH-PCBs exposure and the odds of MS, PFAS and OH-PCB concentrations were divided into quartiles. The quartiles of PFOS, 4-OH-CB187, and 3-OH-CB153 were also significantly associated with higher odds of MS. In the fully adjusted model, 4-OH-CB187 was associated with higher odds of MS in all quartiles compared to Q1. The second and third quartiles were associated with > 50 % increased MS odds compared to Q1 (Q2 vs Q1: OR = 1.561, 95 % CI: 1.061–2.302, p = 0.024, and Q3 vs Q1: OR = 1.526, 95 % CI: 1.024–2.281, p = 0.038), and Q4 was associated with a doubling of MS odds (OR = 2.31, 95 % CI: 1.494–3.591, p = 1.8e-4). Interestingly, for 3-OH-CB153 and PFOS, only Q4 was associated with a significant increase in MS odds (3-OH-CB153: OR = 2.001, 95 % CI: 1.257–3.207, p = 3.62e-3; PFOS: OR = 1.865, 95 % CI: 1.236–2.825, p = 3.1e-3). After adjusting for multiple comparisons, the significance (q < 0.05) of Q4 vs Q1 remained for all three compounds (Table 3).

Furthermore, new associations also emerged, among them, three PFAS compounds (perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluorododecanoic acid (PFDoA)) demonstrated a significant increase odds of MS when comparing Q2 vs Q1 (PFNA: OR = 1.753, 95 % CI: 1.2–2.569, and p = 3.82e-3; PFDA: OR = 1.507, 95 % CI: 1.036–2.197, and p = 0.032; PFDoA: OR = 1.605, 95 % CI: 1.091–2.349, and p = 0.015), while no associations were observed in the other quartile comparison. On the other hand, perfluorodecanesulfonic acid (PFDS) Q2 vs Q1 demonstrated a significant association with decreased odds of MS (OR = 0.509, 95 % CI: 0.298–0.885, and p = 0.012). PFHpS demonstrated a significant association with increased odds of MS in the Q3 vs Q1 comparison (OR = 1.494, 95 % CI: 1.013–2.109, and p = 0.043). Finally, PFOA exposure was associated with increased odds of MS across all quantiles (Q2 vs Q1: OR = 1.621, 95 % CI 1.097–2.402, and p = 0.016; Q3 vs Q1: OR = 1.56, 95 % CI: 1.045–2.335, and p = 0.03; Q4 vs Q1: OR = 1.677, 95 % CI: 1.098–2.572, and p = 0.017). However, after adjusting for multiple comparisons, none of the association with odds of MS remained significant (q < 0.05), though q-values were below 0.10 (Table 3). The model estimates and likelihood ratio test p-values are presented in Supplementary Table S11. Similar trends were also observed in the base model, adjusting for age, sex, BMI at sample

Table 3
Associations between single serum per- and polyfluoroalkyl substances (PFAS) and hydroxylated polychlorinated biphenyls (OH-PCBs) concentration quantiles, and the odds of multiple sclerosis (MS). Odds ratios are calculated per doubling of serum substance concentrations. Q1 is used as a reference.

Substance (ng/ml)	Q2 vs Q1			Q3 vs Q1			Q4 vs Q1		
	OR (95 % CI)	*p*-value	*q-value*	OR (95 % CI)	*p*-value	*q-value*	OR (95 % CI)	*p*-value	*q-value*
PFHxS	1.149 (0.783–1.686)	0.478	0.580	1.03 (0.691–1.468)	0.885	0.900	1.458 (0.933–2.288)	0.099	0.210
PFHpS	1.248 (0.854–1.828)	0.253	0.538	**1.494 (1.013–2.109)**	**0.043**	0.244	1.498 (0.974–2.311)	0.066	0.161
PFOA	**1.621 (1.097–2.402)**	**0.016**	0.066	**1.56 (1.045–2.335)**	**0.03**	0.244	**1.677 (1.098–2.572)**	**0.017**	0.073
PFOS	1.185 (0.805–1.745)	0.389	0.575	1.097 (0.743–1.622)	0.64	0.879	**1.865 (1.236–2.825)**	**3.1e-3**	**0.021**
FOSA	1.133 (0.773–1.661)	0.521	0.590	1.086 (0.742–1.588)	0.672	0.879	1.456 (0.981–2.167)	0.063	0.161
N-MeFOSAA	0.861 (0.588–1.259)	0.44	0.575	0.969 (0.662–1.418)	0.872	0.900	1.272 (0.867–1.867)	0.219	0.372
N-EtFOSAA	1.464 (0.958–2.244)	0.079	0.191	1.319 (0.856–2.033)	0.206	0.444	1.18 (0.768–1.814)	0.449	0.587
PFNA	**1.753 (1.2–2.569)**	**3.82e-3**	0.065	1.403 (0.956–2.064)	0.084	0.358	1.347 (0.902–2.015)	0.146	0.276
PFDA	**1.507 (1.036–2.197)**	**0.032**	0.092	1.323 (0.902–1.942)	0.152	0.431	1.249 (0.844–1.851)	0.266	0.392
PFDS	**0.509 (0.298–0.885)**	**0.012**	0.066	1.315 (0.785–2.215)	0.299	0.508	0.998 (0.592–1.673)	0.993	0.993
PFUnA	1.211 (0.83–1.766)	0.321	0.546	1.299 (0.886–1.909)	0.181	0.440	1.04 (0.694–1.558)	0.848	0.961
PFDoA	**1.605 (1.091–2.349)**	**0.015**	0.066	1.242 (0.846–1.826)	0.27	0.508	0.955 (0.64–1.427)	0.822	0.961
PFTrDA	0.926 (0.637–1.346)	0.688	0.691	0.932 (0.631–1.377)	0.725	0.880	0.803 (0.54–1.192)	0.277	0.392
8:2 FTS	1.165 (0.804–1.686)	0.419	0.575	1.156 (0.794–1.683)	0.449	0.694	1.395 (0.979–1.992)	0.066	0.161
4-OH-CB187	**1.561 (1.061–2.302)**	**0.024**	0.082	**1.526 (1.024–2.281)**	**0.038**	0.244	**2.31 (1.494–3.591)**	**1.8e-4**	**3.06e-3**
3-OH-CB153	0.904 (0.545–1.485)	0.691	0.691	1.445 (0.904–2.315)	0.124	0.422	**2.001 (1.257–3.207)**	**3.62e-3**	**0.021**
4-OH-CB107	0.801 (0.523–1.223)	0.306	0.546	0.972 (0.626–1.509)	0.9	0.9	1.025 (0.648–1.618)	0.914	0.971

The model was adjusted for age, sex, BMI at sample collection, BMI at the age of 20, number of childbirths, regular smoking, irregular smoking, history of infectious mononucleosis, sun exposure, Swedish-born status, and residential area as well as the six alleles of interest; *DRB1*15:01*, *DRB1*13:03*, *DRB1*03:01*, *DRB1*08:01*, *A*02:01*, and *B*44:02*.
q-value: the False Discovery Rate (FDR) correction was used.
Statistical significance ($p < 0.05$) is indicated with bold.

collection, and residential area (as a random effect) (Supplementary Table S12-S13), and model 1, which included lifestyle factors (Supplementary Tables S14-S15). Sensitivity analyses adjusting for genetic ancestry and heritability (PC1–PC5) and, separately for allele count yielded similar non-linear associations with MS odds (Supplementary Tables S16–S19). These non-linear associations between PFOS, 4-OH-CB187, and 3-OH-CB153 exposure and odds of MS have been illustrated in Fig. 1. Similar illustrations for the remaining PFAS and OH-PCBs are presented in Supplementary Fig. S2.

Further, we investigated the possibility of an interaction between individual PFAS and OH-PCB quartile concentrations and six HLA-alleles of interest. Nominal interaction effects were observed between PFDS and *DRB1*13:03* (p = 0.017), PFHpS and *DRB1*08:01* (p = 0.008) and *B*44:02* (p = 0.013), N-methylperfluoro-1-octanesulfonamido-acetic (N-MeFOSAA) and PFDoA and *A*02:01* (N-MeFOSAA; p = 0.046, and PFDoA; p = 0.006), however none remained significant after correcting for multiple comparisons (Supplementary Table S20). These compounds association with odds of MS depending on the interaction gene status are presented in Supplementary Tables S21-S24, with the exception of PFDS due to low number of *DRB1*13:03* carriers. Interestingly, PFOS significantly interacted with *B*44:02* (p = 4.48e-3), which remained significant (q < 0.05) after adjusting for multiple comparisons (Supplementary Table S20). Individuals with *B*44:02* demonstrated a significant increase in MS odds when comparing Q2 to Q1 (OR = 9.633, 95 % CI: 2.922–31.756 and p = 2e-4), Q3 to Q1 (OR = 5.314, 95 % CI: 1.734–16.283, and p = 0.004), and Q4 to Q1 (OR =

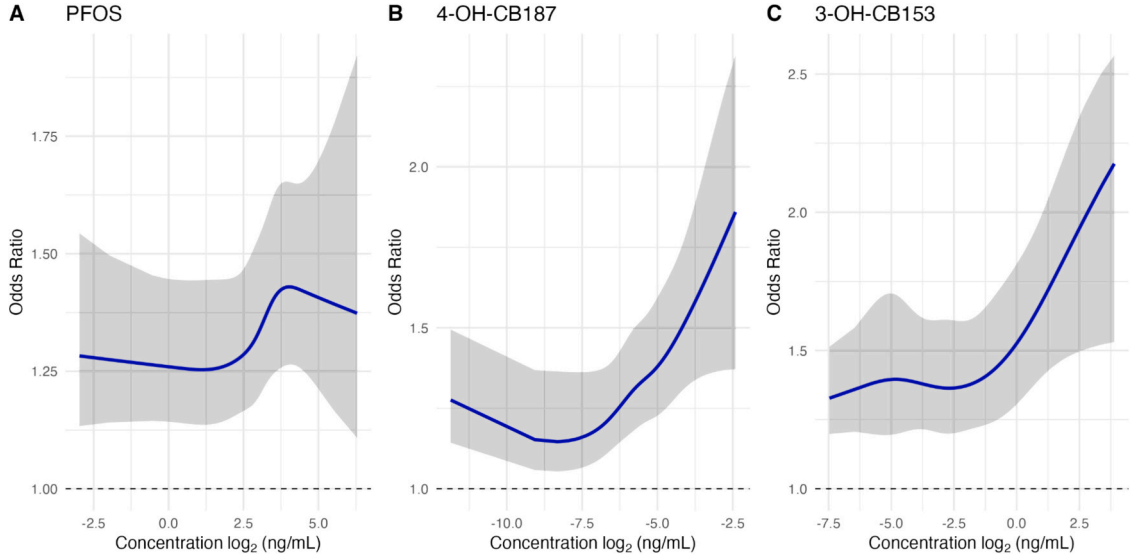

Fig. 1. Illustration of the non-linear association between PFAS and OH-PCB exposure and odds of MS. (A) PFOS, (B) 4-OH-CB187, and (C) 3-OH-CB153. The blue line demonstrates the mean association between compound concentrations and the odds of MS using restricted cubic splines, with the top 1% of exposure values excluded to minimize the influence of extreme observations. The gray area is the 95% confidence interval. All analyses have been performed on $\log_2$ concentrations adjusting for age, sex, BMI at sample collection, BMI at the age of 20, number of childbirths, regular smoking, irregular smoking, history of infectious mononucleosis, sun exposure, Swedish-born status, and residential area as well as the six alleles of interest; *DRB1*15:01*, *DRB1*13:03*, *DRB1*03:01*, *DRB1*08:01*, *A*02:01*, and *B*44:02*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.911, 95 % CI: 1.503–16.047, and p = 0.008). However, in individuals without *B*44:02* only Q4 vs Q1 demonstrated a significant association with increased MS odds (OR = 1.668, 95 % CI: 1.077–2.582, and p = 0.022) (Supplementary Table S25). Similar trends were also observed in the sensitivity analysis including the base model and MS-associated HLA-alleles (*DRB1*15:01*, *DRB1*13:03*, *DRB1*03:01*, *DRB1*08:01*, *A*02:01*, and *B*44:02*), however in individuals with *B*44:02* Q4 vs Q1 did not remain significant (Supplementary Table S26).

3.3. OH-PCBs and PFAS mixtures association with odds of MS

Exposure to these compounds often co-occurs; thus, to consider the effect of the co-exposure on the odds of MS, mixture analyses were performed using quantile g-computations. This type of analysis provides insight into the partial and cumulative dose–response relationship between exposure and health outcomes, relationships that are often obscured in single-compound models. Due to the differences between PFAS and OH-PCBs regarding use, exposure, associated health effects, and their chemical structures, these mixtures were analyzed separately. However, since exposure to PFAS and OH-PCBs co-occurs, the combined mixture effect was also considered. The combined PFAS and OH-PCB mixture demonstrated a significant association with increased odds of MS (Base model: OR = 1.179, 95 % CI: 1.106–1.257, and p = 3.91e-7, Model 1: OR = 1.236, 95 % CI: 1.092–1.4, and p = 7.93e-4; Model 2: OR = 1.306, 95 % CI: 1.095–1.558, and p = 2.94e-3) which remained after adjusting for multiple comparisons. Similar results were also observed for the PFAS mixture (Base model: OR = 1.156, 95 % CI: 1.118–1.195, and p = 2.06e-17, Model 1: OR = 1.157, 95 % CI: 1.091–1.228, and p = 1.06e-6; Model 2: OR = 1.158, 95 % CI: 1.065–1.26, and p = 6.34e-4) as well as the OH-PCB mixture (Base model: OR = 1.067, 95 % CI: 1.049–1.086, and p = 6.27e-13, Model 1: OR = 1.147, 95 % CI: 1.123–1.171, and p = 2.55e-38; Model 2: OR = 1.214, 95 % CI: 1.159–1.272, and p = 2.53e-16) separately. Moreover, sensitivity analyses including genetic ancestry and heritability (PC1 to PC5) and allele count, respectively, demonstrated similar trends (Supplementary Table S27-S28). Thus, demonstrating that exposure to OH-PCBs and PFAS are associated with higher odds of MS independent of lifestyle factors or HLA-alleles *DRB1*15:01*, *DRB1*13:03*, *DRB1*03:01*, *DRB1*08:01*, *A*02:01*, and *B*44:02* status (Fig. 2).

The relative contributions (weights) of the individual compounds in the mixture models are shown in Supplementary Fig. S3-S5. In brief, PFOS and N-ethylperfluoro-1-octanesulfonamidoacetic acid (N-EtFOSAA), along with the OH-PCBs 3-OH-CB153 and 4-OH-CB187 had the highest positive weights in the quantile g-computation model, indicating that increases in their concentrations were strongly associated with a higher MS odds. In contrast to the other OH-PCBs, 2,3,3′,4′,5-Pentachloro-4-biphenylol (4-OH-CB107) had a substantial negative weight, suggesting a protective association with MS odds.

4. Discussion

Increasing evidence points to a rise in the prevalence and incidence of autoimmune diseases (Wen and Li, 2023), with EDCs emerging as potential risk factors (Ehrlich et al., 2023). We have previously demonstrated an association between exposure to OH-PCBs, specifically 4-OH-CB187 and 3-OH-CB153, and increased odds of MS (Vaivade et al., 2025). In the present study, we further investigate the relationship between PFAS and OH-PCBs and odds of MS, evaluating individual compounds and mixtures, linear and non-linear relationships, and interactions with MS-associated HLA alleles. Our findings reveal significant non-linear associations between individual PFAS and OH-PCB compounds and MS odds. Notably, PFOS quartiles exhibited a significant interaction with the MS-protective HLA allele *B*44:02*, where each increase in PFOS quartile among carriers was associated with more than a fourfold higher odds of MS, whereas in non-carriers only the highest quartile was associated with 60 % higher odds. Finally, recognizing that individuals are typically exposed to multiple compounds simultaneously, we conducted a mixture analysis that revealed increased odds of MS, underscoring the importance of evaluating co-exposure scenarios in environmental health research.

Among the various health effects attributed to PFAS, immunomodulation, particularly immunosuppression, has been reported, as

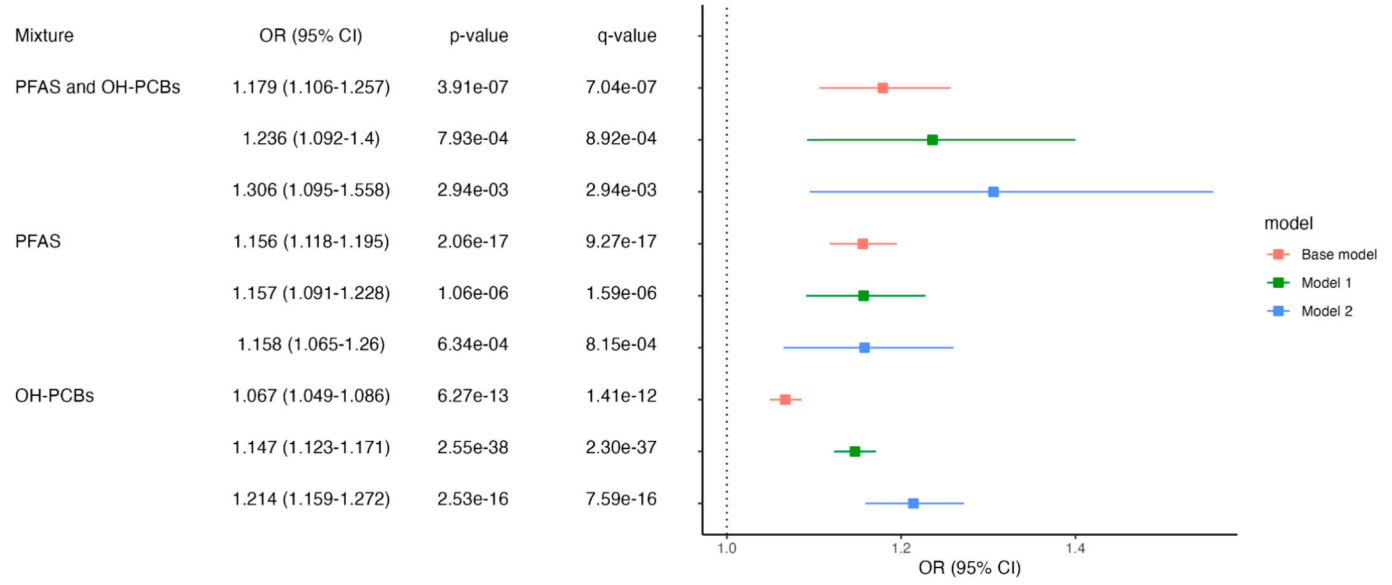

Fig. 2. Forestplot of compound mixture association with odds of MS. Odds ratios (OR), interpreted as the change in outcome odds for a one-quartile increase in the weighted exposure mixture, are reported with 95% confidence intervals (CI) and p-values calculated using quantile g-computations analysis. The p-value was adjusted using FDR. The base model (red) was adjusted for age, sex, BMI at the sample collection, and residential area. Model 1 (green) was adjusted for age, sex, BMI at sample collection, BMI at the age of 20, number of childbirths, regular smoking, irregular smoking, history of infectious mononucleosis, sun exposure, Swedish-born status, and residential area. Model 2 (blue) was adjusted for the same covariates as Model 1, as well as the six alleles of interest: *DRB1*15:01*, *DRB1*13:03*, *DRB1*03:01*, *DRB1*08:01*, *A*02:01*, and *B*44:02*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

evidenced by reduced antibody levels following vaccination in PFOA and PFOS exposed children (Ehrlich et al., 2023; von Holst et al., 2021). Moreover, in vitro and in vivo studies further demonstrate PFAS associated alterations in cytokine expression, induction of oxidative stress, modulation of nuclear receptors and Ca^{2+} signaling, and the suppression of the T cell-dependent antibody response (Ehrlich et al., 2023; Chang et al., 2016; National Toxicology Program, 2016). Likewise, PCB exposure has been associated with oxidative stress in rats, particularly in the cerebral cortex, hippocampus, and cerebellum, as well as in cultured nerve cells (Venkataraman et al., 2007; Venkataraman et al., 2008), with PCB 29 shown to induce concentration-dependent neuronal cell death in vivo (Idda et al., 2020).

Despite these biological effects, the role of PFAS and OH-PCBs in MS remain underexplored, and findings on the effect of EDCs across autoimmune diseases are generally inconsistent. In females, PFAS exposure has shown non-linear inverse associations with RA risk (Qiao et al., 2024), whereas PCB exposure demonstrated positive associations (Lee et al., 2007). Similarly, PFOA exposure has been linked to an increased risk of ulcerative colitis (Steenland et al., 2013), and long-term exposure to PCBs has been associated with increased mortality among females with systemic lupus erythematosus (Tsai et al., 2007; Huang et al., 2023), as well as increased levels of antinuclear antibodies (Dinse et al., 2022). However, limited research has specifically explored the relationship between EDC exposure and the risk of developing MS. Previous studies report either no associations between estimated past PFOA exposure and MS incidences (Steenland et al., 2013), or reduced PFOS concentrations in pwMS compared to controls, but no associations with known MS risk factors (Ammitzbøll, 2019). More recently, Mendelian randomization analysis has suggested a causal relationship between genetically predicted PFOS levels and increased MS risk (Liu et al., 2025). Our previous work observed a linear association between exposure to OH-PCBs (4-OH-CB187 and 3-OH-CB153) and increased odds of MS, whereas no significant associations were observed for individual PFAS compounds (Vaivade et al., 2025). In the current study, we extended this investigation to explore potential non-linear exposure–response relationships and gene-environment interactions involving HLA alleles associated with MS susceptibility. Individual OH-PCBs remained significantly associated with MS odds even after adjustment for lifestyle factors and HLA alleles, demonstrating non-linear patterns with the highest exposure levels corresponding to more than a twofold increase compared to the lowest. PFAS compounds exhibited more complex patterns, with several PFAS, including PFOS, showing significant non-linear associations with odds of MS. Such non-linear exposure–response patterns have also been reported for RA (Qiao et al., 2024), type 2 diabetes (Wang et al., 2025), and non-alcoholic fatty liver disease (Wu et al., 2024), among others.

Given that the average human is exposed to various EDCs simultaneously, evaluating how the combined exposure can influence health outcomes is crucial. While individual compounds may not display associations with disease risk, their co-exposure may have synergistic, antagonistic, or cumulative effects, as shown in vitro for PFAS mixtures depending on the species, exposure levels, ratios, and the specific composition of the mixture (Ojo et al., 2021; Wolf et al., 2014; Hu et al., 2014; Ding et al., 2013; Ojo et al., 2020). However, few studies have explored the health implications of EDC co-exposure in autoimmune diseases. Co-exposure to seven PFAS compounds has been associated with reduced RA risk, mainly in females (Qiao et al., 2024), and to lower prevalence of immune-mediated conditions, specifically allergies and eczema (Rudzanova et al., 2023). In contrast, our findings reveal a significant association between the co-exposure to PFAS and OH-PCBs and an increased odds of MS, independent of sex. Importantly, while most individual PFAS compounds did not exhibit significant associations on their own, their combined exposure was linked to a notable increase in MS odds. These findings highlight single-chemical risk assessment limitations and emphasize the importance of adopting mixture-based approaches that better reflect real-world exposure scenarios.

4.1. Gene-environment interaction between PFOS and HLA alleles in MS

Furthermore, gene-environment interactions have been previously observed in MS. The HLA system plays a dominant role among genetic factors, with both HLA class I and II molecules influencing MS susceptibility through distinct immunological pathways (Attfield et al., 2022; Hollenbach and Oksenberg, 2015). HLA class II alleles, specifically *HLA-DRB1*15:01*, are the strongest known genetic risk factors (International Multiple Sclerosis Genetics Consortium, 2011), promoting autoreactive $CD4^+$ T cell activation via presentation of extracellular antigens (Attfield et al., 2022; Kaskow and Baecher-Allan, 2018). Conversely, specific HLA class I alleles, such as *HLA-A*02:01* and *HLA-B*44:02*, appear protective by presenting intracellular antigens to $CD8^+$ T cell (Attfield et al., 2022). Environmental exposures like smoking, including passive smoking, have been shown to interact with *HLA-DRB1*15:01*, substantially increasing MS risk, and with *HLA-A*02:01*, with evidence also suggesting a three-way interaction (Hedström et al., 2021; Hedström et al., 2014; Hedström et al., 2017). Studies by Hedström et.al., also identified similar interactions involving organic solvents, alcohol consumption, and these HLA alleles (Hedström et al., 2018; Hedström et al., 2021).

This study observed a significant interaction between PFAS exposure, specifically PFOS, and the HLA class I alleles *HLA-B*44:02*. Although *HLA-B*44:02* has been described as protective, carriers exposed to higher PFOS levels exhibited a stronger association with increased odds of MS. While the mechanism remains unclear, PFAS may modulate immune function by affecting cytokine signaling, redox balance, or antigen processing pathways, thereby potentially influencing the repertoire of peptides presented by HLA molecules. In the context of *HLA-B*44:02*, such environmental modulation could alter the activation threshold of autoreactive $CD8^+$ T cells or affect regulatory cell function.

Recent Mendelian randomization analysis suggests a causal link between genetically predicted PFOS levels and increased MS risk, through effects on immune-regulatory genes and pathways such as PPAR signaling (Liu et al., 2025). Moreover, twin-cohort data show that PFOS serum levels are partially genetically determined, with monozygotic twins displaying lower within-pair variability than dizygotic twins, implicating nuclear receptor-related genes in the regulation of PFOS metabolism (Raza et al., 2025). These findings support the idea that genetic variation may influence both PFAS toxicokinetic and immune responsiveness.

Interestingly, Lundtoft et.al. demonstrated that the protective effects of HLA class I alleles was associated with increased expression of the interferon-α/β receptor subunit 2 in B and T cells. Paradoxically, this was linked to reduced type I interferon responsiveness, suggesting a non-classical mechanism of protection beyond antigen presentation (Lundtoft et al., 2020). Thus, PFOS exposure could interfere with these immune-regulatory processes and potentially weaken the allele's protective role against MS. However, the observed interactions between PFAS exposure and class I alleles are unexpected and challenging to explain, nevertheless they highlight the complexity of MS pathogenesis, wherein environmental contaminants may selectively modulate disease risk in genetically susceptible individuals.

4.2. Plausible mode of action of PFAS and OH-PCBs in MS pathogenesis

Exposure to EDCs has been associated with autoimmune response and systemic inflammation. However, the underlying mechanisms remain unclear due to the heterogeneity of both EDCs and autoimmune diseases. EDCs exert adverse effects on the endocrine system primarily by interacting with nuclear hormone receptors, which in turn can bind sex hormones, PPARs, and aromatic hydrocarbon receptors (AhR) (reviewed 2023) (Ehrlich et al., 2023; Huang et al., 2023).

PFAS have been suggested to modulate PPARs (reviewed 2023) (Ehrlich et al., 2023), which regulate immune response, lipid metabolism, and macrophage polarization, and T cell regulation and function, thereby influencing innate and adaptive immunity (Christofides

et al., 2021). In experimental autoimmune encephalomyelitis (EAE), a widely used MS mouse model, PPARδ deficiency leads to a more severe clinical course (Kanakasabai et al., 2011), likely due to impaired microglia-mediated neuroprotection (Doroshenko et al., 2021), whereas PPARγ agonists have demonstrated a potential in reducing new gadolinium-enhancing lesions in relapsing-remitting MS over a six-month period (Weinstein et al., 2017). Recent Mendelian randomization analysis supports a causal link between genetically predicted PFOS levels and increased MS risk, possibly acting through PPAR signaling pathways (Liu et al., 2025). Thus, PFAS exposure may contribute to MS pathophysiology through PPAR-mediated immune dysregulation. However, further studies are needed to establish causal relationships due to the complex interaction of these pathways and the structural variability of PFAS.

AhR, another immune regulator, influencing innate and adaptive immunity, including immune cell differentiation and activation (reviewed 2023) (Huang et al., 2023), has emerged as a potential target for EDCs. Many OH-PCBs are highly potent AhR activators, exceeding the effectiveness of their parent PCBs (Kamata et al., 2009). Activating AhR by EDCs can trigger nuclear factor kappaB (NF-κB), enhancing $CD4^+$ T cell activity and the production of proinflammatory cytokines, which may worsen autoimmune disease severity (Huang et al., 2023; Kobayashi et al., 2008; Quintana et al., 2008). However, the effect appears to be ligand-specific: for instance, 2,3,7,8-Tetrachlorodibenzo-p-dioxin has shown to induce regulatory T (Treg) differentiation, suppressing EAE (Quintana et al., 2008; Yang et al., 2016). This dual role suggests that while some AhR ligands may exert protective effects, others could worsen autoimmunity. Thus, it is plausible that OH-PCBs contribute to MS odds via AhR-mediated mechanisms, though further investigation is warranted.

NF-κB is a central transcription factor regulating immune and inflammatory response, and has been implicated in the pathogenesis of various autoimmune diseases (reviewed 2017) (Liu et al., 2017). Genome-wide association studies have implicated NF-κB signaling pathways in MS (Hussman et al., 2016), further supported by its role in EAE (reviewed 2013) (Mc Guire et al., 2013), where NF-κB promotes T helper 17 (Th17) differentiation (Chen et al., 2011) and function (Li et al., 2016). Most PFAS tested in vitro and in vivo have been shown to activate NF-κB signaling, however, contradictory effects have also been observed (reviewed 2023) (Ehrlich et al., 2023). Given the central role of NF-κB in both immune activation and inflammation, it presents a plausible pathway through which PFAS exposure could contribute to MS odds.

Both PFAS and OH-PCBs have also been shown to compromise blood–brain barrier integrity, facilitating the infiltration of peripheral immune cells into the CNS. In vivo and in vitro studies indicate that these compounds alter the expression of key tight junction proteins, thereby increasing paracellular permeability of the brain endothelial cells (Peixoto-Rodrigues, 2025; Eum et al., 2008; Seelbach et al., 2010; Wang et al., 2011; Yu et al., 2020). Additionally, both compound classes have been shown to induce oxidative stress, increasing reactive oxygen species production and impairing antioxidant defenses (reviewed 2025) (Peixoto-Rodrigues, 2025). These effects may contribute to the disruption of CNS immune privilege, allowing immune cells and inflammatory mediators to penetrate the CNS and damage myelin, thereby playing a role in MS pathogenesis.

The exposure to PFAS and OH-PCBs may thus contribute to the odds of MS through partly overlapping effects on immune regulation and neuroinflammation. Although these compound classes engage different upstream targets, PPARs for PFAS (Ehrlich et al., 2023; Christofides et al., 2021) and AhR for OH-PCBs (Kamata et al., 2009), they share similar downstream responses, including oxidative stress, activation of NF-κB-dependent inflammatory signaling, and disruption of tight-junction integrity at the blood–brain barrier (Ehrlich et al., 2023; Peixoto-Rodrigues, 2025). These processes can collectively disrupt cytokine balance, enhance pro-inflammatory Th17 activity, and weaken immune tolerance within the CNS. The mixture effect observed in this study may therefore reflect the simultaneous amplification of these shared pathways, rather than independent receptor-specific mechanisms. While current data suggest a potential link between EDC exposure and MS odds, the mechanisms are complex and context-dependent, warranting further mechanistic and epidemiological investigations.

4.3. Study limitations

The data in this study come from the Epidemiological Investigation of Multiple Sclerosis (EIMS) cohort, which was initially designed to assess the impact of environmental factors on MS. A key limitation of this study is the reliance on a single-time serum sample to infer long-term effects of PFAS and OH-PCB exposure. Additionally, samples were taken post-diagnosis, and analyses were conducted assuming that similar concentrations can be considered prior to diagnosis, given due to the long half-lives of PFAS and OH-PCBs. Although these compounds are highly persistent and have long biological half-lives, this does not fully address the potential for reverse causality, where disease processes or treatments could influence circulating compound concentrations. Moreover, MS development likely starts years before the first detectable symptoms and the clinical diagnosis (Bjornevik, 2020), thus there is a temporal misalignment between measurement timing and the etiologically relevant exposure window. Therefore, the impact of PFAS and OH-PCB exposure on odds of MS may only represent part of a more complex and prolonged disease process.

Moreover, only OH-PCBs were measured, as parent PCBs could not be analysed using the applied mass spectrometry method. Consequently, it is not possible to distinguish whether the observed associations are attributable to toxic effects unique to these metabolites, reflect underlying exposure to parent PCBs, or a combination of both. PCBs' toxicity has been suggested to partially arise from their hydroxylated metabolites, which exhibit toxic effects not observed in their parent compound (Tehrani and Van Aken, 2014). In addition, as a case–control study, causal inference cannot be drawn, and residual confounding from unmeasured factors, such as family history, comorbidities, diet, or socioeconomic conditions, cannot be excluded. The study population consisted predominantly of Swedish adults of European ancestry, which limits the generalizability of our findings to other populations. Finally, interaction analyses between HLA-allele and compound quartiles were constrained by limited statistical power, as approximately 20 % of the study population had missing data related to HLA alleles. HLA genotyping was performed prior to this study, and HLA data were not available for all participants. However, the missingness was random and unrelated to exposure or disease status.

5. Conclusion

This study investigated the association between exposure to PFAS and OH-PCBs with the odds of MS, considering both individual compounds and their combined effect, while adjusting for lifestyle factors and MS-associated HLA variants.

In conclusion, combined exposure to PFAS and OH-PCBs was significantly associated with an increased odds of MS. Given that individuals are typically exposed to multiple chemicals simultaneously, these findings underscore the importance of considering chemical mixtures in environmental risk assessments. Additionally, we found a non-linear association between individual PFAS and OH-PCB compounds, particularly PFOS, 4-OH-CB187, and 3-OH-CB153, and an increased odds of MS, independent of sex. Notably, PFOS quartiles showed a significant interaction with *HLA-B*44:02*, an MS-associated protective allele, increasing PFOS exposure was associated with more than a fourfold higher odds of MS, whereas in non-carriers only the highest exposure quartile was linked to a ~ 60 % increase compared to the lowest. These findings highlight the complex interplay between environmental exposures and genetic susceptibility in MS. However, further

studies are warranted to explore how PFAS and OH-PCBs contribute to the increased risk of MS.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT-5 to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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Author contributions

L.A. T.O., I.K. and A.K.H. conceptualized the EIMS cohort. The methods were developed by K.K., H.C., I.E., A.V., E.F., and P.E. A.A.G conducted the experimental analysis. A.V. implemented the methods and analysis. The results were interpreted by K.K., J.B., I.E., A.P.S, and A.V. The manuscript was written by A.V., A.P.S., I.E., J.S., H.C., T.Å., O. S., J.B., and K.K., and all the authors were involved in the review and editing process. All authors read and approved the final manuscript.

CRediT authorship contribution statement

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109993.

Data availability

Aggregated data are available upon reasonable request from the corresponding author (KK). Data are not public due to Swedish privacy laws and Ethics Committee restrictions.

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