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Original article

Air Pollution

Association between exposure to combustion-related air pollution and multiple sclerosis risk

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Abstract

Background: Smoking and occupational pulmonary irritants contribute to multiple sclerosis (MS) development. We aimed to study the association between ambient air pollution and MS risk and potential interaction with the human leukocyte antigen (HLA)-DRB1*15:01 allele.

Methods: Exposure to combustion-related air pollution was estimated as outdoor levels of nitrogen oxides (NO_x) at the participants' residence locations, by spatially resolved dispersion modelling for the years 1990–18. Using two population-based case-control studies (6635 cases, 8880 controls), NO_x levels were associated with MS risk by calculating odds ratios (OR) with 95% confidence intervals (CI) using logistic regression models. Interaction between high NOx levels and the HLA-DRB1*15:01 allele regarding MS risk was calculated by the attributable proportion due to interaction (AP). In addition, a register study was performed comprising all MS cases in Sweden who had received their diagnosis between 1993 and 2018 ($n = 22\,173$), with 10 controls per case randomly selected from the National Population register.

Results: Residential air pollution was associated with MS risk. NO_x levels (3-year average) exceeding the 90th percentile (24.6 $\mu g/m^3$) were associated with an OR of 1.37 (95% CI 1.10–1.76) compared with levels below the 25th percentile (5.9 $\mu g/m^3$), with a trend of increasing risk of MS with increasing levels of NO_x ($P < 0.0001$). A synergistic effect was observed between high NOx levels (exceeding the lower quartile among controls) and the HLA-DRB1*15:01 allele regarding MS risk (AP 0.26, 95% CI 0.13–0.29).

Conclusions: Our findings indicate that moderate levels of combustion-related ambient air pollution may play a role in MS development.

Key words: Multiple sclerosis, air pollution, nitrogen oxides, smoking, HLA-DRB1*15:01

Key Messages

- Combustion-related air pollution is associated with risk of developing multiple sclerosis (MS) in a dose-dependent manner.
- At the population level, 13% of the MS cases in Sweden are attributable to combustion as measured by high nitrogen oxide (NO_x) levels (>75th percentile).
- A synergistic effect occurs between high NO_x levels and the HLA-DRB1*15:01 allele regarding association with MS risk.

Introduction

Multiple sclerosis (MS) is characterized by multifocal inflammation, demyelination and axonal damage within the central nervous system (CNS), and is one of the foremost causes of non-traumatic neurological disability in young adults. Both genetic and environmental factors contribute to disease development.

Lung-irritating agents, such as smoking, passive smoking and exposure to organic solvents, have been associated with increased risk of the disease.[1–3] Genetic susceptibility to MS centres on the class II DRB1*15:01 allele of the human leukocyte antigen (HLA) complex.[4] A synergistic effect between this allele and the above-mentioned lung-irritating agents has repeatedly been demonstrated.[3,5,6] One hypothesis is that the pulmonary inflammation itself drives the increased risk of MS. Exposure to ambient air pollution may cause low-level pulmonary inflammation that may contribute to CNS pathology, but studies of air pollution and MS risk have been mainly uninformative.[7–10] Two were based on cohorts with very good outcome and confounder data, but with a very limited number of cases.[7,8] Others were registry-based with no individual confounder information.[9,10] The only study that had residential history during follow-up, detailed outcome and exposure assessment, and information on other environmental exposures and lifestyle habits, was the only study that showed a positive result, albeit based on few cases.[7] Using a large case-control study with detailed spatiotemporal exposure assessment, we aimed at studying the influence of nitric oxide (NO_x) as a measure of combustion-related ambient air pollution on the risk of MS. We also assessed potential synergistic effects between air pollution and the HLA-DRB1*15:01 allele that has been reported to interact with other lung-irritating agents regarding association with MS risk.

Methods

Main study

Design and study population

We used data from Epidemiological Investigation of Multiple Sclerosis (EIMS) and Genes and Environment in Multiple Sclerosis (GEMS), which are Swedish population-based, case-control studies. The target population was the Swedish general population aged 16–70 years.

EIMS recruited incident cases of MS from hospital-based and privately run neurology units. Cases were diagnosed according to the McDonald criteria[11,12] by local neurologists. Two controls per case were randomly selected from the national population register, matched for the case's age 5-year age strata, sex and region (one of 21 counties). The study period was April 2005 to December 2018.

GEMS identified prevalent cases fulfilling the McDonald criteria from the Swedish National MS registry. One control per case, matched by age, sex and region at the time of disease onset, was randomly selected from the national population register. The study participants were recruited between November 2009 and November 2011. GEMS cases did not overlap with cases in EIMS.

The EIMS and GEMS questionnaires on environmental exposures and lifestyle factors were similar, with most questions identically worded. The response rate was 93% for cases and 73% for controls in EIMS, and 82% for cases and 66% for controls in GEMS.

All participants in EIMS/GEMS were asked to provide blood samples for genetic analyses. For those who donated blood, *HLA-DRB1* and *HLA-A* alleles were determined using the MS single nucleotide polymorphism (SNP) genotype from the replication chip[13] followed by imputation of classical four-digit HLA alleles imputed with HLA*IMP :

02.[14] Subjects were categorized based on presence or absence of the HLA-DRB1-15:01 and HLA-A*02:01 alleles, respectively.

National register-based study

The analysis based on EIMS/GEMS was complemented with an analysis comprising all registered cases of MS in Sweden who had developed MS between 1993 and 2018. Cases from EIMS and GEMS were included, as well as all patients from the Swedish MS registry and from the in- and outpatient registers not participating in any of the case-control studies ($n = 22\,173$). For cases only registered in the in- or outpatient registry, the disease onset was estimated to have occurred 3 years prior to the first registration in the patient registry.

For each case, five controls were randomly selected from the national population register, matched by age at index in 5-year intervals and sex. Another five controls were randomly selected, additionally matched by region ($n = 21$).

For each participant in EIMS/GEMS and in the register study, information regarding ancestry, educational level and yearly income between 1990 and 2018 was retrieved from the National Board of Health and Welfare. For employees, information was also obtained regarding occupational socioeconomic status and line of work. These variables are presented in the Supplementary Material (available as Supplementary data at *IJE* online). The number of cases and controls in EIMS/GEMS as well as in both samples comprising the register study are presented in Table 1 and Supplementary Figure S1 (available as Supplementary data at *IJE* online).

Definition of exposure

For all participants (in EIMS/GEMS and in the register study), residential history between 1990 and 2018 was provided by the Swedish Tax Agency, and the geographical coordinates were used to estimate the annual exposure to combustion-related air pollution by the outdoor NO_x levels derived from a combination of chemical transport modelling at regional scale and Gaussian dispersion modelling at local scale. The emission inventory used for modelling at regional scale comes from the Nordic WelfAir project.[15] For local scale modelling, a complementary inventory was compiled where emissions from road traffic and major point sources were represented using a national bottom-up inventory for Sweden. A modelling concept was applied which avoids double-counting the local sources when adding contributions from regional and local scale (defined as contribution from emission sources within 15 km). Emissions from shipping, residential wood combustion (RWC) and 'other sources' (including emissions from mobile machinery and smaller power generators) were treated as area sources also in the local scale modelling. The spatial resolutions of the modelling grid at local scale were 100 × 100 m for road traffic; 200 × 200 m for RWC, shipping and large point sources, and 500 × 500 m for other sources. Dispersion modelling was carried out for the years 1990, 2000, 2011 and 2015. Figure 1 shows the modelled average concentration of NO_x (year 2015) over Sweden (left panel) and the three largest cities in Sweden: Stockholm, Gothenburg and Malmö (right panel).

For the years between the modelling years, concentrations were interpolated linearly to reflect gradual changes in emissions and subsequently adjusted using a ventilation factor that accounts for meteorological year-to-year variations. The contribution from long-range transport (including all sources at a distance >15 km) was estimated for each year using Chemical Transport Modelling at 5 × 5 km spatial resolution, with a semi-Lagrangean post-processing scheme to remove the contribution of local sources. The estimated total concentration of NO_x represents urban background and is comparable to measurements at roof level or at least ~50 m away from major roads. Enhanced concentrations in street canyons were not considered. The exposure assessment has been described in detail elsewhere.[16]

Table 1 Number of cases and controls included in EIMS/GEMS as well as in the two data samples comprising the national register-based study. Index between 1993 and 2018

EIMS/GEMS		Register-based study			
		Regional controls		National controls	
Cases	Controls	Cases	Controls	Cases	Controls
6725	8988	23 164	101 800	23 164	102 104
Place of residence identified during the 3-year period prior to the index year					
6635	8880	22 173	100 930	22 173	100 986

EIMS, Epidemiological Investigation of Multiple Sclerosis; GEMS, Genes and Environment in Multiple Sclerosis; Index, the year of clinical disease onset among cases, and the corresponding year among matched controls.

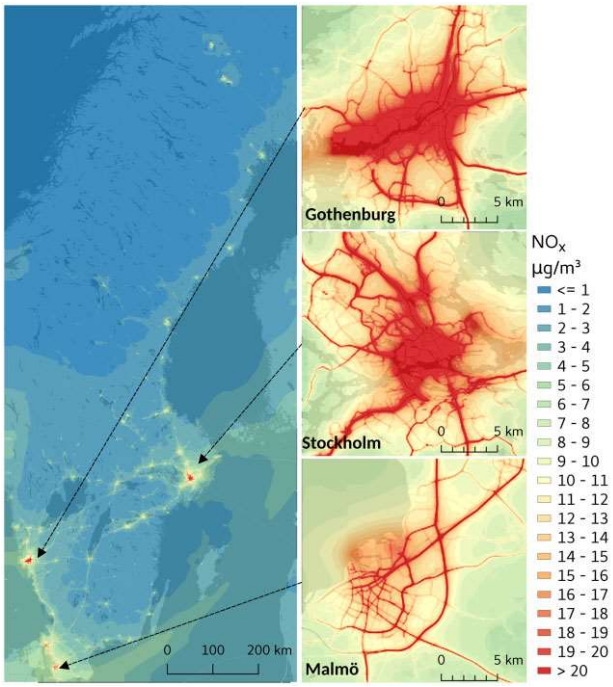

Figure 1 Average concentration of nitrogen oxides (year 2015) over Sweden (left panel) and the three largest cities in Sweden: Stockholm, Gothenburg, and Malmö (right panel). NO_x = nitrogen oxides

For the cases, the index year was defined as the year of clinical disease onset (when the first symptom appeared, leading to diagnosis). The controls were given the same index year as their corresponding case. The average level of NO_x during the 3 years prior to index was considered. Exposure below the lowest quartile among controls was considered as the reference.

Statistical analysis

Exposure to combustion-related air pollution was compared regarding MS occurrence by calculating odds ratios (OR) with 95% confidence intervals (CI) using logistic regression models.[17] The analysis was performed overall and stratified by sex. Our main focus was on NO_x from all sources, but traffic-related and RWC-related NO_x levels were also analysed separately. We also studied the association between NO_x and MS risk in consecutive 3-year intervals before the estimated index. Both conditional and unconditional logistic regression were performed. Only the results from the unconditional analyses are presented since these were almost identical to those from the conditional analyses but showed higher precision.

A trend test for a dose-response relationship regarding NO_x levels and occurrence of MS was performed by using a continuous variable in a logistic regression model. In order to illustrate the influence of increasing exposure to NO_x on risk of MS, we used polynomial regression of order 4 to fit the regression lines to the estimates of ORs. The proportion of cases attributable to high NO_x levels (>25th percentile) was calculated in percentage as an indicator of the impact of combustion-related air pollution on the occurrence of MS in the population. The formula ((OR-1)/OR)xf), where f is the proportion of exposed cases, was used.

Additive interaction, defined as departure from additivity of effects, was evaluated between high NO_x levels and the HLA-DRB1*15:01 allele by calculating the attributable proportion due to interaction (AP) with 95% CI.[18] The AP between two interacting factors reflects the joint effect beyond the sum of their independent effects. Presence of interaction between two causal factors implies that there exists a pathway towards disease where the presence of both risk factors is needed.

Our main results, based on data from EIMS and GEMS, were adjusted for study, age, sex, region, ancestry, sun exposure habits, adolescent body mass index (BMI), smoking and passive smoking. The interaction analysis was also adjusted for HLA-A*02:01. The HLA- A*02:01 allele has a protective effect against MS, and the influence of the HLA-DRB1*15:01 allele becomes more pronounced in its absence due to interaction between these alleles.[4]

The following potential confounding variables were not kept in the final analyses since they had minor influence on the results (<1% change of the OR): educational level, income level, MS heredity, a diagnosis of asthma, EBNA-1 antibody levels, infectious mononucleosis and alcohol consumption. The register study, based on two data samples, was adjusted for the matching variables and ancestry. Definitions of the variables are provided in Supplement 1, available as Supplementary data at *IJE* online.

We performed several supplementary analyses. Since the exposure to air pollution is linked to several neighbourhood-level characteristics in some countries, we stratified the analyses by educational level and income level. Among employees, the analysis was performed adjusted for occupational socioeconomic status and line of work (52% of the cases and 48% of the controls). We also performed the analysis restricted to those who reported no history of infectious mononucleosis (IM). Finally, we performed our main analysis adjusted for number of pack-years (20 cigarettes daily for 1 year) before index. All analyses were conducted using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Residential history in the 3-year period preceding index could be retrieved for 98% of cases and controls derived from EIMS and GEMS, and for 96% and 99% for cases and controls, respectively, in the register study (Table 1). Characteristics of cases and controls in each dataset are presented in Table 2.

Table 2 Characteristics of cases and controls in EIMS/GEMS and in the two data samples comprising the validation study

	Total		NOx exposure < 25th percentile		NOx exposure > 25th percentile	
EIMS/GEMS	Cases	Controls	Cases	Controls	Cases	Controls
N	6635	8880	1581	2208	5054	6672
Women, *n* (%)	4840 (73)	6378 (72)	1172 (74)	1598 (72)	3368 (73)	4780 (72)
Men, *n* (%)	1795 (27)	2502 (28)	409 (26)	610 (28)	1386 (27)	1892 (28)
Swedish, *n* (%)	5170 (78)	6670 (75)	1352 (86)	1844 (84)	3818 (76)	4826 (72)
University studies, *n* (%)	2515 (41)	3535 (43)	456 (32)	696 (35)	2059 (43)	2839 (46)
MS heredity, *n* (%)	1284 (20)	471 (5.4)	353 (23)	130 (6.1)	931 (19)	341 (5.2)
Smoking, *n* (%)	3504 (53)	3853 (44)	769 (49)	896 (41)	2735 (54)	2957 (44)
Exposure to passive smoking, *n* (%)	3465 (52)	3710 (42)	789 (50)	1016 (46)	2676 (53)	3269 (49)
Snuff use, *n* (%)	1006 (16)	1405 (16)	303 (20)	439 (20)	703 (15)	966 (15)
Alcohol, gram/week (SD)	49 (65)	53 (74)	42 (64)	46 (65)	51 (66)	55 (76)
Mean sun exposure (SD)	5.9 (1.8)	6.3 (1.9)	5.6 (1.7)	5.9 (1.8)	6.0 (1.8)	6.4 (1.9)
Mean body mass index, kg/m (SD)	22.4 (3.9)	22.0 (3.5)	22.9 (4.2)	22.4 (4.1)	22.3 (3.8)	21.8 (3.3)
A diagnosis of asthma, *n* (%)	758 (12)	1137 (13)	193 (13)	300 (14)	565 (11)	837 (13)
Infectious mononucleosis, *n* (%)	1057 (16)	845 (9.7)	240 (16)	202 (9.4)	817 (16)	643 (9.8)
Age at disease onset (SD)	35.2 (10.9)		37.0 (11.3)		34.6 (10.6)	
	Total		NO_x exposure < 25th percentile		NO_x exposure ≥ 25th percentile	
Register-based study, regional controls	Cases	Controls	Cases	Controls	Cases	Controls
N	22 173	100 930	5507	25 292	16 666	75 638
Women, *n* (%)	15 364 (69)	69 763 (69)	3796 (69)	17 209 (68)	11 568 (69)	52 554 (69)
Men, *n* (%)	6809 (31)	31 167 (31)	1711(31)	8083 (32)	5098 (31)	23 084 (31)
Swedish, *n* (%)	15 849 (71)	67 360 (67)	4390 (80)	19 127 (76)	11 459 (69)	48 233 (64)
Post-secondary education,[a] *n* (%)	5790 (26)	26 512 (26)	1115 (20)	5072 (20)	4675 (28)	21 440 (28)
Age at disease onset (SD)	43.9 (15.9)		44.9 (14.9)		42.5 (15.3)	
	Total		NO_x exposure < 25th percentile		NO_x exposure ≥ 25th percentile	
Register-based study, national controls	Cases	Controls	Cases	Controls	Cases	Controls
N	22 173	100 986	5628	25 258	16 545	75 728
Women, *n* (%)	15 364 (69)	69 817 (69)	3882 (69)	17 155 (68)	11 482 (69)	52 662 (70)
Men, *n* (%)	6809 (31)	31 169 (31)	1746 (31)	8103 (32)	5063 (31)	23 066 (30)
Swedish, *n* (%)	15 849 (71)	67 018 (66)	4487 (80)	18 952 (75)	11 362 (69)	48 066 (63)
Post-secondary education,[a] *n* (%)	5790 (26)	26 658 (26)	1144 (20)	5011 (20)	4646 (28)	21 647 (29)
Age at disease onset (SD)	43.9 (15.9)		45.9 (15.2)		43.2 (16.0)	

EIMS, Epidemiological Investigation of Multiple Sclerosis; GEMS, Genes and Environment in Multiple Sclerosis; NO_x, nitrogen oxides ($\mu g/m^3$); MS, multiple sclerosis; SD, standard deviation.

[a]2 years or longer.

Based on the EIMS and GEMS combined (6635 cases and 8880 controls), an association was observed between residential NO_x levels and risk of MS. An average level of NO_x from all sources exceeding the 90th percentile (24.6 $\mu g/m^3$) was associated with an OR of 1.37 (95% CI 1.20–1.57) compared with NO_x levels below the 25th percentile (5.9 $\mu g/m^3$) (Table 3). Trends showed increasing risk of MS with increasing levels of NO_x (OR 1.03, 95% CI 1.02–1.05, per 10 $\mu g/m^3$) (Supplementary Figure S2, available as Supplementary data at *IJE* online). When we studied the association between NO_x and MS risk in consecutive 3-year intervals before the estimated index, it was more pronounced in the interval closest to index than in preceding intervals (Supplementary Table S1, available as Supplementary data at *IJE* online). As with other lung-irritating agents, the association was stronger among men than among women (Table 3). Approximately 13% of the cases in the population could be attributable to high NO_x levels (≥25th percentile) (OR being 1.2, 95% CI 1.10–1.31) (not in Table).

Table 3 Odds ratios (OR) with 95% confidence intervals (CI) of multiple sclerosis for different quantiles of outdoor combustion-related air pollution (as NO_x; $\mu g/m^3$)

Total				
NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[b]	OR (95% CI)[c]	*P* for trend
<25% (<5.92)	1581/2208	1.0 (reference)	1.0 (reference)	
25–50% (5.92–9.93)	1733/2231	1.14 (1.03–1.26)	1.16 (1.06–1.28)	
50–75% (9.93–16.42)	1653/2228	1.14 (1.03–1.27)	1.19 (1.07–1.32)	
75–90% (16.42–24.6)	979/1326	1.17 (1.04–1.32	1.23 (1.09–1.39)	
>90% (>24.58)	689/887	1.26 (1.10–1.43)	1.37 (1.20–1.57)	<0.0001
Women				
NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[d]	OR (95% CI)[e]	*P* for trend
<25% (<5.92)	1172/1598	1.0 (reference)	1.0 (reference)	
25–50% (5.92–9.93)	1292/1605	1.16 (1.04–1.30)	1.17 (1.05–1.31)	
50–75% (9.93–16.42)	1168/1597	1.10 (0.98–1.24)	1.14 (1.01–1.28)	
75–90% (16.42–24.6)	710/934	1.19 (1.03–1.36)	1.23 (1.07–1.42)	
>90% (>24.58)	499/644	1.22 (1.05–1.43)	1.32 (1.13–1.54)	0.0007
Men				
NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[d]	OR (95% CI)[e]	*P* for trend
<25% (<5.92)	409/610	1.0 (reference)	1.0 (reference)	
25–50% (5.92–9.93)	442/626	1.09 (0.90–1.32)	1.15 (0.95–1.39)	
50–75% (9.93–16.42)	485/631	1.22 (1.02–1.52)	1.32 (1.09–1.64)	
75–90% (16.42–24.6)	269/392	1.15 (0.90–1.43)	1.26 ()0.98–1.57	
>90% (>24.58)	190/243	1.34 (1.03–1.73)	1.52 (1.17–1.97)	0.002

NO_x, nitrogen oxides ($\mu g/m^3$); ca/co, cases/controls; index, the year of clinical disease onset among cases, and the corresponding year among matched controls.
[a]Average level of NO_x from all sources during the 3 years prior to index.
[b]Adjusted for study, age, sex and region.
[c]Adjusted for study, age, sex, region, ancestry, smoking, passive smoking, sun exposure and adolescent body mass index.
[d]Adjusted for study, age and region.
[e]Adjusted for study, age, region, ancestry, smoking, passive smoking, sun exposure and adolescent body mass index.

There was a correlation between traffic-related and RWC-related NO_x levels ($r = 0.34$, $P < 0.0001$). The risk of MS increased with increasing levels of NO_x regardless of its source (Supplementary Tables S2 and S3, available as Supplementary data at *IJE* online). We observed trends showing increasing MS risk with increasing traffic-related and RWC-related NO_x levels, respectively. When run in the same model, both trends remained significant ($P = 0.01$ and 0.002, respectively).

NO_x levels exceeding the lower quartile among controls were associated with increased risk of MS among both ever and never smokers, but more pronounced among never smokers ($P < 0.0001$) (Table 4). Trends were observed between MS risk and NO_x levels both among ever smokers ($P = 0.02$) and never smokers ($P = 0.0004$).

A synergistic effect was observed between high NO_x levels (exceeding the lower quartile among controls) and presence of the HLA-DRB1*15:01 allele regarding MS risk (AP 0.26, 95% CI 0.13–0.29) (Table 5). The interaction remained similar when the analysis was restricted to include subjects of Swedish origin.

Our finding of a dose-dependent association between residential NO_x levels and risk of MS was replicated in the register study comprising all registered patients in Sweden who had developed MS between 1993 and 2018 ($n = 22\,173$) and up to 10 matched controls per case (Table 6). Both total NO_x levels as well as traffic-related and RWC-related NO_x levels were associated with MS risk (Supplementary Tables S3 and S4, available as Supplementary data at *IJE* online), with a trend showing increased risk of MS with increasing NO_x levels ($P < 0.0001$). The association was more pronounced among men than among women (Table 6).

Supplementary analyses

There was a positive correlation between educational level and air pollution ($r = 0.15$, $P < 0.0001$). The risk of MS

Table 4 Odds ratios (OR) with 95% confidence intervals (CI) of multiple sclerosis for different quantiles of outdoor combustion-related air pollution (as NO_x; $\mu g/m^3$), stratified by smoking habits

	Ever smokers (with/without exposure to passive smoking)		Never smokers (without exposure to passive smoking)	
NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[b]	ca/co	OR (95% CI)[b]
<25% (<5.92)	769/896	1.0 (reference)	466/681	1.0 (reference)
25–50% (5.92–9.93)	920/934	1.18 (1.02–1.36)	461/594	1.31 (1.08–1.58)
50–75% (9.93–16.42)	866/970	1.17 (1.01–1.36)	431/593	1.37 (1.11–1.68)
75–90% (16.42–24.6)	559/595	1.27 (1.08–1.52)	229/340	1.39 (1.08–1.78)
>90% (>24.58)	390/458	1.23 (1.02–1.48)	156/196	1.81 (1.36–2.40)
P for trend		0.02		0.0004

NO_x, nitrogen oxides ($\mu g/m^3$); ca/co, cases/controls; index, the year of clinical disease onset among cases, and the corresponding year among matched controls.
[a]Average level of NO_x from all sources during the 3 years prior to index.
[b]Adjusted for study, age, sex, region, ancestry, sun exposure and adolescent body mass index.

Table 5 Odds ratios (OR) with 95% confidence intervals (CI) of multiple sclerosis for different quantiles of outdoor combustion-related air pollution (as NO_x; $\mu g/m^3$), by DRB1*15:01 status

NOx level[a]	DRB1*15:01	ca/co	OR (95% CI)[b]	OR (95% CI)[c]	AP (95% CI)
Low (<5.92)	–	459/739	1.0 (reference)	1.0 (reference)	
High (≥5.92)	–	1666/2430	1.12 (0.97–1.29)	1.48 (1.24–1.76)	
Low (<5.92)	+	570/318	2.98 (2.48–3.58)	3.00 (2.40–3.71)	
High (≥5.92)	+	1993/935	3.64 (3.01–4.21)	4.91 (4.08–5.91)	0.26 (0.13–0.39)

NO_x, nitrogen oxides ($\mu g/m^3$); ca/co, cases/controls; index, the year of clinical disease onset among cases, and the corresponding year among matched controls; AP, attributable proportion due to interaction; DRB1, allele of the human leukocyte antigen complex.
[a]Average level of NO_x from all sources during the 3 years prior to index; high NO_x level was defined as a value in the three upper quartiles among controls.
[b]Adjusted for study, age, sex and region.
[c]Adjusted for study, age, sex, region, ancestry, smoking, passive smoking, sun exposure and adolescent body mass index.

associated with NO_x exposure remained increased in all exposure groups compared with the reference group after stratification by educational level. Comparing the highest exposure group (>90%) with the reference group (<25%) rendered OR 1.48 (95% CI 0.95–2.33) among those with compulsory school, OR 1.38 (95% CI 1.01–1.90) among those with upper secondary school for 2 years, OR 1.36 (95% CI 1.02–1.82) among those with upper secondary school for 3 years or longer and OR 1.31 (95% CI 1.06–1.60) among those with post-secondary education.

There was also a weak positive correlation between air pollution exposure and both family income ($r = 0.04$, $P < 0.0001$) and individual income ($r = 0.02$, $P = 0.02$). Family income during the 3-year period before index was categorized into quartiles based on control distribution. Comparing the highest NO_x exposure group with the reference group, stratification by income level rendered OR 1.29 (95% CI 0.99–1.74) among those with lowest income, OR 1.39 (95% CI 1.02–1.90) among those in the second quartile, OR 1.37 (95% CI 1.04–1.80) among those in the third quartile and OR 1.31 (95% CI 1.00–1.67) among those with highest income.

Among employees, the association between NO_x exposure and MS risk was similar to that of those who were not employed (data not shown). After adjustment for occupational socioeconomic status and line of work, the OR of MS in the highest NO_x exposure group was 1.35 (95% CI 1.12–1.63), compared with the reference group.

Our results remained similar when we restricted the analysis to include only participants with no history of IM (data not shown). Our results also remained similar when we further adjusted our main analysis for number of pack-years of smoking before index (Supplementary Table S4). When cumulative NO_x exposure and number of pack-years were run as continuous variables in the same logistic regression model, both were significant ($P < 0.0001$ and $P = 0.0002$, respectively).

Discussion

Our analyses revealed a dose-dependent association between 3-year average NO_x levels and risk of MS. We also observed a synergistic effect between NO_x levels and presence of the HLA-DRB1*15:01 allele, supporting the

Table 6 Odds ratios (OR) with 95% confidence intervals (CI) of multiple sclerosis for different quantiles of outdoor combustion-related air pollution (as NO_x; $\mu g/m^3$), overall and stratified by sex

Register–based study, regional controls			Register–based study, national controls		
Total			Total		
NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[b]	NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[c]
<25% (<5.16)	5507/25 292	1.0 (reference)	<25% (<5.23)	5628/25 258	1.0 (reference)
25–50% (5.16–8.43)	5401/25 164	1.01 (0.98–1.05)	25–50% (5.23–8.43)	5418/25 223	1.00 (0.96–1.03)
50–75% (8.43–14.41)	5594/25 215	1.06 (1.02–1.11)	50–75% (8.43–14.43)	5469/25 266	1.01 (0.98–1.06)
75–90% (14.41–22.48)	3414/15 184	1.10 (1.05–1.15)	75–90% (43.43–22.34)	3355/15 128	1.06 (1.01–1.11)
>90% (>22.48)	2257/10 075	1.10 (1.04–1.15)	>90% (>22.34)	2303/10 109	1.08 (1.03–1.14)
Women			Women		
NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[d]	NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[e]
<25% (<5.16)	3796/17 209	1.0 (reference)	<25% (<5.23)	3882/17 155	1.0 (reference)
25–50% (5.16–8.43)	3756/17 304	1.01 (0.96–1.06)	25–50% (5.23–8.43)	3765/17 368	0.98 (0.93–1.03)
50–75% (8.43–14.41)	3858/17 537	1.04 (0.99–1.10)	50–75% (8.43–14.43)	3772/17 540	1.00 (0.96–1.05)
75–90% (14.41–22.48)	2376/10 641	1.08 (1.02–1.14)	75–90% (43.43–22.34)	2337/10 625	1.04 (1.00–1.10)
>90% (>22.48)	1578/7072	1.08 (1.01–1.15)	>90% (>22.34)	1608/7129	1.06 (1.01–1.13)
Men			Men		
NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[d]	NO_x level, quantile (values)[a]	ca/co	OR (95% CI)[e]
<25% (<5.16)	1711/8083	1.0 (reference)	<25% (<5.23)	1746/8103	1.0 (reference)
25–50% (5.16–8.43)	1645/7860	1.01 (0.93–1.08)	25–50% (5.23–8.43)	1653/7856	1.00 (0.93–1.07)
50–75% (8.43–14.41)	1736/7678	1.10 (1.03–1.19)	50–75% (8.43–14.43)	1697/7727	1.05 (0.99–1.13)
75–90% (14.41–22.48)	1038/4543	1.13 (1.04–1.24)	75–90% (43.43–22.34)	1018/4503	1.10 (1.02–1.19)
>90% (>22.48)	679/3003	1.12 (1.01–1.23)	>90% (>22.34)	695/2980	1.13 (1.04–1.24)

NO_x, nitrogen oxides ($\mu g/m^3$); ca/co, cases/controls; index, the year of clinical disease onset among cases, and the corresponding year among matched controls.
[a]average level of NO_x from all sources during the 3 years prior to index.
[b]Adjusted for age, sex, region and ancestry.
[c]Adjusted for age, sex and ancestry.
[d]Adjusted for age, region and ancestry.
[e]Adjusted for age and ancestry.

hypothesis that low-level pulmonary inflammation plays an important role in MS development.

The association with residential outdoor pollution was more pronounced among never smokers who had never been exposed to passive smoking than among ever smokers. It is possible that the impact of exposure to ambient air pollution becomes less evident among those exposed to cigarette smoke, which contains high levels of similar particulates, vapours and gases.[19]

The association between NO_x and MS risk was most pronounced in the 3-year interval closest to index than in preceding 3-year intervals. This may indicate that current exposure is more important than previous exposure. Similarly, the impact of smoking on MS risk is more pronounced among current smokers than among past smokers, and the risk associated with smoking slowly abates after smoking cessation.[20]

Air pollution, including particulate matter and a mixture of gases such as NO_x, has been associated with a range of respiratory effects[21] and has been linked with numerous diseases, such as pulmonary, cardiovascular and neurological diseases.[22] Mechanisms linking air pollution exposure to MS may include local pulmonary inflammation, increased permeability of the epithelial wall and oxidative stress that leads to the release of pro-inflammatory cytokines and systemic inflammation.[23,24] Air pollution may also trigger epigenetic changes, resulting in increased production of pro-inflammatory cytokines.[25]

The local inflammation in the lungs stimulates immune responses which may activate potentially autoreactive T cells and allow them to enter the CNS.[26] Moreover, high levels of air pollution may induce disruption of the blood-brain barrier,[27] which has been suggested as an important component in air pollution-induced neuro-inflammation

and neurodegeneration.[28,29] Air pollutants might also reach the CNS by crossing the blood-brain barrier through the olfactory system.[30]

Air pollution also acts as an atmospheric filter for ultraviolet light and could reduce the cutaneous synthesis of vitamin D.[31] An association has been reported between high levels of air pollution and deficiency in vitamin D.[32] However, Swedish air quality is rather good from an international perspective. Furthermore, our results of an association between NO_x and MS risk remained significant after adjustment for sun exposure habits.

Numerous studies have investigated the relationship of MS with the gut microbiome, and the gut microbiota has emerged as a potential factor associated with the pathobiology of the disease.[33] Animal and human studies suggest that components of air pollution such as NO_x may contribute to alterations of the gut microbiota, which in turn may alter gut physiology including immune responses, metabolism and intestinal permeability.[34,35] However, international large-scale studies would be needed to better understand the role of the gut microbiome in CNS inflammation.

An interaction on the additive scale has repeatedly been observed between the HLAl-DRB1*15:01 allele and several lung-irritating agents regarding risk of developing MS.[3,5,6] However, the exact mechanisms behind the interaction remain speculative. HLA molecules are involved in regulating thymic selection of the mature T cell repertoire. By central tolerance mechanisms, potentially auto-aggressive T cells with a propensity to recognize CNS auto-antigens may to a higher degree survive in HLA-DRB1*15:01-positive subjects. The lungs hold potentially auto-aggressive T cells that may become activated by chronic pulmonary inflammation and enter the CNS after assuming migratory properties.[26] The local inflammation may also induce post-translational modifications of peptides which could promote a CNS-directed autoimmune response in genetically predisposed individuals. Epigenetic modifications induced by exposure to air pollution may further contribute to mediate the interaction between air pollutants and HLA alleles in MS development.[25]

The strengths of our study include its population-based design, the large number of cases and controls, the possibility to adjust for a large number of potential confounding variables, the availability of genetic data for a large proportion of the participants and the high spatial resolution at which NO_x levels were estimated.

Although we were able to adjust for several potential confounding factors, there may exist neighbourhood-level characteristics linked to air pollution which we did not adjust for. We observed a positive correlation between educational level and NO_x exposure, which is probably explained by the fact that the prevalence of highly educated individuals is higher in the larger cities in Sweden than in the smaller ones.[36] Similarly, we observed a weak positive correlation between income level and NO_x exposure. However, our findings remained similar after stratification for educational level and family income level.

Combustion-related air pollution is a complex mixture of both gases and particulates, and our results should not be interpreted as pertaining to NO_x per se, but rather to combustion-related air pollution as a whole. Whereas NO_x is generally considered to be a good representative of this mixture, the relation between NO_x and other components will differ for different sources and with temperature.[37] In this perspective, it is interesting to note that in our study the upper quantiles of NO_x from RWC seemed to entail a similar risk as the upper quantiles of NO_x from other sources. An advantage of NO_x as an indicator instead of the today more common $PM_{2.5}$ (particulate matter with a diameter <2.5 μm) is that it focuses more directly on combustion, having fewer other sources. It should be noted that since the lifetime of NO_x in the atmosphere is limited to a day or two, the long-distance range contribution is less pronounced.

The use of outdoor residential levels is very appropriate from a public health point of view, as these may be related directly to environmental standards. In the pursuit of disease aetiology, however, they are far from optimal, as they do not consider the fact that in a temperate climate as in Sweden most of the time is spent indoors, and that the penetration probabilities of components of air pollutant into the indoor environment will differ between components, between buildings and because of individual habits.[38] Exposure at school or work as well as in transport is further not considered. In a previous study from Stockholm, we observed that spatial differences in outdoor residential levels of NO_2 explained 20% of the variation in individually measured levels.[39] In spite of these shortcomings, a great number of studies using similar exposure assessment have successfully associated low levels of long-term air pollution exposure with a range of health effects, both in Sweden[40–42] and internationally.[43,44]

Neurologist-verified MS diagnosis and year of disease onset were not available for cases identified only through the patient registers, which may have contributed to why we observed a weaker association between NO_x levels and MS risk than in our main study.

EIMS recruited newly diagnosed cases to minimize recall bias. The potential for recall bias is higher in GEMS which used prevalent cases, but the magnitude of memory errors related to place of residency—and consequently to air pollution levels—does probably not differ between cases and controls.

Our register study included all registered cases of MS in Sweden diagnosed between 1993 and 2018, minimizing selection bias. Information regarding NO_x levels was missing only for a minor proportion of the subjects. Selection bias may be greater in EIMS/GEMS. However, there were no differences with respect to age, sex ratio, ancestry, educational level or NO_x levels between cases in Sweden who were included in EIMS/GEMS and those who were not.

The participation rate was lower among controls than among cases in EIMS/GEMS. However, educational level and socioeconomic status were consistent between the controls in EIMS/GEMS, the register study and the general population.[45] The prevalence of lifestyle factors, such as smoking, among the controls in EIMS/GEMS was also consistent with that of the general population.[45] Furthermore, there were no differences with respect to age, sex or smoking habits between those who donated blood and those who did not. We thus believe that our findings are not affected by selection bias to a large extent.

Air pollution is one of the major public health concerns. At the population level, 13% of all cases in Sweden could be attributable to high NO_x levels ($\geq$25th percentile). Although combustion-related emissions have been decreasing in many areas,[46] they remain major contributors to current air pollution, and the annual air quality standard for NO_2 is still exceeded at many European monitoring stations.[47] Globally, the combustion-related emissions and the source contribution profiles differ greatly between countries, and the impact of NO_x exposure may be considerably higher in areas with higher levels of emissions than Sweden.[48]

Conclusion

In conclusion our finding, that exposure to moderate levels of combustion-related ambient air pollution influences the risk of MS, supports the hypothesis that pulmonary irritation and ensuing inflammation play an important role in MS development.

Ethics approval

The study was approved by the Regional Ethical Review Board at Karolinska Institutet (2004/1–4:6 and 2018/030–31/2) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Data availability

Anonymized data underlying this article will be shared on reasonable request from any qualified investigator who wants to analyse questions that are related to the published article.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

Concept and design of the study: A.K.H., L.A., T.B. Acquisition of data: A.K.H., L.A., J.H., D.S., P.S., I.K. Statistical analysis: A.K.H. Drafting of the manuscript: A.K.H. Drafting of the figure: D.S. All authors commented on the draft and approved the final version of the manuscript to be published. All authors agree to be accountable for all aspects of the work.

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Conflict of interest

J.H. has received honoraria for serving on advisory boards for Biogen, Celgene, Sanofi-Genzyme, Merck KGaA, Novartis and Sandoz and speaker's fees from Biogen, Novartis, Merck KGaA, Teva and Sanofi-Genzyme; he has served as principal investigator for projects, or received unrestricted research support from, Biogen, Bristol-Myers-Squibb, Merck KGaA, Novartis, Roche and Sanofi-Genzyme, his MS research is funded by the Swedish Research Council and the Swedish Brain foundation. T.O. has academic grants from the Knut and Alice Wallenberg foundation, the Swedish Research Council and the Swedish Research Council; has received lecture and/or advisory board honoraria, as well as non-restricted MS research grants, from Biogen, Novartis, Sanofi and Merck on projects not related to the one reported here. L.A. reports grants from the Swedish Research Council, grants from the Swedish Research Council for Health Working Life and Welfare and grants from the Swedish Brain Foundation, during the conduct of the study; and personal fees from Teva and Biogene Idec, outside the submitted work.

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