



Association between environmental air pollution and olfactory functioning among Italian adolescents and young adults in the province of Brescia, Italy

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ABSTRACT

Olfactory receptor neurons are in direct contact with the ambient air, making olfactory function particularly susceptible to airborne pollutants. This study investigates the relationship between air pollution and olfactory function among adolescents and young adults residing in the province of Brescia, Italy. It included 169 participants (53.3% female, 15–25 years) of the ongoing longitudinal Public Health Impact of Metals Exposure (PHIME) study. Participants completed assessments of olfactory function using a short version of the “Sniffin’ Sticks” identification test at baseline (2008–2014) and the extended test at follow-up (2017–2021). Annual average concentrations of particulate matter (PM₁₀, PM_{2.5}) and nitrogen dioxide (NO₂) were estimated on a 4 × 4 km² spatial resolution grid using the Regional Chemical Transport Model ARIA for the target area between 2016 and 2019 and averaged over time. We applied multivariable linear regression, Bayesian Kernel Machine Regression and Weighted Quantile Sum (WQS) regression to investigate the associations between air pollutants and olfactory function. A significant negative association was observed between the air pollutants (PM_{2.5}: mean 18.5 µg/m³ Standard Deviation ±5.2 µg/m³; PM_{COARSE}: 2.7 µg/m³ ±1.2 µg/m³; NO₂: 32.3 µg/m³ ±10.1 µg/m³), treated as a mixture, and the olfactory functioning measured with the Sniffin’ total score (µ −1.44, 95%CI -2.42, −0.34), and the Sniffin’ threshold score (µ −1.48, 95%CI -2.91, −0.6) when applying WQS regression. This association was mainly driven by NO₂ and PM_{COARSE}. Findings suggest that air pollution exposure to NO₂ and PM_{COARSE} can reduce olfactory function among adolescents and young adults residing in a polluted area in northern Italy.

Abbreviations: AIC, Akaike Information Criterion; ANOVA, Analysis of variance; BKMR, Bayesian Kernel Machine Regression; BM, Bagnolo Mella; CI, confidence interval; GL, Garda Lake; IQ, intelligence quotient; K-BIT, Kaufman Brief Intelligence Test; NO₂, nitrogen dioxide; PM, particulate matter; PM₁₀, PM with a diameter <10 µm; PM_{2.5}, PM with a diameter <2.5 µm; PM_{COARSE}, PM with a diameter between 2.5 and 10 µm; SD, standard deviation; SEM, structural equation model; TDI, Threshold Discrimination Identification; VC, Valcamonica; VIF, variance inflation factor; WISC-III, Wechsler Intelligence Scale for Children edition III; WQS, weighted quantile sum.

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1. Introduction

Air pollution is a major global public and environmental health problem (Brunekreef and Holgate, 2002; Landrigan, 2017). It is estimated to cause 4.2 million deaths per year worldwide (2018), ranking as the fourth risk factor for mortality (Brauer, 2016). International studies on the effects of air pollution on health have considered exposure to particulate matter (PM) and nitrogen dioxide (NO₂), while the most widely explored health outcomes are respiratory diseases (i.e., asthma, chronic obstructive pulmonary disease) and cardiovascular diseases (mainly stroke). Evidence about associations with mental disorders was also found with cognitive function as the most explored outcome (Dominski et al., 2021). Few environmental health studies assessed the direct relationship between air pollution and olfactory functions. Four of these studies highlighted a harmful effect of NO₂ (Adams et al., 2016) and PM_{2.5} (Ajmani et al., 2016; Trentin et al., 2022) among older adults and PM with a diameter <10 μm (PM₁₀) (Guarneros et al., 2020) in children, while one study found a protective effect of PM with a diameter <2.5 μm (PM_{2.5}) on olfaction (Andersson et al., 2021). Olfactory dysfunction, like loss of smell, has been widely associated with neurodegenerative conditions like Parkinson's and Alzheimer's diseases and with mild cognitive impairment that may lead to later dementia. Thus, olfactory function may be a biomarker for early detection and progression of cognitive impairment (Attems et al., 2014; Devanand, 2016; Doty, 2017; Doty and Hawkes, 2019; Godoy et al., 2015; Jung et al., 2019; Marin et al., 2018; Waldmann et al., 2020). Olfactory functions are especially vulnerable to air pollution exposure because of the direct exposure of the olfactory receptors and bulbs to ambient air. The olfactory system provides a nose-to-brain route for nanoscale particles in PM to enter the brain where they interact with olfactory neurons in the olfactory epithelium, they can deposit in the olfactory bulb via retrograde transport and might be translocated to anatomically connected areas in more remote brain regions such as the cerebrum and cerebellum (Lucchini et al., 2012a; Oberdörster et al., 2004).

Exploring PM exposure during adolescence and young adulthood is of great importance: in a previous study, an increase in PM_{2.5} exposure was associated with differences in cortical thickness during childhood suggesting that exposure during critical time-windows could substantially impact an individual's brain growth trajectory with potential lifelong consequences (Cserbik et al., 2020).

In Europe, the Po River Valley of Italy is among the most polluted areas in terms of PM with a small aerodynamic diameter (PM₁₀ and PM_{2.5}) and NO₂ (2019) due to its orographic and climatic conditions. In particular, the Brescia province is one of Italy's most industrialized and polluted regions located in the Po River Valley. Within this region, we identified three different areas: Valcamonica (VC), Bagnolo Mella (BM) and Garda Lake (GL), with different levels of PM and NO₂ exposures and with different histories of industrial emissions. VC is an area where three ferroalloy plants have been operating for decades until early 2000s, BM is in the southern part of the province where there is a currently operating ferroalloy plant, while GL is an area with no history of industrial ferroalloy plant activity (Lucchini et al., 2012b). This study aims to investigate associations between environmental exposure to PM_{2.5} (PM with a diameter <2.5 μm), PM with a diameter between 2.5 and 10 μm (PM_{COARSE}), NO₂ and the olfactory function of adolescents and young adults living in these areas of the province of Brescia, Italy.

2. Material and methods

2.1. Population and study design

The examined cohort is part of the ongoing longitudinal Public Health Impact of Metals Exposure (PHIME) study, designed to assess the effect of metal exposure on cognitive and behavioral function in young people (Lucchini et al., 2012b). The participants were selected through convenience sampling. Adolescents and young adults residing in the

Brescia province in northern Italy were enrolled in the study through the public school system using a community-based participatory approach that actively engaged local communities. The study's objectives and methodology were communicated through community meetings and conferences and promoted via local media outlets to reach the majority of the population and avoid a selection bias despite voluntary participation. The participants were recruited in the three target areas (VC, BM and GL; see Fig. 1) between 2008 and 2014 during the first assessment (i.e., baseline) and a follow-up visit took place between 2017 and 2021. Inclusion criteria for the study were: i) born and raised within the study area, ii) age between 10 and 14 years at enrollment, and iii) born into a family that had lived in the study area for at least two generations. Exclusion criteria were: i) a diagnosis of neurodegenerative disease, ii) a family history of neurodegenerative disease, iii) use of drugs with known neurological side effects, iv) visual or motor deficits. In total, 169 individuals participated in the baseline and follow-up study visits. Among these, 14 subjects performed the second visit after the onset of the COVID-19 pandemic. None of them declared having experienced COVID-19 at the time of the visit. Consent from subjects participating in the study was received before conducting the study. The project has been reviewed and approved by the ethical committees of the University of Brescia, and the Icahn School of Medicine at Mount Sinai (the first study was approved on January the 23rd, 2007, reference number 19; the follow-up study was approved on February the 7th, 2017, reference number 2610). Timeline of the visits and air pollution assessment.

2.2. Olfactory test

To investigate the olfactory performance, we administered the Burghart "Sniffin' Sticks" (Hummel et al., 1997, 2007b) at baseline and follow-up using pen-like dispensers for standardized odor presentation. The extended test consists of subtests that measure the ability to (i) identify smells (Identification Test), (ii) discriminate smells (Discrimination Test), and (iii) assess the smell threshold (Threshold Test). The sum of the three individual test scores provides the total score (Threshold Discrimination Identification (TDI) score). The Identification test presents single pens containing common odors (e.g. apple, coffee) to the participant, and after smelling this odor a score sheet with a list of four alternative smells was given to the participant. In a forced-choice procedure, the correct odor must be indicated. In total, 16 odors are presented to each participant and the score ranges from 0 (no correct answers) to 16 (all correct answers). The Discrimination test presents three odorants (one odorant once and another odorant twice), and the participant is asked to indicate the stick/smell that is different. This comparison is performed for 16 triplets; the score ranges from 0 (no correct answers) to 16 (all correct answers). The Threshold test uses n-butanol, a well-established test odorant in olfaction research. Sixteen dilution steps of n-butanol (lower numbers indicate higher concentrations) are presented to assess the odor threshold. Following a 3-alternative forced choice procedure, a triplet of sticks is presented to the participant. Only one stick contains the odorant while the two others are blanks; after successive presentations of the sticks, the participant is asked to indicate which of the three sticks contains the odorant. Starting with the lowest odor concentration, a staircase paradigm is used where two subsequent correct identifications of the odorous pen or one incorrect answer mark a so-called turning point, and result in a decrease or increase, respectively, of concentration in the next triplet. The threshold score is the mean of the last four turning points in the staircase, with the final score ranging between 1 and 16 points. Based on this psychophysical assessment, the four scores mentioned above are calculated where the TDI score ranges between 1 and 48. Age- and sex-matched normative data were used to classify each participant as unimpaired normosmic smeller (TDI score ≥31), slightly impaired hyposmic smeller (16 ≤ TDI score ≤30), or impaired anosmic smeller (TDI score ≤15). A short version of the Burghart "Sniffin' Sticks" smell test was used at the first visit to assess each participant's ability to

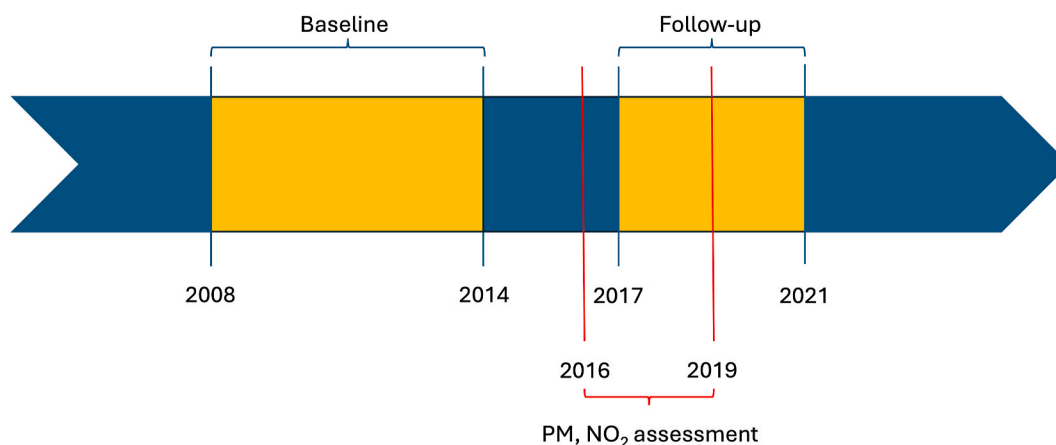


Fig. 1. Timeline of the visits and air pollution assessment.

identify common smells considering a subset of 12 odors among the 16 of the adult version (Lucchini et al., 2012b) that was already successfully used in children (Hummel et al., 2007a). Only the identification test was administered during the baseline visit.

2.3. Air pollution assessment

Annual average concentrations of PM₁₀, PM_{2.5} and NO₂ were estimated across the Lombardy region using a 4 × 4 km² spatial resolution grid with the Regional Chemical Transport Model ARIA. These estimates were integrated with air quality data from the regional monitoring network through assimilation techniques (ARPA Lombardia). Model runs were validated by comparing the measurements with model estimates. The Regional Agency for Environmental Protection (ARPA) of Lombardy tests the accuracy of the air quality network measurements daily and yearly. After incorporating the annually tested measurements, model estimates for PM and NO₂ concentrations were released for the 2016–2019 period.

The modelled PM and NO₂ concentrations on the grid were processed to estimate the area-weighted mean concentration for each municipality (ARPA Lombardia). Given that yearly tested modelled data for PM₁₀ and NO₂ were available from 2011 to 2019, and for PM_{2.5} from 2016 to 2019, we computed the PM and NO₂ exposure as the average concentration over the four years from 2016 to 2019 (Fig. 1). The concentration of particles with a diameter between 2.5 and 10 μm (PM_{COARSE}) was estimated as the difference between the concentrations of PM₁₀ and PM_{2.5} (Guxens et al., 2022).

2.4. Covariates

Variables including age, sex, symptoms of allergic rhinitis, total intelligence quotient (IQ) score, passive smoking exposure and seasonality were assessed at both visits and considered as covariates in the analyses. Self-reported allergic rhinitis symptoms were assessed through a questionnaire (Yes/No) at the time of assessment. Passive smoking was defined as if at least one of the two parents was an active smoker. Participant IQ was measured using the Wechsler Intelligence Scale for Children edition III (WISC-III) at the baseline visit and the Kaufman Brief Intelligence Test (K-BIT) (Kaufman, 1990) at the follow-up visit. Seasonality was defined based on the month of the year during which the visits were performed to account for the conditions of temperature, humidity and other variables characterizing colder and warmer months of the year that could affect the olfactory capacity of the participants. Sniffin' sticks identification baseline score (assessed at 10–14 years of age) was also included in the analyses. Active smoking information was collected only at the second visit since the children were too young to have already started smoking at the baseline visit. This information was

assessed through a questionnaire (Yes/No) at the time of the assessment. The area of residence was used as a proxy of the air pollution exposure that occurred before the baseline visit due to the unavailability of PM_{2.5} data before 2016 and the significant difference in the exposure among the three areas as shown in the results section.

2.5. Statistical analysis

The mean and standard deviation (SD) were considered as descriptive statistics for continuous variables while counts and percentages were calculated for categorical variables. Analysis of variance (ANOVA) and chi-squared tests were used to test the difference among the areas of residence (i.e., VC, BM and GL) for continuous and categorical variables, respectively. A Structural Equation Model (SEM) was applied to assess the concordance between WISC-III and KBIT scores used to measure IQ at baseline and follow-up visits, respectively (Astrua et al., 2007). Paired sample *t*-test and McNemar tests were applied to assess the difference between baseline and follow-up characteristics for continuous and categorical variables, respectively. Spearman correlation coefficients were calculated to measure the correlation among the three air pollutants.

To test our hypothesis that air pollution exposure adversely impacted olfactory function, we first applied linear regression models to estimate the associations between the 4-year average of individual PM_{2.5}, PM_{COARSE} and NO₂ concentrations and the four Sniffin' Sticks scores (Identification, Discrimination, Threshold, and TDI). These models estimated the impact of a 10 μg/m³ increase of PM_{2.5}, PM_{COARSE} and NO₂ concentrations on each of the Sniffin' stick scores. To assess the impact of multicollinearity on multiple regression estimates, we applied the variance inflation factor (VIF): if VIF was greater than 5 we applied separate linear regression models for each exposure (Sheather, 2009). We then examined the impact of a mixture of PM_{2.5}, PM_{COARSE}, and NO₂ using Bayesian Kernel Machine Regression (BKMR) (Bobb et al., 2015) and Weighted Quantile Sum (WQS) regression model (Carrico et al., 2015). BKMR was used to estimate the mixture effect and to identify possible non-linear effects between the exposures and the outcomes, or any interactions among the three pollutants. BKMR is a statistical method that can be used to flexibly model the individual and joint effects of exposure to mixtures of chemicals by using a kernel function. It allows for visualization of individual exposure-response functions while accounting for the other exposures and allowing potential non-linear relationships with the outcome and potential interactions among the exposures. Given the lack of evidence for non-linearity from BKMR models, we used WQS to assess the association between the environmental mixture made of PM_{2.5}, PM_{COARSE}, and NO₂ and the olfactory functions of the subjects. Pairwise interaction variables were included in the model if an interaction was suggested by BKMR. WQS regression is a statistical method that both characterizes the effect of the mixture on the

outcome and identifies which components have the higher contribution to the association through the empirical estimate of a weighted index. The regression parameter associated with the WQS index represents the overall effect of the mixture on the outcome (i.e., olfactory function) while the weights that form the index show the contribution of each component in the mixture to the association. In the WQS algorithm, the dataset is split into a training set where the weights are estimated, and a validation set where the final regression model is fitted. A repeated holdout validation step was applied in this analysis to obtain more stable results (Tanner et al., 2019). Concentrations of pollutants were categorized as tertiles when considering the mixture effect. The threshold for identifying the components with the higher contribution in the association between the mixture and the olfactory outcomes was set equal to the inverse of the number of pollutants included in the mixture (1/3) (Curtin et al., 2019) and the pollutants in the mixture were considered probable contributors or possible contributors of the association if the estimated weights showed a value greater than the threshold at least 90% or 50% of the time across the repeated holdouts, respectively (Busgang et al., 2022). A penalization term was included in the WQS regression models if a lower Akaike Information Criterion (AIC) was observed to obtain better weights and regression parameter estimates (Renzetti et al., 2023).

The Sniffin' Sticks scores measured at baseline and follow-up visits were included in all multivariable regression models as the residuals of the linear regression models where each score was included as the dependent variable and all the covariates (age, sex, symptoms of allergic rhinitis, total IQ score, passive smoking exposure and seasonality) measured at the corresponding visit were included as independent variables. This step provided an adjusted score for each test at the

corresponding visit. The adjusted Sniffin' Sticks scores measured at the follow-up visit were then included as the outcome of the multiple regression models while the adjusted Sniffin' Sticks score measured at the baseline visit, the time difference between the two visits, the area of residence, and active smoking exposure were included as covariates. The Benjamini and Hochberg false discovery rate method (Benjamini and Hochberg, 1995) was used to obtain adjusted p-values for multiple testing when the ANOVA, the paired sample t-test, the chi-square and the McNemar tests were performed, while Tukey's method was applied to adjust for multiple comparisons. All statistical tests were two-sided, and the statistical significance level was set to 5%. All statistical analyses were performed with R (version 4.4.0).

3. Results

Among the 169 participants included in the present study, the overall average age was 12.0 years (SD 0.9) at baseline and 20.0 years (SD 2.4) at the follow-up visit. Participants residing in BM were significantly younger than the other two municipalities both at the first (mean 11.8 years, SD 0.9) and second visit (mean 18.5 years, SD 1.7) (Table 1). 53.3% were females and the sex distribution was similar across areas of residence. The overall average IQ was 110.2 (SD 11.9) at baseline and 104.9 (SD 10.8) at follow-up; the difference in the score ($p < 0.001$) could be due in part to the different tests administered at the two visits while the SEM showed a concordance between the two methods estimating the slope of the structural equation $\beta = 0.924$ which was not significantly different from 1 ($p = 0.790$). No differences in IQ were observed across municipalities at both visits. A total of 13 (7.7%) and 34 (21.7%) individuals reported allergic rhinitis at baseline and at follow-

Table 1
Socio-demographic characteristics for all participants and by area of residence.

	Baseline					Follow-up					p value ^c
	Total (N = 169)	VC (N = 52)	BM (N = 73)	GL (N = 44)	p value ^a	Total (N = 169)	VC (N = 52)	BM (N = 73)	GL (N = 44)	p value ^b	
n (%)											
Biological Sex					0.313						0.313
Females	90 (53.3%)	30 (57.7%)	34 (46.6%)	26 (59.1%)		90 (53.3%)	30 (57.7%)	34 (46.6%)	26 (59.1%)		
Allergic rhinitis					0.188						<0.001
Yes	13 (7.7%)	2 (3.8%)	5 (6.8%)	6 (13.6%)		34 (21.7%)	7 (14.3%)	14 (20.9%)	13 (31.7%)		
Passive smoking					0.259						0.530
Yes	15 (8.9%)	2 (3.8%)	9 (12.3%)	4 (9.1%)		15 (11.1%)	7 (15.2%)	5 (9.8%)	3 (7.9%)		0.546
Active smoking											0.200
Yes						23 (16.8%)	10 (22.2%)	10 (18.5%)	3 (7.9%)		
Season					<0.001						0.197
Winter	61 (36.1%)	20 (38.5%)	35 (47.9%)	6 (13.6%)		48 (28.4%)	10 (19.2%)	22 (30.1%)	16 (36.4%)		
Spring	52 (30.8%)	13 (25.0%)	12 (16.4%)	27 (61.4%)		36 (21.3%)	17 (32.7%)	12 (16.4%)	7 (15.9%)		
Summer	5 (3.0%)	4 (7.7%)	0 (0.0%)	1 (2.3%)		34 (20.1%)	9 (17.3%)	18 (24.7%)	7 (15.9%)		
Autumn	51 (30.2%)	15 (28.8%)	26 (35.6%)	10 (22.7%)		51 (30.2%)	16 (30.8%)	21 (28.8%)	14 (31.8%)		
Mean (SD)											
Age (years)	12.0 (0.9)	12.1 (0.9)	11.8 (0.9)	12.2 (0.8)	0.010	20.0 (2.4)	21.6 (1.8)	18.5 (1.7)	20.7 (2.4)	<0.001	<0.001
IQ score	110.2 (11.9)	109.3 (12.5)	110.4 (12.5)	110.8 (10.1)	0.796	104.9 (10.8)	104.0 (11.9)	104.6 (10.4)	106.7 (10.3)	0.440	<0.001
Time between two visits (years)						7.5 (2.0)	8.8 (1.8)	6.2 (1.3)	8.1 (2.1)		<0.001

Abbreviations: ANOVA, analysis of variance; BM, Bagnolo Mella; GL, Garda Lake; IQ, intelligence quotient assessed using the Wechsler Intelligence Scale for Children edition IV (WISC-III); SD, standard deviation; VC, Valcamonica.

Notes: ^a p-values are related to the comparison of the variables across areas of residence measured at baseline; ^b p-values are related to the comparison of the variables across areas of residence measured at follow-up; ^c p-values are related to the comparison of the variables between baseline and follow-up. Counts and percentages or mean and SD are shown for categorical and continuous variables respectively. For ^a and ^b p-values were obtained through chi-squared and ANOVA tests for categorical and continuous variables respectively while for ^c p-values were obtained through McNemar and paired sample t-test for categorical and continuous variables respectively and adjusted for multiple comparisons through the Benjamini and Hochberg false discovery rate method.

up, respectively, showing a significant increase of cases over time ($p < 0.001$). No significant difference was observed in passive smoking due to having at least one of the two parents as an active smoker either between the two visits or among the three areas at the two visits. At the second visit, 23 (16.8%) participants reported being active smokers and no significant differences were observed among the three areas. An average of 7.5 (SD 2.0) years passed between the two visits with a longer time length among VC participants (mean 8.8, SD 1.8) compared to BM (mean 6.2, SD 1.3). While the follow-up visits were distributed more uniformly over the seasons, the baseline visits were mainly performed during Winter, Spring and Autumn, with a few participants attending the visits during the summertime (3%).

No statistically significant differences in Sniffin' Sticks TDI score and three subscores were observed among areas of residence (Table 2). However, the prevalence of hyposmia (TDI score ≤ 30) was higher in BM (16%) compared to GL and VC (11% and 6%, respectively) while no functional anosmia was observed among participants. TDI, threshold and identification scores (identification score measured both at baseline and follow-up visits) were slightly higher among participants from the GL area, compared to participants from other areas, regardless of whether Sniffin' Sticks scores were unadjusted or adjusted for age, sex, symptoms of allergic rhinitis, total IQ score, passive smoking exposure and seasonality measured at the corresponding visit.

Fig. 2 shows the map of the Brescia province with the estimates of the exposure to PM_{2.5} (A), PM_{COARSE} (B) and NO₂ (C) for each municipality of residence of the participants which are grouped by area of residence. Table 3 confirms what can also be seen graphically from Fig. 2: BM shows higher concentrations of PM_{2.5} (mean (SD): 23.8 $\mu\text{g}/\text{m}^3$ (0.5)) and NO₂ (mean (SD): 41.6 $\mu\text{g}/\text{m}^3$ (2.0)) while higher concentrations of

PM_{COARSE} were observed in GL (mean (SD): 4.0 $\mu\text{g}/\text{m}^3$ (1.0)). All these differences were statistically significant ($p < 0.001$).

When considering multivariable models, the VIF and the Spearman correlation (Fig. 3) coefficient highlighted the presence of multicollinearity between PM_{2.5} and NO₂ (VIF PM_{2.5} = 9.45; VIF NO₂ = 9.44; $r_{\text{Spearman}} = 0.95$). Each exposure was then included in separate regression models. No significant association was estimated between any exposure and outcome (Table S1).

In our BKMR models, the mixture effect did not show a significant non-linear association with any Sniffin' Sticks scores (Fig. S1). An interaction effect in an adverse direction was observed only between PM_{COARSE} and NO₂ in association with the adjusted discrimination score (Fig. S2); the pairwise interaction (PM_{COARSE} x NO₂) was included as an additional component of the mixture in the subsequent WQS regression models. No suggestion of non-linear association with the outcomes was observed considering the individual pollutants (Fig. S3).

In our WQS model with repeated holdout, a penalization term was only included for the discrimination Sniffin' Sticks score since it showed a lower AIC. We observed a statistically significant association between the air pollution mixture and TDI and Threshold scores as the outcome variables. Each pollutant in the mixture being one tertile higher was associated with an average lower adjusted TDI score of 1.77 points ($\mu - 1.77$, 95% confidence interval (CI) -2.65 , -0.62) and an average lower adjusted threshold score of 1.62 points ($\mu - 1.62$, 95%CI -2.65 , -0.63) (Fig. 4, Table S2). A major role of NO₂ and PM_{COARSE} was observed in both associations (Fig. 5 and Table S2): weights for these pollutants for both associations (with TDI and threshold scores) were higher than the threshold (1/3) between 50% and 90% of the time across the repeated holdouts, resulting in being considered possible contributors.

Table 2

Summary statistics for the Sniffin' Sticks TDI score and subscores, for all participants and by area of residence.

	Total (N = 169)	BM (N = 73)	GL (N = 44)	VC (N = 52)	p value
n (%)					
Total categories					0.569
Normosmic	149 (88.2%)	61 (83.6%)	39 (88.6%)	49 (94.2%)	
Hyposmic	20 (11.8%)	12 (16.4%)	5 (11.4%)	3 (5.8%)	
Mean (SD)					
Total (TDI)	35.1 (3.9)	34.8 (4.4)	35.7 (3.7)	35.1 (3.3)	0.623
Total (TDI) adj	0.1 (3.7)	0.01 (4.4)	0.6 (3.8)	-0.1 (3.0)	0.678
Threshold	9.4 (3.0)	9.1 (3.0)	10.0 (2.8)	9.3 (2.9)	0.569
Threshold adj	0.1 (2.8)	-0.3 (3.0)	0.6 (2.7)	-0.1 (2.7)	0.569
Discrimination	12.8 (1.7)	12.9 (1.7)	12.5 (1.8)	13.1 (1.6)	0.569
Discrimination adj	0.0 (1.7)	-0.1 (1.8)	-0.3 (1.9)	0.2 (1.5)	0.599
Identification	12.9 (1.6)	12.8 (1.8)	13.1 (1.5)	12.7 (1.4)	0.569
Identification adj	0.1 (1.4)	0.3 (1.4)	0.3 (1.2)	-0.3 (1.3)	0.569
Identification at baseline	9.5 (1.6)	9.4 (1.7)	9.8 (1.4)	9.5 (1.6)	0.569
Identification at baseline adj	0.0 (1.4)	-0.1 (1.6)	0.2 (1.2)	-0.1 (1.3)	0.678

Abbreviations: ANOVA, analysis of variance; BM, Bagnolo Mella; GL, Garda Lake; VC, Valcamonica; SD, standard deviation; adj, adjusted.

Notes: The adjusted scores were obtained from the residuals of the linear regression models where age, sex, symptoms of allergic rhinitis, total IQ score, passive smoking exposure and seasonality measured at the corresponding visit were included as independent variables. P-values were obtained from the ANOVA test and adjusted for multiple comparisons through the Benjamini and Hochberg false discovery rate method.

4. Discussion

In this study, recent exposure to a mixture of PM_{2.5}, PM_{COARSE}, and NO₂ was associated with lower total and threshold scores of olfactory functioning assessed using the well-established Sniffin' Sticks methods. NO₂ and PM_{COARSE} showed higher weights in this association compared to PM_{2.5}. This means that, with increasing levels of exposure to NO₂ and PM_{COARSE}, we observed a lower total Sniffin' Sticks score: the overall olfactory functions (comprising the ability to perceive, discriminate and identify an odorant) decrease with higher levels of exposure. The estimated mixture effect was strongest for the threshold score: subjects needed higher n-butanol concentrations to correctly identify this odorant.

The subjects were enrolled in the province of Brescia, one of Italy's most polluted and industrialized regions (European Environment Agency, 2024). Three areas were identified with different levels of exposure to the pollutants of interest, due to the prevalence of industry in each area. Valcamonica is a valley in the pre-Alps with a historic activity of ferroalloy plants until the beginning of the 21st century. An area with a more recent industrial activity is Bagnolo Mella, located on the Padana plains where a ferroalloy plant started production in the 1970s and was fully active until 2015. A reference community with no history of industrial ferroalloy plant activity was identified in the Garda Lake area of the province (Lucchini et al., 2012b). The pollutants were measured between 2016 and 2019, corresponding approximately to the time elapsed between the baseline and follow-up visits performed by the participants during which the olfactory functions were assessed.

To our knowledge, this is the first study that examines the combined effect of PM and NO₂, treating them as a mixture, on olfactory functions. Previous studies have shown the effects of PM or NO₂ on olfaction, but they considered these pollutants separately. These studies consistently found that both PM and NO₂ have harmful effects on olfactory functions (Adams et al., 2016; Ajmani et al., 2016; Guarneros et al., 2020). Our study evaluates the joint impact of these pollutants when present together, providing a more comprehensive understanding of their

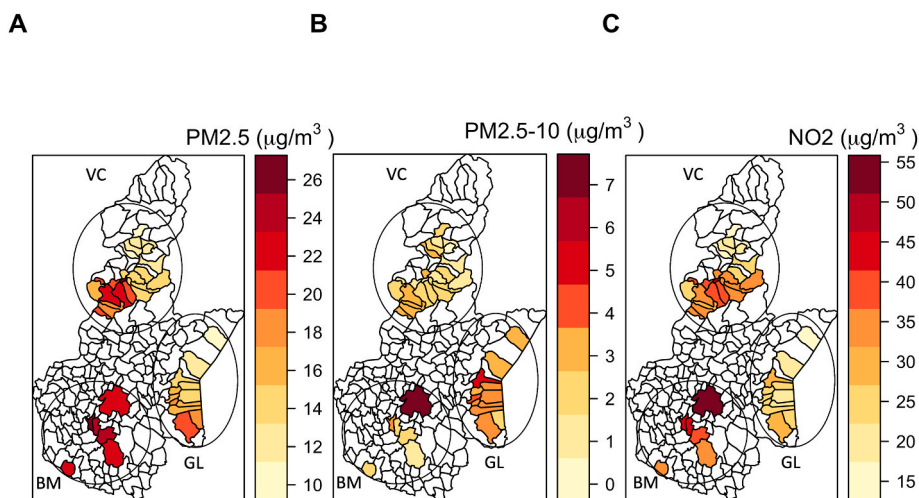


Fig. 2. Spatial representation of the average levels of PM_{2.5} (A), PM_{COARSE} (B) and NO₂ (C) concentrations at the municipality level in the province of Brescia averaged across 2016 and 2019. The three circles identify the three areas of residence. The unshaded municipalities are those where no subjects are enrolled in the study.

Table 3

Overall and by area of residence summary statistics (mean (SD)) for the PM and NO₂ concentration measurements (µg/m³) as mean of annual concentrations over the 4-year period from 2016 to 2019. P-values were obtained from the ANOVA test and adjusted for multiple comparisons through the Benjamini and Hochberg false discovery rate method.

	Total (N = 164)	BM (N = 71)	GL (N = 42)	VC (N = 51)	p value
PM _{2.5}	18.5 (5.2)	23.8 (0.5)	14.1 (2.7)	14.9 (3.7)	<0.001
PM _{COARSE}	2.7 (1.2)	2.6 (0.7)	4.0 (1.0)	1.6 (0.8)	<0.001
NO ₂	32.3 (10.1)	41.6 (2.0)	22.2 (4.4)	27.9 (9.1)	<0.001

Abbreviations: ANOVA, analysis of variance; BM, Bagnolo Mella; GL, Garda Lake; VC, Valcamonica; NO₂, nitrogen dioxide; PM, particulate matter; SD, standard deviation.

combined effects. Our results demonstrate that PM_{COARSE} and NO₂ play a significant role in affecting olfactory functions, which aligns with findings from previous literature. We found that PM_{2.5} appears to be less relevant in this association, suggesting that the size and specific composition of particulate matter may influence its impact on olfaction. Additionally, our study differs from previous research by adjusting the Sniffin' Sticks scores based on a baseline measurement of odor identification ability (identification score). Although this approach does not allow for a longitudinal design except when focusing on the identification score, it enabled us to account for an index that is moderately to highly correlated with the other scores (Hummel et al., 1997), meaning that we can assume that a significant portion of olfactory function at baseline is still captured by the identification score. In contrast, all previous studies only included a single assessment, leading to a loss of information about prior olfactory performance. Moreover, we focused on the effect of recent exposure to the pollutants that occurred between the two olfactory assessments. This focus on recent exposure is particularly relevant for understanding the acute impacts of air pollution on olfactory health. In our study we followed the participants from childhood to adolescence and young adulthood, a growth period during which humans are still undergoing significant developmental changes. This focus on a younger demographic provides valuable insights into how exposure to air pollution during adolescence might influence olfactory function and could have implications for understanding long-term health outcomes.

Because of the anatomical localization of the olfactory system towards the external environment, particularly to airborne pollutants, odorants access the nasal cavity through the nasal vestibule and travel to the olfactory epithelium. Using computational fluid dynamics models, Garcia et al. (2015) showed that especially ultrafine particles can reach the olfactory region of the human nose to a limited extent (Garcia et al., 2015). Similar results were found using different breathing rates (Tian et al., 2017). As outlined in the International Commission on Radiological Protection (ICRP) report (1994) and illustrated by Oberdörster et al. (2004), these nano-sized particles exhibit a deposition profile similar to particles in the 2.5–10 µm range, which primarily deposit in the nasopharyngeal/laryngeal (NPL) region (ICRP, 1994; Oberdörster et al., 2004). Consequently, particles from air pollution may also reach the olfactory region of the nasal cavity to some degree. However, these pollutants have never been measured in the olfactory cleft, so we can only assume they can reach this region. Here, in addition to olfactory testing, nasal lavage or brushing techniques could be used to gather information on inflammatory reactions and to identify biomarkers of

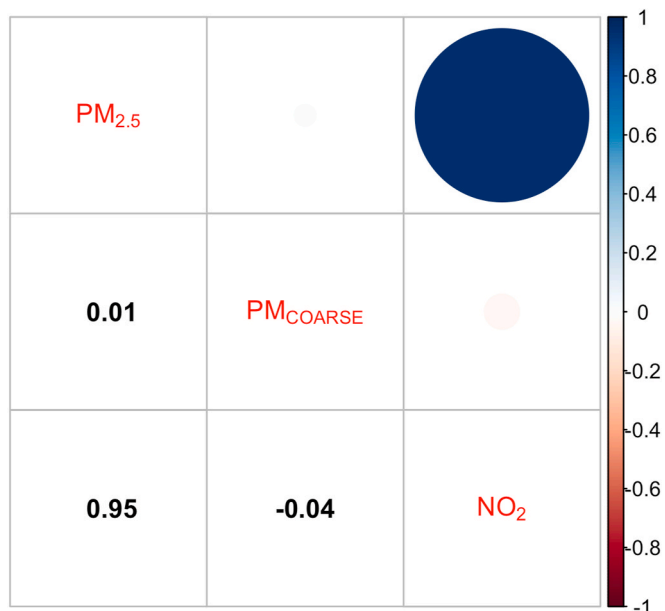


Fig. 3. Pairwise Spearman correlation coefficient between PM_{2.5}, PM_{COARSE} and NO₂.

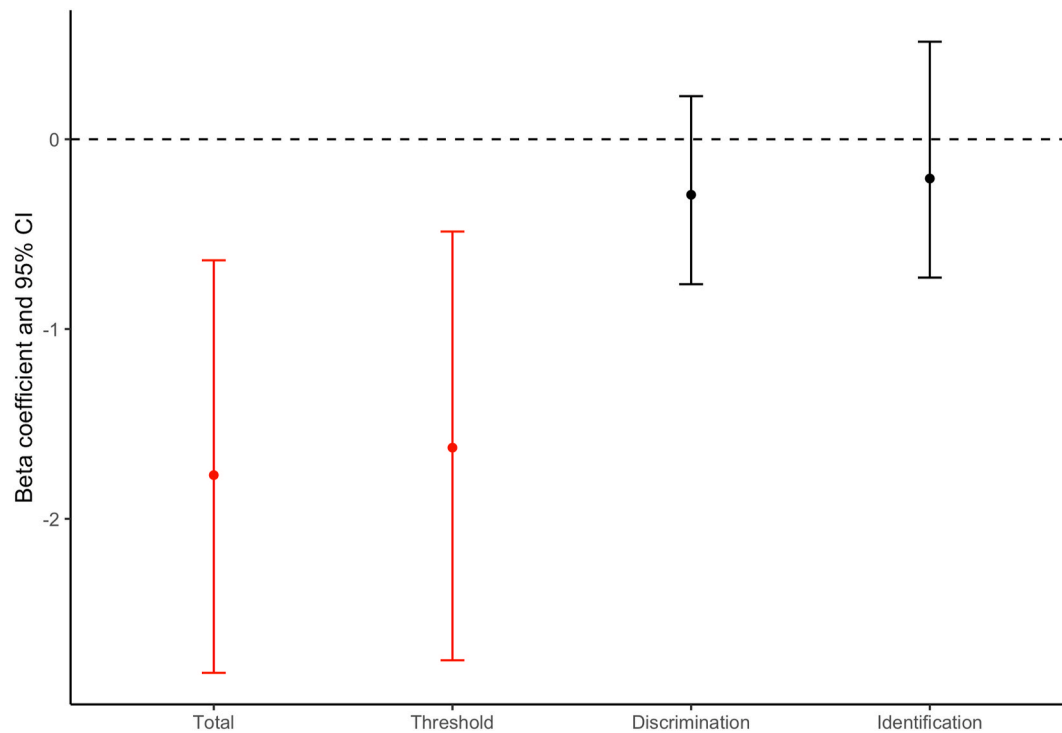


Fig. 4. Estimates of the regression parameter and relative 95% Confidence Interval (95%CI) associated with the weighted index estimated by Weighted Quantile Sum (WQS) regression with repeated holdout for each Sniffin' Sticks score. Red points and error bars highlight the statistically significant results.

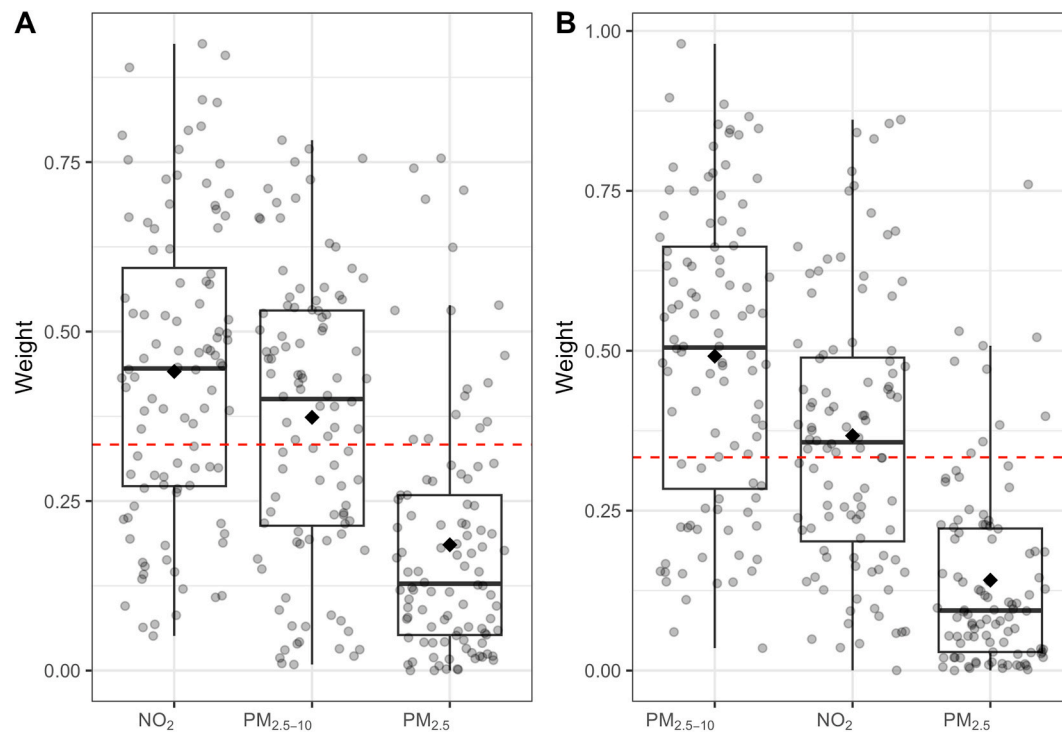


Fig. 5. Boxplots of the distribution of weights estimated through the WQSRH regression for each component included in the mixture. The results obtained for the association between the air pollution mixture and the TDI (A) and threshold (B) Sniffin' Sticks score. The dashed red line is equal to the inverse of the number of the components included in the mixture (1/3 in this case) and it is used as a threshold to identify the components with higher contribution.

exposure, such as metal species linked to air pollution. This approach could help address existing weaknesses in the proposed association. This epithelium contains olfactory receptor neurons with cilia reaching out into the nasal fossa and axons innervate the olfactory bulb via

projections through the cribriform plate (Cullen and Leopold, 1999; Pinto, 2011). Based on the evidence of previous studies demonstrating that ultrafine particles can reach the olfactory region of the human nose, it is plausible that not only odorants but also airborne pollutants can

directly reach and possibly damage the olfactory system. However, the proportion of inhaled air that reaches the olfactory epithelium varies depending on individual nasal anatomy (Borojeni et al., 2020). Moreover, when pollutants enter the nasal cavity, they can cause inflammation and oxidative stress in the olfactory epithelium. This damage can lead to olfactory dysfunction as the inflammatory response and oxidative stress negatively affect the sensory neurons and supporting cells responsible for detecting odors (Gamon et al., 2015; Li et al., 2023; Valko et al., 2007). Threshold tests, which measure the minimum concentration of an odorant required for detection, are particularly sensitive to the peripheral aspects of olfactory function (Hummel and Welge-Lüssen, 2006). This sensitivity indicates that the initial contact of pollutants with the olfactory epithelium can be a critical step in the deterioration of olfactory function. The ongoing exposure to pollutants can thus progressively impair their ability to detect and recognize odors, leading to a decline in olfactory function over time. The implications of such damage are significant, as olfactory dysfunction can affect the quality of life, including the ability to enjoy food, detect hazards like smoke or gas leaks, and engage in social interactions (Boesveldt and Parma, 2021; Hoffman et al., 1998, 2016; Lafreniere and Mann, 2009; Murphy et al., 2002; Santos et al., 2004). Understanding the mechanisms by which airborne pollutants cause olfactory damage can help in developing strategies to protect this sensory system. This might include public health measures to reduce pollutant exposure, as well as medical interventions to mitigate the inflammatory and oxidative effects of pollutants on the olfactory epithelium. Overall, the direct access of airborne pollutants to the olfactory pathway underscores the need for continued research into the environmental factors contributing to olfactory dysfunction, particularly in vulnerable populations like children and adolescents.

In the present study, we applied multiple, advanced statistical models to assess the association between air pollution and olfactory functions. All methods identified negative associations, except for associations estimated through linear regression models between PM_{2.5} and NO₂ with the discrimination test and PM_{COARSE} with the identification test, which were small in magnitude and statistically non-significant. When using BKMR, we did not find any significant effect of the pollutant mixture on the outcomes, although all effect estimates were negative, consistent with other methods. This lack of significance could be attributed to BKMR's requirement for a large sample size due to its use of a non-parametric kernel function to estimate the smooth shape of the mixture-response relationship, which results in less statistical power for a given sample size (Gibson et al., 2019). In contrast, WQS regression revealed a significant negative association of the pollutant mixture on the total and threshold Sniffin' Sticks scores. This may be due to the higher statistical power of WQS regression, which benefits from the linearity assumption compared to the non-parametric nature of BKMR. Our results suggest that there might be an additive effect of the components in the mixture, as indicated by the significant findings from the WQS regression. This highlights the importance of considering the combined effects of multiple pollutants in environmental health studies rather than examining them in isolation. Exposures often occur as complex mixtures rather than as individual pollutants. Therefore, our findings underscore the necessity for environmental health research to adopt a more holistic approach. By evaluating the cumulative impact of multiple pollutants, we can gain a more accurate understanding of their true health implications, improve risk assessments, and develop more effective public health interventions to mitigate the adverse effects of environmental exposures.

The major strengths of the present study are the ability to estimate the impact of the exposure to PM and NO₂ on the participants' olfactory functions while accounting for a prior olfactory performance, even though this was assessed using only a short version of the identification test; the assessment of a mixture effect that allowed to account for multiple exposures and to estimate a cumulative effect; finally, having enrolled the subjects in three areas with different levels of pollution

allowed to have a higher gradient of exposure and to better identify the effect of the exposure on the olfactory functions.

The present study is not without limitations: we did not have information about the exposure that occurred before the first visit which prevented us from assessing the effect of long-term exposure; however, we accounted for antecedent exposure including the area of residence as a proxy of the exposure based on the differences observed in the collected air pollution levels. We approximated the time-varying exposure between the two visits using a constant value based on the average exposure. The spatial resolution of pollutant exposure estimates could be further refined to achieve more precise estimates and capture greater variability in exposure levels. In addition, we measured only a short version (12 items) of the Sniffin' Sticks identification score at the baseline visit, which captures only one aspect of overall olfactory function and precluded us from performing longitudinal analyses. In our analysis, we only had information on PM_{2.5}, PM_{COARSE} and NO₂. An improvement to this study could be the inclusion of other environmental pollutants commonly found in industrialized areas where metals are processed and can affect olfactory functions (like manganese (Guarneros et al., 2013) and hydrogen sulfide (Rumbeiha et al., 2016)) and a more detailed characterization of PM composition. Finally, the relatively small sample size allowed to only find significant associations when using the WQS regression which grants a higher statistical power.

5. Conclusion

This study contributes to understanding the potential effects that recent exposure to air pollution can have on olfactory functions among adolescents and young adults. Among residents of a polluted area in northern Italy, a combined effect of PM and NO₂, mainly driven by NO₂ and PM_{COARSE}, on the Sniffin' Sticks threshold score was detected. This is an understudied problem that needs further attention and should be further explored given the implications that olfactory functions can have on the quality of life and their possible link with the onset of neurological disorders later in life.

CRedit authorship contribution statement

Stefano Renzetti: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Marialisa Volta:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Christoph van Thriel:** Writing – review & editing, Writing – original draft, Supervision. **Roberto G. Lucchini:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition. **Donald R. Smith:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition. **Alessandra Patrono:** Data curation. **Giuseppa Cagna:** Data curation. **Azzurra Invernizzi:** Writing – review & editing, Writing – original draft, Supervision. **Elza Rechtman:** Writing – review & editing, Writing – original draft. **Elisa Ongaro:** Data curation. **Elena De Angelis:** Data curation. **Stefano Calza:** Writing – review & editing, Writing – original draft, Supervision. **Matteo Rota:** Writing – review & editing, Writing – original draft. **Robert O. Wright:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition. **Birgit Claus Henn:** Writing – review & editing, Writing – original draft, Conceptualization. **Megan K. Horton:** Writing – review & editing, Writing – original draft, Conceptualization. **Donatella Placidi:** Writing – review & editing, Writing – original draft, Conceptualization.

Ethical approval

Consent from subjects participating in the study was received prior to conducting the study and the study has been reviewed and approved by the ethics committee of University of Brescia, and the Icahn School of Medicine at Mount Sinai. The first study was approved on January the 23rd, 2007, reference number 19; the follow-up study was approved on February the 7th, 2017, reference number 2610.

Data availability statement

Data are available from the corresponding author upon reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.apr.2024.102391>.

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