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RESEARCH LETTER

WILEY

Association between long-term occupational exposure to PM_{10} and allergic diseases in subway workers

To the Editor,

Persistent or repetitive exposure to environmental pollutants, in particular, exposure to ambient particulate matter with a median aerodynamic diameter of <10 μm (PM_{10}) in air pollution, cigarette smoking and other irritants is associated with an increased risk of development and exacerbation of allergic diseases.[1–3] Inflammation and oxidative stress play a central role in the pathophysiology of allergic diseases and could be measured using biomarkers.[4,5] For that purpose, exhaled breath condensate (EBC), a noninvasively collected biological matrix, allows the measurement of different biomarkers of oxidative stress directly in the lung.[6]

Within the Franco-Swiss project 'Respiratory disease Occupational Biomonitoring Collaborative Project' (ROBoCoP), we assessed whether a long-term occupational exposure to subway PM_{10} is associated with the prevalence of allergic diseases and whether the latter are associated with biomarkers measured in EBC of subway workers.[7]

We adopted a cross-sectional study design with an aetiological focus, combining a retrospective exposure assessment and contemporary outcome measurements to meet the temporality condition. Participants were randomly selected from a 15,000-subway worker cohort. All data and biological samples were collected from March through May 2021 according to the study protocol.[7] The outcomes variables (i.e., current asthma, current rhinitis and current eczema) were assessed using an electronic self-administered questionnaire addressed to workers who consented to participate. Moreover, atopic sensitization defined as a positive skin prick test to one or more of the tested allergens, according to the recommendations from the European Academy of Allergology and Clinical Immunology, was assessed by an occupational physician at the company occupational medicine centre. Finally, EBC samples were collected, during 20 min of tidal breathing using Turbo-Deccs® (Medivac, Parma, Italy) and nose clips, according to the latest recommendations.[6]

Individual inhaled PM_{10} mass (iPM_{10}) per work shift was estimated using a company-specific job-exposure-matrix (JEM) based on PM_{10} measurements conducted from 2004 through 2019.[8] iPM_{10} was modelled as a function of PM_{10} exposure averaged over the participant's employment in the Parisian subway, inhalation rate and filtration efficiency of the respiratory protections used. A detailed description of these methods and results is available elsewhere.[9] Associations between iPM_{10}, health outcomes and biomarkers, were assessed using multivariable logistic regression models adjusted for potential confounders.

Among 287 participants, 35% reported a current rhinitis and 12% a current eczema and 5% a current asthma. Mean exposure duration of PM_{10} was 23.3 years at a mean estimated concentration of 76.7 μg/m^3. This corresponds to an iPM_{10} of 0.6 μg/shift.

The first research hypothesis tested in this study was that iPM_{10} will be positively associated with the prevalence of at least one of the three allergic diseases. We found that iPM_{10} was associated with the prevalence of current asthma among locomotive operators. The adjusted OR was equal to 1.05 [95%CI = 1.00–1.10] per 10 ng/shift, corresponding to 5%-increase in current asthma risk per every 10 ng/shift PM_{10} inhaled (Table 1). Among station agents, the association between iPM_{10} and the prevalence of current asthma was not statistically significant. However, station agents were found to be at higher risk of current asthma when compared to locomotive operators (aOR = 7.47 [95%CI = 1.02–54.74]). No interaction was found between iPM_{10} and job. Moreover, exposure duration was not associated with asthma prevalence.

The second research hypothesis tested in this study was that biomarkers measured in EBC would be associated with the prevalence of the outcomes considered. We found an association of nitrite concentration in EBC with atopic and poly-atopic sensitization, and current asthma (aOR = 2.95 [95%CI = 1.21–7.19], 3.94 [95%CI = 1.35–11.54] and 9.13 [95%CI = 1.23–67.96] per μmol/L, respectively). Nitrate level was negatively associated with current eczema but not associated with current asthma and current rhinitis (Table 1). More detailed information on study results is available at the Unisanté data repository (https://doi.org/10.16909/dataset/47).

Among the study strengths, the use of an original retrospective exposure assessment strategy is noteworthy. This strategy combines the JEM-based estimates of external exposure to subway PM_{10} with inhalation rates accounting for age, sex and physical activity of participants and the filtration efficacy of respiratory protection used at the workplace. The JEM used in this study is the first and unique JEM for subway PM available in the world.[8] It enables, for the first time, assessing the health effects of subway PM_{10} exposure accumulated during more than 23 years of employment. Although personal

exposure monitoring is considered the reference method, it is challenging to implement in Parisian subway, where workers are not allowed wearing measurement devises for security reasons. Another strength of this study is the 84%-response rate. Moreover, EBC sample analysis was robust, with only 0.4% results below the limit of detection and very few results below the limit of quantification.

Among limitations, the absence of PM_{10} measurements prior to 2004 and post-2020 is noteworthy; the missing PM_{10} levels had to be extrapolated. The number of asthma cases was limited and by design, only prevalence of current asthma could be analysed. Indeed, in studies relying on self-reported data, information bias might arise. Therefore, we focussed on current effects of allergic diseases, with diagnosis and/or symptoms within the last year. Finally, the study sample was small, and these study findings need further confirmation.

This study showed for the first time the relationship between long-term exposure to subway PM_{10} and prevalence of asthma in some categories of subway workers. This finding is important for occupational allergology practice pointing out the risk of allergic asthma in the underground railway settings and the need of its screening and appropriate management. The study also confirmed nitrite in EBC as a biomarker of atopy and current asthma, indicating the diagnostic interest of this biomarker. The use of such noninvasively measured biomarkers may facilitate further research in occupational allergology.

KEYWORDS

asthma, atopy, exhaled breath condensate, nitrite, PM_{10} exposure

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Summary box

- In locomotive operators, subway PM_{10} exposure is associated with asthma prevalence.
- Nitrite in exhaled breath condensate is associated with prevalent allergic diseases.

AUTHOR CONTRIBUTIONS

IGC, PW, JAP, JJS and GS was involved in conceptualization; RF, IGC and PW were involved in Methodology; RF, TC and PW were involved in software and formal analysis; AD, KS, VJ and JAP were involved in validation; AD, KS, VJ and JJS were involved in investigation; TC was involved in data curation; RF, JJS and IGC were involved in writing—original draft preparation; All authors were involved in writing—review and editing; IGC was involved in project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

FUNDING INFORMATION

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to ethical and privacy restrictions.

TABLE 1 Relationship between mean inhaled PM_{10} mass per work shift (iPM_{10}), biomarker concentration in EBC and health outcomes.

	Current asthma			Current rhinitis			Current eczema		
Logistic regression adjusted model ($n=240$)	**aOR**	**95%-CI**	***p*[a]**	**aOR**	**95%-CI**	***p*[a]**	**aOR**	**95%-CI**	***p*[a]**
iPM_{10} in locomotive operators (per 10 ng/shift)	1.05[b]	1.00–1.10	**.04**	0.98[b]	0.96–1.00	.13	0.99[b]	0.96–1.02	.55
iPM_{10} in station agents (per 10 ng/shift)	1.05[b]	0.98–1.13	.19	0.95[b]	0.91–0.98	**<.01**	0.99[b]	0.94–1.05	.83
Job category (ref: locomotive operators)	7.47	1.02–54.74	**.05**	1.14	0.63–2.08	.67	0.63	0.26–1.51	.30
Exposure duration (per year)	0.94	0.85–1.04	.25	1.07	1.02–1.12	**.01**	1.02	0.96–1.10	.50
Sex (ref: male)	2.18	0.48–9.93	.31	0.73	0.38–1.39	.34	0.65	0.26–1.65	.36
Atopic sensitization (ref: no)	3.87	1.09–13.73	**.04**	1.17	0.66–2.09	.59	0.50	0.19–1.30	.16
EBC biomarkers[c] $n=280$									
Nitrite (μmol/L)	9.13	1.23–67.96	**.03**	1.20	0.51–2.84	.67	0.53	0.15–1.85	.32
Nitrate (μmol/L)	0.70	0.12–3.97	.69	2.19	0.79–6.10	.13	0.25	0.08–0.75	**.01**

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; EBC, exhaled breath condensate; iPM_{10}, mean inhaled; PM_{10}, mass per shift; *p*, *p*-value; PM_{10}, particulate matter less than 10 microns.

[a]Associations with a *p*-value of <.05 are bolded.

[b]Interaction not significant.

[c]Logistic regression models adjusted are adjusted on age, sex, and smoking status.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the French Personal Protection Committees South-Est IV (N°2020-A03103–36), Declaration of conformity to the French National Commission for Computing and Freedoms (CNIL) N° 2,220,108 (protocol code ID RCB 2020-A03103-36).

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study.

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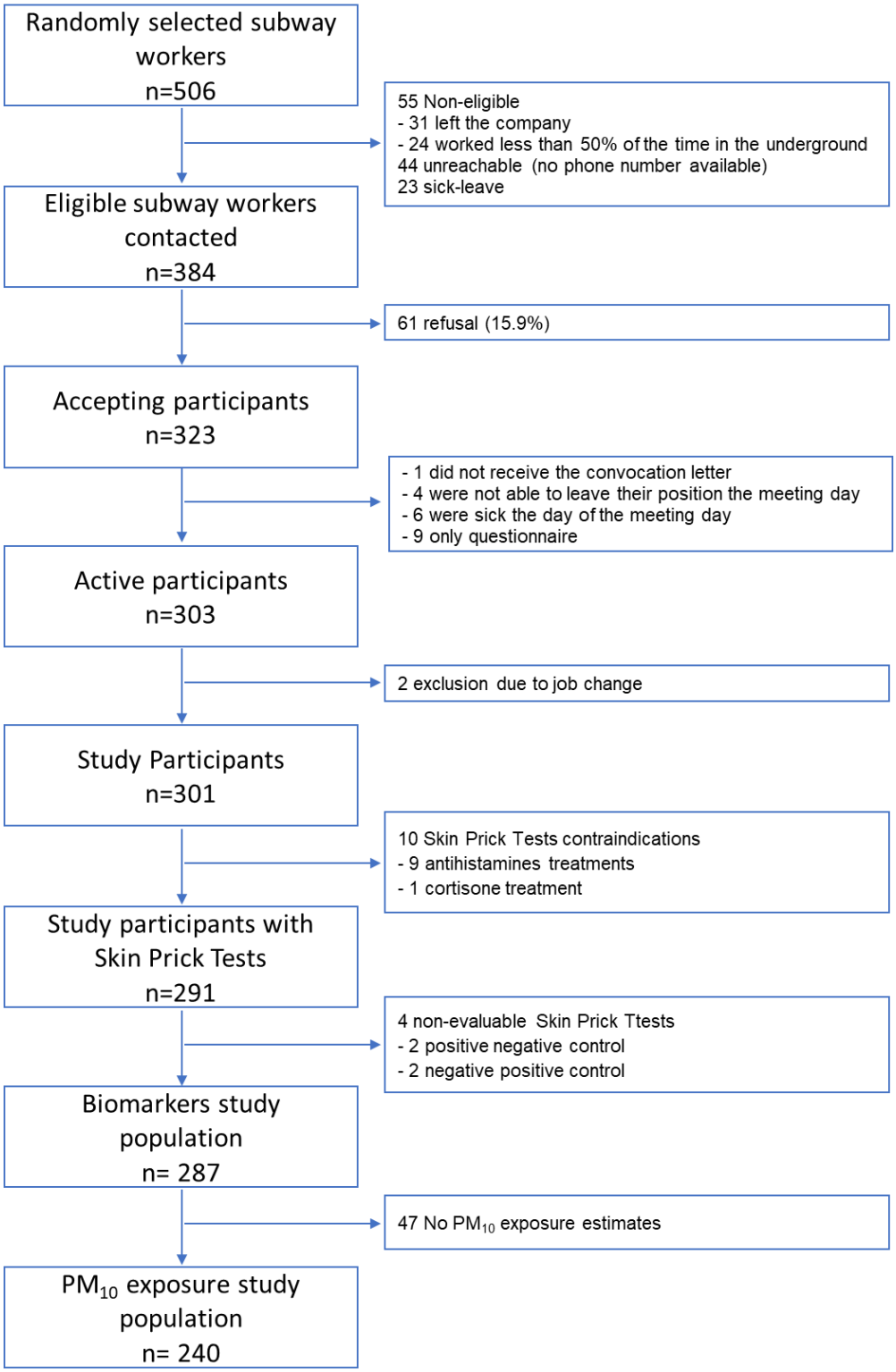
Supplementary materials for Online Open Access Repository

- **Supp figure 1:** Flow Chart of participant selection
- **Supp table 1:** Sample description
- **Supp table 2**: Relationship between EBC nitrite or nitrate levels and atopic sensitization
- **Supp figure 2:** Circular Venn diagram illustrating the prevalence of current rhinitis, current asthma, and current eczema; and the overlap between the conditions (Biomarkers study population n=287)
- **Supp figure 3:** Circular Venn diagram illustrating the prevalence of current rhinitis, current asthma, and current eczema; and the overlap between the conditions (PM_{10} exposure study population n=240)
- **Supp table 3:** Eight measured biomarkers concentration
- **Supp material 1:** Description of the 12 allergen extracts

Supplementary figure 1: Flow Chart of participant selection



Abbreviations: PM_{10} Particulate matter less than 10 microns

Supplementary Table 1: Sample description

Variable	PM_{10} exposure study population n=240	Biomarkers study population n=287
Gender, male, n (%)	102 (42.5%)	144 (50.2%)
Mean age, years, m (SD)	52.6 (5.3)	52.3 (5.3)
Age category		
40-45	31 (12.9%)	38 (13.2%)
45-50	30 (12.5%)	41 (14.3%)
50-55	80 (33.3%)	96 (33.4%)
55-60	89 (37.1%)	102 (35.5%)
60+	10 (4.2%)	10 (3.5%)
BMI (kg/m^2), m (SD)	26.0 (4.6) 4*	26.0 (4.3) 4*
Subway occupations, n (%)		
Station agents	121 (50.4%)	121 (42.2%)
Locomotive operators	119 (49.6%)	120 (41.8 %)
Security guards	0 (0%)	46 (16.0%)
Smoking category, n (%)		
Non smoker	116 (48.3%)	144 (50.2%)
Current smoker	90 (37.5%)	105 (36.6%)
Ex-smoker	34 (14.2%)	38 (13.2%)
Tobacco exposure, pack-years, m (SD)	16.6 (15.4)	15.5 (14.9)
Employement duration in years, m (SD)	24.6 (6.5)	24.2 (6.3)
Exposure duration in years, m (SD)	23.3 (7.4)	23.1 (7.0)
Mean PM_{10} concentration at workplace in $\mu g/m^3$, m (SD)	76.7 (34.5)	
Mean inhaled PM_{10} mass (iPM_{10}) in µg/shift, m (SD)	0.6 (0.2)	-
Atopic sensitization	84 (35.0%)	111 (38.7%)
Mono-sensitization (1 allergen in SPT)	30 (12.5%)	39 (13.6%)
Poly-sensitization (>1 allergen in SPT)	54 (22.5%)	72 (25.1%)
Mugwort (*Artemisia vulgaris*)	10 (4.2%) 6*	12 (4.2%) 8*
Ragweed (*Ambrosia artemisiifolia*)	4 (1.7%) 6*	4 (1.4%) 8*
Timothygrass (*Phleum pratense*)	37 (15.4%) 6*	50 (17.4%) 8*
Birchtree (*Betula verrucosa*)	26 (10.8%)	29 (10.1%)
Cypress (*Cupressus Arizonica*)	7 (2.9%)	8 (2.8%)
Platane (*Platanus acerifolia*)	12 (5.0%)	14 (4.9%)
Aspergillus fumigatus	7 (2.9%)	9 (3.1%)
Alternaria	11 (4.6%)	12 (4.2%)
European Dust Mites (*Dermatophagoïde pteronyssius*)	42 (17.5%)	57 (19.9%)
American Dust Mite (*Dermatophagoides farinae*)	37 (15.4%)	47 (16.4%)
Cat Air	17 (7.1%)	25 (8.7%)
Dog air	13 (5.4%)	17 (5.9%)
Asthma		
Ever asthma	21 (8.8%)	25 (8.7%)
Current asthma	12 (5.0%)	14 (4.9%)
Rhinitis		
Ever rhinitis	94 (39.2%)	113 (39.4%)
Current rhinitis	82 (34.2%)	100 (34.8%)
Eczema		
Ever Eczema	45 (18.8%)	55 (19.2%)
Current Eczema	27 (11.3%)	33 (11.5%)

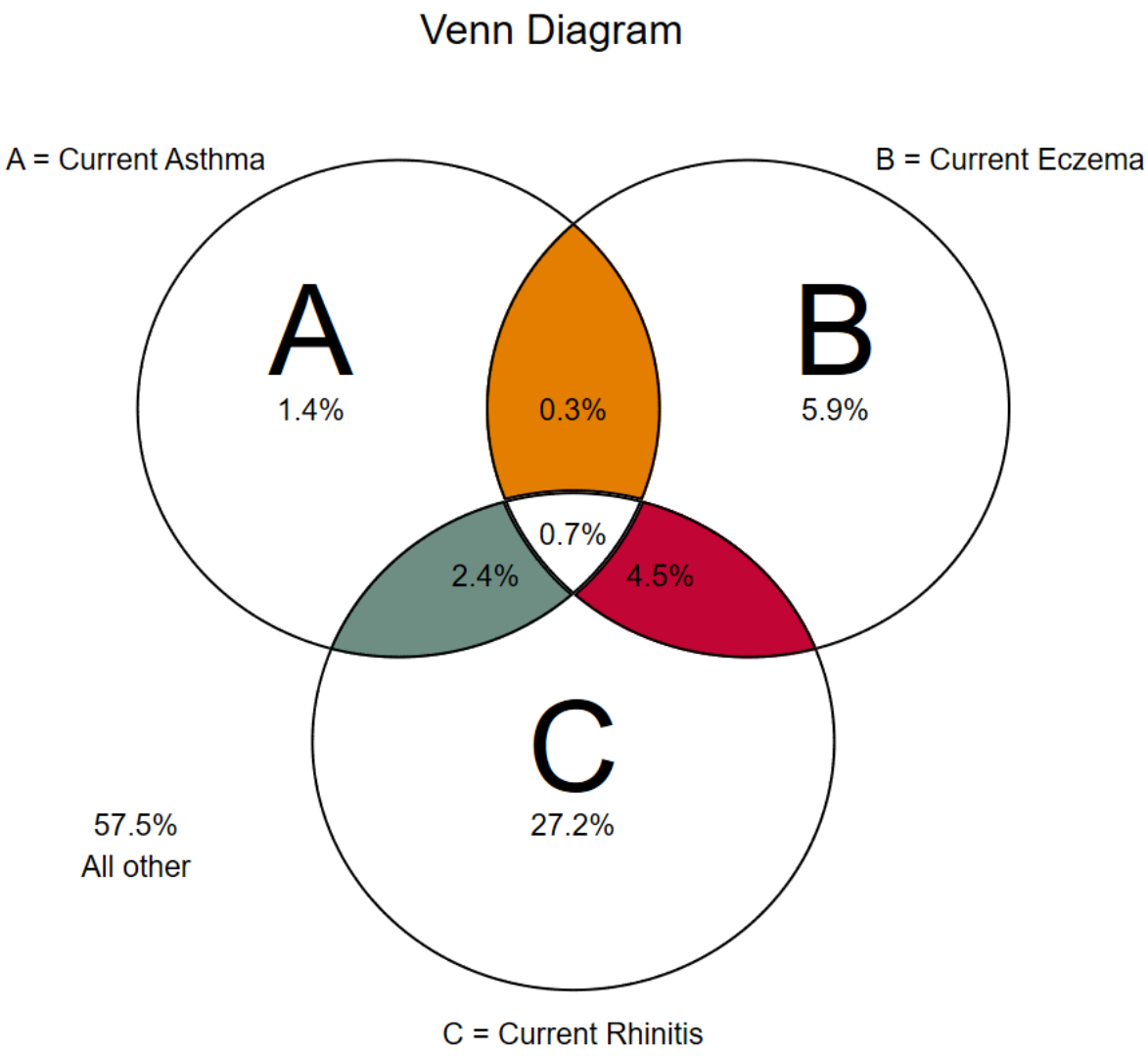
Note: values shown are mean (SD) or number (%) of subjects where appropriate. * number of missing data (missing allergen extracts for SPT). Abbreviations: BMI body mass index, m mean, PM_{10} Particulate matter less than 10 microns, SD standard deviation, SPT Skin Prick Tests. Lifetime smoking exposure was calculated by multiplying the estimation of cigarette packs smoked per day by the number of years smoking.

Supplementary Table 2: Relationship between EBC nitrite or nitrate levels and atopic sensitization

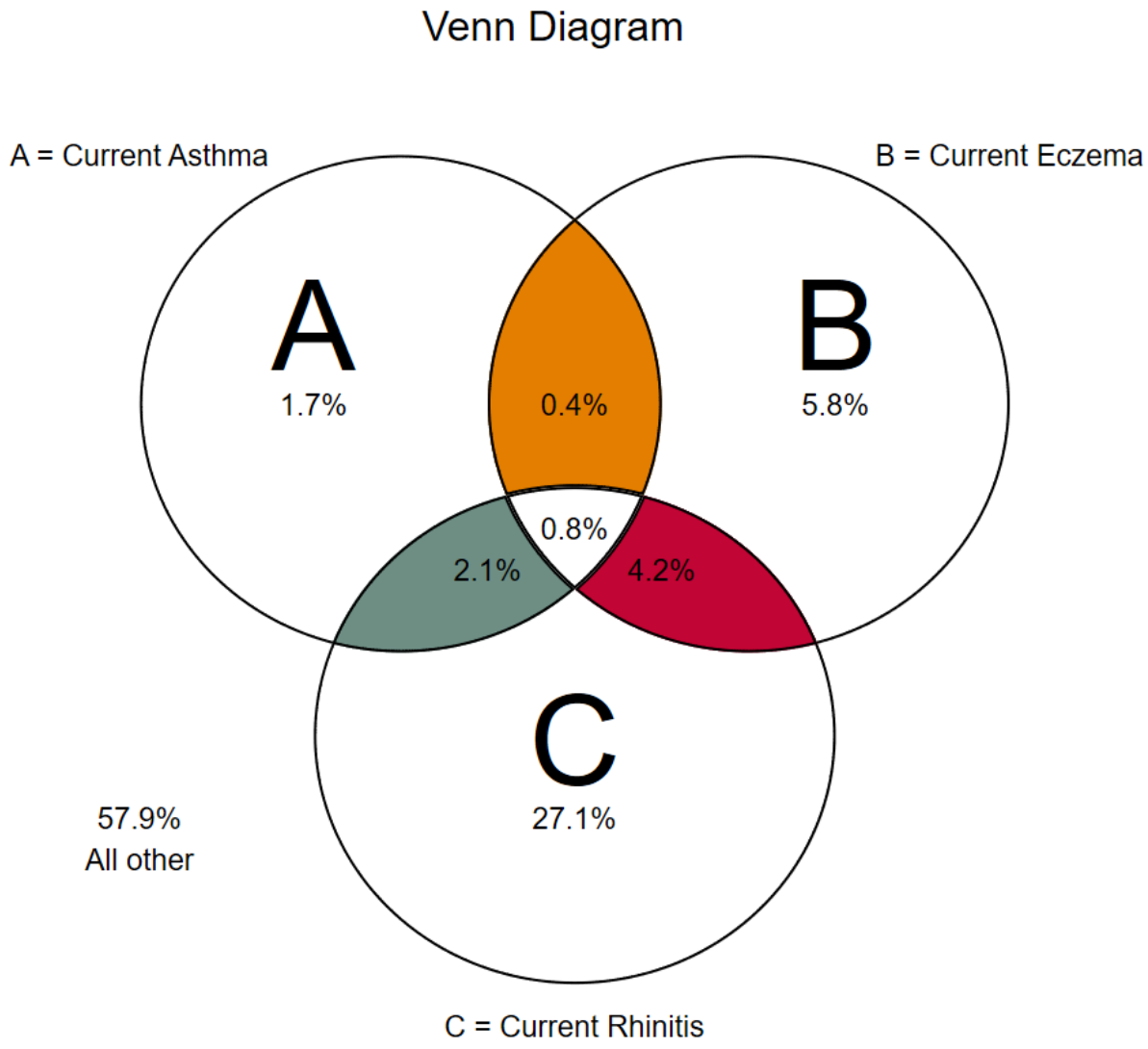
Logistic regression adjusted model	n	Nitrite (µmol/L)				Nitrate (µmol/L)			
		aOR	95%-CI		*p* [a]	aOR	95%-CI		*p* [a]
Atopic sensitization	280	2.95	1.21	- 7.19	**0.02**	2.81	0.94	- 8.45	0.07
Poly-Atopic sensitization (vs no atopic sensitization)	243	3.94	1.35	- 11.54	**0.01**	2.51	0.70	- 9.01	0.16

Logistic regression adjusted models are adjusted on age, sex, and smoking status.
[a] Associations with a p-value of <0.05 are bolded.
Abbreviations: aOR adjusted Odds Ratio, CI confidence interval, OR Odds Ratios, *p* p-value.

Supplementary Figure 2: Circular Venn diagram illustrating the prevalence of current rhinitis, current asthma and current eczema; and the overlap between the conditions (Biomarkers study population n=287)



Supp figure 3: Circular Venn diagram illustrating the prevalence of current rhinitis, current asthma and current eczema; and the overlap between the conditions (PM_{10} exposure study population n=240)



Supplementary Material Table 3: Eight measured biomarkers concentration

Biomarker Median [IQR], missing data	**No Atopic sensitization** n = 176	**Atopic sensitization** n = 111	**Total** n=287	**[0;LOD]** n (%)	**[LOD;LOQ]** n (%)	**LOD** Value	**LOQ** value
Nitrite (µmol/L)	1.0 [0.7-1.7], 5	1.2 [0.7-1.7], 2	1.1 [0.7-1.7], 7	1 (0.4%)	8 (2.8%)	0,1	0,3
Nitrate (µmol/L)	12.5 [8.3-15.9], 5	13.3 [9.4-16.3], 2	12.6 [8.8-16.0], 7	1 (0.4%)	3 (1.1%)	0,25	0,75
Lactate (µmol/L)	2.5 [1.0-4.5], 5	1.8 [0.4-4.1], 2	2.2 [0.6-4.4], 7	14 (4.9%)	30 (10.5%)	0,1	0,3
Butyrate (µmol/L)	1.0 [0.5-1.7], 5	0.7 [0.4-1.6], 2	0.9 [0.4-1.7], 7	3 (1.1%)	41 (14.3%)	0,1	0,3
Formate (µmol/L)	1.5 [1.0-2.1], 5	1.4 [1.1-2.1], 2	1.5 [1.1-2.1], 7	2 (0.7%)	1 (0.4%)	0,1	0,3
Propionate (µmol/L)	9.6 [4.6-18.3], 5	9.2 [5.0-16.0], 2	9.3 [4.7-17.2], 7	1 (0.4%)	0 (0.0%)	0,1	0,3
Acetate (µmol/L)	35.9 [22.8-58.2], 5	34.8 [21.8-49.1], 2	35.1 [22.5-55.5], 7	0 (0.0%)	0 (0.0%)	0,25	0,75
MDA (pg/mL)	268.9 [164.7-434.1], 1	239.8 [124.8-396.6], 2	261.3 [147.9-411.3], 3	6 (2.1%)	17 (5.9%)	25	75

Abbreviations: IQR Interquartile range, LOD Limit of detection, LOQ Limit of quantification, MDA Malondialdehyde

Supp material 1: List of the 12 allergen extracts

We used the following allergen extracts:

- Mugwort (Artemisia vulgaris)
- Ragweed (Ambrosia artemisiifolia)
- Timothygrass (Phleum pratense)
- Birchtree (Betula verrucosa)
- Cypress (Cupressus Arizonica)
- Platane (Platanus acerifolia)
- Aspergillus fumigatus
- Alternaria
- European Dust Mites (Dermatophagoïde pteronyssius)
- American Dust Mite (Dermatophagoides farinae)
- Cat Air
- Dog air