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Lung function-associated exposome profile in the era of climate change: Pooled analysis of 8 population-based European cohorts within the EXPANSE project

Ayoung Jeong [a,b,*], Gianfranco Lovison [a,b], Alonso Bussalleu [a,b], Marta Cirach [c], Payam Dadvand [c,d,e], Kees de Hoogh [a,b], Claudia Flexeder [f,g,h], Gerard Hoek [i], Medea Imboden [a,b], Stefan Karrasch [f,g,h], Gerard H. Koppelman [j,k], Sara Kress [l], Petter Ljungman [m,n], Renata Majewska [o], Göran Pershagen [m], Regina Pickford [f], Youchen Shen [i], Roel C.H. Vermeulen [i], Jelle J. Vlaanderen [i], Megi Vogli [f], Kathrin Wolf [f], Zhebin Yu [m], Erik Melén [p,1], Agnieszka Pac [o,1], Annette Peters [f,q,1], Tamara Schikowski [l,1], Marie Standl [f,h,r,1], Ulrike Gehring [i,1], Nicole Probst-Hensch [a,b,1,*]

[a] Swiss Tropical and Public Health Institute, Allschwil, Switzerland
[b] Department of Public Health, University of Basel, Basel, Switzerland
[c] ISGlobal, Barcelona, Spain
[d] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[e] CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[f] Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health (GmbH), Neuherberg, Germany
[g] Institute and Clinic for Occupational, Social and Environmental Medicine, LMU University Hospital, LMU Munich, Munich, Germany
[h] Comprehensive Pneumology Center Munich (CPC-M), German Center for Lung Research (DZL), Munich, Germany
[i] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands
[j] University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatric Pulmonology and Pediatric Allergology, Groningen, the Netherlands
[k] University of Groningen, University Medical Center Groningen, GRIAC Research Institute, Groningen, the Netherlands
[l] IUF - Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
[m] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[n] Department of Cardiology and Clinical Physiology, Danderyd Hospital, Stockholm, Sweden
[o] Chair of Epidemiology and Preventive Medicine, Jagiellonian University Medical College, Kraków, Poland
[p] Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
[q] Chair of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology, Medical Faculty, Ludwig-Maximilians-Universität München, Munich, Germany
[r] German Center for Child and Adolescent Health (DZKJ), partner site Munich, Munich, Germany

ABSTRACT

Background: The independent and interrelated long-term effects of the exposome such as air pollution, greenness, and ambient temperature on lung function are not well understood, yet relevant in the light of climate change.

Methods: Pre-bronchodilation FEV1 from five mature birth cohorts (N = 4724) and three adult cohorts (N = 6052) from five European countries were used to assess cross-sectional associations with air pollution, greenness, and ambient temperature, assigned to their residential address. All two-way interactions and square terms were *a priori* included in building the final elastic net regression model. Elastic net regression results were put into the context of different environmental scenarios such as improvement of air quality, improvement of greenness, climate change, or their combinations.

Results: Elastic net regression of FEV1 z-scores identified non-zero coefficients for many interaction terms, indicating the importance of joint effects of exposure to air pollution, greenness, and temperature. The non-zero coefficients were bigger and more stable in adults than in children. Upon exploring lung function benefits for different environmental scenarios, an improvement of FEV1 was expected in the scenario of improving air quality or greenness. In contrast, negative changes in FEV1

* Corresponding authors at: Swiss Tropical and Public Health Institute, Kreuzstrasse 2, 4123 Allschwil, Switzerland.
E-mail addresses: a.jeong@swisstph.ch (A. Jeong), nicole.probst@swisstph.ch (N. Probst-Hensch).

[1] Equal contribution

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z-scores were expected in the scenario of climate change, characterized by daily temperature increase in summer and decrease in winter. The beneficial FEV1 effects of improving air pollution or greenness were attenuated in the presence of climate change.

Conclusion: Complex exposome profiles of long-term exposure to air pollution, greenness, and temperature showed associations with FEV1 in European adults, and to less extent in children and adolescents. Climate change seems to have a negative impact on lung function and modifies the association of air pollution and greenspace with lung function.

1. Introduction

Low lung function contributes to disease burden and to diminished quality of life. The Global Burden of Disease 2019 reported chronic obstructive pulmonary disease (COPD), an important outcome of low attained and/or accelerated decline in lung function, as the 6th largest leading cause of disability-adjusted life years (DALYs)(Vos, 2020). Impaired lung function is also considered an independent predictor of other chronic non-communicable diseases and mortality (Cheng, 2021; Higbee et al., 2021).

Lung function progresses through distinct trajectories over the life-course (Agusti and Faner, 2019; Melén, 2024). Low attainment of lung function, and in particular of forced expiratory volume in 1 s (FEV1), in early life and accelerated FEV1 decline in later life is important in the development of COPD (Lange, 2015; Marott et al., 2020). Low FEV1 in adult life is a marker of premature death from all causes (Young et al., 2007; Agustí et al., 2017), and can be measured with less measurement error compared to other spirometry parameters in large-scale epidemiology studies.

Ambient air pollution is the best studied environmental risk factor for lung function. Higher long-term exposure to NO_2 (nitrogen dioxide) and PM_{10} (particulate matter with aerodynamic diameter equal to or less than 10 μm) has been associated with lower lung function in European adults (Adam, 2015). Decreases in PM_{10} concentrations were found to attenuate lung function decline in Swiss adults (Downs, 2007). Higher levels of NO_2, NO_x, $PM_{2.5}$ (particulate matter with aerodynamic diameter equal to or less than 2.5 μm), and $PM_{2.5}$ absorbance were associated with lower lung function in European children (Gehring, 2013). In a recent study of Swedish children and young adults, decreases in $PM_{2.5}$ and NO_x concentrations were associated with higher rates of lung function growth (Yu, 2023). Long-term exposure to ozone has been consistently associated with lung function in children but less consistent in adults (Holm and Balmes, 2022).

Green space has been receiving increasing attention for respiratory health effects, but with inconsistent findings (Johannessen et al., 2023; Markevych, 2023; Fuertes, 2020). While acute effects of temperature on respiratory outcomes, in particular exacerbations of respiratory symptoms and mortality, are relatively well understood (Lepeule, 2018; Scheerens, 2022; Evoy, 2022), chronic effects of ambient temperature have been scarcely studied (Miao, 2022). Considering the rising trend in weather extremes in the recent years – Europe witnessed the hottest summer in 2022 (Copernicus Climate Change Service., 2022) and May 2024 marked as the warmest May ever globally (Copernicus Climate Change Service. May, 2024) – and the trend foreseen to continue in the coming years, there is an urgent need to fill the knowledge gap with regard to chronic effects of extreme temperature on respiratory health.

Given that one is never exposed to a single environmental factor but to a mixture thereof and that exposure to one factor may modify the effect of other exposures, the research focus is shifting towards the "exposome", a concept that encompasses the totality of exposures throughout the life-course (Wild, 2005). This is the focus in the "EXposome Powered tools for healthy living in urbAN SEttings (EXPANSE)", a large European project aimed to investigate exposome effects on cardio-metabolic and pulmonary diseases (Vlaanderen, 2021), in the context of which this study was conducted.

The exposome score approach relies on supervised modeling techniques to develop a prediction model for a specific health outcome. This approach allows comparing exposures in terms of their contributions to prediction, in the context of other exposures.

This study *a priori* focused on three domains of exposures – air pollution, greenness, and temperature. These three domains are considered more proximal cause of impaired lung function among the external exposome for which the EXPANSE project made available pan-European models (Fig. 1). There is an urgent need for better understanding their direct or joint effects on respiratory health in the context of climate change.

In this cross-sectional analysis of a multi-cohort study, we applied the exposome score approach to understand how long-term exposure to air pollution, greenness, and temperature, as well as their interactions, are associated with pre-bronchodilation FEV1. We studied five mature birth cohorts (MBC) and three adult cohorts (AC) separately, to explore if the external exposome effects differ between the phase of lung function growth and the phase of lung function decline.

2. Methods

2.1. Study population

We analyzed a combined data set of population-based cohorts (5 MBC and 3 AC) from 5 European countries. The 5 MBCs include GINIplus/LISA North and South (Germany), PIAMA (Netherlands), Krakow Birth Cohort (Poland), and BAMSE (Sweden). The 3 AC include KORA (Germany), SALIA (Germany), and SAPALDIA (Switzerland). More detailed descriptions of these cohorts are provided in the Supplement. We included a total of 10 336 participants with non-missing information on spirometry measured around the year 2010, geocoded residential addresses, estimated exposure at the residential address, and information on sex, age, height, and smoking at the time of spirometry.

2.2. Pre-bronchodilation FEV1 z-scores

Pre-bronchodilation spirometry respecting guidelines of the American Thoracic Society (Miller, 2005) was conducted around the year 2010. Z-scores were derived by applying the Global Lung Function Initiative equations (Quanjer, 2012). We analyzed z-scores of forced expiratory volume in 1 s (FEV1) as the dependent variables. Given that FEV1 is more widely used in previous studies than other spirometry parameters, we prioritized FEV1 as the outcome.

2.3. External exposome

We analyzed external exposome features in the domains of air pollution, greenness, and temperature. All exposome features were harmonized across Europe and specifically obtained or derived for the EXPANSE project.

2.3.1. Annual mean exposure to NO_2, $PM_{2.5}$, and PM_{10}

Annual mean concentrations of NO_2 ("no2"), $PM_{2.5}$ ("pm25"), and PM_{10} ("pm10") were estimated across Europe by geographically and temporally weighted regression. The model development and validation is described previously (Shen, 2022). Each individual is assigned a 365-day average exposure using the individual annual mean exposures for the year of spirometry and the previous year proportional before the date of spirometry as follows:

$$x_i = (n_{y_0,i}x_{y_0,i} + (365 - n_{y_0,i})x_{y_0-1,i})/365$$

where y_0 is the year of spirometry; $n_{y_0,i}$ is the number of days passed before the spirometry in the year y_0; $x_{y_0,i}$ is the annual mean exposure of the year of spirometry at the home address of the individual i; $x_{y_1,i}$ is the annual mean exposure of the previous year of spirometry at the home address of the individual i.

2.3.2. Warm season mean exposure to ozone

Monthly mean concentrations of ozone were estimated from geographically weighted regression across Europe (Shen, 2024). We used the monthly mean concentrations from April to September (183 days) to define warm season ozone (“o3w”). Each individual is assigned a 183-day average exposure before the date of spirometry as follows:

$$x_i = (n_{y_0,i}x_{y_0,i} + (183 - n_{y_0,i})x_{y_0-1,i})/183$$

where y_0 is the year of spirometry; $n_{y_0,i}$ is the number of warm season days passed before the spirometry in the year y_0; $x_{y_0,i}$ is the warm season mean exposure of the year of spirometry at the home address of the individual i; $x_{y_1,i}$ is the warm season mean exposure of the previous year of spirometry at the home address of the individual i.

2.3.3. Greenness

Mean Normalized Difference Vegetation Index (NDVI) within 300 m buffer (“ndvi3”) was derived across Europe using the Vegetation Indices (MOD13Q1) product of the Terra Moderate Resolution Imaging Spectroradiometer (MODIS) with 250 m x 250 m resolution for the years 2005, 2010, and 2015. Each individual was assigned to the nearest year, with years preceding spirometry being preferred if the date of spirometry is in the middle of one of these intervals.

2.3.4. Distance to the nearest green space

Euclidean distance to the nearest green space (“gsc”) was calculated across Europe using Corine Land Cover database for the years 2006 and 2012. Each individual was assigned to the nearest year, while the past year was preferred in case the date of spirometry is in the middle of the interval.

2.3.5. Aggregated temperature variables

Daily mean, maximum, and minimum temperatures were estimated based on ambient temperature networks, remote sensing, and land use data (Bussalleu, 2024). Each individual was assigned four aggregated variables from the daily temperature estimates: (1) 365-day average of daily mean temperature before spirometry (“tav”); (2) 365-day standard deviation of daily mean temperature before spirometry (“tsd”); (3) warm season (April 1st to September 30th) average of daily maximum temperature up to 365 days before spirometry (“tmxw”); (4) cold season (January 1st to March 31st and October 1st to December 31st) average of daily minimum temperature up to 365 days before spirometry (“tmnc”). We derived these four aggregated variables as an attempt to capture various aspects of long-term exposure to temperature: tav to provide the simplest summary of temperature; tsd to capture the degree of temperature fluctuation; tmxw and tmnc to capture the chronic exposure to high and low extreme temperature separately.

$$tav_i = \sum_d tmp\_avg_{d,i}/365$$

$$tsd_i = \sum_d \left(tmp\_avg_{d,i} - tav_i\right)^2/365$$

$$tmxw_i = \sum_{d_w} tmp\_max_{d_w,i}/183$$

$$tmnc_i = \sum_{d_c} tmp\_min_{d_c,i}/182$$

where $tmp\_avg_{d,i}$, $tmp\_max_{d,i}$, and $tmp\_min_{d,i}$ are daily mean, maximum, and minimum temperature for the day d at the home address of individual i. d ranges from 1 to 365 days before spirometry. d_w and d_c range from 1 to 365 days before spirometry, restricted to warm and cold season respectively.

Each of the 10 exposure variables was standardized to have 0 mean and 1 standard deviation.

Table 1 enumerates the abbreviations used throughout this study to refer to exposome variables.

Table 1
Abbreviations for exposome variables used in this study.

Abbreviation	Description
gsc	Euclidean distance to the nearest green space, using Corine Land Cover database, from the nearest year of spirometry
ndvi3	Mean Normalized Difference Vegetation Index within 300 m buffer, from the nearest year of spirometry
no2	Nitrogen dioxide, 365-day average before spirometry
o3w	Warm season average ozone before spirometry
pm10	Particulate matter with aerodynamic diameter equal to or less than 10 μm, 365-day average before spirometry
pm25	Particulate matter with aerodynamic diameter equal to or less than 2.5 μm, 365-day average before spirometry
tav	365-day average of daily mean temperature before spirometry
tmnc	Cold season (January 1st to March 31st and October 1st to December 31st) average of daily minimum temperature up to 365 days before spirometry
tmxw	Warm season (April 1st to September 30th) average of daily maximum temperature up to 365 days before spirometry
tsd	365-day standard deviation of daily mean temperature before spirometry

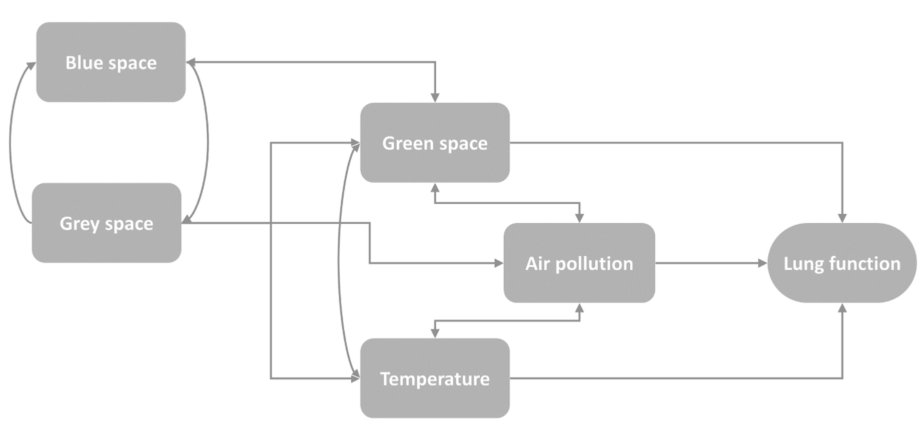

Fig. 1. Conceptual causal diagram.

2.4. Covariates

Age in years was derived from the date of birth and the date of spirometry. Sex (female vs male) was self-reported. Height in centimeters and weight in kilograms were measured. Body mass index (BMI) was calculated from height and weight. AC models were adjusted for participant's education, while MBC models were adjusted for education level of the participant as well as of the father and the mother. Self-reported highest educational level was classified as low (primary school or less), middle (secondary school or equivalent), or high (university degree or higher). Acknowledging that the information on education is difficult to harmonize and young participants in the MBC have not completed education yet, the educational level of the individual in MBC was constructed as a five-category variable, additionally including two categories: other (cannot be assigned to a specific school type) and NA (not available/not completed). Smoking status (current smoker, ex-smoker, or never smoker) was self-reported. Passive smoking was defined as a binary variable (yes/no to regular exposure to passive smoking) using cohort-specific definitions of regular exposure. In MBC only, maternal and paternal smoking were additionally defined as a binary passive smoking indicator (yes/no to maternal/paternal smoked regularly in childhood). Asthma was defined as doctor-diagnosed asthma self-reported by participants or their parents.

Asthma and smoking were *a priori* investigated as effect modifiers. For that purpose, smoking exposure was dichotomized as never-smoker vs ever-smoker (either current or ex-smoker) in AC, and as the absence of active and parental smoking vs smoking-exposed (either the individual was current or ex-smoker or maternal or paternal smoking was reported) in MBC.

2.5. Elastic net regression

We applied the exposome score approach to identify external exposome features and their interactions that show the strongest adjusted associations with FEV1 z-score. We decided to use elastic net regression as it is known to work well with correlated predictor variables. Elastic net regression tends to shrink the coefficients to be zero, and therefore performs variable selection, by introducing penalty terms to the standard least-square objective function (Zou and Hastie, 2005). After observing potential heterogeneity between AC and MBC from the single exposure models (for details see the Supplementary methods and Figs. S1-S2), and in order to investigate the potentially different effects of the external exposome on the lung function growth phase versus the lung function decline phase, we decided to apply the elastic net in AC ($N = 6052$) and MBC ($N = 4724$) separately, adjusting for slightly different sets of covariates. Elastic net was applied to the residuals of the spirometry parameter from regression on covariates *a priori* selected based on previous studies: age, age squared, sex, height, education, smoking status, passive smoking for MBC and AC; additionally paternal education, maternal education, and parental smoking for MBC. Even though the z-scores are by design independent from age, sex, and height, we decided to adjust the z-scores for age, sex, height, after observing remaining associations of the z-scores with age, sex, and height.

Given that the external exposome profile is largely driven by the cohort membership, we *a priori* decided not to adjust for cohort, at the cost of residual confounding. We also *a priori* decided not to adjust for BMI, considering BMI as a potential mediator of associations between air pollution or greenness and lung function. Adjustment for cohort or for BMI was explored as sensitivity analysis.

We developed the elastic net regression models in two steps. In the first step, the residuals of FEV1 z-scores were regressed on the 10 exposure variables, quadratic terms of each, and all possible two-way interaction terms (total number of predictors $N_p = 65$). The mixing parameter alpha was *a priori* fixed at 0.5, using the same weights for both penalty terms L1-norm as in LASSO and L2-norm as in ridge regression. The penalizing parameter lambda was determined from cross-validation to minimize cross-validation errors. The final penalty term is calculated as lambda $\times$ (0.5 $\times$ L1-norm + 0.5 $\times$ L2-norm). In the second step, elastic net was repeated but without penalizing (i) the variables for which the first step elastic net estimated non-zero coefficients and (ii) their lower order terms. This second step was necessary to ensure that when an interaction term was selected, its corresponding lower order terms were also included. For example, the interaction term of no2 and gsc had a non-zero coefficient in the first step, thus its lower order terms no2 and gsc were not penalized in the second step and therefore forced into the model.

The final coefficients indicate the effect estimate by 1 standard deviation change in the corresponding exposure, conditional on all other variables.

2.6. Sensitivity analysis

While the elastic net regression using the entire sample was reported and interpreted as the main finding, model performance was assessed by 10-fold cross-validation. For AC and MBC separately, the observations were randomly assigned to 10 groups. One group was set aside (a test set), and the two step elastic net regression was applied to the remaining 9 groups (a training set). This procedure was iterated 10 times, each of the 10 groups being used as a test set. Stability of the selection of non-zero coefficients across 10 groups was inspected qualitatively.

To explore if the findings are driven by between-cohort differences, we conducted leave-one-out cross-validation. For AC and MBC separately, one cohort was set aside and the two step elastic net regression was applied to the remaining cohorts. This procedure was repeated until every cohort was left out once.

The same procedure was repeated stratified by smoking exposure and by asthma, for AC and MBC separately.

2.7. Interpretation of elastic net regression results in the context of different scenarios

A non-zero coefficient out of the elastic net regression means the effect of a single predictor conditional on all other predictors at the mean values, which is not informative. The non-linear terms and penalized nature make it even more difficult to interpret the results from the elastic net regression. Individual exposome risk scores may be calculated as weighted sum of all predictors using the non-zero coefficients from the elastic net regression as weights. However, such aggregated exposome risk scores would not be useful for our study aims, i.e. to explore three domains of external exposome and their interplay in relation to lung function. We therefore put them into context by assuming different environmental scenarios such as: (1) improving air quality: reductions in NO_2, PM_{10}, and warm season ozone by 10 $\mu g/m^3$ and in $PM_{2.5}$ by 5 $\mu g/m^3$; (2) increasing greenness: increase in NDVI by 0.1 and reduction in the distance to the nearest green space by 100 m; (3) climate change: increase in 365-day average of daily mean temperature by 0.5 °C, 365-day standard deviation of daily mean temperature by 1 °C, warm season average of daily maximum temperature by 2 °C, and decrease in cold season average of daily minimum temperature by 1 °C; (4) improving air quality in the presence of climate change; (5) increasing greenness in the presence of climate change; (6) improving air quality and increasing greenness in the presence of climate change. (4)-(6) are defined as relevant combinations of (1)-(3). For air pollution and greenness, increments correspond roughly to 1 standard deviation change, except for the distance to the nearest green space for which its right-skewed distribution made it unrealistic to assume 1 standard deviation reduction. In the scenario of improving air quality, average exposure to air pollution would be close to the WHO Air Quality Guidelines (WHO, 2021). For aggregated temperature, increments correspond roughly to when daily mean temperature increases by 2 °C in summer and decreases by 1 °C in winter, considering that more frequent extreme temperature events are expected in the current climate change trend. Marginal effects were calculated in each scenario, assuming the corresponding increments compared to the observed mean exposures. Table 2 summarizes the environmental scenarios.

To further facilitate interpreting the results, the FEV1 z-scores were converted to absolute FEV1 values, taking four representative individuals of European ethnicity: 15-year old boy with 175 cm height, 15-year old girl with 165 cm height, 60-year old man with 176 cm height, and 60-year old woman with 163 cm height. They correspond roughly to the mean age and sex-specific mean height in MBC and AC, respectively.

All statistical analyses were conducted in R v4.1 (R Core Team. R: A Language and Environment for Statistical Computing., 2023) using "glmnet" (Friedman et al., 2010) package for elastic net regression and "rspiro" (Lytras and rspiro, 2023) for z-score conversion.

3. Results

Table 3 describes the characteristics of the study sample in total per MBC and AC and per cohort. We analyzed 4724 MBC participants (15.4 ± 2.2 years) and 6052 AC participants (59.6 ± 10.9 years). All MBC participants were below 20 years; participants of the Krakow birth cohort were younger than participants of the other MBCs (8 vs 15–16 years). SALIA consists of women only, older than participants of other ACs, with less frequent active smokers but with substantial exposure to passive smoking. Fig. 2 illustrates the distribution of external exposome features used in this study. All cohorts showed similar distributions of no2, ndvi3, and gsc, while exposure varied across cohorts for o3w and aggregated temperature variables. Participants of the Krakow birth cohort had particularly high exposures to pm25 and pm10. Fig. S3 visualizes the distribution of pre-bronchodilation FEV1 z-scores.

3.1. *Elastic net regression identified interactions within and between domains*

Final elastic net regression of FEV1 z-score identified 13 and 26 non-zero coefficients for MBC and for AC respectively (Fig. 3 and Tables S1-S2). Large numbers of second order terms were identified with non-zero coefficients, including quadratic terms and interaction terms within and between domains. For MBC, one quadratic term and one interaction within air pollution domain (o3wsq and no2_pm10), one between air pollution and greenness (no2_ndvi3), two between air pollution and temperature (o3w_tav and o3w_tmnc), and one between greenness and temperature (ndvi3_tmxw) were identified. For AC, three quadratic terms and two interaction terms within air pollution domain (no2sq, pm10sq, o3wsq, no2_o3w, and pm25_o3w), one quadratic term within greenness domain (ndvi3sq), one interaction term within temperature domain (tsd_tmxw), three between air pollution and greenness (no2_ndvi3, no2_gsc, and o3w_ndvi3), four between air pollution and temperature (no2_tmxw, o3w_tav, o3w_tsd, and o3w_tmnc), two between greenness and temperature (ndvi3_tsd and ndvi3_tmnc) were identified. The first order terms were often forced to the final model because of their higher order terms. Three out of the 7 first order terms included in the final model for MBC (pm10, ndvi3, and tmnc) were not penalized in the second step. For AC, all 10 exposures were included in the final model but six were forced due to their higher order terms (no2, pm25, pm10, ndvi3, tav, and tmnc). One quadratic term (o3wsq) and three interaction terms (no2_ndvi3, o3w_tav, and o3w_tmnc) were selected in both MBC and AC, although the direction of the effect for o3wsq and no2_ndvi3 is opposite in MBC and AC.

The 10-fold cross-validation showed that stability of selection varied by variables. Two out of the four interaction terms and the one quadratic term in MBC were stably selected, i.e. at least in 8 folds, while in AC 7 out of the 12 interaction terms and 3 out of the 4 quadratic terms were stably selected (Tables S1-S2 and Fig. S4).

The leave-one-out cross-validation showed that the variable selection was often affected by which cohort was left out (Tables S1-S2 and Fig. S5). For example, o3w_tmnc was not consistently selected, i.e. non-zero coefficient in the same direction as the final model, when any of the five MBCs but GINIplus/LISA South was left out or when any of the three ACs was left out. Selection of o3wsq, as another example, was more consistent in both MBC and AC, being selected with non-zero coefficient in the same direction regardless of which MBC was left out except PIAMA and regardless of which AC was left out except SAPALDIA.

In the sensitivity analysis, the additional adjustment for cohort or for BMI did not change the results considerably (Fig. S6).

3.2. *Environmental scenarios*

Based on the elastic net results, we explored different environmental scenarios (Table 4). Improving air quality or greenness appeared to increase FEV1 z-score in MBC and AC, while climate change predicted lower FEV1 z-scores, to larger extent in AC. The positive changes in FEV1 z-score by improving air quality diminished when at the same time climate change was assumed in the scenario. When the scenario of improving air quality in the presence of climate change was compared with the scenario of climate change alone, the negative changes in FEV1 z-score by climate change were attenuated by improving air quality. In the presence of climate change, increasing greenness was associated with lower FEV1 z-score in MBC.

Table 2
Assumed changes in exposures in different environment scenarios.

Scenario	Assumed changes in exposures									
	no2	pm25	pm10	o3w	ndvi3	gsc	tav	tsd	tmxw	tmnc
1. Improving air quality*	-10	-5	-10	-10	0	0	0	0	0	0
2. Increasing greenness**	0	0	0	0	0.1	-100	0	0	0	0
3. Climate change***	0	0	0	0	0	0	0.5	1	2	-1
4. Improving air quality in the presence of climate change	-10	-5	-10	-10	0	0	0.5	1	2	-1
5. Increasing greenness in the presence of climate change	0	0	0	0	0.1	-100	0.5	1	2	-1
6. Improving air quality and increasing greenness in the presence of climate change	-10	-5	-10	-10	0.1	-100	0.5	1	2	-1

Values are in original units: μg/m^3 for no2, pm25, pm10, o3w; m for gsc; °C for tav, tsd, tmxw, tmnc.
* Increments correspond to ca 1 standard deviation change and average exposure to air pollution would be close to the WHO Air Quality Guidelines.
** Increments correspond to ca 1 standard deviation change in NDVI.
*** Increments correspond to when daily mean temperature increases by 2 °C in summer and decreases by 1 °C in winter.

Table 3
Study sample characteristics and pre-bronchodilation spirometry parameters.

		MBC						AC			
		BAMSE	GINI/ LISANorth	GINI/ LISASouth	Krakow birth cohort	PIAMA	Total	KORA	SALIA	SAPALDIA	Total
N		1924	759	1084	280	677	4724	1050	700	4302	6052
Year of spirometry		2011-2013	2011-2013	2011-2014	2009-2011	2012-2014	2009-2014	2010-2010	2007-2010	2010-2011	2007-2011
Age [years]		16.7 (0.4)	15.0 (0.3)	15.3 (0.3)	7.8 (0.9)	16.4 (0.2)	15.5 (2.1)	54.6 (5.7)	73.5 (3.1)	58.6 (11.0)	59.6 (10.9)
Sex	Female	1043 (54.2)	398 (52.4)	561 (51.8)	140 (50.0)	361 (53.3)	2503 (53.0)	550 (52.4)	700 (100.0)	2140 (49.7)	3390 (56.0)
	Male	881 (45.8)	361 (47.6)	523 (48.2)	140 (50.0)	316 (46.7)	2221 (47.0)	500 (47.6)	0 (0.0)	2162 (50.3)	2662 (44.0)
Height [cm]		172.9 (9.0)	172.3 (8.1)	170.7 (8.1)	129.2 (7.5)	175.4 (8.7)	170.1 (13.4)	170.0 (9.3)	163.1 (5.9)	169.0 (9.3)	168.5 (9.2)
BMI [kg/m^2]		21.8 (3.1)	21.4 (3.5)	20.5 (3.0)	16.4 (2.2)	20.8 (2.6)	21.0 (3.3)	27.3 (4.9)	27.3 (4.5)	26.3 (4.5)	26.6 (4.6)
Education	Low	284 (14.8)	0 (0.0)[b]	47 (4.3)	280 (100.0)	110 (16.2)	721 (15.3)	501 (47.7)	124 (17.7)	223 (5.2)	848 (14.0)
	Middle	1637 (85.1)	0 (0.0)[b]	254 (23.4)	0 (0.0)	313 (46.2)	2204 (46.7)	266 (25.3)	334 (47.7)	2762 (64.2)	3362 (55.6)
	High	0 (0.0)	0 (0.0)[b]	743 (68.5)	0 (0.0)	252 (37.2)	995 (21.1)	281 (26.8)	239 (34.1)	1317 (30.6)	1837 (30.4)
	Other[a]	0 (0.0)	0 (0.0)[b]	38 (3.5)	0 (0.0)	0 (0.0)	38 (0.8)	–	–	–	–
	N/A	3 (0.2)	759 (100.0)[b]	2 (0.2)	0 (0.0)	2 (0.3)	766 (16.2)	2 (0.2)	3 (0.4)	0 (0.0)	5 (0.1)
Maternal education[c]	Low	126 (6.5)	89 (11.7)	71 (6.5)	0 (0.0)	3 (0.4)	289 (6.1)	–	–	–	–
	Middle	954 (49.6)	398 (52.4)	332 (30.6)	96 (34.3)	591 (87.3)	2371 (50.2)	–	–	–	–
	High	844 (43.9)	272 (35.8)	681 (62.8)	184 (65.7)	83 (12.3)	2064 (43.7)	–	–	–	–
Paternal education[c]	Low	157 (8.2)	222 (29.2)	126 (11.6)	3 (1.1)	7 (1.0)	515 (10.9)	–	–	–	–
	Middle	989 (51.4)	216 (28.5)	186 (17.2)	116 (41.4)	548 (80.9)	2055 (43.5)	–	–	–	–
	High	778 (40.4)	321 (42.3)	772 (71.2)	161 (57.5)	122 (18.0)	2154 (45.6)	–	–	–	–
Smoking	Current	222 (11.5)	36 (4.7)	83 (7.7)	0 (0.0)	78 (11.5)	419 (8.9)	207 (19.7)	16 (2.3)	757 (17.6)	980 (16.2)
	Former	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (5.6)	38 (0.8)	438 (41.7)	125 (17.9)	1660 (38.6)	2223 (36.7)
	Never	1702 (88.5)	723 (95.3)	1001 (92.3)	280 (100.0)	561 (82.9)	4267 (90.3)	405 (38.6)	559 (79.9)	1885 (43.8)	2849 (47.1)
Passive smoking		70 (3.6)	99 (13.0)	54 (5.0)	35 (12.5)	42 (6.2)	300 (6.4)	174 (16.6)	426 (60.9)	541 (12.6)	1141 (18.9)
Maternal smoking[c]		27 (1.4)	84 (11.1)	53 (4.9)	11 (3.9)	101 (14.9)	276 (5.8)				
Paternal smoking[c]		43 (2.2)	90 (11.9)	41 (3.8)	15 (5.4)	138 (20.4)	327 (6.9)				
FEV1 [L]		3.9 (0.7)	3.5 (0.6)	3.5 (0.6)	1.6 (0.3)	3.9 (0.7)	3.6 (0.9)	3.3 (0.8)	2.2 (0.4)	3.0 (0.8)	3.0 (0.8)
FVC [L]		4.7 (0.9)	4.1 (0.8)	4.0 (0.8)	1.7 (0.3)	4.7 (0.9)	4.2 (1.1)	4.3 (1.0)	2.9 (0.5)	4.1 (1.0)	4.0 (1.1)
FEV1/FVC		0.85 (0.07)	0.86 (0.06)	0.88 (0.06)	0.94 (0.06)	0.84 (0.06)	0.86 (0.07)	0.77 (0.07)	0.76 (0.07)	0.73 (0.07)	0.74 (0.07)
FEV1 z-score		−0.04 (0.93)	−0.68 (0.91)	−0.45 (0.93)	−0.22 (1.01)	−0.53 (0.92)	−0.32 (0.96)	0.32 (1.20)	0.21 (1.04)	−0.03 (1.04)	0.06 (1.08)
FVC z-score		0.15 (0.91)	−0.56 (0.91)	−0.47 (0.94)	−0.68 (0.97)	−0.37 (0.89)	−0.23 (0.97)	0.48 (1.00)	0.26 (0.95)	0.41 (0.90)	0.40 (0.92)
FEV1/FVC z-score		−0.34 (0.96)	−0.23 (0.95)	0.03 (1.00)	1.01 (1.16)	−0.31 (0.98)	−0.15 (1.04)	−0.34 (0.91)	−0.18 (0.89)	−0.70 (0.91)	−0.58 (0.93)
Asthma ever	Yes	333 (17.5)	35 (4.6)	103 (10.9)	32 (11.4)	93 (13.8)	596 (13.1)	45 (4.3)	61 (8.8)	539 (12.5)	645 (10.7)
	No	1571 (82.5)	718 (95.4)	845 (89.1)	248 (88.6)	580 (86.2)	3962 (86.9)	1004 (95.7)	633 (91.2)	3763 (87.5)	5400 (89.3)

Continuous variables presented as mean (standard deviation) and categorical variables as count (%).
MBC: mature birth cohort; AC: adult cohort; BMI: body mass index.
[a] only defined in MBC as "cannot be assigned to a specific school type".
[b] no information was available on the number of current school years or on the completed educational level in GINI/LISA North.
[c] only considered in MBC.

Fig. 4 illustrates the predicted changes in the different scenarios, converting the FEV1 z-scores to absolute FEV1 values for representative individuals: 15-year old boy with 175 cm height, 15-year old girl with 165 cm height, 60-year old man with 176 cm height, and 60-year old woman with 163 cm height. For example, change in FEV1 z-score predicted by improving air quality (reduction of no2, pm10, and o3w by 10 μg/m^3 and pm25 by 5 μg/m^3) corresponds to 0.18 L higher FEV1 for 60 year-old man with 176 cm height, which is equivalent to age-related decline in FEV1 for 6 years on average in the elderly.

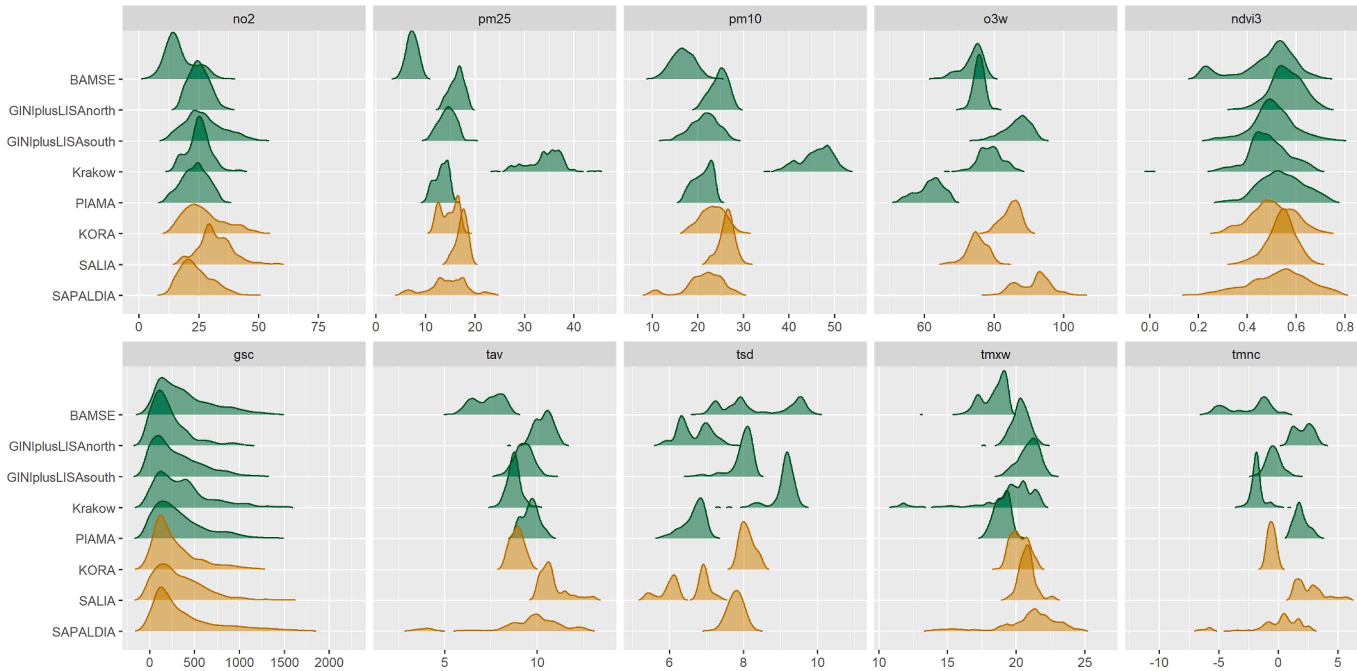

Fig. 2. Distribution of external exposome features per cohort.
Units in x-axis: μg/m^3 for no2, pm25, pm10, o3w; m for gsc; °C for tav, tsd, tmxw, tmncDistribution is drawn in green for mature birth cohorts and yellow for adult cohorts. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

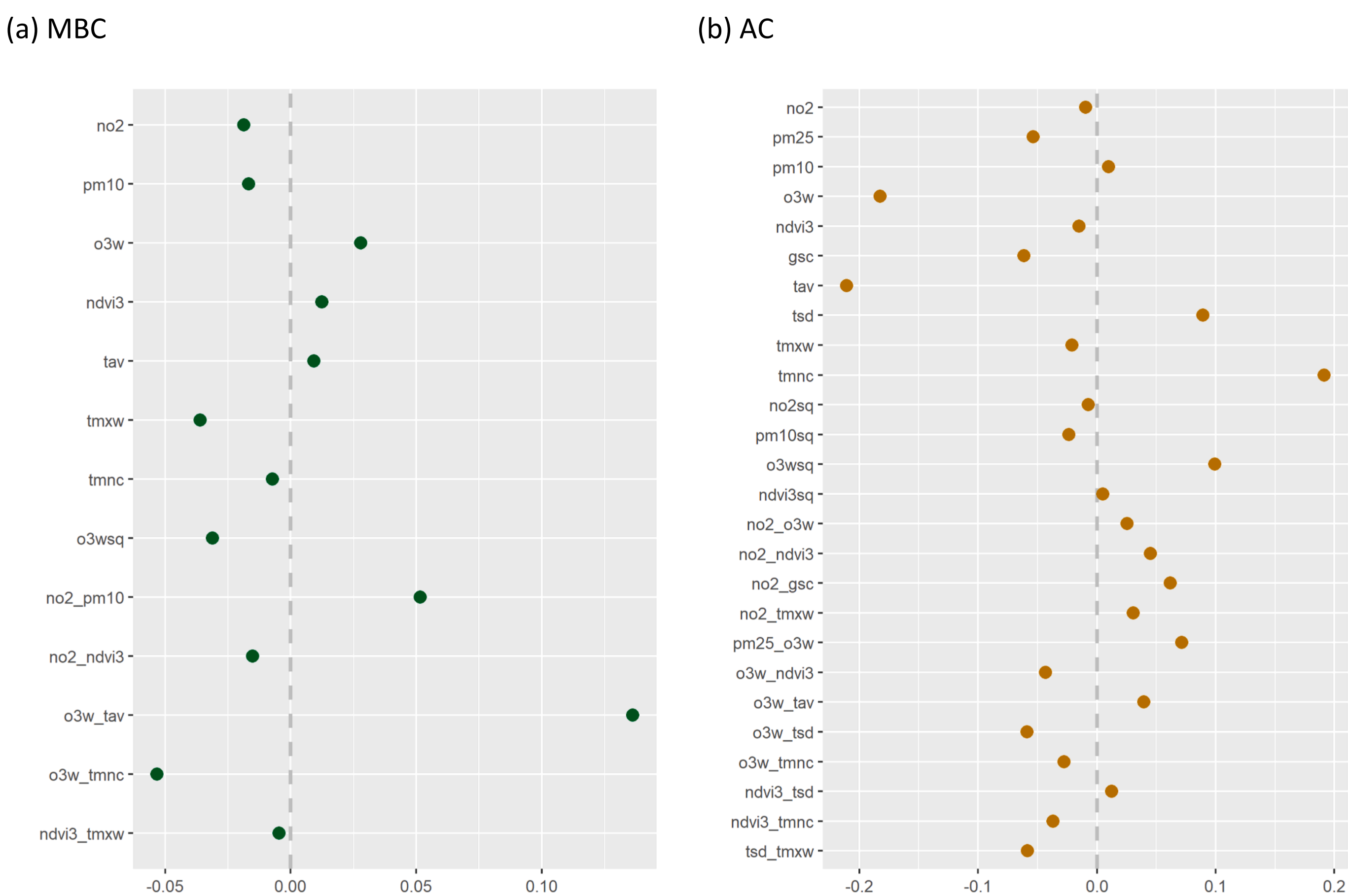

Fig. 3. Non-zero coefficients from elastic net regression of FEV1 z-score*.
* Residuals from regression on a priori selected sets of covariates: age, age squared, sex, height, education, smoking status, passive smoking for MBC and AC; additionally paternal education, maternal education, and parental smoking for MBC. Coefficients refer to the effect size of increase in the corresponding exposure by 1 standard deviation, conditional on all other exposures at the mean values; MBC: mature birth cohort; AC: adult cohort.

Table 4
FEV1 z-score changes predicted by the elastic net regression in different environmental scenarios.

Scenario	MBC					AC				
	All(N = 4724)	Smoking-free(N = 3917)	Smoking-exposed(N = 807)	Asthma (N = 596)	Non-asthma (N = 3962)	All(N = 6052)	Smoking-free(N = 2849)	Smoking-exposed(N = 3203)	Asthma (N = 645)	Non-asthma(N = 5400)
1. Improving air quality	+0.11	+0.12	−0.12	+1.66	+0.065	+0.35	+0.47	+0.36	+0.046	+0.36
2. Increasing greenness	+0.011	+0.00	+0.00	+0.012	+0.0094	+0.0093	−0.0055	+0.00019	−0.050	+0.014
3. Climate change	−0.033	−0.043	−0.029	+0.19	−0.048	−0.16	−0.15	−0.19	+0.00	−0.19
4. Improving air quality in the presence of climate change	+0.0086	+0.034	−0.31	+1.96	−0.014	+0.16	+0.24	+0.17	+0.046	+0.16
5. Increasing greenness in the presence of climate change	−0.026	−0.043	−0.029	+0.25	−0.056	−0.12	−0.14	−0.19	−0.050	−0.15
6. Improving air quality and increasing greenness in the presence of climate change	+0.033	+0.034	−0.31	+1.94	−0.0032	+0.21	+0.19	+0.17	+0.093	+0.21

MBC: mature birth cohort; AC: adult cohort; smoking-free is defined in AC if the individual was never smoker and in MBC if the individual was never smoker and neither maternal nor paternal smoking was reported; smoking-exposed is defined in AC if the individual was current or ex-smoker and in MBC if either the individual was current or ex-smoker or maternal or paternal smoking was reported.

Fig. 4. FEV1 changes predicted by the elastic net regression in different environmental scenarios for representative individuals.
Observed: Mean values of exposure observed in the current study sample, MBC and AC combined. Scenario 1: Improving air quality (reductions in NO_2, PM_{10}, and warm season ozone by 10 μg/m^3 and in $PM_{2.5}$ by 5 μg/m^3; increments correspond to ca 1 standard deviation change and average exposure to air pollution would be close to the WHO Air Quality Guidelines). Scenario 2: Increasing greenness (increase in NDVI by 0.1 and reduction in the distance to the nearest green space by 100 m; increments correspond to ca 1 standard deviation change in NDVI). Scenario 3: Climate change (increase in 365-day average of daily mean temperature by 0.5 °C, 365-day standard deviation of daily mean temperature by 1 °C, warm season average of daily maximum temperature by 2 °C, and decrease in cold season average of daily minimum temperature by 1 °C; increments correspond to when daily mean temperature increases by 2 °C in summer and decreases by 1 °C in winter). Scenario 4: Improving air quality in the presence of climate change (combination of scenarios 1 and 3). Scenario 5: Increasing greenness in the presence of climate change (combination of scenarios 2 and 3). Scenario 6: Improving air quality and increasing greenness in the presence of climate change (combination of scenarios 1, 2, and 3). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. *Smoking exposure stratified analyses*

While elastic net regression produced differences in non-zero coefficients in never- and ever-smokers in AC (Fig. S7 (b) and Table S4), they resulted in similar predicted FEV1 z-scores in the environmental scenarios (Table 4). In MBC, elastic net regression produced different results in smoking-free and smoking-exposed individuals (Fig. S7 (a) and Table S3). When the results were explored in the environmental scenarios, differences between smoking strata in the expected changes in FEV1 z-score were observed in the scenarios of improving air quality. Improving air quality was associated with positive changes in FEV1 z-score in smoking-free but not in smoking-exposed. More generally, the predicted FEV1 z-score changes under different environmental scenarios in smoking free participants followed the principles as observed and described above for the total study population more closely than in smoking exposed in MBC (Table 4).

3.4. *Asthma stratified analyses*

In the asthma-stratified analysis, the non-asthmatics stratum showed similar results to the main results, while the elastic net on the asthmatics resulted in none or much fewer non-zero coefficients in AC (Fig. S8 (b) and Table S6). In MBC, elastic net regression in the non-asthmatics resulted in non-zero coefficients larger in number and magnitude than in the asthmatics (Fig. S8 (a) and Table S5). Improving air quality was associated with much larger positive changes in FEV1 z-score in asthmatics than in non-asthmatics. Climate change was associated with negative changes in FEV1 z-score in non-asthmatics but not in asthmatics. The expected changes in FEV1 z-score under different exposure scenarios in non-asthmatics were more similar to the main results for both MBC and AC than in the asthmatics (Table 4).

4. Discussion

We explored cross-sectional associations of long-term exposure to air pollution, greenness, and temperature with lung function separately in two different age groups representing both, the lung function growth and the lung function decline phase. By applying elastic net regression, we were able to associate extensive number of exposome features, i.e. 10 exposure variables across the three domains and square terms of each exposure as well as all two-way interactions to select variables with mutually adjusted, strong effect estimates. Elastic net regression selected large numbers of quadratic terms and interactions, which reinforces the relevance of an exposome perspective in studying environmental factors for respiratory health, where exposures are correlated and can impact on shared or dependent biological pathways (Peters et al., 2021).

Interactions indicate that the lung function association of one exposure depends on the level of the second exposure. The joint effects can be synergistic – exposure to one risk factor may induce a pathway that aggravates the effect of the other risk factor – or they may exhibit shielding effects – two exposures share the biological mechanism which may become saturated. Conceivably, by including interaction terms, we may also capture different characteristics of the exposure and therefore mitigate misclassification risks and unmask different pathways affected by subgroups of an exposure domain. For example, while NDVI does not distinguish the types of green, its interaction terms as we observed with no2, o3w, tsd, tmnc in AC and no2 and tmxw in MBC, may capture the climate- and temperature-dependent type or use of the green, or the vegetation type. Vegetation type may have an adverse effect on lung function if allergenic. Lambert et al observed that exposure to pollen in infancy was associated with reduced lung capacity at age 15 years (Lambert, 2021). Proximity to greenspace may invite physical activity and therefore have a positive effect on lung function (Fuertes, 2018).

The large number of non-zero coefficients for interaction terms makes it difficult to translate the results. The coefficient resulting from the elastic net regression is interpreted as the effect size of increase in the corresponding exposure by 1 standard deviation, conditional on all other exposures at the mean values, which is not informative when the aim is to understand the effects of multiple exposures in the context of each other.

To provide more informative interpretation, we applied different environmental scenarios. Substantial improvement in air quality predicted better FEV1 in both AC and MBC, but to a substantially lower extent in MBC. When stratified by asthma in MBC, children with asthma appeared to strongly benefit from improving air quality, while increasing greenness or climate change made little difference given the predominant effect of improving air quality. When stratified by smoking in MBC, improving air quality did not predict better FEV1 in smoking-exposed children but in smoking-free children. Adults appeared to benefit from improving air quality regardless of their smoking status or asthma status. In both age groups, this benefit appeared to diminish in the presence of climate change, pointing to the potential co-benefit of climate change mitigation policies (see Box).

Equivalently, substantial increase in greenness predicted slightly better FEV1 in both age groups, but not in the presence of climate change. Rising temperature may change the duration and intensity of pollen and other aeroallergens (Zhang and Steiner, 2022; Storkey et al., 2014).

Climate change alone predicted lower FEV1 in AC and to less extent in MBC. Previous studies reported respiratory effects of short-term exposure to temperature. High temperature was associated with lower lung function (Lepeule, 2018), higher risk of asthma exacerbations in children (Schinasi, 2022), and higher risk of COPD hospitalization (Konstantinoudis, 2022). Both heat and cold were associated with respiratory prescriptions (Royé, 2021), respiratory mortality (Iñiguez et al., 2021), and respiratory symptoms in COPD patients (Scheerens, 2022). We observed that the negative changes in FEV1 z-score by climate change were attenuated by improving air quality and to much lower extent by increasing greenness.

We analyzed MBC and AC separately, to explore difference in the external exposome effects on lung function growth phase and lung function decline phase. The elastic net regression results from MBC and AC differed in terms of the selected variables, the direction and magnitude of effect estimates, and the stability of the selection. More variables were selected with larger effect estimates in AC than in MBC. The expected changes in FEV1 z-scores in the environmental scenarios were consistent in the direction but larger in AC than in MBC. This observed difference may indicate life-course differences in exposure susceptibility or latency of complex environment effects on lung function. What we observed in the adults' lung function may be the results of accumulated exposure.

Our study has several strengths and limitations. We took advantage of well-characterized population-based cohorts from multiple European countries with spirometry performed according to the American Thoracic Society/European Respiratory Society. While our study sample covered late adulthood (38 – 81 years), our sample does not cover the whole life-course. The age range 19–37 years, which includes the lung function plateau phase, preceding the decline at older ages, is neither covered by MBC nor by AC. Every individual in our study sample was assigned to high resolution exposure estimates derived from the same pan-European models specifically developed in the EXPANSE project. However, our study is still subject to differential measurement error by exposures. Type, likelihood, and magnitude of measurement error vary across exposures, presenting a common challenge in exposome studies. We applied the exposome approach to examine comprehensive interactions between air pollution, greenness, and temperature, which is rarely done in environmental epidemiology studies. Elastic net regression works well with collinearity and performs variable selection on the grounds of the strength of their association with the outcome variable, which suits the aim of this study. However, the variable selection may be

Box

Potential Policy Implications in the Context of Future Replication of the Results

- The benefit of air quality improvement on lung function may decrease in the presence of climate change.
- The benefit of residential greenspace on lung function may decrease in the presence of climate change possibly through temperature effects on vegetation.
- Climate change itself, characterized by daily temperature increase in summer and decrease in winter, predicts lower lung function.
- Urban planning and environmental policies should consider the interdependency of respiratory health effects of air pollution, greenspace, and temperature.

unstable in case of strong collinearity. Cross-validation showed various degree of stability in the variable selection. Such unstably selected variables may be a chance finding or a result of high correlation between variables. In case of highly correlated predictor variables, the elastic net regression may select either of them, leading to unstable selection. But this unstable selection would likely not affect the prediction performance. Another limitation of the elastic net regression is the difficulty to obtain unbiased standard error. The cross-sectional and observational nature of this study does not allow causal inference. We acknowledge that by assigning the same season cutoffs for warm season ozone, we may have added different misclassification of this exposure in different countries. The four aggregated temperature variables may not capture extreme temperature changes over short periods sufficiently and the climate change scenario may not reflect the temperature trends and patterns currently being observed in Europe. Although spirometry was performed in all participating cohorts according to the ATS/ERS recommendations, the spirometry measurement may still be affected by differences in device and fieldworker. One mitigation measure was to focus on FEV1 as the lung function outcome of interest in this study, as FEV1 is measured with least error. Bias due to different spirometry devices would have been addressed in part by adjustment for cohort (or for study center in case of multi-center studies), but we *a priori* decided against it, because large proportion of the variation in the exposome profile is driven by cohort membership and therefore adjustment for study center would lead to inflated standard error. Indeed, we observed that variable selection was less stable in the leave-one-out cross-validation. By not adjusting for cohort, we cannot rule out that our findings may be biased by residual confounding. Finally, we conducted a complete case analysis, which may have introduced bias and therefore limited the generalizability of our findings.

5. Conclusions

Long-term exposure to air pollution, greenness, and temperature and their interactions showed associations with FEV1 in European adults, and to less extent in children and adolescents. The lung function associations of exposure domains are best characterized in an exposome approach.

CRediT authorship contribution statement

Ayoung Jeong: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Gianfranco Lovison:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Alonso Bussalleu:** Writing – review & editing, Data curation. **Marta Cirach:** Writing – review & editing, Data curation. **Payam Dadvand:** Writing – review & editing, Data curation. **Kees de Hoogh:** . **Claudia Flexeder:** Writing – review & editing, Data curation. **Gerard Hoek:** Writing – review & editing, Data curation. **Medea Imboden:** Writing – review & editing, Supervision, Project administration, Investigation. **Stefan Karrasch:** Writing – review & editing, Investigation, Data curation. **Gerard H. Koppelman:** Writing – review & editing, Funding acquisition, Conceptualization. **Sara Kress:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Petter Ljungman:** Writing – review & editing, Data curation. **Renata Majewska:** Writing – review & editing, Investigation, Data curation. **Göran Pershagen:** Writing – review & editing, Project administration, Funding acquisition. **Regina Pickford:** Writing – review & editing, Project administration. **Youchen Shen:** Writing – review & editing, Data curation. **Roel C.H. Vermeulen:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Jelle J. Vlaanderen:** Writing – review & editing, Project administration, Funding acquisition. **Megi Vogli:** Writing – review & editing, Project administration, Data curation. **Kathrin Wolf:** Writing – review & editing, Data curation. **Zhebin Yu:** Writing – review & editing, Project administration, Data curation. **Erik Melén:** Writing – review & editing, Investigation, Funding acquisition, Data curation, Conceptualization. **Agnieszka Pac:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation. **Annette Peters:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation. **Tamara Schikowski:** Writing – review & editing, Supervision, Resources, Funding acquisition, Data curation. **Marie Standl:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation. **Ulrike Gehring:** Writing – review & editing, Project administration, Data curation, Conceptualization. **Nicole Probst-Hensch:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109269.

Data availability

The data that support the findings of this study are available upon reasonable request separately from the participating cohorts.

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