



Lifelong exposure to air pollution and greenness in relation to asthma, rhinitis and lung function in adulthood

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ABSTRACT

Objectives: To investigate if air pollution and greenness exposure from birth till adulthood affects adult asthma, rhinitis and lung function. **Methods:** We analysed data from 3428 participants (mean age 28) in the RHINESSA study in Norway and Sweden. Individual mean annual residential exposures to nitrogen dioxide (NO₂), particulate matter (PM₁₀ and PM_{2.5}), black carbon (BC), ozone (O₃) and greenness (normalized difference vegetation index (NDVI)) were averaged across susceptibility windows (0–10 years, 10–18 years, lifetime, adulthood (year before study participation)) and analysed in relation to physician diagnosed asthma (ever/allergic/non-allergic), asthma attack last 12 months, current rhinitis and low lung function (lower limit of normal (LLN), z-scores of forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC below 1.64). We performed logistic regression for asthma attack, rhinitis and LLN lung function (clustered with family and study centre), and conditional logistic regression with a matched case-control design for ever/allergic/non-allergic

Abbreviations: BC, black carbon; CI, confidence interval; DAG, directed acyclic graph; DEHM, Danish Eulerian Hemispheric; ESCAPE, European Studies of Cohorts for Air Pollution Effects; EU, European Union; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; GIS, geographic information system; GLI, Global Lung Function Initiative; LLN, lower limit of normal; LUR, land-use regression; NDVI, normalized difference vegetation index; NIR, near-infrared light; NO₂, nitrogen dioxide; O₃, ozone; OLI, Operational Land Imager; OR, odds ratio; PM_{2.5}, particulate matter with an aerodynamic diameter lower than 2.5 μm; PM₁₀, particulate matter with an aerodynamic diameter lower than 10 μm; RED, visible red light; RHINESSA, Respiratory health in Northern Europe, Spain and Australia; SD, standard deviation; TM, thematic mapper; WHO, World Health Organization.

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asthma. Multivariable models were adjusted for parental asthma and education. **Results:** Childhood, adolescence and adult exposure to NO_2 , PM_{10} and O_3 were associated with an increased risk of asthma attacks (ORs between 1.29 and 2.25), but not with physician diagnosed asthma. For rhinitis, adulthood exposures seemed to be most important. Childhood and adolescence exposures to $\text{PM}_{2.5}$ and O_3 were associated with lower lung function, in particular FEV_1 (range ORs 2.65 to 4.21). No associations between NDVI and asthma or rhinitis were revealed, but increased NDVI was associated with lower FEV_1 and FVC in all susceptibility windows (range ORs 1.39 to 1.74). **Conclusions:** Air pollution exposures in childhood, adolescence and adulthood were associated with increased risk of asthma attacks, rhinitis and low lung function in adulthood. Greenness was not associated with asthma or rhinitis, but was a risk factor for low lung function.

1. Introduction

Air pollution is one of the world's largest known environmental health threats and an important cause of both respiratory mortality and morbidity (World Health Organization (WHO), 2005). Individuals with pre-existing health conditions such as asthma are especially vulnerable for exposure to air pollution, as it can trigger exacerbations. However, although contemporary and early life air pollution has been linked to asthma, the role of air pollution exposure throughout the lifespan in the development of asthma is still not fully resolved (Khreis et al., 2017). Regarding lung function, studies have shown a decrease in forced expiratory volume in 1 s (FEV_1) in children (Yang et al., 2016; Mölter et al., 2013). Less is known regarding adult lung function after lifetime exposure to air pollution (Schultz et al., 2017; Adam et al., 2015).

Contrary to air pollution, greenness has been linked to beneficial health effects such as reduced risk of diabetes and hypertension. However, the effects of greenness on respiratory health and allergy are limited and results are heterogeneous depending on whether residence is in urban or rural areas (Fuertes et al., 2014; Davdand et al., 2014; Lambert et al., 2017). Both local vegetation and season may affect population exposure to allergenic pollen and fungal spores, which at least partly can explain the varying associations in different locations

(Fuertes et al., 2014; Ghiani et al., 2012). Also, regarding lung function the results are heterogeneous; a recent study found an association with higher lung function after growing up nearby green spaces (Fuertes et al., 2020), while other studies did not find any associations (Boeyen et al., 2017).

Lung development starts in the embryonic phase and continues gradually with further growth and lung maturation in utero and post-natally until the lung matures and lung function peaks by the age of 20–25 years (Sharma and Goodwin, 2006). During development, the lungs are particularly vulnerable, and several chronic respiratory diseases in adulthood originate from effects associated with exposures in this period (Ranganathan, 2010; Saglani et al., 2007). However, it remains unclear in which particular time windows the lungs are most susceptible to harmful and beneficial exposures, such as air pollution and greenness.

The aim of this study was to examine whether exposure to air pollution and greenness during different susceptibility windows can be associated with respiratory health in adulthood (Fig. 1). All exposures were calculated from birth up to adulthood based on detailed individual-level residential moving history. Asthma, rhinitis and lung function were selected as indicators of respiratory health.

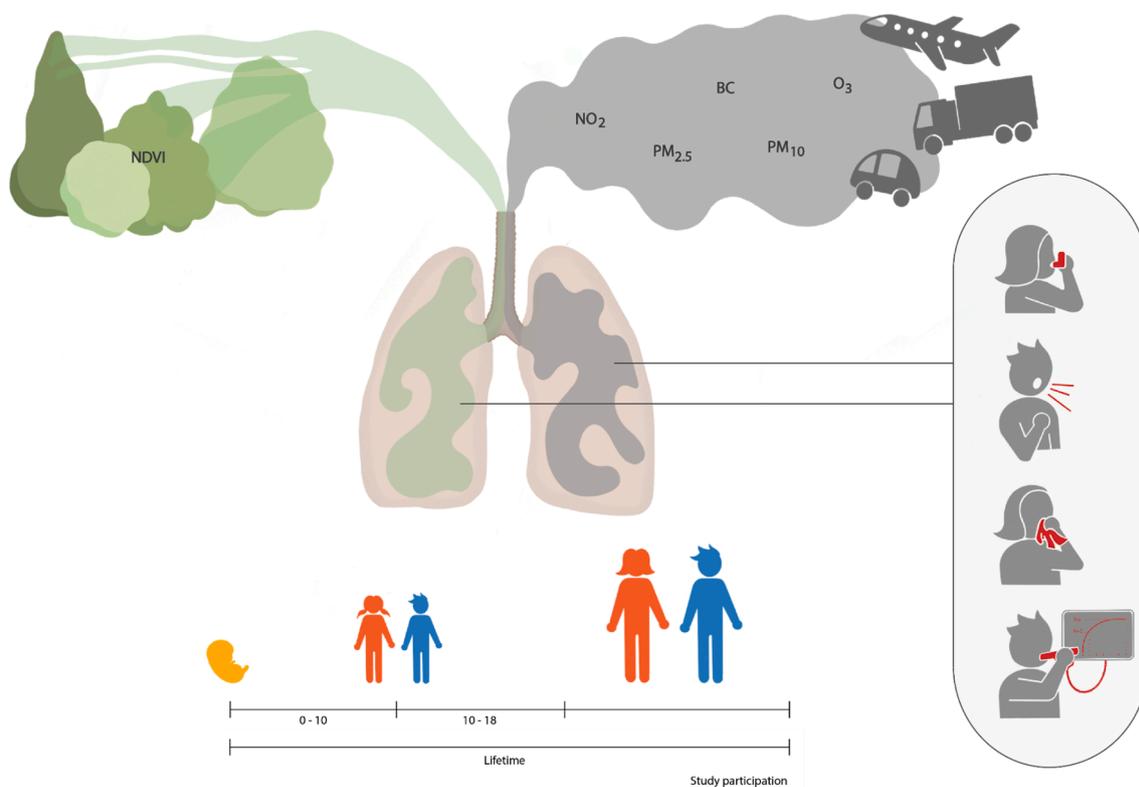


Fig. 1. Longitudinal study, retrospective design with a lifelong history of exposure based on registry-based residential moving history. Overview of the exposures (greenness and air pollutants), the susceptibility windows (0–10 years, 10–18 years and lifetime from birth until study participation) and the outcomes (physician diagnosed asthma (allergic and non-allergic), asthma attack, rhinitis and lung function) in the study. Illustration by Taran Johanne Neckelmann.

2. Methods

2.1. Study design and population

We included participants born after 1975 from the Norwegian (Bergen) and Swedish (Umea, Gothenburg and Uppsala) centres in the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) study (RHINESSA Generation Study Homepage, 2020), conducted from 2013 to 2015 (Fig. 2). Participants born earlier than 1975 were excluded, as individual residential address histories were not available for the years before. All the participants answered questionnaires, with a response rate of 44% and 40% in Sweden and Norway, respectively (Kuiper et al., 2018), while a sub-sample in each centre also underwent clinical examinations. Regional committees of medical research ethics approved the study according to national legislations and written informed consent was obtained from all participants before participation (Overview of ethics committees and approval numbers of RHINESSA centers, 2020).

2.2. Outcomes

2.2.1. Asthma and rhinitis

The following outcomes were analysed: ever asthma, allergic and non-allergic asthma, asthma attack last 12 months and rhinitis. They were collected through questionnaires in the study period between 2013 and 2015. Ever asthma was defined by a positive answer to “Have you ever had asthma diagnosed by a doctor?”, and self-reported age of diagnosis. Allergic and non-allergic asthma was defined based on the same question as ever asthma in addition to a question on rhinitis: “Do you have any nasal allergies including rhinitis?”. Asthma attack was defined as a positive answer to “Have you had an attack of asthma in the

last 12 months?”.

2.2.2. Lung function

Pre-bronchodilator spirometry was conducted using an EasyOne Spirometer and performed with assistance from trained technicians. The participants conducted up to eight manoeuvres until adequate measures of maximum forced expiratory volume in one second (FEV₁) and maximum forced vital capacity (FVC) were achieved. Impaired lung function was defined as lung function below the lower limit of normal (LLN). To calculate the LLN for FEV₁, FVC and FEV₁/FVC we used reference values from Global Lung Function Initiative (GLI 2012) with LLN defined as a z-score < 1.64 standard deviations (SD) (Quanjer et al., 2012).

2.3. Exposure assignments

Geocoded residential addresses for each year from birth onwards were used to assign individualized exposures for all the participants. The address history information was retrieved from the Swedish and Norwegian national population registries.

2.3.1. Air pollution

Annual mean concentrations for nitrogen dioxide (NO₂), particulate matter with diameter < 2.5 µm (PM_{2.5}), and < 10 µm (PM₁₀), ozone (O₃) (µg/m³) and black carbon (BC) (10⁻⁵m⁻¹) were assigned to each participant’s individual geocoded residential history based on air pollution rasters previously developed (Vienneau et al., 2013; de Hoogh et al., 2018, 2016) (Table S1). The rasters are based on Western Europe-wide hybrid land use regression (LUR) models that combine predictor variables from satellite-derived and chemical transport model estimates of air pollution concentrations, geographic information system (GIS)

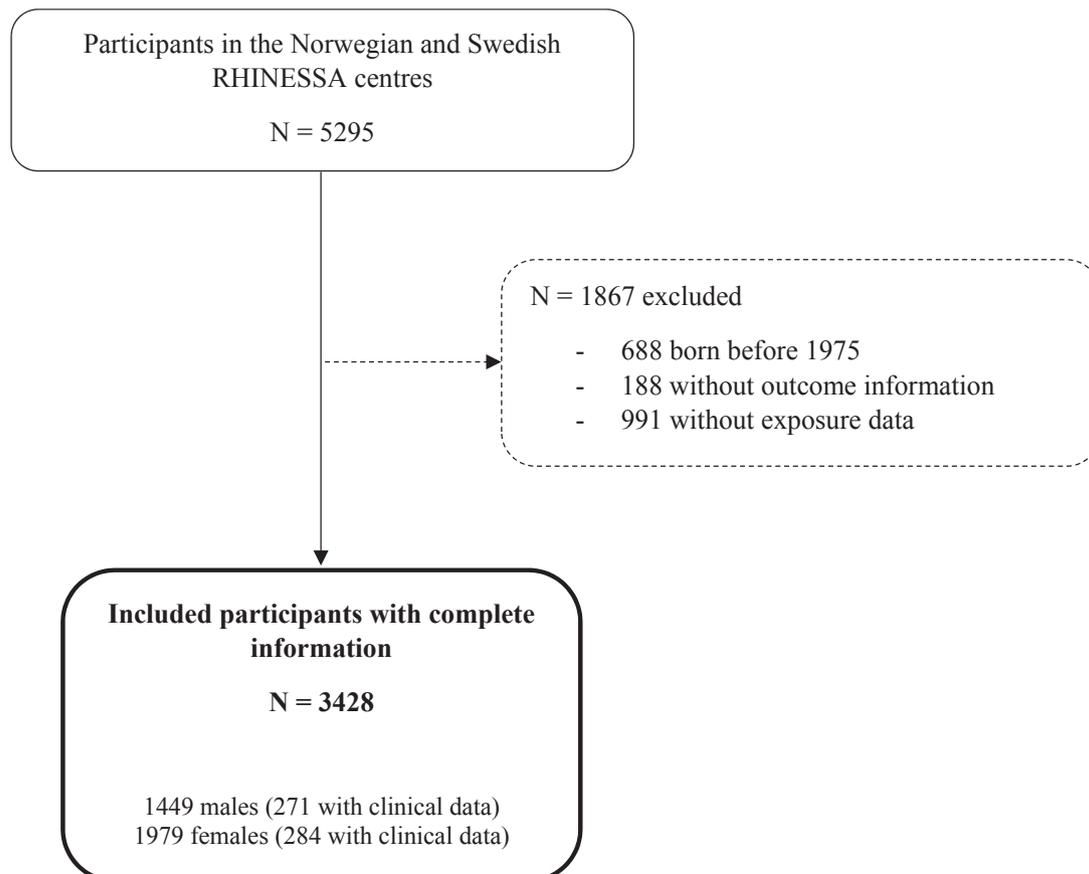


Fig. 2. Flowchart of the RHINESSA study population.

variables representing roads, land use and altitude with measurement data from the AIRBASE monitoring network, except for BC where measurements from the European Study of Cohorts for Air Pollution Effects (ESCAPE) were used (Eeftens et al., 2012). Annual mean PM₁₀ exposures were extracted from LUR models from 2007 (Vienneau et al., 2013), while for assessing the annual mean NO₂, PM_{2.5}, O₃ and BC exposures hybrid LUR models from 2010 were used (de Hoogh et al., 2018, 2016). Annual concentrations for other years than the model years were back-and-forward-extrapolated using the ratio method following the procedure in line with the ESCAPE procedure (Procedure for back-extrapolation, 2020). Extrapolation was based on calculation data from the Danish Eulerian Hemispheric (DEHM) model (Christensen, 1997) and done for each year from 1990 to the study years. For the years prior to 1990, there was no estimated air pollution data available for these areas. Consequently, we applied the estimations for the year 1990 as a proxy.

2.3.2. Greenness

Greenness (vegetation degree) was measured by the Normalized Difference Vegetation Index (NDVI) (Tucker, 1979) derived from cloud-free Landsat 4–5 Thematic Mapper (TM) and 8 Operational Land Imager (OLI) satellite images (Satellite images, United States Geological Survey, 2020) (Table S2). NDVI ranges from -1 to 1 , where values close to 1 indicate highly vegetated areas (Vegetation, 2000). During the most vegetation rich months (May, June, July) satellite images were retrieved every 5 years from 1984 till 2014 (Table S3) for the areas of interest. The same values were kept until next retrieval. Residential greenness was defined as mean NDVI in four circular buffer zone around the participants' address. We selected the 300-m buffer for NDVI as the main analyses, in accordance with the World Health Organization (WHO) recommendations (WHO, 2016). Other buffer zones (100-m, 500-m and 1000-m) served as sensitivity analyses (Table S7).

2.3.3. Susceptibility windows

Annual mean exposures to greenness and the air pollutants were averaged over different time windows: 0–10 years, 10–18 years, from birth until time of participation in the study (lifetime) and also separately for one year prior to participation. Furthermore, cumulative exposures were calculated for the asthmatics from birth till time of asthma diagnosis to be used in the matched analysis (explained in further detail in paragraph 2.5).

2.4. Covariates

Directed Acyclic Graphs (DAGs) were made to identify which potential confounders to include in the statistical models (Figures S1 and S2) (Greenland et al., 1999; DAGitty, 2020). We included all covariates in the DAG that we a priori considered to be of potential importance for the analyses. Parental education level and parental asthma were the only variables selected as true confounders in the DAG, i.e. associated with both the exposures and the outcomes and preceding the childhood exposures in time. The participants reported their own and their parents' educational level by the categories primary school, secondary school/technical school and college/university, while parental asthma was defined from at least one of the parents having asthma, with the question "Have your biological parents ever had asthma?" and with separate answer categories for "mother" and "father".

2.5. Statistical analysis

For lung function, asthma attack and rhinitis, we analysed associations between annual mean exposures in the following time windows: childhood (0–10 years) and adolescence (10–18 years) in addition to annual mean lifetime exposures. For asthma attack and rhinitis, we also analysed associations of exposures the last year before participation in RHINESSA. For the asthma outcomes, we analysed associations of

cumulative exposures for each year up to the age of asthma diagnosis using a matched case-control design. We defined cases as participants with physician diagnosed asthma. Controls were sampled from the non-asthmatic participants and matched to the cases (2 controls per case) by study centre, sex and age at participation, with cumulative exposures defined at the age corresponding to age of diagnosis for the cases. Separate matched case-control datasets were set up for asthma, allergic asthma and non-allergic asthma. In the asthma dataset, all asthma cases were included. In the allergic asthma dataset, the subjects with non-allergic asthma were excluded and, in the non-allergic asthma dataset, the subjects with allergic asthma were excluded. Matching was performed using R version 3.5.1 (R Core Team, 2018).

Exposures of air pollution and greenness in relation to the outcomes were analysed using the following methods: logistic regression for asthma attack, rhinitis, and LLN FEV₁, FVC and FEV₁/FVC; and conditional logistic regression for ever asthma, allergic asthma and non-allergic asthma. The measure of associations used were odds ratios (ORs). For the logistic regression analyses, we constructed a variable combining family and centre and added it to the model. The conditional logistic regression was performed on the matched case control dataset and no clustering was therefore necessary. In all these analyses the following increments of exposures were used: BC per 1- $\mu\text{g}/\text{m}^3$ increase, NDVI per 0.1-unit increase. NO₂, PM exposures and O₃ per 10- $\mu\text{g}/\text{m}^3$ increase.

NO₂, PM_{2.5}, PM₁₀ and BC were highly correlated with each other and therefore not included in the same models. For each of these pollution exposures, we included O₃ and NDVI in the multivariable models together with the covariates from the DAG. O₃ was included since correlations between O₃ and other pollutants was more moderate (WHO, 2013). NDVI was included because greenness and air pollution are the two main exposures of interest in our study, and not correlated with each other (Table S4a-S4c). Following this line of reasoning, we also adjusted the O₃ analysis for NDVI and NO₂, and the NDVI analyses for O₃ and NO₂. Air pollution and greenness variables were included in the models as continuous variables without transformation. We performed separate analyses for each time window due to high correlations between them (all air pollutant correlation coefficients > 0.86 , Table S5a-S5f).

Imputation of missing values was performed on the covariates (parental education and parental asthma), air pollution exposures and greenness to retain all available information. Proportion of missing ranged from 2% (parental education) to 9% (NDVI during certain years in early childhood). Some subjects lacked exposure data in early childhood due to missing address information from the Norwegian population registry where the first registered address is the first moving address instead of birth address. The imputation model included the same variables as those contained in the final analytical models. For the matched case-control datasets, five values were imputed for each missing observation using a multilevel approach as implemented in the *mice*-package in R (van Buuren and Groothuis-Oudshoorn, 2011). This imputation was done using the long-format of (exposure) data for all individuals (one line per year) before deriving cumulative air pollution and greenness estimates and before extracting cases and controls. The pooling of estimates with 95% confidence intervals (CIs) across imputed datasets were performed using Rubiñs combination rules. For the lung function, asthma attack and rhinitis analyses, multiple imputation and pooling of estimates was performed using Stata. Missing values were filled in with the "mi impute mvn" procedure, using an iterative Markov chain Monte Carlo method with 200 imputations (StataCorp., 2019).

An association was interpreted to be present if the effect estimate from the adjusted model reached statistical significance at alpha-level 0.05. R version 3.5.1 and Stata version 16.0 were used to perform the statistical analyses.

3. Results

3.1. Study population

The majority (58%) of participants were female with a median age for the total study population of 28.4 years, ranging from 18 to 40 years. All participants were born between 1975 and 1997 (Table 1).

3.2. Air pollution

None of the mean air pollution exposure values exceeded the limit values of the European Union (EU) (Table S6), while PM_{2.5} surpassed the WHO guidelines values in all centers and PM₁₀ exceeded the WHO guideline in two of the centers (Uppsala and Gothenburg). Mean greenness exposure values ranged between 0.5 and 0.6 across centres and time windows (Table S7). NO₂, PM_{2.5}, PM₁₀ and BC were highly correlated with each other, with coefficients ranging from 0.603 to 0.917 (Table S4a-S4c).

3.3. Ever asthma, allergic and non-allergic asthma

NO₂ was a risk factor for ever asthma and allergic asthma before (OR 1.01 (1.00–1.03) and 1.02 (1.00–1.04), respectively) but not after adjustment for confounders (OR 1.00 (0.98–1.02) and 1.02 (0.99–1.05),

respectively, Table 2). BC was a risk factor for ever asthma in univariable analysis (OR 1.03 (1.00–1.07)) but was a protective factor for non-allergic asthma after adjustment (OR 0.92 (0.85–1.00)). O₃ was associated with less risk for non-allergic asthma (OR 0.91 (0.84–1.00)).

Greenness was not associated with asthma diagnosis.

3.4. Asthma attacks last 12 months

Exposure to NO₂, PM₁₀ and O₃ was significantly associated with an increased risk of asthma attack both in the time window 10–18 years and lifetime exposure (ORs ranging from 1.29 for NO₂ in the time window 10–18 years to 2.25 for lifetime O₃ exposure (Table 3). Exposure to PM₁₀ and O₃ also increased the risk for asthma attack in the time window 0–10 years (ORs 1.59 and 1.94, respectively). For all pollutants in all time windows, however, there was a tendency for increased risk for asthma attacks with increasing pollution exposures (ORs ranging from 1.24 to 1.85, although with p-values > 0.05). Additional analysis showed that exposures of NO₂, PM_{2.5}, PM₁₀, BC and O₃ the year before study participation were all associated with increased risk of asthma attack (Table S8). Greenness was not associated with asthma attack in any of the time windows.

3.5. Current rhinitis

None of the exposures were associated with a higher risk of rhinitis when limiting the focus to the first susceptibility window 0–10 years or lifetime exposure (Table 4). PM₁₀ exposure in the time windows 0–10 years and 10–18 years, as well as lifetime exposure, was associated with increased risk of rhinitis before (ORs 1.21, 1.28 and 1.29, respectively) but not after adjustment for confounders (ORs 1.14, 1.7 and 1.21, respectively). Unadjusted analyses for the susceptibility window 10–18 years revealed an increased risk of rhinitis after exposure to NO₂, PM_{2.5}, PM₁₀ and BC (ORs from 1.13 to 1.29); but after adjustment for covariates only NO₂ remained statistically significant (1.14 (1.01–1.28)), although the tendencies remained the same in all exposures (ORs from 1.14 to 1.27, Table 4). Additional analysis (Table S9) showed that NO₂, PM_{2.5}, PM₁₀ and BC exposures the year before study participation were all associated with increased risk for rhinitis, both before and after adjustment for confounders. Greenness was not associated with rhinitis.

3.6. Lung function

O₃ exposure increased the risk of low lung function in all time windows (Table 5). The OR for FEV₁ < LLN ranged from 2.74 to 3.69 before adjustment, and from 3.84 to 4.47 after adjustment. The OR for FVC < LLN was statistically significant for all time windows before adjustment (OR from 3.22 to 4.23), with the same tendency also after adjustment although this was only significant for the time window 0–10 years (ORs across time windows ranging from 4.04 to 5.95). PM_{2.5} exposure was a risk factor for low FEV₁ in both the 0–10 year and 10–18 year time windows (ORs 2.65 and 3.21, respectively), and for low FVC in the time window 10–18 years and lifetime exposure (ORs 3.70 and 3.50, respectively). Even the estimates that were not statistically significant (for all pollutants in all time windows), showed a clear tendency for increased risk for low lung function with increasing pollution exposures (ORs ranging from 1.50 to 3.43, although with p-values > 0.05). Greenness exposures increased the risk of low FEV₁ in all time windows, and for lifetime exposure and exposure during the period 10–18 years it also increased the risk of low FVC. For FEV₁/FVC < LLN, only BC exposure in the time window 10–18 years was identified as a risk factor (Table S10-S11).

4. Discussion

In this retrospective cohort study with a lifelong exposure based on registry-based residential moving history, we found an increased risk of

Table 1
Study population characteristics. N = 3428 participants.

| Characteristics ^a | RHINESSA N |
|------------------------------------|---------------|
| N | 3428 |
| Bergen (%) | 1502 (43.8) |
| Gothenburg (%) | 487 (14.2) |
| Umea (%) | 676 (19.7) |
| Uppsala (%) | 763 (22.3) |
| Female (%) | 1979 (57.7) |
| Mean age (SD) | 28.2 (6.1) |
| Physician diagnosed asthma (%) | 549 (16.0) |
| Asthma type | |
| Allergic asthma (%) | 283 (8.3) |
| Non-allergic asthma (%) | 262 (7.6) |
| Rhinitis (%) | 965 (28.4) |
| Asthma attack last 12 months (%) | 157 (4.6) |
| Lung function ^b | |
| FEV ₁ in liter (SD) | 3.9 (0.8) |
| FEV ₁ z-score (SD) | −0.4 (0.9) |
| FEV ₁ < LLN (%) | 42 (7.6) |
| FVC in liter (SD) | 4.8 (1.0) |
| FVC z-score (SD) | −0.2 (0.9) |
| FVC < LLN (%) | 27 (4.9) |
| FEV ₁ /FVC ratio (SD) | 0.8 (0.1) |
| FEV ₁ /FVC z-score (SD) | −0.4 (0.8) |
| FEV ₁ /FVC < LLN (%) | 41 (7.4) |
| Paternal education (%) | |
| Primary school | 509 (15.0) |
| Secondary school | 1154 (34.0) |
| College/university | 1734 (51.0) |
| Maternal education (%) | |
| Primary school | 407 (11.9) |
| Secondary school | 1095 (32.1) |
| College/university | 1912 (56.0) |
| Parental asthma (%) | |
| Paternal | 305 (9.1) |
| Maternal | 399 (11.9) |

Abbreviations: FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; LLN, lower limit of normal; SD, standard deviation.

^a Missing information on the following variables: age (17), rhinitis (29), asthma attack last 12 months (8), paternal education (31), maternal education (14), paternal asthma (63), maternal asthma (61). ^b Lung function data collected in a subsample N = 555. Z-scores and LLN are based on the GLI-2012 (Quanjer et al., 2012), with LLN defined as z-score < 1.64 SD.

Table 2

Conditional logistic regression analyses of physician diagnosed asthma (522 cases and 1044 controls), allergic asthma (276 cases and 552 controls) and non-allergic asthma (245 cases and 490 controls) in relation to air pollution and greenness exposures from birth until age of asthma diagnosis for cases and from birth until corresponding age for controls.

| Exposure ^{1*} | Physician diagnosed asthma | | | | Allergic asthma | | | | Non-allergic asthma | | | |
|------------------------|----------------------------|----------------|----------------------------|----------------|----------------------------|----------------|----------------------------|----------------|---------------------|----------------|----------------------------|----------------|
| | Univariable | | Multivariable ² | | Univariable | | Multivariable ² | | Univariable | | Multivariable ² | |
| | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ |
| NO ₂ | 1.01 (1.00–1.03) | 0.022 | 1.00 (0.98–1.02) | 0.993 | 1.02 (1.00–1.04) | 0.046 | 1.02 (0.99–1.05) | 0.271 | 1.00 (0.98–1.02) | 0.813 | 0.98 (0.95–1.01) | 0.162 |
| PM _{2.5} | 1.03 (1.00–1.06) | 0.094 | 1.01 (0.96–1.05) | 0.788 | 1.02 (0.98–1.07) | 0.318 | 1.01 (0.95–1.07) | 0.812 | 1.01 (0.96–1.07) | 0.656 | 1.01 (0.94–1.08) | 0.851 |
| PM ₁₀ | 1.04 (1.00–1.09) | 0.081 | 1.00 (0.94–1.06) | 0.949 | 1.04 (0.98–1.11) | 0.197 | 1.01 (0.93–1.10) | 0.817 | 1.00 (0.94–1.07) | 0.919 | 1.00 (0.91–1.10) | 0.979 |
| BC | 1.03 (1.00–1.07) | 0.039 | 0.98 (0.93–1.04) | 0.539 | 1.04 (1.00–1.09) | 0.059 | 1.01 (0.94–1.09) | 0.695 | 0.98 (0.94–1.03) | 0.481 | 0.92 (0.85–1.00) | 0.040 |
| O ₃ | 0.95 (0.91–0.98) | 0.003 | 0.95 (0.90–1.01) | 0.106 | 0.95 (0.90–1.00) | 0.071 | 1.00 (0.91–1.08) | 0.931 | 0.97 (0.92–1.02) | 0.278 | 0.91 (0.84–1.00) | 0.043 |
| NDVI (300 m) | 0.99 (0.98–1.00) | 0.112 | 1.00 (0.98–1.01) | 0.587 | 0.99 (0.97–1.01) | 0.203 | 1.00 (0.98–1.02) | 0.771 | 1.00 (0.99–1.02) | 0.664 | 1.00 (0.98–1.02) | 0.078 |

Abbreviations: BC, black carbon; CI, confidence interval; NDVI, normalized difference vegetation index; NO₂, nitrogen dioxide; O₃, ozone; OR, odds ratio; PM_{2.5}, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM₁₀, particulate matter with an aerodynamic diameter lower than 10 µm. ¹ All air pollutants exposures were extrapolated in time with the ratio method. ² All models were adjusted for O₃ and NDVI (300 m buffer), except for the O₃-model that was adjusted for NO₂ and NDVI (300 m buffer) and the NDVI-model that was adjusted for O₃ and NO₂. All models were also adjusted for parental education and parental asthma. ³ All p-values < 0.05 = significant and marked bold. * BC per 1-µg/m³ increase, NDVI per 0.1-unit increase. NO₂, PM exposures and O₃ per 10-µg/m³ increase.

Table 3

Logistic regression analyses of asthma attack last 12 months in relation to air pollution and greenness for all time windows in the full (imputed) study population (N = 3428 participants).

| Exposure ^{1*} | 0–10 years | | | | 10–18 years | | | | Lifetime | | | |
|------------------------|---------------------|----------------|----------------------------|----------------|---------------------|----------------|----------------------------|----------------|---------------------|----------------|----------------------------|----------------|
| | Univariable | | Multivariable ² | | Univariable | | Multivariable ² | | Univariable | | Multivariable ² | |
| | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ |
| NO ₂ | 1.06 (0.89–1.26) | 0.511 | 1.24 (1.00–1.53) | 0.052 | 1.04 (0.87–1.26) | 0.644 | 1.29 (1.02–1.63) | 0.036 | 1.07 (0.86–1.33) | 0.545 | 1.32 (1.02–1.71) | 0.034 |
| PM _{2.5} | 1.06 (0.75–1.49) | 0.750 | 1.30 (0.89–1.89) | 0.171 | 1.04 (0.70–1.53) | 0.857 | 1.45 (0.90–2.36) | 0.129 | 1.19 (0.75–1.91) | 0.461 | 1.53 (0.94–2.48) | 0.086 |
| PM ₁₀ | 1.22 (0.86–1.73) | 0.276 | 1.59 (1.06–2.40) | 0.026 | 1.12 (0.75–1.67) | 0.577 | 1.90 (1.06–3.41) | 0.032 | 1.45 (0.89–2.38) | 0.135 | 1.95 (1.14–3.35) | 0.015 |
| BC | 1.04 (0.72–1.50) | 0.844 | 1.49 (0.85–2.60) | 0.165 | 1.14 (0.75–1.73) | 0.535 | 1.78 (0.98–3.24) | 0.059 | 1.15 (0.69–1.93) | 0.585 | 1.85 (0.96–3.57) | 0.065 |
| O ₃ | 1.21 (0.75–1.94) | 0.438 | 1.94 (1.06–3.57) | 0.033 | 1.18 (0.76–1.85) | 0.458 | 2.00 (1.11–3.58) | 0.021 | 1.35 (0.80–2.26) | 0.262 | 2.25 (1.15–4.38) | 0.017 |
| NDVI (300 m) | 0.99 (0.84–1.17) | 0.926 | 1.01 (0.83–1.23) | 0.930 | 0.97 (0.83–1.13) | 0.679 | 0.96 (0.81–1.14) | 0.615 | 0.98 (0.82–1.16) | 0.783 | 0.95 (0.77–1.17) | 0.629 |

Abbreviations: BC, black carbon; CI, confidence interval; NDVI, normalized difference vegetation index; NO₂, nitrogen dioxide; O₃, ozone; OR, odds ratio; PM_{2.5}, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM₁₀, particulate matter with an aerodynamic diameter lower than 10 µm. ¹ All air pollutants exposures were extrapolated in time with the ratio method. ² All models were adjusted for O₃ and NDVI (300 m), except for the O₃-model that was adjusted for NO₂ and NDVI (300 m) and the NDVI-model that was adjusted for O₃ and NO₂. All models were also adjusted for age, sex and parental education and asthma. ³ All p-values < 0.05 = significant and marked bold. *BC per 1-µg/m³ increase, NDVI per 0.1-unit increase. NO₂, PM exposures and O₃ per 10-µg/m³ increase.

asthma attack after childhood and adolescence exposure to NO₂, PM₁₀ and O₃ as well as after exposures in the year before study participation. For rhinitis, recent exposures seemed to be more important than lifelong or early exposures. In addition we revealed an association between childhood and adolescence exposures to PM_{2.5} and O₃ and low lung function, in particular with regard to FEV₁. Air pollution exposures did not increase the risk of physician diagnosed asthma. Higher exposure to greenness was a risk factor for low FEV₁ and FVC but not for asthma and rhinitis.

To our knowledge, there are no previous studies with similarly detailed moving history and the following individualized exposure calculations on both greenness and air pollutants that have examined lung health in adults after exposures during different vulnerability windows throughout the entire lifespan. Consequently, a direct comparison with previous literature is difficult. However, a systematic review reported associations between exposure to traffic related pollutants and the development of childhood asthma (Khreis et al., 2017), with more associations for PM_{2.5}, PM₁₀ and NO₂ compared to BC. Also in our study

NO₂ and PM₁₀ (in addition to O₃) exposures from birth onwards were particularly important risk factors for adult asthma severity measured through asthma attacks last 12 months. We did not observe higher risk of physician diagnosed asthma or allergic asthma in adults after exposure to any of the pollutants. On the contrary, regarding non-allergic asthma we found an association of lower risk after exposure to BC and O₃. These latter findings are somewhat unexpected and may reflect a chance finding or a result of including two relatively high correlated pollutants in one model (Table S4). We note that in single pollutant models, ORs were highly non-significant.

Air pollution exposures in the year before study participation were risk factors for current rhinitis in our study, while early life exposures seemed to be less important. This is in contrast with existing literature that has showed how early life air pollution exposures increase the risk of rhinitis in children (Deng et al., 2016) and also that long-term air pollution exposures are associated with increased disease severity among subjects with rhinitis (Burte et al., 2020).

Several studies have found that exposure to air pollution in early life

Table 4

Logistic regression analyses of rhinitis in relation to air pollution and greenness for all time windows in the full (imputed) study population (N = 3428 participants).

| Exposure ^{1*} | 0–10 years | | | | 10–18 years | | | | Lifetime | | | |
|------------------------|-----------------------------------|----------------|----------------------------|----------------|-----------------------------------|----------------|-----------------------------------|----------------|-----------------------------------|----------------|----------------------------|----------------|
| | Univariable | | Multivariable ² | | Univariable | | Multivariable ² | | Univariable | | Multivariable ² | |
| | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ |
| NO ₂ | 1.07 (0.99–1.16) | 0.072 | 1.07 (0.96–1.19) | 0.210 | 1.13 (1.04–1.23) | 0.006 | 1.14 (1.01–1.28) | 0.037 | 1.11 (1.00–1.22) | 0.046 | 1.12 (0.98–1.27) | 0.091 |
| PM _{2.5} | 1.16 (0.99–1.35) | 0.062 | 1.11 (0.93–1.32) | 0.239 | 1.26 (1.06–1.51) | 0.010 | 1.17 (0.93–1.46) | 0.170 | 1.23 (0.99–1.52) | 0.061 | 1.18 (0.94–1.48) | 0.145 |
| PM ₁₀ | 1.21 (1.03–1.43) | 0.023 | 1.14 (0.94–1.37) | 0.174 | 1.28 (1.07–1.54) | 0.008 | 1.17 (0.90–1.52) | 0.244 | 1.29 (1.02–1.63) | 0.030 | 1.21 (0.95–1.55) | 0.129 |
| BC | 1.16 (0.97–1.38) | 0.094 | 1.17 (0.89–1.55) | 0.263 | 1.29 (1.07–1.57) | 0.009 | 1.27 (0.96–1.67) | 0.091 | 1.26 (1.00–1.60) | 0.049 | 1.32 (0.97–1.78) | 0.077 |
| O ₃ | 0.88 (0.71–1.10) | 0.260 | 0.99 (0.75–1.32) | 0.963 | 0.88 (0.72–1.08) | 0.224 | 1.10 (0.83–1.46) | 0.498 | 0.91 (0.72–1.15) | 0.444 | 1.09 (0.80–1.48) | 0.581 |
| NDVI (300 m) | 0.99 (0.91–1.07) | 0.778 | 1.02 (0.94–1.12) | 0.597 | 0.98 (0.91–1.05) | 0.552 | 1.02 (0.94–1.10) | 0.694 | 0.97 (0.89–1.06) | 0.519 | 1.01 (0.92–1.11) | 0.850 |

Abbreviations: BC, black carbon; CI, confidence interval; NDVI, normalized difference vegetation index; NO₂, nitrogen dioxide; O₃, ozone; OR, odds ratio; PM_{2.5}, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM₁₀, particulate matter with an aerodynamic diameter lower than 10 µm. ¹ All air pollutants exposures were extrapolated in time with the ratio method. ² All models were adjusted for O₃ and NDVI (300 m), except for the O₃-model that was adjusted for NO₂ and NDVI (300 m) and the NDVI-model that was adjusted for O₃ and NO₂. All models were also adjusted for age, sex and parental education and asthma. ³ All p-values < 0.05 = significant and marked bold. *BC per 1-µg/m³ increase, NDVI per 0.1-unit increase, the rest per 10-µg/m³ increase.

Table 5Logistic regression analyses of lower limit of normal (LLN) FEV₁ and FVC in relation to mean air pollution and greenness exposures for all time windows in the full (imputed) study population (N = 3428 participants).

| Exposure ^{1*} | 0–10 years | | | | 10–18 years | | | | Lifetime | | | |
|------------------------|------------------------------------|----------------|------------------------------------|----------------|-----------------------------------|----------------|------------------------------------|----------------|------------------------------------|----------------|------------------------------------|----------------|
| | Univariable | | Multivariable ² | | Univariable | | Multivariable ² | | Univariable | | Multivariable ² | |
| | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ | OR (95% CI) | p ³ |
| FEV₁ | | | | | | | | | | | | |
| NO ₂ | 0.93 (0.56–1.53) | 0.763 | 1.60 (0.92–2.80) | 0.096 | 0.79 (0.48–1.29) | 0.344 | 1.66 (0.85–3.27) | 0.140 | 0.85 (0.44–1.61) | 0.611 | 1.76 (0.92–3.39) | 0.089 |
| PM _{2.5} | 1.51 (0.61–3.71) | 0.372 | 2.65 (1.13–6.21) | 0.025 | 1.15 (0.43–3.06) | 0.784 | 3.21 (1.03–10.07) | 0.045 | 1.80 (0.52–6.29) | 0.355 | 2.87 (0.96–8.54) | 0.058 |
| PM ₁₀ | 1.31 (0.51–3.35) | 0.572 | 2.46 (0.90–6.75) | 0.081 | 0.97 (0.34–2.77) | 0.953 | 3.29 (0.88–12.26) | 0.076 | 1.54 (0.40–5.94) | 0.531 | 2.71 (0.72–10.21) | 0.139 |
| BC | 0.63 (0.25–1.59) | 0.327 | 1.84 (0.46–7.30) | 0.387 | 0.56 (0.19–1.66) | 0.298 | 2.18 (0.44–10.74) | 0.340 | 0.56 (0.14–2.26) | 0.416 | 2.36 (0.42–13.21) | 0.330 |
| O ₃ | 2.74 (1.10–6.82) | 0.031 | 3.84 (1.08–13.64) | 0.037 | 3.05 (1.35–6.92) | 0.008 | 4.21 (1.06–16.77) | 0.042 | 3.69 (1.51–9.02) | 0.004 | 4.47 (1.25–15.96) | 0.021 |
| NDVI (300 m) | 1.43 (1.06–1.92) | 0.019 | 1.42 (0.99–2.05) | 0.060 | 1.69 (1.25–2.28) | 0.001 | 1.68 (1.18–2.39) | 0.004 | 1.84 (1.26–2.67) | 0.001 | 1.74 (1.15–2.63) | 0.008 |
| FVC | | | | | | | | | | | | |
| NO ₂ | 0.81 (0.44–1.46) | 0.474 | 1.56 (0.78–3.12) | 0.205 | 0.75 (0.43–1.30) | 0.300 | 1.50 (0.65–3.43) | 0.341 | 0.82 (0.41–1.67) | 0.589 | 1.71 (0.81–3.61) | 0.162 |
| PM _{2.5} | 1.68 (0.60–4.71) | 0.323 | 3.04 (1.17–7.90) | 0.023 | 1.44 (0.47–4.36) | 0.522 | 3.70 (1.06–12.92) | 0.040 | 2.43 (0.64–9.19) | 0.192 | 3.50 (1.08–11.36) | 0.037 |
| PM ₁₀ | 1.49 (0.53–4.16) | 0.450 | 2.87 (0.98–8.41) | 0.055 | 1.14 (0.33–3.99) | 0.836 | 3.43 (0.85–13.83) | 0.083 | 1.85 (0.43–7.91) | 0.409 | 2.99 (0.75–11.96) | 0.121 |
| BC | 0.46 (0.20–1.10) | 0.081 | 1.89 (0.35–10.37) | 0.462 | 0.57 (0.20–1.65) | 0.301 | 2.30 (0.42–12.56) | 0.335 | 0.55 (0.15–2.03) | 0.372 | 2.74 (0.43–17.66) | 0.288 |
| O ₃ | 4.23 (1.60–11.17) | 0.004 | 5.95 (1.16–30.45) | 0.032 | 3.22 (1.29–8.04) | 0.012 | 4.04 (0.67–24.56) | 0.129 | 4.03 (1.48–10.94) | 0.006 | 4.95 (0.96–25.47) | 0.056 |
| NDVI (300 m) | 1.42 (0.99–2.04) | 0.054 | 1.32 (0.87–2.00) | 0.198 | 1.55 (1.13–2.15) | 0.007 | 1.53 (1.04–2.25) | 0.030 | 1.66 (1.10–2.51) | 0.016 | 1.57 (1.00–2.45) | 0.050 |

Abbreviations: BC, black carbon; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; NDVI, normalized difference vegetation index; NO₂, nitrogen dioxide; O₃, ozone; OR, odds ratio; PM_{2.5}, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM₁₀, particulate matter with an aerodynamic diameter lower than 10 µm. ¹ All air pollutants exposures were extrapolated in time with the ratio method. ² All models were adjusted for O₃ and NDVI (300 m), except for the O₃-model that was adjusted for NO₂ and NDVI (300 m) and the NDVI-models that were adjusted for O₃ and NO₂. All models were also adjusted for age, sex and parental education and asthma. ³ All p-values < 0.05 = significant and marked bold. *BC per 1-µg/m³ increase, NDVI per 0.1-unit increase. NO₂, PM exposures and O₃ per 10-µg/m³ increase.

and in school-age has a negative impact on lung function in childhood and adolescence (Schultz et al., 2017, 2016; Gehring et al., 2013), but the effects into adulthood remain unclear. Our analyses of adult lung function revealed that participants exposed to PM₁₀ and O₃ had a higher risk for lung function below LLN for both FEV₁ and FVC, but not for the ratio – indicating that the effects are on lung volumes rather than obstructive effects. The associations were observed in all susceptibility

windows suggesting that early life exposures to air pollution impacts lung function all the way into adulthood. This is in line with a recent study that found NO_x and PM₁₀ exposures during the first year of life to be associated with FEV₁ and FVC below LLN at the age of 16 (Schultz et al., 2016).

Our study did not reveal any associations between greenness and asthma outcomes or rhinitis, but we found greenness to be a risk factor

for low lung function. Previous literature on the effects of greenness on respiratory health, and especially lung function is limited and heterogeneous. Some studies have found no associations, in line with our analyses of asthma attack and rhinitis (Boeyen et al., 2017; Agier et al., 2019). However, one recent study found higher FEV₁ and FVC among 24-year olds that grew up nearby green spaces within 300 m of their homes (Fuertes et al., 2020). This is in contradiction to our analyses where greenness was in fact a risk factor for low lung function. An explanation for discrepant results between studies may be because the index used for greenness does not differentiate between type of vegetation which may influence the time spent in and around the green areas, for instance a nicely facilitated park with trees and flowers may be used more than an agricultural field. A recent study from Germany showed how residence in places with many trees, and allergenic trees specifically, increase the prevalence of allergic rhinitis (Iana Markevych et al., 2020). In addition, our exposure assessment has the shortcoming that it is based on the participant's home addresses and we cannot account for the time spent in other places (e.g. kindergarten, school, work etc.). Children spend 40–50% of their time at home and the rest at school/kindergarten or commuting, and air pollutant levels are usually lower at home than when commuting (Khreis and Traffic-Related, 2017). Nevertheless, most families in Scandinavia live close to the schools and kindergartens and it is therefore likely that the calculations based on the residential addresses reflect the actual daily exposures.

The results regarding greenness and lung function are in line with a recent paper including 100 000 persons from the UK Biobank (Sarkar et al., 2019) showing that although greenness overall decreases the risk for COPD, it has a curvilinear effect on lung function with a beneficial effect up to a NDVI threshold of 0.21 followed by a negative effect. Also results from the European FP7 HEALS project (Health and Environment-wide Associations based on Large population Surveys) have shown that exposure to green space is associated with increased respiratory disease (Parmes et al., 2020). The negative effect may be due to increased exposures to pollens with higher susceptibility to allergic reactions.

Greenness and air pollution were adjusted for each other in multivariate analyses, but potential interactions between them were not evaluated in the present study. In a recent study by Sun and co-workers (Sun et al., 2020), a synergistic effect was observed between low greenness and high air pollution levels with regard to preterm birth. These results suggest that unfavourable combinations of greenness and air pollution levels may be more harmful to health than greenness and air pollution are separately by themselves. Due to the vast amount of analyses already included in the present study, we have not looked further into this issue. However, it would be valuable for a future study to disentangle this further.

In our analyses, we had a particular focus on susceptibility windows up to 18 years of age. The rationale for examining exposures in childhood and adolescence was the aim to look at exposures of the lungs when they are at their most vulnerable (Sharma and Goodwin, 2006). Children are extra susceptible as the lungs are developing and their immune and metabolic systems are less mature than in adults. Also, they tend to be more outdoors and to be more physically active than adults, as well as to have a greater ventilator rate. Consequently, children's exposure to air pollution is higher compared to adults. Previous studies exploring these windows, have found puberty to be of particular importance especially in men (Svanes et al., 2017). However, in our study a minority of participants changed their residences during childhood and adolescence, which made it difficult to determine if some susceptibility windows were more important than others. Our results nevertheless suggest that all the investigated time windows are of importance in relation to adult lung health.

The percentage of missing in our imputed variables ranged from 2% to 9%. We performed analyses with imputation rather than complete case analyses to avoid the deletion of observations from our dataset, with the following consequences of loss of statistical power and risk of bias due to missing data. An important criterion to avoid imputation bias

is that variables included in the final analytical model make up the set of predictors and outcomes specified in the imputation model. Also, the assumption that data are missing at random is crucial. The largest percentage of missing observations in our data (9%) were greenness exposures in the first years of life. One reason for this was that we failed to obtain enough satellite images to cover the entire study area completely throughout all selected years. Another reason is that the Norwegian population registry provided the first moving address for all participants and not the birth address. Although we have greenness exposures for some time points in the window 0–10 years for all participants, 9% had at least one year missing within this time window. To allow for the uncertainty about missing data, we performed multiple imputation through creating multiple different plausible imputed data sets and appropriately combining results obtained from each of them (Sterne et al., 2009).

One of the major strengths of our study is the availability of detailed information on lung health in two generations from the RHINESSA study, enabling to adjust for the identified confounders and investigate possible susceptibility windows for disease development later in life. Furthermore, the detailed residential addresses, including moving history for each participant is unique and made it possible to calculate individualized exposures. With complex extrapolation formulas from LUR models, accurate estimations were achieved. This enabled us to grasp both spatial and temporal variation in air pollution, even if fine within-city contrasts are not perfectly captured.

Certain limitations should be addressed. First, limitations regarding the exposure assessments must be mentioned. The estimates for 1990 were used as a proxy for each year from 1975 to 1990, because air pollution measurements before this time point were not available. For these years we expect a possible underestimation of the exposures as there was a downwards trend for air pollution from 1975 till 1990 in Europe, especially for PM_{2.5} and PM₁₀ and partly also for NO₂ (Crippa et al., 2016). Also, the LUR models do not encompass detailed exposure data on pollution that is not traffic-related, such as for example pollution coming from residential wood combustion. Such exposures would be important to obtain a deeper understanding of air pollution and health. With the present study we can only draw conclusions about traffic-related air pollution, and exposures to air pollution other than traffic-related pollution will be underestimated. The effects on our results from these sources of underestimation may be that observed associations are in reality stronger than what we have found. Second, we only have mean annual pollution estimates, and not detailed daily or weekly measurements. With finer temporal resolution, we could have used e.g. Bayesian distributed lag model (BDLM) for a more thorough investigation of susceptibility periods (Buckley et al., 2019; Wilson et al., 2017). With a BDLM we could identify lagged effects of air pollution on the outcomes, taking into account fluctuations and acute pollution spikes. Thirdly, information bias is a concern for all studies using self-reported data, especially when including reports regarding family-members. Nevertheless, numerous validation studies from the RHINESSA study have shown recall bias to be minimal for cross-generational reports (Kuiper et al., 2018; Pape et al., 2019; Lonnebotn et al., 2018). Also, allergic asthma is in this context defined as asthma without rhinitis. Subjects with atopic asthma who are allergic to e.g. mites or animal hair but do not have rhinitis may therefore have been classified as non-allergic asthmatics. Lastly, the response rate of RHINESSA was fairly low, approximately 40% (Fincham, 2008). A general decreasing trend of the response rate is reported in the latest years, levelling out at about 50% (Baruch and Holtom, 2008). A low response rate increases the possibility of selection bias, which may lead to distorted estimates. We have earlier shown in a related study population how selection bias affected prevalence estimates, but not exposure-outcome associations (Johannessen et al., 2014). Also, a large Norwegian study of selection bias in the Norwegian Mother and Child Cohort Study found that even if a representative sample is important when the aim is to describe prevalence, it is not essential if the aim is to investigate risk associations

(Nilsen et al., 2009). Since the focus in our paper was to investigate effects of air pollution and greenness on health outcomes, and not on determining prevalence of diseases in a population, it is likely that the internal validity of our results are not compromised.

5. Conclusion

In conclusion, this study found that air pollution exposures throughout the lifespan increased the risk for asthma attacks, rhinitis and low lung function in adulthood, but not for physician-diagnosed asthma. Greenness was not associated with asthma attacks, rhinitis or asthma diagnosis, but it was a risk factor for FEV₁ and FVC below lower limit of normal. Our results confirm that recent air pollution exposures are associated with lung health outcomes, but suggest that also air pollution exposures as far back in time as childhood and adolescence increase the risk of poor lung health in adulthood.

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CRedit authorship contribution statement

Ingrid Nordeide Kuiper: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Cecilie Svanes:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Iana Markevych:** Investigation, Writing - review & editing. **Simone Accordini:** Methodology, Writing - review & editing. **Randi J. Bertelsen:** Writing - review & editing. **Lennart Bråbäck:** Writing - review & editing. **Jesper Heile Christensen:** Investigation, Writing - review & editing. **Bertil Forsberg:** Writing - review & editing. **Thomas Halvorsen:** Writing - review & editing, Supervision. **Joachim Heinrich:** Writing - review & editing. **Ole Hertel:** Investigation, Writing - review & editing. **Gerard Hoek:** Writing - review & editing. **Mathias Holm:** Writing - review & editing. **Kees Hoogh:** Investigation, Writing - review & editing. **Christer Janson:** Writing - review & editing. **Andrei Malinowski:** Writing - review & editing. **Alessandro Marcon:** Methodology, Writing - review & editing. **Roy Miodini Nilsen:** Methodology, Writing - review & editing. **Torben Sigsgaard:** Writing - review & editing. **Ane Johannessen:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article to disclose.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.106219>.

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