Environmental Research 274 (2025) 121328

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Associations of parental air pollution and greenness exposures with offspring asthma outcomes☆

Robin M. Sinsamala [a,*], Alessandro Marcon [b], Randi J. Bertelsen [c], Simone Accordini [b], Jørgen Brandt [d], Lise M. Frohn [d], Camilla Geels [d], Thorarinn Gislason [e,f], Mathias Holm [g], Christer Janson [h], Andrei Malinovschi [i], Iana Markevych [j,k,l], Hans Orru [m], Anna Oudin [n], Francisco Gomez Real [c,o], Torben Sigsgaard [p], Svein M. Skulstad [c], Cecilie Svanes [a,q], Ane Johannessen [r]

[a] Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, 5020 Bergen Norway
[b] Unit of Epidemiology and Medical Statistics, Department of Diagnostics and Public Health, University of Verona, 37134 Verona, Italy
[c] Department of Clinical Science, University of Bergen, 5021 Bergen Norway
[d] Department of Environmental Science, Aarhus University, Frederiksborgvej 399, 4000 Roskilde, Denmark
[e] Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[f] Department of Sleep, Landspitali University Hospital, Iceland
[g] Occupational and Environmental Medicine, School of Public Health and Community Medicine, Institute of Medicine Sahlgrenska Academy, University of Gothenburg, 405 30 Gothenburg, Sweden
[h] Department of Medical Sciences, Respiratory, Allergy & Sleep Research, Uppsala University, 75185 Uppsala Sweden
[i] Department of Medical Sciences, Clinical Physiology, Uppsala University, 75185 Uppsala, Sweden
[j] Institute of Psychology, Jagiellonian University, Krakow, Poland
[k] Health and Quality of Life in a Green and Sustainable Environment, SRIPD-MUP, Medical University of Plovdiv, Plovdiv, Bulgaria
[l] Environmental Health Division, Research Institute at Medical University of Plovdiv, Medical University of Plovdiv, Plovdiv, Bulgaria
[m] Institute of Family Medicine and Public Health, University of Tartu, Tartu, Estonia
[n] Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden
[o] Department of Obstetrics and Gynecology, Haukeland University Hospital, 5021 Bergen, Norway
[p] Department of Public Health, Environment Occupation and Health, Danish Ramazzini Centre, Aarhus University, Aarhus, Denmark
[q] Department of Occupational Medicine, Haukeland University Hospital, 5021 Bergen, Norway
[r] Department of Global Public Health and Primary Care, University of Bergen, 5020 Bergen Norway

ARTICLE INFO

Keywords:
Asthma
Air pollution
Greenness
Preconception

ABSTRACT

Background: Air pollution and greenness impact respiratory health, but intergenerational effects remain unclear. We investigated whether pre-conception parental residential exposure to air pollution and greenness at age 20–44 years is associated with offspring asthma outcomes in the Lifespan and inter-generational respiratory effects of exposures to greenness and air pollution (Life-GAP) project.

Methods: We analyzed data on 3684 RHINESSA study participants born after the year 1990 (mean age 19, standard deviation 4), offspring of 2689 RHINE study participants. Modelled annual concentrations of particulate matter ($PM_{2.5}$, PM_{10}), nitrogen dioxide (NO_2), elemental carbon (EC), and ozone (O_3), and greenness (Normalized Difference Vegetation Index, NDVI) were assigned to parental residential addresses in 1990, corresponding to 1–18 years prior to birth (mean: 6 years, SD: 5). We analyzed associations using generalized structural equation modelling (GSEM), with cluster-robust standard errors allowing for intra-family correlation, while adjusting for potential confounders.

☆ The authors declare they have no conflicts of interest related to this work to disclose.

* Corresponding author.
E-mail addresses: robin.sinsamala@uib.no (R.M. Sinsamala), alessandro.marcon@univr.it (A. Marcon), randi.j.bertelsen@uib.no (R.J. Bertelsen), simone.accordini@univr.it (S. Accordini), jbr@envs.au.dk (J. Brandt), lmf@envs.au.dk (L.M. Frohn), cag@envs.au.dk (C. Geels), thorarig@landspitali.is (T. Gislason), mathias.holm@amm.gu.se (M. Holm), christer.janson@medsci.uu.se (C. Janson), andrei.malinovschi@medsci.uu.se (A. Malinovschi), iana.markevych@uj.edu.pl (I. Markevych), hans.orru@ut.ee (H. Orru), anna.oudin@umu.se (A. Oudin), francisco.real@uib.no (F.G. Real), ts@ph.au.dk (T. Sigsgaard), svein.skulstad@k2.uib.no (S.M. Skulstad), cecilie.svanes@helse-bergen.no (C. Svanes), ane.johannessen@uib.no (A. Johannessen).

https://doi.org/10.1016/j.envres.2025.121328
Received 20 December 2024; Received in revised form 10 February 2025; Accepted 5 March 2025
Available online 6 March 2025
0013-9351/© 2025 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Results: Among offspring participants, 18% reported lifetime asthma, 9% active asthma, 8% asthma medication, 5% asthma attacks, and 37% any asthma symptom. An interquartile range (IQR) increase in parental residential NDVI exposure was associated with less lifetime asthma (OR = 0.79, 95%CI: 0.64, 0.98 per 0.3 units). Similar associations were observed for active asthma and asthma medication use. Associations of air pollution with asthma outcomes were inconclusive.
Conclusion: Parental exposure to residential green spaces before conception was associated with lower asthma risk in offspring. Urban planning policies prioritizing green spaces may be a key public health intervention for future cities.

1. Background

An increasing body of evidence has consistently linked air pollution with respiratory diseases and symptoms (Khreis et al., 2019). Both short-term and long-term exposure to air pollution have been linked to the development and exacerbation of respiratory diseases and symptoms, including asthma, nasal disorders, and wheezing (Jacquemin et al., 2015; Liu et al., 2021). Emerging evidence also suggests that the timing of air pollution exposure is critical for respiratory disease outcomes, with in utero and early postnatal exposures playing a particularly important role (Hehua et al., 2017; Kuiper et al., 2020; Pedersen et al., 2023; Svanes et al., 2023). Biological mechanisms such as oxidative stress, inflammatory and immunological responses have been suggested to explain the association between air pollution exposure and respiratory disease (Gowers et al., 2012; Squillacioti et al., 2024).

Potential beneficial effects of greenness exposure on respiratory health among different populations have been reported, although with some inconsistent findings (Johannessen et al., 2023; Liu et al., 2023). While most of the studies have found protective effects of greenness on the risk of asthma development, others have reported opposite or null findings (Ferrante et al., 2020; Kuiper et al., 2020; Lambert et al., 2017; Mueller et al., 2022; Rantala et al., 2024). Suggested underlying mechanisms of the benefits of greenness include promoting human microbiome diversity, which enhance airway immune homeostasis, and reducing harmful environmental exposures, such as air pollution and excess heat (Burbank et al., 2017; Johannessen et al., 2023). On the other hand, trees and grass are a source of pollen and fungal spores, which may potentially lead to allergic reactions and asthma. Furthermore, trees canopies along trafficked roads can trap ground-level air pollution, potentially increasing exposure to air pollutants (Johannessen et al., 2023).

The pregnancy period is considered as a critical window for fetal development, and exposure to air pollution in this period may alter lung development and influence the development of various respiratory diseases in childhood and later in life (Nordeide Kuiper et al., 2021). Additionally, increasing evidence shows that parental exposures occurring before conception may also be critical in determining respiratory outcomes in the next generation (Accordini et al., 2018; HYCecilie Svanes, 2016; Kuiper et al., 2020; Svanes et al., 2023). Exposure to greenness and/or air pollution before conception may cause heritable epigenetic changes such as DNA methylation, which can be relevant in influencing negative or positive health outcomes in the offspring (Kitaba et al., 2023; Mørkve et al., 2018; Svanes et al., 2023). Several studies have addressed the effects of air pollution and greenness exposure during pregnancy on respiratory outcomes, but few have so far considered the health effects on future offspring of parents' exposure in the years preceding conception (Deng et al., 2016; Kuiper et al., 2020). It is plausible that parents' long-term exposure to air pollution and greenness, even many years before conception, may contribute to the etiopathology of respiratory diseases (Pedersen et al., 2023) in the offspring. Therefore, more insight in this area would provide significant opportunities in disease prevention from a public health perspective. Thus, using data from Respiratory Health in Northern Europe, Spain, and Australia (RHINESSA) (offspring data) and Respiratory Health in Northern Europe (RHINE) studies (parental data), we aimed to investigate whether parental residential exposure to air pollution and greenness in young adulthood is associated with asthma status and respiratory symptoms in offspring.

2. Methods

2.1. Study population and data sources

This study used questionnaire data from participants aged 4–26 at baseline (2013–17) in the RHINESSA cohort (https://rhinessa.net), which comprises offspring of participants from the RHINE study (https://rhine.w.uib.no/). The parents were aged 20–44 years at baseline in 1990 and have been followed up every decade since (Svanes et al., 2022). We included RHINESSA participants from seven study centres: Bergen (Norway, aged 4–25); Gothenburg, Umea, and Uppsala (Sweden, aged 18–25, 17–25, and 17–25, respectively); Aarhus (Denmark, aged 10–24), Reykjavik (Iceland, aged 18–25) and Tartu (Estonia, aged 10–26) who answered detailed questionnaires on demographic and lifestyle factors, and respiratory health. The study was approved by the ethical committees of all the centres in accordance with national legislation, and written informed consent was obtained from all participants. This analysis included offspring participants born after 1990 due to available parental information and modelled residential exposure (RHINE I, baseline) (Fig. 1).

2.2. Exposure assessment

We examined preconception parental residential exposure (in RHINE I) to particulate matter with diameter $\leq$2.5 μm and $\leq$10 μm ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), elemental carbon (EC) and ozone (O_3) as air pollution exposures, and Normalized Difference Vegetation Index (NDVI) as an indicator of vegetation density (greenness). Annual average modelled air pollution and greenness exposures were assigned to parental residential addresses reported at baseline in RHINE I (1990), which corresponded to a mean time before conception of 6 years (SD 5, time range 1–18 years). The year 1990 was selected as the parental exposure year because it was the first of the three years with residential information available for all parents participating in the RHINE study, retrieved from the population registries (the other years were 2000 and 2010). Consequently, 1990 was the only year before the offspring were born in which geocodes could be assigned and exposures calculated.

2.2.1. Air pollutants

Air pollution concentrations (micrograms per cubic meter, μg/m3) were obtained from the NordicWelfAir air pollution modelling system (https://projects.au.dk/nordicwelfair) for all the study centres except Tartu. Concentrations were calculated based on a combined multiscale air pollution modeling system including, long-range transported air pollution (regional sources), from the Danish Eulerian Hemispheric Model (DEHM) (Brandt et al., 2012; Christensen, 1997), and local background source at 1 km × 1 km resolution from the Urban Background Model (UBM) (Brandt et al., 2001; Brandt J, 2001; Frohn et al., 2022). The DEHM covers the Northern Hemisphere, Europe and Scandinavia with resolutions of 150 km × 150 km, 50 km × 50 km and 16.67 km × 16.67 km, respectively. It describes atmospheric transport,

dispersion, deposition, and chemistry of both anthropogenic and natural emissions (Brandt et al., 2012; Skamarock et al., 2008). The UBM calculates the transport and dispersion of primary emitted air pollutants from all local sources, such as traffic and residential heating, industry, agriculture, power plants, etc. and calculates air pollution concentrations including chemical transformations of NO, NO_2 and O_3 (Brandt J, 2001; Frohn et al., 2022; Geels et al., 2021). Both DEHM and UBM are driven with data from the Weather Research and Forecasting model (WRF) (Skamarock et al., 2008). This study utilized combined outputs of DEHM/and UBM with a spatial resolution of 1 km × 1 km. The air pollution concentrations were evaluated against measurements with correlation coefficients ranging from 0.43 to 0.96 for $PM_{2.5}$, 0.72–0.89 for NO_2 and 0.60–0.73 for O_3 in Denmark, Finland, Norway, and Sweden where results from the combined models were validated against measured concentrations (Hvidtfeldt et al., 2018).For Tartu, data of EC and O_3 were not available during the study period and $PM_{2.5}$, PM_{10} and NO_2 were modelled using the Eulerian air quality dispersion model with the resolution of 1 km × 1 km across Estonia that is part of the Airviro Air Quality Management System (SMHI, Sweden; AirViro, 2011). Airviro is a web-based data management tool that uses data on air pollution emissions, ground-level concentrations, and meteorological variables to perform air pollution dispersion modelling and mapping (AirViro, 2011). This data has been used in several epidemiological studies (Orru et al., 2010, 2018).

2.2.2. Greenness

NDVI was used as a proxy for overall greenness measured using satellite imagery. NDVI is derived as the ratio of the difference between near-infrared (NIR) light and red reflectance to the sum of these two measures (NIR-red/NIR + red) (Tucker, 1979), and ranges from −1 to +1, with values closer to +1 indicating greener and denser vegetation. Values close to zero indicate arid areas of rocks, sand, or snow, while negative values usually denote water (Weier and Herring, 2011). For all the study centres, NDVI rasters were calculated and NDVI values were assigned to residential addresses of the parents, using Landsat 4–5 Thematic Mapper TM satellite images retrieved during the most vegetation-rich months (around July–August) in the years closest in time to the RHINE I survey. We used mean NDVI values calculated in circular buffers of 300 m around the participants residential address ($NDVI_{300m}$) in accordance with WHO recommendations (WHO, 2016).

2.3. Asthma outcomes

The outcomes were identified through self-report by participants and ascertained as follows:

- Lifetime asthma (yes/no), defined as a positive response to “Have you ever had asthma?”
- Use of Asthma medication (yes/no), defined as a positive response to “Are you currently using asthma medication?”
- Asthma attacks (yes/no), defined as a positive response to “Have you had an attack of asthma in the last 12 months?”
- Active asthma (yes/no), defined as meeting the criteria for asthma medication and/or asthma attack, as listed above.
- Lifetime asthma phenotypes, a three-category variable (no asthma, non-allergic asthma, allergic asthma) defined by the combination of lifetime asthma and a positive or negative responses to “Do you have nasal allergies including hay fever?”, indicating the presence of allergic and non-allergic asthma, respectively.
- Asthma score, ranging from 0 to 4, defined as the count of symptoms experienced in the past 12 months among breathless when wheezing, waking up with a feeling of chest tightness, waking up due to an attack of shortness of breath, attack of coughing. The score is based on the 5-level score introduced in the European Community Respiratory Healthy Study (ECRHS), (Sunyer et al., 2007) however, one item was not available in our questionnaire hence four symptoms were included.
- Asthma symptoms (yes/no), defined as the presence of at least one of the aforementioned asthma symptoms.

2.4. Covariates

We obtained information on lifestyle and socioeconomic characteristics through questionnaires from offspring and parents. Variables to be considered in the analysis were identified a priori based on direct acyclic graph (DAG, Fig. S1) in relation to their potential role in the associations between exposures and outcomes on the basis of existing literature. We included offspring and parental information. Offspring-specific variables, sex (male or female) and age (continuous, years) were considered as precision variables (Schisterman et al., 2009), due to their strong association with the study outcomes. Parental education level (primary,

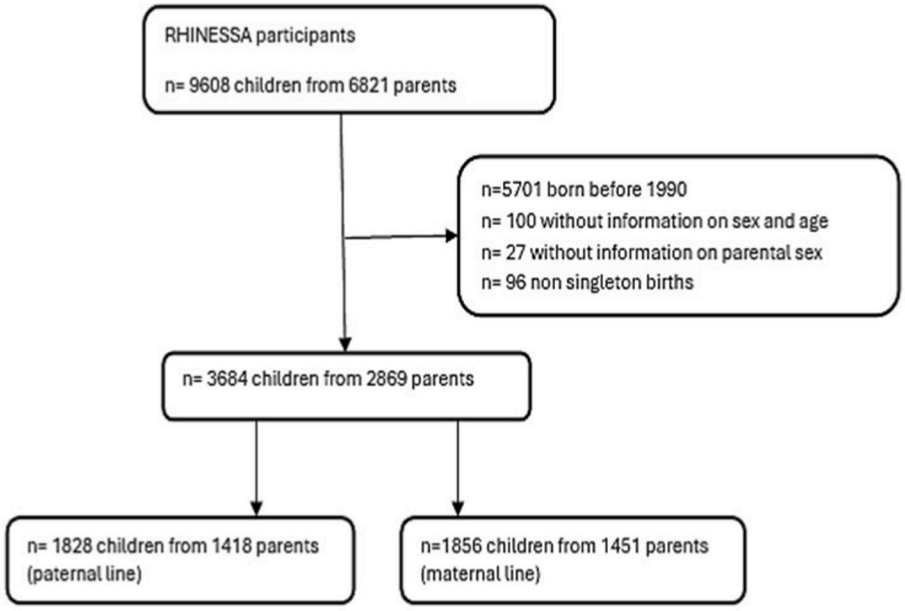

Fig. 1. Flowchart of the Respiratory Health in Northern Europe (RHINESSA) study participants.

secondary, or college/university) and parental smoking status in offspring childhood (one parent smoked, both parents smoked, or neither smoked) were included as potential confounders. These variables were considered as indicators of family deprivation, a determinant of the offspring's health status that may also be linked to living in more polluted and less green areas. Furthermore, we considered parental asthma status as a potential mediator, since it may lie on a causal pathway between air pollution/greenness exposures and asthma outcomes, for example through heritable epigenetic alterations.

2.5. Statistical analysis

All statistical analyses were performed using Stata 18 (StataCorp, College Station, TX, USA). Descriptive statistics were used to describe characteristics of adjustment covariates, exposures, and outcomes. Mean (standard deviation, SD), percentages (%) and median (interquartile range, IQR) were used to describe the variables. Pearson's correlation was used to examine the correlation among exposure variables.

2.5.1. Main analysis

Generalized structural equation modelling (GSEM) was used to estimate the association of air pollution and greenness exposures with asthma outcomes while considering potential mediators. We utilized Bernoulli and multinomial probability distributions with logit link function for binary and categorical outcomes, respectively, and negative binomial probability distribution with logarithm link function for count outcomes. Estimates were presented as odds ratio (OR) with 95% CIs for the binary outcomes, relative-risk ratio (RRR) with 95% CIs for categorical outcomes, and ratios of mean scores (RMS) with 95% CIs for count outcomes, computed per interquartile range (IQR) increases in concentrations of $PM_{2.5}$, PM_{10}, NO_2, EC and O_3, and $NDVI_{300m}$. Missing values were handled through a list-wise deletion approach.

All the models used cluster-robust standard errors, allowing for intra-family correlation (offspring from the same parent), and included centres as a fixed effect. Three progressively elaborate adjustment sets were considered. Model 1 (crude) included each exposure variable separately. Model 2 was initially adjusted for offspring sex, age, parental smoking status and parental educational level. At this stage, we also tested the role of parental asthma status as a mediator (Fig. S4). Mediated or indirect effects were estimated by analysing the association of exposures with mediator (path *a*) and mediator with outcome (path *b*) (Nguyen et al., 2020). Here, the term "effect" is not meant to imply causality, we are merely adhering to the standard use in the mediation analysis literature (Singh et al., 2024). Given that the exposures and mediator were parent-specific path *a* was adjusted for centre, parental sex (precision variable), education level and smoking status. Path *b* was further adjusted for offspring sex, age, and parental asthma status (Preacher et al., 2010; StataCorp, 2023). Indirect effects were defined as the product of path *a* and *b* coefficients (*a* x *b*). Indirect and total ($a \times b + c$) effects were estimated using the nonlinear combination command in STATA (nlcom). Since we found no evidence of mediation by parental asthma status, we eventually included this variable as a further potential confounder in model 2. Finally, model 3 (co-exposure model) included each air pollutant ($PM_{2.5}$, PM_{10}, NO_2, EC and O_3) in the greenness model separately as an additional covariate, and NDVI in the air pollution models as an additional covariate as well. Post hoc Wald tests were performed to assess heterogeneity of associations across asthma phenotypes in model 2 and 3. As a sensitivity analysis we evaluated the association of greenness exposure in 100m and 500m buffers with lifetime asthma and active asthma.

2.5.2. Effect modification

Previous studies reported sex differences in the impact of environmental exposures, epigenetics, and sex hormones (Chowdhury et al., 2021; Litonjua et al., 1998) on asthma prevalence, incidence and severity. Therefore, we assessed effect modification by offspring sex. Effect modification was considered to be present if pvalue for the sex *exposure interaction term ($P_{interaction}$) was below 0.05.

3. Results

In total we included 3684 offspring participants born to 2869 parents. The mean age of the offspring was 19.3 years and 57% were female (Table 1). The majority of the offspring had parents with college/university education (58%) and were never-smokers (66%). The prevalence of asthma outcomes was 18% for lifetime asthma, 9% for active asthma. Furthermore, 8% reported asthma medication and 5% asthma attacks within the last 12 months. For asthma symptoms, 11% reported an asthma score of $\geq$2, while 37% reported having had at least one asthma symptom in the past 12 months (Table 2). The prevalence of asthma outcomes varied by centre, with Reykjavik and Umea having the highest prevalence. Fig. S2 shows a Venn diagram indicating the overlap of cases of asthma outcomes.

Overall, the median (IQR) concentration for $PM_{2.5}$, PM_{10}, NO_2, EC, and O_3 were 9.2 (6.8) $\mu g/m^3$, 19.3 (8.3) $\mu g/m^3$, 14.4 (11.5) $\mu g/m^3$, 0.4 (0.5) $\mu g/m^3$ and 55.7 (13.3) $\mu g/m^3$, respectively. The median (IQR) for $NDVI_{300}$ was 0.31 (0.40) (Fig. 2 and Table S1). Pearson's correlation coefficients (r) among air pollutants ranged from 0.65 (EC and PM_{10}) to 0.88 (EC and $PM_{2.5}$) (Fig. S3). O_3 and NDVI were negatively correlated with all pollutants (-0.36 to -0.84) and positively correlated with each other (0.66).

3.1. Mediation by parental asthma outcomes

We observed no mediation by parental asthma status in the causal pathways between exposures and asthma outcomes (Table 3 and Table S2).

3.2. Association of air pollution and greenness with lifetime asthma and active asthma

Table S3 (Model 1) and Fig. 3 (Models 2 and 3) show associations of air pollution exposures with asthma outcomes. In general, $PM_{2.5}$, PM_{10}, NO_2, EC and O_3 exposures were neither associated with lifetime asthma nor active asthma. Similarly, no association was observed in the co-exposure models including NDVI.

An IQR increase in NDVI exposure in a 300 m buffer was associated with lower odds for lifetime asthma both in the unadjusted (Table S3) and in the adjusted analysis (OR: 0.79, 95%CI: 0.64, 0.98, model 2) (Fig. 4). All associations remained consistent after adjusting for air pollution in the co-exposure models. An association of similar magnitude and direction was observed for active asthma though it included the null (OR: 0.81, 95%CI: 0.63, 1.04, model 2). Further adjustment for air pollutant exposures strengthened the estimated associations. (Fig. 3). Protective associations were also observed for NDVI in 500m buffer with lifetime asthma (Table S4).

3.3. Association of air pollution and greenness with asthma medication and asthma attacks

Overall, we observed no clear pattern of associations for air pollution exposures with use of asthma medication and having had an asthma attack in the past 12 months, the two components of the active asthma definition (Table S3 and Fig. 3).

Fig. 4 shows estimated associations of NDVI exposure with asthma medication and asthma attack. Associations with asthma medication were consistent with those observed for active asthma, remaining consistent across the analyses, and becoming stronger in co-exposure models. No association was observed between greenness and asthma attack.

Table 1
Characteristics of the study participants (offspring, n = 3684).

Characteristics	Aarhus n = 919	Bergen n = 1199	Gothenburg n = 260	Reykjavik n = 276	Tartu n = 324	Umea n = 307	Uppsala n = 399	Overall n = 3684
Age, years, (mean ± SD)	18.7 (3.5)	17.1(4.6)	22.3 (2.0)	21.5 (2.1)	18.7 (4.2)	22.3 (2.1)	22.1 (2.1)	19.3 (4.2)
Female, n (%)	518 (56.4)	680 (56.7)	131 (50.4)	165 (60.0)	195 (60.2)	169 (55.1)	225 (56.4)	2083 (56.5)
Parental education level, n (%)[a] [b]								
primary	130 (14.3)	132 (11.4)	99 (38.4)	89 (33.7)	76 (24.4)	101 (33.1)	87 (22.0)	714 (19.8)
secondary	162 (17.8)	189 (16.3)	89 (34.5)	67 (25.4)	92 (29.6)	92 (30.2)	94 (23.7)	785 (21.8)
college	619 (68.0)	836 (72.3)	70 (27.1)	108 (41.0)	143 (46.0)	112 (36.7)	216 (54.4)	2104 (58.4)
Parental smoking in childhood, n (%)[b]								
one smoker	209 (23.2)	221 (19.2)	44 (17.1)	69 (26.0)	94 (30.0)	51 (16.7)	59 (14.8)	747 (20.8)
both smokers	82 (9.1)	144 (12.5)	38 (14.8)	44 (16.5)	42 (13.4)	24 (7.9)	18 (4.5)	392 (11.0)
no smoker	601 (66.8)	759 (66.1)	171 (66.5)	149 (56.0)	160 (51.1)	226 (74.1)	314 (79.0)	2380 (66.3)
don't know	8 (0.9)	25 (2.2)	4 (1.6)	4 (1.5)	17 (5.4)	4(1.3)	7 (1.8)	69 (1.9)
Parental asthma, n (%)[b]	191 (21.1)	256 (22.1)	14 (5.4)	44 (16.0)	27 (8.4)	25 (8.1)	28 (7.0)	585 (16.1)

Abbreviations: SD, standard deviation.
[a] Maximum attained by at least one parent.
[b] Missing values: Parental education level (n = 81), parental smoking (n = 96) and parental asthma (n = 31).

Table 2
Prevalence of asthma outcomes in the offspring (%).

	Aarhus n = 919	Bergen n = 1199	Gothenburg n = 260	Reykjavik n = 276	Tartu n = 324	Umea n = 307	Uppsala n = 399	Overall n = 3684
Lifetime asthma[c]	16.7	19.0	15.4	26.2	8.7	24.7	19.0	18.0
Asthma phenotype [c]								
allergic	7.1	7.7	5.0	12.4	4.4	11.6	9.6	8.0
non-allergic	9.3	11.0	10.4	13.8	4.4	13.2	9.1	10.2
no asthma	83.5	81.3	84.6	73.8	91.3	75.6	81.3	82.0
Active asthma[a] [c]	7.2	9.0	9.2	13.1	6.0	15.0	12.6	9.4
Asthma Medication[c]	6.5	8.0	9.2	9.8	5.0	14.0	10.3	8.3
Asthma Attack[c]	3.8	4.0	3.5	9.1	3.4	7.9	7.0	4.8
Asthma score[c], no. of symptoms								
0	65.1	65.4	70.2	55.5	55.5	60.0	59.0	63.0
1	27.2	22.0	19.8	30.3	33.3	24.4	30.0	26.0
2	4.8	7.9	6.0	10.2	7.5	9.0	8.1	7.2
3	2.1	3.5	3.6	3.0	2.8	4.4	2.3	3.0
4	0.8	1.2	0.4	1.1	0.9	2.3	0.5	1.0
Asthma symptom[b]	35.0	34.0	31.8	44.6	44.4	40.1	41.4	37.0

[a] Asthma activity (combined asthma medication and/or asthma attack).
[b] binary indicator of presence of at least one asthma symptom.
[c] Missing values: Lifetime asthma (n = 46), phenotypes (n = 52), active asthma (n = 39), asthma medication (n = 35), asthma attack (n = 40) and asthma score (n = 65).

3.4. Association of air pollution and greenness with lifetime asthma phenotypes

Fig. S5 shows the associations of air pollution and NDVI with allergic and non-allergic asthma. In line with the analysis on lifetime asthma, we observed no association for air pollution exposures with neither allergic nor non-allergic asthma. The association with NDVI exposure was similar for allergic and non-allergic asthma (heterogeneity p value > 0.05).

3.5. Association of air pollution and greenness with asthma score and asthma symptoms

There was a positive association between $PM_{2.5}$ exposure and having asthma symptoms (OR: 1.51, 95%CI: 1.01, 2.25). However, this association was attenuated after further adjustment for NDVI in model 3. Associations with PM_{10}, NO_2 and EC were in the same direction but weaker (Table 4). Though less precise, a negative (protective) association of NDVI with asthma symptoms was observed in model 2 (OR: 0.87, 95%CI: 0.72, 1.04), but not with asthma score.

3.6. Effect modification

No effect modification by offspring sex was observed in the association of air pollution and greenness with lifetime asthma (Table S5). However, the association of air pollution ($PM_{2.5}$ and EC) on active asthma was strongest for male offspring, compared to female offspring, and inverse associations were observed for O_3 ($P_{interaction}$ <0.05). In contrast, the protective association of greenness with active asthma was more pronounced in male compared to female offspring ($P_{interaction}$ <0.05). Decomposing active asthma revealed that the differences observed were present for asthma medication, but not for asthma attack (Table S6). Additionally, no effect modification was observed for asthma score or asthma symptoms (Table S7).

4. Discussion

In this longitudinal study of RHINESSA participants (offspring) and their RHINE participant parents from five Northern Europe countries, we found that higher parental residential exposure to greenness before conception was consistently related to a lower risk of having lifetime asthma and using asthma medication. Estimated associations were consistent when adjusting for potential confounders, as well as in co-

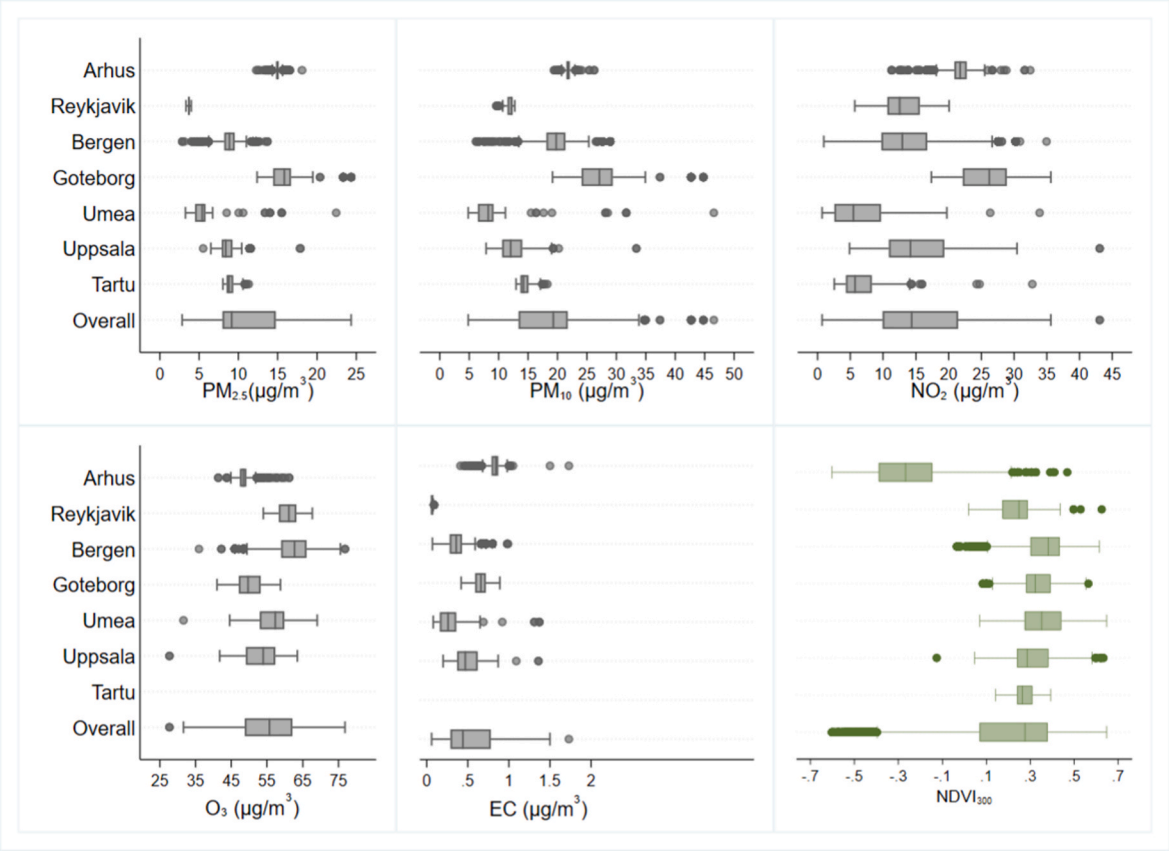

Fig. 2. Distribution of parental residential exposures to air pollution and greenness in 1990 by centre and overall. EC and O_3 from all centres except Tartu

Tables 3
Estimated direct, indirect and total effects of parental residential exposure to air pollution and greenness in 1990 on lifetime asthma and active asthma, with parental asthma as a potential mediator.

Exposure	Lifetime asthma			Active asthma		
	Indirect effect (a*b) OR (95% CI)	Direct effect (c) OR (95% CI)	Total effect (a*b + c) OR (95% CI)	Indirect effect (a*b) OR (95% CI)	Direct effect (c) OR (95% CI)	Total effect (a*b + c) OR (95% CI)
$PM_{2.5}$ (IQR: 6.8 μg/m^3)	1.16 (0.69, 1.95)	1.24 (0.80, 1.94)	1.45 (0.75, 2.79)	1.21 (0.62, 2.35)	1.20 (0.71, 2.01)	1.45 (0.64, 3.30)
PM_{10} (IQR:8.3 μg/m^3)	1.12 (0.85, 1.47)	1.12 (0.88, 1.42)	1.25 (0.88, 1.77)	1.15 (0.81, 1.63)	1.08 (0.82, 1.43)	1.24 (0.83, 1.93)
NO_2 (IQR: 11.5 μg/m^3)	1.12 (0.88, 1.43)	1.03 (0.82, 1.28)	1.15 (0.84, 1.58)	1.16 (0.85, 1.58)	1.00 (0.77, 1.31)	1.16 (0.77, 1.75)
EC (IQR: 0.5 μg/m^3)	1.14 (0.83, 1.58)	1.05 (0.80, 1.38)	1.20 (0.79, 1.83)	1.19 (0.78, 1.82)	0.98 (0.71, 1.35)	1.17 (0.68, 2.02)
O_3 (IQR: 13.3 μg/m^3)	0.92 (0.68, 1.25)	1.02 (0.78, 1.33)	0.94 (0.64, 1.38)	0.90 (0.60, 1.34)	0.99 (0.72, 1.36)	0.89 (0.54, 1.47)
NDVI (IQR: 0.3)	0.86 (0.69, 1.09)	0.79 (0.64, 0.98)	0.68 (0.50, 0.93)	0.82 (0.61, 1.12)	0.81 (0.63, 1.04)	0.67 (0.45, 0.99)

Abbreviations: OR, odds ratio; CI, confidence interval; IQR, Interquartile range; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm; NO_2, nitrogen dioxide; O_3, ozone; EC, Elemental Carbon; NDVI, Normalized Difference Vegetation Index within 300-m buffer. OR with 95% CI calculated per IQR increase in exposures. Since there was no mediated effects in the main outcomes, we did not perform mediation analysis for their components (asthma phenotypes and asthma medication and attacks). $PM_{2.5}$ (n = 3365), PM_{10} (n = 3365), NO_2 (n = 3364), EC (n = 3062), O_3 (n = 3062), $NDVI_{300m}$ (n = 3308).

exposure models including air pollution exposures. These associations were not mediated by parental asthma. There were no differences in the associations with greenness between allergic and non-allergic asthma phenotypes. We found that male offspring were also more sensitive to the benefits of greenness. Air pollution exposures before conception were not associated with asthma outcomes, except for a possible detrimental association in male offspring, which was not seen among female offspring.

4.1. Greenness exposure in parents in relation to offspring asthma outcomes

Consistent protective associations of parental greenness exposure with asthma status and activity were found. To our knowledge, there is only one study that has investigated the impact of preconception greenness exposure with asthma outcomes, conducted in Norway and Sweden using RHINESSA data (Kuiper et al., 2020). Though inconclusive, this study suggested protective association of greenness (500

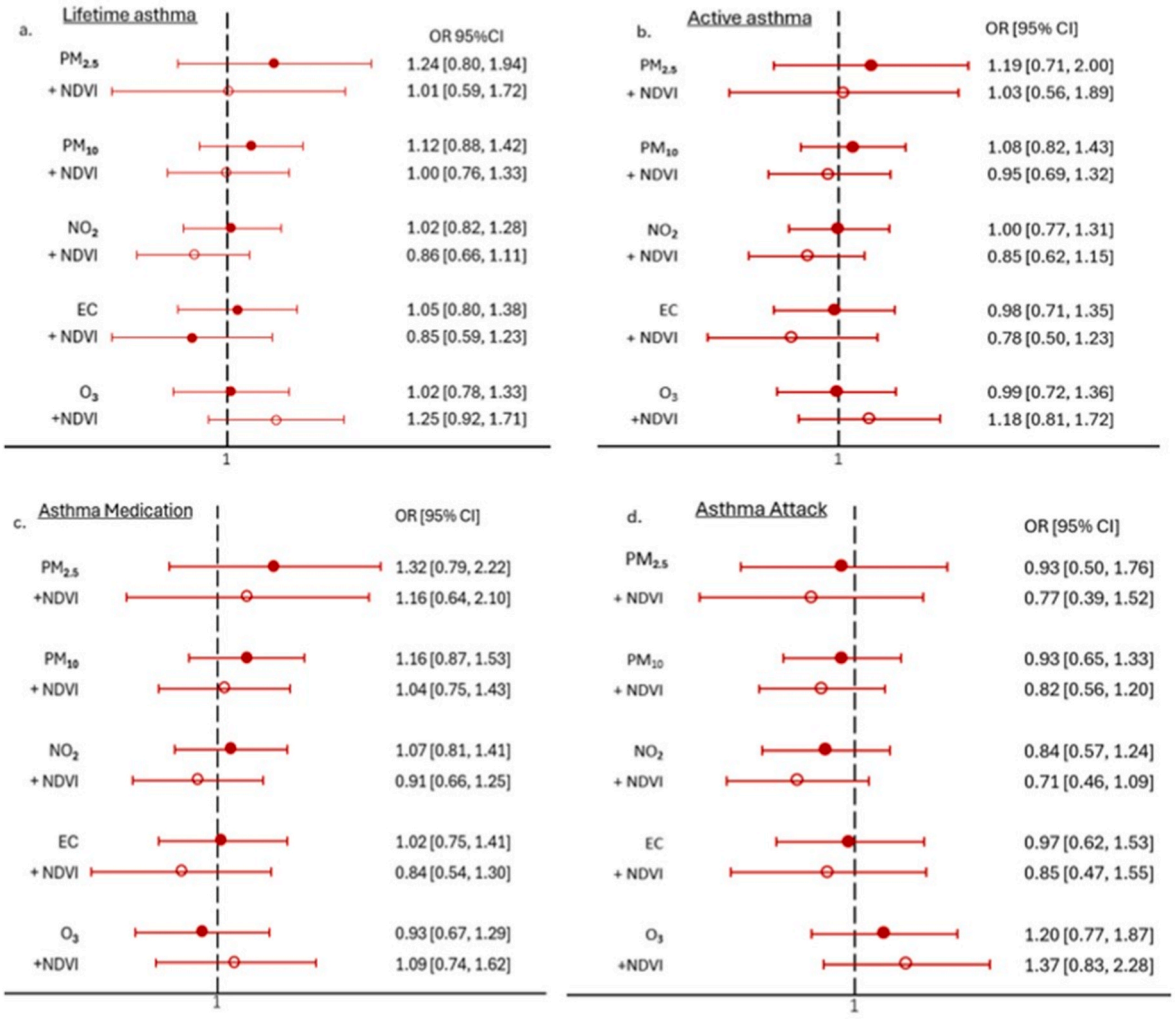

Fig. 3. Estimated associations of parental residential exposures to air pollution in 1990 with offspring asthma outcomes. The analyses are adjusted for offspring age and sex, parental smoking, education level, and asthma status (centre as a fixed effect and clustering by family), and further adjusted for NDVI where stated ("+ NDVI"). ORs are per IQR difference of the exposures. $PM_{2.5}$ (n =3346), PM_{10} (n=3346), NO_2 (n=3345), EC (n=3045), O_3 (n=3045).

m–1000 m buffers) exposure with offspring early onset asthma (Kuiper et al., 2020). While they assessed parental exposure during childhood years, the present study focused on exposure occurring in adulthood. In addition, our study employed more detailed and robust definitions of asthma outcomes. Other studies that investigated this relationship differed in timing of exposure, as they considered pregnancy and post-natal periods, and results have been heterogeneous (Hartley et al., 2020; Lambert et al., 2017; Tang et al., 2023). Our results showed that greenness exposure during the preconception period is beneficially related with asthma outcomes. The associations remained consistent after including air pollution exposures, except for EC, where the estimates changed substantially. This could be due to a strong correlation with NDVI. Generally, there is no consensus on correlation coefficient cutoffs for determining multicollinearity, as some investigators suggest a cutoff of 0.5, while the classical threshold is 0.8 (Vatcheva et al., 2016).

Regarding the lifetime asthma phenotypes, we did not find evidence of heterogeneity in the association with greenness exposure between allergic and non-allergic asthma (heterogeneity p-value >0.05). This could be attributed to low statistical power to detect existing heterogeneity. Our study also revealed a "protective" association of greenness with the presence of asthma symptoms which may be indicative of the beneficial role greenness may play in reducing asthma symptoms in the future generation.

The exact underlying mechanisms of the beneficial effects of greenness on asthma outcomes are not fully understood. Current knowledge suggests a biodiversity hypothesis, with studies reporting that exposure to more diverse vegetation strengthens microbial diversity (Johannessen et al., 2023). Microbial diversity may in turn be beneficial for the immune system and protect against sensitization and allergies (Jackson et al., 2023). Therefore, we could speculate that parental greenness exposure contributes to a potent microbiome influencing epigenetic changes that get transferred to the next generation, potentially protecting against asthma outcomes (Donovan et al., 2018). Recent evidence linking maternal exposure to greenness during pregnancy with cord blood DNA methylation supports this hypothesis (Alfano et al., 2023; Xu et al., 2021). Additional mechanisms, such as the promotion of parental physical activity and lower air pollution levels in green areas, may also contribute to respiratory health benefits in the next generation's offspring.

4.2. Air pollution exposure in parents in relation to offspring asthma outcomes

A limited number of studies have assessed the association of parental exposure to air pollution with asthma outcomes in offspring. In contrast to our results, the other studies have reported positive associations related to preconception air pollution exposure with asthma development in the offspring. Methodological differences exist between these

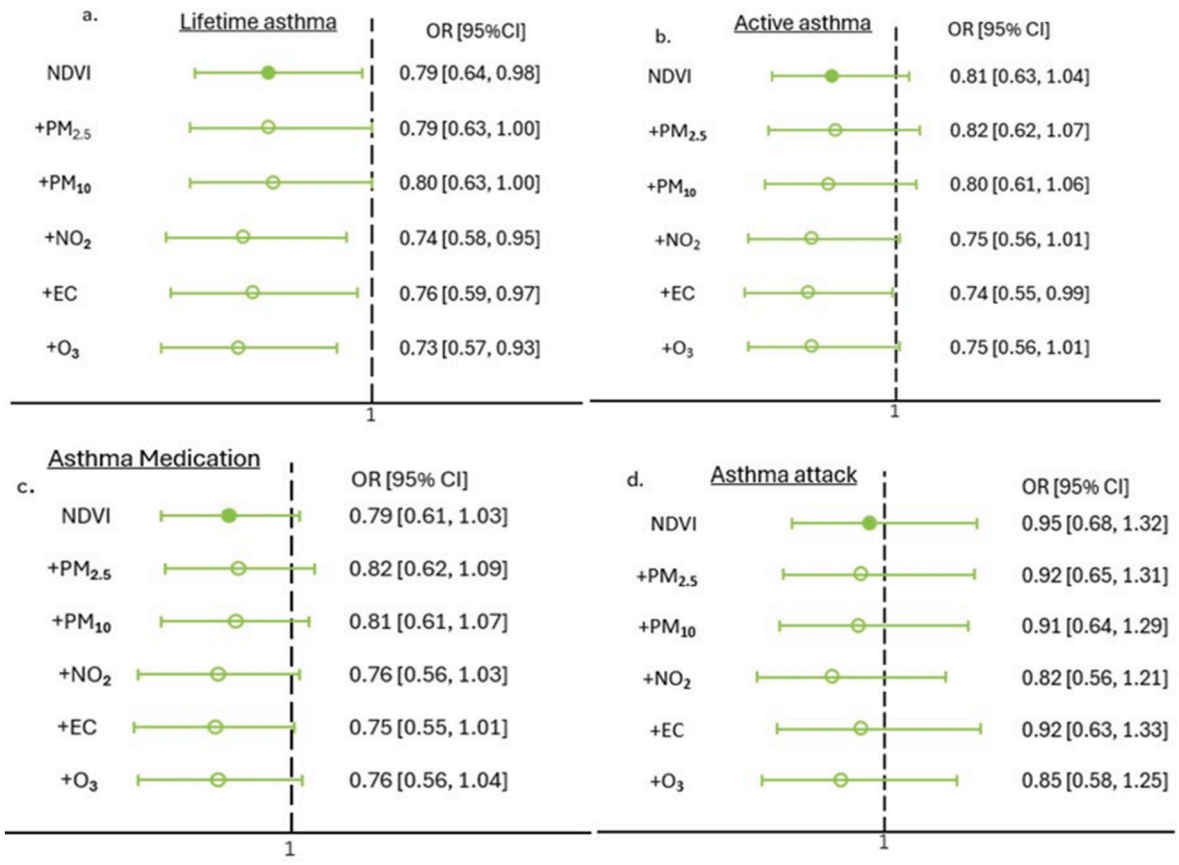

Fig. 4. Estimated associations of parental residential exposures to greenness in 1990 with offspring asthma outcomes. The analyses are adjusted for offspring age and sex, parental smoking, education level, and asthma status (centre as a fixed effect and clustering by family), and further adjusted for each of the air pollutants where stated ("+pollutant") . ORs are per IQR difference of the exposures. $NDVI_{300m}$ (n=3308).

Table 4
Estimated associations of parental residential exposure to air pollution and greenness in 1990 with offspring asthma score (count variable) and asthma symptom (binary variable).

	Asthma score RMS (95%CI)	asthma symptoms OR 95%CI
Air pollution		
$PM_{2.5}$	1.21 (0.93, 1.57)	1.51 (1.01, 2.25)
+NDVI	1.11 (0.83. 1.47)	1.25 (0.82, 1.92)
PM_{10}	1.08 (0.93, 1.25)	1.21 (0.98, 1.51)
+ NDVI	1.02 (0.87, 1.19)	1.09 (0.87, 1.37)
NO_2	1.01 (0.88, 1.15)	1.13 (0.87, 1.48)
+ NDVI	0.96 (0.82, 1.11)	1.00 (0.81, 1.23)
EC	1.06 (0.88, 1.28)	1.16 (0.87, 1.54)
+ NDVI	1.00 (0.82, 1.23)	1.04 (0.78, 1.38)
O_3	0.96 (0.81, 1.13)	0.89 (0.71, 1.12)
+NDVI	1.03 (0.85, 1.24)	0.94 (0.72, 1.23)
Greenness		
NDVI	0.94 (0.83, 1.06)	0.87 (0.72, 1.04)
+ $PM_{2.5}$	0.95 (0.84, 1.08)	0.89 (0.74, 1.09)
+ PM_{10}	0.94 (0.83, 1.07)	0.89 (0.74, 1.07)
+ NO_2	0.92 (0.80, 1.05)	0.87 (0.71, 1.06)
+ EC	0.94 (0.82, 1.08)	0.89 (0.73, 1.08)
+ O_3	0.98 (0.83, 1.16)	0.89 (0.73, 1.10)

Abbreviations: RMS, Ratio of mean score; OR, odds ratio; CI, confidence interval. Estimated association are per IQR difference in the exposures. All analysis adjusted for child's age and sex and parental smoking, education level, and asthma status. +: co-exposure models, further adjusted for greenness in air pollution models and each air pollution in greenness model. $PM_{2.5}$ (n = 3365), PM_{10} (n = 3365), NO_2 (n = 3364), EC (n = 3062), O_3 (n = 3062), $NDVI_{300m}$ (n = 3308).

studies and our study. For instance, the mean age of the offspring in the present study was 19 years, whereas the mean age in a study with both Norwegian and Swedish participants was 5 and 6 years between maternal and paternal line respectively (Kuiper et al., 2020). Additionally, their study averaged parental childhood exposure (0–18 years), while our study used the mean parental exposures assigned in 1990 with a mean preconception window of 6 years (SD 5). Moreover, the mean air pollution concentration levels for their exposure time window were higher compared to ours, which could explain the weaker associations in the present study. Their study reported that maternal childhood exposure to $PM_{2.5}$ and PM_{10} was associated with offsprings early onset asthma. Furthermore, PM_{10} was positively associated with higher risk of hay fever (OR:2.66, 95%CI:1.19–5.91) and similar associations were reported in the paternal line with O_3 exposure (Kuiper et al., 2020). Another study in China found that exposure to outdoor NO_2 1 year before conception was associated with asthma in children (age ranges 3 to 6) (OR: 1.51, 95%CI: 1.09, 2.09), and further adjustment for indoor environmental conditions did not attenuate the association (Deng et al., 2016). Generally, associations of air pollution with asthma score and presence of asthma symptoms were inconclusive in the present study. Previous studies have reported positive associations of air pollution with asthma score (Jacquemin et al., 2009; Keirsbulck et al., 2023), however their findings are not comparable to the current study due to differences in exposure assessments. Our findings could reflect the persistent contribution of air pollution to the pathology of asthma activity and severity.

We did not find evidence that parental asthma status mediated the effect of air pollution with offspring asthma outcomes. There was some suggestive evidence that greenness could affect asthma outcomes through parental asthma status, although the estimates were less

precise. The imprecise effect estimates could be attributed to reduced power in the mediated pathway following decomposition of total effect into direct and indirect (Cheng et al., 2021).

We found evidence that air pollution was more strongly associated with the use of asthma medication in male as opposed to female offspring. Despite these results, we found no effect modification by sex on asthma symptoms or asthma attacks, which is surprising since both medication use and symptoms are considered markers of asthma severity (Ungar et al., 2002). Therefore, interpreting these findings can be challenging within the context of this study. Notwithstanding the inconsistencies, some studies have reported similar findings of effect modification by sex, with male infants having higher risk of developing asthma for exposure to $PM_{2.5}$ during pregnancy, compared to female infants (Hsu et al., 2015; Lavigne et al., 2018).

Concerning the impact of the exposure we consider the developmental origins of health and disease (DOHaD) framework as the basis for understanding how exposure before conception may impact long-term health outcomes (Goyal et al., 2019; Svanes et al., 2023). The DOHaD framework considers the preconception period as a critical window for long-term effects on the offspring health. While the exact pathways are not well known some studies emphasized that preconception exposures may alter germ cell quality leading to intergenerational health effects (Svanes et al., 2023). Moreover, short term preconception exposure (right before conception) has shown to have an impact on DNA methylation at multiple loci linked to higher risk of respiratory diseases in the offspring later in life (Joubert et al., 2016). To date, the strongest evidence of epigenetic pathways of preconception environmental exposures on respiratory outcomes relates mostly to tobacco smoking (Accordini et al., 2018; Kitaba et al., 2023; Svanes et al., 2023). It is plausible that air pollution exposure before conception could express similar epigenetic mechanisms and influence asthma outcomes in the offspring.

4.3. Strengths and limitations

A key strength of this study is its prospective design and the availability of detailed information on offspring-parent pairs from the RHINESSA and RHINE cohorts, which enabled us to investigate the health effects of exposures across generations over various susceptibility windows, such as the preconception period. We also assessed numerous asthma outcomes reported for the last 12 months, thereby minimizing recall bias and ensuring a detailed characterisation of asthma in the offspring population.

In spite of the strengths, there are also several limitations. In common with most epidemiological studies, we assigned parental residential exposure as a proxy for personal exposure in 1990, and did not account for factors that could potentially impact within-subject exposure variability such as time-activity patterns (Dons et al., 2011). However, we expect the resulting exposure misclassification to be non-differential and, consequently, to affect precision and effect size of the estimated associations. We acknowledge the uncertainty as to whether parental exposure directly influenced the observed associations or acted indirectly through the offspring's own exposure. Due to the large proportion of offspring participants with missing data on residential addresses, we were unable to account for offspring's own exposure as a potential mediator. However, disentangling offspring's own residential exposure from parental residential exposure would not be possible since we lacked data on offspring addresses, making it impossible to ascertain if they lived with their RHINE participating parent or not. Despite the use of a state-of-the-art modelling system for exposure assessment, some degree of non-differential exposure misclassification is unavoidable since the DEHM/UBM underperformed in some countries such as Denmark where the correlation coefficient of measured versus modelled $PM_{2.5}$ was lower (0.43) compared to other Nordic countries. Preconception exposure windows varied among parents since all residential exposures were assigned at baseline (1990). NDVI is a general indicator of green vegetation, but it does not capture relevant measures such as microbiome diversity and access to and use of greenness, that are relevant in explaining the suggested pathways. Self-reported data on outcomes and individual level covariates may potentially be affected by reporting bias. Nevertheless, the questionnaire tools are validated and used widely in other studies (Svanes et al., 2022). In the mediation models, we were unable to fully account for the hierarchical structure of our data due to convergence issues encountered when attempting to fit multilevel GSEM models. These issues are not uncommon in complex models with multiple levels and limited sample size per cluster (families). To address this, we simplified the hierarchical structure and used cluster-robust standard errors to account for correlations between siblings. Additionally, the potential for reverse causality cannot be ignored when interpreting the relationship between air pollution and greenness exposure with parental asthma status. For example, we cannot know for sure whether parental asthma status affected parental air pollution exposures (parents with asthma moving to less polluted areas as a self-protection strategy) or vice-versa (parents developing asthma because they live in high-polluted areas). Finally, there was potential for residual confounding from unaccounted lifestyle factors and area-level socioeconomic status (SES), still individual-level SES tends to be highly positively correlated with area-level SES in most urban settings and one could account for the other (Xie et al., 2020).

5. Conclusion

In summary, despite the inconclusive evidence for inter-generational detrimental associations of air pollution, this study found consistent protective associations between parental residential exposure to greenness before conception and asthma outcomes in offspring. These results support the emerging paradigm that preconception exposures may be important determinants of offspring respiratory health. Early preventive strategies including green city planning could have long-term benefits for respiratory health across generations.

CRediT authorship contribution statement

Robin M. Sinsamala: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Alessandro Marcon:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Randi J. Bertelsen:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Simone Accordini:** Writing – review & editing. **Jørgen Brandt:** Writing – review & editing. **Lise M. Frohn:** Writing – review & editing. **Camilla Geels:** Writing – review & editing. **Thorarinn Gislason:** Writing – review & editing. **Mathias Holm:** Writing – review & editing. **Christer Janson:** Writing – review & editing. **Andrei Malinovschi:** Writing – review & editing. **Iana Markevych:** Writing – review & editing. **Hans Orru:** Writing – review & editing. **Anna Oudin:** Writing – review & editing. **Francisco Gomez Real:** Writing – review & editing. **Torben Sigsgaard:** Writing – review & editing. **Svein M. Skulstad:** Writing – review & editing. **Cecilie Svanes:** Writing – review & editing. **Ane Johannessen:** Writing – review & editing, Validation, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used ChatGPT4 to improve language and readability of the text. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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.

Acknowledgements

The following funding supported this study: The Research Council of Norway (grant number 300765) and University of Bergen funded The Lifespan and inter-generational respiratory effects of exposures to Greenness and Air Pollution project (Life-GAP).

The RHINESSA study has received funding from the Research Council of Norway (Grants No. 274767, 214123, 228174, 230 827 and 273838), ERC StG project BRuSH #804199, the European Union's Horizon 2020 research and innovation programme under grant agreement No. 633 212 (the ALEC Study WP2), the Bergen Medical Research Foundation, and the Western Norwegian Regional Health Authorities (Grants No. 912011, 911 892 and 911631).

Study centres have further received local funding from the following: Bergen: the.

above grants for study establishment and co-ordination, and, in addition, World University Network (REF and Sustainability grants), Norwegian Labour Inspection, the Norwegian Asthma and Allergy Association and Trond Mohn Foundation (Grant ID BFS2017TMT02). Gøteborg, Umeå and Uppsala: the Swedish Heart and Lung Foundation, the Swedish Asthma and Allergy Association. Reykjavik: Iceland University. Melbourne: Australian National.

Health and Medical Research Council (NHMRC) Project Grant ID1128450. Tartu:

the Estonian Research Council (Grant No. PUT562). Århus: The Danish Wood.

Foundation (Grant No. 444508795), the Danish Working Environment Authority.

(Grant No. 20150067134), Aarhus University (PhD scholarship).

The RHINE study was funded by the Swedish Heart and Lung Foundation, the Swedish Association Against Asthma and Allergy, the Swedish Association against Heart and Lung Disease, the Swedish Council for Working Life and Social Research, the Bror Hjerpstedt Foundation, The Faculty of Health, Aarhus University, Denmark (Project No. 240008), The Wood Dust Foundation (Project No. 444508795), The Danish Lung Association, The Norwegian Research Council project 135773/330, The Norwegian Asthma and Allergy Association, The Icelandic Research Council and the Estonian Science Foundation (Grant No. 4350). The project exposure data was funded by Nordforsk under the Nordic Programme on Health and Welfare (Project No. 75007: NordicWelfAir – Understanding the link between Air pollution and Distribution of related Health Impacts and Welfare in the Nordic countries). The sponsors did not have any role in the conduct of this research or preparation of the article. Iana Markevych is partially supported by the Strategic research and innovation program for the development of Medical University Plovdiv" No BG-RRP-2.004-0007-C01, Establishment of a network of research higher schools, National plan for recovery and resilience, financed by the European Union—NextGenerationEU.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2025.121328.

Data availability

The data that has been used is confidential.

References

Accordini, S., Calciano, L., Johannessen, A., Portas, L., Benediktsdottir, B., Bertelsen, R. J., Braback, L., Carsin, A.E., Dharmage, S.C., Dratva, J., Forsberg, B., Gomez Real, F., Heinrich, J., Holloway, J.W., Holm, M., Janson, C., Jogi, R., Leynaert, B., Malinovschi, A., 2018. Ageing lungs in European cohorts, S. A three-generation study on the association of tobacco smoking with asthma. Int J Epidemiol 47 (4), 1106–1117. https://doi.org/10.1093/ije/dyy031.

AirViro, 2011. Working with the dispersion Module.How to simulate the dispersion of pollutants. http://www.smhi.se/polopoly_fs/1.12792!/Volume2_Dispersion_3.20.pdf.

Alfano, R., Bijnens, E., Langie, S.A.S., Nawrot, T.S., Reimann, B., Vanbrabant, K., Wang, C., Plusquin, M., 2023. Epigenome-wide analysis of maternal exposure to green space during gestation and cord blood DNA methylation in the ENVIRONAGE cohort. Environ. Res. 216 (Pt 4), 114828. https://doi.org/10.1016/j.envres.2022.114828.

Brandt, J., Christensen, J.H., Frohn, L.M., Berkowicz, R., 2001. Operational air pollution forecasts from regional scale to urban street scale. Part 2: performance evaluation. Phys. Chem. Earth 26, 825–830. https://doi.org/10.1016/S1464-1909(01)00092-2.

Brandt, J., C J, H., Frohn, L.M., Berkowicz, R., 2001. Operational air pollution forecasts from regional scale to urban street scale.Part 1: system description. Atmos. Environ. 26 (10), 781–786.

Brandt, J., Silver, J.D., Frohn, L.M., Geels, C., Gross, A., Hansen, A.B., Hansen, K.M., Hedegaard, G.B., Skjøth, C.A., Villadsen, H., Zare, A., Christensen, J.H., 2012. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. Atmos. Environ. 53, 156–176. https://doi.org/10.1016/j.atmosenv.2012.01.011.

Burbank, A.J., Sood, A.K., Kesic, M.J., Peden, D.B., Hernandez, M.L., 2017. Environmental determinants of allergy and asthma in early life. J. Allergy Clin. Immunol. 140 (1), 1–12. https://doi.org/10.1016/j.jaci.2017.05.010.

Cheng, C., Spiegelman, D., Li, F., 2021. Estimating the natural indirect effect and the mediation proportion via the product method. BMC Med. Res. Methodol. 21 (1), 253. https://doi.org/10.1186/s12874-021-01425-4.

Chowdhury, N.U., Guntur, V.P., Newcomb, D.C., Wechsler, M.E., 2021. Sex and gender in asthma. Eur. Respir. Rev. 30 (162), 210067. https://doi.org/10.1183/16000617.0067-2021.

Christensen, J.H., 1997. The Danish Eulerian Hemispheric Model-A Three-dimensional air pollution model used for the arctic. Atmos. Environ. 31 (24), 4169–4191.

Deng, Q., Lu, C., Ou, C., Chen, L., Yuan, H., 2016. Preconceptional, prenatal and postnatal exposure to outdoor and indoor environmental factors on allergic diseases/symptoms in preschool children. Chemosphere 152, 459–467. https://doi.org/10.1016/j.chemosphere.2016.03.032.

Donovan, G.H., Gatziolis, D., Longley, I., Douwes, J., 2018. Vegetation diversity protects against childhood asthma: results from a large New Zealand birth cohort. Nat. Plants 4 (6), 358–364. https://doi.org/10.1038/s41477-018-0151-8.

Dons, E., Int Panis, L., Van Poppel, M., Theunis, J., Willems, H., Torfs, R., Wets, G., 2011. Impact of time–activity patterns on personal exposure to black carbon. Atmos. Environ. 45 (21), 3594–3602. https://doi.org/10.1016/j.atmosenv.2011.03.064.

Ferrante, G., Asta, F., Cilluffo, G., De Sario, M., Michelozzi, P., La Grutta, S., 2020. The effect of residential urban greenness on allergic respiratory diseases in youth: a narrative review. World Allergy Organization Journal 13 (1), 100096. https://doi.org/10.1016/j.waojou.2019.100096.

Frohn, L.M., Geels, C., Andersen, C., Andersson, C., Bennet, C., Christensen, J.H., Im, U., Karvosenoja, N., Kindler, P.A., Kukkonen, J., Lopez-Aparicio, S., Nielsen, O.-K., Palamarchuk, Y., Paunu, V.-V., Plejdrup, M.S., Segersson, D., Sofiev, M., Brandt, J., 2022. Evaluation of multidecadal high-resolution atmospheric chemistry-transport modelling for exposure assessments in the continental Nordic countries. Atmos. Environ. 290. https://doi.org/10.1016/j.atmosenv.2022.119334.

Geels, C., Winther, M., Andersson, C., Jalkanen, J.-P., Brandt, J., Frohn, L.M., Im, U., Leung, W., Christensen, J.H., 2021. Projections of shipping emissions and the related impact on air pollution and human health in the Nordic region. Atmos. Chem. Phys. 21 (16), 12495–12519. https://doi.org/10.5194/acp-21-12495-2021.

Gowers, A.M., Cullinan, P., Ayres, J.G., Anderson, H.R., Strachan, D.P., Holgate, S.T., Mills, I.C., Maynard, R.L., 2012. Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence; a review. Respirology 17 (6), 887–898. https://doi.org/10.1111/j.1440-1843.2012.02195.x.

Goyal, D., Limesand, S.W., Goyal, R., 2019. Epigenetic responses and the developmental origins of health and disease. J. Endocrinol. 242 (1), T105–t119. https://doi.org/10.1530/joe-19-0009.

Hartley, K., Ryan, P., Brokamp, C., Gillespie, G.L., 2020. Effect of greenness on asthma in children: a systematic review. Public Health Nurs. 37 (3), 453–460. https://doi.org/10.1111/phn.12701.

Hehua, Z., Qing, C., Shanyan, G., Qijun, W., Yuhong, Z., 2017. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: a systematic review. Environ. Res. 159, 519–530. https://doi.org/10.1016/j.envres.2017.08.038.

Hsu, H.H., Chiu, Y.H., Coull, B.A., Kloog, I., Schwartz, J., Lee, A., Wright, R.O., Wright, R. J., 2015. Prenatal particulate air pollution and asthma onset in urban children. Identifying sensitive windows and sex differences. Am. J. Respir. Crit. Care Med. 192 (9), 1052–1059. https://doi.org/10.1164/rccm.201504-0658OC.

Hvidtfeldt, U.A., Ketzel, M., Sørensen, M., Hertel, O., Khan, J., Brandt, J., Raaschou-Nielsen, O., 2018. Evaluation of the Danish AirGIS air pollution modeling system against measured concentrations of PM2.5, PM10, and black carbon. Environmental Epidemiology 2 (2), e014. https://doi.org/10.1097/ee9.0000000000000014.

Jackson, C.M., Kaplan, A.N., Järvinen, K.M., 2023. Environmental exposures may hold the key; impact of air pollution, greenness, and rural/farm lifestyle on allergic outcomes. Curr. Allergy Asthma Rep. 23 (2), 77–91. https://doi.org/10.1007/s11882-022-01061-y.

Jacquemin, B., Sunyer, J., Forsberg, B., Aguilera, I., Bouso, L., Briggs, D., de Marco, R., Garcia-Esteban, R., Heinrich, J., Jarvis, D., Maldonado, J.A., Payo, F., Rage, E., Vienneau, D., Kunzli, N., 2009. Association between modelled traffic-related air pollution and asthma score in the ECRHS. Eur. Respir. J. 34 (4), 834–842. https://doi.org/10.1183/09031936.00138208.

Jacquemin, B., Siroux, V., Sanchez, M., Carsin, A.E., Schikowski, T., Adam, M., Bellisario, V., Buschka, A., Bono, R., Brunekreef, B., Cai, Y., Cirach, M., Clavel-Chapelon, F., Declercq, C., de Marco, R., de Nazelle, A., Ducret-Stich, R.E., Ferretti, V.V., Gerbase, M.W., Kauffmann, F., 2015. Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). Environ. Health Perspect. 123 (6), 613–621. https://doi.org/10.1289/ehp.1408206.

Johannessen, A., Xu, S., Abbah, A.P., Janson, C., 2023. Greenness exposure: beneficial but multidimensional. Breathe 19 (2). https://doi.org/10.1183/20734735.0221-2022.

Joubert, B.R., Felix, J.F., Yousefi, P., Bakulski, K.M., Just, A.C., Breton, C., Reese, S.E., Markunas, C.A., Richmond, R.C., Xu, C.J., Küpers, L.K., Oh, S.S., Hoyo, C., Gruzieva, O., Söderhäll, C., Salas, L.A., Baïz, N., Zhang, H., Lepeule, J., London, S.J., 2016. DNA methylation in newborns and maternal smoking in pregnancy: genome-wide consortium meta-analysis. Am. J. Hum. Genet. 98 (4), 680–696. https://doi.org/10.1016/j.ajhg.2016.02.019.

Keirsbulck, M., Savoure, M., Lequy, E., Chen, J., de Hoogh, K., Vienneau, D., Goldberg, M., Zins, M., Roche, N., Nadif, R., Jacquemin, B., 2023. Long-term exposure to ambient air pollution and asthma symptom score in the CONSTANCES cohort. Thorax 78 (1), 9–15. https://doi.org/10.1136/thoraxjnl-2021-218344.

Khreis, H., Cirach, M., Mueller, N., de Hoogh, K., Hoek, G., Nieuwenhuijsen, M.J., Rojas-Rueda, D., 2019. Outdoor air pollution and the burden of childhood asthma across Europe. Eur. Respir. J. 54 (4). https://doi.org/10.1183/13993003.02194-2018.

Kitaba, N.T., Knudsen, G.T.M., Johannessen, A., Rezwan, F.I., Malinovschi, A., Oudin, A., Benediktsdottir, B., Martino, D., González, F.J.C., Gómez, L.P., Holm, M., Jõgi, N.O., Dharmage, S.C., Skulstad, S.M., Watkins, S.H., Suderman, M., Gómez-Real, F., Schlünssen, V., Svanes, C., Holloway, J.W., 2023. Fathers' preconception smoking and offspring DNA methylation. Clin. Epigenet. 15 (1), 131. https://doi.org/10.1186/s13148-023-01540-7.

Kuiper, I.N., Markevych, I., Accordini, S., Bertelsen, R.J., Braback, L., Christensen, J.H., Forsberg, B., Halvorsen, T., Heinrich, J., Hertel, O., Hoek, G., Holm, M., de Hoogh, K., Janson, C., Malinovschi, A., Marcon, A., Sigsgaard, T., Svanes, C., Johannessen, A., 2020. Associations of preconception exposure to air pollution and greenness with offspring asthma and hay fever. Int J Environ Res Public Health 17 (16). https://doi.org/10.3390/ijerph17165828.

Lambert, K.A., Bowatte, G., Tham, R., Lodge, C., Prendergast, L., Heinrich, J., Abramson, M.J., Dharmage, S.C., Erbas, B., 2017. Residential greenness and allergic respiratory diseases in children and adolescents - a systematic review and meta-analysis. Environ. Res. 159, 212–221. https://doi.org/10.1016/j.envres.2017.08.002.

Lavigne, E., Belair, M.A., Rodriguez Duque, D., Do, M.T., Stieb, D.M., Hystad, P., van Donkelaar, A., Martin, R.V., Crouse, D.L., Crighton, E., Chen, H., Burnett, R.T., Weichenthal, S., Villeneuve, P.J., To, T., Brook, J.R., Johnson, M., Cakmak, S., Yasseen 3rd, A.S., Walker, M., 2018. Effect modification of perinatal exposure to air pollution and childhood asthma incidence. Eur. Respir. J. 51 (3). https://doi.org/10.1183/13993003.01884-2017.

Litonjua, A.A., Carey, V.J., Burge, H.A., Weiss, S.T., Gold, D.R., 1998. Parental history and the risk for childhood asthma. Does mother confer more risk than father? Am. J. Respir. Crit. Care Med. 158 (1), 176–181. https://doi.org/10.1164/ajrccm.158.1.9710014.

Liu, S., Jørgensen, J.T., Ljungman, P., Pershagen, G., Bellander, T., Leander, K., Magnusson, P.K.E., Rizzuto, D., Hvidtfeldt, U.A., Raaschou-Nielsen, O., Wolf, K., Hoffmann, B., Brunekreef, B., Strak, M., Chen, J., Mehta, A., Atkinson, R.W., Bauwelinck, M., Varraso, R., Andersen, Z.J., 2021. Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project. Eur. Respir. J. 57 (6). https://doi.org/10.1183/13993003.030992020.

Liu, W., Liu, K., Cai, J., Ma, S., Yang, M., Yang, Q., Yuan, Y., 2023. Associations between residential greenness and asthma and allergic rhinitis in children: a systematic review and meta-analysis. Sustain. Cities Soc. 94. https://doi.org/10.1016/j.scs.2023.104566.

Mørkve, K.T., Rezwan, F.I., Jiang, Y., Karmaus, W., Svanes, C., Holloway, J.W., 2018. Transgenerational and intergenerational epigenetic inheritance in allergic diseases. J. Allergy Clin. Immunol. 142 (3), 765–772. https://doi.org/10.1016/j.jaci.2018.07.007.

Mueller, W., Milner, J., Loh, M., Vardoulakis, S., Wilkinson, P., 2022. Exposure to urban greenspace and pathways to respiratory health: an exploratory systematic review. Sci. Total Environ. 829, 154447. https://doi.org/10.1016/j.scitotenv.2022.154447.

Nguyen, T.Q., Schmid, I., Stuart, E.A., 2020. Clarifying causal mediation analysis for the applied researcher: defining effects based on what we want to learn. Psychol. Methods. https://doi.org/10.1037/met0000299.

Nordeide Kuiper, I., Svanes, C., Markevych, I., Accordini, S., Bertelsen, R.J., Braback, L., Heile Christensen, J., Forsberg, B., Halvorsen, T., Heinrich, J., Hertel, O., Hoek, G., Holm, M., de Hoogh, K., Janson, C., Malinovschi, A., Marcon, A., Miodini Nilsen, R., Sigsgaard, T., Johannessen, A., 2021. Lifelong exposure to air pollution and greenness in relation to asthma, rhinitis and lung function in adulthood. Environ. Int. 146, 106219. https://doi.org/10.1016/j.envint.2020.106219.

Orru, H., Maasikmets, M., Lai, T., Tamm, T., Kaasik, M., Kimmel, V., Orru, K., Merisalu, E., Forsberg, B., 2010. Health impacts of particulate matter in five major Estonian towns: main sources of exposure and local differences. Air Qual. Atmos. Health 4 (3–4), 247–258. https://doi.org/10.1007/s11869-010-0075-6.

Orru, K., Nordin, S., Harzia, H., Orru, H., 2018. The role of perceived air pollution and health risk perception in health symptoms and disease: a population-based study combined with modelled levels of PM(10). Int. Arch. Occup. Environ. Health 91 (5), 581–589. https://doi.org/10.1007/s00420-018-1303-x.

Pedersen, C.E.T., Eliasen, A.U., Ketzel, M., Brandt, J., Loft, S., Frohn, L.M., Khan, J., Brix, S., Rasmussen, M.A., Stokholm, J., Chawes, B., Morin, A., Ober, C., Bisgaard, H., Pedersen, M., Bonnelykke, K., 2023. Prenatal exposure to ambient air pollution is associated with early life immune perturbations. J. Allergy Clin. Immunol. 151 (1), 212–221. https://doi.org/10.1016/j.jaci.2022.08.020.

Preacher, K.J., Zyphur, M.J., Zhang, Z., 2010. A general multilevel SEM framework for assessing multilevel mediation. Psychol. Methods 15 (3), 209–233. https://doi.org/10.1037/a0020141.

Rantala, A.K., Paciencia, I., Antikainen, H., Hjort, J., Hugg, T.T., Jaakkola, M.S., Jaakkola, J.J.K., 2024. Residential greenness during pregnancy and early life and development of asthma up to 27 years of age: the Espoo Cohort Study. Environ. Res. 252 (Pt 1), 118776. https://doi.org/10.1016/j.envres.2024.118776.

Schisterman, E.F., Cole, S.R., Platt, R.W., 2009. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology 20 (4), 488–495. https://doi.org/10.1097/EDE.0b013e3181a819a1.

Singh, N., Buczyłowska, D., Baumbach, C., Bratkowski, J., Mysak, Y., Wierzba-Łukaszyk, M., Sitnik-Warchulska, K., Skotak, K., Lipowska, M., Izydorczyk, B., Szwed, M., Dzhambov, A.M., Markevych, I., 2024. Pathways linking greenspace to behavioural problems in Polish children. Heliyon 10 (10), e31435. https://doi.org/10.1016/j.heliyon.2024.e31435.

Skamarock, W.C., Klemp, J.B., Dudhia, J., Gill, O.D., Barker, D.M., Duda, M.G., Huang, X., Wang, W., Powers, J.G., 2008. A description of the advanced research WRF version 3. https://doi.org/10.5065/D68S4MVH.

Squillacioti, G., Bellisario, V., Ghelli, F., Marcon, A., Marchetti, P., Corsico, A.G., Pirina, P., Maio, S., Stafoggia, M., Verlato, G., Bono, R., 2024. Air pollution and oxidative stress in adults suffering from airway diseases. Insights from the Gene Environment Interactions in Respiratory Diseases (GEIRD) multi-case control study. Sci. Total Environ. 909, 168601. https://doi.org/10.1016/j.scitotenv.2023.168601.

StataCorp, 2023. STRUCTURAL EQUATION MODELING REFERENCE MANUAL. StataCorp LLC, College Station, TX. *Release 18*.

Sunyer, J., Pekkanen, J., Garcia-Esteban, R., Svanes, C., Künzli, N., Janson, C., De Marco, R., Antó, J.M., Burney, P., 2007. Asthma score: predictive ability and risk factors. Allergy 62 (2), 142–148. https://doi.org/10.1111/j.1398-9995.2006.01184.x.

Svanes, Cecilie, M, PhD, et al., 2016. Father's environment before conception and asthma risk in his children: A multigeneration analysis of the Respiratory Health in Northern Europe study 46 (1), 235–245.

Svanes, C., Johannessen, A., Bertelsen, R.J., Dharmage, S., Benediktsdottir, B., Braback, L., Gislason, T., Holm, M., Jogi, O., Lodge, C.J., Malinovschi, A., Martinez-Moratalla, J., Oudin, A., Sanchez-Ramos, J.L., Timm, S., Janson, C., Real, F.G., Schlunssen, V., Collaboration, R.I., 2022. Cohort profile: the multigeneration respiratory health in northern Europe, Spain and Australia (RHINESSA) cohort. BMJ Open 12 (6), e059434. https://doi.org/10.1136/bmjopen-2021-059434.

Svanes, C., Holloway, J.W., Krauss-Etschmann, S., 2023. Preconception origins of asthma, allergies and lung function: the influence of previous generations on the respiratory health of our children. J. Intern. Med. 293 (5), 531–549. https://doi.org/10.1111/joim.13611.

Tang, M., Liu, W., Li, H., Li, F., 2023. Greenness and chronic respiratory health issues: a systematic review and meta-analysis. Front. Public Health 11, 1279322. https://doi.org/10.3389/fpubh.2023.1279322.

Tucker, C.J., 1979. Red and Photographic Infrared L,lnear Combinations for Monitoring Vegetation, vol. 8, pp. 127–150.

Ungar, W.J., Chapman, K.R., Santos, M.T., 2002. Assessment of a medication-based asthma Index for population research. Am. J. Respir. Crit. Care Med. 165, 190–194. https://doi.org/10.1164/rccm2102012.

Vatcheva, K.P., Lee, M., McCormick, J.B., Rahbar, M.H., 2016. Multicollinearity in regression analyses conducted in epidemiologic studies. Epidemiology 6 (2). https://doi.org/10.4172/2161-1165.1000227.

Weier, J., Herring, D., 2011. Measuring vegetation (NDVI & EVI). Retrieved September 14 from. http://earthobservatory.nasa.gov/Features/MeasuringVegetation/.

WHO, 2016. Urban green spaces and health: a review of evidence. http://www.euro.who.int/pubrequest.

Xie, S., Hubbard, R.A., Himes, B.E., 2020. Neighborhood-level measures of socioeconomic status are more correlated with individual-level measures in urban areas compared with less urban areas. Ann. Epidemiol. 43, 37. https://doi.org/10.1016/j.annepidem.2020.01.012, 43 e34.

Xu, R., Li, S., Li, S., Wong, E.M., Southey, M.C., Hopper, J.L., Abramson, M.J., Guo, Y., 2021. Residential surrounding greenness and DNA methylation: an epigenome-wide association study. Environ. Int. 154, 106556. https://doi.org/10.1016/j.envint.2021.106556.