Effects of air pollution and greenness on asthma and allergy — over time and across generations

Ingrid Nordeide Kuiper

Thesis for the degree of Philosophiae Doctor (PhD)
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UNIVERSITY OF BERGEN

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Scientific environment

The work in this thesis was conducted at the Department of Occupational Medicine at Haukeland University Hospital and the Department of Global Public Health and Primary Care at the University of Bergen (UiB). It was financed by Helse Vest. During the PhD-period I have been an affiliate member of the National Research School in Population-Based Epidemiology (EPINOR).

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Bergen, August 2020

Contents

Abbreviations

AirBase	The European Air quality Database
BC	Black carbon
BMI	Body mass index
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
DAG	Directed Acyclic Graph
DEHM	Danish Eulerian Hemispheric Model
DOHaD	Developmental Origins of Health and Disease
EEA	European Environment Agency
ECRHS	European Community Respiratory Health Survey
ESCAPE	European Studies of Cohorts for Air Pollution Effects
EU	European Union
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GIS	Geographic Information System
GDPR	General Data Protection Regulation
GLI	Global Lung Function Initiative
ISAAC	International Study of Asthma and Allergies in Childhood
LLN	Lower limit of normal

LUR	Land-use regression
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
NDVI	Normalized difference vegetation index
NIR	Near-infrared light
NO_2	Nitrogen dioxide
NPV	Negative Predictive Value
O_3	Ozone
OLI	Operational Land Imager
OR	Odds ratio
$PM_{2.5}$	Particulate matter with an aerodynamic diameter lower than 2.5 μm
PM_{10}	Particulate matter with an aerodynamic diameter lower than 10 μm
PPV	Positive Predictive Value
RED	Visible red light
RHINE	Respiratory Health in Northern Europe
RHINESSA	Respiratory Health in Northern Europe, Spain and Australia
SD	Standard deviation
TM	Thematic Mapper
TRAP	Traffic related air pollution

USGS	United States Geological Survey
VOC	Volatile organic compound
WHO	World Health Organization

Thesis at a glance

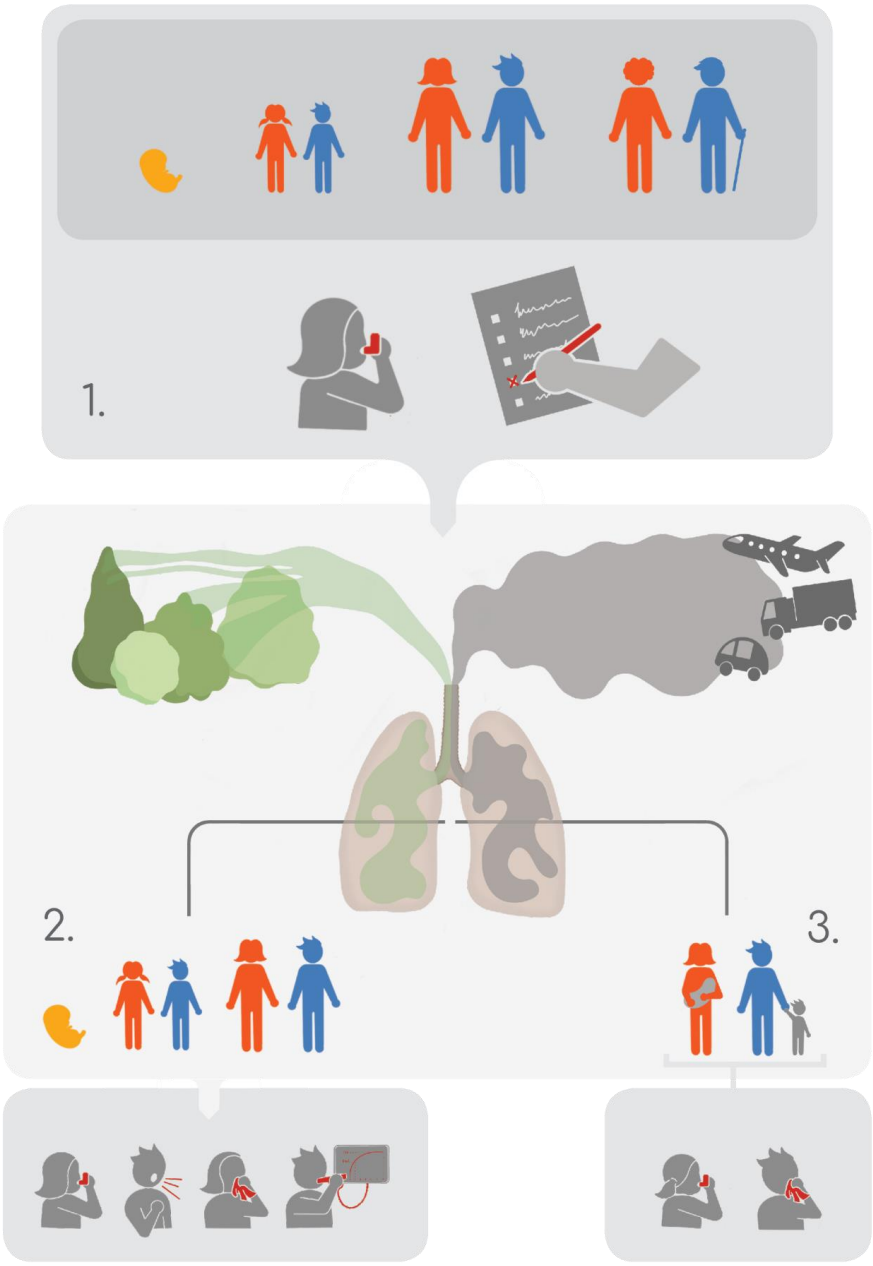

Figure 1. Overview of the three papers included in the thesis: 1) Investigation of the agreement of asthma reports from questionnaires across generations in the RHINESSA study. 2) Longitudinal study with retrospective design of lifelong exposure to air pollution and greenness in relation to: asthma, asthma attack, rhinitis and lung function (the grey figures bottom left). 3) Longitudinal study with retrospective cross-generational design of preconception exposure to air pollution and greenness in relation to: offspring asthma and rhinitis (the grey figures bottom right). Illustration by Taran Johanne Neckelmann.

Abstract

Background: The prevalence of asthma and allergies have increased in the last decades, likely due to complex interaction of genes and environmental factors; however, causal pathways are still far from understood. Environmental factors like air pollution and greenness play a part, but the impact of relatively low levels of air pollution and greenness on the development of asthma and allergies throughout the lifespan and across generations has not been elucidated. When studying intergenerational risk factors, the use of reports on asthma across generations is essential. Before using such reports, however, it is important to validate them.

Objectives: I) To determine the agreement between parental and offspring asthma reports in the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) generation study, and identify predictors of disagreement. II) To investigate the risk of adult asthma, rhinitis and low lung function after lifelong exposure to air pollution and greenness. III) To investigate the associations between parental childhood exposure to air pollution and greenness in relation to their future offspring asthma and rhinitis, and assess if the associations were direct effects or if they were mediated through parental asthma, pregnancy exposure to greenness/air pollution and offspring own exposure.

Material and methods: I) Asthma reports from 6752 offspring and their 5907 parents from the RHINESSA study regarding themselves and each other were analysed. Cohen's kappa, sensitivity, specificity, positive and negative predictive values (PPV and NPV) were calculated to determine agreement. The participant's own answers regarding themselves were defined as the gold standard. Logistic regression analyses were performed to identify predictors for disagreement.

II) and III) Individual annual mean residential exposures to nitrogen dioxide (NO_2), particulate matter (PM_{10} and $PM_{2.5}$), black carbon (BC), ozone (O_3) and greenness (normalized difference vegetation index (NDVI)) were calculated and averaged across the following susceptibility windows: Paper II (N = 3428): 0-10 years, 10-18 years,

from birth until age of diagnosis, lifetime and year before study participation. Paper III (N = 1106 parents, 1949 offspring): parents 0-18 years and offspring 0-10 years.

In paper II, logistic regression was performed for the outcomes asthma attack, rhinitis and impaired lung function (below lower limit of normal (LLN: z-score <1.64 SD)), while conditional logistic regression with a matched case-control design was performed for asthma (ever/allergic/non-allergic). In paper III, logistic regression and mediation analyses were performed for the outcomes offspring asthma and rhinitis.

Results: I) Agreement of parental reports of offspring early (<10 years) and late (>10 years) onset asthma was good and moderate, respectively (Cohen's kappa 0.72 and 0.46). Agreement of offspring reports of maternal and paternal asthma was good (Cohen's kappa 0.69 and 0.68). For both parents and offspring, the most common disagreement was to report no asthma in asthmatic relatives rather than to report asthma in non-asthmatic relatives. Current smokers (odds ratio (OR) 1.46 95% confidence interval (CI) 1.05, 2.02) and fathers (OR 1.31 95% CI 1.08, 1.59) were more likely to report offspring asthma incorrectly. Offspring wheeze was associated with reporting parental asthma incorrectly (OR 1.60 95% CI 1.21, 2.11). II) Exposures to NO_2, PM_{10} and O_3 were associated with increased risk for asthma attacks (range ORs 1.29 to 2.25). Exposures to $PM_{2.5}$ and O_3 increased the risk for low lung function, in particular forced expiratory volume in one second (FEV_1) (range ORs 2.65 to 4.21). Increased NDVI was associated with lower FEV_1 and forced vital capacity (FVC) in all susceptibility windows (range ORs 1.39 to 1.74). III) Maternal exposures to $PM_{2.5}$ and PM_{10} was associated with higher offspring asthma risk (OR 2.23 95% CI 1.32, 3.78; OR 2.27, 95% CI 1.36, 3.80) and paternal high BC exposure was associated with lower offspring asthma risk (OR 0.31, 95% CI 0.11, 0.87). Risk for rhinitis increased for offspring of fathers with medium O_3 exposure (OR 4.15, 95%CI 1.28, 13.50) and mothers with high PM_{10} exposure (OR 2.66, 95% CI 1.19, 5.91). The effect of maternal PM_{10} exposure on offspring asthma was direct, while it for rhinitis was mediated through exposures in pregnancy and offspring's own exposures. Paternal O_3 exposure had a direct effect on offspring rhinitis.

Conclusions: I) Agreement of self-reported asthma across generations in the RHINESSA study showed moderate to good agreement, although with some risk of under-report. II) Lifelong air pollution exposure was associated with asthma attacks, rhinitis and low lung function. Exposure to greenness was associated with low lung function. III) Parental air pollution exposures in their childhood were associated with increased risk of asthma and rhinitis in future offspring.

Consequences: Exposure to air pollution and greenness impact numerous people. Further research is warranted to entirely understand the complex underlying interactions between air pollution and greenness and respiratory health. However, results from this PhD project suggest that existing air pollution limit values may be too high, and that exposures below the upper limit values may have harmful health effects. From a public health perspective, one should continuously strive for cleaner air, not only for today's population, but also for the next generations.

List of Publications

The thesis is based on the following three original papers:

I. Kuiper IN, Svanes C, Benediktsdottir B, Bertelsen RJ, Bråbäck L, Dharmage SC, Holm M, Janson C, Jögi R, Malinovschi A, Matheson M, Moratalla JM, Real FG, Sánchez-Ramos JL, Schlünssen V, Timm S, Johannessen A. Agreement in reporting of asthma by parents or offspring – the RHINESSA generation study. *BMC Pulmonary Medicine* (2018) 18:122.

II. Kuiper IN, Markevych I, Accordini S, Bertelsen RJ, Bråbäck L, Christensen JH, Forsberg B, Halvorsen T, Heinrich J, Hertel O, Hoek G, Holm M, de Hoogh K, Janson C, Malinovschi A, Marcon A, Nilsen RM, Sigsgaard T, Svanes C, Johannessen A. Lifelong exposure to air pollution and greenness in relation to asthma, rhinitis and lung function in adulthood. (Submitted to Env Int 23rd August 2020)

III. Kuiper IN, Markevych I, Accordini S, Bertelsen RJ, Bråbäck L, Christensen JH, Forsberg B, Halvorsen T, Heinrich J, Hertel O, Hoek G, Holm M, de Hoogh K, Malinovschi A, Marcon A, Sigsgaard T, Svanes C, Johannessen A. Associations of preconception exposure to air pollution and greenness with offspring asthma and hay fever. *Int. J. Environ. Res. Public Health 2020, 17, 5828.*

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1. Introduction

The prevalence of asthma and allergies have increased during the last decades (1, 2) and contributes to a heavy morbidity burden both for the individual and the society. An increasing amount of research regarding asthma and allergies has developed, and a complex interaction between individual susceptibility and environmental exposures has been identified (2-4). However, the causal pathways are still far from understood.

From 2000 onwards, there was a growing interest in the importance of early life and prenatal risk factors for developing disease later in life, also known as the Developmental Origins of Health and Disease (DOHaD) hypothesis developed by Forsdahl and Barker twenty years earlier (3, 5, 6). Recently, research has emerged suggesting that also risk factors before conception may be of importance (3).

As a consequence of the increasing interest in studying environmental risk factors for asthma and allergy, one of modern time biggest public health threats, air pollution, has also been studied in relation to these diseases. However, since most of the studies have focused on high air pollution levels and acute health effects, we know relatively little of long-term exposures and disease development, and nothing about inter-generational associations. Contrary to air pollution, another environmental exposure that during the last decade has received increasing interest is greenness, which has been suggested to have beneficial health effects.

To summarize, there is a need to examine air pollution exposure in relation to asthma and allergies – as well as potential beneficial effects of greenness exposures. There is a need for increased knowledge about exposures in a truly long-term perspective; throughout the life-span and across generations. To accomplish knowledge also about inter-generational associations, we need to know if reports of asthma provided by relatives can be used in situations when reports from the generation of interest are not available.

In the following sections brief introductions are provided of the outcomes, exposures and key terms used in this thesis. In addition, an overview of studies on air pollution

and greenness exposures in this field, existing before the initiation of this PhD project, has been included.

1.1 Asthma

Asthma is defined as a chronic inflammation of the airways, triggered by several different factors such as allergens, infections, physical activity and smoking. It is associated with airway hyper responsiveness and reversible airway obstruction that can lead to recurrent episodes of wheezing, breathlessness, chest tightness and coughing (7). Asthma affects all age groups, but often starts in childhood (7). During the first decade of life, asthma is more prevalent in boys, but after puberty it appears to be more prevalent in girls (8). These sex differences have been explained by boys having smaller airway size compared with girls of same height and weight and age (under 10 years), which predisposes to increased airway reactivity (8). After decades with more asthma in women than men during adulthood, however, the sex differences in asthma burden narrows again in the fifth decade of life, suggesting that also sex hormones may play a role (9-11). Worldwide, asthma is among the most common chronic diseases in children, but also in adults it inflicts a heavy morbidity burden on society. It is estimated to affect more than 339 million people throughout the world (12). The prevalence in Norway is eight percent for adults and approximately 20 percent for children between two to ten years (13). Asthma is often categorized by phenotypes due to its heterogeneity. Phenotype is defined as "subtypes of the disease that have recognizable properties produced by interactions of the genotype and the environment" (8, 14). The phenotypes are often based on clinical and/or pathophysiological characteristics or age of onset. Non-allergic asthma and allergic asthma are two of the most common, the latter often starting in childhood and being associated with a positive family history of allergic diseases (7). Diagnosing asthma in young children is a challenge due to the varied and unspecific symptoms, and the absence of a gold standard diagnostic test (8). Guidelines are developed to help diagnose asthma in children based on symptoms, to avoid over and under treatment (7). However, for epidemiological studies there is no clear consensus of the definition of childhood

asthma. In fact, across 122 published studies, 60 different definitions of "childhood asthma" were used (9). Due to the challenges in diagnosis, there are also no standards for the age cut-off for early and late onset childhood asthma in epidemiological studies (9). Some studies have used cut-offs based on phenotypes; early onset transient (0-3 years of age), early onset persistent (0-6 years of age) and late onset (4-6 years of age) (15), while others have used 0-3 years of age as early onset and 4-15 years of age as late onset asthma (16). In this thesis, the definition of asthma onset before 10 years of age is used for early onset and asthma onset after 10 years of age is used for late onset asthma. The cut-off of 10 years was chosen to capture pre-puberty asthma as early onset asthma.

Due to the complexity and heterogeneity of asthma, the pathogenic mechanisms remain unclear and it is therefore still a "hot topic" in the field of epidemiological research.

1.2 Rhinitis

Rhinitis is characterised by one or more of the following symptoms: sneezing, runny nose (rhinorrhoea), stuffy nose (nasal congestion) and nasal itching (17) , and is associated with an inflammation of the mucous membrane. The most common classification is by aetiology; divided into allergic and non-allergic rhinitis. The mucosal inflammation in allergic rhinitis is caused by exposure to different allergens such as pollen, dust mites, moulds, animal allergens or occupational allergens, which initiate an IgE–mediated response (17). The characteristics of non-allergic rhinitis are periodic symptoms of rhinitis that are not caused by allergy, thus not IgE-dependent events, but are due to e.g. infections or underlying immunological pathology (17). In this thesis, the term rhinitis is used for allergic rhinitis, also commonly termed hay fever. An increased risk of allergic rhinitis is seen in persons with eczema or asthma. Up to 25 percent of school age children, 30 percent of adolescents and 23 percent of adults suffer from allergic rhinitis in Western Europe (18). The prevalence is, as for asthma, higher among boys until puberty, but more frequent in women than men after puberty (18, 19). The risk of developing asthma is higher in persons with allergic rhinitis (17). A study among 10-year old children in Norway found a high degree of

multimorbidity between asthma and allergic diseases, with up to 87 percent of the children with rhinitis also having asthma, atopic eczema or conjunctivitis (itchy/runny eyes) (20). Both uncontrolled asthma and persistent rhinitis can cause loss of work and school days and have a huge impact on the quality of life of the affected person. In addition it adds a substantial economic burden on society due to loss of workplace productivity and due to use of health services (17).

1.3 Lung function

Spirometry is an important lung function test in persons with respiratory symptoms. It measures the volume of exhaled air at different time points during a complete exhalation after maximal inhalation, recording among other variables the forced vital capacity (FVC) which represents the total exhaled volume; the forced expiratory volume in one second (FEV_1) which represents the volume exhaled in the first second; and their ratio (FEV_1/FVC) (21). The obtained patterns are important in differentiating obstructive airway diseases (e.g. chronic obstructive pulmonary disease (COPD) and asthma) from restrictive diseases (e.g. fibrotic lung disease). The ratio (FEV_1/FVC) is reduced in obstructive airway disease, while restrictive airway disease is suggested by a reduced FVC in combination with a normal or increased ratio. Results obtained from spirometry are also commonly compared against reference values or predicted values. To calculate predicted normal values for adults, the following patient details are usually used: age, gender, height and ethnicity. Asthma is a reversible obstructive disease, thus spirometry usually shows normal values when the person is not experiencing an exacerbation (22). Spirometry performed during an exacerbation or asthma attack, usually shows a reduced FEV_1/FVC ratio. Reversibility testing is often performed to diagnose asthma and to separate it from other causes of airflow obstruction (22). The test involves spirometry before and after a bronchodilator is given. The presence of reversibility, often defined by an improvement in FEV_1 exceeding 12 %, is suggestive of asthma (22).

1.4 Air pollution

"Pollution is the introduction of substances into the environment, resulting in deleterious effects of such a nature as to endanger human health, harm living resources and ecosystems." (European Environment Agency)

Air pollution is one of the greatest concerns of modern times, not only due to its impact on climate change but also because it affects entire populations and therefore poses a major public health threat. Throughout modern history, several episodes with extremely high levels of air pollution have been investigated in the field of environmental epidemiology. The London smog in 1952 is likely the most famous incident in Europe for its detrimental effects on deaths from respiratory- and cardiovascular related causes. It is estimated that the heavy pollution from coal burning in combination with unfortunate meteorological conditions, caused 4000 deaths among Londoners, and made tens of thousands suffering from acute respiratory illness. Ever since, there has been an increased interest among scientists of the possible harmful effects of high levels of air pollution on health. In addition, governments and politicians have since then been involved in regulating air pollution. The European Union (EU) started in the 1970s their work on developing measurement techniques and implementing several legislations and public health interventions to improve outdoor air quality. However, air pollution is still considered one of the most important environmental risk factors for health problems and disease worldwide (23). According to the World Health Organization (WHO), outdoor air pollution causes almost 500 000 premature annual deaths across Europe, corresponding to a total of 500-2000 persons in Norway (23, 24). However, these high mortality numbers are only the tip of the iceberg if additionally also considering the effects of air pollution on morbidity. Figure 2 is based on the pyramid of health effects in the ERS Report "Air Quality and Health" (25), and illustrates how a large proportion of a population exposed to air pollution will experience milder outcomes such as lung function decline and respiratory symptoms, while a smaller proportion of the population will experience more severe outcomes

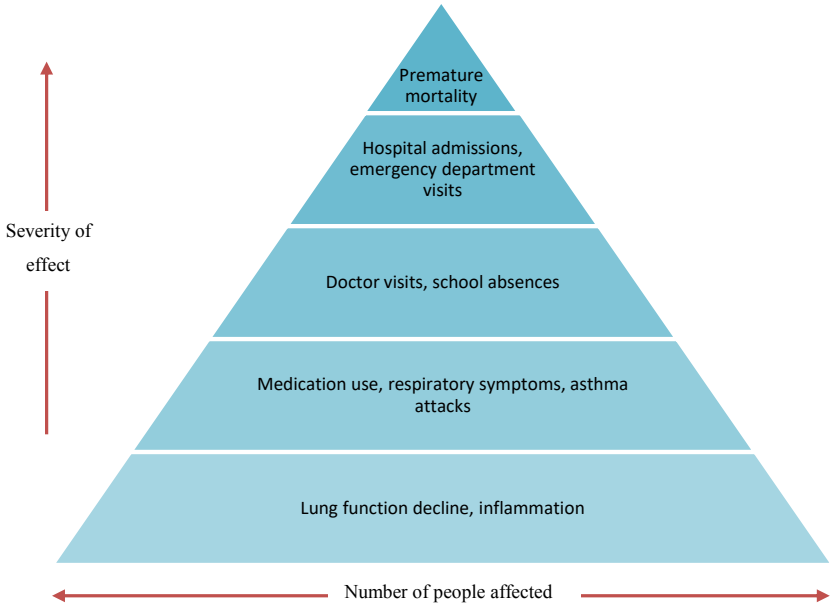

Figure 2. Pyramid of health effects caused by air pollution. (The figure is based on an illustration from the ERS Report "Air Quality and Health", 2010, available online https://www.ersnet.org/images/stories/pdf/web-AQ2010-ENG.pdf).

such as hospital admissions and deaths. Nonetheless, even milder outcomes such as decreased lung function and increased respiratory symptoms impose a heavy burden on individuals and society.

Several different pollutants are major factors causing health issues. In this thesis, the following pollutants were investigated: Particulate matter (PM) in two sizes, $PM_{2.5}$ and PM_{10}, nitrogen dioxide (NO_2), black carbon (BC) and ozone (O_3). PM contains a complex mixture of liquid and solid particles and is mostly a result of chemical reactions between different pollutants. The major components are sulphate, nitrates, ammonia, sodium chloride, BC, mineral dust and water (23). PM comprises particles of different sizes, referred to by the size of the particles aerodynamic diameter in micrometres (µm) after the abbreviation PM. Particles between 2.5 and 10 µm (PM_{10}) are coarse particles, while particles less then 2.5 µm ($PM_{2.5}$) are fine particles (26). PM_{10} causes harm as it enters the upper respiratory tract, while $PM_{2.5}$ poses an even

greater risk to human health as the smaller particles can penetrate the alveolar epithelium (27).

O_3 in the stratosphere protects against ultraviolet irradiation, while ground-level O_3 is one of the major components of photochemical smog and has toxic effects on human health as it can penetrate deeply into the lungs. It is a gas formed from other pollutants such as NO_x from vehicles, industry emissions and volatile organic compounds (VOCs) in reaction with sunlight (23). NO_2 is a toxic gas mainly emitted by combustion processes from engines in vehicles and ships. It is the main source of nitrate aerosols, which is a major fraction of $PM_{2.5}$ and O_3. BC, also called soot, is a short-lived pollutant (days to weeks), and is as mentioned one of the major components of fine PM. The particles are formed from incomplete combustion of biomass and fossil fuels, e.g. diesel engines (23).

Air pollution thus consists of gases and pollutants in various sizes that occur in a complex mixture. Correlation and chemical reactions between pollutants as well as seasonal patterns of the pollutants, makes the task of disentangling the separate effects of each pollutant in epidemiological studies extremely challenging.

Table 1 gives an overview of selected studies regarding the associations between exposure to air pollution with asthma, lung function and rhinitis. The literature overview is based on a systematic search for relevant original publications up to the starting point of my PhD-project (July 2017). The following search-terms in PubMed were used: ((long-term exposure[Title/Abstract]) NOT ((short-term exposure[Title/Abstract])) AND (traffic[Title/Abstract]) AND (air pollution[Title/Abstract]) AND ((asthma[Title/Abstract]) OR (lung function[Title/Abstract]) OR (rhinitis[Title/Abstract]))) AND (("1950/01/01"[Date - Publication] : "2017/07/01"[Date - Publication])) AND (english[Filter]). Relevant papers not identified by the search terms, but identified from the reference lists of review papers were also included in the overview. Studies using different exposure metrics than our studies (NO_2, $PM_{2.5}$, PM_{10}, BC or O_3) were not included in the

overview. The Table is organised by childhood and adolescence outcomes (above the bold line) and adult outcomes (below the bold line).

The twelve presented studies regarding childhood and adolescence outcomes are all cohort studies, mostly birth cohorts. Nine of the studies were conducted in Europe, two in Asia and one in the United States. Regarding the exposure calculations, a majority of the studies used cross-sectional measures based on the school/kindergarten addresses or residential addresses at birth or time of study participation/follow-up, while two of the studies had complete residential address histories from birth until 10 years of age (28, 29). Several different asthma and rhinitis definitions were used, but all of them where parental reports and most of them were defined as physician-diagnosed. Three of the studies used the validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (30-32). One study defined asthma as episodes of wheeze and the use of inhaled corticosteroids, without having a respiratory infection (33). Five of the selected studies investigated childhood lung function with spirometry, some of them including bronchodilator response (28, 32, 34-36). The exposure metrics varied, but the most commonly used were NO_2/NO_x and PM in different sizes.

Seven studies examined the effects of air pollution on asthma and/or rhinitis. Five of them found associations with the outcomes. One study with three year exposure time based on the school addresses revealed an association between asthma in children aged 9-11 years and several pollutants (PM_{10} and NO_x), while allergic rhinitis was associated with PM_{10} (30). Another study looked at exposure during pregnancy and in early life based on kindergarten addresses for all the exposure periods, and found associations of allergic rhinitis in children aged 3-6 years with exposure to NO_2 and PM_{10} during pregnancy and the first year of life (37). A Swedish study (33) calculated lifetime exposure based on residential, day care and school addresses registered from birth till 12 years, and revealed possible associations between exposure to PM_{10} and NO_x during the first year of life and asthma up to 12 years of age. A study of several European birth cohorts (38) found that the risk of incident asthma up to age 14-16 years increased with increasing exposure to NO_2 and $PM_{2.5}$ at the birth address, but no associations with

rhinoconjunctivitis was found. The last study regarding asthma (31), found associations of O_3, CO and NO_x with asthma. However, the exposure calculations were based on current exposure as a proxy of previous exposure because residential address history was not available. Consequently, the author's conclusion on long-term effects of air pollution in this particular study is dubious.

Two studies did not reveal any associations with asthma; one study had exposure calculations of NO_2 till 10 years of age based on complete residential moving history (29), another study conducted in two areas in Germany looked at O_3, NO_2 and $PM_{2.5}$ exposure and asthma in 6-10 year old children (39). For rhinitis however, the German study revealed a protective effect of $PM_{2.5}$ exposure in one of the areas (OR 0.83 95% CI 0.72, 0.96).

The five cohorts regarding lung function examined different exposure metrics and different exposure times and the results were varying. Rice et al. (34), found that lifetime exposure (median exposure time 7.7 years) to $PM_{2.5}$ and BC was associated with lower FVC. The same pattern was seen for FEV_1, but no effect was revealed for ratio or bronchodilator response. Another study examined the effects of NO_2 (32), and revealed associations with lower FVC and FEV_1. It is worth mentioning that this study claims to investigate long-term exposure, however it is a cross-sectional study where the calculations are based on geocoded residential addresses at the time of study participation. Oftedal et al. (28) looked at 10 year exposure time and was the only study using complete residential address history for the exposure calculations. The study revealed an association of NO_2, $PM_{2.5}$ and PM_{10} with reduced expiratory flow variables, especially in girls. No effects were seen on the forced volumes. A decrease in lung function in children aged 6 to 8 years was seen in the study by Gehring et al. (36), looking at several European birth cohorts. This study used residential address at birth and follow-up and back-extrapolated exposure from the years 2008-2010 to the birth years 1994-1999. The last study (35) did not reveal any associations between air pollution exposure and reduced lung function in 15 year old children.

The seven last studies in Table 1 focused on adult outcomes. One of the studies is conducted in the United States, the rest are conducted in Europe where three of them are multi-centre studies consisting of multiple cohorts. Five studies looked at self-reported asthma, one looked at self-reported physician-diagnosed rhinitis, and one investigated lung function. The assessed exposure metrics were NO_2 or PM in different sizes, or a combination of these.

Regarding asthma, all seven studies based their exposure calculations on the participant's residential addresses. All of the selected studies found effects on self-reported physician-diagnosed asthma, but the studies differed in exposure metrics. Two studies found association between $PM_{2.5}$ exposure and asthma (40, 41). Two other studies revealed an effect of NO_2 exposure (42, 43), while one study found a borderline significant effect on asthma (44). An association between exposure to PM_{10} and asthma was found in the two last studies (43, 45). An increased risk of rhinitis was revealed for proximity to major roads (300m), while regarding lung function, FEV_1 was inversely related to NOx and PM_{10} in a multi-centre cohort study (46).

The described selection of literature shows a large variety of included exposure metrics, definition of exposure time, methods of exposure calculations and outcome definitions. Furthermore, the overview reveals that no studies have so far studied continuous air pollution exposure for as much as 30 years. Although some studies claim to investigate lifelong exposure to air pollution (47), the scientific evidence is made up of several studies covering separate time windows rather than continuous lifetime exposure. To understand how air pollution exposure throughout the lifespan affects health, there is a need to follow subjects in the same cohort for a prolonged period of time. Furthermore, to our knowledge no studies have so far addressed the health effects on future offspring of parents' air pollution exposure in the years preceding conception. Several studies have addressed the effects of air pollution exposure in utero on health outcomes in offspring (34, 48), but there is a need to fill the gap on possible damaging effects across generations.

Table 1. Overview of selected studies of associations between exposure to air pollution and asthma, lung function and rhinitis.

First author, year, country	Design	Study population	Exposures, exposure time	Outcomes	Main findings
Pénard-Morand et al. (30), 2010, France	Cross-sectional study	N = 6683 urban children aged 9-11 years	PM_{10}, NO_x, NO_2, CO, benzene, volatile organic compounds, SO_2 3 year annual mean concentrations based on school address	Asthma and rhinitis (ISAAC questionnaires filled in by parents), eczema (skin-prick test)	Asthma was associated with exposure to benzene, SO_2, PM_{10}, NO_x and CO, while allergic rhinitis was associated with PM_{10}.
Deng et al. (37), 2016, China	Cross-sectional study	N = 2598 children aged 3-6 years	NO_2, PM_{10}, SO_2 Based on kindergarten address, pre- and postnatal period (during pregnancy (divided by trimesters), first year of life and from 2-6 years)	Allergic rhinitis, parental questionnaire reporting	Allergic rhinitis was associated with exposure during the third trimester of pregnancy with adjusted (OR 1.40 95% CI 1.08, 1.82) for a 15 $\mu g/m^3$ increase in NO_2 and during the first-year of life with adjusted (OR 1.36 95% CI 1.03, 1.78) and (OR 1.54 95% CI 1.07, 2.21) respectively for 11 and 12 $\mu g/m^3$ increase in NO_2 and PM_{10}.
Gruzieva et al. (33), 2013, Sweden	Birth cohort (BAMSE)	N = 4089 children aged 0-12 years	PM_{10}, NOx, dispersion modelling Based on lifetime residential, daycare, and school addresses (follow up 1, 2, 4, 8 and age 12 years)	Parental reports of wheeze and asthma. Asthma defined as several episodes of wheeze depending on age and use of inhaled corticosteroids, without infection.	Increased asthma risk in children age 8-12 years (OR 2.0 95% CI 1.1, 3.5), for non-allergic asthma, (OR 3.8 95% CI 0.9, 16.2) for a 5th to 95th percentile increase in time-weighted average exposure to PM_{10} (corresponding to 7.2 $\mu g/m^3$). Results were similar for NO_x
Fuertes et al. (39), 2013, Germany	Birth cohorts (GINIplus and LISAplus)	N = 6604 children aged 0-10 years	O_3, NO_2, $PM_{2.5}$ LUR modelling using residential addresses at birth, age 6 and 10 years	Parental reporting of physician-diagnosed asthma, allergic rhinitis and aeroallergen sensitization	No associations for the overall population. Heterogeneous results for area-specific analyses. No associations for GINI/LISA North. LISA east: associations with O_3 was elevated for all outcomes. GINI/LISA south: protective effect of $PM_{2.5}$ exposure on allergic rhinitis (OR 0.83 95% CI 0.72, 0.96), and also for aeroallergen sensitization.

Hwang et al. (31), 2005, Taiwan	Cross-sectional study	N = 32 672 school children aged 6-15 years	SO_2, NOx, O_3, CO, PM_{10} Calculated as annual mean of the year 2000 monthly averages from 22 monitoring stations. Residential history not available	Parental reports of physician diagnosed asthma using ISAAC questionnaire	Asthma was associated with O_3 (OR 1.14 95% CI 1.00, 1.29), CO (OR 1.05 95% CI 1.02, 1.07), and NOx (OR 1.01, 95% CI 0.95, 1.12). Asthma was weakly or not related to SO_2 (OR 0.87, 95% CI 0.73, 1.05) and PM_{10} (OR 0.93, 95% CI 0.91, 0.96).
Rice et al. (34), 2016, U.S.	Prospective prebirth cohort	N = 614 mother-child pairs	$PM_{2.5}$, BC First year of life, lifetime (median age 7.7), prior-year exposure Based on address at birth and at study visit	Childhood lung function, FEV_1, FVC, ratio and bronchodilator response	Residential proximity to roadway, prior-year and lifetime $PM_{2.5}$ and BC exposure were all associated with lower FVC. The same pattern was seen for FEV_1. No associations were found for FEV_1/FVC ratio and bronchodilator response.
Rosenlund et al. (32), 2009, Italy	Cohort study	N = 2107 children aged 9-14 years	NO_2 levels at residential address using LUR models, unknown exposure time	Parental reports of asthma, wheeze, rhinitis and eczema using the ISAAC questionnaire and spirometry	Association between NO_2 exposure and decreased expiratory flow; FEV_1 (−62 ml/s (95% CI −102 to −21) and FVC (−85 ml/s (95% CI −135 to −35). Not consistent associations between rhinitis.
Gehring et al. (36), 2013, Germany, Sweden, the Netherlands and the United Kingdom	Birth cohorts (ESCAPE: BAMSE, GINIplus, LISAplus, MAAS, PIAMA)	N = 5921 aged 6-8 years	NO_2, NOx, $PM_{2.5}$, PM_{10} and PMcoarse estimated with LUR models for residential birth address and current address. Including back-extrapolation from measurement time (2008-2010) till birth-years (1994-1999)	Lung function performed at age 6 and 8 years (FEV_1, FVC and PEF)	Estimated exposure to NO_2, NOx, $PM_{2.5}$ absorbance and $PM_{2.5}$ at current address were associated with some decrease in lung function in all the birth cohorts. Not confounded by short-term exposures to the same pollutants.
Gehring et al. (38), 2015, Germany, Sweden and the Netherlands	Birth cohorts (BAMSE, GINIplus, LISAplus and PIAMA)	N = 14 126 children aged 0-16 years	NO_2, $PM_{2.5}$, PM_{10}, annual averages at residential addresses at birth and follow-ups, calculated with LUR models	Questionnaire reports of rhinoconjunctivitis and physician-diagnosed asthma (follow-ups at age 1, 2, 4, 6-8, 14-16 years). IgE-levels, blood samples	The risk of incident asthma up to age 14–16 years increased with increasing exposure to NO_2 (OR 1.13 per 10 μg/m^3 95% CI 1.02, 1.25) and $PM_{2.5}$ absorbance (1.29 per 1 unit [1.00, 1.66]) at the birth address. No association between air pollution and rhinoconjunctivitis.

Fuertes et al (35), 2015, Germany	Birth cohorts (GINIplus and LISAplus)	N = 2266 children aged 0-15 years	NO_2, $PM_{2.5}$ mass, PM_{10} mass, $PM_{2.5}$ absorbance and ozone, calculated for residential address at birth, age 10 years and age 15 years using LUR models	Spirometry before and after bronchodilation at 15 years of age	No associations between air pollution exposure and reduced lung function at 15 years. Associations among asthmatics with current long-term air pollution exposures, especially NO_2, and lung function.
Oftedal et al. (28), 2008, Norway	Birth cohort	N = 2307 children aged 9-10 years	NO_2, $PM_{2.5}$ and PM_{10}, dispersion models, based on current residential address several time-scales exposures were calculated: first, second year life, total lifetime exposure, several short-term exposures (10 year exposure)	Spirometry (PEF, FVC, FEV_1)	Reduced PEF and reduced forced expiratory flow at 25% and 50% of FVC, especially in girls. One interquartile increase of lifetime exposure to NO_2, PM_{10}, and $PM_{2.5}$ was associated with change in adjusted peak respiratory flow of, respectively, −79 mL/s (95% confidence interval = −128 to −31), −66 mL/s (−110 to −23), and −58 mL/s (−94 to −21). Short-term effects of NO_2 were found, but not for PM.
Oftedal et al. (29), 2009, Norway	Birth cohort	N = 2871 children aged 9-10 years	NO_2, dispersion model, based on complete residential address history from 1992-2002 Distance to major road based on birth address and address by date of questionnaire	Parental report of physician-diagnosed asthma	No association between long-term traffic-related exposure and physician-diagnosed asthma onset.
Young et al. (40) 2014, U.S.	Cohort study	N = 43 352 women	$PM_{2.5}$ and NO_2, annual mean concentrations at residential addresses	Self-reported wheeze, chronic cough and physician-diagnosed asthma	Association between $PM_{2.5}$ and asthma development (OR1.20 95% CI 0.99,1.46, p = 0.063)
Jacquemin et al. (44), 2015, eight European countries	Six cohort studies	N = 23 704 adults	$PM_{2.5}$, PM_{10}, PM_{coarse}, NO_x, NO_2 through LUR models based on residential address at follow-up	Adult asthma incidence	Asthma incidence was positively, but not significantly associated with all exposure metrics except PMcoarse. Borderline statistically significant for a 10-$\mu g/m^3$ increase in NO_2 (OR = 1.10; 95% CI: 0.99, 1.21) and significant with back-extrapolated NO_2 (OR = 1.10; 95% CI: 1.00, 1.20).

Modig et al. (42), 2009, Sweden	Cohort study (RHINE)	N = 3609 adults	NO_2, dispersion model, linked to residential address at time of study inclusion	Adult asthma, self-reported physician-diagnosed asthma	Association between asthma onset (OR per 10 $\mu g/m^{-3}$ 1.46, 95% CI 1.07, 1.99) and incident asthma (OR per 10 $\mu g/m^{-3}$ 1.54, 95% CI 1.00, 2.36) and the levels of nitrogen dioxide (NO_2).
Künzli et al. (45), 2009, Switzerland	Cohort study	N = 2725 adults (aged 18-60 years), never smokers	PM_{10}, dispersion model, linked to residential address	Self-reported physician-diagnosed asthma	Asthma incidence was associated with a change in PM_{10}: The hazard ratio (1.30; 95% CI 1.05, 1.61) per 1 $\mu g/m^3$ change in PM_{10} (IQR).
Cai et al. (43), 2017, three European countries	Cohort studies (HUNT3, Lifelines and UK Biobank)	N = 646 731 aged > 20 years	NO_2, PM_{10} Annual mean estimates was calculated with LUR models using residential addresses	Self-reported adult asthma, physician-diagnosed in Lifelines and UK Biobank	Association between PM_{10} and both ever asthma and current asthma, NO_2 was associated with ever asthma: PM_{10} or NO_2 higher by 10 µg/m−3 was associated with 12.8% (95% CI 9.5, 16.3%) and 1.9% (95% CI 1.1, 2.8%) higher lifetime asthma prevalence.
Schultz et al. (41), 2017, USA	Cohort study	N = 3381 adults aged 21-72 years	$PM_{2.5}$, TRAP (distance to major road) using residential address at time of participation.	Self-reported physician diagnosed asthma and rhinitis, wheeze	$PM_{2.5}$ exposure was associated with asthma (OR3.58 95% CI 2.36-5.43), while current rhinitis was associated with proximity to major roads (300m). No associations for wheeze.
Adam et al. (46), 2015, five cohorts in eight European countries	Five cohort studies (ECRHS, EGEA, NSH, SALIA and SAPALDIA)	N = 7613 adults from the ESCAPE study	NO_2, NO_x, $PM_{2.5}$ and PM_{10}, at residential address at time of spirometry including back-extrapolation with LUR-models	Adult lung function, FEV_1 and FVC	A 10 $\mu g/m^{-3}$ increase in NO_2 exposure was associated with lower levels of FEV_1 (−14.0 mL, 95% CI −25.8, −2.1) and FVC (−14.9 mL, 95% CI −28.7, −1.1). An increase of 10 $\mu g/m^{-3}$ in PM_{10} was associated with a lower level of FEV_1 (−44.6 mL, 95% CI −85.4, −3.8) and FVC (−59.0 mL, 95% CI −112.3, −5.6).

Abbreviations: BC, black carbon; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; LLN, lower limit of normal; LUR, land use regression; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm; TRAP, traffic related air pollution.

1.5 Greenness

Greenness is defined as all forms of vegetation, and during the latest years, there has been an increasing interest in the potential beneficial health effects of living in close proximity to green areas. However, the idea that green environments are beneficial for human health evolved already in the 1800s, when several organisations in London had a special interest in providing accessible open spaces and parks, which they referred to as the "lungs" in the city (49, 50). Also today, this view is supported by the WHO, saying that urban green spaces, such as parks and residential greenery can promote human health (51).

The most common measure of vegetation is the Normalized Difference Vegetation Index (NDVI) that determines the density of green on a patch of land, based on satellite images (52, 53). The first reported studies using NDVI was in 1973 by Rouse et al. from the Remote Sensing Centre of Texas A&M University (52).

Table 2 shows an overview of selected studies regarding the associations between greenness with asthma and rhinitis. The literature overview is based on a systematic search for relevant original publications up to the starting point of my PhD-project (July 2017). The following search terms were used in PubMed: ((greenness[Title/Abstract]) AND ((asthma[Title/Abstract]) OR (lung function[Title/Abstract]) OR (rhinitis[Title/Abstract]))) AND (("1950/01/01"[Date - Publication] : "2017/07/01"[Date - Publication])) AND (english[Filter])). Relevant papers not identified by the search terms, but identified from the reference lists of review papers were also included in the overview. Only studies using NDVI as a metric to define greenness were included. All studies identified were regarding childhood and adolescent asthma and/or rhinitis outcomes. The studies presented include six cohorts and one cross-sectional study (Table 2). Two studies focused on rhinitis, two on both asthma and rhinitis, and three only on asthma. Four of the studies were conducted in Europe, two in Canada and one study was a multinational study (Europe, Canada, and United States). Regarding the exposure calculations, all of the studies used cross-

sectional measures; at time of outcome measure, at birth or during pregnancy. Several different methods were used to classify asthma, the most common was parental report of physician diagnosis. Two of the studies (54, 55) used the validated ISAAC questionnaire, and in addition they required the use of asthma medication during the last 12 months to categorise participants as asthmatics. Two studies by Sbihi et al. (56, 57) defined asthma by linking administrative records with children who had more than two physician visits during the last 12 months and/or one or more hospital admissions due to asthma. In one of the papers, asthma was defined by four trajectories (no asthma, transient asthma, late-onset chronic asthma and early-onset chronic asthma) (57). Regarding allergic rhinitis, most of the studies used parental reports of physician diagnosis or parental reports of rhinitis symptoms.

The reported effects vary in the papers presented (Table 2). Four cohort studies investigated the outcome asthma (54, 56, 58). One of them found a decreased risk of asthma with increasing greenness exposure among pre-school children (0-5 years of age), while no effect was found for school aged children (6-10 years) (56). The same study population was investigated in another study regarding asthma trajectories (57), which revealed an increased risk of late onset chronic asthma (> 3 years) relative to non-asthma trajectory. The protective effect of greenness was strengthened after accounting for co-exposure to air pollutants (NO, NO_2, $PM_{2.5}$ and BC) and proximity to roads for the pre-school period. Another study conducted in several different areas in Spain investigated the effects of asthma and allergic rhinitis in children up to four years of age, did not reveal any associations in the overall study population (58). In region-specific analyses however, increased greenness was associated with an increased risk of asthma in the Euro-Siberian region, characterised by an Atlantic climate. The third cohort study was conducted in 4-6 year old children in Lithuania and showed that surrounding greenness in a 100m buffer size around the residential address, increased the risk of asthma (54). The fourth and last study regarding asthma, a cross-sectional study investigating children aged 9-12 years, did not find any associations with NDVI in neither of the included buffer zones (100m, 250m, 500m and 1000m) around the current home addresses (55).

Regarding rhinitis, four cohorts are presented in Table 2 (55, 58-60). Two of the studies did not reveal any associations of greenness with allergic rhinitis (55, 58). The two other studies, both by Fuertes et al. (59, 60), found heterogeneous results, depending on the study area. One study was performed in Germany, investigating the effects of mean NDVI in 500m residential buffer zones on allergic rhinitis in 3-10 year old children. Positive associations were observed for the urban area (GINA/LISA South area OR 1.16 95% CI 0.99, 1.36), while they were negative in the rural area (GINA/LISA Northern area OR 0.75 95% CI 0.60, 0.93), indicating a protective effect of greenness.

To summarize the presented literature in Table 2, the evidence regarding the effects of greenness on asthma and allergies is limited and inconclusive. Some studies have investigated greenness and the effects on children and adolescents, but no studies have so far investigated long-term greenness exposure up to 30 years. In addition, there are no studies on inter-generational effects after parental preconception exposure to greenness.

Table 2. Overview of selected studies of associations between exposure to greenness with asthma and rhinitis.

First author, year, country	Design	Study population	Exposure measure, exposure time	Outcomes assessed, outcome measure	Main findings
Fuertes et al. **(60)**, 2016, Sweden, Australia, The Netherlands, Canada, Germany	Birth cohorts (BAMSE, PIAMA, SAGE, LISAplus, GINIplus) and high-risk birth cohorts (MACS, CAPPS)	N = 13 016 children	NDVI (500m and 1000m buffer around home address), at outcome age (varied from age 6-8 and 10-12 years	Allergic rhinitis (physician-diagnosis/symptoms), age range: 6-8 years in six cohorts and 10-12 years in five cohorts	Positive association with allergic rhinitis (6-8 years) in BAMSE (OR 1.42 95% CI 1.13, 1.79) and GINI/LISA South (OR 1.69 95% CI 1.19, 2.41), but inversely associated in GINI/LISA North (OR 0.61 95% CI 0.36, 1.01) and PIAMA (OR 0.67 95% CI 0.47, 0.95).
Fuertes et al. **(59)**, 2014, Germany	Birth cohorts (GINIplus and LISAplus)	N = 5803 children	Mean NDVI 500m, 800m, 1000m and 3000m buffer around residential addresses, at birth, age 6 and 10 years	Childhood physician-diagnosed allergic rhinitis including eye and nose symptoms and aeroallergen sensitisation, yearly from 3-10 years	Associations of rhinitis: increase in South (urban) OR 1.16 (95% CI 0.99, 1.36), decrease in North (rural) OR 0.75 (95% CI 0.60, 0.93).
Dadvand et al. **(55)**, 2014, Spain	Cohort study	N = 3178, 9-12 year old children in Spain in 2006	NDVI (100m, 250m, 500m and 1000m around current residential address), at outcome measure	Current asthma (ISAAC questionnaire), allergic rhinitis, 9-12 years	No associations with current asthma or allergic rhinitis for none of the NDVI buffer zones.
Sbihi et al. **(56)**, 2015, Canada	Cohort study	N = 51 857 children born between 1999-2002 in Vancouver	NDVI (100m around residential postal code), exposure during the perinatal period	Asthma incident during preschool (0-5 years) and school years (5-10 years)	Decreased risk of asthma for 0-5 years of age, per interquartile NDVI decrease (OR 0.96 95% CI 0.93, 0.99). No associations for 5-10 years of age.
Tisher et al. **(58)**, 2017, Spain	Birth cohorts (INMA)	N = 2472 children	NDVI (300m buffer around residential birth address and at age 4 years), green space, Urban Atlas map	Asthma, allergic rhinitis up to 4 years from parent completed questionnaires	No associations with asthma or allergic rhinitis overall. Associations of asthma differed in direction in region-specific analyses. In the Euro-Siberian region, higher residential surrounding greenness was associated with increased risk of asthma.

Andrusaityte et al. **(54)**, 2016, Lithuania	Cohort study	N = 1489 children	NDVI (100, 300 and 500m areas of exact residential address), at outcome measure	Clinically diagnosed asthma (ISAAC questionnaire completed by parents) 4-6 years	An increased risk of asthma within 100m NDVI buffer (OR 1.43 95% CI 1.10, 1.85)
Sbihi et al. **(57)**, 2017, Canada	Birth cohort	N = 65 254 children	NDVI, (100m around residential areas), exposure during the perinatal period	Asthma trajectory (no asthma, transient, late-onset chronic asthma (< 3 years) , early onset chronic asthma (< 1 years)), 0-10 years	Risk of late onset chronic asthma relative to non-asthma for the second highest greenness quartile (RR 1.29 95% CI 1.12, 1.49)

Abbreviations: ISAAC, International Study of Asthma and Allergies in Childhood; NDVI, Normalized Difference Vegetation Index; OR, odds ratio.

1.6 Epidemiology

The general definition of epidemiology is: “The study of distribution and determinants of disease frequency” (61). Epidemiological research is an important contributor for improving public health. Already more than 2000 years ago, Hippocrates introduced several epidemiological ideas that are considered the fundamentals of modern epidemiology today (62). The main idea was that disease causality can be explained by environmental factors. Since then, modern epidemiology has evolved enormously, in particular during the nineteenth and twentieth century, to consist of systematized principles and methods to discover causation between exposure and outcome (63). An important domain of epidemiology is the environmental epidemiology, which investigates the associations between external environmental factors and human diseases in population-based studies. One of the earliest studies in this field was published already in 1767, where Baker provided proof that lead poisoning was the cause of the Devonshire colic (63). He started with observations, as is often done in epidemiological research, of regional differences in disease rates, continued with examinations of symptoms and discovery of a suspected cause, and at last confirmed the association (63). Typical for environmental exposures is that it is largely involuntary. While some exposures like active tobacco smoke is a lifestyle choice, exposure to polluted air can be impossible to avoid and can affect entire populations. Consequently, it poses a major public health threat.

1.7 Epigenetics and windows of susceptibility

Previous epidemiological studies have suggested that environmental exposures in utero and in early life play a role in development of disease later in life (5, 6), and that these effects can even be passed on to the next generation through epigenetic mechanisms. Environmental impact, beyond factors causing genetic alterations, appears to be transferred across generations through epigenetic phenomena, altering gene expression rather than the nucleotides in the DNA double helix itself. Epigenetic features include DNA methylation, histone modification, and non-coding RNA (64, 65). These

modified gene expressions often affect the health status within the individual. Although asthma and allergic diseases are among the most common non-communicable childhood diseases (7), the pathogenesis is still not understood, but both genetic susceptibility and environmental exposures are known to be involved. Consequently, the interest in the role of epigenetic mechanisms in the disease development has been increasing, since it links gene regulation to environmental exposures and developmental trajectories (65).

Which exact windows of susceptibility in early life that influence the development of asthma and allergies are not known. Epigenetic mechanisms are also potentially transferred across generations. Increasing evidence suggests that the preconception environment may influence health in the next generation (Figure 3) (64, 66). Previous

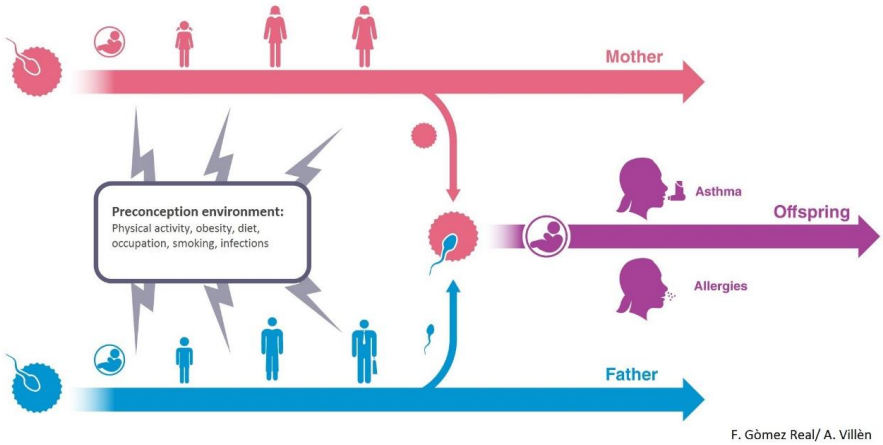

*Figure 3. Maternal, paternal and offspring lifeline and possible environmental influence on asthma and allergies in the offspring. (The figure is designed by F. Gómez Real and A. Villén used in Lønnebotn, M., et al. (2018). "Environmental Impact on Health across Generations: Policy Meets Biology. A Review of Animal and Human Models." **9**(2): 42, under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/.*

studies have discovered associations between parental and grandparental smoking prior to conception and increased risk of asthma in their offspring, and also overweight onset in adolescent boys was associated with offspring asthma (66-69). However, results are inconclusive – e.g. parental occupational exposure was not clearly associated with offspring asthma (16). With regard to intergenerational effects of exposure to air

pollution and greenness on asthma and allergic diseases, there is a knowledge gap with no human studies, to our knowledge. The role of preconception exposures for asthma and allergies is far from clear (66, 67, 70, 71), and there is a large need for generation studies in this field, to investigate parental risk factors and offspring outcomes.

1.8 Generation studies

The increasing interest in epigenetics and intergenerational risk factors, requires detailed information on more than one generation. In humans, in whom generations span decades, this represents a major challenge. Cross-generational research studies can contribute to identify risk factors and particular susceptibility windows that may predispose for disease. Multi-generational data may be of particular importance in identifying susceptible windows with impact not only on the exposed generation but also on their future children. Such research is highly relevant to give a knowledge basis to efficiently improve public health potentially across generations. However, due to lack of optimal multi-generation data, it is sometimes necessary to use reports across generations. For this purpose, it is of great importance to know if data reported on behalf of family members are reliable. So far, validity of intergenerational reports, especially with regard to asthma, is poorly investigated.

Literature review completed August 2020.

2. Aims of thesis

2.1 Main objective

The overall aim of this thesis was to investigate how air pollution and greenness affects lung health over time and across generations. We hypothesised that there is an association of air pollution exposure and poorer lung health due to an inflammatory response in the airways, and that this response takes on a chronic expression over time and also across generations, possibly through epigenetic mechanisms. On the other hand, we hypothesized that there is an association of greenness exposure and improved lung health. Data from the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) generation study provided data to study this, and to ensure high data quality in papers II and III, an additional aim was to investigate the agreement of asthma reports by offspring and parents in the RHINESSA generation study.

2.2 Specific objectives

Paper I. To investigate agreement between parental and offspring reports of asthma regarding themselves and each other (offspring versus parents and parents versus offspring), compared to their own report. In addition, we wanted to identify predictors for discrepant answers.

Paper II. To examine lifelong exposure to air pollution and greenness in association with respiratory health (asthma, rhinitis and lung function) in adulthood, and especially investigate whether susceptibility windows during childhood and adolescence are predisposing for respiratory diseases later in life.

Paper III. To explore associations between parental childhood exposures of greenness and air pollution in relation to their future offspring's asthma and allergies, in areas with relatively low levels of air pollution – and also to assess if observed associations were direct or mediated by other factors.

3. Material and Methods

Table 3. Overview of material and methods used in the three papers in the thesis.

	Paper I	Paper II	Paper III
Aims	To investigate the agreement of asthma reports between parents and offspring.	To investigate the association of lifelong exposure to air pollution and greenness and adult asthma, rhinitis and lung function.	To investigate the association between parental childhood exposure to air pollution and greenness and asthma and rhinitis in their offspring.
Design	Multigeneration cohort study	Cohort study National registry data used to retrospectively determine exposure	Two-generation data from cohort study
Data source	RHINE/ECRHS and RHINESSA	RHINESSA Exposure data sources: Air pollution: AirBase, ESCAPE Greenness (NDVI): satellite images from USGS	
Study population	5907 parents from RHINE/ECRHS and 6752 offspring from RHINESSA	Participants from the Norwegian and Swedish RHINESSA centres born after 1975:	
		3428 participants (555 with clinical data)	1106 parents and their 1949 offspring
Exposures	Main exposures: asthma reports Secondary exposures: Smoking status, education level, respiratory symptoms, comorbidities Study centre, sibling status	Air pollutants (NO_2, $PM_{2.5}$, PM_{10}, BC, O_3) and NDVI	
		Exposure in susceptibility windows: 0-10 years, 10-18 years, lifetime (from birth until study participation) and one year before study participation	Exposure in susceptibility windows: Parental 0-18 years Offspring 0-10 years
Outcomes	Agreement of reports across generations regarding physician diagnosed asthma and ever asthma	Physician diagnosed asthma, allergic asthma, non-allergic asthma, rhinitis, asthma attack, lung function (<LLN FEV_1, FVC and FEV1/FVC)	Offspring early onset asthma and offspring rhinitis (as reported by parent)
Covariates	Same as the variables listed under "Secondary exposures"	Parental education level and parental asthma	Grandparental education level, grandparental asthma Potential mediators: parental asthma, offspring's own pollution/greenness exposures, pollution/greenness exposure during pregnancy
Statistics	Logistic regression analyses Cohen's kappa Sensitivity Specificity Positive and negative predictive values	Logistic regression (asthma attack, rhinitis, <LLN lung function) (clustered by family and study centre) Conditional logistic regression (general asthma, allergic and non-allergic asthma) in a matched case-control dataset.	Multilevel logistic regression analyses (clustered by family and study centre, stratified by parental sex) Mediation analyses

Abbreviations: AirBase, The European air quality database; BC, black carbon; ECRHS, European Community Respiratory Health Survey; ESCAPE, European Study of Cohorts for Air Pollution Effects; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LLN, lower limit of normal; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μm; RHINE, Respiratory Health in Northern Europe; RHINESSA, Respiratory Health in Northern Europe, Spain and Australia; USGS, United States Geological Survey.

3.1 Data sources

This thesis is mainly based on survey data from the RHINESSA generation study, and enriched with data from the Respiratory Health in Northern Europe (RHINE) study and the European Community Respiratory Health Survey (ECRHS), all explained in more detail in paragraph 3.2 and Figure 4. Residential moving history was retrieved from the Norwegian and Swedish population registries for all participants, to use in the exposure assignments. Air pollution data were assigned through an already existing project: European Studies of Cohorts for Air Pollution Effects (ESCAPE), while greenness was assessed using NDVI (paragraph 3.3).

3.2 Study-populations and design

RHINESSA is a cohort dedicated to study asthma, allergy and lung health across generations and throughout the lifespan (Figure 4). The aim is to understand and identify the part that particular susceptibility windows in early life plays for developing disease later in life. The RHINESSA study consists of offspring (mostly adult, but for some centres (Bergen, Tartu and Melbourne) also adolescents and children) of parents from two large cohort studies of respiratory health in adults: the ECRHS study (72) and the RHINE study (73). ECRHS is a population based longitudinal study that started in 1990 using both questionnaires and clinical examination in 29 centres in 14 countries (mostly European). ECRHS had clinical follow up 10 and 20 years after baseline, with a third follow-up planned in 2020/21. The RHINE study was a follow up of the first ECRHS questionnaire-stage using extensive postal questionnaires in two stages (2000 and 2010) with a third follow-up planned for 2020/21. RHINE consists of seven Northern European centres (Reykjavik (Iceland), Bergen (Norway), Umea, Uppsala and Gothenburg (Sweden), Aarhus (Denmark) and Tartu (Estonia)). These centres and three centres from the ECRHS (Huelva and Albacete (Spain) and Melbourne (Australia)) form the 10 included centres in the RHINESSA generation study. All eligible offspring from participants in the seven RHINE centres and the Spanish/Australian ECRHS centres were invited to participate in the questionnaire part of RHINESSA, while offspring of participants from the ten centres who had taken part

in the clinical part of ECRHS were in addition invited to the clinical part of RHINESSA.

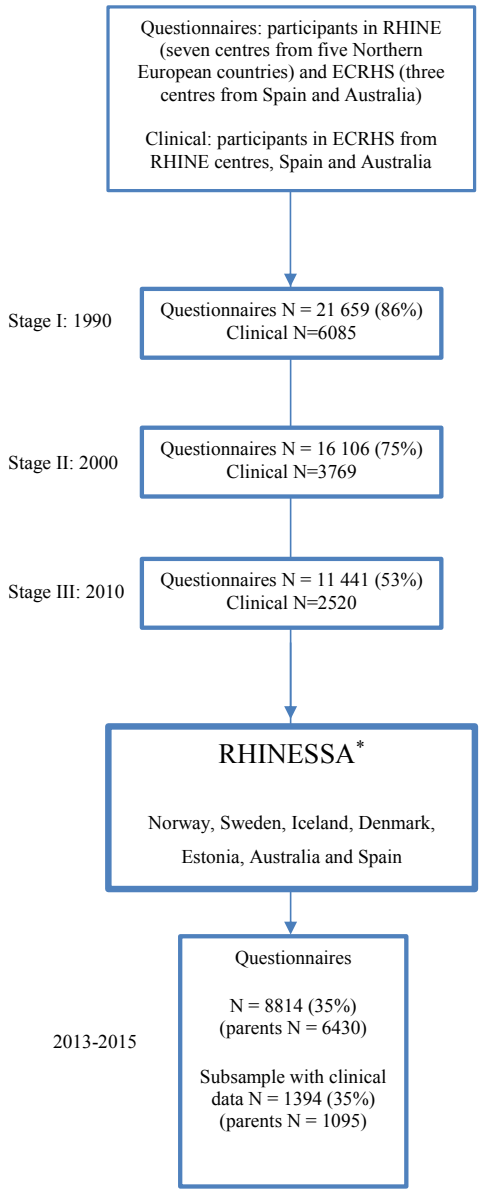

*Figure 4. Flowchart of the RHINESSA study population. *The RHINESSA study population are offspring from participants from the Northern European RHINE centres (Norway, Sweden, Iceland, Denmark and Estonia) and the ECRHS centres in Australia and Spain.*

The RHINESSA participants received questionnaires between 2013 and 2015, where they provided information regarding themselves, in addition to their parents and their offspring. The overall response rate for RHINESSA was 34.7%, see Table 4 for response rates per centre. A sub-sample was invited for clinical examination. The collection of information is still ongoing for the next generation.

Table 4. Response rates RHINESSA study per country.

Country (centre)	Response rate %
Denmark (Aarhus)	21.8
Iceland (Reykjavik)	60.0
Norway (Bergen)	39.4
Sweden (Gothenburg, Umea, Uppsala)	36.9
Estonia (Tartu)	29.1
Spain (Huelva, Albacete)*	21.2
Australia (Melbourne)*	25.4

* The study population (offspring) were identified through parental contact. Offspring from the other centres were identified through register data.

Data from RHINE/ECRHS and RHINESSA were used for paper I. For paper II only data from RHINESSA were used, including both questionnaire and spirometry data, while for paper III only RHINESSA questionnaire data were used. The number included (N) in paper I is lower than the total RHINESSA study population (Figure 5), as the data collection was still ongoing when the paper was published. For paper III, N is lower than in paper II due to the additional inclusion criteria “having children”.

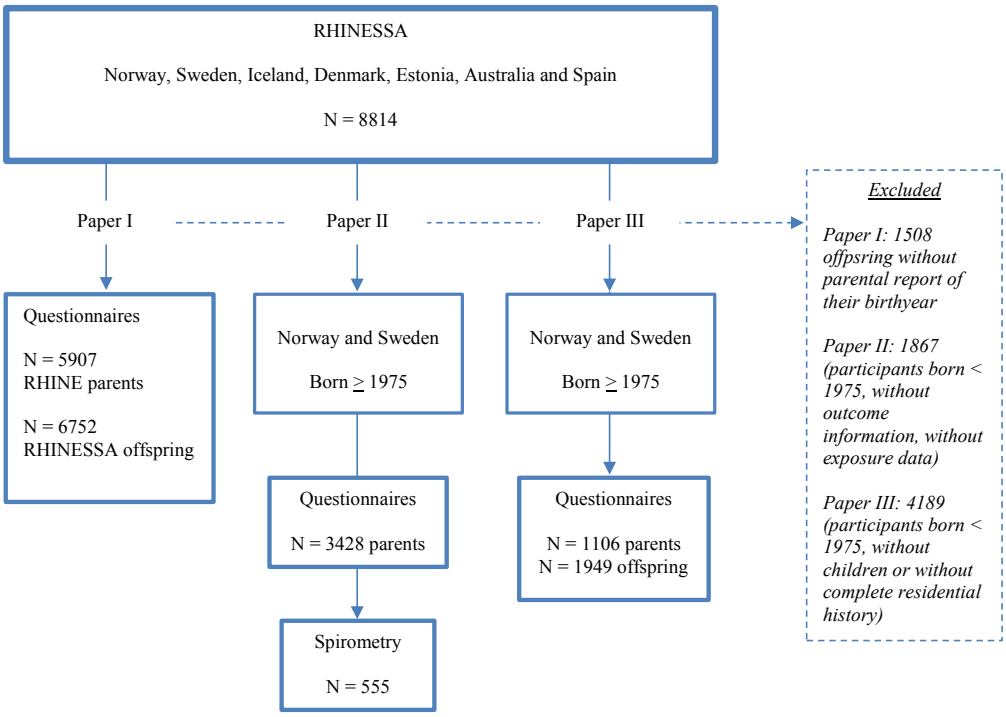

Figure 5. Flowchart of the study populations included in the three papers in the thesis.

3.3 Questionnaires

Analyses in this thesis were based on the questionnaires from the RHINE study for the seven Northern European centres / the ECRHS study for the Australian and Spanish centres (Paper I) and the RHINESSA study (Papers I, II and III) (Appendix A and B). For all the RHINE centres, postal questionnaires were used. For the Spanish and Australian ECRHS centres, interview-based questionnaires were used. For RHINESSA, the questionnaires were web-based in Norway, while Sweden used postal questionnaires. The questionnaires included questions on respiratory symptoms and allergies, smoking habits, education and occupation, indoor environment, sleeping habits, body shape, general health and comorbidities. The participants also answered several questions concerning their grandparents, parents and children, e.g. where

grandparents were raised, parental health and smoking habits, offspring asthma and allergies.

3.4 Spirometry

A sub-sample of the RHINESSA participants performed spirometry in the period between 2013 and 2015. The procedure was performed according to standardized protocols and performed by trained staff. The EasyOne Spirometer was used for the spirometry, lung function was measured by spirometry according to established guidelines (74). The equipment was calibrated every day before use. The participants performed up to eight manoeuvres until adequate flow volume loops were produced, while they were in a seated position wearing a nose clip. The reference values from Global Lung Function Initiative (GLI 2012) were used to calculate percentages of predicted values, normalized for height, age, sex and ethnicity (74). The lower limit of normal (LLN) FEV_1, FVC and FEV_1/FVC (75) were also calculated, defined as a z-score <1.64 standard deviations (SD) (75), thus equal to the fifth percentile of a healthy non-smoking population. The LLN is recommended by the GLI as a cut-off for impaired lung function. Using the GLI software for calculating reference values and LLN cut-off enables us to interpret the results without bias caused by age, height, sex, and ethnicity (75).

3.5 Exposure variables

Air pollution and greenness were the primary exposures in paper II and III.

3.5.1 Air pollution assignment

We assigned annual mean concentrations for five different pollutants (NO_2, $PM_{2.5}$, PM_{10}, BC, and O_3) to each participant's individual geocoded residential history (from 1975-2015). The calculations were based on previous developed air pollution rasters and Western Europe-wide hybrid land use regression models (LURs) (Table 5) (76-78). LURs combine predictor variables from geographic information systems (GIS) (i.e. roads, land use, altitude and meteorology) and routine monitoring of air pollution

with satellite derived and chemical transport model estimates (78, 79). The routine air pollution monitoring data derives from AirBase; the European air quality database which is maintained by the European Environment Agency (EEA) (80). It consists of multi-annual time series of air quality measurement data and statistics for several air pollutants. Annual mean PM_{10} exposures were extracted for 2005 to 2007 from surfaces (100x100m) based on these Western Europe-wide hybrid LURs (76), while annual mean NO_2, $PM_{2.5}$, O_3 and BC exposures were extracted for 2010 (77, 78). An overview of the models used for the different pollutants can be found in Table 3. For each year from 1990 to 2015 we back-and-forth-extrapolated the air pollution concentrations from the LUR-models using the ratio method. This was done with the procedure from the ESCAPE study (81) which is based on the Danish Eulerian Hemispheric Model (DEHM) (82). ESCAPE is a study designed to investigate the long-term effects on human health of exposures to air pollution in Europe. An additional aim is to develop a flexible methodology for assessment of long-term population exposures to air pollution (83). The ratio method used in the extrapolation process is explained in detail in Appendix C.

Table 5. Overview of the models used to calculate air pollution exposures.

Air pollution measure	Model-year and source	
	2007	**2010**
Nitrogen dioxide (NO_2)	-	de Hoogh et al 2016 (78)
Particulate matter with an aerodynamic diameter lower than 2.5 µm ($PM_{2.5}$)	-	de Hoogh et al 2016 (78)
Particulate matter with an aerodynamic diameter lower than 2.5 µm (PM_{10})	Vienneau et al 2013 (76)	-
Black Carbon (BC)	-	de Hoogh et al 2018 (77)
Ozone (O_3)	-	de Hoogh et al 2018 (77)

3.5.2 Greenness assignment

The common indicator for green vegetation, NDVI, was used to assess greenness (84). NDVI refers to all vegetation including both structured green spaces in parks and unstructured vegetation such as forests. Estimates were derived from the cloud-free

Landsat 4-5 Thematic Mapper (TM) and 8 Operational Land Imager (OLI) satellite images (53) (Table 6). Calculations of NDVI are based on the knowledge that plants strongly absorb visible red light (RED) for use in photosynthesis while strongly reflecting near-infrared light (NIR) for cooling. The equation for NDVI is based on spectral reflectance measurements acquired in corresponding light wavelengths: NDVI = (NIR – RED) / (NIR + RED). NIR and RED wavelengths are ratios of the reflected over absorbed light. Their values range from 0 to +1, therefore NDVI values range from -1 to +1, with +1 indicating highly vegetated areas and -1 indicating water (52). For the four study areas included, satellite images were retrieved for approximately every five years from 1984 until 2014 during the most vegetation rich months (May, June, July), and NDVI maps were calculated with residential greenness defined as mean NDVI in a circular 100-m, 300-m, 500-m and 1000-m buffer around each participant's residential address. The WHO recommends the 300-m buffer for main analyses as it corresponds to approximately five minutes walking distance (51). Additional distances are however recommended to provide more in-depth analyses, therefore sensitivity analyses were performed for the other buffer zones.

Table 6. Landsat images used for NDVI calculations.

	Bergen, 201/18	Gothenburg, 195/20	Gothenburg, 196/19	Umea, 193/15	Umea, 193/16	Uppsala, 193/18	Uppsala, 193/19
2014	18/06/201, 8OLI	27/08/2014, 8OLI	21/08/2015, 8OLI	12/07/2014, 8OLI	25/07/2013, 8OLI	10/06/2014, 8OLI	10/06/2014, 8OLI
2009	03/07/2008, 5TM	26/06/2009, 5TM	01/06/2009, 5TM	28/06/2009, 5TM	28/06/2009, 5TM	28/06/2009, 5TM	28/06/2009, 5TM
2004	06/07/2003, 5TM	07/06/2002, 5TM	14/06/2002, 5TM	17/06/2005, 5TM	03/07/2005, 5TM	14/07/2003, 5TM	14/07/2003, 5TM
1999	03/06/1997, 5TM	17/06/2000, 5TM	08/06/2000, 5TM	20/07/1997, 5TM (194/15)	13/07/1997, 5TM	17/06/1999, 5TM	17/06/1999, 5TM
1994	29/07/1994, 5TM	30/06/1993, 5TM	24/06/1994, 5TM	05/07/1994, 5TM	05/07/1994, 5TM	05/07/1994, 5TM	05/07/1994, 5TM
1989	13/06/1989, 5TM	05/07/1989, 5TM	29/08/1989, 5TM	21/06/1989, 5TM	21/06/1989, 5TM	07/07/1989, 5TM	07/07/1989, 5TM
1984	18/06/1985, 5TM	27/06/1986, 5TM	02/06/1986, 5TM	26/06/1985, 5TM	26/06/1985, 5TM	09/07/1984, 5TM	09/07/1984, 5TM

Abbreviations: NDVI, normalized difference vegetation index; OLI, operational land imager; TM, thematic mapper.

3.6 Outcomes and covariates

Outcomes

The outcome variable is the disease or health-related event of interest in a study. It is also often termed the dependent variable and defined as the variable measured in statistical modelling by changing the exposure or independent variable (63). The main

outcome in paper I was self-reported asthma. Reports regarding the participants' own asthma was based on the question "Have you ever had asthma diagnosed by a doctor?", labelled "physician diagnosed asthma. Reports regarding asthma in parents and offspring were labelled "ever asthma". Reports regarding parental asthma were based on the question "Did your biological parents ever suffer from asthma?" with separate reports provided for mothers and fathers, and reports regarding asthma in offspring were based on the question "Please write the years when your children were born, and tick "yes" if they have had any of the following" with separate reports provided for "asthma before 10 years" and "asthma after 10 years".

The outcomes in paper II were physician diagnosed asthma, allergic asthma, non-allergic asthma, rhinitis, asthma attack and LLN for FEV_1, FVC and FEV_1/FVC. Physician diagnosed asthma was defined as a positive answer to the question "Have you ever had asthma diagnosed by a doctor?". Allergic and non-allergic asthma was based on this question and in addition the question regarding rhinitis: "Do you have any nasal allergies including rhinitis?". The definition of asthma attack was based on the question: "Have you had an attack of asthma in the last 12 months?". The lung function outcomes are described in detail in paragraph 3.4.

In paper III, the outcomes were early onset asthma and rhinitis in the offspring reported by the parents. In this paper the term "hay fever" is used instead of rhinitis, the definition however is the same for both papers. The outcomes were defined as affirmative answers to the questions "For each of your biological children, please tick yes if they have had asthma before 10 years", and "For each of your biological children please tick yes if they have had hay fever/rhinitis", respectively.

Susceptibility windows

We investigated several susceptibility windows when looking at risk for disease later in life and in the next generation. The annual mean exposures were averaged across the following time windows in paper II; 0-10 years, 10-18 years, lifetime (from birth until study participation) and year before study participation. In paper III we investigated

one parental window and one offspring window: parental 0-18 years and offspring 0-10 years.

Covariates

The multivariate analyses in this thesis were adjusted for several covariates to increase the accuracy of the results (63). Covariates are characteristics of the study population and can be either independent variables or confounders. A confounder is defined as having an association with both the exposure and the outcome, and not being in the causal pathway between the exposure and outcome in time (63, 85). Potential confounders were considered and discussed based on knowledge from previous literature and identified by using Directed Acyclic Graphs (DAGs) (86) (paper II and III). DAGs offers a unified framework for researchers to provide a systematic representation and analysis of causal inference in epidemiology (87). DAGitty has become an established web application (88) for creating and analysing DAGs containing graphical tools and automated algorithms specifying all minimal sufficient adjustment sets (87). A DAG is thus a presentation about the relationships between variables by acyclic graphs, i.e. not containing feedback loops (63).

Paper I aimed to identify predictors for discrepant asthma reports across generations and included a variety of covariates where every one of them was of interest and they were therefore all included as potential exposure variables rather than confounders: smoking status (never-, ex- or current smoker), education level (primary school, secondary school or college/university), respiratory symptoms (wheeze, wheeze with shortness of breath, awoken with tightness in chest, awoken with attack of cough in the past 12 months and currently taking medication) and comorbidities (hypertension, stroke, ischemic heart disease, diabetes mellitus, COPD and serious respiratory infections before the age of 5 years). In paper II, analysing associations of lifelong exposure to air pollution and greenness on adult asthma and allergies, the following covariates were evaluated as confounders: age, sex, gestational age at birth, childhood respiratory infections, occupational exposure to dust or gas, personal smoking and exposure to passive smoking during childhood, physical activity level, body mass index (BMI), birth weight, exposure to greenness/air pollution in childhood, parental

education level and parental asthma. Only parental education level and parental asthma were identified as relevant confounding variables using DAGs, as they were the only covariates associated with both the exposure and the outcome without lying in the causal pathway between them. DAGs were also made to identify confounders for the analyses in paper III, based on the following covariates: offspring greenness/air pollution exposure, offspring passive smoking, offspring birth weight, parental smoking before conception, parental education, parental asthma, grandparental education and grandparental asthma. Grandparental education level and grandparental asthma and rhinitis are all associated with the exposure and outcomes but are not in the causal pathway between them and were consequently included in the analyses as confounders.

3.7 Quality assurance

All questionnaire data collected in the RHINESSA study, except the Swedish data, were recorded directly in the online software CheckWare by the participants themselves. The Swedish centres used postal questionnaires, where the participants registered their answers on paper, which was later recorded into a database by trained staff. Similar procedures with postal questionnaires were used for data collection in the seven Northern European centres in the RHINE study, while in the Spanish and Australian ECRHS centres, questionnaires were interview based and the participants' answers were registered by trained fieldworkers. The database software used in all the data collection included certain integrated validation procedures, e.g. continuous variables had minimum and maximum values and the categorical variables had predefined answers. After registering the data using appropriate software, data were de-identified and encrypted and sent from the study centres to the coordinating centre in Bergen. There, inconsistency analyses were performed to detect possible recording errors, e.g. participants younger than 18 years who recorded having a completed university degree. In addition, manual controls were performed randomly to identify possible typing errors. Inconsistencies were documented and corrected to ensure that all data used in the analyses of this thesis have been thoroughly quality assured. For

RHINE/ECRHS and the Swedish RHINESSA centres, the faulty values in the databases were corrected through comparison with the original paper forms. For the Norwegian RHINESSA centres, the faulty values were inspected with regard to other information that the participants had provided. If possible to deduce the correct value based on this, it was corrected. If not possible to deduce the correct value, the faulty value was set to missing, e.g. completed education was set to missing for a participant aged 18 years who had ticked "completed university education".

3.8 Statistical analyses

All analyses were performed using STATA versions 14.0-16.1 (Stata Statistical Software, Statacorp, College station, TX: StataCorp LLC) and R Studio version 3.5.1 (R Studio, Inc., part of the R statistical software package, Development Core Team, Boston, MA) (89).

A p-value < 0.05 was considered statistically significant and 95% confidence intervals (CIs) were calculated.

Cohen's kappa and validation

In the study of agreement between parents' and offspring's asthma reports, Cohen's kappa was used to investigate overall agreement. Kappa is a measure of the magnitude of interobserver variation and gives a numerical rating of the degree to which the agreement may have occurred by chance (90, 91). The difference in observed and expected agreement is given as Kappa, a value on a scale between -1 and 1, where 1 is perfect agreement and 0 indicates agreement as expected purely by chance. A value less than 0 is rare and indicates agreement less than chance but can occur due to potential systematic disagreement between observers. The following interpretation categories were used in paper I: poor agreement, <0.2; fair, 0.21–0.40; moderate, 0.41–0.60; good, 0.61–0.80; and very good, 0.81–1.00 (91). The validity of a test can be addressed by calculating sensitivity, specificity and positive and negative predictive values (PPV and NPV). This was done in paper I using the participants' own answers regarding themselves as the golden standard, referred to in the following as being

with/without the disease. Reports given about the other generation (reports about parent's asthma and offspring's asthma) are in the following referred to as positive/negative "test". Sensitivity is the proportion of those with the disease who have a positive test and is calculated by dividing the number of persons with a positive test result by the number of persons with the disease [a/(a+c)], Figure 6) (63). Specificity is calculated by dividing the number of persons with negative test by the number of persons who do not have the disease [d/(b+d)], Figure 6). It describes the proportion of those without the disease who have a negative test (63). PPV and NPV were used to find the number of participants with a positive asthma report from their relative that reported asthma themselves, and the number of participants where their relative reported no asthma and they did the same themselves (92). PPV is calculated by dividing the number of true positive persons by the total number of persons with a positive test result [a/(a+b)], while NPV is calculated by dividing the number of true negative persons by the total of persons with a negative test [d/(c+d)], (Figure 6) (63). All the analyses in paper I were stratified by sex to investigate possible differences between mother and fathers and daughters and sons.

	Disease	**No disease**
Positive test	**a**	**b**
Negative test	**c**	**d**

Figure 6. Calculation of sensitivity [a/(a+c)], specificity [d/(b+d)], PPV [a/(a+b)] and NPV [d/(c+d)].

Regression analyses

In all three papers, regression analyses were used to estimate associations between the exposures of interest and the outcomes. In regression analyses, it is assumed that all observations are independent. In multi-centre studies, there may be certain dependencies within centres: for some characteristics participants from e.g. Reykjavik

in Iceland will be more similar to each other than they are to participants from Huelva in Spain. Furthermore, since all offspring of RHINE/ECRHS participants in ten study centres were invited to the RHINESSA study, some participants in RHINESSA are siblings. The siblings will have the same parental information and therefore not be independent of each other. In paper II and III family was therefore nested into the centre variable to a double cluster to account for both centre and sibling dependency. Odds ratios (ORs) with 95% confidence intervals were used to report the results from the logistic regression analyses. OR is a measure representing the odds of the occurrence of an outcome given a specific exposure divided by the odds of the occurrence of an outcome without that exposure, while the 95% CI gives an estimation of the precision of the OR (63, 93). ORs are calculated using two-by-two frequency tables: a = exposed with asthma, b = exposed without asthma, c = non-exposed with asthma, d = non-exposed without asthma, were OR = ad/bc. An OR = 1 reflects that exposure does not affect the outcome. An OR greater than 1 and if the 95% CI does not include 1, implies that the exposure is associated with higher odds of the outcome; in our analyses corresponding to exposed participants having a higher odds of asthma compared to non-exposed and that the exposure is therefore considered a risk factor for the disease. Contrary, an OR lower than 1 indicates that the exposed have a lower odds of the outcome.

In paper I, univariate logistic regression analyses were performed with each covariate as predictor and discrepant answers (yes/no) in parent-offspring pairs as outcome. The significant predictors from the univariate analyses were used in the multivariate logistic regression analyses, which in addition were adjusted for study centre and sibling status. Logistic regression is used to analyse binary dependent variables and were also used in paper II for the outcomes asthma attack, rhinitis and LLN FEV_1, FVC and FEV_1/FVC (defined as a Z-score <1.64 SD). The multivariate logistic regression analyses in paper II were multilevel analyses, i.e. clustered for family and centre as described earlier in this section. For the outcomes general asthma, allergic and non-allergic asthma conditional, however, logistic regression analyses were performed in a matched case-control dataset. Conditional logistic regression is a specialized version of the logistic regression and has become standard for analysing matched case-control data. Matching

in our analyses were performed for participants with physician-diagnosed asthma who had also reported the age of diagnosis. Controls were sampled from the participants without asthma, and matched to the cases by study centre, sex and age at participation. For each case, we selected two controls per case and separate matched datasets were set up for asthma, allergic asthma and non-allergic asthma. By using matched case-control data for these analyses we were able to examine exposure up to the time of diagnosis for the asthmatics compared with exposure up to the corresponding age for the matched controls.

In paper III, we performed multilevel logistic regression analyses of associations between exposure to air pollution and greenness and the outcomes. As described earlier, multilevel logistic regression is used when the data are nested, i.e. the data of individuals are organized in more than one level and are therefore clustered (94). In our analyses, the data were clustered by family and study centre.

Mediation analyses

Mediating variables are in a causal sequence between an independent variable and a dependent variable (95), and the mechanism by which one variable transmits the effect on another through a mediator variable can be identified by mediation analyses. The mediator (M) can explain all or some of the observed relationship between the independent variable (X) and the dependent variable (Y) (Figure 7). Full mediation occurs if the effect of X on Y disappears after including the mediator (the effect of X on Y is only indirect), while if M accounts for only some of the relationship between X and Y it is called partial mediation, and some direct effect of X in Y still remains.

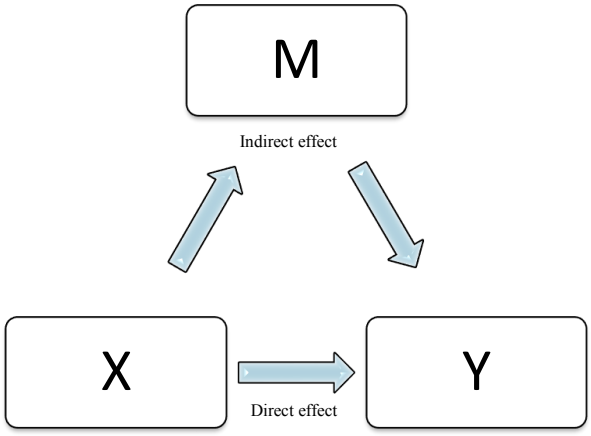

Figure 7. Simple mediation model: M, mediator; X independent variable; Y, dependent variable.

In paper III, we included the following potential mediators based on a priori hypothesis that they lie in the pathway between the exposures (air pollution and greenness) and the outcomes (offspring's asthma and rhinitis): parental asthma, offspring's own pollution and greenness exposures in early childhood, pollution and greenness exposure during pregnancy. Several requirements have to be fulfilled to run the mediation analyses: 1) significant associations from the multivariable analyses; 2) the exposure must be associated with the mediator; 3) the mediator must be associated with the outcome. The mediation tests revealed that the following mediators fulfilled these criteria's: offspring's own exposure and exposure during pregnancy, between maternal PM_{10} exposure and both offspring's outcomes (asthma and rhinitis). In addition, for the paternal line, exposure during pregnancy (O_3), was a potential mediator between paternal O_3 exposure and offspring rhinitis. We used a simple counterfactual mediation method by Buis that decomposes the total effect of a categorical variable into direct and indirect effects, requiring a binary outcome, and that allows any distribution of the mediator (96, 97). The analyses were performed with the "ldecomp" command in Stata that produces three OR estimations for each exposure level: the total effect (direct and indirect paths combined), the direct path and the indirect path (through the mediator). To obtain the 95% CIs we performed bootstrapping with 1000 iterations.

Multiple imputation for missing data

Missing data are relatively common and usually unavoidable in epidemiological research. The problem of missing data is loss of information, with bias and possible erroneous scientific conclusions as a result (98). If assuming the data are missing at random, one approach to deal with this is multiple imputation. This method, replacing missing values by imputed values, is done by creating multiple datasets where the distribution of the observed data is used to estimate multiple values that reflect the uncertainty of the true value (98). In paper II this was done with Stata using the "mi impute mvn" procedure with 200 imputations (99) for the following covariates: parental education, parental asthma, air pollution exposures and greenness; and for the lung function, asthma attack and rhinitis analyses. The proportion of missing data ranged from 2% for parental education to 9% for NDVI during certain years in early childhood. The imputation model included the same variables as those contained in the final analytical models. For the matched-case control datasets, a multilevel approach was used with the mice-package in R where five values were imputed for each missing observation (100).

3.9 Ethical considerations

This thesis involves the use of data collected over more than 20 years. The RHINESSA study, as well as the parental studies RHINE and ECRHS were approved according to national legislations in each study centre by regional committees of medical research ethics (101). All data collection has complied with the principles of the Declaration of Helsinki, and all participants have provided written informed consent prior to participation. Their consents covered the collection of questionnaire data, the collection of clinical data for a sub-sample, and also the retrieval of data from national registries. The risk and inconveniences for participants has been minimal due to focus on questionnaire data and registry data, and only low-risk clinical examinations including lung function testing. Appropriate Data Protection measures have been taken to ensure safe storage of information. The regulation by EU law on data protection and privacy, the General Data Protection Regulation (GDPR) was not applicable for our studies, as

the studies were performed before the law was introduced (May 25th 2018). Data protection has however, been highly prioritized to avoid non-authorized access and misuse. The overall study database was stored on a designated research server at the Haukeland University Hospital, in accordance with hospital regulations for research (102). The server is developed by the IT department at the hospital for secure processing of sensitive personal data for research purposes. The storage system adheres to the "Norwegian Code of conduct for information security in the healthcare and care services sector" (103) and ensures that confidentiality, integrity, and availability are preserved when processing sensitive personal data.

4. Summary of main results

4.1 Paper I. Can intergenerational reports regarding asthma be used as a proxy in the absence of direct reports?

In this paper, we analysed the agreement between asthma reports by parents (N = 5907) and offspring (N = 6752) in the RHINESSA generation study. Figure 8 gives an

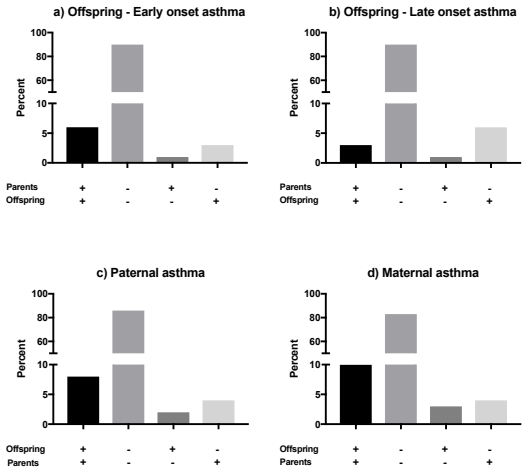

Figure 8. Parent-reported offspring early onset asthma (a) and late onset (b) asthma as compared to offspring's own report; and offspring-reported paternal (c) and maternal (d) asthma as compared to parents' own report.

overview of offspring early/late onset asthma as reported by the offspring themselves and the corresponding parent report (a and b), and paternal and maternal asthma as reported by the parents themselves and the corresponding offspring reports (c and d). Cohen's kappa was calculated to find the overall agreement between asthma reports from offspring and parents. In this study, we found that intergenerational asthma reports show moderate to good agreement. For parental reports of offspring early onset asthma (<10 years of age) the agreement was good (Cohen's kappa 0.72) while they were moderate for offspring late onset asthma (>10 years of age, Cohen's kappa 0.46). Contrary, offspring reports of paternal and maternal asthma were both good (Cohen's

kappa 0.69 and 0.68). Fathers (OR 1.31; 95% CI 1.08, 1.59) and current smokers (OR 1.46, 95% CI 1.05-2.02) were more likely to report offspring asthma incorrectly, while offspring wheeze was associated with reporting parental asthma incorrectly (OR 1.60; 95% CI 1.21, 2.11). The specificity was high for all groups (0.96-0.99), while the sensitivity varied more ranging from 0.36-0.72. The negative predictive value was high for all groups (0.94-0.97) while the positive predictive value varied from 0.75 (maternal asthma) to 0.83 (early onset asthma).

In paper I, we concluded that a moderate to good agreement was found between self-reported asthma and asthma reported by family-members in the RHINESSA generation study, with some risk of under-reporting. Our results suggest that offspring asthma reported by parents and parental asthma reported by offspring may be used as a proxy in epidemiological studies in the absence of direct reports.

4.2 Paper II. Is lifelong exposure to air pollution and greenness associated with asthma, rhinitis or lung function in adulthood?

Paper II is a retrospective cohort study with the aim to study the associations between lifetime exposure to air pollution and greenness, with adult asthma (physician diagnosed asthma, allergic/non-allergic asthma, asthma attack last 12 months), current rhinitis and lung function (LLN FEV_1, FVC and FEV_1/FVC). We analysed 3428 participants born after 1975 (mean age 28), from the Norwegian (Bergen) and Swedish (Umea, Uppsala, Gothenburg) centres in the RHINESSA study conducted from 2013 to 2015. Individualized annual mean exposures of five different air pollutants (NO_2, $PM_{2.5}$, PM_{10}, BC, and O_3) and greenness (NDVI) were assigned to all participants. The assignments were based on geocoded residential address histories, retrieved from Norwegian and Swedish population registries. The exposures were averaged across the following susceptibility windows: 0-10 years, 10-18 years, birth until diagnosis (or corresponding age for non-asthmatics), birth until participation in the study (lifetime) and the year before study participation (adulthood).

We analysed associations between the exposures and asthma attack, rhinitis and LLN lung function using logistic regression; and associations between the exposures and physician diagnosed asthma, allergic asthma and non-allergic asthma using conditional logistic regression on a matched case control dataset.

No associations were observed between any of the exposures with physician diagnosed asthma or allergic asthma in the adjusted analyses. For non-allergic asthma, exposure to both BC and O_3 (OR 0.92; 95% CI 0.85, 1.00 and OR 0.91; 95% CI 0.84, 1.00) were associated with lower risk of non-allergic asthma. Exposure to PM_{10} and O_3 were associated with an increased risk of asthma attack last 12 months in all the susceptibility windows 0-10 years, 10-18 years and lifetime, while NO_2 was an additional risk factor in the time window 10-18 years (Table 7). In the adjusted analyses, only exposure to NO_2 from 10-18 years of age was associated with an increased risk of rhinitis. Exposure to $PM_{2.5}$ and O_3 in childhood and adolescence was associated with increased risk of low lung function, especially FEV_1. In addition, exposure to NDVI in all susceptibility windows increased the risk of low FEV_1 and FVC.

Results from this paper indicate that lifelong exposure to air pollution and greenness increase the risk of poor respiratory health in adulthood. Our findings also suggest that exposure windows in childhood and adolescence may be independent risk factors for adverse lung health in adulthood.

Table 7. Multivariable[1] logistic regression analyses of asthma attack last 12 months and rhinitis and LLN FEV_1 and FVC in relation to air pollution and greenness for all time windows in the full (imputed) study population. The original table published in the paper, included also the other asthma outcomes (physician diagnosed asthma, allergic and non-allergic asthma) in addition to the univariable analyses.

	Asthma attack last 12 months						**Rhinitis**					
	0-10 years		10-18 years		Lifetime		0-10 years		10-18 years		Lifetime	
Exposure[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	1.24 (1.00, 1.53)	0.052	**1.29 (1.02, 1.63)**	**0.036**	**1.32 (1.02, 1.71)**	**0.034**	1.07 (0.96, 1.19)	0.210	**1.14 (1.01, 1.28)**	**0.037**	1.12 (0.98, 1.27)	0.091
$PM_{2.5}$	1.30 (0.89, 1.89)	0.171	1.45 (0.90, 2.36)	0.129	1.53 (0.94, 2.48)	0.086	1.11 (0.93, 1.32)	0.239	1.17 (0.93, 1.46)	0.170	1.18 (0.94, 1.48)	0.145
PM_{10}	**1.59 (1.06, 2.40)**	**0.026**	**1.90 (1.06, 3.41)**	**0.032**	**1.95 (1.14, 3.35)**	**0.015**	1.14 (0.94, 1.37)	0.174	1.17 (0.90, 1.52)	0.244	1.21 (0.95, 1.55)	0.129
BC	1.49 (0.85, 2.60)	0.165	1.78 (0.98, 3.24)	0.059	1.85 (0.96, 3.57)	0.065	1.17 (0.89, 1.55)	0.263	1.27 (0.96, 1.67)	0.091	1.32 (0.97, 1.78)	0.077
O_3	**1.94 (1.06, 3.57)**	**0.033**	**2.00 (1.11, 3.58)**	**0.021**	**2.25 (1.15, 4.38)**	**0.017**	0.99 (0.75, 1.32)	0.963	1.10 (0.83, 1.46)	0.498	1.09 (0.80, 1.48)	0.581
NDVI 300m	1.01 (0.83, 1.23)	0.930	0.96 (0.81, 1.14)	0.615	0.95 (0.77, 1.17)	0.629	1.02 (0.94, 1.12)	0.597	1.02 (0.94, 1.10)	0.694	1.01 (0.92, 1.11)	0.850

	0-10 years		10-18 years		Lifetime	
Exposure[2*]	OR (95% CI)	p[3]	OR (95% CI)	p[3]	OR (95% CI)	p[3]
LLN FEV_1						
NO_2	1.60 (0.92, 2.80)	0.096	1.66 (0.85, 3.27)	0.140	1.76 (0.92, 3.39)	0.089
$PM_{2.5}$	**2.65 (1.13, 6.21)**	**0.025**	**3.21 (1.03, 10.07)**	**0.045**	2.87 (0.96, 8.54)	0.058
PM_{10}	2.46 (0.90, 6.75)	0.081	3.29 (0.88, 12.26)	0.076	2.71 (0.72, 10.21)	0.139
BC	1.84 (0.46, 7.30)	0.387	2.18 (0.44, 10.74)	0.340	2.36 (0.42, 13.21)	0.330
O_3	**3.84 (1.08, 13.64)**	**0.037**	**4.21 (1.06, 16.77)**	**0.042**	**4.47 (1.25, 15.96)**	**0.021**
NDVI 300m	1.42 (0.99, 2.05)	0.060	**1.68 (1.18, 2.39)**	**0.004**	**1.74 (1.15, 2.63)**	**0.008**
LLN FVC						
NO_2	1.56 (0.78, 3.12)	0.205	1.50 (0.65, 3.43)	0.341	1.71 (0.81, 3.61)	0.162
$PM_{2.5}$	3.04 (1.17, 7.90)	0.023	**3.70 (1.06, 12.92)**	**0.040**	**3.50 (1.08, 11.36)**	**0.037**
PM_{10}	2.87 (0.98, 8.41)	0.055	3.43 (0.85, 13.83)	0.083	2.99 (0.75, 11.96)	0.121
BC	1.89 (0.35, 10.37)	0.462	2.30 (0.42, 12.56)	0.335	2.74 (0.43, 17.66)	0.288
O_3	**5.95 (1.16, 30.45)**	**0.032**	4.04 (0.67, 24.56)	0.129	4.95 (0.96, 25.47)	0.056
NDVI 300m	1.32 (0.87, 2.00)	0.198	**1.53 (1.04, 2.25)**	**0.030**	**1.57 (1.00, 2.45)**	**0.050**

Abbreviations: BC, black carbon; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm. [1] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-models that were adjusted for O_3 and NO_2. All models were also adjusted for age, sex and parental education and asthma. [2] All air pollutants exposures were extrapolated in time with the ratio method. [3] All p-values < 0.05 = significant and marked bold. *BC per 1-µg/m^3 increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-µg/m^3 increase.

Paper III. Is preconception exposure to air pollution and greenness associated with future offspring asthma and rhinitis?

In paper III, a two-generation analysis of a cohort study, we investigated if exposure to air pollution and greenness in parents' childhood (N = 1106, mean age 35) affected offspring asthma and rhinitis (N = 1949, mean age 6). Additional analyses were performed to examine if effects were mediated through parental asthma, pregnancy exposure and offspring's own early life exposure to greenness and air pollution. The residential exposures were assessed back in time, based on data from the Norwegian and Swedish population registries, land use regression models for air pollutants, and satellite images for greenness.

Annual mean concentrations for NO_2, $PM_{2.5}$, PM_{10}, BC, O_3 and NDVI were assigned to all participants based on their geocoded residential address history. The exposures were averaged across the following time windows: 0-18 years of age for the parents and 0-10 years of age for the offspring.

The risk of early onset asthma in offspring was higher after maternal medium exposure to $PM_{2.5}$ and PM_{10} compared with low exposure (OR 2.15; 95% CI 1.28, 3.61, OR 2.19; 95% CI 1.32, 3.64), while paternal high BC exposure was associated with lower early onset asthma risk in the offspring (OR 0.29; 95% CI 0.11, 0.80). Offspring had increased risk of rhinitis after paternal medium exposure to O_3 (OR 3.30; 95% CI 1.16, 9.40) and after maternal high PM_{10} exposure (OR 2.73; 95% CI 1.23, 6.08). No associations were found after exposure to NO_2 or NDVI with any of the outcomes. Mediation analyses showed a direct effect of maternal PM_{10} exposure on offspring asthma, while the effect on offspring rhinitis was indirect through exposures in pregnancy and offspring's own exposures. Paternal O_3 exposure was not mediated through O_3 exposure during pregnancy but had a direct and total effect on offspring rhinitis.

Thus, this paper revealed that air pollution exposure in the childhood of mothers appeared to be a risk factor for early onset asthma ($PM_{2.5}$ and PM_{10}) and rhinitis (PM_{10})

in her future offspring. The effects on early onset asthma was direct, while the effect on rhinitis was mediated by exposures during pregnancy and offspring's own childhood. Furthermore, exposure in father's childhood was associated with higher risk of rhinitis (O_3) in the offspring, not mediated by other factors. Our results suggest that long-term exposures to air pollution may have harmful effects even across generations.

5. Discussion

In this chapter, the methodological strengths and limitations of the papers included in the thesis are discussed. Furthermore, the main findings of the papers are discussed and compared to existing knowledge in the field.

5.1 Methodological considerations

When investigating frequency of disease or the effect of selected exposures on disease occurrence in epidemiological studies, the aim is to obtain valid and precise estimates that are generalizable to target populations (61, 63). There are two key concepts in this regard: validity and reliability. Validity refers to if we measure what we intended to measure: to what extent are the results from our studies valid for the study population (internal validity) and to what extent are the results from our studies generalizable for a wider population (external validity). Reliability refers to the precision of a measurement, the extent to which results will be replicated if the test is repeated. A study designed to measure depression that actually asks about anxiety will for instance have low validity, the same applies for a study of a disease in the general population that only includes female participants above 60 years. A study of lung function with numerous fieldworkers who do not receive a standard training in how to perform spirometries, on the other hand, will most likely have low reliability. High reliability is a prerequisite for high validity, but validity may be low even if reliability is high.

To achieve valid and precise estimates it is a goal to minimize measurement error in all stages of the study, from the study design through the data collection and in the analyses of the study results (61, 63). Errors can occur in each stage and be either systematic or random. Systematic errors are also termed bias and can be classified as confounding, selection and information bias (63). The remaining error after elimination of systematic error is called random error (61). Random error occurs by chance and is usually not considered a threat to the validity of a study. However, a large proportion of random errors may threaten the reliability of the estimates, indirectly also

threatening the validity. The goal in epidemiological studies is therefore high validity and high precision to assure correct estimations (63).

5.1.1 Study design issues

The data used in this thesis are based on the ECRHS, RHINE and RHINESSA studies, three large prospective cohort studies aiming to study respiratory health over time and across generations. In international multi-centre studies like ECRHS, RHINE and RHINESSA, there is a possibility that differences in methodology between centres and over time could influence the results. This challenge is hard to elude, however to minimize the chance of discrepancies between the centres, standardized protocols and questionnaires were used in all centres, as well as harmonized across the three studies. Provided they take measures to ensure minimal error in the data collection, large international multi-centre cohorts can contribute with valuable insight about exposure outcome associations, and also about health differences across the studied areas. The RHINESSA study includes 10 centres from seven countries (Denmark, Norway, Sweden, Iceland, Estonia, Spain and Australia), all of which were included in paper I. The diversity in the included countries in RHINESSA contributes to high potential generalizability of the results to a wider European/Australian population. A prerequisite is of course that the study population is representative for the target population. The RHINESSA study has a low response rate (35%), which may threaten its representativeness. For more details regarding this, see section 1.1.3 below.

To analyse air pollution and greenness in this thesis, RHINESSA data from Norway and Sweden were enriched with registry data. A major strength of the Nordic countries is the possibility to retrieve additional information from national population registries. Complete geocoded residential moving history was retrieved for all the Swedish and Norwegian participants born after 1975, and used to calculate individualized exposures for analyses in paper II and III. Consequently, the exposure assessment was highly objective and not dependent on the participants' memories.

5.1.2 Reliability

Reliability refers to the consistency of measurements, or in other words the agreement between replicate measurements when a measurement is performed multiple times under the same conditions (104). In paper 2, impaired lung function was analysed by using data collected through spirometry testing. To accomplish good reliability, the spirometry testing in the RHINESSA study was performed according to the American Thoracic Society (ATS) criteria for repeatability and standardisation of spirometry (74, 105), and both standard operating procedures and standardized equipment were used. The procedure was performed by trained personnel that followed detailed instructions to ensure measurements were performed in the same way in all participants. Furthermore, participants performed up to eight spirometry tests to accomplish acceptable and reproducible measures. An acceptable manoeuvre was defined as free from error, while a reproducible manoeuvre was defined as being without excessive variability from other manoeuvres. To achieve reproducibility, three acceptable manoeuvres were needed and the two highest values for FVC and FEV_1 should not vary more than 200 millilitres from each other. At last, calibration checks on the equipment were performed daily according to recommended standards.

5.1.3 Validity

Validity is defined by the degree to which a method measures what it is intended to measure (63), and is divided into internal and external validity.

Internal validity

Internal validity refers to the degree the results from the study represent the truth in the study population, and is not influenced by methodological errors (63). Systematic errors distorting the internal validity are often categorized into selection bias, information bias and confounding.

Selection bias is a systematic error from factors influencing study participation and from the methods used to select participants (61). Such error may distort the measured association between exposure and outcome, and affect estimates of disease occurrence such as prevalence. In ECRHS, the participants were selected randomly from available

population registers, with an overall response rate of 78% (72, 106). Paper I was based on data from both RHINE3 (second follow-up of ECRHS) and RHINESSA, with an overall response rate of 61% and 35%, respectively (107). Regarding the parent generation, RHINE had a loss to follow-up with response rate 86% in the initial stage (coinciding with the Northern European ECRHS1 response rate) and 61% in RHINE3 (the data used in this thesis). More men than women were lost to follow-up, as well as those who were youngest at baseline (107).

As the RHINESSA study population are offspring of the RHINE and ECRHS participants, they cannot be described as a random population sample. In paper I the RHINESSA study population was initially considered not to be skewed in any direction with respect to demographic characteristics such as sex, smoking habits and educational level compared to the general population in the same age range. However, for further inspection we compared the RHINESSA offspring population (age range 18-50 years, data collected in the years 2013-2015) with corresponding detailed data from Statistics Norway for the Norwegian population (selected year 2014 to match the time of RHINESSA data collection). As shown in Table 8 below, smoking prevalence in RHINESSA was indeed representative for the wider Norwegian population, with a prevalence of 13% smokers in both RHINESSA (Bergen study centre) and in Norway. Distribution of sex and education, on the other hand, was skewed for the RHINESSA population – with an over-representation of female sex and higher education in RHINESSA compared with the Norwegian general population.

Table 8. Demographic characteristics of the RHINESSA study population (total) and the RHINESSA study population (Bergen) compared to numbers from Statistics Norway.

	Study population all centres %	Study population Norway %	Statistics Norway %*
Education			
Primary school	3.0	2.5	20.3
Secondary school	37.9	36.3	39.9
College/university	59.1	61.2	39.8
Sex (female)	58,1	58,1	48,6
Smokers	12,3	12,8	13,0

* Numbers retrieved from Statistics Norway for the age range 20-49 years for education and sex, and age range 16-74 years for smoking prevalence. Numbers retrieved from RHINESSA for age range 18-50 years.

In other words, both the parent and offspring study populations have some degree of selection bias. However, since the aim of this PhD project was to elucidate exposure outcome associations and not present prevalence estimates for disease, this will fortunately not pose a large threat to the internal validity of our results. A previous study investigating follow-up in RHINE found that even if prevalence estimates were somewhat affected by selection bias in the follow-up stages, exposure-outcome associations were mainly unaffected (107). Also a large Norwegian study of selection bias in the Norwegian Mother and Child Cohort Study reached the same conclusion: they 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 (108).

Information bias is a systematic error that originates from the data collection or the classification of the exposure or outcome in a study (61, 63). It is often referred to as misclassification and can be further divided into differential or non-differential misclassification (61).

Differential misclassification

Misclassification in the exposure or outcome is differential if it is dependent of the other: if misclassification in the exposure is different for those with the disease and those without the disease – or if misclassification in the outcome is different for those

with the exposure and those without the exposure (61). Recall bias is a common type of differential misclassification that can lead to both an over- and underestimation of the exposure-outcome association. An example of recall bias is when for instance offspring asthma diagnosis is better recalled by the parents who have asthma diagnosis themselves, leading to an overestimation of the association between parental and offspring asthma. Also, a potential recall bias may be that subjects with well controlled asthma may not recall that they have a diagnosis of asthma (109). In paper I, the participants' own answers regarding themselves were defined as gold standard, which may have resulted in either over-reporting or under-reporting of the asthma diagnosis and age of diagnosis if they do not remember correctly. Recall bias may be reduced if the questions used are formulated in such a manner that accurate recall is triggered, for instance "have a doctor ever told you that you have asthma?" will give more accurate recall than the question "have you ever had asthma?" (61). To ensure the data was not biased by recall, we could have compared our data to primary care records of the participants or to prescription registry data. Unfortunately, this information was not available in our study, but could serve as a basis for a future research project.

If participants with an outcome (e.g. asthmatics) have thoughts regarding which exposures are harmful for their disease development and which are not, the risk of recall bias through over-reporting such exposures will be high (110). In papers II and III in this thesis, potential recall bias could be if participants with the outcome over-reported higher exposure levels of air pollution compared with participants without the outcome. For this reason, we did not rely upon self-reported exposures in this study but collected objective data on air pollution and greenness exposures based on each participants' residential addresses history. There is of course always a risk for recall bias also in the reporting of outcomes – which in our study was self-reported for asthma and rhinitis, but it is unlikely that misclassification of outcomes would be differential, i.e. dependent on the residential addresses.

Non-differential misclassification

Misclassification in exposure and outcome is non-differential if it is independent of the other (61), if it affects equally exposed and non-exposed, or those with and without a disease.

In paper I, we analysed agreement in parents' reports of offspring asthma, and in offspring reports of parents' asthma. The analyses were stratified by sex to see if misclassification of the outcome was dependent on differences between mothers and fathers, and between daughters and sons. In this respect, parental and offspring sex can be considered exposures. If sensitivity and/or specificity for disease classification do not vary by exposure category, misclassification is non-differential (111). In paper I, we did not find any discrepancy between specificity for neither daughters/sons nor mothers/fathers with regard to asthma report agreement. Also, sensitivity varied little between daughters and sons, indicating only non-differential misclassification for the offspring's reports of parental asthma. However, for the parents, sensitivity was much higher for mothers than fathers, suggesting a presence of non-differential misclassification that was further confirmed in logistic regression analysis where fathers had a significant risk of misclassifying their offspring's asthma status.

In paper II, the outcomes allergic and non-allergic asthma were based on the questions regarding physician-diagnosed asthma and "Do you have any nasal allergies including rhinitis?". A result of this outcome definition may be a non-differential misclassification where subjects with atopic asthma who are allergic to e.g. mites or animal hair but do not have rhinitis have been misclassified as non-allergic asthmatics. This kind of misclassification will however be non-differential since it is not dependent on how much air pollution and greenness exposure the misclassified subjects have been exposed to.

Exposure assignments in paper II and III were done based on the participants' residential addresses. Unfortunately, we were not able to account for time spent elsewhere due to lack of information on school/kindergarten/work addresses. Children spend 40-50% of their time at school/kindergarten and the rest of their time at home or

commuting. Levels of air pollution are usually lower at home than when commuting and children are often inside when they are at home (112). Consequently, it is plausible that the true exposures may be different from the exposures assigned in our study. However, the exposure calculations for the first years of life is likely to be correct due to the length of the maternity leave in both Sweden and Norway (29). In addition, most schools and kindergartens in Scandinavia are located nearby the home, further decreasing the chance of misclassification. Any remaining misclassification due to this issue will be non-differential since exposure misclassification is not dependent on whether or not the children have asthma.

Confounding is when the association between exposure and outcome can be explained by a third factor (63). A confounder is defined as being associated with both the exposure and the outcome and not being in the causal pathway between the exposure and outcome in time (61, 63). To avoid incorrect conclusions, it is important to adjust for confounders in analyses. In epidemiological analyses, confounding can be controlled for through study design or through the analyses. In paper I, we performed exploratory analysis to identify risk factors for discrepant reports and potential confounding factors were therefore not evaluated. In paper II and III, potential confounders were identified through previous literature, and DAGs were used to determine minimal sufficient covariate adjustment set. In paper II, parental education and parental asthma were the only variables associated with both air pollution/greenness exposure and the respiratory outcomes, while in paper III grandparental education and grandparental asthma/rhinitis were identified as associated with both exposure and outcome and preceding them both in time. Education status was used as a proxy for socio-economic status, which may affect place of residence and consequently influence the air pollution and greenness exposures.

External validity

External validity is the generalizability of the results, and is the degree to which the results of a study apply to other populations (63). Requirements for high external validity are both high reliability and high internal validity, which consequently will lead to representability of other populations.

The main inclusion criteria in RHINESSA is that they must be offspring of the ECRHS/RHINE participants. As such, we cannot claim to have a sample of the general population in RHINESSA, and we cannot generalize results regarding prevalences to a general population. However, as outlined in the section on selection bias earlier in this thesis, exposure outcome associations may very well be valid for a general population even if prevalence estimates are not. We have no reason to believe that our results are only valid for subjects with parents who have participated in large health surveys. However, other characteristics of the study population are more important in this context and must be acknowledged with regard to generalizability. In paper I, we included adult offspring from all RHINESSA centres. This means that none of our results can be generalized to children below 18 years of age. Also, the parents' age range yield restrictions for generalizability. No parents were older than 66 years. Thus, we cannot generalize our findings on parental recollection of offspring asthma status to older parents. It is possible that an 85-year-old person will have weaker recollection of details in his/her offspring's health status than a 50-year-old person.

In papers II and III, participants from centres other than the Norwegian and Swedish RHINESSA centres and participants born before 1975 were excluded due to non-availability of address information. Both Norway and Sweden have well organized population registers where information can easily be extracted, but for the Swedish participants address information was only available from 1975 onwards. Although also some other countries, like Denmark and Iceland, have well-functioning population registries with detailed address information, data from these centres were unfortunately not available at the time of analyses. The Norwegian and Swedish participants included in the analyses of paper II and III form a relatively homogeneous study population with similar air pollution exposure levels. Consequently, we must refrain from generalising our results to other populations than Nordic populations with similar levels of air pollution exposures. Inclusion of all the 10 RHINESSA centres would have contributed to greater diversity and have given the opportunity to compare regions with different air pollution levels, i.e. high O_3 levels in Australia and Spain versus low levels in the Nordic countries.

5.1.4 Missing data bias

It is a frequent challenge in epidemiological studies that some participants lack information on some of the study variables (63). If not accounting appropriately for missing data in analyses, this may lead to bias and loss of precision (98). Unless the missing data are random, a highly selected study population is formed and selection bias is introduced. And even if the missing data are random, complete case analyses where participants with missing data are excluded will decrease the study population size and may lead to insufficient power.

Missing data are usually classified into three different categories (63, 98): Missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR). MCAR is when the probability of missing values is totally independent of both observed and unobserved values: when the missing data are missing purely by chance. An example may be that questionnaires have been lost in the mail, or that a small sample of a study population cannot be weighed because the fieldworker's weight ran out of batteries. A variable is MAR if other variables in the dataset can be used to predict the missing on that variable, for instance can gender predict missingness of weight if men are more likely than women to report their weight. In this example, weight would be MAR. At last, MNAR is if the missing depends on unobserved and not observed data. In our studies, this could be the case if all smoking mothers had missing on the smoking questions because they were afraid their smoking reports would reveal they were exposing their children to passive smoking – or if all participants with only compulsory schooling refrained from answering the question about educational level.

Complete case analyses can be an appropriate choice in some situations and give unbiased estimates if the variables are MCAR or if the proportion of missing data is very low (98, 113). In papers I and III, our study populations were sufficiently large to run compete case analyses without it negatively affecting power. In paper II, the study population for the clinical analyses with lung function was small, and we decided to perform analyses with imputation rather than complete case analyses to avoid unnecessary deletion of observations. Multiple imputation is a commonly used

approach to deal with missing data, where the purpose is to create several different plausible imputed data sets and combining them to create values that accounts for the uncertainty of the missing values (63, 98). We imputed using multivariate normal regression in Stata, under the assumption that the missing was MAR. We chose to impute with MAR as assumption to ensure appropriate handling of the missingness. If missing was MCAR, both complete case analysis and multiple imputation are valid, while with MAR multiple imputation is valid. In other words, MCAR implies MAR, but MAR does not imply MCAR.

5.1.5 Exposure measurement and assessment

One of the main concerns in environmental studies is the measurement and assessment of exposures, since the quality of this is a critical factor for the study validity (63). Paper II and III in this thesis are unique with regard to the exposure assessment, which was based on complete individual geocoded residential moving history retrieved from population registers. This forms an exclusive source to unbiased exposure data in the Nordic countries, covering an impressing long time span. However, there are some issues of uncertainty concerning the calculations and the back-extrapolation of both air pollution and greenness. To estimate concentrations of the air pollutants for papers II and III, extrapolation formulas from LUR models were used. The exact accuracy of the assignments for our study centres is not known, even if validation studies from the ESCAPE project have shown that the model has satisfactory overall accuracy (78, 114). Furthermore, the LUR models do not encompass detailed exposure data on other sources of air pollution than traffic-related pollution, for instance pollution from residential wood combustion is not accounted for. Both traffic and wood combustion are primary sources of NO_2 and PM and due to the strong correlation it can be hard to disentangle the independent effect of each of them. In papers II and III, results cannot be generalized to other sources of air pollution than traffic, and total exposures will presumably be underestimated.

5.2 Main findings and previous literature

5.2.1 Asthma reports across generations

To the best of our knowledge, no previous studies have addressed the agreement of generational reports on each other's asthma status. Our findings suggest that offspring asthma status reported by parents and vice versa may be used as a proxy in the absence of direct reports. However, the agreement of parental reports of offspring early onset asthma was substantially higher than the agreement of parental reports of late onset asthma (Cohen's kappa 0.72 and 0.46, respectively), which makes it debatable if parental reports of offspring late onset asthma may be used as a proxy. For the analyses in paper III, parental reports of offspring early onset asthma were used as outcome to ensure a high validity. Offspring rhinitis was the second outcome in paper III. Rhinitis was not included in the agreement analyses in paper I due to lack of information on offspring reported parental rhinitis. However, we do have information on parent-reported offspring rhinitis. For further inspection, we have now performed additional agreement analyses comparing these parental reports of offspring rhinitis to offspring's own rhinitis reports, following the same methodology as in paper I (Table 9).

Table 9. Parameter estimates (95% CI) for Cohen's kappa, sensitivity, specificity, PPV and NPV for parental reported offspring rhinitis. N = 4067 parents from RHINE/ECRHS and 5513 adult offspring from RHINESSA.

	Agreement[1] N (%)	Disagreement[2] N (%)	Cohen's kappa	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Both parents	4507 (82)	1006 (18)	0.52	0.80 (0.77, 0.82)	0.82 (0.81, 0.83)	0.53 (0.50, 0.55)	0.94 (0.93, 0.95)
Mother	2545 (82)	562 (18)	0.53	0.78 (0.75, 0.81)	0.83 (0.81, 0.84)	0.56 (0.53, 0.59)	0.93 (0.92, 0.94)
Father	1962 (82)	444 (18)	0.50	0.81 (0.77, 0.85)	0.82 (0.80, 0.83)	0.49 (0.45, 0.52)	0.95 (0.94, 0.96)

[1]Agreement: when both parents and offspring answered the same (yes/yes or no/no). [2]Disagreement: when parents and offspring answered differently (yes/no or no/yes).

Agreement for parent-reported offspring rhinitis is lower than what was shown for early onset asthma in paper I a similar kappa statistic was found for mothers (Cohen's kappa 0.53 for both), while the agreement of paternal reported rhinitis was notably better than for late onset asthma (Cohen's kappa 0.50 and 0.36, respectively). In addition, the overall parental agreement appeared to be somewhat better for rhinitis than late onset asthma (Cohen's kappa 0.52 versus 0.46). Cohen's kappa for parent-reported offspring rhinitis shows a moderate agreement, which indicates that parental reports can be used as a proxy in the absence of direct offspring reports – but should

be used with caution. With a higher kappa, like for early onset asthma, the validity in paper III would be higher.

Several predictors were found to be associated with discrepant answers across generations in paper I. In a previous study regarding bias of self-reported asthma, smoking habits were not associated with misclassification of own asthma status (109). This was not a generational study, but it is nevertheless noteworthy that the results contradict with our findings that smoking parents more often than non-smoking parents reported offspring asthma incorrectly. Our findings may be explained by non-smokers being more aware of both their own and their relatives' health (115).

As an extension to the additional analyses of agreement between parental reports of offspring rhinitis and offspring's own rhinitis reports, we explored which characteristics that were associated with discrepant rhinitis reports (Table 10). In univariate analyses, the following parental characteristics were identified as potential predictors: lower educational level, diabetes, COPD, rhinitis, wheeze and nocturnal attack of cough. In multivariate analyses, however, only two predictors were significantly associated with reporting offspring rhinitis incorrectly: parental primary school education and parents' own rhinitis. Adults with lower levels of education are more likely to have unhealthy habits (116), e.g. smoke, lack of exercise and an unhealthy diet, and may have decreased awareness about health issues compared with adults with higher education. That parents with their own rhinitis diagnosis are more likely to report offspring rhinitis incorrectly was unexpected, but one can speculate that the offspring diagnosed with rhinitis in our study population have few symptoms or that the rhinitis has developed after they grew up and moved away from home. Unfortunately, we did not have any data on age of onset for rhinitis in the RHINESSA study, so we could not further elaborate on this hypothesis.

Table 10. Odds ratios for discrepant answers in parent's rhinitis reports, univariate and multivariate logistic regression analysis.

Predictor	Univariate analyses		Multivariate analyses[1]	
	OR (95%CI)	p	OR (95%CI)	p
Gender	0.98 (0.85, 1.12)	0.727		
Age	1.01 (1.00, 1.02)	0.090		
Smoking				
Current smoker	1.00			
Never smoker	0.93 (0.76, 1.14)	0.511		
Ex-smoker	1.07 (0.87, 1.32)	0.523		
Education				
College/university	1.00		1.00	
Primary school	1.25 (1.01, 1.55)	**0.039**	1.30 (1.03, 1.62)	**0.024**
Secondary school	1.11 (0.95, 1.28)	0.178	1.10 (0.94, 1.29)	0.223
Comorbidity				
Hypertension	1.02 (0.87, 1.20)	0.786		
Stroke	1.22 (0.74, 2.00)	0.440		
Ischemic heart	0.99 (0.66, 1.48)	0.943		
Diabetes	1.40 (1.01, 1.94)	**0.042**	1.37 (0.98, 1.92)	0.064
COPD	1.55 (1.04, 2.32)	**0.031**	1.38 (0.90, 2.12)	0.141
Serious childhood infection <5years	1.09 (0.99, 1.20)	0.071		
Rhinitis	1.49 (1.29, 1.72)	**<0.001**	1.42 (1.12, 1.68)	**<0.001**
Severity of asthma				
Wheeze	1.20 (1.02, 1.42)	**0.030**	1.09 (0.91, 1.32)	0.348
Wheeze with shortness of breath	1.20 (0.98, 1.47)	0.086		
Awoken with tightness in chest	1.06 (0.84, 1.33)	0.628		
Awoken with attack of breathlessness	1.31 (0.98, 1.75)	0.070		
Awoken with attack of cough	1.46 (1.05, 2.03)	**0.024**	1.20 (0.83, 1.73)	0.326
Currently taking asthma medication	1.23 (0.98, 1.54)	0.074		

[1]Adjusted for all predictors that were significant in the univariate analyses as well as for study centre and sibling status.

5.2.2 Lung health after exposure to air pollution and greenness in one generation

Our detailed individualized lifelong exposure calculations for both air pollution and greenness are unique. To our knowledge, no previous studies have examined equally long exposure time, meaning up to 30 years, and associations of air pollution and greenness with asthma, rhinitis and lung function.

Our study did not reveal any associations of air pollution and greenness with increased risk for neither general physician diagnosed asthma nor allergic asthma, when analysing cumulative exposures from birth up to age of asthma diagnosis. As reviewed, several studies have addressed the effects of exposure to air pollution on childhood and adolescent asthma, but with various results. Two of the studies did not reveal any effects on asthma (29, 39), which is in line with our study. One of these null-finding

studies was conducted in Oslo (1992-2002), thus with comparable exposure levels to our studies, and the lack of associations with asthma diagnosis may be because higher levels of air pollution exposures are needed than the levels we observed for our study population (29). We observed associations with both asthma attacks, rhinitis and low lung function, consequently the pollution levels were obviously high enough to lead to harmful health effects. But there is a possibility that even higher levels are needed for it to be associated with a physician diagnosis of asthma, in particular since the exposure time for asthma diagnosis is shorter than for the other outcomes. While asthma attack, rhinitis and low lung function was reported and measured at the time of participation in the study (with mean age 28 years, ranging from 18 to 40), asthma diagnosis was related to considerably younger ages: 53% of the asthmatics got their diagnosis before the age of 10 years, and as many as 90% of the asthmatics got their diagnosis before the age of 19 years. It is important to bear in mind that in Sweden and Norway air pollution levels are relatively low, and therefore it is likely that the exposure time must be longer here than in high-exposure areas like for instance Poland or China to trigger disease.

Several recent studies have, unlike our results, revealed associations of air pollution exposure and asthma. One study of a Dutch birth cohort investigated age-specific associations of exposure to air pollution with asthma development during the transition from childhood and adolescence into young adulthood (117), and found higher incidence of asthma until age 20 years with higher exposure to NO_2, PM_{10}, $PM_{2.5}$ and $PM_{2.5}$ absorbance at birth address. An American study found a decrease in asthma incidence with reductions of NO_2 and $PM_{2.5}$ levels among participants aged 10-18 years in California, but did not reveal any associations for O_3 or PM_{10} (118).

In our study, we had particular focus on the susceptibility windows up to 18 years of age, due to the hypothesis that the lungs are most vulnerable during the years of development and we wanted to explore the effects of exposures in this period. However, disentangling different susceptibility windows for when exposures have the largest effect on adult outcomes was difficult due to the majority of participants not changing place of residence during their childhood and adolescence. Even if we did

observe slightly larger and more significant effect estimates in the 10-18 years window than in the 0-10 year window, the differences were too small for us to draw conclusions with any certainty. Hence, it is hard to point out one window to be more important than the other based on our results and we therefore encourage future studies to further explore this.

Lack of observed significant associations could perhaps also be due to not stratifying by sex. One could argue that our analyses should have been stratified by sex due to gender differences in effects of exposures on lung health. It has been suggested that women are more susceptible than men to adverse effects of cigarette smoking (119). Women have smaller airways than men, and the same amount of exposure will because of this perhaps have a relatively stronger effect on women. With a larger study population, it would be interesting to look further into possible sex-specific associations, but with the large number of analyses in our study as well as the somewhat limited sample size (especially for the clinically examined subpopulation), we prioritized to optimize statistical power and chose not to stratify by sex.

Regarding lung function in our study, we revealed somewhat unexpectedly that higher exposure to greenness was a risk factor for low FEV_1 and FVC. This is in contrast with a recent publication from the UK Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, which found evidence for a better lung function up to 24 years of age for children with residential addresses in more vegetated places or in proximity of green spaces (120). The ALSPAC study registered air pollution exposures at birth and at ages 8, 15 and 24 years. Another study, emanating from the ECRHS, revealed that higher greenness was associated with higher FEV_1 levels (121), but no beneficial longitudinal associations between lung function change and greenness were detected. In fact, FVC decline was steeper with increasing greenness although numbers were modest: 1.8 ml decline per year per 0.2 change in NDVI.

Even if many studies confirm the beneficial effects of greenness to respiratory health, our observed association between greenness and lower lung function may not be as

implausible as first envisaged. A nation-wide cross-sectional study in China recently found that neighbourhood greenness was a significant risk factor for COPD (122). The authors hypothesized that plants emit various kinds of VOCs, and that some species of VOCs may lead to reduced lung function. Also, another aspect of greenness may be negative in a health perspective. Airborne pollen has been linked to hospital admissions and impaired health (123), and may hinder the beneficial effects of greenness.

We defined impaired lung function as lung function below LLN, based on reference values from GLI with LLN defined as a z-score <1.64 SD. Some of the more recent studies addressing lung function have used similar z-scores (120), while other studies have used percent predicted lung function or used litres as measure (28, 36). For further in-depth investigation of our results, additional analyses of lung function expressed in percent predicted and in litres were performed (Appendix D and E). Regarding lung function analyses expressed in litres, we did not reveal any associations with the air pollutants or greenness within the 300 m buffer zone. For the additional NDVI buffer zones, however, we found associations for FEV_1 (1000m buffer, mean life exposure) and FEV_1/FVC ratio (100m buffer, 0-18 years, 10-18 years and mean life exposure). For percent predicted lung function, a reduction of 2-4% of predicted FEV_1 was found in all susceptibility windows per 10-µg/m_3 increase in $PM_{2.5}$ exposure, and a reduction of 2% predicted FEV_1 per 10-µg/m3 increase in NO_2 exposure for all periods except 0-10 years. In addition, a reduction of 3% per 10-µg/m3 increase in PM_{10} exposure was found for the period 0-18 years. For predicted FVC, we revealed a reduction of 2-4% for exposure to $PM_{2.5}$ and PM_{10} for all time periods. For predicted FEV_1/FVC-ratio we found that each 0.1 unit increase in exposure to NDVI (300m) in the period 10-18 years was associated with a ratio decrease of 0.6%. Greenness was not associated with any of the other outcomes.

These additional results show that the initially observed associations between increased greenness and lower lung function were not dependent on our definition of low lung function, the associations were present also for lung function in absolute values and in percent predicted.

5.2.3 Lung health after exposure to air pollution and greenness across generations

Due to our unique exposure data, we were able to investigate preconception exposure in parents' childhood and adolescence (0-18 years) in relation to asthma and rhinitis in their future offspring.

In this study, we revealed that maternal PM_{10} and $PM_{2.5}$ exposure increased the risk of offspring asthma, while rhinitis risk increased for offspring of fathers exposed to O_3 and mothers exposed to PM_{10}.

In addition, an apparently protective association between paternal BC exposure and offspring early onset asthma was revealed, which is also in line with one of the findings in paper II where exposure to BC was associated with lower risk of non-allergic asthma. The reasons for these unexpected findings are not clear, but high correlations between pollutants may play a role in the challenge of disentangling the long-term health effects of pollutants. This is supported by the fact that in single pollutant models in paper II of the odds ratio for BC exposure with regard to non-allergic asthma was very close to 1 (OR 0.98 (95%CI 0.94-1.03)).

Another aspect of uncertainty that may have played a role is the use of spatial LUR models and the back- and forward extrapolation for the periods before 1990 and after the model years that may have impacted the analysed pollutants differently depending on their source. The pollution exposures calculated closest to the model years have the best prediction, while the extrapolation depends on how much the emission landscape has changed during the years not covered (124). We do not suspect this to be a problem in the forth-extrapolation (using the 2010 models to extrapolate to the years up to 2015), but extrapolating back to 1975 based on 1990 formulas may pose a problem. There is reason to believe that exposures to several pollutants were higher in the 1970s in Europe, with a downward trend from the 1980s (125). Consequently, the exposures in the 1970s and 1980s may be lower in our analyses than what they actually were. Together with a potential lack of statistical power, in particular regarding analyses of the paternal line, this may have resulted in an under-estimation of negative health effects of pollution.

Overall, we observed more associations in the maternal line than in the paternal line. Another study, although not directly comparable due to different exposures, found fathers' smoking before conception to be a risk factor for asthma in his future offspring (66). One could hypothesize that for men, the exposure must be quite strong to make the epigenetic leap across generations. Active cigarette smoking will in this regard represent a higher exposure dose than air pollution exposure, especially in the Nordic countries with relatively low air pollution levels. For women, on the other hand, one could envisage that preconception exposure interacts with exposure during pregnancy, and that the exposure dose needed to trigger harmful health effects in the next generation therefore may be smaller in women than in men. For some outcomes, this is likely important. As reported from paper III, the effects of maternal air pollution exposures with regard to offspring rhinitis were mediated by exposures during pregnancy. However, for some outcomes, pregnancy exposures are not necessarily the reason why maternal preconception exposures seem relevant. In paper III, the maternal preconception exposure effects on offspring asthma were direct and not mediated through pregnancy exposures.

6. Conclusions

The overall objective of this PhD project was to investigate how air pollution and greenness affect lung health over time and across generations. This objective was addressed through three scientific papers. To ensure optimal data quality, paper I in this project focused on investigating the agreement of asthma reports by offspring and parents in the RHINESSA generation study. With the reassurance from paper I that offspring outcomes reported by parents are a valid proxy for direct reports from the offspring themselves, we moved on to investigating how air pollution and greenness affects lung health over time and across generations in papers II and III. Overall, results from this PhD project show that long-term air pollution exposures increase the risk of asthma-related outcomes later in life and even in the next generation, while results regarding long-term exposures to greenness are less consistent and need further investigations.

6.1 Asthma reports across generations

Agreement between self-reported asthma and asthma reported by family-members was moderate to good, although with some risk of under-report. Agreement was higher for parental reports of offspring early onset asthma than for offspring late onset asthma. Smokers and fathers were more likely to report offspring asthma incorrectly, while offspring wheeze was associated with incorrect reports of parental asthma status. Overall, asthma reports across generations may be used as a proxy in the absence of direct reports, and may be of particular importance in epidemiological studies where information regarding several generations is not directly available.

6.2 Lifetime exposure to air pollution and greenness

Lifelong air pollution exposure was associated with asthma attacks (NO_2, PM_{10} and O_3), rhinitis (NO_2) and low lung function ($PM_{2.5}$ and O_3) in adulthood. No associations were found for asthma diagnosis. Exposure to greenness was associated with FEV_1 and FVC below the lower limit of normal, but not with asthma attacks, rhinitis or asthma

diagnosis. Disentangling the importance of the susceptibility windows was not feasible due to stable residential patterns, but the results suggest that all the investigated exposure windows are of importance for adult lung health. The results confirm that air pollution exposures are associated with respiratory outcomes one year later, and suggests that also air pollution exposure in childhood and adolescence increases the risk of poor lung health in adulthood.

6.3 Preconception exposure to air pollution and greenness

This study suggests that exposure to air pollution may have harmful effects even across generations. Maternal childhood air pollution exposure was associated directly with early onset asthma in future offspring ($PM_{2.5}$ and PM_{10}). There was also an association between maternal childhood exposure to PM_{10} and offspring rhinitis, but this effect was partly mediated through offspring's own childhood exposure and exposure during pregnancy. Offspring with fathers who had been exposed to O_3 had higher risk of rhinitis, while results regarding fathers and other pollutants in association with the outcomes were inconclusive. Overall, parental exposure to air pollution appears to influence the risk of asthma and allergies in future offspring.

7. Future perspectives

With this thesis we have added new insights to the current knowledge on lifetime and cross-generational effects of air pollution and greenness on respiratory health, with truly long-term air pollution and greenness exposures and even analyses of the effects of preconception exposures on future generations. We revealed that long-term air pollution exposures were associated with increased risk of asthma-related outcomes later in life and in the next generation. Less clear associations were found regarding long-term exposure to greenness.

The impact of exposures in utero and early childhood with regard to subsequent health and susceptibility to disease, has received increasing interest over the past decades. Currently, emerging research focuses on the possibility of susceptible time windows even before conception. To investigate this properly, we need data from generation cohorts. When such data is not available, our results revealed that health reports on behalf of the generations below or above show a moderate to good agreement and may be used as a proxy in the absence of direct reports.

The scientific input from this thesis is an important contribution to policy makers and city planners to increase the awareness of the long-term effects of air pollution and greenness. Although further research is warranted to entirely understand the complex underlying interactions between air pollution and greenness and respiratory health, results from this thesis suggest that existing international limit values for air pollution exposure are in fact too high, and that even lower levels of pollution exposures may have harmful health effects in the population.

Although the present thesis is a valuable contribution to this field of knowledge, and although it will hopefully have an impact on policy making and international recommendations, more knowledge is still needed. In that regard, this thesis may serve as a platform that future research can build upon. Specifically, a better understanding of the underlying epigenetic mechanisms can contribute to disentangling the contribution of different susceptibility windows and increase our knowledge of the interaction between genes and environmental factors in the development of respiratory

disease. Future studies should focus on this and include not only questionnaire data and spirometry, but also cord-blood to investigate the epigenetic mechanisms through fetal and parental DNA methylation and samples from later ages to assess potential persistent epigenetic signals.

8. References

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9. Appendices

Appendix A. Questionnaire from the RHINE study.

Appendix B. Questionnaire from the RHINESSA study.

Appendix C. Calculation of back-extrapolation, the ratio method.

Appendix D. Lung function analyses, liters.

Appendix E. Lung function analyses, % predicted.

Appendix A. Questionnaire from the RHINE study.

Kompetansesenter for klinisk forskning
HAUKELAND SYKEHUS

Institutt for indremedisin
Seksjon for lungemedisin

Ernst Omenaas

Airways symptoms

1. Have you had wheezing or whistling in your chest at any time **in the last 12 months?** ☐ No ☐ Yes

   If NO go to question 2, if YES:

   1.1 Have you been at all breathless when the wheezing noise was present? ☐ No ☐ Yes

   1.2 Have you had this wheezing or whistling when you did not have a cold? ☐ No ☐ Yes

2. Have you woken up with a feeling of tightness in your chest at any time **in the last 12 months?** ☐ No ☐ Yes

3. Have you been woken by an attack of shortness of breath at any time **in the last 12 months?** ☐ No ☐ Yes

4. Have you been woken by an attack of coughing at any time **in the last 12 months?** ☐ No ☐ Yes

5. Have you had an attack of asthma **in the last 12 months?** ☐ No ☐ Yes

6. Are you currently taking any medicine *(including inhalers, aerosols or tablets)* for asthma? ☐ No ☐ Yes

7. Do you have any nasal allergies including hay fever? ☐ No ☐ Yes

8. Do you have any nasal allergies including hay fever? ...../...../.....

9. What is today's date? ...../...../.....

10. Are you male or female ☐ Male ☐ Female

11. How tall are you? ..... cm

12. How much do you weigh? ..... kg

13. In recent years, have you been troubled by a protracted cough? ☐ No ☐ Yes

14. Do you usually bring up phlegm or do you have phlegm in your lungs which you have difficulty bringing up? ☐ No ☐ Yes

    If NO go to question 18, if YES:

15. Do you bring up phlegm in this way almost every day for **at least three months every year?** ☐ No ☐ Yes

    If NO go to question 18, if YES:

16. Have you had periods of this kind for at least two years in a row? NO YES

    If NO go to question 18, if YES:

17. How old were you when these problems began? ..... years

Smoking habits

18. Are you a smoker *(this applies even if you only smoke the odd cigarette/cigar or pipe every week)?* ☐ No ☐ Yes

19. Are you an ex-smoker?

If NO to question 18 and 19 go to question 20, if YES:

19.1 Smoke/smoked .....cigarettes/day

.....cigars/week

.....pkts pipe tobacco/week

How old were you when you started smoking? .....(age)

Smoked for .....years *(applies to both smokers and ex-smokers)*

Stopped smoking in.....(year)

Upper and lower airways

20. Do you have or have you ever had asthma? ☐ No ☐ Yes

If NO go to question 24, if YES:

21. Have you ever had asthma diagnosed by a doctor? ☐ No ☐ Yes

22. How old were you when you first experienced asthma symptoms? ..... years

23. In which year did you last experience asthma symptoms? 19...../ 20.....

24. Has a doctor ever told that you have COPD (BOLD) ☐ No ☐ Yes

25. Have you ever had wheezing or whistling in your chest? ☐ No ☐ Yes

25.1 If "Yes", how old were you when you first noticed wheezing or whistling in your chest? ..... years

25.2. If "Yes", when was the last year you noticed wheezing and whistling in your chest? 19...../ 20.....

26. Have you ever experienced nasal symptoms such as nasal congestion, rhinorrhoea (runny nose) and/or sneezing attacks without having a cold? ☐ No ☐ Yes

If NO go to question 25, if YES:

26.1 How old were you when you experienced them for the first time? ..... years

26.2 Have you had these kind of nasal symptoms in the last 12 months? ☐ No ☐ Yes

26.3 At which time of the year are your nasal symptoms worst?

Spring	Summer	Autumn	Winter	Always	Don't know
☐	☐	☐	☐	☐	☐

27. Has your nose been blocked **for more than 12 weeks during the last 12 months?** ☐ No ☐ Yes

28. Have you had pain or pressure around the forehead, nose or eyes **for more than 12 weeks during the last 12 months?** ☐ No ☐ Yes

29. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat **for more than 12 weeks during the last 12 months?** ☐ No ☐ Yes

30. Has your sense of smell been reduced or absent **for more than 12 weeks during the last 12 months?** ☐ No ☐ Yes

In-door and out-door environment

31. In which type of accommodation do you live?

Detached house ☐ Semidetached or terraced house ☐ Apartment ☐ Other ☐

32 When did you move to your current home? 19 .....

33. How many hours per day do you spend in your home most days? Approx. ..... hours/day

34. Does tobacco smoking take place in your present home?

Yes every day ☐ Yes, frequently 1-4 times/week ☐ Yes, sometimes 1-3 times/month ☐ No never ☐

35. Have any of the following been identified in your home during **the past 12 months:**

35.1 *Water leakage or water damage indoors in walls, floor or ceilings ☐ No ☐ Yes

35.2 *Bubbles or yellow discoloration on plastic floor covering, or black discoloration of parquet floor ☐ No ☐ Yes

35.3 *Visible mould growth indoors on walls, floor or ceilings. ☐ No ☐ Yes

36. Have you seen any signs of damp, water leakage or mould in your home at any time during the past X years? ☐ No ☐ Yes

37. Have you seen any signs of damp, water leakage or mould in your workplace at any time during the past X years? ☐ No ☐ Yes

38. Is your bedroom window towards a nearby street (<20 m)?

☐ No
☐ Yes a street with little traffic
☐ Yes a street with moderate traffic
☐ Yes a street with much traffic

39. Can you in your bedroom hear traffic noise?

- ☐ Not at all
- ☐ A little
- ☐ Much
- ☐ Very much

40. How much time do you usually spend walking or travelling along streets with busy traffic a typical weekday? Approx ..... minutes/day

Marital status

41. What is your marital status? *(more than one alternative may be true)*

- ☐ 1.Single
- ☐ 2 Currently married
- ☐ 3 Cohabitating
- ☐ 4 Separated or divorced
- ☐ 5 Widowed
- ☐ 6 Do not wish to answer

Marital status

42. Please mark the educational level which best describes your level:

- ☐ 1) Primary school
- ☐ 2) Lower or upper secondary school, or technical school
- ☐ 3) College or university

Occupation and work

43. Are you currently working? ☐ No ☐ Yes

44.. Which is your current or most recent work or occupation?

…….

How many years have you worked or did you work in this occupation? .....years

45. We assume that your work ability, when it was as best, was 100 percent. How would you rate your current work ability, expressed in percent? ..... %

46. Have you ever changed job because the job affected your breathing? ☐ No ☐ Yes

46.1 If "Yes", in which years? .....

46.2 If "Yes", from which occupation/job did you change? *(could be several)* .....

47. Have you ever changed job because of hayfever or nasal symptom ☐ No ☐ Yes

47.1 If Yes, in which years? .....

47.2 If "Yes", from which occupation/job did you change? *(could be several)* .....

48 Have you ever changed job because of other health problems/diseases? ☐ No ☐ Yes

48.1 If Yes, in which years? .....

48.2 If "Yes", which occupation/job did you change from? *(could be several)* .....

49. Have you ever worked as a painter? ☐ No ☐ Yes

If "Yes", between which years? .....

50. Have you ever worked as a cleaner? ☐ No ☐ Yes

If "Yes", between which years? .....

51. Have you been reporting any days of sick leave during the last 12 months? ☐ No ☐ Yes

51.1 If yes, how many days have you been on sick leave?

☐ 1 – 7 days ☐ 8-30 days ☐ 31 days – 90 days ☐ More than three months

52. Have you been reporting any days of sick leave because of breathing problems during the last 12 months? ☐ No ☐ Yes

52.1 If yes, how many days have you been on sick leave for breathing problems?

1 – 7 days	8-30 days	31 days – 90 days	More than three months
☐	☐	☐	☐

Childhood and family

53. What term best describes the place you lived most of the time when you were under the age of five years?

☐ Farm with livestock
☐ farm without livestock
☐ village in rural area
☐ small town
☐ suburb of city
☐ inner city

54. When you were a child, which of the following were regularly used for heating?

Open wood	Coke or coal fire	Paraffin	Electricity	Gas or oil fired boiler
☐	☐	☐	☐	☐

55. Did you have a serious respiratory infection before the age of five years? ☐ Yes ☐ No ☐ Don't know

56.1. Did your father ever smoke regularly during your childhood? ☐ Yes ☐ No ☐ Don't know

56.2 Did your mother ever smoke regularly during your childhood? ☐ Yes ☐ No ☐ Don't know

56.3 Did other people (other than parents) smoke regularly at home during your childhood? ☐ Yes ☐ No ☐ Don't know

57. When you were a child, how often did you eat fresh fruits?

Never	Rarely	Every week	Almost daily	Almost daily in the autumn season
☐	☐	☐	☐	☐

58. Did your biological parents ever suffer from any of the following:

	Mother (yes)	Father (yes)
Asthma	☐	☐
Chronich bronchitis, emphysema and/or COPD	☐	☐
Heart disease	☐	☐
Hypertension	☐	☐
Stroke	☐	☐
Diabetes	☐	☐
Cancer	☐	☐

59. Do you have children (including grown-up children)? ☐ No ☐ Yes

If yes, how many? ..... children

Please write the years when your children were born, and tick "yes" if they have had any of the following:

Child	Birth year of child (year)	Asthma before 10 year (yes)	Asthma after 10 years (yes)	Hayfever/ rhinitis (yes)	Atopic eczema/Skin allergies (yes)
1					
2					
3					
4					
5					
6					
7					

Sleep and daytime symptoms

The numbers mean
1: Never or almost never
2: Less than once a week
3: once or twice a week
4: 3- 5 nights/days a week
5: Almost every day or night

How often has it occurred in the last months:

60. that You snore loudly and disturbingly?	1	2	3	4	5
61. that You have heartburn or belching when you have gone to bed?	1	2	3	4	5
62. that You have difficulty in getting to sleep at night?	1	2	3	4	5
63. that You wake up repeatedly during the night?	1	2	3	4	5
64. that You perspire heavily during the night?	1	2	3	4	5
65. that You feel drowsy in the daytime?	1	2	3	4	5
66. that You wake up too early and have difficulty in getting to sleep again?	1	2	3	4	5

67. Have you ever had sleep apnoea diagnosed by a doctor? ☐ No ☐ Yes

If "No" go to question 69, if "Yes":

67.1 What year did you get the diagnosis of sleep apnoea? Year .....

67.2 If you are currently treated for sleep apnoea, what treatment do you have?

- ☐ CPAP
- ☐ Oral appliance (bite splint)
- ☐ Previous surgery in the throat or nose
- ☐ Others

68 How long time do you usually sleep per night?

I usually sleep .....hours and .....minutes.

Other diseases

69. Have ever had hypertension (high blood pressure) diagnosed by a doctor? ☐ No ☐ Yes

If yes:

69.1 When did you get the diagnosis hypertension (high blood pressure)? Year .....

69.2 Are you currently taking any medication for hypertension (high blood pressure)? ☐ No ☐ Yes

70. Have you ever had stroke? ☐ No ☐ Yes

70.1 If you have had stroke, in which year was it? Year .....

71. Have you ever been treated in hospital because of heart infarction or angina pectoris? ☐ No ☐ Yes

If yes:

71.1 When were you treated (for the first time) at a hospital because of heart infarction or angina pectoris? Year .....

72. Have you ever had diabetes diagnosed by a doctor? ☐ No ☐ Yes

If yes:

72.1 What year did you get the diagnosis diabetes? Year: .....

72.2 What treatment are you currently using for diabetes?
- ☐ Insulin
- ☐ Tablets
- ☐ Both insulin and tablets
- ☐ Only diet

73. Do you have or have you ever had ulcerative collitis? ☐ No ☐ Yes

73.1 If yes: how old were you when the disease started? ..... years

74. Do you have or have you ever had Crohn's disease? ☐ No ☐ Yes

74.1 If, yes, how old were you when the disease started? .....years

General health

75 Does your gum bleed when you brush your teeth?
- ☐ Always
- ☐ Often
- ☐ Sometimes
- ☐ Rarely
- ☐ Never

76 How often do you usually brush your teeth?
- ☐ 2 times/day or more
- ☐ Once daily
- ☐ Less than daily

77. How frequently do you exercise? (Give an average)

Never	Less than once a week	Once a week	2-3 times a week	Almost every day
☐	☐	☐	☐	☐

77.1. If you do such exercise as frequently as once or more times a week: How hard do you push yourself? *(Give an average)*
- ☐ I take it easy without breaking into a sweat or losing my breath /
- ☐ I push myself so hard that I lose my breath and break into a sweat /
- ☐ I push myself to near-exhaustion

77.2. How long does each session last? (Give an average)

Less than 15 minutes	6-30 minutes	30 minutes to 1 hour	More than 1 hour
☐	☐	☐	☐

78. Body silhouettes

Information and contact conscent

In case we need to get in touch with you again please write your telephone number below

Telephone number: Daytime .....

Evening .....

THANK YOU FOR YOUR HELP

Appendix B. Questionnaire from the RHINESSA study.

Lungehelseundersøkelsens Generasjonsstudie

– translated «The lung health investigation's Generation Study"
Name chosen in order to be as similar as possible to

Airways symptoms and allergic symptoms

1. Have you had wheezing or whistling in your chest at any time **in the last 12 months?** ☐No ☐Yes

If NO go to question 2, if YES:

1.1. Have you been at all breathless when the wheezing noise was present? ..... ☐No ☐Yes

1.2. Have you had this wheezing or whistling when you did not have a cold?..... ☐No ☐Yes

2. Have you woken up with a feeling of tightness in your chest at any time **in the last 12 months?** ..... ☐No ☐Yes

3. Have you been woken by an attack of shortness of breath at any time **in the last 12 months?** ..... ☐No ☐Yes

4. Have you been woken by an attack of coughing at any time **in the last 12 months?**... ☐No ☐Yes

5. Have you had an attack of asthma **in the last 12 months**? ..... ☐No ☐Yes

6. Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?..... ☐No ☐Yes

7. Do you have any nasal allergies including hay fever?..... ☐No ☐Yes

8. What is your date of birth? (day/month/year) ..... ____dd ____mm_____yyyy

9. What is today's date? (day/month/year) ..... ____dd ____mm _____yyyy

10. Gender ☐Man ☐Woman

11. How tall are you? ..... _____cm

12. How much do you weigh? ..... _____ kg

13. In recent years, have you been troubled by a protracted cough?..... ☐No ☐Yes

14. Do you usually bring up phlegm or do you have phlegm in your lungs which you have difficulty bringing up? ☐No ☐Yes

If NO to question 13 and 14 go to question 15, if YES:

14.1. Do you cough or bring up phlegm in this way almost every day for at least three months every year? ..... ☐No ☐Yes

14.2. Have you had periods of this kind for at least two years in a row? ☐No ☐Yes

15. Do you have or have you ever had asthma?..... ☐No ☐Yes

If NO go to question 16, if YES:

15.1. Have you ever had asthma diagnosed by a doctor?..... ☐No ☐Yes

15.2. How old were you when you first experienced asthma symptoms? _____years

15.3. How old were you when you last experienced asthma symptoms?..... _____years

16. Has a doctor ever told you that you have chronic obstructive pulmonary disease (COPD)? ☐No ☐Yes

17. Have you been woken by an attack of shortness of breath at any time in **the last 3 days**? ☐No ☐Yes

18. Have you been woken by an attack of coughing at any time in **the last 3 days**? ☐No ☐Yes

19. Have you had wheezing or whistling in your chest in **the last 3 days**? ☐No ☐Yes

20. Have you **ever** had wheezing or whistling in your chest? ☐No ☐Yes

If NO go to question 21, if YES:

20.1 How old were you when you first noticed wheezing or whistling in your chest? ..... _____ years

21. Have you ever experienced nasal symptoms such as nasal congestion, rhinorrhoea (runny nose) and/or sneezing attacks without having a cold? ☐No ☐Yes

If No go to question 22, if YES:

21.1. How old were you when you experienced such nasal symptoms for the first time? _____ years

21.2. Have you had such nasal symptoms in **the last 12 months**?..... ☐No ☐Yes

21.3. Has this nose problem been accompanied by itchy or watery eyes? ☐No ☐Yes

21.4. In which months of the year did this nose problem occur?

January / February ..... ☐
March / April ..... ☐
May / June..... ☐
July / August ..... ☐
September / October..... ☐

November / December…… ☐

22. Have you ever had eczema or any kind of skin allergy? ☐No ☐Yes

If NO go to question 23,if YES:

22.1. How old were you when you first had eczema or skin allergy? _____ years

23. Have you ever had an itchy rash that was coming and going for at least 6 months? ☐No ☐Yes

If NO go to question 24, if YES:

23.1. Have you had this itchy rash in **the last 12 months**? ☐No ☐Yes

23.2. Has this itchy rash at any time affected any of the following places:
the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes? ☐No ☐Yes

23.3. Has this itchy rash affected your hands at any time in **the last 12 months?** ☐No ☐Yes

24. Have you ever had an illness or truoble caused by eating **a particular** food or foods? ☐No ☐Yes

If NO go to question 25, if YES:

24.1. Have you nearly always had the same illness or trouble after eating this type of food? ☐No ☐Yes

If NO go to question 25, if YES:

24.2. What type of food was this (*list up to three foods*)?

_____

24.3. Did this illness or truoble include:

24.3.1. a rash or itchy skin? ☐No ☐Yes

24.3.2. diarrhea or vomiting? ☐No ☐Yes

24.3.3. runny or stuffy nose? ☐No ☐Yes

24.3.4. severe headaches? ☐No ☐Yes

24.3.5. breathlessness? ☐No ☐Yes

24.4. How soon after eating this food did/do you get the first sympoms?

Less than half an hour	½ - 1 hour	1-2 hours	2-4 hours	More than 4 hours
☐	☐	☐	☐	☐

24.5. How old were you when you **first** had this attack? _____years

24.6. How old were you when you **last** had this attack? _____years

Smoking habits

25. Do you smoke? (this applies even if you only smoke the odd cigarette/cigar or pipe every week) ☐No ☐Yes

26. Did you smoke previously?..... ☐No ☐Yes

If NO to question 25 and 26 go to question 27, if YES:

26.1. How much do or did you smoke? *(give an average)*

Cigarettes/day	Cigars/week	Pkts pipe tobacco/week

26.2. How old were you when you started smoking? _____ years

26.3. For how long have you smoked? (applies to both smokers and ex-smokers) _____ years

26.4. If you are an ex- smoker, how old were you when you stopped smoking? _____years

27. Do you use moist snuff, nicotine patches, or other products containing nicotine? ☐No ☐Yes

28. Did you use moist snuff, nicotine patches, or other products containing nicotine previously? ☐No ☐Yes

If NO to question 27 and 28 go to question 30, if YES:

29. What kind of nicotine-containing product do /did you use?

29.1. Moist Snuff ☐No ☐Yes

If you use/have used moist snuff:

29.1.1. How old were you when you started using moist snuff? _____ years

29.1.2. For how long have you been using moist snuff? (applies to both current users and past users) _____ years

29.1.3. If you did use moist snuff previously, how old were you when you stopped using it? _____ years

29.2. Nicotine patches/ gum /tablets ☐No ☐Yes

If you have been using nicotine patches/gum/tablets:

29.2.1. For how long have you used nicotine patches/gum/tablets: _____ months

Childhood and family

30. What term best describes **the place you lived most of the time before the age of 5 years**? (tick one box only)

Farm with livestock	Farm without livestock	Village in rural area	Small town	Suburb of city	Inner city
☐	☐	☐	☐	☐	☐

30.1. What term best describes the place **your father** lived as a child? (tick one box only)

Farm with livestock	Farm without livestock	Village in rural area	Small town	Suburb of city	Inner city	Don't know
☐	☐	☐	☐	☐	☐	☐

30.2. What term best describes the place **your mother** lived as a child? (tick one box only)

Farm with livestock	Farm without livestock	Village in rural area	Small town	Suburb of city	Inner city	Don't know
☐	☐	☐	☐	☐	☐	☐

30.3. What term best describes the place **your grandparents'** lived as a child? (tick one box for each grandparent)

	Farm	Village in rural area	Small town	Inner city	Don't know
Father's father	☐	☐	☐	☐	☐
Father's mother	☐	☐	☐	☐	☐
Mother's father	☐	☐	☐	☐	☐
Mother's mother	☐	☐	☐	☐	☐

31. How many persons, including yourself, lived in your home when you were 5 years old (where you lived most of the time)? (number)……

32. Did you have a serious respiratory infection before the age of five years?....☐No ☐ Yes ☐ Don't know

33. Did your father ever smoke regularly during your childhood? .....☐No ☐ Yes ☐ Don't know

34. Did your mother ever smoke regularly during your childhood? .....☐No ☐ Yes ☐ Don't know

If NO / DON'T KNOW go to question 35, if YES:

34.1. Did your mother smoke when she was pregnant with you? ☐No ☐ Yes ☐ Don't know

35. Did other people (other than parents) smoke regularly at home during your childhood?..... ☐No ☐ Yes ☐ Don't know

36. How often did you take cod liver oil when you were a child? (tick one box only)

Never	Rarely	Every week	Daily
☐	☐	☐	☐

37. How often did you eat fresh fruits and berries when you were a child? (tick one box only)

Never	Rarely	Every week	Almost daily	Almost daily in the autumn season
☐	☐	☐	☐	☐

38. How often did you eat potatoes or vegetables that **you or your family had cultivated** when you were a child? (tick one box only)

Never	Rarely	Almost weekly in the growing season	Almost daily in the growing season
☐	☐	☐	☐

39. Was there a cat in your home?

39.1. During your first year of life ☐No ☐ Yes ☐ Don't know

39.2. When you were aged 1 to 4 years ☐No ☐ Yes ☐ Don't know

39.3. When you were aged 5- 15 years ☐No ☐ Yes ☐ Don't know

40. Was there a dog in your home?

40.1. During your first year of life ☐No ☐ Yes ☐ Don't know

40.2. When you were aged 1 to 4 years ☐No ☐ Yes ☐ Don't know

40.3. When you were aged 5- 15 years ☐No ☐ Yes ☐ Don't know

41. What was the highest level of education your mother has/had? (tick one box only)

Primary school (up to the minimum school leaving age)..... ☐

Secondary school / technical school (past the minimum age)..... ☐

College or university ..... ☐

42. What was the highest level of education your father has/had? (tick one box only)

Primary school (up to the minimum school leaving age)..... ☐

Secondary school / technical school (past the minimum age)..... ☐

College or university ..... ☐

43. Did your biological parents ever suffer from any of the following:

	Mother (tick box if YES)	Father (tick box if YES)
Asthma	☐	☐
Chronich bronchitis, emphysema and/or COPD	☐	☐
Heart disease	☐	☐
Hypertension	☐	☐
Stroke	☐	☐
Diabetes	☐	☐
Cancer	☐	☐

44. Do you have any biological children? ☐No ☐ Yes

If NONE go to question 45, if you have (had) biological children:

44.1. How many children? NUMBER_____

44.2. Please write the years when your biological children were born, and tick "YES" if they have had any of the following:

	Year of birth	Girl/ boy	Asthma before 10 years	Asthma after 10 years	Hayfever/ Rhinitis	Atopic eczema/ skin allergies
Child 1						
Child 2						
Child 3						
Child 4						
Child 5						
Child 6						

Education and occupation

45. Please mark the educational level which best describes your level: *(tick one box only)*)

Primary school ..... ☐

Secondary school/technical school..... ☐

College or University ..... ☐

46. Which is your current or most recent work or occupation?

Employed	Self- employed	Homemaker	Student	Unemployed	Other
☐	☐	☐	☐	☐	☐

47. Do you currently have /have you ever had paid work?..... ☐No ☐Yes

*Please **do not** include occupations of shorter duration than three months.*
*Please **do** include part time jobs of 20 or more hours per week.*
If NO go to question 54, if YES:

48. Which is your current or most recent work or occupation? *(please use capital letters)*

.....

48.1. How many years have you worked / did you work in this occupation? .....years

49. Does being at your current workplace ever cause breathing problems (chest tightness, wheezing, coughing)? ☐No ☐Yes

50. In your current job, are you regularly exposed to vapours, gas, dust or fumes? ☐No ☐Yes

51. Have you ever changed job because the job affected your breathing?..... ☐No ☐Yes

52. Have you ever changed job because of hay fever or nasal symptom?..... ☐No ☐Yes

53. Have you ever changed job because of eczema or skin disease?..... ☐No ☐Yes

In-door environment

54. Do you keep a cat? ☐No ☐Yes

If NO go to 55,if YES:

54.1. Is your cat (are your cats) allowed inside the house? ☐No ☐Yes

54.2. Is your cat (are your cats) allowed in the bedroom? ☐No ☐Yes

55. Do you keep a dog? ☐No ☐Yes

If NO go to question 56, if YES:

55.1. Is your dog (are your dogs) allowed inside the house? ☐No ☐Yes

55.2. Is your dog (are your dogs) allowed in your bedroom? ☐No ☐Yes

56. In which type of accommodation do you live? *(tick one box only)*

Detached house ☐

Semidetached or terraced house ☐

Apartment ☐

Other ☐

57. When did you move to your current home?..... Year_____

58. Have you ever moved house because of breathing problems?..... ☐No ☐Yes

59. When was your present home built?..... Year _____

60. Does tobacco smoking take place in your present home? *(tick one box only)*

Yes, every day	Yes, frequently 1-4 times/week	Yes, sometimes 1-3 times/month	No, never
☐	☐	☐	☐

61. Have any of the following been identified in your home in **the last 12 months:**

61.1. Water leakage or water damage indoors in walls, floor or ceilings?..... ☐No ☐Yes

61.2. Bubbles or yellow discoloration on plastic floor covering, or black discoloration of parquet floor? ..... ☐No ☐Yes

61.3. Visible mould growth indoors on walls, floor or ceilings..... ☐No ☐Yes

62. Have you seen any signs of damp, water leakage or mould in your home at any time **in the last 10 years**? ..... ☐No ☐Yes

63. Have you noticed the odour of mould or mildew (not from food) in your home at any time **in the last 12 months**?..... ☐No ☐Yes

General health

64. Have you had a course of antibiotics in **the last 12 months**?..... ☐No ☐Yes
(*i.e. Apocillin, Azitromax, Imacillin) LIST the three most commonly used antibiotics in your country*

64.1. If YES, how many courses of antibiotics..... (number) _____

65. Have you had a course of antibiotics in **the last 14 days**?..... ☐No ☐Yes

66. Does your gum bleed when you brush your teeth? *(tick one box only)*

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

67. How often do you usually brush your teeth? *(tick one box only)*

2 times/day or more	Once daily	Less than daily
☐	☐	☐

68. How frequently do you exercise? *(give an average, tick one box only)*

Never	Less than once a week	Once a week	2-3 times a week	Almost every day
☐	☐	☐	☐	☐

If you do such exercise as frequently as one or more times a week:

68.1. How hard do you push yourself? *(tick one box only)*

I take it easy without breaking into a sweat or losing my breath..... ☐
I push myself so hard that I lose my breath and break into a sweat..... ☐
I push myself to near-exhaustion..... ☐

68.2. How long does each session last? *(give an average, tick one box only)*

Less than 15 minutes ..... ☐
16-30 minutes ..... ☐

30 minutes to 1 hour ..... ☐

More than 1 hour ..... ☐

Sleep and daytime symptoms

69. How often has it occurred **in the last months** *(circle one number for each question):*

1: *Never or almost never*	**2**: *Less than once a week*	**3**: *Once or twice a week*	**4**: *3- 5 nights/days a week*	**5**: *Almost every day or night*

69.1. ... that you snore loudly and disturbingly?.....	1	2	3	4	5
69.2. ...that you have heartburn or belching when you have gone to bed?	1	2	3	4	5
69.3. ... that you have difficulty in getting to sleep at night?...	1	2	3	4	5
69.4. ... that you wake up repeatedly during the night?.....	1	2	3	4	5
69.5. ... that you perspire heavily during the night?	1	2	3	4	5
69.6. ... that you feel drowsy in the daytime?	1	2	3	4	5
69.7. ...that you wake up too early and have difficulty In getting to sleep again?.....	1	2	3	4	5

70. How long time do you usually sleep per night? _____Hours _____Minutes

Other diseases

71. Has a doctor or health professional ever told you that you have?

71.1. Diabetes? ☐No ☐Yes

If NO go to question 71.2, if YES:

71.1.1. How old were you when you were diagnosed with diabetes? _____years

71.1.2. What treatment are you currently using for diabetes? *(tick one box only)*

Insulin	Tablets	Both insulin and tablets	Only diet
☐	☐	☐	☐

71.1.3. Which type of diabetes do/did you have:

☐ Type 1 ☐ Type 2 ☐ Only in pregnancy ☐ Don't know

71.2. Psoriasis? ☐No ☐Yes

If NO go to question 71.3, if YES::

71.2.1. How old were you when you were diagnosed with psoriasis? _____years

71.3. Bechterew's disease? ☐No ☐Yes

If NO go to question 71.4, if YES:

71.3.1. How old were you when you were diagnosed with Bechterew's disease? _____years

71.4. Rheumatiod arthritis? ☐No ☐Yes

If NO go to question 71.5, if YES:

71.4.1. How old were you when you were diagnosed with rheumatoid arthritis? _____years

71.5. Ulcerous Colitis? ☐No ☐Yes

If NO go to question 71.6, if YES:

71.5.1. How old were you when the disease started? ..... _____years

71.6. Crohn's disease? ☐No ☐Yes

If NO go to question 71.7, if YES:

71.6.1. How old were you when the disease started? ..... _____years

71.7. Sleep apnea? ☐No ☐Yes

If NO go to question 71.8, if YES:

71.7.1. How old were you when you were diagnosed with sleep apnea? _____years

71.7.2. What treatment are you currently using for sleep apnea? (more than one box may apply)

CPAP	Oral appliance (bite splint)	Other
☐	☐	☐

71.8. Hypertension (high blood pressure)? ☐No ☐Yes

If NO go to question 71.9, if YES:

71.8.1. How old were you when you were diagnosed with hypertension (high blood pressure)? _____years

71.8.2. Are you currently taking any medication for hypertension (high blood pressure)? ☐No ☐Yes

71.9. Heart infarction or angina pectoris? ☐No ☐Yes

If NO go to question 72, if YES:

71.9.1. Have you ever been treated in hospital because of heart infarction or angina pectoris? ☐No ☐Yes

If NO go to question 72, if YES:

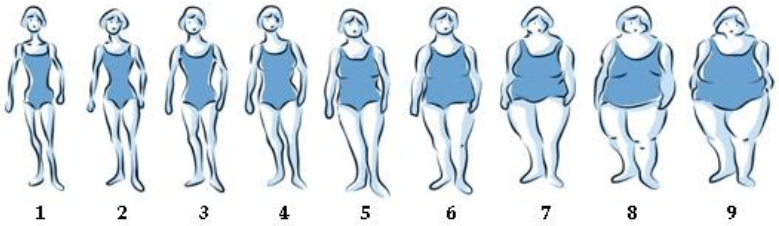
71.9.2. How old were you when you were treated in hospital (for the first time) for heart infarction or angina pectoris? _____years

Body shape

72. Gender: ☐Man ☐Woman

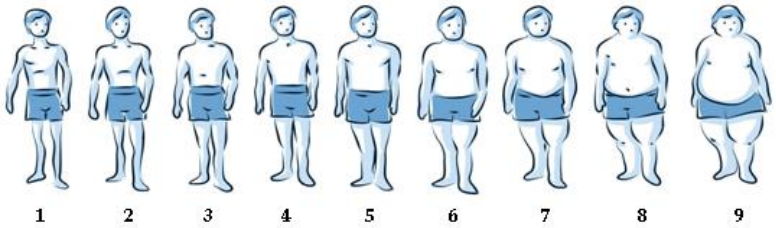
What picture best describes your body shape at each age
(tick one box only for each age/ period you have reached)

72.1. WOMEN



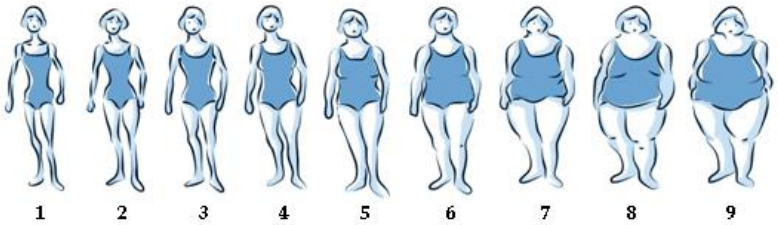
Current	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 8 years	☐	☐	☐	☐	☐	☐	☐	☐	☐
At first menstruation	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 20	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 30	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 45	☐	☐	☐	☐	☐	☐	☐	☐	☐

72.2. MEN



Current	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 8 years	☐	☐	☐	☐	☐	☐	☐	☐	☐
At voice break	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 20	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 30	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 45	☐	☐	☐	☐	☐	☐	☐	☐	☐

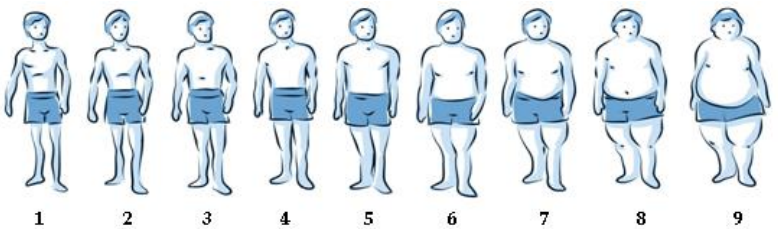
73. What picture best describes the body shape of your biological mother at



Don't know

Age 30	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 45	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

74. What picture best the body shape of your biological father at



Don't know

Age 30	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 45	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Food and drinks

75. How many days each week do you usually eat/ drink the following:

	Never	Rarely	1 day a week	2 days a week	3 days a week	4 days a week	5 days a week	6 days a week	7 days a week
Meat or sausage	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fish	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vegetables	☐	☐	☐	☐	☐	☐	☐	☐	☐
Raw vegetables, salad, vegetable juice	☐	☐	☐	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐	☐	☐	☐
Potatoes or vegetables you or your family have cultivated yourselves	☐	☐	☐	☐	☐	☐	☐	☐	☐
Olive oil	☐	☐	☐	☐	☐	☐	☐	☐	☐
Citrus fruit or citrus fruit juice	☐	☐	☐	☐	☐	☐	☐	☐	☐
Any fruit (except citrus fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Milk (not including milk you have in tea or coffe)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Soft drinks	☐	☐	☐	☐	☒	☐	☐	☐	☐
Dark (not white) bread	☐	☐	☐	☐	☐	☐	☐	☐	☐
Food heated in plastic container in microwave	☐	☐	☐	☐	☐	☐	☐	☐	☐
Unpasteurized milk?	☐	☐	☐	☐	☐	☐	☐	☐	☐
Beer or wine	☐	☐	☐	☐	☐	☐	☐	☐	☐
Naturally fermented foods	☐	☐	☐	☐	☐	☐	☐	☐	☐

76. To collect data on outdoor exposures in places you have lived, we would like to ask for your address history. Some countries provide address information through registries, others do not.

Which country do you live in?

If you live in NORWAY, SWEDEN, DENMARK or SWITZERLAND:

Your country provides address history through registries.
Thank you for participation in this survey.

If you live in AUSTRALIA, ICELAND, SPAIN, or ESTONIA:

76.1. We would like to know where you have lived since January 1990.
Please give the address, including postcode, of all homes you have lived in **for at least one year since 1990, starting with your current address**

House number	**Street name**	**City**	**Postcode**	**Moved in**	**Lived there until (YEAR)**
					current

Norwegian consent form
To be signed before submitting the *postal* questionnaire

Respondent number

Project title	Project number
The Lung Health Investigation's Generation study	

Project leader

Department/hospital

Participation in the study is voluntary. If you want to participate, you have to sign this consent form. If you agree to participate, you can at any time and without giving a reason, withdraw your consent. Further, this will not have any consequences for your future contact with the health care system.

If you want to withdraw, or have any questions about the study, you can contact the project leader.

I would like to participate in this study

Name in capitals

Date	Signed
__ __ /__ __ / 20 __ __	

Thank you for your help!

Consent form - translation for web:

Participation in the study is voluntary. If you want to participate, you have to sign this consent form by ticking 'yes' at the bottom of this page. If you agree to participate, you can at any time and without giving a reason, withdraw your consent. Further, this will not have any consequences for your future contact with the health care system.

If you want to withdraw, or have any questions about the study, you can contact the project leader.

I would like to participate in this study:

Appendix C. Calculation of back-extrapolation, the ratio method.

Ratio method

1. DEHM modelled annual mean concentrations for 2010 (the year the ELAPSE models were modelled for): C_{DEHM_2010}.

2. DEHM modelled annual mean concentrations for years prior and post 2010 were extracted: C_{DEHM_year}

3. Ratio's were calculated by dividing the DEHM modelled annual mean concentrations for years prior and post 2010 by DEHM modelled annual mean concentrations for 2010: $Ratio_{DEHM\_year} = C_{DEHM\_year} / C_{DEHM\_2010}$,

4. Calculate for each participant the back or forward extrapolated concentration ($C_{extrapolated}$) by multiplying the modelled ELAPSE annual mean concentration (for 2010) with the ratio: $C_{extrapolated} = C_{ELAPSE} * Ratio_{DEHM\_year}$

The DEHM estimates from 1990 were used as proxies for the years prior to 1990 in our calculations.

Appendix D. Lung function analyses, liters.

Appendix D.

Univariable and multivariable analyses for lung function, liters

Table S1. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FEV_1 (liters) in the full (imputed) study population. Univariable mixed model regression analyses.

Exposure[1*]	0-18 years Coef. (95% CI)	p[2]	0-10 years Coef. (95% CI)	p[2]	10-18 years Coef. (95% CI)	p[2]	Mean life time exp Coef. (95% CI)	p[2]
NO_2	-0.03 (-0.13-0.06)	0.510	-0.03 (-0.12-0.06)	0.560	-0.03 (-0.12-0.06)	0.478	-0.02 (-0.14-0.09)	0.683
$PM_{2.5}$	-0.12 (-0.31-0.06)	0.196	-0.10 (-0.28-0.07)	0.254	-0.14 (-0.33-0.05)	0.153	-0.15 (-0.39-0.09)	0.210
PM_{10}[3] (male)	**-0.24 (-0.44- -0.04)**	**0.018**	**-0.19 (-0.38- 0.00)**	**0.045**	**-0.32 (-0.53- -0.12)**	**0.002**	-0.18 (-0.45-0.09)	0.183
PM_{10}[3] (female)	**-0.15 (-0.30- .0.01)**	**0.036**	-0.12 (-0.25-0.02)	0.098	**-0.18 (-0.33- -0.04)**	**0.011**	-0.14 (-0.32-0.05)	0.153
BC	-0.05 (-0.26-0.15)	0.594	-0.04 (-0.23-0.14)	0.664	-0.05 (-0.25-0.15)	0.603	-0.09 (-0.34-0.17)	0.497
O_3	-0.05 (-0.27-0.16)	0.647	-0.04 (-0.26-0.18)	0.719	-0.05 (-0.25-0.15)	0.623	-0.12 (-0.35-0.12)	0.331
NDVI (100m)	-0.06 (-0.12-0.01)	0.082	-0.05 (-0.11-0.01)	0.110	-0.05 (-0.11-0.01)	0.131	-0.07 (-0.14-0.00)	0.067
NDVI (300m)	-0.05 (-0.13-0.02)	0.148	-0.04 (-0.11-0.03)	0.287	-0.06 (-0.13-0.01)	0.092	-0.06 (-0.14-0.02)	0.132
NDVI (500m)	-0.06 (-0.13-0.02)	0.136	-0.04 (-0.11-0.03)	0.263	-0.06 (-0.13-0.01)	0.079	-0.07 (-0.14-0.01)	0.098
NDVI (1000m)	-0.06 (-0.13-0.01)	0.088	-0.05 (-0.12-0.02)	0.132	-0.06 (-0.13-0.00)	0.066	**-0.08 (-0.15-0.00)**	**0.039**

*Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All p-values < 0.05 = significant and marked bold. [3] The PM_{10}-models were stratified by sex. *BC per 1-μg/m³ increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m³ increase.*

Table S2. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FEV_1 (liters) in the full (imputed) study population. Multivariable[2] mixed model regression analyses.

Exposure[1*]	0-18 years Coef. (95% CI)	p[3]	0-10 years Coef. (95% CI)	p[3]	10-18 years Coef. (95% CI)	p[3]	Mean life exp Coef. (95% CI)	p[3]
NO_2	-0.03 (-0.11-0.06)	0.517	-0.02 (-0.10-0.05)	0.575	-0.03 (-0.12-0.06)	0.478	-0.03 (-0.12-0.06)	0.531
$PM_{2.5}$	-0.07 (-0.21-0.07)	0.329	-0.05 (-0.17-0.08)	0.435	-0.11 (-0.27-0.05)	0.183	-0.07 (-0.23-0.09)	0.361
PM_{10}[4] (male)	-0.01 (-0.26-0.23)	0.911	-0.01 (-0.23-0.21)	0.939	-0.07 (-0.37-0.23)	0.647	0.04 (-0.25-0.32)	0.808
PM_{10}[4] (female)	-0.02 (-0.20-0.15)	0.811	-0.01 (-0.16-0.15)	0.933	-0.03 (-0.24-0.18)	0.799	-0.04 (-0.24-0.16)	0.697
BC	-0.01 (-0.20-0.18)	0.920	-0.02 (-0.20-0.16)	0.809	0.01 (-0.19-0.20)	0.953	-0.04 (-0.26-0.18)	0.710
O_3	-0.02 (-0.21-0.16)	0.827	-0.02 (-0.20-0.16)	0.823	-0.02 (-0.20-0.16)	0.832	-0.04 (-0.23-0.16)	0.713
NDVI (100m)	-0.02 (-0.07-0.02)	0.362	-0.02 (-0.06-0.03)	0.465	-0.21 (-0.61-0.19)	0.308	-0.04 (-0.09-0.01)	0.147
NDVI (300m)	-0.03 (-0.08-0.03)	0.339	-0.02 (-0.07-0.03)	0.518	-0.04 (-0.08-0.01)	0.144	-0.04 (-0.10-0.01)	0.128
NDVI (500m)	-0.03 (-0.08-0.02)	0.261	-0.02 (-0.07-0.03)	0.510	-0.04 (-0.09-0.00)	0.077	-0.05 (-0.11-0.00)	0.063
NDVI (1000m)	-0.03 (-0.08-0.01)	0.179	-0.02 (-0.07-0.02)	0.337	-0.04 (-0.09-0.00)	0.055	**-0.06 (-0.11-0.01)**	**0.022**

*Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for sex, age, parental education and asthma. [3] All p-values < 0.05 = significant and marked bold. [4] The PM_{10}-analyses were stratified by sex and adjusted for O_3, NDVI (300m buffer), age, parental education and parental asthma. *BC per 1-μg/m³ increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m³ increase.*

Table S3. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FVC (liters) in the full (imputed) study population. Univariable mixed model regression analyses.

	0-18 years		0-10 years		10-18 years		Mean life exposure	
Exposure[1*]	Coef. (95% CI)	p[2]	Coef. (95% CI)	p[2]	Coef. (95% CI)	p[2]	Coef. (95% CI)	p[2]
NO_2	0.01 (-0.11-0.13)	0.885	0.00 (-0.11-0.12)	0.982	0.02 (-0.10-0.14)	0.745	0.02 (-0.13-0.16)	0.811
$PM_{2.5}$	-0.01 (-0.25-0.23)	0.938	-0.01 (-0.24-0.21)	0.916	0.02 (-0.23-0.26)	0.899	-0.08 (-0.38-0.23)	0.628
PM_{10}	0.01 (-0.24-0.26)	0.924	0.02 (-0.22-0.25)	0.886	0.04 (-0.21-0.29)	0.761	-0.05 (-0.38-0.28)	0.766
BC	0.05 (-0.21-0.30)	0.707	0.02 (-0.22-0.25)	0.883	0.11 (-0.15-0.36)	0.402	-0.03 (-0.35-0.29)	0.857
O_3	-0.09 (-0.36-0.19)	0.530	-0.07 (-0.35-0.20)	0.606	-0.09 (-0.34-0.17)	0.505	-0.17 (-0.46-0.13)	0.258
NDVI (100m)	-0.05 (-0.13-0.04)	0.271	-0.05 (-0.13-0.03)	0.227	-0.03 (-0.10-0.05)	0.454	-0.07 (-0.15-0.02)	0.146
NDVI (300m)	-0.05 (-0.15-0.04)	0.266	-0.04 (-0.13-0.04)	0.332	-0.05 (-0.14-0.04)	0.256	-0.07 (-0.17-0.03)	0.165
NDVI (500m)	-0.06 (-0.15-0.03)	0.200	-0.05 (-0.14-0.04)	0.253	-0.06 (-0.15-0.03)	0.170	-0.08 (-0.18-0.02)	0.109
NDVI (1000m)	-0.05 (-0.14-0.03)	0.224	-0.05 (-0.14-0.04)	0.259	-0.06 (-0.14-0.03)	0.198	-0.08 (-0.18-0.01)	0.090

*Abbreviations: BC, black carbon; CI, confidence interval; FVC, forced vital capacity; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All p-values < 0.05 = significant and marked bold. *BC per 1-μg/m³ increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m³ increase.*

Table S4. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FVC (liters) in the full (imputed) study population. Multivariable[2] mixed model regression analyses.

	0-18 years		0-10 years		10-18 years		Mean life exposure	
Exposure[1*]	Coef. (95% CI)	p[3]	Coef. (95% CI)	p[3]	Coef. (95% CI)	p[3]	Coef. (95% CI)	p[3]
NO_2	-0.00 (-0.10-0.10)	0.991	-0.00 (-0.09-0.09)	0.986	-0.00 (-0.11-0.10)	0.946	-0.01 (-0.12-0.11)	0.919
$PM_{2.5}$	-0.07 (-0.24-0.10)	0.420	-0.04 (-0.20-0.11)	0.579	-0.13 (-0.32-0.07)	0.201	-0.07 (-0.26-0.13)	0.493
PM_{10}	-0.07 (-0.25-0.12)	0.488	-0.03 (-0.20-0.13)	0.702	-0.15 (-0.38-0.07)	0.184	-0.05 (-0.26-0.17)	0.678
BC	0.08 (-0.16-0.31)	0.518	0.06 (-0.16-0.28)	0.617	0.10 (-0.14-0.34)	0.404	0.00 (-0.26-0.27)	0.971
O_3	-0.02 (-0.25-0.20)	0.857	-0.03 (-0.26-0.19)	0.775	-0.01 (-0.23-0.21)	0.955	-0.05 (-0.29-0.19)	0.688
NDVI (100m)	0.01 (-0.04-0.07)	0.696	0.00 (-0.05-0.06)	0.850	0.01 (-0.04-0.06)	0.628	-0.01 (-0.07-0.05)	0.797
NDVI (300m)	-0.00 (-0.07-0.06)	0.895	-0.00 (-0.07-0.06)	0.883	-0.01 (-0.07-0.05)	0.701	-0.02 (-0.09-0.05)	0.508
NDVI (500m)	-0.02 (-0.08-0.05)	0.622	-0.01 (-0.07-0.05)	0.702	-0.03 (-0.08-0.03)	0.362	-0.04 (-0.11-0.03)	0.250
NDVI (1000m)	-0.01 (-0.07-0.05)	0.676	-0.01 (-0.06-0.05)	0.801	-0.02 (-0.08-0.03)	0.386	-0.04 (-0.10-0.02)	0.199

Abbreviations: BC, black carbon; CI, confidence interval; FVC, forced vital capacity; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with

*the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for sex, age, 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. NO_2, PM exposures and O_3 per 10-μg/m³ increase.*

Table S5. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FEV1/FVC ratio in the full (imputed) study population. Univariable mixed model regression analyses.

	0-18 years		0-10 years		10-18 years		Mean life exposure	
Exposure[1*]	Coef. (95% CI)	p[2]	Coef. (95% CI)	p[2]	Coef. (95% CI)	p[2]	Coef. (95% CI)	p[2]
NO_2	**-0.01 (-0.02- -0.00)**	**0.011**	-0.01 (-0.01-0.00)	0.066	**-0.01 (-0.02- -0.01)**	**0.001**	**-0.01 (-0.02- -0.00)**	**0.049**
$PM_{2.5}$[3] (male)	**-0.02 (-0.04- -0.01)**	**0.007**	**-0.02 (-0.04- -0.00)**	**0.018**	**-0.03 (-0.05- -0.12)**	**0.001**	**-0.02 (-0.04- -0.00)**	**0.049**
$PM_{2.5}$[3] (female)	**-0.04 (-0.06- -0.01)**	**0.002**	**-0.03 (-0.06- -0.01)**	**0.005**	**-0.04 (-0.06- -0.02)**	**0.000**	-0.03 (-0.06-0.00)	0.078
PM_{10}[3] (male)	**-0.03 (-0.05- -0.01)**	**0.001**	**-0.03 (-0.04- -0.01)**	**0.002**	**-0.04 (-0.06- -0.02)**	**0.000**	**-0.03 (-0.05- -0.01)**	**0.015**
PM_{10}[3] (female)	**-0.04 (-0.06- -0.02)**	**0.000**	**-0.04 (-0.06- -0.01)**	**0.001**	**-0.04 (-0.06- -0.02)**	**0.000**	**-0.04 (-0.07- -0.00)**	**0.028**
BC[3] (male)	**-0.03 (-0.05- -0.01)**	**0.001**	Convergence not achieved	-	**-0.04 (-0.06- -0.02)**	**0.000**	**-0.02 (-0.05- -0.00)**	**0.030**
BC[3] (female)	-0.02 (-0.04-0.00)	0.106	-0.01 (-0.03-0.01)	0.379	**-0.03 (-0.05- -0.01)**	**0.011**	-0.01 (-0.04-0.02)	0.449
O_3	0.01 (-0.01-0.03)	0.234	0.01 (-0.01-0.03)	0.223	0.01 (-0.01-0.03)	0.289	0.01 (-0.01-0.03)	0.192
NDVI (100m)	-0.00 (-0.01-0.00)	0.070	-0.00 (-0.01-0.00)	0.324	**-0.00 (-0.01-0.00)**	**0.026**	-0.00 (-0.01-0.00)	0.321
NDVI (300m)	-0.00 (-0.01-0.00)	0.335	-0.00 (-0.01-0.00)	0.833	-0.00 (-0.01-0.00)	0.109	-0.00 (-0.01-0.00)	0.791
NDVI (500m)	-0.00 (-0.01-0.00)	0.648	-0.00 (-0.00-0.01)	0.817	-0.00 (-0.01-0.00)	0.326	0.00 (-0.01-0.01)	0.935
NDVI (1000m)	-0.00 (-0.01-0.00)	0.247	-0.00 (-0.01-0.00)	0.394	-0.00 (-0.01-0.00)	0.182	-0.00 (-0.01-0.00)	0.481

Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; FVC, forced vital capacity; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m.
*[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All p-values < 0.05 = significant and marked bold. [3] The models were stratified by sex. *BC per 1-μg/m³ increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m³ increase.*

Table S6. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FEV1/FVC ratio in the full (imputed) study population. Multivariable[2] mixed model regression analyses.

	0-18 years		0-10 years		10-18 years		Mean life exposure	
Exposure[1*]	Coef. (95% CI)	p[3]	Coef. (95% CI)	p[3]	Coef. (95% CI)	p[3]	Coef. (95% CI)	p[3]
NO_2	-0.01 (-0.01-0.00)	0.266	-0.00 (-0.01-0.00)	0.358	-0.01 (-0.01-0.00)	0.250	-0.00 (-0.01-0.01)	0.402
$PM_{2.5}$[4] (male)	-0.00 (-0.02-0.02)	0.851	-0.00 (-0.02-0.02)	0.825	-0.00 (-0.02-0.02)	0.932	-0.00 (-0.03-0.02)	0.746
$PM_{2.5}$[4] (female)	-0.00 (-0.02-0.01)	0.827	0.00 (-0.02-0.02)	0.931	0.01 (-0.02-0.03)	0.718	0.00 (-0.02-0.03)	0.893
PM_{10}[4] (male)	-0.01 (-0.03-0.02)	0.601	-0.01 (-0.03-0.01)	0.496	-0.00 (-0.03-0.03)	0.962	-0.01 (-0.03-0.02)	0.623
PM_{10}[4] (female)	0.01 (-0.01-0.03)	0.356	0.01 (-0.01-0.03)	0.556	0.02 (-0.01-0.05)	0.185	0.01 (-0.02-0.03)	0.568
BC[4] (male)	-0.02 (-0.05-0.01)	0.140	Convergence not achieved	-	-0.02 (-0.06-0.01)	0.109	-0.01 (-0.05-0.02)	0.483
BC[4] (female)	-0.00 (-0.03-0.03)	0.924	-0.00 (-0.03-0.02)	0.809	-0.00 (-0.03-0.02)	0.893	-0.00 (-0.03-0.03)	0.951
O_3	-0.00 (-0.02-0.02)	0.908	0.00 (-0.02-0.02)	0.879	-0.00 (-0.02-0.02)	0.695	-0.00 (-0.02-0.02)	0.955
NDVI (100m)	**-0.01 (-0.01-0.00)**	**0.010**	-0.00 (-0.01-0.00)	0.058	**-0.01 (-0.01- -0.00)**	**0.003**	**-0.01 (-0.01- -0.00)**	**0.019**
NDVI (300m)	-0.00 (-0.01-0.00)	0.175	-0.00 (-0.01-0.00)	0.471	-0.00 (-0.01-0.00)	0.052	-0.00 (-0.01-0.00)	0.158

NDVI (500m)	-0.00 (-0.01-0.00)	0.369	-0.00 (-0.01-0.00)	0.837	-0.00 (-0.01-0.00)	0.150	-0.00 (-0.01-0.00)	0.311
NDVI (1000m)	-0.00 (-0.01-0.00)	0.116	-0.00 (-0.01-0.00)	0.229	-0.00 (-0.01-0.00)	0.069	-0.00 (-0.01-0.00)	0.083

Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; FVC, forced vital capacity; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m. [1] *All air pollutants exposures were back-extrapolated in time with the ratio method.* [2] *All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for sex, age, parental education and asthma.* [3] *All p-values < 0.05 = significant and marked bold.*
[4] *The models were stratified by sex and adjusted for O_3, NDVI (300m), age, parental education and asthma.* [*] *BC per 1-μg/m^3 increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m^3 increase.*

Appendix E. Lung function analyses, % predicted.

Appendix E.

Univariable and multivariable analyses for lung function, % predicted

Table 1a. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FEV_1 (% predicted) in the full (imputed) study population. Univariable mixed model regression analyses.

Exposure[1*]	0-18 years Coef. (95% CI)	p[2]	0-10 years Coef. (95% CI)	p[2]	10-18 years Coef. (95% CI)	p[2]	Mean life exposure Coef. (95% CI)	p[2]
NO_2	-0.74 (-2.00-0.52)	0.248	-0.66 (-1.86-0.54)	0.280	-0.70 (-1.95-0.55)	0.274	-0.53 (-2.03-0.97)	0.486
$PM_{2.5}$	-2.17 (-4.68-0.34)	0.090	-2.00 (-4.37-0.36)	0.096	-1.92 (-4.51-0.68)	0.147	-2.94 (-6.15-0.27)	0.073
PM_{10}	-1.81 (-4.42-0.81)	0.175	-1.86 (-4.32-0.61)	0.140	-1.08 (-3.73-1.58)	0.426	-2.81 (-6.25-0.64)	0.110
BC	-0.39 (-3.08-2.29)	0.775	-0.16 (-2.62-2.31)	0.902	-0.47 (-3.16-2.23)	0.734	-0.60 (-4.00-2.80)	0.729
O_3	-0.79 (-3.66-2.09)	0.591	-0.77 (-3.69-2.14)	0.605	-0.72 (-3.42-1.98)	0.600	-2.01 (-5.12-1.09)	0.204
NDVI (300m)	-0.40 (-1.38-0.58)	0.421	-0.08 (-1.02-0.86)	0.867	-0.70 (-1.63-0.22)	0.135	-0.87 (-1.93-0.18)	0.105

Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All p-values < 0.05 = significant and marked bold. [*]BC per 1-μg/m³ increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m³ increase.

Table 1b. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FEV_1 (% predicted) in the full (imputed) study population. Multivariable mixed model regression analyses.

Exposure[1*]	0-18 years Coef. (95% CI)	p[3]	0-10 years Coef. (95% CI)	p[3]	10-18 years Coef. (95% CI)	p[3]	Mean life exposure Coef. (95% CI)	p[3]
NO_2	**-1.89 (-3.621- -0.16)**	**0.032**	-1.46 (-3.07-0.15)	0.075	**-2.25 (-4.09-0.42)**	**0.016**	**-2.07 (-4.05- -0.09)**	**0.041**
$PM_{2.5}$	**-3.40 (-6.29- -0.50)**	**0.021**	**-2.81 (-5.45- -0.17)**	**0.037**	**-4.17 (-7.52- -0.83)**	**0.014**	**-3.72 (-7.10- -0.35)**	**0.031**
PM_{10}	**-3.28 (-6.51- -0.06)**	**0.046**	-2.74 (-5.60-0.13)	0.061	-3.74 (-7.66-0.18)	0.062	-3.46 (-7.16-0.25)	0.067
BC	-2.32 (-6.37-1.73)	0.261	-1.70 (-5.54-2.14)	0.385	-2.58 (-6.68-1.51)	0.217	-3.38 (-7.95-1.20)	0.148
O_3	-3.06 (-6.95-0.83)	0.123	-2.95 (-6.83-0.93)	0.137	-3.15 (-6.96-0.65)	0.104	-3.76 (-7.91-0.39)	0.076
NDVI (300m)	-0.56 (-1.65-0.53)	0.312	-0.22 (-1.27-0.85)	0.694	-0.84 (-1.84-0.15)	0.097	-0.85 (-2.03-0.32)	0.155

Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for sex, age, 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. NO_2, PM exposures and O_3 per 10-μg/m³ increase.

Table 2a. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FVC (% predicted) in the full (imputed) study population. Univariable mixed model regression analyses.

Exposure[1*]	0-18 years Coef. (95% CI)	p[2]	0-10 years Coef. (95% CI)	p[2]	10-18 years Coef. (95% CI)	p[2]	Mean life exposure Coef. (95% CI)	p[2]
NO_2	-0.26 (-1.47-0.96)	0.680	-0.21 (-1.36-0.95)	0.725	-0.22 (-1.43-0.98)	0.715	-0.11 (-1.55-1.33)	0.880
$PM_{2.5}$	-1.42 (-3.84-1.01)	0.252	-1.30 (-3.57-0.97)	0.262	-0.99 (-3.48-1.51)	0.438	-2.26 (-5.36-0.83)	0.153
PM_{10}	-0.97 (-3.49-1.54)	0.452	-0.99 (-3.36-1.39)	0.415	-0.19 (-2.75-2.37)	0.884	-2.12 (-5.45-1.20)	0.210
BC (male)[3]	**3.64 (0.12-7.15)**	**0.043**	**3.41 (0.14-6.68)**	**0.041**	3.45 (-0.10-6.99)	0.057	**5.30 (-0.76-9.84)**	**0.022**
BC (female)[3]	-2.08 (-5.76-1.59)	0.266	-1.47 (-4.83-1.88)	0.389	-1.81 (-5.50-1.87)	0.334	-4.25 (-8.83-0.33)	0.069
O_3	-1.08 (-3.84-1.68)	0.443	-1.26 (-4.05-1.54)	0.377	-0.80 (-3.38-1.79)	0.547	-2.19 (-5.17-0.81)	0.152
NDVI (300m)	-0.13 (-1.07-0.82)	0.790	-0.01 (-0.92-0.89)	0.980	-0.25 (-1.14-0.64)	0.579	-0.63 (-1.65-0.39)	0.227

Abbreviations: BC, black carbon; CI, confidence interval; FVC, forced vital capacity; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All p-values < 0.05 = significant and marked bold. [3] The BC-models were stratified by sex. [*]BC per 1-μg/m³ increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m³ increase.

Table 2b. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FVC (% predicted) in the full (imputed) study population. Multivariable mixed model regression analyses.

Exposure[1*]	0-18 years Coef. (95% CI)	p[3]	0-10 years Coef. (95% CI)	p[3]	10-18 years Coef. (95% CI)	p[3]	Mean life exposure Coef. (95% CI)	p[3]
NO_2	-1.41 (-3.08-0.26)	0.097	-1.08 (-2.63-0.47)	0.172	-1.74 (-3.51-0.03)	0.054	1.63 (-3.55-0.28)	0.095
$PM_{2.5}$	**-3.44 (-6.22- -0.645)**	**0.016**	**-2.78 (-5.32- -0.24)**	**0.032**	**-4.34 (-7.55- -1.13)**	**0.008**	**-3.59 (-6.86- -0.33)**	**0.031**
PM_{10}	**-3.59 (-6.69- -0.49)**	**0.023**	**-2.77 (-5.520- -0.01)**	**0.049**	**-4.66 (-8.43- -0.89)**	**0.015**	**-3.61 (-7.19- -0.04)**	**0.047**
BC (male)[4]	1.82 (-4.01-7.65)	0.541	2.53 (-2.93-7.98)	0.364	1.08 (-4.88-7.03)	0.723	1.68 (-4.91-8.27)	0.617
BC (female)[4]	-2.28 (-7.59-3.03)	0.400	-1.82 (-6.92-3.29)	0.485	Convergence not achieved	-	-4.84 (-10.84-1.16)	0.114
O_3	-3.02 (-6.77-0.73)	0.114	-3.12 (-6.86-0.61)	0.101	-2.87 (-6.53-0.80)	0.125	-3.79 (-7.80-0.22)	0.064
NDVI (300m)	-0.22 (-1.27-0.83)	0.682	-0.05 (-1.07-0.97)	0.919	-0.36 (-1.32-0.60)	0.465	-0.45 (-1.58-0.69)	0.440

Abbreviations: BC, black carbon; CI, confidence interval; FVC, forced vital capacity; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for sex, age, parental education and parental asthma. [3] All p-values < 0.05 = significant and marked bold. [4] The BC-models were stratified by sex and adjusted for O_3, NDVI (300m), age, parental education and asthma. [*]BC per 1-μg/m³ increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m³ increase.

Table 3a. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FEV1/FVC ratio in the full (imputed) study population. Univariable mixed model regression analyses.

Exposure[1*]	0-18 years Coef. (95% CI)	p[2]	0-10 years Coef. (95% CI)	p[2]	10-18 years Coef. (95% CI)	p[2]	Mean life exposure Coef. (95% CI)	p[2]
NO_2	-0.45 (-1.18-0.28)	0.223	-0.45 (-1.14-0.25)	0.209	-0.41 (-1.13-0.32)	0.273	-0.32 (-1.25-0.49)	0.390
$PM_{2.5}$	-0.59 (-2.04-0.86)	0.428	-0.59 (-1.96-0.77)	0.395	-0.66 (-2.15-0.84)	0.391	-0.58 (-2.44-1.27)	0.538
PM_{10}	-0.59 (-2.10-0.92)	0.442	-0.70 (-2.12-0.72)	0.336	-0.52 (-2.05-1.01)	0.508	-0.52 (-2.51-1.47)	0.606

BC	-1.35 (-3.03-0.33)	0.115	-1.39 (-2.95-0.17)	0.081	-1.25 (-2.88-0.39)	0.134	-0.69 (-2.66-1.28)	0.490
O_3	0.33 (-1.33-2.00)	0.695	0.67 (-1.13-2.46)	0.465	0.07 (-1.49-1.64)	0.927	0.18 (-1.62-1.97)	0.849
NDVI (300m)	-0.37 (-0.94-0.21)	0.211	-0.13 (-0.68-0.42)	0.646	**-0.55 (-1.08- -0.01)**	**0.046**	-0.37 (-0.98-0.25)	0.240

Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; FVC, forced vital capacity; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All p-values < 0.05 = significant and marked bold. [*]BC per 1-μg/m^3 increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m^3 increase.

Table 3b. Associations of air pollution and greenness in different time windows (0-18 years, 0-10 years, 10-18 years, mean life exposure) with FEV1/FVC ratio in the full (imputed) study population. Multivariable mixed model regression analyses.

	0-18 years		0-10 years		10-18 years		Mean life exposure	
Exposure[1*]	Coef. (95% CI)	p[3]	Coef. (95% CI)	p[3]	Coef. (95% CI)	p[3]	Coef. (95% CI)	p[3]
NO_2	-0.53 (-1.52-0.47)	0.299	-0.43 (-1.35-0.50)	0.366	-0.54 (-1.59-0.51)	0.311	-0.47 (-1.61-0.67)	0.418
$PM_{2.5}$	-0.05 (-1.72-1.62)	0.952	-0.07 (-1.66-1.51)	0.927	0.10 (-1.81-2.02)	0.918	-0.22 (-2.17-1.72)	0.821
PM_{10}	0.22 (-1.65-2.09)	0.819	Convergence not achieved	-	0.85 (-1.39-3.10)	0.457	0.04 (-2.08-2.17)	0.968
BC	-1.44 (-3.95-1.07)	0.262	-1.46 (-3.82-0.89)	0.224	-1.35 (-3.87-1.16)	0.292	-0.66 (-3.28-1.97)	0.623
O_3	-0.02 (-2.25-2.20)	0.983	0.21 (-2.04-2.45)	0.856	-0.27 (-2.44-1.90)	0.806	0.03 (-2.35-2.42)	0.978
NDVI (300m)	-0.44 (-1.07-0.19)	0.174	-0.23 (-0.84-0.39)	0.470	**-0.58 (-1.15- -0.00)**	**0.049**	-0.50 (-1.18-0.18)	0.149

Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; FVC, forced vital capacity; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.[1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for sex, age, parental education and asthma. [3] All p-values < 0.05 = significant and marked bold. [*]BC per 1-μg/m^3 increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m^3 increase.

10. Papers I-III

I

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RESEARCH ARTICLE Open Access

Agreement in reporting of asthma by parents or offspring – the RHINESSA generation study

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Abstract

Background: Self-report questionnaires are commonly used in epidemiology, but may be susceptible to misclassification, especially if answers are given on behalf of others, e.g. children or parents. The aim was to determine agreement and analyse predictors of disagreement in parents' reports of offspring asthma, and in offspring reports of parents' asthma.

Methods: In the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) generation study, 6752 offspring (age range 18–51 years) and their parents (age range 39–66 years) reported their own and each other's asthma status. Agreement between asthma reports from offspring and parents was determined by calculating sensitivity, specificity, positive and negative predictive value and Cohen's kappa. The participants' own answers regarding themselves were defined as the gold standard. To investigate predictors for disagreement logistic regression analyses were performed to obtain odds ratios (OR) with 95% confidence intervals (CI) for sex, smoking status, education, comorbidity and severity of asthma.

Results: Agreement was good for parental report of offspring early onset asthma (< 10 years, Cohen's kappa 0.72) and moderate for offspring later onset asthma (Cohen's kappa 0.46). Specificity was 0.99 for both, and sensitivity was 0.68 and 0.36, respectively. For offspring report of maternal and paternal asthma the agreement was good (Cohen's kappa 0.69 and 0.68), specificity was 0.96 and 0.97, and sensitivity was 0.72 and 0.68, respectively. The positive predictive value (PPV) was lowest for offspring report of maternal asthma (0.75), and highest for parents' report of early onset asthma in the offspring (0.83). The negative predictive value (NPV) was high for all four groups (0.94–0.97). In multivariate analyses current smokers (OR = 1.46 [95% CI 1.05, 2.02]) and fathers (OR = 1.31 [95% CI 1.08, 1.59]) were more likely to report offspring asthma incorrectly. Offspring wheeze was associated with reporting parental asthma incorrectly (OR = 1.60 [95% CI 1.21, 2.11]), both under- and over reporting.

Conclusions: Asthma reports across generations show moderate to good agreement, making information from other generations a useful tool in the absence of direct reports.

Keywords: Agreement, Validation, Asthma, Questionnaire, Self-report, Transgenerational

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Background

Asthma is the most common non-communicable disease among children and one of the most prevalent chronic diseases worldwide [1, 2]. The World Health Organization [3] estimated in 2011 that 235 million people suffer from asthma, but later studies have indicated numbers as high as 300 million and projected that the worldwide prevalence will increase to 400 million by 2025 [4].

The investigation of asthma is complex. Questionnaires are often preferred in epidemiological studies to determine disease occurrence because they are cost-efficient and simple to perform compared to clinical examination. Questionnaire data on the prevalence of asthma have been used for epidemiological research since the mid 1960s. In 1995 the International Study of Asthma and Allergies in Childhood [5] developed a standardized questionnaire to improve the investigation of asthma in an epidemiological setting [5–7]. Even though clinical examination has been regarded as the gold standard for assessing asthma, recent studies show that questionnaires are a useful epidemiological tool, being reasonably valid [8–10].

Nevertheless, self-reported information is susceptible to misclassification such as recall bias, and it may be particularly susceptible to misclassification if participants are asked to provide information on behalf of others, for example their children or their parents [11, 12]. At the same time, in absence of direct reports, asthma reports on behalf of family members can be highly valuable in a clinical setting if the patient cannot report on behalf of himself/herself or in absence of prior patient history. However, validity of such intergenerational reports with regard to asthma has been poorly investigated, mostly focusing on current asthma status asked at the same time, and only including young children and adolescents [13, 14]. With an increasing interest in intergenerational risk factors [15–19] more attention should be given to validate this kind of information across generations.

The Respiratory Health in Northern Europe, Spain and Australia generation study (RHINESSA) uses questionnaires, interviews, and clinical examinations to study asthma and lung health throughout the lifespan and across generations. Participants are asked to provide information about themselves as well as their children and parents. To underpin the research of RHINESSA and to shed light on this important part of epidemiological methodology, the aim of the present paper was to assess agreement between parental report of offspring asthma as compared to offspring's own report, to assess agreement between offspring's report of parent's asthma as compared to parents' own report, and to investigate predictors for discrepant answers.

Methods

Study design and population

This agreement study compares questionnaires about asthma from two generations. The primary sources of data are parents from the Respiratory Health in Northern Europe study (RHINE, www.rhine.nu) and the European Community Respiratory Health Survey (ECRHS, www.ecrhs.org) and their offspring included in the RHINESSA study (www.rhinessa.net). The parent and offspring pairs provided information on asthma status regarding both themselves and each other.

Parent population

RHINE is a prospective questionnaire-based cohort study comprising subjects from seven Northern European centres: Reykjavik (Iceland), Bergen (Norway), Umea, Uppsala and Gothenburg (Sweden), Aarhus (Denmark) and Tartu (Estonia). All subjects participated in stage 1 of the ECRHS I in 1990, together with many other centres, among others Melbourne (Australia) and Huelva and Albacete (Spain) [20, 21]. Both ECRHS and RHINE had follow-ups after 10 and 20 years, and have investigated incidence, prevalence and risk factors for respiratory diseases, allergies and symptoms related to asthma and chronic obstructive pulmonary disease (COPD) throughout this time period. Response rate in RHINE III was 61%. The ECRHS subjects from the Spanish and Australian study centres filled in the ECRHS stage 3 screening questionnaire; which includes identical questions as in RHINE III for all characteristics needed in the present study.

Offspring population

In the period 2013–2015 questionnaires were sent to all adult offspring (> 18 years) of parents from the RHINE centres and the Spanish and Australian ECRHS centres, and a sub-sample was invited for clinical examination. The questionnaires were web-based in all centres except Sweden where they used postal questionnaires. Overall response rate was 33.5%, varying across centres from 18.6% in Tartu to 73.7% in Melbourne (See Additional file 1: Table S1).

Predictors and outcomes

The main outcome in this agreement study was physician diagnosed asthma self-reported by the participants. Reports of one's own asthma were "doctors-diagnosed asthma" while reports of asthma in others were "ever asthma". In more detail, the asthma outcomes were built on the following wordings:

> Parents reported doctor-diagnosed asthma about themselves by answering yes to the questions "Do you

have or have you ever had asthma?" and "Has it been confirmed by a medical doctor?"

Parents reported asthma about their offspring by answering yes to the questions "For each child, please tick yes if they had asthma before 10 years" and/or "For each child, please tick yes if they had asthma after 10 years". The former was classified as early onset asthma in the offspring, while the latter was classified as late onset asthma.

Offspring reported doctor-diagnosed asthma about themselves by answering yes to the questions "Do you have or have you ever had asthma?" and "Has it been confirmed by a medical doctor?"

Offspring were also asked how old they were when they first experienced asthma symptoms.

Offspring reported asthma about their parents defined by answering yes to the questions "Did your mother ever suffer from asthma?" and "Did your father ever suffer from asthma?". Questionnaires are available from www.rhinessa.net.

A discrepant asthma report by parents was defined as parents reporting absence of asthma in their offspring when the offspring report presence of asthma, or parents reporting presence of asthma in their offspring when the offspring state they do not have asthma. In the same manner, a discrepant asthma report by offspring was defined as offspring reporting absence of asthma in their parents when the parents report presence of asthma, or offspring reporting presence of asthma in their parents when the parents themselves state they do not have asthma.

Predictors for discrepant reports between parent and offspring pairs were investigated for the following covariates in each generation: smoking status (never-, ex- or current smoker), education (primary school, secondary school or college/university), respiratory symptoms (wheeze, wheeze with shortness of breath, awoken with tightness in chest, awoken with attack of cough in the past 12 months and currently taking medication) and comorbidities (hypertension, stroke, ischemic heart disease, diabetes mellitus, COPD and serious respiratory infections before the age of 5 years).

Statistical analyses

All analyses were performed using Stata version 14.0.

The overall agreement between asthma reports from offspring and parents was calculated by Cohen's kappa. The following interpretation categories were used: poor agreement, < 0.2; fair, 0.21–0.40; moderate, 0.41–0.60; good, 0.61–0.80; and very good, 0.81–1.00 [22]. Sensitivity, specificity and predictive values were calculated using the participants' own answers regarding themselves as the golden standard. Descriptive analyses and estimations of Cohen's kappa, sensitivity, specificity and predictive values were performed stratified by sex to investigate any specific differences between mothers and fathers, and between daughters and sons.

We performed univariate logistic regressions with each covariate as predictor and discrepant report (yes/no) in parent-offspring pairs as outcome. The participants' own answers regarding themselves were considered the gold standard also in these analyses. Significant predictors ($p < 0.05$) from the univariate analyses were carried forward to multivariate logistic regression. Separate models were constructed for discrepant reports by parents and discrepant reports by offspring. In addition, the multivariate analyses were adjusted for study centre and sibling status (siblings in RHINESSA/no siblings in RHINESSA).

Ethical approval

In all study centres written informed consent was obtained from each participant, and the study was approved by regional committees of medical research ethics in each study centre according to national legislations.

Results

Reports of 6752 offspring and their parents who had answered questions regarding their own and each other's asthma status were included from the ten study centres. Table 1 shows the characteristics of the study population by parents and offspring. A slight majority of the population was female. The mean age for the mothers and fathers were 54.0 (±6.5) and 54.7 (±6.1) respectively. More mothers than fathers and more daughters than sons reported having asthma. For the offspring, mean age was 30 years and did not differ significantly between males and females. More mothers than fathers and more daughters than sons had obtained university education. Slightly more mothers than fathers were current smokers, whereas in offspring more sons than daughters smoked. The reports of respiratory symptoms were comparable across gender for the parents, but in the offspring, all respiratory symptoms, except the symptoms awoken with attack of breathlessness and wheeze with shortness of breath, were significantly higher for the daughters (Table 1).

Figure 1 summarizes offspring early/late onset asthma and the corresponding parent report (Fig. 1a and b), as well as paternal and maternal asthma and the corresponding offspring report (Fig. 1c and d). The vast majority of parents answered correctly concerning their offspring's asthma status: in 4798 (90%) of the reports on early onset asthma, both parents and offspring

Table 1 Study population characteristics, 5907 parents and 6752 offspring included in the RHINESSA generation study

Characteristics	Parents (RHINE/ECRHS)			Children (RHINESSA)		
	Mother	Father	P[a]	Daughter	Son	P[a]
	N (%)	N (%)		N (%)	N (%)	
N (%)	3377 (57)	2530 (43)		3910 (58)	2842 (42)	
Albacete	39 (57)	30 (43)		39 (53)	34 (47)	
Bergen	593 (53)	518 (47)		706 (60)	480 (40)	
Gothenburg	413 (56)	322 (44)		491 (53)	439 (47)	
Huelva	42 (69)	19 (31)		44 (64)	25 (36)	
Melbourne	96 (55)	80 (45)		42 (62)	26 (38)	
Reykjavik	409 (55)	328 (45)		543 (61)	342 (39)	
Tartu	205 (68)	97 (32)		177 (60)	119 (40)	
Umea	629 (60)	423 (40)		735 (57)	545 (43)	
Uppsala	602 (59)	420 (41)		713 (56)	556 (44)	
Aarhus	349 (54)	293 (46)		420 (60)	276 (40)	
Mean age (SD)	54.0 (6.5)	54.7 (6.1)	**< 0.001**	30.3 (7.7)	30.4 (7.8)	0.930
Asthma (%)	478 (14)	292 (12)	**0.004**	671 (17)	420 (15)	**0.008**
Smoking			**0.009**			**< 0.001**
Never-smokers	1496 (46)	1155 (47)		2602 (67)	1942 (69)	
Ex-smokers	1400 (43)	1100 (45)		850 (22)	503 (18)	
Current smokers	337 (10)	197 (8)		445 (11)	382 (14)	
Education			**< 0.001**			**< 0.001**
Primary school	385 (12)	296 (12)		97 (3)	91 (3)	
Secondary school	1224 (38)	1029 (44)		1282 (33)	1259 (44)	
College/university	1576 (50)	1068 (45)		2521 (65)	1487 (52)	
Parental asthma			0.058			**< 0.001**
Mother	295 (10)	206 (9)		476 (12)	272 (10)	
Father	218 (7)	124 (6)		309 (8)	179 (6)	
No one	2518 (83)	1922 (85)		3038 (79)	2333 (83)	
Both	12 (0.4)	12 (0.5)		39 (2)	23 (1)	
Other diseases[b]						
Comorbidity	892 (26)	778 (31)	**< 0.001**	165 (4)	124 (4)	0.770
Hypertension	778 (23)	659 (26)	**0.005**	120 (3)	96 (4)	0.390
Stroke	54 (2)	46 (2)	0.510	–	–	–
Ischemic heart disease	64 (2)	116 (5)	**< 0.001**	5 (0.1)	8 (0.3)	0.150
Diabetes mellitus	106 (3)	107 (5)	**0.027**	53 (1)	30 (1)	0.270
COPD	73 (2)	60 (2)	0.600	10 (0.3)	5 (0.2)	0.490
Serious childhood infection < 5 years	254 (8)	126 (5)	**< 0.001**	331 (9)	185 (7)	**< 0.001**
Respiratory symptoms			0.246			**0.001**
Wheeze[c]	669 (20)	530 (21)	0.330	697 (18)	468 (17)	0.150
Wheeze with shortness of breath[c]	421 (13)	297 (12)	0.380	457 (62)	256 (49)	**< 0.001**
Awoken with tightness in chest[c]	364 (11)	245 (10)	0.170	497 (13)	286 (10)	**< 0.001**
Awoken with attack of breathlessness[c]	220 (7)	126 (5)	**0.013**	173 (4)	136 (5)	0.48
Awoken with attack of cough[c]	1093 (33)	533 (21)	**< 0.001**	1343 (34	562 (20)	**< 0.001**
Currently taking asthma medication	327 (10)	216 (9)	0.130	383 (10)	212 (8)	**< 0.001**

[a]All *p*-values < 0.05 = significant and are marked bold. *P*-values are estimated from two-group mean comparison test (unpaired t-test) for continuous values and chi-squared test for categorical values

[b]Comorbidity includes the variables: hypertension, stroke, ischemic heart disease, diabetes mellitus, COPD, serious childhood infection < 5 years. Questions about stroke and COPD were not included in the offspring-questionnaires

[c]In the past 12 months

answered "no" and 323 (6%) "yes" to the presence of asthma in the offspring. The reports about late onset asthma followed the same pattern: in 4816 (90%) reports both parents and offspring answered "no asthma" in the offspring, and both parts reported late onset asthma in the offspring among 185 (3%). Parents' discrepant answers were most often that they reported no asthma for asthmatic offspring rather than reporting asthma for non-asthmatic offspring (Fig. 1a and b).

In 86% of the cases, both offspring and fathers reported absence of paternal asthma, compared to 83% for maternal asthma status. In 8% of the reports, offspring and fathers both reported a present asthma diagnosis; the corresponding frequency for maternal asthma was 10%. It was also more common for offspring to report no asthma in asthmatic parents than to report asthma in non-asthmatic parents.

The specificity was high for all four groups (Table 2), while sensitivity was lower. The sensitivity was lowest for the late onset asthma in the offspring (0.36), and highest for the maternal asthma (0.72). The positive predictive value (PPV) was lowest for the maternal asthma (0.75), and highest for the early onset asthma in the offspring (0.83). The negative predictive value (NPV) was high for all four groups (0.94–0.97).

Agreement between the parental reports and early onset asthma in offspring was good (Cohen's kappa 0.72), and moderate for late onset asthma in offspring (Cohen's kappa 0.46). The agreement between offspring reports and maternal and paternal asthma were both good (Cohen's kappa 0.69 and 0.68, respectively). Additional analyses stratified by study centres are given in the additional file (See Additional file 1: Table S2) and show some variability between the centres. To investigate if offspring reports of parental asthma differed in agreement with the parental reports according to age of asthma onset in parents, we performed an additional analysis (See Additional file 1: Table S3) stratifying by the timing of parental asthma onset. This analysis showed that offspring reported asthma in their parents more correctly if the parents had their asthma before the children were 20 years old, than if the parents got their asthma diagnosis after their offspring were 20 years old.

Table 3 shows univariate and multivariate logistic regression analyses of the association between covariates and offspring/parent discrepant asthma reports. In the univariate analyses regarding parent-reported offspring asthma, several parental factors were associated with reporting incorrect: male gender, current smoker, ex-smoker, ischemic heart disease, diabetes, COPD, wheeze and wheeze with shortness of breath. In the univariate analyses regarding the offspring-reported parental asthma, the following factors on the offspring level were associated with

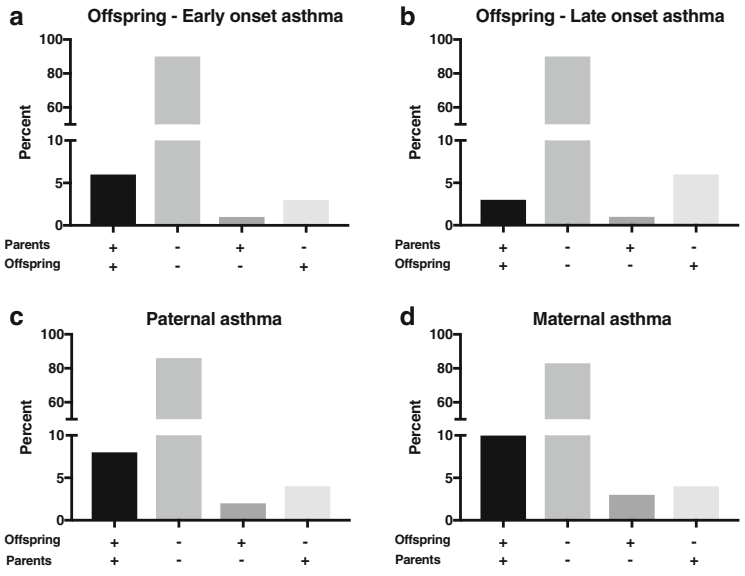

Fig. 1 Parent-reported offspring asthma as compared to offspring's own report (**a**, **b**); and offspring-reported paternal (**c**) and maternal (**d**) asthma as compared to parents' own report

Table 2 Parameter estimates (95% CI) for Cohen's kappa, sensitivity, specificity, PPV and NPV for offspring-reported parental asthma and parent-reported offspring asthma

Offspring asthma	Agreement[a] N (%)	Disagreement[b] N (%)	Cohens kappa	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI
Early onset asthma	5121 (96)	219 (4)	0.72	0.68	0.64, 0.72	0.99	0.98, 0.99	0.83	0.79, 0.86	0.97	0.96, 0.97
Mother	2935 (96)	110 (4)	0.75	0.72	0.66, 0.77	0.99	0.98, 0.99	0.83	0.77, 0.88	0.98	0.97, 0.98
Father	2186 (95)	109 (5)	0.69	0.64	0.57, 0.70	0.99	0.98, 0.99	0.83	0.76, 0.88	0.96	0.95, 0.97
Late onset asthma	5001 (93)	376 (7)	0.46	0.36	0.32, 0.41	0.99	0.98, 0.99	0.79	0.73, 0.84	0.94	0.93, 0.94
Mother	2891 (94)	199 (6)	0.53	0.43	0.37, 0.49	0.99	0.98, 0.99	0.82	0.75, 0.88	0.94	0.93, 0.95
Father	2110 (92)	177 (8)	0.36	0.26	0.21, 0.33	0.99	0.98, 0.99	0.73	0.61, 0.82	0.93	0.92, 0.94
Parental asthma											
Maternal	3477 (93)	276 (7)	0.69	0.72	0.68, 0.75	0.96	0.95, 0.97	0.75	0.71, 0.79	0.95	0.95, 0–96
Daughter	2009 (92)	163 (8)	0.69	0.75	0.69, 0.79	0.95	0.94, 0.96	0.71	0.66, 0.76	0.96	0.95, 0.97
Son	1468 (93)	113 (7)	0.70	0.68	0.61, 0.74	0.97	0.96, 0.98	0.81	0.75, 0.86	0.95	0.93, 0.96
Paternal	2817 (94)	182 (6)	0.68	0.68	0.63, 0.73	0.97	0.96, 0.98	0.76	0.71, 0.80	0.96	0.95, 0.97
Daughter	1637 (94)	101 (6)	0.71	0.72	0.65, 0.78	0.97	0.96, 0.98	0.77	0.70, 0.83	0.96	0.95, 0.97
Son	1180 (94)	81 (6)	0.64	0.63	0.54, 0.71	0.97	0.96, 0.98	0.74	0.65, 0.82	0.96	0.94, 0.97

[a]Agreement: when both parents and offspring answered the same (yes/yes or no/no)
[b]Disagreement: when parents and offspring answered differently (yes/no or no/yes)

reporting incorrectly: ex-smoker, wheeze, currently taking asthma medication and late onset of own asthma.

The statistically significant predictors from the univariate analyses were included in the multivariate logistic regression. After adjustment, the only predictors associated with reporting incorrectly for the parent-reported offspring asthma were gender (OR 1.31 for fathers versus mothers, 95% CI 1.08–1.59) and current smoker (OR 1.46, 1.05–2.02). For the offspring-reported parental asthma, only wheeze was associated with reporting incorrectly in the multivariate model (OR 1.60, 1.21–2.11). No factors were associated with reporting correctly for either the parent-reported offspring asthma or the offspring-reported parental asthma.

Further inspection of the discrepant answers given by offspring with wheeze, showed that they reported both asthma in non-asthmatic parents as well as *no* asthma in asthmatic parents slightly more often than offspring with no wheeze (Table 4). Fathers and smoking parents, on the other hand, (See Additional file 1: Table S4) showed that fathers and current smokers were more likely to report *no* asthma in asthmatic offspring than the mothers and never-smokers were. With regard to reporting asthma in non-asthmatic offspring, however, the fathers and current smokers were as correct as the mothers and never-smokers.

Discussion

In this study, agreement between self-reported asthma and asthma reported by family-members were moderate to good. The specificity was high in both offspring reports of parental asthma and parent reports of offspring asthma, suggesting a high fraction of non-asthmatics correctly identified as such by their relatives. Conversely, the sensitivity was lower for all groups, especially for the late onset asthma in the offspring i.e. a lower fraction of those with asthma after 10 years of age are correctly identified as asthmatics by their parents. The same trend was observed for the offspring; a lower fraction of asthmatic parents are correctly identified as asthmatics, while a higher fraction of the non-asthmatic parents are correctly identified. Overall, however, the vast majority of parents and offspring were in accordance with each other when reporting each other's asthma status. In multivariate analyses, never smokers and mothers were more likely to report offspring asthma correctly. In offspring, wheeze was associated with incorrect reports of parental asthma status.

Our results showed that parents seem to have more knowledge about the asthma status of their offspring than the offspring have about their parents' asthma condition. This may be reasonable if we assume that parents are in general more concerned with their children's health than the children are with their parents' health. In addition, the offspring's awareness of the respiratory health of their parents likely depends on the severity of the parents' asthma. Where asthma in the past was a disease with severe exacerbations, it is today a disease mostly without hospital admissions, indicating that parental asthma may be "invisible" for the offspring.

To our knowledge this is the first agreement study comparing generational reports on each other's adult asthma status in general. Previous studies have only addressed parent-reports of current offspring asthma

Table 3 Odds ratios for discrepant answers in offspring/parent asthma reports, univariate and multivariate logistic regression analysis

Predictor	Univariate analyses Parents		Multivariate analyses[a] Parents		Univariate analyses Offspring		Multivariate analyses[a] Offspring	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Male gender	1.33 (1.11, 1.60)	**0.002**	1.31 (1.08, 1.59)	**0.007**	1.01 (0.84, 1.23)	0.905		
Age	1.00 (0.99, 1.02)	0.630			1.01 (1.00, 1.02)	0.058		
Smoking								
Never smoker	1.00		1.00		1.00			
Current smoker	1.51 (1.11, 2.05)	**0.009**	1.46 (1.05, 2.02)	**0.023**	1.14 (0.85, 1.52)	0.392		
Ex-smoker	1.28 (1.05, 1.56)	**0.013**	1.22 (0.99, 1.50)	0.062	1.31 (1.04, 1.64)	**0.021**	1.22 (0.95, 1.55)	0.114
Education								
College/university	1.00				1.00			
Primary school	1.25 (0.94, 1.66)	0.127			1.59 (0.97, 2.59)	0.065		
Secondary school	1.04 (0.86, 1.28)	0.641			1.03 (0.85, 1.26)	0.756		
Comorbidity								
Hypertension	0.93 (0.75, 1.15)	0.505			1.42 (0.89, 2.28)	0.140		
Stroke	1.03 (0.52, 2.06)	0.930			–	–		
Ischemic heart	1.88 (1.23, 2.86)	**0.003**	1.54 (0.96, 2.46)	0.071	–	–		
Diabetes	1.64 (1.09, 2.46)	**0.018**	1.46 (0.96, 2.24)	0.077	1.07 (0.47, 2.48)	0.868		
COPD	1.75 (1.07, 2.87)	**0.026**	1.49 (0.89, 2.50)	0.129	–	–		
Serious childhood infection < 5 years	1.12 (0.99, 1.27)	0.080			1.11 (0.98, 1.25)	0.106		
Respiratory symptoms								
Wheeze	1.32 (1.07, 1.63)	**0.010**	1.02 (0.72, 1.46)	0.902	1.58 (1.26, 1.97)	**< 0.001**	1.60 (1.21, 2.11)	**0.001**
Wheeze with shortness of breath	1.47 (1.15, 1.89)	**0.002**	1.22 (0.81, 1.84)	0.343	1.37 (0.92, 2.04)	0.127		
Awoken with tightness in chest	1.01 (0.76, 1.36)	0.924			1.16 (0.87, 1.53)	0.313		
Awoken with attack of breathlessness	1.26 (0.89, 1.80)	0.193			1.11 (0.72, 1.72)	0.634		
Awoken with attack of cough	1.28 (1.05, 1.55)	**0.013**	1.25 (1.00, 1.57)	**0.046**	0.94 (0.76, 1.16)	0.557		
Currently taking asthma medication	1.32 (1.00, 1.76)	0.058			1.42 (1.06, 1.91)	**0.020**	0.95 (0.60, 1.49)	0.823
Age of onset								
Early onset	–	–			1.12 (0.78, 1.62)	0.528		
Late onset	–	–			1.76 (1.32, 2.34)	**< 0.001**	1.45 (1.01, 2.07)	**0.042**

[a]Adjusted for all predictors that were significant in the univariate analyses as well as for study centre and sibling status

and not vice versa, and the children have been young [1, 23–25]. The observed high validity in parent-reported offspring asthma is in accordance with for instance a study by Cornish et al. [26] comparing parent-reported asthma to electronic patient records. That parent-reports of children's asthma has high specificity although not so high sensitivity has also been observed in a relatively recent Canadian study [24]. High validity in parent reports of offspring atopic disease status has also been reported [27].

Cohen's kappa and sensitivity were both lower for late onset asthma compared to early onset asthma, which may be explained by the fact that parents are more aware of their offspring's health while they are young and still living at home. The impact on the parents and their ability to recall may be less when an offspring is diagnosed with asthma as a grownup. This is rendered particularly likely with a disease such as asthma, which is not continuously visible, but comes in attacks of various intervals – sometimes with a substantial amount of time between each attack.

In the same manner, it is likely to suspect offspring reporting their parents' asthma more correctly if they witnessed asthma in the parents during childhood when they saw their parents on a daily basis, then if the parents developed asthma after the offspring had grown up and left home. This suspicion was confirmed in the additional analysis (See Additional file 1: Table S3), where we analysed separately offspring-reported parental asthma with onset *after* the offspring was 20 years old, and with onset *before* the offspring was 20 years old. Offspring reported asthma in their parents more correctly if the parents had their asthma during the offspring's childhood.

Table 4 Frequency (absolute and relative) of discrepant asthma reports according to wheezing/non-wheezing

Discrepant asthma reports	N (%)
Offspring with wheeze reporting asthma in their non-asthmatic mothers	31/655 (4.7)
Offspring without wheeze reporting asthma in their non-asthmatic mothers	94/3091 (3.0)
Offspring with wheeze reporting no asthma in their asthmatic mothers	33/655 (5.0)
Offspring without wheeze reporting no asthma in their asthmatic mothers	117/3091 (3.8)
Offspring with wheeze reporting asthma in their non-asthmatic fathers	22/510 (4.3)
Offspring without wheeze reporting asthma in their non-asthmatic fathers	52/2483 (2.1)
Offspring with wheeze reporting no asthma in their asthmatic fathers	24/510 (4.7)
Offspring without wheeze reporting no asthma in their asthmatic fathers	83/2483 (3.3)

We found that never-smokers and mothers were more likely to report offspring asthma correctly. Non-smokers have higher health-risk awareness than smokers [28], thus it is plausible that this group also have more knowledge regarding their offspring health. That mothers report more correctly than fathers may be explained by them generally being the primary care givers of children and consequently spending more time with them in the daily life. Today this is probably not as rigid a pattern as before, but the present agreement study is based on a parent population born between 1945 and 1973, and their offspring born between 1963 and 1997.

Wheeze in the offspring is a significant predictor for incorrect reports of parental asthma. One could speculate that offspring with wheeze over-report asthma in their parents because of a hyper alertness concerning asthma and its symptoms. This would be in accordance with what has been observed for instance in atopic diseases, where fathers were more likely to recall their own atopic disease history if their children currently had severe atopic diseases [29]. In addition, Danell et al. [30] showed that children reported more asthma-related issues than their parents regarding their own symptoms. However, in our study, the discrepant answers given by offspring with wheeze were associated with both under-reporting and over-reporting (See Additional file 1: Table S4), and further studies are needed to appropriately investigate the mechanisms behind these discrepancies. Although seemingly random, the observed misclassification may lead to a bias towards the null and yield weaker associations than what actually exist in real life.

Regarding the parents, we observed an increased risk for differential misclassification of offspring asthma among men and smokers, with a tendency for under-estimating asthma in their offspring. As suspected, we also observed that this type of misclassification was more widespread regarding late onset asthma in the offspring than early onset asthma. The same pattern was also observed for offspring reporting parental asthma with onset after the offspring had grown up and left home.

Apart from male gender and current smoking in parents, and wheeze in offspring, we did not observe any other significant predictors for discrepant asthma reports across generations. This leads us to believe that discrepant reports concerning offspring health status are mostly due to minor and random misclassification with little consequences for the validity of asthma reports.

Nevertheless, the observed predictors for discrepant answers should be taken into consideration in any future studies relying on asthma reports on behalf of family members.

The main strengths of this study are population size and study design; to our knowledge RHINESSA is the largest population-based generational study so far, and this is the first study to compare self-report questionnaires across generations. In addition to the agreement analyses, we also identified predictors for disagreement, which was possible through the large dataset collected in the RHINE, ECRHS and RHINESSA.

However, some limitations to our study should also be acknowledged. First, the response rate in the offspring population was low: Only a third of the offspring of ECRHS/RHINE participants agreed to participate in the RHINESSA generation study. However, the offspring population was not severely skewed in any direction – distribution of demographic characteristics such as sex, smoking habits and educational level did not seem to differ substantially from that of a general population in the same age range. We also examined distribution of sex, smoking habits, educational level and asthma status of parents with participating offspring and parents with non-participating offspring to further examine any potential response bias. Our data showed that the groups were very similar. There was a miniscule overrepresentation in RHINESSA of offspring who had parents with asthma (13.6% versus 11.5% in non-participating offspring), parents who were non-smokers (84.3% versus 80.6%), and female parents (mothers, 55.3% versus 50.6%). In addition, slightly less parents with higher education had offspring who participated in RHINESSA (46.1% versus 47.9% of the parents with

non-participating offspring). These very small differences are reassuring, and do not provide any evidence of differential misclassification due to response bias. In addition, we were not aiming to assess disease prevalence in the present study, but to assess associations between two variables (parent reports and offspring reports). Although a low response rate may have impact on prevalence rates, internal exposure-outcome associations are less affected [20, 31]. However, we cannot be entirely certain that the observed differences in agreement between centres (Additional file 1: Table S2a and b), are valid for the general populations in these centres or if they apply only to the select group of participants.

Secondly, self-report questionnaires are susceptible to misclassification in the form of recall bias, especially if the outcomes date far back in time. Through comparing offspring-reports on parental asthma and parent-reports on offspring asthma, we set as a prerequisite that the reports they have given regarding themselves are correct. A comparison with primary care records for the study participants would have helped us assess presence or absence of recall bias in our study. Other possibilities would be to use prescription registry data. Data on dispensed antiasthmatics from the Norwegian Prescription Database (NorPD) has previously been validated in the Norwegian mother and child cohort study (MoBa), and they found that the use of prescription data for 7-year old children had high validity [32]. Unfortunately, such data was not available in our study. However, while clinical assessment is often considered the best method for validating self-reported asthma, recent studies presented self-report questionnaires to be a reliable tool in an epidemiological setting [8, 26].

Thirdly, we used "doctor-diagnosed asthma" when subjects reported about themselves, but "ever asthma" when subjects reported about each other. A recent Danish study showed how asthma prevalence in children is highly dependent on the method of measuring asthma, being lowest when measured with hospitalization data and highest when measured with prescription data, and with self-reports by parents in between the two other methods [4].

Since the asthma report on behalf of the other generation in our study was ever asthma and not doctor-diagnosed, one could suspect an over-report of asthma on behalf of the other generation. However, the results of our study did not show any such tendency. This is in line with previous research by de Marco et al., who found that the question "Do you have or have you ever had asthma?" gave prevalence estimates comparable to clinical diagnosis [33].

Furthermore, in RHINESSA only one of the parents is included, while ideally both parents should have been included. However, mothers and fathers were approximately equally distributed in RHINESSA and consequently we have no reason to believe that there is a gender bias present.

Conclusion

In conclusion, this agreement study shows a moderate to good agreement between the self-reported asthma and asthma reported by family-members, although we observed some risk of under-report. In the absence of direct reports, offspring asthma status reported by parents and parental asthma status reported by offspring may be used as a proxy, both in epidemiological studies and in a clinical setting before undergoing further clinical examination.

Additional file

Additional file 1: Table S1. Response rates of the offspring population, RHINESSA. **Table S2a and 2b.** Parameter estimates and 95% confidence intervals for Cohen's kappa, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for offspring-reported parental asthma and parent- reported offspring asthma, stratified by study centers. **Table S3.** Parameter estimates and 95% confidence intervals for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for offspring-reported parental asthma and parent-reported offspring asthma, according to timing of parental asthma onset. **Table S4.** Frequency (absolute and relative) of discrepant asthma reports according to fathers/mothers, and current smoking parents/never-smoking parents. (DOCX 36 kb)

Abbreviations

CI: Confidence interval; COPD: Chronic obstructive lung disease; ECRHS: European Community Respiratory Health Survey; MoBa: Norwegian mother and child cohort study; NorPD: The Norwegian Prescription Database; NPV: Negative predictive value; OR: Odds ratio; PPV: Positive predictive value; RHINE: Respiratory Health in Northern Europe; RHINESSA: Respiratory Health in Northern Europe, Spain and Australia

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

INK: Principal author, conception and design of the work, statistical analysis, interpretation of data, drafting the work. CS, BB, RJB, LB, SCD, MH, CJ, RJ, AM, MM, JMM, FGR, JLSR, VS, ST, AJ: Conception and design of the work, acquisition and interpretation of data and revising for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

In all study centres written informed consent was obtained from each participant, and the study was approved by regional committees of medical research ethics in each study centre according to national legislations, see online supplement for names of ethics committees and approval numbers).

Consent for publication
Not applicable.

Competing interests
The last author, Ane Johannessen is a member of the Editorial Board of BMC Pulmonary Medicine. All of the other authors declare that they have no competing interests.

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Additional files.

Table S1. Response rates of the offspring population, RHINESSA.

Country (center)	**Response rate (%)**
Denmark (Aarhus)	30.5
Iceland (Reykjavik)	25.0
Norway (Bergen)	40.1
Sweden (Gothenburg, Umea, Uppsala)	43.7
Estonia (Tartu)	18.6
Spain (Albacete, Huelva)	24.6
Australia (Melbourne)	73.7

Table S2a and b. Parameter estimates and 95% confidence intervals for Cohen's Kappa, sensitivity, specificity, PPV, and NPV for offspring-reported parental asthma and parent-reported offspring asthma, stratified by study centers.

a) Offspring asthma	**Agreement[1] N (%)**	**Disagreement[2] N (%)**	**Cohen's kappa**	**Sensitivity**	**95% CI**	**Specificity**	**95% CI**	**PPV**	**95% CI**	**NPV**	**95% CI**
Early onset asthma	*4845 (96)*	*204 (4)*	*0.71*	*0.66*	*0.61, 0.71*	*0.99*	*0.98, 0.99*	*0.81*	*0.76, 0.85*	*0.97*	*0.97, 0.98*
Aarhus	568 (97)	19 (3)	0.69	0.68	0.50, 0.83	0.99	0.97, 0.99	0.74	0.55, 0.88	0.98	0.97, 0.99
Reykjavik	625 (93)	47 (7)	0.68	0.66	0.55, 0.75	0.97	0.96, 0.98	0.79	0.68, 0.87	0.95	0.93, 0.96
Bergen	974 (96)	38 (4)	0.65	0.57	0.44, 0.68	0.99	0.98, 1.00	0.83	0.69, 0.92	0.97	0.96, 0.98
Gothenburg	653 (97)	20 (3)	0.74	0.76	0.60, 0.88	0.98	0.97, 0.99	0.76	0.60, 0.88	0.98	0.97, 0.99
Umea	882 (96)	39 (4)	0.74	0.66	0.56, 0.76	0.99	0.98, 1.00	0.90	0.81, 0.96	0.96	0.95, 0.97
Uppsala	882 (96)	35 (4)	0.74	0.70	0.58, 0.80	0.99	0.98, 0.99	0.83	0.72, 0.91	0.97	0.96, 0.98
Tartu	284 (98)	6 (2)	0.56	0.67	0.22, 0.96	0.99	0.96, 1.00	0.50	0.16, 0.84	0.99	0.97, 1.00
Albacete/Huelva	108 (96)	4 (4)	0.83	0.85	0.55, 0.98	0.98	0.93, 1.00	0.85	0.55, 0.98	0.98	0.93, 1.00
Melbourne	145 (93)	11 (7)	0.83	0.79	0.65, 0.90	0.99	0.95, 1.00	0.97	0.87, 1.00	0.92	0.85, 0.96
Late onset asthma	*4750 (94)*	*304 (6)*	*0.48*	*0.37*	*0.33, 0.42*	*0.99*	*0.99, 0.99*	*0.78*	*0.72, 0.84*	*0.95*	*0.94, 0.95*
Aarhus	313 (97)	11 (3)	0.55	0.60	0.39, 0.79	1.00	0.98, 1.00	0.94	0.70, 1.00	0.97	0.94, 0.98
Reykjavik	597 (93)	46 (7)	0.45	0.34	0.23, 0.48	0.99	0.98, 1.00	0.78	0.58, 0.91	0.94	0.91, 0.95
Bergen	962 (93)	74 (7)	0.42	0.33	0.24, 0.44	0.99	0.98, 0.99	0.72	0.56, 0.85	0.94	0.92, 0.95
Gothenburg	647 (94)	41 (6)	0.47	0.36	0.23, 0.50	0.99	0.98, 1.00	0.80	0.59, 0.93	0.95	0.93, 0.96
Umea	857 (90)	91 (10)	0.43	0.34	0.25, 0.43	0.99	0.98, 0.99	0.80	0.67, 0.90	0.91	0.89, 0.93
Uppsala	864 (93)	65 (7)	0.47	0.35	0.25, 0.46	0.99	0.98, 1.00	0.84	0.69, 0.94	0.93	0.92, 0.95
Tartu	198 (99)	2 (1)	0.61	0.60	0.15, 0.95	1.00	0.98, 1.00	1.00	0.29, 1.00	0.99	0.96, 1.00

Albacete/Huelva	101 (86)	16 (14)	0.39	0.39	0.17, 0.64	0.95	0.89, 0.98	0.58	0.28, 0.85	0.90	0.82, 0.95
Melbourne	116 (93)	9 (7)	0.63	0.53	0.28, 0.77	0.99	0.95, 1.00	0.90	0.28, 0.85	0.93	0.87, 0.97

b) Parental asthma	**Agreement[1] N (%)**	**Disagreement[2] N (%)**	**Cohen's kappa**	**Sensitivity**	**95% CI**	**Specificity**	**95% CI**	**PPV**	**95% CI**	**NPV**	**95% CI**
Maternal	*3347 (93)*	*255 (7)*	*0.68*	*0.70*	*0.65, 0.74*	*0.96*	*0.96, 0.97*	*0.74*	*0.70, 0.78*	*0.96*	*0.95, 0-96*
Aarhus	357 (95)	18 (5)	0.78	0.78	0.63, 0.88	0.98	0.96, 0.99	0.84	0.71, 0.94	0.97	0.94, 0.98
Reykjavik	412 (88)	56 (12)	0.54	0.55	0.44, 0.66	0.95	0.92, 0.97	0.69	0.56, 0.80	0.91	0.88, 0.94
Bergen	565 (92)	50 (8)	0.66	0.64	0.54, 0.74	0.97	0.95, 0.98	0.80	0.69, 0.88	0.94	0.91, 0.96
Gothenburg	487 (96)	22 (4)	0.76	0.78	0.65, 0.89	0.98	0.96, 0.99	0.78	0.65, 0.89	0.98	0.96, 0.99
Umea	690 (94)	43 (6)	0.74	0.79	0.70, 0.87	0.96	0.94, 0.98	0.75	0.66, 0.84	0.97	0.95, 0.98
Uppsala	673 (92)	55 (8)	0.66	0.69	0.59, 0.78	0.96	0.94, 0.97	0.71	0.61, 0.80	0.95	0.94, 0.97
Tartu	189 (93)	15 (7)	0.48	0.62	0.32, 0.86	0.95	0.91, 0.98	0.44	0.22, 0.69	0.97	0.94, 0.99
Albacete/Huelva	89 (82)	20 (18)	0.51	0.65	0.44, 0.83	0.87	0.78, 0.93	0.61	0.41, 0.79	0.89	0.80, 0.95
Melbourne	34 (97)	1 (3)	0.65	1.00	0.89, 1.00	0.50	0.01, 0.99	0.97	0.85, 1.00	1.00	0.03, 1.00
Paternal	*2803 (93)*	*193 (7)*	*0.67*	*0.64*	*0.58, 0.69*	*0.97*	*0.96, 0.98*	*0.70*	*0.64, 0.75*	*0.96*	*0.95, 0.97*
Aarhus	308 (96)	13 (4)	0.74	0.72	0.53, 0.87	0.98	0.96, 0.99	0.81	0.61, 0.93	0.97	0.95, 0.99
Reykjavik	373 (89)	44 (11)	0.38	0.35	0.22, 0.51	0.97	0.94, 0.98	0.57	0.37, 0.75	0.92	0.89, 0.95
Bergen	532 (93)	39 (7)	0.69	0.64	0.53, 0.75	0.98	0.96, 0.99	0.84	0.72, 0.92	0.94	0.92, 0.96
Gothenburg	407 (97)	14 (3)	0.76	0.77	0.59, 0.90	0.98	0.96, 0.99	0.77	0.59, 0.90	0.98	0.96, 0.99
Umea	511 (93)	36 (7)	0.60	0.60	0.45, 0.73	0.97	0.95, 0.98	0.67	0.52, 0.81	0.96	0.94, 0.97
Uppsala	517 (96)	24 (4)	0.77	0.87	0.75, 0.95	0.97	0.95, 0.98	0.73	0.60, 0.83	0.99	0.97, 0.99
Tartu	88 (96)	4 (4)	0.48	0.40	0.05, 0.85	0.99	0.94, 1.00	0.67	0.09, 0.99	0.97	0.91, 0.99
Albacete/Huelva	86 (85)	15 (15)	0.58	0.54	0.34, 0.73	0.97	0.91, 1.00	0.88	0.64, 0.99	0.85	0.75, 0.92
Melbourne	29 (88)	4 (12)	0.68	1.00	0.85, 1.00	0.60	0.26, 0.88	0.85	0.66, 0.96	1.00	0.54, 1.00

[1] Agreement: When both parents and offspring answered the same (yes/yes or no/no).

[2] Disagreement: When parents and offspring answered differently (yes/no or no/yes).

Table S3. Parameter estimates and 95% confidence intervals for sensitivity, specificity, PPV, and NPV for offspring-reported parental asthma and parent-reported offspring asthma, according to timing of parental asthma onset.

Parental asthma	**Agreement[1] N (%)**	**Disagreement[2] N (%)**	**Sensitivity**	**95% CI**	**Specificity**	**95% CI**	**PPV**	**95% CI**	**NPV**	**95% CI**
Asthma onset in mothers < offspring age 20	3982 (91)	371 (9)	0.75	0.70, 0.79	0.93	0.92, 0.94	0.52	0.48, 0.56	0.97	0.97, 0.98
Asthma onset in mothers ≥ offspring age	3814 (88)	539 (12)	0.61	0.52, 0.70	0.89	0.88, 0.89	0.14	0.12, 0.18	0.99	0.98, 0.99

20										
Asthma onset in fathers < offspring age 20	3351 (94)	233 (6)	0.72	0.66, 0.77	0.95	0.95, 0.96	0.58	0.53, 0.63	0.97	0.97, 0.98
Asthma onset in fathers ≥ offspring age 20	3224 (90)	360 (10)	0.48	0.33, 0.63	0.91	0.90, 0.92	0.06	0.04, 0.09	0.99	0.99, 1.00

[1] Agreement: When both parents and offspring answered the same (yes/yes or no/no).

[2] Disagreement: When parents and offspring answered differently (yes/no or no/yes).

Table S4. Frequency (absolute and relative) of discrepant asthma reports according to fathers/mothers, and current smoking parents/never-smoking parents.

Discrepant asthma reports	**N (%)**
Fathers reporting early onset asthma in early non-asthmatic offspring	28/2293 (1.2)
Mothers reporting early onset asthma in early non-asthmatic offspring	39/3047 (1.3)
Fathers reporting no asthma in offspring with early onset asthma	80/2293 (3.5)
Mothers reporting no asthma in offspring with early onset asthma	72/3047 (2.4)
Fathers reporting late onset asthma in late non-asthmatic offspring	21/2285 (0.9)
Mothers reporting late onset asthma in late non-asthmatic offspring	28/3092 (0.9)
Fathers reporting no asthma in offspring with late onset asthma	156/2285 (6.8)
Mothers reporting no asthma in offspring with late onset asthma	171/3092 (5.5)
Current smoking parents reporting early onset asthma in early non-asthmatic offspring	5/466 (1.1)
Never-smoking parents reporting early onset asthma in early non-asthmatic offspring	25/2413 (1.0)
Current smoking parents reporting no asthma in offspring with early onset asthma	13/466 (2.9)
Never-smoking parents reporting no asthma in offspring with early onset asthma	59/2413 (2.4)
Current smoking parents reporting late onset asthma in late non-asthmatic offspring	7/483 (1.4)
Never-smoking parents reporting late onset asthma in late non-asthmatic offspring	20/2433 (0.8)
Current smoking parents reporting no asthma in offspring with late onset asthma	39/483 (8.1)
Never-smoking parents reporting no asthma in offspring with late onset asthma	129/2433 (5.3)

II

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

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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; NO_2, nitrogen dioxide; O_3, ozone; OLI, Operational Land Imager; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m; RED, visible red light; RHINESSA; Respiratory health in Northern Europe, Spain and Australia; SD, standard deviation; TM, thematic mapper; WHO, World Health Organization.

Keywords:
Air pollution
Greenness
Asthma
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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 (NO_2), particulate matter (PM_{10} and $PM_{2.5}$), black carbon (BC), ozone (O_3) 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 (FEV_1), forced vital capacity (FVC) and FEV_1/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 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 to 2.25), but not with physician diagnosed asthma. For rhinitis, adulthood exposures seemed to be most important. Childhood and adolescence exposures to $PM_{2.5}$ 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 (1). 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 (2). Regarding lung function, studies have shown a decrease in forced expiratory volume in 1 second (FEV_1) in children (3, 4). Less is known regarding adult lung function after lifetime exposure to air pollution (5, 6).

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 (7-9). 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 (7, 10). Also, regarding lung function the results are heterogeneous; a recent study found an association with higher lung function after growing up nearby green spaces (11), while other studies did not find any associations (12, 13).

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 (14). During development, the lungs are particularly vulnerable, and several chronic respiratory diseases in adulthood originate from effects associated with exposures in this period (15, 16). 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 (Figure 1). All exposures were calculated from birth up to adulthood based on detailed

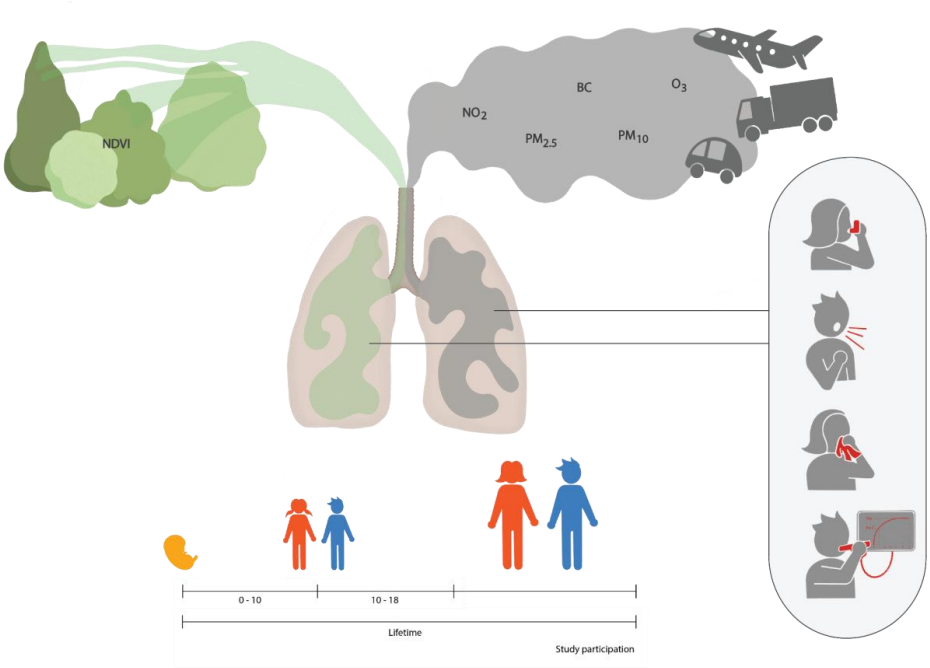

Figure 1. Longitudinal study, retrospective design with a lifelong history of exposure based on registry-based residential moving history. Overview of the exposures (greenness and air pollutants), the susceptibility windows (0-10 years, 10-18 years and lifetime from birth until study participation) and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

individual-level residential moving history. Asthma, rhinitis and lung function were selected as indicators of respiratory health.

2. Methods

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 (17), conducted from 2013 to 2015 (Figure 2). Participants born

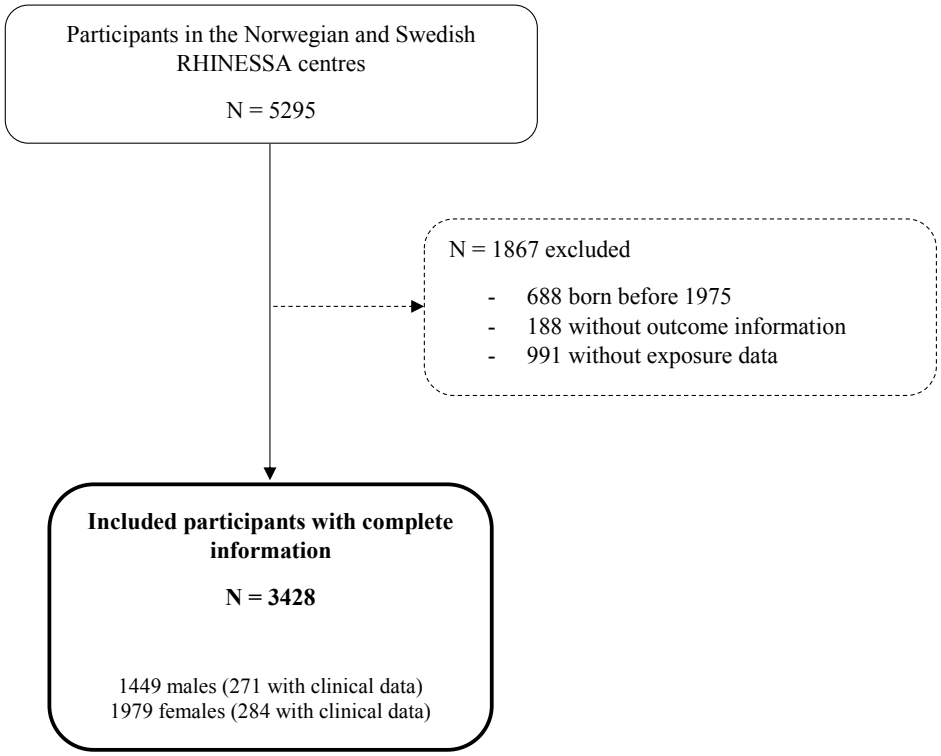

Figure 2. Flowchart of the RHINESSA study population.

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 (18), 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 (19).

2.2 Outcomes

Asthma and rhinitis

The following outcomes were analysed: ever asthma, allergic and non-allergic asthma, asthma attack last 12 months and rhinitis. 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?”.

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 (FEV_1) 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 FEV_1, FVC and FEV_1/FVC we used reference values from Global Lung Function Initiative (GLI 2012) with LLN defined as a z-score <1.64 standard deviations (SD) (20).

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.

Air pollution
Annual mean concentrations for nitrogen dioxide (NO_2), particulate matter with diameter < 2.5 μm ($PM_{2.5}$), and < 10 μm (PM_{10}), ozone (O_3) ($\mu g/m^3$) and black carbon (BC) ($10^{-5}m^{-1}$) were assigned to each participant’s individual geocoded residential history based on air pollution rasters previously developed (21-23) (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) 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 (24). Annual mean PM_{10} exposures were extracted from LUR models from 2007 (21), while for assessing the annual mean NO_2, $PM_{2.5}$, O_3 and BC exposures hybrid LUR models from 2010 were used (22, 23). 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 (25). Extrapolation was based on calculation data from the Danish Eulerian Hemispheric (DEHM) model (26) 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.

Greenness
Greenness (vegetation degree) was measured by the Normalized Difference Vegetation Index (NDVI) (27) derived from cloud-free Landsat 4-5 Thematic Mapper (TM) and 8 Operational Land Imager (OLI) satellite images (28) (Table S2). NDVI ranges from -1 to 1, where values close to 1 indicate highly vegetated areas (29). 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 (30). Other buffer zones (100-m, 500-m and 1000-m) served as sensitivity analyses (Table S7).

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) (31, 32). 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 (33).

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 FEV_1, FVC and FEV_1/FVC; and conditional logistic regression for ever asthma, allergic asthma and non-allergic asthma. 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.

NO_2, $PM_{2.5}$, PM_{10} and BC were highly correlated with each other and therefore not included in the same models (correlation coefficients ranging from 0.603 to 0.917, Table S4a-S4c). For each of these pollution exposures, we included O_3 and NDVI in the multivariable models together with the covariates from the DAG. O_3 was included since correlations between O_3 and other pollutants was more moderate (34). 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 O_3 analysis for NDVI and NO_2, and the NDVI analyses for O_3 and NO_2. 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 (35). 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 Rubin´s 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 (36).

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

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).

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 PM_{10} 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).

NO_2 was a risk factor for ever asthma and allergic asthma before but not after adjustment for confounders (Table 2). BC was a risk factor for ever asthma in univariable analysis but was a protective factor for non-allergic asthma after adjustment. O_3 was associated with less risk for ever asthma and non-allergic asthma. Greenness was not associated with asthma diagnosis.

Exposure to NO_2, PM_{10} and O_3 was associated with an increased risk of asthma attack both in the time window 10-18 years and lifetime exposure (Table 3). Exposure to PM_{10} and O_3 also increased the risk for asthma attack in the time window 0-10 years. Additional analysis showed that exposures of NO_2, $PM_{2.5}$, PM_{10}, BC and O_3 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.

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). PM_{10} exposure in all time windows was associated with increased risk of rhinitis before but not after adjustment for

confounders. Unadjusted analyses for the susceptibility window 10-18 years revealed an increased risk of rhinitis after exposure to NO_2, $PM_{2.5}$, PM_{10} and BC; but after adjustment for covariates only NO_2 remained statistically significant (Table 4). Additional analysis (Table S9) showed that NO_2, $PM_{2.5}$, PM_{10} 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.

O_3 exposure increased the risk of FEV_1<LLN in all time windows (Table 5) and $PM_{2.5}$ exposure was a risk factor for low FEV_1 across all time windows. O_3 was also a risk factor for low FVC in the time window 0-10 years, and in univariate analyses also for the other time windows. $PM_{2.5}$ exposure during lifetime and in the time window 10-18 years, was associated with low FVC after adjusting for confounders. Greenness exposures increased the risk of low FEV_1 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 FEV_1/FVC<LLN, only BC exposure in the time window 10-18 years was identified as a risk factor (Table S10-S11).

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]	
FEV1 in liter (SD)	3.9 (0.8)
FEV1 z-score (SD)	-0.4 (0.9)
FEV1 < 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)
FEV1/FVC ratio (SD)	0.8 (0.1)
FEV1/FVC z-score (SD)	-0.4 (0.8)
FEV1/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: FEV_1, 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 reference equations (20), 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.

	Physician diagnosed asthma				Allergic asthma				Non-allergic asthma			
	Univariable		Multivariable[2]		Univariable		Multivariable[2]		Univariable		Multivariable[2]	
Exposure[1*]	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	**1.01 (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 (300m)	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; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m.[1] All air pollutants exposures were extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m buffer), except for the O_3-model that was adjusted for NO_2 and NDVI (300m buffer) and the NDVI-model that was adjusted for O_3 and NO_2. 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. NO_2, PM exposures and O_3 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).

	0-10 years				10-18 years				Lifetime			
	Univariable		Multivariable[2]		Univariable		Multivariable[2]		Univariable		Multivariable[2]	
Exposure[1*]	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 300m	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; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m. [1] All air pollutants exposures were extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. 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. NO_2, PM exposures and O_3 per 10-μg/m³ increase.*

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).

0-10 years	10-18 years	Lifetime

Exposure[1*]	Univariable OR (95% CI)	p[3]	Multivariable[2] OR (95% CI)	p[3]	Univariable OR (95% CI)	p[3]	Multivariable[2] OR (95% CI)	p[3]	Univariable OR (95% CI)	p[3]	Multivariable[2] 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 300m	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; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m.[1] All air pollutants exposures were extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. 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 5. Logistic 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 Univariable OR (95% CI)	p[3]	Multivariable[2] OR (95% CI)	p[3]	10-18 years Univariable OR (95% CI)	p[3]	Multivariable[2] OR (95% CI)	p[3]	Lifetime Univariable OR (95% CI)	p[3]	Multivariable[2] OR (95% CI)	p[3]
FEV_1												
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 300m	**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 300m	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; FEV, forced expiratory volume in 1 second; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m.[1] All air pollutants exposures were extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-models that were adjusted for O_3 and NO_2. 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. NO_2, PM exposures and O_3 per 10-μg/m³ increase.

4. Discussion

In this retrospective cohort study with a lifelong exposure based on registry-based residential moving history, we found an increased risk of asthma attack after childhood and adolescence exposure to NO_2, PM_{10} and O_3 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 O_3 and low lung function, in particular with regard to FEV_1. Air pollution exposures did not increase the risk of physician diagnosed asthma. Higher exposure to greenness was a risk factor for low FEV_1 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 (2), with more associations for $PM_{2.5}$, PM_{10} and NO_2 compared to BC. Also in our study NO_2 and PM_{10} (in addition to O_3) 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 O_3. 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 (37) and also that long-term air pollution exposures are associated with increased disease severity among subjects with rhinitis (38).

Several studies have found that exposure to air pollution in early life and in school-age has a negative impact on lung function in childhood and adolescence (5, 39, 40), but the effects into adulthood remain unclear. Our analyses of adult lung function revealed that participants exposed to PM_{10} and O_3 had a higher risk for lung function below LLN for both FEV_1 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 NOx and PM_{10} exposures during the first year of life to be associated with FEV_1 and FVC below LLN at the age of 16 (40).

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 (12, 13). However, one recent study found higher FEV_1 and FVC among 24-year olds that grew up nearby green spaces within 300 m of their homes (11). 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 may be used more than an agricultural field. Also, urban areas tend to have more allergenic trees than rural areas. A recent study from Germany showed how residence in places with many trees, and allergenic trees specifically, increase the prevalence of allergic rhinitis (41). 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 (42). 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 (43) 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 (44). The negative effect may be due to increased exposures to pollens with higher susceptibility to allergic reactions.

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 (14). 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 (45). 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 (46).

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 PM_{10} and partly also for NO_2 (47). 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, 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 (18, 48, 49). 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% (50). A general decreasing trend of the response rate is reported in the latest years, levelling out at about 50% (51). The importance of the participants being representative of the general population is emphasized to be at least as important as the response rate. The RHINESSA study population was not skewed in any direction and has the same distribution of demographic characteristics (e.g. education level, sex, asthma status) as the same age range in the general population (18).

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 FEV_1 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.

CRediT authorship contribution statement

Ingrid Nordeide Kuiper: Conceptualization, Methodology, Formal analysis, Writing – Original draft, Writing – review & editing. **Thomas Halvorsen:** Writing – review & editing, Supervision. **Iana Markevych:** Investigation, Writing – review & editing. **Joachim Heinrich:** Writing – review & editing. **Randi J. Bertelsen:** Writing – review & editing. **Mathias Holm:** Writing – review & editing. **Lennart Bråbäck:** Writing – review & editing. **Andrei Malinovschi:** Writing – review & editing. **Simone Accordini:** Methodology, Writing

– review & editing. **Alessandro Marcon:** Methodology, Writing – review & editing. **Bertil Forsberg:** Writing – review & editing. **Torben Sigsgaard:** Writing – review & editing. **Christer Janson:** Writing – review & editing. **Kees de Hoogh:** Investigation, Writing – review & editing. **Gerard Hoek:** Writing – review & editing. **Ole Hertel:** Investigation, Writing – review & editing. **Jesper Heile Christensen:** Investigation, Writing – review & editing. **Roy Miodini Nilsen**: Methodology, Writing – review and editing. **Cecilie Svanes:** Conceptualization, Methodology, Writing – review & editing, Supervision. **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.

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Appendix A. Supplementary material

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Appendix A. Supplementary material

Table S1. Overview of the models used to calculate air pollution exposures.

Air pollutant	Study center	Model-year and source	
		2007	2010
NO_2	Umea, Uppsala, Gothenburg	-	de Hoogh et al 2016 (1)
	Bergen	-	de Hoogh et al 2016 (1)
$PM_{2.5}$	Umea, Uppsala, Gothenburg	-	de Hoogh et al 2016 (1)
	Bergen	-	de Hoogh et al 2016 (1)
PM_{10}	Umea, Uppsala, Gothenburg	Vienneau et al 2013 (2)	-
	Bergen	Vienneau et al 2013 (2)	-
BC	Umea, Uppsala, Gothenburg	-	de Hoogh et al 2018 (3)
	Bergen	-	de Hoogh et al 2018 (3)
O_3	Umea, Uppsala, Gothenburg	-	de Hoogh et al 2018 (3)
	Bergen	-	de Hoogh et al 2018 (3)

Abbreviations: BC, black carbon; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.

Table S2. Landsat images used for NDVI calculations.

	Bergen, 201/18	Gothenburg, 195/20	Gothenburg, 196/19	Umea, 193/15	Umea, 193/16	Uppsala, 193/18	Uppsala, 193/19
2014	18/06/201, 8OLI	27/08/2014, 8OLI	21/08/2015, 8OLI	12/07/2014, 8OLI	25/07/2013, 8OLI	10/06/2014, 8OLI	10/06/2014, 8OLI
2009	03/07/2008, 5TM	26/06/2009, 5TM	01/06/2009, 5TM	28/06/2009, 5TM	28/06/2009, 5TM	28/06/2009, 5TM	28/06/2009, 5TM
2004	06/07/2003, 5TM	07/06/2002, 5TM	14/06/2002, 5TM	17/06/2005, 5TM	03/07/2005, 5TM	14/07/2003, 5TM	14/07/2003, 5TM
1999	03/06/1997, 5TM	17/06/2000, 5TM	08/06/2000, 5TM	20/07/1997, 5TM (194/15)	13/07/1997, 5TM	17/06/1999, 5TM	17/06/1999, 5TM
1994	29/07/1994, 5TM	30/06/1993, 5TM	24/06/1994, 5TM	05/07/1994, 5TM	05/07/1994, 5TM	05/07/1994, 5TM	05/07/1994, 5TM
1989	13/06/1989, 5TM	05/07/1989, 5TM	29/08/1989, 5TM	21/06/1989, 5TM	21/06/1989, 5TM	07/07/1989, 5TM	07/07/1989, 5TM
1984	18/06/1985, 5TM	27/06/1986, 5TM	02/06/1986, 5TM	26/06/1985, 5TM	26/06/1985, 5TM	09/07/1984, 5TM	09/07/1984, 5TM

Abbreviations: NDVI, normalized difference vegetation index; OLI, operational land imager; TM, thematic mapper.

Table S3. NDVI assignment to addresses.

NDVI map	Address year
1984	1975 to 1986
1989	1987 to 1991
1994	1992 to 1996
1999	1997 to 2001
2004	2002 to 2006
2009	2007 to 2011
2014	2012 to 2015

Abbreviations: NDVI, normalized difference vegetation index.

Table S4. Pearson correlation coefficients for the included air pollutants and NDVI and the different susceptibility windows.

S4a. 0-10 years

Exposure	$PM_{2.5}$	PM_{10}	NO_2	BC	O_3	NDVI
$PM_{2.5}$	1.0	0.913	0.848	0.638	-0.376	-0.225
PM_{10}	0.913	1.0	0.765	0.603	-0.281	-0.237
NO_2	0.848	0.765	1.0	0.791	-0.654	-0.409
BC	0.638	0.603	0.791	1.0	-0.787	-0.240
O_3	-0.376	-0.281	-0.654	-0.787	1.0	0.310
$NDVI_1$	-0.225	-0.237	-0.409	-0.240	0.310	1.0

Abbreviations: BC, black carbon; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.1300-m buffer.

S4b. 10-18 years

Exposure	$PM_{2.5}$	PM_{10}	NO_2	BC	O_3	NDVI
$PM_{2.5}$	1.0	0.908	0.812	0.697	-0.329	-0.170
PM_{10}	0.908	1.0	0.728	0.674	-0.266	-0.187
NO_2	0.812	0.728	1.0	0.821	-0.663	-0.360
BC	0.697	0.674	0.821	1.0	-0.677	-0.216
O_3	-0.329	-0.266	-0.663	-0.677	1.0	0.333
$NDVI_1$	-0.170	-0.187	-0.360	-0.216	0.333	1.0

Abbreviations: BC, black carbon; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.1300-m buffer.

S4c. Lifetime

Exposure	$PM_{2.5}$	PM_{10}	NO_2	BC	O_3	NDVI
$PM_{2.5}$	1.0	0.917	0.830	0.712	-0.194	-0.074
PM_{10}	0.917	1.0	0.753	0.670	-0.101	-0.101
NO_2	0.830	0.753	1.0	0.862	-0.101	-0.300
BC	0.712	0.670	0.862	1.0	-0.857	-0.162
O_3	-0.194	-0.101	-0.587	-0.628	1.0	0.320
NDVI1	-0.074	-0.101	-0.300	-0.162	0.320	1.0

Abbreviations: BC, black carbon; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.1300-m buffer.

Table S5. Pearson correlation coefficients for different susceptibility windows for each exposure.

S5a. $PM_{2.5}$

Susceptibility window	0-10 years	10-18 years	Lifetime
0-10 years	1.0	0.900	0.973
10-18 years	0.900	1.0	0.900
Lifetime	0.973	0.900	1.0

Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μ m.

S5b. PM_{10}

Susceptibility window	0-10 years	10-18 years	Lifetime
0-10 years	1.0	0.876	0.970
10-18 years	0.876	1.0	0.864
Lifetime	0.970	0.864	1.0

Abbreviations: PM_{10}, particulate matter with an aerodynamic diameter less than 10 μ m.

S5c. NO_2

Susceptibility window	0-10 years	10-18 years	Lifetime
0-10 years	1.0	0.883	0.952
10-18 years	0.883	1.0	0.925
Lifetime	0.952	0.925	1.0

Abbreviations: NO_2, nitrogen dioxide.

S5d. BC

Susceptibility window	0-10 years	10-18 years	Lifetime
0-10 years	1.0	0.879	0.945
10-18 years	0.879	1.0	0.906
Lifetime	0.945	0.906	1.0

Abbreviations: BC, black carbon.

S5e. O_3

Susceptibility window	0-10 years	10-18 years	Lifetime
0-10 years	1.0	0.900	0.941
10-18 years	0.900	1.0	0.942
Lifetime	0.941	0.942	1.0

Abbreviations: O_3, ozone.

S5f. NDVI (300m)

Susceptibility window	0-10 years	10-18 years	Lifetime
0-10 years	1.0	0.701	0.850
10-18 years	0.701	1.0	0.845
Lifetime	0.850	0.845	1.0

Abbreviations: NDVI, normalized difference vegetation index

Table S6. Mean annual average exposure (range) for air pollutants per center for the exposure time windows (0-10 years, 10-18 years and lifetime).

Mean annual average exposure (range)[a]		NO_2 µg/m_3	$PM_{2.5}$ µg/m_3	PM_{10} µg/m_3	BC $10^{-5}m^{-1}$	O_3 µg/m_3
Umea	**0-10 years**	14.1 (0.2-38.6)	10.5 (1.0-22.5)	16.6 (10.7-26.8)	0.10 (0.00-1.07)	68.4 (62.8-74.8)
	10-18 years	12.6 (0.1-37.3)	8.9 (0.5-21.9)	14.0 (8.0-26.2)	0.11 (0.00-1.13)	68.2 (60.0-75.7)
	Lifetime	13.6 (0.3-33.1)	9.3 (0.7-20.4)	14.4 (9.7-25.1)	0.17 (0.00-1.17)	67.8 (62.8-75.2)
Uppsala	**0-10 years**	22.7 (2.7-47.7)	16.8 (7.0-29.5)	23.0 (12.7-34.1)	0.68 (0.03-1.76)	67.4 (60.9-74.3)
	10-18 years	18.3 (2.2-49.0)	13.2 (5.7-24.8)	18.3 (10.1-31.7)	0.56 (0.00-1.60)	68.1 (60.9-77.3)
	Lifetime	19.9 (2.5-39.8)	13.8 (7.0-22.5)	19.1 (11.7-26.4)	0.63 (0.02-1.54)	67.6 (61.0-74.7)
Gothenburg	**0-10 years**	36.5 (7.0-72.4)	23.6 (11.5-30.7)	27.7 (16.3-40.6)	1.07 (0.42-2.06)	64.5 (59.0-73.2)

	10-18 years	29.7 (5.5-69.0)	18.1 (6.1-29.8)	21.6 (9.8-35.7)	0.92 (0.15-2.20)	65.5 (54.3-77.2)
	Lifetime	30.7 (9.1-60.0)	18.6 (9.8-24.8)	22.3 (13.8-31.0)	0.95 (0.14-1.66)	65.1 (58.8-73.6)
Bergen	**0-10 years**	24.0 (3.0-49.0)	14.4 (2.9-24.4)	19.4 (12.0-27.8)	0.91 (0.00-2.58)	62.7 (50.0-74.4)
	10-18 years	22.0 (2.9-47.9)	12.1 (2.1-22.6)	16.6 (9.4-26.5)	0.72 (0.00-2.58)	62.8 (49.9-74.4)
	Lifetime	21.2 (4.5-43.5)	11.5 (2.5-16.7)	15.9 (8.6-21.5)	0.68 (0.00-2.01)	62.7 (50.1-74.5)
EU limit values		40[b]	25[b]	40[b]	-	-[c]
WHO guideline values		40[b]	10[b]	20[b]	-	-[c]

Abbreviations: BC, black carbon; EU, European Union; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m; WHO, World Health Organization. [a] *All air pollutants exposures were extrapolated in time with the ratio method.* [b] *Annual mean values.* [c] *Only maximum daily 8-hour mean values available*

Table S7. Mean annual average exposure (range) for all NDVI buffer zones per centre for the exposure time windows (0-10 years, 10-18 years and lifetime).

Mean annual average exposure (range)		**NDVI 100m**	**NDVI 300m**	**NDVI 500m**	**NDVI 1000m**
Umea	**0-10 years**	0.550 (0.137-0.840)	0.551 (0.204-0.797)	0.555 (0.215-0.781)	0.559 (0.230-0.770)
	10-18 years	0.559 (0.147-0.831)	0.558 (0.198-0.803)	0.561 (0.273-0.794)	0.568 (0.198-0.770)
	Lifetime	0.530 (0.127-0.840)	0.531 (0.184-0.797)	0.536 (0.192-0.811)	0.544 (0.222-0.796)
Uppsala	**0-10 years**	0.565 (0.240-0.851)	0.570 (0.281-0.789)	0.577 (0.300-0.778)	0.594 (0.286-0.782)
	10-18 years	0.580 (0.210-0.848)	0.583 (0.268-0.801)	0.590 (0.325-0.807)	0.602 (0.317-0.791)
	Lifetime	0.559 (0.251-0.816)	0.562 (0.347-0.783)	0.569 (0.192-0.811)	0.582 (0.369-0.766)
Gothenburg	**0-10 years**	0.546 (0.209-0.814)	0.551 (0.222-0.767)	0.560 (0.198-0.768)	0.564 (0.208-0.751)
	10-18 years	0.580 (0.168-0.833)	0.585 (0.232-0.796)	0.592 (0.206-0.782)	0.594 (0.228-0.774)
	Lifetime	0.558 (0.225-0.815)	0.563 (0.241-0.777)	0.570 (0.224-0.770)	0.574 (0.231-0.748)
Bergen	**0-10 years**	0.534 (0.121-0.779)	0.549 (0.155-0.802)	0.545 (0.128-0.799)	0.533 (0.146-0.782)
	10-18 years	0.549 (0.108-0.786)	0.553 (0.133-0.774)	0.548 (0.136-0.770)	0.537 (0.121-0.764)
	Lifetime	0.522 (0.121-0.776)	0.532 (0.163-0.758)	0.528 (0.147-0.772)	0.519 (0.164-0.768)

Abbreviations: NDVI, normalized difference vegetation index.

Table S8. Logistic regression analyses of asthma attack last 12 months in relation with mean air pollution and greenness exposures the year before RHINESSA participation, in the full (imputed) study population.

Exposure[1*]	Univariable OR (95% CI)	p[3]	Multivariable[2] OR (95% CI)	p[3]
NO_2	1.10 (0.88-1.38)	0.400	**1.60 (1.20-2.13)**	**0.001**
$PM_{2.5}$	1.67 (0.96-2.91)	0.067	**2.10 (1.22-3.62)**	**0.008**
PM_{10}	**2.03 (1.13-3.65)**	**0.017**	**2.46 (1.34-4.54)**	**0.004**
BC	1.34 (0.82-2.20)	0.238	**2.14 (1.21-3.78)**	**0.008**
O_3	1.40 (0.93-2.09)	0.104	**2.44 (1.39-4.26)**	**0.002**
NDVI 300m	0.99 (0.89-1.10)	0.857	0.97 (0.85-1.10)	0.598
NDVI 100m	0.96 (0.87-1.06)	0.408	0.93 (0.84-1.04)	0.212
NDVI 500m	0.99 (0.89-1.10)	0.889	0.97 (0.85-1.10)	0.593
NDVI 1000m	0.99 (0.89-1.10)	0.859	0.97 (0.85-1.10)	0.619

Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m. [1] All air pollutants exposures were extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. 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/m^3 increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m^3 increase.

Table S9. Logistic regression analyses of current rhinitis in relation with mean air pollution and greenness exposures the year before RHINESSA participation, in the full (imputed) study population.

Exposure[1*]	Univariable OR (95% CI)	p[3]	Multivariable[2] OR (95% CI)	p[3]
NO_2	**1.15 (1.03-1.28)**	**0.012**	**1.25 (1.08-1.45)**	**0.003**
$PM_{2.5}$	**1.32 (1.01-1.73)**	**0.040**	**1.35 (1.02-1.77)**	**0.033**
PM_{10}	**1.45 (1.09-1.93)**	**0.011**	**1.45 (1.08-1.94)**	**0.014**
BC	**1.40 (1.11-1.76)**	**0.004**	**1.50 (1.15-1.96)**	**0.003**
O_3	0.96 (0.80-1.15)	0.633	1.22 (0.95-1.57)	0.119
NDVI 300m	0.98 (0.93-1.03)	0.446	1.00 (0.94-1.05)	0.894
NDVI 100m	0.99 (0.94-1.03)	0.562	1.00 (0.95-1.05)	0.978
NDVI 500m	0.98 (0.93-1.03)	0.346	0.99 (0.93-1.05)	0.677
NDVI 1000m	0.98 (0.93-1.03)	0.364	0.99 (0.93-1.05)	0.685

Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m. [1] All air pollutants exposures were extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-model that was adjusted for O_3 and NO_2. 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/m^3 increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m^3 increase.

Table S10. Logistic regression analyses of lower limit of normal (LLN) FEV_1/FVC in relation with mean air pollution and greenness exposures for all time windows in the full (imputed) study population.

	0-10 years				10-18 years				Lifetime			
	Univariable		Multivariable[2]		Univariable		Multivariable[2]		Univariable		Multivariable[2]	
Exposure[1*]	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]
FEV_1/FVC												
NO_2	1.34 (0.87-2.05)	0.180	1.16 (0.64-2.07)	0.628	1.39 (0.90-2.16)	0.139	1.16 (0.57-2.38)	0.676	1.36 (0.79-2.35)	0.272	1.15 (0.52-2.56)	0.734
$PM_{2.5}$	1.44 (0.61-3.37)	0.402	1.00 (0.34-2.91)	0.998	1.89 (0.75-4.72)	0.174	1.34 (0.31-5.77)	0.698	1.54 (0.45-5.26)	0.488	1.11 (0.25-4.94)	0.887
PM_{10}	1.27 (0.49-3.31)	0.618	0.82 (0.23-2.84)	0.750	1.56 (0.60-4.07)	0.363	0.79 (0.13-4.93)	0.801	1.31 (0.34-5.10)	0.695	0.85 (0.16-4.67)	0.856
BC	2.47 (0.94-6.49)	0.067	2.88 (0.69-12.03)	0.146	**2.66 (1.02-6.90)**	**0.045**	2.27 (0.48-10.69)	0.299	2.59 (0.72-9.31)	0.146	2.22 (0.37-13.42)	0.386
O_3	0.50 (0.18-1.42)	0.192	0.49 (0.13-1.83)	0.289	0.52 (0.20-1.36)	0.183	0.49 (0.12-2.03)	0.328	0.55 (0.17-1.75)	0.313	0.49 (0.11-2.17)	0.348
NDVI 300m	0.98 (0.71-1.35)	0.900	1.12 (0.77-1.64)	0.541	1.10 (0.80-1.52)	0.551	1.22 (0.85-1.75)	0.286	1.01 (0.71-1.44)	0.962	1.22 (0.82-1.81)	0.333
NDVI 100m	1.03 (0.78-1.37)	0.826	1.16 (0.87-1.55)	0.312	1.11 (0.83-1.48)	0.473	1.25 (0.93-1.67)	0.144	1.03 (0.74-1.43)	0.867	1.22 (0.89-1.68)	0.222
NDVI 500m	0.98 (0.72-1.34)	0.906	1.09 (0.77-1.55)	0.637	1.11 (0.83-1.50)	0.479	1.22 (0.86-1.71)	0.260	1.03 (0.74-1.43)	0.857	1.23 (0.84-1.79)	0.285
NDVI 1000m	1.07 (0.78-1.46)	0.692	1.15 (0.82-1.63)	0.420	1.18 (0.86-1.63)	0.300	1.30 (0.90-1.87)	0.165	1.09 (0.79-1.50)	0.617	1.26 (0.86-1.86)	0.238

*Abbreviations: BC, black carbon; CI, confidence interval; FEV, forced expiratory volume in 1 second; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μ m; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μ m. [1] All air pollutants exposures were extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-models that were adjusted for O_3 and NO_2. 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/m[3] increase, NDVI per 0.1-unit increase. NO_2, PM exposures and O_3 per 10-μg/m[3] increase.*

Table S11. Logistic regression analyses of lower limit of normal (LLN) FEV_1 and FVC in relation to mean greenness exposures (buffer zones 100 m, 500 m and 1000 m) for all time windows in the full (imputed) study population.

	0-10 years				10-18 years				Lifetime			
	Univariable		Multivariable[1]		Univariable		Multivariable[1]		Univariable		Multivariable[1]	
Exposure*	OR (95% CI)	p[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]
FEV_1												
NDVI 100m	**1.47 (1.13-1.91)**	**0.004**	**1.44 (1.07-1.92)**	**0.014**	**1.46 (1.11-1.92)**	**0.008**	**1.39 (1.04-1.86)**	**0.026**	**1.68 (1.21-2.34)**	**0.002**	**1.55 (1.09-2.19)**	**0.015**
NDVI 500m	**1.45 (1.05-2.02)**	**0.026**	1.41 (0.94-2.12)	**0.101**	**1.68 (1.22-2.31)**	**0.002**	**1.62 (1.12-2.35)**	**0.011**	**1.86 (1.24-2.79)**	**0.003**	**1.72 (1.11-2.66)**	**0.015**
NDVI 1000m	**1.50 (1.05-2.14)**	**0.027**	1.42 (0.93-2.17)	**0.108**	**1.68 (1.15-2.45)**	**0.008**	**1.55 (1.02-2.35)**	**0.041**	**1.82 (1.19-2.79)**	**0.006**	**1.61 (1.02-2.52)**	**0.039**
FVC												
NDVI 100m	1.26 (0.93-1.70)	0.141	1.14 (0.80-1.62)	0.461	1.19 (0.89-1.60)	0.239	1.13 (0.81-1.57)	0.466	1.30 (0.90-1.87)	0.161	1.17 (0.77-1.79)	0.458
NDVI 500m	1.50 (1.00-2.27)	0.052	1.36 (0.84-2.21)	0.211	**1.66 (1.16-2.39)**	**0.006**	**1.61 (1.07-2.43)**	**0.023**	**1.87 (1.15-3.04)**	**0.011**	**1.74 (1.05-2.90)**	**0.032**
NDVI 1000m	1.55 (0.96-2.50)	0.071	1.39 (0.81-2.38)	0.227	**1.61 (1.05-2.47)**	**0.030**	1.48 (0.93-2.37)	0.098	**1.86 (1.08-3.21)**	**0.025**	1.64 (0.93-2.87)	0.085

*Abbreviations: CI, confidence interval; FEV, forced expiratory volume in 1 second; NDVI, normalized difference vegetation index; OR, odds ratio; [1] All models were adjusted for O_3 and NDVI (300m), except for the O_3-model that was adjusted for NO_2 and NDVI (300m) and the NDVI-models that were adjusted for O_3 and NO_2. All models were also adjusted for age, sex and parental education and asthma. [2] All p-values < 0.05 = significant and marked bold. * NDVI per 0.1-unit increase.*

Figure S1. Directed Acyclic Graph for greenness.

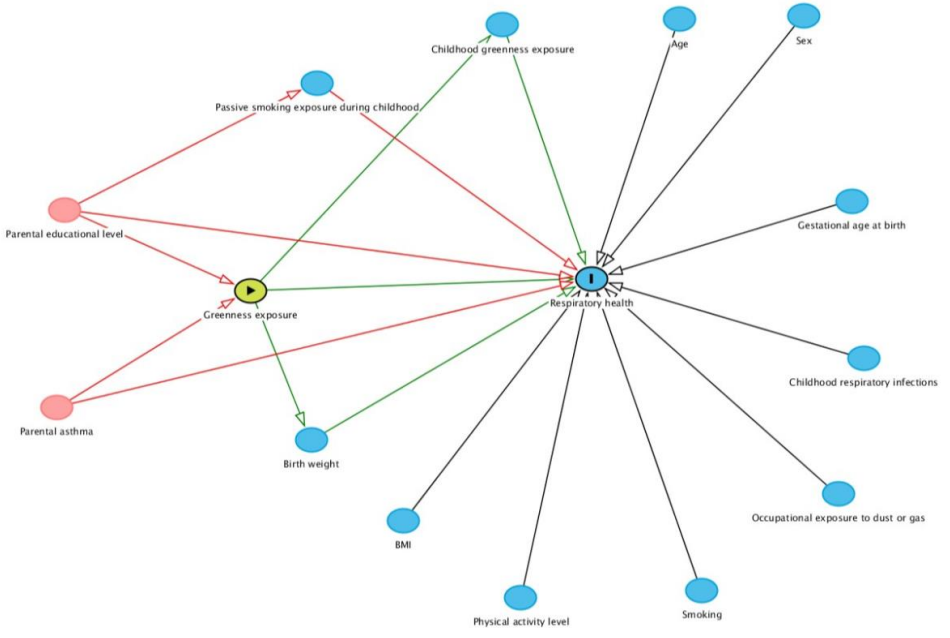
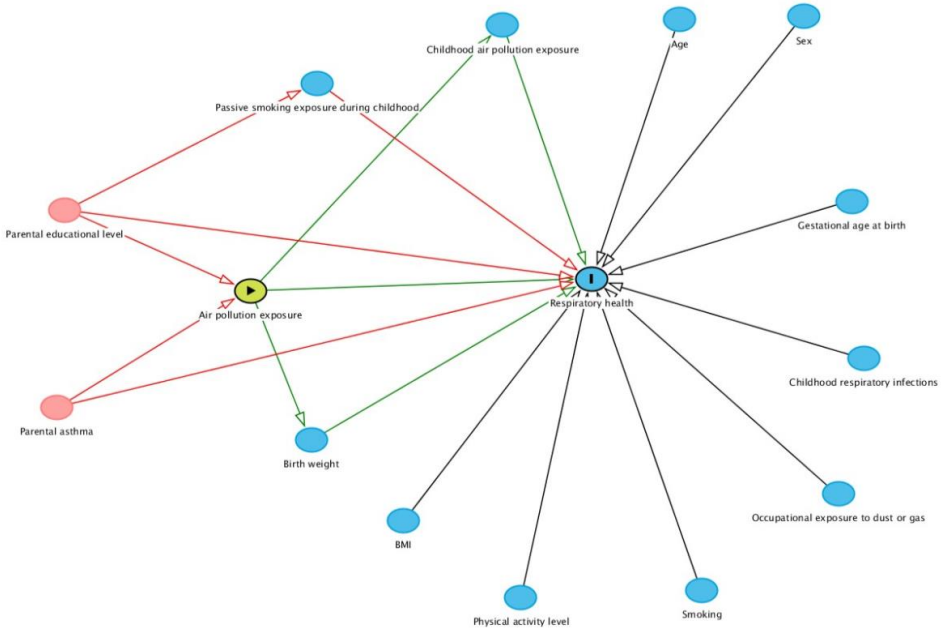


Figure S2. Directed Acyclic Graph for air pollution.



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III

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Article

Associations of Preconception Exposure to Air Pollution and Greenness with Offspring Asthma and Hay Fever

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Abstract: We investigated if greenness and air pollution exposure in parents' childhood affect offspring asthma and hay fever, and if effects were mediated through parental asthma, pregnancy greenness/pollution exposure, and offspring exposure. We analysed 1106 parents with 1949 offspring (mean age 35 and 6) from the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) generation study. Mean particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), black carbon

(BC), ozone (O_3) (μg/m^3) and greenness (normalized difference vegetation index (NDVI)) were calculated for parents 0–18 years old and offspring 0–10 years old, and were categorised in tertiles. We performed logistic regression and mediation analyses for two-pollutant models (clustered by family and centre, stratified by parental lines, and adjusted for grandparental asthma and education). Maternal medium $PM_{2.5}$ and PM_{10} exposure was associated with higher offspring asthma risk (odds ratio (OR) 2.23, 95%CI 1.32–3.78, OR 2.27, 95%CI 1.36–3.80), and paternal high BC exposure with lower asthma risk (OR 0.31, 95%CI 0.11–0.87). Hay fever risk increased for offspring of fathers with medium O_3 exposure (OR 4.15, 95%CI 1.28–13.50) and mothers with high PM_{10} exposure (OR 2.66, 95%CI 1.19–5.91). The effect of maternal PM_{10} exposure on offspring asthma was direct, while for hay fever, it was mediated through exposures in pregnancy and offspring's own exposures. Paternal O_3 exposure had a direct effect on offspring hay fever. To conclude, parental exposure to air pollution appears to influence the risk of asthma and allergies in future offspring.

Keywords: air pollution; greenness; preconception exposure; childhood asthma; childhood hay fever

1. Introduction

Air pollution is a major risk factor for disease worldwide and is estimated to cause almost 500,000 premature annual deaths across Europe [1]. Studies have shown that long-term exposure to high levels of air pollution affects multiple organs in the human body, causing cardiovascular and respiratory diseases [2]. Regarding the development of asthma, some studies have found childhood exposure to air pollution to be a risk factor [3], while other studies did not reveal those effects [4]. Less is known regarding the intergenerational effects of exposure to lower levels of air pollution, e.g., levels below recommended limits from the European Union (EU) and the World Health Organisation (WHO) [5,6], on offspring asthma and hay fever.

Exposure to greenspace has, on the other hand, been associated with beneficial health effects such as reduced risk of mortality, diabetes, and high blood pressure [7]. However, effects of greenness on asthma and allergies are less clear [8–11]. Some studies have indicated decreased respiratory morbidity in adulthood due to living near green areas [7,12–14] while the effects of residential greenness on childhood allergic rhinitis and aeroallergen sensitization have depended on the region [15–18]. Access to green areas may decrease stress through rest, increase opportunities for physical activity and increase social interaction [19]. Furthermore, vegetation may remove pollutants such as ozone (O_3), particulate matter (PM) and nitrogen dioxide (NO_2) from the air and may reduce exposure to harmful noise [9,20]. Negative effects of greenness, on the other hand, may be explained by higher exposure to pollen triggering allergic responses [17].

Asthma and allergies may result from both genetic susceptibility and environmental exposures, and the importance of early life factors have been widely acknowledged [21–23]. Emerging research suggests that even preconception exposures may be of relevance, and that epigenetic mechanisms may be at play across generations [24]. Recent studies have found that father's smoking and overweight onset in adolescence was associated with higher asthma risk in their future offspring [25–27], suggesting vulnerable time windows many years before conception of offspring. There are, however, no studies investigating such intergenerational effects of exposures to air pollution and greenness.

To address the knowledge gaps of these long-term effects of exposure to air pollution and greenness on asthma and hay fever, the aims of our study were to (1) explore the associations between parental childhood exposures of greenness and air pollution in relation to their future offspring asthma and allergies, in areas with relatively low air pollution and to (2) assess if the observed associations were direct or mediated by other factors.

2. Materials and Methods

2.1. Study Design and Population

We included participants born after 1975 as well as their offspring from centres with available pollution data and relatively low air pollution levels in the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) generation study, conducted in 2013–2015 [28,29]: Bergen (Norway); and Umea, Uppsala, and Gothenburg (Sweden), as shown in Figure 1. Individual residential address history was only available from 1975 onwards and participants born before that were therefore not included. The participants answered questionnaires regarding their lung health and provided information on their offspring asthma and allergies. The overall response rate was 40% in Norway and 44% in Sweden [28]. Informed consent was obtained from each participant, and the study was approved by regional committees of medical research ethics according to national legislations [30].

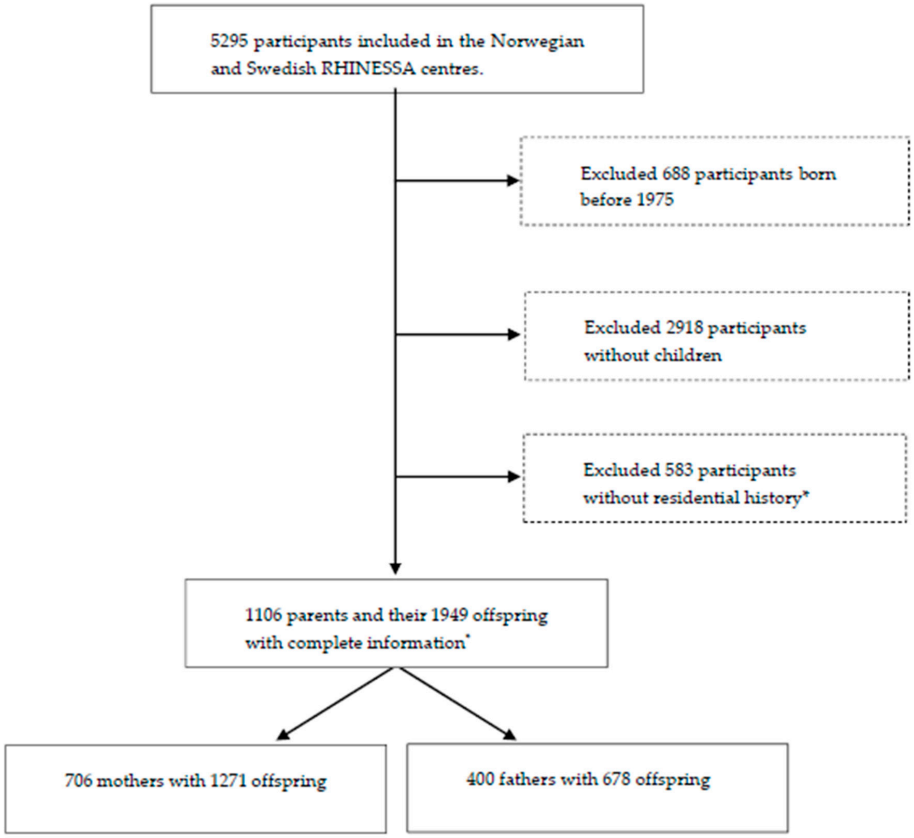

Figure 1. Flowchart of the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) generation study population. * Lack of residential history due to lack of registered addresses in the population registries or lack of consent to address history retrieval.

2.2. Residential Address History

We retrieved the parents' geocoded residential addresses from the Swedish and Norwegian national population registries for each year ranging from parents' birth until the age of 18 years, as well as for offspring from birth until the age of 10 years.

2.3. Outcomes

The main outcomes in this study were offspring early-onset asthma and hay fever, defined as affirmative answers to the questions "For each of your biological children, please tick yes if they have had asthma before 10 years of age", and "For each of your biological children please tick yes if they have had hay fever/rhinitis", respectively.

2.4. Exposure Assessment

2.4.1. Air Pollution

We assigned annual mean concentrations ($\mu g/m^3$) of 5 different air pollutants—NO_2, $PM_{2.5}$, PM_{10}, black carbon (BC) and O_3—to each participant based on their geocoded residential history. The exposures were assigned from air pollution rasters developed previously [31–33]. Annual mean PM_{10} exposures were extracted for 2005 to 2007 from surfaces (100 × 100 m) based on western Europe-wide hybrid land use regression (LUR) models [31]. Annual mean NO_2, $PM_{2.5}$ and O_3 exposures and BC exposures for 2010 originate from similar hybrid LUR models [32,33]. An overview of the models used for the different pollutants can be found in the online supplement (Table S1).

We back-and-forth extrapolated the air pollution concentrations from the LUR models using the ratio method for each year from 1990 to 2015 following the procedure from the European Study of Cohorts for Air Pollution Effects (ESCAPE) project [34], that is based on the Danish Eulerian Hemispheric (DEHM) model [35]. For the years before 1990, we used 1990 estimates as proxies.

2.4.2. Greenness

Greenness was assessed using the normalized difference vegetation index (NDVI) [36], which refers to both structured and unstructured vegetation. NDVI estimates were derived from cloud free Landsat 4–5 TM and 8 OLI satellite images [37] (Table S2). NDVI values range from −1 to +1, with +1 indicating highly vegetated areas [38].

Satellite images were retrieved for every 5 years during the most vegetation rich months (May, June, July) (Table S3), and NDVI maps were calculated with mean NDVI in a circular 100 m, 300 m, 500 m and 1000 m buffer around each participant's residential address. In the main analysis, we included the 300 m buffer, while the other buffer zones were included in sensitivity analysis (Tables S4 and S6a,b).

2.5. Time Windows for Exposures

We averaged mean annual exposures for the air pollutants and greenness across the period 0–18 years of age for parents and 0–10 years of age for offspring. Although desirable to estimate separate exposures for parents' childhood and adolescence, stable residential patterns made this unfeasible (Table S7a–f).

2.6. Covariates and Mediators

To identify the minimal sufficient covariate adjustment set, we used a directed acyclic graph (DAG) (Figures S1–S4) [39,40]. To be considered as a confounder variable, the covariate had to be associated with both the exposure and the outcome and precede them both in time. Based on the DAG, we adjusted the multivariable analyses for grandparental education and grandparental asthma. Grandparental asthma was defined based on positive report by the parents on the question: "Have your biological parents ever had asthma?" with separate answer categories for "mother" and "father". Grandparental education level was defined based on the question: "What was the highest level of education your mother/father has/had?", with categories primary school, secondary school and college/university.

In addition, parental asthma, offspring's own pollution/greenness exposures and pollution/greenness exposures during pregnancy (defined as birth year and the preceding year)

were included as potential mediators based on a priori hypothesis that they may lie in the pathway between parental air pollution/greenness exposures and offspring asthma/allergies.

2.7. Statistical Analyses

All statistical analyses were performed using Stata version 16.0.

Descriptive analyses were stratified by parental sex.

We performed multilevel logistic regression analyses to investigate associations between air pollutants and greenness categorized in tertiles (low, medium and high exposures; see definition for all categories in Table S5), and early-onset asthma and hay fever as binary outcomes. The analyses were complete case analyses, clustered by family (to account for siblings) and study centre, and stratified by parental sex. All models were adjusted for O_3 and NDVI (300 m buffer), except for the O_3 model which was adjusted for NO_2 and NDVI (300 m buffer) and the NDVI model which was adjusted for O_3 and NO_2. All models were also adjusted for grandparental education and grandparental asthma.

As sensitivity analyses, we fitted regression models separately for each country (Table S8a,b) and for parents born after 1985 (Table S9a,b). p-values < 0.05 were considered statistically significant.

Correlation analyses were performed for all exposures to decide which pollutants to include in the same models (Tables S10a,b and S11a–f).

Mediation analyses were performed to decompose the total effects of parental exposures to greenness and each air pollutant on offspring's outcomes into their direct and indirect (mediated) effects (Figure 2). Parental asthma, offspring's exposure during pregnancy and offspring's own exposure were all evaluated as potential mediators. In order to be a mediator, the exposure must be associated with the mediator and the mediator must be associated with the outcome. Mediation tests showed that offspring's own exposure and exposure during pregnancy were potential mediators between maternal pollution exposure (PM_{10}) and both offspring's outcomes. For the paternal line, exposure during pregnancy (O_3) was a potential mediator between paternal O_3 exposure and offspring hay fever.

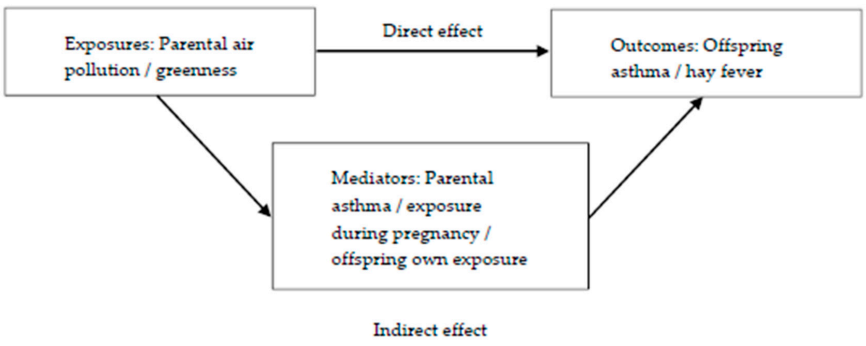

Figure 2. Mediation models for the effects of parental exposures (air pollution/greenness) on offspring's outcomes (asthma or hay fever).

The mediation analyses were conducted using ldecomp in Stata, a simple counterfactual mediation method that requires a categorical main exposure variable and a binary outcome, and allows any distribution of the mediator [41,42]. We used bootstrapping (1000 iterations) to obtain the 95% confidence interval (95%CI).

3. Results

The parents were on average 35 years old, and there were more mothers than fathers in the study population (Table 1). More mothers had asthma and hay fever compared to the fathers. The majority of the parents were never-smokers.

Table 1. Study population characteristics. *N* = 706 mothers and 400 fathers and their 1949 offspring.

Characteristics [a]	RHINESSA	
	Fathers	Mothers
	N (%)	*N* (%)
N	400 (36.2)	706 (63.8)
Umea	88 (22.0)	166 (23.5)
Uppsala	85 (21.3)	136 (19.3)
Gothenburg	58 (14.5)	93 (13.1)
Bergen	169 (42.2)	311 (44.1)
Offspring sex (male)	327 (48.2)	630 (49.6)
Offspring mean age (SD)	5.4 (3.6)	6.1 (4.2)
Offspring early-onset asthma (<10 years of age)	60 (15.0)	141 (20.0)
Offspring hay fever	27 (6.8)	70 (9.9)
Parental mean age (SD)	35.0 (3.8)	34.6 (3.9)
Parental asthma	62 (15.5)	128 (18.1)
Early-onset asthma	31 (7.8)	35 (5.0)
Late-onset asthma	28 (7.0)	88 (12.5)
Parental hay fever	125 (31.3)	193 (27.3)
Parental smoking onset		
Never-smokers	271 (67.8)	427 (60.5)
Smokers before 18 years old	103 (25.8)	246 (34.8)
Smokers after 18 years old	26 (6.5)	31 (4.4)
Parental education		
Primary school	9 (2.3)	22 (3.1)
Secondary school	137 (34.3)	185 (26.2)
College/university	253 (63.3)	498 (70.5)
Grandparental asthma	45 (11.3)	74 (10.5)

Abbreviations: SD, standard deviation. [a] Missing information (N): parental early-onset asthma (13), parental late-onset asthma (13), parental hay fever (14), parental smoking onset (4), parental education (4), grandparental asthma (31).

Mean air pollution exposures in the parents' childhood were lowest in Umea and highest in Gothenburg (NO_2 14.0 and 38.0 μg/m$_3$, $PM_{2.5}$ 10.3 and 24.4 μg/m^3, PM_{10} 16.5 and 28.6 μg/m$_3$, BC 0.09 and 1.09 μg/m^3), except for O_3, which was lowest in Bergen (62.7 μg/m^3) and highest in Umea (68.4 μg/m^3) (Table S12). Only annual mean values for $PM_{2.5}$ and PM_{10} exceeded WHO recommendations in some centres ($PM_{2.5}$ for parents 0–18 years old in Umea, Uppsala and Bergen; parents 0–18 years old and offspring 0–10 years old in Gothenburg; PM_{10} for parents 0–18 years old in Uppsala and Gothenburg). No annual mean exposures exceeded the recommended EU-values (Table S12).

The correlations between $PM_{2.5}$, PM_{10}, NO_2 and BC were medium to strong, while O_3 showed weaker correlation with the other pollutants (Table S10a,b).

Maternal medium $PM_{2.5}$ and PM_{10} exposure was associated with a higher risk of offspring early-onset asthma when compared to low exposure (Table 2). Maternal high PM_{10} exposure was associated with a higher risk of hay fever in offspring. Paternal medium O_3 exposure increased the risk of offspring hay fever, while paternal high BC exposure reduced the risk of offspring early-onset asthma when compared to low exposure. NO_2 and NDVI were not associated with any outcomes, neither in the maternal nor the paternal line.

Table 2. Univariable and multivariable analyses: associations between paternal (*N* = 400) and maternal (*N* = 706) exposure to air pollutants and NDVI and offspring (*N* = 1949) early-onset asthma (a) and hay fever (b) in the RHINESSA generation study.

(a) Early-Onset Asthma.									
		Univariable		Multivariable [3]		Univariable		Multivariable [3]	
Exposure [1]	Exposure Level [2]	Fathers (OR, 95% CI)	*p* [4]	Fathers (OR, 95% CI)	*p* [4]	Mothers (OR, 95% CI)	*p* [4]	Mothers (OR, 95% CI)	*p* [4]
NO_2	Medium	1.15 (0.58–2.30)	0.690	1.09 (0.51–2.32)	0.824	**1.69 (1.05–2.73)**	**0.032**	1.78 (0.96–3.31)	0.067
	High	0.70 (0.34–1.44)	0.332	0.50 (0.21–1.20)	0.120	**1.68 (1.04–2.72)**	**0.034**	1.79 (0.89–3.60)	0.101
$PM_{2.5}$	Medium	0.56 (0.27–1.14)	0.111	0.48 (0.20–1.14)	0.098	**2.09 (1.30–3.37)**	**0.002**	**2.23 (1.32–3.78)**	**0.003**
	High	0.70 (0.35–1.41)	0.320	0.53 (0.24–1.17)	0.115	1.55 (0.94–2.57)	0.088	1.66 (0.96–2.88)	0.072
PM_{10}	Medium	0.49 (0.23–1.04)	0.064	0.46 (0.20–1.09)	0.077	**2.13 (1.35–3.38)**	**0.001**	**2.27 (1.36–3.80)**	**0.002**
	High	0.82 (0.42–1.62)	0.567	0.65 (0.31–1.40)	0.273	1.39 (0.83–2.31)	0.209	1.46 (0.84–2.53)	0.183
BC	Medium	1.26 (0.64–2.46)	0.501	0.86 (0.40–1.87)	0.707	1.60 (1.00–2.58)	0.051	1.45 (0.83–2.54)	0.186
	High	0.48 (0.22–1.04)	0.064	**0.31 (0.11–0.87)**	**0.026**	1.57 (0.98–2.53)	0.060	1.33 (0.69–2.58)	0.393
O_3	Medium	1.90 (0.95–3.80)	0.071	1.93 (0.93–4.01)	0.079	0.81 (0.52–1.27)	0.366	0.86 (0.53–1.39)	0.542
	High	1.25 (0.60–2.60)	0.550	1.09 (0.42–2.82)	0.852	0.67 (0.42–1.06)	0.084	0.97 (0.52–1.82)	0.923
NDVI (300 m)	Medium	0.65 (0.30–1.42)	0.279	0.56 (0.26–1.20)	0.138	1.17 (0.74–1.85)	0.505	1.25 (0.79–2.00)	0.341
	High	0.76 (0.39–1.47)	0.411	0.67 (0.31–1.42)	0.297	0.78 (0.46–1.31)	0.341	1.00 (0.59–1.72)	0.987
(b) Hay Fever.									
		Univariable		Multivariable [3]		Univariable		Multivariable [3]	
Exposure [1]	Exposure Level [2]	Fathers (OR, 95% CI)	*p* [4]	Fathers (OR, 95% CI)	*p* [4]	Mothers (OR, 95% CI)	*p* [4]	Mothers (OR, 95% CI)	*p* [4]
NO_2	Medium	1.67 (0.65–4.26)	0.285	2.72 (0.82–9.02)	0.103	1.13 (0.55–2.34)	0.740	1.52 (0.51–4.56)	0.454
	High	1.24 (0.45–3.40)	0.680	2.41 (0.60–9.65)	0.213	**2.01 (1.04–3.90)**	**0.039**	2.84 (0.88–9.19)	0.081
$PM_{2.5}$	Medium	1.46 (0.48–4.45)	0.510	1.72 (0.44–6.80)	0.438	1.69 (0.83–3.46)	0.151	1.85 (0.85–4.00)	0.121
	High	2.26 (0.75–6.85)	0.149	2.78 (0.77–10.10)	0.120	1.97 (0.99–3.91)	0.052	1.90 (0.91–3.97)	0.086
PM_{10}	Medium	1.24 (0.40–3.88)	0.708	1.90 (0.46–7.87)	0.375	1.71 (0.83–3.52)	0.147	1.85 (0.85–4.01)	0.121
	High	2.34 (0.78–7.00)	0.127	3.41 (0.87–13.30)	0.078	**2.44 (1.26–4.72)**	**0.008**	**2.66 (1.19–5.91)**	**0.017**
BC	Medium	2.10 (0.75–5.89)	0.160	2.52 (0.81–7.88)	0.112	1.50 (0.74–3.04)	0.257	1.70 (0.70–4.16)	0.243
	High	1.37 (0.46–4.05)	0.575	2.56 (0.70–9.37)	0.157	1.99 (1.00–3.97)	0.052	2.71 (0.96–7.65)	0.060
O_3	Medium	**3.30 (1.16–9.40)**	**0.025**	**4.15 (1.28–13.50)**	**0.018**	1.33 (0.70–2.52)	0.383	1.56 (0.79–3.06)	0.198
	High	1.91 (0.63–5.80)	0.253	2.78 (0.58–13.26)	0.199	0.84 (0.42–1.68)	0.618	1.62 (0.54–4.82)	0.389
NDVI (300 m)	Medium	0.80 (0.27–2.36)	0.683	0.72 (0.24–2.14)	0.551	1.18 (0.60–2.33)	0.629	1.29 (0.65–2.57)	0.460
	High	1.22 (0.48–3.13)	0.681	1.35 (0.44–4.19)	0.602	1.15 (0.58–2.30)	0.683	1.57 (0.72–3.43)	0.257

Abbreviations: BC, black carbon; CI, confidence interval; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 μm. [1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] The low exposure group was used as the reference group. [3] All models were adjusted for O_3 and NDVI (300 m buffer), except for the O_3 model which was adjusted for NO_2 and NDVI (300 m buffer) and the NDVI model which was adjusted for O_3 and NO_2. All models were also adjusted for grandparental education and grandparental asthma. [4] All *p*-values < 0.05 = significant and marked bold.

Sensitivity analyses revealed protective associations of paternal high NDVI exposure (1000 m) for offspring early-onset asthma (Table S6b). Sensitivity analyses stratified by country and for parents born after 1985 gave roughly the same patterns, but with some variations due to low numbers (Tables S8a,b and S9a,b).

Maternal PM_{10} exposure had a direct effect on offspring early-onset asthma (Table 3) and an indirect effect on offspring hay fever (mediated by offspring's own exposure and by exposure during pregnancy) (Table 3). Paternal O_3 exposure was associated with increased odds for offspring hay fever through a direct and total effect, and was not mediated by O_3 exposure during pregnancy.

Table 3. Mediation analysis of the association between parental exposure and offspring early-onset asthma and hay fever (outcome) through exposure during pregnancy and offspring own exposure (potential mediators).

(a) Early-Onset Asthma.				
Mediator	**Parental exposure**	**Offspring Early-Onset Asthma**		
		Total Effect	**Indirect Effect**	**Direct Effect**
		OR (95% CI) *	**OR (95% CI) ***	**OR (95% CI) ***
Exposure during pregnancy (PM_{10})	**PM_{10} (maternal)**			
	Low	1.00	1.00	1.00
	Medium	**2.08 (1.31–3.31)**	1.10 (0.97–1.25)	**1.89 (1.17–3.06)**
	High	1.36 (0.85–2.19)	1.20 (0.96–1.50)	**1.13 (0.67–1.93)**
(b) Hay Fever.				
Mediator	**Parental exposure**	**Offspring Hay Fever**		
		Total Effect	**Indirect Effect**	**Direct Effect**
		OR (95% CI) *	**OR (95% CI) ***	**OR (95% CI) ***
Offspring own exposure (PM_{10})	**PM_{10} (maternal)**			
	Low	1.00	1.00	1.00
	Medium	1.75 (0.75–4.04)	**1.24 (1.08–1.44)**	1.40 (0.60–3.27)
	High	**2.70 (1.20–6.08)**	**1.73 (1.25–2.39)**	1.56 (0.66–3.69)
Exposure during pregnancy (PM_{10})	**PM_{10} (maternal)**			
	Low	1.00	1.00	1.00
	Medium	1.79 (0.79–4.08)	**1.49 (1.22–1.83)**	1.20 (0.52–2.74)
	High	**2.71 (1.24–5.93)**	**2.02 (1.49–2.76)**	1.34 (0.61–2.94)
Exposure during pregnancy (O_3)	**O_3 (paternal)**			
	Low	1.00	1.00	1.00
	Medium	**5.48 (1.50–20.1)**	1.10 (0.80–1.50)	**5.00 (1.31–19.1)**
	High	4.14 (0.69–24.9)	1.16 (0.70–1.94)	3.55 (0.53–24.0)

Abbreviations: CI, confidence interval; O_3, ozone; OR, odds ratio; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm. * All p-values < 0.05 = significant and marked bold.

4. Discussion

Exposure to $PM_{2.5}$ and PM_{10} in mothers' childhood was associated with higher risk of offspring early-onset asthma, and exposure to PM_{10} was associated with higher risk of offspring hay fever. Fathers' exposure to O_3 was associated with more offspring hay fever, while fathers' BC exposure was associated with less offspring early-onset asthma. NO_2 and NDVI were not significantly associated with any of offspring's outcomes in neither the maternal nor paternal line, although a protective NDVI association was suggested with a larger buffer zone. The association between maternal exposure to PM_{10} and offspring early-onset asthma was a direct effect, while the effect on offspring hay fever was indirect, mediated by exposures during pregnancy and offspring's own childhood. The association between paternal O_3 exposure and offspring hay fever was direct and not mediated by other factors.

To the best of our knowledge, this is the first study to investigate the associations between individual exposures to air pollution and greenness during childhood of one generation on lung health and allergy in the second generation. In previous literature, the focus on the parents' role in offspring's health revolves around maternal factors and in particular exposures during pregnancy. Recent studies associating prenatal air pollution exposure in mothers with childhood asthma show how maternal

environmental exposure just before and during pregnancy is critical for fetal lung development and future respiratory health [43–45]. Our results expand and elaborate on this, suggesting that also exposures as far back in time as the childhood of the parents may play an important role in offspring health.

A possible explanation for our findings is that potential epigenetic processes can be induced in response to environmental exposures and influence disease risk also in the next generation [46]. Even air pollution levels that are below recommended limit values may through such epigenetic processes have a potential harmful effect on the respiratory health of future offspring. While we found clearer signals in the maternal than in the paternal line, previous studies have identified associations between paternal exposures and offspring asthma. One study discovered an association between paternal smoking prior to conception and offspring non-allergic early-onset asthma, while other studies found associations between smoking and overweight onset in adolescent boys and increased risk of asthma in the next generation [25,27,47]. A similar pattern was observed in our study were fathers' exposure to O_3 was associated with higher risk of offspring hay fever. However, we also found a seemingly protective association between paternal BC exposure and offspring early-onset asthma. The estimates in the paternal line should be interpreted with caution due to low number of fathers in our analysis, but this is nevertheless a surprising result that should be investigated further. Ideally, information on both parents should be included in the same analyses to give a complete picture of the possible epigenetic processes. Unfortunately, we only had information on one parent and his/her offspring in our study, and not on entire family units. Analyses of offspring with both parents in a long timeframe should be emphasized in future research.

Our study revealed few associations between exposure to greenness and early-onset asthma or hay fever in offspring. This may be because we do not have data on the time spent in green spaces. In the sensitivity analyses performed for wider NDVI buffer zones, we observed protective associations for offspring early-onset asthma after parental exposure to high levels of NDVI. For offspring hay fever, NDVI exposure was on the contrary associated with increased risk. The latter is in line with existing literature, and is possibly due to pollen exposure triggering allergic disease [17,48].

A noteworthy feature in our study was that medium parental exposure levels were associated with significantly increased risk for offspring asthma and hay fever, despite the fact that these levels are quite low—even high exposure levels in our study were in fact well beyond the international recommended limit values. It appears that there were no clear dose–response relation between parental air pollution exposures and offspring disease risk—for offspring asthma, the risk was actually highest for those whose parents were medium exposed. This may be related to the importance of the exposure time window and the epigenetic processes discussed above. In a study by Svanes et al. [25], the age of smoking onset in the parents was an important risk factor for asthma in their offspring, even after adjustment for the number of cigarettes they had smoked before conception. Moreover, a recent epigenome-wide association study showed associations between pre-conception paternal smoking and DNA methylation characteristics in adult and adolescent offspring—independent of the amount smoked [49]. Our findings suggest that the same patterns may be present for air pollution exposures as for smoking exposures. Given the low levels of exposures, these results suggest the need for re-evaluation of the recommended limit values.

Associations between air pollutants are complex, and one could hypothesize that there are interactive effects at play. The focus of the present study on inter-generational effects of relatively low air pollution exposure is however still in its early days. There is a need to establish evidence that there are certain basic associations before moving on to disentangle whether these exposures depend on interactions and/or which pollutants are of most importance with regard to respiratory health in the next generation. The exploration of interactive inter-generational effects of air pollution components on lung health would be a valuable next step for future studies.

We focused on residential air pollution exposures, but exposures can be substantially higher when commuting, compared to being at home. Children spend only around 40–50% of their time

at home [50]. However, in most Scandinavian cities, it is common to live in close proximity of the children's school or kindergarten and it is therefore likely that the true everyday air pollution and greenness exposures are similar to the residential exposure levels.

Associations between maternal PM_{10} childhood exposure and offspring hay fever were mediated by offspring's own exposure and by maternal pregnancy exposure, while the effect was direct and unmediated with regard to early-onset asthma in offspring. These findings may suggest that asthma risk is susceptible for an epigenetic transmission across generations, while risk for hay fever is more likely triggered by own exposures. This could in turn imply a different transmission susceptibility for allergic asthma and non-allergic asthma. Unfortunately, we could not distinguish between allergic and non-allergic asthma in our study.

Correlation analyses revealed a strong correlation between pregnancy exposure and offspring childhood exposure, but weaker correlation between parental childhood exposures and pregnancy/offspring childhood exposures. Many parents moved to other areas with other levels of exposures after they grew up, and then settled in the same area during pregnancy and upbringing of children. This was also illustrated by the mediation analyses, where the effects of maternal childhood exposures to pollutants on offspring hay fever were mediated in the same manner by exposure during pregnancy and offspring's own childhood exposure.

There are several strengths of this study. The RHINESSA generation study was designed to study respiratory health across generations with detailed information on mothers and fathers and their offspring, making it possible to investigate different susceptibility time windows for developing disease. The detailed address history was collected for each participant, together with the standardized exposure assessment of numerous air pollutants. The extrapolation formulas from the LUR models enabled us to estimate concentrations for specific areas and time points by integrating data on topography, road network, traffic information and land use within geographic information systems, resulting in accurate exposure calculations also for unmonitored locations and years. Although we do not know the precise accuracy of our selected study centres, previous validation studies from the ESCAPE project have shown that the model has satisfactory accuracy, with 68 to 71% explained variance for the PM variables and 82% explained variance for NO2 [32,51].

Another strength is the mediation analysis to disentangle the effects of the exposures on the outcomes into the direct and indirect (mediated through offspring's own exposure and maternal exposure during pregnancy) components, and the use of DAGs to avoid over-adjustment in our analyses and to identify the possible mediators.

Some limitations should be acknowledged. First, population-based studies are vulnerable to bias. The response rate in RHINESSA was fairly low (around 40%). However, compared to the general population in the same age range, the RHINESSA population did not differ substantially when looking at demographic distributions (e.g., sex, smoking habits, educational level and asthma status) [28]. Additionally, recall bias is a challenge in many population-based studies. However, we do not suspect this in our study—partly due to exposure data being objectively registered based on residential address histories from the Norwegian and Swedish population registries, and with air pollution exposures being modelled by land-use regression models and greenness exposures being assigned through satellite images. Furthermore, the outcomes (offspring asthma and offspring hay fever) were not dependent on the parents' memory far back in time since their offspring were still young (mean age of 6 years). Second, in the current study, we tested numerous exposures for associations with the outcomes. This multiple testing can increase the possibility of more false positive findings due to type 1 error [52]. However, due to a relatively low sample size, we believe instead that there may be an under-estimation rather than over-estimation of the associations in our analyses. Thirdly, the use of back extrapolation methods in the air pollution assignments may be a weakness for assignments before 1990 since the 1990 estimates were used as a proxy for these years. Air pollutants (except for O_3) had a large variation over time, which may cause error in the earliest years. However, in additional analyses where we excluded all parents born before 1985, the patterns remained roughly unchanged, with pollutants as

asthma risk factors in the maternal line but not in the paternal line. Lastly, the information on included parents was self-reported through questionnaires, and information about children and grandparents was parent-reported, thus, posing a potential information bias. However, validation studies carried out in RHINESSA showed a minimal risk of bias for asthma, smoking status, body silhouettes and overweight status reported across generations [28,53,54].

5. Conclusions

In conclusion, this study found that air pollution exposure in a mother's childhood appeared to be a risk factor for early-onset asthma and hay fever in her future offspring. The observed effect of maternal exposures on asthma was direct, while the effect on hay fever was partly mediated through both offspring's own exposure and exposure during pregnancy. Results regarding fathers were inconclusive and should be investigated further. Furthermore, future research with larger study populations are needed to fully understand the intergenerational effects of air pollution and greenness on offspring asthma and hay fever. However, our results suggest that the current air pollution limit values may be too high and that the long-term effects of exposure to air pollution may have harmful effects even across generations.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/16/5828/s1, Table S1. Overview of the models used to calculate air pollution exposures. Table S2. Landsat images used for NDVI calculations. Table S3. NDVI assignment to addresses. Table S4. Mean annual average exposure (range) for NDVI buffer zones per center for parental exposure (0–18 years) and offspring's exposure (0–10 years). Table S5. Low, medium and high exposure categories for air pollutants for the time windows: parents (0–18 years) and offspring (0–10 years). Table S6. Associations of paternal (N = 400) and maternal (N = 706) exposure to additional buffer zones of NDVI with offspring (N = 1949) early-onset asthma (Table S6a) and hay fever (Table S6b) in the RHINESSA generation study. Table S7a–f. Correlation coefficients for the exposure time windows: parent (0–10 years) and parent (10–18 years) for each exposure. Table S8. Analyses stratified per country (Swedish centers versus Bergen): Associations between paternal (N = 400) and maternal (N = 706) exposure to air pollution and NDVI (300 m) and offspring (N = 1949) early-onset asthma (Table S8a) and hay fever (Table S8b) in the RHINESSA generation study. Table S9. Analyses for parents born after 1985: associations of paternal (N = 73) and maternal (N = 154) exposure to air pollutants and NDVI with offspring (N = 309) early-onset asthma (Table S9a) and hay fever (Table S9b) in the RHINESSA generation study. Table S10. Correlation coefficients for the included air pollutants and NDVI: parental exposure (S10a) and offspring exposure (S10b). Table S11a–f. Correlation coefficients for the exposure time windows: parent (0–18 years), pregnancy and offspring (0–10 years) per exposure. Table S12. Mean annual average exposure (range) for air pollutants and NDVI (300 m) per center for parent exposure (0–18 years) and offspring exposure (0–10 years). Figure S1. Directed acyclic graph for parental air pollution exposure and offspring's early-onset asthma. Figure S2. Directed acyclic graph for parental greenness exposure and offspring's early-onset asthma. Figure S3. Directed acyclic graph for parental air pollution exposure and offspring's hay fever. Figure S4. Directed acyclic graph for parental greenness exposure and offspring's hay fever.

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Conflicts of Interest: The second author, Iana Markevych, is an assistant guest editor of the Special Issue "Environmental Exposures and Health–Mechanisms and Their Contingencies in a Developmental Perspective" of IJERPH. The co-author, Joachim Heinrich, is a co-editor of IJERPH. All other authors declare that they have no conflicts of interest.

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Supplementary material

Table S1. Overview of the models used to calculate air pollution exposures.

Air pollutant	Study center	Model-year and source	
		2007	2010
NO_2	Umea, Uppsala, Gothenburg	-	de Hoogh et al 2016 (1)
	Bergen	-	de Hoogh et al 2016 (1)
$PM_{2.5}$	Umea, Uppsala, Gothenburg	-	de Hoogh et al 2016 (1)
	Bergen	-	de Hoogh et al 2016 (1)
PM_{10}	Umea, Uppsala, Gothenburg	Vienneau et al 2013 (2)	-
	Bergen	Vienneau et al 2013 (2)	-
BC	Umea, Uppsala, Gothenburg	-	de Hoogh et al 2018 (3)
	Bergen	-	de Hoogh et al 2018 (3)
O_3	Umea, Uppsala, Gothenburg	-	de Hoogh et al 2018 (3)
	Bergen	-	de Hoogh et al 2018 (3)

Abbreviations: BC, black carbon; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm.

Table S2. Landsat images used for NDVI calculations.

	Bergen, 201/18	Gothenburg, 195/20	Gothenburg, 196/19	Umea, 193/15	Umea, 193/16	Uppsala, 193/18	Uppsala, 193/19
2014	18/06/201, 8OLI	27/08/2014, 8OLI	21/08/2015, 8OLI	12/07/2014, 8OLI	25/07/2013, 8OLI	10/06/2014, 8OLI	10/06/2014, 8OLI
2009	03/07/2008, 5TM	26/06/2009, 5TM	01/06/2009, 5TM	28/06/2009, 5TM	28/06/2009, 5TM	28/06/2009, 5TM	28/06/2009, 5TM
2004	06/07/2003, 5TM	07/06/2002, 5TM	14/06/2002, 5TM	17/06/2005, 5TM	03/07/2005, 5TM	14/07/2003, 5TM	14/07/2003, 5TM
1999	03/06/1997, 5TM	17/06/2000, 5TM	08/06/2000, 5TM	20/07/1997, 5TM (194/15)	13/07/1997, 5TM	17/06/1999, 5TM	17/06/1999, 5TM
1994	29/07/1994, 5TM	30/06/1993, 5TM	24/06/1994, 5TM	05/07/1994, 5TM	05/07/1994, 5TM	05/07/1994, 5TM	05/07/1994, 5TM
1989	13/06/1989, 5TM	05/07/1989, 5TM	29/08/1989, 5TM	21/06/1989, 5TM	21/06/1989, 5TM	07/07/1989, 5TM	07/07/1989, 5TM
1984	18/06/1985, 5TM	27/06/1986, 5TM	02/06/1986, 5TM	26/06/1985, 5TM	26/06/1985, 5TM	09/07/1984, 5TM	09/07/1984, 5TM

Abbreviations: NDVI, normalized difference vegetation index; OLI, operational land imager; TM, thematic mapper.

Table S3. NDVI assignment to addresses.

NDVI map	Address year
1984	1975 to 1986

1989	1987 to 1991
1994	1992 to 1996
1999	1997 to 2001
2004	2002 to 2006
2009	2007 to 2011
2014	2012 to 2015

Abbreviations: NDVI, normalized difference vegetation index.

Table S4. Mean annual average exposure (range) for NDVI buffer zones per center for parental exposure (0-18 years) and offspring's exposure (0-10 years).

Average exposure (range)	Umea		Uppsala		Gothenburg		Bergen	
	Parent (0-18 years)	Offspring (0-10 years)	Parent (0-18 years)	Offspring (0-10 years)	Parent (0-18 years)	Offspring (0-10 years)	Parent (0-18 years)	Offspring (0-10 years)
NDVI 100m	0.565 (0.224-0.787)	0.514 (0.077-0.841)	0.581 (0.260-0.786)	0.574 (0.106-0.892)	0.532 (0.271-0.781)	0.608 (-0.056-0.862)	0.541 (0.097-0.747)	0.532 (0.107-0.771)
NDVI 300m	0.561 (0.276-0.777)	0.515 (0.154-0.815)	0.585 (0.376-0.768)	0.581 (0.216-0.846)	0.542 (0.236-0.710)	0.615 (0.170-0.833)	0.548 (0.188-0.773)	0.545 (0.096-0.788)
NDVI 500m	0.562 (0.296-0.780)	0.515 (0.169-0.823)	0.593 (0.391-0.758)	0.589 (0.212-0.871)	0.554 (0.211-0.723)	0.623 (0.150-0.838)	0.537 (0.157-0.751)	0.541 (0.116-0.762)
NDVI 1000m	0.564 (0.311-0.737)	0.518 (0.221-0.807)	0.611 (0.378-0.748)	0.599 (0.281-0.857)	0.561 (0.224-0.729)	0.620 (0.154-0.825)	0.527 (0.169-0.731)	0.523 (0.116-0.743)

Abbreviations: NDVI, normalized difference vegetation index.

Table S5. Low, medium and high exposure categories for air pollutants for the time windows: parents 0-18 years, offspring 0-10 years.

Range for exposure categories (based on tertiles)		Low	Medium	High	EU limit values	WHO guideline values
NO_2	**Parents 0-18 years**	<18.975	18.975-26.281	>26.281	40	40
	Offspring 0-10 years	<12.209	12.209-17.466	>17.466	40	40
$PM_{2.5}$	**Parents 0-18 years**	<13.655	13.655-16.859	>16.859	25	10
	Offspring 0-10 years	<8.208	8.208-10.102	>10.102	25	10
PM_{10}	**Parents 0-18 years**	<18.644	18.644-22.238	>22.238	40	20
	Offspring 0-10 years	<12.151	12.151-13.980	>13.980	40	20
BC	**Parents 0-18 years**	<0.443	0.443-0.903	>0.903	-	-
	Offspring 0-10 years	<0.297	0.297-0.558	>0.558	-	-
O_3	**Parents 0-18 years**	<63.700	63.700-67.144	>67.144	-	-
	Offspring 0-10 years	<64.289	64.289-67.823	>67.823	-	-
NDVI (100m)	**Parents 0-18 years**	<0.513	0.513-0.600	>0.600	-	-
	Offspring 0-10 years	<0.509	0.509-0.610	>0.610	-	-

NDVI (300m)	**Parents 0-18 years**	<0.520	0.520-0.597	>0.597	-	-
	Offspring 0-10 years	<0.522	0.522-0.612	>0.612	-	-
NDVI (500m)	**Parents 0-18 years**	<0.527	0.527-0.597	>0.597	-	-
	Offspring 0-10 years	<0.521	0.521-0.610	>0.610	-	-
NDVI (1000m)	**Parents 0-18 years**	<0.527	0.527-0.605	>0.605	-	-
	Offspring 0-10 years	<0.510	0.510-0.608	>0.608	-	-

Abbreviations: BC, black carbon; EU, European Union; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm; WHO, World Health Organization.

Table S6. Associations of paternal (N = 400) and maternal (N = 706) exposure to additional buffer zones of NDVI with offspring (N = 1949) early onset asthma (table S8a) and hay fever (table S8b) in the RHINESSA generation study.

S6a. Early onset asthma

Exposure	Exposure level	Univariable Fathers (OR, 95% CI)	p[2]	Multivariable[1] Fathers (OR, 95% CI)	p[2]	Univariable Mothers (OR, 95% CI)	p[2]	Multivariable[1] Mothers (OR, 95% CI)	p[2]
NDVI (100m)	Medium	0.60 (0.28-1.27)	0.180	0.53 (0.26-1.08)	0.080	1.19 (0.75-1.87)	0.465	1.23 (0.78-1.96)	0.374
	High	0.76 (0.39-1.49)	0.421	0.69 (0.33-1.45)	0.325	0.76 (0.46-1.25)	0.273	0.94 (0.55-1.60)	0.820
NDVI (500m)	Medium	0.55 (0.26-1.20)	0.132	0.55 (0.24-1.25)	0.156	0.97 (0.62-1.52)	0.881	1.00 (0.63-1.59)	0.999
	High	0.67 (0.34-1.31)	0.238	0.62 (0.30-1.28)	0.194	0.61 (0.37-1.01)	0.055	0.75 (0.44-1.29)	0.303
NDVI (1000m)	Medium	**0.36 (0.15-0.83)**	**0.018**	**0.33 (0.14-0.79)**	**0.012**	0.97 (0.62-1.53)	0.904	1.05 (0.65-1.68)	0.844
	High	0.62 (0.32-1.18)	0.143	0.49 (0.23-1.07)	0.086	**0.59 (0.36-0.96)**	**0.034**	0.68 (0.41-1.15)	0.152

Abbreviations: CI, confidence interval; NDVI, normalized difference vegetation index; OR, odds ratio. [1] Performed for all significant results from the univariable analyses. All models were adjusted for O_3 and NO_2, and in addition adjusted for grandparental education and grandparental asthma.[2] All p-values < 0.05 = significant and marked bold.

S6b. Hay fever

Exposure	Exposure level	Univariable Fathers (OR, 95% CI)	p[2]	Multivariable[1] Fathers (OR, 95% CI)	p[2]	Univariable Mothers (OR, 95% CI)	p[2]	Multivariable[1] Mothers (OR, 95% CI)	p[2]
NDVI (100m)	Medium	0.76 (0.26-2.23)	0.620	0.69 (0.26-1.84)	0.460	1.66 (0.85-3.24)	0.141	1.92 (0.94-3.90)	0.072
	High	1.68 (0.62-4.58)	0.308	2.04 (0.62-6.73)	0.240	1.45 (0.72-2.91)	0.296	1.92 (0.83-4.46)	0.129
NDVI (500m)	Medium	0.88 (0.30-2.61)	0.818	0.87 (0.30-2.54)	0.799	1.75 (0.91-3.37)	0.096	1.89 (0.96-3.73)	0.065
	High	1.27 (0.50-3.26)	0.613	1.24 (0.43-3.62)	0.691	1.18 (0.57-2.47)	0.657	1.45 (0.63-3.34)	0.381
NDVI (1000m)	Medium	1.55 (0.51-4.72)	0.441	1.45 (0.50-4.23)	0.495	1.33 (0.66-2.66)	0.420	1.34 (0.66-2.72)	0.415
	High	2.08 (0.73-5.92)	0.170	1.80 (0.58-5.58)	0.310	1.39 (0.69-2.82)	0.360	1.69 (0.79-3.63)	0.180

Abbreviations: CI, confidence interval; NDVI, normalized difference vegetation index; OR, odds ratio. [1] *Performed for all significant results from the univariable analyses. All models were adjusted for O_3 and NO_2, and in addition adjusted for grandparental education and grandparental asthma.* [2] *All p-values < 0.05 = significant and marked bold.*

Table S7. Correlation coefficients for the exposure time windows: parent (0-10 years) and parent (10-18 years).

S7a. NO_2

	Parents (0-10 years)	**Parents (10-18 years)**
Parents (0-10 years)	1.0	0.876
Parents (10-18 years)	0.876	1.0

Abbreviations: NO_2, nitrogen dioxide.

S7b. $PM_{2.5}$

	Parents (0-10 years)	**Parents (10-18 years)**
Parents (0-10 years)	1.0	0.909
Parents (10-18 years)	0.909	1.0

Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm.

S7c. PM_{10}

	Parents (0-10 years)	**Parents (10-18 years)**
Parents (0-10 years)	1.0	0.879
Parents (10-18 years)	0.879	1.0

Abbreviations: PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm.

S7d. BC

	Parents (0-10 years)	**Parents (10-18 years)**
Parents (0-10 years)	1.0	0.922
Parents (10-18 years)	0.922	1.0

Abbreviations: BC, black carbon.

S7e. O_3

	Parents (0-10 years)	**Parents (10-18 years)**

Parents (0-10 years)	1.0	0.903
Parents (10-18 years)	0.903	1.0

Abbreviations: O_3, ozone.

S7f. NDVI

	Parents (0-10 years)	**Parents (10-18 years)**
Parents (0-10 years)	1.0	0.728
Parents (10-18 years)	0.728	1.0

Abbreviations: NDVI, normalized difference vegetation index.

Table S8. Analyses stratified per country (Swedish centers versus Bergen): Associations between paternal (N = 400) and maternal (N = 706) exposure to air pollution and NDVI (300m) and offspring (N = 1949) early onset asthma (table S8a) and hay fever (table S8b) in the RHINESSA generation study.

S8a. Early onset asthma

Exposure[1]	**Centre**	**Exposure level**	**Univariable Fathers (OR, 95% CI)**	**p[3]**	**Multivariable[2] Fathers (OR, 95% CI)**	**p[3]**	**Univariable Mothers (OR, 95% CI)**	**p[3]**	**Multivariable[2] Mothers (OR, 95% CI)**	**p[3]**
NO_2	Swedish	Medium	2.14 (0.84-5.48)	0.113	1.77 (0.93-3.37)	0.081	1.53 (0.78-3.00)	0.213	**2.04 (1.07-3.87)**	**0.030**
		High	1.09 (0.44-2.75)	0.848	1.80 (0.80-4.05)	0.158	1.77 (0.94-3.36)	0.078	2.20 (1.00-4.84)	0.051
	Bergen	Medium	0.44 (0.17-1.18)	0.104	0.61 (0.15-2.41)	0.478	1.38 (0.69-2.78)	0.368	1.03 (0.43-2.47)	0.941
		High	**0.26 (0.08-0.86)**	**0.027**	0.43 (0.09-2.08)	0.295	1.28 (0.63-2.62)	0.497	0.91 (0.33-2.49)	0.857
$PM_{2.5}$	Swedish	Medium	1.12 (0.32-3.84)	0.862	1.19 (0.59-2.36)	0.629	1.36 (0.64-2.87)	0.422	1.39 (0.68-2.86)	0.368
		High	1.14 (0.46-2.84)	0.775	1.40 (0.70-2.82)	0.339	1.52 (0.81-2.85)	0.194	1.56 (0.77-3.15)	0.215
	Bergen	Medium	**0.28 (0.12-0.68)**	**0.005**	**0.23 (0.08-0.69)**	**0.009**	**2.45 (1.26-4.75)**	**0.008**	**2.69 (1.25-5.80)**	**0.011**
		High	-	-	-	-	1.76 (0.73-4.26)	0.207	2.13 (0.83-5.44)	0.115
PM_{10}	Swedish	Medium	0.65 (0.17-2.43)	0.524	1.02 (0.49-2.11)	0.954	1.46 (0.68-2.16)	0.330	1.26 (0.61-2.59)	0.536
		High	1.07 (0.43-2.62)	0.886	1.35 (0.72-2.52)	0.348	1.49 (0.81-2.74)	0.205	1.53 (0.82-2.87)	0.181
	Bergen	Medium	**0.33 (0.13-0.84)**	**0.020**	0.37 (0.13-1.07)	0.068	**2.22 (1.18-4.19)**	**0.014**	**2.31 (1.17-4.55)**	**0.016**
		High	0.56 (0.13-2.41)	0.433	0.80 (0.14-4.37)	0.792	1.04 (0.31-3.55)	0.948	0.98 (0.28-3.41)	0.974
BC	Swedish	Medium	1.21 (0.53-2.75)	0.644	1.23 (0.69-2.21)	0.483	1.46 (0.78-2.72)	0.233	1.27 (0.71-2.25)	0.421
		High	0.48 (0.16-1.45)	0.193	**0.34 (0.12-0.96)**	**0.043**	1.16 (0.58-2.30)	0.679	0.86 (0.38-1.98)	0.727
	Bergen	Medium	1.15 (0.28-4.67)	0.844	1.76 (0.41-7.59)	0.448	1.82 (0.70-4.75)	0.222	1.38 (0.49-3.92)	0.545
		High	0.42 (0.10-1.77)	0.236	0.94 (0.16-5.71)	0.950	1.95 (0.78-5-02)	0.166	1.51 (0.48-4.69)	0.480

O_3	Swedish	Medium	1.63 (0.41-6.41)	0.485	2.17 (0.60-7.86)	0.236	1.64 (0.59-4.53)	0.339	2.08 (0.74-5.86)	0.165
		High	1.09 (0.28-4.23)	0.901	2.30 (0.58-9.19)	0.237	1.31 (0.48-3.55)	0.600	2.16 (0.66-7.03)	0.201
	Bergen	Medium	2.21 (0.86-5.67)	0.098	1.81 (0.50-6.50)	0.362	0.72 (0.37-1.40)	0.337	0.75 (0.34-1.63)	0.467
		High	2.92 (0.52-16.4)	0.224	1.09 (0.09-12.6)	0.947	0.82 (0.30-2.24)	0.699	1.25 (0.33-4.64)	0.742
NDVI (300m)	Swedish	Medium	0.64 (0.22-1.84)	0.408	1.14 (0.64-2.05)	0.656	1.73 (0.86-3.48)	0.124	1.49 (0.84-2.64)	0.175
		High	0.54 (0.23-1.26)	0.153	0.93 (0.47-1.83)	0.841	1.02 (0.46-2.27)	0.966	1.08 (0.55-2.12)	0.814
	Bergen	Medium	0.68 (0.22-2.09)	0.507	0.63 (0.18-2.17)	0.463	0.81 (0.43-1.53)	0.516	0.80 (0.42-1.54)	0.509
		High	1.36 (0.47-3.93)	0.566	1.23 (0.43-3.49)	0.701	0.65 (0.33-1.28)	0.212	0.69 (0.32-1.49)	0.341

Abbreviations: BC, black carbon; CI, confidence interval; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm. [1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m buffer), except for the O_3-model that was adjusted for NO_2 and NDVI (300m buffer) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for grandparental education and grandparental asthma. [3] All p-values < 0.05 = significant and marked bold. - = Too few observations.

S8b. Hay fever

Exposure[1]	Centre	Exposure level	Univariable Fathers (OR, 95% CI)	p[3]	Multivariable[2] Fathers (OR, 95% CI)	p[3]	Univariable Mothers (OR, 95% CI)	p[3]	Multivariable[2] Mothers (OR, 95% CI)	p[3]
NO_2	Swedish	Medium	**4.63 (1.34-16.01)**	**0.016**	**2.96 (1.28-6.89)**	**0.011**	2.24 (0.90-5.59)	0.083	**3.81 (1.60-9.14)**	**0.003**
		High	2.54 (0.72-9.02)	0.149	2.02 (0.57-7.11)	0.275	**3.10 (1.33-7.22)**	**0.009**	**3.80 (1.22-11.85)**	**0.021**
	Bergen	Medium	0.32 (0.07-1.43)	0.135	0.33 (0.04-3.05)	0.327	0.36 (0.11-1.21)	0.098	0.32 (0.05-2.21)	0.247
		High	0.18 (0.02-1.56)	0.119	0.52 (0.02-12.6)	0.688	0.80 (0.27-2.32)	0.676	0.76 (0.11-5.22)	0.778
$PM_{2.5}$	Swedish	Medium	1.95 (0.41-9.29)	0.402	1.05 (0.41-2.68)	0.915	1.15 (0.37-3.58)	0.804	1.32 (0.52-3.39)	0.561
		High	2.41 (0.62-9.41)	0.205	1.44 (0.58-3.54)	0.428	2.02 (0.93-4.39)	0.075	1.96 (0.84-4.60)	0.119
	Bergen	Medium	1.28 (0.26-6.23)	0.757	1.93 (0.32-11.6)	0.473	2.56 (0.84-7.85)	0.100	**3.02 (1.07-8.56)**	**0.037**
		High	-	-	-	-	0.51 (0.06-4.62)	0.553	-	-
PM_{10}	Swedish	Medium	1.34 (0.25-7.19)	0.736	1.04 (0.35-3.05)	0.947	1.31 (0.33-5.20)	0.699	1.46 (0.52-4.13)	0.471
		High	2.52 (0.66-9.66)	0.178	2.31 (0.94-5.69)	0.069	**2.83 (1.31-6.08)**	**0.008**	**2.94 (1.23-7.03)**	**0.016**
	Bergen	Medium	1.23 (0.25-6.11)	0.798	3.57 (0.33-39.1)	0.298	1.81 (0.64-5.07)	0.261	2.69 (0.83-8.77)	0.101
		High	-	-	-	-	-	-	-	-
BC	Swedish	Medium	2.38 (0.78-7.28)	0.128	1.87 (0.88-3.97)	0.104	**2.35 (1.05-5.26)**	**0.038**	**2.31 (1.08-4.96)**	**0.031**
		High	1.49 (0.42-5.29)	0.538	1.00 (0.28-3.53)	0.997	**3.00 (1.26-7.10)**	**0.013**	2.74 (0.95-7.93)	0.063
	Bergen	Medium	1.26 (0.32-4.98)	0.746	0.82 (0.21-3.18)	0.772	0.53 (0.12-2.24)	0.385	0.68 (0.11-4.35)	0.683
		High	-	-	-	-	0.94 (0.27-3.36)	0.919	1.15 (0.21-6.40)	0.874
O_3	Swedish	Medium	2.16 (0.46-10.26)	0.331	1.09 (0.28-4.24)	0.900	0.85 (0.34-2.14)	0.731	0.91 (0.34-2.42)	0.855

		High	1.03 (0.21-4.93)	0.975	0.86 (0.17-4.32)	0.853	0.54 (0.21-1.34)	0.181	0.97 (0.26-3.65)	0.961
	Bergen	Medium	3.06 (0.70-13.40)	0.139	1.95 (0.50-7.59)	0.334	1.28 (0.46-3.55)	0.635	1.09 (0.26-4.68)	0.904
		High	5.52 (0.50-60.90)	0.163	-	-	-	-	-	-
NDVI	Swedish	Medium	0.66 (0.18-2.38)	0.526	1.10 (0.52-2.35)	0.798	1.19 (0.53-2.68)	0.666	1.26 (0.62-2.56)	0.523
(300m)		High	0.76 (0.25-2.31)	0.623	1.46 (0.57-3.74)	0.425	0.76 (0.32-1.84)	0.545	1.36 (0.60-3.06)	0.462
	Bergen	Medium	2.16 (0.20-23.32)	0.527	1.95 (0.50-7.59)	0.334	1.13 (0.32-4.00)	0.851	1.00 (0.30-3.32)	0.997
		High	5.53 (0.63-48.49)	0.122	-	-	2.31 (0.75-7.14)	0.147	1.70 (0.44-6.66)	0.443

Abbreviations: BC, black carbon; CI, confidence interval; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm. [1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m buffer), except for the O_3-model that was adjusted for NO_2 and NDVI (300m buffer) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for grandparental education and grandparental asthma. [3] All p-values < 0.05 = significant and marked bold. - = Too few observations.

Table S9. Analyses for parents born after 1985: Associations of paternal (N = 73) and maternal (N = 154) exposure to air pollutants and NDVI with offspring (N = 309) early onset asthma (Table 9a) and hay fever (Table 9b) in the RHINESSA generation study.

Table S9a. Early onset asthma

Exposure[1]	**Exposure level**	**Univariable Fathers (OR, 95% CI)**	**p[3]**	**Multivariable[2] Fathers (OR, 95% CI)**	**p[3]**	**Univariable Mothers (OR, 95% CI)**	**p[3]**	**Multivariable[2] Mothers (OR, 95% CI)**	**p[3]**
NO_2	Medium	1.21 (0.24-6.25)	0.816	0.39 (0.04-4.04)	0.430	2.40 (0.66-8.70)	0.183	7.76 (0.88-68.03)	0.064
	High	0.77 (0.14-4.42)	0.772	0.10 (0.00-3.09)	0.190	2.99 (0.85-10.47)	0.087	**14.0 (1.32-147.58)**	**0.028**
$PM_{2.5}$	Medium	-	-	-	-	2.22 (0.67-7.41)	0.195	2.65 (0.63-11.22)	0.184
	High	0.37 (0.05-2.99)	0.353	0.13 (0.01-3.27)	0.216	1.95 (0.51-7.49)	0.331	3.63 (0.85-15.48)	0.081
PM_{10}	Medium	0.18 (0.02-1.61)	0.126	**0.09 (0.01-0.88)**	**0.039**	1.61 (0.46-5.66)	0.456	1.92 (0.49-7.46)	0.349
	High	0.40 (0.05-3.28)	0.396	0.11 (0.00-4.77)	0.250	1.82 (0.49-6.80)	0.371	3.36 (0.89-12.71)	0.074
BC	Medium	1.83 (0.36-9.23)	0.462	1.15 (0.17-7.61)	0.885	3.06 (0.82-11.37)	0.095	4.84 (0.84-28.00)	0.078
	High	1.05 (0.16-6.66)	0.961	0.21 (0.01-4.23)	0.307	2.22 (0.59-8.30)	0.236	3.66 (0.44-30.84)	0.232
O_3	Medium	0.86 (0.16-4.56)	0.858	0.59 (0.06-5.48)	0.638	0.61 (0.14-2.59)	0.501	0.49 (0.11-2.07)	0.330
	High	0.33 (0.05-2.22)	0.256	0.08 (0.00-2.82)	0.163	0.61 (0.19-1.96)	0.407	3.79 (0.52-27.78)	0.190
NDVI (300m)	Medium	0.20 (0.02-1.73)	0.144	0.25 (0.03-2.32)	0.214	1.15 (0.31-4.22)	0.834	1.20 (0.29-5.01)	0.807
	High	0.59 (0.12-2.87)	0.511	0.41 (0.07-2.55)	0.340	0.25 (0.04-1.52)	0.132	0.26 (0.05-1.36)	0.111

Abbreviations: BC, black carbon; CI, confidence interval; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm. [1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m buffer), except for the O_3-model that was adjusted for NO_2 and NDVI (300m buffer) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for grandparental education and grandparental asthma. [3] All p-values < 0.05 = significant and marked bold. - = Too few observations.

Table S9b. Hay fever

Exposure[1]	Exposure level	Univariable Fathers (OR, 95% CI)	p[3]	Multivariable[2] Fathers (OR, 95% CI)	p[3]	Univariable Mothers (OR, 95% CI)	p[3]	Multivariable[2] Mothers (OR, 95% CI)	p[3]
NO_2	Medium	-	-	-	-	2.14 (0.29-15.97)	0.458	5.78 (0.36-93.52)	0.216
	High	3.36 (0.19-59.54)	0.408	-	-	3.55 (0.56-22.46)	0.178	8.93 (0.32-245.97)	0.196
$PM_{2.5}$	Medium	-	-	-	-	3.67 (0.49-27.35)	0.205	4.68 (0.76-28.92)	0.097
	High	0.30 (0.02-5.56)	0.415	-	-	5.24 (0.83-33.13)	0.078	4.23 (0.54-33.17)	0.169
PM_{10}	Medium	-	-	-	-	3.62 (0.49-26.97)	0.209	3.80 (0.59-24.45)	0.160
	High	0.21 (0.01-3.85)	0.291	-	-	5.55 (0.88-35.14)	0.069	3.90 (0.60-25.41)	0.155
BC	Medium	-	-	-	-	2.28 (0.37-14.15)	0.376	3.11 (0.26-37.33)	0.371
	High	0.31 (0.02-5.48)	0.423	-	-	1.83 (0.24-13.91)	0.561	3.93 (0.17-90.61)	0.393
O_3	Medium	-	-	-	-	6.23 (0.71-54.25)	0.098	3.59 (0.36-35.86)	0.276
	High	1.94 (0.11-33.82)	0.648	-	-	2.54 (0.23-28.46)	0.450	6.57 (0.24-180.40)	0.266
NDVI (300m)	Medium	-	-	-	-	1.02 (0.14-7.38)	0.988	1.48 (0.14-15.50)	0.741
	High	0.38 (0.02-6.63)	0.506	-	-	1.11 (0.19-6.67)	0.906	1.84 (0.21-15.89)	0.580

Abbreviations: BC, black carbon; CI, confidence interval; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm. [1] All air pollutants exposures were back-extrapolated in time with the ratio method. [2] All models were adjusted for O_3 and NDVI (300m buffer), except for the O_3-model that was adjusted for NO_2 and NDVI (300m buffer) and the NDVI-model that was adjusted for O_3 and NO_2. All models were also adjusted for grandparental education and grandparental asthma. [3] All p-values < 0.05 = significant and marked bold. - = Too few observations.

Table S10. Correlation coefficients for the included air pollutants and NDVI.

S10a. Parental exposure

Air pollutant	$PM_{2.5}$	PM_{10}	NO_2	BC	O_3	NDVI
$PM_{2.5}$	1.0	0.917	0.873	0.657	-0.404	-0.267
PM_{10}	0.917	1.0	0.793	0.639	-0.291	-0.251
NO_2	0.873	0.793	1.0	0.786	-0.651	-0.432
BC	0.657	0.629	0.786	1.0	-0.814	-0.310
O_3	-0.404	-0.291	-0.651	-0.814	1.0	0.380
NDVI[1]	-0.267	-0.251	-0.432	-0.310	0.380	1.0

Abbreviations: BC, black carbon; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm.
[1]300-m buffer.

S10b. Offspring's exposure

Air pollutant	$PM_{2.5}$	PM_{10}	NO_2	BC	O_3	NDVI

$PM_{2.5}$	1.0	0.966	0.742	0.697	-0.298	0.190
PM_{10}	0.966	1.0	0.725	0.738	-0.310	0.213
NO_2	0.742	0.725	1.0	0.872	-0.318	0.013
BC	0.697	0.738	0.872	1.0	-0.230	0.112
O_3	-0.298	-0.310	-0.318	-0.230	1.0	0.007
NDVI[1]	0.190	0.213	0.013	0.112	0.007	1.0

Abbreviations: BC, black carbon; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm.
[1]300-m buffer.

Table S11. Correlation coefficients for the exposure time windows: parent (0-18 years), pregnancy and offspring (0-10 years).

S11a. NO_2

	Parents (0-18 years)	**Pregnancy**	**Offspring (0-10 years)**
Parents (0-18 years)	1.0	0.418	0.433
Pregnancy	0.418	1.0	0.859
Offspring (0-10 years)	0.433	0.859	1.0

Abbreviations: NO_2, nitrogen dioxide.

S11b. $PM_{2.5}$

	Parents (0-18 years)	**Pregnancy**	**Offspring (0-10 years)**
Parents (0-18 years)	1.0	0.542	0.590
Pregnancy	0.542	1.0	0.839
Offspring (0-10 years)	0.590	0.839	1.0

Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm.

S11c. PM_{10}

	Parents (0-18 years)	**Pregnancy**	**Offspring (0-10 years)**
Parents (0-18 years)	1.0	0.522	0.574
Pregnancy	0.522	1.0	0.801
Offspring (0-10 years)	0.574	0.801	1.0

Abbreviations: PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm.

S11d. BC

	Parents (0-18 years)	Pregnancy	Offspring (0-10 years)
Parents (0-18 years)	1.0	0.467	0.476
Pregnancy	0.467	1.0	0.857
Offspring (0-10 years)	0.476	0.857	1.0

Abbreviations: BC, black carbon.

S11e. O_3

	Parents (0-18 years)	Pregnancy	Offspring (0-10 years)
Parents (0-18 years)	1.0	0.465	0.478
Pregnancy	0.465	1.0	0.841
Offspring (0-10 years)	0.478	0.841	1.0

Abbreviations: O_3, ozone.

S11f. NDVI

	Parents (0-18 years)	Pregnancy	Offspring (0-10 years)
Parents (0-18 years)	1.0	0.205	0.176
Pregnancy	0.205	1.0	0.737
Offspring (0-10 years)	0.176	0.737	1.0

Abbreviations: NDVI, normalized difference vegetation index.

Table S12. Mean annual average exposure (range) for air pollutants and NDVI (300m) per center for parent exposure (0-18 years) and offspring exposure (0-10 years).

Average exposure (range)[a]	Umea		Uppsala		Gothenburg		Bergen		EU limit values	WHO limit values
	Parent (0-18 years)	Offspring (0-10 years)	Parent (0-18 years)	Offspring (0-10 years)	Parent (0-18 years)	Offspring (0-10 years)	Parent (0-18 years)	Offspring (0-10 years)		
NDVI 300m	0.561 (0.276-0.777)	0.515 (0.154-0.815)	0.585 (0.376-0.768)	0.581 (0.216-0.846)	0.542 (0.236-0.710)	0.615 (0.170-0.833)	0.548 (0.188-0.773)	0.545 (0.096-0.788)		
NO_2 µg/m³	14.0 (1.3-33.4)	10.9 (0.3-34.1)	22.5 (5.4-46.3)	14.4 (2.6-33.5)	38.0 (15.3-69.7)	19.0 (2.3-40.5)	23.7 (2.9-44.9)	16.1 (3.4-33.4)	40[b]	40[b]
$PM_{2.5}$ µg/m³	10.3 (1.2-20.0)	7.3 (0.5-19.1)	17.4 (9.8-25.7)	9.9 (4.5-17.6)	24.4 (14.8-29.8)	11.9 (6.0-17.1)	14.5 (3.9-22.8)	8.9 (2.4-14.9)	25[b]	10[b]
PM_{10} µg/m³	16.5 (11.8-25.1)	11.3 (7.6-19.3)	23.7 (16.7-32.5)	14.2 (9.2-20.2)	28.6 (19.8-37.0)	15.0 (10.8-20.9)	19.7 (13.3-27.0)	13.0 (7.7-18.9)	40[b]	20[b]
BC µg/m³	0.09 (0-1.09)	0.23 (0-1.50)	0.64 (0.20-1.42)	0.52 (0-1.45)	1.09 (0.51-1.89)	0.67 (0.10-1.59)	0.91 (0-2.43)	0.45 (0-1.21)	-	-

O_3 µg/m³	68.4 (62.6-73.3)	67.6 (58.1-75.0)	67.4 (62.3-71.3)	68.4 (56.3-75.5)	64.2 (57.6-70.5)	67.1 (57.3-76.2)	62.7 (51.2-74.6)	64.0 (54.3-76.6)	-[c]	-[c]

Abbreviations: BC, black carbon; EU, European Union; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 µm; PM_{10}, particulate matter with an aerodynamic diameter lower than 10 µm; WHO, World Health Organization.[a] All air pollutants exposures were back-extrapolated in time with the ratio method. [b] Annual mean values. [c] Only maximum daily 8-hour mean values available.

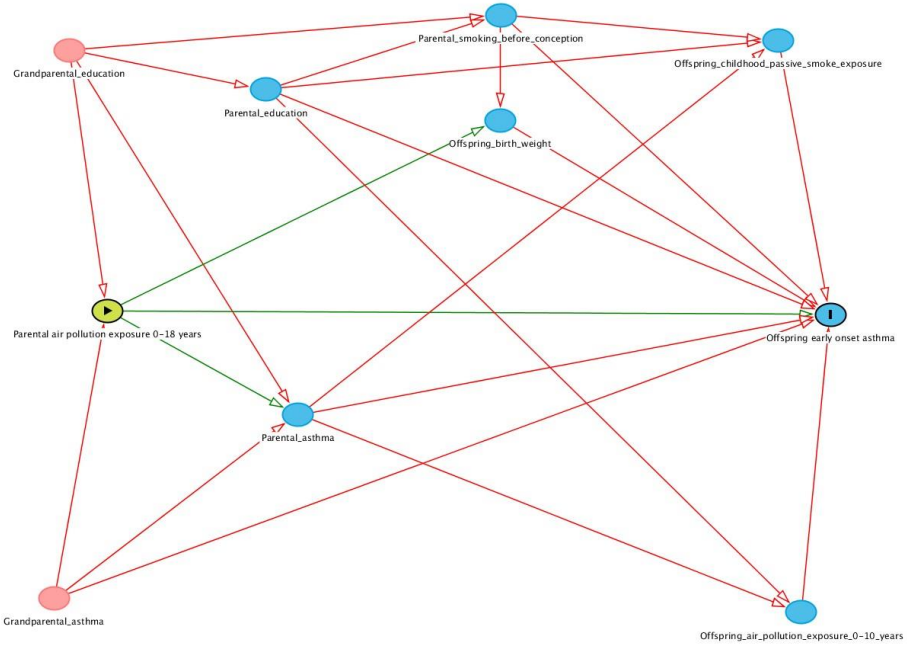

Figure S1. Directed Acyclic Graph for parental air pollution exposure and offspring's early onset asthma. Green circle with arrow: main exposure in the analysis. Blue circle with "I": main outcome. Other blue circles: risk factors for the outcome that are not risk factors for the exposure. Red circles: risk factors for both the outcome and the main exposure. Green arrows: paths from the main exposure. Red arrows: paths from other risk factors.

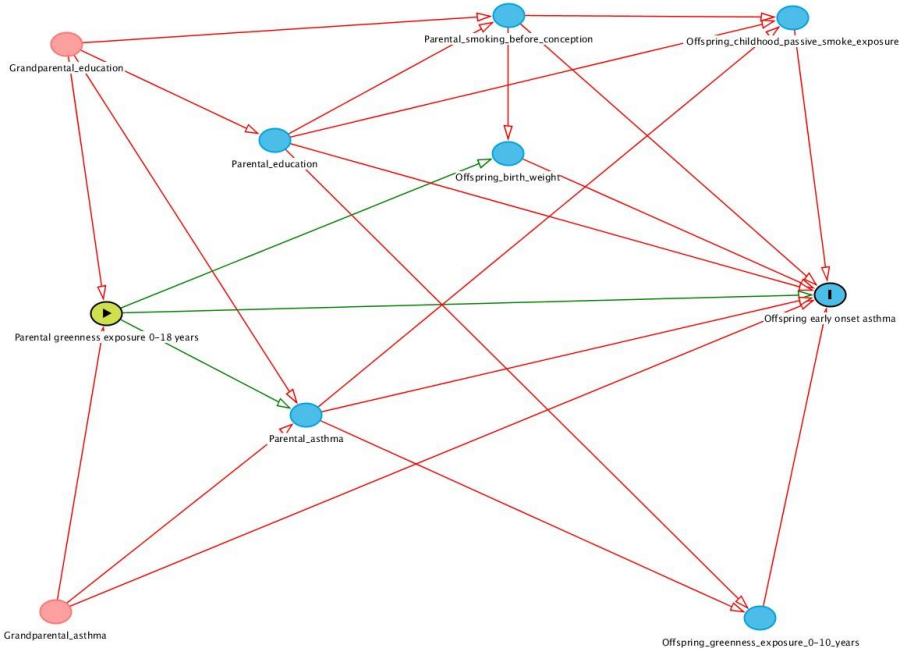

Figure S2. Directed Acyclic Graph for parental greenness exposure and offspring's early onset asthma. Green circle with arrow: main exposure in the analysis. Blue circle with "I": main outcome. Other blue circles: risk factors for the outcome that are not risk factors for the exposure. Red circles: risk factors for both the outcome and the main exposure. Green arrows: paths from the main exposure. Red arrows: paths from other risk factors.

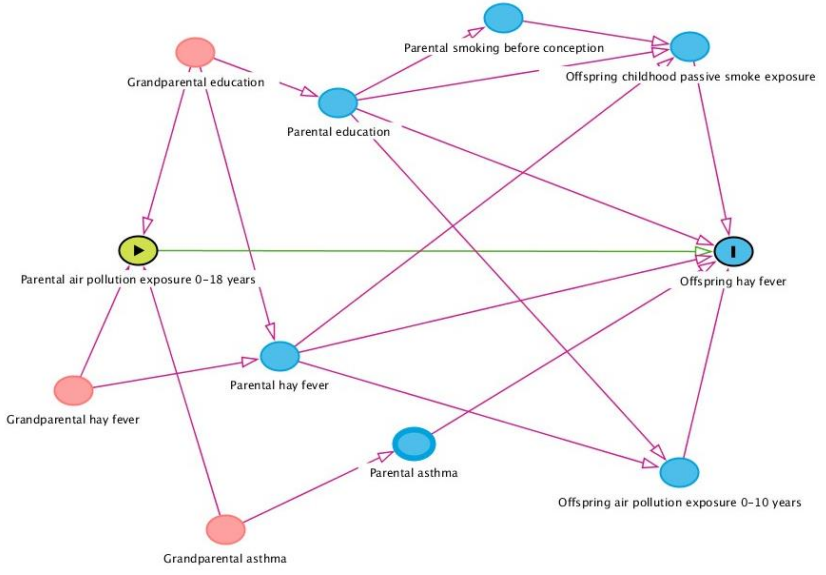

Figure S3. Directed Acyclic Graph for parental air pollution exposure and offspring's hay fever.
Green circle with arrow: main exposure in the analysis. Blue circle with "I": main outcome. Other blue circles: risk factors for the outcome that are not risk factors for the exposure. Red circles: risk factors for both the outcome and the main exposure. Green arrows: paths from the main exposure. Red arrows: paths from other risk factors.

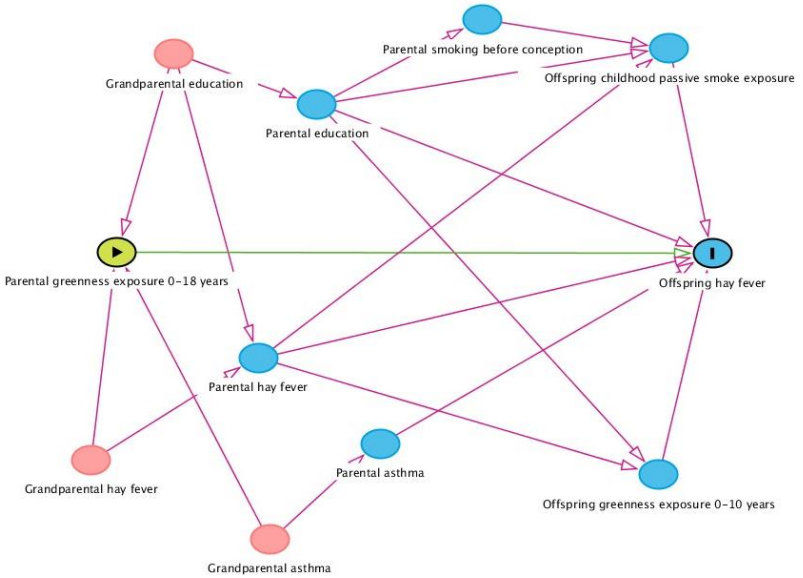

Figure S4. Directed Acyclic Graph for parental greenness exposure and offspring's hay fever. Green circle with arrow: main exposure in the analysis. Blue circle with "I": main outcome. Other blue circles: risk factors for the outcome that are not risk factors for the exposure. Red circles: risk factors for both the outcome and the main exposure. Green arrows: paths from the main exposure. Red arrows: paths from other risk factors.

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