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Report on the relationships of early-life stressors with transient and persistent common allergies, and the extent to which these mediate associations of early-life stressors with life course chronic obstructive respiratory health and disease trajectories

Work package 5 - Task 5.3 - Deliverable 5.3

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1. Summary

Background: Asthma is a major non-communicable disease affecting over 12% of children and estimated to affect 339 million people worldwide (1). Exposure to outdoor air pollutants such as particulate matter (PM) and nitrogen dioxide (NO_2) have been associated with both childhood asthma and allergies (2–9). However, whether allergies such as atopic dermatitis (eczema) and allergic rhinitis (hay fever) mediate the relationship has not been well-characterized.

Aim: To examine the relationship between exposure to air pollutants in early life with the development of childhood asthma and whether common allergies mediate this relationship.

Methods: We included cohorts with harmonized variables for childhood asthma diagnosis at 5 years of age and older, air pollution data during the pregnancy, and data on common allergies. Five cohorts with available data and stable Opal servers are reported here: ALSPAC, GenR, INMA, MoBa, NINFEA. A directed acyclic graph (DAG) was produced to determine potential confounding factors. Distribution of air pollutants and prevalence of childhood allergy and asthma and confounding variables were examined. Unadjusted and adjusted logistic regressions were performed with childhood asthma at 5 years of age or older as the dependent variable and with NO_2 and PM_{10} as separate exposures. The Baron and Kenny method was used to examine mediation by allergies on the relationship between air pollution on childhood asthma, and variables were standardized. Pooled analyses and study-level random effects meta-analyses were performed and forest plots generated. All analyses were carried out using DataSHIELD.

Results: Pooled analyses with NO2 and PM10 exposure showed significant total effect, direct, and indirect effects, indicating that air pollutants were associated with childhood asthma and that this effect was partially mediated through allergies. These results were not replicated in study-level meta-analyses where no total, direct, or indirect effects observed.

Conclusion: We observed inconsistent results between analytical approaches. These will be further explored in future analyses with new indicator variables for the mediator and outcome to ensure appropriate temporal ordering of variables, inclusion of a larger number of participating cohorts, and use of a DataSHIELD function currently under development which will allow for greater statistical power.

2. Introduction

Workpackage 5 of the LifeCycle project focuses on the associations between early-life stressors during preconception, pregnancy, infancy, and early childhood with lung function developmental trajectories and the risk of asthma from childhood until young adulthood. The specific objective of Task 5.3 is to examine the relationship between early-life stressors with transient and persistent common allergies and the extent to which these mediate the associations of early-life stressors with childhood asthma and adult chronic obstructive respiratory disease.

For our task, we focused on examining whether childhood allergies mediates the relationship between exposure to air pollution in early life and childhood asthma. The etiology of asthma is thought to be a complex interplay between environmental exposures (such as air pollution, mold, pollen, and the weather), genetic susceptibility, and host factors (such as infections and nutrition); the underlying mechanisms, while not fully understood, may include airway inflammation and control of reactivity and airway tone (10). In this proposal, we hypothesize that relationships between early-life stressors such as exposure to air pollutants and childhood asthma are at least partly mediated by common allergies. The atopic march, the linear progression starting with eczema with subsequent allergic rhinitis and asthma in later childhood is a well-known concept but it may not capture the trajectories of most children (11–13). Asthma often co-occurs with allergies like eczema and allergic rhinitis but the causal nature of this progression is unknown. Studies suggest that a dysfunctional skin barrier may be a site for allergic sensitization and contributes to the onset of eczema and progression to allergic rhinitis and childhood asthma (14). Eczema has often been found to precede development of asthma, but this is not always the case, with only an estimated 1-in-3 children with eczema developing childhood asthma later on (15,16). Similarly, asthma often co-occurs with allergic rhinitis due to shared common physiology such as heightened reactivity and bronchial hyper-responsiveness (17,18). It is considered a risk factor for asthma, with a 23-year follow-up finding allergic rhinitis three times more likely to develop asthma than those without allergic rhinitis (12,13) . However, the evolution of the two appear to be bidirectional; a study in Italy following 99 patients with only allergic rhinitis or allergic asthma over 10 years found that 31.8% of participants with allergic rhinitis developed asthma, while 50% of those with asthma went on to develop allergic rhinitis (19).

In this report, we describe which cohorts were included, the variable selection, the methods used and current results. We also describe the future direction of this work.

3. Data harmonization

Air pollution data

Workpackage 3 created the integrated harmonized indices for stressors in the urban environment using Geographic Information Systems (GIS) approahces. A GIS environment was set up at ISGlobal for centralized processing of the data in collaboration with each participating cohort. Cohorts provided address histories of cohort participants from pregnancy up to twelve years of age for geocoding. Exposures of interest, including air pollution, were assigned within the GIS environment to all geocoded addresses.

Exposure estimates for outdoor air pollutants were based on the land use regression (LUR) modelling approach developed in the European Study of Cohorts for Air Pollution Effects (ESCAPE) framework (20). For some cohorts such as ALSPAC and some exposures in INMA, exposure estimates using the LUR approach was not possible and models developed within the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) study were used (21).

Air pollution experienced during the pregnancy period were examined and log-transformed prior to analyses.

Mediator and outcome data

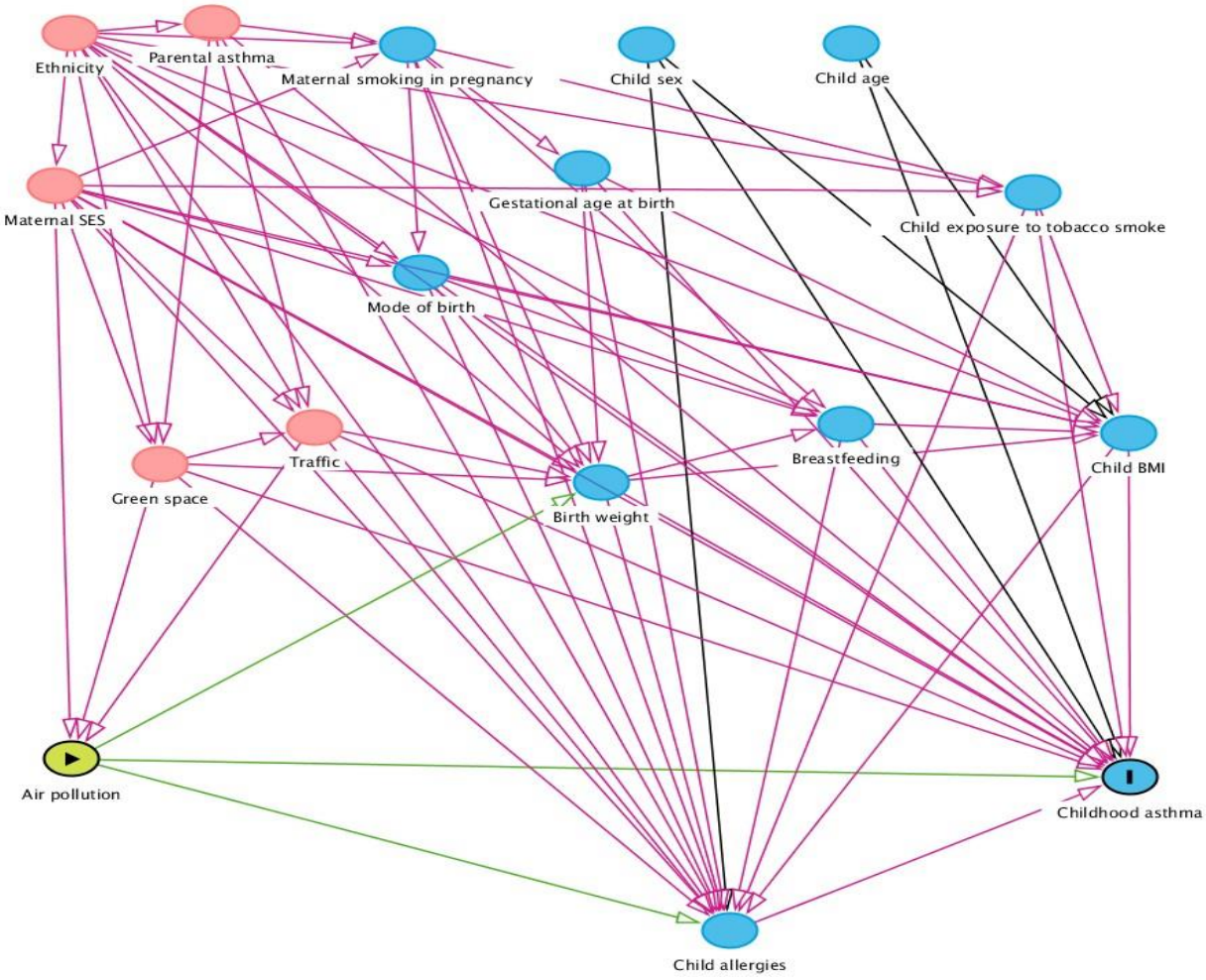
Tasks 5.1, 5.2, 5.3, and 5.4 of workpackage 5 developed a harmonization manual for respiratory and allergic variables based on data availability in the participating cohorts and prior experience. These included asthma and allergy diagnoses during each year of the child's life, as well as the child ever having allergies or asthma.

Doctor-diagnosed childhood asthma (yes; no) was defined according to the ISAAC-defined diagnosis of asthma occurring at age 5 and older (22). The ISAAC definiton requires that the child has a doctor-diagnosis of asthma as well as either wheezing in the previous 12 months or use of asthma medication in the previous 12 months.

Childhood allergies harmonized by cohorts include ever having had eczema, any inhalant allergy, and urticaria. A new indicator variable was derived where an individual was considered as having an allergy if they were recorded as ever having eczema, inhalant allergy, or urticaria. They were considered as never having an allergy if they were recorded as never having had eczema, inhalant allergy, and urticaria.

Covariate data

A directed acyclic graph (DAG) was drawn to identify potential confounding variables. In the following DAG, the minimum sufficient adjustment set for the total effect to close all biasing paths and leave causal paths open includes green space, maternal SES, and traffic. Traffic was not available across all cohorts and was not adjusted for in the final models.The final models adjusted for green space, maternal SES, child sex, mother's age, and mother's asthma.



4. Scientific output

Paper: Early-life exposure to air pollutants and childhood asthma: potential mediation by common allergies

Partners involved: **ERASMUS, ISGlobal, UNITO, UNIVBRIS, NIPH**

Summary: We examined associations between early-life exposure to nitrogen dioxide (NO_2) and particulate matter (PM_{10}) with childhood asthma at age 5 and older and whether this relationship is partly mediated by allergy. We used individual participant data of 19,765 children from 5 birth cohorts with NO_2 exposure and individual participant data of 13,073 children from 4 birth cohorts with PM_{10} exposure.

In cohorts participating in the NO_2 exposure analysis, exposure during the pregnancy period varied across cohorts with the lowest exposure occuring among MoBa participants (median [interquartile range; IQR]: 20.7 [15.6, 26.9] µg/m^3) and the highest among NINFEA participants (56.6 [47.2, 67.6] µg/m^3). Conversely, MoBa participants had the highest prevalence of any allergy (39.7%) and NINFEA participants the lowest (2.3%). ALSPAC participants had the highest prevalence of childhood asthma at age 5 years or older (22.3) and GenR participants the lowest (1.2%).

Cohort (N)		NO_2 exposure (µg/m^3) Median (IQR)	Any allergy N (%)	Childhood asthma N (%)
ALSPAC	5428	27.2 (24.4, 29.7)	816 (15.0)	1213 (22.3)
GenR	3728	38.4 (34.8, 42.3)	965 (25.9)	44 (1.2)
INMA	1237	26.6 (15.6, 39.9)	440 (35.5)	81 (6.5)
MoBa	6329	20.7 (15.6, 26.9)	2511 (39.7)	705 (11.1)
NINFEA	514	56.6 (47.2, 67.6)	12 (2.3)	25 (4.8)

N and values are from fully-adjusted models

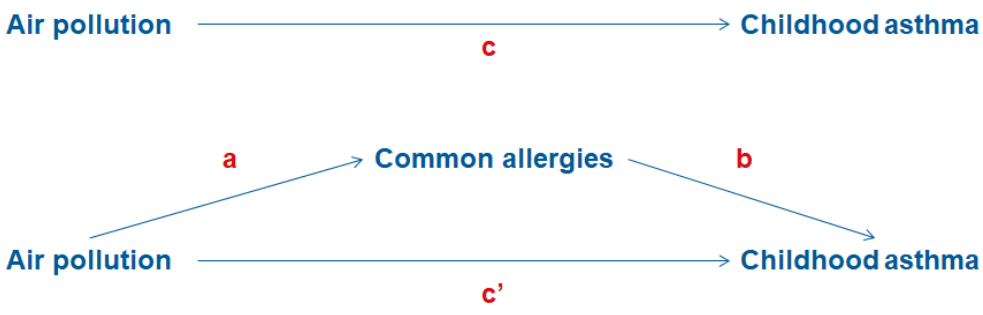
Similar patterns were observed among cohorts participating in the PM_{10} exposure analysis.

Cohort (N)		PM_{10} exposure ($\mu g/m^3$) Median (IQR)	Any allergy N (%)	Childhood asthma N (%)
GenR	3728	31.5 (28.6, 34.9)	965 (25.9)	44 (1.2)
INMA	426	32.7 (30.1, 34.9)	156 (36.6)	14 (3.3)
MoBa	6346	13.5 (11.6, 16.1)	2518 (39.7)	707 (11.1)
NINFEA	513	44.6 (37.9, 57.4)	12 (2.3)	25 (4.9)

N and values are from fully-adjusted models

We conducted mediation analysis using both a pooled (independent participant data) as well as a study-level meta-analysis using random effects models with exisitng DataSHIELD functions. In a mediation analysis, we presume that the exposure works at least partially through the mediator to affect the otucome; in our analysis, we preseume air pollution works at least partially through allergy to increase the risk of childhood asthma and that allergy would at least partially explain the underlying mechanism of the relationship between air pollution and childhood asthma. One support for undertaking a mediation analysis is that if mediation exists, then interventions could be created to modifying the mediating variable in order to have an impact on the health outcome.

We used the steps for mediation analysis following those laid out by Baron and Kenny (23). In their proposed method, a series of regressions are performed to establish relationships between corresponding variables to obtain unstandardized regression coefficients for paths *a, b, c,* and *c'*. Path *c* is known as the total effect and path *c'* is known as the direct effect.



In ordinary leart squares regression, an indirect effect can be computed as the product of the unstandardiazed coefficients from paths *a* and *b*; it can also be computed as the difference between

the total and direct effect $c - c'$ (24). This indirect effect gives the change in the outcome for each unit change in the exposure as mediated through the mediator and a significant indirect effect coefficient provides evidence of a mediation model. Perfect mediation occurs when the effect of the exposure on the outcome decreases to zero in the direct effect model; partial mediation occurs when the effect decreases.

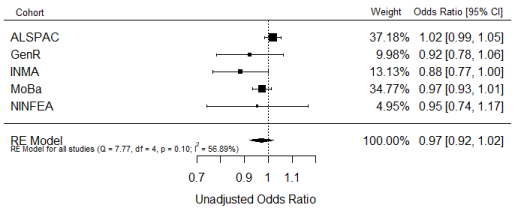
However, as the outcome under consideration is binary, the methods of calculating the indirect effect ab and $c - c'$ are no longer equivalent. Therefore, standardization of the variables were carried out prior to computing the indirect effect and the Sobel test for its standard error (25,26).

In pooled independent participant data analyses, we found a significant total effect where NO_2 exposure in pregnancy was associated with a reduced odds of childhood asthma. The direct effect shows that air pollution, when controlling for allergy, is associated with reduced odds of childhood asthma. The indirect effect shows the effect on childhood asthma of changes in NO_2 exposure which operate through allergies.

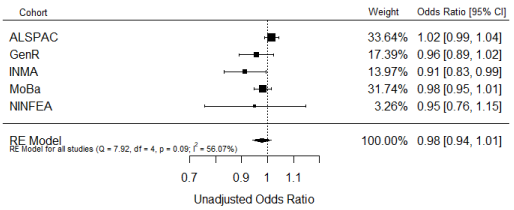
NO_2 exposure	N	Total effect (95% CI)	Direct effect (95% CI)	Indirect effect (95% CI)
Unadjusted	19765	0.87 (0.85, 0.89)	0.88 (0.87, 0.90)	0.96 (0.95, 0.97)
Adjusted	17236	0.86 (0.84, 0.89)	0.88 (0.86, 0.91)	0.96 (0.94, 0.97)

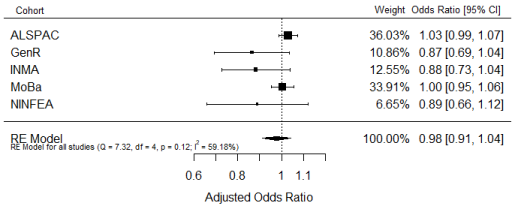
These results are in contrast to those from the study-level meta-analysis where no relationship was observed between NO_2 exposure and childhood asthma and all calculated effects were null.

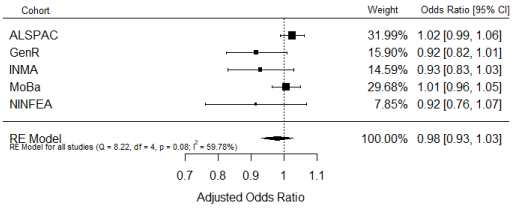
Total Effect - NO2



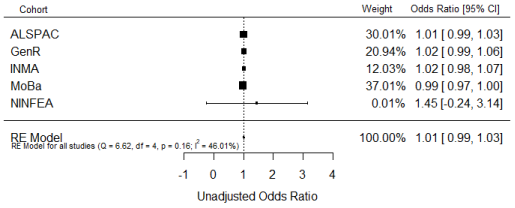
Direct Effect - NO2

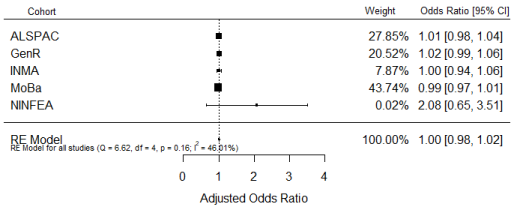






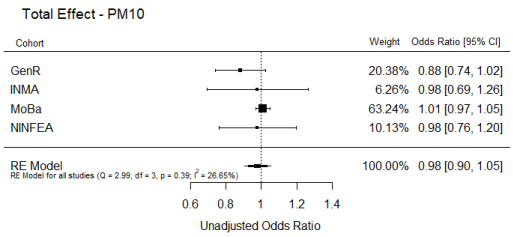
Indirect Effect - NO2

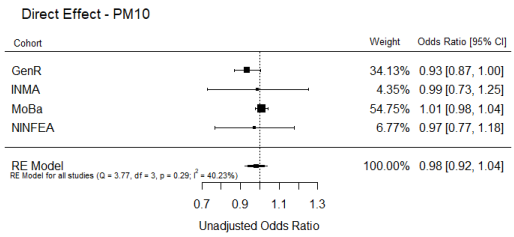


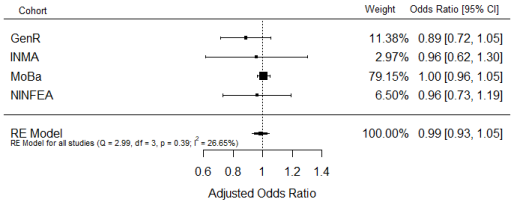


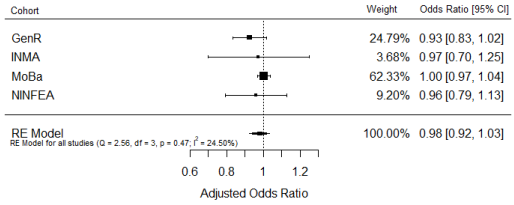
Similar observations were found with PM_{10} exposure during the pregnancy period.

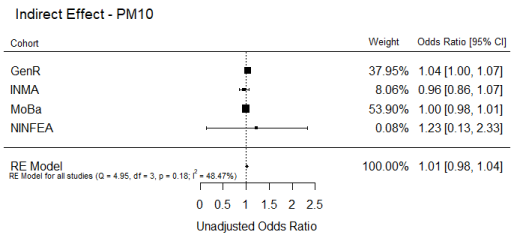
PM_{10} exposure	N	Total effect (95% CI)	Direct effect (95% CI)	Indirect effect (95% CI)
Unadjusted	13073	0.70 (0.67, 0.72)	0.77 (0.75, 0.79)	0.90 (0.88, 0.92)
Adjusted	11013	0.71 (0.68, 0.75)	0.77 (0.74, 0.81)	0.90 (0.88, 0.93)

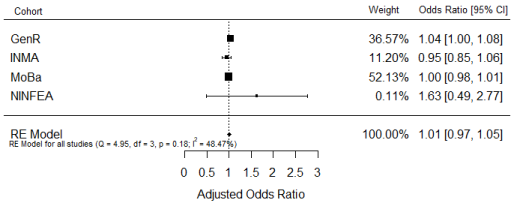












The differences in results reported from the pooled and study-level meta-analysis may be a result of how these two studies are conducted. In pooled indepedent participant data analyses all cohort

participants are equally weighted and contribute the same amount of information to the overall effect size. In study-level random-effect model analyses, studies with larger samples sizes receive a greater weight in the study-level analysis. Further discussion of limitations of the current analyses and how they will be redressed are discussed in the following section.

Conclusions: Exposure to air pollutants during pregnancy was associated with a reduction in childhood asthma and this relationship is mediated through childhood allergies in pooled analyses. No relationships were observed in the study-level meta-analyses. These inconsistent results will be further explored in future analyses with creation of appropriate temporal ordering of variables, larger number of participating cohorts, and use of a DataSHIELD function currently under development which will allow for greater statistical power.

5. Further work

Future work for task 5.3 will include examining alternative methods of capturing the information from missing variables, such as ethnicity, widening the exposure window to the first year of life, and examining additional potential mediators and whether moderation is present, such as by child sex. We could also consider sensitivity analyses investigating only cohorts only with fully harmonized data or those whose asthma diagnoses are extracted from medical records rather than questionnaires.

In the current analysis, the available outcome variable was defined as those with a diagnoses at 5 years of age and older but the mediator was not age-bound. Therefore, it is possible that the mediator occurred after the outcome. To ensure allergy diagnoses occured prior to asthma diagnoses, future work will use harmonized mediator and outcome variables which were derived on a yearly repeated basis. Cohorts will be examined separately to assess which ages contain the majority of allergy and asthma diagnoses and new indicator variables will be created to ensure the most appropriate new allergy and asthma variables are in the correct temporal order within cohorts.

Additional cohorts with the necessary data will also be included in future work. Three further cohorts have the appropriate data but were unable to be included in this analysis due to Opal server versioning and data audits. Additionally, the *mediation* package currently being developed for DataSHIELD will be used in place of the Baron and Kenny method used in this analysis, which was the only method currently supported within DataSHIELD (27). The *mediation* package is a more flexible and statistically powerful approach to mediation and allows for bootstrapping to test the indirect effect rather than the more conservative Sobel test.

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