LifeCycle

More info on LIFECYCLE online:
lifecycle-project.eu

Report on the associations of 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

Work package 5 - Task 5.1 - Deliverable 5.1

Authors:

Liesbeth Duijts, Annemiek Mian

Version 1.0

Delivery date: Month 48

Submission date June, 30th, 2021

Dissemination level: Confidential

LIFECYCLE Project
Coordination and leadership:

Erasmus MC
Generation R (Na-2918)
PO box 2040
3000 CA Rotterdam
The Netherlands

Phone: +31 (0)10 704 3405
Email: lifecycle@erasmusmc.nl
Web: lifecycle-project.eu

This project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733206 (LifeCycle).

Table of Contents

1. Summary

Background: Individual birth cohorts have added valuable knowledge on the role of early life sociodemographic, lifestyle, and growth factors on the risk of developing respiratory outcomes such as wheezing, asthma, respiratory tract infections, and related allergy and eczema outcomes. The impact of these cohorts and their data could be further increased by combining data from different cohorts. Combining data will lead to the opportunity to better identify risk groups and risk factors leading to respiratory disease across the lifecycle across countries. This enables research on better causal understanding and modelling of life course health trajectories.

Aim: Task 5.1 aims to identify early-life stressors during preconception, pregnancy, infancy and early childhood related to lung function trajectories and the risk of asthma from childhood until young adulthood.

Methods: We identified relevant respiratory health data across cohorts, and aimed to harmonize these according to four main groups: 1) maternal respiratory health related characteristics, 2) respiratory diseases in childhood, 3) allergic diseases in childhood, 4) skin diseases in childhood, and 5) respiratory diseases in adulthood. Additionally, 1-stage or 2-stage meta-analyses were performed to study associations of various early-life stressors with respiratory health trajectories.

Results: More than 50 respiratory health and related disease variables of thirteen European and Australian cohorts were harmonized into a federated library. Results of meta-analyses mostly using the novel federated analysis platform DataSHIELD showed that lower respiratory tract infections before age 3 years, lifetime maternal eating disorders, and an adverse urban environment during pregnancy were associated with lower lung function or increased risk of asthma in later childhood. Cat and dog ownership during pregnancy were not associated with childhood asthma, while child's allergic sensitization to cat and dog were associated with increased risk of childhood asthma.

Conclusion: A federated library consisting harmonized respiratory health data of European children and Australian cohorts is a useful framework for identifying early-life risk stressors to be associated with adverse respiratory health trajectories. Findings can be used for development of novel e-learning modules and preventive strategies with focus on early-life infectious, environmental, and nutritional stressors to optimize respiratory health during childhood.

2. Introduction

Work package 5 of the LifeCycle Project focuses on 'Early-life stressors and respiratory health life course trajectories'. The specific objective of Task 5.1 was to identify early-life stressors during preconception, pregnancy, infancy and early childhood related to lung function trajectories and the risk of asthma from childhood until young adulthood. For this, we aimed to use individual participant data from the EuroCHILD Cohort Network to identify early-life stressors, individually and integrated in the early-life exposome, with lung function trajectories and symptoms, diagnosis and medication related to asthma. Main outcomes included lung function (spirometry) and symptoms and diseases (respiratory infections, wheezing, asthma).

In this report we present the results of our deliverable. First, we describe the identification and harmonization process of respiratory health data across cohorts. These data formed the base for originally planned projects of Task 5.1 to study the relation of early-life stressors and respiratory health life course trajectories. Second, we report the scientific output based on 1-stage (multilevel) or 2-stage meta-analyses on associations of early-life stressors in critical periods with respiratory health life course trajectories, taking relevant confounders and causal inference models in collaboration with **WP7** into account. Additionally, scientific output of a LifeCycle Exchange Fellowship, and educational output of a developed e-learning module on 'Early-life exposures and childhood asthma' in collaboration with **WP11** are reported. Last, during the LifeCycle project, additional interest of participating institutes was gained in studying early-life stressors and respiratory health life course trajectories. Therefore, additional meta-analysis projects have been proposed, of which two in collaboration with recently started HZ2020-funded projects, and preliminary results of this further work are presented. In total, eleven research projects related to task 5.1 have been finalized or are currently ongoing (**Table 1**).

Table 1. Overview of research projects of task 5.1

Title	Lead institute	Status
Main projects as originally planned		
1. Respiratory outcomes across the life course	ERASMUS	Finalized
2. Respiratory tract infections, lung function and asthma	ERASMUS	Finalized
3. Pet exposures and asthma and allergy	UCPH	Finalized
4. Maternal eating disorders, asthma and lung function	UNITO	Finalized
5. Urban environment, lung function and asthma[#]	INMA, ERASMUS	Finalized
Additional planned projects		
6. Breastfeeding, solid foods, respiratory/allergy outcomes	ERASMUS	In progress
7. Prediction of respiratory outcomes*	ERASMUS	In progress
8. Green spaces and child health outcomes**	INMA	In progress
9. Mode of delivery and childhood asthma	SOUTHAMPTON	In progress
10. Childcare attendance, role RTI, and allergy/asthma	UWA	In progress
11. Social inequalities and respiratory health	UCPH	In progress

[#]As part of a LifeCycle exchange fellowship. *In collaboration with HZ2020-funded project EUCAN-Connect. **Collaboration with WP3, and in collaboration with HZ2020-funded project ATHLETE.

3. Data harmonization

General harmonization concept

A list of respiratory and related health variables that were of interest for the EU Child Cohort Network has been developed (see also the previous report of WP1). These variables have been selected based on prior experience with meta-analyses and data availability in the participating cohorts, and in close collaboration with **task 5.2, 5.3, and 5.4**. The respiratory health variables were grouped into five groups: 1) maternal respiratory health related characteristics, 2) respiratory diseases in childhood, 3) allergic diseases in childhood, 4) skin diseases in childhood, and 5) respiratory diseases in adulthood (**Table 2**). In total, 13 cohorts had available data on any of the respiratory health variables. Respiratory health variables could be linked to harmonized variables of **WP3, 4 and 6** through unique mother and child identifier numbers.

All cohorts that indicated to have measured respiratory and related health outcomes were asked to harmonize their data in wide format and to use the cleanest (e.g. after an internal check per cohort for outliers and distribution) variables for this process. For repeated measures, the actual age at time of the measurement, as opposed to the average age of the cohort at follow-up was used. If no repeated data existed on a specific variable available within a cohort, the cohort was allowed to harmonize the variable at that specific age point. As an illustration of this: if only one measure of inhalant allergic sensitization by skin prick test at the age of 7.5 years was available, the cohort created the variable inh_all_sens_SPT_7. Detailed descriptions of harmonization processes were entered in the online catalogue (https://catalogue.lifecycle-project.eu/menu/main/app-molgenis-app-lifecycle) [1-3]. This includes a description of the source variables and whether the variable is fully or partially harmonized. Where a variable is only partially harmonized, an explanation for why the variable was partially harmonized is provided in the harmonization description. Whether a variable is partially harmonized depends on specific data gathering within cohorts. Sometimes a variable was measured in a slightly different way. As example, a variable was considered partially harmonized if cohorts used other questions than the International Study on Asthma and Allergy in Childhood (ISAAC)-based questionnaires to define asthma and allergy, which is a most common method to assess respiratory and related diseases in large-scale epidemiological studies.

Maternal respiratory health related characteristics

Maternal history of asthma, allergy, and eczema, preferably doctor-diagnosed, was defined using questionnaires, medical records, or hospital registries.

Respiratory diseases in childhood

Wheezing and asthma Wheezing and asthma were defined using International Study on Asthma and Allergy in Childhood (ISAAC)-based questionnaires, medical records, or hospital registries [4]. Since most cohorts used ISAAC Questionnaires, commonly used in epidemiological studies to define asthma, the variable created by this method was considered as fully harmonized. If other methods were used, the variable was considered partially harmonized. Since previous consortia used several definitions for current asthma, multiple variables were created. This included the CHICOS (http://chicosproject.eu/the-project/; https://www.birthcohorts.net/) definition, based on at least a doctor diagnosed asthma, combined with wheezing or use of asthma medication in the past 12 months, as well as the MeDALL definition based on two out of the following three questions: 1). Doctor diagnosed asthma; 2). Wheezing in the past 12 months; 3). Use of asthma medication in the past 12 months [5].

Asthma medication use Asthma medication in the last 12 months was defined on general use (no, yes) and specific medication use (no use, inhaled bronchodilator (reliever) use only, inhaled corticosteroid (preventer) use only, both inhaled bronchodilator and corticosteroid use, other or unspecified medication use) mostly based on parental-reported questionnaires.

Respiratory tract infections Physician-attended upper and lower respiratory tract infections were mostly defined by parental reported questionnaires. Upper respiratory tract infections included ear infection, throat infection, laryngitis, croup, whooping cough or equivalent, and lower respiratory tract infections included bronchitis, bronchiolitis, pneumonia, chest infection and equivalent.

Lung function Lung function measures were obtained by spirometry according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria and included forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), mid forced expiratory flow ($FEF_{25–75}$), and forced expiratory flow at 75% of FVC (FEF_{75}). Both absolute values and sex-, age-, height-, and ethnicity adjusted Z-scores according to the Global Lung Initiative (GLI) reference criteria were included. Additionally, reproducibility was defined according to the ATS/ERS criteria [6]. Other lung function measures included bronchial hyper reactivity (BHR), as measured by metacholine challenge test, and fractional exhaled nitric-oxide (FeNO), expressed as parts per billion (ppb).

Allergic diseases in childhood

Physician-diagnosed inhalant and food allergies were defined using International Study on Asthma and Allergy in Childhood (ISAAC)-based questionnaires, medical records or hospital registries [4]. If data were available allergy should preferably be obtained by ISAAC questionnaires, as commonly used in large-scale epidemiological studies. If this was not the case, the variable was considered

partially harmonized. If no information was available on diagnosis of allergy by a phycisian, the variable was considered partially harmonized. Allergic sensitization for inhalant or food allergens were measured by skin prick tests or specific IgE measurements.

Skin diseases in childhood

Physician-diagnosed eczema was defined using International Study on Asthma and Allergy in Childhood (ISAAC)-based questionnaires, medical records or hospital registries [4]. For itchy rash, an additional variable was added that noted the location on the body of the itchy rash. Similarly as for asthma and allergy, eczema should preferably be obtained by ISAAC questionnaires, as commonly used in large-scale epidemiological studies. If this was not the case, or if it was not known if the diagnosis was mad by a physician, the variable was considered partially harmonized.

Respiratory diseases in adulthood

Physician-diagnosed chronic obstructive pulmonary disease (COPD) was defined using the GOLD criteria, which encompasses an obstructive pre-bronchodilator spirometry ($FEV_1/FVC < 0.70$). Additionally, COPD was defined according to the lower limit of normal (LLN), as described in J.L. Hankinson et al, Am J Respir Crit Care Med, 1999, or more generally as phycisian-diagnosed COPD by self-reported questionnaires, commonly used in large-scale epidemiological studies. If these critere were not present or if it was unknown if the diagnosis was mad by a physician, the variable was considered partially harmonized.

Table 2. Overview of number of cohorts with main available and harmonized data on respiratory health

	Number of cohorts
Maternal respiratory health related characteristics	
Asthma	13
Any allergy	10
Inhalant allergy	9
Food allergy	6
Eczema	12
Respiratory diseases in childhood	
Wheezing	12
Ever asthma ever*	12
Current asthma*	13
Asthma medication use	13
Upper respiratory tract infection	11
Lower respiratory tract infection	11
FEV_1 (L)	8
FVC (L)	8
FEV_1/FVC	7
FEF_{25} (L/s)	6
FEF_{50} (L/s)	6
FEF_{75} (L/s)	6
Bronchial hyperresponsiveness	2
Fractional exhaled nitric oxide	1
Allergic diseases in childhood	
Food allergy ever, phycisian-diagnosed	12
Inhalant allergy ever, phycisian-diagnosed	8
House dust mite, IgE	2
Cat, IgE	2
Rye, IgE	1
Mould, IgE	1
Any inhalant allergens, SPT	5
Grass mix, SPT	4
Cat, SPT	4
Dog, SPT	3
House dust mite, SPT	4
Birch, SPT	4
Food allergens, IgE	1
Food allergens, SPT	4
Cow milk, SPT	2
Chicken egg, SPT	2
Wheat, SPT	0
Peanut, SPT	2
Nut mix, SPT	2
Sesame, SPT	1
Fish mix, SPT	1
Shell fish mix, SPT	0
Kiwi fruit, SPT	0
Skin diseases in childhood	
Eczema	11
Itchy rash	10
Respiratory diseases in adulthood	
COPD*	1

Data available on the LifeCycle catalogus (https://catalogue.lifecycle-project.eu/menu/main/app-molgenis-app-lifecycle/child_health).*Multiple definitions according to previous consortia definitions (CHICOS, MeDALL, or GOLD criteria) available. Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), mid forced expiratory flow ($FEF_{25–75}$), and forced expiratory flow at 75% of FVC (FEF_{75}). Skin prick test (SPT). Immunoglobuline E (IgE). Chronic obstructive pulmonary disease (COPD).

4. Scientific output

Originally planned projects

Below, we present a list of summaries of finalized projects related to this deliverable. Involved partners are ordered according to the partner numbers in the LifeCycle Project.

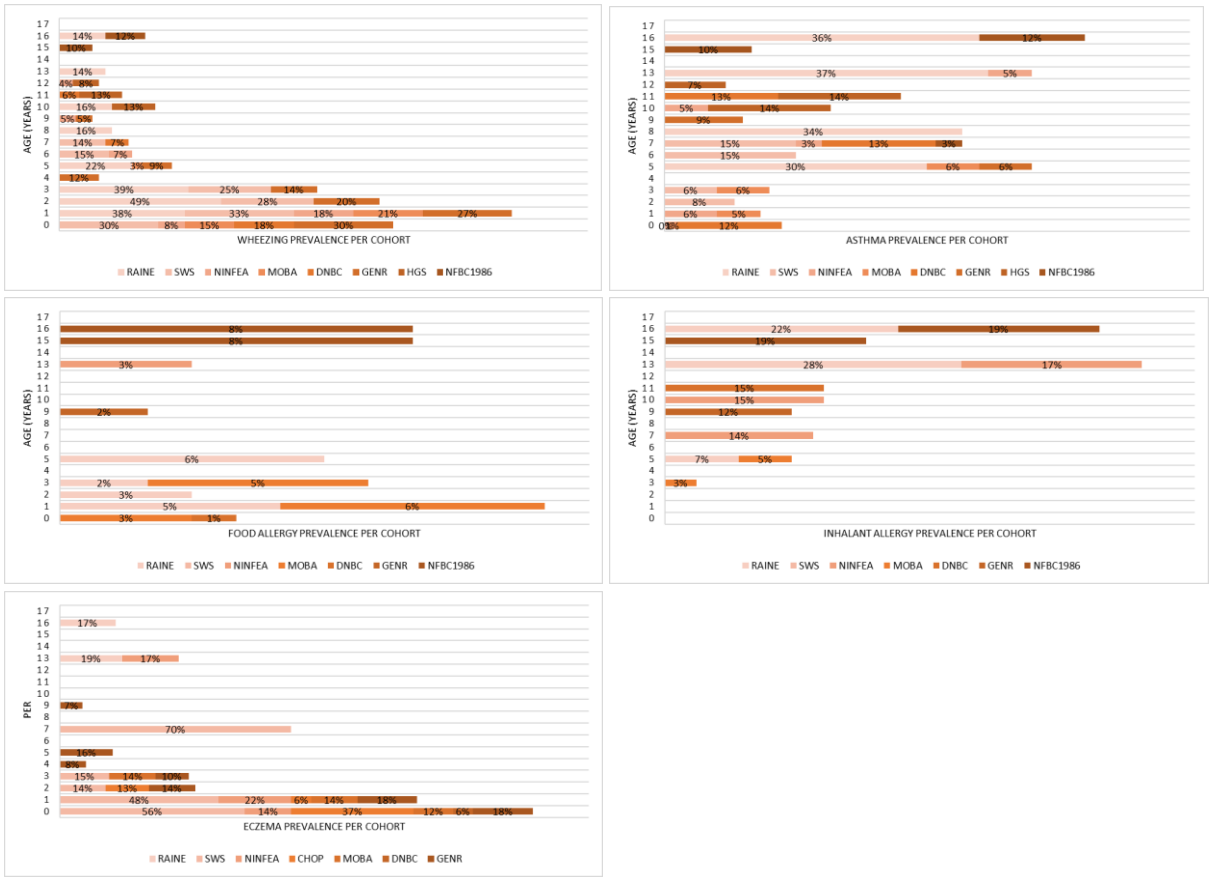
Paper 5.1.1. A resource for research into the early life origins of asthma, allergy, and eczema across the life course. EU Child Cohort Network – Respiratory Health Working Group.

Partner(s) involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIBRIS, UCPH, BTHFT, NIPH, INSERM, UOULU, LMU, UWA. **Additional cohort:** HGS

Summary: Individual birth cohorts have added valuable knowledge on the role of early life sociodemographic, lifestyle, and growth factors on the risk of developing respiratory outcomes such as wheezing, asthma, and related diseases such as allergy and eczema. The impact of these cohorts and their data could be further increased by combining data from different cohorts. We harmonized data on any respiratory and related diseases from birth until adulthood of >125,000 children participating in 13 cohorts. With this, we created a federated library consisting of more than 50 harmonized variables in three main outcome groups including respiratory diseases, allergic diseases, and skin diseases (**Table 2**). Main results showed that wheezing tended to be highly prevalent until age 5 years (8-39%), after which prevalences declined until age 16 years (12-14%)(**Figure 1**). The prevalence of asthma from age 6 years onwards was 3-14%, except for the Australian cohort (up to 37%). Prevalences of food and inhalant allergies ranged from 2 to 8% and 3 to 28%, respectively, from birth until adulthood. The range of prevalences of respiratory and related diseases was, except for a lower prevalence of asthma in Italy, not different among North and Southern European, and Australian children. Data on lung function, most prominently obtained by spirometry, and allergic sensitization by skin prick test or specific IgE blood measurements were only available at specific ages.

Conclusion: This federated library consisting of more than 50 harmonized respiratory health data of European children of 13 European and Australian cohorts provides a framework for further research into early-life risk stressors, and mediating pathways such as common allergies and DNA methylation related to respiratory health trajectories. This leads to the opportunity to better identify risk groups and risk factors leading to respiratory disease across the lifecycle across countries.

Figure 1. Prevalence of wheezing, asthma, food and inhalant allergies, and eczema from birth until adulthood among children of European birth cohorts



Paper 5.1.2. Early-life respiratory tract infections and the risk of lower lung function and asthma: a meta-analysis of 154,492 children.

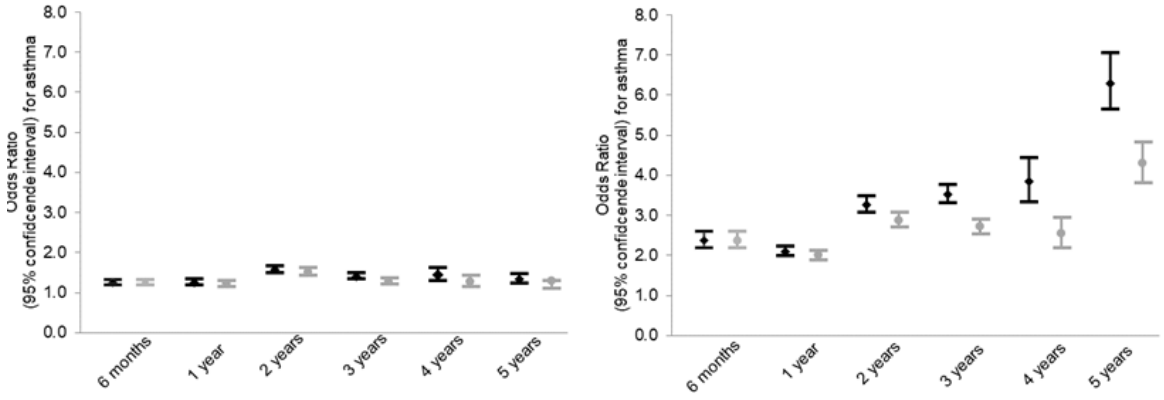
Partner(s) involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, BTHFT, UOC, NIPH, INSERM

Summary: We examined the associations of early-life respiratory tract infections with lung function and asthma in children. We used individual participant data of 154,492 children from 37 birth cohorts to examine the associations of upper (URTI) and lower respiratory tract infections (LRTI) by the age of 6 months, 1, 2, 3, 4 and 5 years with forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) FEV_1/FVC, forced expiratory flow at 75% of FVC (FEF_{75}) and asthma at a mean age of 7 (SD 2) years. We used multilevel mixed effect models, to take clustering of participants within cohorts into account, and adjusted for socio-economic, lifestyle and growth factors. URTI were not associated with lung function. URTI at all ages were associated with an increased risk of asthma (OR (95% CI): ranging from 1.25 (1.15, 1.34) to 1.56 (1.47, 1.66))(**Figure 2**). LRTI at all ages were associated with a lower FEV_1, FEV_1/FVC and FEF_{75} (Z-score (95% CI): ranging from -0.07 (-0.14, -0.00)

to -0.24 (-0.38, -0.10)), except for LRTI at age 6 months with FEF_{75}, and an increased risk of asthma (OR (95% CI): ranging from 2.00 (1.85, 2.10) to 3.72 (3.19, 3.85)). Figure 1 graphically shows these associations.

Conclusion: Early-life lower respiratory tract infections are associated with lower lung function and increased risk of asthma in later life, while upper respiratory tract infections are associated with asthma only. These findings provide support for the hypothesis that early-life respiratory tract infections might have a direct effect on lung development.

Figure 2. Associations of early-life upper (A) and lower (B) respiratory tract infections with school-age asthma.
Values are adjusted odds ratio's with 95% confidence interval, derived from multilevel logistic regression models (black diamonds). Models were additionally adjusted for preceding upper (A) or lower (B) respiratory tract infections (grey circles)..



Paper 5.1.3. Associations of early-life pet ownership with childhood asthma and allergic sensitization: a federated meta-analysis of >75,000 participants from the EU Child Cohort Network.

Partner(s) involved: ERASMUS, ISGlobal, UNITO, UOS, UNIVBRIS, UCPH, NIPH, INSERM, UWA.

Summary: We used individual participant data from up to 77,227 children from 9 birth cohorts to examine associations between early-life pet ownership and the development of asthma and pet-specific allergic sensitization in childhood. We specifically examined how these associations were influenced by type of pet (cat vs. dog), timing (never, pregnancy and early childhood), and number of pets owned. Additionally, we examined whether there was evidence for pet-specific allergic sensitization mediating associations between pet ownership and childhood asthma. All analyses were conducted using the federated analysis platform DataSHIELD. Logistic regression models were fitted separately for each cohort and the results combined using random effects meta-analysis.
Neither early-life cat-ownership nor early-life dog-ownership were strongly associated with childhood asthma (**Figure 3**). For both cat and dog ownership, ownership in pregnancy only was associated with greatest odds of childhood asthma (OR (95% CI): 1.14 (0.94, 1.38) and 1.11 (0.90, 1.36) respectively), whilst continuous dog ownership during both pregnancy and infancy was associated with lowest odds of childhood asthma (OR (95% CI): 0.90 (0.81, 1.01)). Odds of current

asthma at school age were relatively constant for one versus multiple cats or dogs, and were consistent with no or only a very weak association (**Table 3**). Consistent with these findings for childhood asthma, cat and dog ownership were also not strongly associated with allergic sensitization to the respective allergen (OR (95% CI): 0.92 (0.75, 1.13) and 0.93 (0.57, 1.54) respectively), whereas both cat- and dog-specific allergic sensitization were strongly associated with childhood asthma (OR (95% CI): 6.89 (5.14, 9.25) and 5.98 (3.14, 11.36) respectively).

Conclusion: Our findings provide little evidence for early-life cat and dog ownership increasing the odds of childhood asthma or respective specific allergic sensitization, but strong evidence for cat- and dog-specific allergic sensitisation increasing the odds of childhood asthma. These findings suggest that avoidance of cats and dogs in early-life is unlikely to prevent the development of asthma in susceptible children.

Figure 3. Forest plots for associations of (A) cat and (B) dog ownership in pregnancy and infancy with school age asthma

*Adjusted odds ratios with 95% confidence intervals, including mutually adjusted for cat and dog ownership.

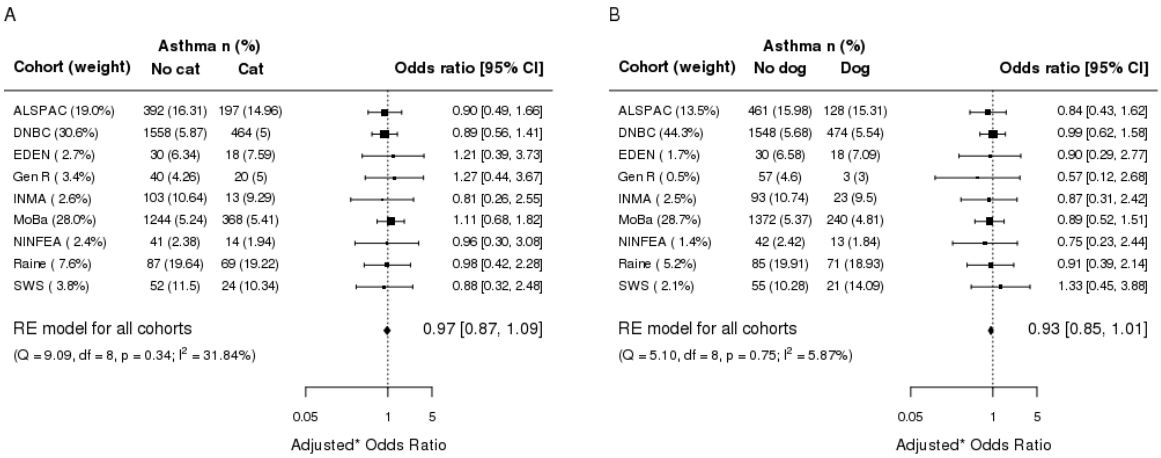


Table 3. Associations between number[a] of cats and dogs owned and odds of current asthma at school age

		Odds of current asthma at school-age			
	N	Crude OR (95%	I2	Adjusted[b] OR	I2
Cats					
None	6288	reference		reference	
1	1498	0.94 (0.78, 1.12)	0	0.94 (0.78, 1.12)	0
>1	970	1.03 (0.66, 1.63)	60	1.07 (0.66, 1.74)	62
Dogs					
None	6810	reference		reference	
1	1558	0.94 (0.79, 1.12)	0	0.88 (0.73, 1.05)	0
>1	388	1.02 (0.75, 1.40)	0	0.85 (0.61, 1.18)	0

[a] Average number of cats and dogs across early-life (prenatally and early childhood). Cohorts with relevant data were: ALSPAC, INMA, NINFEA, RAINE and SWS. In SWS, data on number of cats and dogs were only available for the prenatal period.

[b] Adjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, ethnic background, maternal age at birth, maternal smoking during pregnancy, birth order, number of children living in the home and sex of the child; mutually adjusted for number of cats or dogs owned

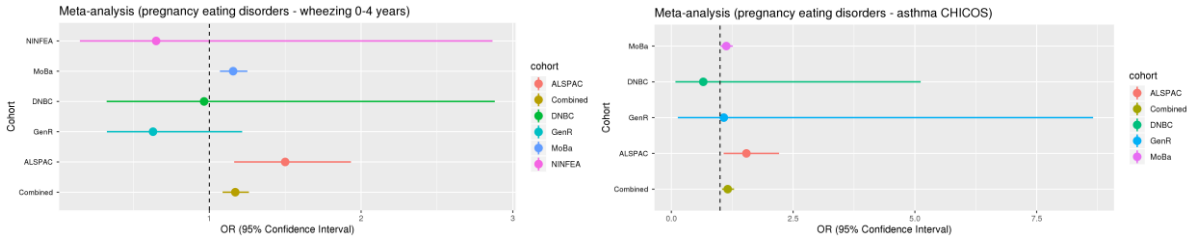
Paper 5.1.4. Maternal eating disorders in childhood respiratory outcomes: The LifeCycle multi-cohort analysis.

Partner(s) involved: ERASMUS, UNITO, UNIVBRIS, UCPH, BTHFT, UMCG, NIPH, LMU

Summary: Maternal eating disorders have been associated with several adverse pregnancy and childhood outcomes, like premature birth, foetal and infant growth restriction, and abnormal neurodevelopmental outcomes, and are usually accompanied by dysfunctional behaviours and unhealthy lifestyle, such as restrictive eating and poor diet, excessive exercise, high smoking prevalence, and purge episodes with laxative abuse that could severely compromise the homeostatic balance of the body. Anxiety and depressive symptoms are also ubiquitous in these disorders, and together with unhealthy behaviours and lifestyle factors are implicated in poorer infant health. We aimed to evaluate the associations of maternal eating disorders with offspring wheezing, asthma and lung function within the LifeCycle project. We use individual participant data of more than 120,000 mother-child pairs from 7 birth cohorts to examine the associations of maternal eating disorders before and during pregnancy with offspring respiratory outcomes. The analyses were performed using DataSHIELD both as study-level meta-analyses, and by pooling individual-level data and the obtained estimates using logistic and linear regression models adjusted for a priori selected covariates. Data from 6 cohorts have been analyzed (Generation R, NINFEA, ALSPAC, DNBC, MoBa, and CHOP) with the overall lifetime any eating disorder prevalence of 2.5% (ranging from 0.4 (DNBC cohort, registry-based data) to 16.6% (CHOP cohort, self-reported any eating disorder). Lifetime diagnosis of eating disorders was associated with preschool wheezing (0-4 years), with an adjusted odds ratio of 1.25 (95% confidence intervals [CI]: 1.15-1.35), and to a lesser extent with school-age asthma (1.09; 95% CI: 0.97-1.23; based on 4 cohorts) (**Figure 4**). The estimates were stronger for maternal lifetime anorexia nervosa diagnosis (wheezing 1.23 [1.04-1.47], asthma 1.35 [1.01-1.81] based on 5 cohorts) than for bulimia nervosa diagnosis. Similar estimates were also observed when mothers suffered from eating disorders during pregnancy . The results remained robust after adjustment for maternal pre-pregnancy depression and anxiety.

Conclusion: Maternal eating disorders are associated with an increased risk of wheezing and asthma in childhood, independently of comorbid depression and anxiety.

Figure 4. Study-level meta-analysis of maternal pregnancy eating disorders and offspring preschool wheezing and school-age asthma



LifeCycle Exchange Fellowship

Within the LifeCycle Exchange Fellowship program, Alicia Abellan from ISGLOBAL (Barcelona, Spain) visited ERASMUS (Rotterdam, The Netherlands) for a research fellowship to study the exposome in relation to respiratory health. The project was partly remotely during the corona pandemic. The project was cohort specific to gain knowledge on the complex statistical analyses. The project formed the base for further meta-analyses on 'Green spaces and respiratory, cardiometabolic, and mental health outcomes' including multiple cohorts (see project 5.1.8).

Paper 5.1.5. Maternal exposure to urban environment during pregnancy and lung function, wheeze, and asthma in school-age children.

Partner(s) involved: ERASMUS, ISGLOBAL

Summary: Many early life environmental exposures are associated with the development of lower lung function and risk of asthma in childhood. Evidence on the many exposures related to the urban environment during pregnancy and especially the concurrence of them in relation to children's respiratory health is lacking. We examined the associations of exposure to the full urban environment during pregnancy, including air pollution, noise, traffic, green and blue spaces, and built environment with lung function, wheeze, and asthma during childhood. We included 5,624 mother-child pairs participating in the Generation R birth cohort. We estimated a total of 44 urban environment exposures including air pollution, road traffic noise, traffic, green spaces, blue spaces, and built environment during pregnancy (**Figure 5**). At 10 years of age, lung function was measured by spirometry and asthma from questionnaires. Wheezing patterns were constructed from questionnaires across childhood. We performed single, multiple exposure and cluster analyses to assess the associations. A higher maternal exposure to NO_2 and $PM_{2.5}$ during pregnancy was associated with lower lung function only in mid-to-small airways in childhood (z-score for $PM_{2.5}$=-0.10, 95%CI=-0.15, -0.05). Higher levels of $PM_{2.5}$ increased FEV_1 and FVC, but these associations were not observed when considering the urban environment as a whole in cluster analyses. High road traffic noise was associated with increased asthma at 10 years, and increasing size of the nearest major blue spaces with higher lung function (FEV_1 z-score=0.02, 95%CI=0.00, 0.04) and lower odds of asthma (OR=0.92, 95%CI=0.84, 1.00). Cluster analyses revealed that living during pregnancy in an urban environment with higher levels of air pollution, noise, urbanisation and lower levels of natural spaces may contribute to lower lung function in mid-to-small airways (z-score=-0.08, 95%CI=-0.17, 0.01), and to increased odds of early and late wheeze during childhood (OR early=1.23, 95%CI=1.00, 1.51)(**Table 4**).

Conclusion: This study shows that the urban environment during pregnancy is of relevance to the offspring's respiratory health through childhood. Air pollution, road traffic noise, and blue spaces were the main determinants of childhood respiratory health.

Figure 5. Description of the clusters of urban exposures

Bars represent exposure level of each urban exposure in the cluster vs. mean level of exposure in the overall population (mean=0).

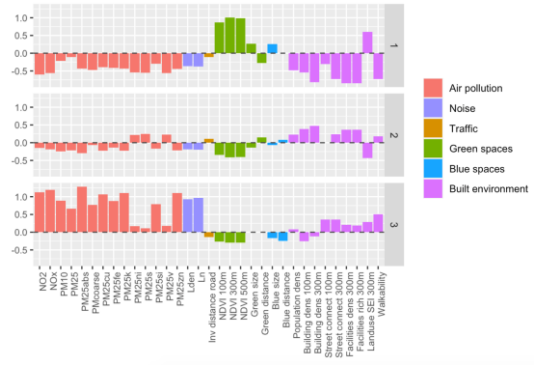


Table 4. Associations of maternal exposure to the full urban environment in clusters with and lung function, wheezing patterns, and asthma in school-age children

	Cluster 2		**Cluster 3**	
	Estimate (95%CI)	p-value	Estimate (95%CI)	p-value
Lung function (z-score change)				
FEV_1	-0.03 (-0.10, 0.03)	0.294	-0.04 (-0.12, 0.04)	0.278
FVC	-0.02 (-0.08, 0.04)	0.470	-0.03 (-0.10, 0.05)	0.519
FEV_1/FVC	-0.01 (-0.07, 0.05)	0.791	-0.03 (-0.11, 0.04)	0.393
$FEF_{25-75\%}$	-0.03 (-0.10, 0.04)	0.425	-0.08 (-0.17, 0.01)	0.069
Wheezing patterns and asthma (OR)				
Early wheezing	1.13 (0.95, 1.36)	0.164	1.23 (1.00, 1.51)	0.054
Late wheezing	1.22 (0.86, 1.76)	0.282	1.48 (0.99, 2.25)	0.059
Persistent wheezing	0.85 (0.67, 1.07)	0.166	0.75 (0.56, 1.01)	0.060
Asthma	1.14 (0.85, 1.54)	0.388	0.98 (0.67, 1.42)	0.907

Lung function models were adjusted for maternal education, pre-pregnancy BMI, age, smoking during pregnancy, history of asthma or atopy, and child's ethnicity and season of birth. Wheezing and asthma models were additionally adjusted for child's sex. Abbreviations: FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; $FEF_{25-75\%}$: mid expiratory flow; OR: odds ratio; CI: confidence interval.

Educational Module

In **collaboration with WP11**, an educational module on 'Early-life exposures and childhood asthma' including a selft test and a Continuing Medical Education (CME) test assessment was developed. The module contains three lessons: 1. ' Asthma from birth until adulthood' comprising the definition, treatment, and prognosis of asthma, the link of asthma with neonatal and adult respiratory diseases, and the meaning of lung function; 2. 'Developmental origins of asthma' comprising historical landmark exposures, and the role of early growth and nutrition on developing asthma; and 3. ' Biological pathways and prediction of asthma'. The module is currently being processed for online availability and will be presented in **deliverable D11.4 (Mo 60)**.

5. Further work

During the LifeCycle project, additional meta-analysis projects in relation to Task 5.1 have been proposed, and preliminary results of this further work are presented below.

Additional planned projects

Project 5.1.6. A federated individual participant meta-analysis on infant breastfeeding and introduction of solid foods in relation to respiratory and allergy outcomes throughout childhood. In progress.

Partner(s) involved: ERASMUS, ISGLOBAL, UOS, UCPH, BTHFT, NIPH, INSERM, UWA and HGS

Summary: More insight into individual participant data across different cohorts worldwide, which uses harmonized data and have detailed information on infant feeding and respiratory and allergy outcomes at different ages potentially leads to identification of smaller effect estimates, specific subgroups, and mediator effects, and capitalizes on existing published and unpublished data potentially leading to less publication bias. Therefore, our aim is to perform an individual participant meta-analysis with harmonized exposure and outcome variables among children of nine cohorts to examine the associations of the duration and exclusivity of breastfeeding, and timing of introduction of solid foods with wheezing, asthma, lung function, inhalant allergic sensitisation and physician diagnosed inhalant allergy from birth until adolescence.

Preliminary results: We have obtained cohort approval and DataShield credentials, and are currently exploring regression models.

Project 5.1.7. Prediction of respiratory outcomes. In progress.

Partner(s) involved: ERASMUS. This project will be performed cohort specific first.

In collaboration with HZ2020 funded EUCAN-connect project: https://eucanconnect.com/

Summary: Asthma in childhood is associated with increased risk of lower lung function and chronic obstructive respiratory diseases in adulthood. Therefore, early identification of children at risk for asthma is important to improve quality of life by effective prevention strategies, or to monitor and apply appropriate treatment strategies. A third of children with asthma related symptoms at preschool age will eventually develop asthma at school age. A large proportion of preschool children with transient asthma related symptoms might therefore have unnecessary drug treatment with potential side effects. To develop innovative prevention strategies, better prediction models and risk stratification is needed. The strongest predictors for childhood asthma are the number of wheezing episodes and eczema at preschool age, and subsequently sex, parental education, and parental asthma. However, an overall evaluation of our and other prediction models showed that none of the

models have an optimal predictive performance. This is most likely due to the lack of inclusion of novel identified risk factors from fetal life onwards and genetic variants, which are potentially related to the complex developmental process of asthma, and missing critical early age windows. Incorporating novel early-life factors and genetic variants in currently available prediction models may contribute to better risk stratification and identification of yet unknown subgroups. Therefore, we aim to develop a new personalized prediction model integrating risk factors form fetal life onwards, and genetic variants to better predict the development of asthma in later childhood.
Preliminary results: We have performed a literature search to obtain the most relevant predictors, and are currently exploring the most optimal predication models.

Project 5.1.8. Green spaces and child health outcomes (WP3). In progress.
Partner(s) involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, BTHFT, UOC, NIPH, INSERM
Summary: We aim to investigate the associations between prenatal and postnatal exposure to green spaces with multiple outcomes related to cardiometabolic, respiratory, and mental health in children at preschool age and primary school age in Lifecycle, HELIX, and EUChild Network cohorts, using an outcome-wide analysis approach. We will follow the outcome wide approach to assess causal effects of a single exposure over numerous outcomes in all cohorts with urban exposome data available including ALSPAC, BiB, DNBC-Copenhagen, EDEN, GEN R, INMA (Gipuzkoa, Sabadell, Valencia), MoBa-Oslo, NINFEA, RHEA, ABCD, KANC, PiccoliPiù (**Figure 6**). Regression models for each outcome in each cohort will be performed: (i) Prenatal exposure to green space and outcomes at 3-5 yrs (ii) Postnatal exposure to green spaces and outcomes at 3-5 yrs (iii) Prenatal exposure to green space and outcomes at 6-12 yrs (iv) Postnatal exposure to green spaces and outcomes at 6-12 yrs. We have already obtained cohort approval and DataShield credentials for ALSPAC, DNBC, EDEN, GEN R, INMA, MoBA, and NINFEA. The selection of confounders has been defined through directed acyclic graphs for each outcome. From the health outcome variables harmonised within LifeCycle, we will include those variables for which at least 3 cohorts per age band have data, so far, we have in the two age-bands: ADHD, Externalization and Internalization Problems, Fluid Intelligence, Gross and Fine Motor, BMI, Asthma, and Wheezing (Figure 1).
Preliminary results: Exposure to green spaces [NDVI 300m] in pregnancy and childhood adjusted for sex and age of the child, pregnancy smoking, asthma of mother, maternal_education and area-level socioeconomic status is not associated with wheezing at 3-5 (0.31 [-0.27;0.89], -0.13 [-0.68;0.42]) and 6-12 years (-0.58 [-1.77;0.61], -0.09 [-1.11;1.28]) of age. The next steps will be to include the remaining cohorts into the analysis, and create DataShield scripts to e-values for sensitivity analysis and multiple metrics tests.
Project 5.1.9. An Individual Participant Data Meta-Analysis Examining the Associations Between Mode of Delivery and Respiratory Outcomes. In progress.

Partner(s) involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, UWA, BTHFT, NIPH, INSERM, LMU

Summary: In this study, we aim to assess the association between mode of delivery and childhood asthma. We use individual participant data of 155,180 children from 12 birth cohorts involved within the LifeCycle project. The identification of the available data was conducted via the EU Child Cohort Network Variable Catalogue. Initially, descriptive analysis of the harmonised variables accessed via DataSHIELD were conducted in order to get an understanding of the datasets (i.e. main exposure, outcomes and covariates) (**Table 5**). At this stage of the project we are assessing the longitudinal associations between mode of delivery and asthma using various regression models for each cohort adjusting for important covariates such as sex and pregnancy hypertension. The model results will be added in a two random-effects meta-analysis models. We aim also to apply a generalised linear mixed model that will enable us to perform the analysis in one-stage, with the possibility of providing us with more accurate inferences. Depending on software availability, we are interested to examine whether we can assess the potential mediation effect on the exposure/outcome relationship due to other covariates, using a mediation analysis via the product method.

Preliminary results: We have obtained cohort approval and DataShield credentials, and are currently exploring various regression models.

Table 5. Descriptive characteristics for children born by caesarean and non-caesarean section

		Mode of Delivery	
		Caesarean	No caesarean
Asthma Ever	Yes	3127 (2%)	16281 (10.5%)
	No	19464 (12.5%)	116308 (70%)
Sex	Males	4178 (4.0%)	23151 (22.3%)
	Females	10511 (10.1%)	66104 (63.6%)
Ever breastfed	Yes	18703 (13%)	112847 (78.7%)
	No	2030 (1.4%)	9867 (6.9%)
Preeclampsia	Yes	622 (0.5%)	1106 (0.8%)
	No	18034 (13.7%)	111945 (85.0%)
Pregnancy hypertension	Yes	1816 (1.3%)	7364 (5.4%)
	No	17628 (12.8%)	110521 (80.5%)
Gestational diabetes	Yes	474 (7.7%)	1305 (21.1%)
	No	832 (13.5%)	3566 (57.7%)
Size for Gestational age	AGA	16933 (11.8%)	111084 (77.3%)
	LGA	3185 (2.2%)	12585 (8.8%)
	SGA	1422 (1.0%)	3640 (2.5%)

Project 5.1.10 Associations between childcare attendance and age of introductions on respiratory infections, allergy and asthma. In progress.

Partner(s) involved: UWA, ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, BTHFT, UOC, INSERM

Summary: Childcare attendance in early-life is a potential risk factor for asthma, however results are conflicting, with studies showing both a positive, negative and no association for asthma or recurrent wheeze with childcare attendance. There is also strong evidence for increased respiratory infections in children attending day-care. Respiratory infections are an independent risk factor for asthma.

Therefore, it is plausible that due to increased exposure to viral pathogens in a childcare setting, respiratory infections act as a mediator for an increased risk for asthma. The overall hypothesis is that early-life exposure to childcare leads to an increased risk for asthma. We also hypothesize that the increased risk is mediated by increased respiratory infections in children attending childcare compared to children who stay at home. We used individual participant data of 59 352 children from nine birth cohorts. Multivariable analyses using logistic regression was used to determine the associations between childcare attendance in the first years of life with asthma at any time in childhood and lower respiratory tract infections (LRTI) in infancy. Models were adjusted for significant co-variates including maternal asthma, birth weight, household income, and sibling position. Multivariable logistic regression models showed that childcare attendance was associated with a lower odds for the presence of asthma ever (OR: 0.79, 95% CI:0.74- 0.85) (**Table 6**). Childcare attendance was associated with an increased odds for LRTI in infancy (OR: 1.04, 95% CI:1.00- 1.09). **Conclusion: Preliminary results suggest that early-life childcare attendance does not increase risk of asthma. There was however a significant association between early-life childcare attendance and LRTIs. These findings do not support for the hypothesis that early-life childcare attendance increases the risk of asthma through increased respiratory infections.**

Table 6. Association between early-life childcare attendance with doctor-diagnosis of asthma ever in children
Analyses were adjusted for age, sex, weight for gestational age, maternal asthma, sibling number.

	Doctor-diagnosed Asthma (Odds ratio (95% CI); p-value)	
	Unadjusted	**Adjusted**
DNBC	1.01 (0.94, 1.09);p=0.74	1.02 (0.94, 1.10); p=0.71
NINFEA	0.93 (0.51, 1.68); p=0.80	0.99 (0.53, 1.87); p=0.98
EDEN	0.53 (0.27, 1.05); p=0.07	0.59 (0.34, 2.11); p=0.14
Raine	0.96 (0.71, 1.31); p=0.80	0.94 (0.66, 1.34); p=0.73
SWS	2.19 (0.43, 11.12); p=0.34	1.93 (0.37, 10.02); p=0.43
ALSPAC	1.13 (0.86, 1.48); p=0.38	1.09 (0.81, 1.46); p=0.57
Pooled analysis	**0.78 (0.73, 0.83); p<0.001**	**0.79 (0.74, 0.85); p<0.001**

Project 5.1.11. Social inequalities and respiratory health. In progress.

Partners involved: Institutes are currently responding to the proposed project.

Summary: Asthma disproportionately affects children from disadvantaged backgrounds. A better understanding of the drivers of these differences is essential for effectively addressing social inequalities in respiratory health. This study will build on findings from the WP5 (5.1.3) descriptive study which aims in part to describe how social inequalities in respiratory health vary across LifeCycle cohorts/countries. It will apply methods currently being developed in DataSHIELD by Melis et al. to assess the mediating role of a limited set of risk factors for asthma. Mediators that will be considered include smoking in pregnancy and the home, birth weight, gestational age, breastfeeding, mode of delivery, access to green space and ambient air pollution.

Preliminary results: Data access of cohorts is currently being approved legally after which data analyses will be performed.

6. References

1. Swertz, M.A., et al., *The MOLGENIS toolkit: rapid prototyping of biosoftware at the push of a button.* BMC Bioinformatics, 2010. **11 Suppl 12**: p. S12.
2. Swertz, M.A. and R.C. Jansen, *Beyond standardization: dynamic software infrastructures for systems biology.* Nat Rev Genet, 2007. **8**(3): p. 235-43.
3. van der Velde, K.J., et al., *MOLGENIS research: advanced bioinformatics data software for non-bioinformaticians.* Bioinformatics, 2019. **35**(6): p. 1076-1078.
4. Asher, M.I., et al., *International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods.* Eur Respir J, 1995. **8**(3): p. 483-91.
5. Hohmann, C., et al., *The development of the MeDALL Core Questionnaires for a harmonized follow-up assessment of eleven European birth cohorts on asthma and allergies.* Int Arch Allergy Immunol, 2014. **163**(3): p. 215-24.
6. Quanjer, P.H., et al., *Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations.* Eur Respir J, 2012. **40**(6): p. 1324-43.