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Report on early-life stressors that are related to both asthma throughout childhood and lung function and COPD in adulthood

Work package 5 - Task 5.2 - Deliverable 5.2

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1. Summary

Background: Early life is an important window of opportunity to improve respiratory health across the full lifecycle. Optimizing early-life conditions has the yet unfulfilled potential to improve life course health trajectories.

Aim: To examine whether individual early-life stressors and the integrated early-life exposome related to impaired respiratory health at younger age also affect lung function and risk of chronic obstructive pulmonary problems (COPD) in adulthood.

Methods: We used data from The Northern Finland Birth Cohort 1966 (NFBC1966) (n = 12 000). The prevalence of asthma and COPD was measured by a postal questionnaire at age 14, 31 and 46 years. Exposure to early life stressors was measured by a postal questionnaire at birth. Odds ratios (OR) and their 95% confidence intervals (95% CI) were obtained from multinomial logistic regression, stratified by gender.

Results: Being born in a farmer family predicted lower prevalence of asthma in females at age 14 (OR 0.11, 95% CI 0.01, 0.94), 31 (OR 0.62, 95% CI 0.39, 0.97) and 46 (OR 0.60, 95% CI 0.38, 0.97) years and in males at age 31 years (OR 0.59, 95% CI 0.35, 0.99). Working as a farmer was not associated with asthma at age 31 and 46 years. Birth length was associated with COPD at age 31 (OR 0.91, 95% CI 0.84, 0.99) (Table 4). Higher weight in <1 month after delivery predicted lower prevalence of COPD at age 31 (OR 0.64, 95% CI 0.45, 0.89). Other early life stressors were not associated with COPD at age 31 years.

Conclusions: Exposure to farming environment in childhood demonstrates a protective effect on asthma from birth to 46 years, indicating that 'immune deviation' may take place throughout life. The effect is more consistent in females compared to males. Birth length and weight in infancy may determine later onset of COPD. However, the pathways and mechanisms involved in the relationships between early-life events and chronic respiratory diseases in adulthood warrant further investigation.

2. Introduction

Early life is an important window of opportunity to improve health across the full lifecycle. Exposure to stressors just before or during pregnancy or during early childhood leads to developmental adaptations, which subsequently affect life course and disease risk (1). Optimizing early-life conditions has the yet unfulfilled potential to improve life course health trajectories for individuals themselves, and also their offspring through transgenerational effects (2). Therefore, novel strategies for optimizing early life will help to maximize the human developmental potential for current and future European generations. Prospective cohort studies starting from pregnancy or childhood provide the opportunity to study the effects of early-life stressors in relation to lifecycle health trajectories, and their potential for targeted prevention or intervention strategies (3).

Workpackage 5 of the LifeCycle Project examines respiratory tract development and disease trajectories throughout the life course, focusing on asthma and chronic obstructive pulmonary problems (COPD). We examined the associations of exposure to early-life stressors during preconception, pregnancy, infancy and early childhood with respiratory health and disease during childhood, adolescence and adulthood. Main groups of early-life stressors were socio-economic, migration, urban environment and lifestyle indicators, individually and combined in the early-life exposome created in WP3. We use the same analytical models as WP4 and WP6 to compare different life course models including those assuming specific critical periods and those assuming interactive and cumulative effects throughout the life course. Our main outcomes are asthma and COPD and their life course trajectories.

The specific objective of Task 5.2 is to explore whether individual early-life stressors and the integrated early-life exposome related to impaired respiratory health at younger age also affect lung function and risk of COPD in adulthood. The main hypothesis for this task is that asthma and COPD, the major chronic obstructive respiratory problems in childhood and adulthood, respectively, have at least partly a common origin in early life. We will use data from partners in the EuroCHILD Cohort Network that have measured lung function and collected information about chronic respiratory diseases in adults of age 20 to 60 years. ALSPAC and RAINE have longitudinal information until age 25 years, and NFBC and HBCS have information until age 60 years.

In this report, we describe how exposure to farming environment in childhood demonstrates a protective effect on asthma from birth to 46 years, and how early life stressors related to lung function and asthma in childhood also affect the risk of COPD in adulthood. The output of this task will lead to identification of common early-life stressors and related epigenetic pathways that lead to both asthma symptoms at younger ages and decreased lung function or COPD at older ages.

3. Data harmonization

The work performed under this task provide guidance and potential for harmonization of adult outcomes (the latest age harmonized in the EuChildNetwork catalogue being 17 y), in collaboration with Task 5.1, 5.3 and 5.4.

4. Scientific output

Congress abstract. Influence of farm environment on asthma during the life-course: A population-based birth cohort study in Northern Finland. Submitted to ERS International Congress 2021. (4)

Partner(s) involved: University of Oulu

Summary: In this study, we investigated the influence of farming environment on asthma in three time points from birth to 46 years using data from the Northern Finland Birth Cohort 1966 (n = 10 926). The prevalence of asthma was measured by a postal questionnaire at age 14, 31 and 46 years. Exposure to farming environment was measured by a postal questionnaire at birth and at age 31 and 46 years. Odds ratios (OR) and their 95% confidence intervals (95% CI) for the prevalence of asthma were obtained from multinomial logistic regression, stratified by gender. The analyses were adjusted for smoking, socio-economic position, birthweight, BMI, family size, living place, pets, sports, diet and occupational farming. Being born in a farmer family predicted lower prevalence of asthma in females at age 14 (OR 0.11, 95% CI 0.01, 0.94), 31 (OR 0.62, 95% CI 0.39, 0.97) and 46 (OR 0.60, 95% CI 0.38, 0.97) years and in males at age 31 years (OR 0.59, 95% CI 0.35, 0.99). Working as a farmer was not associated with asthma at age 31 and 46 years.

Conclusions: Exposure to farming environment in childhood demonstrates a protective effect on asthma from birth to 46 years, indicating that 'immune deviation' may take place throughout life. The effect is more consistent in females compared to males.

Paper 1. Influence of farm environment on asthma during the life-course: A population-based birth cohort study in Northern Finland. Article manuscript. (5)

Partne(s) involved: University of Oulu

Summary: Using the Northern Finland Birth Cohort 1966 (n = 10 926), we investigated the influence of farming environment on asthma from birth to 46 years. The prevalence of asthma was measured by a postal questionnaire at age 14, 31 and 46 years. Exposure to farming environment was measured by a postal questionnaire at birth and at age 31 and 46 years. Odds ratios (OR) and their 95% confidence intervals (95% CI) for the prevalence of asthma were obtained from multinomial logistic regression, stratified by gender. The analyses were adjusted for smoking, socio-economic position, birthweight, BMI, family size, living place, furry pets, physical activity, diet and occupational farming. Being born in a farmer family predicted lower prevalence of asthma in females at age 14 (OR 0.11, 95% CI 0.01, 0.94) (Table 1), 31 (OR 0.62, 95% CI 0.39, 0.97) (Table 2) and 46 (OR 0.60, 95% CI 0.38, 0.97) (Table 3) years and in males at age 31 years (OR 0.59, 95% CI 0.35, 0.99). Working as a farmer was not associated with asthma at age 31 and 46 years.

Conclusions: Exposure to farming environment in childhood demonstrates a protective effect on asthma from birth to 46 years, indicating that 'immune deviation' may take place throughout life. The effect is more consistent in females compared to males. Multi-factorial clinical phenotypes of asthma and the heterogeneity of farming exposures may explain the inconsistent relationship between farming environment and asthma in males and older age groups.

Paper 2. Early life stressors predicting chronic obstructive pulmonary problems in NFBC1966. Article manuscript. (6)

Partner(s) involved: University of Oulu – Invitation to others via LifeCycle network

Summary: We used NFBC1966 to examine whether early life stressors related to lung function and asthma in childhood also affect the risk of chronic pulmonary problems (COPD) in adulthood. The report hereby includes the analytical protocol and the first descriptives.

Study population: NFBC1966

Outcomes:

Lung function at young adult stage (31 y)

- Chronic pulmonary problems: Self-reported (own estimate, verified by doctor)
- Spirometry values: Forced vital capacity (litre, %) (sex and height adjusted), forced expiratory volume 1 (litre, %) (sex and height adjusted)

Lung function at middle-age adult stage (46 y)

- Chronic pulmonary problems: Self-reported (own estimate, verified by doctor)

Early life stressors:

- At birth and in infancy (age range: 0 y to 23 months): birth weight, birth length, gestational age, placental weight, mode of delivery, paternal asthma, maternal asthma, sibling asthma, number of persons in household, farmer family, residence, type of place of residence, maternal smoking, maternal weight, maternal height
- In infancy (age): maternal occupational status, maternal occupational status (< 1 year), maternal education (< 1 year), peak height/weight velocity, height (< 1 months), height (≥ 1 and < 2 months), weight (< 1 months), weight (≥ 1 and < 2 months), BMI at adiposity peak (or at 9 months), age at adiposity rebound (or BMI at 7 y)

Covariates:

- In childhood (7 y): furry pet(s)

- In adolescence (14 y): maternal occupation, paternal occupation, own smoking, maternal smoking, paternal smoking, weight, height, sports (frequency, type), sports club membership
- In adulthood (31 y): socioeconomic position (occupation), basic education, occupational education, weight, height, smoking, frequency of light and moderate to vigorous physical activity, duration of light and moderate to vigorous physical activity, MET minutes of light and moderate to vigorous physical activity, total MET minutes, pet (cat, dog, other)

Intermediaries:

- In adolescence (14 y): asthma
- In adulthood (31 y): asthma (own estimate, verified or treated by doctor)

Statistical analyses:

1) **Step 1:** multiple imputation for missing data.
2) **Step 2 (descriptive screening):** logistic regression on early life stressors predicting chronic pulmonary problems in adulthood (each exposure and outcome separately)
3) **Step 3:** logistic regression on early life stressors predicting chronic pulmonary problems in adulthood adjusted for early life parental confounders.
    a. **Parental confounders:** SEP, asthma, type and place of residence, smoking, weight, height
4) **Step 4 (path analysis):** early life stressors predicting lung function in adulthood via asthma in adolescence (including child/adolescent covariates).
    a. **Mediators:** adolescent asthma
    b. **Childhood covariates:** furry pet(s) at age 7 y
    c. **Adolescent covariates:** smoking, weight, height, physical activity (frequency), parental occupation, parental smoking

Preliminary results: The analyses included 8 668 participants (4 154 males, 4 514 females) who had valid data on COPD. The reported prevalence of COPD was 7% (n = 606) at age 31 years. Birth length was associated with COPD at age 31 (OR 0.91, 95% CI 0.84, 0.99) (Table 4). Higher weight in < 1 month after delivery predicted lower prevalence of COPD at age 31 (OR 0.64, 95% CI 0.45, 0.89). Other early life stressors were not associated with COPD at age 31 years.

Conclusions: Shorter birth length and higher weight in infancy (< 1 month after delivery) predicted lower prevalence of COPD in adulthood. Our findings support a growing body of data showing that early-life factors may play a fundamental part in the later onset of COPD. However, the pathways and mechanisms involved in the relationships between early-life events and chronic respiratory diseases in adulthood warrant further investigation.

Table 1. Regression analysis of farm environment and asthma at age 14 years.

	Females				Males			
	Model 1 (n = 4 810)		Model 2 (n = 2 302)		Model 1 (n = 4 849)		Model 2 (n = 2 043)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Birth								
Farmer family	0.445	0.159, 1.244	0.112	0.013, 0.937	0.818	0.412, 1.627	0.710	0.193, 2.614
Living place	0.642	0.386, 1.067	0.816	0.379, 1.759	0.706	0.462, 1.081	0.527	0.248, 1.119
Socio-economic	0.978	0.749, 1.279	0.685	0.466, 1.007	0.958	0.769, 1.193	1.001	0.672, 1.491
Birth weight	1.024	0.974, 1.076	1.012	0.937, 1.093	1.005	0.969, 1.043	0.978	0.917, 1.042
Family size	0.889	0.763, 1.037	1.004	0.805, 1.252	1.001	0.897, 1.118	1.105	0.922, 1.325
Maternal	1.278	0.739, 2.210	1.938	0.845, 4.448	1.188	0.760, 1.858	1.560	0.748, 3.252
Maternal BMI	0.997	0.916, 1.084	1.026	0.904, 1.166	0.990	0.927, 1.057	0.959	0.847, 1.085
7 years								
Pet(s)			0.558	0.263, 1.185			0.788	0.378, 1.643
14 years								
Smoking			0.454	0.135, 1.530			0.816	0.308, 2.166
BMI			1.013	0.874, 1.174			1.038	0.910, 1.185
Sports			1.079	0.903, 1.288			0.940	0.774, 1.141
Paternal			0.964	0.428, 2.173			2.557	0.882, 7.412
R^2	0.024		0.006		0.064		0.045	

Table 2. Regression analysis of farm environment and asthma at age 31 years.

	Females				Males			
	Model 1 (n = 3 859)		Model 2 (n = 2 162)		Model 1 (n = 3 465)		Model 2 (n = 1 889)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Birth								
Farmer family	0.757	0.539, 1.064	0.615	0.389, 0.971	0.704	0.492, 1.007	0.585	0.345, 0.992
Living place	0.855	0.681, 1.073	0.935	0.689, 1.270	0.803	0.632, 1.021	0.817	0.580, 1.152
Socio-economic position	0.894	0.795, 1.005	0.870	0.742, 1.021	0.926	0.820, 1.046	0.908	0.760, 1.084
Birth weight	1.002	0.981, 1.022	0.991	0.963, 1.019	0.998	0.978, 1.018	0.997	0.969, 1.026
Family size	1.028	0.973, 1.086	1.067	0.991, 1.148	1.600	1.000, 1.123	1.104	1.019, 1.196
Maternal smoking	1.302	1.022, 1.658	1.378	0.988, 1.921	1.094	0.846, 1.416	1.138	0.791, 1.637
Maternal BMI	0.982	0.948, 1.016	0.979	0.936, 1.025	1.009	0.975, 1.045	0.995	0.946, 1.047
7 years								
Pet(s)			0.885	0.654, 1.198			0.988	0.703, 1.387
14 years								
Smoking			0.841	0.582, 1.217			0.927	0.606, 1.419
BMI			1.029	0.967, 1.096			0.984	0.917, 1.056
Sports			1.057	0.989, 1.131			0.998	0.919, 1.085
Paternal smoking			0.873	0.646, 1.180			1.167	0.815, 1.671
31 years								
Farmer			1.120	0.385, 3.255			0.976	0.366, 2.602
Socio-economic position			1.013	0.844, 1.215			1.039	0.878, 1.230
BMI			1.051	1.018, 1.086			1.301	0.946, 1.790
Smoking			1.209	0.879, 1.663			1.051	1.002, 1.102
Sports			1.164	1.050, 1.289			1.127	1.008, 1,261
Healthy diet			0.958	0.887, 1.035			0.962	0.877, 1.055
Unhealthy diet			1.042	0.936, 1.162			0.990	0.897, 1.093
Furry pet(s)			0.584	0.430, 0.793			0.870	0.628, 1.206
R^2	0.007		0.046		0.006		0.026	

Table 3. Regression analysis of farm environment and asthma at age 46 years.

	Females				Males			
	Model 1 (n = 3 106)		Model 2 (n = 1 718)		Model 1 (n = 2 569)		Model 2 (n = 1 324)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Birth								
Farmer family	0.805	0.573, 1.130	0.604	0.377, 0.967	0.762	0.514, 1.129	0.782	0.441, 1.386
Living place	0.833	0.668, 1.040	0.889	0.655, 1.208	0.934	0.707, 1,232	0.911	0.596, 1.394
Socio-economic position	1.020	0.907, 1.147	0.958	0.812, 1.131	0.901	0.785, 1.035	0.836	0.677, 1.034
Birth weight	0.996	0.976, 1.016	1.012	0.983, 1.042	0.986	0.964, 1.008	0.969	0.936, 1.002
Family size	1.026	0.972, 1.084	1.101	1.023, 1.185	1.014	0.948, 1.084	1.072	0.977, 1.177
Maternal smoking	1.323	1.042, 1.681	1.292	0.918, 1.820	1.253	0.934, 1.680	1.094	0.696, 1.719
Maternal BMI	0.994	0.961, 1.027	0.966	0.923, 1.012	1.053	1.013, 1.094	1.057	0.998, 1.120
7 years								
Pet(s)			0.789	0.583, 1.069			1.240	0.809, 1.899
14 years								
Smoking			0.980	0.683, 1.406			0.826	0.484, 1.410
BMI			1.064	0.998, 1.136			0.962	0.881, 1.049
Sports			1.024	0.956, 1.096			1.018	0.924, 1.121
Paternal smoking			1.226	0.890, 1.689			1.687	1.071, 2.657
31 years								
Farmer			1.812	0.681, 4.820			0.612	0.183, 2.045
Socio-economic position			1.007	0.833, 1.218			0.998	0.819, 1.216
BMI			1.044	1.009, 1.080			1.165	0.786, 1.726
Smoking			1.319	0.957, 1.819			1.048	0.988, 1.112
Sports			1.001	0.903, 1.110			1.078	0.942, 1.233
Healthy diet			0.965	0.893, 1.044			1.038	0.933, 1.156
Unhealthy diet			1.047	0.937, 1.169			0.888	0.786, 1.003
Furry pet(s)			0.703	0.520, 0.950			1.042	0.704, 1.543
R^2	0.008		0.057		0.009		0.046	

Table 4. Results of the logistic regression model on COPD (yes/no) at 31 years (n = 8 668, 4 154 males, 4 514 females) adjusted for sex.

Exposure		n	OR	95% CI		p
Gender	2 = female	8 668	0.91	0.78	1.08	0.29
Farmer family	1 = yes	8 252	0.84	0.67	1.05	0.12
Father asthma	1 = yes	5 622	1.22	0.85	1.73	0.28
Mother asthma	1 = yes	5 623	1.09	0.79	1.52	0.59
Sibling asthma	1 = yes	5 625	1.19	0.88	1.62	0.26
Mother smoking	1 = yes	8 479	1.13	0.90	1.42	0.29
Living place	1 = urban	8 668	1.09	0.92	1.30	0.30
Birth weight		8 668	0.97	0.89	1.05	0.45
Birth length		8 593	0.91	0.84	0.99	**0.03**
Gestational age		8 376	0.96	0.89	1.05	0.38
Placental weight		7 473	1.00	0.92	1.09	0.95
Mother BMI		7 912	1.02	0.93	1.11	0.71
BMI at adiposity peak (or at 9 months)		3 248	0.98	0.85	1.13	0.77
Age at adiposity rebound (or BMI at 7y)		4 100	0.98	0.87	1.11	0.79
Peak height velocity		5 256	1.04	0.91	1.19	0.54
Height < 1 months		300	0.70	0.44	1.12	0.14
Height ≥ 1 and < 2 months		1 922	1.15	0.97	1.36	0.10
Weight < 1 months		732	**0.64**	0.45	0.89	**0.01**
Weight ≥ 1 and < 2 months		2 358	0.99	0.83	1.17	0.89
Household size		8 511	0.98	0.90	1.06	0.61
Delivery mode	ref. No					
Caesarian		3 357	1.20	0.80	1.78	0.37
Forceps. vacuum		3 357	1.36	0.77	2.40	0.29
Helping in brech birth		3 357	1.10	0.69	1.74	0.69
Maternal education	ref. High					
Medium		8 533	0.93	0.54	1.59	0.78
Low		8 533	0.87	0.59	1.29	0.50
Maternal occupation	ref. No					
Unskilled		8 534	1.26	0.93	1.70	0.14
Skilled		8 534	1.12	0.89	1.41	0.32
Professional		8 534	1.06	0.81	1.39	0.65
Farmer		8 534	0.88	0.70	1.11	0.29
Paternal occupation	ref. No					
Unskilled		8 309	1.45	0.45	4.69	0.54
Skilled		8 309	1.39	0.43	4.48	0.58
Professional		8 309	1.30	0.40	4.23	0.66
Farmer		8 309	1.16	0.36	3.76	0.81

5. Further work

- We will invite partners in the EuroCHILD Cohort Network (ALSPAC, HBCS and RAINE study) that have measured lung function and collected information about chronic respiratory diseases in adults of age 20 to 60 years to join the study on early life stressors predicting chronic obstructive pulmonary problems (6). ALSPAC and RAINE have longitudinal information until age 25 years, and NFBC and HBCS have information until age 60 years.
- To justify our preliminary findings on the associations between birth length and weight in infancy and COPD in adulthood, we will further investigate the pathways involved in the relationships between early-life stressors and COPD in adulthood. Specifically, we will examine early life stressors predicting lung function in adulthood via asthma in adolescence.
- Also, in view of the current literature in the field, the pathways underlying these apparent protective effects of being born in a farm need further understanding. As illustrated by the diagram of the Figure 1, future work will include testing the role of genetics and epigenetics factors in explaining part of these relationships. The hygiene hypothesis will be partially inferred by including early antibiotic exposures in the models.

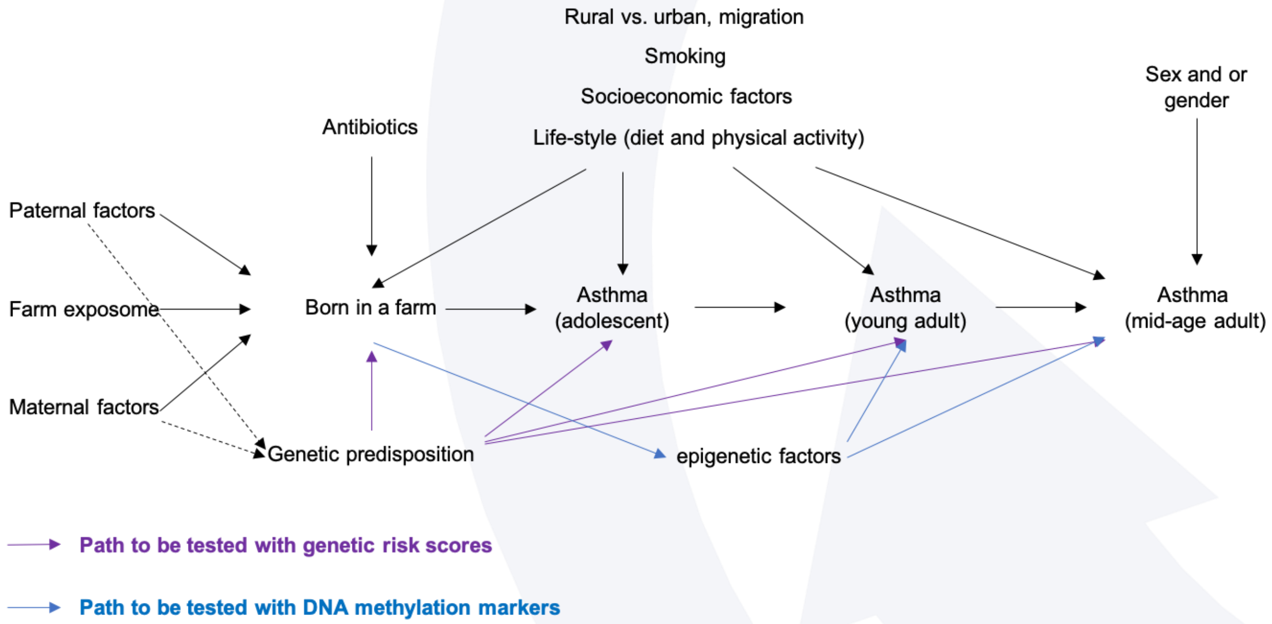

Figure 1. Directed acyclic diagram describing the possible pathways pertaining an association between being born in a farm and the risk of asthma in later life.

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