

RESEARCH ARTICLE

Early Life Origins of Lung Ageing: Early Life Exposures and Lung Function Decline in Adulthood in Two European Cohorts Aged 28–73 Years

Julia Dratva^{1,2*}, Elisabeth Zemp^{1,2}, Shyamali C. Dharmage³, Simone Accordini⁴, Luc Burdet⁵, Thorarinn Gislason⁶, Joachim Heinrich^{7,8}, Christer Janson⁹, Deborah Jarvis¹⁰, Roberto de Marco⁴, Dan Norbäck¹¹, Marco Pons¹², Francisco Gómez Real^{13,14}, Jordi Sunyer¹⁵, Simona Villani¹⁶, Nicole Probst-Hensch^{1,2}, Cecilie Svanes^{17,18}



OPEN ACCESS

Citation: Dratva J, Zemp E, Dharmage SC, Accordini S, Burdet L, Gislason T, et al. (2016) Early Life Origins of Lung Ageing: Early Life Exposures and Lung Function Decline in Adulthood in Two European Cohorts Aged 28–73 Years. PLoS ONE 11(1): e0145127. doi:10.1371/journal.pone.0145127

Editor: Philipp Latzin, University Children's Hospital Basel, SWITZERLAND

Received: July 29, 2015

Accepted: November 27, 2015

Published: January 26, 2016

Copyright: © 2016 Dratva et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: ECRHS and SAPALDIA cohort studies are bound to the local ethical and legal restrictions with respect to study data. At the time of SAPALDIA 1 and 2, and ECRHS I and II providing data publicly was not considered and participants were not asked for consent to provide individual data to the public. The data are available on request to scientists. Requests are to be addressed to the study primary investigators (www.ecrhs.org/; www.sapaldia.ch) or via the first and/or last authors of the manuscript.

1 Swiss Tropical and Public Health Institute, Dept. Epidemiology and Public Health, Basel, Switzerland, **2** University of Basel, Basel, Switzerland, **3** Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, Australia, **4** Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy, **5** Hôpital Interkantonal de la Broye, Payerne, Switzerland, **6** Dept. of Respiratory Medicine and Sleep, Landspítali University Hospital Reykjavik, Reykjavik, Iceland, **7** Helmholtz Center Munich, National Research Centre for Environmental Health, Munich, Germany, **8** Ludwig Maximilians University Munich, University Hospital Munich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine and German Center for Lung Research (DZL), Munich, Germany, **9** Department of Medical Sciences: Respiratory Medicine & Allergology, Uppsala University, Uppsala, Sweden, **10** Department of Public Health Sciences, Imperial College London, London, United Kingdom, **11** Department of Medical Sciences: Occupational & Environmental Medicine, Uppsala University, Uppsala, Sweden, **12** Division of Pulmonary Medicine, Regional Hospital of Lugano, Lugano, Switzerland, **13** Department of Clinical Science, University of Bergen, Bergen, Norway, **14** Department of Obstetrics and Gynaecology, Haukeland University Hospital, Bergen, Norway, **15** Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain, **16** University of Pavia, Faculty of Medicine, Dept. of Public Health, Neurosciences, Experimental and Legal Medicine, Pavia, Italy, **17** Bergen Respiratory Research Group, Centre for International Health, University of Bergen, Bergen, Norway, **18** Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway

* julia.dratva@unibas.ch

Abstract

Objectives

Early life environment is essential for lung growth and maximally attained lung function. Whether early life exposures impact on lung function decline in adulthood, an indicator of lung ageing, has scarcely been studied.

Methods

Spirometry data from two time points (follow-up time 9–11 years) and information on early life exposures, health and life-style were available from 12862 persons aged 28–73 years participating in the European population-based cohorts SAPALDIA ($n = 5705$) and ECRHS ($n = 7157$). The associations of early life exposures with lung function (FEV_1) decline were analysed using mixed-effects linear regression.

Funding: The first author was supported by a Marie Heim-Vögtlin grant from the Swiss National Science Foundation (grant # PMPDP3_129021/1; # PMPDP3_141671/1), the Lung league Beider Basel, Lung league Graubünden, the Stiftung ehemals Bündner Heilstätten and the COST action BM1201. Research support received by the SAPALDIA and ECRHS cohorts can be found in the online supplement (e-supplement). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Results

Early life exposures were significantly associated with FEV₁ decline, with estimates almost as large as personal smoking. FEV₁ declined *more rapidly* among subjects born during the winter season (adjusted difference in FEV₁/year of follow-up [95%CI] -2.04ml [-3.29;-0.80]), of older mothers, (-1.82 ml [-3.14;-0.49]) of smoking mothers (-1.82ml [-3.30;-0.34] or with younger siblings (-2.61ml [-3.85;-1.38]). *Less rapid* FEV₁-decline was found in subjects who had attended daycare (3.98ml [2.78;5.18]), and indicated in subjects with pets in childhood (0.97ml [-0.16;2.09]). High maternal age and maternal smoking appeared to potentiate effects of personal smoking. The effects were independent of asthma at any age.

Conclusion

Early life factors predicted lung function decline decades later, suggesting that some mechanisms related lung ageing may be established early in life. Early life programming of susceptibility to adult insults could be a possible pathway that should be explored further.

Introduction

Early childhood is a critical time window for subsequent lung health. Adverse childhood environmental exposures can restrain growth[1], modulate lung function [1, 2] and induce changes to gene-expression, modulating airway pathophysiology.[3, 4] The impact of a range of early life factors have been evidenced such as parental life-style [5, 6], nutrition [7] ambient air pollution [8, 9] or viral infections.[10] Epigenetic programming has been suggested as an underlying mechanism leading to less favourable long term respiratory health outcomes. [7, 11–13]

Emerging research suggests that not only lung growth, but also lung ageing, may be programmed early in life [14, 15]. Lung ageing encompasses the physiological as well as pathological processes which lead to altered lung function and lung diseases with increasing age. [16] Lung function decline is on one hand a normal ageing process, on the other hand it can be potentiated by risk factors, such as smoking [17, 18] or obesity.[17, 19] Early life impact on adult respiratory health is relatively well documented [20–23]. However, the potential impact on lung function decline by early life factors has been scarcely studied and remains inconsistent. Svanes et al., for example, shows that a childhood disadvantage score, including childhood asthma, predicted more rapid lung function decline in middle aged adults [21] and Jackson et al. evidenced earlier and quicker lung function decline for young adults with lower childhood SES [24] whereas Marossy et al. found no significant association between lung function decline in adults age 35–45 and early life respiratory infections.[25]

Smoking is known as the main adult risk factor for accelerated lung function decline; however, causes for varying susceptibility to tobacco exposure between individuals are not well understood. Early life factors, in particular parental smoking, have been hypothesized to play a role for modifying susceptibility.[26–28]. No previous study on early life factors has yet followed participants into old age or had the power to investigate individual early life factors in sufficient detail. We wished to investigate the hypotheses i) that early life factors may predict lung function decline, independent of childhood or parental asthma and ii) that one potential pathway might be through altered susceptibility to adult insults like smoking.

The combined data of the two cohorts, the Swiss Study on Air Pollution And Lung and Heart Disease In Adults (SAPALDIA) and the European Community Respiratory Health

Study (ECRHS) offered the opportunity, the necessary population size and age range to study these hypotheses.

Material and Methods

Study population

The study population consists of 12862 subjects of the SAPALDIA [29] and the ECRHS cohort. [30] Both studies have been described in detail elsewhere. In short, the SAPALDIA study population was recruited in 1991 as a population-based, random sample of adults ($N = 9651$, age 20–60 years) from eight study areas in Switzerland. [29] In the second assessment in 2002/03, lung function measures as well as the questionnaire on socio-demographic characteristics, life-style factors, living, housing and work related characteristics and health status, were repeated. Lung function data from both surveys was available for 5705 participants and mean follow-up time was 10.9 years. In ECRHS I, a random sample of adults aged 20–44 years were recruited in 29 centres ($N = 13\,359$). [30] 7157 participants with lung function measures at two time points (at ECRHS I in 1991–1993 and at ECRHS II in 1998–2002), were included into the analyses. The mean follow-up time was 8.8 years. The two cohorts have coordinated study design, questionnaires and common standards for interview and clinical examinations which allows for analyses of the combined data sets. Each study centre received approval by the institutional or regional ethics committee (S1 Text), and all participants signed informed consents.

Because of the large number of study centres, and the large number of study participants from Switzerland, the study centres were categorised into four European regions: Southern (Spain, France-Montpellier, Central (Switzerland, France-Grenoble and Italy-Pavia, -Turin, -Verona), Northern (Iceland, Sweden, Norway, Estonia) and Western Europe (Great-Britain, Belgium, France-Bordeaux and -Paris; S1 Fig).

Early life factors

Information on early life characteristics was collected by an interview-led questionnaire assessing serious respiratory infection <2 years, day care attendance <5 years, bedroom sharing, older and younger siblings, maternal age at delivery, season of birth (winter, defined as born in November to end of January, versus other seasons), paternal and/or maternal smoking during childhood, childhood pet keeping and urban living environment (large town vs. small town or farm/village) (S5 Table).

Lung function measurements

Spirometry testing in both studies was performed according to the ECRHS protocol following the American Thoracic Society guidelines. [31] The maximum FEV_1 and maximum forced vital capacity (FVC) of up to five technically acceptable manoeuvres were determined. Annual decline in FEV_1 ($\Delta FEV_1/yr.$) was calculated by subtracting the baseline from the follow-up value and dividing the difference by the individual time of follow-up in years, a negative value representing a decline. SAPALDIA used identical spirometry devices (model 2200, SensorMedics Corp., Yorba Linda, CA, USA) and protocols in both examinations, [32] as did ECRHS centres using same or comparable spirometers (Spiro Medics; Biomedin). [21]

Covariates

Asthma status: Participants reported doctor diagnosed asthma and age of onset. Childhood and teenage asthma was defined based on the age of reported first asthma attack (<10 yrs. of

age, respectively <20 yrs.). Adult asthma was defined as having the first asthma attack after the age of 20 yrs.

Other: Socio-demographic, individual, lifestyle factors associated with respiratory health and family predisposition, such as parental and sibling asthma, were considered as confounders. Smoking status was defined on self-reported smoking history. Pack years at the 2nd survey were calculated based on an estimation of the average number of cigarettes smoked per year. Missing data for pack years (N = 225) and maternal age at birth (N = 237) were imputed by a “simple” imputation technique based on multivariate regression models to predict the missing information. Imputed data were only used as confounders in multivariate analyses.

Statistical methods

Descriptive analyses, including comparative lung function (FEV₁) at first survey and lung function decline (Δ FEV₁/yr.), were ran by European region and by smoking status. We studied the impact of early life factors on lung function decline in a mixed-effects linear regression model; in a first step, for single early life factors (S1 Table), and secondly, adjusting mutually for all early life exposures. Model adjustments were made for mid age, mid age square, mid BMI (mid = [survey 1 + survey 2]/2), change in BMI (between survey 1 and 2), height, pack years smoked, age at highest education, based on the significance level of $p \leq 0.2$. Different regional adjustments, including the four European regions (main analyses), the cohorts (ECRHS, SAPALDIA) or study centre as random factors, were performed. To investigate independency of the investigated early life factors from childhood & teenage and adult asthma, we ran additional models adjusting for the reported asthma status, as well as sensitivity analyses excluding subjects who reported 1.) asthma as a child (<10 yrs.) 2.) ever having had asthma, 3.) COPD, defined as pre-bronchodilator FEV₁/FVC <0.70 [33]. The potentially increased susceptibility to adult smoking was investigated by interaction terms between significant adverse early life factors and participants' current smoking exposure (e.g. smoking*maternal smoking), and by stratified analyses by smoking status and sex. Significance of interaction was assumed at a p-value of ≥ 0.1 . Furthermore, we ran a sensitivity analysis excluding participants under 25 yrs. at the first survey and stratified analyses by gender, smoking status and European region. To take regional differences in population size into account we performed meta-analyses by European region. All analyses were conducted using STATA 12 (www.stata.com/stata12). The final significance level was $p = 0.05$ for all results.

Results

Characteristics of the 12862 study participants by European region are provided in table 1. The early life factors, except season of birth ($p = 0.7$), differed significantly between the regions ($p < 0.001$, Table 1). Age-and height-adjusted lung function and lung function decline is presented in table 2. In both men and women FEV₁ decline was higher in the Northern European region and among current smokers (Table 2).

The associations of early life factors with adult FEV₁ decline, analysed with mixed-effects linear regression analyses and mutual adjustment for all the early life factors, are presented in Table 3. The lung function decline was significantly more rapid in participants who were born during the winter season, to mothers >31 years at delivery, with ≥ 2 younger siblings or exposed to maternal smoking. Significantly less rapid lung function decline was observed in persons who had attended day care in childhood and was indicated for early life pet exposure (Table 3).

Sensitivity analyses excluding asthmatic participants (S4 Table) and adjusting for reported asthma at any age (S5 Table) showed consistent results.

Table 1. Characteristics of the study population of the ECRHS and SAPALDIA cohorts, by European region.

	European Regions								All	
	Southern		Central		Northern		Western			
	N = 1517		N = 6530		N = 3089		N = 1726		N = 12862	
Socio-demographic factors†	Mean	s.d.	Mean	s.d.	Mean	s.d.	Mean	s.d.	Mean	s.d.
Age, 2 nd survey (yrs.)	42	7	51	11	43	7	44	7	47	10
BMI, 2 nd survey (kg/m ²)	27	5	26	4	26	4	26	5	26	4
Age at highest (yrs.) educational degree	19	5	20	4	23	6	19	4	20	5
Pack years, 2 nd survey										
in all	15	20	11	19	9	14	10	17	11	18
in current smokers	25	20	23	21	19	16	24	20	22	20
Early life factors†	no.	%	no.	%	no.	%	no.	%	no.	%
Season of birth (winter)	395	26	1624	25	777	25	422	24	3218	25
Maternal age (>31 yrs.)	546	36	2023	31	871	28	474	27	3914	30
Maternal smoking	60	4	833	13	982	32	511	30	2386	19
Paternal smoking	1032	68	3716	57	1835	59	1158	67	7741	60
Severe respiratory infection	124	8	560	9	364	12	156	9	1204	9
Urban living environment	488	32	1972	30	1550	50	694	40	4704	37
Sharing bedroom	784	52	1728	27	917	30	950	55	4379	34
Daycare attendance	730	48	3029	46	1422	46	692	40	5873	46
Family pet (< 5 yrs.)	916	60	2880	44	1134	37	592	34	5522	43
Older siblings	993	65.5	3942	61	1747	57	1040	60	7722	60
Younger siblings	987	65	4012	62	1769	57	1035	60	7803	61
Asthma†										
Childhood asthma	49	3	190	3	155	5	107	6	501	4
Adult asthma	116	8	213	3	258	9	150	10	737	6
Paternal asthma	117	8	409	6	181	6	88	5	795	6
Maternal asthma	93	6	310	5	235	8	107	6	745	6
Sibling asthma	199	13	760	12	263	9	186	11	1408	11

† Differences across European regions tested by ANOVA or Chi2 as appropriate, all $p < 0.001$ with exception of season of birth (p -value = 0.7)

doi:10.1371/journal.pone.0145127.t001

Analyses stratified by sex yielded consistent results in men and women, with the exception of parental smoking and respiratory infections ([S2 Table](#), [S2 Fig](#)): Differential effects were observed for maternal smoking by sex, with higher effect estimates in men ($\Delta\text{FEV}_1/\text{yr.}$ -2.23 ml [-5.11 to -0.33]) than in women (-0.57 ml [-2.34 to 1.20], $p_{\text{heterogeneity}} = 0.08$). In non-smokers, respiratory infections were more strongly associated with FEV_1 decline in men ($p_{\text{heterogeneity}} = 0.053$). Separate analysis for synergistic effects between adverse early life factors and adult smoking showed that maternal smoking and higher maternal age were more strongly associated with FEV_1 decline among current smokers than among never-smokers ([S3 Table](#)). In participants exposed to both early life factors we observed a significantly larger effect estimates compared to a single exposure ([Table 4](#)). The synergistic effects were larger in men than in women (higher maternal age & smoking -4.45 ml [-7.04 to -1.85] vs. (-3.98 ml [-6.80 to -1.14]; maternal smoking & smoking -5.87 [-10.01 to -1.7] vs. -3.17 [-6.39 to -0.08]). Further stratified analyses by sex yielded a significant interaction between maternal age and current smoking status among men ($p_{\text{interaction}} = 0.023$) but not in women. Synergistic effects were not observed for season of birth or younger siblings.

Table 2. Age and height adjusted FEV₁ and FEV₁ decline per follow-up year (Δ FEV₁/yr.) in women and men, by European region and by smoking status.

	Adjusted FEV ₁ † (ml)	s.e.	Adjusted FEV ₁ decline/year‡ (ml)	s.e.
Women				
Southern European Region (N = 750)	2886	15	-25.2	-1.1
Central European Region (N = 3407)	2848	7	-27.4	-0.6
Northern European Region (N = 1578)	2871	10	-30.5	-0.8
Western European Region (N = 914)	2856	13	-26.9	-1.0
Never smoker (N = 4959) §	2874	6	-26.9	-0.4
Current smoker (N = 1690) §	2816	11	-30.4	-0.7
Men				
Southern European Region (N = 767)	3886	22	-34.2	-1.4
Central European Region (N = 3123)	3876	11	-34.7	-0.8
Northern European Region (N = 1511)	3872	15	-39.6	-1.1
Western European Region (N = 812)	3867	20	-35.8	-1.3
Never smoker (N = 4341) §	3916	9	-34.9	-0.5
Current smoker (N = 1872) §	3781	14	-38.3	-0.8

s.e. standard error; † age and height adjusted FEV₁ at 2nd survey;

‡ age and height adjusted difference in FEV₁ (ml) per year of follow up;

§ additionally adjusted for European regions (fixed effect)

doi:10.1371/journal.pone.0145127.t002

Meta-analyses showed that the associations of early life factors with FEV₁ decline were generally consistent across European regions (adjusted for study centres within each region) (Fig 1, S2 Fig). Only the association with urban living environment showed a significant heterogeneity, with protective effects in Central Europe whereas adverse effects were present in Western and Southern Europe (heterogeneity p-value 0.016, Fig 1).

Table 3. The associations of early life factors with lung function decline (mutually adjusted models).

Early life factors		Adjusted difference in FEV ₁ decline †			p-value
		in ml ‡		95% CI	
Season of birth	(winter vs. other)	-2.04	-3.29	-0.80	0.001
Maternal age	(>31 vs <31 yrs.)	-1.82	-3.14	-0.49	0.007
Maternal smoking	(yes vs. no)	-1.82	-3.30	-0.34	0.016
Paternal smoking	(yes vs. no)	0.56	-0.57	1.69	0.332
Severe respiratory infection	(yes vs. no)	-0.57	-2.42	1.29	0.549
Urban living environment	(urban vs. rural)	0.62	-0.84	2.08	0.408
Daycare attendance	(yes vs. no)	3.98	2.78	5.18	0.000
Sharing bedroom	(yes vs. no)	-0.42	-1.57	0.74	0.481
Family pet (<5 years)	(yes vs. no)	0.97	-0.16	2.09	0.091
Older siblings ≥2	(≥2 vs. <2)	0.56	-1.00	2.12	0.479
Younger siblings <2	(<2 vs. ≥2)	-2.61	-3.85	-1.38	0.000

† Change in FEV₁ (ml) by follow up year—a negative coefficient implies more rapid FEV₁ decline and a positive coefficient implies less rapid decline.

‡ Estimates from mixed-effects linear regression, mutually adjusted for all other early life factors investigated, and for sex, mid age, mid age square, mid BMI, change in BMI (between survey 1 and 2), height, pack years smoked, age at highest education, European region (random effect)

CI = Confidence Interval

doi:10.1371/journal.pone.0145127.t003

Table 4. Synergistic effects of early life factors and participants' current smoking status with regard to lung function decline.

		Adjusted difference in FEV1 decline†			
Early life exposure		in ml ‡	CI 95%		p-value
maternal age >31 yrs.	participant smoking				
No	No	Ref.			
Yes	No	-0.44	-1.92	1.04	0.559
No	Yes	-1.21	-2.87	0.44	0.150
Yes	Yes	-4.20	-6.44	-1.97	0.000
maternal smoking	participant smoking				
No	No	Ref.			
Yes	No	-1.75	-3.55	0.04	0.056
No	Yes	-1.82	-3.38	-0.25	0.023
Yes	Yes	-4.44	-7.04	-1.85	0.001

† Change in FEV₁ (ml) by follow up year—a negative coefficient implies more rapid FEV₁ decline and a positive coefficient implies less rapid decline.

‡ Estimates from mixed-effects linear regression, mutually adjusted for all other early life factors and for sex, mid age, mid age square, mid BMI, change in BMI (between survey 1 and 2), height, age at highest education, pack-years, European region (random effect).

CI = Confidence Interval

doi:10.1371/journal.pone.0145127.t004

Discussion

In two European multi-centre cohort studies, including 12862 persons aged 28–73 at follow-up and relying on comparable methodology, we found that early life factors predicted lung function decline into old age, suggesting that lung ageing is programmed early in life. Our analyses show a substantial impact on lung function decline by early life factors, ranging from adverse effects almost as large as the effects of personal smoking, to “protective” effects of similar magnitude for having older siblings. The early life impact was independent of participant's lifetime asthma status. A more rapid lung function decline was associated with season of birth, higher maternal age at delivery, maternal smoking and the presence of younger siblings, whereas early day-care attendance, older siblings and childhood pet keeping appeared to be associated with a less rapid decline. One must consider, that these early life factors may reflect underlying mechanisms, [34] having led to or potentiated the observed lung function decline. The main findings were consistent across European regions with the exception of urban living environment. There was some evidence of a differential impact of early life factors by sex, suggesting that early life programming may be related to gender. Accelerated decline related to adverse early life factors was more pronounced among current smokers than never-smokers, possibly pointing to an increased susceptibility to smoking in subjects exposed to higher maternal age and maternal smoking.

This is the first study to investigate early life impact on lung function decline into old age, and to address the hypothesis on interaction with adult insults like smoking. Our findings agree with some of the earlier studies showing association between early life environment, e.g. maternal smoking, and lung function decline in younger adults.[6, 21, 26, 27]. We did not observe a significant effect for respiratory disease on lung function decline, neither did Svanes et al.[21] or Marossy et al.,[25] although early infections have been associated with lung growth and function.[15] In our study, non-differential misclassification by retrospective recall or different severity of childhood disease may explain the null-finding. Such imprecision would most likely attenuate the true association.

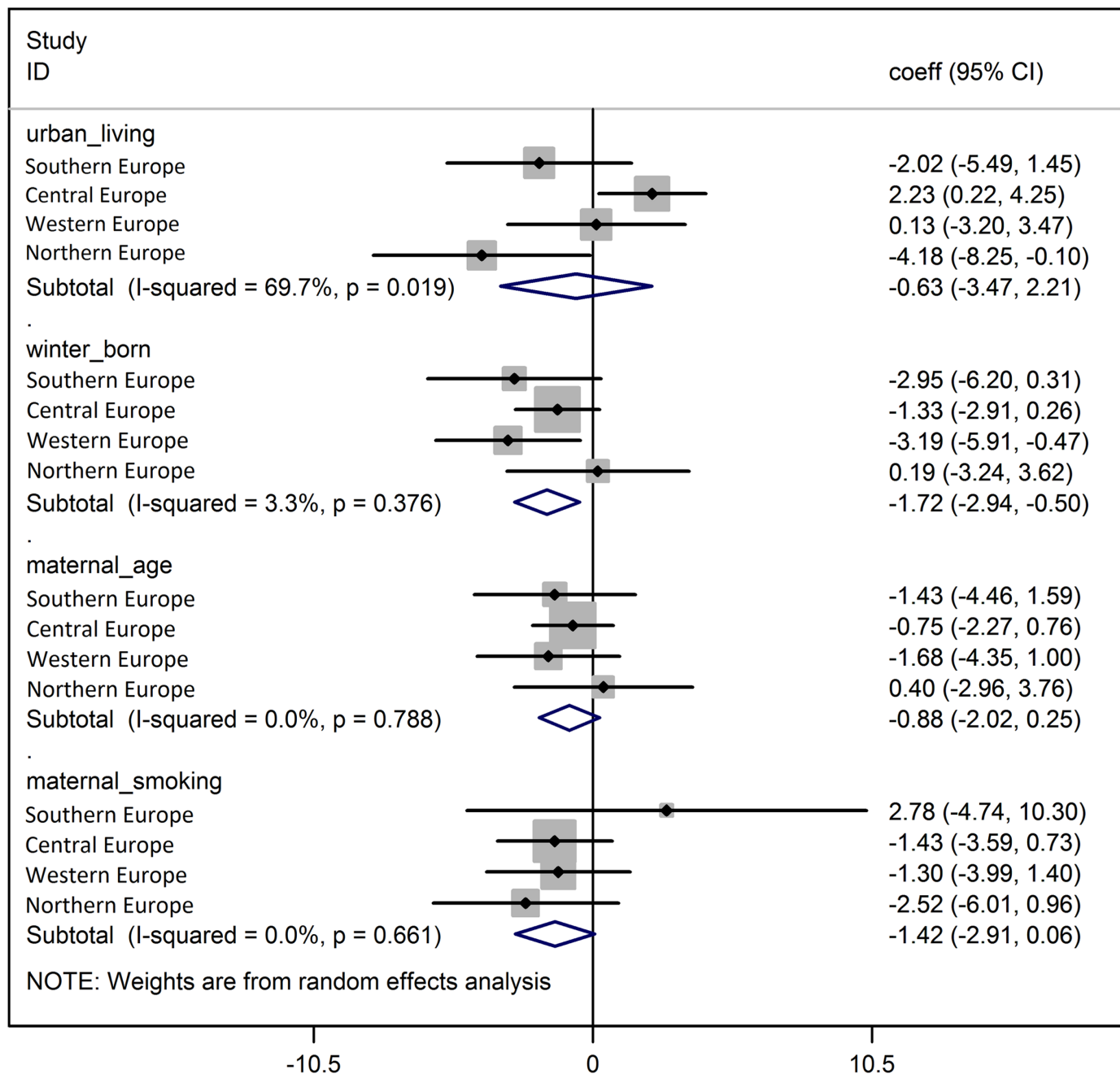


Fig 1. Meta-analyses across European regions: selected early life factors and FEV₁ decline. Δ FEV₁/yr. corresponds to change in FEV₁ (ml) per year of follow-up—a negative coefficient implies more rapid FEV₁ decline and a positive coefficient implies less rapid decline. Meta-Analyses by European region, mutually adjusted for all other early life factors investigated and for sex, mid age, mid age square, mid BMI, change in BMI (between survey 1 and 2), height, lifetime pack years smoked, age at highest education, study area (random effect).

doi:10.1371/journal.pone.0145127.g001

Among the novel findings is the association of lung function decline with season of birth. This association was strong and consistent between European regions. Participants born in winter months had a more rapid decline in lung function. Being born in winter has been related to in-utero exposures to viral infections or allergens and to a higher frequency of respiratory

infections in the first months of life,[35] both likely major influences on the subsequent establishment of immune response.[36] Low maternal vitamin D levels, more frequent in winter season, have also been discussed as possible factor influencing childhood wheeze and asthma.[37] Season of birth cannot be separated, however, from season of conception and pregnancy. Our finding that season of birth is somehow related to early life programming of lung ageing should fuel further research into underlying mechanisms.

We found a more pronounced lung function decline in participants born to older mothers. Maternal age at delivery reflects biological ageing of the mother as well as sociocultural characteristics. Pregnancy complications [38] and Caesarean section are more common in older mothers, and may be of importance for immunological functions in infants [39] and beyond [40]. A birth cohort effect may also play a role, as participants born between 1930 and 1950 were more often born to older mothers than younger participants (data not shown). Our result conflict with earlier publications,[41, 42] but are in line with a recent study by Caudri et al. observing a differential impact of maternal age depending on the wheeze phenotypes, implying older age to be associated with late onset wheeze. [43] We also observed that maternal smoking is a significant predictor for accelerated lung function decline even in older age. Long-term impact of maternal smoking have previously been shown with regard to asthma [5] and lung function in young to mid-age adults.[21, 26, 27] Inflammatory pathways are believed to be central; however, many open questions remain regarding the underlying mechanisms.[26, 34] In our cohorts lung function decline was more pronounced in smokers who in addition were exposed to either maternal smoking or higher maternal age. This indicates that susceptibility to later adult insults might be programmed early in life. A synergistic effect of parental smoking has been described by Guerra et al. [26] who found a steeper decline of lung function in young adults exposed to both parental and individual smoking. Upton et al. showed that the effect on airflow limitation by 10 cigarettes/day maternal smoking was numerically equivalent to 10 years active smoking. [27] The importance of the early life environment for susceptibility to adult insults has already been discussed by Ramsey et al., who found an additive influence on FEV₁ decline by parental and individual socio-economic position. Previous findings on synergistic effects support our novel finding on an increased susceptibility to smoking in subjects born to older mothers. Our data further support some heterogeneity by gender: we found a stronger overall impact of maternal age and current smoking in men as compared to women, even after adjustment for pack years. There are several known mechanisms which may explain different susceptibility by sex to life-time exposures, [13, 44, 45] and several studies have shown a higher respiratory vulnerability in men. [5, 46–48] The concept of increased vulnerability at certain time-points in life is also underlying the analyses of both older and younger siblings, representing an early and a later prolonged exposure to a variety of microbes. While the effect of older siblings was non-significant, we found an independent and adverse effect of the presence of younger siblings. The analytic approach and the result is supported by a publication by Svanes et al. that found a U-shaped association between number of siblings and adult asthma,[23] and a recent publication by Grabenhenrich et al. also observing a U-form association between asthma and age at entering day care.[42]

Day care attendance was related to less rapid lung function decline, independent of gender or smoking status, and similar “protective effects” were indicated for childhood pet keeping and having older siblings. This is the first analysis of lung function decline in relation to these early life exposures. Our findings are in agreement with previous research in younger populations and other respiratory health outcomes, in particular allergic diseases.[49] The data imply that these factors, generally discussed in view of the hygiene hypothesis,[50] can induce long-term modifications of the immune system.

While a study within ECRHS showed that some childhood exposures are reported with high consistency, irrespective of respiratory health status,[51] residual confounding due to recall bias cannot be excluded. All factors except maternal age were recorded at baseline, prior to measurement of lung function at baseline and at follow-up. The retrospective reporting of these factors might have led to imprecise recall, which is likely to have attenuated true associations. It is, however, unlikely that recall would be differential with regard to the outcome of the present analysis—the difference between two objectively measured lung function values. It is also unlikely that recall bias should be uniform across different cohorts and European countries.

The consistent results across European regions suggest that the associations may be due to homogeneous biological mechanisms rather than heterogeneous socio-cultural differences. Heterogeneity between regions was only found for the impact of urban living environment. We observed a significant protective effect on lung function decline by urbanity in Central Europe, while the opposite was found in Western and Southern Europe. Urbanity can be considered a proxy for opposite health determinants, e.g. higher pollutant exposure versus better access to health care. Our data did not allow investigating the latent construct urbanity any further.

With respect to parental smoking, we could not assess how much parents have smoked and for how long. This limitation possibly reduced the power of our study, since one would assume that the synergy would increase with higher doses of exposure in childhood.[27] Residual confounding is also possible due to a lack of information on further potentially influencing factors e.g. nutrition, air pollution exposure in childhood or birth characteristics. Individuals with particularly poor early life development could possibly be more or less likely to participate in the cohort, thus, the prevalence of early life factors might not reflect the true population prevalence. In view of our study hypothesis, this bias would limit the generalizability of our study, but not produce spurious associations. As some study participants were younger than 25 years at the first survey, late lung growth may have confounded the analyses. However, excluding these subjects resulted in consistent associations. The analytical strategy, including all factors in mutually adjusted analyses, may have introduced over-adjustment, potentially reducing the power to identify less strong direct associations.

Investigating early life factors and potential interactions demands large study populations, which was achieved by combining the cohorts SAPALDIA and ECRHS. We had the power to study even potentially small effects of early life factors and to identify sub-groups at risk, given the inclusion of persons in the 7th decade with the advantage of rich information about declining lung function in this aging cohort. This multinational study population constitutes both strengths and limitations. On one hand, our homogenous results across the European regions underline the importance of early life environment in Europe. On the other hand regional differences in the effects of childhood factors may attenuate the overall effects when adjusted for regions and regional specific risks may not have been picked up. The results cannot be generalized to countries where the investigated childhood factors, such as day care, must be considered proxies of considerably different exposures.

In conclusion, our results showed that lung function decline into old age were predicted by early life factors. This novel finding supports the hypothesis that lung ageing, which is captured by lung function decline, is programmed early in life. We further found that lung function decline was more rapid in those with early life disadvantages who subsequently smoked, suggesting that altered individual susceptibility to adult insults could be one possible pathway for persisting effects of early life factors decades later. Interestingly, lung function was found to decline more rapidly in people born during the winter season, consistently across European regions; this effect merits further investigation. From a public health point of view, early life impact on lung function decline and on susceptibility to adult exposures offers possibilities for

intervention, and from a clinical point of view, these findings identify a population at risk for accelerated lung function decline.

Supporting Information

S1 Fig. European map and regional distribution of SAPALDIA and ECRHS study centers.
(PDF)

S2 Fig. Meta-analyses across European regions: Association of early life factors and lung function decline.
(PDF)

S1 Table. Impact of single early life factors on lung function decline.
(PDF)

S2 Table. Impact of early life factors on lung function decline, stratified by sex.
(PDF)

S3 Table. Impact of early life factors on lung function decline, stratified by smoking status.
(PDF)

S4 Table. Sensitivity analyses.
(PDF)

S5 Table. Sensitivity analyses: Association between lung function decline and early life factors adjusting for childhood and adult asthma.
(PDF)

S6 Table. Definitions of early life factors as used in SAPALDIA and ECRHS questionnaires.
(PDF)

S1 Text. Funding and ethical committees.
(DOCX)

S2 Text. Cohort funding information.
(DOC)

Author Contributions

Conceived and designed the experiments: JD CS SD. Performed the experiments: EZ SD SA LB TG JH CJ DJ RM DN MP JS SV NP CS. Analyzed the data: JD CS. Wrote the paper: JD EZ SD SA LB TG JH CJ DJ RM DN MP JS SV NP CS FGR.

References

1. Apostol GG, Jacobs DR Jr., Tsai AW, Crow RS, Williams OD, Townsend MC, et al. Early Life Factors Contribute to the Decrease in Lung Function between Ages 18 and 40: The Coronary Artery Risk Development in Young Adults Study. *Am J Respir Crit Care Med*. 2002; 166(2):166–72. doi: [10.1164/rccm.2007035](https://doi.org/10.1164/rccm.2007035) PMID: [12119228](https://pubmed.ncbi.nlm.nih.gov/12119228/)
2. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *Bmj*. 1991; 303(6804):671–5. PMID: [1912913](https://pubmed.ncbi.nlm.nih.gov/1912913/).
3. London SJ, James Gauderman W, Avol E, Rappaport EB, Peters JM. Family history and the risk of early-onset persistent, early-onset transient, and late-onset asthma. *Epidemiology*. 2001; 12(5):577–83. PMID: [11505179](https://pubmed.ncbi.nlm.nih.gov/11505179/).

4. Martinez FD. The Origins of Asthma and Chronic Obstructive Pulmonary Disease in Early Life. *Proceedings of the American Thoracic Society*. 2009; 6(3):272–7. doi: [10.1513/pats.200808-092RM](https://doi.org/10.1513/pats.200808-092RM) PMID: [19387029](https://pubmed.ncbi.nlm.nih.gov/19387029/)
5. Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney P. Parental smoking in childhood and adult obstructive lung disease: results from the European Community Respiratory Health Survey. *Thorax*. 2004; 59(4):295–302. doi: [10.1136/thx.2003.009746](https://doi.org/10.1136/thx.2003.009746) PMID: [15047948](https://pubmed.ncbi.nlm.nih.gov/15047948/)
6. Ramsay SE, Whincup PH, Lennon LT, Morris RW, Wannamethee SG. Longitudinal associations of socioeconomic position in childhood and adulthood with decline in lung function over 20 years: results from a population-based cohort of British men. *Thorax*. 2011; 66(12):1058–64. doi: [10.1136/thoraxjnl-2011-200621](https://doi.org/10.1136/thoraxjnl-2011-200621) PMID: [21784770](https://pubmed.ncbi.nlm.nih.gov/21784770/)
7. Palmer DJ, Huang R-C, Craig JM, Prescott SL. Nutritional Influences on Epigenetic Programming: Asthma, Allergy, and Obesity. *Immunology and Allergy Clinics of North America*. 2014; 34(4):825–37. doi: [10.1016/j.jac.2014.07.003](https://doi.org/10.1016/j.jac.2014.07.003) PMID: [25282294](https://pubmed.ncbi.nlm.nih.gov/25282294/)
8. Carlsen K-Hk, Carlsen KCLd. Respiratory effects of tobacco smoking on infants and young children. *Paediatric Respiratory Reviews*. 2008; 9(1):11–20. doi: [10.1016/j.prrv.2007.11.007](https://doi.org/10.1016/j.prrv.2007.11.007) PMID: [18280975](https://pubmed.ncbi.nlm.nih.gov/18280975/)
9. Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy*. 2015; 70(3):245–56. doi: [10.1111/all.12561](https://doi.org/10.1111/all.12561) PMID: [25495759](https://pubmed.ncbi.nlm.nih.gov/25495759/)
10. Tennant PW, Gibson GJ, Parker L, Pearce MS. Childhood respiratory illness and lung function at ages 14 and 50 years: childhood respiratory illness and lung function. *Chest*. 2009; 137(1):146–55. PMID: [19581355](https://pubmed.ncbi.nlm.nih.gov/19581355/). doi: [10.1378/chest.09-0352](https://doi.org/10.1378/chest.09-0352)
11. von Mutius E. Gene-environment interactions in asthma. *The Journal of allergy and clinical immunology*. 2009; 123(1):3–11; quiz 2–3. PMID: [19130922](https://pubmed.ncbi.nlm.nih.gov/19130922/). doi: [10.1016/j.jaci.2008.10.046](https://doi.org/10.1016/j.jaci.2008.10.046)
12. Hollingsworth JW, Maruoka S, Boon K, Garantziotis S, Li ZW, Tomfohr J, et al. In utero supplementation with methyl donors enhances allergic airway disease in mice. *J Clin Invest*. 2008; 118(10):3462–9. doi: [10.1172/Jci34378](https://doi.org/10.1172/Jci34378) WOS:000259828600027. PMID: [18802477](https://pubmed.ncbi.nlm.nih.gov/18802477/)
13. Krauss-Etschmann S, Bush A, Bellusci S, Brusselle GG, Dahlen SE, Dehmel S, et al. Of flies, mice and men: a systematic approach to understanding the early life origins of chronic lung disease. *Thorax*. 2013; 68(4):380–4. doi: [10.1136/thoraxjnl-2012-201902](https://doi.org/10.1136/thoraxjnl-2012-201902) PMID: [22781122](https://pubmed.ncbi.nlm.nih.gov/22781122/)
14. Krauss-Etschmann S, Bush A, Bellusci S, Brusselle GG, Dahlen SE, Dehmel S, et al. Of flies, mice and men: a systematic approach to understanding the early life origins of chronic lung disease. *Thorax*. 2012. doi: [10.1136/thoraxjnl-2012-201902](https://doi.org/10.1136/thoraxjnl-2012-201902)
15. Stocks J, Sonnappa S. Early life influences on the development of chronic obstructive pulmonary disease. *Ther Adv Respir Dis*. 2013; 7(3):161–73. doi: [10.1177/1753465813479428](https://doi.org/10.1177/1753465813479428) WOS:000336023700004. PMID: [23439689](https://pubmed.ncbi.nlm.nih.gov/23439689/)
16. Thannickal VJ, Murthy M, Balch WE, Chandel NS, Meiners S, Eickelberg O, et al. Blue Journal Conference. Aging and Susceptibility to Lung Disease. *American Journal of Respiratory and Critical Care Medicine*. 2015; 191(3):261–9. doi: [10.1164/rccm.201410-1876PP](https://doi.org/10.1164/rccm.201410-1876PP) PMID: [25590812](https://pubmed.ncbi.nlm.nih.gov/25590812/)
17. Chinn S, Jarvis D, Melotti R, Luczynska C, Ackermann-Liebrich U, Anto JM. Smoking cessation, lung function, and weight gain: a follow-up study. *Lancet*. 2005; 365:1629–35. doi: [10.1016/S0140-6736\(05\)66511-7](https://doi.org/10.1016/S0140-6736(05)66511-7) PMID: [15885295](https://pubmed.ncbi.nlm.nih.gov/15885295/)
18. Petersen H, Sood A, Meek PM, Shen X, Cheng Y, Belinsky SA, et al. RAPid lung function decline in smokers is a risk factor for copd and is attenuated by angiotensin-converting enzyme inhibitor use. *CHEST Journal*. 2014; 145(4):695–703. doi: [10.1378/chest.13-0799](https://doi.org/10.1378/chest.13-0799)
19. Pistelli F, Bottai M, Carrozzi L, Pede FD, Baldacci S, Maio S, et al. Changes in obesity status and lung function decline in a general population sample. *Respiratory Medicine*. 2008; 102(5):674–80. doi: [10.1016/j.rmed.2007.12.022](https://doi.org/10.1016/j.rmed.2007.12.022) PMID: [18261894](https://pubmed.ncbi.nlm.nih.gov/18261894/)
20. de Marco R, Accordini S, Marcon A, Cerveri I, Anto JM, Gislason T, et al. Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults. *Am J Respir Crit Care Med*. 2013; 183(7):891–7. PMID: [20935112](https://pubmed.ncbi.nlm.nih.gov/20935112/)
21. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, et al. Early life origins of chronic obstructive pulmonary disease. *Thorax*. 2009;thx.2008.112136. doi: [10.1136/thx.2008.112136](https://doi.org/10.1136/thx.2008.112136)
22. Svanes C, Heinrich J, Jarvis D, Chinn S, Omenaas E, Gulsvik A, et al. Pet-keeping in childhood and adult asthma and hay fever: European community respiratory health survey. *The Journal of allergy and clinical immunology*. 2003; 112(2):289–300. PMID: [12897734](https://pubmed.ncbi.nlm.nih.gov/12897734/)
23. Svanes C, Jarvis D, Chinn S, Omenaas E, Gulsvik A, Burney P, et al. Early exposure to children in family and day care as related to adult asthma and hay fever: results from the European Community Respiratory Health Survey. *Thorax*. 2002; 57(11):945–50. PMID: [12403876](https://pubmed.ncbi.nlm.nih.gov/12403876/); PubMed Central PMCID: PMC1746215.

24. Jackson B, Kubzansky LD, Cohen S, Weiss S, Wright RJ. A matter of life and breath: childhood socio-economic status is related to young adult pulmonary function in the CARDIA study. *International journal of epidemiology*. 2004; 33(2):271–8. doi: [10.1093/ije/dyh003](https://doi.org/10.1093/ije/dyh003) PMID: [15082626](https://pubmed.ncbi.nlm.nih.gov/15082626/)
25. Marossy AE, Strachan DP, Rudnicka AR, Anderson HR. Childhood chest illness and the rate of decline of adult lung function between ages 35 and 45 years. *Am J Respir Crit Care Med*. 2007; 175(4):355–9. doi: [10.1164/rccm.200607-1023OC](https://doi.org/10.1164/rccm.200607-1023OC) PMID: [17023728](https://pubmed.ncbi.nlm.nih.gov/17023728/).
26. Guerra S, Stern DA, Zhou M, Sherrill DL, Wright AL, Morgan WJ, et al. Combined effects of parental and active smoking on early lung function deficits: a prospective study from birth to age 26 years. *Thorax*. 2013; 68(11):1021–8. doi: [10.1136/thoraxjnl-2013-203538](https://doi.org/10.1136/thoraxjnl-2013-203538) PMID: [23847259](https://pubmed.ncbi.nlm.nih.gov/23847259/)
27. Upton MN, Smith GD, McConnachie A, Hart CL, Watt GCM. Maternal and Personal Cigarette Smoking Synergize to Increase Airflow Limitation in Adults. *American Journal of Respiratory and Critical Care Medicine*. 2004; 169(4):479–87. doi: [10.1164/rccm.200211-1357OC](https://doi.org/10.1164/rccm.200211-1357OC) PMID: [14630616](https://pubmed.ncbi.nlm.nih.gov/14630616/)
28. Svanes O, Skorge TD, Johannessen A, Bertelsen RJ, Bratveit M, Forsberg B, et al. Respiratory Health in Cleaners in Northern Europe: Is Susceptibility Established in Early Life? *PloS one*. 2015; 10(7): e0131959. doi: [10.1371/journal.pone.0131959](https://doi.org/10.1371/journal.pone.0131959) PMID: [26168149](https://pubmed.ncbi.nlm.nih.gov/26168149/); PubMed Central PMCID: PMC4500550.
29. Ackermann-Lieblich U, Kuna-Dibbert B, Probst-Hensch NM, Schindler C, Felber Dietrich D, Stutz EZ, et al. Follow-up of the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA 2) 1991–2003: methods and characterization of participants. *Soz Präventivmed*. 2005; 50(4):245–63. PMID: [16167509](https://pubmed.ncbi.nlm.nih.gov/16167509/).
30. Burney P, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J*. 1994; 7(5):954–60. PMID: [8050554](https://pubmed.ncbi.nlm.nih.gov/8050554/)
31. American Thoracic Society Nat. Standardization of Spirometry, 1994 Update. *American Thoracic Society. Am J Respir Crit Care Med*. 1995; 152(3):1107–36. doi: [10.1164/ajrccm.152.3.7663792](https://doi.org/10.1164/ajrccm.152.3.7663792) PMID: [7663792](https://pubmed.ncbi.nlm.nih.gov/7663792/).
32. Kunzli N, Kuna-Dibbert B, Keidel D, Keller R, Brandli O, Schindler C, et al. Longitudinal validity of spirometers—a challenge in longitudinal studies. *Swiss Med Wkly*. 2005; 135(33–34):503–8. PMID: [16208589](https://pubmed.ncbi.nlm.nih.gov/16208589/).
33. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD 2013 update, accessed May 2013.
34. Carraro S, Scheltema N, Bont L, Baraldi E. Early-life origins of chronic respiratory diseases: understanding and promoting healthy ageing. *The European respiratory journal*. 2014; 44(6):1682–96. doi: [10.1183/09031936.00084114](https://doi.org/10.1183/09031936.00084114) PMID: [25323240](https://pubmed.ncbi.nlm.nih.gov/25323240/).
35. Gazala E, Ron-Feldman V, Alterman M, Kama S, Novack L. The association between birth season and future development of childhood asthma. *Pediatric Pulmonology*. 2006; 41(12):1125–8. PMID: [17034060](https://pubmed.ncbi.nlm.nih.gov/17034060/)
36. Gold DR, Bloomberg GR, Cruikshank WW, Visness CM, Schwarz J, Kattan M, et al. Parental characteristics, somatic fetal growth, and season of birth influence innate and adaptive cord blood cytokine responses. *Journal of Allergy and Clinical Immunology*. 2009; 124(5):1078–87. doi: [10.1016/j.jaci.2009.08.021](https://doi.org/10.1016/j.jaci.2009.08.021) PMID: [19895995](https://pubmed.ncbi.nlm.nih.gov/19895995/)
37. Ginde AA, Sutherland ER. Vitamin D in asthma: Panacea or true promise? *Journal of Allergy and Clinical Immunology*. 2010; 126(1):59–60. doi: [10.1016/j.jaci.2010.05.030](https://doi.org/10.1016/j.jaci.2010.05.030) PMID: [20620566](https://pubmed.ncbi.nlm.nih.gov/20620566/)
38. Cleary-Goldman J, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, et al. Impact of maternal age on obstetric outcome. *Obstet Gynecol*. 2005; 105(5 Pt 1):983–90. PMID: [15863534](https://pubmed.ncbi.nlm.nih.gov/15863534/).
39. Magnus MC, Håberg SE, Stigum H, Nafstad P, London SJ, Vangen S, et al. Delivery by Cesarean Section and Early Childhood Respiratory Symptoms and Disorders. *American Journal of Epidemiology*. 174(11):1275–85. doi: [10.1093/aje/kwr242](https://doi.org/10.1093/aje/kwr242) PMID: [22038100](https://pubmed.ncbi.nlm.nih.gov/22038100/)
40. Salminen S, Gibson GR, McCartney AL, Isolauri E. Influence of mode of delivery on gut microbiota composition in seven year old children. *Gut*. 2004; 53(9):1388–9. doi: [10.1136/gut.2004.041640](https://doi.org/10.1136/gut.2004.041640)
41. Sherriff A, Peters TJ, Henderson J, Strachan D, Team aTAS. Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3 ½ years. *International journal of epidemiology*. 2001; 30(6):1473–84. doi: [10.1093/ije/30.6.1473](https://doi.org/10.1093/ije/30.6.1473) PMID: [11821366](https://pubmed.ncbi.nlm.nih.gov/11821366/)
42. Grabenhenrich LB, Gough H, Reich A, Eckers N, Zepp F, Nitsche O, et al. Early-life determinants of asthma from birth to age 20 years: A German birth cohort study. *Journal of Allergy and Clinical Immunology*. (0:). doi: [10.1016/j.jaci.2013.11.035](https://doi.org/10.1016/j.jaci.2013.11.035)
43. Caudri D, Savenije OEM, Smit HA, Postma DS, Koppelman GH, Wijga AH, et al. Perinatal risk factors for wheezing phenotypes in the first 8 years of life. *Clinical & Experimental Allergy*. 2013; 43(12):1395–405. doi: [10.1111/cea.12173](https://doi.org/10.1111/cea.12173)

44. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax*. 1999; 54(12):1119–38. doi: [10.1136/thx.54.12.1119](https://doi.org/10.1136/thx.54.12.1119) PMID: [10567633](https://pubmed.ncbi.nlm.nih.gov/10567633/)
45. Harding R, Maritz G. Maternal and fetal origins of lung disease in adulthood. *Semin Fetal Neonatal Med*. 2012; 17(2):67–72. doi: [10.1016/j.siny.2012.01.005](https://doi.org/10.1016/j.siny.2012.01.005) PMID: [22277111](https://pubmed.ncbi.nlm.nih.gov/22277111/).
46. Hayatbakhsh MR, Sadasivam S, Mamun AA, Najman JM, Williams GM, O'Callaghan MJ. Maternal smoking during and after pregnancy and lung function in early adulthood: a prospective study. *Thorax*. 2009; 64(9):810–4. doi: [10.1136/thx.2009.116301](https://doi.org/10.1136/thx.2009.116301) PMID: [19525264](https://pubmed.ncbi.nlm.nih.gov/19525264/)
47. Dong GH, Chen T, Liu MM, Wang D, Ma YN, Ren WH, et al. Gender Differences and Effect of Air Pollution on Asthma in Children with and without Allergic Predisposition: Northeast Chinese Children Health Study. *PLoS one*. 2011; 6(7). ARTN e22470 doi: [10.1371/journal.pone.0022470](https://doi.org/10.1371/journal.pone.0022470) WOS:000292929500069. PMID: [21811617](https://pubmed.ncbi.nlm.nih.gov/21811617/)
48. Dong G-H, Chen T, Liu M-M, Wang D, Ma Y-N, Ren W-H, et al. Gender Differences and Effect of Air Pollution on Asthma in Children with and without Allergic Predisposition: Northeast Chinese Children Health Study. *PLoS ONE*. 2011; 6(7):e22470. doi: [10.1371/journal.pone.0022470](https://doi.org/10.1371/journal.pone.0022470) PMID: [21811617](https://pubmed.ncbi.nlm.nih.gov/21811617/)
49. Kozyskyj AL, Bahreinian S, Azad MB. Early life exposures: impact on asthma and allergic disease. *Curr Opin Allergy Clin Immunol*. 2011; 11(5):400–6. doi: [10.1097/ACI.0b013e328349b166](https://doi.org/10.1097/ACI.0b013e328349b166) PMID: [21772139](https://pubmed.ncbi.nlm.nih.gov/21772139/).
50. Ege MJ, Mayer M, Normand A-Cc, Genuneit J, Cookson WOCM, Braun-Fahrlander C, et al. Exposure to Environmental Microorganisms and Childhood Asthma. *New England Journal of Medicine*. 2011; 364(8):701–9. doi: [10.1056/NEJMoa1007302](https://doi.org/10.1056/NEJMoa1007302) PMID: [21345099](https://pubmed.ncbi.nlm.nih.gov/21345099/)
51. Svanes C, Dharmage S, Sunyer J, Zock JP, Norback D, Wjst M, et al. Long-term reliability in reporting of childhood pets by adults interviewed twice, 9 years apart. Results from the European Community Respiratory Health Survey I and II. *Indoor Air*. 2008; 18(2):84–92. PMID: [18333988](https://pubmed.ncbi.nlm.nih.gov/18333988/). doi: [10.1111/j.1600-0668.2008.00523.x](https://doi.org/10.1111/j.1600-0668.2008.00523.x)