

## **Supplementary tables and figures**

**Early-life respiratory tract infections and the risk of school-age lower lung function and asthma: a meta-analysis of 150,000 European children.**

## Supplementary methods

ALSPAC recruited 14,541 pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992. 14,541 is the initial number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a "Children in Focus" clinic by 19/07/99. Of these initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper: <http://ije.oxfordjournals.org/content/early/2012/04/14/ije.dys064.full.pdf+html>. The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 fetuses. Of this total sample of 15,458 fetuses, 14,775 were live births and 14,701 were alive at 1 year of age. A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon.

Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool" and reference the following webpage:

<http://www.bristol.ac.uk/alspac/researchers/our-data/>

Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

## **REFERENCES**

1. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: The 'Children of the 90s'; the index offspring of The Avon Longitudinal Study of Parents and Children (ALSPAC). *International Journal of Epidemiology* 2013; 42: 111-127.
2. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology* 2013; 42:97-110.

**Supplementary Table S1.** Data collection on respiratory tract infections, lung function and asthma among children per cohort.

Cohort name (country)	Respiratory tract infections		Respiratory outcomes		Covariates
	Method of assessment	Available at ages	Spirometry protocol	School-age asthma	
ABIS (Sweden)	Questionnaire, parental report	1, 3, 5 years	N/A	Confirmed doctor diagnosis, derived from the national health care register, at age 5 years	Questionnaires and register data
ALSPAC (United Kingdom)	Questionnaire, parental report	6 months, 1, 3, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis at age 8 years	Questionnaires and register data
BAMSE (Sweden)	Questionnaire, parental report	1, 2, 4 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 8 years	Questionnaires and register data
BiB (United Kingdom)	Questionnaire, parental report	6 months, 1, 2, 3, 4 years	N/A	Confirmed doctor diagnosis, derived from health care registry data, at age 5 years	Questionnaire and register data
BILD	Questionnaire and interview by study	2, 3, 4 years	ATS/ERS	Questionnaire, parental report at	Questionnaire

(Swiss)	team member, parental report				age 6 years (ISAAC based)	
CoNER (Italy)	Questionnaire, parental report	6 months, 1, 3 years	Other		Questionnaire, parental report of doctor diagnosis at age 8 years	Questionnaire and parental report
COPSAC 2000 (Denmark)	Parental report of symptoms	3 years	ATS/ERS		Diagnosed by physicians in the research clinic according to symptom algorithm, at age 7 years	Interview questionnaire
COPSAC 2010 (Denmark)	Parental report of symptoms	1, 2, 3 years	ATS/ERS		Diagnosed by physicians in the research clinic according to symptom algorithm, at age 5 years	Interview questionnaire
DNBC (Denmark)	Questionnaire, parental report	6 months, 1 year	N/A		Questionnaire, ISAAC based, at age 7 years	Questionnaire and register data
EDEN (France)	Questionnaire, parental report	6 months, 1, 2, 3 years	ATS/ERS		Questionnaire, ISAAC based, at age 6 years	Questionnaire
FLEHS	Questionnaire, parental report	6 months, 1, 2, 3, 4, 5 years	N/A		Questionnaire, parental report of doctor diagnosis, at	Questionnaire

(Belgium)				age 10 years	
GASPII (Italy)	Questionnaire, parental report	6 months, 1, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis at age 9 years	Questionnaire
Generation R (Netherlands)	Questionnaire, parental report of doctor diagnosis	6 months, 1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 10 years	Questionnaire
Generation XXI (Portugal)	Questionnaire, parental report of doctor diagnosis	6 months, 2, 4 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 7 years	Questionnaire
GINI (Germany)	Questionnaire, parental report of doctor diagnosis	1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 15 years	Questionnaire
HUMIS (Norway)	Questionnaire, parental report of doctor diagnosis	6 months, 1, 2, 3 years	N/A	Registry data, hospital or specialist visit for asthma at age 9 years	Questionnaire and register data
IMNA Gipuzkoa	Questionnaire, parental report	1, 4 years	ATS/ERS	N/A	Questionnaire

(Spain)					
INMA Menorca (Spain)	Questionnaire, parental report	1, 2, 3, 4 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 12 years	Questionnaire
INMA Sabadell (Spain)	Questionnaire, parental report	6 months, 1, 2, 4 years	ATS/ERS	N/A	Questionnaire
INMA Valencia (Spain)	Questionnaire, parental report	1, 2, 4 years	ATS/ERS	N/A	Questionnaire
Isle of Wight (United Kingdom)	Questionnaire, parental report	1, 2, 4 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 10 years	Questionnaire
KOALA (Netherlands)	Questionnaire, parental report	6 months, 1, 2 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 7 years	Questionnaire
LRC (United Kingdom)	Questionnaire, parental report	1, 2-3, 3-5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis at age 12 years	Questionnaire and register data

Lifeways Cross-Generation Cohort Study (Ireland)	Parental record of health care visit	1, 2, 3, 4 years	N/A	Health care record, at age 9 years	Questionnaire and register data
LISA (Germany)	Questionnaire, parental report	1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis, at age 15 years	Questionnaire
LucKi (Netherlands)	Questionnaire, parental report	6 months, 1, 3 years	N/A	Questionnaire ISAAC based, at age 6 years	Questionnaire and register data
LUKAS (Finland)	Questionnaire, parental report of doctor diagnosis	1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis, at age 6 years	Questionnaire
MAS-90 (Germany)	Questionnaire, ICD-9 coding	6 months, 1, 2, 3, 4, 5 years	Other	Questionnaire, ISAAC based, at age 7 years	Interview and questionnaire
MCS (United Kingdom)	Questionnaire, parental report	1, 3, 5 years	N/A	Questionnaire, parental report, at age 11 years	Questionnaire
MoBa (Norway)	Questionnaire, parental report of doctor diagnosis	6 months, 2, 3 years	N/A	Questionnaire, parental report of doctor diagnosis, at	Questionnaire and register data



NINFEA (Italy)	Questionnaire, parental report of doctor diagnosis	6 months, 1 year	N/A	age 7 years Questionnaire, parental report of doctor diagnosis, at age 7 years	Questionnaire
Pelagie (France)	Questionnaire, parental report of doctor diagnosis	2 years	N/A	Questionnaire, ISAAC based, parental report of doctor diagnosis, at age 6 years	Questionnaire
PIAMA (Netherlands)	Questionnaire, parental report of doctor diagnosis	1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report, at age 11 years	Questionnaire
REPRO_PL (Poland)	Questionnaire, parental report of doctor diagnosis	1, 2 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis at age 7 years	Questionnaire and registry data
Rhea (Greece)	Questionnaire, parental report of doctor diagnosis	1, 4 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis, at age 7 years	Questionnaire
STEPS (Finland)	Symptom diary, doctor diagnosis	6 months, 1, 2 years	N/A	Questionnaire, ISAAC based, at age 5 years	Questionnaire, diary and registry data

SWS (United Kingdom)	Questionnaire, parental report of doctor diagnosis	6 months, 1, 2, 3 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 6 years	Questionnaire
Whistler (Netherlands)	Registry data	6 months, 1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 5 years	Questionnaire

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ATS/ERS: American Thoracic Society/European Respiratory Society; N/A: not available.

**Supplementary Table S2.** Characteristics of respiratory tract infections among children in participating cohorts

Cohort name	Upper respiratory tract infections						Lower respiratory tract infections					
	6 months	1 year	2 years	3 years	4 years	5 years	6 months	1 year	2 years	3 years	4 years	5 years
ABIS	N/A	98.3 (10,303)	N/A	99.1 (8,722)	N/A	99.3 (7,346)	N/A	40.9 (3,942)	N/A	58.8 (4,849)	N/A	60.4 (4,314)
ALSPAC	9.7 (778)	30.4 (2,403)	N/A	25.0 (1,928)	N/A	32.2 (2,426)	10.5 (825)	12.2 (929)	N/A	8.8 (674)	N/A	9.4 (678)
BAMSE	N/A	30.8 (1,032)	43.7 (1,451)	N/A	9.4 (319)	N/A	N/A	10.4 (347)	14.2 (473)	N/A	14.1 (475)	N/A
BiB	13.0 (166)	22.4 (440)	18.3 (314)	20.7 (253)	35.0 (422)	N/A	8.2 (105)	18.1 (356)	14.0 (240)	14.9 (183)	19.9 (240)	N/A
BILD	N/A	N/A	45.3 (115)	40.7 (103)	41.1 (104)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CoNER	71.1 (150)	95.5 (191)	N/A	46.2 (92)	N/A	N/A	12.8 (27)	22.5 (45)	N/A	6.9 (8)	N/A	N/A
COPSAC 2000	N/A	N/A	N/A	99.7 (289)	N/A	N/A	N/A	N/A	N/A	55.9 (162)	N/A	N/A
COPSAC 2010	N/A	35.0 (192)	48.2 (261)	27.6 (147)	N/A	N/A	N/A	15.7 (86)	25.1 (136)	13.5 (72)	N/A	N/A
DNBC	81.5 (24,450)	98.6 (28,903)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
EDEN	55.1 (496)	94.7 (852)	46.8 (421)	48.3 (435)	N/A	N/A	10.2 (92)	41.7 (375)	35.8 (322)	33.4 (301)	N/A	N/A

FLEHS	59.6 (65)	81.3 (87)	77.4 (82)	75.2 (79)	85.0 (85)	82.1 (78)	14.2 (15)	24.3 (26)	14.3 (15)	16.3 (17)	13.0 (13)	11.6 (11)
GASPII	6.0 (28)	19.1 (88)	N/A	N/A	30.8 (137)	N/A	13.8 (64)	24.7 (114)	N/A	N/A	N/A	16.8 (78)
Generation R	11.8 (368)	27.0 (1,009)	32.2 (1,259)	25.4 (960)	22.1 (841)	21.66 (1,055)	7.5 (234)	6.9 (261)	11.1 (442)	6.5 (248)	4.4 (167)	4.8 (232)
Generation XXI	14.3 (158)	N/A	49.4 (257)	N/A	60.6 (3,285)	N/A	N/A	N/A	17.7 (116)	N/A	2.4 (129)	N/A
GINI	N/A	69.2 (1,298)	80.9 (1,509)	80.6 (1,502)	83.1 (1,524)	87.2 (1,653)	N/A	N/A	N/A	N/A	N/A	N/A
HUMIS	18.8 (390)	33.3 (682)	35.8 (742)	N/A	N/A	N/A	3.6 (74)	9.0 (184)	11.8 (244)	N/A	N/A	N/A
IMNA Gipuzkoa	N/A	4.01 (111)	N/A	N/A	23.2 (63)	N/A	N/A	52.0 (144)	N/A	N/A	33.3 (90)	N/A
INMA Menorca	N/A	33.9 (122)	38.4 (162)	33.2 (140)	28.7 (121)	N/A	N/A	49.3 (183)	61.6 (260)	47.4 (200)	33.2 (140)	N/A
INMA Sabadell	11.1 (43)	22.9 (104)	26.9 (121)	N/A	29.7 (121)	N/A	22.1 (87)	65.4 (267)	66.1 (281)	N/A	49.9 (203)	N/A
INMA Valencia	N/A	31.6 (129)	32.1 (127)	N/A	30.5 (135)	N/A	N/A	47.7 (217)	66.2 (301)	N/A	41.0 (181)	N/A
Isle of Wight	N/A	15.8 (198)	15.7 (178)	N/A	17.0 (198)	N/A	N/A	7.4 (101)	12.8 (144)	N/A	N/A	N/A
KOALA	85.0 (1,535)	88.3 (2,241)	93.7 (1,726)	N/A	N/A	N/A	N/A	13.0 (224)	17.4 (311)	N/A	N/A	N/A

LRC	N/A	98.8 (3,930)	N/A	99.1 (2,210)	N/A	97.3 (2,684)	N/A	19.0 (721)	N/A	N/A	N/A	N/A
Lifeways	N/A	20.3 (28)	13.0 (18)	1.4 (2)	0.0 (0)	N/A	N/A	20.3 (28)	13.0 (18)	1.4 (2)	0.0 (0)	N/A
LISA	43.2 (402)	69.9 (644)	87.5 (819)	84.6 (766)	82.5 (741)	87.7 (782)	N/A	N/A	N/A	N/A	N/A	N/A
LucKi	88.1 (273)	93.3 (277)	N/A	97.7 (292)	N/A	N/A	7.0 (21)	11.7 (33)	N/A	14.7 (42)	N/A	N/A
LUKAS	N/A	44.6 (165)	96.0 (333)	99.4 (335)	87.7 (314)	82.5 (292)	N/A	8.1 (30)	9.0 (31)	10.4 (35)	5.3 (19)	7.9 (28)
MAS-90	49.8 (381)	71.2 (532)	63.2 (504)	48.8 (392)	50.7 (409)	78.4 (625)	6.3 (48)	13.7 (102)	16.4 (131)	10.8 (87)	11.4 (92)	16.7 (133)
MCS	N/A	11.7 (1,679)	N/A	7.7 (1,030)	N/A	2.4 (351)	N/A	28.0 (4,020)	N/A	0.2 (30)	N/A	0.7 (101)
MoBa	15.1 (4,964)	N/A	43.5 (13,693)	53.0 (13,969)	N/A	N/A	5.1 (1,661)	N/A	13.4 (4,192)	13.7 (3,619)	N/A	N/A
NINFEA	21.0 (210)	N/A	N/A	N/A	N/A	N/A	7.0 (70)	20.0 (206)	N/A	N/A	N/A	N/A
Pelagie	N/A	N/A	64.4 (580)	N/A	N/A	N/A	N/A	N/A	61.3 (576)	N/A	N/A	N/A
PIAMA	N/A	22.1 (605)	31.3 (861)	30.0 (832)	27.5 (745)	28.8 (772)	N/A	15.4 (425)	12.5 (344)	10.0 (274)	7.4 (200)	7.7 (208)
REPRO_PL	N/A	45.5 (46)	67.0 (65)	N/A	N/A	N/A	N/A	29.7 (30)	26.8 (26)	N/A	N/A	N/A

Rhea	N/A	21.2 (117)	N/A	N/A	53.5 (318)	N/A	N/A	22.8 (126)	N/A	N/A	75.1 (405)	N/A
STEPS	78.1 (557)	97.4 (686)	99.1 (566)	N/A	N/A	N/A	3.6 (26)	9.2 (65)	13.0 (74)	N/A	N/A	N/A
SWS	83.3 (1,010)	N/A	N/A	N/A	N/A	N/A	12.0 (238)	17.7 (349)	19.4 (388)	16.0 (314)	N/A	N/A
Whistler	9.7 (140)	35.0 (503)	66.4 (955)	80.9 (1,163)	88.8 (1,277)	94.6 (1,360)	N/A	N/A	N/A	N/A	N/A	N/A
Total	41.2 (36,564)	62.9 (58,949)	46.0 (27,119)	47.7 (35,641)	42.8 (11,159)	42.6 (19,424)	6.7 (3,587)	23.0 (13,297)	16.0 (9,045)	16.0 (11,117)	11.8 (2,354)	15.0 (5,783)

Values are valid percentages (absolute numbers). N/A: not available.

**Supplementary Table S3.** Characteristics of covariates

	<b>Participants</b>
<b>Maternal characteristics</b>	
Age, mean (SD)	30.0 (4.69)
Ethnicity	
European (%)	68,534 (89.1)
Non-European (%)	8,354 (10.9)
Education	
Low (%)	33,432 (25.2)
Middle (%)	44,238 (33.3)
High (%)	55,145 (41.5)
Smoking during pregnancy	
Yes (%)	21,680 (15.4)
No (%)	119,272 (84.6)
Asthma	
Yes (%)	16,362 (11.5)
No (%)	126,038 (88.5)
Atopy	
Yes (%)	35,744 (28.7)
No (%)	88,871 (71.3)
Parity	
Nulliparous (%)	62,547 (25.3)
Multiparous (%)	65,848 (74.7)
<b>Child characteristics</b>	
Gender	
Female (%)	72,871 (49.9)

Male (%)	72,964 (50.1)
Gestational age at birth, median (5-95% range)	40.0 (36.7, 42.0)
Birth weight, mean (SD)	3,502 (571)
Season of birth	
Spring (%)	36,781 (26.0)
Summer (%)	38,220 (27.0)
Autumn (%)	33,376 (23.6)
Winter (%)	33,040 (23.4)
Breastfeeding	
Yes (%)	94,231 (88.2)
No (%)	12,554 (11.8)
Daycare attendance	
Yes (%)	24,603 (19.5)
No (%)	101,247 (81.5)
Pet keeping	
Yes (%)	53,722 (41.1)
No (%)	76,835 (58.9)

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Numbers are means (SD), valid percentages (absolute numbers) or medians (9-95% range).



**Supplementary Table S4.** Unadjusted associations of any upper and lower respiratory tract infections with lung function and asthma

	<b>FEV<sub>1</sub></b> <b>Z-score (95% CI)</b> <b>n = 25,903</b>	<b>FVC</b> <b>Z-score (95% CI)</b> <b>n = 25,903</b>	<b>FEV<sub>1</sub>/FVC</b> <b>Z-score (95% CI)</b> <b>n = 25,903</b>	<b>FEF<sub>75</sub></b> <b>Z-score (95% CI)</b> <b>n = 14,426</b>	<b>Asthma</b> <b>Odds Ratio (95% CI)</b> <b>n = 140,385</b>
<b>Upper respiratory tract infections</b>					
Age 6 months	0.06 (0.01, 0.11)*	0.03 (-0.02, 0.08)	0.05 (0.00, 0.10)*	0.10 (0.03, 0.19)*	1.27 (1.20, 1.33)**
Age 1 year	0.00 (-0.03, 0.03)	0.02 (-0.02, 0.05)	-0.02 (-0.05, 0.01)	-0.02 (-0.07, 0.03)	1.28 (1.21, 1.37)**
Age 2 years	0.02 (-0.02, 0.05)	0.01 (-0.02, 0.05)	0.00 (-0.03, 0.04)	-0.01 (-0.06, 0.05)	1.65 (1.56, 1.74)**
Age 3 years	0.02 (-0.02, 0.05)	0.03 (-0.01, 0.06)	-0.02 (-0.06, 0.01)	-0.02 (-0.04, 0.07)	1.47 (1.39, 1.55)**
Age 4 years	0.03 (-0.01, 0.07)	0.02 (-0.02, 0.06)	0.02 (-0.02, 0.06)	0.02 (-0.03, 0.07)	1.57 (1.42, 1.74)**
Age 5 years	0.04 (0.00, 0.08)*	0.03 (-0.01, 0.07)	0.01 (-0.03, 0.05)	0.03 (-0.04, 0.09)	1.37 (1.25, 1.49)**
<b>Lower respiratory tract infections</b>					
Age 6 months	-0.15 (-0.21, -0.09)**	-0.05 (-0.11, 0.01)	-0.15 (-0.21, -0.09)**	-0.00 (-0.13, 0.12)	2.57 (2.37, 2.80)**
Age 1 year	-0.20 (-0.24, -0.15)**	-0.09 (-0.13, -0.05)**	-0.17 (-0.21, -0.13)**	-0.17 (-0.24, -0.11)**	2.27 (2.15, 2.41)**
Age 2 years	-0.10 (-0.15, -0.05)**	-0.04 (-0.09, 0.01)	-0.10 (-0.15, -0.05)**	-0.13 (-0.20, -0.06)**	3.49 (3.28, 3.71)**
Age 3 years	-0.18 (-0.23, -0.12)**	-0.02 (-0.07, 0.04)	-0.26 (-0.31, -0.20)**	-0.14 (-0.23, -0.05)**	3.73 (3.50, 3.97)**
Age 4 years	-0.09 (-0.14, -0.02)**	0.00 (-0.06, 0.06)	-0.13 (-0.19, -0.07)**	-0.11 (-0.20, -0.02)*	4.09 (3.56, 4.70)**
Age 5 years	-0.18 (-0.25, -0.11)**	0.01 (-0.05, 0.08)	-0.30 (-0.36, -0.23)**	-0.23 (-0.38, -0.08)**	6.66 (5.98, 7.42)**

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF<sub>75</sub>).

**Supplementary Table S5.** Associations of any upper and lower respiratory tract infections with lung function and asthma

	FEV <sub>1</sub> Z-score (95% CI) n = 25,903	FVC Z-score (95% CI) n = 25,903	FEV <sub>1</sub> /FVC Z-score (95% CI) n = 25,903	FEF <sub>75</sub> Z-score (95% CI) n = 14,426	Asthma Odds Ratio (95% CI) n = 140,385
<b>Upper respiratory tract infections</b>					
Age 6 months	0.04 (-0.01, 0.09)	0.02 (-0.03, 0.07)	0.05 (0.00, 0.10)*	0.10 (0.02, 0.18)*	1.25 (1.18, 1.32)**
Age 1 year	0.01 (-0.02, 0.04)	0.02 (-0.01, 0.05)	-0.02 (-0.05, 0.01)	-0.03 (-0.08, 0.02)	1.25 (1.18, 1.34)**
Age 2 years	0.02 (-0.02, 0.05)	0.01 (-0.02, 0.05)	0.01 (-0.03, 0.04)	-0.01 (-0.06, 0.04)	1.57 (1.48, 1.67)**
Age 3 years	0.02 (-0.02, 0.05)	0.03 (-0.01, 0.06)	-0.02 (-0.06, 0.01)	0.01 (-0.05, 0.06)	1.41 (1.34, 1.49)**
Age 4 years	0.04 (-0.00, 0.08)	0.02 (-0.02, 0.06)	0.02 (-0.02, 0.06)	0.01 (-0.04, 0.06)	1.44 (1.29, 1.61)**
Age 5 years	0.05 (0.01, 0.08)*	0.04 (-0.00, 0.07)	0.01 (-0.03, 0.05)	0.03 (-0.04, 0.10)	1.34 (1.23, 1.46)**
<b>Lower respiratory tract infections</b>					
Age 6 months	-0.14 (-0.20, -0.08)**	-0.04 (-0.10, 0.01)	-0.15 (-0.21, -0.09)**	-0.01 (-0.13, 0.11)	2.38 (2.18, 2.60)**
Age 1 year	-0.19 (-0.23, -0.15)**	-0.08 (-0.12, -0.04)**	-0.17 (-0.21, -0.13)**	-0.18 (-0.24, -0.11)**	2.10 (1.98, 2.22)**
Age 2 years	-0.09 (-0.14, -0.04)**	-0.03 (-0.08, 0.02)	-0.10 (-0.15, -0.05)**	-0.14 (-0.21, -0.06)**	3.26 (3.06, 3.48)**
Age 3 years	-0.16 (-0.22, -0.11)**	-0.01 (-0.06, 0.04)	-0.25 (-0.30, -0.20)**	-0.15 (-0.23, -0.06)**	3.53 (3.30, 3.77)**
Age 4 years	-0.09 (-0.15, -0.02)**	-0.01 (-0.07, 0.06)	-0.13 (-0.19, -0.07)**	-0.12 (-0.21, -0.03)*	3.84 (3.33, 4.42)**
Age 5 years	-0.18 (-0.24, -0.11)**	0.02 (-0.05, 0.08)	-0.30 (-0.36, -0.23)**	-0.24 (-0.39, -0.09)**	6.30 (5.64, 7.04)**

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. Models are adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birth weight, season of birth, breastfeeding and daycare attendance. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF<sub>75</sub>).

**Supplementary Table S6.** Associations of any upper and lower respiratory tract infections with lung function and asthma, additionally adjusted for preceding respiratory tract infections

	<b>FEV<sub>1</sub></b> <b>Z-score (95% CI)</b> <b>n = 25,903</b>	<b>FVC</b> <b>Z-score (95% CI)</b> <b>n = 25,903</b>	<b>FEV<sub>1</sub>/FVC</b> <b>Z-score (95% CI)</b> <b>n = 25,903</b>	<b>FEF<sub>75</sub></b> <b>Z-score (95% CI)</b> <b>n = 14,426</b>	<b>Asthma</b> <b>Odds Ratio (95% CI)</b> <b>n = 140,385</b>
<b>Upper respiratory tract infections</b>					
Age 6 months	0.04 (-0.01, 0.09)	0.02 (-0.03, 0.07)	0.05 (0.00, 0.10)*	0.10 (0.02, 0.18)*	1.25 (1.18, 1.32)**
Age 1 year	0.00 (-0.03, 0.04)	0.02 (-0.01, 0.05)	-0.03 (-0.06, 0.00)	-0.04 (-0.09, 0.01)	1.23 (1.16, 1.31)**
Age 2 years	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	-0.01 (-0.06, 0.05)	1.52 (1.44, 1.62)**
Age 3 years	0.01 (-0.02, 0.05)	0.02 (-0.01, 0.06)	-0.02 (-0.06, 0.01)	0.02 (-0.04, 0.08)	1.28 (1.21, 1.36)**
Age 4 years	0.03 (-0.01, 0.07)	0.01 (-0.03, 0.05)	0.03 (-0.01, 0.07)	0.02 (-0.04, 0.07)	1.28 (1.15, 1.43)**
Age 5 years	0.05 (0.01, 0.09)*	0.03 (-0.01, 0.07)	0.02 (-0.02, 0.06)	0.03 (-0.04, 0.10)	1.30 (1.10, 1.31)**
<b>Lower respiratory tract infections</b>					
Age 6 months	-0.14 (-0.20, -0.08)**	-0.04 (-0.10, 0.01)	-0.15 (-0.21, -0.09)**	-0.01 (-0.13, 0.11)	2.38 (2.18, 2.60)**
Age 1 year	-0.17 (-0.22, -0.13)**	-0.08 (-0.12, -0.04)**	-0.16 (-0.20, -0.12)**	-0.18 (-0.25, -0.11)**	2.00 (1.88, 2.12)**
Age 2 years	-0.05 (-0.10, 0.01)	-0.01 (-0.06, 0.04)	-0.06 (-0.11, -0.01)*	-0.11 (-0.18, -0.03)**	2.88 (2.70, 3.08)**
Age 3 years	-0.12 (-0.17, -0.06)**	0.01 (-0.04, 0.07)	-0.21 (-0.26, -0.15)**	-0.10 (-0.19, -0.01)*	2.72 (2.54, 2.91)**
Age 4 years	-0.05 (-0.11, 0.01)	0.01 (-0.07, 0.08)	-0.09 (-0.15, -0.02)**	-0.08 (-0.17, 0.01)	2.55 (2.20, 2.95)**
Age 5 years	-0.11 (-0.18, -0.04)**	0.03 (-0.04, 0.10)	-0.21 (-0.28, -0.15)**	-0.21 (-0.36, -0.06)**	4.29 (3.82, 4.82)**

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. Models are adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birth weight, season of birth, breastfeeding and daycare attendance. Additionally, upper respiratory tract infections were adjusted for preceding upper respiratory tract infections, and lower respiratory tract infections for preceding lower respiratory tract infections. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF<sub>75</sub>).

**Supplementary Table S7.** Associations of any upper and lower respiratory tract infections with lung function, stratified for wheezing

	FEV <sub>1</sub> , wheeze - Z-score (95% CI)	FEV <sub>1</sub> , wheeze + Z-score (95% CI)	FVC, wheeze - Z-score (95% CI)	FVC, wheeze + Z-score (95% CI)	FEV <sub>1</sub> /FVC, wheeze - Z-score (95% CI)	FEV <sub>1</sub> /FVC, wheeze + Z-score (95% CI)	FEF <sub>75</sub> , wheeze - Z-score (95% CI)	FEF <sub>75</sub> , wheeze + Z-score (95% CI)
<b>Upper respiratory tract infections</b>								
Age 6 months	0.05 (-0.01, 0.11)	0.17 (0.08, 0.27)**	0.03 (-0.03, 0.09)	0.13 (0.02, 0.23)*	0.05 (-0.01, 0.11)	0.09 (-0.01, 0.19)	0.11 (0.02, 0.21)*	0.16 (-0.01, 0.32)
Age 1 year	0.01 (-0.03, 0.05)	0.04 (-0.03, 0.11)	0.02 (-0.02, 0.05)	0.03 (-0.04, 0.10)	-0.01 (-0.05, 0.03)	0.03 (-0.05, 0.10)	-0.02 (-0.08, 0.04)	0.00 (-0.10, 0.11)
Age 2 years	0.01 (-0.04, 0.05)	0.11 (0.02, 0.21)*	-0.01 (-0.05, 0.03)	0.08 (-0.01, 0.18)	0.02 (-0.02, 0.06)	0.03 (-0.07, 0.13)	0.01 (-0.05, 0.07)	0.08 (-0.04, 0.20)
Age 3 years	0.03 (-0.01, 0.07)	0.04 (-0.07, 0.15)	0.04 (-0.00, 0.08)	0.01 (-0.10, 0.11)	-0.02 (-0.06, 0.02)	0.07 (-0.04, 0.19)	0.07 (-0.04, 0.08)	0.07 (-0.10, 0.24)
Age 4 years	0.03 (-0.02, 0.08)	0.10 (0.00, 0.21)*	0.04 (-0.04, 0.05)	0.04 (-0.06, 0.14)	0.04 (-0.01, 0.09)	0.11 (0.01, 0.22)*	0.03 (-0.04, 0.09)	0.12 (-0.05, 0.29)
<b>Lower respiratory tract infections</b>								
Age 6 months	-0.06 (-0.21, 0.10)	-0.05 (-0.13, 0.03)	-0.03 (-0.18, 0.13)	-0.01 (-0.10, 0.07)	-0.03 (-0.18, 0.12)	-0.05 (-0.14, 0.04)	0.23 (0.04, 0.43)*	-0.13 (-0.33, 0.07)
Age 1 year	-0.14 (-0.20, -0.07)**	-0.17 (-0.24, -0.10)**	-0.07 (-0.14, -0.01)*	-0.09 (-0.16, -0.02)*	-0.11 (-0.17, -0.04)**	-0.10 (-0.18, -0.03)**	-0.19 (-0.31, -0.07)**	-0.03 (-0.17, 0.10)
Age 2 years	-0.03 (-0.04, 0.10)	-0.08 (-0.18, 0.01)	0.04 (-0.29, 0.11)	-0.11 (-0.21, -0.01)*	0.03 (-0.09, 0.04)	0.04 (-0.05, 0.14)	-0.01 (-0.11, 0.09)	-0.04 (-0.17, 0.10)
Age 3 years	-0.08 (-0.17, 0.01)	-0.04 (-0.14, 0.06)	-0.03 (-0.12, 0.06)	0.03 (-0.07, 0.13)	-0.08 (-0.17, 0.00)	-0.11 (-0.21, -0.00)*	-0.03 (-0.14, 0.08)	-0.14 (-0.30, 0.03)
Age 4 years	-0.04 (-0.12, 0.06)	-0.11 (-0.25, 0.04)	0.03 (-0.06, 0.12)	-0.11 (-0.25, 0.02)	-0.10 (-0.18, 0.01)*	0.00 (-0.14, 0.14)	-0.01 (-0.16, 0.14)	-0.07 (-0.34, 0.19)

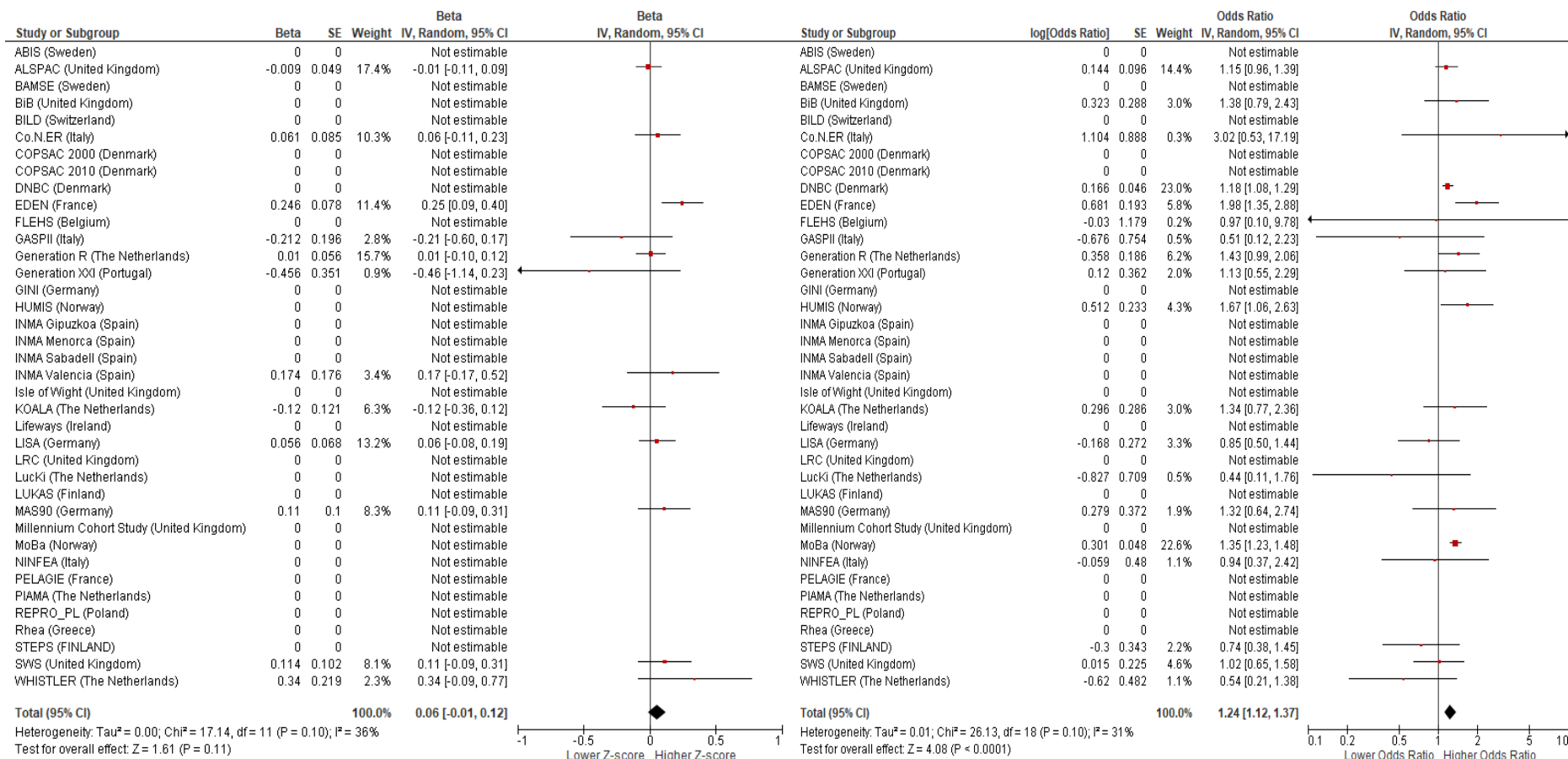
Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic regression models. \*p-value <0.05, \*\*p-value <0.01. Models are adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birth weight, season of birth, breastfeeding and daycare attendance. Wheeze – or + reflects whether the child did not or did wheeze in the first year of life (infections at age 6 months or 1 year), the second year of life (infections age 2 years), the third year of life (infections age 3 years) or the fourth year of life (infections age 4 years).

**Supplementary Figure S8.** Associations of any upper or lower respiratory tract infections with lung function and asthma assessed by a two-stage individual participant meta-analysis

**Upper respiratory tract infections age 6 months**

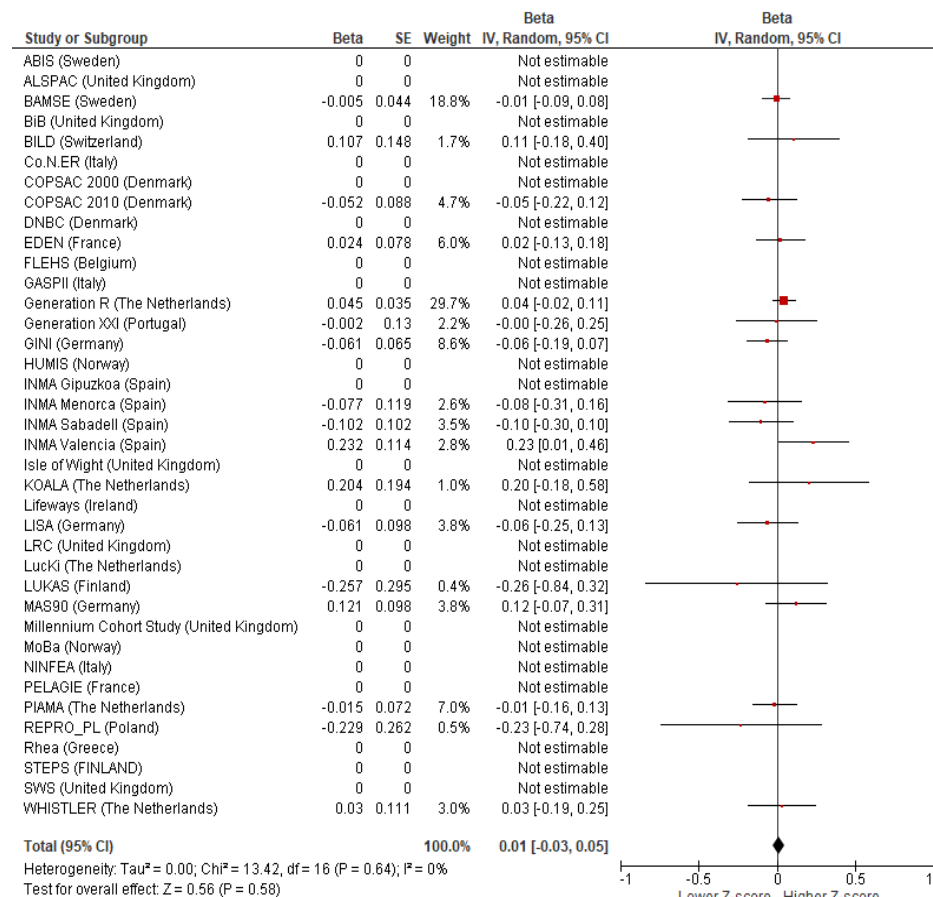
**A. FEV<sub>1</sub>/FVC**

**B. Asthma**

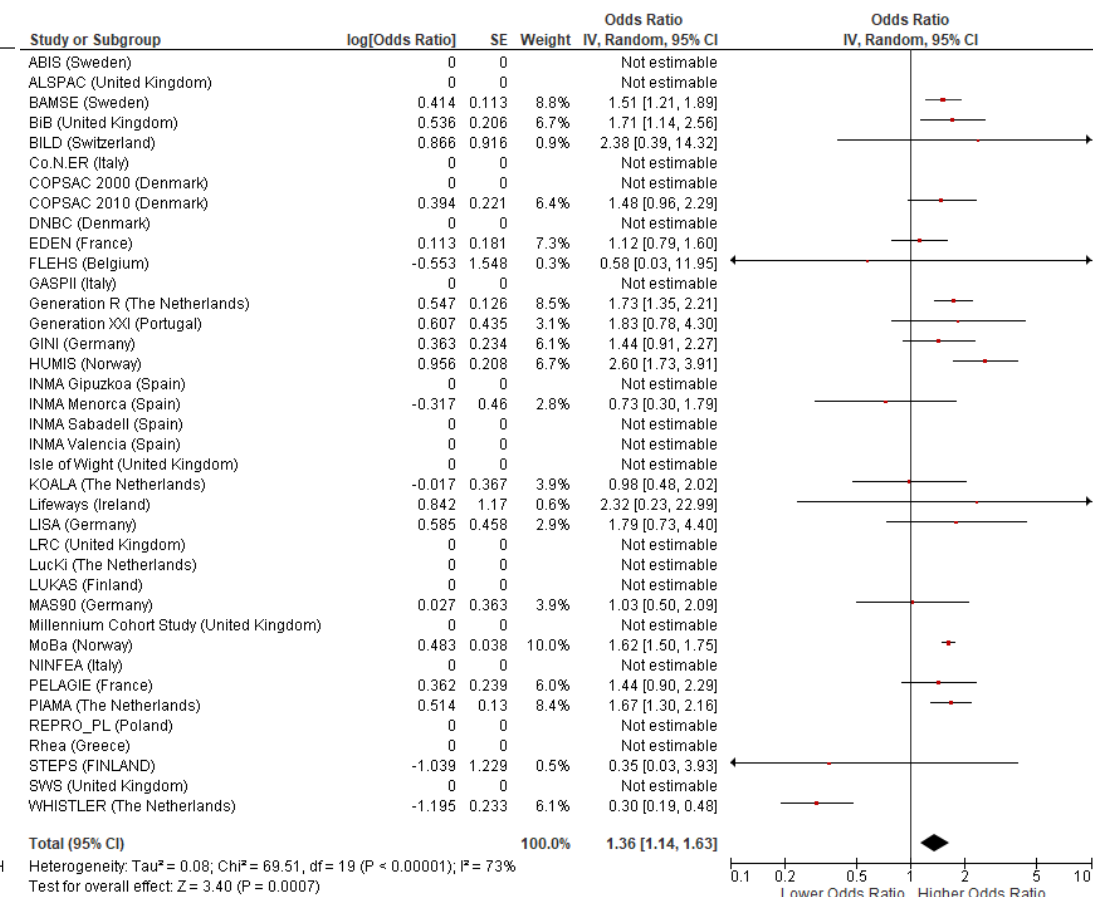


## Upper respiratory tract infections age 2 years

### A. FEV<sub>1</sub>/FVC



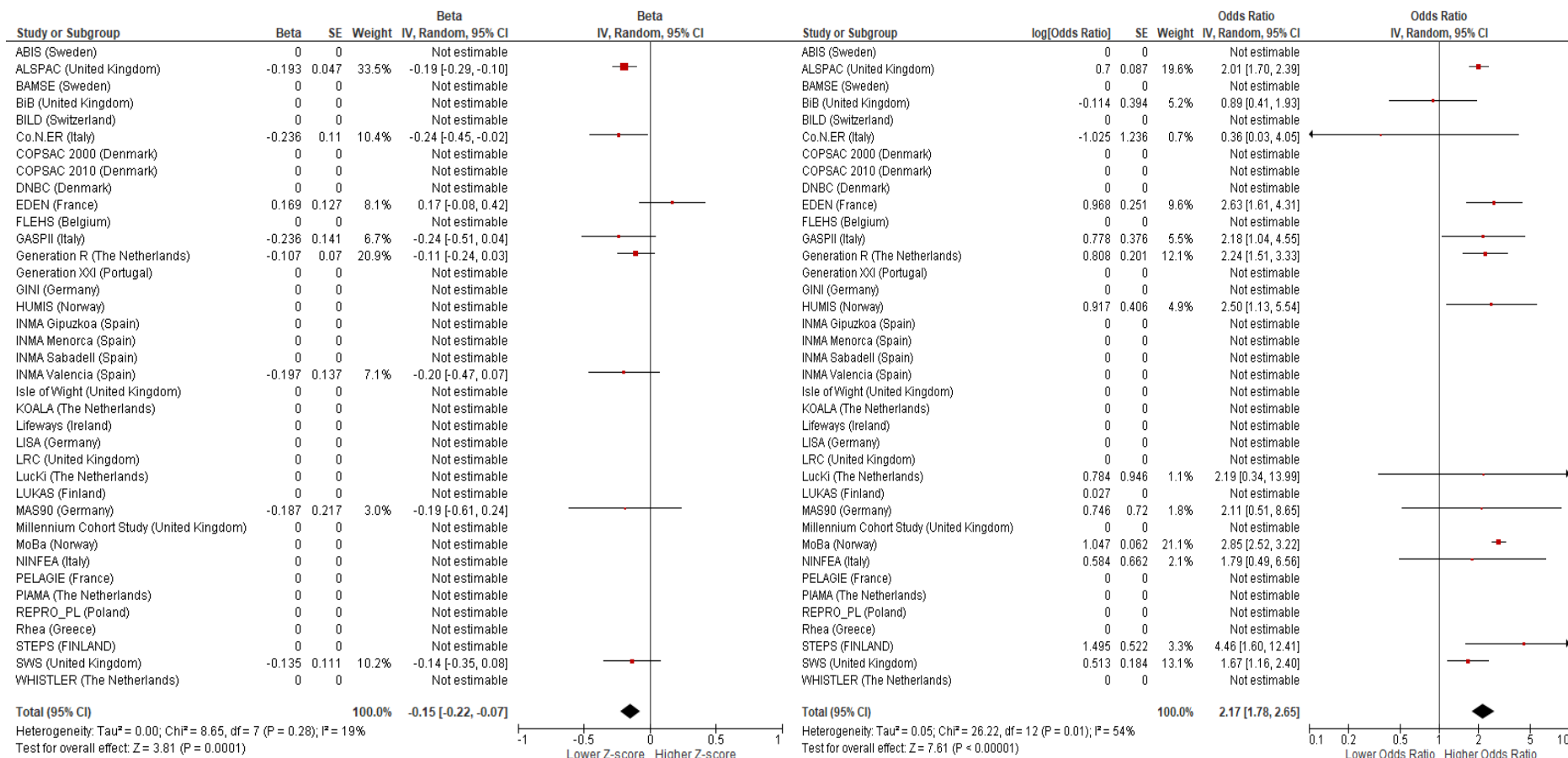
### B. Asthma



## Lower respiratory tract infections age 6 months

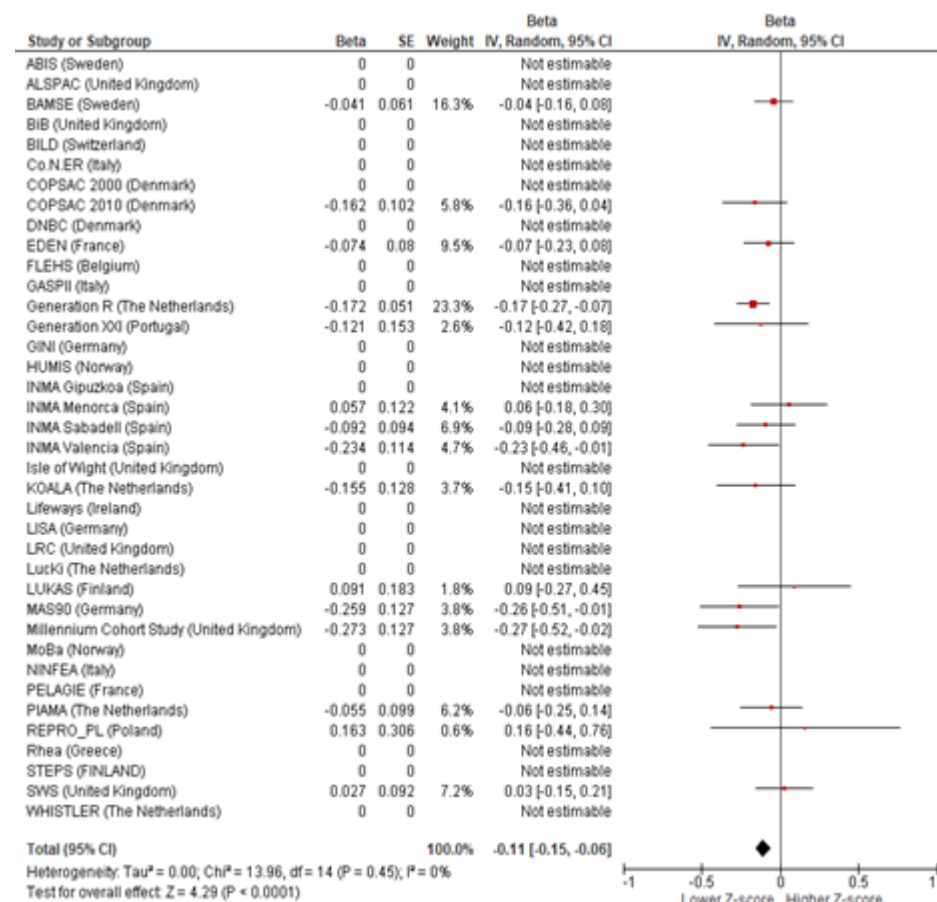
### A. FEV<sub>1</sub>/FVC

### B. Asthma

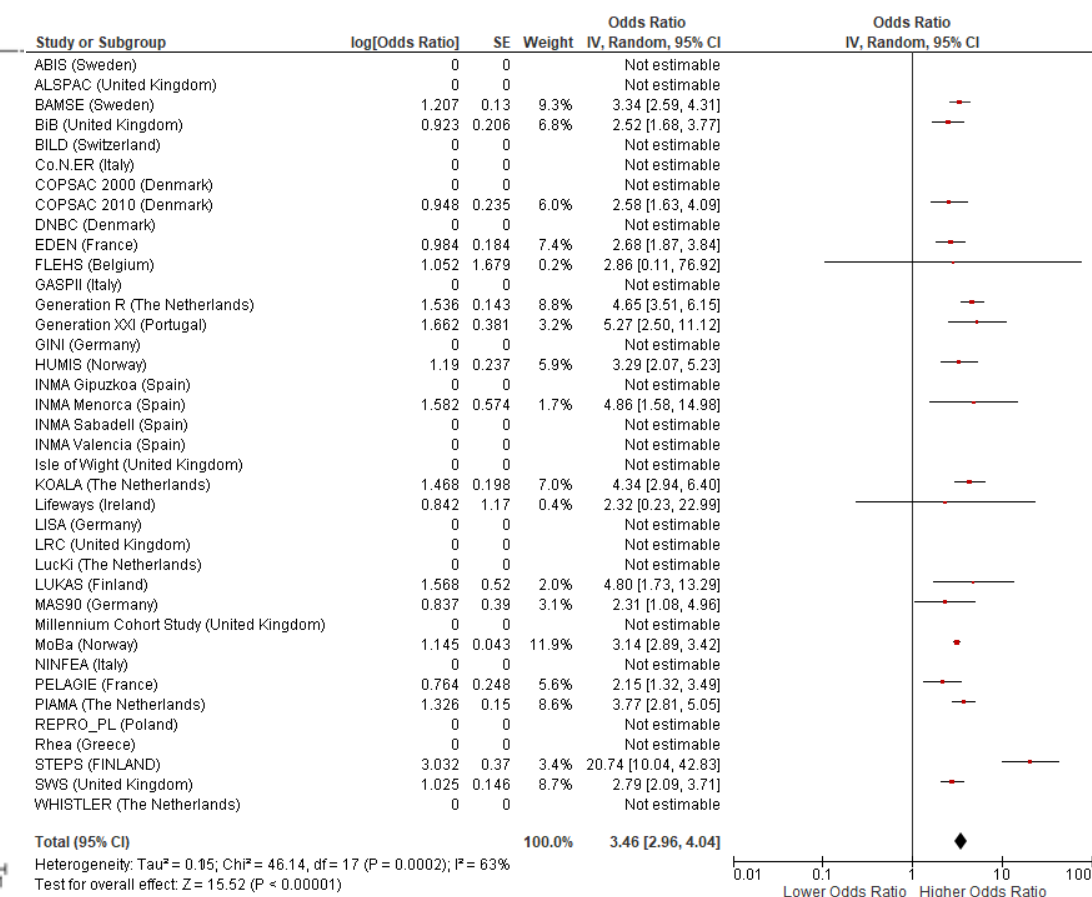


## Lower respiratory tract infections age 2 years

### A. FEV<sub>1</sub>/FVC



### B. Asthma



Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from logistic or linear regression models, respectively. The cohorts for which no estimate was provided had no or not sufficient data available for that particular analysis. Models are adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birth weight, season of birth, breastfeeding and daycare attendance. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC).



**Supplementary Table S9.** Associations of any upper and lower respiratory tract infections with lung function and asthma in complete cases, in cohorts who used an ISAAC based questionnaire to assess asthma, in cohorts that assessed respiratory tract infections by questionnaire and in children aged < 9 years and ≥ 9 years, respectively

	Complete cases	Asthma assessed by ISAAC based questionnaire	Respiratory tract infections assessed by questionnaire	Age <9 years	Age ≥ 9 years
<b>FEV<sub>1</sub>/FVC</b>					
Upper respiratory tract infections, age 6 months	n = 2,586 0.15 (0.06, 0.25)**	NA	n = 24,268 0.05 (-0.00, 0.10)	n = 9,368 0.07 (0.01, 0.13)*	n = 4,135 0.00 (-0.08, 0.09)
Upper respiratory tract infections, age 2 years	n = 5,431 0.01 (-0.04, 0.07)	NA	n = 24,268 0.00 (-0.04, 0.04)	n = 5,911 0.01 (-0.04, 0.07)	n = 7,468 -0.00 (-0.05, 0.05)
Lower respiratory tract infections, age 6 months	n = 2,183 -0.10 (-0.23, 0.04)	NA	n = 24,268 -0.15 (-0.21, -0.09)**	n = 8,499 -0.16 (-0.23, -0.09)**	n = 3,214 -0.13 (-0.26, -0.01)*
Lower respiratory tract infections, age 2 years	n = 5,381 -0.09 (-0.16, -0.03)**	NA	n = 24,268 -0.09 (-0.14, -0.04)**	n = 6,335 -0.09 (-0.15, -0.02)**	n = 4,873 -0.11 (-0.20, -0.03)**
<b>Asthma</b>					
Upper respiratory tract infections, age 6 months	n = 8,201 1.31 (1.05, 1.63)*	n = 57,212 1.20 (1.11, 1.30)**	n = 142,576 1.25 (1.19, 1.33)	n = 82,059 1.21 (1.17, 1.31)**	n = 6,689 1.24 (0.98, 1.57)
Upper respiratory tract infections, age 2 years	n = 12,807 1.47 (1.27, 1.70)**	n = 57,212 1.32 (1.16, 1.49)**	n = 142,576 1.32 (1.52, 1.72)	n = 44,504 1.54 (1.44, 1.64)**	n = 12,363 1.70 (1.47, 1.96)**
Lower respiratory tract infections, age 6 months	n = 5,915 2.22 (1.63, 3.03)**	n = 57,212 2.02 (1.62, 2.52)**	n = 142,576 2.38 (2.18, 2.60)	n = 48,075 2.38 (2.17, 2.60)**	n = 6,199 2.21 (1.64, 2.99)**
Lower respiratory tract infections, age 2 years	n = 12,700 3.34 (2.88, 3.86)**	n = 57,212 3.46 (3.50, 3.93)**	n = 142,576 3.24 (3.03, 3.46)	n = 44,844 3.20 (2.98, 3.42)**	n = 10,020 3.68 (3.08, 4.40)**

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. Models are adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birth weight, season of birth, breastfeeding and daycare attendance. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC).

**Supplementary Table S10.** Associations of any upper and lower respiratory tract infections with lung function and asthma, after excluding cohorts who determine >5% of the population

Omitted cohort	FEV <sub>1</sub> /FVC Z-score (95% CI)	Asthma Odds Ratio (95% CI)
<b>Upper respiratory tract infections</b>		
<b>age 6 months</b>		
ABIS	NA	NA
ALSPAC	n = 19,939 0.08 (0.02, 0.13)**	n = 138,978 1.26 (1.19, 1.33)**
DNBC	NA	n = 111,932 1.27 (1.19, 1.37)**
MoBa	NA	n = 111,827 1.20 (1.12, 1.28)**
<b>Lower respiratory tract infections</b>		
<b>age 6 months</b>		
ABIS	NA	NA
ALSPAC	n = 19,939 -0.11 (-0.20, -0.03)**	n = 138,978 2.56 (2.31, 2.83)**
DNBC	NA	n = 111,932 2.39 (2.19, 2.61)**
MoBa	NA	n = 111,827 1.16 (1.01, 1.32)*

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. Models are adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birth weight, season of birth, breastfeeding and daycare attendance. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC), not applicable (NA).

**Supplementary Figure S1.** Flowchart of included cohorts and participants

