Online data supplement

Title: Does early-onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts

Authors:

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Table E1. Distribution of maternal and child characteristics comparing those excluded due to missing

data to those included in our study

	Excluded at baseline due to missing exposure/outcome information[*], n=5,420		Total study population at baseline†, n=21,130	
	Total n with data	No. (%)	Total n with data	No. (%)
Child sex				
male	5420	2806 (51.8)	21130	10791 (51.1)
Maternal education				
low/medium	5186	3120 (60.2)	19943	10975 (55.0)
Parity				
multiparous	5281	2508 (47.5)	20754	9819 (47.3)
Birthweight (g)				
median (IQR)	5229	3460 (640)	20689	3460 (645)
Breastfeeding				
≥3 months	5063	3195 (63.1)	20507	13874 (67.7)
Parental asthma				
yes	4507	876 (19.4)	20519	3407 (16.6)
Smoking during pregnancy				
yes	5304	797 (15.0)	20012	2737 (13.7)
Passive smoke				
yes	5178	1464 (28.3)	21096	5916 (28.0)

[*]Excluded at baseline due to not having information for at least 1 exposure of interest & BMI information for at least 2 follow-ups

†Total study population after excluding the 5,420 participants with missing exposure/outcome information and 567 prevalent obesity cases

Table E2.Information on data collection for early-onset asthma and asthma-related phenotypes by cohort

	Asthma diagnosis ever prior to baseline visit	Wheeze	Wheeze in the last 12 months of baseline visit	Allergic rhinitis in the last 12 months of baseline visit	Medication in the last 12 months of baseline visit
ABCD	Not collected	Ever wheeze collected at 1y	Not collected	Not collected	Not collected
BAMSE	Ever physician diagnosed asthma collected at 1 y, 2 y, 4 y	Wheeze in last 12 months collected at 1 y, 2y, 4 y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4y	Treatment for asthma or breathing problems in the last 24 months collected at 4y
DARC	Not collected	Wheeze in last 12 months collected at 3m, 6m, 9m, 18m, 3y	Wheezing in the last 12 months collected at 3 y	Allergic rhinitis in the last 12 months collected at 3 y	Treatment for asthma or breathing problems in the last 12 months collected at 3y
EDEN	Ever physician diagnosed asthma collected at 4y	Wheeze in last 12 months collected at 1 y, 2y, 3y, 4 y	Wheezing in the last 12 months collected at 4y	Allergic rhinitis in the last 12 months collected at 4 y	Not collected
GENR	Not collected	Wheeze in last 12 months collected at 2y, 4y	Wheeze in the past 12 months at 4 y	Not collected	Not collected
GINIplus	Ever physician diagnosed asthma collected at 1 y, 2 y, 3 y, 4 y	Wheeze in last 12 months collected at 1y, 2y, 3y, 4y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4 y	Treatment for asthma in the last 12 months collected at 3 y
INMA_M	Ever physician diagnosed asthma collected at 2 y, 3 y, 4 y	Wheeze in last 12 months collected at 1y, 2y, 3y, 4y	Wheezing in the last 12 months collected at 4 y	Not collected	Not collected
INMA_V	Ever physician diagnosed asthma in the last 12 months collected at 4 y	Wheeze in last 12 months collected at 2y, 4y	Wheezing in the last 12 months collected at 4 y	Self-report of allergic rhinitis in the last 12 months collected at 4 y	Medication for wheezing in the last 12 months collected at 4 y
KOALA	Doctor diagnosed asthma collected at 4 y	Wheeze in last 12 months collected at 2y, 4y	Wheeze in the past 12 months collected at 4 y	Not collected	Medication in the last 12 months at 4 y
LISAplus	Ever physician diagnosed asthma collected at 1 y, 2 y, 3 y, 4 y	Wheeze in last 12 months collected at 1y, 2y, 4y;	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months at 4 y	Not collected
MAS	Not collected	Wheeze in last 12 months collected at 1y, 2y, 3y, 4y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4 y	Not collected
PIAMA	Ever physician diagnosed asthma collected at 1 y, 2y, 3 y, 4y	Wheeze in last 12 months collected at 1y, 2y, 3y, 4y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4 y	Treatment for respiratory or lung problems in the last 12 months collected at 4 y
RHEA	Ever physician diagnosed asthma collected at 4 y	Ever wheeze collected at 9m; wheeze in last 12 months collected at 4y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4 y	Treatment for asthma or breathing problems in the last 12 months collected at 4 y
ROBBIC	Ever physician diagnosed asthma collected at 6m, 15m, 3-4 y	Wheeze in last 12 months collected at 6m, 15m, 3y	Wheezing in the last 12 months collected at 3-4 y	Allergic rhinitis in the last 12 months collected at 3-4 y	Treatment for asthma or breathing problems in the last 12 months at 3-4 y
SWS	Ever physician diagnosed asthma collected at 3 y	Wheeze in last 12 months collected at 2y, 4y	Wheeze in the past 12 months collected at 3 y	Not collected	Not collected

Table E3.Prevalence of baseline early-onset asthma and asthma-related phenotypes by cohort

	Baseline asthma		Baseline wheeze in the last 12 months		Early wheeze at 0-2 years		Baseline allergic rhinitis in the last 12 months		Baseline medication use for asthma/breathing difficulties in the last 12 months	
	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)
ABCD	NA	NA	NA	NA	2783	272 (9.8)	NA	NA	NA	NA
BAMSE	2239	246 (11.0)	2258	343 (15.2)	2265	441 (19.5)	2240	275 (12.3)	2249	588 (26.1)
DARC	NA	NA	348	51 (14.7)	348	60 (17.2)	348	35 (10.1)	348	130 (37.4)
EDEN	592	81 (13.7)	560	60 (10.7)	587	83 (14.1)	592	128 (21.6)	NA	NA
GENR	NA	NA	1072	109 (10.2)	1149	195 (17.0)	NA	NA	NA	NA
GINI	3241	106 (3.3)	3231	321 (9.9)	3302	362 (11.0)	3246	318 (9.8)	3309	54 (1.6)
INMA_M	249	5 (2.0)	249	25 (10.0)	249	67 (26.9)	NA	NA	NA	NA
INMA_V	426	17 (4.0)	426	83 (19.5)	426	149 (35.0)	425	14 (3.3)	417	69 (16.6)
KOALA	1449	98 (6.8)	1452	149 (10.3)	1467	213 (14.5)	NA	NA	1439	143 (9.9)
LISA	1844	28 (1.5)	1847	209 (11.3)	1873	647 (34.5)	1857	193 (10.4)	NA	NA
MAS	NA	NA	963	96 (10.0)	966	116 (12.0)	963	125 (13.0)	NA	NA
PIAMA	2988	217 (7.3)	2921	333 (11.4)	2981	512 (17.2)	2917	599 (20.5)	2533	355 (12.3)
RHEA	500	28 (5.6)	502	19 (3.8)	486	119 (24.5)	500	112 (22.4)	497	298 (60.0)
ROBBIC	641	25 (3.9)	641	98 (15.3)	639	178 (27.9)	641	87 (13.6)	641	425 (66.3)
SWS	1507	94 (6.2)	1508	358 (23.7)	1509	400 (26.5)	NA	NA	NA	NA

Abbreviations: NA, not available.

Table E4. Distribution of obese at baseline and incident obesity up to age 8 years in a pooled sample of children from 16 European birth cohorts

	Total at baseline including prevalent obese cases	Obese at baseline	Total at baseline after excluding prevalent obese cases	Obesity incidence by end of follow-up
	N	Yes No. (%)		Yes No. (%)
ABCD	2872	89 (3.1)	2783	24 (0.9)
BAMSE	2357	89 (3.8)	2268	60 (2.7)
DARC	356	8 (2.3)	348	7 (2.0)
EDEN	598	6 (1.0)	592	10 (1.7)
GENR	1189	20 (1.7)	1169	10 (0.8)
GINIplus	3358	49 (1.5)	3309	47 (1.4)
INMA_M	263	14 (5.3)	249	6 (2.4)
INMA_V	453	27 (6.0)	426	44 (10.3)
KOALA	1484	13 (0.9)	1471	9 (0.6)
LISAplus	1903	22 (1.2)	1881	21 (1.1)
MAS	987	18 (1.8)	969	26 (2.7)
PIAMA	3061	72 (2.4)	2989	81 (2.7)
RHEA	557	31 (5.6)	526	53 (10.1)
ROBBIC		53 (7.6)	641	39 (6.1)
SWS	1565	56 (3.6)	1509	46 (3.1)
All participants	21697	567 (2.6)	21130	483 (2.3)

Table E5. Distribution of maternal and child characteristics by cohort

	Child sex (male)		Maternal education (low/medium)		Parity (multiparous)		Birthweight (g)		Breastfeeding (≥3 months)		Parental asthma (yes)		Smoking during pregnancy (yes)		Passive smoke (yes)	
	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Median (IQR)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)
ABCD	2783	1404 (50.5)	2773	1293 (46.6)	2783	1161 (41.7)	2783	3492 (655)	2783	1821 (65.4)	2667	409 (15.3)	2783	232 (8.3)	2783	340 (12.2)
BAMSE	2268	1153 (50.8)	2257	1309 (58.0)	2268	1073 (47.3)	2251	3540 (675)	2219	2107 (95.0)	2255	456 (20.2)	2268	272 (12.0)	2268	319 (14.1)
DARC	348	174 (50.0)	348	267 (76.7)	348	188 (54.0)	348	3594 (700)	326	260 (79.8)	336	65 (19.3)	348	103 (29.6)	348	58 (16.7)
EDEN	592	322 (54.4)	587	349 (59.5)	592	300 (50.7)	591	3320 (600)	592	290 (49.0)	592	101 (17.1)	592	102 (17.2)	592	251 (42.4)
GENR	1169	590 (50.5)	1162	399 (34.3)	1169	481 (41.2)	1169	3540 (655)	882	565 (64.1)	962	121 (12.6)	1169	263 (22.5)	1163	270 (23.2)
GINIplus	3309	1670 (50.5)	3212	1737 (54.1)	3191	1587 (49.7)	3263	3455 (615)	3262	2448 (75.1)	3208	443 (13.8)	3267	430 (13.1)	3307	825 (25.0)
INMA_M	249	118 (47.4)	237	200 (84.4)	NA	NA	249	3220 (530)	249	150 (60.2)	248	25 (10.1)	249	86 (34.5)	249	158 (63.5)
INMA_V	426	215 (50.5)	426	297 (69.7)	426	190 (44.6)	426	3250 (600)	423	227 (53.7)	426	57 (13.4)	426	95 (22.3)	426	224 (52.6)
KOALA	1471	752 (51.1)	1454	677 (46.6)	1471	825 (56.1)	1471	3530 (595)	1471	1017 (69.1)	1452	237 (16.3)	1471	79 (5.4)	1471	287 (19.5)
LISAplus	1881	905 (51.9)	1863	808 (43.4)	1879	853 (45.4)	1881	3450 (590)	1772	1557 (87.9)	1811	229 (12.6)	1822	256 (14.1)	1858	476 (25.6)
MAS	969	508 (52.4)	NA	NA	969	392 (40.4)	963	3400 (590)	968	585 (60.4)	940	143 (15.2)	NA	NA	969	544 (56.2)
PIAMA	2989	1518 (50.8)	2975	1877 (63.1)	2989	1479 (49.5)	2981	3520 (650)	2966	1378 (46.5)	2968	398 (13.4)	2972	476 (15.7)	2989	938 (31.4)
RHEA	526	286 (54.4)	503	323 (64.2)	522	284 (54.4)	411	3200 (620)	499	257 (51.5)	522	41 (7.9)	500	103 (20.6)	523	216 (41.3)
ROBBIC	641	330 (51.5)	641	393 (61.3)	638	283 (44.4)	641	3351 (570)	639	463 (72.5)	639	126 (19.7)	636	62 (9.8)	641	354 (55.2)
SWS	1509	786 (52.1)	1505	1046 (69.5)	1509	723 (47.9)	1509	3470 (646)	1456	749 (51.4)	1493	556 (37.2)	1509	187 (12.4)	1509	656 (43.5)

Abbreviations: NA, not available.

Table E6.Individual participant meta-analyses results for the association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years after omitting one cohort at a time[*]

	Baseline asthma	Baseline wheeze in the last 12 months	Baseline allergic rhinitis in the last 12 months
Overall	1.87 (1.32, 2.64)	1.38 (1.06, 1.80)	1.35 (1.02, 1.79)
Cohort omitted			
ABCD	NA	NA	NA
BAMSE	2.13 (1.46, 3.13)	1.45 (1.09, 1.93)	1.29 (0.95, 1.76)
DARC	NA	1.38 (1.05, 1.82)	NE
EDEN	1.82 (1.28, 2.61)	1.35 (1.03, 1.77)	1.34 (1.01, 1.78)
GENR	NA	1.39 (1.05, 1.82)	NA
GINIplus	1.86 (1.30, 2.67)	1.31 (0.98, 1.74)	1.42 (1.07, 1.89)
INMA_M	NE	1.37 (1.04, 1.80)	NA
INMA_V	1.60 (1.10, 2.33)	1.37 (1.01, 1.86)	1.32 (0.99, 1.75)
KOALA	1.87 (1.32, 2.66)	1.32 (1.01, 1.73)	NA
LISAplus	NE	1.36 (1.02, 1.80)	1.37 (1.03, 1.82)
MAS	NA	1.41 (1.08, 1.86)	1.38 (1.03, 1.83)
PIAMA	1.85 (1.24, 2.77)	1.34 (0.98, 1.81)	1.31 (0.94, 1.84)
RHEA	1.92 (1.34, 2.75)	1.38 (1.04, 1.84)	1.31 (0.96, 1.78)
ROBBIC	1.89 (1.33, 2.71)	1.47 (1.12, 1.93)	1.43 (1.07, 1.91)
SWS	1.89 (1.31, 2.72)	1.34 (0.99, 1.83)	NA

Abbreviations: NA, not applicable; NE, cohort-specific estimate not estimable due to no exposed incident obesity cases within the cohort.

[*]Hazard ratios (95% CIs) by cohort were obtained by using Cox proportional hazards models adjusted for age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, & birthweight with sex-specific baseline hazard. Combined estimates were obtained by using a random-effects meta-analysis.

Table E7.Association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years in a pooled sample of 21130 children from 16 European birth cohorts with additional adjustment for overweight children at baseline

Asthma/asthma-related phenotypes	n (%)	aHR[*] (95% CI)
Baseline asthma		
Yes	945 (6.0)	1.47 (1.05, 2.08)
No	14731 (94.0)	ref
Baseline wheeze in the last 12 months		
Yes	2254 (12.5)	1.15 (0.89, 1.50)
No	15724 (87.5)	ref
Asthma history		
Active asthma (have baseline asthma and baseline wheeze)	543 (3.5)	1.75 (1.15, 2.66)
Have baseline asthma, but no baseline wheeze	387 (2.5)	1.22 (0.69, 2.16)
Have no baseline asthma, but have baseline wheeze	1438 (9.3)	1.06 (0.76, 1.46)
Have no baseline asthma and no baseline wheeze	13084 (84.7)	ref
Early wheeze at 0-2 years of age		
Yes	3814 (18.1)	1.11 (0.90, 1.38)
No	17216 (81.9)	ref
Wheezing history		
Persistent wheezing (have early wheeze and baseline wheeze)	1133 (6.3)	1.28 (0.92, 1.80)
Late onset wheezing (have no early wheeze but have baseline wheeze)	1135 (6.3)	1.08 (0.74, 1.57)
Transient wheezing (have early wheeze but no baseline wheeze)	2355 (13.1)	1.00 (0.76, 1.31)
Never wheezing (have no early wheeze and no baseline wheeze)	13417 (74.4)	ref
Baseline allergic rhinitis in the last 12 months		
Yes	1886 (13.7)	1.30 (0.99, 1.70)
No	11843 (86.3)	ref
Asthma and allergic rhinitis		
Have baseline asthma and allergic rhinitis	241 (2.2)	1.41 (0.74, 2.69)
Have baseline asthma and no allergic rhinitis	491 (4.5)	2.12 (1.36, 3.30)
Have no baseline asthma and no allergic rhinitis	10092 (93.2)	ref

Abbreviations: aHR, adjusted hazard ratio; ref, reference category.
[*]Cox proportional hazards model adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, birthweight, & overweight status at baseline with sex-specific baseline hazard.

Table E8. Association of early-onset asthma and asthma-related phenotypes with incident overweight or obesity up to age 8 years in a pooled sample of 19230 children from 16 European birth cohorts among children who were normal weight at baseline

Asthma/asthma-related phenotypes	n (%)	Incident obesity (n=210) aHR* (95% CI)	Incident overweight or obesity (n=1816) aHR* (95% CI)
Baseline asthma			
Yes	830 (5.9)	1.25 (0.70, 2.23)	1.10 (0.89, 1.35)
No	13334 (94.1)	ref	ref
Baseline wheeze in the last 12 months			
Yes	1997 (12.3)	1.18 (0.78, 1.78)	1.10 (0.95, 1.27)
No	14310 (87.8)	ref	ref
Asthma history			
Active asthma (have baseline asthma and baseline wheeze)	468 (3.4)	1.40 (0.67, 2.89)	1.04 (0.78, 1.37)
Have baseline asthma, but no baseline wheeze	349 (2.5)	1.18 (0.48, 2.92)	1.24 (0.92, 168)
Have no baseline asthma, but have baseline wheeze	1277 (9.2)	1.22 (0.75, 1.98)	1.16 (0.97, 1.38)
Have no baseline asthma and no baseline wheeze	11862 (85.0)	ref	ref
Early wheeze at 0-2 years of age			
Yes	3374 (17.6)	1.22 (0.88, 1.69)	1.07 (0.95, 1.20)
No	15768 (82.4)	ref	ref
Wheezing history			
Persistent wheezing (have early wheeze and baseline wheeze)	980 (6.0)	1.30 (0.75, 2.24)	1.05 (0.85, 1.28)
Late onset wheezing (have no early wheeze but have baseline wheeze)	1030 (6.3)	1.22 (0.70, 2.13)	1.18 (0.97, 1.42)
Transient wheezing (have early wheeze but no baseline wheeze)	2105 (12.9)	1.22 (0.82, 1.81)	1.11 (0.96, 1.28)
Never wheezing (have no early wheeze and no baseline wheeze)	12254 (74.9)	ref	ref
Baseline allergic rhinitis in the last 12 months			
Yes	1700 (13.7)	1.45 (0.98, 2.14)	0.98 (0.84, 1.14)
No	10727 (86.3)	ref	ref
Asthma and allergic rhinitis			
Have baseline asthma and allergic rhinitis	209 (2.1)	1.45 (0.65, 3.11)	0.98 (0.65, 1.48)
Have baseline asthma and no allergic rhinitis	434 (4.5)	1.43 (0.65, 3.11)	1.24 (0.96, 1.62)
Have no baseline asthma and no allergic rhinitis	9114 (93.4)	ref	ref

Abbreviations: aHR, adjusted hazard ratio; ref, reference category.

*Cox proportional hazards model adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, & birthweight with sex-specific baseline hazard.

Table E9. Association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years in a pooled sample of 21130 children from 16 European birth cohorts with additional adjustment for baseline BMI

Asthma/asthma-related phenotypes	n (%)	aHR[*] (95% CI)
Baseline asthma		
Yes	945 (6.0)	1.32 (0.93, 1.86)
No	14731 (94.0)	ref
Baseline wheeze in the last 12 months		
Yes	2254 (12.5)	1.09 (0.84, 1.41)
No	15724 (87.5)	ref
Asthma history		
Active asthma (have baseline asthma and baseline wheeze)	543 (3.5)	1.60 (1.05, 2.43)
Have baseline asthma, but no baseline wheeze	387 (2.5)	1.05 (0.59, 1.86)
Have no baseline asthma, but have baseline wheeze	1438 (9.3)	1.00 (0.72, 1.38)
Have no baseline asthma and no baseline wheeze	13084 (84.7)	ref
Early wheeze at 0-2 years of age		
Yes	3814 (18.1)	1.03 (0.84, 1.29)
No	17216 (81.9)	ref
Wheezing history		
Persistent wheezing (have early wheeze and baseline wheeze)	1133 (6.3)	1.15 (0.82, 1.60)
Late onset wheezing (have no early wheeze but have baseline wheeze)	1135 (6.3)	1.06 (0.73, 1.54)
Transient wheezing (have early wheeze but no baseline wheeze)	2355 (13.1)	0.95 (0.73, 1.25)
Never wheezing (have no early wheeze and no baseline wheeze)	13417 (74.4)	ref
Baseline allergic rhinitis in the last 12 months		
Yes	1886 (13.7)	1.19 (0.90, 1.56)
No	11843 (86.3)	ref
Asthma and allergic rhinitis		
Have baseline asthma and allergic rhinitis	241 (2.2)	1.42 (0.74, 2.73)
Have baseline asthma and no allergic rhinitis	491 (4.5)	1.71 (1.10, 2.66)
Have no baseline asthma and no allergic rhinitis	10092 (93.2)	ref

Abbreviations: aHR, adjusted hazard ratio; ref, reference category.
[*]Cox proportional hazards model adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, birthweight & baseline BMI with sex-specific baseline hazard.
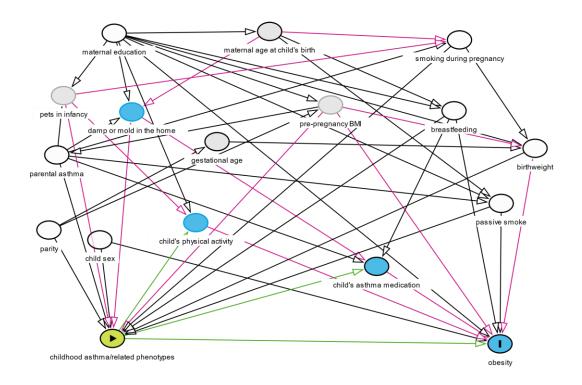
Figure E1. Directed acyclic graph for assessing the impact of early-onset asthma and asthma-related phenotypes on obesity risk. Yellow node represents our exposures of interest. Blue nodes represent our outcome of interest or risk factors for the outcome. All white nodes are variables we controlled for in adjusted models. Gray nodes denote other variables which we did not adjust for in our final analysis. Pink paths denote potentially biasing paths. Green paths denote potentially causal paths.