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Supplemental Material

Maternal Smoking during Pregnancy and Early Childhood and Development of Asthma and Rhinoconjunctivitis – a MeDALL Project

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Table S1. Definitions of smoking variables in the participating birth cohorts.

Birth cohort	Maternal smoking		Any SHS exposure			
	Maternal Smoking during pregnancy	**Infancy (first year of life)**	**When children were ages 1-2 years**	**When children were ages 4-6 years**	**When children were ages 8-10 years**	**When children were ages 14-16 years**
BAMSE	Mother smoked at least 1 cig/day during any trimester of pregnancy.	Mother, father, or others actively smoke at home at age 2 months.	Mother, father, or others actively smoke at home at age 2 year.	Mother, father, or others actively smoke at home at age 4 years.	Mother, father, or others actively smoke at home at age 8 years.	Mother, father, or others actively smoke at home at age 16 years.
GINIplus	Mother smoked during any trimester of pregnancy.	Mother actively smoking inside the home between age 5 and 12 months (asked in intervention arm only).	Smoking inside the home (in general) at age 2 years.	Mother, father, or others actively smoke inside the home at age 6 years.	Mother, father, or others actively smoke inside the home at age 10 years.	Mother, father, or others actively smoke inside the home at age 15 years.
LISAplus	Mother smoked during any trimester of pregnancy.	Mother, father, or others actively smoke inside the home at age 1 year.	Mother, father, or others actively smoke inside the home at age 2 years.	Mother, father, or others actively smoke inside the home at age 6 years.	Mother, father, or others actively smoke inside the home at age 10 years.	Mother, father, or others actively smoke inside the home at age 15 years.
MAS	Mother smoked during any trimester of pregnancy.	Mother, father, or others actively smoke inside the home at age 1 month.	Mother, father, or others actively smoke inside the home at age 18 months.	Mother, father, or others actively smoke inside the home at age 4 years.	Mother, father, or others actively smoke inside the home at age 9 years.	No data
PIAMA	Mother smoked during any trimester of pregnancy.	Cigarettes, pipes, cigars smoked in the house by mother, father and/or other household member at age 3 months.	Cigarettes, pipes, cigars smoked in the house by mother, father and/or other household member at age 2 years.	Cigarettes, pipes, cigars smoked in the house by mother, father and/or other household member at age 4 years.	Cigarettes, pipes, cigars smoked in the house by mother, father and/or other household member at age 8 years.	Cigarettes, pipes, cigars smoked in the house by mother, father and/or other household member at age 14 years.

Table S2. Definitions of asthma and rhinoconjunctivitis variables in the participating birth cohorts.

Outcome	Age 4-6 years	Age 8-10 years	Age 14-16 years
Asthma	Positive answer to two out of three: 1) Doctors diagnosed asthma ever (parental reported); 2) Asthma medication in the past 12 months (parental reported); 3) Wheezing in the past 12 months (parental reported).	Positive answer to two out of three: 1) Doctors diagnosed asthma ever (parental reported); 2) Asthma medication in the past 12 months (parental reported); 3) Wheezing in the past 12 months (parental reported).	Positive answer to two out of three: 1) Doctors diagnosed asthma ever (parental reported); 2) Asthma medication in the past 12 months (child reported, if available); 3) Wheezing in the past 12 months and/or breathing difficulties, where available (child reported, if available).
Rhinoconjunctivitis	Positive answer to the following questions: 1) In the past 12 months problems with sneezing, or a runny, or blocked nose when child did not have a cold or flu (parental reported); 2) In the past 12 months, has this nose problem been accompanies by itchy-watery eyes (parental reported).	Positive answer to the following questions: 1) In the past 12 months problems with sneezing, or a runny, or blocked nose when child did not have a cold or flu (parental reported); 2) In the past 12 months, has this nose problem been accompanies by itchy-watery eyes (parental reported).	Positive answer to the following questions: 1) In the past 12 months problems with sneezing, or a runny, or blocked nose when child did not have a cold or flu (child reported, if available); 2) In the past 12 months, has this nose problem been accompanies by itchy-watery eyes (child reported, if available).

Table S3. Overview of follow-ups of participating cohorts and outcome assessment intervals.

Birth cohort	0	1y	2y	3y	4y	5y	6y	7y	8y	9y	10y	11y	12y	13y	14y	15y	16y
BAMSE	X	X	X		X				X				X				X_c
GINIplus	X	X	X	X	X		X				X					X_c	X
LISAplus	X	X	X		X		X				X					X_c	
MAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
PIAMA	X	X	X	X	X	X	X	X	X			X			X_c		X

X indicates all follow-ups conducted in each cohort.
X indicates outcome interval used.
X_c indicates where children reported symptoms were utilized.

Table S4. Participant characteristics of five European birth cohorts at baseline.

Characteristic	BAMSE	GINIplus	LISAplus	MAS	PIAMA
Number of children at recruitment	4089	5991	3094	1314	3963
Maternal smoking during pregnancy, n (%)	527 (12.9)	723 (15.1)	536 (18.0)	308 (25.4)	700 (17.8)
SHS during infancy, n (%)	855 (21.0)	583 (20.9)	506 (19.7)	590 (49.6)	998 (25.4)
Male sex, n (%)	2065 (50.5)	2991 (51.3)	1585 (51.2)	684 (52.1)	2054 (51.8)
Mean birth weight (grams), mean±sd[a]	3529±558	3472±465	3473±445	3409±466	3507±546
Mean gestation age (weeks), mean±sd[a]	39.8±2.0	39.8±1.5	39.8±1.2	40.0±1.5	39.8±1.7
Parental education, n (%)					
Low	720 (17.6)	432 (10.4)	188 (6.2)	76 (8.2)	502 (13.1)
Medium	1201 (29.5)	1200 (28.9)	906 (29.6)	317 (34.1)	1402 (36.8)
High	2161 (52.9)	2523 (60.7)	1964 (64.2)	536 (57.7)	1908 (50.1)
Parental allergy[b], n (%)	1200 (29.7)	2020 (44.4)	1449 (50.8)	575 (46.2)	1690 (43.2)
Older siblings, n (%)	1980 (48.4)	2389 (49.8)	1348 (43.7)	464 (35.3)	1986 (50.2)
Breastfeeding (≥4 months), n (%)	3116 (79.5)	3112 (67.1)	2082 (79.0)	627 (47.8)	1370 (35.2)
Early mold or dampness in dwelling (0-2 years), n (%)	1034 (25.4)	1156 (24.2)	1091 (40.9)	162 (14.2)	1643 (46.9)
Early day-care (0-2 years), n (%)	3205 (83.4)	190 (4.6)	709 (46.2)	277 (28.9)	2131 (57.6)

Based on entire cohort data.

[a]sd = standard deviation.

[b]Mother and/or father with asthma and/or hay fever.

Table S5. Association between SHS exposure during pregnancy and during infancy in relation to prevalent asthma and rhinoconjunctivitis up to 14 to 16 years from one-stage IPD-MA[a].

Outcome	Maternal smoking during pregnancy		SHS during infancy	
	Crude	Adjusted[b]	Crude	Adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Asthma	1.21 (1.03, 1.42)	1.08 (0.90, 1.29)	1.21 (1.07, 1.37)	1.05 (0.90, 1.22)
Rhinoconjunctivitis	1.11 (0.99, 1.25)	1.10 (0.95, 1.28)	1.07 (0.96, 1.19)	1.14 (1.00, 1.31)

[a]Individual participant data meta-analysis.

[b]ORs and 95% CIs obtained from GEE analyses adjusted for sex, parental education level, parental allergy, older siblings, breastfeeding, study center, intervention arm, and early day-care attendance.

Table S6. The development of early-onset and persistent phenotypes of asthma and rhinoconjunctivitis in relation to intensity of SHS during infancy.

Outcome	SHS exposure during infancy			
	N[a]	n[a]	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
Early-transient asthma				
No smoking	5599	184	Reference catg.	Reference catg.
Total of 1-9 cigarettes/day	664	29	1.34 (0.90, 2.01)	1.44 (0.94, 2.21)
Total of ≥10 cigarettes/day	561	30	1.66 (1.12, 2.47)	1.08 (0.71, 1.66)
Persistent asthma				
No smoking	5639	224	Reference catg.	Reference catg.
Total of 1-9 cigarettes/day	663	28	1.07 (0.71,1.59)	1.07 (0.69, 1.65)
Total of ≥10 cigarettes/day	565	34	1.55 (1.07, 2.24)	1.08 (0.72, 1.61)
Early-transient rhinoconjunctivitis				
No smoking	4968	74	Reference catg.	Reference catg.
Total of 1-9 cigarettes/day	571	13	1.54 (0.85, 2.80)	1.65 (0.87, 3.12)
Total of ≥10 cigarettes/day	534	9	1.13 (0.56, 2.28)	1.12 (0.54, 2.33)
Persistent rhinoconjunctivitis				
No smoking	5015	121	Reference catg.	Reference catg.
Total of 1-9 cigarettes/day	579	21	1.52 (0.95, 2.44)	1.65 (0.97, 2.80)
Total of ≥10 cigarettes/day	535	10	0.77 (0.40, 1.48)	0.92 (0.43,1.94)

[a]N = total number of exposed children and n = number of exposed cases.
[b]ORs and 95% CIs obtained from multinomial logistic regression analyses adjusted for sex, parental education level, parental allergy, older siblings, breastfeeding, study center, intervention arm, and early day-care attendance.

Table S7. Asthma and rhinoconjunctivitis development in relation to smoking during pregnancy stratified by parental allergy.

Outcome	No parental allergy	Yes parental allergy	Interaction p-value
Asthma			
Maternal smoking during pregnancy	1.12 (0.88, 1.42)	1.03 (0.80, 1.35)	0.55
Rhinoconjunctivitis			
Maternal smoking during pregnancy	1.16 (0.93, 1.45)	1.07 (0.87, 1.31)	0.61

ORs and 95% CIs obtained from GEE analyses adjusted for sex, parental education level, older siblings, breastfeeding, study center, intervention arm, and early day-care attendance.

Table S8. Asthma and rhinoconjunctivitis development in relation to smoking during infancy stratified by parental allergy.

Outcome	No parental allergy	Yes parental allergy	Interaction p-value
Asthma			
SHS during infancy	1.11 (0.91, 1.36)	1.00 (0.78, 1.27)	0.30
Rhinoconjunctivitis			
SHS during infancy	1.28 (1.06, 1.53)	1.01 (0.82, 1.23)	0.12

ORs and 95% CIs obtained from GEE analyses adjusted for sex, parental education level, older siblings, breastfeeding, study center, intervention arm, and early day-care attendance.

Table S9. Asthma and rhinoconjunctivitis development in relation to smoking during pregnancy stratified by sex.

Outcome	Males	Females	Interaction p-value
Asthma			
Maternal smoking during pregnancy	1.19 (0.94, 1.51)	1.02 (0.79, 1.33)	0.47
Rhinoconjunctivitis			
Maternal smoking during pregnancy	1.09 (0.88, 1.34)	1.10 (0.89, 1.36)	0.87

ORs and 95% CIs obtained from GEE analyses adjusted for parental education level, parental allergy, older siblings, breastfeeding, study center, intervention arm, and early day-care attendance.

Table S10. Asthma and rhinoconjunctivitis risk in relation to smoking during infancy stratified by sex.

Outcome	Males	Females	Interaction p-value
Asthma			
SHS during infancy	1.10 (0.90, 1.36)	0.94 (0.75, 1.18)	0.34
Rhinoconjunctivitis			
SHS during infancy	1.06 (0.88, 1.27)	1.08 (0.89, 1.31)	0.94

ORs and 95% CIs obtained from GEE analyses adjusted for parental education level, parental allergy, older siblings, breastfeeding, study center, intervention arm, and early day-care attendance.

Table S11. Association between SHS exposure during pregnancy and during infancy in relation to prevalent asthma and rhinoconjunctivitis up to 14 to 16 years from one-stage IPD-MA[a] excluding preterm infants.

Outcome	**Not excluding (N = 9052)**	**Excluding (N = 8751)**
Asthma		
Maternal smoking during pregnancy	1.08 (0.90, 1.29)	1.10 (0.92, 1.32)
SHS during infancy	1.05 (0.90, 1.22)	1.08 (0.92, 1.26)
Rhinoconjunctivitis		
Maternal smoking during pregnancy	1.10 (0.95, 1.28)	1.10 (0.95, 1.29)
SHS during infancy	1.14 (1.00, 1.31)	1.15 (1.01, 1.32)

ORs and 95% CIs obtained from GEE analyses adjusted for sex, parental education level, parental allergy, older siblings, breastfeeding, study center, intervention arm, and early day-care attendance. Preterm defined as infants born <36 weeks gestation.

[a]Individual participant data meta-analysis.

Figure S1. Prevalence of parental tobacco smoking in five European birth cohorts.

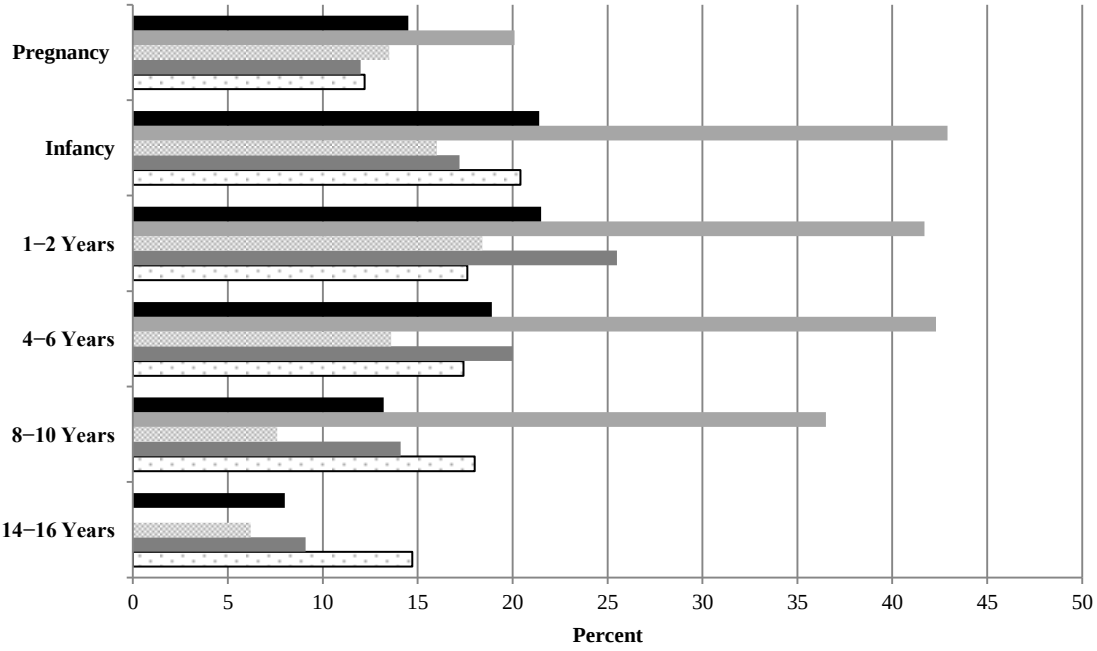


Figure S2. Prevalence of clinical phenotypes in five European birth cohorts.

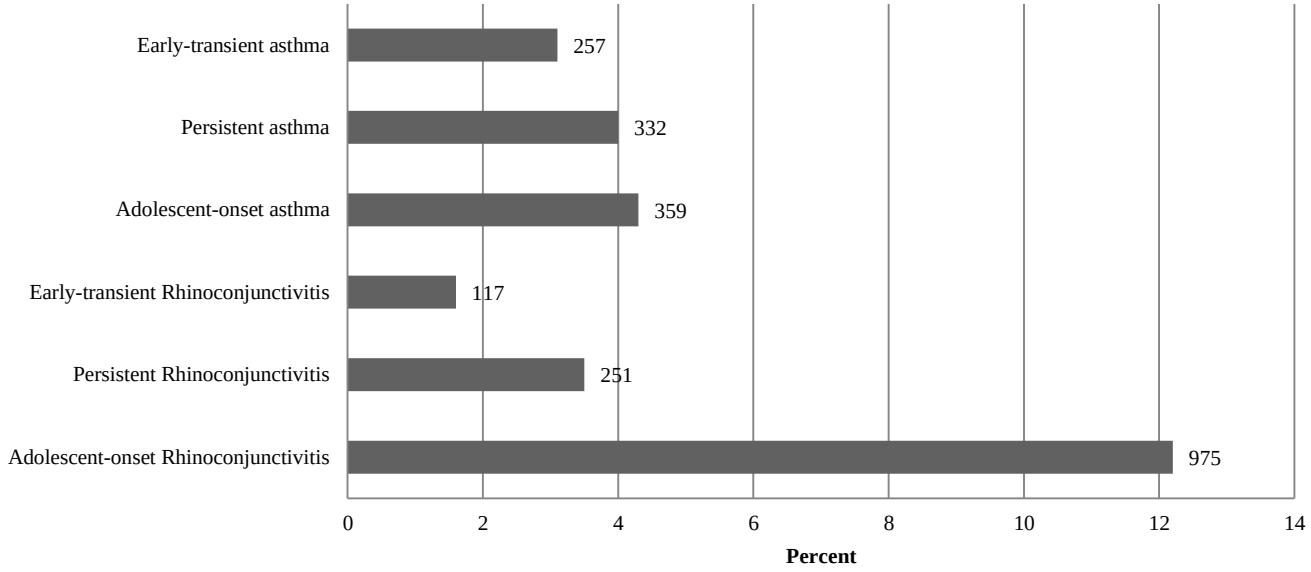
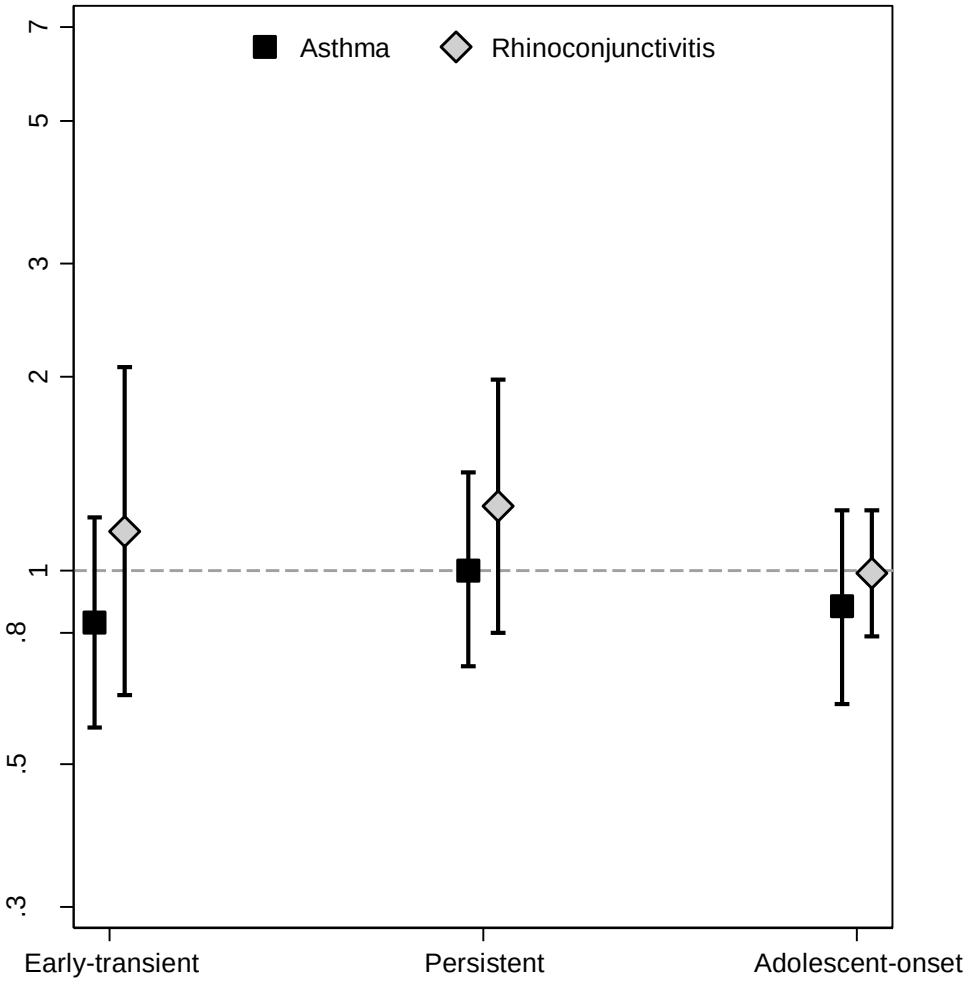
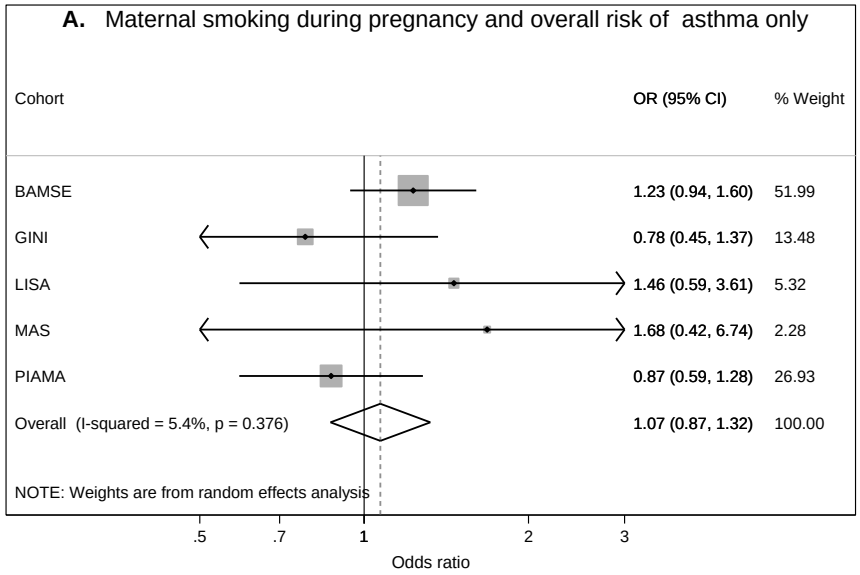


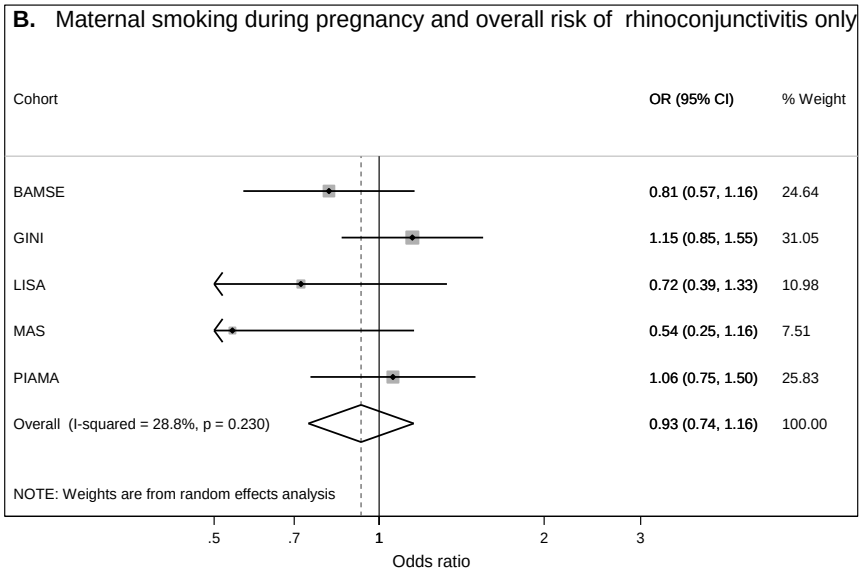
Figure S3. Secondhand smoking during infancy and the development of early-transient, persistent, and adolescent-onset disease phenotypes.*

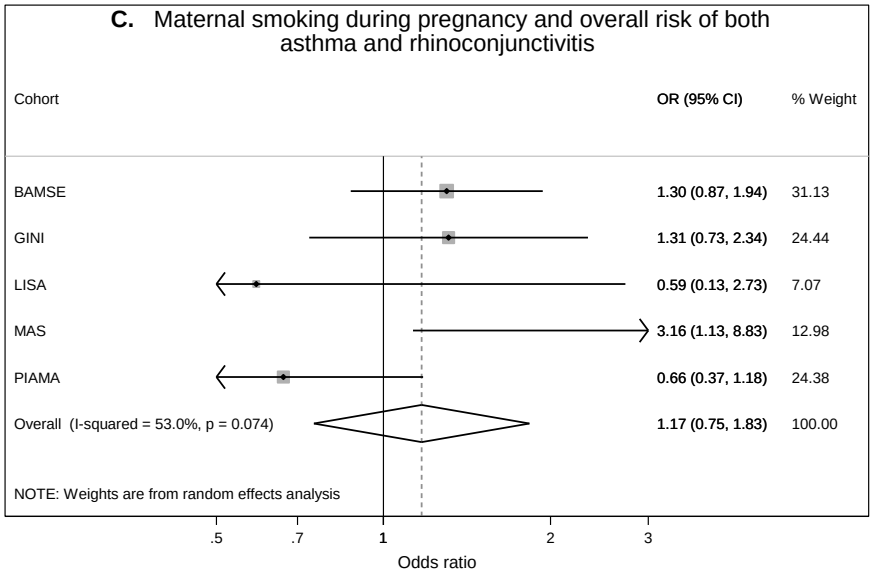


*OR and 95% CI were obtained by logistic regression adjusted for sex, parental education, parental allergy, maternal smoking during pregnancy, siblings, breastfeeding, study center, intervention arm, and early day-care attendance.

Figure S4. Association between maternal smoking during pregnancy and asthma only, rhinoconjunctivitis only, or concurrent asthma and rhinoconjunctivitis up to 14 to 16 years of age in five European birth cohorts. Cohort specific odds ratios (OR) and 95% confidence intervals (CI) were obtained by GEE models adjusted for sex, parental education level, parental allergy, older siblings, breastfeeding, study center, intervention arm, and early day-care attendance. Combined OR and 95% CI were derived from cohort-specific OR and 95% CI using a random effects model.







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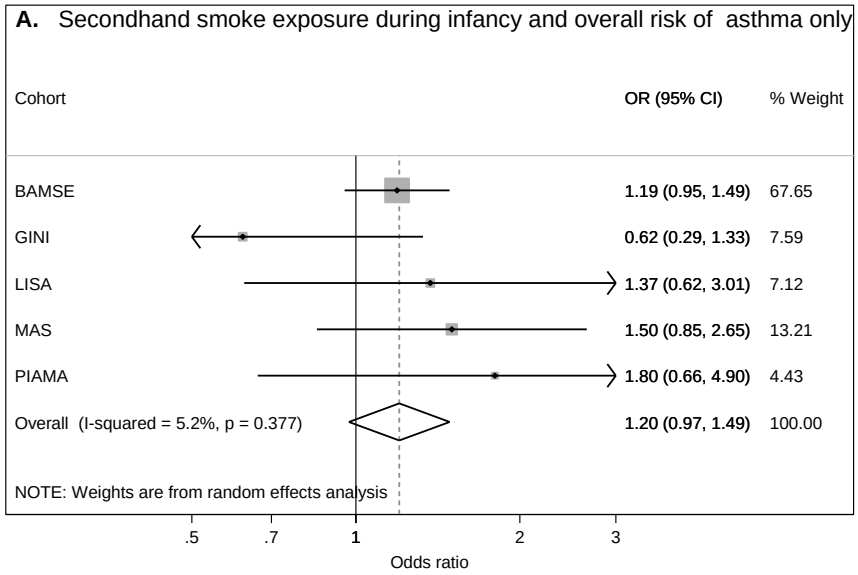

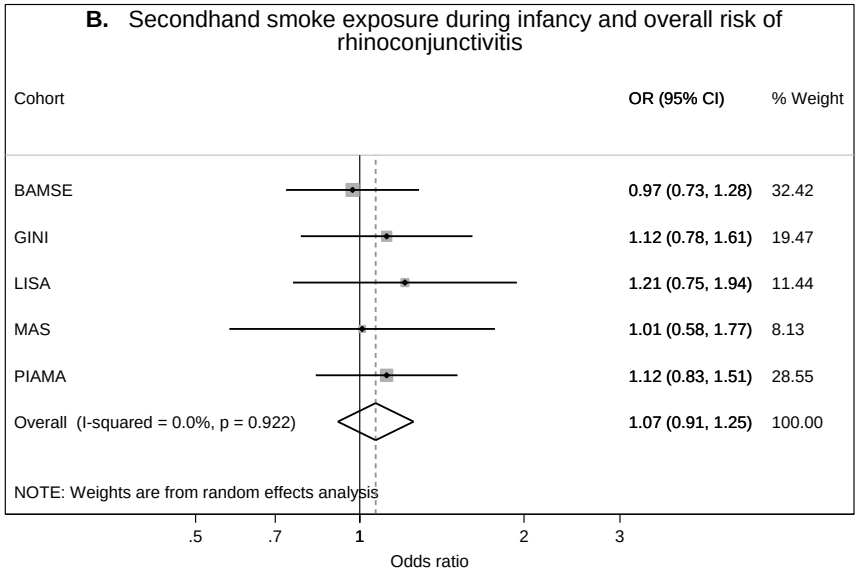

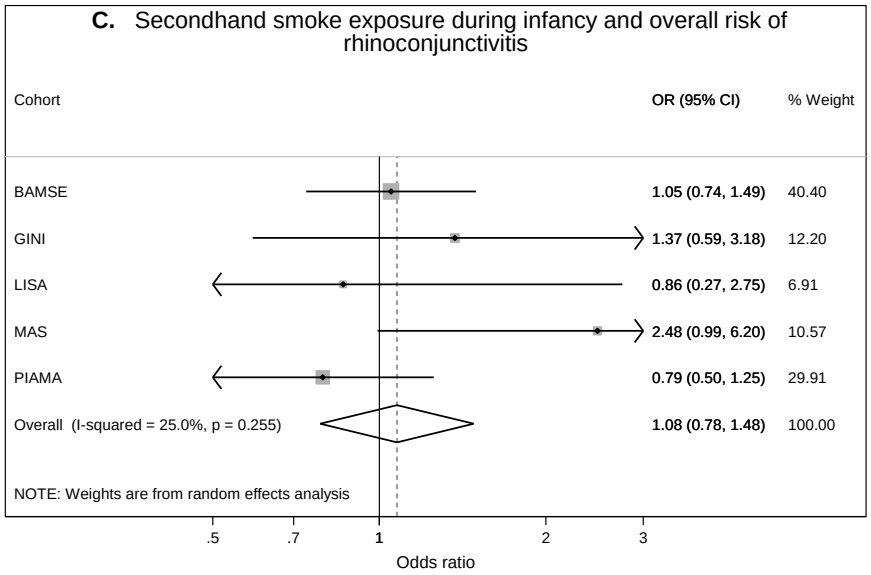

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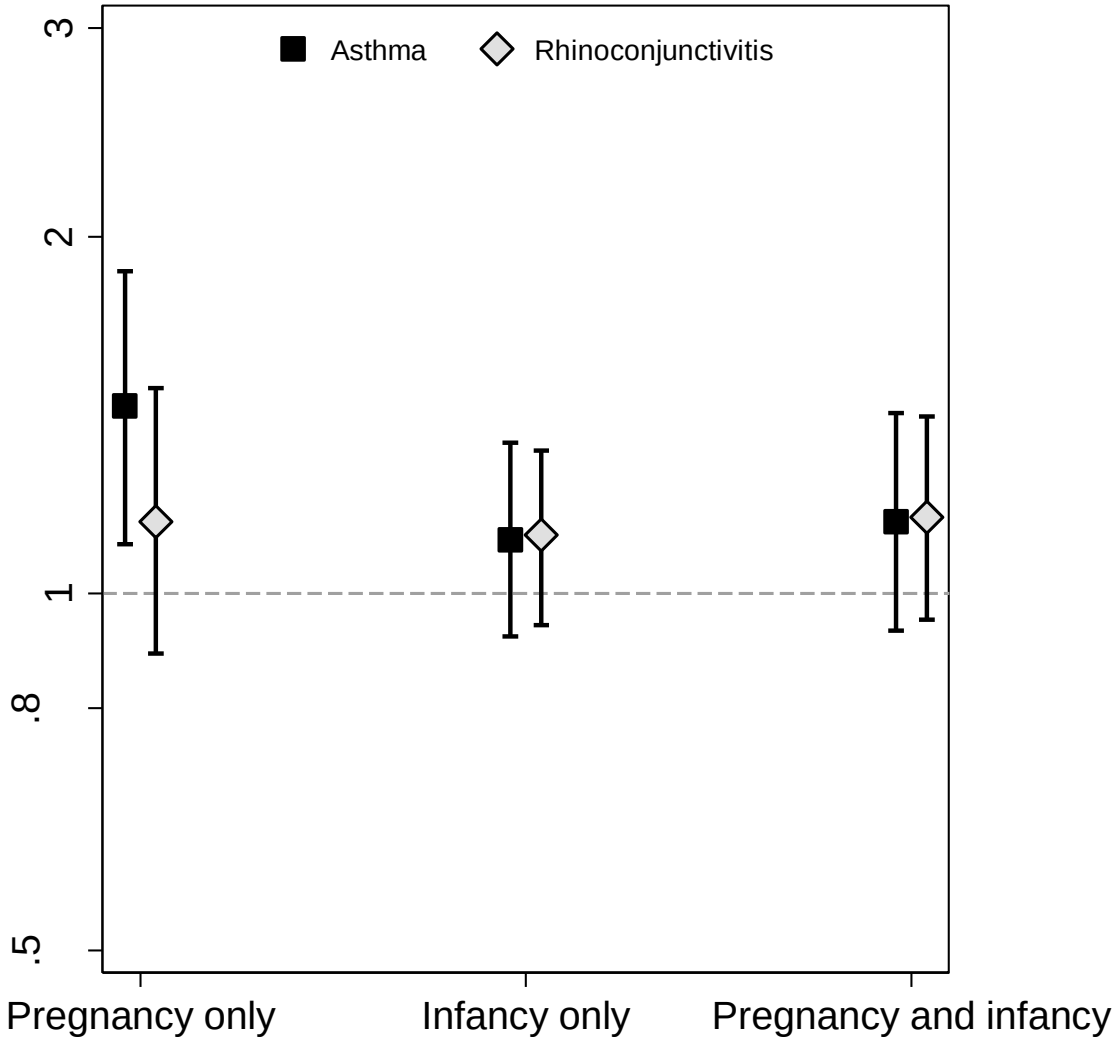

*OR and 95% CI were obtained by a GEE model adjusted for sex, parental education, parental allergy, siblings, breastfeeding, study centre, intervention arm, and early daycare attendance.

Figure S7. Associations between any tobacco smoke exposure during pregnancy or SHS during infancy and prevalence of asthma and rhinoconjunctivitis up to 14 to 16 years of age in five European birth cohorts. Cohort specific odds ratios (OR) and 95% confidence intervals (CI) were obtained by generalized estimating equation models adjusted for sex, parental education level, parental allergy, older siblings, breastfeeding, study center, intervention arm, and early day-care attendance. Combined OR and 95% CI were derived from cohort-specific OR and 95% CI using a random effects model. Participants unexposed to tobacco smoke during pregnancy and infancy comprised the reference category.