Maternal Smoking in Pregnancy and Asthma in Preschool Children

A Pooled Analysis of Eight Birth Cohorts

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***Rationale*: Although epidemiological studies suggest that exposure to maternal smoking during fetal and early life increases the risk of childhood wheezing and asthma, previous studies were not able to differentiate the effects of prenatal from postnatal exposure.**

***Objectives*: To assess the effect of exposure to maternal smoking only during pregnancy on wheeze and asthma among preschool-age children.**

***Methods*: A pooled analysis was performed based on individual participant data from eight European birth cohorts. Cohort-specific effects of maternal smoking during pregnancy, but not during the first year, on wheeze and asthma at 4 to 6 years of age were estimated using logistic regression and then combined using a random effects model. Adjustments were made for sex, parental education, parental asthma, birth weight, and siblings.**

***Measurements and Main Results*: Among the 21,600 children included in the analysis, 735 children (3.4%) were exposed to maternal smoking exclusively during pregnancy but not in the first year after birth. In the pooled analysis, maternal smoking only during pregnancy was associated with wheeze and asthma at 4 to 6 years of age, with adjusted odds ratios of 1.39 (95% confidence interval, 1.08–1.77) and 1.65 (95% confidence interval, 1.18–2.31), respectively. The likelihood to develop wheeze and asthma increased statistically significantly in a linear dose-dependent manner in relation to maternal daily cigarette consumption during the first trimester of pregnancy.**

***Conclusions*: Maternal smoking during pregnancy appears to increase the risk of wheeze and asthma among children who are not exposed to maternal smoking after birth.**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Several epidemiological studies suggest that exposure to maternal smoking during fetal and early life increases the risk of childhood wheezing and asthma. However, previous studies were not able to differentiate effects of prenatal from postnatal exposure.

What This Study Adds to the Field

This large pooled analysis of eight birth cohorts with data on more than 21,000 children showed that maternal smoking during pregnancy is associated with wheeze and asthma in preschool children, even among children who are not exposed to maternal smoking late in pregnancy or after birth.

Keywords: asthma; cohort studies; epidemiology; preschool children; tobacco smoking

Children are especially susceptible to environmental toxicants due to their growing and differentiating organs and tissues (1–3). There are critical windows of lung growth and maturation in fetal life and in the first years after birth. Thus, the impact of tobacco smoke exposure is most prominent during these periods (4). Nicotine, carcinogens, and other toxic substances pass the placental barrier and are also found in the amniotic fluid, affecting the fetus (5, 6).

An association has been reported between smoking in pregnancy and respiratory morbidity in the child, such as impaired lung function and lower airway obstruction (7–10). Because most women who smoke during pregnancy continue doing so

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after delivery (11), it has been difficult to disentangle the effects of smoking during and after pregnancy (10). However, human and animal studies indicate that different biological mechanisms influence respiratory disease development before and after birth (9, 12–14). Although pregnant women may quit smoking (11, 15), the challenge for assessment of fetal smoke exposure effects on airway disease has been identifying a sufficient number of children exposed only during pregnancy.

Our principal objective was to assess the effect of exposure to maternal smoking only during pregnancy on wheeze and asthma in European children at 4 to 6 years of age followed from pregnancy or birth. Some of the results of this study have been previously reported in the form of an abstract (16).

METHODS

We conducted a pooled analysis based on individual participant data from European birth cohorts from the ENRIECO (Environmental Health Risks in European Birth Cohorts) collaboration (17). Cohorts were included if they satisfied the following criteria: (*1*) population-based cohort focusing on allergy and asthma with ethical approval, (*2*) recruitment during pregnancy or shortly (i.e., in the first months) after birth, (*3*) at least one follow-up assessment of the outcomes wheeze or asthma during 4 to 6 years of age, and (*4*) information on maternal smoking from at least one time point during pregnancy and from the first year after birth. Eight cohorts met these criteria: ALSPAC (Bristol, UK); AMICS-Menorca (Island of Menorca, Spain); BAMSE (Stockholm, Sweden); DARC (Odense, Denmark); GINIplus, LISAplus, MAS (all multicenter, Germany); and PIAMA-NHS (multicenter, The Netherlands).

Definition of Exposures and Health Outcomes

All exposure information was based on parental questionnaires. The information on maternal smoking during pregnancy and the child's first year of life available in each birth cohort is described in Tables E1 and E2 in the online supplement. "Maternal smoking during pregnancy" was defined as smoking of at least one cigarette daily during any trimester. "Maternal smoking during the first year of life" was defined as maternal smoking in the dwelling or near the child during the child's first year of life. GINIplus lacked information on maternal smoking when the children were 1 year of age; therefore, information from 4 months were used as a proxy. "Any tobacco smoke exposure during the first year of life" was defined as mother, father, partner, or other person smoking in the dwelling or near the child during the child's first year of life. "Current maternal smoking" was defined as smoking in the dwelling or near the child at the time of outcome assessment (4–6 yr). "Any current smoke exposure" was defined as mother, father, or other person smoking in the dwelling or near the child at the time of outcome assessment. ALSPAC lacked information on paternal and other persons smoking when the child was 4 to 6 years of age and was not included in the analyses of any current smoke exposure. To evaluate the effect of smoking during pregnancy, maternal smoking during pregnancy and during the first year of the child's life was allocated into four categories: (*1*) no smoking during pregnancy or in the first year (reference category), (*2*) maternal smoking during pregnancy only, (*3*) maternal smoking in the first year only, and (*4*) maternal smoking during pregnancy and during the first year. The effect of maternal smoking during the first trimester was evaluated, irrespective of maternal smoking in the latter trimesters, as well as among mothers who smoked in the first but not in the third trimester. DARC lacked trimester-specific information and was excluded from these analyses.

Information on symptoms of wheeze and asthma were obtained from parental questionnaires (the information on wheeze and asthma available in each cohort is described in Table E3). "Current wheeze" was defined as parental-reported wheezing during the last 12 months according to the International Study of Asthma and Allergy in Childhood (ISAAC) core questions. This information was available from all cohorts. "Current asthma" was defined as satisfying at least two out of three of the following criteria: (*1*) a doctor's diagnosis of asthma ever, (*2*) parental-reported wheezing during the last 12 months according to the ISAAC core questions (18), or (*3*) asthma medication in the last 12 months. ALSPAC lacked information on doctor's diagnosis of asthma and was not included in the analyses of asthma. The time point for outcome assessments was 5 years of age, except for BAMSE and ALSPAC, which had available outcome data at 4 and 6 years of age, respectively.

Statistical Analysis

A pooled analysis of eight birth cohorts was performed using a two-stage approach. In stage 1, cohort-specific crude and adjusted estimates, including dose-response effects, were calculated using logistic regression analyses. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). Different potential confounder models were tested. The final logistic model included adjustments for sex, parental asthma based on mother's and/or father's history of asthma, parental education counting the parent with the highest educational level, siblings (having older siblings at birth or not), and birth weight in grams as a continuous variable, because these covariates resulted in an OR change of more than 5% or due to prior knowledge. To further exclude the effect of smoke exposure in childhood, we performed an additional analysis among children with no current maternal smoking or any other current smoke exposure at the time of outcome assessment (i.e., at 4–6 yr of age).

In stage 2, the cohort-specific OR estimates were combined using a random effects model, which considers within-cohort and between-cohort variation (19). The results are presented as forest plots with central point estimates and 95% CI of adjusted ORs, where the size of the square represents the inverse of the variance of the individual cohort. Statistical heterogeneity among studies was evaluated using the Q-test and I^2 statistics (20).

To examine dose-response relations between the numbers of cigarettes smoked per day and current wheeze or asthma, a two-stage multivariate random effects dose-response pooled analysis was performed. In the first stage, a quadratic logistic model was estimated for each study. In the second stage, we combined the two regression coefficients and the variance/covariance matrix that had been estimated within each study using a restricted maximum likelihood method in a multivariate, random effects metaanalysis. A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the quadratic term is equal to zero. For DARC, MAS, and PIAMA-NHS, information on number of cigarettes from any time during pregnancy was used as a proxy due to lack of trimester-specific data.

All statistical analyses were performed with STATA software, version 11 (Stata Corp., College Station, TX), and $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 presents characteristics of the eight birth cohorts, including the prevalence of maternal smoking during pregnancy, in the first year after delivery, and at the time of outcome assessment as well as wheeze and asthma prevalence at 4 to 6 years of age. The proportion of internal missing on the main exposure or outcome variables (often due to loss to follow-up) ranged between 5 and 42% across the cohorts, and the final proportion of children included in the pooled analyses was 66% out of the recruited children, in total 21,600 children. These children were somewhat less exposed to maternal smoking during pregnancy (19.2%; 95% CI, 18.7–19.7) compared with all eligible children (22.7%; 95% CI, 22.3–23.2). Moreover, their parents more often had a high educational level (55.9%; 95% CI, 55.3–56.6) compared with the parents of all eligible children (52.8%; 95% CI, 52.1–53.2). No statistically significant differences were seen for other potential confounders or for wheeze and asthma prevalence (data not shown).

The prevalence of maternal smoking during pregnancy and the first year of the child's life allocated into four disjunctive categories are presented in Table 2. On average, 23.5% of the children were exposed to maternal smoking during pregnancy or the first year of life, with a range of 16.9 to 39.2% between the cohorts. About 80% of the mothers who smoked during pregnancy continued smoking during the first postnatal year. In total, 735 children were identified who had been exposed to maternal smoke during pregnancy but not in the first year of life. The prevalence

TABLE 1. CHARACTERISTICS OF THE EIGHT EUROPEAN BIRTH COHORTS, INCLUDING PREVALENCE OF MATERNAL SMOKING DURING PREGNANCY, IN THE FIRST YEAR AFTER DELIVERY AND AT THE TIME OF OUTCOME ASSESSMENTS AS WELL AS PREVALENCE OF WHEEZE AND ASTHMA AT 4 TO 6 YEARS OF AGE

Birth Cohort	Country	Enrolment Period	Number of Recruited Children	Child's Age at Recruitment	Mean Birth Weight (*g*)	Mother Smoked during Pregnancy, n (%)*	Mother Smoked First Year after Delivery, n (%)†	Mother Smoked when the Child Was 4–6 yr of Age, n (%)‡	Wheeze at 4–6 yr of Age, n (%)§	Asthma at 4–6 yr of Age, n (%)§
ALSPAC	UK	1991–1992	14,057	During pregnancy	3,384	3,670 (27.5)	3,606 (33.9)	1,918 (24.8)	829 (9.9)	na‖
AMICS-Menorca	Spain	1997–1998	482	During pregnancy	3,187	182 (37.9)	152 (32.8)	112 (24.3)	41 (8.9)	34 (7.4)
BAMSE	Sweden	1994–1996	4,089	2 mo	3,530	529 (12.9)	584 (14.8)	534 (14.3)	546 (14.7)	512 (13.7)
DARC	Denmark	1998–1999	562	1 mo	3,541	183 (32.6)	154 (29.8)	88 (19.1)	27 (5.9)	18 (4.1)
GINIplus	Germany	1995–1998	5,991	Shortly before or after birth	3,472	709 (14.8)	713 (14.9)¶	428 (12.4)	341 (8.9)	135 (3.5)
LISAplus	Germany	1997–1999	3,097	3 d	3,473	536 (18.0)	362 (16.4)	177 (8.8)	208 (9.5)	70 (3.2)
MAS	Germany	1990	1,314	1 mo	3,409	308 (25.4)	443 (38.9)	272 (27.6)	103 (10.5)	34 (3.8)
PIAMA-NHS	The Netherlands	1996–1997	3,182	During pregnancy	3,515	676 (21.3)	546 (17.6)	419 (14.5)	278 (9.7)	122 (4.4)

* Mother smoked at least one cigarette daily during any time of pregnancy.
† Mother smoked during the first year after delivery.
‡ Mother smoked at the time of outcome assessment (i.e., when the child was 4, 5, or 6 yr of age).
§ Outcome data are from follow-up visits when the children were 5 yr of age except for BAMSE (4 yr of age), and ALSPAC (6 yr of age).
‖ Not assessed.
¶ Information on maternal smoking collected 4 mo after delivery for GINIplus.

of wheeze at 4 to 6 years of age was 10.4% among the included children, and the prevalence of asthma was 6.6% (Table 2).

In Figure 1, the cohort-specific and combined adjusted ORs of maternal smoking during pregnancy, but not in the first year after delivery, on current wheeze (Figure 1A) and asthma (Figure 1B) are displayed. The combined estimates were statistically significant for wheeze with an adjusted OR of 1.39 (95% CI, 1.08–1.77) and for asthma with an adjusted OR of 1.65 (95% CI, 1.18–2.31). No significant heterogeneity was observed between the studies ($Q = 5.03$, $P = 0.656$ for wheeze; $Q = 4.96$, $P = 0.55$ for asthma).

In Figure 2, the cohort-specific and combined adjusted ORs of maternal smoking in the first year of life, but not during pregnancy, on current wheeze (Figure 2A) and asthma (Figure 2B) are displayed. No increased risk for current wheeze or asthma was seen, the combined adjusted ORs being 0.91 (95% CI, 0.71–1.17) for wheeze and 1.20 (95% CI, 0.84–1.71) for asthma. There was no heterogeneity between the studies ($Q = 2.23$, $P = 0.946$; $Q = 2.60$, $P = 0.627$).

Figure 3 displays the cohort-specific and combined adjusted ORs for children exposed to maternal smoking during pregnancy as well as in the first year of life. The combined estimates were significant for wheeze (Figure 3A) (adjusted OR, 1.25; 95% CI, 1.09–1.43) and asthma (Figure 3B) (adjusted OR, 1.30; 95% CI, 1.00–1.68). Again, there was no heterogeneity ($Q = 2.32$, $P = 0.940$; $Q = 7.26$, $P = 0.297$).

Excluding children with smoke exposure not only by the mother but also by the father or other persons in the household (i.e., any smoke exposure) in the child's first year of life resulted in similar results for all three exposure categories as those presented above (data not shown). We also restricted the analysis to children with no current maternal smoke exposure (i.e., at 4–6 yr of age) (n = 16,241; 507 children were exposed to maternal smoking during pregnancy but not thereafter). Exposure to maternal smoking during pregnancy but not during the first year of life was associated with an increased risk of wheeze (adjusted OR, 1.63; 95% CI, 1.25–2.12) and asthma (adjusted OR, 1.95; 95% CI, 1.34–2.85) among these children. Similar results were observed among children with no current smoke exposure from any persons as well as during the first year of life (n = 9,882; data not shown).

Clear effects of maternal smoking during pregnancy were seen already for the first trimester. Maternal smoking during the first trimester of pregnancy only but not during the third trimester

TABLE 2. PREVALENCE OF MATERNAL SMOKING DURING PREGNANCY AND DURING THE FIRST YEAR AFTER DELIVERY IN EIGHT EUROPEAN BIRTH COHORTS COMPRISING 21,600 CHILDREN INCLUDED IN THE POOLED ANALYSES

Birth cohort	No Smoking (Reference), n (%)*	Smoking during Pregnancy Only, n (%)†	Smoking in the First Year Only, n (%)‡	Smoking during Pregnancy and First Year, n (%)§	Wheeze at 4–6 yr of Age, n (%)‖	Asthma at 4–6 yr of age, n (%)‖
ALSPAC	5,460 (71.2)	157 (2.1)	407 (5.3)	1,584 (20.8)	742 (9.7)	na¶
AMICS-Menorca	268 (60.8)	28 (6.3)	12 (2.7)	133 (30.2)	39 (8.8)	33 (7.5)
BAMSE	3,051 (83.1)	93 (2.5)	153 (4.2)	376 (10.2)	537 (14.7)	503 (13.7)
DARC	315 (63.6)	35 (7.1)	17 (3.4)	128 (25.9)	26 (6.2)	18 (4.2)
GINIplus	3,159 (83.3)**	123 (3.2)**	137 (3.6)**	375 (9.9)**	333 (8.9)	129 (3.4)
LISAplus	1,421 (80.7)	106 (6.0)	67 (3.8)	166 (9.4)	181 (10.4)	61 (3.5)
MAS	561 (63.6)	18 (2.0)	127 (13.9)	188 (20.6)	95 (10.7)	33 (4.0)
PIAMA-NHS	2,291 (78.1)	175 (6.0)	56 (1.9)	413 (14.1)	275 (9.6)	121 (4.4)
Total	16,526 (76.5)	735 (3.4)	976 (4.5)	3,363 (15.6)	2,228 (10.4)	898 (6.6)

* No maternal smoking during pregnancy or in the first year after delivery.
† Maternal smoking of at least one cigarette daily during any time of pregnancy but no smoking during the first year after delivery.
‡ No maternal smoking during pregnancy but maternal smoking during the first year after delivery.
§ Maternal smoking of at least one cigarette daily during any time of pregnancy and during the first year after delivery.
‖ Outcome data are from follow-up visits when the children were 5 yr of age except for BAMSE (4 yr of age) and ALSPAC (6 yr of age).
¶ Not assessed.
** Information on maternal smoking collected 4 mo after delivery.

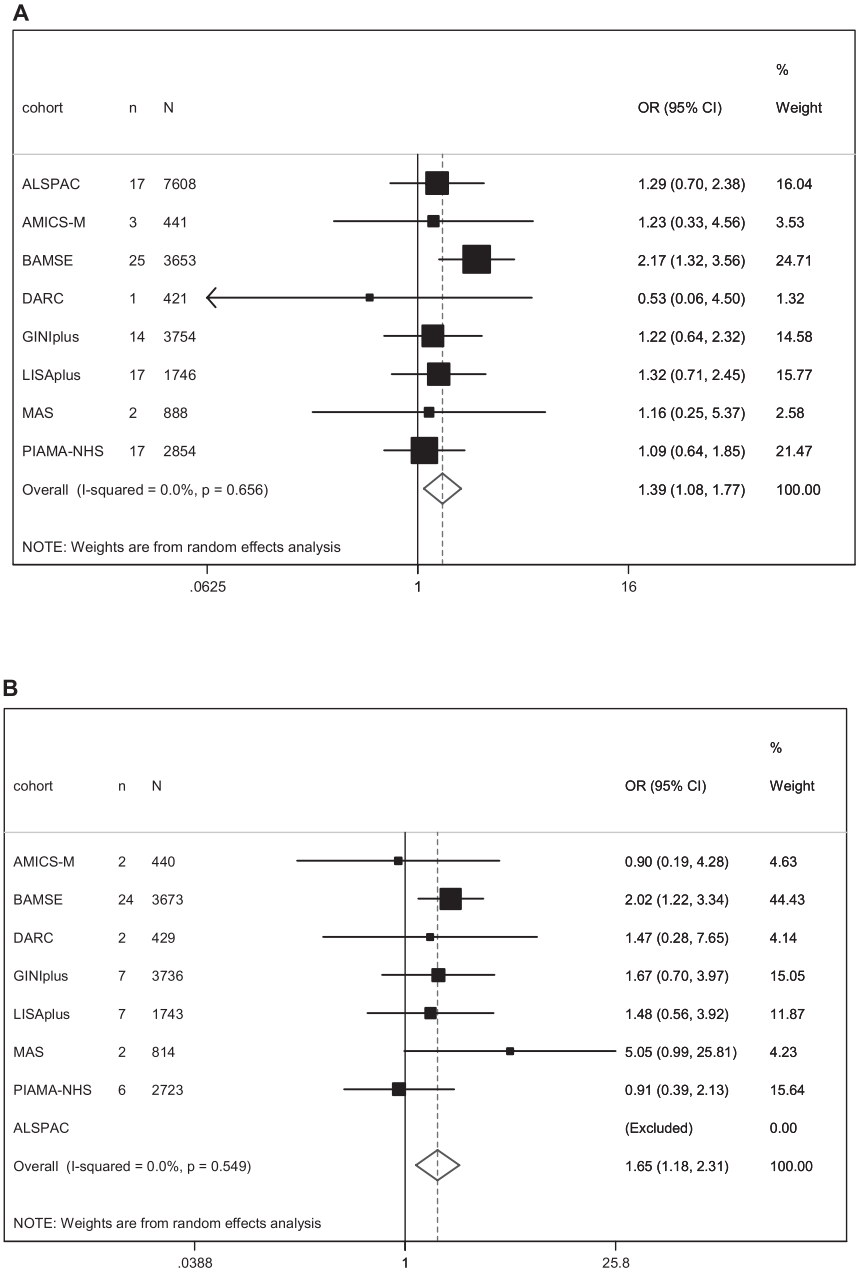

Figure 1. Associations between maternal smoking during pregnancy only (no maternal smoking during the first year of life) in relation to preschool wheeze and asthma in eight European birth cohorts. Cohort-specific odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by logistic regression adjusted for sex, parental asthma, parental education, siblings, and birth weight. Combined ORs and 95% CIs derived by random effects methods are shown. AMICS-M = AMICS-Menorca; N = total number of cases in each birth cohort; n = number of exposed cases in each cohort. (*A*) Wheeze, 4 to 6 years of age. (*B*) Asthma, 4 to 6 years of age. ALSPAC (UK) lacked information on doctor's diagnosis of asthma and was not included in the analyses of asthma.

or the first year after birth was associated with an increased risk of wheeze (adjusted OR, 1.45; 95% CI, 1.00–2.12) and asthma (adjusted OR, 2.10; 95% CI, 1.38–3.21). Of the 735 women that smoked during pregnancy but not in the first year after delivery, 496 (67%) quitted smoking during the first or second trimester. In dose-response analyses of maternal smoking during the first trimester of pregnancy and the risk of wheeze and asthma at 4 to 6 years of age, there was no evidence of nonlinearity of the association with the number of cigarettes smoked for wheeze ($P = 0.505$) and asthma ($P = 0.268$). Every five cigarette increase in daily consumption conferred an adjusted OR of 1.18 (95% CI, 1.02–1.38) for wheeze and 1.23 (95% CI, 1.03–1.47) for asthma.

DISCUSSION

This pooled analysis of individual participant data from eight European birth cohorts including 21,600 children enabled us to estimate the independent effect of maternal smoking during pregnancy on wheeze and asthma in preschool children. The results were consistent, showing an increased risk for preschool wheeze and for asthma among children exposed to cigarette smoke by their mothers during pregnancy. The effect appeared to be particularly strong for smoking during the first trimester of pregnancy with a significant dose-response effect relation.

There were several strengths with this study. Individual participant data from eight European birth cohorts were used, enabling us to assess the effect from different patterns of smoke exposure from various populations. To our knowledge, this is the largest database assessing the specific influence of maternal smoking during pregnancy on childhood respiratory disease. Information on maternal smoking during pregnancy was collected at baseline assessment in all cohorts before development of childhood respiratory disease. Moreover, data were harmonized before analyses, reducing between-study heterogeneity. Separation of pre- and postnatal smoke exposure was also possible, as well as assessment of dose-response effects for amount of cigarettes smoked in the first trimester in relation to preschool wheeze and asthma.

There were some possible limitations. In total, 66% of the eligible children in the selected cohorts were included in our

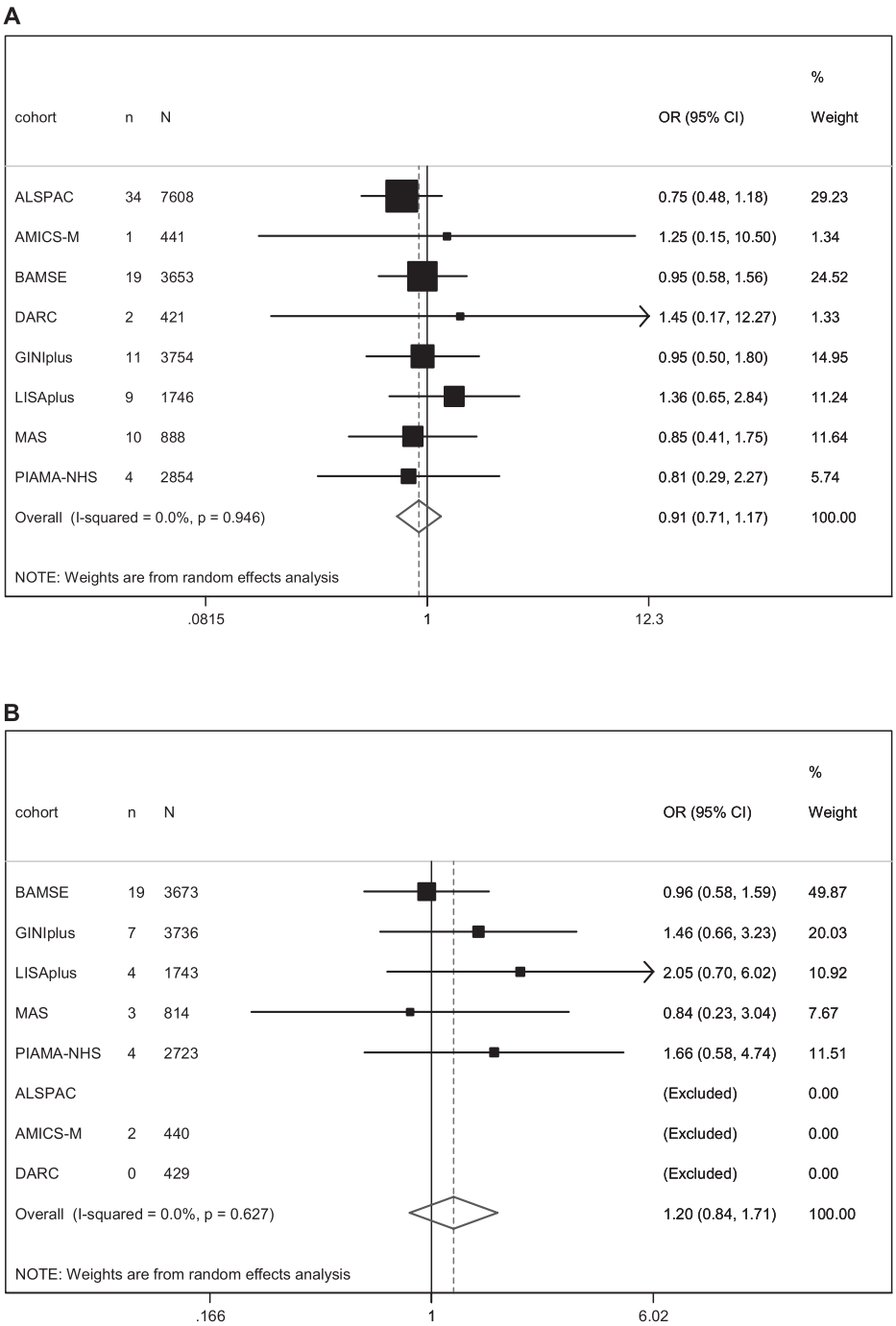

Figure 2. Associations between maternal smoking during the first year only (no maternal smoking during pregnancy) in relation to preschool wheeze and asthma in eight European birth cohorts. Cohort-specific odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by logistic regression adjusted for sex, parental asthma, parental education, siblings, and birth weight. Combined ORs and 95% CIs derived by random effects methods are shown. AMICS-M = AMICS-Menorca; N = total number of cases in each birth cohort; n = number of exposed cases in each cohort. (*A*) Wheeze, 4 to 6 years of age. (*B*) Asthma, 4 to 6 years of age. ALSPAC (UK) lacked information on doctor's diagnosis of asthma and was not included in the analyses of asthma. AMICS-Menorca (Spain) and DARC (Denmark) were excluded due to insufficient numbers of cases.

analyses. Fewer children exposed to tobacco smoke during pregnancy met our inclusion criteria compared with the original cohorts. In contrast, there was no difference in the prevalence of wheeze and asthma among the included children and those not included. Thus, it is unlikely that our finding of an increased risk among children born to smoking mothers would be explained by selection.

All exposure information was based on parental questionnaire answers. The questions were not entirely standardized, but we were able to extract comparable exposure information from all cohorts. Exposure information on maternal smoking during pregnancy was collected during pregnancy or in the first months after delivery (i.e., before disease occurrence). Thus, any misclassification of prenatal smoke exposure is likely to be nondifferential. Moreover, pregnant women have been shown to report smoking accurately, although women who quit smoking may underreport smoking (21). Maternal smoking during the first year of life was assessed when the child was 1 year of age. A validation study including four of our birth cohorts demonstrated a fair agreement between parental reported tobacco smoking and indoor air nicotine or urinary cotinine measurements (22).

Questionnaire information on wheeze and asthma during the past 12 months was comparable among the cohorts. To enhance asthma outcome accuracy, we used a composite variable satisfying at least two out of three conditions to define asthma. Although some studies suggest that smoking parents may underreport symptoms of wheeze or underutilize health care for mild respiratory symptoms in their children (23, 24), such bias would primarily lead to an underestimation of the true effect of maternal smoking if nondifferential in relation to exposure.

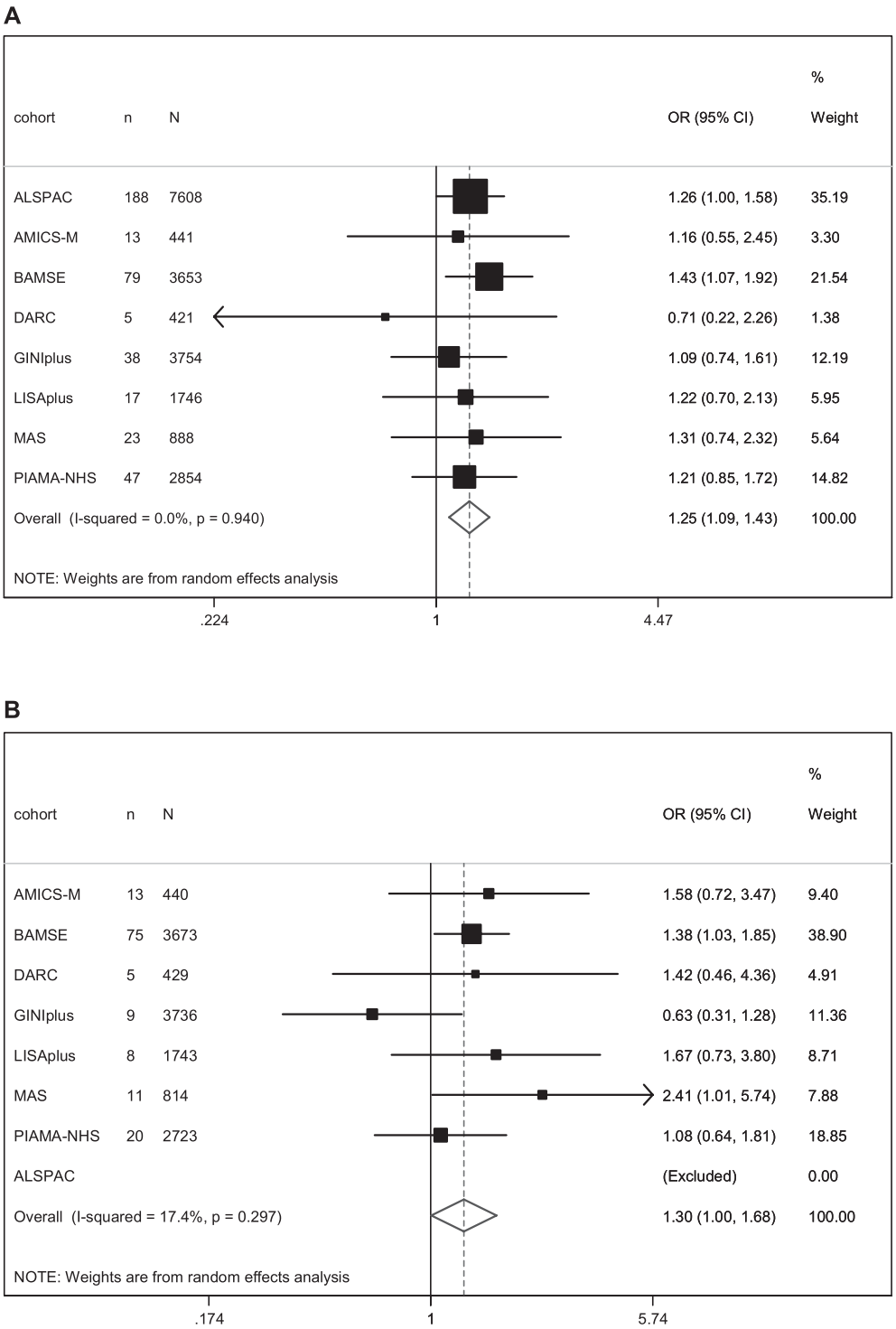

Figure 3. Associations between maternal smoking during pregnancy and in the first year after delivery in relation to preschool wheeze and asthma in eight European birth cohorts. Cohort-specific odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by logistic regression adjusted for sex, parental asthma, parental education, siblings, and birth weight. Combined ORs and 95% CIs derived by random effects methods are shown. AMICS-M = AMICS-Menorca; N = total number of cases in each birth cohort; n = number of exposed cases in each cohort. (*A*) Wheeze, 4 to 6 years of age. (*B*). Asthma, age 4 to 6 years of age. ALSPAC (UK) lacked information on doctor's diagnosis of asthma and were not included in the analyses of asthma.

Our results showing an increased risk of asthma and wheeze among children whose mothers smoked during pregnancy are in line with earlier findings (8–10, 25, 26). However, in none of the previous studies was it possible to disentangle the effect of pre- versus postnatal smoking, mainly due to small sample sizes. A positive dose-dependent effect was shown in our study estimating the odds ratio for every five-cigarette increase in daily consumption during the first trimester. The risk remained statistically significant even for the group of mothers smoking in the first but not in the third trimester. This indicates that the hazardous effects of maternal smoking on the fetal respiratory system might be present before the woman knows that she is pregnant.

An effect of maternal smoking during pregnancy on the subsequent development of childhood asthma is biologically plausible, although the underlying mechanisms remain unclear. Changes in airway sensory innervation, thickening of the airway smooth muscle layer, and altered smooth muscle relaxation causing airway hyperresponsiveness have been seen in animals exposed to tobacco smoke *in utero* (13, 14, 27, 28). Airway remodeling by collagen deposition rendering stiffer airways and increased lung inflammation and a TH2-biased immune response were also observed (13, 27). Several tobacco smoke constituents have been proposed as causative agents for asthma development. For example, nicotine can interfere with various aspects of lung development, disturbing

alveolar architecture or changing tissue elasticity (12, 29, 30). The fetal lung begins to develop in the fourth week of pregnancy, and terminal bronchioles have been formed early in the second trimester (31). Our data indicate that the early stage of organogenesis may be affected by maternal smoking.

In our study, children exposed to maternal smoking during pregnancy and in the first year of life had an increased risk of preschool wheeze and asthma, whereas no significant associations were observed for children exposed to maternal smoking only during the first year of life. Previous studies have shown such an association (1, 3, 7), and the lack of effect in our study may be an effect of the parents avoiding direct smoke exposure of their children during early childhood (10). This might be due to increased awareness of the health hazards from second-hand smoke exposure (3). Early signs of respiratory disease in toddlers might also result in adjusted parental smoking behavior (25). Moreover, given the strong effect of maternal smoking during pregnancy, the potential adverse effects of postnatal maternal smoking might only be visible beyond preschool age.

This large pooled analysis of eight birth cohorts with data on more than 21,000 children showed that maternal smoking during pregnancy is associated with wheeze and asthma in preschool children and among children who are not exposed to maternal smoking late in pregnancy or after birth. Policy makers should be aware of the important role of motivating tobacco smoking teenage girls and young women to stop before getting pregnant to prevent asthma in their children.

Author disclosures are available with the text of this article at www.atsjournals.org.

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Maternal Smoking in Pregnancy and Asthma in Preschool Children: a Pooled Analysis of 8 Birth Cohorts

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Online data supplement

Table E1. Trimester specific information on maternal smoking during pregnancy in the participating birth cohorts

	Maternal smoking during pregnancy			Daily amount of cigarettes smoked by mother during pregnancy		
Birth cohort	**First trimester**	**Second trimester**	**Third trimester**	**First trimester**	**Second trimester**	**Third trimester**
ALSPAC	yes	yes	yes	yes	no	yes
AMICS-Menorca	yes	yes	yes	yes	no	yes
BAMSE	yes	yes	yes	yes	yes	yes
DARC	no*	no*	no*	no*	no*	no*
GINIplus	yes	yes	yes	yes	yes	yes
LISAplus	yes	yes	yes	yes	yes	yes
MAS	yes	yes	yes	no†	no†	no†
PIAMA-NHS	yes	yes	yes	no‡	no†	no†

*No trimester specific information available, information was only obtained for the whole pregnancy.

†No trimester specific information available on number of cigarettes. Information on number of cigarettes was collected when the woman completed the baseline questionnaire.

Table E2. Definition of maternal and any smoke exposure in the first year after delivery and at outcome assessment in the participating birth chorts

	Maternal smoking		Any smoke exposure	
Birth cohort	**First year after delivery**	**When the child was 4-6 years**	**First year after delivery**	**When the child was 4-6 years**
ALSPAC	Actively smoking, not limited to smoking in the dwelling, age 0 and/or 1 years	Actively smoking, not limited to smoking in the dwelling, age 5 years	Mother actively smoking, not limited to smoking in the dwelling, age 0 or 1 years, and/or child in smoky room, age 0 years	Not assessed
AMICS-Menorca	Smoking location not specified at age 0 years and/or currently smoking at home age 1 year	Currently smoking at home, age 6 years	Maternal smoking (location not specified) at age 0 years and/or father and/or other persons currently smoking in the dwelling age 0 years and/or mother, father and/or other persons currently smoking in the dwelling at age 1 year	Mother, father and/or other persons currently smoking in the dwelling at age 6 years
BAMSE	Smoking at home at age 0 and/or 1 years	Smoking at home at age 4 years	Mother, father, siblings or others smoking in the dwelling at age 0 and/or 1 years	Mother, father, siblings or others smoking in the dwelling at age 4 years
DARC	Smoking inside at age 0 and/or 1 years	Smoking inside at age 5 years	Smoking inside by mother, father, siblings or others at age 0 and/or 1 years	Smoking inside by mother, father, siblings or others at age 5 years
GINIplus	Smoking, not specified where, at age 0 years	Smoking, not limited to smoking in dwelling, at age 5 years	Mother smoking, not specified where, at age 0 years and/or someone smoking (mother and/or other) in the dwelling at age 0 and/or 1 years	Someone smoking (mother and/or other) in the dwelling at age 5 years
LISAplus	Smoking at home at age 0 and/or 1 years	Smoking at home at age 5 years	Mother, father and/or others smoking in the dwelling at age 0 and/or 1 years	Mother, father and/or others smoking in the dwelling at age 5 years
MAS	Smoking at home at age 0 and/or 1 years	Smoking at home at age 5 years	Mother, father and/or others smoking at home at age 0 and/or 1 years	Mother, father and/or others smoking at home at age 5 years
PIAMA-NHS	Cigarettes, pipes, cigars smoked in the house age 0 and/or 1 years	Cigarettes, pipes, cigars smoked in the house	Cigarettes, pipes, cigars smoked in the house by mother, father and/or other household members age 0 and/or 1 years	Cigarettes, pipes, cigars smoked in the house by mother, father and/or other household member at age 5 years

Table E3. Definition of current wheeze and asthma in the participating birth cohorts. Current asthma is defined as satisfying at least 2 out of 3 criteria of wheeze in the last 12 months, a diagnosis of asthma ever and/or asthma medication in the last 12 months

		Outcome	
Birth cohort	**Current wheeze**	**Doctor's diagnosis of asthma ever**	**Current asthma medication**
ALSPAC	Doe she/she have wheezing with whistling on the chest when he/she breathes?	Not assessed	Asthma medication in the last 12 months.
AMICS-Menorca	Did your child ever wheeze in the last 12 months?	Has a doctor ever diagnosed asthma?	Asthma medication intake in the last 12 months: reliever inhaler, preventer inhaler, reliever syrup/tablets, oral corticoids.
BAMSE	Has your child had trouble with wheezing or raspy breathing in the last 12 months?	Has a doctor diagnosed your child as having asthma?	Has your child received treatment for breathing difficulties?
DARC	Has or has had the child occasionally suffered from wheezing since the last follow-up/last 12 months?	Do you think your child has asthma? Yes, this was doctor diagnosed.	Has the child received any prescriptive medication since last follow-up like: local steroid, teophyllin, short-term B2-agonist, other?
GINIplus	Did your child suffer from wheezing in the chest while breathing in the last 12 months?	Has a doctor diagnosed asthma on your child? Combined variable for diagnosis in the last 12 months at 0, 1, 3 and 5 years.	Was your child treated for asthma in the last 12/24 months?
LISAplus	Did your child suffer from wheezing in the chest while breathing in the last 12 months?	Has a doctor diagnosed asthma on your child? Combined variable for diagnosis in the last 12 months at 0, 1, 3 and 5 years.	Was your child treated for asthma in the last 12/24 months?
MAS	Did your child suffer from wheezing in the last 12 months?	Did your child ever get a doctor diagnosis of asthma?	Did your child receive medication for breathing difficulties in the last 12 months?
PIAMA-NHS	Has your child had wheezing or whistling in the chest during the past 12 months?	Has a doctor ever diagnosed asthma in your child?	Has your child had asthma medication prescribed by a doctor in during the last 12 months?