

*Original article***Preterm delivery and asthma: A systematic review and meta-analysis**

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Background: Accumulating evidence suggests that reduced duration of pregnancy predicts increased risk of asthma, but the studies published have been inconsistent.

Objective: We sought to synthesize the evidence on the relation between preterm delivery and the risk of asthma later in life and to assess differences between the studies as potential sources for heterogeneity of the results.

Methods: We conducted a MEDLINE search (until the end of May 2005). The outcome was asthma. The determinant of interest was preterm delivery defined as a gestational age of less than 37 weeks.

Results: We identified 19 articles that provided estimates for the meta-analysis. The summary effect estimates for asthma (fixed-effects odds ratio, 1.074 [95% CI, 1.072-1.075]; heterogeneity $P = .000$; random-effects odds ratio, 1.366 [95% CI, 1.303-1.432]) showed an increased risk in relation to preterm delivery, with substantial heterogeneity between study-specific estimates. The effect of preterm delivery on asthma was stronger in cross-sectional studies; studies with broad outcome criteria, a small sample size, and a younger study population; and studies conducted in English-speaking populations, outside Europe, and published more recently. In metaregression, adjusting for other determinants, the effect estimate was significantly associated only with the mean age of the study population.

Conclusions: The weight of evidence shows that preterm babies have an increased risk of asthma compared with term babies. **Clinical implications:** Recognition of prematurity as a determinant of asthma emphasizes the importance of active treatment of physiologic airflow obstruction and a need for special preventive measures against known environmental determinants of asthma in preterm babies. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Asthma, preterm delivery, gestational age, fetal development, meta-analysis

Abbreviation used

CI: Confidence interval
OR: Odds ratio
SE: Standard error

Disturbances in fetal development predispose individuals to cardiovascular diseases and diabetes later in life.¹ It has been suggested that the fetal period and early childhood play an important role also for asthma and other allergic diseases.² Reduced duration of pregnancy can be considered an indicator of disturbance in fetal development, and preterm delivery terminates normal fetal development, both of which might increase susceptibility to ill health. Thus a relation between preterm delivery and the risk of asthma would be consistent with the hypothesis that the fetal period plays an essential role in the development of asthma. Recognition of prematurity as a determinant of asthma could have clinical importance because it would favor active treatment of any physiologic airflow obstruction in preterm babies.³ In addition, prematurely born children could get special attention with respect to preventive measures against known or suspected environmental and nutritional determinants of asthma. However, previous studies on the relation between preterm delivery and asthma have provided somewhat controversial results. To our knowledge, there are no previous systematic reviews that have estimated the overall effect of preterm delivery on the risk of asthma.

To fill in this important gap in current knowledge, we conducted a systematic review and a meta-analysis of the existing evidence on the relation between preterm delivery and the risk of asthma. We also assessed reasons for heterogeneity of results between the studies.

METHODS**Search strategy and inclusion criteria**

We performed a systematic literature search of the MEDLINE database from 1966 through May 2005 using the following search command: asthma [Epidemiology, Etiology, Genetics, Pathology] AND preterm delivery [Premature labor, Premature Infant, Gestational Age]. The abstracts identified by this search were screened to eliminate the obviously irrelevant ones. For the remaining, copies of

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the full articles were retrieved and screened according to the following *a priori* inclusion criteria: (1) provides information that can be used to estimate the relation between preterm delivery and the risk of asthma as an odds ratio, incidence rate ratio, cumulative incidence ratio, hazard ratio, or prevalence ratio; (2) is an original study; (3) is a cohort, case-control, or cross-sectional study in design; and (4) includes a study population of children, adults, or both. Reference lists of the articles that fulfilled the aforementioned inclusion criteria were also reviewed, and further articles fulfilling these criteria were included. All studies providing sufficient information on the relation between preterm delivery and asthma were included, irrespective of whether this question was their primary or secondary objective.

The outcome of interest was asthma. Our definition of asthma was based on a physician's diagnosis; hospitalization for asthma; asthma reported by the child/patient, his or her parent, or both; or a history of asthma. Our exposure was preterm delivery, which was defined as a gestational age of less than 37 weeks according to the World Health Organization criterion.⁴ For any study to be included in our analysis, its outcome and exposure definitions had to be consistent or adaptable with ours.

Data extraction

The most relevant characteristics of each selected article were recorded in a data extraction form by 4 coauthors independently. After this, the forms were compared. The characteristics of interest included authors, year of publication, study design, sample size, age of the study population, geographic region, language of the study population, definition of diagnosis of asthma, definition of prematurity, adjustment for confounding, and effect measures. In the case of disagreement in the data extracted, discussion was carried out to achieve agreement. The summarized data were rechecked to avoid transcription errors.

Statistical methods

We calculated summary effect estimates by using both the fixed- and the random-effects models. The fixed-effects model applied the Mantel-Haenszel method with inverse variances of individual effect estimates as weights.⁵ The random-effects model applied the method of DerSimonian and Laird.⁶ The natural log and SE of the natural log of effect estimates were calculated from the raw data or from the CIs presented in the articles. When available, the adjusted effect estimates were preferred to the crude estimates. Fixed- and random-effects models were run on Stata 8.2 by using the "meta" command.⁷ Heterogeneity between study-specific effect estimates was tested by using the Q statistics and distribution. A funnel plot was created, and potential publication bias was tested in metaregression of the effect estimates and their variance⁸ by using the "metareg" module.⁹ Finally, we assessed determinants of the heterogeneity between the study-specific estimates in a metaregression analysis using the "metareg" module,⁷ fitting all the study characteristics in the model.

RESULTS

Studies

The MEDLINE search identified 62 articles. On the basis of their abstracts, 38 studies were eliminated as being obviously irrelevant. The remaining 24 studies were retrieved and reviewed in detail: 11 met the criteria defined in the "Methods" section and were included in the analysis. Reference lists of the articles that fulfilled our inclusion criteria were checked; 17 further articles were identified and reviewed, and 8 of these fulfilled our inclusion criteria and consequently were included in the analyses. The meta-analysis was based on 19 studies displayed in Table I.¹⁰⁻²⁸

Design characteristics

Design characteristics of the studies included in the meta-analysis are shown in Table I. Of the 19 studies selected, 10 were published in 1990-2000, and 9 were published more recently in 2001-2005. Fourteen studies were cohort studies, 4 were cross-sectional studies, and 1 was a prevalent case-control study. The majority of the studies ($n = 13$) were carried out in Europe (Denmark, Finland, Germany, Norway, Sweden, and the United Kingdom). Three studies were conducted in the United States, 2 in New Zealand, and 1 in Canada.

The reasons for excluding 24 studies were the following: outcome measures incompatible with our criteria ($n = 5$), determinants incompatible with our criteria ($n = 4$), lack of quantitative results compatible with the criteria ($n = 2$), study population comprised of preterm infants only ($n = 2$), prematurity not examined as a potential risk factor for asthma ($n = 2$), and other reasons ($n = 9$).

Exposure, outcome, and effect measures

Six studies used the definition of preterm delivery compatible with our criteria (ie, <37 vs ≥ 37 weeks' gestation). The rest elaborated the risk of asthma according to different durations of gestational age ranging from 28 to 45 weeks. General variance-based methods using CIs²⁹ were applied to combine the results according to the 2 levels of gestational age when gestational age was divided into more than 2 levels in the original articles. Using this approach, we were able to include the results from altogether 13 studies contrasting less than 37 weeks with 37 or more weeks of gestational age, 2 studies contrasting 37 weeks or less with greater than 37 weeks, 2 studies contrasting less than 36 weeks with 36 weeks or more, and 2 studies that did not specify a cutoff point for prematurity but that we assumed to be 37 weeks.

Definition of asthma was based on symptoms and signs related to asthma ($n = 3$), use of asthma medication ($n = 1$), hospitalization caused by asthma ($n = 1$), and a physician's diagnosis of asthma ($n = 13$). The sources for outcome information included registries, medical records, self- or parent-administered questionnaires, and personal interview, clinical examination, or both (Table I). Some studies presented results for several different outcomes. In those cases we selected the effect estimate for the most objective and specific outcome measure available.

The measure of effect varied among the studies: 13 studies presented odds ratios (ORs), 1 study applied hazard ratios, and 5 studies presented prevalences according to preterm delivery. Prevalences were converted into crude ORs, and hazard ratios and ORs were treated as comparable measures of effect ("relative risks").

Preterm delivery and asthma

Table I shows the study-specific effect estimates used in the meta-analysis. Six of the 19 estimates are directly from the original articles, and 13 are transformed from the information available to comply with our categorization used in the meta-analysis. In 15 of the 19 studies, the effect estimate was greater than 1, and of these, 9 studies had the lower

TABLE I. Selected design characteristics of the studies included in the analysis

Reference	Study design	Size of study population	Time of birth	Age at end of study (y)	Region, country	Preterm delivery contrast	Asthma definition/information	Adjusted	Effect estimate used in meta-analysis (RR [95% CI])
Schwartz et al, 1990 ¹⁰	Cross-sectional	5627	1967-1979	<11	United States	Preterm vs full term	Physician diagnosis, questionnaire	Yes	1.28 (0.81-1.94)
Rona et al, 1993 ¹¹	Cross-sectional	5573	1980-1985	5-11	England and Scotland	≤37 vs >37 wk	Asthma attack, questionnaire	No	1.0716 (0.7632-1.5045)
von Mutius et al, 1993 ¹²	Cross-sectional	4827	1978-1980	9-11	Munich, Germany	<37 vs ≥37 wk	Physician diagnosis, questionnaire	Yes	1.9272 (1.3409-2.7698)
Kelly et al, 1995 ¹³	Cohort study	3746	1980-1986, 1982-1988	5-11	Merseyside, United Kingdom	Preterm vs full term	Physician diagnosis, questionnaire	Yes	1.40 (1.10-1.79)
Fergusson et al, 1997 ¹⁴	Cross-sectional	869	—	16	New Zealand	<37 vs ≥37 wk	Physician diagnosis, medical records	No	1.1673 (0.5693-2.3934)
Svanes et al, 1998 ¹⁵	Cohort study	688	1967-1971	20-24	Bergen, Norway	<37 vs ≥37 wk	Symptoms and signs, questionnaire	Yes	1.86 (0.23-12.0)
Bråbäck and Hedberg, 1998 ¹⁶	Cohort study	149398	1973-1975	17-20	Sweden	<37 vs ≥37 wk	Physician diagnosis, examination	No	1.042 (1.0398-1.0443)
Leadbitter et al, 1999 ¹⁷	Cohort study	652	1972-1973	13	Dunedin, New Zealand	<37 vs ≥37 wk	Symptoms and signs, questionnaire	No	0.6852 (0.2028-2.3154)
Räsänen et al, 2000 ¹⁸	Cohort study	3968	1975-1979	16	Finland	<37 vs ≥37 wk	Physician diagnosis, questionnaire	Yes	0.8911 (0.7293-1.0889)
Steffensen et al, 2000 ¹⁹	Cohort study	4794	1973-1975	18	Denmark	<37 vs ≥37 wk	Physician diagnosis, medical records	Yes	0.9284 (0.6221-1.3853)
Annesi-Maesano et al, 2001 ²⁰	Cohort study	4065	1958	1-18	United Kingdom	<37 vs ≥37 wk	Symptoms and signs, interview	No	1.26 (0.90-1.76)
Pekkanen et al, 2001 ²¹	Cohort study	4919	1966	31	Northern Finland	<36 vs ≥36 wk	Physician diagnosis, questionnaire	Yes	1.1376 (0.9216-1.4043)
Miller, 2001 ²²	Cohort study	6159	1988	3	United States	<36 vs ≥36 wk	Physician diagnosis, medical records	No	1.4902 (1.2786-1.7367)
Yuan et al, 2003 ²³	Cohort study	9694	1996-1997	1	North Jutland, Denmark	<37 vs ≥37 wk	Asthma medication, registry	Yes	2.2759 (2.1787-2.3774)
Katz et al, 2003 ²⁴	Cohort study	10809	1975-1980	11-16	Sheffield, United Kingdom	<37 vs ≥37 wk	Physician diagnosis, questionnaire	No	0.9134 (0.4312-1.7615)
Jaakkola and Gissler, 2004 ²⁵	Cohort study	58841	1987	7	Finland	<37 vs ≥37 wk	Physician diagnosis, registry	Yes	1.64 (1.38-1.95)
Bolte et al, 2004 ²⁶	Cross-sectional	741	1990	5-7	Munich, Germany	<37 vs ≥37 wk	Physician diagnosis, questionnaire	No	1.5946 (1.4913-1.7051)
Dik et al, 2004 ²⁷	Cohort study	170960	1980-1990	6	Manitoba, Canada	≤37 vs >37 wk	Physician diagnosis, registry	Yes	1.1027 (1.1002-1.1051)
Debley et al, 2005 ²⁸	Case-control	Case: 2028 Control: 8293	1987-1994	6-12	Washington, United States	<37 vs ≥37 wk	Hospitalized, registry	No	1.70 (1.39-2.08)

RR, Relative risk.

TABLE II. Summary ORs for the relation between preterm delivery and the risk of asthma: main analysis (n = 19) and stratified analyses

Stratification	Model		Heterogeneity statistics	
	Fixed-effects model (OR [95% CI])	Random-effects model (OR [95% CI])	Q (n)	P value
Main analysis				
Single stratum including total population	1.074 (1.072-1.075)	1.366 (1.303-1.432)	2632.175 (19)	.000
Stratified analyses				
Outcome definition				
Physician-diagnosed asthma	1.073 (1.071-1.074)	1.207 (1.155-1.261)	1470.078 (13)	.000
Other	2.198 (2.107-2.292)	1.490 (1.066-2.083)	40.099 (6)	.000
Study design				
Cross-sectional	1.543 (1.457-1.635)	1.518 (1.365-1.688)	8.233 (7)	.222
Longitudinal	1.073 (1.072-1.075)	1.316 (1.248-1.388)	2472.256 (12)	.000
Study population size				
<5000	1.430 (1.353-1.512)	1.243 (1.024-1.510)	41.703 (10)	.000
≥5000	1.073 (1.072-1.075)	1.383 (1.309-1.461)	2478.328 (9)	.000
Mean age of study population				
<10 y	1.105 (1.103-1.108)	1.405 (1.111-1.904)	1219.57 (10)	.000
≥10 y	1.042 (1.040-1.045)	1.192 (0.939-1.513)	169.187 (9)	.000
Geographic location				
Other	1.103 (1.100-1.105)	1.325 (1.054-1.665)	33.649 (6)	.000
Europe	1.045 (1.042-1.047)	1.302 (0.997-1.701)	1419.816 (13)	.000
Language				
English	1.103 (1.100-1.105)	1.293 (1.103-1.516)	37.648 (9)	.000
Other	1.045 (1.042-1.047)	1.324 (0.963-1.821)	1413.428 (10)	.000
Year of publication				
2001-2005	1.105 (1.103-1.108)	1.434 (1.077-1.908)	1215.913 (9)	.000
1990-2000	1.042 (1.040-1.044)	1.139 (0.985-1.317)	21.138 (10)	.012

limit of the 95% CI at greater than 1. In the remaining 4 studies, the point estimate was less than 1, but the 95% CI included 1.

Table II presents the summary effect estimates from the main analyses including all 19 studies (fixed-effects and random-effects models) and also from analyses stratified by 7 main characteristics of the studies. The summary OR from the fixed-effects model was 1.074 (95% CI, 1.072-1.075), indicating a significantly increased risk of asthma. However, the Q statistics showed significant heterogeneity between the study-specific estimates (Table II). The random-effects model that allowed for heterogeneity yielded a summary OR of 1.366 (95% CI, 1.303-1.432), suggesting an even greater risk of asthma in relation to preterm delivery. The stratified analyses showed a greater effect estimate in the 6 studies using broad outcome criteria compared with 13 studies using physician-diagnosed asthma as the outcome criterion; in the 7 cross-sectional studies, including also a prevalent case-control study, compared with the 12 cohort studies; and in studies with a small sample size (<5000 subjects) compared with those with a larger sample size. The effect estimate was also higher in studies with young participants (mean age, <10 years) compared with those with an older study population, in non-European compared with European populations, and in English-speaking populations compared with other populations. Nine more recently published studies had greater effect estimates compared with those of the earlier 10 studies published in 1990-2000. In

general, there was substantial heterogeneity remaining after stratification, which indicates that each of the examined characteristics explained only a fraction of the total heterogeneity between the study-specific estimates.

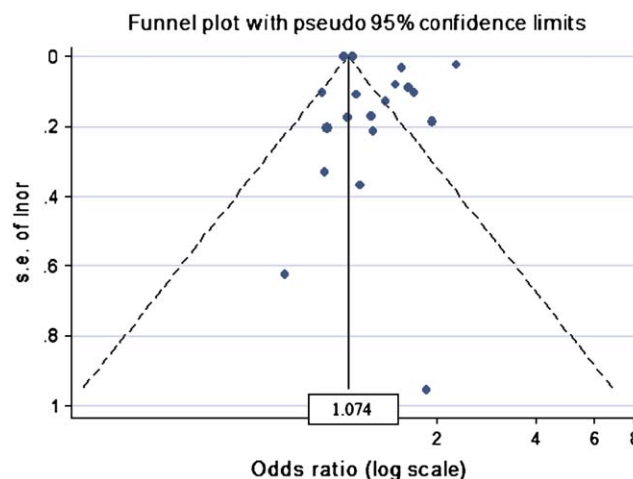
Finally, we fitted metaregression models to assess potential determinants of heterogeneity, adjusting for each other (Table III). In the bivariate analyses outcome definition, mean age, and study design were significant determinants of the effect estimate (ln OR). In multivariate metaregression analysis with all the studied determinants in the model, the effect of mean age remained unchanged, showing a decreasing effect of preterm delivery on the risk of asthma with increasing age of the study population. The effects of both outcome definition and study design reduced, and their effect on ln OR could be explained by chance alone.

Publication bias

We assessed the potential for publication bias by using a funnel plot, as shown in Fig 1. The vertical line indicates the summary effect estimate from the fixed-effects model (1.074) and the corresponding pseudo 95% confidence limits converging as a function of the SE of the effect estimate. The smaller studies with large SEs of ln OR seem to be scattered symmetrically around the summary effect estimate, whereas the funnel plot shows substantial heterogeneity among the large studies with small SEs, with an imbalance toward large positive effect estimates. The pattern differs from a typical publication bias, in which the

TABLE III. Metaregression analysis of the determinants of the heterogeneity between study-specific effect estimates

Determinant	Bivariate analyses			Multivariate model		
	Regression coefficient	95% CI	P value	Regression coefficient	95% CI	P value
Mean age of the study population (y)	-0.0208	-0.0448 ~ 0.0032	.089	-0.0207	-0.0364 ~ -0.0051	.009
Outcome definition (physician diagnosed = 1; other = 0)	-0.5124	-0.6056 ~ -0.4192	.000	-0.137	-0.4010 ~ 0.1267	.308
Study design (cross-sectional = 1; cohort = 0)	0.1478	0.0408 ~ 0.2548	.007	0.1133	-0.1434 ~ 0.3701	.387
Size of study population (per 1000)	-0.0012	-0.0036 ~ -0.0011	.305	-0.0008	-0.0028 ~ 0.0011	.405
Geographic location (other = 1; Europe = 0)	-0.0167	-0.4936 ~ 0.4602	.945	0.0863	-0.2493 ~ 0.4219	.614
Language (English = 1; other = 0)	-0.0471	-0.4829 ~ 0.3886	.832	-0.2535	-0.5658 ~ 0.0588	.112
Time from the first article (y; 1990 = 0)	0.0090	-0.0399 ~ 0.0580	.718	0.0084	-0.0211 ~ 0.0380	.577
Constant	—	—	—	0.6011	—	—

**FIG 1.** Funnel plot of the effect estimates (ln OR) by their SEs (*s.e. of ln OR*). The vertical line indicates the summary effect estimate (1.074) from the fixed-effects model according to the SE, and the dashed lines show pseudo 95% confidence limits for the summary effect estimate.

effect estimates from small studies would be biased toward large positive values. In meta-regression the association between the effect estimates (ln OR) and their variance (*se* [ln OR]) was negative, as indicated by the plot, but this was statistically nonsignificant (ln OR = 0.3437 - 0.5682 *se* [ln OR], *P* = .339).

DISCUSSION

This systematic review and meta-analysis based on 19 epidemiologic studies fulfilling *a priori* inclusion criteria indicates that children born prematurely have an approximately 7% higher risk of asthma compared with term children. The magnitude of the study-specific estimates varied substantially. Taking into account this heterogeneity, preterm babies could have, on average, a 36% higher risk of asthma than term babies.

In stratified analyses the effect of preterm delivery on asthma was stronger in cross-sectional studies; studies with broad outcome criteria, a small sample size, and a younger study population; and studies conducted in English-speaking populations, outside Europe, and published more recently. In meta-regression, adjusting for other determinants, the effect estimate was significantly associated only with the mean age of the study population. The effect of preterm delivery on the risk of asthma seems to be strongest in young age and decreases later in life.

Validity of results

The selection of studies was based on a clearly defined search strategy. In addition to the primary MEDLINE search, we used secondary references that were cited by the articles identified in the primary search. Many of the secondary references investigated the relation between preterm delivery and asthma as a secondary objective or

reported relevant figures as part of describing the effect of covariates for other relations.

Four observers checked independently the eligibility of the studies according to *a priori* set inclusion and exclusion criteria and decided on the most appropriate effect or prevalence estimate. Any disagreements were settled by discussion. Incompatibility of the determinant or outcome criteria with our preset criteria were the main reasons for exclusion. We used the World Health Organization criterion⁴ for prematurity, which is based on gestational age of less than 37 weeks. Only 5 studies provided effect estimates based identically on this definition, but we were able to use data of 8 more studies by converting their results to comply with our criterion for prematurity. The remaining studies used a slightly different cut point or did not indicate the cut point clearly.

The weight of evidence showed that preterm delivery is a significant determinant of asthma, but there was substantial heterogeneity between the study-specific estimates. We elaborated the reasons for this heterogeneity both in stratified analyses and in metaregression, which takes into account several potential determinants of heterogeneity, adjusting for each other. In the stratified analyses the cross-sectional studies provided a substantially greater effect estimate (1.543) than cohort studies (1.073). This could be explained by information bias related to recall of prematurity, which is likely to be more dominant in cross-sectional studies assessing preterm delivery, usually after the onset of asthma. The summary effect estimate of cross-sectional studies was also more homogeneous than that of cohort studies, which could be related to publication bias; that is, it might be more difficult to publish negative findings from cross-sectional than from cohort studies. The summary effect estimates from the random-effects model were more similar between cross-sectional (1.518) and longitudinal studies (1.316). However, it should be noted that the summary effect estimates were statistically significant for both cross-sectional and longitudinal studies, independently from the chosen model. Moreover, in metaregression the study design was not a significant determinant of heterogeneity after adjustment was made for other determinants.

Studies using a physician's diagnosis as the outcome criterion showed a lower summary effect estimate than studies with broad outcome criteria. This difference disappeared in the metaregression analysis, adjusting for other factors.

The summary effect estimate appeared to be less heterogeneous for smaller studies compared with larger studies. The funnel plot revealed no typical pattern of publication bias, and both small and large studies provided statistically significantly increased effect estimates.

The magnitude of the summary effect estimates was greater in studies with a younger compared with an older study population (Table II). The mean age of the study population was also a statistically significant determinant of heterogeneity in the metaregression, as shown in Table III. This could mean that prematurity has a stronger role in early-onset asthma and that its importance diminishes with increasing age. But this finding would also be compatible

with an explanation that the same environmental exposures that increase the risk of preterm delivery increase the risk of asthma in early childhood, whereas they have less importance in older age.

The summary effect estimate was greater in studies conducted among non-European and English-speaking populations. Whether this reflects some true differences in environmental conditions of pregnant women and young children or is merely a reflection of publication bias remains an open question. It is also possible that the diagnostic procedures for asthma differ between European countries and English-speaking countries outside Europe.

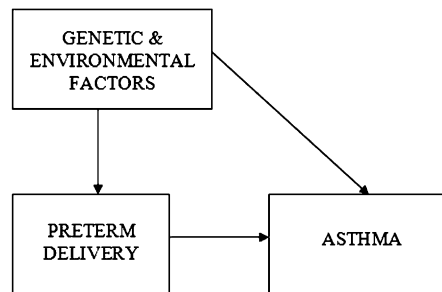
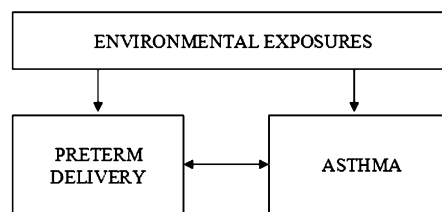
The magnitude of effect estimate was greater in more recent studies published in 2001–2005 than in the older studies published in 1990–2000. Again, this could be related to a publication bias because it might have been easier to publish negative studies early on when the study question was brand new.

The interpretation of meta-analysis is more challenging when the study-specific effect estimates differ substantially from each other, especially if there are estimates both below and above unity. The fixed-effects model is based on an assumption that there is theoretically one true estimate. The random-effects model assumes heterogeneity in the true effect estimates between different populations and takes between-study variation into account. The random-effects model has become a standard approach to incorporate heterogeneity. Poole and Greenland³⁰ have criticized this practice by pointing out that if study-specific results are too heterogeneous, the reasons for heterogeneity should be elaborated instead of aggregating the results. We elaborated the heterogeneity between the study-specific effect estimates but systematically present summary estimates from both fixed- and random-effects models to offer the readers a possibility to form their own informed judgment.

The effect estimates from random-effects models were usually greater than those from fixed-effects models. This could technically be explained by a tendency of the fixed-effects model to give more weight to large studies compared with the random-effects model. In the present meta-analysis the larger studies had smaller effect estimates. In particular, the 2 largest studies, by Bråbäck and Hedberg¹⁶ ($n = 149,398$) and Dik et al²⁷ ($n = 170,960$), had rather small effect estimates (OR, 1.042 and 1.027, respectively).

Causal pathways/models explaining the association between preterm delivery and asthma

Different causal pathways could explain the observed association between preterm delivery and the development of asthma, as presented in the 3 simplified models in Fig 2. There is some evidence in the current literature supporting each of the 3 models. First, preterm delivery *per se* might increase the risk of asthma through the mechanism that the lungs of a preterm infant are not fully developed anatomically or immunologically, and this immaturity might make the child more susceptible to later exposures capable of causing asthma. This would make direct

Model 1**Model 2****Model 3****FIG 2.** Models for potential causal pathways between preterm delivery and asthma.

genetic and environmental determinants of preterm delivery indirect determinants of asthma (Model 1). There is recent evidence that prenatal exposure to tobacco smoke products caused by maternal smoking increases the risk of asthma later in life independently from postnatal exposure to environmental tobacco smoke.^{25,31-35} Part of this effect could be through reduced gestational age. Second, preterm delivery and asthma might have common genetic determinants (Model 2). For example, there is some evidence that the duration of pregnancy is shorter among women with asthma,³⁶ and on the other hand, maternal asthma is shown to be a strong determinant of the child's asthma.³⁷⁻³⁹ Thus maternal genetic constitution is likely to be partially responsible for the studied association. In addition to common genetic determinants, some environmental exposures during pregnancy might increase both the risk of preterm delivery and of such fetal development of the respiratory and immunologic systems that favors susceptibility of the child to asthma (Model 2). For example, there is evidence that both maternal smoking^{25,40} and exposure to environmental tobacco smoke during pregnancy^{41,42} increase the risk of preterm delivery. There is also some evidence that these exposures during pregnancy are sufficient to increase the child's risk of asthma independently from postnatal exposure (Model 2).^{33,34} This type of mechanism might not be limited to just sharing the environmental exposures that increase the risk of both preterm delivery and asthma, but it is also possible that preterm delivery modifies the relations between environmental exposures and the development of asthma. For

example, the effect of maternal smoking during pregnancy on development of the child's asthma might be stronger in preterm infants because of the immaturity of their respiratory system at the time of birth. Third, some of the prenatal exposures might be closely related to postnatal exposures, in which case the same exposure could induce preterm delivery during pregnancy and asthma postnatally (Model 3). Thus the association between preterm delivery and asthma would be due to an association between prenatal and postnatal exposures rather than mechanistic changes in pregnancy leading to development of asthma. An example of this is again the child's exposure to environmental tobacco smoke during pregnancy and then in early or later childhood. As stated, environmental tobacco smoke is a known determinant of preterm delivery, and there is also strong evidence on the relation between postnatal exposure to environmental tobacco smoke and the risk of asthma.⁴³

When trying to disentangle which of the suggested pathways is responsible for the observed relation between preterm delivery and increased risk of asthma or whether all of them play a role, we face the problem that most of the studies have had an interest in looking at risk factors for preterm delivery and risk factors for asthma without making an attempt to deduce the underlying mechanisms. As presented above, there are some empiric data supporting the role of each of the pathways. Indeed, the heterogeneity observed between the results from different studies could be explained by different mechanisms operating in different populations and settings.

From the clinical and preventive point of view, the recognition of prematurity as a determinant of asthma has at least 2 important implications. First, this association indicates that any physiologic airflow obstruction in preterm babies should be treated actively because it might be a sign of development of a more chronic type of asthma. Second, if the same environmental exposures are responsible for this association, prematurely born children should get special attention with respect to preventive measures against known or suspected environmental and nutritional determinants of asthma.

Concluding remarks

The weight of evidence shows that preterm delivery increases significantly the child's risk of asthma. The mechanisms underlying this association are not well understood, and several pathways might be of importance. The effect of preterm delivery on the risk of asthma seems to be strongest in young age and decreases later in life.

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