A meta-analysis of adverse perinatal outcomes in women with asthma

Running Title:

Adverse perinatal outcomes in women with asthma

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Abstract

Objective: This meta-analysis sought to establish if maternal asthma is associated with an increased risk of adverse perinatal outcomes and to determine the size of these effects.

Search Strategy: Electronic databases were searched for the following terms: (asthma or wheeze) and (pregnan* or perinat* or obstet*).

Selection Criteria: Cohort studies published between 1975 and March 2009 were considered for inclusion. Studies were included if they reported at least one perinatal outcome in pregnant women with and without asthma.

Data Collection and Analysis: 103 articles were identified, and 40 publications involving 1,637,180 subjects were included. Meta-analysis was conducted with subgroup analyses by study design and active asthma management.

Main Results: Maternal asthma was associated with an increased risk of low birth weight (relative risk[RR]1.46, 95% confidence interval[CI]1.22,1.75), small for gestational age (RR 1.22, CI 1.14,1.31), preterm delivery (RR 1.41, CI 1.22,1.61) and pre-eclampsia (RR 1.54, CI 1.32,1.81) The relative risk of preterm delivery and preterm labor were reduced to non-significant levels by active asthma management (RR 1.07, CI 0.91, 1.26 for preterm delivery and RR 0.96, CI 0.73, 1.26 for preterm labor).

Conclusions: Pregnant women with asthma are at increased risk of perinatal complications including pre-eclampsia and outcomes which affect the baby's size and timing of birth. Active asthma management with a view to reducing the exacerbation rate may be clinically useful in reducing the risk of perinatal complications, particularly preterm delivery.

Key Words: Meta-analysis, Asthma, Pregnancy, Perinatal Outcomes

Introduction

Asthma is the most common chronic medical condition to affect pregnancy, with a prevalence of between 8 and 13% worldwide [1-3]. It has been suggested that asthma may have an effect on pregnancy outcomes, and also that pregnancy may affect the course of asthma [4]. Since 1970, there have been reports that maternal asthma is associated with an increased risk of perinatal complications [5], but the published data have been conflicting, with studies varying substantially in terms of design and sample size. In general, larger database studies have reported increased risks [6-12], while smaller clinical prospective cohort studies have not found significantly increased risks [13-19]. There are two primary explanations for this discrepancy. The first is that the smaller studies individually lack sufficient power to detect the increased risks. The second is that these smaller, prospective, clinical studies are associated with better asthma management and disease control, which mitigates the increased risk. Indeed, several studies have reported a relationship between increased asthma severity or decreased asthma control and increased perinatal complications [18, 20-28].

To address these issues we have undertaken a systematic review of the literature and performed meta-analyses of cohort studies to investigate whether maternal asthma is associated with an increased risk of perinatal complications related to size at birth, timing of birth, and maternal pre-eclampsia in cohort studies.

Sources

Systematic review of the literature – Search strategy

A review protocol was established by the investigators prior to commencement. English language studies published between 1975 (when inhaled corticosteroids were introduced) and March 2009 were identified for possible inclusion from Medline (n=1642), Embase (n=1755), CINAHL (n=417), and the Cochrane Clinical Trials Register (n=75), using the search terms ((asthma or wheeze) and (pregnan* or perinat* or obstet*)). All identified abstracts were independently

assessed by two reviewers. The full text version of each potential article was obtained for assessment by two independent reviewers to establish whether it met the inclusion criteria. Hand searching and reference checking of articles was not conducted and it was considered unfeasible to search non-English language publications.

Inclusion criteria

Articles were included if they contained data from a group of pregnant women with asthma and a control group of pregnant women without asthma, reported at least one perinatal outcome of interest, and were cohort studies (either prospective or retrospective in design). Asthma was defined as physician diagnosed asthma (whether confirmed or subject self-report), or an asthma diagnosis as coded in a database, or asthma fulfilling American Thoracic Society criteria. In this paper, we report our evaluation of perinatal outcomes related to size at birth (low birth weight, mean birth weight, small for gestational age [SGA], high birth weight), timing of birth (preterm delivery, preterm labor) and pre-eclampsia.

Study Selection

Description of studies

103 papers were identified for possible inclusion in the review. 63 publications were excluded for the following reasons: no control group (n=27), no clear asthma group (n=5), asthma subjects selected by exacerbation only (n=3), study published after 1975 but conducted prior to 1975 (n=2), cross-sectional survey (n=3), abstract only (n=3), asthma subgroups only compared to control group (n=8), no perinatal outcomes reported (n=3), review article (n=1) and case control study design (n=8). Of the 40 remaining publications which met the inclusion criteria, 33 papers describing 11 prospective and 15 retrospective cohort studies were included in analyses reported in this paper as they contained data on size at birth and timing of birth outcomes, and maternal pre-eclampsia (Table 1).

Data Extraction

Data was extracted using a standardised form by one reviewer and checked by a second reviewer. Any discrepancies were discussed by the investigators in order to reach a consensus. Study authors were contacted to clarify an outcome definition where necessary. Data were extracted for: study design, study characteristics (including year, country of study), subject characteristics (including gestational age at recruitment, subject exclusions, maternal age, body mass index, age, smoking, socioeconomic status, prenatal care, race/ethnicity, co-morbidities), asthma diagnosis, severity, management, and perinatal outcome data for asthma and control groups (mostly as n [%], mean [SD] or adjusted odds ratios). Active asthma management was indicated when the study investigators were involved in the management and treatment of subjects with asthma (Table 1). Perinatal outome data from each study was entered into a database for electronic extraction prior to analysis.

Study quality was assessed independently and scored by two reviewers using the Newcastle-Ottawa Scale (NOS) [29]. The NOS is a validated tool for assessing the quality of non-randomized studies including cohort and case-control studies and has a maximum score of 9. Quality scores of the 40 studies ranged from 4-9 (mean 7.7, Table 1) with most studies (76%) having a score of 8 or 9. All were considered of adequate quality for inclusion in analyses.

Included Studies

Schatz et al. published overlapping data in 1988 and 1995 [14, 30]. Only the most recent data, which covered the longest time period (1978-1989) and included the most definitively matched subjects was included [14]. Stenius-Aarniala et al. published two papers with the same total number of subjects in 1995 and 1996 [20, 31] and outcome data was included from the original publication only [31]. Data

from Mirhshahi et al [16] was not included in the analysis of low birth weight as recruitment after 36 weeks gestation could bias results by an underestimate of the effect size.

Meta-Analysis

While there are potential challenges inherent in conducting a meta-analysis of observational studies related to biases and diversity in the original studies, performing such analyses is an accepted technique with well-described guidelines [32], which we have followed in this report. The relative risk of the perinatal outcome was examined in women with asthma compared to women without asthma using Review Manager software (Version 4.2.7, Wintertree Software Inc, Ontario, Canada). For dichotomous outcomes the relative risk with 95% confidence interval was calculated using a random effects model. The difference between relative risks for the active management and no active management subgroups was determined using the method of Altman and Bland [33] and expressed as a relative risk ratio (RRR) with 95% confidence intervals. Where original data had been adjusted for potential confounders (Table 1), adjusted odds ratios were pooled using the generic inverse variance method. For continuous outcomes, the weighted mean difference was calculated, with 95% confidence interval. Heterogeneity was examined using the Chi-squared test ($P<0.1$ considered significant heterogeneity), the I-square parameter and meta-regression. When outcomes were reported in at least 10 studies, Funnel plots and the Egger test were used to investigate study size effects, indicative of possible publication bias (Stata 7). Power calculations were conducted using the PS Power and Sample size Program (version 2.1.30) [34]. In reporting results of the meta-analysis we followed recommendations from the recent PRISMA consensus statement [35].

Meta-Regression

For meta-analyses with more than 10 studies, meta-regression was performed using Stata 7 (Stata Corporation, College Station, TX). Simple and multiple meta-regression was conducted for possible

explanatory differences among the studies where possible. Potential explanatory variables were control event rate, study design (retrospective/prospective), continent of study, decade conducted and participant characteristics (proportion experiencing an exacerbation, proportion using ICS, difference between asthma and control groups for current smokers and maternal age).

Results

Low birth weight

Data on low birth weight (defined as birth weight <2500g [6, 11, 13, 14, 16, 21, 22, 30, 36-39] or ≤2500g [40]) was reported in 13 publications involving 1,109,907 subjects. The presence of asthma was associated with a significantly increased risk for low birth weight when compared to women without asthma (Figure 1, RR 1.46, 95% confidence interval [CI] 1.22, 1.75). The mean birth weight of infants of mothers with asthma was 93 g lower (95% CI -160, -25 g)[17, 22, 36, 38, 41-44] than that of infants of control mothers. The funnel plot indicated no significant publication bias (P=0.336), however there was significant heterogeneity between studies (I^2 = 87.7%, P<0.1) that was not improved by removing the three smaller studies [21, 38, 39] (also the studies of lowest quality) nor was it explained by variables included in univariate and multivariate meta-regression analyses (Table 2). However, sub-group analyses of prospective and retrospective studies were suggestive of study design as a possible source of the heterogeneity, since there was no effect of asthma on low birth weight in the prospective sub-group (n=3, RR 1.07, 95% CI 0.76, 1.49, I^2 = 4%, P>0.1), while only the retrospective sub-group was significant (n=8, RR 1.54, 95% CI 1.26, 1.87, I^2=90.9%, P<0.1), although significant heterogeneity remained in this sub-group.

Sub-group analysis of 3 studies where subjects had active management of their asthma by the study investigators or local hospital [14, 22, 38] and 8 studies where no active management of asthma was given [6, 11, 13, 21, 36, 37, 39, 40], demonstrated similar effect sizes (active management: RR 1.55, 95% CI 0.69, 3.46, no active management: RR 1.50, 95% CI 1.23, 1.82, ratio of relative risk (RRR) 1.03,

95% CI 0.45, 2.37, P=0.938) [33]), although only the no active management sub-group remained significant.

Small for gestational age (SGA)

Infants born SGA were defined as <10th percentile for gestational age, based on normal data from the population [2, 14, 18, 21, 25, 30, 37, 40, 45], or by a fetal growth ratio <0.85 (birth weight divided by the mean birth weight of the study population) [6, 10, 44]. There was a significantly increased risk of SGA with maternal asthma (Figure 2, <10th centile: RR 1.23, 95% CI 1.11, 1.37, fetal growth ratio <0.85: RR 1.20, 95% CI 1.12, 1.27). If all studies were combined regardless of the SGA definition, the overall result was an increased risk of SGA with maternal asthma (RR 1.22, 95% CI 1.14, 1.31). Publication bias was not present (p=0.604). Although heterogeneity was moderate, this was likely due to the very large sample size of some of the studies (significant heterogeneity was not found among the smaller studies with <2000 asthma subjects, but remained among larger studies with >2000 asthma subjects, data not shown). Results obtained from retrospective and prospective study sub-groups were similar (<10th centile, RR 1.24, 95% CI 1.07, 1.42 for retrospective and RR 1.21, 95% CI 1.00, 1.46 for prospective), and when adjusted for confounders, analysis of 2 studies [6, 10] showed a similar effect size of asthma on SGA (fetal growth ratio <0.85, OR 1.21, 95% CI 1.10, 1.34). Analysis of data from 3 studies on high birth weight (>4 kg) [6, 16, 46] was supportive of the effect of maternal asthma on fetal growth (RR 0.84, 95% CI 0.74, 0.96, no heterogeneity).

Preterm Delivery

Preterm delivery (birth prior to 37 completed weeks gestation) was reported in 18 publications including 988,252 subjects [6, 10, 13, 14, 18, 20-22, 25, 30, 31, 36-40, 45, 46]. Maternal asthma was associated with a significant increased risk of preterm delivery (Figure 3, RR 1.41, 95% CI 1.23, 1.62). There was significant heterogeneity between studies (I^2 = 85.4%, P<0.1), driven mainly by differences between the retrospective studies . The seven prospective cohort studies showed a significant effect

(RR 1.15, 95% CI 1.01, 1.32) without heterogeneity (I^2 = 0%). Multiple meta-regression (Table 2) indicated that the location of the study (Scandinavia [37]), also explained some of the variance (P=0.013). The funnel plot was not significant (P=0.224). Further adjustment for covariates in four studies [6, 10, 13, 25] similarly confirmed the effect of asthma on preterm delivery (OR 1.38, 95% CI 1.24, 1.53, heterogeneity P=0.97, I^2=0%).

There were 5 studies where subjects' asthma was actively managed [14, 18, 22, 31, 38] and 10 studies where no active asthma management was described [6, 10, 13, 21, 25, 36, 37, 39, 40, 45]. There was a significant effect of maternal asthma on preterm labor in the no active management sub-category (Figure 4, RR 1.50, 95% CI 1.28, 1.75, heterogeneity P<0.1, I^2=89.6%,), but not in the active management sub-category (RR 1.07, 95% CI 0.91, 1.26, heterogeneity not significant). The active management studies had 100% power to detect a RR of 1.50, as observed in the no active management studies. The difference between the relative risks of the no active management and active management sub-groups was also significant (ratio of relative risk (RRR) 0.71, 95% CI 0.57, 0.89, P=0.003) [33].

Maternal asthma was also associated with a significantly increased risk of preterm labor (premature uterine contractions prior to 37 completed weeks gestation) [6, 9, 10, 13, 14, 20-22, 36, 44] (RR 1.71, 95% CI 1.14, 2.57, p=0.009). This pooled estimate showed significant heterogeneity (I^2 = 98.2%, P<0.1) that was partly explained by study design, and age differences among subjects (meta-regression, data not shown). In particular, the retrospective sub-group of studies showed a significant effect on preterm labor (RR 2.18, 95% CI 1.30, 3.66 with heterogeneity), while analysis of the prospective sub-group was not significant (RR 1.08, 95% CI 0.77, 1.51, no heterogeneity). There was no significant publication bias in the studies reporting preterm labor (p=0.967).

Sub-group analysis by active asthma management demonstrated a significant effect of asthma on preterm labor (RR 2.19, 95% CI 1.35, 3.57, heterogeneity 98.7%, P<0.1), but not in the active

management sub-category (RR 0.96, 95% CI 0.73, 1.26, heterogeneity not significant). This sub-category was adequately powered to detect a RR of 2.19 (100% power) as observed in the no active management sub-category. The difference between the relative risks of the no active management and active management sub-groups was significant (ratio of relative risk (RRR) 0.44, 95% CI 0.25, 0.77, P=0.004) [33].

Pre-eclampsia

Data on pre-eclampsia (defined as elevated blood pressure of either >140 mm Hg systolic, or > 90 mm Hg diastolic, which was accompanied by proteinuria) was analysed from 15 cohort studies [6, 9, 10, 14, 18, 19, 21, 26, 31, 36, 41-43, 47, 48]. Two studies excluded cases of pre-existing hypertension [26, 47], and one study specifically stated that subjects with chronic hypertension were included [14]. The remaining studies used ICD9 codes or textual descriptions to define pre-eclampsia. There was a significantly increased risk of pre-eclampsia among mothers with asthma (RR 1.54, 95% CI 1.32, 1.81) compared to mothers without asthma (Figure 5), although there was heterogeneity (I^2=80.3%). Meta-regression analysis did not reveal the source of the heterogeneity (P>0.05, Table 2) and additional sub-group analysis by study design did not explain the heterogeneity (data not shown). Publication bias was not significant (P=0.328). Adjustment for various covariates in six studies [6, 9, 10, 19, 26, 36] confirmed the effect of asthma on pre-eclampsia, as the adjusted odds of pre-eclampsia remained significantly increased in women with asthma compared to women without asthma (OR 1.57, 95% CI 1.24, 1.98, p=0.0002).

Sub-group analysis by active asthma management demonstrated that both sub-categories showed significant effects of maternal asthma on pre-eclampsia (6 studies with active management: RR 1.70, 95% CI 1.11, 2.59) and 9 studies with no active management: RR 1.54, 95% CI 1.28, 1.85). The difference between the relative risks of the no active management and active management sub-groups was not significant (ratio of relative risk (RRR) 1.10, 95% CI 0.70, 1.75, P=0.675) [33].

Discussion

Asthma is a common chronic disease among pregnant women, and the extent of the risks for both the mother and baby during the perinatal period make this a significant health issue. This meta-analysis indicates that pregnant women with asthma are at a significantly increased risk of a range of adverse perinatal outcomes including low birth weight, SGA, preterm labour and delivery and pre-eclampsia. These observations are derived from a substantial body of literature spanning several decades and including very large numbers of pregnant women, (over 1,000,000 for low birth weight and over 250,000 for preterm labor) suggesting these results are robust across many settings. Since the majority of women with asthma have asthma of mild severity, the size of these risks may be greater in sub-groups of asthmatic women, such as those with severe or uncontrolled asthma, or those experiencing exacerbations during pregnancy [49].

Maternal asthma reduces fetal growth, with data from our meta-analyses consistently indicating an increased risk of low birth weight and SGA and a significant reduction in mean birth weight among women with asthma. Significant heterogeneity in the retrospective studies may have been due to differences in ethnicity between study populations since the studies from Asia [38] and the Middle East [39] reported the highest risks of low birth weight among women with asthma. The effect of asthma itself on low birth weight is not as large as that previously described in a smaller meta-analysis for the risk of low birth weight among asthmatic women with severe exacerbations (RR 2.54, 95% CI 1.52, 4.25) [49], suggesting that a sub-group of women with exacerbations of asthma may contribute to this overall risk. Other work has suggested that the use of ICS during pregnancy may protect against low birth weight [24]. Further analyses and meta-analyses of sub-groups of asthmatic women, perhaps at an individual patient data level, stratified by treatment and disease control are needed to directly verify these findings.

Maternal asthma significantly increases the risk of both preterm labor and delivery prior to 37 weeks. The pooled analysis was confirmed by a smaller analysis of four studies which adjusted their results for important confounding factors such as maternal age, education, race and co-morbid conditions such as diabetes and hypertension. Several large cohort studies have also shown a significant effect of maternal asthma on preterm delivery which may be related to oral steroid use [18, 25]. Dombrowski et al. found that only the sub-group of women with severe asthma (FEV_1 <60% predicted and/or used oral steroids in the 4 weeks prior to study enrolment) had a significantly increased risk of preterm delivery compared to non-asthmatic women (adjusted OR 2.2, 95% CI 1.2, 4.2) [18]. Schatz et al. found a significant relationship between lower lung function and premature birth, consistent with the concept that more severe asthma is a risk factor [50]. Importantly, our results demonstrated that the risk of preterm labor and delivery is greatly reduced to a non-significant level, when active asthma management was provided to women, suggesting a beneficial effect of active asthma management. This is plausible, given that one of the assumed benefits of active management would be a reduction in the number of exacerbations, or courses of oral steroids used, both of which have been implicated as contributing to the risk of preterm delivery [25, 51].

Maternal asthma significantly increases the risk of pre-eclampsia, by at least 50%, and this finding was supported by an analysis of 6 studies where data were adjusted for possible confounders. Data from case control studies also support a relationship between pre-eclampsia and asthma, where women were symptomatic during pregnancy [27] or had admissions or emergency department visits for asthma prior to pregnancy [52, 53]. A recent cohort study found a significant association between hypertension during pregnancy and lower FEV_1 after adjustment for covariates [50] suggesting that the underlying severity of asthma may be important.

It is possible that asthma itself is not causing the increased risk of these perinatal outcomes, and rather that the risks described are associations due to confounding factors such as socioeconomic

status. All studies had a control group of women drawn from the same population which makes this possibility unlikely, and where possible, we investigated studies which presented odds ratios adjusted for important confounders and these were supportive of the unadjusted analyses. If the association between maternal asthma and poor perinatal outcome is indeed real, there are three main explanations could account for the increased risk. Firstly, uncontrolled asthma during pregnancy may lead to adverse outcomes, as a result of chronic maternal hypoxia. Maternal hypoxia could influence fetal oxygenation [54] with consequences for fetal growth via alterations of placental function [55-61]. A specific mechanism has been proposed for the effect of maternal asthma on reduced fetal growth, with a reduction in placental 11beta-hydroxysteroid dehydrogenase enzyme activity (resulting in higher cortisol transfer to the fetus) in women who did not use inhaled steroids associated with reduced birth weight [58, 68]. The findings of Schatz et al. [50] indicate that reduced lung function may be a marker of poor control of asthma, which could influence outcomes such as preterm delivery and pre-eclampsia via hypoxic mechanisms. Alternatively, the release of inflammatory mediators from the mother in response to asthma may also be involved [4]. Other inflammatory diseases, when they are active, are also associated with adverse perinatal outcomes such as low birth weight and preterm delivery [62-64]. Secondly, there may be a common pathogenesis of both severe asthma and perinatal complications [50]. A common pathway leading to hyperactivity of the smooth muscle in both the bronchioles and the myometrium has been proposed to explain the increased incidence of preterm labour in women with asthma [13, 65, 66]; a common pathway of mast cell infiltration has been proposed to explain the connection between asthma and pre-eclampsia [67]. Finally, asthma medications may have a direct adverse effect on the mother or fetus during pregnancy. However, the preponderance of the evidence to date suggests that commonly used asthma medications, such as ICS and inhaled short-acting beta agonists, do not increase perinatal risk, and that ICS treatment may actually be protective against outcomes such as low birth weight [4]. Further meta-analyses of perinatal outcomes in sub-groups of women with asthma using particular

medications (theophylline, short acting β_2-agonists, ICS and oral steroids in particular) will be useful in further examining this possibility.

While meta-analyses of observational studies in epidemiology (MOOSE) is well described and accepted [32], consideration should be given to the observational nature of the cohort studies used in this review and the influence of potential confounders, the extent of heterogeneity between studies and the possibility of publication bias for some outcomes. However, for several outcomes, including SGA, preterm labor and delivery and pre-eclampsia, we investigated adjusted data where possible and found similar results. In addition we investigated confounders as contributors to the heterogeneity between studies using meta-regression and in almost all cases there was no change in effect size making it less likely that confounding explains the observations in the current meta-analysis. It is likely that the heterogeneity is overstated in our meta-analysis compared to traditional meta-analyses due to the very large sample sizes of some of the retrospective cohort studies. We have also investigated the consistency between retrospective and prospective studies, and where there is similarity between these, the analyses are less likely to be influenced by bias or confounding. The risk of publication bias appears small since none of the formal tests for publication bias reached significance, making it unlikely that the pooled estimates are inflated. This review has provided the most comprehensive analysis to date of the risks of poor perinatal outcomes in women with asthma and shows a consistently moderate effect of asthma on these outcomes.

These results have implications for the antenatal care of these women. Some of the reported complications may be minimised by effective asthma management strategies; in particular preterm labor and delivery. Exacerbations are key events which may contribute to poor perinatal outcomes [49] and are common in pregnancy, being related to asthma severity, viral infection, poor adherence, and other risk factors such as obesity [28, 68]. Active asthma management has the potential to reduce

the number and severity of exacerbations in pregnancy, but further improvements in this area are needed. Since changes in asthma course during pregnancy can be unpredictable and not always consistent between pregnancies for the same woman [69], it is recommended that women have their asthma monitored at least monthly during pregnancy [70]. Further studies should define optimal management strategies to improve asthma control during pregnancy and prevent exacerbations, with the aim of reducing perinatal complications. In the meantime, despite some heterogeneity, the increased risks demonstrated in these analyses of pregnancies of asthmatic women, suggest that careful medical and obstetric monitoring of the asthmatic mother and her developing baby are warranted.

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Contribution to Authorship

Vanessa Murphy: conception, study search & identification, inclusion/exclusion, data extraction, quality assessment, interpretation and writing.

Jennifer Namazy: study search & identification, inclusion/exclusion, data extraction, quality assessment and interpretation

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Michael Schatz: conception, interpretation, writing and editing.

Christina Chambers: interpretation and editing

John Attia: statistical advice and editing

Peter Gibson: study design and conception, interpretation, writing and editing

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Table 1: Details of Included Studies. R=Retrospective; P=Prospective

Study	Asthma Participants	Control Participants	Study Design	Data Source	Asthma Diagnosis	Active Asthma Management	Study Year	Study Country	Adjusted Data	Excluded	Quality Score
Acs[36]	N=757	N=37394	R	Database	Self report	No	1980-1996	Hungary	Maternal age, birth order, employment status, anti-asthmatic drugs, pregnancy supplements	Mild congenital abnormalities, chromosome syndrome, non-Hungarian citizens	9
Bakhireva[45]	N=654	N=303	P	Interview, medical records	Dr diagnosis	No	1998-2003	USA/ Canada			6
Bracken[25 71],	N=873, 778 with active treatment	N=1333, 449 had symptoms or med use during pregnancy.	P	Interview	Self report	No	1997-2000	USA	Maternal age, gravidity, marital status, race, education, pre pregnancy	Still born, molar pregnancy, abortion, multiple birth, loss to follow-	9
Triche[26]	N=656,						1997-2004				

	568 had asthma symptoms or took meds during pregnancy	N=1052, 353 had asthma symptoms during pregnancy							weight, height, smoking, caffeine consumption, parity, prenatal vitamin use	up, inadequate information on asthma #23: preexisting hypertension, non English speaking, insulin dependent diabetes	
Breton[40]	N=13100, 23% > 1 pregnancy)	N=28042, 33% random sample, 23% > 1pregnancy	R	Database	Database code	No	1990-2002	Canada	Pregnancy induced hypertension, gestational diabetes, placental abruption, infection amniotic cavity		8
Clark[2]	N=718	N=718	R	Database	Self report	No	2001-2003	UK		Excluded diabetes, ITTN,	9

										renal disease, epilepsy, preterm delivery, twins, preeclampsia	
Demissie[6], Demissie[7]	N=2289	N=9156	R	Database -	Database code	No	1989-1992	USA	Maternal age, education, marital status, parity, race, diabetes, preexisting hypertension, smoking, alcohol use		9
Dombrowski[43]	N=121, 153 pregnancies	N=116, Matched by parity	R	Medical Records	Not stated	No	1982-1985				8
Dombrowski[18], Hendler[68]	N=1739, 50% mild, 50% mod/severe	N=881	P	Clinical, Medical records	Self report	Yes Monthly visits including spirometry, data on	1994-1999	USA		Multiple gestation, intrauterine fetal demise, major	9

						symptom frequency, medication use and exacerbations collected				congenital malformation, active pulmonary disease other than asthma, gestational age>26 weeks, inability to attend ultrasound	
Doucette[13]	N=32	N=3859	P	Interview, medical records	Not stated	No	1980-1982	USA	Education, race, vaginal bleeding during pregnancy, smoking during 2nd month of pregnancy, number of pregnancies		8
Enriquez[44]	N=9154, Asthma subjects	N=131145	R	Database	Database code	No	1995-2003	USA		None	9

	more likely to smoke , more comorbities than controls										
Jana [22]	N=182, 182 pregnancies in 158 women, 2 x twins	N=364, Matched for age & parity, delivered within 48hrs of asthma cases, 6 x twins	P	Clinical, case notes	ATS criteria	Yes Referred to specialist clinic - included instruction on continuing asthma meds, exacerbation management and regular assessment by chest physician	1983-1992	Not stated		Emphysema, bronchitis, other lung disease	8
Kallen[48], Kallen[37],	N=24369 N=24750	N=835848 N=849254	R	Database	Self report	No	1995-2004	Sweden	Year of birth, maternal age, parity, smoking,	High BMI, subfertility, non-nordic country of	9

	Multiple pregnancies included	Multiple pregnancies included							years of unwanted childlessness	birth	
Karimi[39]	N=76	N=152	R	Unsure	Not stated	No	Not stated	Iran			4
Lao[38]	N=87	N=87, matched for age & parity	R	Case Notes	Not stated	Yes Asthma subjects closely followed up in antenatal clinic	1984-1987	Hong Kong			8
Littner[17]	N=28, infants only	N=29, infants only	R	Medical Records	Dr diagnosis	No	1998-2001	Israel		Gestational diabetes, Type I Diabetes, abruption placenta, assisted delivery, ETOH/drug/tobacco use, placenta previa, perinatal infections,	6

										abnormal intrapartum monitoring, low apgar scores, perinatal blood loss, meconium, hemolysis, or chromosomal abnormalities	
Liu[10]	N=2193, Likely to represent non severe asthma	N=8772	R	Database	Database code	No	1991-1992 & 1995-1996	Canada	Maternal age, diabetes, preexisting hypertension	Fetal death, birth weight <500gms, <22>45weeks, multiple births	8
Mihrshahi[16]	N=340	N=271, 21 without asthma were using medications	P	Clinical, medical records	Dr diagnosis	No		Australia		Delivery prior to 36 weeks	9
Perlow[21]	N=81	N=130, matched for	R	Database	Dr diagnosis	No	1985-1990	USA		Intermittent asthma	5

		time of delivery – next 2 deliveries after asthma cases							medication use	
Schatz, Schatz [14, 30]	N=486 N=360	N=486 N=295	P	Clinical, medical records	Dr diagnosis, objective lung function	Yes Monthly assessment in the allergy clinic including symptom and medication diaries and treatment adjustment	1978-1989 1978-1984	USA	Total lung capacity <80% predicted, miscarriage<20 wks, multiple gestation, prior matched pregnancy in study	9
Sheiner[11]	N=1963	N=137205	R	Database	Database code	No	1998-2002	Israel	<3 visits antenatal care	9
Sobande[42]	N=88, Acute asthma	N=106	P	Medical records	Dr diagnosis	Yes Hospital admission for asthma –	1997-2000	Saudi Arabia		7

						managed by specialist and treated			
Stenius Aarniala[47]	N=181, 198 pregnancies	N=198, matched for age, parity & time of delivery	P-asthma R-control	Clinical, medical records	ATS criteria	Yes Seen in dept of pulmonary medicine including regular symptom assessment and peak flow monitoring	1978-1982	Finland	7
Stenius-Aarniala[20, 31]	N=504	N=237, matched for age & parity	P-asthma, R-control	Clinical, medical records	ATS criteria	Yes Women referred to pulmonary medicine departments for regular checkups	1982-1992	Finland	8

						during pregnancy. Asthma follow-up and treatment provided by study authors.					
Tamasi[41]	N=48	N=18, similar age & gestational age	P	Clinical	Not stated	Yes Referred to 'Asthma ambulance' including history, asthma medication use and treatment adjustment during the pregnancy.	Not stated	Hungary		Current respiratory tract infection	6
Tata[19]	N=37585, Includes multiple	N=243434, Includes multiple	R	Database	Database code	No	1998-2004	UK	Maternal age, smoking, BMI		9

	pregnancies – similar between groups	pregnancies – similar between groups									
Wen[9]	N=8672	N=34688	R	Database	Database code	No	1989-1990 & 1995-1996	Canada	Maternal age, diabetes, preexisting hypertension, cesarean also adjusted for pregnancy complications		7

Table 2: Results of Meta-Regression Analyses

Outcome	Covariate	No. of studies	exp (b)	P value
Low Birth Weight (univariate analysis)	Control event rate	11	0.01(.03)	0.194
	Retrospective vs Prospective design	11	1.62 (0.86)	0.390
	Country vs USA:	10		
	Europe		0.85 (0.93)	0.889
	Asia/Middle East		2.24 (1.91)	0.378
	Scandinavia		0.64 (0.69)	0.689
	Decade vs 1980s	8		
	1990s		0.86 (0.31)	0.693
	2000s		0.66 (0.33)	0.449
	Proportion with exacerbation	4	1.04 (0.04)	0.356
	Proportion using ICS	5	0.98 (0.03)	0.633
	Smokers (asthma- control)	4	0.74 (1.40)	0.888
	Age (asthma-control)	5	0.01(.03)	0.194
Preterm Delivery (univariate analysis)	Control event rate	15	0.04 (0.08)	0.161
	Retrospective vs Prospective design	15	1.24 (0.20)	0.210
	Country vs USA:	14		

	Europe		1.07 (0.28)	0.801
	Asia/Middle East		3.88 (3.96)	0.214
	Scandinavia		0.77 (0.17)	0.282
	Decade vs 1980s	12		
	1990s		0.84 (0.15)	0.345
	2000s		0.73 (0.30)	0.472
	Proportion with exacerbation	5	0.98 (0.02)	0.372
	Proportion using ICS	8	1.0 (0.004)	0.580
	Smokers (asthma- control)	8	0.99 (0.02)	0.625
	Age (asthma-control)	5	1.64 (0.67)	0.312
Preterm Delivery (multivariate analysis)	Retrospective vs Prospective design	14	1.10 (0.21)	0.625
	Country vs USA:	14		
	Europe		1.02 (0.14)	0.898
	Asia/Middle East		34.16 (4.78)	0.250
	Scandinavia		0.74 (0.04)	**0.001**
Pre-eclampsia (univariate analysis)	Control event rate	15	0.04 (0.11)	0.261
	Retrospective vs Prospective design	15	1.09 (0.20)	0.663
	Country vs USA:	15		
	Europe		0.83 (0.19)	0.440
	Asia/Middle		11.65(17.24)	0.125

	East			
	Scandinavia		1.10 (0.25)	0.670
	Decade vs 1980s	14		
	1990s		0.92 (0.18)	0.673
	2000s		0.69 (0.21)	0.243
	Proportion with exacerbation	5	1.02 (0.01)	0.232
	Proportion using ICS	7	1.00 (0.005)	0.538
	Smokers (asthma- control)	9	0.98 (0.03)	0.407
	Age (asthma-control)	9	1.31 (0.18)	0.093

Figure Legends

Figure 1

Meta-analysis of cohort studies for low birth weight. “Increased Risk” indicates that the outcome was more likely in subjects with asthma. RR=relative risk; CI= confidence interval

Figure 2

Meta-analysis of small for gestational age, by outcome definition (birth weight <10th centile, or fetal growth ratio <0.85). “Increased Risk” indicates that the outcome is more likely in women with asthma. RR= relative risk; CI=confidence interval

Figure 3

Meta-analysis of cohort studies for preterm delivery. “Increased Risk” indicates that outcome is more likely in women with asthma . RR= relative risk; CI= confidence interval

Figure 4

Meta-analysis of cohort studies for preterm delivery by active asthma management. “Increased Risk” indicates that outcome is more likely in women with asthma . RR= relative risk; CI= confidence interval

Figure 5

Meta-analysis of cohort studies for pre-eclampsia. “Increased Risk” indicates that the outcome was more likely in women with asthma. RR=relative risk; CI=confidence interval.

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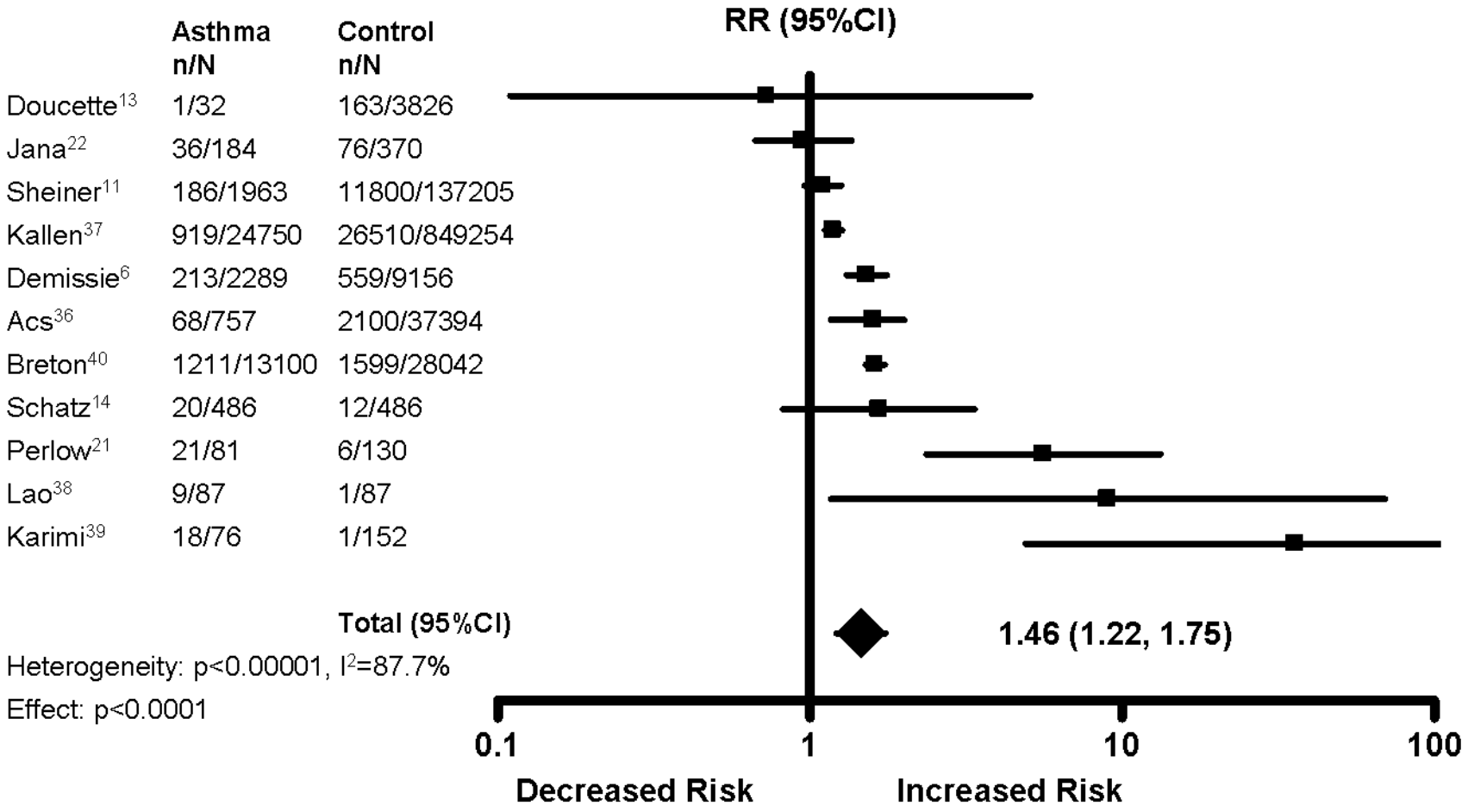
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Sheiner[11] 186/1963 11800/137205
Kallen[37] 919/24750 26510/849254
Demissie[6] 213/2289 559/9156
Acs[36] 68/757 2100/37394
Breton[40] 1211/13100 1599/28042
Schatz[14] 20/486 12/486
Perlow[21] 21/81 6/130
Lao[38] 9/87 1/87
Karimi[39] 18/76 1/152
Total (95%CI)
1.46 (1.22, 1.75)
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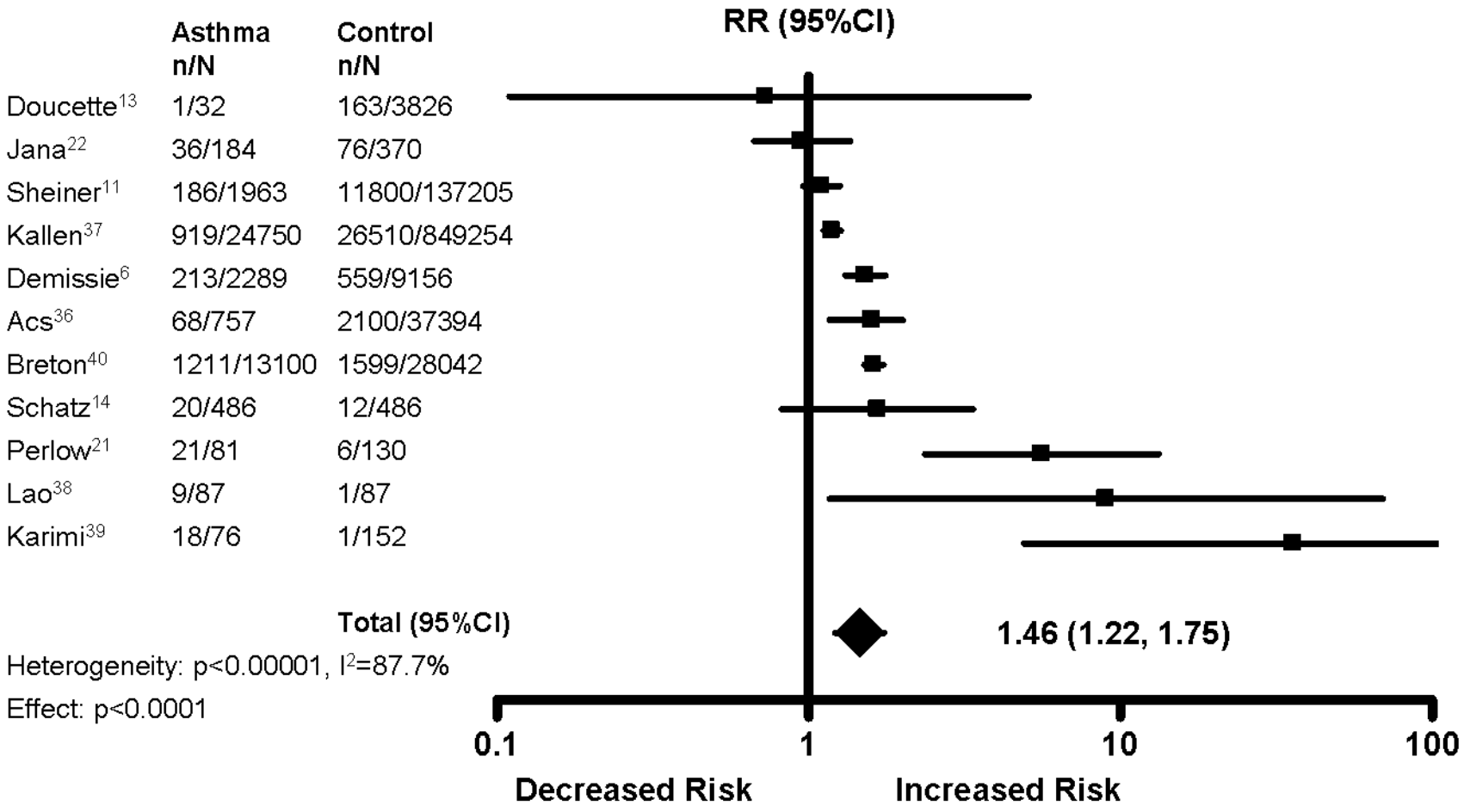
Effect: p<0.0001
0.1
1
10
100
Decreased Risk
Increased Risk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Acs[36] 68/757 2100/37394
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Effect: p<0.0001
0.1
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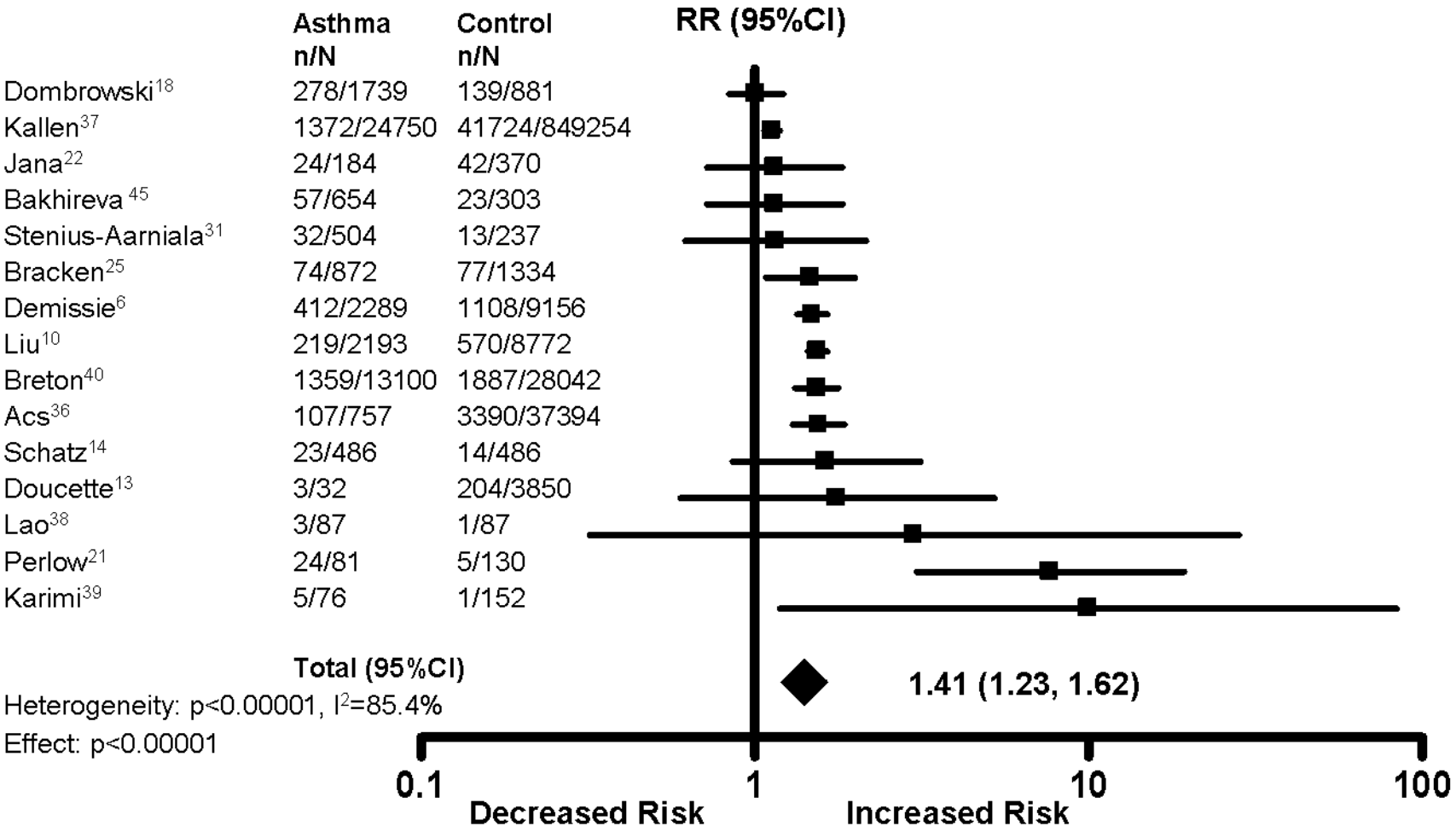
Decreased Risk
Increased Risk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Control n/N
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Bakhireva[45] 57/654 23/303
Stenius-Aarniala[31] 32/504 13/237
Bracken[25] 74/872 77/1334
Demissie[6] 412/2289 1108/9156
Liu[10] 219/2193 570/8772
Breton[40] 1359/13100 1887/28042
Acs[36] 107/757 3390/37394
Schatz[14] 23/486 14/486
Doucette[13] 3/32 204/3850
Lao[38] 3/87 1/87
Perlow[21] 24/81 5/130
Karimi[39] 5/76 1/152
Total (95%CI)
1.41 (1.23, 1.62)
Heterogeneity: p<0.00001, I²=85.4%
Effect: p<0.00001
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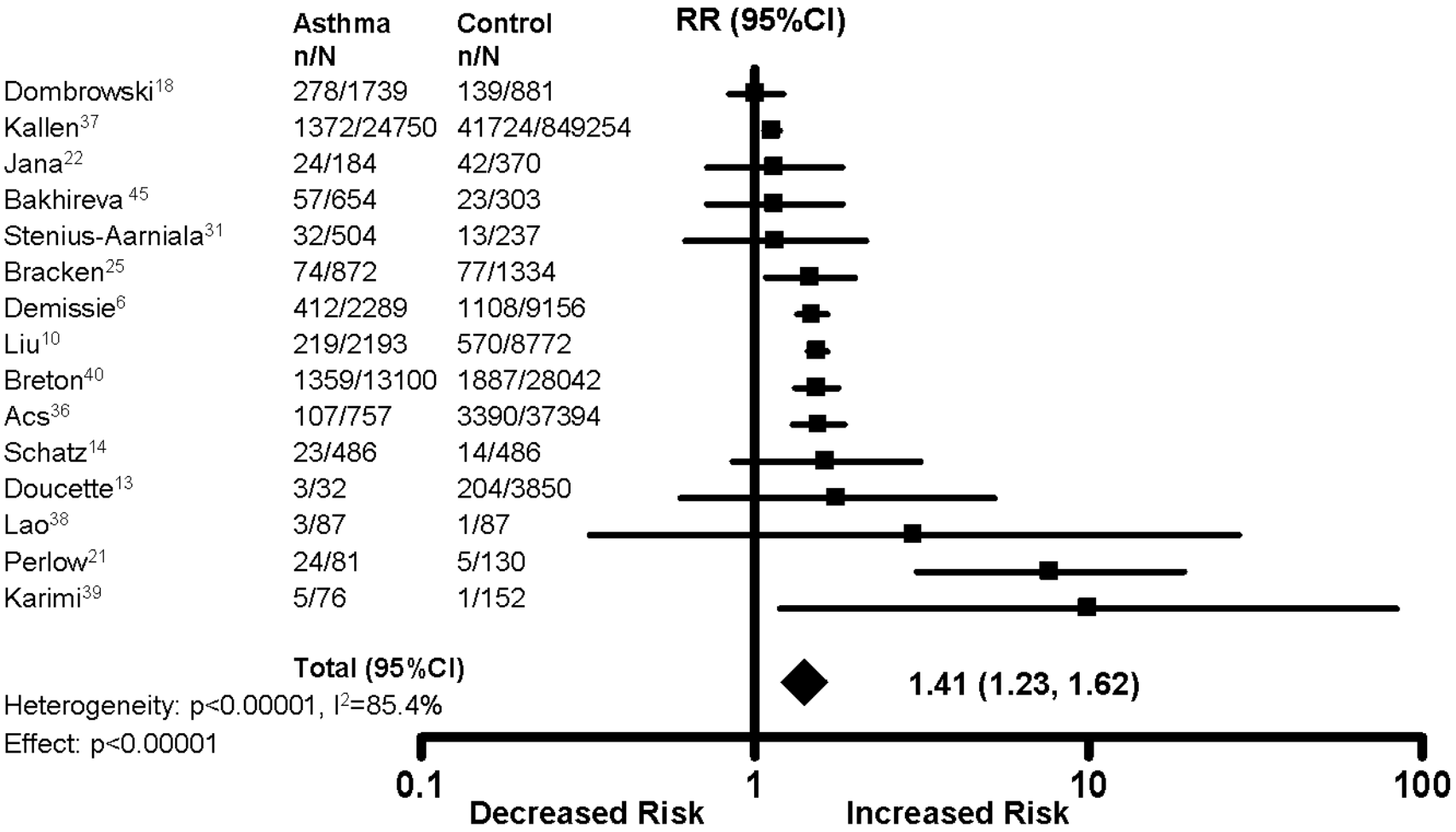
1
10
100
Decreased Risk
Increased Risk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Control n/N
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Jana[22] 24/184 42/370
Bakhireva[45] 57/654 23/303
Stenius-Aarniala[31] 32/504 13/237
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Demissie[6] 412/2289 1108/9156
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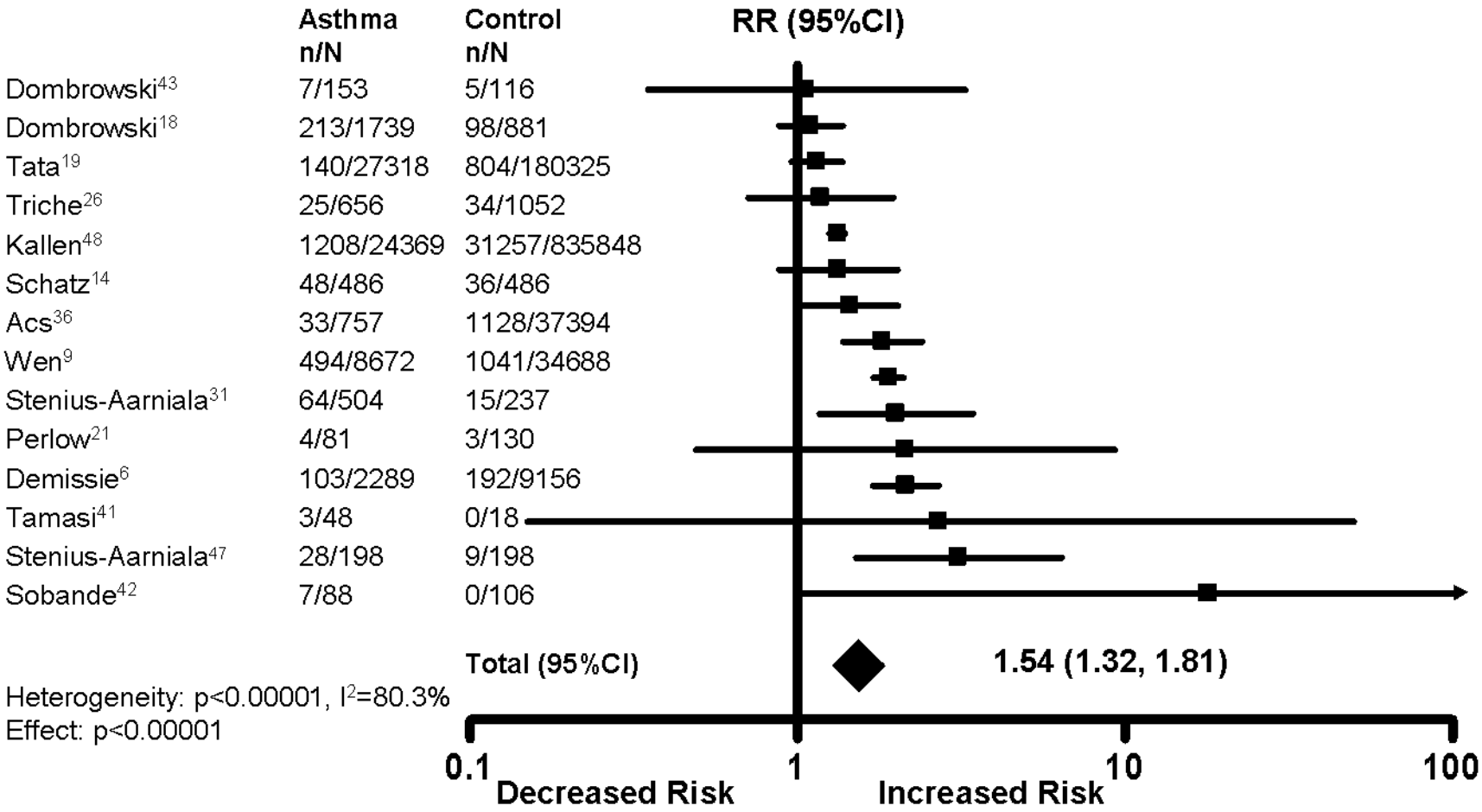
Acs[36] 107/757 3390/37394
Schatz[14] 23/486 14/486
Doucette[13] 3/32 204/3850
Lao[38] 3/87 1/87
Perlow[21] 24/81 5/130
Karimi[39] 5/76 1/152
Total (95%CI)
1.41 (1.23, 1.62)
Heterogeneity: p<0.00001, I²=85.4%
Effect: p<0.00001
0.1
1
10
100
Decreased Risk
Increased Risk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Control n/N
RR (95%CI)
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Tata[19] 140/27318 804/180325
Triche[26] 25/656 34/1052
Kallen[48] 1208/24369 31257/835848
Schatz[14] 48/486 36/486
Acs[36] 33/757 1128/37394
Wen[9] 494/8672 1041/34688
Stenius-Aarniala[31] 64/504 15/237
Perlow[21] 4/81 3/130
Demissie[6] 103/2289 192/9156
Tamasi[41] 3/48 0/18
Stenius-Aarniala[47] 28/198 9/198
Sobande[42] 7/88 0/106
Total (95%CI)
1.54 (1.32, 1.81)
Heterogeneity: p<0.00001, I²=80.3%
Effect: p<0.00001
0.1
1
10
100
Decreased Risk
Increased Risk