

Supplement 2 - Tables

Risk factors for asthma exacerbation during pregnancy: a systematic review and meta-analysis

Table S1. Excluded studies during full text review	
Reference	Exclusion Reason
Adeyemi et al. 2015	Wrong patient population
Ali et al. 2017	Wrong outcomes
Ali et al. 2016	Wrong patient population
Amaral et al. 2018	Wrong study design
Badawy et al. 2014	Wrong patient population
Bakhireva et al. 2008	Wrong patient population
Blais et al. 2008	Wrong outcomes
Blais et al. 2010	Wrong study design
Blais et al. 2015	Wrong study population
Blais et al. 2012	Wrong study population
Chaiprom et al. 2021	Wrong outcomes
Charlton et al. 2013	Duplicate
Charlton et al. 2012	Wrong study design
Cockey 2003	Wrong study design
Cohen et al. 2018	Wrong study design
Cossette et al. 2014	Wrong patient population
Desalu et al. 2020	Wrong patient population
Dombrowski et al. 2005	Wrong study design
Eger et al. 2017	Wrong study design
Gemicioglu et al. 2021	Wrong patient population
Grosso et al. 2018	Wrong patient population
Grzeskowiak et al. 2015 (1)	Wrong study design
Grzeskowiak et al. 2015 (2)	Wrong study design
Grzeskowiak et al. 2015 (3)	Wrong study design
Hernandez et al. 2006	No English
Henderson et al. 2000	Wrong patient population
Hodyl et al. 2011 (1)	Wrong study design
Hodyl et al. 2011 (2)	Wrong study design
Hodyl et al. 2012	Wrong study design
Ibrahim et al. 2019	Wrong patient population
Ivancso et al. 2013	Wrong patient population
Jana et al. 2012	Wrong study design
Johnston and Said 2012	Wrong patient population
Koo et al. 2017 (1)	Duplicate
Koo et al. 2017 (2)	Duplicate
Kwon et al. 2006	Wrong study design
Lacasse-Guay et al. 2010	Wrong study design
Leblanc et al. 2009	Wrong study design
Leblanc and de Castro 2013	No English
Lee et al. 2015 (1)	Wrong patient population
Lee et al. 2015 (2)	Duplicate
Lim et al. 2013 (1)	Wrong study design
Lim et al. 2013 (2)	Wrong study design

Louik et al. 2010	Wrong study design
Martinovic and Pantovic 2009	Wrong study design
Meredith et al. 2014	Wrong study design
Mihrshahi et al. 2003	Wrong patient population
Mirzakhani et al. 2018	Wrong outcomes
Mitchell et al. 2017	Wrong patient population
Murphy et al. 2010	Overlapping study population
Murphy et al. 2014 (1)	Wrong patient population
Murphy et al. 2014 (2)	Wrong patient population
Murphy et al. 2015 (1)	Wrong study design
Murphy et al. 2015 (2)	Wrong study design
Murphy et al. 2016	Wrong study design
Murphy and Gibson 2016	Wrong study design
Nittner-Marszalska et al. 2013	Wrong patient population
Nittner-Marszalska et al. 2013	Duplicate
Novotna et al. 2010	Wrong study design
Oleson et al. 2001	Wrong study design
Osei-Kumah et al. 2010	Wrong patient population
Osei-Kumah et al. 2013	Wrong study design
Otsuka et al. 2005	Wrong patient population
Powell et al. 2011	Wrong outcomes
Powell et al. 2012	Wrong study design
Rastogi et al. 2006	Wrong patient population
Rooney Thompson et al. 2015	Wrong patient population
Shebl and Chakraborty 2019	Wrong study design
Tata et al. 2007	Wrong outcomes
Tata et al. 2008	Wrong patient population
Titova et al. 2019	Wrong study design
Towers et al. 2004 (1)	Wrong patient population
Towers et al. 2004 (2)	Duplicate
Towers et al. 2004 (3)	Duplicate
Valet et al. 2009	Wrong patient population
VanDePutte et al. 2018	Wrong study design
VanDePutte et al. 2019	Wrong patient population
Vanders et al. 2019	Wrong study design
Yland et al. 2019	Wrong study design
Yland et al. 2020	Wrong patient population

Table S2. Characteristics of included studies.				
First Author	Study years and country	Definition Exacerbations	Exacerbators/total population (%)	QA score
Abdullah et al. 2020[8]	April 1 2003 - March 31 2012; Canada	at least 5 GP visits for asthma, or at least 1 ED or hospitalisation during pregnancy	4,455/103,424 (4.3%)	9
Ali et al. 2018 JACI[24]	2007-2015; Denmark	Exacerbations were defined according to the American Thoracic Society/European Respiratory Society guidelines on asthma control and exacerbation. Subcategorised as mild and severe: Mild exacerbations were defined as exacerbations managed by an increase in therapy, but not requiring oral corticosteroids. Severe exacerbations were defined as exacerbations requiring hospital admission, emergency department treatment, and/or a rescue course of systemic corticosteroid. For the purpose of this systematic review we only included the severe exacerbation.	Any 252/1,283 (19.6%) Severe 99/1,283 (7.7%)	9
Ali et al. 2018 CEA[29]	2007-2016; Denmark	Not reported	Unknown	9
Bakhireva et al. 2008[38]	1998-2003; USA and Canada	Hospitalisation for asthma, unscheduled ED for asthma - reported separately.	Hospitalisation 61/819 (7.4%) ED 153/819 (18.7%)	9
Belanger et al. 2010[18]	April 1997-June 2000; USA	Hospitalisation for asthma, unscheduled ED for asthma - reported separately.	Hospitalisation 14/641 (2.2%) ED 99/641 (15.4%)	8
Bokern et al. 2021[27]	2004-2019; Australia	Hospital admission, emergency department presentation, unscheduled doctor visit or the use of oral corticosteroids (OCS)	Any: 135/1461 (9.2%) OCS: 99/1461 (6.8%)	8
Carroll et al. 2005[32]	1995-2001; USA	Asthma-related emergency department visits and hospitalizations were identified by using ICD-9 code 493.	Hospitalisations 272/4,315 (6.3%) ED 479/4,315 (11.1%) OCS 547/4,315 (12.7%)	9
Charlton et al. 2013[39]	2000-2008; UK	i. An asthma exacerbation, asthma attack or asthma diagnosis record on the same date as a hospitalisation or visit to an accident and emergency department, which was classified as a 'definite'	643/19,600 (3.3%)	7

		asthma exacerbation; ii. A prescription for short-term oral corticosteroid treatment associated with a record of asthma (but not explicitly coded by the GP as an exacerbation) on the same day, which was classified as a 'probable' asthma exacerbation; iii. A prescription for short-term oral corticosteroid treatment without any record of the indication for treatment, which was classified as a 'possible' asthma exacerbation.		
Cohen et al. 2019[40]	2000-2013; USA	Asthma related emergency department visit, asthma-related hospitalization, or course of oral corticosteroids (<20 mg prednisone equivalents for 3-28 days associated with an asthma diagnosis within 14 days) from LMP to delivery	MAX database 25,954/120,745 (21.5%) MS database 2,586/20,104 (12.9%)	7
Dombrowski et al. 2004[44]	December 1995-February 2000; USA	Asthma symptoms (cough, dyspnea, or wheezing) that resulted in a medical intervention, including an emergency visit (unscheduled prenatal visit or treatment in an emergency department), need for oral corticosteroids, or hospitalization.	74/385 (19.2%)	Low risk of bias*
Enriquez et al. 2007[31]	1995-2003; USA	Hospital or emergency department (ED) care for asthma during pregnancy	2479/9,154 (27.1%)	9
Firoozi et al. 2009[36]	1990-2002; Canada	A short (<14 days) course of oral corticosteroids dispensed by a pharmacy, an ED visit for asthma, or a hospitalization for asthma	1707/11,240 (15.2%)	9
Grzeskowiak et al. 2016 EJOGRB [52]	May 2009-May 2012; Australia	Hospital admission, emergency department presentation, an unscheduled doctor visit, or a course of oral steroids due to asthma.	27/169 (16.0%)	9
Grzeskowiak et al. 2016 ERJOR[12]	May 2009-May 2012; Australia	Hospital admission, emergency department presentation, an unscheduled doctor visit, or a course of oral steroids due to asthma.	41/189 (21.7%)	7
Grzeskowiak et al. 2017[33]	May 2009-May 2012; Australia	Hospital admission, emergency department presentation, an unscheduled doctor visit, or a course of oral steroids due to asthma.	41/189 (21.7%)	9
Hendler et al. 2006[16]	1994-1999; USA	Asthma symptoms (cough, dyspnea, or wheezing) severe enough to result in a medical intervention, including hospitalization, unscheduled visits (physician office or emergency department), or treatment with oral corticosteroids among subjects who were not already taking regular oral corticosteroids.	549/1,693 (32.4%)	8

Jensen et al. 2020[34]	2007-2010; Australia	Unscheduled physician appointment, emergency department presentation, hospitalization, or OCS	40/103 (38.8%)	8
Kim et al. 2015[42]	2009-2013; South Korea	1) asthma-related hospitalization; (2) asthma-related emergency department (ED) visit; or (3) asthma-related outpatient visit with systemic corticosteroid prescription.	546/10,311 (5.3%)	9
Liu et al. 2019[11]	1997-2012; Denmark	Inpatient treatment, had an emergency room visit for asthma or filled a prescription for an oral corticosteroid.	2,103/83,266 (2.5%)	9
Murphy et al. 2005[4]	January 1997-June 2003; Australia	Hospital admission, emergency department presentation, unscheduled doctor visit or the use of oral corticosteroids (OCS)	53/146 (36.3%)	6
Murphy et al. 2017[15]	June 2007-December 2010; Australia	Hospital admission, emergency department presentation, unscheduled doctor visit or the use of oral corticosteroids (OCS)	Not reported/115	7
Murphy et al. 2020 JA[46]	June 2007-December 2010; Australia	Hospital admission, emergency department presentation, unscheduled doctor visit or the use of oral corticosteroids (OCS)	18/137 (13.1%)	9
Murphy et al. 2020 JACI-IP[65]	June 2007-December 2010; Australia	Hospital admission, emergency department presentation, unscheduled doctor visit or the use of oral corticosteroids (OCS)	72/217 (33.2%)	9
Murphy et al. 2020 R[47]	June 2007-December 2010; Australia	Hospital admission, emergency department presentation, unscheduled doctor visit or the use of oral corticosteroids (OCS)	35/195 (17.9%)	9
Newman et al. 2010[30]	1994-2000; USA	(1) hospitalization, (2) an unscheduled office visit, (3) an ED visit, or (4) treatment with oral corticosteroids	433/2209 (19.6%)	7
Palmsten et al. 2016[50]	2011-2013; USA and Canada	Self-report of any overnight hospitalizations or emergency room visits, unscheduled physician visits, or oral corticosteroid use because of asthma symptoms	Between intake and week 20: 9/124 (7.3%) Between week 20 and week 32: 6/103 (2.8%) Between week 32 and postpartum: 5/118 (4.2%)	7
Powell et al. 2013[49]	June 2007-December 2010; Australia	Uncontrolled asthma requiring oral corticosteroid or unscheduled health care utilization (hospitalization, emergency department visit, or general practitioner visit)	61/175 (34.9%)	8

Powell et al. 2010[53]	June 2007-December 2010; Australia	An unscheduled visit to a doctor, presentation to the emergency room or admission to hospital, or when oral corticosteroids were used for treatment of asthma	73/220 (33.2%)	Low risk of bias*
Robijn et al. 2020[14]	July 2006-November 2013; Sweden	Hospitalisation or unplanned ED visit for asthma (ICD J45/J46) and/or a short oral corticosteroid (OCS) course for asthma during pregnancy	1,430/33,829 (4.2%)	9
Rohn et al. 2021[45]	2015-2019; USA	An unscheduled doctor visit, emergency room/urgent care visit or an overnight hospitalization due to worsening asthma symptoms.	Unknown/275	8
Schatz et al. 2010[48]	December 1995-February 2000; USA	Asthma symptoms requiring a hospitalization, other unscheduled medical visit, or oral corticosteroid course.	64/310 (20.6%)	8
Schatz et al. 2003[5]	December 1994-March 1999; USA	Symptoms severe enough to result in a medical intervention, including hospitalization, unscheduled visits (physician or emergency department), or the prescription of oral corticosteroids (in patients who were not already on regular oral corticosteroids).	346/1,739 (19.9%)	7
Shebl et al. 2019[25]	2015-January 2018; Egypt	(1) Change of the basal condition, which led to adding oral corticosteroids for BA treatment. (2) Unscheduled outpatient visits. (3) Admission to the emergency room or hospitalization.	77/308 (25.0%)	4
Tanacan et al. 2020[41]	2009-2018; Turkey	Significant increase in pre-treatment clinical manifestations or a significant increase in medication. All exacerbation cases were hospitalized and required treatment protocols which were applied according to the current guidelines	43/284 (15.1%)	7
Yoo et al. 2020[26]	2007-2014; USA	International Classification of Diseases, Ninth Revision code 493.xx, then chart review	62/289 (21.5%)	7
*Cochrane Risk of Bias				

Table S3. Associations between risk factors and asthma exacerbations during pregnancy from meta-analyses expressed as mean difference (MD) and relative risks (RR)						
	Studies	Type	Estimate (95%CI)	I ²	P-value	GRADE [†]
Age	6[4, 12, 24–27]	Continuous - MD	0.62 (0.11-1.13)	0.0%	0.79	++
	4[4, 8, 11, 14]	≥35 years vs ≤34 years* - RR	1.27 (1.06-1.52)	87.8%	<0.01	+
Body Mass Index	3[12, 24, 25]	Continuous - MD	1.82 (-1.12-4.75)	95.2%	<0.01	+
	5[12, 14, 16, 26, 27]	Obese vs Non-Obese - RR	1.25 (1.15-1.37)	0.0%	0.74	++
Smoking	9[4, 8, 12, 14, 25–28, 30]	Smoker vs Non-Smoker – RR	1.35 (1.04-1.75)	94.0%	<0.01	++
Ethnicity	2[26, 31]	Black vs White – RR	1.62 (1.52-1.73)	79.5%	0.03	+
Rural Area	3[8, 11, 25]	Rural vs Metropolitan/Regional – RR	0.92 (0.66-1.28)	95.2%	<0.01	+
Mental Health	2[14, 33]	Depression/Anxiety vs None – RR	1.42 (1.27-1.59)	68.7%	0.07	+
	4[11, 14, 26, 33]	All mental health measures combined vs None – RR	1.41 (1.31-1.51)	0.0%	0.22	+
GORD	2[25, 26]	GORD vs No GORD - RR	0.98 (0.61-1.58)	0.0%	0.67	+
Allergic Rhinitis	2[25, 26]	Allergic Rhinitis vs None - RR	1.28 (0.85-1.92)	89.5%	<0.01	+
Gestational Weight Gain	3[4, 12, 24]	Continuous - MD	-2.71 (-4.48 - -0.94)	69.3%	0.03	+
Parity	6[4, 11, 12, 14, 24, 27]	Multiparous vs Nulliparous - RR	1.31 (1.01-1.68)	89.1%	<0.01	++
Plurality	3[24, 26, 27]	Twins/Triplets vs Singletons - RR	2.23 (1.10-4.50)	60.7%	0.07	+
Sex of Baby	10[4, 8, 11, 12, 24–27, 36, 37]	Male vs Female - RR	1.05 (0.89-1.25)	88.9%	<0.01	++
Asthma Severity	6[4, 5, 25, 39–41]	Severe vs Moderate/Mild - RR	2.70 (1.85-3.95)	98.5%	<0.01	++

History of Exacerbations	2[27, 42]	Hospitalisation vs No Hospitalisation - RR	3.75 (2.82-4.97)	39.0%	0.20	+
	2[27, 42]	ED visit vs No ED visit - RR	3.80 (2.94-4.90)	91.6%	<0.01	+
ICS use	2[12, 27]	ICS use vs No ICS use around 18 weeks gestation - RR	1.65 (1.42-1.92)	0.0%	0.66	+
*Includes one study[1] with cut-off value of 34 instead of 35. † GRADE assessment + moderate certainty, ++ high certainty. Abbreviations: GORD Gastro-oesophageal reflux disease, ICS inhaled corticosteroids						

Table S4. Associations between risk factors and asthma exacerbations during pregnancy from meta-analyses by active study involvement status for analysis with significant heterogeneity in main analysis.

	Type	No Active Involvement			Active Involvement		
		N	Estimate (95%CI)	I ²	N	Estimate (95%CI)	I ²
Age	≥35 years vs ≤34 years* - RR	3	1.25 (1.03-1.51)	92.0%	1	1.57 (0.87-2.82)	-
BMI	Continuous - MD	All studies active involvement, no subgroup analysis performed					
Smoking	Smoker vs Non-Smoker – RR	4	1.32 (1.21-1.43)	44.6%	5	1.32 (0.79-2.20)	88.2%
Ethnicity	Black vs White – RR	All studies no active involvement, no subgroup analysis performed					
Rural Area	Rural vs Metropolitan/Regional – RR	2	1.04 (0.80-1.35)	94.4%	1	0.63 (0.43-0.93)	-
Mental Health	Depression/Anxiety vs None – RR	One study in each subgroup, no subgroup analysis performed					
Allergic Rhinitis	Allergic Rhinitis vs None - RR	One study in each subgroup, no subgroup analysis performed					
Gestational Weight Gain	Continuous - MD	All studies active involvement, no subgroup analysis performed					
Parity	Multiparous vs Nulliparous - RR	2	1.22 (1.14-1.30)	0.0%	4	1.35 (0.85-2.14)	79.7%
Plurality	Twins/Triplets vs Singletons - RR	1	3.97 (2.28-6.90)	-	2	1.49 (0.80-2.78)	0.0%
Sex of Baby	Male vs Female - RR	4	1.01 (0.97-1.05)	0.0%	6	1.07 (0.75-1.52)	75.7%
Asthma Severity	Moderate-Severe vs Mild - RR	2	2.31 (1.03-5.19)	99.7%	4	4.80 (2.63-8.74)	80.0%
	Severe vs Moderate/Mild - RR	2	1.91 (1.27-2.90)	98.9%	4	3.61 (2.32-5.64)	82.5%
History of Exacerbations	ED visit vs No ED visit - RR	One study in each subgroup, no subgroup analysis performed					

*Includes one study[1] with cut-off value of 34 instead of 35. Abbreviations: GORD Gastro-oesophageal reflux disease, ICS inhaled corticosteroids