Original Article

The risk factors of meconium aspiration syndrome in newborns: a meta-analysis and systematic review

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Background: Risk factors related to meconium aspiration syndrome (MAS), that were understated or unanalyzed by previous comprehensive studies, have emerged. The aim of the study is to determine the maternal, peripartum and fetal-neonatal risk factors with a meta-analysis method, to provide a more extended vision on high-risk scenarios related to MAS development and an insight for further research.

Methods: Articles were obtained by searching the PubMed, Ovid MEDLINE, Embase.com, Scopus, Web of science, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials databases, yielding 2,090 records from 1978 to 2022. Inclusion criteria of eligible studies were reported on the risk factors for the outcome of MAS within any population; using non-MAS group as control; and providing the sample size and raw data. Risk of bias of the included studies were assessed by Newcastle-Ottawa quality assessment scale. Meta-analysis on pooled odds ratios (ORs) on the extracted risk factors from the literature were calculated by Mantel-Haenszel or Inverse Variance method.

Results: A total of 55 references, including case-control studies (n=17) and observational cohort studies (n=38), were included. The majority of cohort studies, but not case-control studies, were at low risk of bias. Fifteen risk factors were included, of which 6 were related to maternal status, 3 to peripartum status and 5 to fetal-neonatal status. All factors but gender of infant were significant impactor. The factor with the largest valid effect size was Apgar <7 at 5 min [8 studies, OR 14.89, 95% confidence interval (CI): 9.52–23.28, P<0.001]. Induction of labor was a protective factor (6 studies, OR 0.56, 95% CI: 0.47–0.68, P<0.001). Maternal body mass index (BMI) ≥30 kg/m^2 (5 studies, OR 2.27, 95% CI: 1.53–3.35, P<0.001) was a risk factor. Smoking was an unneglectable risk factor that was understated with only one adjusted OR available (1 study, OR 1.47, 95% CI: 1.32–1.64).

Conclusions: The reported factors can be considered as impactors for MAS development by clinicians. Maternal smoking and obesity were understated and should be emphasized and controlled in further clinical practice. The limited quality of relevant case-control studies necessitates further high-quality researches (CRD 42022338176).

Keywords: Risk factors; meconium aspiration syndrome (MAS); smoking; maternal obesity

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Introduction

Meconium aspiration syndrome (MAS) is one of the respiratory morbidities that mainly occurs in term and post-term neonate. Additionally, though rare, MAS may also occur in preterm neonates (1). By mechanically obstructing the airways, chemically damaging the epithelium of airway and alveolar, as well as de-activating surfactant and impairing alveoli compliance, MAS can lead to severe adverse outcomes including respiratory distress syndrome, persistent pulmonary hypertension, the use of extracorporeal membrane oxygenation (ECMO) (2), neurological impairment (3), cardiovascular instability and even death (2).

Previous studies have identified several important risk factors for MAS, such as born through meconium-stained amniotic fluid (MSAF) (2,4-8), non-reassuring fetal heart rate tracing (2,4,9-15), cesarean delivery, poor Apgar score (2,11,14-16), advancing gestational age (1,17,18), etc. However, the aforementioned risk factors were from comprehensive studies on the risk factors for MAS done decades before (2). It was demonstrated by studies that the incidence of MAS varied over decades. Yoder *et al.* reported a reduction of MAS from 1990 to 1998 (15), attributing partially to the medical advancement. Similarly, a population-based study has also reported a declined rate of MAS aligning with the appearance of increase in protective obstetric practice (18). In recent years, there are scattered studies reporting several risk factors related to MAS that were understated previously, such as maternal smoking (4) and maternal obesity (19), and new obstetric strategies that emerged in last decade and were not analyzed in previous clinical settings, such as induction of labor (20). The emerging attention on these factors was a result of changing medial practice and social environment. These factors were not analyzed through meta-analysis. The question raises whether previously overlooked factors have gained significance associating to MAS and the recognized risk factors remained significant with the adding on of new studies done in the era of swift shift of medical practice. The answer to this question may be essential to directing clinical attention.

In this study, we aim to comprehensively review the studies to date and to summarized and meta-analyze, when applicable, the maternal and neonatal risk factors for MAS, to provide a more extended vision on high-risk scenarios related to MAS development for the clinicians and an insight for further research. We present the following article in accordance with the PRISMA reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-23-5/rc).

Highlight box

Key findings

- Maternal obesity, maternal inflammatory response, maternal smoking are risk factors related to meconium respiratory syndrome (MAS), which are not emphasized enough by previous studies. Thick meconium and low Apgar score are the factors with the largest effect size among peripartum and fetal-neonatal related factors, respectively. Induction of labor is a protective factor.

What is known and what is new?

- Meconium-stained amniotic fluid, non-reassuring fetal heart rate tracing, cesarean delivery, poor Apgar score, advancing gestational age were known to be risk factors for MAS
- Risk factors such as maternal obesity, maternal inflammatory response, maternal smoking, are understated by previous studies.
- Induction of labor, which just gained attention in last decade, can be a protective factor for MAS.

What is the implication, and what should change now?

- Maternal smoking and obesity should be controlled in clinical practice.
- The overall limited quality of relevant case-control studies necessitates further high-quality researches.
- The limited number of combinable studies focusing on maternal risk factors indicates more attention on the association of maternal characteristics to MAS should be paid in future studies.

Methods

This review was performed according to a predefined protocol, which was developed according to recommended for systematic reviews (21,22) and registered in the International Prospective Register of Systematic Reviews (CRD 42022338176).

Sources and search strategy

A comprehensive literature search on published literature for records discussing MAS, infants, and risk factors was performed by a researcher. Search strategies applying a combination of keywords and controlled vocabulary was conducted in PubMed, Ovid MEDLINE, Embase.com, Scopus, Web of science, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials from their inception to June 1, 2022. Search terms included "meconium aspiration syndrome", "meconium aspiration

syndrome", "aspiration syndrome, meconium", "syndrome, meconium aspiration", "meconium aspiration", "aspiration, meconium", "meconium inhalation", "newborn", "infant", "infant, newborn", "infants, newborn", "newborn infant", "newborn infants", "newborns", "neonate", "neonates", "infants", "risk factor", "risk factors", "factor, risk", "social risk factors", "factor, social risk", "factors, social risk", "risk factor, social", "risk factors, social", "social risk factor", "health correlates", "correlates, health", "population at risk", "populations at risk", "risk scores", "risk score", "score, risk", "risk factor scores", "risk factor score", "score, risk factor". Additional manual search of bibliographies of identified key articles, use of the "related articles" feature in PubMed, and use of the tool in Web of Science was also performed. No language or location limit were set in the searching strategy. Article with available full text in foreign languages to the researchers was translated using online translator.

Study selection

The inclusion criteria were cohort studies that reported on the risk factors for MAS or case-control studies that aimed on analyzing risk factor for the outcome of MAS within any population; using non-MAS population as control group; the sample size and raw data were provided. Studies were excluded if they were an interventional study, review, meta-analysis or cases report; lack control groups; had incomplete data; did not have available full text; included animals; did not report raw data for the included analyzed risk for MAS. Search strategies for each database can be found in the supplemental materials (Appendix 1). Two investigators screened and evaluated for inclusion independently. If any disagreement occurs, it will be resolved by a third investigator.

All search strategies were completed in June 2022, and a total of 2,090 results, published from 1978 to 2022, were exported to Endnote. Notably, 1,202 records were deleted after using the deduplication.

Risk of bias

The assessment of the risk of bias of the included studies was carried out according to Newcastle-Ottawa Scale. Two investigators conducted evaluation independently. If any disagreement occurs, it will be resolved by a third investigator. A score >7 was considered as low risk of bias; a score <3 as very high risk.

Data extraction

Risk factors that impact the incidence of MAS are of interest to this study. The risk factor reported by the eligible studies were recorded, with special attention on the following fifteen factors: six risk factors related to maternal condition: maternal body mass index (BMI) ≥30 kg/m^2, maternal age >34-year-old, previous cesarean delivery, smoking, nulliparous, as well as maternal fever and chorioamnionitis, which were further combined into maternal inflammatory response according to recent studies (23-25); four peripartum risk factors: oligohydramnios, induction of labor, caesarean section, thick meconium; and five risk factors related to fetal-neonatal factors: abnormal fetal heart rate, male infant, post term, small for gestational age (SGA), and Apgar <7 at 5 min. For each study, when data were available, the raw data and the best estimated effect size of the above factors (the hierarchy being multiple adjusted effect size, and unadjusted effect size) were extracted by one investigator and confirmed by the second. Adjusted effects from subgroups were extracted when adjusted effects were not available in an overall form but detailed in all subgroups, and was dropped when the effect sizes were only provided in selected subgroups. In studies only providing data on rates, manual calculation was performed to convert the rates in the original study into number of cases in the present study.

Statistical analysis

The studies with same extracted risk factors were combined by the factor and meta-analysis was performed using Review Manager (RevMan Version 5.4. The Cochrane Collaboration, 2020). If one or more studies provided data on adjusted effect size of a particular risk factor, the relevant meta-analyses were done by inputting the adjusted effect size from each individual study and combining with Inverse Variance method and other effect sizes from studies only reporting univariate result were displayed in the forest plot but suppressed in the summary estimate. The risk factor of interest with none adjusted effect size available were still analyzed by Mantel-Haenszel method but were marked out in the table to alarm the reader to interpret with caution. Pooled odds ratios (ORs) were calculated as case-control studies were included. In the heterogeneity test, a P value >0.05 and I^2<50% was considered no heterogeneity, 0.01<P<0.05 or 50%<I^2<70% was considered medium heterogeneity, and 0<P<0.01

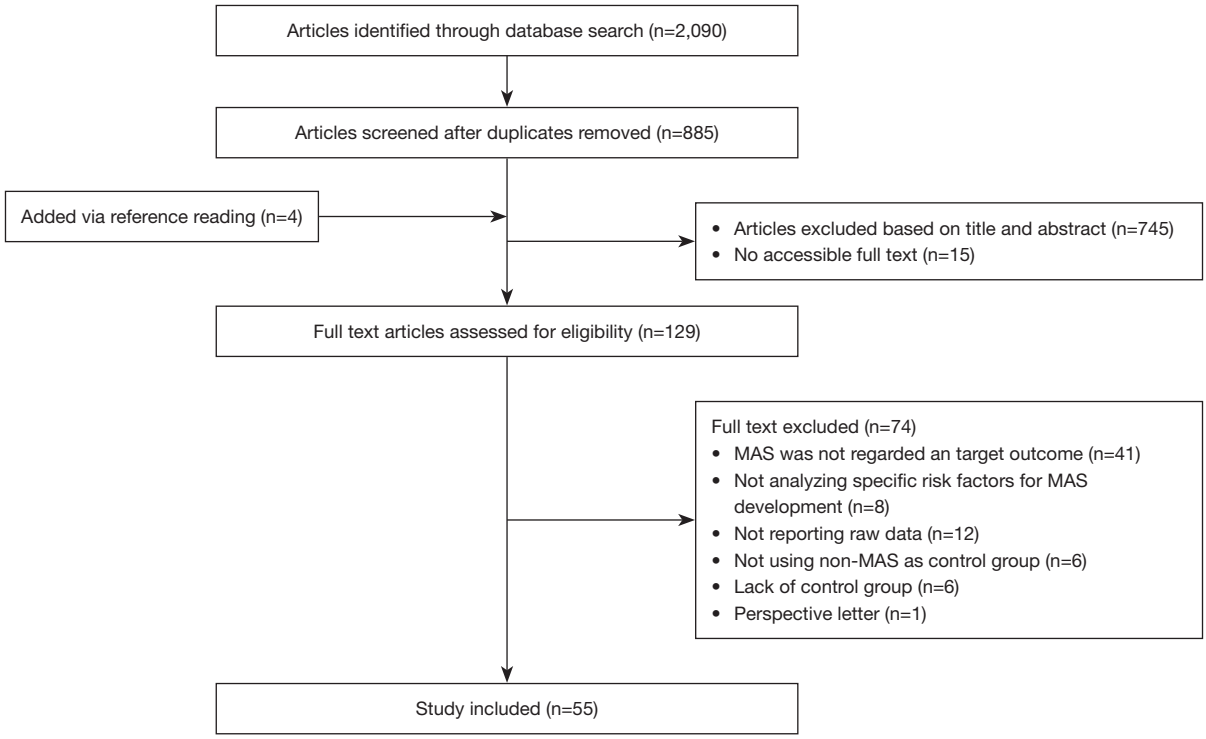

Figure 1 Flow chart of the study. MAS, meconium aspiration syndrome.

or I^2>70% was considered large heterogeneity. Random effects models were used in every analysis due to the non-randomize nature of the enrolled studies. Sensitivity analysis was done manually by repeating the meta-analysis when removing the included studies one at a time to testify the stability of the pooled OR. An unchanged significance of pooled OR after removing a study was considered stable; an altered significance yet similar direction of pooled OR was considered fair stability; an altered significance and direction of pooled OR was considered unstable. Publication bias analysis was conducted by the Egger's test from the metabias add-on program in Stata (Stata Statistical Software: Release 17. StataCorp LLC. College Station, TX, USA) when more than three studies were included. A P value >0.05 in the Egger's test was considered to be significant. Subgroup analyses were further done for analyses with large heterogeneity. The body of evidence was evaluated by GRADE method.

Results

Literature retrieval result

The search yielded 885 unique records published from 1978 to 2022. Four additional studies were found through reference searches. After excluding 759 records by abstract screening, 129 articles were fully read for eligibility evaluation (*Figure 1*). A total of 55 studies, including case-control studies (n=17) (4-16,18,24-26) and observational cohort studies (n=38) with single center (19,23,27-36), multicenter (17,37-39), and regional/national studies (1,20,40-59), were selected for this meta-analysis, published from 1985 to 2022. A flow chart of the process was shown in *Figure 1*. An overview of characteristics of the included studies, including study period, country of objects, study population, number of patients in the reported groups, factors analyzed in the study, are presented in *Tables 1,2*. The list of the excluded fully read studies is presented in Table S1. The detailed results of quality evaluation of the studies by Newcastle-Ottawa quality scale are presented in Tables S2,S3. The study protocol can be found online (https://www.crd.york.ac.uk/PROSPEROFILES/338176_PROTOCOL_20230111.pdf)

Several studies reporting independent risk factors with well-established cohort were not enrolled because of the lack of raw data, including Persson 2014 (60), Björkman 2015 (61), Caughey 2005 (62), Cheng 2006 (63), Darling

Table 1 Characteristics and reported analyzed factors of enrolled case-control studies

Author, year	Country	Study design	Population	N of MAS	N of non-MAS	Analyzed factor related to MAS	NOS
Alchalabi 1999 (9)	Jordan	Single center nested case-control study	All live-born term and post-term pregnancies with a singleton fetus with cephalic presentation and MSAF in the center between March to September 1997. Exclusion: women with risk factors for fetal distress such as hypertensive disorders, diabetes mellitus, antepartum hemorrhage, intrauterine growth retardation and major fetal anomalies	19	325	Maternal age, gestation, non-reassuring FHR, cesarean delivery, Apgar ≤7 at 5 minutes, PROM	5
Amitai Komem 2022 (4)	Israel	Single center case-control study	All singleton gestations with cephalic presentation, delivered in the presence of MSAF between March 2011 and March 2020. Exclusion: suspected major fetal anomalies or genetic abnormalities as well as planned cesarean deliveries	78	11,778	Previous cesarean delivery, cesarean delivery, delivery <38 weeks, fever >38 ℃, nulliparous, smoking, diabetes, hypertensive disorders	7
Avula 2017 (5)	Guntur	Single center nested case-control study	All births with MSAF between October 2015 to February 2016 in the study center. Exclusion: babies born with prematurity and with congenital anomalies and whose parents didn't give consent	21	139	Post term, SGA, oligohydramnios, Apgar <7	6
Bhat 2008 (6)	India	Single center nested case-control study	All births with MSAF between June 2002 and May 2004 in the study center. Exclusion not stated	45	364	Birthweight <2,500 g, gestation >37 weeks, Caesarean section, meconium in trachea, thick meconium consistency, BMI increase, amniotic fluid index, serum white blood cell, k/μ	6
Gad 2020 (7)	Egypt	Single center nested case-control study	All singleton term neonates with MSAF between January, 2013 through December, 2017 in the study center. Exclusion: neonates with congenital anomalies and those with risk factors or evidence of neonatal sepsis	22	79	Gender, Caesarean section, elevated C-reactive protein level, Apgar <7 at 5 min	6
Gurubacharya 2015 (10)	Nepal	Single-center cross-sectional study	All live babies born though MSAF between April 2010 to June 2010. Exclusion: newborns with gross congenital anomalies	7	108	Maternal age, Apgar <3 at 1 minute, Apgar <3 at 5 minutes, resuscitation, parity, post-term	6
Lee 2016 (25)	Korea	Single center nested case-control study	1) Singleton pregnancy; 2) term gestation (gestational age ≥38 weeks); 3) amniotic fluid obtained at the time of cesarean delivery; and 4) MSAF identified at delivery. Exclusion: 1) multiple gestation; 2) stillbirth or fetal death; and 3) presence of major congenital malformations in the study site from July 1995 through June 2009	12	106	Maternal age, nulliparity, non-reassuring FHR pattern, Apgar <7 at 5 minutes, positive amniotic fluid culture, MMP-8 >23 ng/mL, acute histologic chorioamnionitis	6
Liu 2002 (8)	USA	Single center nested case-control study	All infants born through MSAF from May 27, 1994 to June 9, 1997 in the study center. Exclusion not stated	24	660	Apgar <7 at 5 minutes, Apgar <7 at 1 minute, thick meconium, need for resuscitation, infant's stomach suctioned at <5 minutes of age, post-term, Caesarean section, male	6
Mehar 2016 (26)	India	Single center retrospective cohort study	Patients admitted to the neonatal intensive care unit of the center. Study period and exclusion not specified	27	372	Gender, gestation	5

Table 1 (*continued*)

Table 1 (*continued*)

Author, year	Country	Study design	Population	N of MAS	N of non-MAS	Analyzed factor related to MAS	NOS
Meydanli 2001 (11)	Turkey	Single center nested case-control study	Term and post-term pregnant women with a singleton vertex-presenting fetus at 37 weeks' gestation with thick MSAF whose antepartum course were uncomplicated. Study period not specified. Exclusion: multiple gestations, presentation anomalies, previous cesarean section, already ruptured membranes, gestational age <37 weeks, maternal anemia, maternal diabetes mellitus preexisting or gestational, maternal hypertension, intrauterine growth restriction, hydramnios, fetal anomalies and the presence of moderate or light meconium. Study period not stated	15	55	Postdate pregnancy, meconium below vocal cords, non-reassuring FHR tracing, need for endotracheal intubation at delivery room, caesarean section, Apgar score ≤4 at 1 min, Apgar score ≤6 at 5 min, umbilical cord plasma erythropoietin ≥50 mU/mL	5
Oliveira 2019 (12)	Portugal	Single center case-control study	All newborns admitted to the neonatal intensive care unit of the center born through MSAF, with respiratory distress and changes in thoracic radiography compatible with MAS diagnosis between 1 January 2005 and 31 December 2015. Exclusion: newborns with a diagnosis other than MAS that explained the respiratory distress, those with normal thoracic radiography or with no need of oxygen therapy	29	58	Maternal age, maternal education, birthweight, gender, primipara, maternal obesity, smoker, Caesarean section, non-reassuring or abnormal FHR, maternal fever, resuscitation	6
Paudel 2020 (16)	Nepal	Multi-center nested case-control study	All babies born in the study sites between 1 July 2017 to 29 August 2018. Exclusion: out-born, still born and whose parents did not provide consent	122	59,940	Parity, induction of labor, maternal infection, mode of delivery, complications during pregnancy, gestational age, gender, Apgar score <6 at 1 min and 5 min	7
Rossi 1989 (13)	USA	Single center case-control study	Live-born infants delivered through MSAF with birth weight >2300 gm, and gestational age >37 weeks study site June through October, 1986. Exclusion: recognizable congenital anomalies, breech presentation, multiple gestations, prematurity, SGA, or the type of meconium was not recorded	22	216	non-reassuring FHR	5
Usta 1995 (14)	USA	Single center retrospective case-control study	All cases born through thick or moderate MSAF population between January 1990 and April 1993 in the study center. Exclusion: thin or non-specified meconium, abnormal fetal presentation, multi fetal pregnancy, and congenital anomalies	898	39	Cigarette smoking, admitted for non-reassuring FHR tracing, Apgar score ≤4 at 1min, present cesarean delivery, previous cesarean delivery, chorioamnionitis, PROM, SGA, LGA, male	5
Vivian-Taylor 2011 (18)	New South Wales, Australia	Population-based nested case-control study	All liveborn, term (≥37 complete weeks of gestation), singleton infants born in study sites during 1 January 1997–31 December 2007. No exclusion stated	2149	877,037	Maternal age, parity, smoking, labor induction, delivery mode, gestational age, gender, birthweight percentile	9
Yoder 2002 (15)	USA	Single center nested case-control study	The study population consisted of all live infants greater than 37 weeks' completed gestation born through MSAF at the study center from January 1 1990 to December 31 1998. Exclusion not stated	61	1,365	Tracheal meconium, PROM, 5-min Apgar <7, >2 non-reassuring FHR, Cesarean delivery, need for bag mask ventilation, chorioamnionitis	6
Yokoi 2021 (24)	Japan	Single-center retrospective observational study	Term neonates with MSAF between March 2013 and December 2018 in the study center. Exclusion: neonates whose placentae were unavailable, neonates subsequently diagnosed with major congenital anomalies, multiple gestations	88	1,248	Cesarean delivery, PROM >24 h, multipara, elevated C-reactive protein level, elevated haptoglobin level, gender	7

MAS, meconium aspiration syndrome; NOS, Newcastle-Ottawa Scale; MSAF, meconium-stained amniotic fluid; SGA, small for gestational age; FHR, fetal hearty rate; PROM, premature rupture of membrane; BMI, body mass index; MMP, matrix metalloproteinase; LGA, large for gestational age.

Table 2 Characteristics and reported analyzed factors of enrolled cohort studies

Author, year	Country/region of subjects	Study design	Study population	MAS in the observed group	MAS in the reference group	Observed factor of the study	NOS
Andersson 2022 (40)	Denmark	Nationwide cohort study	Singleton births without major congenital malformations, with registered GA, and with in-tended vaginal delivery at GA 41^{+0}–42^{+0}weeks between 2009 and 2018 in Denmark	299/55,717	345/79,160	41^{+0}–41^{+3} week GA (ref) *vs.* 41^{+4}– 42^{+0} week GA	9
Ashwal 2014 (27)	Canada	Single center retrospective cohort study	All singleton pregnancies at term who attempted vaginal delivery at the study center between June 1st and December 31st 2012	4/987	38/22,280	Oligohydramnios *vs.* normal amniotic fluid index (ref)	8
Ashwal 2018 (23)	Canada	Single center retrospective cohort study	All singleton pregnancies at term who attempted vaginal delivery at the study center between 2012–2015	4/309	2/618	Intrapartum fever *vs.* afebrile (ref)	8
Ashwal 2022 (28)	Canada	Single center retrospective cohort study	All women who underwent unplanned intrapartum cesarean delivery following a trial of labor in study site between 2009 and 2016	3/337	16/1,892	an intrapartum cesarean delivery with a history of a previous cesarean delivery *vs.* without (ref)	9
Bailey 2021 (29)	USA	A secondary analysis of a single center prospective cohort	Women admitted for labor at ≥37 weeks of gestation within a single institution from 2010 to 2015. Exclusion: fetal anomalies	5/614	9/5,727	Cord blood PH ≥7.20 vs Cord blood PH 7.11–7.19 (ref)	9
Blankenship 2020 (30)	USA	Retrospective analysis of a single center prospective cohort	Women at 37–38 weeks of gestation; had a singleton, cephalic infant; presented either for induction of labor or in spontaneous labor; and reached 10 cm cervical dilation in the study site from 2010 to 2015. Exclusion: congenital anomalies, had placenta pre-via or other contraindication to vaginal delivery, delivered by cesarean before achieving complete cervical dilation, or had a prior cesarean delivery	2/682	9/6,141	Labour duration ≥ 90th percentile *vs.* <90th percentile (ref)	8
Blomberg 2014 (41)	Sweden	Nationwide prospective cohort study	All singleton primiparous women prospectively registered in the Swedish Medical Birth Register who gave births from 1 January 1992 through 31 December 2010	30/29,816 (17–19 y), 363/185,942 (20–24 y), 563/205,905 (30–34 y), 193/63,193 (35–40y), 42/10,634 (40+ y)	649/300,822	Maternal age (years): 17–29, 20–24, 25–29 (ref), 30–34, 35–39, 40+	9
Cassidy 1985 (31)	Ireland	A secondary retrospective analysis of a single center cohort	Pregnancies resulting in an infant below the 5th centile for an Irish delivered over a 16-month period. Study date and exclusion not stated	1/100	0/100	SGA	8
Cedergren 2004 (42)	Sweden	Nationwide prospective population-based cohort study	Pregnancies delivered in Sweden January 1, 1992, through December 31, 2001. Exclusion: women with insulin-dependent diabetes mellitus	85/69,143 (BMI 29.1–35 kg/m^2), 42/12,402 (BMI 35.1–40 kg/m^2), 11/3,386 (BMI >40 kg/m^2)	731/526,038	Maternal BMI (kg/m^2): 19.8–26 (ref), 29.1–35, 35.1–40, >40	9
Cedergren 2006 (43)	Sweden	Nationwide prospective population-based cohort study	Singletons born in Sweden between January 1, 1992 to December 31, 2001. Exclusions: were made for pre-existing maternal diabetes and pregnancies where the infant had chromosomal anomalies	130/6,346	10,811/770,355	Cardiovascular defects	9
Cederholm 2005 (44)	Sweden	Nationwide prospective population-based cohort study	Women 35 to 49 years old with single births in Sweden during the period 1991–1996	64/21,748 (Amniocentesis), 5/1,984 (chorionic villus sampling)	99/47,854	Amniocentesis or chorionic villus sampling *vs.* not exposed (ref)	9
Cheng 2012 (45)	USA	Nationwide retrospective cohort study	Nulliparous women with singleton, vertex live births delivered at 39–42 weeks' gestation in 2005 in USA	19/23,963 (39 wk' GA)[a], 61/30,263 (40 wk' GA)[a], 57/17,379 (41 wk' GA)[a]	515/177,733 (39 wk' GA)[a], 189/48,518 (40 wk' GA)[a], 11/2,739 (41 wk' GA)[a]	Induction *vs.* expectant (ref)	9
Chiruvolu 2018 (37)	USA	Multicenter cohort study	Nonvigorous newborns born during the retrospective 1-year period before the implementation of new NRP guidelines (October 1, 2015, to September 30, 2016) to infants born during the 1-year prospective period after implementation (October 1, 2016, to September 30, 2017)	7/130	11/101	Born before *vs.* born after implementation of new NRP guidelines (ref)	9
Clausson 1999 (46)	Sweden	Nationwide prospective population-based cohort study	All recorded birth between 1991–1995. Exclusion: multiple births, preterm births, and LGA infants	32/10,321 (term-SGA), 155/39,415 (post term-AGA), 3/1,558 (post term-SGA)	595/458,744	Term SGA/post term SGA/post term AGA *vs.* term AGA (ref)	8
De los Santos-Garate 2011 (17)	Mexico	Multi-center retrospective cohort study	All babies born from April 2006 to April 2009 at the study hospitals in NEOSANO's Perinatal Network in Mexico. Exclusion: Multiple births, babies with congenital malformations or inaccurate gestational age	26/4545 (40 wk' GA), 26/3,024 (41 wk' GA), 12/388 (42–44 wk' GA)	26/5,034 (39 wk' GA)[a]	GA (weeks): 39 (ref), 40, 41, 42–44	9

Table 2 (*continued*)

Table 2 (*continued*)

Author, year	Country/region of subjects	Study design	Study population	MAS in the observed group	MAS in the reference group	Observed factor of the study	NOS
Ding 2021 (1)	USA	Population-based retrospective cohort study	Twin births at a gestational age of 34–40 weeks from national database from 1995 to 2000. Exclusion: (I) extreme birthweights (<500 g or >6,000 g); (II) twin births not delivered at the same gestational week	35/48,942 (34 wk' GA), 56/71,116 (35 wk' GA), 65/95,086 (36 wk' GA)[b], 55/101,874 (37 wk' GA)[b], 44/45,318 (39 wk' GA)[b], 31/20,858 (40 wk' GA)[b]	49/82,844	GA in twin pregnancy (weeks): 34, 35, 36, 37, 38 (ref), 39, 40	9
Greenwood 2003 (32)	Ireland	Single-center prospective cohort study	An established cohort in The National Maternity Hospital, Dublin. Included if they had an early amniotomy that showed clear amniotic fluid	8/435	0/7959	Meconium in amniotic fluid *vs.* clear amniotic fluid (ref)	8
Flemming 2020 (47)	Canada	A population-based retrospective cohort study	All data routinely collected under universal healthcare coverage in Ontario, Canada from 01/01/2000–12/31/2017	11/2,022	57/10,110	Compensated Cirrhosis *vs.* general population (ref)	7
Johnson 2005 (48)	USA	State-wide cohort study	Women who had singleton births in Washington state between 1993 and 2001	52/579	14/2,384 (US-Black), 7/2,453 (US-White)	Somali immigrants *vs.* US-Black (ref) or US-White (ref)	9
King 2012 (38)	USA	Multi-center retrospective cohort study	All women with singleton, term gestations (≥37 weeks) delivered from August 1995 to February 2004. Exclusion: women with a stillbirth or a prior cesarean delivery	10/198	184/12,942	Birthweight >4,500 g *vs.* birthweight <4,000 g (ref)	9
Knight 2017 (49)	UK	National prospective cohort study	Nulliparous women aged 35–50 years delivering at 39 weeks of gestation or beyond	6/3,715 (39 wk' GA), 26/5,908 (40 wk' GA), 41/7,254 (41 wk' GA)	414/55,785 (39 wk' GA), 242/28,190 (40 wk' GA), 62/6,276 (41 wk' GA)	Induction *vs.* expectant management (ref)	9
Kortekaas 2020 (50)	The Netherland	National retrospective cohort study	Women with a singleton birth, no known fetal congenital anomalies, ≥37 weeks of gestation and a fetus in cephalic position. Exclusion: women <18 of age, women with both pre-existing and pregnancy induced hypertensive disorder or both pre-existing or gestational diabetes mellitus. Data from 1999 and 2010 in Perined	291/4,778 (35–39 y), 62/884 (>40 y)	1,168/20,629 (18–34 y)	Maternal age (years): 18–34 (ref), 35–39, >40	9
Levin 2020 (39)	Israel	Multi-center retrospective cohort study	The study cohort included all nulliparous women who delivered neonates weighing ≥4,500 g between 2007 and 2018 in the study center	9/78, 13/50	0/43, 4/28	Trial of labor *vs.* no trial of labor (ref), Vaginal delivery *vs.* failed (ref)	8
Li 2019 (51)	Taiwan	Regional retrospective cohort study	Newly diagnosed with PIH between January 1, 2000 and December 31, 2013 in a regional database	392/29,013	930/116,052	PIH	9
Lindegren 2017 (52)	Sweden	Nationwide prospective population-based cohort study	Singleton cephalic pregnancies from 2001 to 2013 ≥41^{+3} weeks, delivered at maternity units with more than 500 deliveries per year during the study period	213/35,252 (primipara), 50/31,180 (multipara)	148/34,985 (primipara) 63/33,081 (multipara)	Deliveries in units expectant management *vs.* deliveries in units with the most active management of prolonged pregnancies (ref), stratified by parity	9
Lindegren 2020 (20)	Sweden	Nationwide prospective population-based cohort study	Singleton prolonged pregnancies (>41^{+3}) and fetus in cephalic presentation among women with one previous birth. The first birth took place after 1998, and the second delivery took place during the study period 1999–2014	18/13,312	63/45,571	Induction *vs.* spontaneous start of labor (ref)	9
Narchi 2010 (33)	UK	Single-center prospective cohort study	Singleton pregnancy, delivered after 24 completed weeks	2/1537 (BMI 25–30 kg/m^2), 7/804 (BMI 30–35 kg/m^2)	4/3,322 (BMI <25 kg/m^2)	Maternal BMI (kg/m^2) at the first visit: <25, 25–30, 30–35	9
Persson 2016 (53)	Sweden	Nationwide prospective population-based cohort study	Infants of mothers with two consecutive live singleton term births in Sweden between 1992–2012	10/19,608 (weight change <–2)[a], 19/36,538 (–2 to <–1)[a], 51/86,441 (1 to <2)[a], 54/65,060 (2 to <4)[a], 38/24,051 (≥4)[a]	117/198,305 (–1 to <1)[a]	Inter-pregnancy weight change (kg/m^2): <–2, –2 to <–1, –1 to <1 (ref), 1 to <2, 2 to <4, ≥4	9
Petrova 2001 (54)	USA	Nationwide retrospective cohort analysis	Singleton live births in USA from a national database between 1995–1997	39/7,800 (preterm, primipara), 278/39,714 (term, primipara), 44/11,000 (preterm, multipara), 1,013/112,556 (term, multipara)	1,074/537,000 (preterm, primipara), 11,452/5,726,000 (term, primipara), 805/402,500 (preterm, multipara), 12,103/4,034,333 (term, multipara)	Maternal fever, stratified by parity and term	9
Polnaszek 2018 (19)	USA	A secondary analysis of a prospective cohort study from a single center	Singleton deliveries at 37 weeks of gestation or beyond from 2010 to 2014 in the center	11/3,311	5/3,147	Maternal obese (BMI >30 kg/m^2)	9

Table 2 (*continued*)

Table 2 (*continued*)

Author, year	Country/region of subjects	Study design	Study population	MAS in the observed group	MAS in the reference group	Observed factor of the study	NOS
Pyykonen 2018 (55)	Finland	Nationwide prospective population-based cohort study	Term, singleton cephalic deliveries between 2006–2012 in Finland	8/6,874 (40^{+0}–40^{+2} wk' GA), 10/5,533 (40^{+3}–40^{+5} wk' GA), 11/5,104 (40^{+6}–41^{+1} wk' GA), 13/5,568 (41^{+2}–41^{+4} wk' GA), 40/10,127 (41^{+5}–42^{+0} wk' GA)	20/6,862 (40^{+0}–40^{+2} wk' GA), 23/5,520 (40^{+3}–40^{+5} wk' GA), 28/5,087 (40^{+6}–41^{+1} wk' GA), 28/5,553 (41^{+2}–41^{+4} wk' GA), 43/10,124 (41^{+5}–42^{+0} wk' GA)	Labor induction *vs.* Expectant management (ref)	9
Rietveld 2015 (56)	Netherland	National cohort study	Women who delivered for the second time between 2000–2007 in the Netherlands after one previous cesarean	6/5,246	14/7,614	attempted operative vaginal delivery *vs.* emergency repeat cesarean in trial of labor after cesarean (ref)	9
Roos 2011 (57)	Sweden	Nationwide prospective population-based cohort study	Women with singleton pregnancies giving birth between 1995–2007 in Sweden	13/3,787	1,738/1,191,336	Polycystic ovary syndrome	9
Salihu 2011 (58)	USA	State-wide population-based retrospective cohort study	Singleton live births macrocosmic infants born within the gestational age range of 34–42 weeks	81/26,954[a]	180/90,022	Maternal pre-pregnancy obese (BMI >30 kg/m^2)	9
Stotland 2006 (34)	USA	Single-center retrospective cohort study	All women delivering term, singleton infants in the center between 1980–2001 with information on pre-pregnancy weight and weight gain	28/4,112 (gain below)[a], 90/8,860 (gain above)[a]	38/7,492[a]	Maternal gestational weight gain by Institute of Medicine guidelines	9
Tyrberg 2013 (59)	Sweden	A national retrospective cohort study	All singleton deliveries in Sweden between 1973 and 2010. No exclusion stated	22/29,408	1,287/893,505	Maternal age (years) <16–19 *vs.* 20–30 (ref)	9
Usher 1988 (35)	Canada	Single center retrospective cohort study	All births included: The date of the last normal menstrual period was recorded; there was a record of an early ultrasound dating examination; gestational age calculated from early ultrasound examination was concordant within 7 days with that calculated from menstrual history; and delivery occurred at or after 273 days from the last normal menstrual period. Study period between Jan. 1, 1978, and March 31, 1986. No exclusion stated	2/1,407 (41 wk' GA)[a], 6/340 (42+ wk' GA)[a]	13/5,915 (39–40 wk' GA)[a]	41wk, 42+wk *vs.* 39–40 wk (ref)	9
Ward 2022 (36)	USA	Single center retrospective cohort study	All women with the term and post-term singleton pregnancies (>37 weeks' gestation) at the study site from 1990 to 2008. No exclusion stated	9/689 (38 wk GA), 29/1,537 (39 wk GA), 73/2,772 (40 wk GA), 77/1,989 (41 wk GA), 55/1,156 (42 wk GA)	N/A (observing the rate of MAS with advancing GA)	Gestation	9

[a], calculated from the rates provided by the study; [b], converted in to individual twins from the twin pairs in the original study. MAS, meconium aspiration syndrome; NOS, Newcastle-Ottawa Scale; GA, gestational age; SGA, small for gestational age; LGA, large for gestational age; AGA, appropriate for gestational age; NRP, Neonatal Resuscitation Program; PIH, pregnancy-induced hypertension; N/A, not applicable; BMI, body mass index; ref, reference group.

2019 (64), Gould 2004 (65) and Gupta 2021 (66).

Risk of bias of included studies

The results of quality evaluation of the studies by Newcastle-Ottawa quality scale are presented in *Table 1* and details are presented in Tables S2,S3. The case-control studies were published from 1989 to 2021. The majority of case-control studies were single center studies. All but three [Amitai Komem 2022 (4), Paudel 2020 (16), Vivian-Taylor 2011 (18)] were of small sample size. The majority hit a score of six, with none fell below three. One study was considered as low risk of bias (18) that was determined a score of nine. The main limitation of the case-control studies was that the case definition was extracted from established records, rather than individually validation, that controls were from hospitals, and that adjustment for potential confounders were not performed. The observational cohort studies were published from 1985 to 2022, of which the majority hit a score of nine. In general, the cohort studies were of a higher quality.

Risk factor analysis

Results of the meta-analysis and certainty of evidence body are summarized in *Table 3* reviewed below. The forest plots of each analysis, with the presentation with studies providing unadjusted effect size, were provided in the supplementary figures (Figures S1-S15).

Maternal risk factor

Maternal BMI ≥30 kg/m^2 [5 studies, OR 2.27, 95% confidence interval (CI): 1.53–3.35, P<0.001] was a significant risk factor for MAS with large heterogeneity (I^2=74%, P=0.002); there were one unadjusted effect size from Oliveira *et al.* (12), and was similar to the combined result (Figure S1). Maternal age >34 years old was significant (2 studies, OR 1.46, 95% CI: 1.15–1.85, P=0.002) to MAS with large heterogeneity (I^2=83%, P<0.001); there were one unadjusted effect size of maternal age >34 years old from Gurubacharya *et al.* (10) and was similar in trend with the combined result (Figure S2). Previous cesarean delivery was significant risky to MAS (3 studies, OR 1.27, 95% CI: 1.08–1.50, P=0.004) with no heterogeneity (I^2=0%, P=0.52); the unadjusted effect sizes (14,25) were similar to the pooled OR (Figure S3). Maternal inflammatory response (3 studies, OR 2.20, 95% CI: 1.55–3.13, P<0.001) was a significant risk factor with small heterogeneity (I^2=54%, P=0.09); the studies with unadjusted effect size (14,15,23) were similar to the summarized effect size of adjusted result (Figure S4). There was only one adjusted effect size for smoking (1 study, OR 1.47, 95% CI: 1.32–1.64) and the unadjusted effect sizes were consistent with this adjusted OR in terms of direction and significance (Figure S5). Nulliparous was a significant risk factor (2 studies, OR 1.42, 95% CI: 1.29–1.56, P<0.001) for MAS with no heterogeneity (I^2=0%, P=0.99); the remaining unadjusted ORs were also similar (Figure S6). There was no evidence of publication bias for the maternal risk factors and all conclusions were stable. There was no evidence of publication bias and sensitivity test was stable for all maternal factors.

Maternal fever in the domain of maternal inflammatory response showed to be a risk factor (2 studies, OR 2.37, 95% CI: 1.57–3.58, P<0.001). Chorioamnionitis were reported by three studies with only one adjusted OR available (1 study, OR 1.83, 95% CI: 1.18–2.84); the other three unadjusted OR were consistent to this result (Figure S4) (14,15). The subgroup analysis was not done for maternal age >34 years old, since there were only three publications in the meta-analysis. Subgroup analysis was attempted for maternal BMI ≥30 kg/m^2, but none of the grouping strategy diminished the heterogeneity.

Peripartum risk factors

Oligohydramnios (2 studies, OR 2.35, 95% CI: 1.09–5.08, P=0.03) and cesarean section (2 studies, OR 2.50, 95% CI: 1.68–3.73, P<0.001) were risk factors for MAS with no heterogeneity; the remaining unadjusted ORs of the two factors were of the same significance to the corresponding summarized effect size (Figures S7,S9). Induction of labor appeared to be a protective factor (6 studies, OR 0.56, 95% CI: 0.47–0.68, P<0.001) with medium heterogeneity (I^2=60%, P=0.002). There was no adjusted effect size reported for thick meconium in the enrolled studies, and the pooled OR for the univariate effect sizes showed significant risk for MAS (3 studies, OR 3.96, 95% CI: 2.02–7.77, P<0.001). The stability of the conclusion was true for all. There was no evidence of publication bias for the peripartum risk factors.

Fetal-neonatal risk factors

There was no adjusted effect size reported for fetal-neonatal risk factors in the enrolled studies hence the pooled OR

Table 3 Combined studies of risk factors

Risk factor	N of participants [studies]	Combined effect			Heterogeneity test			Publication bias		Sensitivity analysis	Certainty of the evidence (GRADE)	
		Pooled OR	95% CI	P value	I^2	P value	Heterogeneity	P value	conclusion		Certainty	Reason for adjusting grading
Maternal factors												
Maternal BMI ≥30 kg/m^2	1,202,375 [5]	2.27	1.53–3.35	<0.001	74%	0.002	Large	0.404	None	Stable	Low	Inconsistency but large effect size
Maternal age >34 year	3,645,799 [2]	1.46	1.15–1.85	0.002	83%	<0.001	Large	0.210	None	Stable	Very Low	Inconsistency
Previous cesarean delivery	148,962 [3]	1.27	1.08–1.50	0.004	0%	0.52	None	0.470	None	Stable	Very Low	Inconsistency
Maternal inflammatory response[a]	86,091 [3]	2.20	1.55–3.13	<0.001	54%	0.09	Small	0.181	None	Stable	Low	Large effect size but inconsistency
Maternal fever	24,693 [2]	2.37	1.57–3.58	<0.001	41%	0.18	None	0.578	None	Stable	Moderate	Large effect size
Chorioamnionitis	1,336 [1]	1.83	1.18–2.84	0.007	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Smoking[b]	874,865 [1]	1.47	1.32–1.64	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nulliparous	888,893 [2]	1.42	1.29–1.56	<0.001	0%	0.99	None	0.363	None	Stable	Low	N/A
Peripartum factors												
Oligohydramnios	36,837 [2]	2.35	1.09–5.08	0.03	0%	0.97	None	0.739	None	Stable	Moderate	Large effect size
Induction of labor	1,946,604 [6]	0.56	0.47–0.68	<0.001	60%	0.002	Small	0.524	None	Stable	Very low	Inconsistency
Caesarean section	13,191 [2]	2.50	1.68–3.73	<0.001	29%	0.24	None	0.729	None	Stable	Moderate	Large effect size
Thick meconium[c]	2,020 [3]	3.96	2.02–7.77	<0.001	39%	0.20	None	0.482	None	Stable	Low	Large effect size but high risk of bias
Fetal-neonatal Factors												
Abnormal fetal heart rate[c]	14,893 [8]	4.70	3.50–6.32	<0.001	0%	0.60	Small	0.840	None	Stable	Very Low	Large effect size but large inconsistency and high risk of bias
Male infant[c]	953,922 [10]	1.15	0.98–1.36	<0.001	26%	0.20	None	0.335	None	Fair	Very Low	High risk of bias and high risk of bias
Post term[c]	305,786 [7]	4.03	2.84–5.71	<0.001	36%	0.15	None	0.214	None	Stable	Low	Large effect size but high risk of bias
SGA[b]	878,078 [4]	1.97	1.76–2.20	<0.001	0%	0.76	None	0.475	None	Stable	Very Low	High risk of bias
Apgar <7 at 5 min[b]	74,548 [8]	14.89	9.52–23.28	<0.001	47%	0.07	None	0.983	None	Stable	Moderate	Very large effect size but high risk of bias

[a], combined analysis of identified risk factors: maternal fever, chorioamnionitis, maternal infection; [b], only one study provided adjusted effect size; [c], only effect sizes from univariate analysis were available. OR, odds ratio; CI, confidence interval; BMI, body mass index; SGA, small for gestational age; N/A, not applicable.

reported below were conducted on the univariate results. The listed fetal-neonatal risk factors, i.e., abnormal fetal heart rate (8 studies, OR 4.70, 95% CI: 3.50–6.32, P<0.001), male infant (10 studies, OR 1.15, 95% CI: 0.98–1.36, P<0.001), post-term (7 studies, OR 4.03, 95% CI: 2.84–5.71, P<0.001), SGA (4 studies, OR 1.97, 95% CI: 1.76–2.20, P<0.001), and Apgar <7 at 5 min (8 studies, OR 14.89, 95% CI: 9.52–23.28, P<0.001), were significant risk of MAS. There was no heterogeneity between studies for male infant (I^2=26%, P=0.20), SGA (I^2=0%, P=0.76), and post-term (I^2=36%, P=0.15), Apgar <7 at 5 min (I^2=47%, P=0.07), and abnormal fetal heart rate (I^2=0%, P=0.60). There was no evidence of publication bias and the stability of the conclusion was true for all fetal-neonatal risk factors. However, due to the results were from univariate analysis these results should be interpreted with caution.

Certainty of body of evidence

The certainty of evidence were very low for factors including maternal age >34-year-old, previous cesarean delivery, induction of labor, abnormal fetal heart rate, male infant, and SGA, due to the inconsistency from heterogeneity among studies and/or the high risk of bias of included studies (*Table 3*). The certainty of evidence remained at low level for factors including maternal BMI ≥30 kg/m^2 and maternal inflammatory response, due to large effect size but inconsistency and for post term and thick meconium due to large effect size but high risk of bias. The certainty of evidence was also low for nulliparous. The certainty for maternal fever, caesarean section and oligohydramnios were moderate due to large effect size (*Table 3*). The certainty for Apgar <7 at 5 min remained at moderate level due to very large effect size but high risk of bias (*Table 3*).

Discussion

Though the incidence and mortality of MAS decreased among the decades, MAS is still one of the causes leading to severe adverse outcome and may require advanced therapy of life support. To date, the predictor for MAS remains to be one of the topics for studies in this field. Clarifying the risk factors of MAS is of significance to early notify of the development of MAS which paves the way for early diagnosis and intervention, and may further reduce the use of advanced support caused by delayed intervention. In this study, instead of pre-defining risk factors at the start of the literature searching, we set the risks of interest after reading through the included article for reported factors, with the attempt to capture wider spectrum of information related to the topic. And we have identified a few factors that were understated in previous studies.

We included maternal fever and maternal chorioamnionitis specified by the article in terms of maternal inflammatory response, a concept that gained much attention in recent years (23-25). We did not include premature rupture of membrane (PROM) since PROM does not directly translate to maternal inflammatory response. The role of inflammation on MAS has gained increasing attention (23-25). Ashwal *et al.* (23) reported a trend, though not significant, of higher rate of MAS in relation to maternal fever (considering the overall incidence of MAS in the cohort, the insignificance might be due to the small sample size). Lee *et al.* (25) reported that intra-amniotic inflammation was associated to higher rate of MAS. Yokoi *et al.* (24) found that inflammatory biomarkers at birth of the neonate including C-reactive protein, haptoglobin were all relate to increased risk of MAS. Though the main pathological mechanism was considered to be triggered premature bowel peristalsis by intrauterine hypoxia-ischemia, there are studies proposing intrauterine inflammation as an independent variable for MAS development (25). A potential explanation might be that the elevated proinflammatory mediators such as interleukins and cytokine, transferred into the fetus, by swallowing or passing the cord, trigger bowel peristalsis and thus meconium passage in utero (23-25).

The other maternal factors analyzed in this study are all statistically significant. Smoking is reported to be a risk factor of neonatal morbidities other than MAS (67,68). A higher risk of SGA was reported in off-springs born to mothers smoking during pregnancy (68), which is another risk factor for MAS seen in this study. Maternal obesity, or BMI ≥30 kg/m^2, was focused more in industrialized countries. Furthermore, apart from a set high BMI, Persson *et al.* (60) showed that a dynamic increase in the BMI is also associated to higher risk of MAS, based on a nation-wide cohort study. Advanced maternal age was reported to be associated with post-term birth (49), which is also a significant risk factor for MAS demonstrated in this study. However, the limited number of combinable studies the large heterogeneity of studies reporting on maternal factors diminished the certainty of evidence of the reported results, calling for high-quality studies to further investigate into risk factors for MAS surrounding maternal characteristics.

Our data supports the previously identified peripartum and fetal-neonatal risk factors risk factors for MAS, such as oligohydramnios, caesarean section, thick meconium, abnormal fetal heart rate, post-term, SGA, and low Apgar score (2), of which the main pathway leading to MAS is intrauterine hypoxia. Among the aforementioned risk factors, low Apgar score had the largest effect size, which is a straight-forward consequence of intrauterine hypoxia.

Induction of labor seemed to be a protective factor. Paudel *et al.* (16), reported a different result with comparing different induction method to no induction. However, this study was dropped because of the large heterogeinty among studies and unstable results when including this study. The explanation to this result might be the population and medical strategy in Paudel *et al.* (16) varied from those from other studies. Further randomized trials can be an option to validate this finding.

Some of the risk factors reported in the study are highly linked to the socioeconomic and demographic characteristics of the study site and the study period. For example, in earlier articles, the aforementioned cesarean section, reported by a series of studies to be a risk factor for MAS, were not categorized as elective and emergency. Vivian-Taylor *et al.* (18) clarified that it was the emergency cesarean section to be the risk factor for MAS, and the elective cesarean section was seen to be protective. They further pointed out that instrumental delivery was also a risk factor, which was rarely reported by other studies. Industrialized countries tend to conduct more large cohort studies and analyze factors relating to demographic characteristics such as ethnicity, teenage mother and maternal obesity. Additionally, new medical management strategies, i.e., induction of labor, has also gained increasing attention in the latest decade. On the other hand, the developing countries focus more on analyzing direct data from the delivery process, such as Apgar score, meconium-stained amnionic fluids, blood markers. These differences indicated a social-economical and temporal impact on the reported factors. Though a large proportion of the target factors in the large cohort studies are hard to combine due to their uniqueness, we have listed all the analyzed factors in *Table 1*.

To comply to the inclusion criteria for the analysis, several studies reporting independent risk factors with well-established cohort were not enrolled, including birth trauma (66) and large distance from home birth to emergency obstetric services (64), one unit increase in BMI (60) and born to low-risk mothers at low-cesarean delivery hospitals (65).

The strength of this study includes large sample size of cases and controls as the incidence of MAS was low in general. Additionally, we attempted to control selection bias through a predefined protocol. However, there are several limitations to be pointed out. First, the majority of the included studies were small and at overall high risk of bias, especially those case-control studies. As mentioned above, a lot of factors analyzed by the high-quality cohort studies were too unique to combine, resulting in limited number of pooled analyses with limited quality of studies. Second, the standard for MAS diagnosis varied over time. The enrolled studies did not conduct independent evaluation of MAS, but extracted data through medical records, which may lead to heterogeneity in MAS definition. Third, we could not eliminate language bias as only English databases were searched. Moreover, differences in socioeconomic conditions, lifestyles, and available therapies and medical strategies may introduce large inter-study heterogeneity, undermining the certainty of the conclusion. Also, we were unable to run the sub-analysis according to study era for most of the factor due to the large heterogeneity, hence we were not able to answer whether the effect size of risk factor altered over the decades. Last but not least, the majority of certainty of evidence ranged between very low to low due to the observational nature of the studies. However, since risk factors like maternal, peripartum, and fetal-neonatal characteristics cannot be analyzed by randomized controlled trials, our meta-analysis of observational studies can serve as a source of evidence.

Conclusions

In conclusion, despite the limitations, our study provides evidence reporting the risk factors associating to MAS development. As MAS is a disease with multiple risk factors, all 15 risk factors reported can be considered as potential impacting factors. In clinical practice, maternal smoking and obesity should be controlled and induction of labor can serve as a protective factor. The overall limited quality of relevant case-control studies necessitates further high-quality researches. The limited number of combinable studies focusing on maternal risk factors indicates more attention on the association of maternal characteristics to MAS should be paid in future studies.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-23-5/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-23-5/coif). LQ serves as an unpaid managing editor of *Pediatric Medicine*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1

Search date 2022.5.30-6.1

PubMed 265
(((((((((Meconium aspiration syndrome[Mesh]) OR (Meconium aspiration syndrome[Title/Abstract]) OR (Meconium aspiration syndrome[Title/Abstract])) OR (Aspiration Syndrome, Meconium[Title/Abstract])) OR (Syndrome, Meconium Aspiration[Title/Abstract])) OR (Meconium Aspiration[Title/Abstract])) OR (Aspiration, Meconium[Title/Abstract])) OR (Meconium Inhalation[Title/Abstract])) AND ((((((((((“Infant, Newborn”[Mesh]) OR (Infant, Newborn[Title/Abstract])) OR (Infants, Newborn[Title/Abstract])) OR (Newborn Infant[Title/Abstract])) OR (Newborn Infants[Title/Abstract])) OR (Newborns[Title/Abstract])) OR (Newborn[Title/Abstract])) OR (Neonate[Title/Abstract])) OR (Neonates[Title/Abstract])) OR (Infant[Title/Abstract])) OR (Infants[Title/Abstract]))) AND ((((((((((((((((((“Risk Factors”[Mesh]) OR (Risk Factors[Title/Abstract])) OR (Factor, Risk[Title/Abstract])) OR (Risk Factor[Title/Abstract])) OR (Social Risk Factors[Title/Abstract])) OR (Factor, Social Risk[Title/Abstract])) OR (Factors, Social Risk[Title/Abstract])) OR (Risk Factor, Social[Title/Abstract])) OR (Risk Factors, Social[Title/Abstract])) OR (Social Risk Factor[Title/Abstract])) OR (Health Correlates[Title/Abstract])) OR (Correlates, Health[Title/Abstract])) OR (Population at Risk[Title/Abstract])) OR (Populations at Risk[Title/Abstract])) OR (Risk Scores[Title/Abstract])) OR (Risk Score[Title/Abstract])) OR (Score, Risk[Title/Abstract])) OR (Risk Factor Scores[Title/Abstract])) OR (Risk Factor Score[Title/Abstract])) OR (Score, Risk Factor[Title/Abstract]))

EMBASE.com 419
((‘Meconium aspiration syndrome’/exp) OR (‘Meconium aspiration syndrome’:ti,ab,kw) OR (‘Aspiration Syndrome, Meconium’:ti,ab,kw) OR (‘Syndrome, Meconium Aspiration’:ti,ab,kw) OR (‘Meconium Aspiration’:ti,ab,kw) OR (‘Aspiration, Meconium’:ti,ab,kw) OR (‘Meconium Inhalation’:ti,ab,kw)) AND ((‘Newborn’/exp) OR (‘Infant’/exp) OR (‘Infant, Newborn’:ti,ab,kw) OR (‘Infants, Newborn’:ti,ab,kw) OR (‘Newborn Infant’:ti,ab,kw) OR (‘Newborn Infants’:ti,ab,kw) OR (‘Newborns’:ti,ab,kw) OR (‘Newborn’:ti,ab,kw) OR (‘Neonate’:ti,ab,kw) OR (‘Neonates’:ti,ab,kw) OR (‘Infant’:ti,ab,kw) OR (‘Infants’:ti,ab,kw)) AND ((‘Risk Factor’/exp) OR (‘Risk Factors’:ti,ab,kw) OR (‘Factor, Risk’:ti,ab,kw) OR (‘Risk Factor’:ti,ab,kw) OR (‘Social Risk Factors’:ti,ab,kw) OR (‘Factor, Social Risk’:ti,ab,kw) OR (‘Factors, Social Risk’:ti,ab,kw) OR (‘Risk Factor, Social’:ti,ab,kw) OR (‘Risk Factors, Social’:ti,ab,kw) OR (‘Social Risk Factor’:ti,ab,kw) OR (‘Health Correlates’:ti,ab,kw) OR (‘Correlates, Health’:ti,ab,kw) OR (‘Population at Risk’:ti,ab,kw) OR (‘Populations at Risk’:ti,ab,kw) OR (‘Risk Scores’:ti,ab,kw) OR (‘Risk Score’:ti,ab,kw) OR (‘Score, Risk’:ti,ab,kw) OR (‘Risk Factor Scores’:ti,ab,kw) OR (‘Risk Factor Score’:ti,ab,kw) OR (‘Score, Risk Factor’:ti,ab,kw))

WOB 577
http://www.webofscience.com/wos/alldb/summary/eadaf559-9e5e-462a-878c-225c63f41115-3b65c535/relevance/1
(((((TS=(Meconium aspiration syndrome)) OR TS=(Aspiration Syndrome, Meconium)) OR TS=(Syndrome, Meconium Aspiration)) OR TS=(Meconium Aspiration)) OR TS=(Aspiration, Meconium)) OR TS=(Meconium Inhalation)
AND ((((((((((TS=(Infant, Newborn)) OR TS=(Infant)) OR TS=(Infants, Newborn)) OR TS=(Newborn Infant)) OR TS=(Newborn Infants)) OR TS=(Newborns)) OR TS=(Newborn)) OR TS=(Neonate)) OR TS=(Neonates)) OR TS=(Infants)
AND

Ovid medline 265
Ovid MEDLINE(R) ALL <1946 to May 27, 2022>

exp Meconium aspiration syndrome/ OR Meconium aspiration syndrome.mp OR Aspiration Syndrome, Meconium.mp OR Syndrome, Meconium Aspiration.mp OR Meconium Aspiration.mp OR Aspiration, Meconium.mp OR Meconium Inhalation.mp 2013
AND exp Infant, Newborn/ OR exp Infant/ OR Infant, Newborn.mp OR Infants, Newborn.mp OR Newborn Infant.mp OR Newborn Infants.mp OR Newborns.mp OR Newborn.mp OR Neonate.mp OR Neonates.mp OR Infant.mp OR Infants.mp
AND exp Risk Factors/ OR Risk Factors.mp OR Factor, Risk.mp OR Risk Factor.mp OR Social Risk Factors.mp OR Factor, Social Risk.mp OR Factors, Social Risk.mp OR Risk Factor, Social.mp OR Risk Factors, Social.mp OR Social Risk Factor.mp OR Health Correlates.mp OR Correlates, Health.mp OR Population at Risk.mp OR Populations at Risk.mp OR Risk Scores.mp OR Risk Score.mp OR Score, Risk.mp OR Risk Factor Scores.mp OR Risk Factor Score.mp OR Score, Risk Factor.mp 1312081

Scopus 515
(TITLE-ABS-KEY (“Meconium aspiration syndrome” OR “Meconium aspiration syndrome” OR “Meconium aspiration syndrome” OR “Aspiration Syndrome, Meconium” OR “Syndrome, Meconium Aspiration” OR “Meconium Aspiration” OR “Aspiration, Meconium” OR “Meconium Inhalation”) AND TITLE-ABS-KEY (“Newborn” OR “Infant” OR “Infant, Newborn” OR “Infants, Newborn” OR “Newborn Infant” OR “Newborn Infants” OR “Newborns” OR “Newborn” OR “Neonate” OR “Neonates” OR “Infant” OR “Infants”) AND TITLE-ABS-KEY (“Risk Factor” OR “Risk Factors” OR “Factor, Risk” OR “Risk Factor” OR “Social Risk Factors” OR “Factor, Social Risk” OR “Factors, Social Risk” OR “Risk Factor, Social” OR “Risk Factors, Social” OR “Social Risk Factor” OR "Health Correlates" OR “Correlates, Health” OR “Population at Risk” OR “Populations at Risk” OR “Risk Scores” OR “Risk Score” OR “Score, Risk” OR “Risk Factor Scores” OR “Risk Factor Score” OR “Score, Risk Factor”))

Cochrane 46
Search Name:
Date Run: 01/06/2022 01:41:22
Comment:

ID	Search	Hits
#1	MeSH descriptor: [Meconium Aspiration Syndrome] this term only	105
#2	(Meconium Aspiration Syndrome):ti,ab,kw OR (Meconium Inhalation):ti,ab,kw OR (Meconium Aspiration):ti,ab,kw OR (Aspiration, Meconium):ti,ab,kw OR (Aspiration Syndrome, Meconium):ti,ab,kw	311
#3	(Syndrome, Meconium Aspiration):ti,ab,kw	256
#4	{OR #1, #2, #3}	311
#5	MeSH descriptor: [Infant, Newborn] explode all trees	17497
#6	(Infants, Newborn):ti,ab,kw OR (Newborns):ti,ab,kw OR (Newborn):ti,ab,kw OR (Neonates):ti,ab,kw OR (Newborn Infants):ti,ab,kw	33140
#7	(Newborn Infant):ti,ab,kw OR (Neonate):ti,ab,kw	23111
#8	{OR #5, #6, #7}	33803
#9	MeSH descriptor: [Risk Factors] explode all trees	26247
#10	(Populations at Risk):ti,ab,kw OR (Population at Risk):ti,ab,kw OR (Correlates, Health):ti,ab,kw OR (Health Correlates):ti,ab,kw OR (Risk Factor):ti,ab,kw	86352
#11	(Factor, Risk):ti,ab,kw OR (Risk Factors, Social):ti,ab,kw OR (Social Risk Factor):ti,ab,kw OR (Risk Factor, Social):ti,ab,kw OR (Factors, Social Risk):ti,ab,kw	50942
#12	(Factor, Social Risk):ti,ab,kw OR (Social Risk Factor):ti,ab,kw OR (Risk Factor Score):ti,ab,kw OR (Risk Factor Scores):ti,ab,kw OR (Risk Score):ti,ab,kw	36609
#13	(Risk Scores):ti,ab,kw OR (Score, Risk Factor):ti,ab,kw OR (Score, Risk):ti,ab,kw	43540
#14	{OR #9, #10, #11, #12, #13}	131016
#15	{AND #4, #8, #14}	46

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Table S1 Summary of excluded fully read studies

Authors	Title	Year	Journal
Choi W., *et al.*	Risk factors differentiating mild/moderate from severe meconium aspiration syndrome in meconium-stained neonates	2015	*Obstetrics & Gynecology Science*
Kalra V. K., *et al.*	Change in neonatal resuscitation guidelines and trends in incidence of meconium aspiration syndrome in California	2020	*Journal of Perinatology*
Sandal G, *et al.*	The admission rate in neonatal intensive care units of newborns born to adolescent mothers	2011	*Journal of Maternal-Fetal and Neonatal Medicine*
Shah N, *et al.*	Comparision of obstetric outcome among teenage and non-teenage mothers from three tertiary care hospitals of Sindh, Pakistan	2011	*Journal of the Pakistan Medical Association*
Wertheimer A, *et al.*	The effect of meconium-stained amniotic fluid on perinatal outcome in pregnancies complicated by preterm premature rupture of membranes	2020	*Archives of Gynecology and Obstetrics*
Persson M, *et al.*	Maternal Overweight and Obesity and Risks of Severe Birth-Asphyxia-Related Complications in Term Infants: A Population-Based Cohort Study in Sweden	2014	*PLoS Medicine*
Hofer N, *et al.*	Meconium aspiration syndrome - A 21-years' experience from a tertiary care center and analysis of risk factors for predicting disease severity	2013	*Klinische Padiatrie*
Lin H. C, *et al.*	Meconium aspiration syndrome: Experiences in Taiwan	2008	*Journal of Perinatology*
Mohammad N, *et al.*	Meconium stained liquor and its neonatal outcome	2018	*Pakistan Journal of Medical Sciences*
Hiersch L, *et al.*	Meconium-Stained Amniotic Fluid and Neonatal Morbidity in Low-Risk Pregnancies at Term: The Effect of Gestational Age	2017	*American Journal of Perinatology*
Pariente Gali, *et al.*	Meconium-stained amniotic fluid--risk factors and immediate perinatal outcomes among SGA infants	2015	*The Journal of Maternal-fetal & Neonatal Medicine*
Raman Ts Raghu and Jayaprakash D G	Neonatal outcome in meconium stained deliveries - a prospective study	1997	*Medical Journal, Armed Forces India*
Shah S C, *et al.*	Neonatal outcome of macrosomia	2020	*Journal of Nepal Paediatric Society*
Janssen P A, *et al.*	Outcomes of planned home births versus planned hospital births after regulation of midwifery in British Columbia	2002	*CMAJ*
Malik A S, *et al.*	Prelabour rupture of membranes and neonatal morbidity in level II nursery in Kelantan	1994	*The Medical journal of Malaysia*
Urbaniak K J, *et al.*	Risk factors for meconium-aspiration syndrome	1996	*Australian and New Zealand Journal of Obstetrics and Gynaecology*
Addisu Dagne, *et al.*	Prevalence of meconium stained amniotic fluid and its associated factors among women who gave birth at term in Felege Hiwot comprehensive specialized referral hospital, North West Ethiopia: a facility based cross-sectional study	2018	*BMC pregnancy and childbirth*
Adhikari M, *et al.*	Meconium aspiration in South Africa	1995	*South African Medical Journal*
Adhikari S, *et al.*	Morbidities and Outcome of a Neonatal Intensive Care in Western Nepal	2017	*The Journal of the Nepal Health Research Council*
Ahi S, *et al.*	Correlation between Maternal Vitamin D and Thyroid Function in Pregnancy with Maternal and Neonatal Outcomes: A Cross-Sectional Study	2022	*International Journal of Endocrinology*
Arbib N, *et al.*	The pre-gestational triglycerides and high-density lipoprotein cholesterol ratio is associated with adverse perinatal outcomes: A retrospective cohort analysis	2020	*International Journal of Gynecology and Obstetrics*
Baloch K, *et al.*	Assessment of Neonatal Respiratory Distress Incidences with Causes, Mortality and Morbidity in a Tertiary Care Hospital	2020	*Journal of Pharmaceutical Research International*
Baseer Khaled A, *et al.*	Risk Factors of Respiratory Diseases Among Neonates in Neonatal Intensive Care Unit of Qena University Hospital, Egypt	2020	*Annals of Global Health*
Beaver K M and Wright J P	Evaluating the effects of birth complications on low self-control in a sample of twins	2005	*International Journal of Offender Therapy and Comparative Criminology*
Benny P S, *et al.*	Meconium aspiration - role of obstetric factors and suction	1987	*Australian and New Zealand Journal of Obstetrics and Gynaecology*
Bjorkman K and Wesstrom J	Risk for girls can be adversely affected post-term due to underestimation of gestational age by ultrasound in the second trimester	2015	*Acta Obstetricia et Gynecologica Scandinavica*
Bogomazova I M, *et al.*	Neonatal meconium aspiration: Risk factors and adaptation by the newborns	2019	*Obstetrics, Gynecology and Reproduction*
Bowe S, *et al.*	The association between placenta-associated circulating biomarkers and composite adverse delivery outcome of a likely placental cause in healthy post-date pregnancies	2021	*Acta Obstetricia et Gynecologica Scandinavica*
Brocklehurst P, *et al.*	Perinatal and maternal outcomes by planned place of birth for healthy women with low risk pregnancies: The Birthplace in England national prospective cohort study	2012	*BMJ (Online)*
Caughey A B, *et al.*	Neonatal complications of term pregnancy: Rates by gestational age increase in a continuous, not threshold, fashion	2005	*American Journal of Obstetrics And Gynecology*
Cavallin F, *et al.*	Risk factors for mortality among neonates admitted to a special care unit in a low-resource setting	2020	*BMC Pregnancy and Childbirth*
Chand Saroop, *et al.*	Factors Leading To Meconium Aspiration Syndrome in Term- and Post-term Neonates	2019	*CUREUS*
Cheng Yvonne W, *et al.*	The association between persistent occiput posterior position and neonatal outcomes	2006	*Obstetrics and Gynecology*
Colvin Z, *et al.*	Duration of labor induction in nulliparous women with hypertensive disorders of pregnancy and maternal and neonatal outcomes	2020	*Journal of Maternal-Fetal and Neonatal Medicine*
Conway D L, *et al.*	Isolated oligohydramnios in the term pregnancy: is it a clinical entity?	1998	*Journal of Maternal-Fetal and Neonatal Medicine*
Currie J and Rossin-Slater M	Weathering the storm: hurricanes and birth outcomes	2013	*Journal of Health Economics*
Dargaville P A and Copnell B	The epidemiology of meconium aspiration syndrome: Incidence, risk factors, therapies, and outcome	2006	*Pediatrics*
Darling E K, *et al.*	Distance from Home Birth to Emergency Obstetric Services and Neonatal Outcomes: A Cohort Study	2019	*Journal of midwifery & women's health*
David A N, *et al.*	Incidence of and factors associated with meconium staining of the amniotic fluid in a Nigerian University Teaching Hospital	2006	*Journal of Obstetrics and Gynaecology*
De Oliveira C A, *et al.*	Hypertensive syndromes during pregnancy and perinatal outcomes	2006	*Revista Brasileira de Saude Materno Infantil*
Duran R, *et al.*	The impact of Neonatal Resuscitation Program courses on mortality and morbidity of newborn infants with perinatal asphyxia	2008	*Brain & Development*
Espinheira M C, *et al.*	Meconium aspiration syndrome - the experience of a tertiary center	2011	*Revista Portuguesa de neumologia*
Fedakar A	The incidence and clinical features of meconium aspiration syndrome: A two-year neonatal intensive care experience	2019	*European Research Journal*
Firdaus U, *et al.*	Meconium stained amniotic fluid: A clinical study of maternal and neonatal attributes	2013	*Current Pediatric Research*
Fischer C, *et al.*	A Population-Based Study of Meconium Aspiration Syndrome in Neonates Born between 37 and 43 Weeks of Gestation	2012	*International Journal of Pediatrics*
Gluck O, *et al.*	Bloody amniotic fluid during labor - Prevalence, and association with placental abruption, neonatal morbidity, and adverse pregnancy outcomes	2019	*European Journal of Obstetrics & Gynecology and Reproductive Biology*
Gonen N, *et al.*	Placental Histopathology and Pregnancy Outcomes in "Early" *vs.* "Late" Placental Abruption.	2021	*Reproductive Sciences*
Gould J B, *et al.*	Cesarean delivery rates and neonatal morbidity in a low-risk population	2004	*Obstetrics and Gynecology*
Gupta P, *et al.*	Clinical and biochemical asphyxia in meconium stained deliveries	1998	*Indian Pediatrics*
Gupta R and Cabacungan E T	Neonatal Birth Trauma: Analysis of Yearly Trends, Risk Factors, and Outcomes	2021	*Journal of Pediatrics*
Gupta S K, *et al.*	Meconium aspiration syndrome in infants of HIV-positive women: A case-control study	2016	*Journal of Perinatal Medicine*
Gupta V, *et al.*	Meconium stained amniotic fluid: antenatal, intrapartum and neonatal attributes	1996	*Indian Pediatrics*
Hashim N, *et al.*	Primary cesarean section in grandmultiparity	2015	*Rawal Medical Journal*
Hofer N, *et al.*	Inflammatory indices in meconium aspiration syndrome	2016	*Pediatric Pulmonology*
Horgan M J, *et al.*	The relationship of thrombocytopenia to the onset of persistent pulmonary hypertension of the newborn in the meconium aspiration syndrome	1985	*New York State Journal of Medicine*
Khazardoost S, *et al.*	Risk factors for meconium aspiration in meconium stained amniotic fluid	2007	*Journal of Obstetrics and Gynaecology*
Kominiarek M, *et al.*	Gestational weight gain and obesity: Is 20 pounds too much?	2013	*American Journal of Obstetrics and Gynecology*
Lewis L, *et al.*	Obstetric and neonatal outcomes for women intending to use immersion in water for labour and birth in Western Australia (2015-2016): A retrospective audit of clinical outcomes	2018	*Australian and New Zealand Journal of Obstetrics and Gynaecology*
Oddie S J	Perspective on meconium staining of the amniotic fluid	2010	*Archives of Disease in Childhood: Fetal and Neonatal Edition*
Paz Y, *et al.*	Variables associated with meconium aspiration syndrome in labors with thick meconium	2001	*European Journal of Obstetrics and Gynecology and Reproductive Biology*
Perlman J N	Maternal fever and neonatal depression: Preliminary observations	1999	*Clinical Pediatrics*
Pourcyrous M, *et al.*	Significance of serial C-reactive protein responses in neonatal infection and other disorders	1993	*Pediatrics*
Qian L, *et al.*	Current status of neonatal acute respiratory disorders: A one-year prospective survey from a Chinese neonatal network	2010	*Chinese Medical Journal*
Sandstrom A, *et al.*	Durations of second stage of labor and pushing, and adverse neonatal outcomes: a population-based cohort study	2017	*Journal of Perinatology*
Saunders K	Should we worry about meconium? A controlled study of neonatal outcome	2002	*Tropical Doctor*
Schneiderman M and Balayla J	A comparative study of neonatal outcomes in placenta previa versus cesarean for other indication at term	2013	*Journal of Maternal-Fetal and Neonatal Medicine*
Shishavan M K, *et al.*	The association of hair coloring during pregnancy with pregnancy and neonatal outcomes: A cross-sectional study	2021	*International Journal of Women's Health and Reproduction Sciences*
Shrestha M, *et al.*	Profile of asphyxiated babies at Tribhuvan University Teaching Hospital	2009	*Journal of Nepal Paediatric Society*
Smid Marcela C, *et al.*	Maternal Super Obesity and Neonatal Morbidity after Term Cesarean Delivery	2016	*American Journal of Perinatology*
Spain, J. E, *et al.*	Risk factors for serious morbidity in term nonanomalous neonates	2015	*American Journal of Obstetrics and Gynecology*
Swain P K and Thapalial A	Meconium stained amniotic fluid - A potential predictor of Meconium Aspiration Syndrome	2008	*Journal of Nepal Paediatric Society*
Tay, S. K.	Spurious labor: A high risk factor for dysfunctional labor and fetal distress	1991	*International Journal of Gynecology and Obstetrics*
Thornton Patrick D, *et al.*	Meconium aspiration syndrome: Incidence and outcomes using discharge data	2019	*Early Human Development*
Tuuli Methodius G, *et al.*	Umbilical Cord Arterial Lactate Compared With pH for Predicting Neonatal Morbidity at Term	2014	*Obstetrics and Gynecology*

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Table S2 Results of the risk of bias assessment of case-control studies using the Newcastle - Ottawa quality assessment scale assessment tool

Author, year	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Total
Alchalabi 1999 (9)				*	*	*	*	*	5
Amitai Komem 2022 (4)		*		*	**	*	*	*	7
Avula 2017 (5)		*		*	*	*	*	*	6
Bhat 2008 (6)		*		*	*	*	*	*	6
Gad 2020 (7)				*	**	*	*	*	6
Gurubacharya 2015 (10)		*		*	*	*	*	*	6
Lee 2016 (43)		*		*	*	*	*	*	6
Liu 2002 (8)		*		*	*	*	*	*	6
Mehar 2016 (21)				*	*	*	*	*	5
Meydanli 2001 (11)				*	*	*	*	*	5
Oliveira 2019 (12)		*		*	*	*	*	*	6
Paudel 2020 (16)		*		*	**	*	*	*	7
Rossi 1989 (13)				*	*	*	*	*	5
Usta 1995 (14)				*	*	*	*	*	5
Vivian-Taylor 2011 (18)	*	*	*	*	**	*	*	*	9
Yoder 2002 (15)		*		*	*	*	*	*	6
Yokoi 2021 (22)	*	*		*	**	*	*	*	7

https://dx.doi.org/10.21037/pm-23-5

Table S3 Results of the risk of bias assessment of cohort studies using the Newcastle - Ottawa quality assessment scale assessment tool

Author, y	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total
Andersson 2022 (40)	*	*	*	*	**	*	*	*	9
Ashwal 2014 (27)	*	*	*	*	*	*	*	*	8
Ashwal 2018 (23)	*	*	*	*	*	*	*	*	8
Ashwal 2022 (28)	*	*	*	*	**	*	*	*	9
Bailey 2021 (29)	*	*	*	*	**	*	*	*	9
Blankenship 2020 (30)	*	*	*	*	*	*	*	*	8
Blomberg 2014 (41)	*	*	*	*	**	*	*	*	9
Cassidy 1985 (31)	*	*	*	*	*	*	*	*	8
Cedergren 2004 (42)	*	*	*	*	**	*	*	*	9
Cedergren 2006 (43)	*	*	*	*	**	*	*	*	9
Cederholm 2005 (44)	*	*	*	*	**	*	*	*	9
Cheng 2012 (45)	*	*	*	*	**	*	*	*	9
Chiruvolu 2018 (37)	*	*	*	*	**	*	*	*	9
Clausson 1999 (46)	*	*	*	*	*	*	*	*	8
De los Santos-Garate 2011 (17)	*	*	*	*	**	*	*	*	9
Ding 2021 (1)	*	*	*	*	**	*	*	*	9
Greenwood 2003 (32)	*	*	*	*	*	*	*	*	8
Flemming 2020 (47)		*	*	*	*	*	*	*	7
Johnson 2005 (48)	*	*	*	*	**	*	*	*	9
King 2012 (38)	*	*	*	*	**	*	*	*	9
Knight 2017 (49)	*	*	*	*	**	*	*	*	9
Kortekaas 2020 (50)	*	*	*	*	**	*	*	*	9
Levin 2020 (39)	*	*	*	*	*	*	*	*	8
Li 2019 (51)	*	*	*	*	**	*	*	*	9
Lindegren 2017 (52)	*	*	*	*	**	*	*	*	9
Lindegren 2020 (20)	*	*	*	*	**	*	*	*	9
Narchi 2010 (33)	*	*	*	*	**	*	*	*	9
Persson 2016 (53)	*	*	*	*	**	*	*	*	9
Petrova 2001 (54)	*	*	*	*	**	*	*	*	9
Polnaszek 2018 (19)	*	*	*	*	**	*	*	*	9
Pyykonen 2018 (55)	*	*	*	*	**	*	*	*	9
Rietveld 2015 (56)	*	*	*	*	**	*	*	*	9
Roos 2011 (57)	*	*	*	*	**	*	*	*	9
Salihu 2011 (58)	*	*	*	*	**	*	*	*	9
Stotland 2006 (34)	*	*	*	*	**	*	*	*	9
Tyrberg 2013 (59)	*	*	*	*	**	*	*	*	9
Usher 1988 (35)	*	*	*	*	**	*	*	*	9
Ward 2022 (36)	*	*	*	*	**	*	*	*	9

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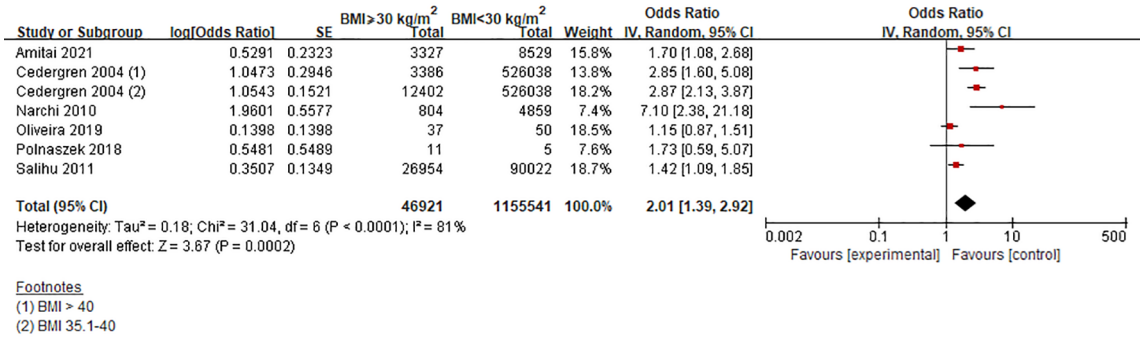


Figure S1 Forest Plot for maternal body mass index (BMI) ≥30 kg/m^2.

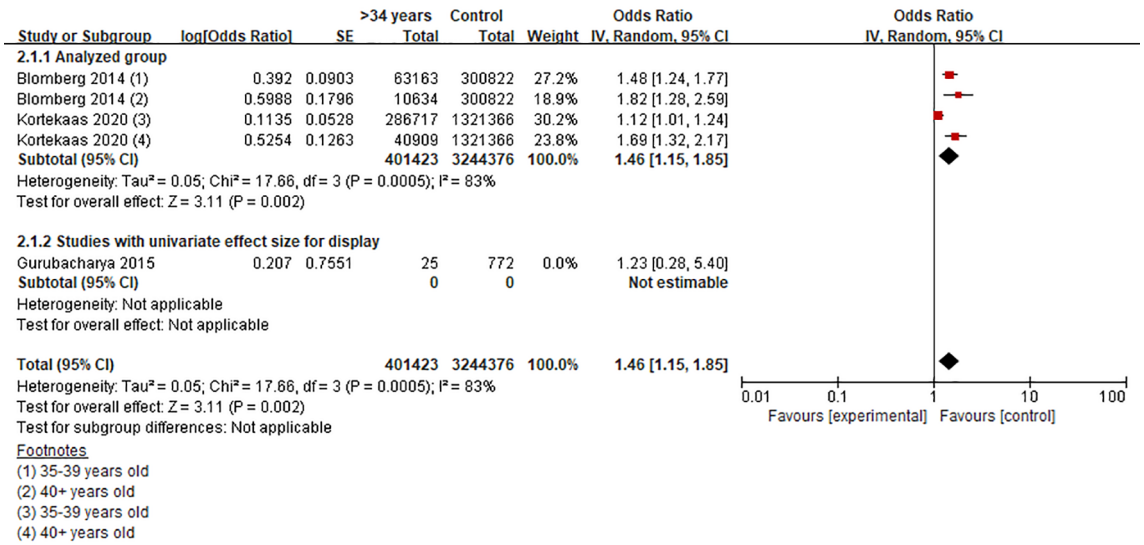


Figure S2 Forest Plot for maternal age >34 years old.

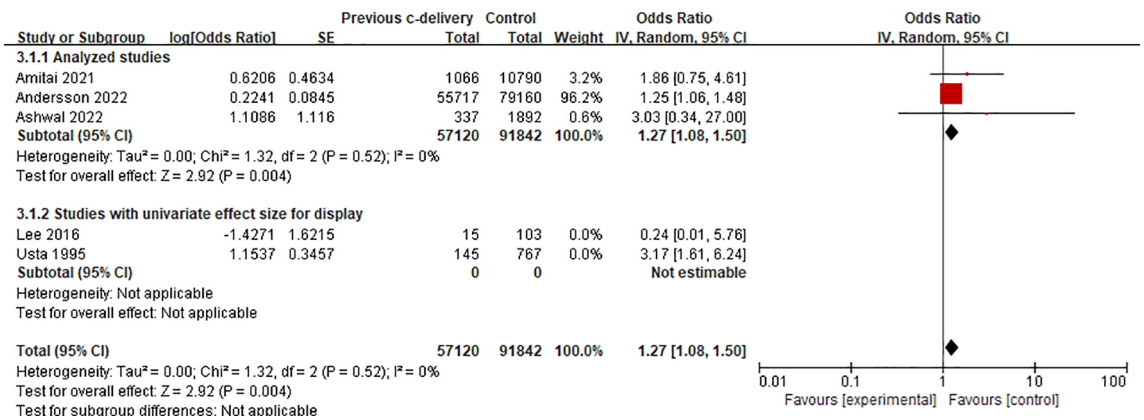


Figure S3 Forest Plot for previous caesarean delivery.

https://dx.doi.org/10.21037/pm-23-5

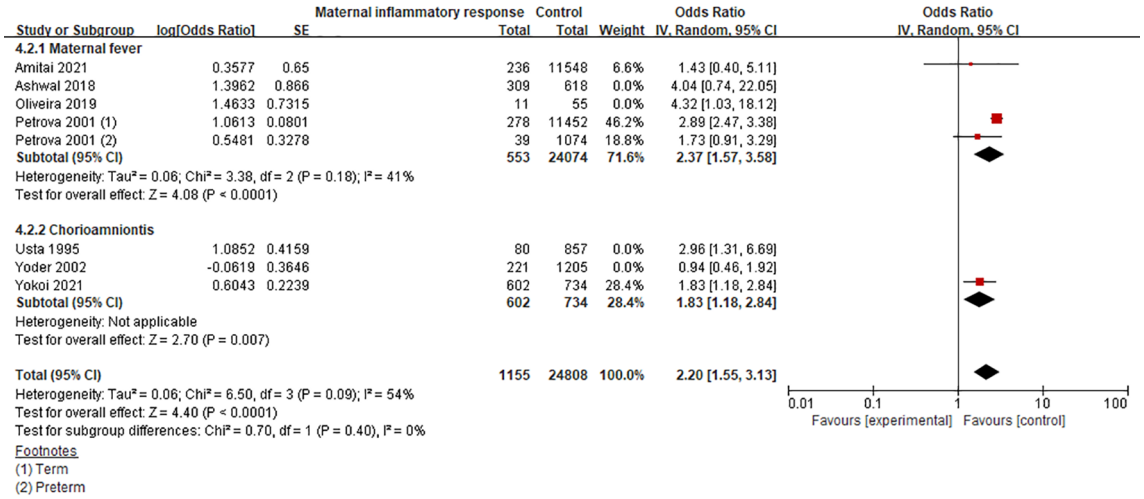


Figure S4 Forest Plot for maternal inflammatory response.

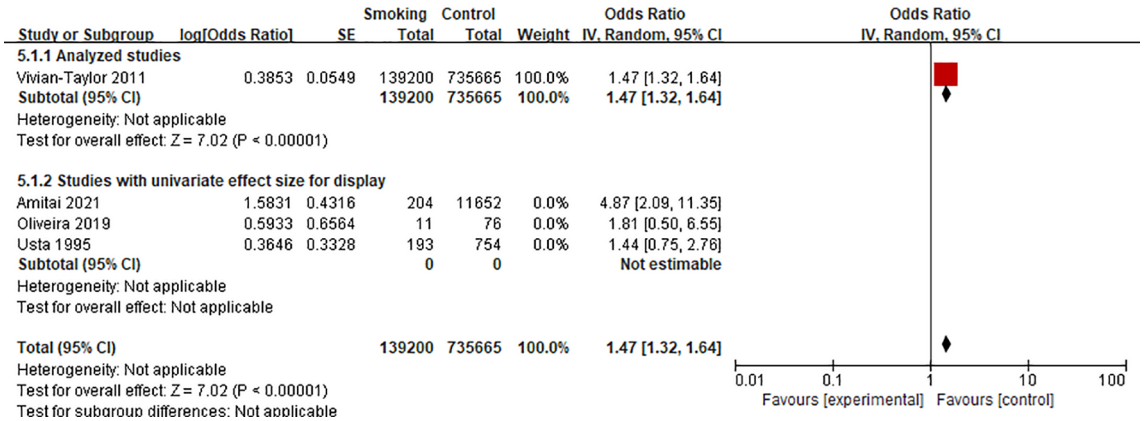


Figure S5 Forest Plot for maternal smoking.

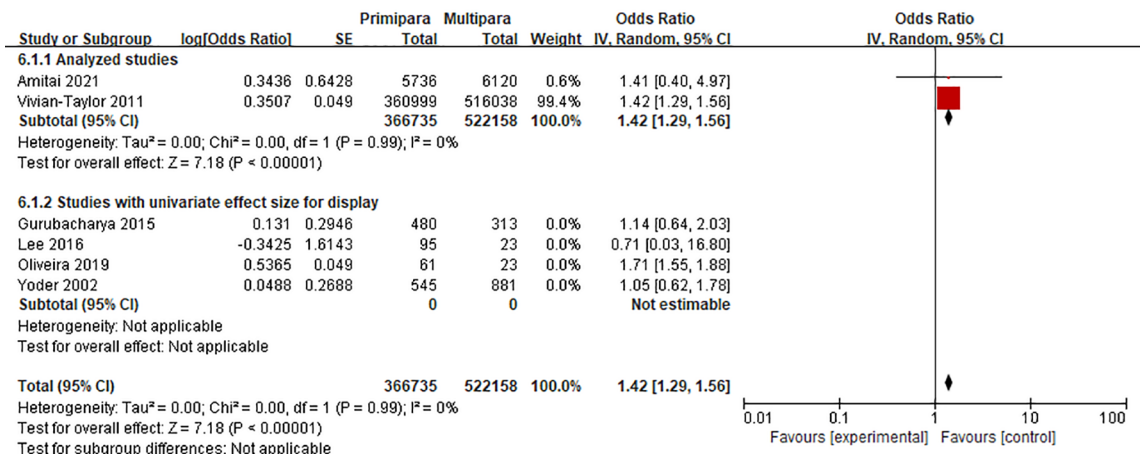


Figure S6 Forest Plot for nulliparous.

https://dx.doi.org/10.21037/pm-23-5

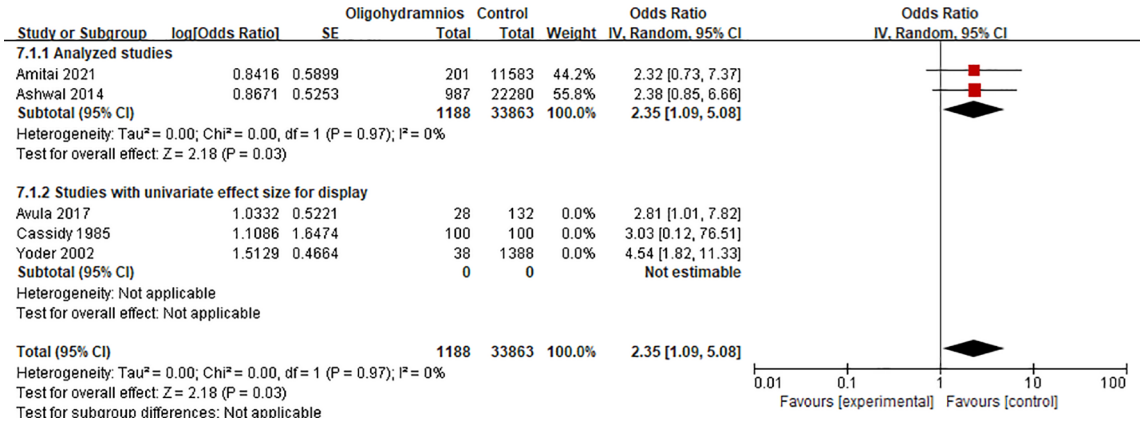
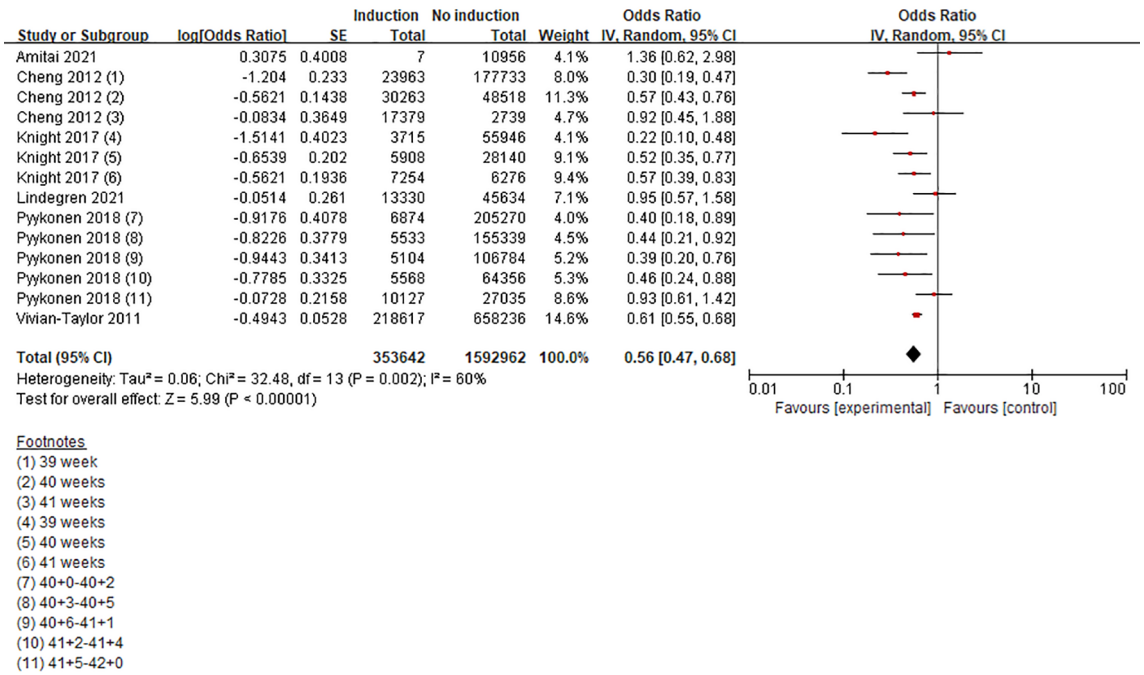


Figure S7 Forest Plot for oligohydramnios.



Footnotes
(1) 39 week
(2) 40 weeks
(3) 41 weeks
(4) 39 weeks
(5) 40 weeks
(6) 41 weeks
(7) 40+0-40+2
(8) 40+3-40+5
(9) 40+6-41+1
(10) 41+2-41+4
(11) 41+5-42+0

Figure S8 Forest Plot for induction of labor.

https://dx.doi.org/10.21037/pm-23-5

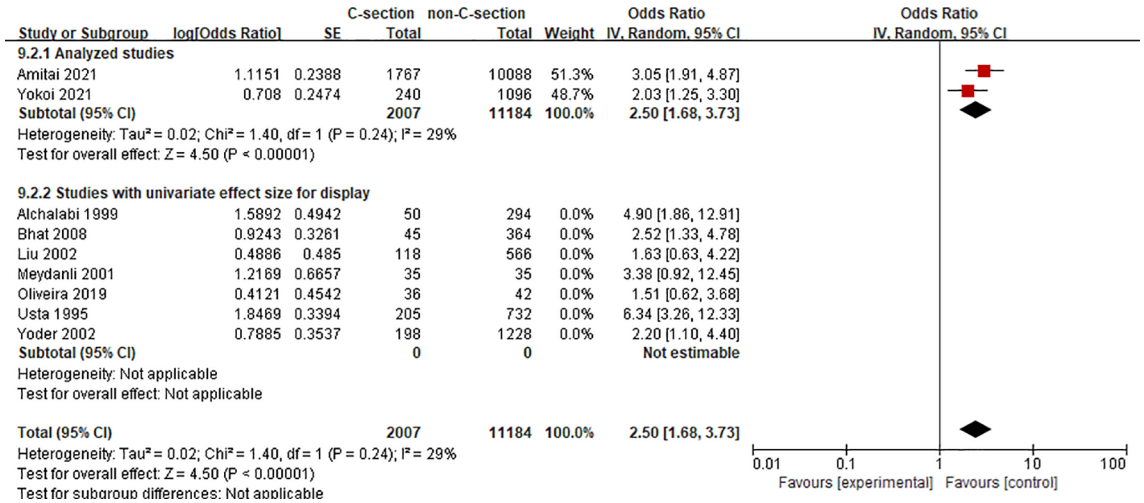


Figure S9 Forest Plot for cesarean delivery.

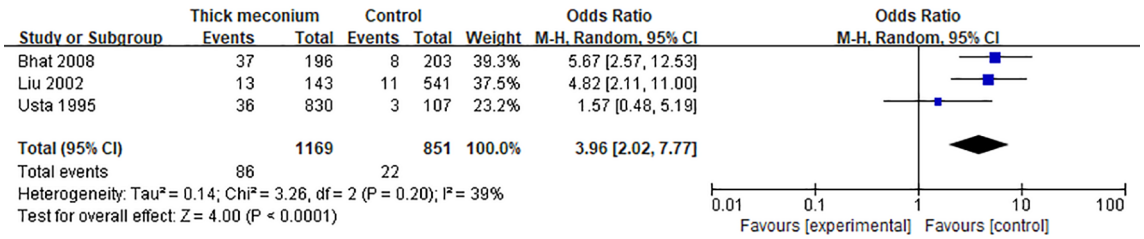


Figure S10 Forest Plot for thick meconium.

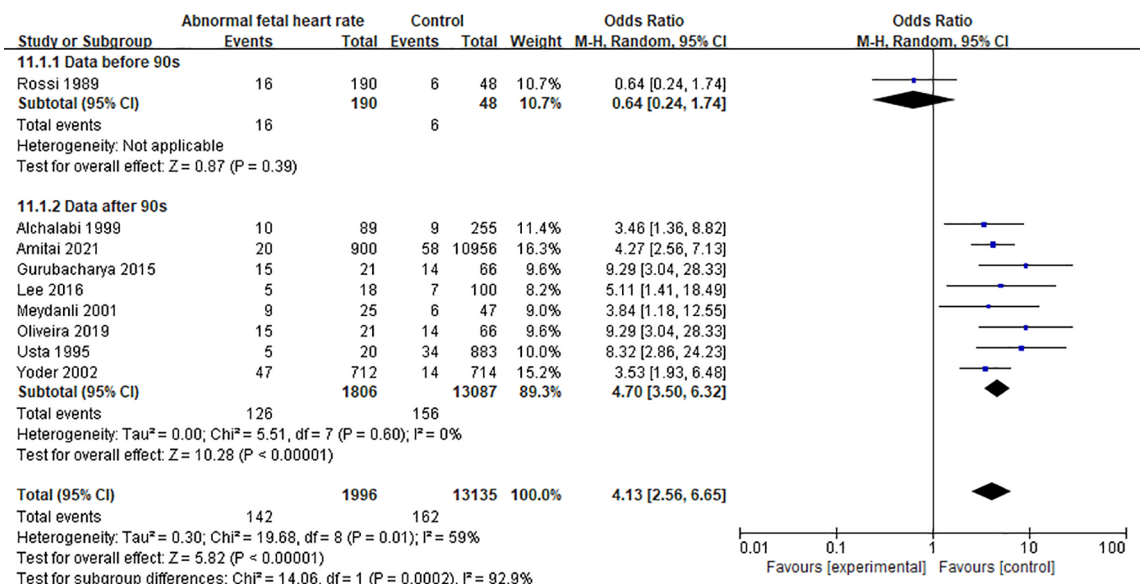


Figure S11 Forest Plot for abnormal fetal heart rate.

https://dx.doi.org/10.21037/pm-23-5

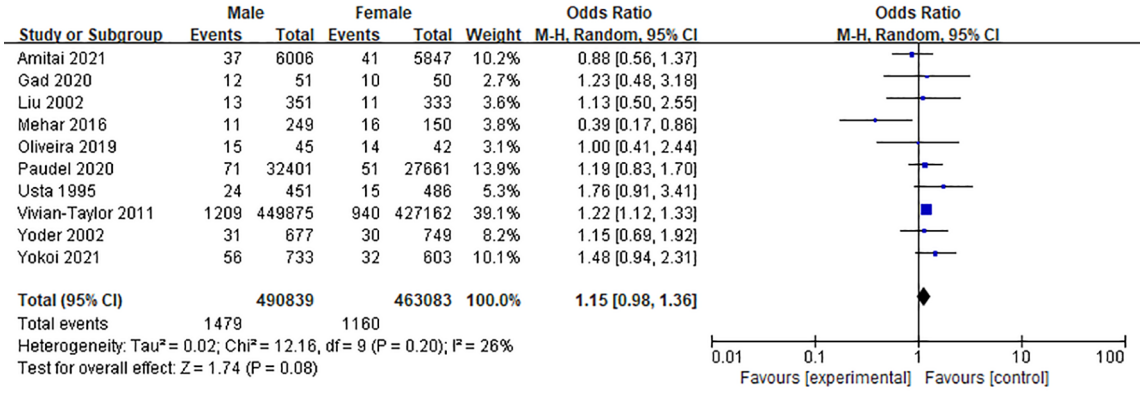


Figure S12 Forest Plot for gender.

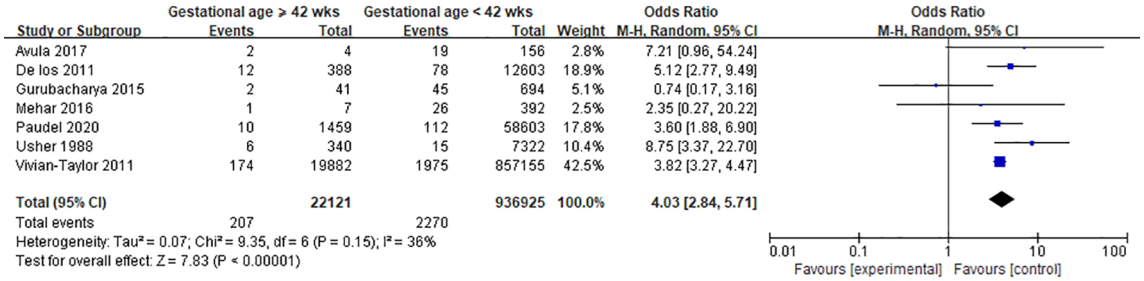


Figure S13 Forest Plot for post-term (gestational age ≥42 weeks).

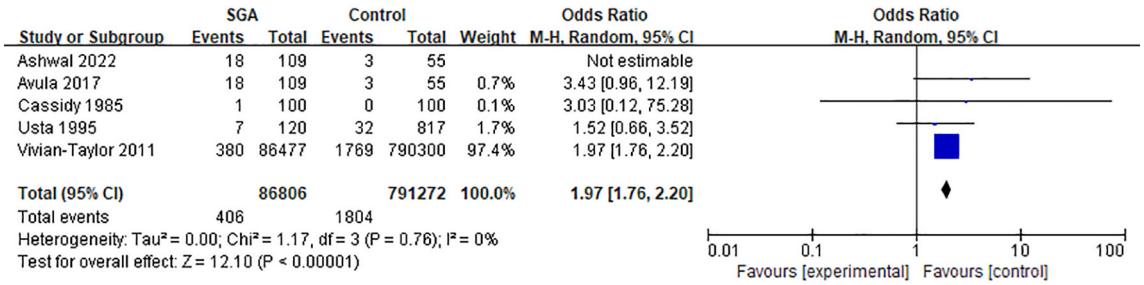


Figure S14 Forest Plot for small for gestational age (SGA).

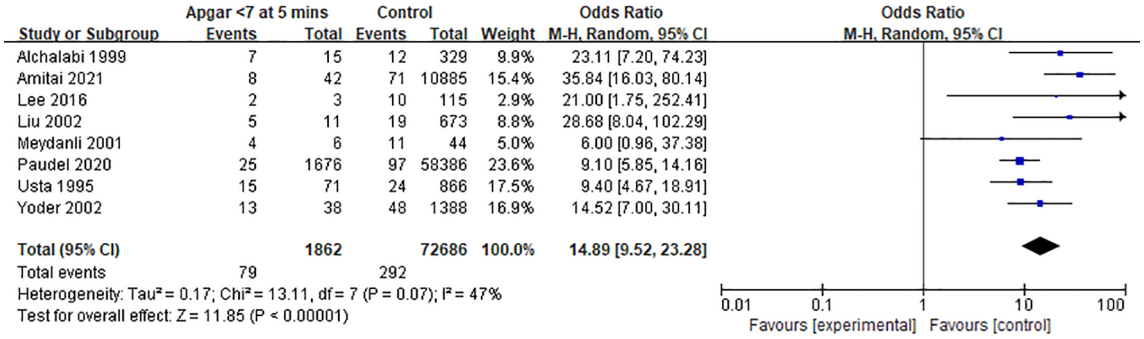


Figure S15 Forest Plot for Apgar <7 at 5 min.

https://dx.doi.org/10.21037/pm-23-5