Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis

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ABSTRACT The aim of this study was to systematically review and meta-analyse observational studies on prenatal maternal psychological stress and the subsequent development of asthma and wheezing in early childhood.

All available published literature from 1960 until November 2013 was systematically searched through electronic databases (PubMed, Embase, PsycInfo and Web of Science). All observational studies assessing associations between any form of prenatal maternal psychological stress and respiratory morbidity in the child were included. Data extraction, quality assessment and meta-analyses were performed.

The overall meta-analysis included 10 studies and showed that the prevalence of wheezing, asthma and other respiratory symptoms is higher in children of mothers who were exposed to or experienced some form of psychological stress during pregnancy than in mothers who did not (pooled OR 1.56 (95% CI 1.36–1.80)). Comparable results were observed in subgroup analyses of stress exposure, perceived stress, asthma and wheezing.

This study demonstrates that prenatal maternal psychological stress is associated with respiratory morbidity, including asthma and wheezing in the child. Future studies examining the early origins of asthma and wheezing need to account for the impact of prenatal maternal stress.

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Introduction

Asthma is a common chronic disease affecting ~300 million people worldwide [1]. The prevalence of asthma is increasing, especially in children [1, 2], and it is now the most common chronic disease in childhood [3]. A diagnosis of asthma is often preceded by wheezing in infancy [4, 5], for which prevalence estimates range 1.7– 32.2% [6].

Recent literature states that asthma originates in early life [5]. The Barker hypothesis [7], also known as "early life programming", describes that maternal disease and lifestyle factors can affect fetal development and growth, and can be linked with adverse effects on health outcomes in the offspring later in life [8]. Early life programming also applies to lung development and functioning. Lung development is influenced by both genetic and environmental factors, as well as by interactions between these factors, which may have persistent effects on lung function and respiratory health in later life [5, 9]. Therefore, the prenatal environment and condition of the fetus are important for the development of the respiratory system and may also play a role in the development of asthma [10].

Several factors may affect developmental processes and are associated with respiratory disease in later life. Potential risk factors during pregnancy include maternal smoking, suboptimal fetal nutrition, insufficient dietary intake, vitamin D deficiency, obesity and exposure to air pollution [10–14].

Associations between maternal psychological factors and *in utero* developmental processes were investigated in several prospective studies, which demonstrated long-term adverse physical and mental health outcomes in the child (*e.g.* emotional problems, attention deficit hyperactivity disorder, impaired cognitive development and diabetes) [15–17]. However, the effects of maternal psychological stress on the prenatal development of the respiratory system and postnatal respiratory health have not been studied extensively. The mechanisms through which psychological stress during pregnancy could influence the *in utero* development of the respiratory system are thought to involve disruption of the balance between the neuroendocrine system, the autonomic nervous system (ANS) and the immune system [18]. More specifically, prenatal maternal stress may influence the neuroendocrine system and hence the immune system through fetal programming of the hypothalamic–pituitary–adrenal (HPA) axis [19]. Based on these theories, it is conceivable that prenatal maternal psychological stress may affect respiratory function in the child. Investigating this relationship could provide new insights into the role of prenatal maternal psychological stress in the origins of asthma.

However, an overview of the influence of psychological stress during pregnancy on lung function in the child is lacking. The purpose of this systematic review and meta-analysis is to assess whether an association exists between prenatal maternal psychological stress (stress exposure and perceived stress) and the development of respiratory morbidity in childhood, specifically asthma and wheezing, and to gain a better understanding of prenatal vulnerabilities for lung development.

Methods

For the analysis of the association between prenatal psychological stress and the development of respiratory morbidity, we used search strategies that followed the Cochrane guidelines [20]. In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for adequate reporting were followed [21].

Search strategy

All available published literature from 1960 until 15 November 2013 was systematically searched using electronic databases. We searched PubMed, Embase, PsycInfo and Web of Science, including the Science Citation Index Expanded, the Social Sciences Citation Index and the Arts & Humanities Citation Index. Search terms were identified based on previous research and discussed by four of the contributing authors (K.F.E. van de Loo, J. Roukema, P.J.F.M. Merkus, and C.M. Verhaak). All search terms were individually adapted for each database, based on standardised subject terms, *e.g.* Medical Subject Headings (MeSH) terms or subject headings, and free-text terms. All search terms were checked by a librarian and the title, keywords and abstract of potentially eligible manuscripts were searched. To prevent bias, a broad search was performed based on separate search terms for participants, exposures and outcome measures. The participant terms were related to pregnant women (search terms were, for example, "pregnancy", "pregnant women", "maternal exposure" and "prenatal exposure"). The exposure variable search terms included all forms of prenatal maternal psychological stress, including all types of stress exposure (experiencing a stressful event) and perceived stress (experiencing stress symptoms) (search terms were, for example, "stress", "psychological stress", "mental health", "anxiety" and "depression"). We used respiratory morbidity, including both asthma and wheezing in childhood, as outcome search terms (search terms were, for example, "respiratory sounds", "asthma" and "bronchial hyperreactivity"). See online supplementary material S1 for a more detailed description of the search strategy. The results of all

databases were merged using reference management software Endnote X5 (www.endnote.com) and duplicates were removed. No studies were excluded based on language.

Inclusion criteria

The inclusion criteria for the systematic review were: 1) data pertaining to an original study (*i.e.* no review articles, editorials or commentaries); 2) no strict definitions necessary for "prenatal stress" (any study reporting "prenatal stress" was eligible regardless of the measurement performed) and "asthma" or "wheezing" (any study assessing any form of respiratory morbidity was included, regardless of the measurement), but a clear statement or understanding that "prenatal stress" was the exposure of interest and "asthma" and/or "wheezing" were the outcomes of interest in each eligible study was necessary; and 3) provision of an adjusted relative risk (RR), odds ratio (OR) or hazard ratio (or adequate data in order to compute these parameters).

Study selection

Studies were first selected based on careful screening of the titles by one author (K.F.E. van de Loo). To ensure no relevant studies were missed, the titles of the first 170 articles were screened by two authors (K.F.E. van de Loo and C.M. Verhaak). The results were compared and checked using the abstracts in case of disagreement. Secondly, two authors (K.F.E. van de Loo and M.M.H.J. van Gelder) independently screened the abstracts and subsequently the remaining full-text articles. Disagreements were resolved by discussion with a third author (C.M. Verhaak) until consensus was reached. κ statistics were calculated to assess the levels of agreement [22]. A snowballing method was also used to search for additional studies. The authors of some primary studies were contacted to provide missing or additional data when needed for the inclusion or exclusion of these studies (n=3).

Data extraction

Data on study design, time period, country, study cohort, number of participants, demographic variables, age of the children, assessment measures, timing of exposure, outcome variables and covariates were extracted by two authors (K.F.E. van de Loo and C.M. Verhaak). For all studies, the adjusted estimates as provided in the articles were extracted. Furthermore, we collected the available data on the number of pregnant women who experienced some form of psychological stress and the number of women who did not experience stress. Within these groups, we were interested in the number of children with and without respiratory morbidity. We contacted all authors by email for additional information when these data were not provided in the publications. On methodological grounds, we excluded studies that used data from identical study populations, based on identical samples, to avoid bias due to duplicate results.

Quality assessment

The methodological quality was scored using an adapted version of the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (online supplementary material S2) [23]. Quality assessment was based on three sets of criteria. First, the selection criteria, including representativeness of the cohort and included population, ascertainment of stress exposure and measurement of stress (prospective, retrospective). Secondly, the comparability criteria were used to investigate whether cohorts were comparable based on design or analyses by inclusion of predefined confounders, such as maternal smoking. Thirdly, the outcome criteria were applied, including the assessment of the outcome measure (asthma, wheezing) and adequacy of follow-up. Two independent authors (K.F.E. van de Loo and M.M.H.J. van Gelder) individually scored the quality assessment checklist for all included articles. Subsequently, the results were compared and discussed. Based on these discussions, the scales were adapted where necessary and were again independently scored, compared and discussed. A third author (C.M. Verhaak) was involved in the final discussion for an independent third opinion, which resulted in final quality ratings. Based on these ratings, the studies were grouped into low-quality (0–3), moderate-quality (4–6) and high-quality (7–8) studies.

Data analysis

To study the overall effect of prenatal maternal psychological stress on the development of any kind of respiratory morbidity in the child, we performed separate meta-analyses based on crude and adjusted measures. First, we performed an overall meta-analysis based on crude measures, calculated using dichotomous data on the number of pregnant women (stress *versus* no stress) and the number of children (asthma/wheezing *versus* no asthma/wheezing) from all included articles. Furthermore, separate meta-analyses (also using these dichotomous data) were performed for the effects of stress exposure and perceived stress, and for the outcome measures asthma and wheezing.

Secondly, we performed a meta-analysis based on the adjusted ORs with 95% confidence intervals (CIs) as mentioned in the original articles, regardless of which factors (for example, maternal age and smoking) were included in the adjusted analyses by the authors. If the adjusted OR was not mentioned, the article was not included in the adjusted meta-analysis. To analyse the results, the generic inverse variance method was used [20].

For all meta-analyses, to avoid bias by using one study sample more than once in each analysis, only one exposure and one outcome measure were included from each study. Regarding prenatal maternal psychological stress, if available, a composite score of multiple stress measures (multiple questionnaires) was used. When this was not possible, the score of only one questionnaire was entered in the meta-analysis. For example, when both an anxiety and a depression questionnaire were applied in a study, only one of these was entered in the meta-analysis. We choose to enter the measure that was most frequently used in the included studies, to make results more comparable. In this case, the anxiety measure was included in the meta-analysis as it was more frequently used than depression. The scores of the alternative measures (for example, depression) were entered exploratively to investigate whether these would have changed the results. As we used dichotomous measures, a differentiation was made between levels of stress exposure and/or perceived stress above *versus* below the clinical cut-off score.

For the overall effect on respiratory health, asthma was used when a study investigated both asthma and wheezing. When multiple types of wheezing were analysed, we divided the results into two groups: wheezing (sum of all different types) *versus* no wheezing. Where studies presented the results of multiple age groups, we used the oldest group for analysis.

All meta-analyses were performed using a random effect model according to the DerSimonian and Laird method [24] to calculate the pooled ORs with 95% CIs. Heterogeneity between the studies was investigated using I^2 [25]. If heterogeneity was >50%, it was rated as substantial. Some heterogeneity was expected beforehand, due to clinical diversity (differences in populations, participants, measurements and outcomes) between the studies. The clinical diversity regarding, for example, psychological stress (which measurements) and respiratory morbidity (which measures, how they were assessed), was investigated by exploring the study characteristics. Additionally, subgroup analyses were performed based on quality scores to investigate methodological bias in both the crude and adjusted meta-analyses. Outliers were not excluded from the analyses to avoid bias, but the results with and without outliers were described. Visual inspection of a funnel plot was used to investigate publication bias when ⩾10 studies were available. All analyses were performed using RevMan version 5.0 (http://www.tech.cochrane.org/revman).

Results
Study selection
The systematic searches of the databases yielded 2572 non-duplicated results of which 2175 articles were excluded based on title only. Reasons for exclusion were, for example, asthma or wheezing in the mother instead of the child, and animal studies. Good agreement was found between the authors for screening of the first 170 titles (κ=0.70). Initial disagreement did not lead to inclusion of any extra articles. The abstracts of the 397 selected articles were independently screened by two authors with "excellent agreement" (κ=0.83). This resulted in 24 full-text articles being screened for eligibility (κ=0.72; "good agreement") and a total of 14 studies that were included based on the inclusion criteria (figure 1). The snowball method revealed no additional studies. Three out of 14 eligible publications were excluded from the meta-analysis because they studied the same cohorts [26–28]. One study was excluded because of insufficient data and unsuccessful contact with the authors [29].

Study characteristics
Table 1 shows a detailed description of the study characteristics. Eight studies were cohort studies, one used a case–control design [36] and one was a cross-sectional study [34]. The quality ratings based on the NOS ranged 5–7 on a scale of 0–8. Three (30%) studies were classified as high quality and seven (70%) were classified as moderate quality (online supplementary material S3). In total, the studies included 58 different potential confounders in the multivariable models used to calculate adjusted risk estimates (between three and 25 per study). However, most studies included all potential confounders in the multivariable models, irrespective of whether these confounded the association of interest or not. The most frequently included co-variables were: preterm birth, breastfeeding, race/ethnicity, parental asthma or allergy (all in four studies), maternal age (five studies), smoking during pregnancy (six studies), maternal educational level and sex of the child (both in eight studies).

The psychological stress measures used in the included studies were diverse. Studies focused on stress exposure [27, 32], perceived stress [30, 31, 35–37] or both [33, 38]. Stress exposure was assessed in terms of experience of general life events (for example, any situation of loss or uneasiness) [32–34] or difficult life circumstances (such as financial strains) [38] in some studies, and as specific events (such as the loss
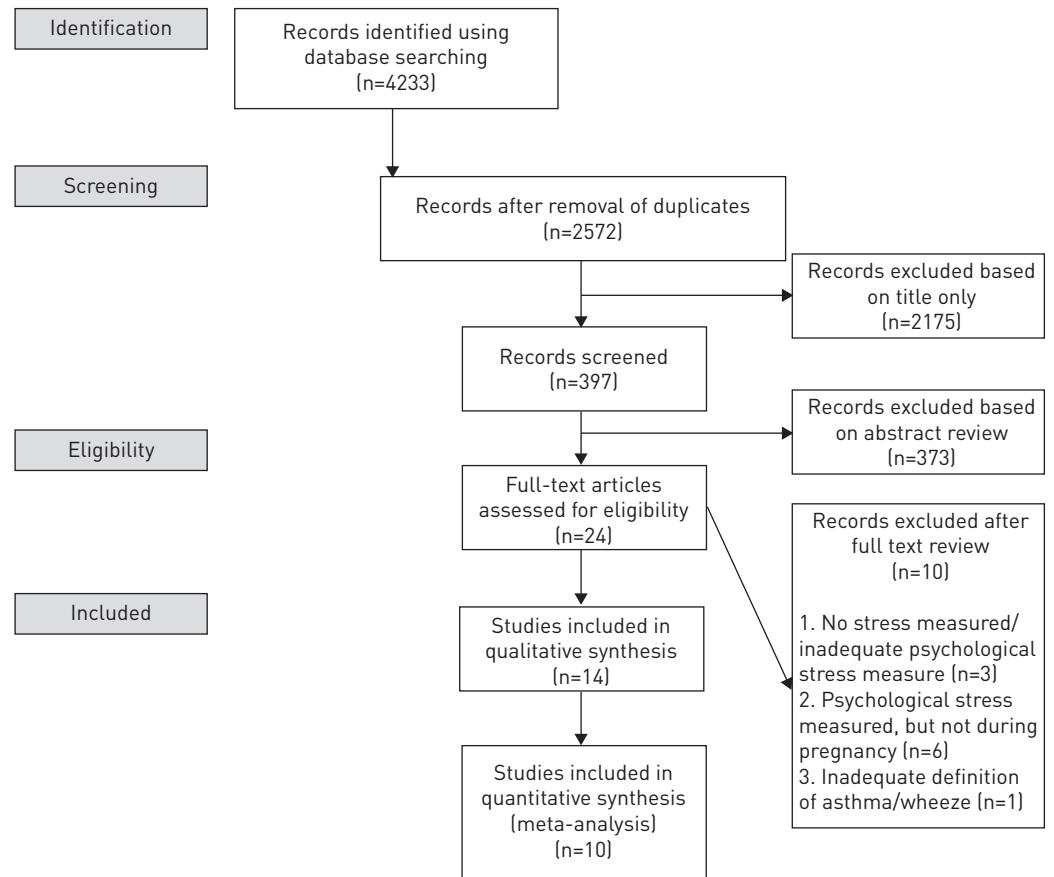
FIGURE 1 Study selection.

of a spouse or child) [27] in other studies. Perceived stress was assessed in terms of general stress symptoms (for example, "I feel unhappy") [30, 31, 35, 37, 38], anxiety ("I feel tense") [33, 36] or depression ("I feel hopeless") [33, 36], as well in relation to a specific source of stress, such as pregnancy-specific anxiety or stress ("I worry about the health of the baby") [31, 38].

Five (50%) studies assessed wheezing as an outcome measure [30, 32, 36–38], while one study assessed asthma [27] and three (30%) studies assessed both [33–35]. One study assessed respiratory health in general as an outcome measure [31]. Wheezing was assessed at different ages in childhood, ranging 0–14 years (table 1 provides a more detailed description). Only one study provided results of wheezing at multiple ages [35]. Three studies reported results for the different types of wheezing: transient, late onset or persistent [35, 37], and single wheeze *versus* multiple wheeze [38]. Asthma was also assessed at different ages: at 6 [35] or 7.5 years of age [33], and at a mean±SD age of 8.5±3.2 years [34]. One study assessed asthma hospitalisation at different ages from birth and also performed an additional analysis on children from 6 years of age onwards [27].

Meta-analyses
Meta-analysis based on dichotomous measures
The overall meta-analysis using the numbers of children with asthma, wheezing and other respiratory morbidity in the groups who were exposed *versus* unexposed to prenatal stress showed a statistically significant result (OR 1.56 (95% CI 1.36–1.80), I^2=18%, 10 studies) with a low level of heterogeneity (figure 2). The subgroup analyses based on quality scores also revealed statistically significant results for the moderate-quality group (OR 1.54 (95% CI 1.30–1.84), I^2=0%, seven studies) and the high-quality group (OR 1.77 (95% CI 1.18–2.67), I^2=74%, three studies) separately. The level of heterogeneity in the high-quality group indicates a large degree of variability, partly due to the small number of studies included. There was no statistically significant difference between the high- and moderate-quality group (p=0.54; I^2=0%), suggesting a negligible chance of methodological bias. The funnel plot revealed a slight asymmetry, indicating some evidence of indirect publication bias (figure 3).

TABLE 1 Characteristics of the studies included in the meta-analysis

First author [ref.]	Subjects n	Design	Psychological stress	Gestational age at exposure	Measurement of psychological stress	Exposure included	Respiratory health	Age at assessment/ diagnosis	Measurement of respiratory health	Outcome measure included	Most relevant effect size[#]	Quality assessment: NOS
Alton [30]	791	Follow-up study of a prenatal care trial	Maternal distress	Gestational weeks 7 and 32–34	Symptom Questionnaire (anxiety, depression, somatic, hostility scales).	Severe maternal distress (sum score of Symptom Questionnaire) *versus* no stress	Wheeze	3 years of age	Maternal report of a diagnosis of chronic breathing problems made by a healthcare worker.	Wheeze/no wheeze	**Severe prenatal stress: OR 2.62 (95% CI 0.92–7.43)[¶]**	6
Beijers [31]	174	Cohort study	General anxiety and stress; pregnancy-related anxiety and stress	Last trimester (mean: 37 weeks of pregnancy)	STAI (general anxiety); Alledaagse Problemen Lijst [Everyday Problem Checklist]; pregnancy-specific anxieties questionnaire revised; Pregnancy Experience Scale.	Sum of all questionnaires	Respiratory health	First 12 months of life	Mothers reported on their infant's illnesses and health complaints in semi-structured interviews at monthly intervals (three in person, nine by telephone). The health data were coded using ICD-10 and summed over 12 months.	Respiratory health (upper *versus* lower quartile)	Anxiety during pregnancy (STAI)[+]: B=1.465, β=0.132, R^2_{model}=0.232, F_{change}=5.614, R^2_{change}=0.093	5
Chiu [32]	653	Cohort study	Negative life events (NLEs)	Within 2 weeks of enrolment; mid-to-late pregnancy (28.4±7.9 week)	Crisis in Family Systems - Revised survey: measuring life events experienced across 11 domains in the past 6 months.	Prenatal NLEs	Wheeze	From birth to 2 years of age	Child wheeze reported by mother at telephone and face-to-face interviews at ~3-month intervals. Mothers were asked, "Since we last spoke with you on [date], has your infant/child had wheezing or whistling in the chest?" Repeated wheeze was defined as two or more episodes.	Repeated wheeze: more than two episodes *versus* less than two episodes	**NLE score ⩾5; OR 3.79 (95% CI 1.39–10.3)[§]**	7
Cookson [33]	5810	Cohort study	Anxiety; maternal depression; life events	Gestational weeks 18 and 32	Crown Crisp Experiential Index; Edinburgh Postnatal Depression Scale; Life Events Inventory.	Anxiety during pregnancy (4th quartile at 18 or 32 weeks)	Asthma; wheeze	7.5 years	Current asthma was defined as a report *via* questionnaire of a doctor's diagnosis of asthma-ever and either reported symptoms of wheeze or treatment for asthma in the previous 12 months.	Asthma/no asthma; wheeze/no wheeze	**Maternal anxiety 4th quartile Asthma 32 weeks: OR 1.65 (95% CI 1.30–2.08)[f]** Asthma 18 weeks: OR 1.53 (95% CI 1.22–1.93)[##]	7

TABLE 1 Continued

First author [ref.]	Subjects n	Design	Psychological stress	Gestational age at exposure	Measurement of psychological stress	Exposure included	Respiratory health	Age at assessment/ diagnosis	Measurement of respiratory health	Outcome measure included	Most relevant effect size [#]	Quality assessment: NOS
DE MARCO [34]	3854	Survey	Stressful life events	Any time during pregnancy (retrospectively assessed)	One question: "During pregnancy, did the mother experience any situations of loss or uneasiness (mourning, loss of her or her husband's job, separation/divorce)?"	Stressful life events during pregnancy Yes/No	Asthma; wheeze	3–14 years of age (mean ±SD 8.5±3.2)	A child was considered to have wheeze/ asthma based on the following questions: "Has your child ever had wheezing or whistling in his/her chest at any time in the past?"; "Has your child ever had asthma?"	Asthma/no asthma; wheeze/no wheeze	**Asthma: OR 1.71 (95% CI 1.02–2.89)[¶¶]** Wheezing: adjusted OR 1.41 (95% CI 1.03–1.94)	5
GUXENS [35]	4848	Cohort study	Psychological distress	20 weeks of gestation	Brief Symptom Inventory	Overall measure, anxiety[##] depression[##]	Wheeze; asthma	Wheeze was assessed at 1, 2, 3 and 4 years of age, asthma at 6 years of age	Adapted questionnaire (ISAAC): 1) no wheezing; 2) early wheezing; 3) late wheezing; 4) preschool persistent wheezing. Physician-diagnosed ever-asthma obtained using questionnaires.	Asthma/no asthma; wheeze (transient + late onset + persistent)/ no wheeze	**Asthma: overall distress-adjusted OR 1.45 (95% CI 0.91–2.31)[++]** Wheezing: overall distress-adjusted OR 1.60 (95% CI 1.32–1.93)	7
KHASHAN [27]	3 193 033	Cohort study	Bereavement	First (0–12 weeks), second (13–24 weeks) and third (25 weeks–birth) trimester	Death of a spouse or child.	Exposed/ unexposed during pregnancy	Asthma	All ages and additional analysis at >6 years of age	Hospital discharges from the National Patient Register. The primary outcome measure was defined according to the ICD codes of asthma (ICD-8, ICD-9 and ICD-10) from hospitalised patients.	Asthma/no asthma	Adjusted RR age of children >6 years of age: 2.01 (95% CI 1.16–3.49)[§§] Adjusted RR all ages: 1.43 (95% CI 1.06–1.92)	6
LEFEVRE [36]	247	Case–control study	Depression, anxiety	Anytime during pregnancy (retrospectively assessed)	Doctor's diagnosis, recorded at the hospital in "cases" and reported using a standardised questionnaire in "controls". In both, diagnoses and troubles were confirmed during an interview with a trained psychologist.	Anxiety during pregnancy, depression during pregnancy[##]	Wheeze	Before 2 years of age	More than three dyspnoeic episodes with wheezing, whatever the age of onset.	Wheeze (more than three episodes)/ no wheeze	**Anxiety: adjusted OR 1.98 (95% CI 0.69–5.68)[ff]** Depression: adjusted OR 1.55 (95% CI 0.12–19.8)[##]	5

Continued

TABLE 1 Continued

First author [ref.]	Subjects n	Design	Psychological stress	Gestational age at exposure	Measurement of psychological stress	Exposure included	Respiratory health	Age at assessment/ diagnosis	Measurement of respiratory health	Outcome measure included	Most relevant effect size[#]	Quality assessment: NOS
REYES [37]	279	Cohort study	Maternal demoralisation	Third trimester	PERI-D	High (score >1.55) versus low demoralisation	Wheeze	Every 3 months in the first 0–2 years, and every 6 months at 2–5 years	Mother/caregiver asked a binary question: "In the last 3 months has your child had wheezing or whistling in the chest?" Divided into: transient, late-onset and persistent wheezers.	Wheeze (transient + late onset + persistent)/ no wheeze	**Adjusted OR 1.66 (95% CI 1.29–2.14)[###]**	5
WOOD [38]	515	Cohort study	Internal stress; external stress	60% in third trimester, most of the remainder in the second trimester	Internal stressors: Pregnancy Anxiety Scale, EPDS, PSS. External stressors: difficult life circumstances, financial strain, neighbourhood violence, housing problems.	External stress (cumulative stress score), internal stress[##]	Wheeze	From birth until 12 months	Wheeze in the first 12 months (zero, one or more than two episodes of wheezing) assessed by telephone surveys performed every 3 months using the Respiratory and Allergy Symptoms questionnaire and during telephone calls at the time of illnesses, from records of hospitalisations caused by respiratory tract illnesses, and from physical examinations at scheduled study visits.	Wheeze (one or more episode)/no wheeze	Multiple wheeze: **External stress: adjusted OR 1.11 (p=0.10)[¶¶¶]** Mean EPDS score: adjusted OR 1.37 (p<0.01)[##] Mean PSS score: adjusted OR 1.59 (p=0.01)[##]	5

[#]: effect sizes in bold are included in the adjusted meta-analysis. [¶]: adjusted for prenatal maternal alcohol use, smoking and vitamin use, postnatal smoking, preterm birth, duration exclusive breastfeeding, maternal education level and out-of-home childcare. [+]: variables in initial regression model: maternal educational level, smoking during pregnancy, alcohol ingestion during pregnancy, birth weight, 5-min Apgar score, sex, number of siblings, postnatal anxiety, postnatal daily hassles, daily hassles, fear of giving birth, fear of bearing a child with disabilities and evening cortisol. Adjusted for duration of breastfeeding, child care attendance, pregnancy-specific hassles and cortisol decline. [§]: adjusted for child's sex, season of birth, race/ethnicity, education and self-reported maternal history of atopy, prenatal traffic-related air pollution (black carbon), household cockroach allergen and neighbourhood disadvantage index. [f]: adjusted for sex, preterm delivery, multiple birth, number of siblings, maternal age, maternal education, maternal history of asthma and allergy, prenatal tobacco smoke exposure and problems during pregnancy (diabetes, hypertension, steroid intake). [##]: analysed exploratively as alternative measures in meta-analyses. [¶¶]: adjusted for sex, age, of foreign descent (both non-Italian parents), parental education, parental smoking, parental asthma, person who filled in the questionnaire, residential area, traffic level near home, exposure to industrial pollution, exposures to mould, farm animals, bedroom sharing with older siblings, ever had a cat at home, ever had a dog at home, pregnancy conditions (hypertension, pre-eclampsia, risk of miscarriage or premature delivery, infection-induced fever, gynaecological infection, use of paracetamol), birth conditions (mother's age at delivery, birth weight, preterm birth, caesarean birth) and breastfeeding. [++]: adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, parity, parental history of asthma or atopy, pet keeping, children's sex, preterm birth, birth weight, breastfeeding, daycare attendance, secondhand smoke at home, eczema and lower respiratory tract infections. [§§]: adjusted for calendar year and age as time-dependent variables, family history of allergy, maternal age, infant sex and maternal level of education. [ff]: adjusted for propensity score, child's age, maternal asthma, maternal smoking habit during pregnancy and birthplace (Paris/outside Paris (France)). [###]: maternal (age at pregnancy, ethnicity, education, history of asthma and IgE) and child characteristics (sex, exposure to secondhand smoke and wheeze reported during the cold and flu season). [¶¶¶]: adjusted for study site, birth season of the child and child's sex. NOS: Newcastle-Ottawa Scale; STAI: Stait-Trait Anxiety Inventory; ICD-8, -9 and -10: International Classification of Diseases, 8th, 9th and 10th revision; B: regression coefficient; β: standardised regression coefficient; R^2_{model}: total explained variance by the model; F_{change}: F statistic corresponding to R^2_{change}; R^2_{change}: partial explained variable by added predictors; ISAAC: International Study of Asthma and Allergies in Childhood; RR: relative risk; PERI-D: Psychiatric Epidemiology Research Interview Demoralisation Scale; EPDS: Edinburgh Postnatal Depression Scale; PSS: Perceived Stress Scale.

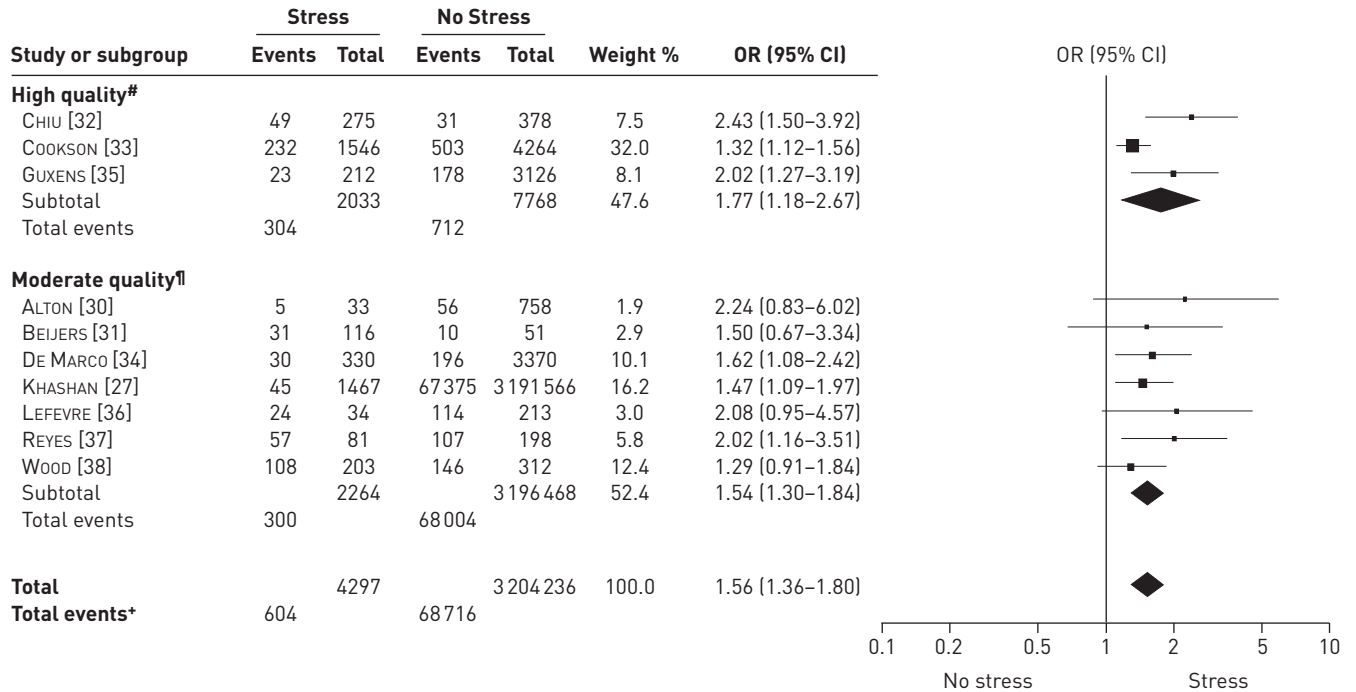| Study or subgroup	Stress Events	Stress Total	No Stress Events	No Stress Total	Weight %	OR (95% CI)
High quality[#]						
Chiu [32]	49	275	31	378	7.5	2.43 (1.50–3.92)
Cookson [33]	232	1546	503	4264	32.0	1.32 (1.12–1.56)
Guxens [35]	23	212	178	3126	8.1	2.02 (1.27–3.19)
Subtotal		2033		7768	47.6	1.77 (1.18–2.67)
Total events	304		712			
Moderate quality[¶]						
Alton [30]	5	33	56	758	1.9	2.24 (0.83–6.02)
Beijers [31]	31	116	10	51	2.9	1.50 (0.67–3.34)
De Marco [34]	30	330	196	3370	10.1	1.62 (1.08–2.42)
Khashan [27]	45	1467	67375	3191566	16.2	1.47 (1.09–1.97)
Lefevre [36]	24	34	114	213	3.0	2.08 (0.95–4.57)
Reyes [37]	57	81	107	198	5.8	2.02 (1.16–3.51)
Wood [38]	108	203	146	312	12.4	1.29 (0.91–1.84)
Subtotal		2264		3196468	52.4	1.54 (1.30–1.84)
Total events	300		68004			
Total		4297		3204236	100.0	1.56 (1.36–1.80)
Total events[+]	604		68716			

FIGURE 2 Overall meta-analysis (dichotomous measures, random effects model) of the association between any form of prenatal maternal psychological stress and respiratory morbidity in childhood, stratified according to study quality. [#]: heterogeneity: Tau^2=0.09, Chi-squared=7.59, df=2 (p=0.02), I^2=74%; test for overall effect: Z=2.75 (p=0.006). [¶]: heterogeneity: Tau^2=0.00, Chi-squared=3.15, df=6 (p=0.79), I^2=0%; test for overall effect: Z=4.89 (p<0.00001). [+]: heterogeneity: Tau^2=0.01, Chi-squared=10.94, df=9 (p=0.28), I^2=18%; test for overall effect: Z=6.21 (p<0.00001); test for subgroup differences: Chi-squared: 0.37, df=1 (p=0.54), I^2=0%.

Stress exposure *versus* perceived stress
Subgroup analyses revealed statistically significant effects of stress exposure during pregnancy (OR 1.58 (95% CI 1.26–1.99), I^2=34%, four studies), as well as perceived stress (OR 1.59 (95% CI 1.29–1.96), I^2=18%, six studies) on respiratory morbidity in the child (online supplementary material S4).

Asthma or wheezing as an outcome measure
Subgroup analyses also showed that children of mothers who experienced some form of stress during pregnancy were more often diagnosed with asthma compared with children of mothers who did not experience stress (OR 1.45 (95% CI 1.25–1.68), I^2=13%, four studies) (online supplementary material S5). In addition, wheezing complaints were more often found among children whose mothers experienced psychological stress during pregnancy compared with mothers who did not (OR 1.87 (95% CI 1.42–2.45),
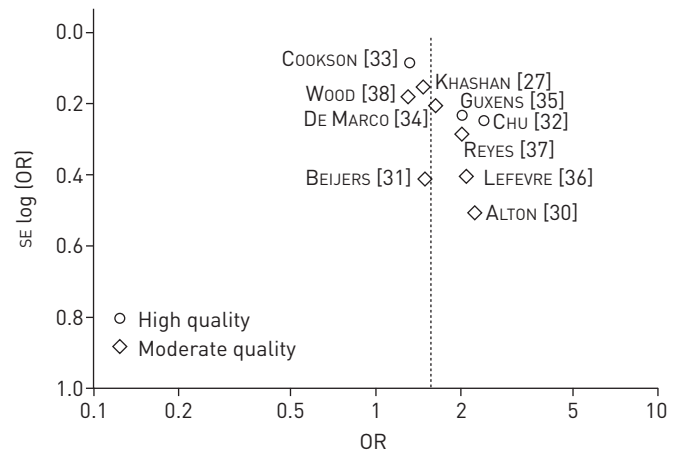

FIGURE 3 Studies included in the overall meta-analysis stratified by study quality.

I^2=76%, eight studies) (online supplementary material S6). A substantial level of heterogeneity was present in the latter subgroup analysis. Visual inspection of the forest plot revealed one potential outlier (OR 3.22 (95% CI=2.38–4.35)) [35]. Exclusion of this outlier decreased the overall OR to 1.57 (95% CI 1.33–1.84) and the I^2 to 25%.

Adjusted meta-analysis

The meta-analysis of the adjusted ORs as reported in the articles also showed that the prevalence of asthma, wheezing and other respiratory morbidity was higher in children whose mothers experienced some form of psychological stress during pregnancy compared with mothers who did not (OR 1.59 (95% CI 1.25–2.01), I^2=68%, eight studies) (figure 4). The OR was similar to the OR from the crude meta-analysis, but the level of heterogeneity was substantial. The potential confounders that were included in the individual studies differed greatly in number and type of confounder (table 1). Subgroup analysis based on quality scores, which were partly based on inclusion of the most important potential confounders (online supplementary material S2), revealed no statistically significant difference between the high- and moderate-quality groups (p=0.58). The results were statistically significant for the moderate-quality group (OR 1.51 (95% CI 1.11–2.05), I^2=68%, five studies) and the high-quality group (OR 1.71 (95% CI 1.25–2.33), I^2=32%, three studies), separately, despite the substantial level of heterogeneity in the moderate-quality group.

Timing of exposure

The exposure to prenatal stress was measured in different time periods (different trimesters, for example) and covered different time frames (the whole pregnancy or a single trimester) (table 1). Subgroup analyses on timings of the exposure were not possible due to this heterogeneity and the small number of studies. Only one study assessed the effect in the three trimesters of pregnancy separately, and found that the RRs of asthma related to exposure to maternal bereavement were elevated in each trimester, but were not statistically significant [27]. However, due to the very small number of exposed cases in each trimester, it was impossible to tell whether there were truly no effects or whether this was because of a lack of study power. Another study assessed the second and third trimester separately, and found evidence of a dose–response relationship for maternal anxiety symptoms reported at 32 weeks of pregnancy compared to 18 weeks, with larger effect sizes for non-atopic compared with atopic asthma [33]. Some studies assessed exposure any time during pregnancy [34, 36], or in the second [35] or third trimester only [31], while one study measured exposure during the third trimester as stress during the past year [37]. One study assessed the second trimester [35]. The remaining studies assessed the results of exposure in different trimesters together: the first and third trimester [30], or the second and third trimester [32, 38].

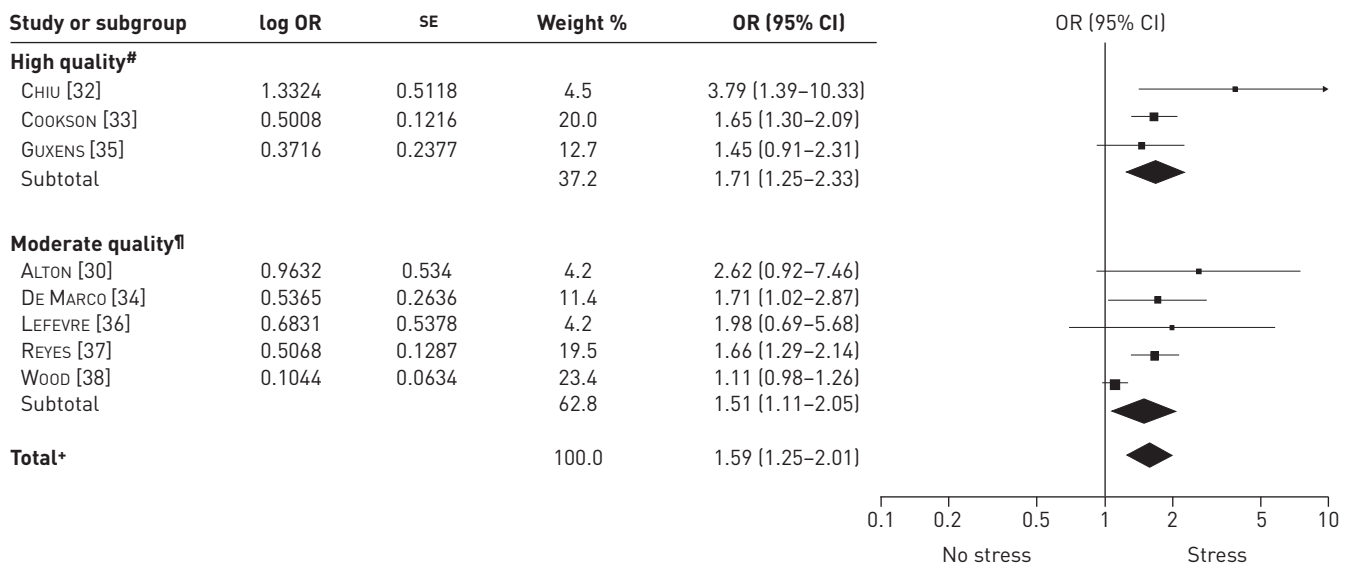| Study or subgroup	log OR	SE	Weight %	OR (95% CI)	OR (95% CI)
High quality#					
CHIU [32]	1.3324	0.5118	4.5	3.79 [1.39–10.33]	
COOKSON [33]	0.5008	0.1216	20.0	1.65 [1.30–2.09]	
GUXENS [35]	0.3716	0.2377	12.7	1.45 [0.91–2.31]	
Subtotal			37.2	1.71 [1.25–2.33]	
Moderate quality¶					
ALTON [30]	0.9632	0.534	4.2	2.62 [0.92–7.46]	
DE MARCO [34]	0.5365	0.2636	11.4	1.71 [1.02–2.87]	
LEFEVRE [36]	0.6831	0.5378	4.2	1.98 [0.69–5.68]	
REYES [37]	0.5068	0.1287	19.5	1.66 [1.29–2.14]	
WOOD [38]	0.1044	0.0634	23.4	1.11 [0.98–1.26]	
Subtotal			62.8	1.51 [1.11–2.05]	
Total+			100.0	1.59 [1.25–2.01]	

0.1 0.2 0.5 1 2 5 10

No stress — Stress

FIGURE 4 Overall adjusted meta-analysis (random effects model) using the generic inverse variance method on the association between any form of prenatal maternal psychological stress and respiratory morbidity in childhood, stratified according to study quality. #: heterogeneity: Tau^2=0.03, Chi-squared=2.93, df=2 (p=0.23), I^2=32%; test for overall effect: Z=3.35 (p=0.0008). ¶: heterogeneity: Tau^2=0.06; Chi-squared=12.39, df=4 (p=0.01), I^2=68%; test for overall effect: Z=2.61 (p=0.009). +: heterogeneity: Tau^2=0.06, Chi-squared=21.59, df=7 (p=0.003), I^2=68%; test for overall effect: Z=3.83 (p=0.0001); test for subgroup differences: Chi-squared=0.31, df=1 (p=0.58), I^2=0%.

Discussion

This is the first systematic review and meta-analysis of the association between prenatal maternal psychological stress and respiratory morbidity in the child. Both the meta-analysis based on crude data and the adjusted meta-analysis showed that prenatal psychological stress is associated with an increased risk of respiratory morbidity in the child. This association was also observed for the separate stress measures, stress exposure and perceived stress, and the individual outcome measures of asthma and wheezing, in both high- and moderate-quality studies. Literature regarding the influence of prenatal psychological stress on the development of respiratory morbidity in the child was searched from 1960 onwards, but the first article on this subject was only published in 2009. Between 2009 and the end of 2013, an additional 13 studies on this topic were published. This underscores the increasing interest in this new topic of research.

Before interpreting the results, it is important to discuss the strengths and limitations of this study. One limitation was the relatively small number of studies that could be included. By performing a meta-analysis, however, small but clinically relevant effects could be detected and a global hypothesis could be formed because of the heterogeneous groups [39]. Because the majority of studies used ORs as effect measures, we also calculated ORs in our meta-analyses. However, a sensitivity analysis in which we calculated RRs for the raw data using the numbers in figure 2, indicated that the ORs in the original studies and in this meta-analysis may overestimate the true effect sizes, due to the relatively frequently occurring outcomes, especially in some studies of moderate quality [36–38]. However, the ORs observed may underestimate the true effect sizes in some studies, because of non-differential misclassification in exposure and outcome variables. Although the RR from the overall meta-analysis (RR 1.38 (95% CI 1.23–1.54)) was somewhat lower than the overall OR (OR 1.56 (95% CI 1.36–1.80)), the result remained statistically significant and does not change the interpretation.

Because we performed separate meta-analyses, based on the crude and the adjusted-effect measures, the results were investigated with and without adjustment for confounders. Although the crude and adjusted-effect measures differed considerably within individual studies, the results of the meta-analyses were remarkably similar, with only slightly larger confidence intervals in the adjusted analyses. However, as all studies included different numbers and types of potential confounders and most did not separate out true confounders, conclusions about the influence of specific confounders could not be drawn. Inferences about indirect effects, such as for smoking or breastfeeding [40], could not be made either. The inclusion of potential confounders was also taken into account in the quality assessment, but the results of the meta-analyses showed no statistically significant differences between the moderate- and high-quality studies.

As dichotomous variables were used in the overall meta-analysis, it was not possible to obtain specific insights into the influence of the quantity and/or quality of stress experienced, or to assess a dose–response relationship. The amount of stress had to be above a cut-off score or in the 4th quartile for women to be classified as exposed, so only serious levels of stress were included in the exposure–outcome associations.

Visual inspection of the funnel plot showed some indication of publication bias. Moderate and high levels of asymmetry are common in meta-analyses with small study sizes, even in the absence of publication bias, and *vice versa* [41]. So there may be many reasons for the slight asymmetry observed in the funnel plot: publication bias, location bias, true heterogeneity, data irregularities, artefacts or chance [42]. It is possible that smaller studies without statistically significant effects remained unpublished. However, the quality assessment indicated that all studies included were of moderate or high quality, and the results showed no differences in the outcomes between the quality scores. Therefore, there seemed to be no indication of methodological bias. One study was excluded based on insufficient data and unsuccessful contact with the authors [29]. Given the size of the study population (n=66 203), inclusion of this study would have changed the overall results somewhat, but not drastically.

Before we performed this meta-analysis, we expected some clinical diversity among the different studies. This was confirmed by substantial levels of heterogeneity in the adjusted overall meta-analysis and in several subgroup meta-analyses. The levels of heterogeneity observed could be explained by true heterogeneity among populations regarding the prevalence of asthma and wheezing [2, 6], or may be due to heterogeneity in different types and measurements of respiratory health, timing of exposure, age of the child, confounders adjusted for, or the small numbers of studies included. Exclusion of one study from the sub-analysis on wheezing revealed low levels of heterogeneity among the remaining studies without substantial consequences for the effect measure.

Heterogeneity in definitions and measurements of psychological stress and respiratory morbidity hampered straightforward interpretation of the results. The psychological stress results showed that the studies included used different conceptualisations and different means of assessment. By exploring "stress" we made a distinction between stress exposure (for example, experiencing a stressful event, which could be major or minor) and perceived stress (experiencing stress symptoms, such as feeling tense), as exposure to

a stressor does not necessarily result in perceived stress [43]. Perceived stress is dependent on individual differences in dealing with the stressor, due to individual differences in perceived social support and/or coping styles, for example [44, 45]. By making this distinction, some important critical notes need to be addressed. First, the conceptualisations of perceived stress in the included studies are rather different, ranging from more global measures of stress (perceiving more or fewer symptoms of stress) to psychological dysfunction (normal *versus* pathological stress). Regarding the subgroup analysis on perceived stress, for example, one study assessed stress as a general measure of experiencing distress [35], while another assessed a diagnosis of anxiety or depression disorder [36]. Comparisons between more global measures of distress and assessment of psychological dysfunction could be interesting, but were not possible in the present study due to the small sample sizes.

Secondly, different types of stress could yield different physiological responses [44]. In cases of acute stress (such a life event), the physiological stress response could be protective and adaptive to maintain homeostasis, but could also be over-activated when stress is chronic; the latter results in allostatic overload and could have damaging effects [46, 47]. As this meta-analysis only encompassed stress exposure and perceived stress, specific conclusions about the distinction between stress exposure, perceived stress, psychological dysfunction or physiological reactions could not be drawn.

In addition to the differences in the concept of stress, a wide range of measurements are available for each definition, which complicates comparisons between studies [48]. As a result, conclusions about specific forms of stress exposure or perceived stress could not be drawn in this study. However, despite the heterogeneity in concepts and assessment methods used, the meta-analyses consistently revealed that prenatal psychological stress, and both stress exposure and perceived stress, are associated with adverse respiratory health outcomes in the child. This is in line with other studies regarding the negative impact of prenatal maternal stress on adverse health outcomes in the child [15, 16, 49–54].

Both asthma and wheezing were studied for child respiratory health. Recent literature shows that asthma is seen as a heterogeneous phenotype that originates in early life [55, 56]. A doctor's diagnosis of asthma is considered the most reliable and robust measure. In the studies included, asthma was often reported through a questionnaire completed by the child's mother [33, 35] or through a patient register [27]. One study asked a single question only, without referring to a doctor's diagnosis [34]. Wheezing has been described in different subtypes: transient early, late-onset, and persistent wheezing [57]. In the majority of children, wheezing is a transient condition in the first 3 years of life and is associated with a diminished airway function. For a small group of children, wheezing is a precursor for asthma. In the studies included, wheezing was measured in multiple ways: some made a distinction between the subtypes described above [35, 37], while others measured repeated wheeze as more than one or two [38], two [32], or three episodes [36], by one single question [34] or through maternal report of a doctor's diagnosis [30, 33]. The differences in diagnostic assessment measures were taken into account in the quality assessment ratings. As differences in methods used for diagnoses are a well-known problem, some protocols were developed to fill this gap, such as the International Study of Asthma and Allergies in Children (ISAAC) initiative [2, 58]. For wheezing, an international consensus group of the European Respiratory Society (ERS) task force classified preschool wheezing and preferred pharmacological treatment [59]. The application of standards is clearly required for future studies to reduce heterogeneity and avoid underestimation of effects.

This meta-analysis supports the hypothesis that prenatal maternal psychological stress has a negative influence on respiratory health in the offspring. However, the underlying mechanisms, such as how the psychophysiological stress responses from the mother are transferred to the child, are only partly understood. The following is hypothesised. *In utero*, lung development passes through several critical periods, starting around 26 days of gestation and following multiple stages [60]. It is known that prenatal stress has an influence on the programming of the immune function, which starts early in pregnancy when the stem cells are formed [61]. Prenatal maternal stress, acting through neuroendocrine, immune/ inflammatory and/or vascular pathways, may affect lung maturation, growth and function [52, 53, 62]. More specifically, maternal stress could disturb the balance between the interrelated neuroendocrine system, the ANS and the immune system, thereby leading to impaired lung function and immunity in the child [18]. It is conceivable that the HPA axis and the ANS are involved in this complex mechanism [18]. Furthermore, it is hypothesised that gene–environment interactions play an important role in the development of asthma [10], suggesting that multiple factors, both genetic and non-genetic, are involved.

For future prospective studies, we recommend the specification of outcome measures, such as different types of wheezing as well as asthma [59], and the incorporation of various types of stress exposure, perceived stress, psychological dysfunction and physiological reactions. Furthermore, the role of mediating factors (for example, smoking and exposure to air pollution) needs to be explored. Future research should also focus on the effects of prenatal maternal stress at different time points in pregnancy, relating to critical developmental

periods, as well as on dose–response relationships. Finally, it would be interesting to investigate the various mechanisms by which different types of prenatal maternal stress may influence *in utero* development of the respiratory system. Although this meta-analysis provides evidence for a negative impact of maternal stress during pregnancy on the development of the child, the clinical implications are still unclear.

In conclusion, this study shows that prenatal psychological stress plays a negative role in the development of asthma and wheezing in offspring. Based on this systematic review and meta-analysis, future studies examining the early origins of asthma need to account for the impact of prenatal maternal psychological stress.

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