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ORIGINAL ARTICLE

Risk and protective factors for childhood asthma and wheezing disorders in the first 1,000 days of life: a systematic review of meta-analyses

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Open acess

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Abstract

Introduction: The first 1,000 days of life of a child, the period from conception to the end of the second year, is a critical stage for the development of respiratory and immune systems. Many factors occurred in this period may be associated to risk of asthma in childhood.

Objective: To condense evidence about risk and protective factors for childhood asthma and/or wheezing disorders occurred in the first 1,000 days of life.

Methods: MEDLINE, CINAHL, and SCOPUS databases were searched. Systematic reviews with meta-analysis, or meta-analysis of observational and interventional studies on risk or protective factors for childhood asthma/wheeze, emphasizing the period between the conception and two first years of age, were included. The quality of studies was evaluated by the Assess Systematic Reviews tool. The pooled odds ratio, 95% confidence interval and homogeneity among studies were analyzed.

Results: Thirty-five studies met the inclusion criteria, with good methodological quality. Parental history of asthma; maternal weight gain during pregnancy, urogenital infections, psychological stress, and smoking; caesarean section; preterm birth; birth weight; and neonatal hyperbilirrubinemia are risk factors for asthma/wheeze in childhood. Intake of fish oil, zinc and vitamin E during pregnancy appear as protective factors, as well as breastfeeding, fish intake in the first two years, and BCG vaccination.

Conclusion: Several modifiable behaviors or exposures can be associated with asthma and wheezing in childhood. The knowledge about these behaviors and exposures can improve early prevention strategies with a view to ensuring a beneficial impact on respiratory health.

Keywords: asthma, child, protective factors, risk factors.

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Authors Summary

Why was this study done?
Asthma prevalence has been increasing worldwide, not only due to the genetic background, but also mainly because of the effect of environmental risk factors. Prenatal and postnatal environment exposures may disturb lung growth and delay immune system maturation, resulting in an increased susceptibility to asthma and wheezing disorders in childhood. Knowledge about the risk factors present in the first 1,000 days of life of children can support approaches and interventions capable of modifying the risk of asthma and/ or changing the course of the disease in childhood.

What did the researchers do and find?
This study condensed evidence about risk and protective factors for childhood asthma and/ or wheezing disorders occurred in the first 1,000 days of life. It was verified that several behaviors and/or exposures were associated with higher risk of asthma and wheezing disorders such as maternal weight gain during pregnancy, maternal urogenital infections, psychological stress, and smoking during pregnancy, caesarean section, preterm birth, birth weight, and neonatal hyperbilirrubinemia. On the other hand, intake of fish oil, zinc and vitamin E during pregnancy appear as protective factors, as well as breastfeeding, fish intake in the first two years, and BCG vaccination.

What do these findings mean?
Asthma is strongly influenced by modifiable environmental factors. The knowledge about these factors in the beginning of life can improve early prevention strategies with a view to ensuring a beneficial impact on respiratory health, changing the course of the disease in childhood.

INTRODUCTION

The first 1,000 days of life of a child, period from conception to the end the second year, has become a core focus to understand the developmental programming of disease predisposition in early life[1]. Initially, the efforts of this approach were focused on the role of nutrition in obesity, adiposity, diabetes and non-communicable diseases[2,3]. However, other exposures during this period can influence many aspects of the development of allergic diseases and should be regarded as a core part of this program[1,4].

The period between birth until the first two years of life is a "window of susceptibility" or a critical stage because both the respiratory and immune systems are immature at birth and have a prolonged period of postnatal maturation[5,6]. For this reason, prenatal and postnatal environment exposures may disturb lung growth and delay immune system maturation, resulting in an increased susceptibility to asthma and wheezing disorders in childhood[7].

Many epidemiological studies have suggested a wide range of factors that occur in the first 1,000 days of life may be associated to risk of asthma. However, for many of these factors, there seems to be not sufficient scientific evidence to support causal pathways between them and the development of asthma in childhood. For this reason, the aim of the present study was to condense evidence about risk and protective factors occurred between the conception and the first two years of age that are involved in childhood asthma and/or wheezing disorders.

METHODS

Data sources and searches

The searches were performed by two investigators in MEDLINE via OVID, Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO, and SCOPUS from inception until the first week of May 2017. Search terms included MeSH terms and free texts [*e.g.*, (risk factors OR protective factors) AND (asthma OR wheeze) AND (child) AND (meta-analysis)]. Searches in the databases were complemented by hand searching reference lists of the included studies. No language or initial time restriction was adopted.

Study selection

The present review included systematic reviews with meta-analysis, or meta-analysis of observational and interventional studies on risk or protective factors for childhood asthma, emphasizing the period between the conception and two first years of age. Meta-analyses from databases, such as cohort studies, were also included. The main outcome was diagnosis of asthma, with or without verification of medical records, or the symptom of wheezing. Studies analyzing the main outcome in wide age range were included only if they included analyses in the childhood. Genetic and molecular research, as well as pharmacologic treatments, were excluded from this review.

This systematic review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[8], and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42017069852). Two researchers analyzed the results of the search independently to find potentially eligible studies. First, the studies were sorted according to title, then the abstracts were analyzed and only the potentially eligible studies were fully assessed. Based on the abstracts, full articles were acquired for full review and considered for analysis. Any disagreement between the researchers was resolved by consensus.

Data extraction and synthesis

Two researchers analyzed and extracted the data from the selected systematic reviews using a standardized form. The extracted information included: 1) number of studies included in each meta-analysis; 2) total number of subjects included in each study; 3) design of the studies included in each meta-analysis; 4) pooled odds ratio (OR) or relative risk (RR) and respective 95% confidence interval (CI); 5) measure of homogeneity among studies, such as I^2 statistic or Cochran's Q statistic. In the interpretation of heterogeneity, I^2 value of 0% indicates no heterogeneity, and larger values show increasing heterogeneity (25% - low, 50% - moderate and 75% - high)[9]. In this present review, the exposures were considered as "risk factor" or "protective factor" when the heterogeneity was null or low.

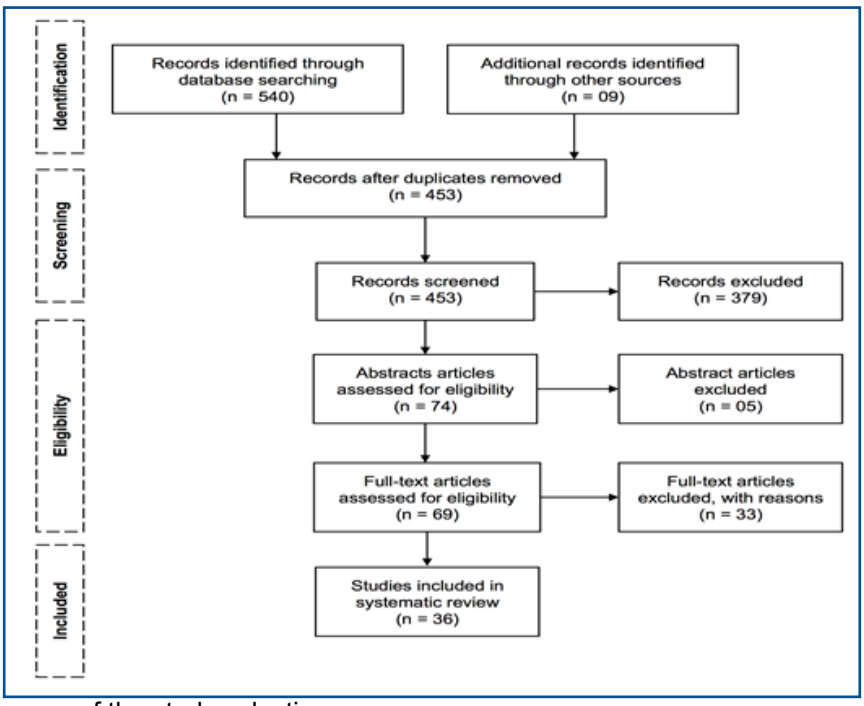

Figure 1: Flow diagram of the study selection process

Quality assessment

Two independent researchers analyzed the methodological quality of the eligible systematic reviews using the AMSTAR tool (A Measurement Tool to Assess Systematic Reviews). The AMSTAR tool consists of 11 items and each item has the options yes; no; cannot answer; or not applicable. Each answer "yes" receives one point. In the present review, studies scoring 8 or more points were considered as having good quality.

RESULTS

A total of 540 articles were identified in the databases. Hand searching identified nine additional titles. Among these articles, 74 were selected by the title and had their abstracts reviewed. Based on the abstracts, 69 studies were selected for a full review. Thirty-six studies met the eligibility criteria, whereas 33 studies were excluded (Figure 1). These exclusions were due to the following reasons: seventeen studies were not limited to analyze exposures occurred in the early life; six studies were systematic reviews without meta-analysis; four studies were narrative reviews; three studies were protocols of systematic reviews; one study had allergic sensitization as outcome; one study had only pulmonary function as outcome; and one study had hospitalizations for asthma as outcome.

The remaining studies examined the follow exposures: family history[10], maternal infections[11], maternal stress[12], maternal weight and gestational weight gain[13], maternal nutrition[14], folate supplementation[15,16], probiotics use[17,18], fish and oil fish intake[19], antibiotic use[20-23], paracetamol use[24-26], parental and household smoking[27,28], caesarean section[29,30], prematurity[31-33], birth weight[33-36], hyperbilirrubinemia[37], breastfeeding[38,39], Bacillus Calmette–Guérin (BCG) vaccination[40,41], pets ownership[42,43], endotoxins[44], and mold/dampness[45]. In Table 1 displays general characteristics of the studies and their main findings. According the AMSTAR tool, all included studies had a good methodological quality, except for one[42] (Table 2). Four studies included in this review were meta-analyses from cohort studies, and did not perform a systematic review in the literature[28,33,43,45]. For this reason, the methodological quality cannot be evaluated by the AMSTAR (Table 1 and Table 2).

Risk factors

Parental history of asthma is a well-known risk factor for childhood asthma. Maternal asthma can represent a 3-fold increased risk, while paternal asthma a 2.4 fold increase in the odds of asthma in childhood. During pregnancy, urogenital maternal infections and psychological stress increase the risk of asthma during childhood (OR = 1.39, CI 95% 1.18 – 1.64, I^2 = 15%; OR = 1.56, CI 95% 1.36 – 1.80, I^2 = 18%; respectively)[10]. Maternal smoking also increases the odds of asthma/ wheezing disorders in offspring (OR = 1.70, CI 95% 1.24 – 2.35, I^2 = 0%)[27]. Due to moderate to high heterogeneity, the risk evidence between asthma in the offspring and maternal overweight and obesity was not consistent. However, each1-kg/m^2 increase in maternal body mass index is associated with a 2% to 3% increase in the odds of childhood asthma[13]. Antibiotic use during pregnancy significantly increase the risk of childhood asthma, especially in the second and third trimesters (OR = 1.14, CI 95% 1.01 – 1.29; OR = 1.33, CI 95% 1.11 – 1.60, respectively; I^2 = 0% for both)[23] as well as paracetamol use (second/third trimesters, OR = 1.49, CI 95% 1.37 – 1.63, I^2 = 0%)[26]. The causal association between asthma and antibiotics exposure after birth until two years of life as well as paracetamol exposure remains inconclusive due to the high heterogeneity between studies and potential biases.

Caesarean section can increase the risk of asthma in the offspring (OR range 1.16 to 1.20, $I^2 \approx 25\%$). However,

Table 1: Characteristics of included studies and main findings of the meta-analyses of risk and protective factors for childhood asthma

Exposure	Study	N. of studies	N. of subjects	Study design	Period of exposure	OR or RR (95% CI) for meta-analysis	Heterogeneity
Family history	Lim et al., 2010[10]	33	254,820	Case-control and cross-sectional studies	-	Maternal asthma: OR = 3.04 (2.59 – 3.56) Paternal asthma: OR = 2.44 (2.14 – 2.79)	Maternal asthma: Q statistic – p = 0.13 Paternal asthma: Q statistic – p = 0.06
Maternal infections	Zhu et al., 2016[11]	10	299,830	Cohort, case-control and cross-sectional studies	Pregnancy	Overall: OR = 1.55 (1.24 – 1.92) Fever episode: OR = 1.73 (1.35 – 2.23) Chorioamnionitis: OR = 1.42 (1.50 – 3.28) Respiratory infection: OR = 1.49 (0.94 – 2.36) Urogenital infection: OR = 1.39 (1.18 – 1.64)	Overall: I2 = 88%; p < 0.001 Fever episode: I2 = 0%; p < 0.001 Chorioamnionitis: I2 = 95%; p < 0.001 Respiratory infection: I2 = 66%; p = 0.09 Urogenital infection: I2 = 15%; p < 0.001
Maternal psychological stress	van de Loo et al., 2016[12]	10	3,210,204	Survey, cohort and case-control studies	Pregnancy	Overall: OR = 1.56 (1.36 – 1.80) High quality studies: OR = 1.77 (1.18 – 2.67) Moderate quality studies: OR = 1.54 (1.30 –1.84) Stress exposure: OR = 1.58 (1.26 – 1.99) Perceived stress: OR = 1.59 (1.29 – 1.96)	Overall: I2 = 18%; p= 0.28 High quality studies: I2 = 74%; p = 0.02 Moderate quality studies: I2 = 0%; p = 0.79 Stress exposure: I2 = 34% Perceived stress: I2 = 18%
Maternal weight and gestational weight gain	Forno et al., 2014[13]	14	108,321	Observational studies	Pregnancy	- Ever asthma/wheeze: Underweight (BMI < 18.5): OR = 0.96 (0.88 – 1.22) Overweight (BMI 25 – 30): OR = 1.13 (0.99 – 1.29) Obese (BMI > 30): OR = 1.49 (1.22 – 1.83) Continuous BMI: OR =1.03 (1.02 – 1.05) Gestational weight gain (in kg): OR = 1.04 (0.97 – 1.11) - Current asthma/wheeze: Underweight (BMI < 18.5): OR =1.03 (0.90 – 1.18) Overweight (BMI 25 – 30): OR = 1.11 (0.98 – 1.25) Obese (BMI > 30): OR = 1.35 (1.08 – 1.68) Continuous BMI: OR = 1.03 (1.02 – 1.04) Gestational weight gain (in kg): OR = 1.01 (1.01 – 1.02)	- Ever asthma/wheeze: Underweight (BMI < 18.5): I2 =15.6%; p= 0.306 Overweight (BMI 25 – 30): I2 = 69.2%; p= 0.011 Obese (BMI > 30): I2 = 78.6%; p = 0.001 Continuous BMI: I2 = 70.4%; p = 0.001 Gestational weight gain (in kg): I2 = 80.1%; p= 0.025 - Current asthma/wheeze: Underweight (BMI < 18.5): I2 = 33.9%; p= 0.209 Overweight (BMI 25 – 30): I2 = 54%; p = 0.089 Obese (BMI > 30): I2 = 68%; p = 0.014 Continuous BMI: I2 = 66.3%; p = 0.007 Gestational weight gain (in kg): I2 = 0%; p= 0.453
Maternal nutrition	Beckhaus et al., 2015[14]	32	167,081,040 paris	Cohort studies	Pregnancy	Vitamin D intake: OR = 0.58 (0.38 – 0.88) Vitamin E intake: OR = 0.54 (0.41 – 0.71) Zinc intake: OR = 0.57 (0.40 – 0.81)	Vitamin D intake: I2 = 59%; p = 0.06 Vitamin E intake: I2 = 0%; p = 0.89 Zinc intake: I2 = 0%; p = 0.60
Fish and fish oil intake	Yang et al, 2013[19]	05	9,488	Cohort studies	Pregnancy and first year of life	Newborn's fish exposure: OR = 0.75 (0.61 – 0.94) Fatty acids in maternal expressed breast milk: OR = 0.71 (0.52 – 0.96)	Newborn's fish exposure: I2 = 11.5%; p = 0.323 Fatty acids in maternal expressed breast milk: I2 = 0%; p = 0.359

Continuation - Table 1: Characteristics of included studies and main findings of the meta-analyses of risk and protective factors for childhood asthma

Exposure	Study	N. of studies	N. of subjects	Study design	Period of exposure	OR or RR (95% CI) for meta-analysis	Heterogeneity
	Crider et al., 2013[15]	14	Not reported	Cohort studies, nested case-control and case-control studies	Periconceptional period through the first trimester of pregnancy	Any versus no supplementation: - Asthma: RR = 1.01 (0.78 - 1.30) - Asthma/wheezing: RR = 1.05 (1.02 – 1.09)	- Asthma: I2 = 0%; p = 0.73 - Asthma/wheezing: I2 = 0%; p = 0.68
Folate	Wang et al., 2015[16]	26	74,656	Cohort, case-control and cross-sectional studies	Pregnancy	- Any use: Asthma: RR = 1.04 (0.94 – 1.16) Wheezing: RR = 1.05 (0.95 – 1.15) - Pre-pregnancy: Asthma: RR = 0.98 (0.73 – 1.33) - Early pregnancy (first trimester): Asthma: RR = 0.98 (0.78 – 1.23) Wheezing: 1.06 (1.02 – 1.09) - Other period in pregnancy: Asthma: RR = 1.03 (0.92 – 1.16) Wheezing: 1.01 (0.98 – 1.03)	- Any use: Asthma: I2 = 0% Wheezing: I2 = 0% - Pre-pregnancy: Asthma: I2 = 0% - Early pregnancy: Asthma: I2 = 0% Wheezing: I2 = 0% - Other period in pregnancy: Asthma: I2 = 0% Wheezing: I2 = 0%
Probiotics	Elazab et al., 2013[17]	25	4,894	Clinical trials	Pregnancy and first 2 years of life	Overall: OR = 0.96 (0.85 – 1.07) Prenatal and postnatal: OR = 0.99 (0.88 – 1.12) Postnatal: OR = 0.79 (0.56 – 1.12)	Overall: I2 = 9.5%; p = 0.350 Prenatal and postnatal: I2 = 26.2%; p = 0.219 Postnatal: I2 = 0%; p = 0.634
	Zuccotti et al., 2015[18]	17	4,755	Clinical trials	Pregnancy and first 2 years of life	Asthma: RR = 0.99 (0.77–1.27) Wheezing: RR = 1.02 (0.89 – 1.17)	Not reported

Continuation - Table 1: Characteristics of included studies and main findings of the meta-analyses of risk and protective factors for childhood asthma

Exposure	Study	N. of studies	N. of subjects	Study design	Period of exposure	OR or RR (95% CI) for meta-analysis	Heterogeneity
Antibiotic use	Marra et al., 2006[20]	08	33,211	Retrospective and prospective observational studies	First year of life	- Exposure at least one course: Overall: OR = 2.05 (1.41 – 2.49) Prospective studies: OR = 1.12 (0.88 – 1.42) Retrospective studies: OR = 2.82 (2.07 – 3.83) - Dose response analysis: Overall: OR = 1.16 (1.05 – 1.28) Prospective studies: OR = 1.07 (0.95 – 1.20) Retrospective studies: OR = 1.37 (1.18 – 1.60)	- Exposure at least one course: Overall: Q = 43.4; p < 0.01 Prospective studies: Q = 1.93; p = 0.38 Retrospective studies: Q = 9.92; p = 0.04 - Dose response analysis: Overall: Q = 34.4; p < 0.01 Prospective studies: Q = 24.1; p < 0.01 Retrospective studies: Q = 1.48; p = 0.22
	Murk et al., 2011[22]	22	685,550	Databases, retrospective and prospective observational studies	Pregnancy and first year of life	- Exposure in pregnancy: Overall: OR= 1.24 (1.02 – 1.50) Prospective: OR = 1.70 (1.11 – 2.60) Database: OR = 1.38 (1.07–177) - Exposure in first year of life: Overall: OR = 1.52 (1.30 –1.77) Prospective: OR = 1.07 (0.89 –1.28) Retrospective: OR = 2.04 (1.83 – 2.27) Database: OR = 1.35 (1.12 – 1.62) - Dose response analysis: > 4 courses: OR = 1.59 (1.18 – 2.14) 3 – 4 courses: 1.44 (1.13 – 1.84) 1 – 2 courses: 1.24 (1.08 – 1.46)	- Exposure in pregnancy: Overall: I2 = 80% Prospective: not applicable (one study) Database: I2 = 73% - Exposure in first year of life: Overall: I2 = 95% Prospective: I2 = 0% Retrospective: I2 = 45% Database: I2 = 96% - Dose response analysis: Overall: I2 = 93% Prospective studies: I2 = 93% Retrospective studies: I2 = 85%
	Penders et al., 2011[21]	21	Not reported	Historical or prospective cohort studies and nested case-control studies within cohort or case-cohort studies	Infancy (up to 2 years)	Overall: OR = 1.27 (1.12 – 1.43) Selected studies*: OR =1.12 (0.98 – 1.26) *Reverse causation and confounding by indication unlikely	Overall: I2 = 75.7%; p = 0.001 Selected studies: I2 = 46.3%; p = 0.061
	Zhao et al., 2015[23]	10	1,118,976	control studies within cohort or case-cohort studies	Pregnancy	Overall: OR = 1.20 (1.13 – 1.27) Case-control: OR = 1.22 (1.02 – 1.45) Cohort: OR = 1.19 (1.13 – 1.26) Strict criteria*: OR = 1.18 (1.11 - 1.26) Stratification by trimesters of pregnancy: Overall: OR = 1.17 (1.07 – 1.27) First trimester: OR = 1.09 (0.92 –1.29) Second trimester: OR = 1.14 (1.01 –1.29) Third trimester: OR = 1.33 (1.11 – 1.60) *Excluded case–control studies. Included studies with adjustment for maternal asthma or parental allergy and studies that achieved high quality	Overall: I^2 = 82.9%; p = 0.001 Case-control: I^2 = 90%; p = 0.001 Cohort: I^2 = 42.3%; p = 0.109 Strict criteria: I^2 = 46.7%; p = 0.095 Stratification by trimesters of pregnancy: Overall: I^2 = 0%; p = 0.699 First trimester: I^2 = 0%; p = 1 Second trimester: I^2 = 0%; p = 0.740 Third trimester: I^2 = 0%; p = 0.638

Continuation - Table 1: Characteristics of included studies and main findings of the meta-analyses of risk and protective factors for childhood asthma

Exposure	Study	N. of studies	N. of subjects	Study design	Period of exposure	OR or RR (95% CI) for meta-analysis	Heterogeneity
Paracetamol use	Etminan et al., 2009[24]	11	126,776	Cohort, case-control and cross-sectional studies	Pregnancy and first year of life	- Exposure in pregnancy: Asthma: OR = 1.28 (1.13 – 1.39) Wheezing: OR = 1.50 (1.10 – 2.05) - Exposure in first year of life: Asthma: OR = 1.47 (1.36 – 1.56) Wheezing: OR = 1.51 (1.24 – 1.83)	- Exposure in pregnancy: Asthma: I2 = 0%; p = 0.40 Wheezing: I2 = 70%; p = 0.001 - Exposure in first year of life: Asthma: I2 = 0%; p = 0.44 Wheezing: I2 = 0%; p = 0.65
	Eyers et al., 2011[25]	06	28,038	Cohort, case-control and cross-sectional studies	Pregnancy	Fixed effects: OR = 1.20 (1.11 – 1.29) Random effects: OR = 1.21 (1.02 – 1.44)	I2 = 76% (95% CI 46.2% – 89.3%)
	Cheelo et al., 2015[26]	11	921,519	Cohort and cross-sectional studies	Pregnancy and first 2 years of life	- Stratification by trimesters of pregnancy: First trimester: OR = 1.39 (1.01 –1.91) Second/third trimester: OR = 1.49 (1.37 –1.63) Third trimester: OR = 1.17 (1.04 – 1.31) - First 2 years of life: Any versus no paracetamol intake unadjusted: OR = 1.56 (1.07 – 2.26) Any versus no paracetamol intake adjusted*: OR = 1.41 (0.96 – 2.08) Frequency of paracetamol intake unadjusted: OR = 1.15 (1.00 – 1.31) Frequency of paracetamol intake adjusted*: OR = 1.06 (0.92 – 1.22) * for respiratory tract infections	- Stratification by trimesters of pregnancy: First trimester: I2 = 64.2%; p = 0.025 Second/third trimester: I2 = 0%; 0.833 Third trimester: I2 = 0%; p = 0.796 - First 2 years of life: Any versus no paracetamol intake unadjusted: I2 = 0%; p = 0.884 Any versus no paracetamol intake adjusted*: I2 = 0%; p = 0.795 Frequency of paracetamol intake unadjusted: : I2 = 0%; p = 0.570 Frequency of paracetamol intake adjusted*: I2 = 0%; p = 0.785
Smoke	Burke et al., 2012[27]	79	Not reported	Cohort studies	Pregnancy and first 2 years of life	- Wheeze (≤ age 2) Prenatal smoking: OR = 1.41 (1.20 – 1.67) Maternal smoking: OR = 1.70 (1.24 – 2.35) Household smoking: OR = 1.35 (1.10 – 1.66) - Asthma (≤ age 2) Prenatal smoking: OR = 1.85 (1.35 – 2.53) Maternal smoking: OR = 2.47 (0.65 – 9.39) Household smoking: OR = 1.14 (0.94 – 1.38)	- Wheeze (≤ age 2) Prenatal smoking: I2 = 85.2%; p = 0.001 Maternal smoking: I2 = 0%; p = 0.586 Household smoking: I2 = 64.5%; p = 0.0004 - Asthma (≤ age 2) Prenatal smoking: I2 = 41.9%; p = 0.142 Maternal smoking: I2 = 3.7%; p = 0.308 Household smoking: I2 = 0.1%; p = 0.367
	Silvestri et al., 2015[28]	43	Not reported	Cohort studies	Pregnancy	- Prenatal exposure to maternal smoking Infants and preschool children: Overall: OR = 1.36 (1.19 – 1.55) Higher quality studies: OR = 1.37 (1.21 – 1.54) Poorer quality studies: OR = 1.51 (0.97 – 2.34) Current asthma/wheezing: Overall: OR = 1.22 (1.03 – 1.44)	- Prenatal exposure to maternal smoking Infants and preschool children: Overall: I2 = 68.9%; p < 0.001 Higher quality studies: I2 = 51.9% Poorer quality studies: I2 = 77.5% Current asthma/wheezing: Overall: I2 = 65.2%; p = 0.005
Caesarean section	Thavagnanam et al., 2007[29]	23	1,194,470	Cohort, case-control and cross-sectional studies	-	OR = 1.20 (1.14 – 1.26)	I^2 = 24.6%; p = 0.128

Continuation - Table 1: Characteristics of included studies and main findings of the meta-analyses of risk and protective factors for childhood asthma

Exposure	Study	N. of studies	N. of subjects	Study design	Period of exposure	OR or RR (95% CI) for meta-analysis	Heterogeneity
	Huang et al., 2015[30]	26	3,390,258	Cohort studies	-	Overall: OR = 1.16 (1.14 – 1.19) Elective caesarean section: OR = 1.21 (1.17 –1.25) Emergency caesarean section: OR = 1.23 (1.19–1.26) Instrumental vaginal delivery: OR = 1.07 (1.04 – 1.11)	Overall: I2 = 26%; p = 0.159 Elective caesarean section: I2 = 39.9%; p = 0.102 Emergency caesarean section: I2 = 84.8%; p = 0.001 Instrumental vaginal delivery: I2 = 54.9%; p = 0.03
	Jaakkola et al., 2006[31]	19	456,651	Cohort, case-control and cross-sectional studies	-	- Overall: Fixed effects: OR = 1.07 (1.07 – 1.07) Random effects: OR =1.36 (1.30 – 1.43) - Cross-sectional studies: Fixed effects: OR = 1.54 (1.45 – 1.63) Random effects: OR =1.51 (1.36 – 1.68) - Longitudinal studies: Fixed effects: OR = 1.07 (1.07 – 1.07) Random effects: OR =1.31 (1.24 – 1.38)	- Overall: Q = 2632.1; p < 0.001 - Cross-sectional studies: Q = 8.233; p = 0.222 - Longitudinal studies: Q = 2472.256; p = 0.001
Prematurity	Been et al., 2014[32]	30	1,543,63	Cohort, case-control and cross-sectional studies	-	Unadjusted data: OR = 1.71 (1.57 – 1.87) Adjusted data: OR = 1.46 (1.29 –1.65) - Dose response analysis: OR = 0.94 (0.92 - 0.96) - 6% (95% CI 4% – 8%) decrease in wheezing disorder risk for every week increase in gestation length up to 40 weeks - Subgroup analysis: Very preterm (<32 week gestation): unadjusted OR = 3.00 (2.61 – 3.44); adjusted: OR = 2.81 (2.52–3.12) Moderately preterm (32 to 36 week gestation): unadjusted: OR = 1.49 (1.34 – 1.66); adjusted: OR = 1.37 (1.17 – 1.62)	Unadjusted data: I2 = 82% (95% CI 75% – 87%) Adjusted data: I2 = 80% (95% CI 68% – 86%) - Dose response analysis: I2 = 90% (95% CI 85% – 92%) - Subgroup analysis: Very preterm: unadjusted I2 = 62% (95% CI 9% – 79%); adjusted I2 = 0% (95% CI 0% – 68%) Moderately preterm: unadjusted I2 = 92% (95% CI 87% – 94%); adjusted I2 = 89% (95% CI 82% – 93%)
	Sonnenschein-van der Voort et al., 2014[33]	31	147,252	Cohort studies	-	- Preschool wheezing: OR = 1.34 (1.25 – 1.43) - School-age asthma: OR = 1.40 (1.18 – 1.67) - Low birth weight: Preschool wheezing: OR = 1.10 (1.00 – 1.21) School-age asthma: OR = 1.13 (1.01 – 1.27)	- Preschool wheezing: Q = 28; p = 0.424; I^2 = 3% - School-age asthma: Q = 29; p = 0.034; I^2 = 42% - Low birth weight: Preschool wheezing: I2 = 15%; p = 0.244 School-age asthma: I2 = 0%; p = 0.787

Continuation - Table 1: Characteristics of included studies and main findings of the meta-analyses of risk and protective factors for childhood asthma

Exposure	Study	N. of studies	N. of subjects	Study design	Period of exposure	OR or RR (95% CI) for meta-analysis	Heterogeneity
	Flaherman & Rutherford, 2006[34]	09	110,402	Cohort studies	-	- High birth weight: RR = 1.2 (1.1 – 1.3)	- High birth weight: Low level of heterogeneity; p = 0.440
	Xu et al., 2014[35]	13	1,105,703	Cohort and case–control studies	-	- Low birth weight: Overall: OR = 1.16 (1.13 – 1.20) Unadjusted data: OR = 1.17 (1.09 – 1.25) Adjusted data: OR = 1.16 (1.12 –1.20)	- Low birth weight: Overall: I2 = 40.2%; p = 0.066 Unadjusted data: I2 = 7.8%; p = 0.370 Adjusted data: I2 = 67.9%; p = 0.014
Birth weight							
	Mebrahtu et al., 2015[36]	37	1,712,737	Cohort and case–control studies	-	- Low birth weight (<2.5kg of birth weight): Overall unadjusted: OR = 1.60 (1.39 – 1.85) Overall adjusted: OR=1.63 (1.32 – 2.01) - High birth weight (>4.0kg birth weight): Overall unadjusted: OR = 1.02 (0.99 – 1.04)	- Low birth weight: Overall unadjusted: I2 = 82% (95% CI: 74% – 88%) Overall adjusted: not reported - High birth weight: Overall unadjusted: I2 = 0% (95% CI: 0 – 45%)
Hyperbilirrubinemia	Das & Naik, 2015[37]	07	127,620	Cohort, case-control and cross-sectional studies	First 2 years of life	- After neonatal hyperbilirrubinemia: OR = 4.26 (4.04 – 4.50) -After neonatal phototherapy: OR = 3.81 (3.53 – 4.11)	- After neonatal hyperbilirrubinemia: I2 = 0%; p = 0.46 -After neonatal phototherapy: I2 = 26%; p = 0.26

Continuation - Table 1: Characteristics of included studies and main findings of the meta-analyses of risk and protective factors for childhood asthma

Exposure	Study	N. of studies	N. of subjects	Study design	Period of exposure	OR or RR (95% CI) for meta-analysis	Heterogeneity
Breastfeeding	Dogaru et al., 2014[38]	117	Not reported	Cohort, case-control and cross-sectional studies	-	- Asthma ever: Age 0 – 2 years (any duration breastfeeding): Ever breastfeeding versus never: OR = 0.65 (0.51 – 0.82) ≥ 3 versus < 3 months: OR = 0.59 (0.50 – 0.70) ≥ 6 versus < 6 months: OR = 0.61 (0.50 – 0.74) Exclusive breastfeeding ≥ 3 versus < 3 months: OR = 0.62 (0.51 – 0.74) ≥ 6 versus < 6 months: OR = 0.69 (0.58 – 0.81) Age 3 – 6 years Ever breastfeeding versus never: OR = 0.79 (0.68, 0.91) ≥ 3 versus < 3 months: OR =0.84 (0.76 – 0.92) ≥ 6 versus < 6 months: OR =0.57 (0.38 – 0.86) Exclusive breastfeeding ≥ 3 versus < 3 months: OR =0.81 (0.59 – 1.11) ≥ 6 versus < 6 months: OR =0.51 (0.24 – 1.08) Age ≥ 7 years Ever breastfeeding versus never: OR = 0.86 (0.77 – 0.96) ≥ 3 versus < 3 months: OR = 0.86 (0.73 – 1.01) ≥ 6 versus < 6 months: OR = 0.94 (0.82 – 1.07) Exclusive breastfeeding ≥ 3 versus < 3 months: OR = 0.73 (0.39 – 1.36) ≥ 6 versus < 6 months: OR = 0.68 (0.37 – 1.24) - Recent asthma: Age 0 – 2 years (any duration breastfeeding): Ever breastfeeding versus never: OR = 0.65 (0.51 – 0.82) ≥ 3 versus < 3 months: OR = 0.59 (0.50 – 0.70) ≥ 6 versus < 6 months: OR = 0.61 (0.50 – 0.74) Exclusive breastfeeding ≥ 3 versus < 3 months: OR = 0.62 (0.51 – 0.74) ≥ 6 versus < 6 months: OR = 0.69 (0.58 – 0.81) Age 3 – 6 years Ever breastfeeding versus never: OR = 0.86 (0.65 – 1.13) ≥ 3 versus < 3 months: OR = 0.79 (0.70 – 0.88) ≥ 6 versus < 6 months: OR = 0.45 (0.30 – 0.69) Exclusive breastfeeding ≥ 3 versus < 3 months: OR = 0.83 (0.56 – 1.23) ≥ 6 versus < 6 months: OR = 0.71 (0.53 – 0.94) Age ≥ 7 years Ever breastfeeding versus never: OR = 0.96 (0.84 – 1.10) ≥ 3 versus < 3 months: OR = 0.87 (0.76 – 1.04) ≥ 6 versus < 6 months: OR = 0.96 (0.86 – 1.08) Exclusive breastfeeding ≥ 3 versus < 3 months: OR = 0.65 (0.34 – 1.26)	- Ever versus never breastfeeding: Overall: I2 = 44% High income countries: 18% Medium/low income countries: 0% - Exclusive breastfeeding ≥ 3-4 months versus less: Cohort: I2 = 81% All types of studies: I2 = 72% - More versus less breastfeeding: Overall: I2 = 63% High income countries: 70% Medium/low income countries: 9% - More versus less breastfeeding with parental or family history of asthma/ atopy With family history: I2 = 78% Without family history: I2 = 64%

Continuation - Table 1: Characteristics of included studies and main findings of the meta-analyses of risk and protective factors for childhood asthma

Exposure	Study	N. of studies	N. of subjects	Study design	Period of exposure	OR or RR (95% CI) for meta-analysis	Heterogeneity
	Lodge et al., 2015[39]	42	Not reported	Cohort, case-control and cross-sectional studies	-	- Ever versus never breastfeeding: Overall: OR = 0.88 (0.82 – 0.95) High income countries: 0.90 (0.83 – 0.97) Medium/low income countries: 0.78 (0.70 –0.88) - Exclusive breastfeeding ≥ 3-4 months versus less: Cohort: OR = 0.94 (0.69 – 1.29) All types of studies: OR = 0.89 (0.71 – 1.11) - More versus less breastfeeding: Overall: OR = 0.90 (0.84 – 0.97) High income countries: 0.93 (0.83 – 1.04) Medium/low income countries: 0.86 (0.79 –0.94) - More versus less breastfeeding with parental or family history of asthma/atopy With family history: OR = 1.08 (0.74 – 1.58) Without family history: OR = 1.2 (0.91 – 1.59)	- Ever versus never breastfeeding: Overall: I2 = 44% High income countries: 18% Medium/low income countries: 0% - Exclusive breastfeeding ≥ 3-4 months versus less: Cohort: I2 = 81% All types of studies: I2 = 72% - More versus less breastfeeding: Overall: I2 = 63% High income countries: 70% Medium/low income countries: 9% - More versus less breastfeeding with parental or family history of asthma/ atopy With family history: I2 = 78% Without family history: I2 = 64%
BCG vaccination	El-Zein et al., 2010[40]	23	75,917	Cohort, case-control cross-sectional studies and randomized controlled trial	First 2 years of life	OR = 0.86 (0.79 – 0.93)	Q = 14.16; p = 0.51; I2 = 0%
	Linehan et al., 2014[41]	22	113,245	Cohort, case-control and cross-sectional studies	First 2 years of life	Overall: OR = 0.946 (0.89 – 1.00) Lower quality studies: OR = 0.90 (0.78 – 1.03)	Overall: I2 = 26%; p = 0.159 Lower quality studies: : I2 = 56%; p = 0.026
Pets ownership	Apelberg et a., 2001[42]	32	Not reported	Cohort studies	First 2 years of life	Fixed effects Overall: OR = 1.11 (0.98 – 1.25) ≤ 6 years: OR = 0.98 (0.80 – 1.20) > 6 years: OR = 1.19 (1.02 – 1.40) Random effects Overall: OR = 1.09 (0.89 – 1.34) ≤ 6 years: OR = 0.99 (0.77 – 1.27) > 6 years: OR = 1.15 (0.86 – 1.56)	Overall: Q = 13.5; p = 0.04 ≤ 6 years: Q = 2.77; p = 0.25 > 6 years: Q = 8.39; p = 0.04
	Lodrup Carlsen et al., 2012[43]	11	22,840	Cohort, case-control and cross-sectional studies	First 2 years of life	- Asthma: Cat versus no pets: OR = 1.00 (0.78 – 1.28) Dog versus no pets: OR = 0.77 (0.58 – 1.03) Cat/dog versus no pets: OR = 1.04 (0.59 – 1.84) Bird versus no pets: OR = 1.03 (0.69 – 1.52) Rodent versus no pets: OR = 1.03 (0.64 – 1.66) - Allergic asthma: Cat versus no pets: OR = 1.09 (0.74 – 1.61) Dog versus no pets: OR = 0.79 (0.52 – 1.21) Cat/dog versus no pets: OR = 0.91 (0.22 – 3.74)	- Asthma: Cat versus no pets: I2 = 9%; p = 0.36 Dog versus no pets: I2 = 0%; p = 0.89 Cat /dog versus no pets: I2 = 33%; p = 0.18 Bird versus no pets: I2 = 21%; p = 0.25 Rodent versus no pets: I2 = 0%; p = 0.84 - Allergic asthma: Cat versus no pets: I2 = 21%; p = 0.26 Dog versus no pets: I2 = 0%; p = 0.95 Cat /dog versus no pets: I2 = 59%; p = 0.06

In this table, the number of studies and participants included in each meta-analysis is specifically related to asthma or wheezing cases, or outcomes during childhood or exposure during pregnancy and first two years. BCG, Bacillus Calmette-Guérin; BMI, body mass index; CI, confidence intervals; OR, odds ratio; PB, population based; PBC, population-based cohort; RR, relative risk.

Table 2: Quality of systematic reviews using the AMSTAR tool

Studies	AMSTAR questions										
	01	02	03	04	05	06	07	08	09	10	11
Apelberg, Aoki and Jaakkola, 2001[42]	yes	no	no	yes	no	yes	no	NA	yes	yes	no
Beckhaus et al., 2015[14]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Been et al., 2014[32]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Burke et al., 2012[27]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	-
Cheelo et al., 2015[26]	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes
Crider et al., 2013[15]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Das and Naik, 2015[37]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Dogaru et al., 2014[38]	yes	yes	yes	yes	no	yes	yes	yes	yes	no	yes
Elazab et al., 2013[17]	yes	yes	yes	yes	no	yes	yes	yes	yes	no	yes
El-Zein et al., 2010[40]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Etminan et al., 2009[24]	yes	no	yes	yes	no	yes	yes	no	yes	yes	yes
Eyers et al., 2011[25]	yes	yes	yes	yes	no	yes	-	-	yes	yes	no
Flaherman & Rutherford, 2006[34]	yes	no	no	yes	yes	yes	no	NA	yes	yes	yes
Forno et al., 2014[13]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Huang et al., 2015[30]	yes	yes	yes	yes	no	yes	no	NA	yes	yes	yes
Jaakkola et al., 2006[31]	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes
Lim, Kobzik and Dahl, 2010[10]	yes	yes	no	yes	no	yes	yes	yes	no	yes	yes
Linehan et al., 2014[41]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Lodge et al., 2015[39]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Marra et al., 2006[20]	yes	yes	yes	-	yes	yes	yes	yes	yes	yes	yes
Mebrahtu et al., 2015[36]	yes	yes	yes	yes	no	yes	yes	no	yes	yes	yes
Mendy et al., 2011[44]	yes	yes	yes	yes	no	yes	yes	yes	yes	no	yes
Murk, Risnes & Bracken, 2011[22]	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes
Penders, Kummeling & Thijs, 2011[21]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Thavagnanam et al., 2008[29]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	no
van de Loo et al., 2016[12]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Wang et al., 2015[16]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Xu et al., 2014[35]	yes	yes	no	yes	no	yes	yes	no	yes	yes	yes
Yang, Xun & He, 2013[19]	yes	yes	yes	-	yes	yes	-	-	yes	yes	yes
Zhao et al., 2015[23]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Zhu et al., 2016[11]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Zuccotti et al., 2015[18]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes

Legend: -, cannot answer; NA, not applicable. AMSTAR's Questions: 1. Was an a priori design provided? 2. Was there duplicate study selection and data extraction? 3. Was a comprehensive literature search performed? 4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? 5. Was a list of studies (included and excluded) provided? 6. Were the characteristics of the included studies provided? 7. Was the scientific quality of the included studies assessed and documented? 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? 9. Were the methods used to combine the findings of studies appropriate? 10. Was the likelihood of publication bias assessed? 11. Was the conflict of interest included?

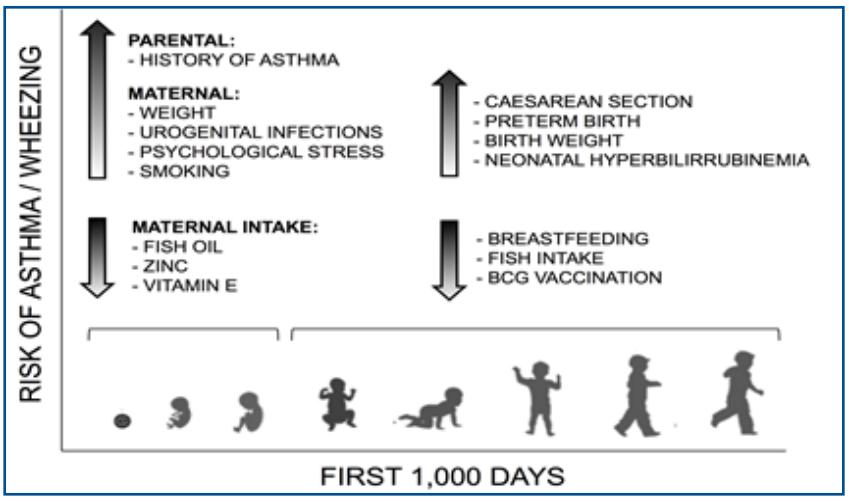

Figure 2: Protective and risk factors for childhood asthma and wheezing disorders in the first 1,000 days

due to the moderate to high heterogeneity between the studies, differences between elective and emergency caesarean sections are not consistent[29,30]. As for birth weight, both low (<2.5kg) and high (>4.0kg) birth weight are associated with a slight increase in asthma and wheezing disorders in preschool and school age[34-36]. Neonatal hyperbilirrubinemia increases more markedly the risk of childhood asthma (OR = 4.26, CI 95% 4.04 – 4.50, I^2 = 0%)[37].

Protective factors

Intake of fish oil, zinc and vitamin E during pregnancy decreases the risk of childhood wheezing[14]. However, this beneficial effect could not be verified when the outcome analyzed was childhood asthma. After birth, ever breastfeeding, especially in middle/low income countries, reduces the risk of childhood asthma when compared to never breastfeeding (OR = 0.78, CI 95% 0.70 – 0.88, I^2 = 0%)[39]. Newborn's fish intake is also a protective factor for asthma (OR = 0.7, CI 95% 0.61 – 0.94, I^2 = 11.5%)[19], as well as BCG vaccination (OR range 0.86 to 0.94, I^2 range 0% to 26%)[40,41]. However, the protective factor BCG vaccination is relatively short-lived, being lost in adolescence. Protective and risk factors for childhood asthma and wheezing disorders in the first 1,000 days are summarized in Figure 2.

The icons used in the elaboration of this figure were extracted from the electronic address: http://www.sarihusada.co.id/en/About-Us/First-1000-Days-of-Life/Detail-For-the-First-1000-Days-of-Life.

DISCUSSION

Summary of evidence

The results from meta-analyses provide evidence that parental history of asthma, maternal weight gain during pregnancy, maternal urogenital infections, maternal psychological stress, maternal smoking, caesarean section, preterm birth, birth weight, and neonatal hyperbilirrubinemia are risk factors for childhood asthma/wheeze. In the other hand, intake of fish oil, zinc and vitamin E during pregnancy appear as protective factors as well as breastfeeding, fish intake in the first two years, and BCG vaccination, although discreetly in the case of the last one. There is insufficient evidence to recommend any dietary pattern or folic acid supplementation and probiotic administration to prevent asthma. Also, there is no evidence that pets' ownership increases or decreases the risk of childhood asthma. The lack of consistence in the findings (moderate to high heterogeneity), coupled with the possible biases of the studies, further hinder conclusions about the role of endotoxins, mold, dampness, antibiotics and paracetamol exposures in the development of asthma and wheezing disorders.

Are there any explanations to these associations?

Several possible biological causal pathways could explain the increased risk of asthma. However, some potential mechanisms are not fully understood. Humans are born Th2-skewed, and gradually develop a Th1/Th2 balance. However, in asthma and other allergic diseases, a Th2-polarized immune deviation has been observed[46]. The imbalance in circulating Th1- and Th2-associated chemokines may precede the onset of wheeze from birth, implicating that these chemokines may sometimes be primarily involved in the pathogenesis of allergic diseases and not only secondarily to a general immune deviation after disease onset[47].

Fetal exposure to inflammatory cytokines has been linked to chronic lung diseases[48]. Since fetal lung and skin are in constant contact with amniotic fluid, exogenous toxins or mediators of inflammation released through the placenta may lead to fetal exposure. Increased inflammation within the placenta may alter fetal cytokine levels thereby affecting the immune system development and resulting in differential response to allergens later in life. This mechanism can explain the association between asthma and maternal infections, as well as the association between asthma and maternal weight gain, since maternal obesity increases concentrations of lipids and pro-inflammatory mediators like TNFα, IL-1, and IL-6 in the placenta[49]. In another way, nutritional components such as long-chain n-3 polyunsaturated fatty acids from fish and fish oil intake have the ability to inhibit the production of prostaglandin E2, suppress Th2 cell's response to allergens and consequently modulate the intensity and duration of inflammatory responses. For this reason, it has been hypothesized that the increased intake of long-chain n-3 polyunsaturated fatty acids can reduce the risk of atopic diseases such as asthma[50].

Maternal smoking, mainly during pregnancy, also has significant immunologic effects that could contribute to increased risk of respiratory infections and asthma. Maternal smoking during pregnancy is associated with higher cord blood immunoglobulin E levels, as well as lowers Th1 responses to polyclonal stimulation. Furthermore, it is associated with stronger neonatal allergen-specific responses, and can affect Toll-like receptor innate defense pathways, which could both explain an increased susceptibility to infection and have implications for subsequent allergen-specific immune development[51]. The release of hypothalamic corticotropin hormone, which can be induced by maternal psychological stress, leads to systemic secretion of glucocorticoids and catecholamines[52]. In this way, it can also influence immune responses in the offspring, because both glucocorticoids and catecholamines mediate a Th2 shift by up-regulating Th2-cytokine production and suppressing antigen-presenting cells and Th1 cells[53].

Oxidative stress plays a critical role in the pathogenesis of asthma[54]. Pro-oxidant and antioxidant imbalance can cause dysfunction in cell signaling and arachidonic acid metabolism and increase airway and systemic inflammation[55]. By acting as an antioxidant, vitamin E may inhibit secretion of IL-4 by T cells[56], and this is possibly one reason for the reduced risk of asthma in children. In another way, bilirubin, at higher levels, might act as a strong pro-oxidant that might induce airway inflammation and development of asthma later in life. Bilirubin also can strongly inhibit the Th1 cell response and lead to a delay in the Th2 to Th1 switch[57]. Besides this, unconjugated bile acids inhibit the growth of intestinal anaerobic bacteria, which change the gut microbiota composition, and the prevention of Th1 response, influencing the development of allergic diseases[58]. Intestinal bacterial flora is important to the children's immune system development. The delivery mode can affect this development, since in caesarean section, children are not exposure to the vaginal flora that cause alterations in intestinal bacterial flora, such as in the case of bifidobacterium species[59]. Human breast milk also plays an important role in the establishment of favorable gut colonization. In addition to having immunomodulating properties, transforming growth factor β is a cytokine present in the human milk that is involved

in the maintenance of intestinal homeostasis and inflammation regulation[60]. These mechanisms can explain the protective effect of breastfeeding in asthma and other allergic diseases.

Other potential explanations for the increase of risk of asthma are anatomical and immunological immaturity. Preterm birth might increase the risk of asthma because the lungs of a preterm infant are not fully developed anatomically or immunologically, and this immaturity might make the child more susceptible to later exposures capable of causing asthma[31]. Similarly, children with low birth weight may have disturbances in lung development, which would cause a greater sensitivity to external environmental stimuli and result in an increased risk of asthma[35]. Also related to lung development, zinc deficiency has been associated with impaired fetal lung growth in rats[61]. Based on this finding, we can postulate that zinc supplementation is beneficial for lung growth, which explain the association between zinc supplementation during pregnancy and decrease in the risk of childhood asthma.

Limitations

In this review, the meta-analyses that were not systematic reviews were included because they brought data from big cohort studies, with a significant number of participants. However, the AMSTAR tool cannot evaluate the methodological quality of these studies. Many meta-analyses showed to have moderate to high heterogeneity, reveling lack of consistence in the findings. The lack of homogeneity, coupled with the possible biases, hinder strong evidences about some exposures in early life. In addition, studies with other potential risk factors, such as respiratory syncytial virus infection, were not included in this review because the meta-analyses published so far do not restrict exposure to the first 1,000 days of life.

Clinical implications

Current findings suggest that several modifiable behaviors or exposures can be associated with asthma and wheezing in childhood. Although the pooled odds ratios in many meta-analyses have found associations, measures of heterogeneity suggest a lack of consistent in many findings. Awareness of these modifiable behaviors and exposures, as well as the knowledge about the close links between early-life lung events, immune maturation and childhood respiratory diseases can improve early prevention strategies with a view to ensuring a beneficial impact on both short- and long-term respiratory health[62].

CONCLUSION

There are still many aspects that need to be considered and further explored. Knowledge about the risk factors present in the first 1,000 days of life of children can support approaches and interventions capable of modifying the risk of asthma and/or changing the course of the disease in childhood. Understanding these potentially modifiable factors is of great interest for the planning of public health policies, being as relevant as new clinical treatments for asthma[63].

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Resumo

Introdução: Os primeiros 1000 dias de vida de uma criança, período desde a concepção até o final do segundo ano, são considerados críticos para o desenvolvimento dos sistemas respiratório e imunológico. Muitos fatores ocorridos nesse período podem estar associados ao risco de asma na infância.

Objetivo: Condensar evidências sobre fatores de risco e proteção para asma infantil e/ ou sibilância ocorridos nos primeiros 1000 dias de vida.

Método: Foram revisadas as bases de dados MEDLINE, CINAHL e SCOPUS. Foram incluídas revisões sistemáticas com meta-análise, ou meta-análise de estudos observacionais e de intervenção sobre fatores de risco ou proteção para asma infantil/ sibilância, enfatizando os primeiros 1000 dias de vida. A qualidade dos estudos foi avaliada pela ferramenta *Assess Systematic Reviews*. *Odds ratio*, intervalos de confiança e homogeneidade entre os estudos foram analisados.

Resultados: Trinta e cinco estudos preencheram os critérios de inclusão, com boa qualidade metodológica. Foram identificados como fatores de risco para asma e/ou sibilância na infância: história parental de asma, ganho de peso materno durante a gestação, infecções urogenitais, estresse psicológico, tabagismo, parto cesárea, prematuridade, peso ao nascer e hiperbilirrubinemia neonatal. A ingestão de óleo de peixe, zinco e vitamina E durante a gestação aparecem como fatores de proteção, bem como amamentação, ingestão de peixe nos dois primeiros anos e vacinação BCG.

Conclusão: Diversos comportamentos ou exposições modificáveis podem estar associados à asma e sibilância na infância. O conhecimento sobre estes comportamentos e exposições pode melhorar as estratégias de prevenção precoce, visando garantir um impacto benéfico na saúde respiratória.

Palavras-chave: Asma, criança, fatores de proteção, fatores de risco.