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Neonatal hyperbilirubinemia and childhood allergic diseases: a systematic review

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ABSTRACT

Background: Studies have found a link between neonatal hyperbilirubinemia (NNH) and/or phototherapy (NPT) and childhood allergic diseases. The present systematic review was conducted to provide updated evidence, and to provide direction regarding future research.

Methods: A systematic search of the published literature was done. Observational studies including children up to 12 years of age were included. Data extraction was done using a standardized data extraction form that was designed and pilot tested *a priori*. The analysis was carried out with the statistical software RevMan (version 5.2) [Protocol is registered at PROSPERO: CRD42014009943].

Results: Of 79 citations retrieved, a total of 7 good quality studies (n=101,499) were included in the final analysis. There was a significant increase in the odds of asthma and allergic rhinitis (AR) after NNH [asthma, OR 4.26 (95% CI 4.04-4.5); AR, OR 5.37 (95% CI 4.16-6.92)] and after NPT [asthma, OR 3.81 (95% CI 3.53-4.11); AR, OR 3.04(95% CI 2.13-4.32)]. A similar increase in the trend was noted for late onset asthma after NNH [OR 4.1 (95% CI 2.82-5.94)], and hospitalization due to asthma after NPT [OR 3.56 (95% CI 2.93-4.33)]. The GRADE evidence generated was of “low-quality”.

Conclusions: The current evidence finds a significant increase in the odds of childhood allergic diseases after NNH and/or NPT. As observational studies were included, the evidence generated was of ‘low-quality’. Future studies should try to elucidate the pathophysiologic link between NNH and/or NPT and childhood allergic diseases.

KEY WORDS

Atopy, allergic rhinitis, asthma, bilirubin, icterus, phototherapy, Th1, Th2

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INTRODUCTION

Worldwide, there has been a gradual increase in the incidence and prevalence of allergic/atopic diseases. Till date, many factors (both atopic and non-topic) have been implicated in the pathogenesis of these diseases (1). One such factor is the neonatal hyperbilirubinemiae (NNH) that has been linked to the development of childhood allergic diseases in the later life (2-8).

In-vivo, reactive oxygen free radicals are generated during cellular metabolism as well as by environmental pollutants. The adverse cellular effects of these oxidants are countered by various antioxidants. An imbalance in this oxidant-antioxidant mechanism plays an important role in the pathogenesis as well as progression of allergic airway diseases (9). Bilirubin is a known antioxidant present in-vivo (10). However, in premature neonates, the anti-oxidant effect of bilirubin might not be seen (11). Moreover, studies have shown that, at higher level (>12.5 mg/dl) bilirubin might act as a strong pro-oxidant (12). During NNH, an increased production of heme (a pro-oxidant) complements a higher bilirubin pro-oxidant effect that might induce airway inflammation with development of asthma later in life.

The immune system of neonates after birth is skewed towards Th-2 response that promotes allergic/atopic sensitization. In order to prevent the development of allergy, there should be a rapid switch from Th-2 to Th-1 response after birth (13). In-vitro experiments have shown that bilirubin could

strongly inhibit the Th-1 cell response leading to a delay in the Th-2 → Th-1 switch (14). Besides this, experimental models have also shown that unconjugated bile acids inhibit the growth of intestinal anaerobic bacteria (particularly bacteroides, lactobacilli, and clostridia). This effect may be exaggerated during NNH with high bilirubin levels (15-17). The changes in the gut microbiota composition and the prevention of Th-1 response could act synergistically along with other factors to influence the development of allergic diseases in later life.

Based on the above hypothesis, studies have found variable association between NNH and/or neonatal phototherapy (NPT) and various childhood allergic diseases. The present systematic review was conducted to provide updated evidence generated from the available studies, and to provide direction regarding future research.

OBJECTIVES

Primary

1. To assess the rate of childhood allergic diseases after NNH and/or NPT

Secondary

1. To assess the rate of hospitalization due to childhood asthma after NNH and/or NPT
2. To assess the rate of late onset of asthma after NNH and/or NPT
3. To assess the dose relationship between NNH and childhood allergic diseases
4. To assess the prevalence of childhood allergic diseases after NNH and/or NPT in various countries.

METHODS

The protocol has been registered at PROSPERO database (No:CRD42014009943).

Type of participants

Children with a history hyperbilirubinemia/jaundice and/or requiring phototherapy during neonatal period and then followed up till the age of 12 years for development of allergic diseases were included.

Children of <1 year age or those with chronic illness, congenital malformations, and kernicterus/bilirubin encephalopathy were excluded [asthma or allergic rhinitis is difficult to label below 1 year age, and various factors play a role in the diagnosis and assessment of allergic diseases in those with chronic illness or congenital malformations or kernicterus/bilirubin encephalopathy].

Types of studies

As the question can rarely be addressed by randomized or quasi-randomized trials, we planned to include observational studies (both hospital and population based) after applying the following eligibility criteria:

1. Cohort studies that enrolled infants in the first 4 weeks of life and followed them up till the age of 12 years.
2. Case-control studies in which
 - Infants having hyperbilirubinemia and/or requiring phototherapy were the 'cases' AND
 - The exposure (i.e. hyperbilirubinemia or phototherapy) occurred in the first 4 weeks of life for all or almost all the cases.
3. Cross-sectional studies that measured the association between hyperbilirubinemia and/or phototherapy starting from the neonatal period till the age of 12 years.

Exposure or intervention

This included physiological (not requiring any treatment and any bilirubin level) or pathological (requiring treatment in form of phototherapy or exchange transfusion) hyperbilirubinemia during the neonatal period.

Outcome measures and their definitions

Primary outcomes

1. Rate of childhood allergic diseases after NNH and/or NPT

Rate of asthma after NNH

Rate of asthma after NPT

Rate of allergic rhinitis after NNH

Rate of allergic rhinitis after NPT

Rate of atopic eczema/dermatitis after NNH

Rate of atopic eczema/dermatitis after NPT

Rate of rhino-conjunctivitis/hay fever after NNH

Rate of rhino-conjunctivitis/hay fever after NPT

Secondary outcomes

1. Rate of late onset of asthma after NNH and/or NPT
2. Rate of hospitalization due to childhood asthma after NNH and/or NPT
3. Relation between serum bilirubin level and childhood allergic diseases
4. Relation between duration of NPT and childhood allergic diseases
5. Rate of childhood asthma requiring steroid after NNH and/or NPT

Neonatal hyperbilirubinemia (NNH) is defined as either clinical jaundice or laboratory confirmation by estimating serum bilirubin during the neonatal period (within 30 days of life). Phototherapy (NPT) is a treatment modality used for NNH when serum bilirubin exceeded 15mg/dl. Childhood allergic diseases encompass asthma, allergic rhinitis (AR), atopic dermatitis/eczema, and allergic rhino-conjunctivitis/hay fever. Asthma is labeled in children >1 year age with the criteria of 'physician diagnosed asthma' with or without ancillary investigations. Allergic rhinitis (AR) is labeled in children with the criteria of 'physician diagnosed AR' with at least three episodes of AR in the past (with or without ancillary investigations). Atopic eczema/dermatitis is defined as an itchy rash which was coming and going for at least 6 months affecting the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears, or eyes. Allergic rhino-conjunctivitis/hay fever is diagnosed in presence of runny nose or blocked nose, sneezing, and itchy eyes.

Search methodology

The following databases were searched independently by the review authors using the following search terms: [(newborn OR infant OR neonat*) AND (hyperbilirubinemia OR icterus OR jaundice) AND (phototherapy OR therapy OR treatment) AND (allergy OR atopy OR asthma OR allergic rhinitis OR rhinitis OR rhino-conjunctivitis OR hay fever OR atopic dermatitis OR allergic eczema)]. The databases searched were: MEDLINE via PubMed (1970 – April 2014), Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, April 2014) (supplementary appendix 1). Searches were limited to human studies. There were no language restrictions. We also checked the cross-references of relevant articles.

Data extraction

Data extraction was done using a standardized data extraction form that was designed and pilot tested *a priori*. The authors independently extracted the data from included studies, including year, setting (country, type of population, gestation, birth weight, maternal risk factors, neonatal risk factors), exposure/intervention (neonatal hyperbilirubinemia, phototherapy, exchange transfusion), results (outcome measures, effect, significance), and funding sources. Any disagreement in the extracted data was resolved through discussion.

Assessment of risk of bias in included studies

The review authors independently assessed the methodological quality of selected studies. Quality assessment was undertaken using the “Newcastle Ottawa Scale (NOS)” for observational studies. This scale assesses the study quality under three major headings namely, selection of the studies (representativeness; exposure assessment/control selection), comparability (adjustment for main/additional confounders), and outcome/exposure (adequacy of outcome measured, exposure measured versus self-report) (18). Any disagreement was resolved through discussion.

Data analysis

For each outcome measure, the total number of participants and the number of participants experiencing the event, and the adjusted odds ratio (aOR) provided by the study authors were extracted. The OR were adjusted for maternal (year of birth, age, parity, education, socio-economic factors, and smoking during pregnancy) and neonatal (gestational age, sex, birth-weight, infections, birth asphyxia, respiratory and other birth conditions) factors. We intended to use only aOR for pooling of the results. If adjusted ratios were not provided in a given study, we used the unadjusted OR.

Meta-analysis was done by the generic inverse variance using the RevMan software version (Review Manager 5.2.0) (19). We used the natural logarithm converted values of aOR and their confidence intervals (CI) for computing the pooled estimates. The heterogeneity among the studies was quantified by use of the I^2 statistics. Given that all the included studies were observational in nature and had an inherent risk of heterogeneity among them, we planned to use fixed-effect model for pooling the results irrespective of the degree of heterogeneity.

Publication bias

For assessment of publication bias, funnel plot was constructed using the OR and 1/SE values obtained from studies measuring one of the primary outcome. In the absence of publication bias, such a plot is expected to have a shape resembling an inverted funnel (20).

RESULTS

Description of studies

Of 79 citations retrieved, a total of 7 good quality studies including 101,499 children (1-12 years age) were included in the final analysis (**Figure 1**) (2-8). Of the 7 included studies, 6 were retrospective studies (case-control studies =3), and 1 was a cohort study (**Table 1**) (2-8). Five studies (2,4,6-8) evaluated the role of NNH and five studies (2-5,7) evaluated the role of NPT in relation to the

development of childhood allergic diseases. Six studies were conducted in upper-middle to high-income countries, and one study was conducted in low-income country (5).

Risk of bias in included studies

All the studies were of good quality as per the New-Castle Ottawa Scale (**Table 2**).

Effect of interventions/exposures

Primary outcomes

Rate of childhood allergic diseases after NNH and/or phototherapy (NPT)

(i) Rate of childhood asthma after NNH: a total of four studies reported this outcome (2,4,6,8). There was no heterogeneity among the studies. Compared to no NNH, the pooled estimate showed a significant increase in the risk of childhood asthma after NNH [OR: 4.26, 95%CI 4.04 to 4.5, $p<0.001$] (**Figure 2**).

(ii) Rate of childhood asthma after NPT: a total of five studies reported this outcome (2-6). Data could be pooled from 4 studies, as one study reported zero events in the exposure group (3). Compared to no NPT, the pooled estimate showed a significant increase in the risk of childhood asthma after NPT [OR: 3.81, 95%CI 3.53 to 4.11, $p<0.001$]. As one of the studies had a small sample size ($n=62$) leading to a very large OR (5), the result was re-pooled after excluding this study. But, the effect size remained unchanged (**Figure 3**).

(iii) Rate of childhood allergic rhinitis (AR) after neonatal hyperbilirubinemia: a single study reported this outcome (7). Compared to NNH, there was a significant increase in the risk of childhood AR after NNH [OR: 5.37, 95%CI 4.16 to 6.92, $p<0.001$].

(iv) Rate of childhood allergic rhinitis after NPT: a total of two studies reported this outcome (2,7). There was no heterogeneity among the studies. Compared to no NPT, the pooled estimate showed a significant increase in the risk of childhood AR after NPT [OR: 3.04, 95%CI 2.13 to 4.32, $p<0.001$].

(v) Rate of childhood allergic rhinitis and/or conjunctivitis after NPT: a single study (n=53) reported this outcome (3). Compared to no NPT, there was a significant increase in the risk of childhood allergic rhinitis and/or conjunctivitis after NPT [OR: 8.36, 95%CI 1.18 to 59.43, p=0.016].

We could not find any study that reported about the risk of childhood atopic dermatitis/eczema after NNH and/or NPT.

Secondary outcomes

(i) Rate of late onset of asthma after NNH and/or NPT: a single study reported this outcome (6). Compared to no NNH, there was a significant increase in the risk of development of late onset childhood asthma after NNH [OR: 4.1, 95%CI 2.82 to 5.94, p<0.001].

(ii) Rate of hospitalization due to childhood asthma after NNH and/or NPT: a single study reported this outcome (2). Compared to no NPT, there was a significant increase in the risk of hospitalization due to childhood asthma after NPT [OR: 3.56, 95%CI 2.93 to 4.33, p<0.001].

(iii) Relation between duration of NPT and childhood allergic diseases: two studies reported this outcome. One study found a longer duration (mean±SD, days) of NPT in childhood asthma group (4.9±1.3) compared to the control group (3.2±1.1) (p=0.001) (5). Another study did not find any statistically significant association between the rate of AR and the icterus lasting days, but the AR attack times (p=0.02) and the use of oral antihistamines (p=0.04) were significantly higher in those with icterus lasting for ≥7 days (7).

(iv) Relation between serum bilirubin level and childhood allergic diseases: two studies reported this outcome. In one study, the increase risk of asthma correlated with maximum serum bilirubin (TSB) level and TSB level at 48 hours postpartum (p< 0.01). TSB levels >15 mg/dl were associated with a 61% increase in the risk of childhood asthma (aOR: 1.61, 95% CI 1.04 to 2.08, p=0.007) (8). In another study, there was no association between TSB level and AR rate or AR attack time or antihistamine use (7).

(v) Rate of childhood asthma requiring steroid after NNH and/or NPT: a single study reported this outcome (4). Compared to no NPT, there was a significant increase in the rate of steroid use in those with childhood asthma after NPT [OR: 4.35, 95%CI 3.31 to 5.72, $p < 0.001$].

Publication bias

To assess whether there was a bias in the published literature, funnel plot was constructed using the OR and 1/SE values obtained from studies measuring the rate of asthma after NNH. From the funnel plot generated, the possibility of publication bias in the analysis is less likely (**Figure 4**).

Grade of evidence

For assessment of the quality of evidence, GRADE Profiler software (version 3.6) was used (21). The software uses five parameters for rating the quality of evidence, and these are - limitations to design of randomized controlled trials, inconsistency of results or unexplained heterogeneity, indirectness of evidence, imprecision of results, and publication bias. The rating is done as – no, serious, and very serious limitation. The evidence generated in the present review was of “low-quality” for following outcomes: rate of childhood asthma after NNH and after NPT (**Table 3**). The evidence generated was of “very low quality” for following outcome: rate of childhood allergic rhinitis after NPT (**Table 3**).

DISCUSSION

Summary of evidence

After an extensive search of the literature, we could find 7 observational studies including 101,499 children (1-12 years age) to be eligible for inclusion in the present systematic review. Our results indicate that there was significant increase in the rate of asthma and allergic rhinitis after NNH and/or NPT, the rate of late onset of asthma after NNH, the rate of hospitalization due to asthma after NPT. Besides this, there was an overall increase in the prevalence of various childhood allergic diseases after NNH and/or NPT. When we constructed the GRADE evidence from available data, it was found to

be of “low quality” for the rates of asthma after NNH and after NPT, and of “very low quality” for the rate of AR after NPT.

Are the above findings/associations real or there are alternative explanations ? This can be made clear if we discuss the following points. First, the sample size was very large with no/little heterogeneity among the included studies. Both these factors reduce the chance of any bias to occur including the publication bias. Second, adjusted ORs (95% CI) were used in the present meta-analyses to calculate the summary estimate, which also makes the association or the direction of association stronger. Third, good quality studies were used to calculate the summary estimate, which also reduce the chance of biases (inherent to observational studies) to occur. Fourth, there was consistency of study results including the strength of association. Taking into account of all these factors, it seems that the associations are real but may be not causal.

Are there any explanations to these associations ?. If yes, then it would be difficult to explain, as both NNH and NPT have been shown to be associated with an increased risk of childhood allergic diseases. From the available literature as well as from the present evidence it seems that both NNH and NPT probably act by different mechanisms to increase the risk. As discussed earlier, though bilirubin is a known antioxidant, it hardly exerts this effect in premature neonates. At a higher level (>12.5 mg/dl), bilirubin acts as a strong pro-oxidant along with increase heme (a pro-oxidant) production during NNH, even in term neonates. Besides this, bilirubin delays the Th-2 to Th-1 switch (by inhibiting IL-2 production and other mechanism), interferes with the lung surfactant function, decreases ADCC (antibody dependent cell cytotoxicity), and modifies the neonatal gut microbiota (14,15-17,22-25). All these factors help in the induction of airway inflammation (both upper and lower airway) that might lead to the development of allergic diseases (asthma and/or allergic rhinitis) later in life. On the other hand, NPT also affects the Th-2 to Th-1 switch (by increasing TNF- α , IL-1 β , IL-8, and decreasing IL-6) besides directly damaging the DNA, decreasing the NK-cell activity (through UV light), and interfering with the CD4+/CD8+ cells (through UV light) (26-29). All these factors also help in the induction of

airway inflammation (both upper and lower airway) that might lead to the development of allergic diseases (asthma and/or allergic rhinitis) later in life.

After discussing all these points it seems that, a dose-response relationship exists between the NNH and NPT (a higher or a lower level of one or the other), that along with the genetic constituent and environmental factors decide the future development of allergic diseases.

Limitations

All the studies were observational, so the evidence generated was of “very low/low-quality”. Before degrading observational studies one should perhaps consider if a randomized clinical study is at all possible. Theoretically one could randomize the intervention for icterus to phototherapy and no phototherapy, but it seems very difficult to randomize icterus. Moreover, the ethics of randomizing phototherapy would also be doubtful. We could not take into account the type of hyperbilirubinemia (unconjugated or conjugated), as none of the studies reported the outcome separately for them. As a cytokine/immunologic study was not undertaken, it was also difficult to find a patho-physiologic link between NNH and/or NPT and allergic diseases. It was also difficult for us to make any suggestion about the dose-response effect as only one study measured this. Besides this, our results may not be applicable to children of other parts of the world (as only one small study was conducted in a developing country), and older children/adolescents of 12-18 years age.

Further area of research

Future studies should report any link between the type of hyperbilirubinemia (unconjugated or conjugated) and the risk of allergic diseases. More studies are needed on the outcomes like the rate of late onset asthma, rate of hospitalization due to asthma, rate of other allergic diseases (atopic dermatitis/eczema, hay fever), rate of medication use in allergic diseases, and the relationship of serum bilirubin level or duration of NPT with allergic diseases. Studies should simultaneously focus on the immunological markers or cytokines/gene polymorphism and allergen tests (e.g., skin prick test).

Finally, the studies should also report the findings from other parts of the world and should include older children/adolescents.

CONCLUSIONS

The current evidence finds a significant increase in the rate of childhood allergic diseases after NNH and/or NPT. As observational studies were included, the evidence generated was of 'low-quality'. Future studies should try to elucidate the pathophysiologic link between NNH and/or NPT and childhood allergic diseases.

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None

COMPETING INTEREST

None

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FIGURE LEGENDS

Figure 1: Study flow

Figure 2: Rate of childhood asthma after NNH

Figure 3: Rate of childhood asthma after phototherapy

Figure 4: Funnel plot assessing the publication bias

Table 1: Observational Studies on neonatal hyperbilirubinemia/phototherapy and childhood allergic diseases

S. No	Study ID/ Site or country	Design, setting	Study population	Number of subjects	Intervention/Exposure	Outcome (effect size)	Comments
1	Aspberg 2007/ Sweden [2]	Retrospective study, hospital based	Data on all children born between 1987 and 1999, who had been hospitalized for asthma before the end of 2001	14,803 children	Neonatal icterus/phototherapy	The association between icterus/phototherapy and hospitalization with asthma: aOR, 1.27 (95% CI: 1.08–1.50) for ≥ 1 hospitalization, aOR 1.52 (95% CI: 1.19–1.95) for ≥ 2 hospitalization, aOR 1.46 (95% CI: 1.02–2.09) for ≥ 3 hospitalization	Exposure data (icterus/phototherapy) is prospective in relation to the outcome. Included children >2 yr age with asthma
2	Gloria-Bottini 2010/Italy [3]	Retrospective survey of a birth cohort, population based	Neonatal phototherapy data from four Italian hospitals.	Data on 53 children	Neonatal phototherapy	Among subjects studied at birth, allergic rhinitis and/or conjunctivitis were more frequent among those treated with phototherapy than among those not treated (p=0.046)	Studied the effect of adenosine enzyme (ADA) co-dominant allele (ADA1*2)

3	Aspberg 2010/ Sweden [4]	Retrospective study, hospital based.	Data on children born between 1990 and 2003	61,256 children	Neonatal icterus/phototherapy	Neonatal phototherapy and/or icterus were risk determinants for children who developed asthma before the age of 12: aOR, 1.30 (95% CI: 1.16–1.47)	Exposure data (icterus/phototherapy) is prospective in relation to the outcome
4	Heidarzadeh 2011/Iran [5]	Analytical case-controlled study, hospital based	Children referred to asthma and allergy clinic of a hospital	Cases = 28; Controls = 34	Neonatal phototherapy	Phototherapy in case group = 26 (92.8%), and in control group = 20 (58.8%) (P value= 0.002). Mean duration of phototherapy in cases = was 4.9 days, and in controls = 3.2 days (P-value<0.0001)	Age group studied was 2-12 years
5	Ku 2012/Taiwan [6]	Case-control study, hospital based	Data on children born between year 1997-2000	Cases = 717; Controls = 10,604	Neonatal icterus	The rate of asthma in icteric children = aOR, 1.64 (95% CI: 1.36–1.98).	Included children >2 yr age with asthma. Found an increased rate and severity of asthma up to the age of 10 yrs
6	Sun 2013/Taiwan [7]	Case-control study, hospital based	Data on children born between 1996-2000	Cases = 717; Controls = 10,601	Neonatal icterus/phototherapy	The rate of allergic rhinitis (AR) in icteric children: aOR, 1.46 (95% CI: 1.24–1.72). Found a higher incidence of AR in children <4 years age. The use of oral antihistamines, and complication rates were higher in the icteric children	Studied only the development of AR from birth to 10 years age. No association between phototherapy and AR noted

7	Huang 2013/USA [8]	Multicenter prospective cohort study, hospital and population based	Data from Collaborative Perinatal Project from 1959 to 1965.	Data on 28,807 subjects	Neonatal icterus without phototherapy	The overall prevalence of asthma was 5.26%. Neonatal maximum TSB levels >15 mg/dL were associated with a 61% increase in the risk of childhood asthma = adjusted OR, 1.61 (95% CI: 1.04, 2.08)	Study was conducted at a time when phototherapy was not available as treatment. Included term infants weighing >2,250 g
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Note: aOR = adjusted odds ratio; TSB = Total serum bilirubin; CI = Confidence interval.

Table 2: Quality assessment of included studies using the New-Castle Ottawa Scale

Study author, year, country	Selection				Comparability of cases and controls on the basis of the design or analysis	Exposure			Comment
	Is the case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment of cases and controls	Non response rate	
Aspberg 2007, Sweden [2]	Yes, record validation (*)	Yes (*)	Yes, from birth register (*)	Yes, children matched for age and same survey area (*)	Yes, groups comparable and also adjusted for potential confounders (**)	Yes, birth record (*)	Yes (*)	4% (*)	Good quality
Gloria-Bottini 2010, Italy [3]	Yes, record validation (*)	Yes (*)	Yes, from clinical records (*)	Yes, from the same birth cohort (*)	Yes, groups comparable. Not adjusted for	Yes, birth record (*)	Yes (*)	0% (*)	Good quality

					potential confounders (*)				
Aspberg 2010, Sweden [4]	Yes, record validation (*)	Yes (*)	Yes, from birth register (*)	Yes, children matched for age and same survey area (*)	Yes, groups comparable and also adjusted for potential confounders (**)	Yes, birth record (*)	Yes (*)	3% (*)	Good quality
Heidarzadeh 2011/Iran [5]	Yes, record validation (*)	Yes (*)	Yes, hospital controls (*)	Yes, children matched for groups (*)	Yes, groups comparable and also adjusted for potential confounders (**)	Yes, hospital records (*)	Yes (*)	0% (*)	Good quality
Ku 2012, Taiwan [6]	Yes, record validation (*)	Yes (*)	Yes, from birth register (*)	Yes, children matched for age and same survey area (*)	Yes, groups comparable and also adjusted for potential confounders (**)	Yes, birth records (*)	Yes (*)	0% (*)	Good quality
Sun 2013, Taiwan [7]	Yes, record validation (*)	Yes (*)	Yes, from birth register (*)	Yes, children matched for age and same survey area (*)	Yes, groups comparable and also adjusted for potential confounders	Yes, birth records (*)	Yes (*)	1.9% (*)	Good quality

					rs (**)				
Huang 2013/USA [8]	Yes, record validation (*)	Yes (*)	Yes, from birth register (*)	Yes, infants matched for birth race, age, birth weight (*)	Yes, groups comparable and also adjusted for potential confounders (**)	Yes, birth records (*)	Yes (*)	28% loss (*)	Good quality

Table 3: GRADE evidence for various outcomes

Quality assessment							Effect		
No of studies (subjects)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Quality	Importance
Rate of childhood asthma after NNH (follow-up: 1-12 years; assessed with: clinical parameters)									
4 (n=90,744)	Observational studies ¹	Serious ¹	No	No	No	Strong association ²	OR 4.26 (4.04 to 4.5)	LOW	CRITICAL
Rate of childhood asthma after phototherapy for NNH (follow-up: 1-12 years; assessed with: clinical parameters)									
4 (n=61,999)	Observational studies ¹	Serious ¹	No	No	No	Strong association ³	OR 3.81 (3.53 to 4.11)	LOW	CRITICAL
Rate of childhood allergic rhinitis after phototherapy for NNH (follow-up: 1-12 years; assessed with: clinical parameters)									

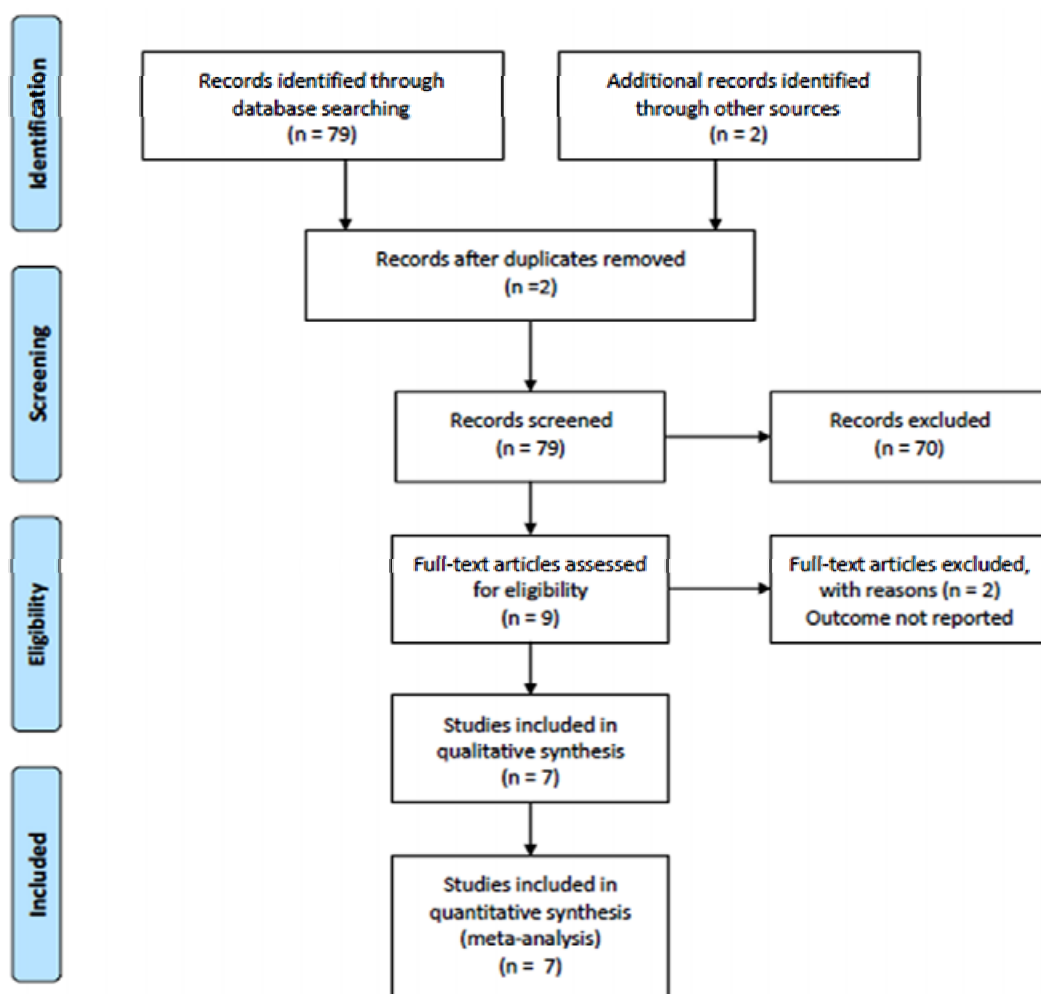
2 (n=11,371)	Observational studies ¹	Serious ¹	No	No	No	Reporting bias ⁴	OR 3.04 (2.13 to 4.32)	VERY LOW	CRITICAL
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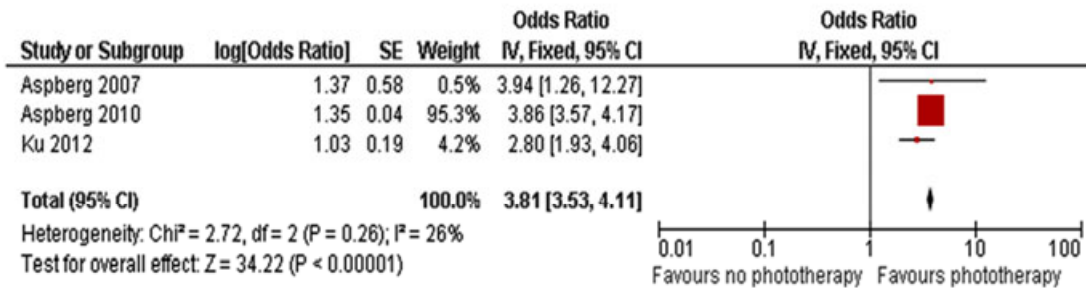
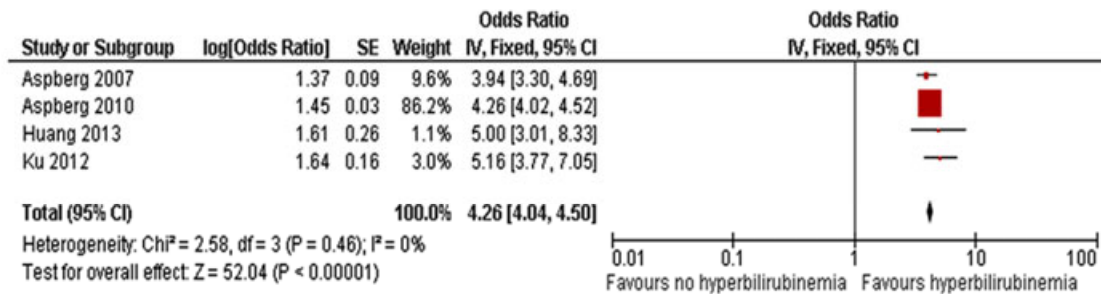
¹ Case-control and other study designs together

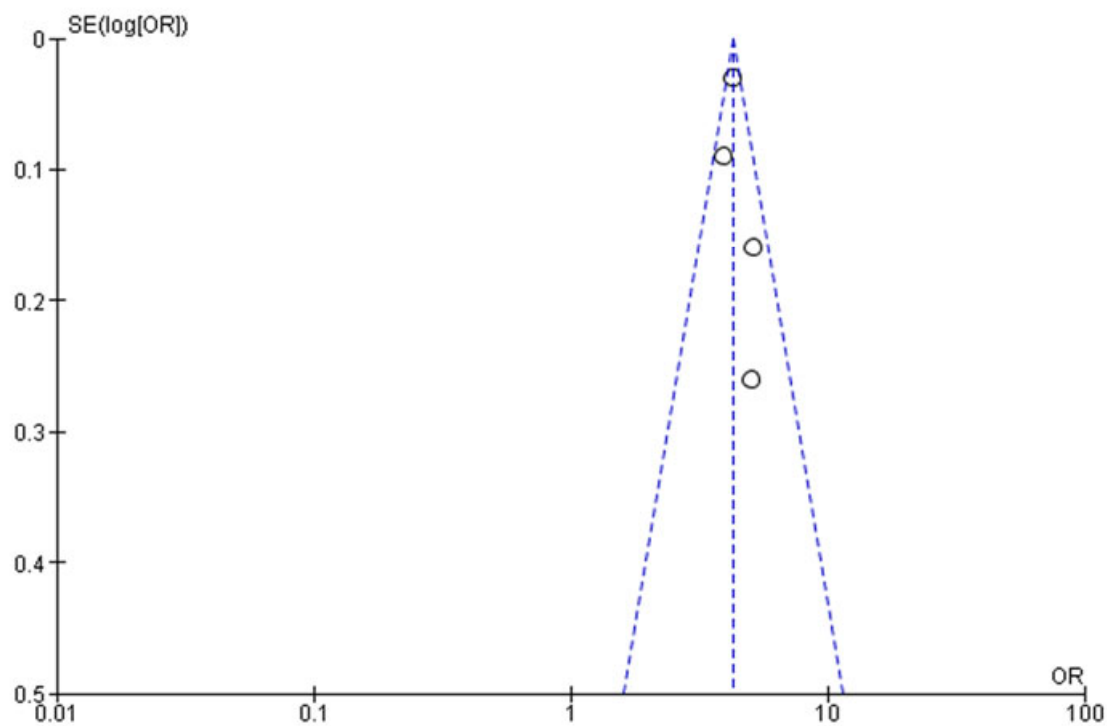
² Large effect size and good precision

³ Large effect size and good precision

⁴ One study has small sample size but very large effect size







Search Details (PubMed/Medline)

1. ("newborn"[MeSH Terms] OR ("neonate"[All Fields] AND "neonatal"[All Fields]) OR "infant"[All Fields]) AND icterus [All Fields] AND ("jaundice"[MeSH Terms] OR "hyperbilirubinemia"[All Fields])
2. ("newborn"[MeSH Terms] OR ("neonate"[All Fields] AND "neonatal"[All Fields]) OR "infant"[All Fields]) AND ("allergy"[MeSH Terms] OR "allergic diseases"[All Fields] OR "atopy"[All Fields] OR "diseases"[All Fields])
3. "asthma"[MeSH Terms] OR "allergic asthma"[All Fields]
4. "rhinitis"[MeSH Terms] OR "allergic rhinitis"[All Fields]
5. "allergic conjunctivitis"[MeSH Terms] OR "atopic conjunctivitis"[All Fields] OR "hay fever" [All Fields]
6. "eczema"[MeSH Terms] OR "atopic eczema"[All Fields] OR "atopic dermatitis" [All Fields]
7. (#1) AND #2
8. (#7) AND #3
9. (#8) AND #4
10. (#9) AND #5
11. (#10) AND #6
12. "child"[MeSH Terms] OR "child"[All Fields]
13. "child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]
14. (#11) AND #12
15. (#13) AND #14
16. "phototherapy"[MeSH Terms] OR "light"[All Fields] OR "therapy" [All Fields]
17. (#15) AND #16