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Neonatal jaundice, phototherapy and childhood allergic diseases: an updated systematic review and meta-analysis

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iii. Abstract and keywords

Background: Neonatal jaundice and phototherapy have been associated with the development of allergic diseases. It has been suggested, however, that effect estimates of the associations might be smaller than expected. We sought to update the evidence of their associations including recently published large longitudinal studies.

Methods: We sought published and unpublished observational studies through the major databases. We used a random-effect meta-analysis model weighted by the inverse variance estimate, the Quality in Prognosis Studies tool to assess the methodological quality for each study, and the Grading of Recommendations, Assessment, Development, and Evaluation approach to assess the certainty of evidence (COE).

Results: Nineteen studies were enrolled in the qualitative syntheses, and fourteen studies were synthesized in the meta-analyses. Neonatal jaundice was associated with a higher risk of childhood-onset asthma (odds ratio [OR], 1.46; 95% confidence interval [95% CI], 1.39–1.53; COE, moderate), atopic dermatitis (AD) (OR, 1.30; 95% CI, 1.07–1.57; COE, moderate), and allergic rhinitis (AR) (OR, 3.01; 95% CI, 0.88–10.30; COE, low). Neonatal phototherapy was also associated with a higher risk of childhood-onset asthma (OR, 1.24; 95% CI, 1.11–1.38; COE, moderate), AD (OR, 1.31; 95% CI, 1.24–1.39; COE, moderate), and AR (OR, 1.38; 95% CI, 0.93–2.04; COE, Very low). There were no studies that reported effect estimates of the associations between childhood-onset food allergies and neonatal jaundice and phototherapy.

Conclusion: Neonatal jaundice and phototherapy were probably a prognostic factor of childhood-onset allergic diseases; however, the associations were likely to be smaller than previously estimated.

Keywords: allergic rhinitis, asthma, atopic dermatitis, food allergy, hyperbilirubinemia, icterus, neonatal jaundice, newborn infant, phototherapy, prognostic factor

Key Message

It has been suggested that the previous review overestimated the effect estimates of the association between neonatal jaundice and/or phototherapy and allergic diseases. We updated the evidence of their associations including recently published studies. From our results, neonatal jaundice and phototherapy were probably prognostic factor of childhood-onset allergic diseases; however, the associations were likely to be smaller than previously estimated.

iv Main text

Introduction

Asthma, allergic rhinitis (AR), atopic dermatitis (AD), food allergies (FA), and other allergic diseases are common chronic medical conditions in childhood and have an increasing prevalence worldwide.^{1,2} Perinatal or neonatal factors could influence the potential risks of childhood-onset allergic diseases.^{3,4}

Fifty to sixty percent of term infants develop neonatal jaundice,^{5,6} and 10%–20%⁷ of these are treated with phototherapy to prevent bilirubin encephalopathy and kernicterus⁵. A possible association between neonatal jaundice and phototherapy and increasing risks of allergic diseases has been reported.⁸ A systematic review by Das et al.,⁸ which included seven studies published before April 2014, showed that neonatal jaundice and phototherapy led to childhood-onset asthma and AR, with a three- to five-fold increase in the odds ratio (OR). This paper, however, was limited to a small number of studies and only evaluated asthma and AR; we have suggested that the results from Das et al. were overestimated and did not prove a meaningful association between neonatal jaundice, phototherapy, and allergic diseases.⁹ Several other large longitudinal studies have been published.^{10–15} Our study will use rigorous methodology to demonstrate a clear association between neonatal jaundice, phototherapy, and childhood-onset allergic diseases.

2 Methods

2.1 Protocol and registration

We conducted a systematic review and meta-analysis in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) (Supporting Information–1). We followed the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) informative statements to communicate the findings of systematic reviews of interventions.¹⁶ We developed a detailed protocol and registered our study with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020183852, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=183852).

2.2 Study inclusion and exclusion criteria

We included studies using the PECO framework: participant, exposure, comparator, and outcome. The participants were any newborn infants; the exposure was neonatal jaundice and phototherapy; the comparators were newborn infants who did not have jaundice or

undergo phototherapy; and the outcomes were childhood-onset (age 19 or younger) allergic diseases: asthma, AD, AR, or FA. We accepted the diagnostic criteria adopted by the original studies and excluded case reports or series, systematic reviews, and other meta-analyses.

2.3 Search strategy

We searched MEDLINE (via PubMed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov; the studies occurred before May 7, 2020, and we did not restrict for language or date of publication (Supporting Information–2). We also confirmed the references included in the eligible studies.

2.4 Study selection and data extraction

Two authors (YK and TA) screened the titles and abstracts of studies according to the inclusion and exclusion criteria and then obtained and independently assessed the full text for eligibility. If we were not sure whether a study met the inclusion criteria, we emailed the study's original authors and requested additional information. We used the Rayyan software¹⁷ for study selection. Two authors (YK and TA) independently extracted data from the studies.

2.5 Quality assessment

Two authors (YK and TA) independently assessed the risk of bias for each study by using the Quality In Prognosis Studies tool^{18,19}. This tool includes six domains, and we assessed each by the confounding factors of gestational week, gender, and birth weight. Any conflicts between the two reviewers were resolved through discussion or with a third reviewer as needed.

2.6 Data synthesis and statistical analysis

All statistical analyses were performed using the “meta” package of R software (version 3.6.1)²⁰. We performed meta-analysis and pooled the adjusted ORs with 95% confidence intervals (CIs) for all outcomes. We used a random-effect meta-analysis model weighted by the inverse variance estimate. We contacted the authors to confirm the ORs if the papers only included the hazard ratios (HRs) and/or incidence rate ratios (IRRs). If ORs were still not available after querying the authors, we performed meta-analyses by pooling log HR and log IRR and reporting them as relative risks. For the presence of jaundice, we used results with total serum bilirubin level (TSB) above 15 mg/dL for studies stratifying TSB levels, rather than a binary variable. We used the results of participants with gestational ages of ≥35–37 weeks for studies reporting multiple effect estimates.

We visually evaluated heterogeneity using forest plots and calculated and analyzed I^2 statistics (I^2 values of 0%–40%: not important; 30%–60%: moderate heterogeneity; 50%–90%: substantial heterogeneity; 75%–100%: considerable heterogeneity).²¹ If heterogeneity was detected ($I^2 > 50\%$), we verified the possible causes. To calculate I^2 statistics, we used the Cochrane chi-square test (Q-test).

Individuals from East Asia have a higher risk factor for neonatal jaundice, so we analyzed subgroups by noting whether a study was performed in an East Asian or non-East Asian region.²² We also indicated the relationship between birth year and effect size. Due to limited data, we could not perform the Egger's regression test and other subgroup and sensitivity analyses that were originally planned in our protocol.

2.7 Rating the certainty of the evidence

We created a summary of findings tables based on the Cochrane Handbook²¹ for each of the following outcomes: asthma, AD, AR, and FA. "Summary of findings" for all outcomes included grading of the certainty of evidence (COE) for the prognostic factors according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)²³. In using GRADE for the prognostic factor approach, we started with "High" COE in the observational research evidence²⁴. If there were any serious concerns in any domain, we lowered the grade from "High" COE. ORs and relative risks were integrated separately. Effect estimates displayed in the Summary of findings table were created using only the results of OR. To determine the inconsistency domain of the GRADE rating, we took into account whether the results of OR and relative risk were consistent.

3 Results

3.1 Literature search results

Figure 1 displays the PRISMA flow chart that details the process of study selection, including reasons for exclusion. We screened 1,129 records, after removal of duplicates, and assessed 31 full texts. Nineteen studies were in the qualitative synthesis.^{10-15,25-37} In the end, fourteen studies reporting the effect estimate were synthesized in the meta-analysis. Our search did not reveal any ongoing and unpublished studies.

3.2 Characteristic of studies included in the qualitative synthesis

Table 1 shows the characteristics of the 19 included studies,^{10-15,25-37} which included three case-control studies,^{26,27,32} two cross-sectional studies,^{25,33} and 14 longitudinal cohort

studies.^{10-14,28-31,34-37} There were 14 articles related to jaundice^{12-15,25-27,29-31,33,34,36,37} and 13 articles related to phototherapy.^{10-14,27,28,30-32,34,35,37} Seven studies were conducted in East Asia: Taiwan, five^{11,14,15,30,31}; China, one²⁶; and Singapore, one¹⁰; 12 studies originated in non-East Asian countries. No studies on the associations between neonatal jaundice and phototherapy and FA were included in the meta-analysis. Only one study³⁶ qualitatively reported an association between jaundice and FA. The characteristics of the outcomes reported in the 19 studies are shown in Supporting Information–3.

3.3 Risk of bias in the included studies

Supporting Information–4 summarizes the risk of bias in the included studies. There was a low or moderate risk of bias for study participation, study attrition, outcome measurements, and statistical analysis. The risk of bias for prognostic factor measurement was moderate because the definitions of jaundice and phototherapy were not provided according to TSB levels. One study¹⁵ was only a conference abstract, and all domains of that study were moderate or high.

3.4 Results of synthesis

3.4.1 Association between neonatal jaundice and childhood-onset allergic diseases

Meta-analyses for the association of neonatal jaundice with allergic diseases are shown in Figure 2. Nine studies investigated the association between neonatal jaundice and asthma.^{12,14,15,25,27,29,31,34,37} Of these, the meta-analysis included eight studies reporting the effect estimate.^{12,14,15,25,29,31,34,37} Neonatal jaundice was slightly associated with a higher risk of childhood-onset asthma: OR, 1.46; 95% CI, 1.39–1.53; $n = 6$ ^{15,25,29,31,34,37}; COE, moderate. This result was not changed when we pooled the studies using relative risk: 1.70; 95% CI, 0.89–3.25; $n = 2$.^{12,14} One case–control study ($n = 600$), which was not included in the meta-analysis, qualitatively reported that children with asthma, AR, and/or acute urticaria were more likely to have jaundice in the neonatal period.²⁷ Two reports have studied the association between TSB and the development of asthma. Huang et al²⁹ reported that the risk for asthma increased with both the maximum TSB and TSB levels at 48 hours postpartum (P for trend < 0.01). However, Kuzniewicz et al¹² reported that there was no dose-response relationship between maximum TSB level and the development of asthma.

Four studies that investigated the association between neonatal jaundice and AD were included in the meta-analysis.^{13-15,33} Neonatal jaundice was probably associated with a

higher risk of childhood-onset AD slightly: OR, 1.30; 95% CI, 1.07–1.57; $n = 2^{15,33}$; COE, moderate. This result was not changed when we pooled the studies using relative risk: 1.67; 95% CI, 0.76–3.65; $n = 2^{13,14}$

Five studies investigated the association between neonatal jaundice and AR.^{14,15,26,27,30} Four studies reporting the effect estimates were included in the meta-analysis.^{14,15,26,30} Neonatal jaundice may be associated with a higher risk of childhood-onset AR: OR, 3.01; 95% CI, 0.88–10.30; $n = 3^{15,26,30}$; COE, low. This result was similar to the HR reported by another retrospective cohort study: 2.52; 95% CI, 2.43–2.61.¹⁴

No study reported an effect estimate for FA. Only one study ($n = 692$) qualitatively reported that children with hyperbilirubinemia in the neonatal period had a higher rate of milk protein intolerance at the age of 12 months.³⁶

3.4.2 Association between neonatal phototherapy and childhood-onset allergic diseases

Meta-analyses of the association of neonatal phototherapy with allergic diseases are shown in Figure 3. In total, 10 studies investigated the association between neonatal phototherapy and asthma.^{10,12,14,27,28,31,32,34,35,37} Among these studies, six^{10,12,14,31,34,37} that reported the effect estimate were included in the meta-analyses. Neonatal phototherapy was probably associated with a higher risk of childhood-onset asthma slightly (OR, 1.24; 95% CI, 1.11–1.38; $n = 5^{10,14,31,34,37}$; COE, moderate). This result remained unchanged when we pooled the studies with relative risk: 1.11; 95% CI, 0.93–1.33; $n = 2^{12,14}$ Four studies, including two retrospective cohort^{28,35} and two case–control studies^{27,32} qualitatively reported that neonatal phototherapy was associated with childhood-onset asthma.

Four studies investigated the association between neonatal phototherapy and AD and were included in the meta-analysis.^{10,11,13,14} Neonatal phototherapy was probably associated with a higher risk of childhood-onset AD slightly: OR, 1.31; 95% CI, 1.24–1.39; $n = 2^{10,11}$; COE, moderate). This association was weakened when we pooled the studies with relative risk: 1.02; 95% CI, 0.82–1.25; $n = 3^{11,13,14}$

Four studies investigated the association between neonatal phototherapy and AR.^{10,14,27,30} Of these, two studies reporting the effect estimate were included in the meta-analysis.^{10,14} Neonatal phototherapy may be associated with a slightly higher risk of

childhood-onset AR, but the evidence is very uncertain: OR, 1.38; 95% CI, 0.93–2.04; n = 2^{10,14}; COE, very low. This result was similar to the HR reported by a retrospective cohort study: HR, 1.37; 95% CI, 1.31–1.43).¹⁴ One case–control study (n = 600) qualitatively reported that children with asthma, AR, and/or acute urticaria were more likely to have jaundice in the neonatal period²⁷; however, a retrospective study (n = 11,328) qualitatively showed that children had equal rates of AR whether they did or did not have phototherapy during the neonatal period.³⁰

No study to date has investigated the association between neonatal phototherapy and FA.

3.5 Subgroup and sensitivity analysis

Subgroup analysis looked at the differences between studies carried out in East Asian countries or in non-East Asian countries. Studies focused on East Asian countries had a similar OR for the relationship between asthma and neonatal jaundice: OR, 1.79; 95% CI, 1.23–2.60; n = 2^{15,31} compared to those carried out in other parts of the world: OR, 1.45; 95% CI, 1.40–1.50; n = 4.^{25,29,34,37} Studies conducted in East Asia had a similar OR for the incidence of asthma in neonates who had phototherapy: 1.06; 95% CI, 0.77–1.45; n = 3^{10,14,31} compared to studies conducted in other parts of the world: OR, 1.35; 95% CI, 1.28–1.42; n = 2^{34,37}.

In three studies in which subgroup analysis was conducted for gender, the direction of effect was the same for both sexes.^{11,14,31} Five studies that limited participants to newborns ≥35–37 weeks of gestation had similar effect estimates to those in our review.^{12,14,29,34,37}

No trend was found between the birth year of the participants and the effect size of the association between neonatal jaundice and asthma.^{12,14,15,25,29,31,34,37} (Supporting Information–5). On the other hand, studies of more recently born children were likely to have a smaller effect size of the association between neonatal phototherapy and asthma^{10,12,14,31,34,37} (Supporting Information–6).

4. Discussion

Our study demonstrated that children who had jaundice and received phototherapy during the neonatal period were more likely to develop childhood-onset asthma, AD, and AR, although the associations might be small. The COEs were all “moderate,” except for the

outcomes of AR. No studies reported the effect estimate of the associations between neonatal jaundice, phototherapy, and childhood-onset FA.

The effect estimates synthesized in our study were smaller than those of the previous meta-analysis by Das et al.,⁸ which can be attributed to the errors in their analysis methodology.⁹ The subgroup analyses by study location showed that the results of the studies conducted in East Asian and Non-East Asian countries were similar. The results of studies that performed subgroup analysis for gender or gestational age were also comparable to our results. Moreover, our results that are based on the latest data, clearly confirmed the findings of the previous review that neonatal jaundice and phototherapy have a slight association with allergic diseases.

The pathogenesis underlying neonatal jaundice or phototherapy in childhood-onset allergic diseases remains unclear. However, several hypotheses have been proposed to explain these associations.³⁸ First, unconjugated bilirubin may inhibit interleukin (IL)-2 production,³⁹ which induces the T-helper type 2 (Th-2)/T-helper type 1 (Th-1) switch disorder. Second, phototherapy for neonatal jaundice could alter the levels of cytokines, such as tumor necrosis factor-alpha, IL-1-beta, IL-8, and IL-6,⁴⁰⁻⁴² as well as directly result in DNA damage in lymphocytes.⁴³ These changes, in addition, may result in the Th-2/Th-1 switch disorder. In general, the neonatal immune system is skewed toward Th-2 type immune responses.⁴⁴ The Th-2/Th-1 switch disorder can influence Th-2 predominance, which may in turn contribute to the subsequent development of allergic diseases.⁴⁵ Therefore, further research is warranted to confirm these mechanisms.

The association between the use of phototherapy and childhood-onset allergic diseases varied depending on the birth year. The present review showed that participants from more recent birth years had lower effect estimates for the association between phototherapy and childhood-onset asthma. Though that cause is unclear, future studies may contribute more insights.

Several different types of phototherapy devices have been proposed since their first introduction in the 1950s.⁴⁶ Although some studies have been performed to determine the short-term efficacy and side-effects of using these devices,⁴⁶ long-term effects have rarely been studied. In fact, no study has still investigated the association between neonatal phototherapy and childhood-onset allergic diseases taking into account the involvement of different types of phototherapy devices and wavelengths. Therefore, further research is

needed to determine the influence of phototherapy using different devices on the development of allergic diseases.^{47,48}

The present study is the first meta-analysis suggesting an association among neonatal jaundice, phototherapy, and childhood-onset AD. The effect estimates of the present study are comparable to those of asthma and AR. The natural history of allergic diseases as they develop during childhood is known as the atopic march,^{49,50} and the presence of any allergic disease increases the risk of the development of additional diseases. AD is in fact associated with the development of asthma and AR.^{50,51} Several studies have also reported an extremely strong association between asthma and AR⁵² and that AR could be an independent risk factor of asthma development.⁵³ Therefore, neonatal jaundice and phototherapy are considered potential risk factors of almost all childhood-onset allergic diseases rather than of a specific allergic disease alone.

This study has several strengths. The major strength of the present study is its rigorous methodology and presentation in accordance with the PRISMA guidelines and GRADE tool. No serious concerns with respect to asthma and AD were identified, except for “risk of bias,” which we have rated as moderate COE. Second, the number of included studies was higher than in the review by Das et al.⁸ As a result, we could demonstrate evidence for the association of childhood-onset asthma or AR with neonatal jaundice and phototherapy. Finally, our review included AD and FA, which were not in the previous review.⁸

The study also had several limitations, which should be considered when interpreting the results. First, it is not known whether jaundice, phototherapy, or the combination influenced the development of allergic diseases since phototherapy is generally the first-line therapy for mild and moderate neonatal jaundice.⁵ Newborn infants can be divided into three groups: 1) non-jaundice and non-phototherapy, 2) jaundice and non-phototherapy, 3) jaundice and phototherapy. Most past studies have compared infants without jaundice with those with jaundice either with or without phototherapy. Accordingly, the effect of phototherapy could be added to the effect estimates of jaundice, which was likely to be over- or underestimated. In addition, we could not assess the presence of publication bias using pre-specified statistical tests owing to the involvement of a limited number of studies. Moreover, we did not find any ongoing or unpublished study in the registries, such as the ICTRP or clinicaltrials.gov; however, it should be noted that studies

with positive results are generally more likely to be published than those with negative results.⁵⁴

Third, we could not perform several planned subgroup analyses to investigate heterogeneity due to the limited data. Finally, some studies, especially those that did not include the intended outcomes in their titles and abstracts, may have been sidelined from our study selection. In this regard, we conducted a cited reference search for the eligible studies to ensure that relevant studies were not omitted.

In conclusion, neonatal jaundice and phototherapy are probably associated with childhood-onset allergic diseases; however, the strength of their association is likely to be smaller than what was previously estimated. The mechanism of the effect modification of birth year on this association has not been answered. Further studies could assess if there is an association between neonatal jaundice and phototherapy on AR and FA.

Author Contributions

YK contributed to the conception and design of the study. All the authors contributed development and implementation of literature search strategy. YK and TA contributed acquisition of data, including review of literature search results and data abstraction, and YK performed meta-analysis. All the authors contributed analysis and interpretation of data. YK wrote the first draft of the manuscript. All the authors contributed critical revisions of the manuscript for important intellectual content. All the authors approved the final version for publication.

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498 publication of research findings: an updated review of related biases. *Health Technol*
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500 Table 1. Characteristics of the included studies
501

Author (Published year)	Design	Setting	Study location	Sample size	Subject			Outcome	
					Gestation week	Birth year	Age (years of age)	Jaundice	Phototherapy
Santos (2020) ²⁵	Cross-sectional	Population	Brazil	820	Not limited	2009	6 or 7	Asthma	
Kang (2019) ²⁶	Case–control	Hospital	China	500	Not limited	Not available	Case: 12.8+/-5.2 Control: 13.7+/-5.2	AR	
Tham (2019) ¹⁰	Prospective cohort	Population	Singapore	1,058	Not limited	2009–2011	Up to 1.5, 3, and 5		Asthma, AD, AR
Safar (2019) ²⁷	Case–control	Hospital	Egypt	600	Not limited	Not available	Case: 3.7+/-0.18 Control: 3.4+/-0.17	Asthma [†] , AR [†]	Asthma [†] , AR [†]
Ku (2018) ¹¹	Retrospective cohort	Population	Taiwan	117,041	Not limited	1997–2008	Up to 5		AD
Yavuz (2018) ²⁸	Retrospective cohort	Hospital	Turkey	293	Not limited	Not available	Case: 8.8 (6.9–11.6) Control: 11.3 (8.0–13.3)		Asthma [†]
Kuzniewicz (2018) ¹²	Retrospective cohort	Population	US	109,212	≥ 35 weeks	2010–2014	3–7	Asthma	Asthma
Gau (2018) ¹⁵	Cohort	Not available	Taiwan	385	Not available	2010	Up to 6	Asthma, AD, AR	
Egeberg (2016) ¹³	Retrospective cohort	Population	Denmark	673,614	Not limited	1997–2007	Up to 1, 2, and 5–	AD	AD
Wei (2015) ¹⁴	Retrospective cohort	Population	Taiwan	83,060	Not limited	2000–2007	1–8	Asthma, AD, AR	Asthma, AD, AR
Huang (2013) ²⁹	Prospective cohort	Population	US	28,807	37–44 weeks	1959–1965	Up to 7	Asthma	
Sun (2013) ³⁰	Retrospective cohort	Population	Taiwan	11,328	Not limited	1997–2000	Up to 10	AR	AR [†]
Ku (2012) ³¹	Retrospective cohort	Population	Taiwan	11,321	Not limited	1997–2000	Up to 10	Asthma	Asthma
Arani (2011) ³²	Case–control	Hospital	Iran	62	Not limited	Not available	Case: 6.33 Control: 6.34		Asthma [†]
Apfelbacher (2011) ³³	Cross-sectional	Population	Germany	17,641	Not limited	Not available	0–17	AD	
Aspberg (2010) ³⁴	Retrospective cohort	Population	Sweden	1,337,472	Not limited	1990–2003	2–11	Asthma	Asthma
Gloria-Bottini (2010) ³⁵	Retrospective cohort	Hospital	Italy	53	Not limited	Not available	By more than 30		Asthma [†]
Raimondi (2008) ³⁶	Retrospective cohort	Hospital	Italy	692	Not limited	2005–2006	12 month of age	FA [†]	
Aspberg (2007) ³⁷	Retrospective cohort	Population	Sweden	1,386,029	Not limited	1987–1990	2–14	Asthma	Asthma

502
503 AD, atopic dermatitis; AR, allergic rhinitis; FA, food allergy

505 Table 2. Summary of findings for the effect of neonatal jaundice on the development of childhood-onset allergic diseases

506

Overview of study design						
Patients or study population: Newborn infant						
Exposure: Neonatal jaundice						
Comparison: No neonatal jaundice						
Outcome	Illustrative comparative risks [†]		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk ratio (95% CI)					
	Assumed risk	Corresponding risk				
	Control	Exposure				
Asthma	Study population		OR; 1.46	2,764,834	⊕⊕⊕⊖	
	48 per 1000	69 per 1000	(1.39; 1.53)	(6 studies)	Moderate ^a	
	Risk ratio; 1.43 (1.36; 1.49)					
Atopic dermatitis	Study population		OR; 1.30	18,026	⊕⊕⊕⊖	
	123 per 1000	154 per 1000	(1.07; 1.57)	(2 studies)	Moderate ^a	
	Risk ratio; 1.25 (1.06; 1.47)					
Allergic rhinitis	Study population		OR; 3.01	12,213	⊕⊕⊖⊖	

174 per 1000	387 per 1000	(0.88; 10.30)	(3 studies)	Low ^{a, b}
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Risk ratio; 2.23

(0.90; 3.94)

[†] The corresponding risk and risk ratio (and its 95% CI) were based on the assumed risk in the comparison group and the relative effect (and 95% CI) before the exposure group. Assumed risk was estimated from all the studies included in the meta-analysis.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

507 CI, confidence interval, OR, odds ratio

508 ^a Downgraded one point because of moderate or high risk of bias associated with prognostic factor measurement, statistical analysis,
509 and reporting.

510 ^b Downgraded one point as imprecise.

511 Table 3. Summary of findings for the effect of neonatal phototherapy on the development of childhood-onset allergic diseases

512

Overview of study design						
Patients or study population: Newborn infant						
Exposure: Phototherapy						
Comparison: No phototherapy						
Outcome	Illustrative comparative risks [†]		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk ratio (95% CI)					
	Assumed risk	Corresponding risk				
	Control	Exposure				
Asthma	Study population		OR; 1.24	2,818,940	⊕⊕⊕⊖	
	45 per 1000	55 per 1000	(1.11; 1.38)	(5 studies)	Moderate ^a	
	Risk ratio; 1.23 (1.10; 1.36)					
Atopic dermatitis	Study population		OR; 1.31	84,118	⊕⊕⊕⊖	
	127 per 1000	161 per 1000	(1.24; 1.39)	(2 studies)	Moderate ^a	
	Risk ratio; 1.26 (1.20; 1.32)					
Allergic rhinitis	Study population		OR; 1.38	84,118	⊕⊖⊖⊖	

399 per 1000	478 per 1000	(0.93; 2.04)	(2 studies)	Very low ^{a, b, c}
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Risk ratio; 1.20

(0.96; 1.44)

[†]The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect (and its 95% CI) estimated for the intervention group. Assumed risk was estimated from all the studies included in the meta-analysis.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

513 CI, confidence interval, OR, odds ratio

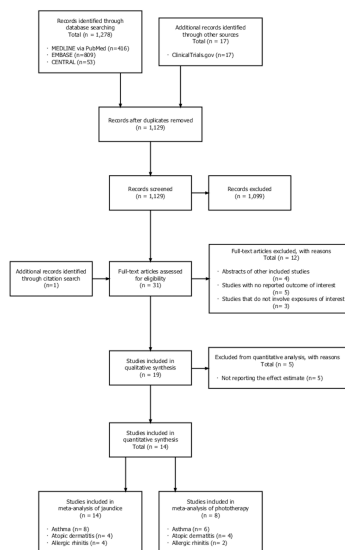
514 ^a Downgraded one point because of moderate or high risk of bias associated with prognostic factor measurement, statistical analysis,
515 and reporting.

516 ^b Downgraded one point for inconsistency.

517 ^c Downgraded one point as imprecise.

ix. **Figure legends**

- Figure 1. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart: results of the search strategy
- Figure 2. Forest plots showing the association between neonatal jaundice and childhood-onset allergic diseases.
- Figure 3. Forest plots showing the association between neonatal phototherapy and childhood-onset allergic diseases.



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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4, Supporting Information–2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5



PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 5-6
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Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 6-7, Table 1, Supporting Information-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 7, Supporting Information-3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 7-9, Table 2, 3 Figure 2, 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 7-9, Figure 2, 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2, 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 10



PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Supportive Information_2 Search strategy

1. MEDLINE search strategy

#1	infant, newborn[mh]
#2	child[mh]
#3	neonat*[tiab]
#4	infant[tiab]
#5	newborn[tiab]
#6	child[tiab]
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	hyperbilirubinemia, neonatal[mh]
#9	phototherapy[mh]
#10	bilirubin[mh]
#11	jaundice[mh]
#12	icterus[tiab]
#13	hyperbilirubinemia[tiab]
#14	phototherapy[tiab]
#15	bilirubin[tiab]
#16	jaundice[tiab]
#17	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	hypersensitivity[mh]
#19	dermatitis, atopic[mh]
#20	eczema[mh]
#21	asthma[mh]
#22	rhinitis[mh]
#23	rhinitis, allergic[mh]
#24	food hypersensitivity[mh]
#25	allerg*[tiab]
#26	atop*[tiab]
#27	hypersensitivity[tiab]
#28	dermatitis[tiab]
#29	eczema[tiab]
#30	wheezing[tiab]
#31	asthma asthma[tiab]
#32	"hay fever"[tiab]

#33 hayfever[tiab]
 #34 rhinitis[tiab]
 #35 food allergy[tiab]
 #36 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR
 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
 #37 #7 AND #17 AND #36

((((((((Infant, Newborn[mh]) OR Child[mh]) OR neonat*[tiab]) OR infant[tiab]) OR
 newborn[tiab]) OR child[tiab])) AND (((((((Hyperbilirubinemia, Neonatal[mh]) OR
 Phototherapy[mh]) OR Bilirubin[mh]) OR Jaundice[mh]) OR icterus[tiab]) OR
 hyperbilirubinemia[tiab]) OR phototherapy[tiab]) OR bilirubin[tiab]) OR jaundice[tiab])) AND
 (((((((((((Hypersensitivity[mh]) OR allerg*[tiab]) OR atop*[tiab]) OR
 hypersensitivity[tiab]) OR Dermatitis, Atopic[mh]) OR Eczema[mh]) OR dermatitis[tiab]) OR
 eczema[tiab]) OR Asthma[mh]) OR wheezing[tiab]) OR asthma[tiab]) OR Rhinitis[mh]) OR
 Rhinitis, Allergic[mh]) OR "hay fever"[tiab]) OR hayfever[tiab]) OR rhinitis[tiab]) OR Food
 Hypersensitivity[mh]) OR "food allergy"[tiab])

2. CENTRAL search strategy

- #1 [mh infant, newborn]
- #2 child:ti,ab,kw
- #3 neonat*:ti,ab,kw
- #4 infant:ti,ab,kw
- #5 newborn:ti,ab,kw
- #6 child:ti,ab,kw
- #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
- #8 hyperbilirubinemia, neonatal:ti,ab,kw
- #9 phototherapy:ti,ab,kw
- #10 bilirubin:ti,ab,kw
- #11 jaundice:ti,ab,kw
- #12 icterus:ti,ab,kw
- #13 hyperbilirubinemia:ti,ab,kw
- #14 phototherapy:ti,ab,kw
- #15 bilirubin:ti,ab,kw
- #16 jaundice:ti,ab,kw
- #17 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
- #18 hypersensitivity:ti,ab,kw
- #19 dermatitis, atopic:ti,ab,kw
- #20 eczema:ti,ab,kw
- #21 asthma:ti,ab,kw
- #22 rhinitis:ti,ab,kw
- #23 rhinitis, allergic:ti,ab,kw
- #24 food hypersensitivity:ti,ab,kw
- #25 allerg*:ti,ab,kw
- #26 atop*:ti,ab,kw
- #27 hypersensitivity:ti,ab,kw
- #28 dermatitis:ti,ab,kw
- #29 eczema:ti,ab,kw
- #30 wheezing:ti,ab,kw
- #31 asthma:ti,ab,kw
- #32 "hay fever":ti,ab,kw
- #33 hayfever:ti,ab,kw
- #34 rhinitis:ti,ab,kw
- #35 food allergy:ti,ab,kw

#36 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR
#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35

#37 #7 AND #17 AND #36

((((((([mh "Infant, Newborn"]) OR [mh Child]) OR neonat*:ti,ab) OR infant:ti,ab) OR
newborn:ti,ab) OR child:ti,ab)) AND (((((((([mh "Hyperbilirubinemia, Neonatal"]) OR [mh
Phototherapy]) OR [mh Bilirubin]) OR [mh Jaundice]) OR icterus:ti,ab) OR
hyperbilirubinemia:ti,ab) OR phototherapy:ti,ab) OR bilirubin:ti,ab) OR jaundice:ti,ab)) AND
((((((((((((([mh Hypersensitivity]) OR allerg*:ti,ab) OR atop*:ti,ab) OR
hypersensitivity:ti,ab) OR [mh "Dermatitis, Atopic"]) OR [mh Eczema]) OR dermatitis:ti,ab)
OR eczema:ti,ab) OR [mh Asthma]) OR wheezing:ti,ab) OR asthma:ti,ab) OR [mh Rhinitis])
OR [mh "Rhinitis, Allergic"]) OR "hay fever":ti,ab) OR hayfever:ti,ab) OR rhinitis:ti,ab) OR
[mh "Food Hypersensitivity"]) OR "food allergy":ti,ab)

3. EMBASE search strategy

- #1 EMB.EXACT.EXPLODE(infant)
- #2 ab(child) OR ti(child)
- #3 ab(neonat*) OR ti(neonat*)
- #4 ab(infant) OR ti(infant)
- #5 ab(newborn) OR ti(newborn)
- #6 ab(child) OR ti(child)
- #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
- #8 EMB.EXACT.EXPLODE(hyperbilirubinemia)
- #9 EMB.EXACT.EXPLODE(phototherapy)
- #10 EMB.EXACT.EXPLODE(bilirubin)
- #11 EMB.EXACT.EXPLODE(jaundice)
- #12 ab(icterus) OR ti(icterus)
- #13 ab(hyperbilirubinemia) OR ti(hyperbilirubinemia)
- #14 ab(phototherapy) OR ti(phototherapy)
- #15 ab(bilirubin) OR ti(bilirubin)
- #16 ab(jaundice) OR ti(jaundice)
- #17 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
- #18 EMB.EXACT.EXPLODE(hypersensitivity)
- #19 EMB.EXACT.EXPLODE(atopic dermatitis)
- #20 EMB.EXACT.EXPLODE(eczema)
- #21 EMB.EXACT.EXPLODE(asthma)
- #22 EMB.EXACT.EXPLODE(rhinitis)
- #23 EMB.EXACT.EXPLODE(allergic rhinitis)
- #24 ab(allerg*) OR ti(allerg*)
- #25 ab(atop*) OR ti(atop*)
- #26 ab(hypersensitivity) OR ti(hypersensitivity)
- #27 ab(dermatitis) OR ti(dermatitis)
- #28 ab(eczema) OR ti(eczema)
- #29 ab(wheezing) OR ti(wheezing)
- #30 ab(asthma) OR ti(asthma)
- #31 ab("hay fever") OR ti("hay fever")
- #32 ab(hayfever) OR ti(hayfever)
- #33 ab(rhinitis) OR ti(rhinitis)
- #34 ab(food allergy) OR ti(food allergy)

#35 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR
#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34
#36 #7 AND #17 AND #35

4. ClinicalTrials.gov

condition/disease;	infant, newborn, child, neonate, infant
intervention/treatment;	hyperbilirubinemia, phototherapy bilirubin, jaundice, icterus

Supporting Information–3. Characteristics of outcomes of the included studies

Author				Exposure: Jaundice				Phototherapy				Confounder	Comment
				Outcome									
				Asthma	Atopic dermatitis	Allergic rhinitis	Food allergy	Asthma	Atopic dermatitis	Allergic rhinitis	Food allergy		
(year)	Design	Exposure definition	Outcome definition										
Santos (2020) ²⁵	Cross sectional	Questionnaire	Modified ISAAC questionnaire	OR, 1.68 (0.94; 3.00)									model of delivery, gestational age, APGAR, birth weight, neonatal hyperbilirubinemia, neonatal respiratory infection, neonatal hospitalization
Kang (2019) ²⁶	Case control	Questionnaire	Otolaryngologist diagnosis			OR: 9.70 (5.00, 18.83)							maternal conditions of pre-pregnancy, pregnancy-related conditions gestational age, delivery manner, disease in early life, direct relatives' allergy, living condition, smoking
Tham (2019) ¹⁰	Prospective cohort	Medical record	Modified ISAAC questionnaire (+ Physician's diagnosis)					OR, 0.6 (0.2; 1.7) by month 18 OR, 0.7 (0.3; 1.4) by month 36 OR, 0.6	OR, 1.4 (0.8; 2.6) by month 18 OR, 1.3 (0.7; 2.4) by month 36 OR, 1.3	OR, 0.7 (0.3; 1.6) by month 18 OR, 1.0 (0.6; 1.8) by month 36 OR, 1.0 (0.6;		sex, ethnicity, breastfeeding levels, family history of allergy, gestational age, maternal education levels, and mode of delivery	

						(0.3; 1.2)	(0.7; 2.3)	1.9)	
						by month 60	by month 60	by month 60	
Safar (2019) ²⁷	Case control	Medical record	Physician diagnosis	Case [§] : 53% (159/300) Control: 39% (117/300) (P=0.001)	Case [§] : 53% (159/300) Control: 39% (117/300) (P=0.001)	Case [§] : 35.8% (57/159) Control: 19.7% (23/117) (P=0.003)		Case [§] : 35.8% (57/159) Control: 19.7% (23/117) (P=0.003)	[§] , Case: asthma, AR, and/or acute urticaria
Ku (2018) ¹¹	Retrospective cohort	ICD9 code	ICD9 code ATC code				IRR 0.871 (0.770; 0.985)		sex, socioeconomic status, urbanization, special healthcare needs, congenital skin disease, neonatal infection, preterm status, low birth weight, high birth weight, other birth, or maternal conditions
Yavuz (2018) ²⁸	Retrospective cohort	Medical record	Pulmonary function test or apparent asthma attack			Case: 17.9% Control: 7.1% (P=0.004)			Subject; children with allergic rhinitis and grass pollen sensitization and age > 6 years
Kuzniewicz (2018) ¹²	Retrospective cohort	Bilirubin measurement	Medical record	TSB <3: HR, 1.00 (0.86; 1.16) TSB 3–5.9: Reference TSB 6–8.9: HR, 1.04 (0.96; 1.14)		HR, 1.01 (0.92; 1.11)			sex, maternal history of asthma, cesarean delivery, birth hospitalization length of stay >7 days, recalibration, race, maternal age, gestational age, birth facility,

				TSB 9–11.0: HR, 1.14 (1.04; 1.26) TSB 12–14.9: HR, 1.12 (1.02; 1.24) TSB 15–17.0: HR, 1.22 (1.10; 1.36) TSB ≥18: HR, 0.99 (0.84; 1.16)						birth year, and feeding type during the birth hospitalization
Gau (2018) ¹⁵	Cohort	Not reported	Physician diagnosis	OR, 2.722 (1.192; 6.214)	OR, 1.946 (0.819; 4.623)	OR, 2.024 (0.843; 4.800)				gender, maternal age, maternal education, and family economic status
Egeberg (2016) ¹³	Retrospective cohort	Register record (ICD code)	ICD10 code, ATC code, and selected exclusion criteria		IRR, 1.12 (1.08; 1.16), prior to fifth birthday IRR, 1.13 (1.08; 1.18), prior to second birthday IRR, 1.13 (1.06; 1.21), prior to first birthday			IRR, 0.97 (0.88; 1.08), prior to fifth birthday IRR, 1.01 (0.88; 1.15), prior to second birthday IRR, 1.11 (0.92; 1.35), prior to first birthday		age, sex, neonatal phototherapy, neonatal jaundice, birthweight, gestation age at birth, season of birth
Wei	Retrospective	ICD9 code	ICD9 code	HR, 2.36	HR, 2.49	HR, 2.55	HR, 1.21	HR, 1.22	HR, 1.37	age, sex, comorbidities of fetal [†] , Subject; full-term only

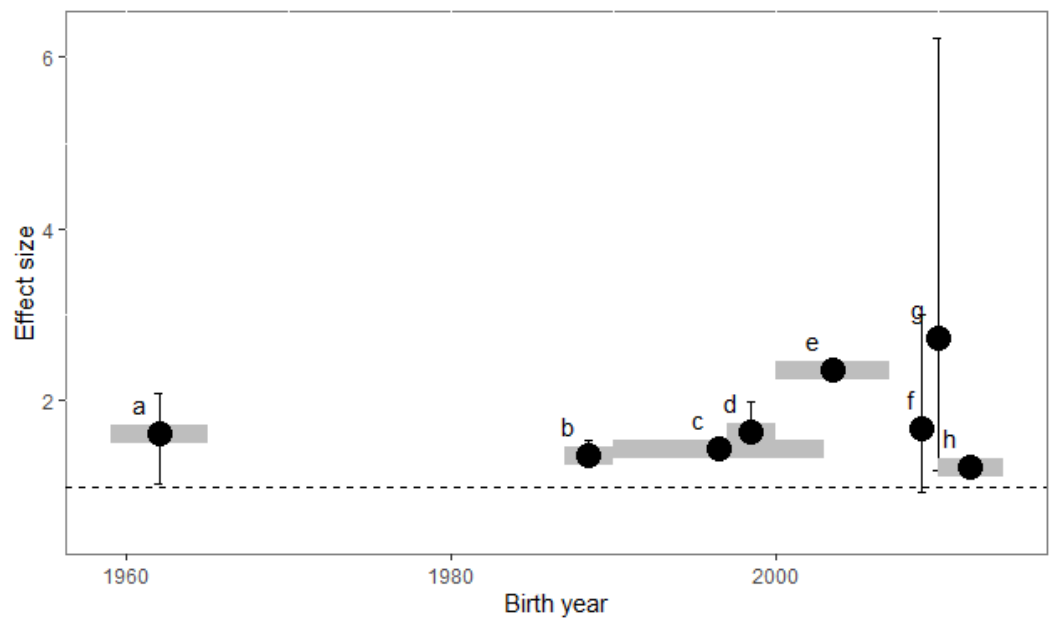
Ku (2012) ³¹	Retrospective cohort	ICD9 code	ICD9 code	OR, 1.64 (1.36; 1.98)	OR, 1.03 (0.72; 1.47)	preterm/low birth weight, neonatal infections, other respiratory conditions, gender, and other birth conditions	
Arani (2011) ³²	Case control	Questionnaire	Pediatric asthma and allergy specialist diagnosis		Case: 92.8% (26/28) Control: 58.8% (20/34) (P < 0.002)	Matching; age, sex, rout of delivery, nutrition, and low birth weight Exclusion; children with history of blood exchange and hospitalization due to any reason but jaundice	
Apfelbacher (2011) ³³	Cross sectional	Computer-assisted personal interview (parent-reported)	Physician diagnosis	OR, 1.27 (1.04; 1.54)		age group, gender, social status, sibling, breastfeeding, maternal smoking during pregnancy, maternal smoking during lactation, smoking in the living place, maternal alcohol consumption during pregnancy, pets, parental allergy, infection	
Aspberg (2010) ³⁴	Retrospective cohort	Resister record (Medical record)	Resister record (ATC code)	OR, 1.45 (1.40; 1.51)	OR, 1.35 (1.28; 1.42) OR, 1.24 (0.92; 1.72) ‡	year of birth, maternal age, parity, smoking during pregnancy, and years of involuntary childlessness	‡, Exclusion of maternal diabetis mellitus, pre-eclampsia, cesarean section, instrumental vaginal delivery, preterm birth

Supporting Information—4 The risk of bias for each study by using the Quality In Prognosis Studies tool

Exposure	Outcome	Author (published year)	Bias domains					
			Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Jaundice	Asthma	Santos (2020) ²⁵	Low	Moderate	Moderate	Low	Low	Moderate
		Kuzniewicz (2018) ¹²	Low	Low	Low	Low	Low	Low
		Gau (2018) ¹⁵	High	High	High	Moderate	Moderate	High
		Wei (2015) ¹⁴	Low	Low	Moderate	Low	Low	Moderate
		Huang (2013) ²⁹	Low	Low	Low	Low	Low	Low
		Ku (2012) ³¹	Low	Low	Moderate	Low	Low	Moderate
		Aspberg (2010) ³⁴	Low	Low	Moderate	Low	Low	Moderate
		Aspberg (2007) ³⁷	Low	Low	Moderate	Low	Low	Moderate
	Atopic dermatitis	Gau (2018) ¹⁵	High	High	High	Moderate	Moderate	High
		Egeberg (2016) ¹³	Low	Low	Moderate	Low	Low	Moderate
		Wei (2015) ¹⁴	Low	Low	Moderate	Low	Low	Moderate
		Apfelbacher (2011) ³³	Moderate	Moderate	Moderate	Low	Low	Moderate
	Allergic rhinitis	Kang (2019) ²⁶	Moderate	Low	Moderate	Low	Moderate	Moderate
		Gau (2018) ¹⁵	High	High	High	Moderate	Moderate	High
		Wei (2015) ¹⁴	Low	Low	Moderate	Low	Low	Moderate
		Sun (2013) ³⁰	Low	Low	Moderate	Low	Low	Moderate
Phototherapy	Asthma	Tham (2019) ¹⁰	Low	Low	Moderate	Low	Low	Moderate
		Kuzniewicz (2018) ¹²	Low	Low	Moderate	Low	Low	Moderate
		Wei (2015) ¹⁴	Low	Low	Moderate	Low	Low	Low

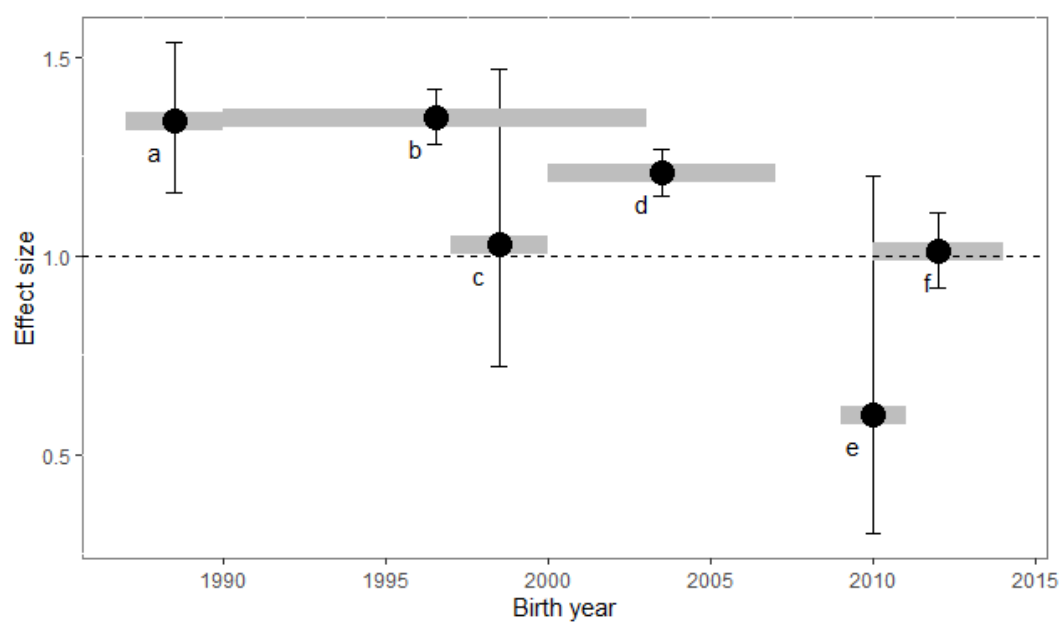
Atopic dermatitis	Ku (2012) ³¹	Low	Low	Moderate	Low	Low	Moderate
	Aspberg (2010) ³⁴	Low	Low	Moderate	Low	Low	Moderate
	Aspberg (2007) ³⁷	Low	Low	Moderate	Low	Low	Moderate
	Tham (2019) ¹⁰	Low	Low	Moderate	Low	Low	Moderate
	Ku (2018) ¹¹	Low	Low	Moderate	Low	Low	Low
	Egeberg (2016) ¹³	Low	Low	Moderate	Low	Low	Moderate
Allergic rhinitis	Wei (2015) ¹⁴	Low	Low	Moderate	Low	Low	Low
	Tham (2019) ¹⁰	Low	Low	Moderate	Low	Low	Moderate
	Wei (2015) ¹⁴	Low	Low	Moderate	Low	Low	Low

Supporting Information–5 Birth year of participants and effect size of the association between neonatal jaundice and childhood-onset asthma



- a: Huang (2013)²⁹, odds ratio
- b: Aspberg (2007)³⁴, odds ratio
- c: Aspberg (2010)³⁷, odds ratio
- d: Ku (2012)³¹, odds ratio
- e: Wei (2015)¹⁴, hazard ratio
- f: Santos (2020)²⁵, odds ratio
- g: Gau (2018)¹⁵, odds ratio
- h: Kuzniewicz (2018)¹², hazard ratio

Supporting Information–6 Birth year of participants and effect size of the association between neonatal phototherapy and childhood-onset asthma



a: Aspberg (2007)³⁷, odds ratio

b: Aspberg (2010)³⁴, odds ratio

c: Ku (2012)³¹, odds ratio

d: Wei (2015)¹⁴, hazard ratio

e: Kuzniewicz (2018)¹², hazard ratio

f: Tham (2019)¹⁰, odds ratio