Pediatr Neonatol. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:
Pediatr Neonatol. 2019 February ; 60(1): 28–34. doi:10.1016/j.pedneo.2018.03.004.

Phototherapy for Neonatal Hyperbilirubinemia and Childhood Eczema, Rhinitis and Wheeze

Elizabeth Huiwen Tham[1,2,*], **Evelyn Xiu Ling Loo**[3,*], **Anne Goh**[4], **Oon Hoe Teoh**[5], **Fabian Yap**[7], **Kok Hian Tan**[8], **Keith M Godfrey**[9,10], **Hugo Van Bever**[1,2], **Bee Wah Lee**[1], **Yap Seng Chong**[2,6], and **Lynette Pei-chi Shek**[1,2,3]

[1]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[2]Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, National University Health System, Singapore

[3]Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR),Singapore

[4]Allergy service, Department of Paediatrics, KK Women's and Children's Hospital, Singapore

[5]Respiratory Service Medicine, Department of Paediatrics, KK Women's and Children's Hospital

[6]Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System

[7]Department of Endocrinology, KK Women's and Children's Hospital, Singapore

[8]Department of Maternal Fetal Medicine, KK Women's and Children's Hospital (KKH), Singapore

[9]NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, SO16 6YD, Southampton, United Kingdom

[10]Medical Research Council Lifecourse Epidemiology Unit, SO16 6YD, Southampton, United Kingdom

Abstract

Background—The pathogenesis of allergic diseases in childhood may be attributed to influences of early environmental stimuli on fetal and neonatal immune regulation. Neonatal hyperbilirubinemia is common in the Asian population and up to 20% of infants require phototherapy.

Aim—We examined the hypothesis that phototherapy for neonatal hyperbilirubinemia modulates the infant's risk of developing eczema, rhinitis and wheeze in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort.

Corresponding author's address: Associate Prof. Lynette Shek, Department of Paediatrics, 1E Kent Ridge Road, Level 12 NUHS Tower Block, Singapore 119228, Telephone: +65 – 67795740, lynette_shek@nuhs.edu.sg.
*co-first authors

Trial registration : NCT01174875 Registered 1 July 2010, retrospectively registered

Europe PMC Funders Author Manuscripts

Methodology—Interviewers collected information on demographics, lifestyle, birth data and allergic outcomes. Atopic sensitization was assessed through skin prick testing (SPT) to aeroallergens and food allergens.

Results—A total of 135 (12.8%) children underwent phototherapy for neonatal hyperbilirubinemia. Infants who underwent phototherapy were of a significantly lower mean (SD) gestational age [37.5 (2.5) weeks] compared to those who did not [38.5 (1.2) weeks p<0.01]. A higher proportion of infants born by Caesarean section underwent phototherapy compared to those who were born vaginally (17.5% vs 10.7%, p < 0.01). There were no differences in prevalence of allergen sensitization, eczema, rhinitis and early onset wheeze with use of nebulizer in the first 5 years of life between subjects that underwent phototherapy and those that did not. There were also no associations between mean bilirubin peak levels within the phototherapy group with development of eczema, rhinitis and early onset wheeze in the first 5 years of life.

Conclusions—We found no evidence for a link between phototherapy for neonatal hyperbilirubinemia and childhood allergic outcomes in this prospective mother-offspring cohort.

Keywords

jaundice; phototherapy; eczema; allergic rhinitis; asthma

Background

The Developmental Origins of Health and Disease (DOHaD) field examines the role of early environmental stimuli on fetal and neonatal immune regulation and the development of diseases in later life.1 One of the earliest environmental influences experienced by many neonates occurs in the setting of phototherapy for neonatal hyperbilirubinemia which involves prolonged exposure of the neonate's entire body surface area to a unique, artificial external environment in the earliest days of life when the effects of developmental influences on immune programming are most significant.

The incidence of neonatal hyperbilirubinemia is significantly higher in Asian infants compared to infants of other ethnicities.2 Up to 80% of Asian newborns are diagnosed with neonatal jaundice, 8–20% of whom require phototherapy.3, 4 Genetic polymorphisms, such as the G71R mutation in the uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) liver enzyme responsible for bilirubin conjugation, are associated with a higher risk of prolonged jaundice and the need for phototherapy.5 These mutations are highly prevalent in the Asian population but have not been reported in Caucasian populations.6

Blue-green phototherapy utilizes monochromatic visible light in the spectrum of 390–470nm to convert unconjugated bilirubin into water soluble, excretable structural photoisomers7 and is the gold standard therapy for significant neonatal hyperbilirubinemia to prevent kernicterus. Known short-term side effects of phototherapy include dehydration through transepidermal water loss,8 thermal dysregulation, electrolyte disturbances and the bronze baby syndrome.9 There are also longer term effects which are less well known – including melanoma, patent ductus arteriosus and retinal damage.9

In a cohort of newborns, phototherapy, but not hyperbilirubinemia itself, was also associated with DNA cell damage and apoptosis of peripheral blood mononuclear cells, which may negatively impact DNA repair ability.10 Two recent retrospective case-control studies by Wickremasinghe et al11 and Newman et al12 indicated that phototherapy could slightly increase the risk of cancer in infancy.

Ultraviolet (UV) light makes up a small component, around 0.3%, of traditional blue-green phototherapy. In vitro studies propose that UV light acutely activates pro-inflammatory pathways in the cutaneous immune system resulting in increased production of inflammatory cytokines, release of sequestered autoantigens and enhancement of immunogenic properties of skin proteins.13

Phototherapy has also recently been linked to alterations of immune pathways, which may predispose towards the development of allergic diseases. Bilirubin is a natural anti-oxidant which, in its physiological state, protects infants against oxidative stress and promotes the natural Th2/Th1 switch.14 Phototherapy interferes with this protective mechanism and in itself causes disruptions in the skin cytokine milieu. Phototherapy increases the production of Th2 pro-inflammatory cytokines such as TNF-alpha, IL-1 beta and IL-8, and also decreases IL-6 levels,15 promoting a Th2 shift towards pro-allergic tendencies.

In this prospective mother-infant birth cohort study, we examined whether the artificial environmental exposure of blue-green phototherapy for neonatal hyperbilirubinemia in early life might modulate the infant's risk of developing eczema, rhinitis and wheeze in early childhood.

Methods

The Growing Up in Singapore Towards healthy Outcomes (GUSTO) study is a large, ongoing mother-infant cohort study in Singapore which recruited pregnant women from the general population and followed their offspring up prospectively, and the methodology has been described in detail previously.16 Information on demographics, family history of allergy, social and lifestyle factors and birth data was collected. Data on neonates who underwent phototherapy for neonatal hyperbilirubinemia were also collected during the hospital stay after birth. Ascertainment of later allergic outcomes was undertaken through standardized questionnaires administered at 3, 6, 9, 12, 15 18, 24, 36, 48 and 60 months of age to ensure consistency during interviews and home visits. We used the modified ISAAC questionnaire, which was also used in many other studies.17–19

A physician's diagnosis of eczema was determined by a positive answer to the written question: "Has your child ever been diagnosed with eczema?" Skin examination and SCORAD assessments were performed by trained physicians at the month 18 and month 36 time-points for eczema diagnosis and its severity. Wheezing was defined as a positive answer to the written questions "Has your child ever wheezed?" and ""Has your child ever been prescribed with nebulizer/inhaler?" Rhinitis was defined as a positive response to the question "Has your child ever had sneezing, running nose, blocked or congested nose, snoring or noisy breathing during sleep or when awake that has lasted for 2 or more weeks

duration?" The diagnosis of rhinitis before 18 months of age required a single episode that lasted for at least 4 weeks or two or more episodes lasting at least 2 weeks each. New cases of rhinitis after 18 months of age were defined by one or more episodes lasting at least 2 weeks.

Atopic sensitization was assessed through skin prick testing (SPT) to aeroallergens (house dust mites *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae,* and *Blomia tropicalis*) and to food allergens (egg, peanut and cow's milk) which were performed at the 18, 36 and 60-month visits. At 60 months, skin prick testing was also carried out to shrimp and crab allergens. All skin prick extracts were obtained from Greer Laboratories (Lenoir, NC, USA), except for *B. tropicalis*, which was obtained from our in-house laboratory. *B. tropicalis* extract was prepared as previously described.20

A wheal of at least 3 mm was defined as a positive SPT and a child was considered as SPT-positive (sensitized) if any one or more of the individual tests was positive with a positive reaction to histamine (positive control) and negative reaction to saline (negative control). We used the ISAAC modified questionnaire as used in other studies.17 At 18 months, outcomes were classified as absent when the answers for all visits were "no." Outcomes at 36 and 60 months were classified as absent when the answers for the visits were "no" for at least 70% of the visits. Family history of allergy was defined as positive if the mother, father or an older sibling had ever had atopic eczema, asthma or allergic rhinitis. "High breastfeeding" was defined by exclusive or predominant breastfeeding for at least 4 months, with subsequent partial breastfeeding to at least 6 months of age, while "low breastfeeding" was defined as exclusive formula feeding or weaning before 3 months. "Intermediate breastfeeding" was defined as breastfeeding to at least 3 months but without meeting the criteria for high breastfeeding.

Ethics approval was obtained from the Domain Specific Review Board of Singapore, National Healthcare Group and the Centralised Institutional Review Board of SingHealth. Informed written consent was obtained from all subjects. Statistical analysis was carried out using IBM SPSS version 20.0 (IBM SPSS Statistics, Armonk, NY). Demographic characteristics between the groups were compared using the chi-square test. The strength of associations between phototherapy and eczema, rhinitis and early-onset wheeze were assessed using univariable and multivariable logistic regression (adjusting for gender, ethnicity, family history of allergy, breastfeeding, gestational age, maternal education levels and mode of delivery), using a p value of 0.05 as significant and reported adjusted odds ratios with exact 95% confidence intervals.

Results

After removal of early dropouts, 1058 (85.5%) subjects had responses to questions on jaundice and formed the study population. There were 135 (12.8%) children who underwent phototherapy for neonatal hyperbilirubinemia, of whom 63 (46.7%) were male and 82 (60.7%) were of Chinese ethnicity. The demographic characteristics of the cohort are shown in Table 1. Infants who underwent phototherapy were of a lower mean (SD) gestational age (37.5 (2.5) weeks) compared to those who did not (38.5 (1.2) weeks, $p < 0.01$, Table 1). A

higher proportion of infants born by Caesarean section (17.5%) underwent phototherapy compared to those who were born vaginally (10.7%, $p < 0.01$, Table 1)

There were generally few differences in demographic variables between subjects included and excluded from the study with the exception of mode of delivery and maternal education levels. A higher proportion of subjects included in this study were delivered by Caesarean delivery compared to those excluded (30.8% vs 20.2%, p=0.04). Subjects included in this study also had mothers of higher education levels compared to those excluded (59.9% vs. 50.9%, p = 0.03).

There were no differences in prevalence of allergen sensitization, eczema, rhinitis and early onset wheeze with use of nebulizer/inhaler in the first 5 years of life between subjects that underwent phototherapy and those that did not (Table 2). Only 31 subjects had complete SCORAD data for eczema severity at month 18 and 43 subjects at month 36. Multivariable analysis showed no association between phototherapy and SCORAD at month 18 [Adj OR 21.7, 95% CI (2.3—45.7), p = 0.1] or month 36 [Adj OR 7.4, 95% CI (30.2 —15.4), p = 0.5]. Findings were similar after adjusting for potential confounding variables, including sex, ethnicity, family history of allergy, maternal education levels, breastfeeding, mode of delivery and gestational age (Table 3). Mean bilirubin peak levels were recorded only in subjects who underwent phototherapy. There were no statistically significant differences in mean bilirubin peak levels between subjects who subsequently developed eczema, rhinitis or wheeze and those who did not (Table 4). Mean bilirubin peak levels in subjects who developed allergen sensitization at months 18 and 36 were lower than in those who did not become sensitized - 18 months [Adj OR 0.97, 95% CI (0.95—0.99), p = 0.02] and at 36 months [Adj OR 0.98, 95% CI (0.96—0.99), p = 0.02]. However, the adjusted odds ratios were very close to 1.0; thus the clinical significance of this very small difference is doubtful. No significant associations were seen at 60 months.

Discussion

This is the first large prospective cohort study to examine for an association between phototherapy for neonatal hyperbilirubinemia and subsequent allergic sensitization or the development of eczema, rhinitis or early onset wheeze; we found no evidence to support such an association. This finding provides an important counterpoint to the current view that neonatal hyperbilirubinemia and phototherapy may increase the risk of development of allergic diseases in later childhood21 and will reassure neonatologists and parents of jaundiced infants who require phototherapy, an essential intervention for the prevention of kernicterus especially in the Asian population where rates of hyperbilirubinemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency are high.22

Existing literature in the field has hitherto suggested a direct association between neonatal hyperbilirubinemia and/or phototherapy and the development of atopic diseases.23–26 Huang et al27 found that the risk of asthma increased with bilirubin levels in a cohort of babies born in the United States before the introduction of phototherapy (OR 1.61, 95% CI 1.04 – 2.08). A retrospective Swedish cohort study23 identified neonatal icterus and/or phototherapy as risk determinants for children who were prescribed anti-asthmatic

medications (OR 1.30, 95% CI 1.16—1.47). In the Asia-Pacific region, retrospective cohort studies in Taiwan described associations between neonatal jaundice and an increased rate and severity of childhood asthma24 as well as allergic rhinitis25, atopic dermatitis and urticarial.26 A recent systematic review including these studies also found a significant increase in the rate of childhood allergic diseases after neonatal hyperbilirubinemia and/or phototherapy, though the evidence base was deemed to be of 'very low/low quality.21

It is possible that that the observed association between bilirubin, phototherapy and atopic outcomes in other studies might have been confounded by other factors such as breastfeeding, as these data were mostly retrospectively obtained from existing databases collated for other purposes such as insurance claims or indirectly assessed through ICD (International Classification of Diseases) codes and surrogate indicators of disease such as the use of asthma medications. These methodological limitations do not allow adjustment for potential confounding influences for which source data were not available and potential sources of bias are inherent in such retrospective studies.

The strengths of GUSTO lie in our extensively well-phenotyped cohort derived from Singapore's general population; prospective capture of all child health information and allergen sensitization data through skin prick testing at multiple time-points and the ability to adjust for multiple potential socio-demographic confounders. Reliance on parental-reported outcomes of rhinitis and early-onset wheezing were limitations of this study, but questionnaires were adapted from the ISAAC questionnaires which have been validated extensively in large epidemiologic studies worldwide for the ascertainment of allergic outcomes.28 Another limitation is the smaller sample size of GUSTO as compared to other studies which results in loss of statistical power. The rates of rhinitis, wheeze and atopic dermatitis in this cohort were nonetheless consistent with the previous ISAAC surveys29. We did not obtain data on mean bilirubin peak levels in neonates who did not undergo phototherapy as this was not routinely performed in non-jaundiced infants. Data on phototherapy intensity and duration were also not collected in this study, which limited our ability to stratify for these effects. None of the above-mentioned, more recent, cross-sectional studies with positive associations had measured bilirubin levels, phototherapy intensity or duration. These factors could have been potential confounders but their contribution to the differences in study findings between ours and theirs is unknown.

Genetic polymorphisms in the Glutathione S-transferase (GST) gene such as GSTM1 and GSTT1 null genotypes may explain the differences observed between populations. The Glutathione S-Transferases (GSTs) are a group of enzymes comprising of five gene classes, alpha (A), mu (M), pi (P), theta (T) and zeta (Z) according to their biochemical properties such as substrate specificity, chemical affinity, structure and amino acid sequences.30, 31 These enzymes are phase II detoxification enzymes involved in detoxification of exogenous or environmental toxins through conjugation with glutathione (GSH), facilitating their removal from cells for excretion. In hepatocytes, they also decrease efflux of bilirubin and bilirubin conjugates back into plasma.32

Polymorphisms in the GST gene have been linked to significant neonatal hyperbilirubinemia33–35 and separately also with allergic diseases such as atopic

Europe PMC Funders Author Manuscripts

dermatitis36–38 and asthma39–43 across several ethnic groups worldwide. The significance of such associations has been analyzed in several meta-analyses,44–46 with conflicting conclusions. Such polymorphisms are involved in immuno-modulation and likely also modify the risk of developing hyperbilirubinemia. Frequency of gene carriage varies between populations, the GSTM1-null genotype is present in around 50% of Caucasians and in only approximately 20% of African Americans.47 Apart from Korea, genetic studies involving this polymorphism and its relationship with allergic diseases are currently lacking in Asia.36, 37 The existence of such genotypes in the Singaporean population and their association with disease is currently unknown.

Another limitation of this study was the lack of data on maternal viral infections during the antenatal period, which may be associated with an increased risk of infantile wheezing in their offspring,48, 49 which precluded our ability to adjust for it as a potential confounder.

In conclusion, we found no evidence in this large prospective birth cohort that phototherapy for neonatal hyperbilirubinemia was associated with childhood eczema, rhinitis, and early-onset wheezing or allergic sensitization. Isolating the differential effects of hyperbilirubinemia and phototherapy on allergic outcomes is challenging, as the current standard of care advocates phototherapy for all neonates with significant hyperbilirubinemia. Randomized controlled trials for this purpose would also likely be ethically implausible. Thus, corroborative data from other large prospective birth cohorts in other parts of the world are preferable and should ideally adjust for confounders such as bilirubin levels, phototherapy intensity and duration, as well as genetic polymorphisms such as the GST gene which may modulate an individual’s risk of both hyperbilirubinemia and atopic outcomes. Nonetheless, in view of the known side effects and reported associations with other non-allergic disease outcomes such as cancer, judicious consideration of the necessity and duration of phototherapy in accordance with established guidelines and risk stratification is essential and unwarranted phototherapy in neonates with no significant hyperbilirubinemia is best avoided.

References

1. Waterland RA, Michels KB. Epigenetic Epidemiology of the Developmental Origins Hypothesis. Annu Rev Nutr. 2007; 27:363–88. [PubMed: 17465856]
2. Newman TB, Easterling MJ, Goldman ES, Stevenson DK. Laboratory Evaluation of Jaundice in Newborns. Frequency, Cost, and Yield. Am J Dis Child. 1990; 144:364–8. [PubMed: 2106258]
3. Fok TF, Lau SP, Hui CW. Neonatal Jaundice: Its Prevalence in Chinese Babies and Associating Factors. Aust Paediatr J. 1986; 22:215–9. [PubMed: 3767789]
4. Huang A, Tai BC, Wong LY, Lee J, Yong EL. Differential Risk for Early Breastfeeding Jaundice in a Multi-Ethnic Asian Cohort. Ann Acad Med Singapore. 2009; 38(3):217–24. [PubMed: 19347075]
5. Zhou YY, Lee LY, Ng SY, Hia CP, Low KT, Chong YS, et al. Ugt1a1 Haplotype Mutation among Asians in Singapore. Neonatology. 2009; 96:150–5. [PubMed: 19325249]
6. Akaba K, Kimura T, Sasaki A, Tanabe S, Ikegami T, Hashimoto M, et al. Neonatal Hyperbilirubinemia and Mutation of the Bilirubin Uridine Diphosphate-Glucuronosyltransferase Gene: A Common Missense Mutation among Japanese, Koreans and Chinese. Biochem Mol Biol Int. 1998; 46:21–6. [PubMed: 9784835]
7. Ennever JF, McDonagh AF, Speck WT. Phototherapy for Neonatal Jaundice: Optimal Wavelengths of Light. J Pediatr. 1983; 103:295–9. [PubMed: 6875728]

8. Raboni R, Patrizi A, Cocchi G, Faldella G, Raone B. Comparison of Two Different Neonatal Skin Care Practices and Their Influence on Transepidermal Water Loss in Healthy Newborns within First 10 Days of Life. Minerva Pediatr. 2014; 66:369–74. [PubMed: 25253185]
9. Xiong T, Qu Y, Cambier S, Mu D. The Side Effects of Phototherapy for Neonatal Jaundice: What Do We Know? What Should We Do? Eur J Pediatr. 2011; 170(10):1247–55. [PubMed: 21455834]
10. Yahia S, Shabaan AE, Gouida M, El-Ghanam D, Eldegla H, El-Bakary A, et al. Influence of Hyperbilirubinemia and Phototherapy on Markers of Genotoxicity and Apoptosis in Full-Term Infants. Eur J Pediatr. 2015; 174:459–64. [PubMed: 25209224]
11. Wickremasinghe AC, Kuzniewicz MW, Grimes BA, McCulloch CE, Newman TB. Neonatal Phototherapy and Infantile Cancer. Pediatrics. 2016; 137(6):e20151353. [PubMed: 27217478]
12. Newman TB, Wickremasinghe AC, Walsh EM, Grimes BA, McCulloch CE, Kuzniewicz MW. Retrospective Cohort Study of Phototherapy and Childhood Cancer in Northern California. Pediatrics. 2016; 137(6):e20151354. [PubMed: 27217477]
13. Maverakis E, Miyamura Y, Bowen MP, Correa G, Ono Y, Goodarzi H. Light, Including Ultraviolet. J Autoimmun. 2010; 34:J247–57. [PubMed: 20018479]
14. Gloria-Bottini F, Bottini E. Is There a Role of Early Neonatal Events in Susceptibility to Allergy? Int J Biomed Sci. 2010; 6:5.
15. Kurt A, Aygun AD, Kurt AN, Godekmerdan A, Akarsu S, Yilmaz E. Use of Phototherapy for Neonatal Hyperbilirubinemia Affects Cytokine Production and Lymphocyte Subsets. Neonatology. 2009; 95(3):262–6. [PubMed: 19005263]
16. Soh SE, Lee SS, Hoon SW, Tan MY, Goh A, Lee BW, et al. The Methodology of the Gusto Cohort Study: A Novel Approach in Studying Pediatric Allergy. Asia Pac Allergy. 2012; 2(2):144–8. [PubMed: 22701865]
17. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Camargo CA Jr, et al. Peanut, Milk, and Wheat Intake During Pregnancy Is Associated with Reduced Allergy and Asthma in Children. J Allergy Clin Immunol. 2014; 133:1373–82. [PubMed: 24522094]
18. Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippila C, Ahonen S, Nevalainen J, et al. Maternal Vitamin D Intake During Pregnancy Is Inversely Associated with Asthma and Allergic Rhinitis in 5-Year-Old Children. Clin Exp Allergy. 2009; 39:875–82. [PubMed: 19522996]
19. Floistrup H, Swartz J, Bergstrom A, Alm JS, Scheynius A, van Hage M, et al. Allergic Disease and Sensitization in Steiner School Children. J Allergy Clin Immunol. 2006; 117:59–66. [PubMed: 16387585]
20. Yi FC, Chew FT, Jimenez S, Chua KY, Lee BW. Culture of Blomia Tropicalis and Ige Immunoblot Characterization of Its Allergenicity. Asian Pac J Allergy Immunol. 1999; 17:189–94. [PubMed: 10697258]
21. Das RR, Naik SS. Neonatal Hyperbilirubinemia and Childhood Allergic Diseases: A Systematic Review. Pediatr Allergy Immunol. 2015; 26(1):2–11. [PubMed: 25229699]
22. Ho NK. Neonatal Jaundice in Asia. Baillieres Clin Haematol. 1992; 5:131–42. [PubMed: 1596589]
23. Aspberg S, Dahlquist G, Kahan T, Kallen B. Confirmed Association between Neonatal Phototherapy or Neonatal Icterus and Risk of Childhood Asthma. Pediatr Allergy Immunol. 2010; 21:e733–9. [PubMed: 20444150]
24. Ku MS, Sun HL, Sheu JN, Lee HS, Yang SF, Lue KH. Neonatal Jaundice Is a Risk Factor for Childhood Asthma: A Retrospective Cohort Study. Pediatr Allergy Immunol. 2012; 23:623–8. [PubMed: 22957782]
25. Sun HL, Lue KH, Ku MS. Neonatal Jaundice Is a Risk Factor for Childhood Allergic Rhinitis: A Retrospective Cohort Study. Am J Rhinol Allergy. 2013; 27:192–6. [PubMed: 23710954]
26. Wei CC, Lin CL, Shen TC, Kao CH. Neonatal Jaundice and Risks of Childhood Allergic Diseases: A Population-Based Cohort Study. Pediatr Res. 2015; 78:223–30. [PubMed: 25950455]
27. Huang L, Bao Y, Xu Z, Lei X, Chen Y, Zhang Y, et al. Neonatal Bilirubin Levels and Childhood Asthma in the Us Collaborative Perinatal Project, 1959–1965. Am J Epidemiol. 2013; 178:1691–7. [PubMed: 24186969]
28. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (Isaac): Rationale and Methods. Eur Respir J. 1995; 8:483–91. [PubMed: 7789502]

29. Wang XS, Tan TN, Shek LP, Chng SY, Hia CP, Ong NB, et al. The Prevalence of Asthma and Allergies in Singapore; Data from Two Isaac Surveys Seven Years Apart. Arch Dis Child. 2004; 89:423–6. [PubMed: 15102631]
30. Listowsky I, Abramovitz M, Homma H, Niitsu Y. Intracellular Binding and Transport of Hormones and Xenobiotics by Glutathione-S-Transferases. Drug Metab Rev. 1988; 19:305–18. [PubMed: 3068032]
31. Hayes JD, Pulford DJ. The Glutathione S-Transferase Supergene Family: Regulation of Gst and the Contribution of the Isoenzymes to Cancer Chemoprotection and Drug Resistance. Crit Rev Biochem Mol Biol. 1995; 30:445–600. [PubMed: 8770536]
32. Wolkoff AW, Goresky CA, Sellin J, Gatmaitan Z, Arias IM. Role of Ligandin in Transfer of Bilirubin from Plasma into Liver. Am J Physiol. 1979; 236:E638–48. [PubMed: 375751]
33. Abdel Ghany EA, Hussain NF, Botros SK. Glutathione S-Transferase Gene Polymorphisms in Neonatal Hyperbilirubinemia. J Investig Med. 2012; 60:18–22.
34. Muslu N, Dogruer ZN, Eskandari G, Atici A, Kul S, Atik U. Are Glutathione S-Transferase Gene Polymorphisms Linked to Neonatal Jaundice? Eur J Pediatr. 2008; 167:57–61. [PubMed: 17318621]
35. Prachukthum S, Nunnarumit P, Pienvichit P, Chuansumrit A, Songdej D, Kajanachumpol S, et al. Genetic Polymorphisms in Thai Neonates with Hyperbilirubinemia. Acta Paediatr. 2009; 98:1106–10. [PubMed: 19397531]
36. Cho HR, Uhm YK, Kim HJ, Ban JY, Chung JH, Yim SV, et al. Glutathione S-Transferase M1 (Gstm1) Polymorphism Is Associated with Atopic Dermatitis Susceptibility in a Korean Population. Int J Immunogenet. 2011; 38:145–50. [PubMed: 21176116]
37. Chung J, Oh SY, Shin YK. Association of Glutathione-S-Transferase Polymorphisms with Atopic Dermatitis Risk in Preschool Age Children. Clin Chem Lab Med. 2009; 47:1475–81. [PubMed: 19842992]
38. Vavilin VA, Safronova OG, Lyapunova AA, Lyakhovich VV, Kaznacheeva LF, Manankin NA, et al. Interaction of Gstm1, Gstt1, and Gstp1 Genotypes in Determination of Predisposition to Atopic Dermatitis. Bull Exp Biol Med. 2003; 136:388–91. [PubMed: 14714091]
39. El Rifai N, Moustafa N, Degheidy N, Wilson M. Glutathione S Transferase Theta1 and Mu1 Gene Polymorphisms and Phenotypic Expression of Asthma in Egyptian Children: A Case-Control Study. Ital J Pediatr. 2014; 40:22. [PubMed: 24559168]
40. Ivaschenko TE, Sideleva OG, Baranov VS. Glutathione- S-Transferase Micro and Theta Gene Polymorphisms as New Risk Factors of Atopic Bronchial Asthma. J Mol Med (Berl). 2002; 80(1): 39–43. [PubMed: 11862323]
41. Karam RA, Pasha HF, El-Shal AS, Rahman HM, Gad DM. Impact of Glutathione-S-Transferase Gene Polymorphisms on Enzyme Activity, Lung Function and Bronchial Asthma Susceptibility in Egyptian Children. Gene. 2012; 497:314–9. [PubMed: 22326267]
42. Piacentini S, Polimanti R, Moscatelli B, Re MA, Fuciarelli R, Manfellotto D, et al. Glutathione S-Transferase Gene Polymorphisms and Air Pollution as Interactive Risk Factors for Asthma in a Multicentre Italian Field Study: A Preliminary Study. Ann Hum Biol. 2010; 37:427–39. [PubMed: 20367187]
43. Tamer L, Calikoglu M, Ates NA, Yildirim H, Ercan B, Saritas E, et al. Glutathione-S-Transferase Gene Polymorphisms (Gstt1, Gstm1, Gstp1) as Increased Risk Factors for Asthma. Respirology. 2004; 9:493–8. [PubMed: 15612961]
44. Liang S, Wei X, Gong C, Wei J, Chen Z, Chen X, et al. Significant Association between Asthma Risk and the GSTM1 and GSTT1 Deletion Polymorphisms: An Updated Meta-Analysis of Case-Control Studies. Respirology. 2013; 18:774–83. [PubMed: 23600494]
45. Minelli C, Granell R, Newson R, Rose-Zerilli MJ, Torrent M, Ring SM, et al. Glutathione-S-Transferase Genes and Asthma Phenotypes: A Human Genome Epidemiology (Huge) Systematic Review and Meta-Analysis Including Unpublished Data. Int J Epidemiol. 2010; 39(2):539–62. [PubMed: 20032267]
46. Saadat M, Ansari-Lari M. Genetic Polymorphism of Glutathione S-Transferase T1, M1 and Asthma, a Meta-Analysis of the Literature. Pak J Biol Sci. 2007; 10:4183–9. [PubMed: 19086569]

47. Ginsberg G, Smolenski S, Hattis D, Guyton KZ, Johns DO, Sonawane B. Genetic Polymorphism in Glutathione Transferases (Gst): Population Distribution of GSTM1, T1, and P1 Conjugating Activity. J Toxicol Environ Health B Crit Rev. 2009; 12:389–439. [PubMed: 20183528]

48. Murphy VE, Mattes J, Powell H, Baines KJ, Gibson PG. Respiratory Viral Infections in Pregnant Women with Asthma Are Associated with Wheezing in the First 12 Months of Life. Pediatr Allergy Immunol. 2014; 25:151–8. [PubMed: 24329935]

49. Stensballe LG, Ravn H, Kristensen K, Agerskov K, Meakins T, Aaby P, et al. Respiratory Syncytial Virus Neutralizing Antibodies in Cord Blood, Respiratory Syncytial Virus Hospitalization, and Recurrent Wheeze. J Allergy Clin Immunol. 2009; 123:398–403. [PubMed: 19101023]

Europe PMC Funders Author Manuscripts

Table 1

Comparison of demographics in children with phototherapy and those without.

	Phototherapy group (N = 135)	No Phototherapy group (N = 923)	p-value
Sex	**N(%)**	**N(%)**	
Male	63 (46.7)	493 (53.5)	0.2
Female	72 (53.3)	430 (46.6)	
Mode of delivery			
Caesarean section	57 (42.2)	269 (29.1)	<0.01
Vaginal Delivery	78 (57.8)	654 (70.9)	
Breastfeeding levels [1]			
Low	50 (39.4)	393 (45.3)	0.4
Mid	62 (48.8)	369 (42.5)	
High	15 (11.8)	106 (12.2)	
Ethnicity			
Chinese	82 (60.7)	518 (56.1)	0.6
Malay	32 (23.7)	237 (25.7)	
Indians	21 (15.6)	168 (18.2)	
Family history of allergy [1]	39 (44.3)	329 (50.8)	0.3
No family history of allergy	49 (55.3)	319 (49.2)	
Gestational weeks [2]	37.5 ± 2.5	38.5 ± 1.2	<0.01
Maternal education levels [1]			
At least 12 years	91 (68.4)	534 (58.6)	0.04
Less than 12 years	42 (31.6)	377 (41.4)	

[1] Sample size ranged from 736 to 1044 due to missing values

[2] Values are mean ± SD

Europe PMC Funders Author Manuscripts

Table 2

Comparison of prevalence of allergic outcomes in children with phototherapy and those without.

	Phototherapy	No Phototherapy	p-value
	N(%)	N(%)	
Outcomes by 18 months			
Allergen sensitization	14 (13.5)	98 (13.6)	0.9
Eczema	27 (25.7)	152 (20.3)	0.2
Rhinitis	13 (14.6)	119 (19.0)	0.4
Early onset of wheeze and use of nebulizer/inhaler	7 (7.8)	60 (10.0)	0.7
Outcomes by 36 months			
Allergen sensitization	22 (21.2)	172 (23.8)	0.6
Eczema	29 (27.6)	180 (24.0)	0.5
Rhinitis	31 (34.8)	221 (35.2)	0.9
Early onset of wheeze and use of nebulizer/inhaler	17 (14.9)	158 (19.5)	0.3
Outcomes by 60 months			
Allergen sensitization	33 (35.5)	232 (34.8)	0.9
Eczema	31 (29.8)	192 (26.0)	0.4
Rhinitis	35 (39.8)	245 (39.9)	0.9
Early onset of wheeze and use of nebulizer/inhaler	16 (17.0)	150 (22.8)	0.2

Europe PMC Funders Author Manuscripts

Table 3

Univariable and multivariable analysis for associations between phototherapy and sensitization, eczema, rhinitis and wheeze.

	Univariable analysis	Multivariable analysis
	OR (95% CI)	**Adjusted OR (95% CI)**
Outcomes by Month 18		
Allergen sensitization	1.0 (0.5-1.8)	1.1 (0.6-2.3)
Eczema	1.4 (0.8-2.2)	1.4 (0.8-2.6)
Rhinitis	0.7 (0.4-1.4)	0.7 (0.3-1.6)
Early onset of wheeze and use of nebuliser/inhaler	0.8 (0.3-1.7)	0.6 (0.2-1.7)
Outcomes by Month 36		
Allergen sensitization	0.9 (0.5-1.4)	1.0 (0.5-1.9)
Eczema	1.2 (0.8-1.9)	1.3 (0.7-2.4)
Rhinitis	1.0 (0.6-1.6)	1.0 (0.6-1.8)
Early onset of wheeze and use of nebuliser/inhaler	0.7 (0.4-1.2)	0.7 (0.3-1.4)
Outcomes by Month 60		
Allergen sensitization	1.0 (0.7-1.6)	1.1 (0.6-2.0)
Eczema	1.2 (0.8-1.9)	1.3 (0.7-2.3)
Rhinitis	1.0 (0.6-1.6)	1.0 (0.6-1.9)
Early onset of wheeze and use of nebuliser/inhaler	0.7 (0.4-1.2)	0.6 (0.3-1.2)

*Adjusted for sex, ethnicity, breastfeeding levels, family history of allergy, gestational age, maternal education levels and mode of delivery

Table 4

Mean Bilirubin peak levels and allergic outcomes.

Allergic outcome by month 18	**Mean Bilirubin Peak ± SD (Outcome = yes)**	**Mean Bilirubin Peak ± SD (Outcome = No)**	**Adjusted OR**	**P value**
Allergen sensitization	206.4 ± 54.2	228.6 ± 39.7	0.97 (0.95–0.99)	0.02
Eczema	234.4± 36.5	226.7± 41.7	1.00 (0.99–1.02)	0.7
Rhinitis	239.8 ± 43.2	226.0 ± 42.8	1.04 (0.99–1.1)	0.1
Wheeze and use of nebulizer	238.3± 48.4	227.5 ± 40.6	1.02 (0.99–1.1)	0.2
Allergic outcome by month 36	**Mean Bilirubin Peak ± SD (Outcome = yes)**	**Mean Bilirubin Peak ± SD (Outcome = No)**	**Adjusted OR**	**P value**
Allergen sensitization	217.8± 48.3	227.5± 43.0	0.98 (0.96–0.99)	0.02
Eczema	235.5 ± 35.5	226.1 ± 42.0	1.0 (0.99–1.03)	0.3
Rhinitis	234.8 ± 45.0	224.4 ± 41.7	1.0 (0.99–1.03)	0.1
Wheeze and use of nebulizer	226.8 ± 46.3	227.1 ± 41.6	1.0 (0.98–1.02)	0.8
Allergic outcome by month 60	**Mean Bilirubin Peak ± SD (Outcome = yes)**	**Mean Bilirubin Peak ± SD (Outcome = No)**	**Adjusted OR**	**P value**
Allergen sensitization	228.1 ± 45.4	228.6 ± 43.2	0.99 (0.98–1.02)	0.7
Eczema	236.8 ± 34.9	225.1 ± 42.5	1.01 (0.99–1.03)	0.3
Rhinitis	235.7 ± 44.0	222.8 ± 42.2	1.02 (0.99–1.04)	0.1
Wheeze and use of nebulizer	224.9 ± 51.4	226.2 ± 41.0	0.99 (0.98–1.02)	0.9

*Adjusted for sex, ethnicity, breastfeeding levels, family history of allergy, gestational age, maternal education levels and mode of delivery