**Distinct risk factors contribute to variations in early life eczema prevalence in ethnically Chinese children from Shanghai and Singapore**

**Summary Box**

* We compared the epidemiology of eczema in ethnically Chinese children from China and Singapore.
* Maternal history of allergy in children born vaginally was a unique risk factor in Singapore.

**To the Editor**

In recent decades, there has been a sharp rise in childhood eczema, especially in the first year of life. Genetic factors alone are insufficient to explain the rapid and non-uniform changes in prevalence across regions. This points towards the involvement of environmental exposures and gene-environment interactions in eczema development. The early life environment is significant in shaping eczema development as genetically comparable populations exhibit variations in disease patterns 1.

There are emerging recommendations to improve the present generic approach to eczema management by taking into account ethnic differences in eczema etiology 2. We propose further enhancement to personalize eczema management and enhance efficacy by considering the local early life risk factors, even within ethnically similar populations. By targeting the earliest precursors of eczema, the aim is to halt the atopic march and reduce the burden of eczema and associated allergic comorbidities in children.

In this study, we compared the epidemiology of eczema in the first year of life in ethnically Chinese children from the Shanghai Birth Cohort (SBC) from China and the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort from Singapore. Demographic and lifestyle information beginning from pregnancy was collected using interviewer-administered questionnaires in SBC and GUSTO, from which we identified 13 predictors with aligned definitions in both cohorts.

At 12 months, SBC parents were asked “Did your child ever had rashes since birth (including eczema and milk allergy)?” and “What is the doctor’s diagnosis of the rash (eczema/milk allergy/atopic dermatitis/others/not diagnosed)?”. Eczema was defined by positive responses to both rash occurrence and doctor’s diagnosis of eczema or atopic dermatitis. The modified International Study of Asthma and Allergies in Childhood questionnaire was administered at 3, 6 and 12 months for GUSTO participants. Eczema was defined by a positive response to “Has your child ever been diagnosed with eczema?”. Ethics approval was obtained from the ethics committee of Shanghai Xinhua Hospital (XHEC-C-2013-001, approved on 7 January 2013) for SBC and SingHealth Centralized Institutional Review Board (2009/280/D, approved on 2 March 2009) and the National Healthcare Group Domain Specific Review Board (D/2009/021, approved on 26 February 2009) for GUSTO. Written informed consent was obtained from all participants/the parents. All analyses were performed using SPSS 26.0 and STATA BE 17.

Of 3720 mother-child pairs from SBC and 691 ethnically Chinese mother-child pairs from GUSTO, 2341 (62.9%) and 520 (75.3%) from SBC and GUSTO, respectively, were included in this study after excluding participants without data on eczema outcomes by 12 months or non-singleton pregnancies. The weighted prevalences of eczema by 12 months were 31.3% (95% CI 29.4-33.3) in SBC and 16.1% (95% CI 11.6-21.8) in GUSTO 3.

No significant associations were observed between all risk factors studied and eczema development in adjusted multivariate Poisson regression analysis in SBC (Table 1). In the GUSTO cohort, longer duration of gestation (ARR 0.75 [0.59-0.93]) was associated with a lower risk of eczema development, while a maternal history of allergy (ARR 3.4 [1.5-8.0]) was associated with higher risk of eczema development. Moreover, in GUSTO, a maternal history of allergy was associated with a higher risk of eczema in children born vaginally (ARR 3.2 [1.6-6.4]) while no association was observed for children born by caesarean section (ARR 0.83 [0.30-2.32]) in the GUSTO cohort. This finding was not observed in SBC.

To our knowledge, this is the first study to examine eczema prevalence and common risk factors among genetically comparable ethnic Chinese children residing in distinct geographical locations. Our findings highlight a potential unique risk factor in Singapore, namely maternal history of allergy in children born vaginally. While the role of maternal history of allergy is strongly recognized, current research has mostly established it as a non-modifiable risk factor linked to the inheritance of high-risk gene variants. There is no consensus on the involvement of other mechanisms, including cellular immunity, immunoglobulin E, inflammatory cytokines and microbiome 4,5. In support of our findings, a study in Jiangsu, China reported stronger association between maternal history of allergy and eczema in children born via vaginal birth as compared to caesarean section 6. We hypothesize that this mechanistic pathway was more prominent in GUSTO as substantially higher proportions of mothers delivered vaginally than in SBC.

In addition, a longer gestational age may also exert stronger protection against childhood eczema in Singapore versus Shanghai, perhaps due to climatic differences, with a more robust skin epithelium at birth protecting against environmental insults in heat-stressed Singapore. A higher gestational age may promote infant skin maturation and induce differential expression of skin protein biomarkers in infants. Notably, filaggrin-processing proteins were found to be downregulated in preterm as compared to full term neonates 7.

This is a unique study featuring comprehensive profiling of participants from two mother-offspring cohorts, allowing a range of demographic and risk factors to be aligned and compared. However, the definition of eczema was not identical. Another limitation is the use of parental reports of symptoms to assess eczema in children. However, we minimized recall bias and subjectivity through interviewer-administered structured questionnaires. In addition, we were unable to identify risk factors in SBC despite the higher prevalence of eczema. This may be explained by the limited panel of common study variables from SBC and GUSTO studied, as well as the different initiation years of the cohorts. Our findings support more in-depth investigations of the possible imprinting of allergic inflammation during vaginal birth in high-risk children.

**Word count:** 895

**Keywords:** allergy, eczema, pediatric study, Shanghai, Singapore

**Funding:** This work was supported in part by the Singapore National Research Foundation under its Translational and Clinical Research (TCR) Flagship Programme and administered by the Singapore Ministry of Health’s National Medical Research Council (NMRC), Singapore (NMRC/TCR/004-NUS/2008, NMRC/TCR/012-NUHS/2014), the Science and Technology Commission of Shanghai Municipal (21410713500), the National Medical Research Council (NMRC) Transition Award grant [MOH-TA18nov-003] from NMRC, Singapore, to EH Tham, the UK Medical Research Council (MC\_UU\_12011/4) to KM Godfrey, the National Institute for Health and Care Research (NIHR Senior Investigator (NF-SI-0515-10042) and NIHR Southampton Biomedical Research Centre (NIHR203319)) to KM Godfrey, the Rosetrees Foundation to KM Godfrey and the Institute for Human Development and Potential, Agency for Science Technology and Research (A\*STAR), Singapore. All funders had no role in 1) the study design; 2) the collection, analysis, and interpretation of data; 3) the writing of the report; and 4) the decision to submit the manuscript for publication. For the purpose of Open Access, the author has applied a Creative Commons Attribution (CC BY) license to any Author Accepted Manuscript version arising from this submission.

**Acknowledgement:** We thank the GUSTO study group and all clinical and home-visit staff involved. The voluntary participation of all subjects is greatly appreciated. The GUSTO study group includes Allan Sheppard, Amutha Chinnadurai, Anne Eng Neo Goh, Anne Rifkin-Graboi, Anqi Qiu, Arijit Biswas, Bee Wah Lee, Birit Froukje Philipp Broekman, Boon Long Quah, Chai Kiat Chng, Cheryl Shufen Ngo, Choon Looi Bong, Christiani Jeyakumar Henry, Daniel Yam Thiam Goh, Doris Ngiuk Lan Loh, Fabian Kok Peng Yap, George Seow Heong Yeo, Helen Yu Chen, Hugo P S van Bever, Iliana Magiati, Inez Bik Yun Wong, Ivy Yee-Man Lau, Jeevesh Kapur, Jenny L. Richmond, Jerry Kok Yen Chan, Joanna Dawn Holbrook, Joshua J. Gooley, Keith M. Godfrey, Kenneth Yung Chiang Kwek, Kok Hian Tan, Krishnamoorthy Naiduvaje, Leher Singh, Lin Lin Su, Lourdes Mary Daniel, Lynette Pei-Chi Shek, Marielle V. Fortier, Mark Hanson, Mary Foong-Fong Chong, Mary Rauff, Mei Chien Chua, Michael J. Meaney, Mya Thway Tint, Neerja Karnani, Ngee Lek, Oon Hoe Teoh, P. C. Wong, Peter David Gluckman, Pratibha Keshav Agarwal, Rob Martinus van Dam, Salome A. Rebello, Seang Mei Saw, Shang Chee Chong, Shirong Cai, Shu-E Soh, Sok Bee Lim, Stephen Chin-Ying Hsu, Victor Samuel Rajadurai, Walter Stunkel, Wee Meng Han, Wei Wei Pang, Yap Seng Chong, Yin Bun Cheung, Yiong Huak Chan and Yung Seng Lee.

**Conflict of interest:** Chong YS has received reimbursement for speaking at conferences sponsored by Abbott Nutrition, Nestle, and Danone. Chong YS and Godfrey KM is part of an academic consortium that has received research funding from Bayer, Nestle and Danone. All other authors declare no conflict of interest.

**Data availability:** Data may be made available on reasonable request from the corresponding author due to ethical and privacy limitations. Supplementary information on predictors not analysed in this study is available at 10.5281/zenodo.15718144.

**Authors’ contributions:**

Hui Xing Lau: Writing-original draft (equal), Writing-review and editing (equal), Project administration (equal)

Qian Chen: Conceptualisation (equal), Methodology (equal), Project administration (Equal), Writing-review and editing (equal)

Qai Ven Yap: Formal analysis (equal), Writing-original draft (equal), Writing-review and editing (equal)

Yun Huang: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Noor Hidayatul Aini Suaini: Formal analysis (equal), Writing-original draft (equal), Writing-review and editing (equal)

Yiong Huak Chan: Formal analysis (equal), Writing-review and editing (equal)

Le Duc Huy Ta: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Gaik Chin Yap: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Lynette Pei-Chi Shek: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Elizabeth Huiwen Tham: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Bee Wah Lee: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Hugo Van Bever: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Anne Eng Neo Goh: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Kok Hian Tan: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Fabian Kok Peng Yap: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Yap Seng Chong: Methodology (equal), Project administration (equal), Writing-review and editing (equal), Funding acquisition (lead)

Keith M Godfrey: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Johan Gunnar Eriksson: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Ying Tian: Methodology (equal), Project administration (equal), Writing-review and editing (equal)

Jun Zhang: Conceptualisation (lead), Methodology (lead), Formal analysis (lead), Project administration (lead), Supervision (lead), Writing-original draft (lead), Writing-review and editing (equal)

Evelyn Xiu Ling Loo: Conceptualisation (lead), Methodology (lead), Formal analysis (lead), Project administration (lead), Supervision (lead), Writing-original draft (lead), Writing-review and editing (equal)

Hui Xing Lau1\*

Qian Chen2\*

Qai Ven Yap3

Yun Huang2

Noor Hidayatul Aini Suaini1

Yiong Huak Chan3

Le Duc Huy Ta4

Gaik Chin Yap4

Lynette Pei-Chi Shek4

Elizabeth Huiwen Tham1,4,5,6

Bee Wah Lee4

Hugo Van Bever4

Anne Eng Neo Goh7

Kok Hian Tan8

Fabian Kok Peng Yap7,9,10

Yap Seng Chong1,11

Keith M Godfrey12,13,14

Johan Gunnar Eriksson1,5,11,15,16

Ying Tian2

Jun Zhang2,17#

Evelyn Xiu Ling Loo1,4,5#^

1. Institute for Human Development and Potential (IHDP), Agency for Science, Technology and Research (A\*STAR), 30 Medical Drive, Singapore 117609, Republic of Singapore
2. Ministry of Education-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China
3. Department of Biostatistics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
4. Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore
5. Human Potential Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
6. Khoo Teck Puat-National University Children’s Medical Institute, National University Hospital, National University Health System, Singapore
7. Department of Paediatrics, KK Women’s and Children’s Hospital (KKH), Singapore
8. Department of Maternal Fetal Medicine, KK Women’s and Children’s Hospital (KKH), Singapore
9. Duke-NUS Medical School, Singapore
10. Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
11. Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore
12. School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
13. NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom
14. MRC Lifecourse Epidemiology Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
15. Folkhälsan Research Center, Helsinki, Finland
16. Department of General Practice and Primary Health Care, University of Helsinki, Finland
17. International Peace Maternity and Child Health Hospital, Shanghai, China

\*co-first authors

#co-senior authors

^corresponding author: Dr Evelyn Loo, Institute for Human Development and Potential, Brenner Centre for Molecular Medicine, 30 Medical Drive, Singapore 117609. Phone: (+65) 6407 0100. Fax: (+65) 6776 6840. Email address: evelyn\_loo@sics.a-star.edu.sg

**Abbreviations:**

ARR: Adjusted risk ratio

CI: Confidence interval

GUSTO: Growing Up in Singapore Towards healthy Outcomes cohort

IQR: Interquartile range

SBC: Shanghai Birth Cohort

SD: Standard deviation

**References**

1. Zhao J, Bai J, Shen K, et al. Self-reported prevalence of childhood allergic diseases in three cities of China: a multicenter study. *BMC Public Health*. 2010/09/13 2010;10(1):551. doi:10.1186/1471-2458-10-551
2. Chiricozzi A, Maurelli M, Calabrese L, et al. Overview of Atopic Dermatitis in Different Ethnic Groups. *J Clin Med*. 2023;12(7). doi:10.3390/jcm12072701
3. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. Wiley; 2014.
4. Ravn NH, Halling A-S, Berkowitz AG, et al. How does parental history of atopic disease predict the risk of atopic dermatitis in a child? A systematic review and meta-analysis. *J Allergy Clin Immunol*. 2020;145(4):1182-1193. doi:10.1016/j.jaci.2019.12.899
5. McCauley KE, Rackaityte E, LaMere B, et al. Heritable vaginal bacteria influence immune tolerance and relate to early-life markers of allergic sensitization in infancy. *Cell Rep Med*. 2022;3(8)doi:10.1016/j.xcrm.2022.100713
6. Hong Z, Jing R, Hui L, et al. A cohort study of intrapartum group B streptococcus prophylaxis on atopic dermatitis in 2-year-old children. *BMC Pediatr*. 2022/12/02 2022;22(1):693. doi:10.1186/s12887-022-03758-5
7. Visscher MO, Carr AN, Winget J, et al. Biomarkers of neonatal skin barrier adaptation reveal substantial differences compared to adult skin. *Pediatr Res*. 2021;89(5):1208-1215. doi:10.1038/s41390-020-1035-y

**Table**

**Table 1.** Analysis of the associations between risk factors and eczema development in first year of life in SBC, Shanghai, China (recruited during pregnancy from 2013-2016) and GUSTO, Singapore (recruited during pregnancy from 2009 to 2010).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | SBC  Unadjusted | | GUSTO  Unadjusted | | SBC  Adjusteda | | | GUSTO  Adjustedb | | | *P*c |
| RR (95% CI) | *p* | RR (95% CI) | *p* | RR (95% CI) | *p* | Wald statistics | RR (95% CI) | *p* | Wald statistics |
| Maternal age at recruitment | 0.99 (0.97- 1.01) | 0.37 | 1.04 (0.99-1.09) | 0.13 | 0.99 (0.96- 1.01) | 0.23 | 1.45 | 1.04 (0.98-1.11) | 0.24 | 1.37 | 0.15 |
| Pre-pregnancy BMI | 1.00 (0.97- 1.02) | 0.79 | 1.03 (0.97-1.10) | 0.39 | 1.01 (0.99- 1.04) | 0.34 | 0.91 | 1.05 (0.97-1.13) | 0.25 | 1.32 | 0.33 |
| Nulliparous | 1.0 (0.8- 1.3) | 0.69 | 1.5 (1.0-2.3) | 0.05 | 0.99 (0.77- 1.27) | 0.91 | 0.01 | 1.4 (0.8-2.4) | 0.26 | 1.28 | 0.18 |
| Female | 0.86 (0.74- 1.01) | 0.06 | 0.75 (0.49-1.15) | 0.19 | 0.87 (0.74- 1.03) | 0.11 | 2.59 | 0.89 (0.52-1.52) | 0.67 | 0.18 | 0.94 |
| Less than university education | 0.99 (0.85- 1.15) | 0.86 | 0.58 (0.38-0.89) | <.05 | 0.97 (0.81- 1.16) | 0.73 | 0.12 | 0.68 (0.38-1.22) | 0.20 | 1.64 | 0.35 |
| Ever or current smoker | 1.3 (0.9- 2.0) | 0.15 | 1.0 (0.5-2.1) | 0.98 | 1.5 (1.0- 2.4) | 0.07 | 3.24 | 1.5 (0.5-4.0) | 0.47 | 0.52 | >0.99 |
| Environmental smoke during pregnancy | 1.0 (0.9- 1.2) | 0.72 | 0.79 (0.47-1.33) | 0.38 | 1.1 (0.9- 1.3) | 0.38 | 0.76 | 0.75 (0.37-1.52) | 0.43 | 0.64 | 0.35 |
| Alcohol consumption before/during pregnancy | 0.94 (0.75- 1.18) | 0.62 | 1.2 (0.8-1.9) | 0.33 | 0.90 (0.69- 1.19) | 0.47 | 0.52 | 1.0 (0.6-1.7) | >0.99 | 0 | 0.74 |
| Caesarean delivery | 1.0 (0.9- 1.2) | 0.77 | 1.0 (0.7-1.7) | 0.85 | 0.93 (0.74- 1.18) | 0.56 | 0.34 | 1.7 (0.7-4.0) | 0.22 | 1.5 | 0.09 |
| GA | 1.01 (0.96- 1.06) | 0.80 | 0.89 (0.79-1.00) | 0.05 | 0.99 (0.93- 1.06) | 0.82 | 0.05 | 0.75 (0.59-0.93) | <.05 | 6.49 | <.05 |
| Birthweight | 1.1 (0.9-1.3) | 0.37 | 1.0 (0.6-1.7) | 0.88 | 1.0 (0.9-1.1) | 0.66 | 0.20 | 2.1 (1.0-4.5) | 0.05 | 3.72 | <.05 |
| Use of antibiotics by M12 | 1.1 (0.9- 1.3) | 0.19 | 1.3 (0.8-2.1) | 0.24 | 1.0 (0.9- 1.3) | 0.69 | 0.16 | 1.7 (0.8-4.0) | 0.20 | 1.65 | 0.10 |
| Maternal history of allergy X mode of delivery |  |  |  |  |  |  |  | 0.28 (0.09-0.89) | <.05 |  |  |
| Maternal history of allergy | 1.1 (0.9- 1.3) | 0.26 | 2.0 (1.3-3.1) | <.05 | 1.0 (0.8- 1.3) | 0.77 | 0.08 | 3.4 (1.5-8.0) | <.05 | 8.22 | <.001 |
| Subgroup: Caesarean | 1.3 (1.0-1.5) | <.05 | 0.86 (0.39-1.90) | 0.71 | 1.2 (0.9-1.5) | 0.13 | 2.24 | 0.83 (0.30-2.32) | 0.73 | 0.12 |  |
| Subgroup: Vaginal | 0.97 (0.79-1.20) | 0.79 | 3.0 (1.7-5.1) | <.001 | 1.1 (0.8-1.3) | 0.68 | 0.18 | 3.2 (1.6-6.4) | <.001 | 11.01 |  |

BMI: Body-mass index; GA: Gestational age; GUSTO: Growing Up in Singapore Towards healthy Outcomes cohort; M12: age 12 months; SBC: Shanghai Birth Cohort.

a1859 out of 2341 (79.4%) SBC subjects were included in the adjusted analysis.

b377 out of 520 (72.5%) GUSTO subjects were included in the adjusted analysis.

c*P*-value for the difference between the two cohorts in the adjusted model.

Two-sided *P*-values are presented.

Interaction between maternal history of allergy and mode of delivery were included in the model but not significant for SBC. The interaction term was derived from the multiplication of maternal history of allergy (1 = yes, 0 = no) by mode of delivery (1 = caesarean section, 0 = vaginal delivery).

Interaction for maternal history of allergy and mode of delivery: *P*=0.496 for SBC.

Interaction between maternal history of allergy and use of antibiotics were included in the model but not significant.

Interaction for maternal history of allergy and use of antibiotics: *P*=0.798 for SBC and p=0.593 for GUSTO.