Published in final edited form as:

Pediatr Allergy Immunol. 2019 February ; 30(1): 122–127. doi:10.1111/pai.12983.

Early childcare enrollment and childhood wheezing phenotypes

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Trial Registration: NCT01174875 Registered 1 July 2010, retrospectively registered

Conflict of Interest Statement

Chong YS has received reimbursement for speaking at conferences sponsored by Abbott Nutrition, Nestle, and Danone. Godfrey KM has received reimbursement for speaking at conferences sponsored by Nestle and Shek LP has received reimbursement for speaking at conferences sponsored by Danone and Nestle and consulting for Mead Johnson and Nestle.

Godfrey KM, Chong YS are part of an academic consortium that has received research funding from Abbot Nutrition, Nestle and Danone. Shek LP has received research funding from Danone.

Statement of Contribution

EH Tham conceptualized the study, performed data analysis and wrote the manuscript. PT Tan performed data analysis and critically reviewed the manuscript. EX Loo, A Goh, OH Teoh, KH Tan, KM Godfrey, H Van Bever, BW Lee, EA Finkelstein, YS Chong and LP Shek critically reviewed the manuscript for intellectual content.

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Keywords

Childcare; wheezing; house dust mite; asthma; allergy

To the Editor

The “hygiene hypothesis” proposes that microbial exposures in early life - such as a farming lifestyle, early childcare attendance, older siblings and pet ownership protect against atopy by maintaining a balanced Th1/Th2 immune cytokine milieu.^{1–3} The newly described “biodiversity hypothesis” or “old friends” hypothesis further suggests that co-evolved trans-generationally transmitted commensal microbiota played important immunoregulatory roles, which have now been diminished due to loss of biodiversity in modern urbanized environments.⁴

Children attending childcare are at increased risk of viral respiratory infections and viral-induced wheezing disorders.⁵ Early onset recurrent viral induced wheezing has been associated with a higher risk of obstructive airway disease in later life,⁶ likely mediated by viral induced inflammation & immunomodulation which incite lung damage, culminating in lung function restriction which may persist through adolescence into adulthood.⁷

Studies have observed either protective or null effects of early childcare attendance against asthma development, and only in high-risk populations with parental atopy⁵ or older siblings.^{1, 8, 9} Cross-sectional studies are also limited in their ability to evaluate the temporal relationship between these variables and to establish the exact window of vulnerability.

We hypothesized that the specific window of childcare enrollment and duration of exposure determine the risks of early onset viral-induced wheezing and the development of wheezing phenotypes and respiratory allergy in later childhood and explored this hypothesis within the Growing Up in Singapore Towards healthy Outcomes (GUSTO) longitudinal mother-offspring cohort.

The GUSTO cohort’s methodology has been described previously (Appendix 1, Supplementary Material).¹⁰ Data were collected prospectively through interviewer-administered questionnaires at 3, 6, 9, 12, 15, 18, 24, 36, 48 and 60 months. *Eczema* was defined as a positive response to the question “Has your child ever been diagnosed with eczema?”. *Wheezing* was defined as positive responses to both questions: “Has your child had wheezing since the last visit?” AND “Has your child been prescribed with nebulizer/inhaler treatment since the last visit?” Definitions of wheezing phenotypes were adapted from the Avon Longitudinal Study of Parents and Children (ALSPAC),¹¹ which was further validated in the Southampton Women’s Survey (SWS).¹²

Transient early wheezing was defined as at least one episode of parental-reported wheezing (as prior defined) before age 2 and none in the 12 months preceding the Year 5 visit. *Late onset wheezing* was defined as no reported wheezing episodes in the first 2 years of life and at least one episode of wheezing in the 12 months preceding the Year 5 visit. *Persistent wheezing* was defined as at least one episode of parental-reported wheezing before the age of two years **and** at least one episode of wheezing in the preceding year before the Year 5 visit.

Skin prick testing (SPT) to house dust mites (HDM) *D. pteronyssinus*, *Dermatophagoides farinae* and *B. tropicalis* was carried out at 18 and 60 months. Ethics approval was obtained from the Centralized Institutional Review Board (CIRB) of SingHealth (reference 2009/280/D) and the Domain Specific Review Board of Singapore National Healthcare Group (reference D/09/021). Written informed consent was obtained from all participants.

Statistical analysis was performed using IBM SPSS version 24. Statistical significance was set at $p < 0.05$.

The demographic characteristics of the subjects are summarized in Supplementary Table 1 and wheezing outcomes by childcare enrolment group are shown in Table 1. Forty-nine children (6%) were enrolled into childcare before 6 months of age, 35 (4%) between 6 and 12 months of age, 143 (19%) between 1 and 2 years of age and 513 (68%) after the age of 2 years.

Wheezing with nebulizer use was reported in 129 (18%) subjects and healthcare utilization for wheezing-related conditions in 83 (12%) subjects by 24 months of age. The prevalence of early wheeze in this cohort is similar to a previous cross-sectional study in Singapore which reported the prevalence of parental-reported wheezing symptoms in the second year of life to be 23.2%.¹³ By 5 years of age, transient onset wheezing was reported in 87 (14%) subjects, late onset wheezing in 35 (6%) children and persistent wheezing in 23 (4%) children.

Childcare enrollment before 6 months of age was associated with an increased risk of wheezing episodes and healthcare utilization by 24 months compared to children who had never attended childcare (Table 2), as well as transient early wheezing and persistent wheezing phenotypes, but not late onset wheezing, by age 5 years (Table 3).

Increasing duration of childcare attendance in the first year of life was significantly associated with episodes of wheezing and increased healthcare utilization by 24 months of age (Table 2), as well as transient early wheezing [adjusted OR 1.31, 95% CI (1.13, 1.51) $p < 0.001$], but not late onset or persistent wheezing, by 5 years of age.

This is the first prospective study demonstrating that early childcare enrollment and before age 6 months and increased exposure duration were associated with higher risks of wheeze-related respiratory morbidity by age 2 years and the development of transient early onset wheezing and persistent wheezing phenotypes at age 5 years, compared to children who were enrolled at an older age.

Our findings contrast with other studies which reported positive associations between early daycare attendance (0-2 years) and increased airway symptoms until age 4 years, but no protection against asthma by age 8 years.⁹ Nicolaos et al. found that children who entered nursery between 6-12 months or after 12 months of age had a reduced risk of current wheeze at age 5 years.⁸ The Home Allergens and Asthma Study found no significant associations between daycare attendance in the first year of life and asthma at age 4 years in a high risk cohort of children with parental atopy.

The precise window of exposure and exposure duration are additional key modulating factors. Nicolaos et al reported a protective effect of childcare attendance between 6-12 months against asthma at age 5 years but no effect in those enrolled before 6 months of age. Ball et al described that childcare attendance before age 6 months increased the risk of recurrent wheeze and later asthma, but only in those with older siblings and its retrospective design may have been influenced by recall bias.¹

Children with transient wheezing phenotypes are more likely to have persistently diminished lung function in later childhood.^{11, 12} Persistent wheezing is modulated by early inflammatory insults such as viral infections, atopic sensitization, immune dysregulation and airway remodelling and confers a high risk for asthma inception.¹¹ This study suggests that the risk of developing this phenotype is likely due to early exposure to respiratory viruses and early onset wheezing illnesses, which is moderated through very early childcare enrollment.

Strengths of the GUSTO cohort include the prospective ascertainment of data at multiple time-points from an unselected mother-offspring cohort, enabling temporal evaluation of relationships between risk factors and outcomes. Limitations include the reliance on parental reported outcomes and exposures and the lack of an objective assessment of asthma such as lung function. However, the ISAAC questionnaires have been validated extensively in large epidemiologic studies worldwide for the ascertainment of allergic outcomes.

The exponential increase in the number of infant and childcare centres in Singapore showcases the rising demand for affordable early childcare to allow working mothers to return to the workforce after just 4 months of government-paid maternity leave. Modifications maternity and family care leave policies could allow families to delay childcare enrollment beyond the first 6 months of life, which may attenuate the risks of developing wheezing disorders through shifting the balance between pathogenic and beneficial environmental microbial exposures towards a null or protective effect, as seen in previous studies.

Preschool education confers long-term neurodevelopmental advantages and economic benefits contributed by the larger pool of working mothers. However, most of this evidence focuses on the preschool age group (3-5 years) and not infants, thus a short delay in childcare enrollment may not translate to any significant loss of the above-mentioned benefits in the long-term, but this will require further investigation.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank the GUSTO study group, operational managers, research fellows, study coordinators, and data management team. The GUSTO study group includes: Pratibha Agarwal, Arijit Biswas, Choon Looi Bong, Birit F.P. Broekman, Shirong Cai, Jerry Kok Yen Chan, Yiong Huak Chan, Cornelia Yin Ing Chee, Yin Bun Cheung, Amutha Chinnadurai, Chai Kiat Chng, Mary Foong-Fong Chong, Shang Chee Chong, Mei Chien Chua, Doris Fok, Marielle V. Fortier, Anne Eng Neo Goh, Yam Thiam Daniel Goh, Joshua J. Gooley, Wee Meng Han, Mark Hanson, Christiani Jeyakumar Henry, Joanna D. Holbrook, ChinYing Hsu, Neerja Karnani, Jeevesh Kapur, Ivy Yee-Man Lau, Bee Wah Lee, Yung Seng Lee, Ngee Lek, Sok Bee Lim, Iliana Magiati, Lourdes Mary Daniel, Cheryl Ngo, Krishnamoorthy Niduvaje, Wei Wei Pang, Anqi Qiu, Boon Long Quah, Victor Samuel Rajadurai, Mary Rauff, Salome A. Rebello, Jenny L. Richmond, Anne Rifkin-Graboi, Lynette Pei-Chi Shek, Allan Sheppard, Borys Shuter, Leher Singh, Shu-E Soh, Walter Stunkel, Lin Lin Su, Kok Hian Tan, Oon Hoe Teoh, Mya Thway Tint, Hugo P S van Bever, Rob M. van Dam, Inez Bik Yun Wong, P. C. Wong, Fabian Yap, and George Seow Heong Yeo.

Sources of Funding

This research is supported by the Singapore National Research Foundation under its Translational and Clinical Research (TCR) Flagship Program 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. Additional funding is provided by the Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A*STAR), Singapore. Tham EH is supported by the National Medical Research Council (NMRC) Research Training Fellowship grant [MH 095:003\008-225] from NMRC, Singapore. K.M Godfrey is supported by the National Institute for Health Research through the NIHR Southampton Biomedical Research Centre and by the European Union's Seventh Framework Program (FP7/2007–2013), projects EarlyNutrition and ODIN under grant agreement numbers 289346 and 613977.

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Table 1
Wheezing outcomes by childcare enrollment age group

Wheezing outcome	Early childcare enrollment ^a (≤12 months) n=84 (%)	Late (>12 months) or no childcare ^a n=676 (%)	p-value
Healthcare utilization for wheezing by 24 months (n=83)	19/78 (24)	64/601 (11)	P<0.001
Wheezing with nebulizer use by 24 months (n=129)	32/81 (40)	97/629 (15)	P<0.001
[†] Wheeze + nebulizer use by 5 years (n= 165)	37/75 (49)	128/578 (22)	P<0.001
Never wheezed (n=488)	38/75 (51)	450/578 (78)	
[§] Transient onset wheezing (n=87)	19/67 (28)	68/566 (12)	P<0.001
[¶] Late onset wheezing (n=35)	5/67 (8)	30/566 (5)	P=0.40
[#] Persistent wheezing (n=23)	5/67 (8)	18/566 (3)	P=0.09

^aDifferences in total numbers are due to missing data

[†]Subjects who reported wheeze + nebulizer use at any of the time-points 3, 6, 9, 12, 18, 24 or 60 months

[§]**Transient early wheezing**: at least one episode of parental-reported wheezing requiring the use of inhalers or nebulizers before age 2 and none in the 12 months preceding the Year 5 visit.

[¶]**Late onset wheezing**: no reported wheezing episodes in the first 2 years of life and at least one episode of wheezing with inhaler or nebulizer use in the 12 months preceding the Year 5 visit.

[#]**Persistent wheezing**: at least one episode of parental-reported wheezing requiring the use of inhalers or nebulizers before the age of two years **and** at least one episode of wheezing as prior defined in the preceding year before the Year 5 visit.

Table 2
Childcare attendance and wheeze-related morbidity by 24 months

	Wheezing with the use of nebulizer by 24 months			Utilization of healthcare facility for wheezing by 24 months		
	Crude (n=710)		Adjusted (n=643)	Crude (n=679)		Adjusted (n=608)
	RR (95% CI)	p value		OR, (95% CI)	p value	
Childcare attendance by 1 year of age	3.36 (2.06, 5.48)	P<0.001	4.24 (2.44, 7.37)	2.70 (1.52, 4.82)	P=0.001	4.28 (2.14, 8.56)
	3.98 (2.20, 7.23)	P<0.001	5.01 (2.60, 9.68)	3.31 (1.65, 6.60)	P=0.001	6.06 (2.62, 14.01)
Age group at childcare enrollment	2.45 (1.15, 5.22)	P=0.02	3.13 (1.37, 7.15)	1.94 (0.77, 4.88)	P=0.16	2.58 (0.89, 7.47)
Duration of childcare attendance in the 1 st year	1.27 (1.15, 1.40)	P<0.001	1.33 (1.19, 1.49)	1.22 (1.08, 1.37)	P=0.001	1.34 (1.16, 1.54)

Adjusted for ethnicity, maternal education, maternal atopy, gender, sibling, antenatal and postnatal smoking exposures and breastfeeding. Healthcare utilization data for wheezing conditions were captured through questions on hospital admission or consultation at an emergency department, specialist outpatient clinic or primary care clinic for wheezing, bronchiolitis, bronchitis or asthma.

Parental-reported data on childcare attendance included the age of enrollment into childcare, the number of days of childcare attendance per week as well as the number of hours of attendance per day.

Duration of childcare attendance in the first year of life was calculated as the average number of days per week spent in childcare from the time of enrollment.

Table 3

Associations between childcare attendance and wheezing phenotypes by age 5 years

		Transient early wheezing				Late onset wheezing				Persistent wheezing			
		Crude (n=630)		Adjusted (n=524)		Crude (n=630)		Adjusted (n=524)		Crude (n=630)		Adjusted (n=524)	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Ethnicity	Chinese	REF		REF		REF		REF		REF		REF	
	Malay	1.59 (0.96, 2.63)	P=0.07	1.70 (0.82, 3.53)	P=0.15	1.37 (0.59, 3.17)	P=0.46	1.70 (0.57, 5.10)	P=0.35	2.06 (0.87, 4.88)	P=0.10	2.59 (0.61, 10.98)	P=0.20
	Indian	0.97 (0.48, 1.94)	P=0.92	0.85 (0.31, 2.34)	P=0.75	2.78 (1.22, 6.35)	P=0.02	3.37 (1.26, 9.03)	P=0.02	0.34 (0.04, 2.63)	P=0.30	0.97 (0.11, 8.95)	P=0.98
Maternal Atopy		1.85 (1.11, 3.08)	P=0.02	1.86 (1.01, 3.43)	P=0.04	2.16 (1.07, 4.36)	P=0.03	1.78 (0.78, 4.07)	P=0.17	2.31 (0.91, 5.85)	P=0.08	2.01 (0.63, 6.35)	P=0.24
Childcare enrolment age	Before 6 months	2.77 (1.32, 5.81)	P=0.01	3.30 (1.31, 8.31)	P=0.01	2.06 (0.69, 6.18)	P=0.20	2.08 (0.53, 8.08)	P=0.29	3.51 (1.13, 10.94)	P=0.03	6.57 (1.45, 29.66)	P=0.01
	6-11 months	2.35 (0.83, 6.66)	P=0.11	3.79 (1.19, 12.11)	P=0.02	0.95 (0.12, 7.33)	P=0.96	1.02 (0.12, 8.55)	P=0.98	1.62 (0.21, 12.75)	P=0.65	2.57 (0.27, 24.58)	P=0.41
	>=12 months	REF		REF		REF		REF		REF		REF	

Further adjusted for maternal education, gender, sibling, antenatal and postnatal smoking exposures, breastfeeding status at 6 months, eczema and HDM sensitization status at 18 months
Bold text indicate significant associations (p<0.05)