Title: Early childcare enrollment and childhood wheezing phenotypes

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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.

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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] Children attending childcare, however, are at increased risk of viral respiratory infections and viral-induced wheezing disorders.[2] Early onset recurrent viral induced wheezing has been associated with a higher risk of obstructive airway disease in later life,[3] likely mediated by viral induced inflammation & immunomodulation which incite lung damage, culminating in lung function restriction which may persist through adolescence into adulthood.[4]

Studies have observed either protective or null effects of early childcare attendance against asthma development, and only in high-risk populations with parental atopy[2] or older siblings.[5-7] 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.[8] 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),[9] which was further validated in the Southampton Women's Survey (SWS).[10]

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. Allergic wheezing phenotypes were further defined by house dust mite sensitization status at 18 months for *HDM sensitized-transient early wheezing*, and at 60 months for *HDM sensitized-late onset wheezing* and *HDM sensitized-persistent wheezing*. 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 are shown in Table 1. Fifty-three children (5.5%) were enrolled into childcare before 6 months of age, 44 (4.6%) between 6 and 12 months of age, 185 (19.2%) between 1 and 2 years of age and 684 (70.8%) after the age of 2 years.

Wheezing with nebulizer use was reported in 134 (18.6%) subjects and healthcare utilization for wheezing-related conditions in 87 (12.6%) subjects by 24 months of age. By 5 years of age, subjects had developed transient onset wheezing was reported in 87 (13.7%)

121 subjects, late onset wheezing in 35 (5.5%) children and persistent wheezing in 23 (3.6%)
122 children.

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

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

131 Childcare enrollment before 1 year of age was associated with the HDM-sensitized
132 persistent wheezing phenotype by age 5 years [adjusted OR 7.59, 95% CI (1.48, 39.01),
133 $p=0.015$] but not with HDM-sensitized late onset wheezing [adjusted OR 1.63, 95% CI (0.47,
134 5.62), $p=0.438$].

135 This is the first prospective study demonstrating that early childcare enrollment and
136 before age 6 months and increased exposure duration were associated with higher risks of
137 wheeze-related respiratory morbidity by age 2 years and the development of transient early
138 onset wheezing and persistent wheezing phenotypes (with and without HDM sensitization) at
139 age 5 years, compared to children who were enrolled at an older age.

140 Our findings contrast with other studies which reported positive associations between
141 early daycare attendance (0-2 years) and increased airway symptoms until age 4 years, but no
142 protection against asthma by age 8 years.[7] Nicolaos et al. found that children who entered
143 nursery between 6-12 months or after 12 months of age had a reduced risk of current wheeze
144 at age 5 years.[6] 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.[6] 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.[5]

Children with transient wheezing phenotypes are more likely to have persistently diminished lung function in later childhood.[9, 10] 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.[9] 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 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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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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Supplementary Table 1. Demographic characteristics of subjects in the GUSTO Cohort

Demographic variable	N (%)
Ethnicity	
• Chinese	691 (55.9)
• Malay	322 (26.1)
• Indian	223 (18.0)
Maternal Education - Tertiary	406 (33.3)
Male Sex	619 (52.9)
Has Sibling	636 (54.3)
Breastfeeding until month 6	390 (39.8)
Maternal atopy	226 (22.1)
Maternal smoke exposure during pregnancy	428 (37.2)
Passive smoking exposure by 1 year of age	349 (37.3)
Childcare enrollment by 1-year of age	
• None	912 (90.4)
• < 6 months	53 (5.3)
• 6 - <= 12 months	44 (4.4)
Childcare enrollment age group	
• < 6 months	53 (5.5)
• 6 – <=12 months	44 (4.6)
• 13 - 23 months	185 (19.2)
• 2 years - <5years	684 (70.8)
Duration of childcare attendance in the 1st year (days/week)†	
• N	96
• Min, Max	0.50. 7.00
• Mean (SD)	4.75 (1.1)

† for those enrolled in childcare

Table 1. Wheezing illness outcomes

Wheezing illness outcome		**N / Total N (%)**	**Outcome in those with childcare attendance by 12 months N=96 n (%)**
Healthcare utilization for wheezing by 24 months		87 / 691 (12.6)	19 (24.4)
Wheeze + nebulizer use by 24 months		134 / 721 (18.6)	32 (39.5)
Wheeze + nebulizer use by 5 years†		176 / 664 (26.5)	37 (49.3)
Never wheezed by 5 years		488 / 964 (50.6)	38 (50.7)
§**Transient onset wheezing†**	Total	87 / 633 (13.7)	19 (28.4)
	% Atopic‡	7 / 74 (9.5)	0 (0.0)
¶Late onset wheezing	Total	35 / 633 (5.5)	5 (7.5)
	% Atopic‡	22 / 32 (68.8)	4 (6.3)
#Persistent wheezing	Total	23 / 633 (3.6)	5 (7.5)
	% Atopic‡	11 / 20 (55.0)	3 (4.7)

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

‡Atopic: sensitized to HDM at age 5 years

Differences in total numbers are due to missing data

§***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			
		Unadj RR, 95% CI	**Unadj p value**	**Adj RR, 95% CI**	**Adj p value**	**Unadj OR, 95% CI**	**Unadj p value**	**Adj OR, 95% CI**	**Adj p value**
Childcare attendance by 1 year of age	No	REF		REF		REF		REF	
	Yes	**3.36 (2.06, 5.48)**	**P<0.001**	**4.24 (2.44, 7.37)**	**P<0.001**	**2.70 (1.52, 4.82)**	**P=0.001**	**4.28 (2.14, 8.56)**	**P<0.001**
Age group at childcare enrollment	None	REF		REF		REF		REF	
	Before 6 months	**3.98 (2.20, 7.23)**	**P<0.001**	**5.01 (2.60, 9.68)**	**P<0.001**	**3.31 (1.65, 6.60)**	**P=0.001**	**6.06 (2.62, 14.01)**	**P<0.001**
	6-12 months	**2.45 (1.15, 5.22)**	**P=0.021**	**3.13 (1.37, 7.15)**	**P=0.007**	1.94 (0.77, 4.88)	P=0.161	2.58 (0.89, 7.47)	P=0.080
Duration of childcare attendance in the 1st year		**1.27 (1.15, 1.40)**	**P<0.001**	**1.33 (1.19, 1.49)**	**P<0.001**	**1.22 (1.08, 1.37)**	**P=0.001**	**1.34 (1.16, 1.54)**	**P<0.001**

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

Variable		Transient early wheezing				Late onset wheezing				Persistent wheezing			
		Unadj OR (95% CI)	**Unadj p-value**	**Adj OR (95%CI)**	**Adj p-value**	**Unadj OR (95% CI)**	**Unadj p-value**	**Adj OR (95%CI)**	**Adj p-value**	**Unadj OR (95% CI)**	**Unadj p-value**	**Adj OR (95%CI)**	**Adj p-value**
Ethnicity	**Chinese**	REF		REF		REF		REF		REF		REF	
	Malay	1.59 (0.96, 2.63)	P=0.074	1.70 (0.82, 3.53)	P=0.153	1.37 (0.59, 3.17)	P=0.463	1.70 (0.57, 5.10)	P=0.346	2.06 (0.87, 4.88)	P=0.099	2.59 (0.61,	P=0.195
	Indian	0.97 (0.48, 1.94)	P=0.921	0.85 (0.31, 2.34)	P=0.748	**2.78 (1.22, 6.35)**	**P=0.015**	**3.37 (1.26, 9.03)**	**P=0.016**	0.34 (0.04, 2.63)	P=0.300	0.97 (0.11, 8.95)	P=0.979
Maternal Atopy	**No**	REF		REF		REF		REF		REF		REF	
	Yes	**1.85 (1.11, 3.08)**	**P=0.019**	1.86 (1.01, 3.43)	P=0.046	2.16 (1.07, 4.36)	P=0.032	1.78 (0.78, 4.07)	P=0.170	2.31 (0.91, 5.85)	P=0.078	2.01 (0.63, 6.35)	P=0.237
Childcare enrollment age	**Before 6 months**	**2.77 (1.32, 5.81)**	**P=0.007**	**3.30 (1.31, 8.31)**	**P=0.011**	2.06 (0.69, 6.18)	P=0.197	2.08 (0.53, 8.08)	P=0.292	**3.51 (1.13, 10.94)**	**P=0.030**	**6.57 (1.45,**	**P=0.014**
	6-11 months	**2.35 (0.83, 6.66)**	**P=0.109**	**3.79 (1.19, 12.11)**	**P=0.024**	0.95 (0.12, 7.33)	P=0.960	1.02 (0.12, 8.55)	P=0.984	1.62 (0.21, 12.75)	P=0.648	2.57 (0.27,	P=0.411
	>=12 months	REF		REF		REF		REF		REF		REF	
HDM sensitized at M18	**No**	REF		REF		REF		REF		REF		REF	
	Yes	0.75 (0.33, 1.71)	P=0.496	0.67 (0.26, 1.72)	P=0.404	2.93 (1.25, 6.86)	P=0.013	2.46 (0.90, 6.73)	P=0.080	3.51 (1.39, 8.86)	P=0.008	1.61 (0.38, 6.83)	P=0.515
Eczema by 18M	**No**	REF		REF		REF		REF		REF		REF	
	Yes	1.70 (0.99, 2.94)	P=0.056	1.80 (0.91, 3.54)	P=0.090	2.10 (1.00, 4.42)	P=0.051	1.76 (0.70, 4.42)	P=0.231	2.60 (1.06, 6.35)	P=0.036	2.91 (0.88, 9.60)	P=0.079

Further adjusted for maternal education, gender, sibling, antenatal and postnatal smoking exposures and breastfeeding status at 6 months
Bold text indicate significant associations