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Prevalence, risk factors and parental perceptions of gastroesophageal reflux disease in Asian infants in Singapore

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ABSTRACT

Introduction: Infant gastroesophageal reflux disease (GERD) is a significant cause of concern to parents. This study seeks to describe GERD prevalence in infants, evaluate possible risk factors and assess common beliefs influencing management of GERD among Asian parents.

Methods: Mother-infant dyads in the Singapore PREconception Study of long-Term maternal and child Outcomes (S-PRESTO) cohort were prospectively followed from preconception to 12 months post-delivery. GERD diagnosis was ascertained through the revised Infant Gastroesophageal Reflux Questionnaire (I-GERQ-R) administered at 4 time points during infancy. Data on parental perceptions and lifestyle modifications were also collected.

Results: The prevalence of infant GERD peaked at 26.5% at age 6 weeks, decreasing to 1.1% by 12 months. Infants exclusively breastfed at 3 weeks of life had reduced odds of GERD by 1 year (adjusted odds ratio 0.43, 95% confidence interval 0.19–0.97, P=0.04). Elimination of "cold or heaty food" and "gas producing" vegetables, massaging the infant's abdomen and application of medicated oil to the infant's abdomen were quoted as major lifestyle modifications in response to GERD symptoms.

Conclusion: Prevalence of GERD in infants is highest in the first 3 months of life, and the majority outgrow it by 1 year of age. Infants exclusively breastfed at 3 weeks had reduced odds of GERD. Cultural-based changes such as elimination of "heaty or cold" food influence parental perceptions in GERD, which are unique to the Asian population. Understanding the cultural basis for parental perceptions and health-seeking behaviours is crucial in tailoring patient education appropriately for optimal management of infant GERD.

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CLINICAL IMPACT

What is New

- The highest prevalence of gastroesophageal reflux disease (GERD) among Asian infants was observed at 6 weeks.
- Children who were exclusively breastfed at 3 weeks had lower risk of GERD.
- Asian mothers appear to adopt cultural-based modifications in relieving infants of their GERD symptoms.

Clinical Implications

- This study highlights the need and importance of understanding the cultural basis of parental perceptions and health-seeking behaviours.
- Findings from this study can help health practitioners develop better therapeutic approaches and to provide culturally aligned education to support mothers of infants with GERD.

INTRODUCTION

Functional gastrointestinal (GI) disorders, such as colic, gastroesophageal reflux (GER) and constipation, are common in infants under 1 year. They are a frequent cause of concern for parents and result in a significant healthcare burden[1,2] due to their negative impact on feeding behaviours, caregivers' mental wellbeing and quality of life for the whole family. Cultural factors may also influence parent-child interactions in response to GER symptoms, particularly lifestyle changes and infant feeding practices.

Current knowledge on the prevalence, natural history and factors contributing to infant GI disorders is limited. No studies have reported the prevalence of gastroesophageal reflux disease (GERD) in infants below 12 months, but some have reported the prevalence of infant regurgitation based on the ROME criteria for paediatric GI disorders.[3,4] This study therefore aimed to describe the prevalence and natural history of GERD in infants during the first year of life in an Asian preconception cohort. We also evaluated possible risk factors for infant GERD and assessed common Asian parental beliefs, together with their influence on lifestyle modifications in response to GERD symptoms in these infants.

METHODS

Study design and participants

The Singapore PREconception Study of long-Term maternal and child Outcomes (S-PRESTO) study was designed to assess the impact of nutrition, lifestyle, mental health and other environmental factors during the preconception, antenatal and postnatal periods on mother-offspring health outcomes. The S-PRESTO study design and participants have been previously described.[5-8] In brief, the study recruited 1,032 women aged 18–45 years of Chinese, Malay and Indian ethnicity (or a combination of these) without significant health conditions and who were planning to conceive. The 373 babies born were evaluated prospectively at multiple time points with ongoing follow-ups from birth. S-PRESTO was granted ethical approval by the SingHealth Centralised Institutional Review Board (Reference 2014/692/D) and written informed consent was obtained from all women at recruitment.

Maternal and infant characteristics

Maternal characteristics including socio-demographic factors, lifestyle habits, anthropometric measurements and clinical data were collected at multiple time points during the preconception and antenatal periods. Infant data, such as mode of delivery, birthweight and sex, were collected at birth, while other clinical data were recorded prospectively at multiple time points from birth. Mothers were also asked about their infant feeding practices at each postnatal visit starting at 3 weeks (see Appendix in the online Supplementary Materials).

Infant GERD symptoms and parental beliefs

Mothers were asked about their child's health status during the standard study follow-up periods at 6 weeks, 3, 6 and 12 months post-delivery using interviewer-administered questionnaires. These included questions from the revised Infant Gastroesophageal Reflux Questionnaire (I-GERQ-R)—a reliable and valid measure of infant GERD—with higher scores indicating greater symptom burden.[9,10] An I-GERQ-R score of ≥16 is diagnostic of GERD. The I-GERQ-R questionnaire was derived from the I-GERQ, which was validated for GERD diagnosis in infants aged 1–14 months. Additional information ascertained through the questionnaire included parental beliefs about their infant's troublesome GI symptoms, and potential factors believed to have caused the GI symptoms (online Supplementary Materials).

Statistical analysis

All data collected were analysed on STATA I/C version 16.0 (StataCorp LLC, College Station, Texas, US) and RStudio software version 1.3.1056 (RStudio, Boston, US), an integrated development environment for R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Chi-square and Fisher's Exact tests were used to analyse differences between infants with and without GERD. Risk factors for GERD were analysed using univariate logistic regression with a categorical outcome of having GERD in the first year of life. Multivariate logistic regression was used to create a model of risk factors that may influence the development of GERD. Results with *P* values ≤0.05 were considered significant.

RESULTS

Characteristics of participants

A total of 1,054 women attended the recruitment visit, with 1,032 enrolled in the study.[8] Of these 1,032 participants, 475 became pregnant and 373 gave birth to liveborn singleton infants. Supplementary Fig. S1 shows the number of participants involved at various time points throughout the study. In all, 347 mothers completed the I-GERQ-R questionnaire or questions regarding their beliefs about GI symptoms at one or more time points and were included in this analysis. The demographic factors of participants are presented in Supplementary Table S1. The median age of mothers at recruitment was 30 years (range 20–40 years). The ethnic breakdowns were Chinese (76.1%), Malay (13.8%), Indian (5.8%) and mixed ethnicity (4.3%), similar to Singapore's general population. The majority of mothers had completed tertiary education (72.6%) and had never smoked (91.6%). All infants were healthy and free of major comorbidities.

Prevalence of infant GERD

The highest prevalence of GERD in infants was 26.5% (67/253) at age 6 weeks. This decreased to 7.7% (21/274) at 3 months, 2.6% (8/302) at 6 months and eventually 1.1% (3/273) at 12 months. The mean I-GERQ-R scores decreased with age alongside the decline in prevalence of GERD across time points (Fig. 1).

Infants with GERD were more likely to cry 3 or more hours a day than those without GERD (23/99 [23.2%] versus 22/1003 [2.2%]; *P*<0.01). Infants with GERD were likely to cry at a particular time of day than those without GERD; this was most often in the evening (32.8%) or night (41.4%), but the difference in evening/night versus morning/afternoon crying was not significant.

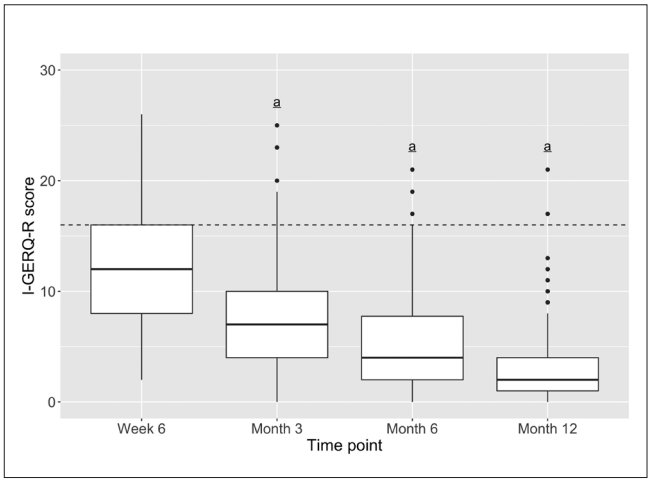

Fig. 1. Distribution of I-GERQ-R scores across 4 time points.

The mean GERD scores decreased with age up to 12 months. The dotted line shows the cut-off of 16, indicating that the prevalence of GERD according to the I-GERQ-R definition also decreased with age. *P* values were calculated from comparison of means to the mean GERD score at week 6.

I-GERQ-R: revised Infant Gastroesophageal Reflux Questionnaire

[a] indicates *P*<0.001

Natural history of GERD

The natural history of GERD was analysed in a subset of 162 participants who had complete data at all 4 time points (Fig. 2). Seven of those with GERD at 6 weeks continued to have GERD at 3 months and only 1 infant with GERD at 3 months continued to have it at 6 months. One infant who had GERD at 6 weeks had no reported symptoms at months 3 and 6, but GERD symptoms were once again reported at 12 months. All other infants outgrew GERD by 12 months.

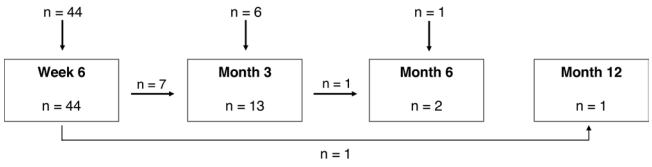

Fig. 2. Natural history of GERD.

Figure shows the longitudinal follow-up of infants diagnosed with GERD in the first year of life, in infants with complete data at all 4 time points (n=162). Vertical arrows indicate new cases while horizontal arrows indicate ongoing cases.

Risk factors for GERD

There were significant differences in GERD prevalence by ethnicity, whereby 48.7% (74/152) of infants born to Chinese mothers reported symptoms of GERD in the first year of life, compared to a significantly smaller 25.0% (11/44, *P*<0.01) of those born to mothers of other

ethnicities. Compared to Chinese infants, Malay infants had lower odds of GERD (Table 1).

Infants who were exclusively breastfed at 3 weeks of life had reduced odds of GERD in first year of life, but this did not differ between various modes of breast milk feeding (expressed breast milk feeding versus a combination of being fed at the breast and being fed expressed breast milk) (Table 1). While a higher number of formula feeds per day at 3 weeks of life was associated with increased odds of GERD during infancy in univariate analyses (Supplementary Table S2), this was no longer apparent after adjusting for confounders (Supplementary Table S3). No other risk factors were associated with GERD in any of the adjusted models.

We also observed an association between GERD and frequency of feed refusal when hungry. Increasing frequency of feed refusal was associated with higher total I-GERQ-R scores at each time point (Table 2). When pooling all time points, 26% of infants who never/rarely refused feeds during the first year of life had GERD, while 72.1% of those who has ever (sometimes/often/always) refused feeds also had GERD. These findings were similar across ethnic groups, with similar proportions of infants who had frequent feed refusals during infancy fulfilling GERD diagnosis in both the Chinese (37/48, 77.1%) and Malay (4/6, 66.7%) ethnic groups.

Parental perceptions: Causes of infant's GI symptoms

Symptom-weighted ranking identified excessive crying and regurgitation as the most important symptoms affecting infants with GERD–31.8% (27/85) and 32.9% (28/85) during the first year, respectively. Other symptoms including "gassiness" or "bloatedness", not eating enough and "wind" in the baby's stomach were also quoted as causes for concern.

Table 1. Multivariate logistic regression model for the association of ethnicity and infant feeding habits at 3 weeks of life with gastroesophageal reflux disease in the first year of life[a,b]

Model 1 (n=127)	**aOR (95% CI)**	***P* value**
Ethnicity		
Chinese	1.00	-
Malay	0.14 (0.03–0.63)	**0.01**
Indian	0.19 (0.02–2.03)	0.17
Mixed ethnicity	0.2 (0.04–1.09)	0.06
Expressed BM (frequency) at week 3	0.96 (0.85–1.09)	0.51
Exclusive breastfeeding at week 3	0.44 (0.19–0.98)	**0.05**
Breast milk (direct + expressed) at week 3	1.12 (0.47–2.66)	0.80
Model 2 (n=127)		
Ethnicity		
Chinese	1.00	-
Malay	0.14 (0.03–0.63)	**0.01**
Indian	0.19 (0.02–2.05)	0.17
Mixed ethnicity	0.20 (0.04–1.11)	0.07
Expressed BM (frequency) at week 3	0.96 (0.84–1.00)	0.57
Exclusive breastfeeding at week 3	0.43 (0.19–0.97)	**0.04**
Expressed BM at week 3	0.98 (0.29–3.31)	0.98

aOR: adjusted odds ratio; BM: breast milk

[a] All models adjusted for household income, maternal highest education level, multiparity, birthweight and gestational age.

[b] For each type of feeding, parents were asked to indicate the frequency of feed. Exclusive breastfeeding was defined as an affirmative response to the question, "Is your baby still breastfeeding?" AND an indicated frequency of direct breastfeeding, expressed breast milk or donor breast milk of >0 time per day AND frequency of formula use, cow's milk, other milk and solid intake indicated as 0 time per day. Information on the mode of breast milk feeding such as fed at the breast (direct), fed expressed breast milk (EBM), or a combination of being fed at the breast and being fed EBM, was also collected among infants who were breastfed at each time point.

Figures in bold are significant

Table 2. Association between frequency of feed refusal and gastroesophageal reflux disease (GERD) status at each time point

Frequency of feed refusal when hungry	No GERD no. (%)	GERD no. (%)	RR (95% CI)[a]	Mean GERD score (SD)	*P* value[b]
Week 6					
Never/rarely	180 (77.3)	53 (22.8)	1.0	11.76 (4.84)	
Sometimes/often/always	6 (30.0)	14 (70.0)	5.04 (2.81–7.26)	16.80 (4.95)	**<0.001**
Month 3					
Never/rarely	235 (95.9)	10 (4.1)	1.0	6.96 (3.98)	
Sometimes/often/always	18 (62.1)	11 (37.9)	7.45 (5.89–9.02)	14.41 (4.71)	**<0.001**
Month 6					
Never/rarely	267 (99.6)	1 (0.4)	1.0	4.37 (3.19)	
Sometimes/often/always	27 (79.4)	7 (20.6)	7.51 (6.31–8.71)	11.89 (4.43)	**<0.001**
Month 12					
Never/rarely	257 (100)	0	1.0	2.77 (2.53)	
Sometimes/often/always	13 (81.3)	3 (18.8)	6.11 (4.72–7.5)	8.88 (5.15)	**<0.001**

95% CI: 95% confidence interval; GERD: gastroesophageal reflux disease; RR: risk ratio; SD: standard deviation
[a] Linear regression analysis carried out with GERD score as a continuous variable
[b] *P* value obtained for both chi-square/Fisher's Exact test and linear regression were identical

A similar proportion of mothers of infants with (78.9%) and without GERD (73.0%) thought that too much wind in their child's stomach caused excessive crying (Fig. 3A). Likewise, 47.4% of parents of infants with GERD and 29.7% of parents of infants without GERD attributed this symptom to an "immaturity of child's GI system". There were no statistically significant differences in parental perceptions of symptom causality between infants with and without GERD.

A significantly larger percentage of parents of infants with GERD believed that their child's regurgitation was caused by "too much wind" (86.7%) ($P<0.01$) compared to parents of infants without GERD (34.3%) (Fig. 3B). Additionally, 47.6% of parents of infants with GERD and 45.7% of parents of infants without GERD attributed this symptom to an "immature GI system". Some parents also indicated other factors such as weaning to solids, excessive food consumption, or insufficient intake of fluids as potential causes.

Parental perceptions: Lifestyle interventions

At 6 weeks, 3 months and 6 months, all parents of infants with GERD had made at least one lifestyle change due to their child's excessive crying or regurgitation. The most common intervention implemented for excessive crying was repositioning the infant at an incline, followed by maternal dietary modifications (Fig. 4A). The dietary modifications commonly included elimination of spicy foods (26.3%), dairy (21.1%) and cold food or drinks (21.1%). Some mothers began taking supplements (10.5%), added probiotics (5.3%) or more vegetables (5.3%) to their diet. For parents of GERD infants, 36.8% reduced the volume of their child's feeds, compared to 18.8% of parents of non-GERD infants ($P=0.08$).

For infants with regurgitation as the primary troublesome GI symptom, all those with GERD were positioned at 30–45° incline during and after feeding, compared to 84.4% of infants without GERD (Fig. 4B). Feed volume reduction and maternal dietary modifications were the next most common interventions. Twenty percent of these mothers stopped consuming spicy food, and 13.3% cut down on dairy and citrus fruits.

Healthcare-seeking behaviours

Parents were most likely to consult a healthcare professional for their infants' GI symptoms in the earlier months of life: 19.2% of parents sought help at 6 weeks and again at 3 months, but only 6.7% did so at 6 months and 5.3% at 12 months. Parents of infants suffering from regurgitation (48.1%, 45.5%, 20.0% and 16.7% at 6 weeks, 3, 6 and 12 months, respectively) or who cried excessively (40.6%, 48.1%, 10% and 12.5% at 6 weeks, 3, 6 and 12 months, respectively) were consistently more likely to seek help than those suffering from other symptoms.

Fig. 3. Parental perceptions regarding the causes of their infant's troublesome gastrointestinal (GI) symptoms.

Common causes reported by mothers when their infant's GI symptoms were due to (A) excessive crying and (B) regurgitation. Other perceived causes included food allergies, being too "heaty" or too "cold", overfeeding and insufficient fluid consumption.

GERD: gastroesophageal reflux disease; GI: gastrointestinal

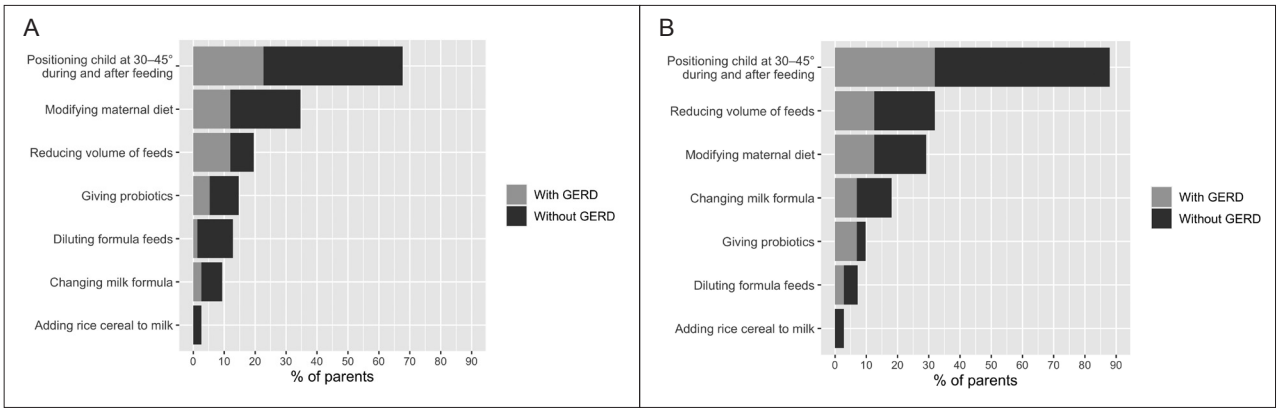

Fig. 4. Lifestyle interventions practised by parents of infants suffering from gastrointestinal (GI) symptoms.

Common lifestyle modifications made by parents where causes of infant's GI symptoms were due to (A) excessive crying and (B) regurgitation. The most common lifestyle change made was a change in the positioning of during and after feeding.

GERD: gastroesophageal reflux disease; GI: gastrointestinal

Fifteen mothers indicated that their baby had turned blue or purple and/or had stopped breathing while awake, or struggled to breathe, due to GERD at any time during the first year of life. Only 7 indicated that they sought medical attention for their child's feeding issues; however, it is unclear whether it was done for this particular indication.

Parents with higher household income were significantly less likely to seek advice at any time in the first year than those with a lower household income (odds ratio 0.78, 95% confidence interval [CI] 0.66–0.93). Maternal education level, multiparity and ethnicity were not associated with healthcare-seeking behaviour.

DISCUSSION

This study provides data on the epidemiology, risk factors, longitudinal course and social impact of GERD in an Asian paediatric population. There is currently a paucity of data on GERD prevalence in Asian infants and much of the published literature is based on adults or children in Western populations. Of the studies in Asian populations, the majority used surrogate indicators of GERD such as individual symptoms of regurgitation/reflux as outcome measures. This study utilised a robust, validated,[9,10] questionnaire-based tool, the I-GERQ-R, to evaluate not only the prevalence but also the natural history of GERD longitudinally across the first 12 months of life in Asian infants. We also identified common Asian parental perceptions of GERD symptoms, causality and behavioural modifications triggered by the infants' GI symptoms, as well as characterised family profiles that might explain health-seeking behaviours.

It is important to distinguish GERD from GER, which is a normal physiological process even in healthy infants in the first few months of life.[11] Immaturity of the oesophagogastric junction allows gastric contents to

move back up into the oesophagus but does not cause vomiting.[12] Infant GERD is characterised by reflux (due to transient lower oesophageal sphincter relaxation) in association with other symptoms and/or complications such as irritability, refusal to feed, failure to thrive and arching of the back,[11,13] as well as chronic cough, choking, wheezing and apnoea. In this study, the I-GERQ-R tool enabled us to distinguish GERD from GER, which other studies utilising single symptoms such as regurgitation were not able to.

The highest prevalence of GERD in our population was at age 6 weeks. The prevalence decreased rapidly with age and almost all infants outgrew GERD by 1 year. As most other studies did not use validated tools for GERD diagnosis, direct comparisons of prevalence across different populations are not possible. The prevalence of GERD was recently estimated at 26.9% (95% CI 20.1–33.7) in a meta-analysis of 4 studies comprising infants from birth to 3 years.[14] Other studies that reported regurgitation as the primary surrogate symptom for GERD estimated prevalence of 20–50%.[14,15]

A major difference in infant GERD between different ethnic groups is the variation in the age at peak prevalence. GERD prevalence peaked at 4 months in Western populations.[16] However, research on Japanese and Indonesian infants showed that peak prevalence of GER was at 1 month of age and prevalence consistently decreased with age until 12 months.[17] Similarly, Thai infants regurgitated most during the first 2 months.[18] Our data showed that the peak prevalence of infant GERD was at 6 weeks, which is consistent with other Asian populations.

Exclusively breastfed infants in this cohort had a reduced odds of GERD, but the mode of breast milk feeding did not appear to impact GERD risk. Some studies have, however, reported a protective effect of feeding at the breast against reflux.[19-22] In a prospective study in the US, any combination of formula feeding (bottled breast milk + formula feeding, formula feeding alone, or mixed breast milk + formula feeding) were found to be risk factors for reflux compared to feeding at the breast.[21] Turkish infants with regurgitation were also less likely to have been breastfed[19] while formula-fed Indonesian infants had an increased frequency of regurgitation and vomiting compared to those who were exclusively breastfed.[20] Formula feeds also differ from breast milk in milk content and hence digestibility, and are also associated with increased risks of bacterial contamination, all of which can increase the risk of reflux symptoms.[23] Additionally, infants exclusively breastfed may be able to self-regulate milk intake compared to formula-fed infants. Infant cues of satiety may be ignored or missed during bottle feeding, potentially resulting in overfeeding or larger volume of milk than is needed, leading to reflux.[24]

We found that infants with a positive response to the feed refusal question were more likely to fulfil GERD criteria. This implies that feed refusal may be a distinguishing feature that clinicians could use in screening for GERD compared to more subjective symptoms such as excessive crying, where the full I-GERQ-R questionnaire cannot be feasibly performed. Additionally, as there is currently little evidence to suggest genetic differences in basic pathophysiological mechanisms of GERD, we postulate that environmental, cultural or dietary factors play a role in symptom recognition/reporting by parents. This is suggested by the higher prevalence of GERD in Asians in the US compared to Asians living in East Asia.[25] Larger studies are needed to elucidate if there are indeed genetic factors linked to GERD pathophysiology.

Infant feeding practices in Singapore are influenced by tradition and social conditioning, and caregivers tend to seek advice from friends and family more often than from health professionals.[26] Maternal dietary modifications were common, and included the elimination of spicy foods, "cold" foods and drinks and "gas-producing" vegetables. Other changes made included massaging and applying of medicated oil to the infant's abdomen, actions thought to relieve gastrointestinal discomfort. The concept of "cold" or "heaty" foods, "wind", and "gas-producing" vegetables are common in complementary and alternative medicine practices such as traditional Chinese medicine, whereby a delicate balance of the yin and yang energies is essential for good health.[27] An imbalance in the yin-yang energy brought about by the consumption of associated foods, therefore, is thought to result in disease manifestations such as the GI symptoms reported here. Furthermore, maternal nutrition during lactation has been known to influence infant health, thus it is plausible that maternal diet and nutrition can also influence the quality of breast milk and therefore the symptoms of GERD in infants. However, further research in this field is required. While our findings are not surprising given that complementary and alternative medicine is a salient part of Asian culture, the study highlights the uniqueness and importance of understanding the cultural basis for parental perceptions, implementation of common non-pharmacological remedies, and health-seeking behaviours for infant GERD in other parts of the world.

There were several limitations in our study. The mothers in the S-PRESTO cohort were not fully representative of the general Singapore population—

72.6% completed a university education compared to 51% of general Singapore population in the same age category (females aged 25 to 39 years in 2014).[28] Although a majority of the respondents were mothers, data on whether respondents were the primary caregivers and time spent with infants in the first year of life were not collected and this may undermine the reporting of symptoms related to the child's feeding and GERD. Objective measures of GERD such as pH impedance studies were not performed due to their invasive nature. Self-reported symptoms may also misclassify disease outcomes. The I-GERQ-R questionnaire has also not been formally validated in a Singaporean/Asian population although it has been used extensively in other populations. However, as English is the primary language in Singapore and the majority of parents in this study were familiar with the terminology used in the I-GERQ-R, this would not likely impact the validity and applicability of the results.

CONCLUSION

The information on caregivers' perceptions and behaviours in response to their infants' GI symptoms can aid healthcare practitioners to develop better therapeutic approaches and provide culturally aligned education for parents and caregivers.[25] More can also be done by healthcare providers and society to support mothers who desire to continue breastfeeding for its numerous advantages, besides the reduction of distressing GERD symptoms. This approach may in turn improve maternal mental health and infant outcomes. Additionally, the use of the I-GERQ-R questionnaire, which has been validated for diagnosis of GERD,[9,10] minimises the need to conduct invasive testing for GERD diagnosis. Further well-designed and sufficiently powered studies in paediatric GERD are needed to aid the development of clinical management and infant feeding guidelines specific to the unique cultural background of each population.

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Conflict of interest

YS Chong, KM Godfrey and LP Shek are part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, and Danone. Godfrey and Shek have received reimbursement for speaking at conferences sponsored by companies selling nutritional products. The funders were not involved in the design and conduct of the study, data analysis and preparation of manuscript.

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