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14 **Children of Asian ethnicity in Australia have higher risk of food allergy and early onset**  
15 **eczema than those in Singapore**

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### 143 **Abstract**

144 **Background:**In Western countries, Asian children have higher food allergy  
145 risk than Caucasian children. The early life environmental exposures for this discrepancy are  
146 unclear. We aimed to compare prevalence of food allergy and associated risk factors between  
147 Asian children in Singapore and Australia.

148 **Methods:**We studied children in the Growing Up in Singapore Towards healthy Outcomes  
149 (GUSTO) birth cohort (n=878) and children of Asian ancestry in the HealthNuts cohort  
150 (n=314). Food allergy was defined as a positive SPT  $\geq 3$  mm to egg or peanut AND either a  
151 convincing history of IgE-mediated reaction at 18 months (GUSTO) or a positive oral food  
152 challenge at 14-18 months (HealthNuts). Eczema was defined as parent-reported doctor  
153 diagnosis.

154 **Results:** Food allergy prevalence was 1.1% in Singapore and 15.0% in Australia ( $p < 0.001$ ).  
155 Egg introduction was more often delayed ( $> 10$  months) in Singapore (63.5%) than  
156 Australia (16.3%;  $p < 0.001$ ). Prevalence of early onset eczema ( $< 6$  months) was lower in  
157 Singapore (8.4%) than Australia (30.5%) ( $p < 0.001$ ). Children with early onset eczema were  
158 more likely to have food allergy than those without eczema in Australia [aOR 5.11 (2.34-  
159 11.14);  $p < 0.001$ ] and Singapore [aOR 4.00 (0.62-25.8);  $p = 0.145$ ].

160 **Conclusions:** Among Asian children, prevalence of early onset eczema and food allergy was  
161 higher in Australia than Singapore. Further research with larger sample sizes and harmonized  
162 definitions of food allergy between cohorts is required to confirm and extend these  
163 findings. Research on environmental factors influencing eczema onset in Australia and  
164 Singapore may aid understanding of food allergy pathogenesis in different parts of the world.

### 165 **Key words:**

166 Asian children, eczema, food allergy, GUSTO, HealthNuts

167 **Abbreviations:**

168 GUSTO: Growing Up in Singapore Towards healthy Outcomes

169 ISAAC: International Study of Asthma and Allergies in Childhood

170 SACC: Standard Australian Classification of Countries

171 SPT: Skin Prick Test

172 OFC: Oral Food Challenge

173 **Introduction**

174 Food allergy rates are rising rapidly worldwide but this phenomenon seems to be  
175 observed mainly in Western populations<sup>1</sup> whereas food allergy prevalence in children living  
176 in Asia remains relatively low.<sup>2</sup>The prevalence of peanut allergy, for example, is as high as 1-  
177 3% in children in the USA, UK and Australia,<sup>3-5</sup> but is <1% in most Asian countries.<sup>2</sup>The  
178 Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study found that  
179 the prevalence of parent-reported peanut allergy was only 0.1-0.3% in children up to 4 years  
180 of age.<sup>6</sup> In contrast, the prevalence of peanut allergy in a longitudinal food allergy cohort in  
181 Melbourne, Australia (HealthNuts) was 3.1% at 1 year of age and 1.9% at 4 years of age.<sup>3</sup>In  
182 the same study, egg allergy prevalence was 9.5% and this dropped to 1.2% by age 4 years.

183 The combined effects of migration, ethnicity and country of birth appear to influence the  
184 burden of allergic diseases,<sup>7</sup> particularly in children of Asian ancestry living in Western  
185 countries. Previous work in the HealthNuts cohort has shown that Australian-born infants of  
186 Asian ancestry were more likely to be food allergic than Australian-born non-Asians. The  
187 prevalence of peanut allergy was 3 times higher in infants with at least one East Asian parent  
188 compared to those with two Australian-born parents.<sup>8</sup>Up to 50% of infants with two East  
189 Asian parents developed eczema and 25% had challenge-proven food allergy by age 1  
190 year.Paradoxically, the parents of these East Asian infants themselves had lower rates of  
191 allergic diseases compared with Australian-born parents.Further, in a separate study, children  
192 who had migrated postnatally from Asia to Australia had a lower risk of peanut allergy<sup>9</sup>,  
193 anyfood allergy and asthma compared to Australian-born non-Asian children.<sup>10</sup> Among those  
194 of Asian ethnicity, being born in Australia conferred significantly higher risks of food allergy  
195 [aOR 6.96(4.14 – 11.74); p<0.001], eczema [aOR 5.50 (3.50-8.66); p<0.001] and asthma  
196 [aOR 2.99 (2.12-4.22); p<0.001] than being born in Asia<sup>10</sup>.

197 The ethnic differences appear to extend to other allergic disorders as well. At age 6 years,  
198 children of Asian descent living in Australia had a higher prevalence of allergic rhinitis and  
199 aeroallergen sensitization compared with Caucasian children.<sup>11</sup>These observations suggest

200 that both genetic and early life environmental factors play a vital role in driving the  
201 development of allergies in individuals of Asian ancestry. However, no direct comparison of  
202 the prevalence and risk factors for food allergy between Asians living in different  
203 geographical locations has been performed before.

204 Using data from the GUSTO cohort in Singapore and the HealthNuts cohort in  
205 Australia, we compared the prevalence of food allergy and evaluated risk factors such as  
206 eczema, environmental exposures and dietary factors in modulating food allergy risk in Asian  
207 children living in Singapore and Australia.

## 208 **Methods**

### 209 **Singapore GUSTO cohort**

210 The GUSTO cohort is a population based birth cohort study in Singapore comprising  
211 extensive longitudinal assessments of mother-infant dyads from pregnancy and through  
212 childhood. The GUSTO study methodology has been previously described in detail.<sup>12</sup> Briefly,  
213 a total of 1247 women of Chinese, Malay and Indian ethnicity who were in their first  
214 trimester of pregnancy from the two major public obstetric hospitals in Singapore – the  
215 National University Hospital (NUH) and the KK Women’s and Children’s Hospital (KKH) –  
216 were included between June 2009 and September 2010.

217 Ethics approval was obtained from the Domain Specific Review Board of Singapore  
218 National Healthcare Group and the Centralised Institutional Review Board of SingHealth.  
219 Written informed consent was taken from all participants.

220 Parental demographic data inclusive of age, ethnicity, education level and socio-  
221 economic status as well as family history of atopy (self-reported diagnosis of asthma, allergic  
222 rhinitis or eczema in the mother, father or sibling) were captured using interviewer-  
223 administered questionnaires. Maternal dietary intake during pregnancy was captured using  
224 food diaries administered in the third trimester. Information on birth and delivery, child  
225 health, pet ownership, childcare attendance, feeding practices in early life and allergic  
226 outcomes were obtained from interviewer-administered questionnaires, including the  
227 modified ISAAC questionnaire<sup>13-15</sup> at 3-monthly time-points from birth until 18 months of age  
228 and 6-monthly thereafter. Skin prick tests (SPT) were offered to all children at age 18, 36 and  
229 60 months, while food reaction data was obtained via questionnaires at ages 6, 12, 18, 36, 48  
230 and 60 months.

## 231 **Australia HealthNuts cohort**

232 The HealthNuts study is a population-based longitudinal study of food allergy that  
233 recruited 11-15 month old children (mean age 12.7 months) recruited at community  
234 immunisation centres in Melbourne, Australia (N=5,276). The HealthNuts study  
235 methodology has previously been described in detail<sup>16</sup>. In summary, all children underwent  
236 skin prick testing to four common allergens (egg, peanut, sesame and either shrimp or cow's  
237 milk) at the immunisation centres. Children with a detectable wheal size  $\geq 1$  mm to any of the  
238 foods were invited to the HealthNuts clinic at the Royal Children's Hospital, Melbourne for  
239 an oral food challenge (OFC) to ascertain their food allergy status (generally between 14-18  
240 months of age). During the clinic visit, children underwent repeat SPT and a blood test to  
241 determine their food specific IgE levels. The children's mean age at the first clinic visit was  
242  $13.9 \pm 1.3$  months (standard deviation). OFCs were carried out using a pre-determined  
243 protocol described previously.<sup>17,18</sup> The following objective criteria were used to define a  
244 positive OFC: three or more concurrent, non-contact urticaria persisting for at least 5 minutes,  
245 perioral or periorbital angioedema, vomiting or evidence of circulatory or respiratory  
246 compromise, occurring within 2 hours of ingestion of a dose during food challenge. The food  
247 challenge was deemed negative if the child was able to complete the challenge with no  
248 reaction.<sup>18</sup>

249 Ethics approval was obtained from the Human Research Ethics Committee (HREC)  
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251 Department of Human Services (reference no. 10/07) as well as the Royal Children's  
252 Hospital HREC (reference no. 27047). Parents gave written consent for child's participation  
253 in the study.

## 254 **Definitions**

### 255 *Ethnicity Definitions*

256 *Asians in GUSTO* were made up of children born in Singapore whose parents and  
257 grandparents were of homogenous Chinese, Malay or Indian ethnicity, which are the  
258 three main ethnic groups in Singapore.

259 *Asians in HealthNuts* consisted of children born in Australia with both parents born in  
260 North East Asia region (China, Hong Kong, Japan, Taiwan, Macau, North Korea, South  
261 Korea), South East Asia region (Vietnam, Philippines, Singapore, Thailand, Indonesia,  
262 Malaysia, Cambodia, Laos) or South Asia region (India and Sri Lanka). These countries were

263 grouped based on the Standard Australian Classification of Countries (SACC) which were  
264 developed to be relevant to Australia's multicultural society for use in analysing Australian-  
265 based country of origin data<sup>19</sup>. Groups in the SACC comprise geographically proximate  
266 countries which have broadly similar social, cultural, economic and political characteristics.  
267 The parent's country of birth act as proxy for ancestry background in HealthNuts. It was  
268 shown previously that parent's country of birth information correlated well with genetically  
269 inferred ancestry in this cohort<sup>20</sup>. All analyses in the HealthNuts cohort were restricted to this  
270 Asian population.

### 271 ***Outcome Definitions – Food Allergy***

272 In GUSTO, food allergy was defined by a positive SPT of  $\geq 3$  mm to egg or peanut at  
273 18 months **AND** a convincing history of an IgE-mediated reaction upon exposure to egg or  
274 peanut.

275 In HealthNuts, food allergy was defined as a positive SPT  $\geq 3$  mm to egg or peanut at  
276 the clinic visit at 14-18 months of age **AND** a positive OFC to egg or peanut. Previous  
277 definitions using the HealthNuts data was based on a positive SPT  $\geq 2$  mm to relevant foods.  
278 This was modified in the current study in order to have a harmonised definition that is in line  
279 with GUSTO.

### 280 ***Exposure definitions***

281 We also used harmonised exposure definitions to ensure they are comparable between  
282 the two studies. Definitions for all exposure variables included in the analysis are  
283 summarized in Table S1. For eczema, the following definitions were used in each cohort:

284 In GUSTO, eczema was defined as a parent-reported doctor's diagnosis of eczema at  
285 any time point up until 18 months. A categorical variable was also created with the following  
286 categories: "No eczema, Eczema that started before 6 months" and "Eczema that started after  
287 6 months".

288 Similarly, in HealthNuts, eczema was defined as a parent-reported diagnosis of  
289 eczema based on an affirmative response to the question "Has your child ever been diagnosed  
290 with eczema?" In conjunction with responses to the question "Age when eczema was first  
291 diagnosed", a categorical variable with the following categories were created "No eczema",  
292 "Eczema that started before 6 months" and "Eczema that started after 6 months".

### 293 ***Statistical Analysis***

294 The prevalence of food allergy in each study was estimated as the observed  
295 proportion with 95% confidence intervals generated using the normal approximation to the  
296 binomial distribution.

297 Baseline characteristics of each study were reported and compared using chi-square  
298 tests. Student's t-test was carried out to compare continuous variables (e.g birthweight).

299 Adjusted logistic regression models were used to analyse the association between  
300 exposure variables and food allergy in each of the two Asian populations separately, to obtain  
301 odds ratios (OR) and 95% confidence intervals. For this, three sets of hypothesis-driven  
302 analyses were carried out:

- 303 i. Association between eczema and food allergy (adjusted for maternal history of self-  
304 reported atopy, child's sex and pet ownership)
- 305 ii. Association between household exposure to tobacco smoke and proxy markers  
306 of hygiene hypothesis (use of antibiotics, dog ownership, cat ownership, childcare  
307 attendance, any siblings and caesarean delivery) with food allergy (adjusted for  
308 maternal history of self-reported atopy and child's sex)
- 309 iii. Association between infant diet and food allergy (adjusted for child's sex, maternal  
310 history of atopy and child history of eczema)

311 Interaction analyses were carried out to assess whether the relationship between each  
312 potential risk factor and food allergy differed between the two cohorts. Regression models  
313 were fitted to the combined group of Singapore and Australian children, with product terms  
314 added to test for interactions between the study cohort and each risk factor. Models with and  
315 without interaction terms were compared using the likelihood ratio test.

316

317

## 318 **Results**

### 319 **Prevalence of food allergy**

320 The prevalence of food allergy among 18 month old Asian children in Singapore was  
321 1.1% (n=10/878) (95% CI 0.6 - 2.1%) compared to 15.0% (n=47/314) (95% CI 11.4-19.4%)  
322 in 14-18 month old Asian children in Australia (p<0.001).

### 323 **Demographics of Asian participants in each study cohort**

324 The demographics of participants in each study are shown in Table S2. In the  
325 Australian cohort this analysis was restricted to children with two Asian-born parents  
326 (n=314) whereas the Singapore cohort consisted of 878 Asian children (Table S2). More

327 Singapore children had siblings (58.2% vs 45.5%,  $p < 0.001$ ) while fewer mothers had  
328 completed tertiary education (34.1% vs 76.9%). Paternal history of allergy was more common  
329 in Australia.

### 330 **Environmental Exposures**

331 Maternal smoking during pregnancy and household exposure to tobacco smoke were  
332 more prevalent in Singapore (Table 1). Childcare attendance in the first 12 months of life was  
333 more common in Australia compared with Singapore ( $p < 0.001$ ). Among those attending  
334 childcare, a larger proportion of Singaporean children started childcare before 6 months  
335 whereas more Australian children started childcare after 6 months. Rates of pet ownership  
336 and use of antibiotics in infancy were similar between the two studies.

### 337 **Eczema**

338 **Error! Reference source not found.** Eczema diagnosis was more common in  
339 Australian children than Singaporean children. In particular, the percentage of children with  
340 early onset eczema (before 6 months) was higher in Australia at 30.5% compared to 8.4% in  
341 GUSTO,  $p < 0.001$ , while the percentage of children with later onset eczema was similar  
342 between the two cohorts (Table 1).

343 Of those with eczema, a higher proportion of Australian children (84.2%) required  
344 topical steroids compared to Singaporean children (61.9%),  $p = 0.001$ .

### 345 **Infant's Diet**

346 Delayed introduction of solids ( $> 6$  months) and egg into the infant's diet was more  
347 common in Singapore compared with Australia (Table 1). A significantly larger proportion  
348 of Singaporean children had not been introduced to egg by 12 months of age compared to only  
349 3.9% of Australian children. Peanut introduction was delayed in both cohorts, with only 10.6%  
350 of Singaporean children and 13.8% of Australian children introducing peanut before 10  
351 months of age. By age 12 months, the majority of Singaporean children and Australian  
352 children had still not been introduced to peanut.

353 We investigated whether the timing of introduction of food in the two cohorts differed  
354 by eczema status, since pre-existing eczema can influence food introduction practices.  
355 Regardless of eczema status, a higher proportion of Singapore children were introduced to  
356 egg after 10 months compared to Australian children (Table S3). Among those with eczema,

357 17.9% of Singapore children were introduced to egg between 10 – 12 months and 59.0% still  
358 had not been introduced to egg by age 12 months. This is compared to in Australia  
359 where 14.4% had been introduced between 10-12 months and 7.2% were still not introduced  
360 by 12 months ( $p < 0.001$  for both). For peanut introduction, 23.8% of Singapore children with  
361 eczema were introduced to peanut between 10-12 months of age compared to only 5.8% of  
362 Australian children with eczema ( $p = 0.022$ ). However, the percentage of children not  
363 introduced to peanut by 12 months was higher in Australia compared to Singapore, regardless  
364 of eczema status.

365 When we examined within group comparisons, we found that among Australian  
366 children, a higher percentage of children with eczema (85.4%) were not introduced to peanut  
367 by 12 months compared to those without eczema (76.0%);  $p = 0.031$  (Table S4). In the  
368 Singapore cohort, there was no difference in proportion of children introduced to peanut by 12  
369 months stratified by eczema status.

370 In both Singapore and Australia, more children with eczema had delayed egg  
371 introduction compared to those without eczema. 7.2% of Australian children with eczema  
372 were still not introduced to egg by 12 months compared to only 1.8% who had no eczema  
373 ( $p = 0.021$ ). Similarly in Singapore, 59% of children with eczema were not introduced to egg  
374 while 43.8% with no eczema were already introduced to egg by 12 months ( $p < 0.001$ ).

375 Additionally, duration of breastfeeding was shorter among Singapore children. 87.5%  
376 of Singaporean children were already on mixed feeding in the first 6 months of life compared  
377 to 63% in Australia (Table 1).

## 378 **Maternal diet**

379 Maternal dietary practices during pregnancy varied between the two studies for all  
380 investigated foods (Table 1). Fewer mothers of Singaporean children consumed nuts, peanuts,  
381 shellfish, egg and soy during pregnancy compared to mothers of Australian children (all  
382  $p < 0.001$ ).

## 383 **Association between food allergy and potential risk factors**

384 In the unadjusted model, family history of allergic disease, particularly maternal and  
385 paternal history, were associated with an increased risk of food allergy in the Australian  
386 cohort but only maternal history was associated with food allergy in the Singapore cohort  
387 (Table 2). We therefore, adjusted for maternal atopic history in our model when examining

388 the association between eczema and food allergy risk. Early onset eczema was associated  
389 with an increased risk of food allergy in both Australia and Singapore (Table 3). Children in  
390 Australia with early onset eczema (<6 months) were 5 times more likely to also have food  
391 allergy compared to those with later onset. The magnitude of association was similar for  
392 GUSTO but lacked precision and included the null [aOR 4.00 (0.62-25.8); p=0.145]. However,  
393 of those with early onset eczema, only 5.7% of Singaporean children also had food allergy  
394 compared to 32.6% of Australian children (p<0.001).

395 Eczema with use of topical steroids were strongly associated with an increased risk of  
396 food allergy in the Australian cohort (p<0.001)(Table S6). There was weak evidence of a  
397 similar association between eczema with use of topical steroids and food allergy in the  
398 Singapore cohort (p=0.074). Conversely, children in Singapore with eczema not requiring use  
399 of topical steroids had greater odds of developing food allergy compared to those without  
400 eczema (p=0.021). Weak evidence for a similar association was observed in the Australian  
401 cohort (p=0.075) (Table S6). When comparing the use of topical steroids among those with  
402 eczema, there was no evidence of an association between eczema and steroid use with risk of  
403 food allergy in both cohorts (data not shown).

404  
405 In the adjusted models assessing environmental factors and infant diet, there was no  
406 evidence of an association between any of the factors examined and food allergy (Table  
407 3). There was also no strong evidence that the association between any of the examined  
408 factors and food allergy differed between cohorts (all interaction P>0.05), apart from paternal  
409 history of atopy and type of milk feeding (Table S5). In the Singapore cohort, those who  
410 were fully breastfed had increased odds of food allergy compared to those who received  
411 mixed feeding [OR 9.89 (2.59-37.87)].

412

## 413 **Discussion**

414 This is the first study directly comparing the prevalence of food allergy and identifying  
415 whether known risk factors for food allergy are different in Asian children living in two  
416 different geographical locations, utilizing combined data from two cohorts – HealthNuts  
417 (Australia) and GUSTO (Singapore). Despite the ethnic similarities between both cohorts, the  
418 prevalence of food allergy in Singapore (1.1%) was substantially lower than in Asians living  
419 in Australia (15%) ( $p < 0.001$ ). Prevalence of eczema was also lower in Singapore. We also  
420 showed that early onset eczema was associated with food allergy in Australia; the magnitude  
421 of association was similar in Singapore but lacked precision with 95% CIs including the null.  
422 These findings suggest that early life environmental factors and gene-environment  
423 interactions are likely to play a significant role in modulating food allergy development in  
424 ethnic Asians.

425 We found that the prevalence of several risk factors and environmental exposures differed  
426 between the cohorts, namely higher maternal and household exposure to tobacco  
427 smoke and larger families in Singapore as well as a higher proportion of children with delayed  
428 introduction of solids and egg and shorter duration of exclusive breastfeeding. More Asian  
429 children in Australia had a family history of atopy, more mothers reported intake of  
430 allergenic foods during pregnancy and more mothers had completed tertiary education. The  
431 differences in these factors may be due to cultural and societal influences, as well as maternal  
432 educational background and awareness of prevailing infant feeding guidelines. Despite the  
433 observed differences, these risk factors were not strongly associated with food allergy in the  
434 respective cohorts. There was also little evidence that the relationship between individual risk  
435 factors and food allergy differed between the two cohorts.

436 Previous allergy guidelines internationally recommended avoidance of allergenic foods  
437 during pregnancy and in early life for the prevention of food allergy in infants.<sup>21,22</sup> However,  
438 as the evidence base for this recommendation was weak, this guideline was later  
439 revoked.<sup>23</sup> More recently, clinical trials, systematic reviews and meta-analyses have shown  
440 early introduction of peanut and egg into the infant diet to be protective against food allergy  
441 <sup>24,25</sup>. Many mothers in Singapore, however, still do not routinely consume allergenic foods  
442 during pregnancy and more mothers in Singapore also delayed the introduction of eggs into  
443 their children's diets compared to Asian mothers in Australia. Peanut introduction mostly  
444 occurred after 12 months in both cohorts. There was no evidence of an association between

445 timing of egg or peanut introduction in the Asian population in Singapore or Australia in  
446 adjusted models, perhaps due to limited power to detect associations. However, we have  
447 previously shown that Singaporean children have a low prevalence of food allergy despite  
448 delayed introduction of allergenic food<sup>6</sup>. Collectively, timing of introduction of allergenic  
449 foods into the infant diet is therefore unlikely to explain the higher prevalence of food allergy  
450 among Asian children in Australia. It may also be that early introduction of certain foods is  
451 beneficial only in groups at high risk of developing food allergy and given that the prevalence  
452 of allergy was generally lower in Singapore, the delay in food introduction seems unlikely  
453 to contribute a detrimental effect on the development of food allergy.

454 We found a much higher prevalence of early onset eczema in Australia, while the  
455 association between early onset eczema and food allergy was similar in Australian and  
456 Singaporean children. The strong association between early onset eczema and food allergy is  
457 consistent with other cohort and mechanistic studies which implicate epicutaneous  
458 sensitization to food allergens through an impaired skin barrier as the primary trigger driving  
459 the development of food allergy.<sup>26-28</sup> Notably, the prevalence of early onset eczema with  
460 increased severity was also higher in Australian-born Asian children than in children in  
461 Singapore. However, guidelines for the management of eczema and use of topical steroids are  
462 similar in the two countries. Use of moisturisers are recommended regardless of severity of  
463 eczema and topical steroids are recommended in the presence of eczema flares. It is possible  
464 that parental attitudes to treatment may differ between these two populations, but parents  
465 from both countries typically do seek medical attention for eczema that is severe and not  
466 responding to moisturizers alone. It is thus likely that the difference in the use of topical  
467 steroids between the two studies reflects a difference in eczema severity of infants in the two  
468 countries. Early risk factors for eczema may also differ in Australia compared to Singapore.

469 Predisposition to eczema among Asians may be compounded by the weaker skin barrier  
470 of the East Asian skin, compared to Caucasians and African Americans<sup>29</sup>. A relatively weaker  
471 skin barrier of East Asians living in Australia may be further compromised by exposure to  
472 environmental risk factors such as a dry climate in Melbourne, further aggravating severity of  
473 eczema. The prevalence of eczema has previously been shown to be inversely related to  
474 relative ambient humidity in US children.<sup>30</sup> Other studies have shown that low humidity and  
475 low temperature decrease skin barrier function, making the skin more reactive towards  
476 irritants and allergens<sup>31</sup>. Therefore, an environment with high humidity, such as that in  
477 Singapore, may moderate the adverse consequences of eczema on epicutaneous food allergen

478 sensitization, contributing to the lower prevalence of eczema and food allergy observed  
479 compared to that in Australia.

480 A combination of factors, such as environmental food allergen exposures and eczema  
481 severity, may also modulate a child's risk of developing food allergy. We have shown here  
482 that maternal allergen consumption during pregnancy was significantly lower in Singapore.  
483 This may in turn be a surrogate indicator of household allergen consumption, which has been  
484 linked with increased risks of allergen sensitization in high-risk children with eczema, in a  
485 series of studies by Brough et al.<sup>32-35</sup> Exposure to airborne peanut protein was associated with  
486 peanut sensitization and peanut allergy in children with eczema. It could thus be speculated  
487 that a combination of lower household food allergen exposures in the homes of children in  
488 Singapore, along with a lower prevalence of eczema compared to Asian children in Australia,  
489 could contribute to the lower prevalence of food allergy in the former. In this study, we were  
490 not able to test this hypothesis as environmental allergen exposures, including household  
491 consumption of peanut or/and egg were not directly measured in both cohorts, but this is an  
492 important research question to be addressed in future studies. Other factors such as vitamin D  
493 levels and childhood vaccinations schedules, which have been shown to influence food allergy  
494 risk, were also not directly measured in this study. However, we speculate that differential  
495 effect of these factors between the two countries could contribute to the difference in  
496 prevalence observed.

497 Data obtained from the World Health Organisation (WHO) showed a stark difference in  
498 UVR exposure between Singapore and Melbourne. In any given year, Singapore's UVR is in  
499 the extreme high range (UV index 10-13) throughout the year whereas Melbourne's UVR  
500 fluctuates according to the different seasons, (UV index 2 in winter and 9 in summer)<sup>36</sup>. A  
501 lower UV-B exposure during fall and winter in Australia, along with reduced vitamin D  
502 synthesis, might play a role in the pathogenesis of food allergy.<sup>38</sup> In addition, childhood  
503 vaccinations can exert an important immunologic effect on the infant's immune  
504 system. Tuberculosis is endemic in Singapore, thus the Bacille-Calmette-Guerin (BCG)  
505 vaccine is part of the compulsory immunization schedule and is routinely given to all infants  
506 at birth. It is, however, not compulsory in Australia, where the incidence of tuberculosis is  
507 low. As a potent immune modulator, there has been much interest in the role of the BCG  
508 vaccine as a primary preventative strategy against childhood atopic disorders.<sup>39</sup> Furthermore,  
509 perturbations in the gut microbiome have also been linked to food allergy. There was a  
510 significant reduction in biodiversity of gut microbiota in self-reported food allergic adults in

511 the Human Gut Project.<sup>40</sup>Gut microbiota comparisons were however not possible in this  
512 study and remains a research gap that could be filled in future inter-geographic studies.

513 A limitation of this study is the difference in food allergy definitions between the two  
514 cohorts. Food allergy in the Singapore cohort was defined as a parental report of a suggestive  
515 history of reaction to the food with a positive SPT, while in the Australia cohort, it was  
516 defined as a positive OFC. However, self-reported prevalence tends to overestimate the true  
517 prevalence, thus the true prevalence of food allergy may be even lower in Singaporean  
518 children, which would further increase the magnitude of difference between the two cohorts  
519 rather than nullifying it. The low food allergy prevalence in Singaporean children is also  
520 consistent with previous published studies.<sup>42,43</sup>Furthermore, the magnitude of differences in  
521 sensitisation to egg and peanut (based on SPT) between the two studies is consistent with the  
522 differences in food allergy prevalence. Additionally, eczema definition and eczema severity in  
523 both cohorts was not based on an objective measure or a validated severity score, but instead  
524 on parent-reported doctor diagnosis and topical steroid use as a proxy measure obtained from  
525 questionnaires. The analysis of risk factors for food allergy in the individual cohorts has  
526 limited statistical power due to the relatively small sample size of the Asian population in the  
527 Australian cohort study and small number of food allergic subjects in Singapore cohort study.  
528 We may be insufficiently powered to detect an association for some of the key  
529 epidemiological risk factors such as that with topical steroids use as the Singapore cohort  
530 were made up of infants with predominantly mild eczema and few severe cases.

531 Despite these limitations, the GUSTO and HealthNuts cohorts are two of the largest,  
532 well-phenotyped and comprehensive population-based childhood cohorts in the Asia Pacific  
533 region, which are unselected for allergy risk and have been shown to be reflective of the  
534 characteristics of the general population<sup>16</sup>. This is also the first inter-geographical comparison  
535 of food allergy and its risk factors in Asian children residing in two different geographical  
536 locations. The statistical comparisons made possible through raw data sharing between the  
537 cohorts is also unparalleled. These findings highlight the children of East Asian-born parents  
538 living in Western countries as a high-risk allergic group. This group of children therefore  
539 might benefit from more frequent monitoring clinically. These findings are also important  
540 clinically with regards to targeted implementation of nutritional strategies as a prevention and  
541 management strategy.

## 542 **Conclusion**

543 The prevalence of food allergy and early onset eczema is much higher in Australian  
 544 children of Asian ancestry compared to Asian children in Singapore. Genetically predisposed  
 545 children of Asian ancestry may have an increased risk of food allergy upon exposure to  
 546 environmental risk factors. Eczema appears to be more severe in Australia, whereas the high  
 547 humidity in Singapore may abrogate the impact of skin barrier deficits on epicutaneous food  
 548 allergen sensitization and food allergy, contributing to the lower prevalence of food allergy in  
 549 Singapore. This calls into question the role of epigenetics and other yet to be identified risk  
 550 factors such as diet, microbiome and meteorological influences.

551

552 **Table 1** Comparison of hygiene hypothesis-associated variables, eczema status, infant and  
 553 maternal dietary intake between Australia (N=314) and Singapore (N=878).

| <b>Exposure</b>                                | <b>Australia<br/>N (%)</b> | <b>Singapore<br/>N (%)</b> | <b>P-value*</b>   |
|--|----------------------------|----------------------------|-------------------|
| <b>Hygiene hypothesis variables</b>            |                            |                            |                   |
| <b>Maternal smoking during pregnancy</b>       | 1 (0.3)                    | 21 (2.4)                   | <b>0.018</b>      |
| <b>Household exposure to tobacco smoke</b>     | 62 (19.8)                  | 276 (38.2)                 | <b>&lt; 0.001</b> |
| <b>Age started childcare</b>                   |                            |                            |                   |
| None (ref)                                     | 254 (81.7)                 | 651 (90.4)                 |                   |
| < 6 months                                     | 11 (3.5)                   | 44 (6.1)                   |                   |
| ≥ 6 months                                     | 46 (14.8)                  | 25 (3.5)                   | <b>&lt; 0.001</b> |
| <b>Cat ownership</b>                           | 10 (3.2)                   | 26 (3.1)                   | 0.956             |
| <b>Dog ownership</b>                           | 24 (7.6)                   | 39 (5.5)                   | 0.176             |
| <b>Infant antibiotic use (ever)</b>            | 124 (40.9)                 | 351 (45.9)                 | 0.137             |
| <b>Eczema</b>                                  |                            |                            |                   |
| <b>Infant eczema</b>                           |                            |                            |                   |
| None (ref)                                     | 168 (59.6)                 | 691 (83.2)                 |                   |
| < 6 months                                     | 86 (30.5)                  | 70 (8.4)                   | <b>&lt; 0.001</b> |
| ≥ 6 months                                     | 28 (9.9)                   | 70 (8.4)                   | <b>0.036</b>      |
| <b>Use of topical steroids to treat eczema</b> |                            |                            |                   |
| No eczema (ref)                                | 168 (67.2)                 | 635 (85.8)                 |                   |
| Eczema + steroids                              | 69 (27.6)                  | 65 (8.8)                   | <b>&lt; 0.001</b> |
| Eczema + no steroids                           | 13 (5.2)                   | 40 (5.4)                   | 0.533             |
| <b>Infant diet</b>                             |                            |                            |                   |

| <b>Exposure</b>   | <b>Australia<br/>N (%)</b> | <b>Singapore<br/>N (%)</b> | <b>P-value*</b>   |
|---|----------------------------|----------------------------|-------------------|
| <b>Age at solid introduction</b>                          |                            |                            |                   |
| ≤ 6 months  | 273 (91.6)                 | 664 (84.1)                 |                   |
| > 6 months  | 25 (8.4)                   | 126 (16.0)                 | <b>0.001</b>      |
| <b>Age at egg introduction</b>                            |                            |                            |                   |
| ≤ 10 months   | 257 (83.7)                 | 295 (36.5)                 |                   |
| > 10 months   | 38 (12.4)                  | 140 (17.3)                 | <b>&lt;0.001</b>  |
| Not yet given by 12 months                                | 12 (3.9)                   | 373 (46.2)                 | <b>&lt;0.001</b>  |
| <b>Age at peanut introduction</b>                         |                            |                            |                   |
| ≤ 10 months   | 40 (13.8)                  | 82 (10.6)                  |                   |
| 10-12 months  | 18 (6.2)                   | 177 (22.9)                 | <b>&lt;0.001</b>  |
| Not yet given by 12 months                                | 232 (80.0)                 | 516 (66.6)                 | 0.696             |
| <b>Type of milk feeding in the first 6 months of life</b> |                            |                            |                   |
| Mixed feeding   | 194 (63.0)                 | 710 (87.6)                 |                   |
| Fully formula fed   | 12 (3.9)                   | 40 (4.9)                   | 0.783             |
| Fully breastfed   | 102 (33.1)                 | 61 (7.5)                   | <b>&lt; 0.001</b> |
| <b>Duration of breastfeeding</b>                          |                            |                            |                   |
| < 1 month   | 21 (6.9)                   | 208 (24.6)                 | <b>&lt; 0.001</b> |
| 1 - 2 months  | 25 (8.2)                   | 157 (18.6)                 | <b>&lt; 0.001</b> |
| 3 - 5 months  | 56 (18.4)                  | 149 (17.6)                 | <b>0.004</b>      |
| 6-11 months   | 82 (27.0)                  | 151(17.9)                  | 0.269             |
| ≥ 12 months   | 120 (39.5)                 | 181(21.4)                  |                   |
| <b>Maternal diet during pregnancy</b>                     |                            |                            |                   |
| <b>Any peanut consumption</b>                             | 244 (85.6)                 | 121 (14.0)                 | <b>&lt; 0.001</b> |
| <b>Any egg consumption</b>                                | 277 (94.5)                 | 486 (56.4)                 | <b>&lt; 0.001</b> |
| <b>Any tree nutconsumption</b>                            | 215 (83.0)                 | 67 (7.8)                   | <b>&lt; 0.001</b> |
| <b>Any shellfish/crustacean consumption</b>               | 189 (69.2)                 | 256 (29.7)                 | <b>&lt; 0.001</b> |
| <b>Any soy consumption</b>                                | 243 (87.4)                 | 343 (39.8)                 | <b>&lt; 0.001</b> |

554 \*For variables with more than 2 categories, P-values shown are pairwise P-values obtained  
555 from comparison of the relevant category against reference category.

556 **Table 2** Univariate analyses of key associations ( $p < 0.05$ ) between environmental exposure and food allergy in Australia and Singapore

|   | Australia (N=314)          |                        | Singapore (N=878)          |                        | Australia (N=314) |                  | Singapore (N=878) |              | P interaction |
|---|----------------------------|------------------------|----------------------------|------------------------|-------------------|------------------|-------------------|--------------|---------------|
|   | Non Food-Allergic<br>N (%) | Food Allergic<br>N (%) | Non Food-Allergic<br>N (%) | Food Allergic<br>N (%) | OR (95% CI)       | P-value          | OR (95% CI)       | P-value      |               |
| <b>Demographics and environmental factors</b> |                            |                        |                            |                        |                   |                  |                   |              |               |
| <b>Gender</b>                                 |                            |                        |                            |                        |                   |                  |                   |              |               |
| Male  | 134 (51)                   | 35 (74.5)              | 451 (52)                   | 7 (70)                 | 1                 | -                | 1                 | -            | -             |
| Female  | 129 (49)                   | 12 (25.5)              | 417 (48)                   | 3 (30)                 | 0.36 (0.18-0.72)  | <b>0.004</b>     | 0.46 (0.12-1.80)  | 0.267        | 0.735         |
| <b>Cat Ownership</b>                          |                            |                        |                            |                        |                   |                  |                   |              |               |
| No  | 261 (97.8)                 | 43 (91.5)              | 797 (96.8)                 | 10 (100)               | 1                 | -                | 1                 | -            | -             |
| Yes   | 6 (2.2)                    | 4 (8.5)                | 26 (3.2)                   | 0 (0)                  | 4.04 (1.1-14.93)  | <b>0.036</b>     | NA                | NA           | NA            |
| <b>Family and personal history of atopy</b>   |                            |                        |                            |                        |                   |                  |                   |              |               |
| <b>Paternal Atopy</b>                         |                            |                        |                            |                        |                   |                  |                   |              |               |
| No  | 184 (68.9)                 | 18 (38.3)              | 612 (71.7)                 | 8 (80)                 | 1                 | -                | 1                 | -            | -             |
| Yes   | 83 (31.1)                  | 29 (61.7)              | 242 (28.3)                 | 2 (20)                 | 3.57 (1.88-6.79)  | <b>&lt;0.001</b> | 0.63 (0.13-3.00)  | 0.564        | <b>0.044</b>  |
| <b>Maternal Atopy</b>                         |                            |                        |                            |                        |                   |                  |                   |              |               |
| No  | 200 (74.9)                 | 24 (51.1)              | 601 (70.4)                 | 3 (30.0)               | 1                 | -                | 1                 | -            | -             |
| Yes   | 67 (25.1)                  | 23 (48.9)              | 253 (29.6)                 | 7 (70.0)               | 2.86 (1.52-5.40)  | <b>0.001</b>     | 5.54 (1.42-21.6)  | <b>0.014</b> | 0.388         |
| <b>Family History</b>                         |                            |                        |                            |                        |                   |                  |                   |              |               |

|  | Australia (N=314)              |                           | Singapore (N=878)              |                           | Australia (N=314) |                  | Singapore (N=878)  |              |                  |
|--|--------------------------------|---------------------------|--------------------------------|---------------------------|-------------------|------------------|--------------------|--------------|------------------|
|  | Non Food-<br>Allergic<br>N (%) | Food<br>Allergic<br>N (%) | Non Food-<br>Allergic<br>N (%) | Food<br>Allergic<br>N (%) | OR (95% CI)       | P-<br>value      | OR (95% CI)        | P-value      | P<br>interaction |
| <b>Atopy</b>                             |                                |                           |                                |                           |                   |                  |                    |              |                  |
| No                                       | 129 (48.3)                     | 11 (23.4)                 | 387 (45.2)                     | 2 (20)                    | 1                 | -                | 1                  | -            | -                |
| Yes                                      | 138 (51.7)                     | 36 (76.6)                 | 469 (54.8)                     | 8 (80)                    | 3.06 (1.49-6.26)  | <b>0.002</b>     | 3.30 (0.70-15.6)   | 0.132        | 0.931            |
| <b>Eczema Diagnosis</b>                  |                                |                           |                                |                           |                   |                  |                    |              |                  |
| No eczema                                | 155 (92.3)                     | 13 (7.7)                  | 687 (99.4)                     | 4 (0.6)                   | 1                 | -                | 1                  | -            | -                |
| Before 6 months                          | 58 (67.4)                      | 28 (32.6)                 | 66 (94.3)                      | 4 (5.7)                   | 5.76 (2.79-11.87) | <b>&lt;0.001</b> | 10.41 (2.54-42.58) | <b>0.001</b> | 0.463            |
| After 6 months                           | 23 (82.1)                      | 5 (17.9)                  | 68 (97.1)                      | 2 (2.9)                   | 2.59 (0.85-7.95)  | 0.096            | 5.05 (0.91-28.09)  | 0.064        | 0.523            |
| <b>Eczema diagnosis with steroid use</b> |                                |                           |                                |                           |                   |                  |                    |              |                  |
| No eczema                                | 155 (92.3)                     | 13 (7.7)                  | 632 (99.5)                     | 3 (0.5)                   | 1                 | -                | 1                  | -            | -                |
| Eczema + steroids                        | 45 (65.2)                      | 24 (34.8)                 | 62 (95.4)                      | 3 (4.6)                   | 6.36 (3.00-13.49) | <b>&lt;0.001</b> | 10.19 (2.01-51.58) | <b>0.005</b> | 0.605            |
| Eczema + no steroids                     | 10 (76.9)                      | 3 (23.1)                  | 37 (92.5)                      | 3 (7.5)                   | 3.58 (0.87-14.63) | 0.076            | 17.08 (3.33-87.55) | <b>0.001</b> | 0.156            |
| <b>Infant Diet</b>                       |                                |                           |                                |                           |                   |                  |                    |              |                  |
| <b>Type of milk feeding</b>              |                                |                           |                                |                           |                   |                  |                    |              |                  |
| Mixed feeding                            | 165 (63)                       | 29 (63)                   | 705 (87.9)                     | 5 (55.6)                  | 1                 | -                | 1                  | -            | -                |

|                                       | Australia (N=314)              |                           | Singapore (N=878)              |                           | Australia (N=314) |              | Singapore (N=878) |              |                  |
|---------------------------------------|--------------------------------|---------------------------|--------------------------------|---------------------------|-------------------|--------------|-------------------|--------------|------------------|
|                                       | Non Food-<br>Allergic<br>N (%) | Food<br>Allergic<br>N (%) | Non Food-<br>Allergic<br>N (%) | Food<br>Allergic<br>N (%) | OR (95% CI)       | P-<br>value  | OR (95% CI)       | P-value      | P<br>interaction |
| Fully formula feed                    | 9 (3.4)                        | 3 (6.5)                   | 40 (5.0)                       | 0 (0)                     | 1.9 (0.48-7.43)   | 0.358        | NA                | NA           | NA               |
| Fully breastfed                       | 88 (33.6)                      | 14 (30.4)                 | 57 (7.1)                       | 4 (44.4)                  | 0.91 (0.45-1.8)   | 0.777        | 9.89 (2.59-37.87) | <b>0.001</b> | <b>0.002</b>     |
| <b>Maternal Diet during pregnancy</b> |                                |                           |                                |                           |                   |              |                   |              |                  |
| <b>Egg consumption</b>                |                                |                           |                                |                           |                   |              |                   |              |                  |
| No                                    | 10 (4)                         | 6 (13.6)                  | 370 (43.4)                     | 6 (66.7)                  | 1                 | -            | 1                 | -            | -                |
| Yes                                   | 239 (96)                       | 38 (86.4)                 | 483 (56.6)                     | 3 (33.3)                  | 0.26 (0.09-0.77)  | <b>0.015</b> | 0.38 (0.10-1.54)  | 0.177        | 0.681            |
| <b>Soy consumption</b>                |                                |                           |                                |                           |                   |              |                   |              |                  |
| No                                    | 25 (10.5)                      | 10 (24.4)                 | 514 (60.3)                     | 5 (55.6)                  | 1                 | -            | 1                 | -            | -                |
| Yes                                   | 212 (89.5)                     | 31 (75.6)                 | 339 (39.7)                     | 4 (44.4)                  | 0.37 (0.16-0.83)  | <b>0.017</b> | 1.21 (0.32-4.55)  | 0.775        | 0.131            |

557 NA- not applicable. Where no children fall into one particular group of a variable (n=0), ORs were not able to be obtained and rows are  
558 indicated as NA.

559 **Table 3** Adjusted models for the risk factors of food allergy in Australia and Singapore.

|                                    | Australia (n=278)   |                | Singapore (n=666)   |                | P<br>interaction |
|------------------------------------|---------------------|----------------|---------------------|----------------|------------------|
| <b>Model 1<sup>†</sup>: Eczema</b> | <b>aOR (95% CI)</b> | <b>P-value</b> | <b>aOR (95% CI)</b> | <b>P-value</b> |                  |
| No eczema                          | 1                   | -              | 1                   | -              | -                |
| < 6 months                         | 5.11 (2.34-11.14)   | <0.001         | 4.00 (0.62-25.8)    | 0.145          | 0.920            |
| ≥ 6 months                         | 2.34 (0.75-7.34)    | 0.145          | 4.16 (0.65-26.49)   | 0.132          | 0.412            |

aOR – adjusted odds ratio. <sup>†</sup>Adjusted for maternal history of atopy, child’s sex and pet ownership.

|  | Australia (n=294)   |                | Singapore (n=622)   |                | P<br>interaction |
|--|---------------------|----------------|---------------------|----------------|------------------|
| <b>Model 2<sup>‡</sup>: Hygiene hypothesis</b> | <b>aOR (95% CI)</b> | <b>P-value</b> | <b>aOR (95% CI)</b> | <b>P-value</b> |                  |
| <b>Use of antibiotics</b>                      | 1.27 (0.64-2.53)    | 0.497          | 1.64 (0.35-7.78)    | 0.532          | 0.857            |
| <b>Dog ownership</b>                           | 0.68 (0.17-2.69)    | 0.579          | 1.98 (0.21-18.34)   | 0.547          | 0.294            |
| <b>Cat ownership</b>                           | 4.87 (0.95-24.95)   | 0.058          | NA                  | NA             | NA               |
| <b>Childcare attendance</b>                    | 0.87 (0.34-2.23)    | 0.772          | 1.07 (0.12-9.68)    | 0.955          | 0.729            |
| <b>Any siblings</b>                            | 1.50 (0.75-3)       | 0.251          | 1.36 (0.28-6.58)    | 0.699          | 0.736            |
| <b>Household exposure to tobacco smoke</b>     | 1.15 (0.49-2.71)    | 0.745          | 0.21 (0.02-1.83)    | 0.157          | 0.178            |
| <b>Caesarean delivery</b>                      | 1.04 (0.50-2.16)    | 0.911          | 0.45 (0.05-3.98)    | 0.473          | 0.486            |

aOR – adjusted odds ratio  
<sup>‡</sup>model adjusted for sex and maternal history of atopy

|                                  | Australia (n=238)   |                | Singapore (n=204) <sup>§</sup> |                | P<br>interaction |
|----------------------------------|---------------------|----------------|--------------------------------|----------------|------------------|
| <b>Model 3<sup>¶</sup>: Diet</b> | <b>aOR (95% CI)</b> | <b>P-value</b> | <b>aOR (95% CI)</b>            | <b>P-value</b> |                  |
| <b>Age of solid introduction</b> |                     |                |                                |                |                  |
| ≤ 6 months                       | 1                   | -              | 1                              | -              | -                |
| > 6 months                       | 1.45 (0.42-5.07)    | 0.560          | NA                             | NA             | NA               |
| <b>Age of egg introduction</b>   |                     |                |                                |                |                  |
| ≤ 10 months                      | 1                   | -              | 1                              | -              | -                |

|                                   |                  |       |                  |       |       |
|-----------------------------------|------------------|-------|------------------|-------|-------|
| 10-12 months                      | 0.94 (0.31-2.88) | 0.915 | NA               | NA    | NA    |
| Not yet given                     | 2.06 (0.46-9.19) | 0.343 | NA               | NA    | NA    |
| <b>Age of peanut introduction</b> |                  |       |                  |       |       |
| Not yet given                     | 1                | -     | 1                | -     | -     |
| ≤ 10 mths                         | 0.73(0.21-2.45)  | 0.605 | NA               | NA    | NA    |
| > 10mths                          | 0.50 (0.06-4.32) | 0.531 | 1.51(0.27-8.46)  | 0.639 | 0.531 |
| <b>Duration of breastfeeding</b>  |                  |       |                  |       |       |
| < 1 mths                          | 1.62 (0.34-7.73) | 0.546 | NA               | NA    | NA    |
| 1-2 mths                          | 1.07 (0.24-4.67) | 0.930 | 0.92 (0.08-10.4) | 0.946 | 0.550 |
| 3-5 mths                          | 1.79 (0.65-4.92) | 0.261 | 0.52 (0.05-5.39) | 0.581 | 0.203 |
| 6-11mths                          | 1.28 (0.46-3.53) | 0.634 | 1.01 (0.16-6.26) | 0.991 | 0.523 |
| ≥ 12mths                          | 1                | -     | 1                | -     | -     |

560 aOR – adjusted odds ratio, NA – not applicable. Odds ratios could not be obtained as there were no children in  
561 that particular group. For example, in model 3, for egg introduction, there were no children introduced to egg  
562 between 10 to 12 months with food allergy in the GUSTO study.

563 §sample size greatly reduced due to missing maternal atopy data which was a confounder in the model and low  
564 food allergy cases that have introduced solids, egg and peanut by the first year of life.

565 ¶model adjusted for sex, eczema diagnosis (<6 months, >=6 months or no eczema) and maternal history of atopy

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