

Letter to the Editor

Atopic dermatitis and early childhood caries: Results of the GUSTO study

To the Editor:

Atopic dermatitis (AD) is a chronic, relapsing form of inflammatory skin disease, affecting approximately 10% of children in the United States.¹ AD has been associated with sleep disturbances, along with various comorbid allergic conditions, resulting in poor quality of life. In the last decade, studies have demonstrated an epidermal skin barrier defect, caused by various genetic mutations, to be an additional predisposing factor.² Early childhood caries (ECC), a chronic diet-mediated infectious oral disease, has been reported to be the most common chronic childhood disease in the United States.³ ECC has a multifactorial etiology, with one of the risk factors being genetic mutations in tooth-formative stages, resulting in structural defects,⁴ thereby increasing dental caries susceptibility. Duverger et al⁵ demonstrated hair keratin mutations in tooth microstructures to significantly increase the risk of dental caries, thus linking structural defects in hair follicles and caries risk. Because both dental caries and AD are associated with defects in structural genes, we hypothesized that there may be a potential link between them (*structural defect hypothesis*). Our study aimed to assess whether the occurrence of AD during the first year of life is associated with the risk of ECC at age 2 and 3 years. A second objective was to assess whether AD is associated with the development of new ECC lesions between age 2 and 3 years.

Data were collected from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study cohort, which recruited pregnant women (≥ 18 years) during their first trimester (< 14 weeks' gestation).⁶ Ethical approval was obtained from the Centralized Institutional Review Board of SingHealth (reference 2009/280/D) and the Domain Specific Review Board of Singapore National Healthcare Group (reference D/09/021). An interviewer-administered questionnaire was provided to parents at 3, 6, and 12 months to identify children who had been diagnosed with AD. AD was assessed *in part* by parent-reported, physician-diagnosed AD, as previously reported,⁷ based on a positive answer to the written question: "Has your child ever been diagnosed with eczema?" The determination of AD was not solely based on parental report of AD; skin prick tests (SPTs) were performed to improve the specificity of the diagnosis. Children underwent SPTs for common inhalant allergens (house dust mites *Dermatophagoides pteronyssinus*, *D. farinae*, and *Blomia tropicalis*) and food allergens (egg, peanut, and cow's milk) at the 18-month visit. All the allergens were obtained from Greer Laboratories (Lenoir, NC), except for *B. tropicalis*, which was obtained from our in-house laboratory. SPT results were categorized as positive if the wheal size was at least 3 mm to any allergen, along with a positive response to histamine and a negative response to saline. On the basis of responses to both the questionnaire and SPTs, individuals were categorized into 3 groups, AD-SPT(+ve), AD-SPT(–ve), and non-AD groups.

Oral examinations were carried out at 2-year and 3-year visits by trained calibrated dental professionals (intraclass correlation coefficient, > 0.80). ECC status was evaluated using modified

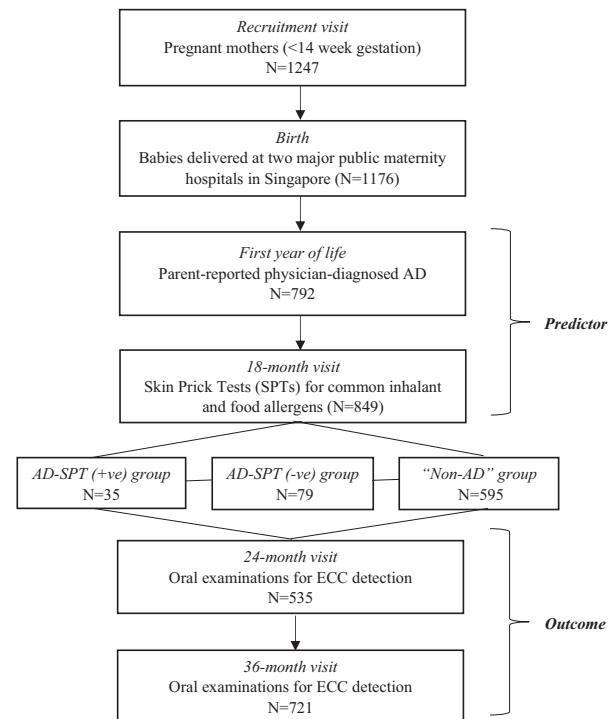


FIG 1. Flowchart describing the study protocol.

International Caries Detection and Assessment System criteria,⁸ grouping the children into caries-affected and caries-free groups. Surface-level, tooth-level, and individual-level increase in ECC was defined as newly affected surfaces, teeth or children, respectively, between 2- and 3-year visits. A flow chart of the study design is illustrated in Fig 1. Data analysis was carried out using SPSS version 23.0 (IBM SPSS Statistics, Armonk, NY). Chi-square tests were used to assess the association between AD and ECC. Logistic regression was used for multivariable analyses to adjust for potential confounding variables, including sex, ethnicity, maternal education, household income, maternal smoke exposure during pregnancy, and postnatal smoke exposure in the first year.

Participants' characteristics are described in Table I. After categorization of AD into 3 groups, 4.9% (35 of 709) of children developed AD with a positive SPT result, AD-SPT(+ve); 11.1% (79 of 709) of children developed AD but had a negative SPT result, AD-SPT(–ve), while 84% (595 of 709) of the children were not diagnosed with AD. Oral examinations were performed in 535 and 721 children at 2- and 3-year visits, respectively. Out of the examined children, 17.8% (95 of 535) had ECC at the 2-year visit, which substantially increased to 42.9% (309 of 721) at the 3-year visit. Of the 397 caries-free children at 2 years who were reexamined at 3 years, 35.8% developed new ECC lesions at the 3-year visit. In addition, the presence of new decayed surfaces and teeth between 2- and 3-year visits was shown to be 42.1% and 40.8%, respectively.

The findings of the present study demonstrated higher ECC risk in the AD-SPT(+ve) group, at both age 2 years (adjusted odds ratio [OR], 3.29; 95% CI, 1.06-10.17) and 3 years (adjusted OR, 3.09; 95% CI, 1.24-7.17), compared with the non-AD group (Table II). However, no difference in ECC risk was observed between the AD-SPT(–ve) group and non-AD groups at both 2- and

TABLE I. Participants' characteristics

Characteristic	Total, n (%)	N (% of those with characteristic)			
		AD	Positive SPT result	ECC at 2 y	ECC at 3 y
Ethnicity					
Malay	193 (26.8)	24 (16.7)	28 (16.3)	27 (19.1)	94 (48.7)
Indian	120 (16.6)	10 (13.3)	7 (6.9)	8 (9.6)	39 (32.5)
Chinese	408 (56.6)	66 (19.5)	45 (12.8)	48 (18.4)	176 (43.1)
Sex					
Male	373 (51.7)	61 (21.6)	45 (14.1)	46 (19.2)	156 (41.8)
Female	348 (48.3)	39 (14.2)	35 (11.5)	37 (15.4)	153 (44.0)
Maternal education levels					
Primary or less	28 (3.9)	4 (21.1)	2 (8.0)	4 (19.0)	13 (46.4)
Secondary	262 (36.6)	33 (16.9)	31 (13.4)	37 (20.7)	125 (47.7)
Preuniversity	176 (24.6)	20 (13.8)	19 (11.9)	17 (13.5)	75 (42.6)
University	249 (34.9)	43 (21.8)	28 (13.7)	24 (16.0)	94 (37.8)
Household income (SGD)					
0-1999	110 (16.4)	15 (18.3)	13 (13.5)	13 (17.1)	58 (52.7)
2000-3999	200 (29.8)	24 (16.1)	18 (10.3)	23 (16.2)	86 (43.0)
4000-5999	168 (25.0)	25 (18.7)	23 (15.1)	22 (18.8)	73 (43.5)
>6000	194 (28.8)	33 (20.6)	20 (12.1)	23 (21.1)	76 (39.2)
Maternal smoke exposure during pregnancy					
Yes	261 (38.2)	31 (15.9)	22 (9.8)	34 (19.2)	124 (47.5)
No	423 (61.8)	63 (18.9)	56 (15.1)	45 (16.7)	166 (39.2)
Postnatal smoke exposure					
Yes	37 (5.4)	9 (29.0)	4 (12.5)	3 (12.5)	14 (37.8)
No	652 (94.6)	84 (16.3)	75 (13.0)	80 (17.5)	285 (43.7)

SGD, Singapore dollar.

TABLE II. Association of AD in the first year of life and the risk of ECC

Presence of ECC	N	Crude OR (95% CI)	N	Adjusted* OR (95% CI)
ECC at 2 y				
Parent-reported physician-diagnosed AD				
Yes	73	1.30 (0.70-2.42)	60	1.57 (0.78-3.15)
No	350	1 [Reference]	267	1 [Reference]
Presence of AD				
AD-SPT (+ve)	18	2.25 (0.81-6.23)	16	3.29 (1.06-10.17) [†]
AD-SPT (−ve)	45	0.97 (0.43-2.19)	38	1.01 (0.40-2.51)
Non-AD	330	1 [Reference]	253	1 [Reference]
ECC at 3 y				
Parent-reported physician-diagnosed AD				
Yes	100	0.92 (0.59-1.43)	85	1.16 (0.71-1.88)
No	458	1 [Reference]	400	1 [Reference]
Presence of AD				
AD-SPT (+ve)	25	2.54 (1.09-5.88) [‡]	23	3.09 (1.24-7.17) [§]
AD-SPT (−ve)	60	0.71 (0.40-1.26)	53	0.80 (0.44-1.48)
Non-AD	435	1 [Reference]	380	1 [Reference]
Surface-level increase in ECC				
Parent-reported physician-diagnosed AD				
Yes	66	0.83 (0.48-1.45)	60	0.93 (0.51-1.71)
No	313	1 [Reference]	267	1 [Reference]
Presence of AD				
AD-SPT (+ve)	17	2.14 (0.79-5.80)	16	3.02 (1.00-9.10) [#]
AD-SPT (−ve)	42	0.53 (0.25-1.10)	38	0.55 (0.24-1.21)
Non-AD	298	1 [Reference]	253	1 [Reference]

SGD, Singapore dollar.

*Adjusted for ethnicity, sex, maternal education levels, household income (in SGD), maternal smoke exposure during pregnancy, and postnatal smoke exposure during first year of life.

[†]*P* = .038.[‡]*P* = .029.[§]*P* = .015.[#]*P* = .049.

3-year visits. In addition, the AD-SPT(+ve) group was shown to have a higher risk of surface-level increase in ECC between the 2- and 3-year visits, compared with the non-AD group (adjusted OR, 3.02; 95% CI, 1.00-9.10).

To our knowledge, ours is the first longitudinal study showing an association between AD and ECC. Our results indicate that children with AD are at an increased risk of developing tooth decay by age 3 years. Although not all cases of AD were associated with ECC, those with a positive SPT result were at a higher risk of ECC at both 2- and 3-year dental examinations. The exact mechanism behind the association still remains unclear. A possible mechanism is through a common pathogenic pathway underlying AD and ECC, potentially due to ectodermal defects during tissue development ("structural defect hypothesis"). One of the strengths of our study is its longitudinal (cohort) study design, accounting for the noncavitated phase of ECC. Second, the categorization of AD cases with a positive SPT result reduces the odds of misclassification of nonallergic rashes as AD. Third, oversampling of Malay and Indian individuals in the GUSTO cohort provides insight into ECC risk in a multiethnic Asian population. Although our GUSTO study cohort design did include visits at 3-monthly time points during the first year, resources did not permit physician examination at those visits. Further studies are needed to validate our diagnostic measure (combined parent-reported AD and SPT) with established criteria such as those of Hanifin and Rajka,⁹ which are based on physician examination. Moreover, AD remains a clinical diagnosis; although there may have been some misclassification of cases, this generally weakens associations unless a systematic bias is present. Also, future studies are needed to confirm our proposed *structural defect hypothesis* or to uncover other mechanisms underlying the association we observed in this study. As such, polymorphisms in certain genes, such as *MBL2* and *TLR2*, have been separately associated

with both AD and ECC in the literature. The distal-less homeobox (Dlx-3) gene, which has been shown to play an important role in both enamel formation and regulation of epidermal differentiation, may be considered a target gene for future investigations.

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