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Evaluation of caregiver-reported criteria for diagnosing eczema in young children

To the Editor,

Eczema or atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease with a peak incidence in the first 2 years of life¹. Physician diagnosis of AD is still problematic as there is variability in diagnosing AD, especially in young children, and validation studies on diagnostic accuracy and criteria of physician diagnosis of AD are lacking. Furthermore, mild to moderate AD is easily controllable with topical treatment, such as moisturizers and corticosteroids², which results in children with AD presenting at the doctor's office with a normal skin. Epidemiological studies often employ caregiver-reported history of a physician-diagnosed AD as a proxy measure to estimate AD prevalence in children^{3,4}. When compared to physician diagnosis using Hanifin and Rajka criteria at the clinic visit, a previous study in 0–17-year-old children/adolescents reported sensitivities/specificities of 70%/96% and 83%/89% for caregiver-reported 1-year recall history of AD diagnosis and history of ever having AD, respectively⁵. Hence, the present study aimed to evaluate the diagnostic accuracy of life-time caregiver-reported history of physician-diagnosed AD in young children (i.e., life-time prevalence) using the physician diagnosis of AD at clinic visit as the gold standard (i.e., point prevalence, potentially influenced by treatment).

Ethical approval was obtained from Centralized Institutional Review Board (CIRB) of SingHealth (reference 2009/280/D) and Domain Specific Review Board (DSRB) of Singapore National Healthcare Group (reference D/09/021). Data was extracted from The Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort, which is a mother-offspring cohort where Singapore citizens or permanent residents of Chinese, Malay and Indian ethnicity with homogenous ethnic background were approached for participation⁶. Life-time caregiver-reported history of physician-diagnosed AD was derived by asking the following question at 6-, 12-, 18- and 36-month clinic visits, “*Has your child ever been diagnosed with eczema?*”, reflecting life-time prevalence. Thereafter, currently active AD diagnosis, reflecting point prevalence, was performed by physicians on the same day using standard Hanifin and Rajka criteria⁷ which were used as the reference to evaluate diagnostic accuracy of caregiver-reported history of physician-diagnosed AD. For the main analysis, data from 18- and 36-month clinic visits were used for assessing the diagnostic accuracy of caregiver reported criteria.

Based on the physician diagnosis at clinic visit, 3.42% (31/906) and 4.70% (43/915) children were diagnosed as having active AD at ages 18-months and 36-months, respectively. Using physician-diagnosed AD at 18-months as

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the gold standard, caregiver-report of physician-diagnosed AD demonstrated high sensitivity (93.3%), specificity (90.4%) and negative predictive value (NPV=99.7%), but a low positive predictive value (PPV=25.2%) (Table 1). Furthermore, at the 36-month visit, caregiver-report of physician-diagnosed AD demonstrated good specificity (86.8%) and NPV (97.5%), but low sensitivity (54.7%) and PPV (16.7%) (Table 1).

An aforementioned cross-sectional study reported reasonable sensitivity/specificity/PPV/NPV (83%/89%/81%/91%) compared to physician diagnosis, with comparable point prevalence (56.0%) and life-time prevalence (58.1%) of AD⁵. In this study, a low PPV (16.7% to 25.2%) of the caregiver-reported criteria was observed in our cohort (Table 1), with inflated false-positive cases at both 18-months (74.8%) and 36-months (83.2%). This may be predominantly attributed to the assessment of a different feature of AD, being past prevalence of ever having had AD *versus* having currently active eczema. Differences might be due to the waxing and waning nature of AD in addition to usage of steroids/moisturizers, which are commonly used and very effective in the treatment, and hereby controlling AD. A substantial discrepancy was noted between point prevalence at the clinic visits (3.42% and 4.70% at 18- and 36-month, respectively) and life-time prevalence (12.3% and 15.0% at 18- and 36-month, respectively) in the present study cohort. While the specificity of the caregiver-reported criteria was good at both 18-month (90.4%) and 36-month visits (86.8%) compared to physician diagnosis, its sensitivity dropped substantially from 93.3% at 18-month to 54.7%, partially due to higher number of false-negative cases at 36-months compared to 18-months (2.5% vs 0.3%).

Interestingly, when only the caregiver-reported criteria, suggesting life-time prevalence of “ever having eczema” was compared across different follow-up visits, 25.9% (28/108) of children with a positive caregiver history of ever having AD diagnosis by 18-months, subsequently reported a negative history of ever being diagnosed with AD at 36-months (Table 2). Additionally, the agreement between the caregiver-reported eczema across the two assessments was poor (Cohen’s kappa = 0.62), which possibly explains the difference observed in the sensitivities between 18-months and 36-months. This discrepancy was slightly higher with a longer follow up period (28.7% and 27.9% between 12-to 36-months and 6- to 36-months, respectively), suggesting that the caregiver-report of previous physician-diagnosed AD may potentially be prone to recall bias, although this cannot be unequivocally proven. While lack of clarity and/or interpretation of the question asked can also possibly mislead the caregivers to report only active/ongoing eczema, future studies are warranted for critical evaluation of recall bias during history taking of AD in epidemiological settings, especially when using caregiver reported measures in young children. Our findings nonetheless suggest that information bias (misreporting) at 18-months is less likely than at 36-months.

A strength of the study is its longitudinal study design which may have partially prevented missed cases arising from waxing and waning of AD over time, since 58.7% (18/31) of children diagnosed with AD at 18-months did not present AD symptoms at 36-month visit. A major limitation of using physician-diagnosis at the clinic visit as the gold standard is that it may be suggestive of point prevalence at the time of clinic visit but not of the actual life-time prevalence, owing to the relapsing/remitting nature of AD, and/or the effect of its treatment. We did not have information from questions that have higher specificity for AD, such as an itchy rash affecting usual locations. Furthermore, the study was limited by the logistic constraint in assessing inter- and intra-examiner reliability among physicians for AD assessment, although Hanifin-Rajka criteria have been shown to exhibit high inter-rater agreement

(ICC>0.80) among physicians/dermatologists.⁸ Another confounder to consider in the future study is the role of symptomatic treatment in AD, which can suppress active AD, mainly in children with mild to moderate AD.

In conclusion, the study findings indicate the significant, yet unexplored, influence of recall bias when using caregiver-report in estimating life-time AD prevalence in young children, potentially leading to underestimation of actual AD cases, which may be especially critical in populations with low disease prevalence rates.

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Conflicts of interest: Lynette Pei-chi Shek has consultant arrangements with Mead Johnson and Nestle; has received payment for lectures from Danone and Nestle; and has received research funding from Danone. Yap Seng Chong have received research collaborations and funding from Abbott, Danone, and Nestec. Bee Wah Lee has received honoraria for serving on an advisory board for Nestle Nutrition, has received payment for lectures from Danone Nutrition, and has received travel support from the Asia Pacific Association of Allergy Asthma and Immunology. Keith Godfrey has received reimbursement for speaking at conferences sponsored by companies selling nutritional products and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, Benevolent AI Bio Ltd. and Danone; he has patents issued for phenotype prediction and predictive use of CpG methylation; and has a patent pending for maternal nutrition composition. The authors have no conflicts of interest relevant to this article to disclose.

Authors' contributions

Tosha Ashish Kalhan conducted the data analyses, drafted, and critically reviewed for important intellectual content. Evelyn Xiu Ling Loo and Carolina Un Lam assisted in obtaining grants/resources for the study, collected data and critically reviewed the manuscript for important intellectual content. Lynette Pei-chi Shek, Michael Kramer, Hugo

Van Bever, Anne Goh, Yap Seng Chong, Bee Wah Lee, Kok Hian Tan, Seang-Mei Saw and Keith M Godfrey obtained grants/resources for the study, conceptualized and designed the study and critically reviewed the manuscript for important intellectual content. Bindu Karunakaran collected data and critically reviewed the manuscript for important intellectual content. Chin-Ying Stephen Hsu obtained grants/resources, conceptualized, and designed the study, conducted the analyses, drafted and revised the manuscript and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Table 1. Comparative evaluation of eczema diagnostic criteria using physician diagnosis at 18-months and 36-months as the gold standard

Caregiver-reported history of physician-diagnosed eczema at 18-months	Physician-diagnosed eczema at 18-month clinic visit* (N=902)		
	No	Yes	
No	789	2	NPV=99.7%
Yes	83	28	PPV=25.2%
	Specificity=90.4%	Sensitivity=93.3%	
Caregiver-reported history of physician-diagnosed eczema at 36-months	Physician-diagnosed eczema at 36-month clinic visit* (N=911)		
	No	Yes	
No	755	19	NPV=97.5%
Yes	114	23	PPV=16.7%
	Specificity=86.8%	Sensitivity=54.7%	

PPV, positive predictive value; NPV, negative predictive value

*using Hanifin-Rajka criteria

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Table 2. Discrepancies of caregiver-reported life-time prevalence of “ever having eczema” across different follow-up visits

			Caregiver-reported history of physician-diagnosed eczema at 36-months	
			Yes	No
Caregiver-reported history of physician-diagnosed eczema	at 6-months	Yes	44 (72.1%)	17 (27.9%)
		No	87 (11.1%)	699 (88.9%)
	at 12-months	Yes	57 (71.3%)	23 (28.7%)
		No	73 (9.4%)	700 (90.6%)
	at 18-months	Yes	80 (74.1%)	28 (25.9%)