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Is self-reported history of eczema and hay-fever a valid measure of atopy in those who report current asthma?

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Conflicts of Interest

JLP has received a travel grant from Boehringer-Ingelheim, KPM have received travel grants from Oticon and Knud Højgaards Fond, MJA holds investigator initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has undertaken an unrelated consultancy for Sanofi and has received a speaker fee from GSK. The remaining authors have no conflicts of interest to declare.

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SUMMARY

This study suggests that in the absence of skin prick test (SPT) or sIgE data, self-reported hayfever "and/or" eczema provides a useful definition of allergic asthma for epidemiological studies.

KEY WORDS

ALLERGIC ASTHMA, ALLERGY, HAYFEVER, ECZEMA, SKIN PRICK TEST, VALIDITY

ABBREVIATIONS

CI = confidence interval

DOR = Diagnostic Odds Ratio

L95 = Lower 95 % Confidence Interval

MACS = Melbourne Atopy Cohort Study

NLR = Negative Likelihood Ratio

PLR = Positive Likelihood Ratio

SPT = Skin Prick Test

sIgE = Specific Immunoglobulin E

TAHS = Tasmanian Longitudinal Health STUDY

U95 = Upper 95 % Confidence Interval

To the Editor: There is growing awareness that "asthma" is a clinical syndrome with multiple distinct pathophysiological mechanisms, or endotypes, leading to variable clinical expression of disease. Distinction of asthma as a clinical syndrome is of increasing importance since the emergence of targeted biological therapies (1). Asthma is most often phenotyped as allergic or non-allergic, based on evidence of sensitisation to specific allergens measured as skin prick tests (SPT) or in vitro immunoglobulin E (sIgE) (2). However, in large scale epidemiological studies, measurement of sIgE or SPT is often not feasible due to cost or

logistical constraints. Allergic asthma has often been classified as asthma with concurrent self-reported hayfever and/or eczema (3,4). Similarly, SPT or sIgE are uncommonly measured in primary care settings, with assessment of "atopy" in those with asthma typically based on reports of other allergic conditions. It is not clear how valid this approach is or how frequently participants are misclassified. We have examined the validity of using self-reported hayfever and/or eczema to define allergic status among asthmatics compared to SPT as a "gold standard".

This analysis used data from two independent studies: The Melbourne Atopy Cohort Study (MACS) (5) and The Tasmanian Longitudinal Health Study (TAHS) (6). MACS is a birth-cohort of children, with family history of allergic diseases, born between 1990 and 1994. Parents and siblings were included in later follow-ups. TAHS is a cohort of children born in Tasmania in 1961, plus their families. Parents and siblings have been studied in later phases. Participants from MACS' 18 year follow-up, together with TAHS probands from the 2012 and TAHS siblings from the 2007 study were included if they fulfilled these criteria: (i) current asthma, (ii) valid skin prick tests, and (iii) complete information on hayfever and eczema ever (supplementary Figure S1).

Current asthma was defined by self-reported doctor diagnosed asthma *and* self-reported concurrent episodes of asthma, wheezing breathing or any asthma medication use within the last 12 months. Hayfever ever was based on self-reported episodes of ever hayfever in MACS and slightly more broadly defined in TAHS by also including nasal allergies. Eczema ever was based on participant reports of ever eczema in MACS and slightly more broadly defined in TAHS by also including any kind of skin allergy.

A positive skin prick test was defined as a mean wheal diameter of at least 3mm greater than the saline control for one or more of the following allergen extracts: dust mite (*D. pteronyssinus*), cat, *Alternaria*, *Penicillium*, mixed grasses or rye grass pollen. Results were deemed invalid if the histamine control reaction was below 3 mm and no other reaction above 3 mm, to any allergen wheals, was identified (7). The period prevalence (in the past 12 months) of reported asthma symptoms was assessed, when the skin prick tests were performed.

Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratios (DOR) were calculated with 95% confidence intervals (CI). Probands, siblings and parents were initially analysed separately, then probands, siblings and parents were pooled in each study. Asthma defined to be allergic or non-allergic was assessed for each individual. Clustering by family was adjusted within each study using the PROC GENMOD procedure in SAS (SAS Institute Inc., Cary, NC, USA) version 9.4. Due to high heterogeneity between MACS and TAHS, as assessed by using I^2, pooled estimates are not shown. Of 937 participants with current asthma, 78% had a positive SPT and 89% ever had hayfever *and/or* eczema (Table I).

Table I Descriptive data of the study population with current asthma in the MACS 18 years follow up and TAHS 2012 and 2007 follow up

	MACS				TAHS			TOTAL
	18 year follow up				2012 follow up	2007 follow up		
	Probands, *n*= 89	Siblings, *n*= 111	Parents, *n*= 156	Total, *n* = 356	Probands, *n*= 225	Siblings, *n*= 356	Total, *n*= 581	*n* = 937
Female	47.2 % (42/89)	50.5 % (56/111)	69.9 % (109/156)	58.2 % (207/356)	55.6 % (125/225)	53.0 % (188/355)	54.0 % (313/580)	55.6 % (520/936)
Mean age in years (SD)	18.2 (1.4)	20.4 (6.2)	50.9 (4.4)	33.2 (16.3)	52.1 (0.9)	49.4 (5.7)	50.5 (4.7)	41.9 (11.5)
Positive skin prick test	87.6 % (78/89)	85.6 % (95/111)	86.5 % (135/156)	86.5 % (308/356)	73.8 % (166/225)	71.6 % (255/356)	72.5 % (421/581)	77.8 % (729/937)
Ever hayfever	73.0 % (65/89)	70.3 % (78/111)	85.3 % (133/156)	77.5 % (276/356)	83.1 % (187/225)	77.8 % (277/356)	79.9 % (464/581)	79.0 % (740/937)
Ever eczema	56.2 % (50/89)	68.5 % (76/111)	44.9 % (70/156)	55.1 % (196/356)	61.8 % (139/225)	53.1 % (189/356)	56.5 % (328/581)	55.9 % (524/937)
Ever hayfever *and* eczema	43.8 % (39/89)	50.5 % (56/111)	42.3 % (66/156)	45.2 % (161/356)	52.9 % (119/225)	43.0 % (153/356)	46.8 % (272/581)	46.2 % (433/937)
Ever hayfever *and/or* eczema	85.4 % (76/89)	88.3 % (98/111)	87.8 % (137/156)	87.4 % (311/356)	92.0 % (207/225)	87.9 % (313/356)	89.5 % (520/581)	88.7 % (831/937)

n = number of participants, SD = Standard deviation, MACS = Melbourne Atopy Cohort Study, TAHS = Tasmanian Longitudinal Health STUDY

Figure I: Sensitivity, specificity and diagnostic odds ratio of hayfever, eczema and combination of these

Supplementary Figure S1: Flowchart – The Melbourne Atopy Cohort Study (MACS) and The Tasmanian Longitudinal Health Study (TAHS) participants

MACS and TAHS estimates of self-reported hayfever ever compared with SPT-defined allergic asthma showed relatively high sensitivity ≥0.82, but moderate specificity ≥0.60, and DOR >4.13, Figure I. The corresponding PLR was ≥1.57 and NLR was ≤0.23, see supplementary Table SI. The results varied between groups, and were higher in older participants (MACS parents and TAHS participants). Using self-reported ever eczema showed lower utility (DOR ≥0.74) as did combining hayfever *and* eczema ever (requiring both) (DOR ≥0.19). In contrast, combining current asthma with hayfever "*and/or*" eczema estimates of sensitivity were at least 0.90, specificity ≥0.69, PLR >2.92, NLR of <0.14, and DOR ≥20.5.

We found that combining self-reported hayfever *and/or* eczema ever, provided high sensitivity, specificity, PLR and a large DOR for defining atopic asthma, and a low NLR. Current asthma combined with hayfever ever alone showed an acceptable sensitivity, moderate specificity and less useful clinical PLR, NLR and DOR when compared with SPT-defined allergic asthma. Combining current asthma with eczema alone or hayfever *and* eczema showed much poorer results.

This is the first study to examine the validity of combining self-reported hayfever *as well as* eczema to identify atopic versus non-atopic asthma in young to middle-aged adults. A previous study of Swiss school children (8) examined the validity of self-reported hayfever ever compared with SPT and showed high specificity (useful in including allergy), but low sensitivity. Even though

hayfever can present in childhood, it is more common in adults than children (9), which may explain the low sensitivity observed in the Swiss study.

It is a limitation that our study is based on an Australian population, as it has one of the highest rates of atopy in the world. Furthermore MACS is a high-risk birth cohort based on children with a family history of allergic diseases resulting in a population with even higher rates of allergy (5). While the rates of allergy would be higher in this study, it is unlikely that this would affect the validity of the symptoms combinations compared with definitions including SPTs. Our results are restricted to the specific allergen extracts measured in the skin prick tests, using the main allergens of Australia. We adopted SPT as gold standard, and it would be useful to also explore the use of in vitro sIgE (2). We used self-reported doctor-diagnosed asthma and self-reported concurrent symptoms of asthma, which are used in most epidemiological studies. While self-reported asthma and clinical diagnosis of asthma showed relatively good agreement (k=0.78) (10), it would be useful also to explore these associations using clinical assessed diagnosis of asthma. It should be noted that in most epidemiological studies, current asthma status is defined by patient report, rather than confirmed clinical diagnosis. The differences between the MACS and TAHS cohorts, including the definition of hayfever and eczema, age of the participants and nature of the cohorts (high risk versus population-based) may have led to highly heterogeneous findings. Hayfever and eczema were furthermore, more broadly defined in TAHS. This is a limitation as it prevented us from pooling of the results.

Our results suggest that a history of self-reported hayfever and/or eczema combined provides the most accurate means to define allergic asthma in epidemiological studies without direct assessment of SPT or sIgE measurements.

Ethics approval and consent to participate

All participants provided written informed consent. The MACS project was approved by the Human Research Ethics Committee of the Mercy Hospital for Women (up to 12 years, reference numbers R07/20 and R88/06) and Royal Children's Hospital (18 years, reference number 28035).

The TAHS was approved by Human Ethics Review Committees at The Universities of Melbourne (approval number 040375), Tasmania (040375.1) and New South Wales (08094), the Alfred (1118/04) and Royal Brisbane and Women's Hospital Health Service District (2006/037).

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Authors' contributions

KP, VS, KSH, SCD and AJL: Conception and design of the analysis, interpretation of data and drafting the work. SCD, AJL, CJL, BE, CS, PST, and MJA: Design of the 18 year follow-up of the MACS for funding proposals and data collection. SCD, JP, HW, DB, BE, CS, GSH, PST, and MJA: Design of the TAHS follow-up studies, writing grant proposals and data collection. All authors contributed to the manuscript drafts revising for important intellectual content and have read and approved the manuscript.

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REFERENCES

1. Kuruvilla ME, Lee FE-H, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol. 2019 Apr;56(2):219–33.

2. Australasian Society of Clinical Immunology and Allergy. Laboratory Tests in the Diagnosis of Allergic Diseases [Internet]. Australasian Society of Clinical Immunology and Allergy (ASCIA). [cited 2019 Jul 1]. Available from: https://www.allergy.org.au/hp/papers/tests-in-the-diagnosis-of-allergic-diseases

3. Svanes C, Koplin J, Skulstad SM, Johannessen A, Bertelsen RJ, Benediktsdottir B, et al. Father's environment before conception and asthma risk in his children: a multi-generation analysis of the Respiratory Health In Northern Europe study. Int J Epidemiol. 2017 Feb 1;46(1):235–45.

4. Christensen BH, Thulstrup AM, Hougaard KS, Skadhauge LR, Hansen KS, Frydenberg M, et al. Maternal occupational exposure to asthmogens during pregnancy and risk of asthma in 7-year-old children: a cohort study. BMJ Open. 2013 Jan 1;3(4):e002401.

5. Lowe AJ, Lodge CJ, Allen KJ, Abramson MJ, Matheson MC, Thomas PS, et al. Cohort Profile: Melbourne Atopy Cohort study (MACS). Int J Epidemiol. 2017 Feb 1;46(1):25–6.

6. Matheson MC, Abramson MJ, Allen K, Benke G, Burgess JA, Dowty JG, et al. Cohort Profile: The Tasmanian Longitudinal Health STUDY (TAHS). Int J Epidemiol. 2017 01;46(2):407–408i.

7. Australasian Society of Clinical Immunology and Allergy. Skin Prick Testing for the Diagnosis of Allergic Disease [Internet]. 2016 [cited 2019 Jul 1]. Available from: https://www.allergy.org.au/hp/papers/skin-prick-testing

8. Braun-Fahrländer C, Wüthrich B, Gassner M, Grize L, Sennhauser FH, Varonier HS, et al. Validation of a rhinitis symptom questionnaire (ISAAC core questions) in a population of Swiss school children visiting the school health services. Pediatr Allergy Immunol. 1997 May 1;8(2):75–82.

9. Owens L, Laing IA, Zhang G, Turner S, Le Souëf PN. Prevalence of allergic sensitization, hay fever, eczema, and asthma in a longitudinal birth cohort. J Asthma Allergy. 2018 Aug 13;11:173–80.

10. Iversen L, Hannaford PC, Godden DJ, Price DB. Do people self-reporting information about chronic respiratory disease have corroborative evidence in their general practice medical records? A study of intermethod reliability. Prim Care Respir J J Gen Pract Airw Group. 2007 Jun;16(3):162–8.