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Diagnosis validation and clinical characterization of atopic dermatitis in Nurses' Health Study 2

A.M. Drucker^{1,2,3}, E. Cho^{3,4,5}, W.-Q. Li^{3,4}, C. A. Camargo^{5,6,7}, T. Li^{3,5}, and A..A Qureshi^{3,4,5,8}

¹Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Canada

²Women's College Research Institute and Department of Medicine, Women's College Hospital, Toronto, Canada

³Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, RI

⁴Department of Epidemiology, School of Public Health, Brown University, Providence, RI

⁵Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

⁶Department of Emergency Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA

⁷Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

⁸Department of Dermatology, Rhode Island Hospital, Providence, RI, United States

Abstract

Background: Epidemiologic studies of atopic dermatitis are often limited by case definitions that have not been validated.

Objective: In this study, we assessed the accuracy of self-report of atopic dermatitis in a large cohort of US female nurses, the Nurses' Health Study 2 (NHS2). We also provide clinical characteristics of atopic dermatitis in the cohort.

Methods: We sent an electronic questionnaire to NHS2 participants who previously reported ever having a diagnosis of atopic dermatitis. This questionnaire was designed to confirm cases of atopic dermatitis using previously validated algorithms with >85% specificity. We assessed the association of atopic dermatitis with asthma, comparing the results when different definitions of atopic dermatitis were applied. We also inquired about various aspects of participants' atopic dermatitis.

Corresponding author: Aaron M Drucker, Room 6401, Women's College Hospital, 76 Greville Street, Toronto, ON M5S1B2, Canada, aaron.drucker@wchospital.ca, Phone: 416-323-7546, Fax: 416-323-6236.

Statement of Contribution

Drs. Drucker, Cho, Li, Camargo and Qureshi contributed to the design of this study. Ms. Li conducted data analysis. Dr. Drucker drafted the manuscript. All authors contributed to data interpretation of the data and provided critical feedback on the manuscript.

Conflicts of interest

None of direct relevance to this study.

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Results: Responses were received from 2,509 of 5,126 (49%) nurses who were sent the questionnaire, with an average age of 62. Most participants (1,996/2,509, 80%) reiterated their previously reported clinician diagnosis of atopic dermatitis. Application of the two diagnostic algorithms yielded confirmation of 1,538 and 1,293 prevalent cases, respectively. The association of atopic dermatitis with asthma was stronger when more stringent atopic dermatitis case definitions were applied. Participants generally reported mild disease (92% with 10% maximal body surface area involved) and a high proportion (57%) reported adult-onset disease.

Conclusions: Self-report of atopic dermatitis diagnosis has good reliability, and future analyses will be strengthened by our ability to conduct sensitivity analyses with refined confirmed atopic dermatitis subgroups.

Keywords

Atopic dermatitis; eczema; validation; epidemiology; asthma

Introduction

Atopic dermatitis (AD) is increasingly recognized to persist into adulthood.^{1–3} This has spurred epidemiologic studies of adults with AD, including investigations of risk factors for development of AD and non-atopic comorbidities. Data sources for these investigations include cross-sectional surveys and cohort studies using insurance claims or electronic health record data.^{4–8} These studies rely on either patient-reported diagnosis or physician coding in the form of *International Classification of Disease* (ICD) or other diagnostic codes, all of which are prone to varying degrees of misclassification of AD.^{9–11} A systematic review found that the method used to identify cases of AD in routinely collected health data can influence the results of analyses, included substantial differences in prevalence estimates.¹² Only 2 of 59 included studies described any validation of their case definition. Similarly, it has been shown that there is often poor agreement between self-reported physician-diagnosed AD and objectively applied diagnostic criteria, also affecting the results of epidemiologic analyses.¹³

Our research group has published AD-related analyses using data from Nurses' Health Study 2 (NHS2), an ongoing cohort of US female nurses, which relies on self-report of ever receiving a clinician diagnosis of AD for its case definition.^{14–18} Participants are also asked what year they were diagnosed. In this study, we aimed to assess the accuracy of self-report of AD among NHS2 participants using a validated questionnaire.¹⁹ We also assessed various characteristics of participants' AD.

Materials and Methods

Atopic Dermatitis Screening and Evaluation Questionnaire 2

The AD Screening and Evaluation Questionnaire (ADSEQ) is a paper-based instrument developed to accurately identify cases of adult AD.¹⁹ It is administered to subjects to complete on their own. ADSEQ asks respondents if they have been diagnosed with AD, if they have a personal or family history (parents, siblings, children) of atopy and if their skin is generally itchy. In a validation study conducted among outpatients in a dermatology

clinic, four algorithms combining answers to these questions were developed and tested, with a specificity ranging between 84% and 93% for a diagnosis of AD.¹⁹

We modified ADSEQ into the ADSEQ2 to be administered electronically, on a computer or mobile device. ADSEQ2 contained all of the questions included in the original ADSEQ that are required for the diagnostic algorithms and added other questions on age of diagnosis, last disease activity and maximal severity, self-assessed disease extent, effect on sleep, AD treatments, treatment satisfaction, and anxiety related to AD flares.

Study population

NHS2 is a prospective cohort study of US female registered nurses that began in 1989 with 116,686 participants between the ages of 25 and 42. Detailed data about participants' lifestyle and environmental factors, health behaviors, and medical histories are collected by mailed questionnaires biennially. Cohort participants' completion and return of the self-administered questionnaire is considered informed consent. The current study was approved by the institutional review board of Brigham and Women's Hospital.

In 2009 and 2013, participants were asked whether they had ever been diagnosed by a clinician as having "eczema (atopic dermatitis)." A total of 10,647 participants reported ever having a diagnosis of AD in either 2009, 2013 or both.

ADSEQ2 was sent to all NHS2 participants in spring 2017 who (1) reported a diagnosis of AD in 2009 or 2013; (2) remained active participants in the cohort; (3) had provided their email address to NHS2 and consented to electronic communication; and (4) were not currently participating in other NHS2 substudies. A total of 5,126 participants were sent an electronic questionnaire (Fig. 1) with a single reminder sent to participants who did not respond to the first invitation.

The first question on ADSEQ2 asked the participant whether they had been diagnosed with AD by a clinician. If they answered "yes," they were invited to continue with the remainder of the questionnaire. If they answered "no," the questionnaire was terminated. Participants were allowed to skip individual questions.

Other study variables

During routine cohort follow-up, NHS2 participants provide detailed information on major health and lifestyle characteristics. Race/ethnicity and height were reported at cohort baseline. Biennially, NHS2 participants were asked about clinician-diagnosed asthma. Information on self-reported body weight, physical activity, alcohol intake, smoking status and asthma are comprehensively collected and updated during the cohort follow-up. Asthma self-report has been validated in this cohort²⁰ and self-report of body weight, physical activity and alcohol intake variables have been validated in a cohort of older nurses.^{21–23} Body mass index (BMI) is calculated by dividing the reported weight (kg) by the height squared (m²). History of ever having hayfever (allergic rhinitis) and food allergy were reported in 2009.

Statistical analysis

We assessed the *reliability* of AD self-report by calculating the proportion of respondents who reiterated that they had been diagnosed with AD on ADSEQ2. Among those who reiterated that they had been diagnosed with AD, we assessed the *validity* of their self-report by applying two published ADSEQ algorithms, with specificity of 86% and 88%, respectively, and calculating the proportion of respondents who met those criteria.¹⁹ Algorithm 1 was positive for AD if, in addition to reporting a diagnosis of AD, participants indicating they had a rash similar to one of the clinical photos from ADSEQ. Algorithm 2 was positive for AD if participants indicating they had a rash similar to one of the clinical photos from ADSEQ and they reported a family history of atopy. Two other published ADSEQ algorithms were not used in this analysis as they incorporate answers to a question on current itch; we aimed to assess the validity of ever having AD, not current disease.

To examine differences between nurses determined to have AD based on each case definition, we described their characteristics according to basic demographic and lifestyle attributes and history of asthma as reported on the main questionnaire. Attributes examined were age, BMI, alcohol intake, physical activity, smoking history, race and history of asthma, hayfever (allergic rhinitis), and food allergy. We also calculated age-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between AD and asthma compared to the general NHS2 population for each of the case definitions. We hypothesized that there would not be substantial differences in major demographic and lifestyle characteristics between the different AD case definitions, but that asthma, hayfever (allergic rhinitis) and food allergy would be more common with the more stringent case definitions. Further, we hypothesized that the association with asthma would be stronger with the more stringent case definitions.

We further characterized respondents' AD by calculating descriptive statistics for their answers to other ADSEQ2 questions.

Results

Reliability and validity of self-report

Responses were received from 2,509 of 5,126 (49%) nurses who were sent the questionnaire. Self-report on the main questionnaire was reliable, with 1,996 (80%) reiterating that they were diagnosed by a clinician as having AD. Just over half (57%) reported being diagnosed by a dermatologist. Application of the two diagnostic algorithms yielded confirmation of 1,538 (61% of all respondents, 79% of those who reiterated their AD diagnosis) and 1,293 (52% of all respondents and 66% of those who reiterated their AD diagnosis) cases, respectively.

Characteristics of participants according to different AD case definitions

Demographic and lifestyle characteristics were similar across the different AD case definitions (Table 1). Compared to all participants who reported having AD in 2009 or 2013, participants with confirmed AD according to the ASDEQ algorithms were somewhat more likely to have asthma, hayfever (allergic rhinitis) and food allergy. The association of AD

with asthma compared with the general NHS2 population was stronger when more stringent AD case definitions were applied.

Characteristics of AD

Among respondents who reiterated their AD diagnosis on ADSEQ2, self-report of age of onset of AD was common between ages 2 and 17 (659/1,967 (34%)), but most participants reported onset in adulthood (1,124/1967, 57%) (Table 2). Similarly, most respondents reported their AD to be at its worst in adulthood (1198/1708, 70%). Very few respondents (6%) reported maximal body surface area involvement over 10%. Sleep disruption was common, with approximately half reporting some sleep disruption when their AD was at its worst (789/1,959, 40%).

Commonly used treatments included topical corticosteroids and calcineurin inhibitors, whereas phototherapy and systemic therapy were not used commonly (Table 3). Oral steroids were the most commonly used systemic therapy. Most participants (1,457/1,939, 75%) agreed that the treatments they used for AD were effective. Respondents whose AD was more extensive at its worst were somewhat less satisfied with treatments (Table 4). When asked if they ever felt anxious or worried that their AD would worsen or flare, 579/1953 (30%) said they did. Among them, there was significant variability as to how strong that anxiety/worry was at its worst and how much it affected their daily life (Supplemental Fig. 1).

Discussion

In this study, we provide evidence that self-report of AD diagnosis is reliable, with regards to repeat self-report, among adult women nurses in NHS2. In addition, we now have sub-populations of refined confirmed AD cases within the cohort. These findings provide some reassurance about the validity of our previous analyses on AD in this cohort and are encouraging for future work.¹⁴⁻¹⁷ Future analyses in NHS2 can explore associations of AD using multiple case definitions, adding to the robustness of their findings.

The AD population in NHS2 has a number of important characteristics that should be kept in mind when interpreting the results of analyses. Similar to other survey-based assessments,^{8,24} many participants report onset of AD in adulthood. It has been questioned whether AD can truly have its first onset in adulthood; perhaps these are cases who had mild or transient disease in early childhood that have since been forgotten.²⁵ Factors associated with forgetting a previous diagnosis of AD include earlier AD onset, less disabling disease, transient disease and a lack of other atopic conditions.^{26,27} As such, NHS2 questionnaires administered during adulthood likely fail to capture resolved cases of mild, transient childhood AD.

Persistence of AD late into adulthood was common; only 10% of participants reported no active lesions after childhood and 32% reported having active patches at the time of the survey. The high rates of persistence in NHS2 are consistent with other recent studies. For example, a cohort study of children with mild-to-moderate AD found that 80% of participants still had periods of active disease into early adulthood³ and a systematic review

found that there was no statistically significant drop year-on-year in the prevalence of AD within cohort studies.²

Participants in NHS2 generally report having milder disease, with estimated maximal body surface area under 10% in more than 90% of cases. However, 20% report use of systemic corticosteroids in the past for their AD suggesting that they had severe enough disease to warrant at least a short-course of systemic therapy at some point. These findings are consistent with an international study which found that severe disease was present in 2 to 21% of adult AD patients, varying depending on the country and scale used to measure disease severity.²⁸

NHS2 participants report a significant personal burden of disease of AD. Sleep disruption was reported by 53%, and anxiety related to anticipated flares was reported by 30%. Sleep disruption is a well-documented consequence of AD. In a US population-based survey, AD and concomitant sleep disruption were associated with major decrements in self-perceived overall health status.²⁹ Anticipatory anxiety related to AD flares has also been suggested previously in an analysis of patient social media posts.³⁰

This study has a number of limitations. We were only able to contact approximately half of all NHS2 participants who ever reported having AD. Further, only half of those we contacted responded to our questionnaire. Despite these participation rates, we are somewhat reassured by the similarity of participants with AD according to the different case definitions across many important lifestyle and demographic factors. We did not record the time required to complete the questionnaire, which is an important consideration for feasibility. ADSEQ validation was conducted in a dermatology clinic population which is different from our population of female nurses. As such, test characteristics that rely on disease prevalence, such as positive predictive value, cannot be extrapolated to our population. We have focused on their specificity. Many of the questions used for the clinical characterization of patients' AD rely on recall over many years, and as such are likely not entirely accurate. Additionally, we assessed age of diagnosis and last disease activity in fairly wide categories and so are unable to calculate precise disease duration for participants. Finally, this validation study was conducted in a cohort of female nurses, and as such the results are not generalizable to questionnaire-based cohort studies in other populations; in the future, the questionnaire could be applied to other cohorts including the Growing Up Today Study (a cohort of male and female children of NHS2 participants) or NHS3 (a newer cohort of nurses with both male and female participants).

In sum, NHS2 participants with AD have mostly mild disease with reported onset and continued activity in adulthood. Self-report of AD diagnosis by NHS2 participants has good reliability, and future analyses will be strengthened by our new ability to conduct sensitivity analyses with refined confirmed AD subgroups. Therefore, we are encouraged that NHS2, and likely other cohorts of health professionals, can continue to be used for epidemiologic studies of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AD	atopic dermatitis
NHS2	Nurses' Health Study 2
ADSEQ	AD Screening and Evaluation Questionnaire
ADSEQ2	AD Screening and Evaluation Questionnaire 2

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Figure 1.

Flow diagram of Nurses' Health Study 2 respondents reporting a history of atopic dermatitis and completing the Atopic Dermatitis Screening and Evaluation Questionnaire 2.

Figure 2.

Age of participants (a) at atopic dermatitis diagnosis (n=1,967), (b) when atopic dermatitis was at its worst (n=1,708) and (c) when atopic dermatitis was last active (n=1,969).

Characteristics of respondents with atopic dermatitis according to each case definition of atopic dermatitis in the Nurses' Health Study 2

Characteristic	Case definitions		
	Self-report in 2009 or 2013 (n=10,647)	Reiterated self-report in 2017 (n=1,996)	Algorithm 1* (n=1,538) Algorithm 2* (n=1,293)
Age in 2017, years	62 (5)	62 (5)	62 (5)
Body mass index in 2009 (kg/m ²)	28 (7)	28 (6)	28 (6)
Alcohol intake in 2009, g/d	6 (10)	7 (11)	6 (10)
Physical activity, metabolic equivalent hours/week in 2009	23 (29)	23 (25)	23 (25)
Current smokers (2009), %	6	5	5
Past smokers (2009), %	30	29	29
Race, % white	95	96	96
Asthma, %	33	33	35
Hayfever (allergic rhinitis), %	46	48	50
Food allergy, %	19	19	21
Association with asthma relative to the general NHS2 population	2.37 (2.27, 2.47)	2.36 (2.15, 2.59)	2.55 (2.29, 2.84) 2.79 (2.49, 3.13)

For continuous variables, data are presented as means (standard deviations). For proportions, data are presented as percentages. For the association with asthma, results are presented as age-adjusted odds ratios (95% confidence intervals).

* Algorithms 1 and 2 have been validated to confirm cases of atopic dermatitis with >85% specificity. Algorithm 1 was positive for AD if, in addition to reporting a diagnosis of AD, participants indicating they had a rash similar to one of the clinical photos from the Atopic Dermatitis Screening and Evaluation Questionnaire (ADSEQ). Algorithm 2 was positive for AD if participants indicating they had a rash similar to one of the clinical photos from ADSEQ and they reported a family history of atopy.

Table 2.

Characteristics of respondents who reiterated their diagnosis of atopic dermatitis on ADSEQ2

Characteristic	Counts (%)
Age in 2017, years (standard deviation)	62 (5)
<i>Atopic history (n=1,996)</i>	
Asthma	606 (30%)
Hayfever	1,298 (65%)
Food allergy	502 (25%)
Family history * of atopic dermatitis	931 (47%)
Family history * of asthma	716 (36%)
Family history * of hayfever	1,303 (65%)
Family history * of food allergy	446 (22%)
<i>Extent of atopic dermatitis at its worst (body surface area) (n=1,960)</i>	
0–10%	1,808 (92%)
11–20%	74 (4%)
>20%	41 (2%)
Don't know	37 (2%)
<i>Sleep disruption when atopic dermatitis was at its worst (n=1,959)</i>	
Never	923 (47%)
One night per month or less	187 (10%)
Less than one night per week but more than once per month	156 (8%)
One or more nights per week	446 (23%)
Do not know	247 (13%)

ADSEQ2: Atopic Dermatitis Screening and Evaluation Questionnaire 2

* includes parents, siblings, children

Table 3.

Treatments used for atopic dermatitis among respondents who reiterated their diagnosis of atopic dermatitis on ADSEQ2 (n/n (%))

Treatment	Never used	Ever used	Duration of use					
<i>Topical treatments</i>			<1 year	1–2 years	3–5 years	6–10 years	11–20 years	21+ years
Corticosteroids	104/1,963 (5%)	1859/1,963 (95%)	401/1855 (22%)	336/1855 (18%)	376/1855 (20%)	283/1855 (15%)	178/1855 (10%)	281/1855 (15%)
Calcineurin inhibitors	1,622/1,957 (83%)	335/1,957 (17%)	148/335 (44%)	92/335 (27%)	59/335 (18%)	20/335 (6%)	10/335 (3%)	6/335 (2%)
<i>Phototherapy and systemic treatments</i>			<1 month	1–6 months	7–12 months	13–24 months	25+ months	
Phototherapy	1,705/1,963 (87%)	258/1,963 (13%)	99/258 (38%)	101/258 (39%)	32/258 (12%)	17/258 (7%)	9/258 (3%)	
Oral corticosteroids	1,559/1,960 (80%)	401/1,960 (20%)	202/401 (50%)	145/401 (36%)	33/401 (8%)	11/401 (3%)	10/401 (2%)	
Cyclosporine	1,949/1,960 (98%)	11/1,960 (1%)	9/11 (82%)	1/11 (9%)	1/11 (9%)	0	0	
Methotrexate	1,927/1,959 (98%)	32/1,959(2%)	8/32 (25%)	8/32 (25%)	8/32 (25%)	2/32 (6%)	6/32 (20%)	
Azathioprine	1,955/1,958 (>99%)	3/1,958 (<1%)	2/3 (66%)	0	1/3 (33%)	0	0	
Mycophenolate	1,953/1,959 (>99%)	6/1,959(<1%)	3/6 (50%)	0	2/6 (33%)	0	1/6(17%)	

Table 4.

Perceived treatment effectiveness and satisfaction among respondents who reiterated their diagnosis of atopic dermatitis on ADSEQ2, stratified by maximal atopic dermatitis extent (n/n (%))

Maximal extent of atopic dermatitis	Completely disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Completely agree
<i>"I feel treatments for my atopic dermatitis have been effective."</i>					
10% body surface area	78/1,778 (4%)	173/1,778 (10%)	169/1,778 (10%)	650/1,778 (37%)	708/1,778 (40%)
11% body surface area	13/114 (11%)	14/114 (12%)	13/114 (11%)	42/114 (37%)	32/114 (28%)
<i>"I have been satisfied with treatments for my atopic dermatitis."</i>					
10% body surface area	93/1,765 (5%)	199/1,765 (11%)	200/1,765 (11%)	554/1,765 (31%)	719/1,765 (41%)
11% body surface area	17/115 (15%)	15/115 (13%)	16/115 (14%)	33/115 (30%)	34/115 (30%)