

## Title Page

### Title

[Strengths and limitations of the](#) United Kingdom Working Party criteria for atopic dermatitis in ~~Danish~~ adults

### Running head

Atopic dermatitis and diagnostic criteria

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### Study/ethical approval

Study approval was obtained from the Danish Data Protection Agency (ref. 2012-58-0004, j.no. VD-2018-286, I-Suite no.: 6528). Review of an ethics committee is not required in Denmark for studies not involving human tissue but where data are based on surveys.

### Declaration of interests

Dr. Thyssen is supported by an unrestricted research grant from the Lundbeck Foundation and has attended an advisory board for Eli-Lilly, Pfizer, Abbvie, and LEO Pharma and Sanofi-Genzyme, and been a speaker on atopic dermatitis for LEO Pharma, Regeneron and Sanofi-Genzyme and an investigator for Abbvie,

Sanofi-Genzyme, LEO Pharma, Pfizer and Eli Lilly & Co. Dr. Andersen has no conflict of interest. Dr. Halling has no conflict of interest. Dr Williams led the UK Working Party of diagnostic criteria for atopic dermatitis. Dr. Egeberg has received research funding from Pfizer and Eli Lilly, and honoraria as consultant and/or speaker from Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals.

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#### **Author Contributions**

Drs. Egeberg and Thyssen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Thyssen and Egeberg. *Acquisition, analysis, and interpretation of data:* All authors. *Drafting of the manuscript:* Thyssen and Egeberg. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Egeberg. *Obtained funding:* Egeberg. *Administrative, technical, or material support:* All authors. *Study supervision:* All authors.

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**Abbreviations and acronyms**

AD – Atopic dermatitis

H&R - Hanifin and Rajka

ICD – International Classification of Diseases

PPV – Positive predictive value

UKWP - United Kingdom Working Party's Criteria

**Key words**

Adults - Atopic dermatitis – Diagnosis – Validity – UK working Party Criteria

**Abstract (2011/300 words)**

**Background:** The United Kingdom Working Party's (UKWP) criteria were developed to improve epidemiological research in atopic dermatitis (AD), but have not been validated in an exclusively adult European population.

**Objective:** To validate the UKWP criteria for AD in adults.

**Methods:** In this cross-sectional study, three independent samples of adult individuals were drawn and interviewed: patients with a hospital diagnosis of AD or plaque psoriasis in adulthood, and general population controls. Various versions of the UKWP criteria for AD were utilized.

**Results:** [A total of 3,490 \(general population\), 3,834 \(AD\), and 4,016 \(psoriasis\) adult individuals were enrolled in the study.](#) The best combination of the UKWP criteria lead to a sensitivity of 0.71 and a specificity of 0.96 in the general population. The criteria better captured 'AD ever' compared to 'AD within the past 12 months', and had a higher sensitivity in patients with moderate (87.2-97.7%) or severe (95.8-100%) AD at the time of interview compared to those who were asymptomatic (12.6-36.8%). ~~The specificity of the UKWP criteria was lower when a group of psoriasis patients was used as control group~~[The UKWP -criteria also captured high proportions of psoriasis patients \(19.7-47.7%\) when applied in a cohort of unique psoriasis patients.](#)

**Conclusions:** It remains a challenge to accurately diagnose a history of AD in adulthood since symptoms are shared with other skin conditions and AD may have resolved or can be waxing and waning, in turn leading to recall bias. ~~The UKWP criteria performed well in the general population for the purpose of determining the prevalence, but should be used cautiously~~[more carefully when studying comorbidity.](#)

## INTRODUCTION

Atopic dermatitis (AD) is a prevalent inflammatory skin condition of childhood and adulthood..

The 1980 Hanifin and Rajka (H&R) criteria were developed to better delineate AD patients for clinical and investigative studies and avoid misclassification.<sup>1</sup> However, some criteria proved to be either unspecific or occur very infrequently. Some criteria were predominately derived from clinical features observed in AD patients with European ancestry,<sup>2</sup> and expectedly, their performance is less good in non-European populations.<sup>3</sup> To further complicate things, some criteria require invasive diagnostic tests, and several clinical features seem to suffer from interobserver variability and be highly dependent on the patients gender, age, and AD severity.<sup>3-7</sup>

To improve epidemiological research in AD, the United Kingdom Working Party's (UKWP) Criteria for AD were developed in 1994, using the original Hanifin and Rajka criteria as a starting point. The UKWP criteria were validated in groups of predominately pediatric patients with AD as well as healthy controls, and patients with other inflammatory skin conditions.<sup>2, 8, 9</sup> Based on these studies, six features were identified that could reliably separate predominately pediatric AD from other inflammatory skin conditions (Table 1). The major criterion, itch, was selected as it was considered very sensitive, whereas the minor criteria were selected as they were considered to be specific.<sup>8</sup>

The UKWP refinement of the Hanifin and Rajka criteria were applied in a cross-sectional survey of 695 British school children aged 3-11 years, and showed a sensitivity of 70%, a specificity of 93%, a positive predictive value (PPV) of 47% and a negative predictive value (NPV) of 97% when compared with dermatologist examination.<sup>10</sup> False positive cases were ascribed to current inactivity of eczema at the time of examination. While two validation studies have since examined the performance of the UKWP criteria for AD in Asian adults,<sup>11, 12</sup> the UKWP criteria for AD have not yet been exclusively validated in a European adult population.

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Importantly, different versions of the adapted UKWP criteria gave different associations between AD and cardiovascular comorbidities in adults in a general population study.<sup>13</sup> Moreover, recent large surveys have attempted to determine the prevalence of adult AD, and study its comorbidity, by using adapted UKWP criteria. This has spawned growing concerns that the UKWP criteria in their current form cannot be used indiscriminantly to study issues such as the co-morbidities of AD in adults.<sup>14, 15</sup>

We validated the UKWP criteria for AD in adults from the general population. Because of the higher prevalence, and increasing incidence of psoriasis, in adults when compared with children,<sup>16</sup> we also included cohorts of patients with a clinical diagnosis plaque psoriasis.<sup>17</sup>

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## MATERIALS AND METHODS

### *Sampling of the Danish Skin Cohort*

The prospective Danish Skin Cohort was first established in 2018 to study AD and plaque psoriasis<sup>18</sup>. Briefly, the cohort was generated based on 3 independent samples, respectively, i) 10,000 adults from the general population sample randomly drawn from the general Danish population (CPR register) with no diagnostic code of psoriasis or AD in the hospital system, ii) 10,000 adult patients with a diagnostic code for AD (but not plaque psoriasis), and iii) 10,000 adult patients with a diagnostic code for plaque psoriasis (but not AD) randomly drawn from the National Patient Registry.<sup>18</sup> The entire Danish adult population, aged 18 years or older, was eligible for selection. The Danish National Patient Register contains information on all diagnoses given predominately by health care providers from public and private hospitals (both inpatient and outpatient clinics).<sup>19</sup> This register was used to sample the AD and psoriasis populations. Specifically, the AD and psoriasis samples consisted of patients that had received at least one dermatologist diagnosis of, respectively, AD (International Classification of Diseases [ICD]-10 L20) or plaque psoriasis (ICD-10 L40.0) given after their 18<sup>th</sup> birthday. Both diagnoses have been validated and show very high PPV (97% for psoriasis and 92-98% for AD).<sup>20,21</sup> Importantly, all patients with AD who also had a diagnosis of psoriasis given by any health care provider in the National Patient Registry were excluded and vice versa. To reduce participation bias, study participants were not informed about the scope or content of the research project before agreeing to participate. All 30,000 individuals from the three samples were contacted with a written invitation. To increase study participation, patients were contacted via phone a total of five times.

### *Interviews*

Enrolled adults were interviewed at baseline in a structured manner.<sup>22</sup> Disease specific questions related to AD and psoriasis were given to participants from all samples. The exact wording used to generate different version of the UKWP criteria for AD is shown in Table E1.

The major UKWP criterion was based on either a 'history of an itchy skin condition' or a 'history of an itchy skin condition within the past 12 months', and the following variations of the five minor UKWP criteria

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were used in the analysis: i) 'onset of this condition <2 years' or 'onset of this condition in childhood', ii) history of flexural involvement, iii) personal history of asthma or hay fever, iv) 'history of dry skin all over the body', or 'history of dry skin all over the body within the past 12 months', v) 'visible flexural dermatitis' which was assessed by asking patients about current flexural involvement (cubital fossa or popliteal fossa). For details about the original UKWP criteria, the practical manual can be reached online<sup>23</sup> and the current criteria are shown in Table 1. AD severity was assessed by the Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD)<sup>24</sup> for 100% of included subjects. AD severity was then categorized into asymptomatic (PO-SCORAD=0), mild (PO-SCORAD=0.1-24.9), moderate (PO-SCORAD=25.0-50.0), and severe (PO-SCORAD>50.0) disease. Psoriasis patients were asked to measure the body surface area (BSA) currently affected by psoriasis, which had previously been shown to accurately reflect physician-reported BSA scores.<sup>25</sup> Psoriasis severity was categorized based on BSA into mild (BSA <3), moderate (BSA 3-10), and severe (BSA ≥10).

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To study the performance of the UKWP criteria across we created the following groups: i) general population controls (respectively, 'all controls', 'controls who never had AD [either physician diagnosed or self-reported]', and 'controls who never had AD or psoriasis [either physician diagnosed or self-reported]'), ii) patients with dermatologist verified AD (patients that had never received a diagnosis of psoriasis), and iii) patients with dermatologist verified plaque psoriasis (patients that had never received a diagnosis of AD). Creation of the subgroups was done to allow for possible detection of individuals where the UKWP criteria would not perform equally well.

### **Statistical analysis**

We examined, respectively, the 'lifetime' and '12-month' prevalence of AD by using two different versions of the major criterion itch (i.e. 'a history of itchy skin condition ever' vs. 'a history of an itchy skin condition within the past 12-months') and, respectively, 2-3 of 4-5 minor criteria (Table 2 and Table E2). The prevalence of AD in adults with a hospital code of AD reflected the sensitivity (selected data are shown in Tables 2, 3 and all data are shown in Tables E2-E9). The specificity was calculated by the following equation  $specificity = true\ negatives / (true\ negative + false\ positives)$ , which was used in both the general



population and psoriasis samples. To calculate the PPV, we used the following equation  $PPV = \frac{\text{true positive}}{\text{true positive} + \text{false positive}}$ . To calculate the NPV, we used the following equation  $NPV = \frac{\text{true negative}}{\text{false negative} + \text{true negative}}$ .

## RESULTS

A total of 3,490 (general population), 3,834 (adults with AD), and 4,016 (adults with psoriasis) individuals accepted the invitation and were enrolled. Among, respectively, general population controls, AD patients, and psoriasis patients, 55.4%, 69.0% and 55.8% were women. Psoriasis patients were, as expected, older than AD patients, e.g. 72.9% of psoriasis patients were 55 years or older compared to 30.7% of AD patients. General population controls were more evenly distributed across age groups.

Table 2 shows the estimated prevalence of AD when using various combinations of the UKWP criteria 2/5 and 3/5. The sensitivity, specificity, PPV and NPV are detailed in Table 3. Only these data will be discussed in this article, but additional results for 2/4 and 3/4 as well as 2/5 or 3/5 minor criteria can be found in the Tables E2-E9. Analyses showed essentially the same results as the data presented here.

Overall, the estimated prevalence (and sensitivity) of AD was slightly lower when a positive response to the question about ‘onset of an itchy skin condition’ was restricted to ‘onset before 2 years of age’ rather than ‘onset during childhood’, and similarly, when ‘a history of dry skin all over the body’ was restricted to ‘within the past 12 months’ rather than ‘ever’. Similar, studying 2/5 minor criteria gave higher prevalence estimates than 3/5 minor criteria. For example, the prevalence of ‘AD ever’ increased from 4.2-7.8% to 13.4-16.2% in the general population sample when using 3/5 and 2/5 minor criteria, respectively.

The sensitivity of the UKWP criteria in the general population reached 0.52-0.82 when 2/5 minor criteria were used compared to 0.40-0.71 when 3/5 minor criteria (Tables 2 and 3 and Fig. 1). The best combination was found for 3 of 5 minor criteria asking about disease onset in childhood and a history of dry skin ‘ever’, leading to a sensitivity of 0.71 and a specificity of 0.96 (Table 3). The sensitivity of the UKWP criteria was highest when attempting to capture individuals with ‘AD ever’ compared to ‘AD within the past 12 months’. The specificity was high for all combinations of the minor criteria (0.89-0.99) in the general population.

The adapted UKWP criteria that were used to diagnose ‘AD in the past 12 months’ performed well in the group of AD patients who did not report any skin problems within the past 12 months, since only 1.9-5.0% reported having AD within the past 12 months. The sensitivity of the UKWP criteria when diagnosing ‘AD

ever' was low (12.6-36.8%) when examined in an AD population who reported being asymptomatic at the time of interview, but who had at least one previous hospital contact due to AD. The UKWP criteria had a high sensitivity when used to diagnose 'AD ever' in patients with moderate (87.2-97.7%) or severe (95.8-100%) disease as assessed by the PO-SCORAD.

These combinations of the UKWP criteria also captured high proportions of psoriasis patients (19.7-47.7%). This tendency can be appreciated graphically in Fig. 2, which shows the proportion of adults with dermatologists verified AD and plaque psoriasis, respectively, that fulfilled the UKWP criteria. Similar patterns were observed when studying 'AD within the past 12 months'.

Fig. 3 shows the percentage of patients with dermatologist-verified plaque psoriasis and AD that met the respective major and minor UKWP criteria for AD by disease severity. Most criteria performed very well in those with moderate to severe AD as high positive response rates were observed. However, the major criterion also lead to very high positive response rates in patients with psoriasis ([78.9%-92.3%](#)), and generally, there seemed to be no differences in the rate of positive responses among psoriasis patients with mild, moderate and severe disease. Accordingly, the PPV was high when using the AD criteria in a group of patients with 'plaque psoriasis but never AD', indicating that the criteria indeed capture psoriasis.

## DISCUSSION

### Main Findings

This large interview-based study examined the validity of various versions of the UKWP criteria for AD. The best combination of the UKWP criteria led to a sensitivity of 0.71 and a specificity of 0.96 in the general population. When compared with an exclusive psoriasis population, the UKWP incorrectly diagnosed a large proportion of psoriasis patients as having AD.

### Interpretation

The UKWP criteria for AD were developed in an attempt to improve diagnostic criteria for this very common inflammatory skin condition of childhood. The criteria were validated in a clinical setting where most participants were children and where patients with other inflammatory skin conditions also were included.<sup>2, 8, 9</sup> The criteria were also successfully validated in a survey including British school children,<sup>10</sup> but proved to be less useful in pediatric South African and Ethiopian populations.<sup>26, 27</sup> Notably, an attempt to validate the UKWP criteria in Iranian children<sup>28</sup> prompted a useful overview of challenges that need to be addressed when performing a good validation of a set of criteria<sup>29</sup>: i) the recommended protocol should be strictly followed, ii) exact translation to a different language, if needed, is crucial and require first translation to the new language and then translation back to the primary language, iii) the criteria should be tested in the setting they were developed for, iv) one needs to ensure that the assessor, as much as possible, is blinded to the criteria that are being evaluated, and v) ensure that the assessor has the same clinical skills as the average clinician who are expected to use them. While the performance of the UKWP criteria in children is not flawless, they are widely accepted to reliably identify pediatric AD. Importantly, few other chronic inflammatory skin diseases than eczemas exist in high numbers in children, e.g. psoriasis, in turn increasing the accuracy of the criteria.

To our knowledge, only two validation studies have so far examined the performance of the UKWP criteria for AD in adults.<sup>11, 12</sup> A Taiwanese study conducted in nursing staff, showed a sensitivity of 42.2%, a specificity of 99.6%, a PPV of 90.5% and a NPV of 95.2%, whereas a Japanese study conducted in staff

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members at health care centers showed that the sensitivity was 70%, the specificity 90%, the PPV 90.5% and the NPV 95.2%. Both studies validated the UKWP criteria in populations where study participants had knowledge about health care and diseases, which might have affected the outcome. However, importantly, both studies did not examine the validity in a group of individuals with other skin conditions such as psoriasis. Indeed, in our study, we included a group of psoriasis patients, since this disorder has become a common condition and now affects up to 8% of adult Danes and 11% of Norwegians.<sup>30-32</sup> Psoriasis is chronic condition characterized by sharply demarcated symmetrical lesions on several body parts, including the knees and elbows. However, it is also an itchy condition and some lesions in flexures may be less well demarcated. Although psoriasis is different from AD, they are not mutually exclusive diseases.<sup>33</sup> Psoriasis patients may suffer from respiratory problems due to smoking or overweight, and they even get diagnosed with asthma more often than the general population.<sup>34</sup> In the light of these clinical characteristics, it is not surprising that the UKWP in their survey form, and when used in adults, may incorrectly capture psoriasis patients as having AD. Importantly, psoriasis is very uncommon in young children, and when the UKWP criteria for AD are used in this age-group, psoriasis is unlikely to have major impacts the accuracy of the UKWP criteria. ~~though it has not been examined.~~ However, due to the high psoriasis prevalence in adults, this may constitute a genuine problem, particularly for studies of disease co-morbidities where one must be certain that index cases really have the disease of interest. A simple way to exclude this problem in future studies could be to ask about a personal history of psoriasis. Other relevant groups with skin conditions that could ideally have been studied in our survey include [stasis dermatitis](#), [lichen planus](#), ~~non-~~unspecific eczemas and contact eczemas,<sup>7</sup> as then when generalized, may also incorrectly be categorized as being AD. In fact, there have been previous concerns about the inclusion of periorbital eczema in the 'visible flexural dermatitis criteria' as this may also occur in allergic contact dermatitis in adults.<sup>35, 36</sup> Importantly, the risk of misclassification is less of not a concern for the prevalence estimatione given the high specificity and relatively high sensitivity. The ideal study design to explore misclassifications is a general population validation study with closer examination of all false positive cases as has been done in previous validation studies

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**Commented [HW1]:** If you want to add something sensible here it could be "The ideal study design to explore such misclassifications is a general population validation study with closer examination of all false positive cases as has been done in previous validation studies" (you don't want people testing the criteria in a sample of 100 cases of flexural eczema dermatitis for example ie looking at the criteria the wrong way round)

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As per the original UKWP manual instructions, the most suitable form of the criteria need to be applied to the appropriate study. For a general population prevalence study, the UKWP criteria provide a fair trade-off between sensitivity and specificity, but for a case control study where one has to be sure that the cases are genuine, more specific versions are needed and are described in the online manual.<sup>37</sup> Highly specific versions of the criteria are also needed for studies of disease co-morbidity in order to minimize inclusion of psoriasis patients and associated psoriasis co-morbidity. As stated in the original UKWP manual “In countries where there is a high prevalence of other skin diseases that could be confused with atopic eczema, such as scabies or onchocerciasis, it seems prudent to stipulate that *the eruption must lack specific features of that dermatosis.*”<sup>38</sup> Those conducting the examination should be capable of identifying eruptions of other common dermatoses, and preferably be dermatologists.

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Collectively, our adult data study indicates that various versions of the UKWP refinement of the Hanifin and Rajka criteria ~~may~~ misclassify cases of psoriasis and possibly other skin conditions as AD. Our findings have important ramifications for the interpretation of prevalence and comorbidity studies using UKWP criteria in adults, and even for surveys using questions based on chronicity and itch to identify AD, since there is a high likelihood that other inflammatory skin conditions have been captured besides AD. For example, ~~since~~ psoriasis is strongly associated with obesity, diabetes, and heart disease, this could explain some of the positive associations between AD and cardiovascular risk factors found in previous studies.<sup>13, 39, 40</sup> Moreover, comorbidities that are infrequent in psoriasis patients, but frequent in AD patients, may be underestimated in case of misclassification. Future epidemiological comorbidity studies using the UKWP criteria in adult populations should therefore be carefully performed to avoid misclassification, and false high prevalence rates.

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### Limitations

This study had several limitations. The participation rate was low, but this is the expected level of such studies in Denmark nowadays. We do not expect that the participation rate influenced the interpretation of the study since the control groups consisted of AD and psoriasis patients who had their diagnosis given by a dermatologist ensuring high accuracy. Our primary aim was to validate the criteria and not to estimate the

prevalence of AD in the general adult population. Importantly, individuals were unaware of the specific content of the survey when enrolled, thereby limiting the risk of participation bias. Difference in time between signs and symptoms of skin disease and questioning may have affected the results given that an itchy skin condition is necessary criterion for the UKWP criteria. Using the UKWP criteria in AD and psoriasis patient populations is a very stringent and arguably artificial test, e.g. the inclusion of asymptomatic AD patients.

### ***Conclusion***

Clinicians and researchers should be cognizant about the important limitations of using the UKWP criteria and should instead use the most appropriate version when designing and interpreting studies.

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## Table and figures

### Table 1 - UKWP criteria for AD in children

### Table 2 – Numbers and percentages of patients meeting the UKWP criteria across populations

### Table 3 - Validity of the UKWP criteria with different control populations

### Figure 1 – Differences in specificity of the UKWP criteria when different control populations are used

**Legend:** These figures show differences in sensitivity and specificity when the general population and patients with psoriasis, respectively, are used as control groups. When the sensitivity is high, the specificity is heterogeneous and dependent on the control population, suggesting that misclassification is high. When the specificity is high in both control populations, the sensitivity is low. AD, atopic dermatitis; UKWP, United Kingdom Working Party

### Figure 2 – Proportion (%) of adults with dermatologists verified atopic dermatitis and plaque psoriasis, respectively, that fulfill the UKWP criteria

**Legend:** In various combinations, the sensitivity of of the United Kingdom Working Party (UKWP) criteria fluctuates considerably. When most sensitive, the UKWP criteria captures 81.7% of adult patients with atopic dermatitis, but at the same time they also capture 47.7% of adult patients with plaque psoriasis.

### Figure 3 – Percentage of patients with dermatologist-verified plaque psoriasis and atopic dermatitis meeting the respective UKWP criteria