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Questionnaire use depends on the study goal, target group and phase of the condition

DOI: 10.1111/bjd.20948

Linked Article: Szabó *et al.* *Br J Dermatol* 2022; **186**:485–495.

Assessment of questionnaires in research and clinical practice has become part of the daily routine, facilitated by the digital opportunities that allow patients to electronically fill out questionnaires in an easy, accessible way in a relatively short amount of time. Moreover, the overall methodological quality has largely improved during the last decade.

Frequently used questionnaires and assessment tools are usually characterized by high standards of reliability and internal and external validity. The choice of questionnaires therefore largely depends on the goal and content of the study and the related target population. Additionally, there are key differences in requests for assessment instruments in different research settings. For example, while a short questionnaire with relatively broad categories might be most useful as a screening and signal detection instrument in clinical practice in large epidemiological studies, a similar questionnaire might not be sensitive enough to use in a large randomized controlled trial to study small changes during new therapies in different subgroups of patients. A well-known example is the EuroQol-5D, which is the most frequently used and best validated scale for cost-effectiveness analyses in skin disease and other conditions, although the sensitivity of the five items has been questioned in skin diseases.[1]

Such differences in questionnaire use are also reflected in the present study in this issue of the BJD.[2] Szabó *et al.* compare the Dermatology Life Quality Index (DLQI), DLQI-Relevant and Skindex-19. The DLQI is the most well-known, easy-to-use and validated questionnaire in many countries, with extended norms for many skin conditions. It is most useful as an overall quality-of-life instrument to get an impression of the impact of the skin disease on daily life. On the other hand, Skindex-19 might be more sensitive than the DLQI when it comes to describing specific psychological and social dimensions that might change during the course of the disease, for example in self-management studies. This may also apply to other questionnaires that have been developed for specific purposes with regard to skin diseases, such as the measurement of itch–scratch problems (e.g. Impact of Chronic Skin Disease on Daily Life),[3] stigmatization (e.g. Weight Self-Stigma Questionnaire)[4] or illness cognitions (e.g. Itch Cognition Questionnaire).[5]

In the end, there is no one-size-fits-all solution to the assessment of the various dimensions that are impacted by the effects of skin diseases. It all depends on the particular perspective of the given study. Further research will benefit from a more detailed and systematic description of the exact purpose and added value of specific questionnaires in particular fields where they would be most useful, along with an overview of which questionnaires might work for whom, in which conditions, and during which phase of the disease.

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Conflicts of interest: the author declares no conflicts of interest.

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Atopic dermatitis: filaggrin and skin barrier dysfunction

DOI: 10.1111/bjd.20946

Linked Article: Hoyer *et al. Br J Dermatol* 2022; **186**:544–552.

Atopic dermatitis (AD) is among the most common skin diseases that affect children and adults. It has been associated with several other atopic illnesses like asthma, seasonal allergies and food allergies and is often considered to be the first illness on the march to these other allergic illnesses.[1] PreventADALL was a randomized controlled trial of 2397 mother–child pairs designed to evaluate AD therapeutic prevention strategies using oil-emulsified baths and topical cream. The results showed no therapeutic benefit on the incidence of AD (AD incidence 8% for non-intervention vs. 11% for intervention).[2]

Filaggrin loss-of-function (LoF) mutations have been associated with the prevalence and severity of AD and are the most prevalent genetic mutations associated with this condition.[3,4] The *FLG* gene is responsible for protein coding of profilaggrin, which is ultimately processed to filaggrin and is important for skin barrier function.[3,5] *FLG* genetic variation varies by ancestry and can vary within race.[3,5,6]

In this issue of the *BJD*, Hoyer *et al.* used, regardless of treatment assignment, the prospectively collected PreventADALL dataset for a post hoc evaluation of the association of filaggrin LoF with the prevalence of AD, eczema and skin barrier dysfunction. The latter was assessed by transepidermal water loss (TEWL), which can be technically difficult to measure.[7,8] Children from PreventADALL were genotyped for the most common European filaggrin LoF mutations – R501X, 2282del4 and R2447X – and were evaluated at 3, 6 and 12 months of age for the presence of dry skin, eczema, AD and skin barrier function (TEWL).[7] About 9% of the cohort had filaggrin LoF, and all subsequent analyses compared patients with filaggrin LoF variants to those without. At all three timepoints filaggrin LoF was associated with eczema, and at the latter two timepoints with AD.[7] Higher TEWL was only noted at month 6 among those with filaggrin LoF.[7]

What did we learn? Filaggrin LoF variants were known to be relatively uncommon in the general population and more common in those with AD.[3,5–7] However, if barrier dysfunction, as measured by TEWL, is the mechanism that drives the causal relationship between filaggrin LoF and AD, then TEWL should have been elevated at all timepoints and preceded the diagnosis of AD in infants.[7–9] It is possible that TEWL might not be a good measure of the causal pathway of filaggrin insufficiency and AD, but a better measure of AD severity.[8] All filaggrin LoF variants are not clinically the same, so by focusing on only three variants, other important variants might not have been measured.[4,5,8] Keratinocyte filaggrin production is also diminished by T helper 2 cytokines that are common to AD, and this might occur later in life.[10] As a result, immune pathways may have a greater effect on TEWL than filaggrin LoF. Filaggrin insufficiency resulting in an impaired barrier function and then AD is likely to occur both genetically via LoF variants and also via immune inhibition, making filaggrin a not so innocent bystander. As noted by Hoyer *et al.*, further study is needed.

Acknowledgment: this commentary was reviewed by Dr Zelma Chiesa Fuxench MD MSCE and Dr Katrina Abuabara MD MSCE. I am grateful for their review and criticism.

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Conflicts of interest: the author declares they have no conflicts of interest.

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