An association of atopic dermatitis with depression and anxiety has been observed in several epidemiological studies, such as that by Schonmann et al.\(^1\) However, the underlying mechanisms, and whether this association is causal, is not yet clear. The study by Baurecht et al.\(^2\) in the current issue of the BJD is the first to investigate this important and frequently reported association using Mendelian randomization. This approach allows the causality of the observed effect to be studied, controlling for reverse causation, confounding and biases such as reporting or recall bias.\(^3\)

Mendelian randomization relies on the definition of instrumental variables based on genetic variants.\(^4\) These genetic variants should be robustly associated with the exposure of interest and can serve as a proxy for it. A significant association between the instrumental variable and the outcome indicates causality, as the instrumental variable is independent of external factors and is randomly allocated at conception, hence the method name. In two-sample Mendelian randomization, the associations of the instrumental variable with the exposure and with the outcome are assessed in two different populations. This approach has some advantages to one-sample Mendelian randomization and increases the statistical power and the validity of the results.\(^5\)

With the rise of large-scale genome-wide association studies (GWAS) becoming available over the past decade, the possibilities of better understanding the genetic architecture and identifying risk variants of a broad variety of health outcomes have increased dramatically. As the summary statistics of GWAS consortia are often made publicly available, the results can be used for two-sample Mendelian randomization studies. Baurecht et al. obtained summary statistics from large, sufficiently powered GWAS studies on atopic dermatitis, broad depression, major depressive disorder and anxiety. The results did not show any evidence for a causal relationship of atopic dermatitis with depression or anxiety, with all odds ratios close to 1.

Mendelian randomization relies on the fulfilment of several assumptions,\(^6\) including a robust association of the genetic variants with the exposure but independence from confounding factors and outcome. Accordingly, the authors of the present analysis conducted several sensitivity analyses to test for these assumptions, such as validity of the instruments or pleiotropy. The known causal association of atopic dermatitis with asthma, which was included as a positive control outcome. Although a higher risk for depression or anxiety was reported for patients suffering from atopic dermatitis, the present Mendelian randomization study does not provide evidence of a causal role of atopic dermatitis with respect to the development of these disorders. The authors discuss potential reasons for this discrepancy, such as residual confounding by an unknown factor or a comorbidity. Nevertheless, this well designed study by Baurecht and colleagues offers important novel evidence indicating a lack of causality, calling for further research to identify the mechanism responsible for the observed association of atopic dermatitis with depression and anxiety.

Addressing the causality of the association of atopic dermatitis with depression and anxiety using Mendelian randomization

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An association of atopic dermatitis with depression and anxiety has been observed in several epidemiological studies, such as that by Schonmann et al.\(^1\) However, the underlying mechanisms, and whether this association is causal, is not yet clear. The study by Baurecht et al.\(^2\) in the current issue of the BJD is the first to investigate this important and frequently reported association using Mendelian randomization. This approach allows the causality of the observed effect to be studied, controlling for reverse causation, confounding and biases such as reporting or recall bias.\(^3\)

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Although a higher risk for depression or anxiety was reported for patients suffering from atopic dermatitis, the present Mendelian randomization study does not provide evidence of a causal role of atopic dermatitis with respect to the development of these disorders. The authors discuss potential reasons for this discrepancy, such as residual confounding by an unknown factor or a comorbidity. Nevertheless, this well designed study by Baurecht and colleagues offers important novel evidence indicating a lack of causality, calling for further research to identify the mechanism responsible for the observed association of atopic dermatitis with depression and anxiety.
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Getting to the core of peripheral vascular malformations: measuring what matters

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The management of peripheral vascular malformations – previously limited to sclerotherapy, laser treatments and surgical excision – is progressing into the realm of molecular targeted therapies. Thus, it is timely that in this issue of the BJD, development of a patient-reported outcome measure addressing symptoms and appearance in vascular malformations (OVAMA questionnaire) is presented.1

Advances in cell biology and genomics have led to recognition of the role of gene mutations in the development of vascular malformations in at least two intracellular signalling pathways: RAS/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), and phosphatidylinositol 3 kinase (PIK3)/protein kinase B/mammalian target of rapamycin (mTOR).2 These discoveries, providing insight into pathogenesis, have consequently led to the development of targeted interventions.3

The median cost for research and development of therapeutic agents to introduce a new drug to market, inclusive of costs for failed trials, has been estimated at US$980 million (in 2018 dollars). Within the class of antineoplastic and immunomodulatory interventions, the estimated cost was three times higher at US$2771 million.4 However, despite these investments, there has been inadequate attention to the data in trials to inform healthcare utilization rather than simply to achieve regulatory drug approval. This lack of outcome concordance was shown in dermatology research evaluating a random sample of 10 Cochrane Skin systematic reviews and their associated dermatology trials. It was found that, of the outcomes sought by the reviews, 17 of 60 were not reported in any trial, while 12 of 60 were used in less than half of the trials. Major shortcomings identified included lack of standardized outcome measures, inadequate outcome reporting and poor concordance of outcomes used in reviews and clinical trials. The results of these deficiencies and lost opportunities resonate into the future as they negate the potential for meta-analyses and obfuscate attempts at comparative effectiveness research.5 These issues represent an unnecessary waste of research resources.

The identification, development and subsequent application of core outcome sets, a minimum set of outcome domains and their relevant measures for clinical trials of a specific disease, may help to address these shortcomings.6 Prior consensus for trials on vascular malformations had identified the following core domains: radiological assessment, physician-reported location-specific signs, patient-reported severity of symptoms, pain, quality of life, satisfaction and adverse events.7 In the absence of a measure addressing the core domains of symptom severity and appearance, the authors undertook development of such a patient-reported outcome measure for interventional clinical trials in peripheral vascular malformations.1 As we enter a new era of formal clinical trials of innovative treatments uncovered by careful iterative research, let us hope that the same care and attention will also be applied by trialists to selecting the outcome measures that matter most: to patients, clinicians and other relevant stakeholders – core outcome sets.

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1 Lokhorst MM, Horbach SER, Young-Afat DA et al. Development of a condition-specific patient-reported outcome measure for measuring symptoms and appearance in vascular malformations: the OVAMA questionnaire. Br J Dermatol 2021; 185:797–803.