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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]

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, could be successfully demonstrated, confirming the feasibility of the approach.

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

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