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Relationship between atopic dermatitis, depression and anxiety: a two-sample Mendelian randomization study

H. Baurecht[1] C. Welker,[1] S.-E. Baumeister,[2,3,4] S. Weidnger,[5] C. Meisinger,[2,3] M.F. Leitzmann[1] and H. Emmert[5]

[1]Department of Epidemiology and Preventive Medicine, University of Regensburg, Germany
[2]Chair of Epidemiology, LMU München, UNIKA-T Augsburg, Augsburg, Germany
[3]Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany
[4]University Hospital Münster, Münster, Germany
[5]Department of Dermatology, Allergology and Venereology, University Hospital Schleswig-Holstein, Kiel, Germany

Correspondence
Hansjörg Baurecht.
Email: hansjoerg.baurecht@ukr.de

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Summary

Background Growing evidence suggests that atopic dermatitis (AD) is associated with an increased risk of depressive disorders and anxiety. However, existing studies were observational and may have uncovered correlations but could not easily disentangle noncausal or reverse-causal associations because these associations could be confounded and may not reflect true causal relationships.
Objectives To examine, in a two-sample Mendelian randomization study, the potential effect of AD on the risk of depressive disorders and anxiety.
Methods Genetic instruments from the largest available genome-wide association study (GWAS) for AD (10 788 cases and 30 047 controls) were used to investigate the relationship to broad depression (170 756 cases and 329 443 controls), major depressive disorder (MDD; 30 603 cases and 143 916 controls) and anxiety (5580 cases and 11 730 controls). A set of complementary approaches were carried out to assess horizontal pleiotropy and related potential caveats occurring in MR studies.
Results We observed no causal impact of AD on the risk of depressive disorders and anxiety, with close-to-zero effect estimates. The inverse weighted method revealed no associations of AD on broad depression [odds ratio (OR) 1·014; P = 0·431], probable MDD (OR 1·002; P = 0·568), International Classification of Diseases, Ninth/Tenth Revision-based MDD (OR 1·001; P = 0·466) or anxiety (OR 1·097; P = 0·180).
Conclusions This MR study does not support a causal effect of AD on depression and anxiety.

What is already known about this topic?

- There is growing evidence that atopic dermatitis (AD) is related to depressive disorders and anxiety.
- Observational studies are prone to reverse causation and confounding, distorting true relationships.
- Observational study results are inconclusive regarding the effect of AD on depression and anxiety.

What does this study add?

- Using Mendelian randomization as an alternative approach to investigate causality, we did not find a causal relationship between AD and depressive disorders or anxiety.

Depression was found to be the third leading cause of nonfatal health loss in the 2017 Global Burden of Disease Study,[1] affecting > 300 million people worldwide.[2] The World Health Organization ranks depression as the single largest contributor to global disability and as a major contributor to death by suicide, with about 800 000 fatalities per annum. Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder. It has a complex pathophysiology encompassing a genetic predisposition and environmental triggers,[3] and affects 15–20% of children and 5–10% of adults.[4]

Emerging evidence has suggested that AD is associated with depression and anxiety,[5] reducing the quality of life of those affected.[6] In a matched case–control study exploiting routinely collected data from the UK Clinical Practice Research Datalink, the results showed a significantly increased risk of incident depression and anxiety in patients with AD.[7] These potential associations between AD and depression and anxiety have been further substantiated by systematic reviews and meta-analyses.[8,9]

However, previous studies were based on observational epidemiological designs, which are prone to reverse causation and unmeasured confounding.[10] Mendelian randomization (MR) provides an alternative approach to investigating causality by using genetic variants as instrumental variables and thereby accounting for observational study bias.[11,12] We present a MR study on the association of AD and the risks of depression and anxiety.

Materials and methods

We carried out a two-sample MR analysis based on summary statistics, where the instrument–exposure and instrument–outcome associations were estimated in independent samples. We retrieved associations of single-nucleotide polymorphisms (SNPs) with AD from a subset of the largest genome-wide association study (GWAS) of European descent.[13] SNP–outcome associations were derived from genetic association data on depression and anxiety.[14–16] Additionally, we carried out positve and negative control outcome analyses to assess the potential biasing influences from horizontal pleiotropy and selection bias,[17–19] and tested for reverse causation bias.[17,20] A positive control outcome is an outcome for which it is already well established that the exposure is causal. A negative control is an outcome lacking a causal link with the exposure. Reverse causation is present if the outcome influences the exposure leading to distorted SNP–outcome associations and thus misleading inference.

Selection of genetic instrumental variables for atopic dermatitis

For AD genome-wide summary statistics from a GWAS of 10 788 patients with AD and 30 047 controls from 20 studies of European descent were publicly available, excluding the 23andMe study.[13] All analyses were based on this dataset. These samples had been genotyped, imputed to 1000 Genomes Project Phase 1 (release March 2012), harmonized and variants with minor allele frequencies > 1% were analysed across studies. Summary statistics were reported for variants with high imputation quality ($r^2 > 0{\cdot}3$ for MACH and proper info > 0·4 for IMPUTE). In order to exclude variants with spurious linkage disequilibrium, we used a clumping algorithm (r^2 threshold = 0·001; window size = 10 mB) (Table S1; see Supporting Information).

For instrument selection we chose two strategies. Firstly, we used genetic instruments on a lower significance threshold ($P < 5 \times 10^{-4}$) in order to increase the explained phenotypic variance and thus the statistical power. Secondly, we selected the 25 established genome-wide significant ($P < 5 \times 10^{-8}$) sentinel SNPs reported in the largest GWAS of AD conducted in a European discovery cohort of 18 900 cases and 84 166 controls (the sample above plus the 23andMe study) and replicated in independent samples comprising 30 588 cases and 226 537 controls of European descent,[13] totalling 49 488 cases of AD and 310 703 controls (Table S2; see Supporting Information). This approach can be considered a three-sample MR analysis because genetic instruments were obtained from the complete genetic study on AD (including discovery and replication),[13,17] while available exposure summary statistics were derived from a subsample representing 11·3% of the total sample size.

Genome-wide association study summary statistics for depression and anxiety

SNP–outcome associations were retrieved from the most recent and largest GWAS meta-analyses on broad depression, excluding 23andMe, from 33 studies of the Psychatric Genomics Consortium and the UK Biobank,[14,15] totalling 170 756 cases and 329 443 controls. GWAS summary statistics for probable and International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10)-coded major depressive disorder (MDD) were obtained from the UK Biobank with 30 603 cases and 143 916 controls, and 8276 cases and 209 308 controls, respectively. Broad depression was defined as self-reported past help-seeking for problems with nerves, anxiety, tension or depression, while probable MDD was acertained by self-reported depressive symptoms with associated impairment, and ICD-9/10-coded MDD was based on hospital admission records. GWAS summary statistics for anxiety were derived from the Anxiety NeuroGenetics Study (ANGST) Consortium,[16] comprising seven independent studies totalling 5580 patients with diagnosed anxiety disorder and 11 730 controls (Table S2).

Genome-wide association study summary statistics for negative and positive control outcomes

A systematic review reported high asthma risk in young children with AD;[21] thus, we used asthma as a positive control outcome. GWAS summary statistics for asthma were obtained from the most recent GWAS meta-analysis.[22] Summary

statistics for the negative control outcome body height were retrieved from the GIANT consortium (Table S2).[23]

Statistical analyses

Primary analysis

A priori statistical power was calculated according to Brion *et al.*[24] Summary statistics results were harmonized to ensure effect size alignment and to prohibit strand mismatch. Wald ratios were obtained by dividing the log odds ratio (OR) from the SNP–outcome associations by the log OR of the corresponding SNP–AD association, standard errors were calculated using the delta method. Wald ratios were combined using the multiplicative random effects inverse-variance weighted (IVW) model for weak instruments, as well as for established AD risk SNPs retrieved from an external sample.[17] To adjust for multiple testing, we applied the false-discovery rate and present q values.[25]

Heterogeneity analysis and test for directional pleiotropy

Valid estimation of a causal effect using MR requires that all instruments are independent of the outcome conditional on the exposure and confounders.[18] Violations of this assumption through horizontal pleiotropy, whereby the instruments exert an effect on the outcome independent of the exposure, can introduce bias. To address the issue of pleiotropy, we examined the heterogeneity of ratio estimators, based on Cochran's Q, the I^2 statistic, and the MR Egger intercept.[18] In the case of balanced pleiotropy (i.e. pleiotropic effects are independent of the magnitude of the SNP–exposure associations; and if the mean pleiotropic effect is zero), the effect can be reliably estimated by the multiplicative random effects IVW method.[17,18]

Analyses using pleiotropy-robust methods

If the mean pleiotropic effect is nonzero, robust meta-analytic methods are indicated.[18] Thus, for sensitivity analyses, we carried out a suite of pleiotropic-robust methods (weighted median; robust-adjusted profile score; radial regression MR; and MR pleiotropy residual sum and outlier),[26] applied leave-one-out analysis to assess whether the IVW estimate was driven by a single SNP, and performed positive and negative control outcome analyses. Complementary MR analysis was carried out using the causal analysis using summary effect estimates (CAUSE) approach.[27] By incorporating all genetic variants, which increases statistical power, CAUSE assesses whether GWAS summary statistics for the exposure and outcome are consistent with a causal model, where the majority of variants affect the outcome through the exposure, or with a shared model, where the majority of variants affect an unobserved heritable confounder acting on both exposure and outcome. An integrated formal analysis tests the null hypothesis that there is no difference in model fit between the sharing and causal model. For this Bayesian approach, which estimates the parameters γ, the causal effect estimate, η, the effect of the unobserved confounders on the outcome and q, the proportion of variants acting via the confounders by a posterior distribution, parameter priors were set to default, as described elsewhere.[27] CAUSE has been demonstrated to make fewer false detection of causal relationship in the presence of pleiotropy than other established methods.

Three-sample Mendelian randomization

In a two-sample MR study, weak instrument bias may mitigate the estimated causal effect towards null. To overcome this problem, three-sample MR studies have been proposed for which genetic instruments are selected by one dataset, whereas exposure outcome association by MR analysis is carried out using two different datasets.[17]

Test for reverse causation, and negative and positive control outcome

Further approaches to sensitivity analysis and assessment of the robustness of the MR analysis are to test for reverse causation, and negative and positive control outcome.[17] Reverse causation (i.e. the outcome influencing the exposure) can be tested using genetic instruments associated with the outcome and carrying out MR analysis on the exposure. A positive control outcome is an outcome for which the causal exposure outcome association is already established. A negative control outcome is an outcome for which a causal link to the outcome is lacking.

All analyses were performed using the packages metafor (2.4.0), MendelianRandomization (0.4.2), TwoSampleMR (0.5.5), MRPRESSO (1.0) and cause (1.2.0) in R, version 4.0.2. Reporting follows the STROBE-MR (Strengthening the Reporting of Observational studies in Epidemiology – Mendelian randomization) statement.[28]

Results

Primary analysis

In total, 470 SNPs as weak genetic instruments ($P < 5 \times 10^{-4}$) for AD explained 18·7% of the phenotypic variance. With a type I error rate of 5%, there was ≥ 95% power to detect a causal association of an OR > 1·10 with broad depression, probable MDD and ICD-9/10-based MDD. We detected an expected OR > 1·15 for anxiety with a power of > 96% (Table S1). With regard to reverse causation, the explained phenotypic variance of the 647 and 342 genetic instruments for broad depression and anxiety is 2·5% and 29·7%, respectively. We had ≥ 80% power to detect an expected OR of > 1·22 for depression and > 1·06 for anxiety on AD. Applying standard IVW MR analysis, we found no evidence for effects of genetically instrumented AD on broad depression [OR 0·995, 95% confidence interval (CI) 0·99–1·00; P = 0·068, q = 0·356)], probable MDD (OR 0·999, 95% CI 0·998–

1·001; P = 0·413, q = 0·596), ICD-9/10-based MDD (OR 1·00, 95% CI 0·999–1·000; P = 0·345, q = 0·596) or anxiety (OR 1·011, 95% CI 0·962–1·063; P = 0·668, q = 0·668) (Table 1, Figure 1).

Heterogeneity analysis and test for directional pleiotropy

The strength of all 470 SNPs as genetic instruments measured by the F statistics was greater than the common threshold of 10 (range 12·13–117·19). Substantial heterogeneity between Wald ratios in the IVW estimate was observed only for broad depression, but low hetereogeneity was seen for all other outcomes (Table S3; see Supporting Information). For all considered outcomes, the intercept test from the MR Egger regression was not statistically significant and did not indicate directionaly pleiotropy (Table S3), although the test might have been underpowered.[18] When more robust models towards directional pleiotropy were employed, we observed strikingly similar estimates of ORs close to 1 ($0{\cdot}599 \leq q \leq 0{\cdot}780$; Table 1). In addition, leave-one-out analyses showed no single SNP driving the results (Table S4; see Supporting Information).

Analysis using pleiotropy-robust methods

Robust methods also indicated no relation of AD to depression, probable and ICD-9/10-based MDD or anxiety ($0{\cdot}246 \leq q \leq 0{\cdot}668$; Table 1). The null associations were futher supported by the CAUSE analysis, which did not indicate that a causal model better fits the data than a shared model for depression [OR 1·01, 95% credible interval (CredIn) 1·00–1·03; P = 0·431], probable MDD (OR 1·00, 95% CredIn 1·00–1·01; P = 0·763), ICD-9/10-based MDD (OR 1·00, 95% CredIn 1·00–1·00; P = 0·983) or anxiety (OR 1·02, 95% CredIn 0·914–1·13; P = 0·987).

Three-sample Mendelian randomization

To further corroborate the null findings, we adopted an approach related to three-sample MR to select instruments from the complete genetic study on AD (discovery and replication)[13] and carry the established instruments explaining 1·5% of the phenotypic variance forward to the subset with available summary statistics representing 11·3% of the complete study (Table S5; see Supporting Information). Again, we observed no association of genetic instrumented AD with broad depression and anxiety (Figure 1, Table 1).

Test for reverse causation, and negative and positive control outcome

For further sensitivity analyses, we calculated reverse causation and carried out positive and negative control outcome analyses. Neither reverse causation nor negative control outcome revealed a significant effect of any mental outcome with AD (Tables S6 and S7; see Supporting Information). However, an observed association with the positve control outcome of asthma showed a well-known strong causal association, confirming our analyses (Table S7).

Table 1 Mendelian randomization (MR) estimates for the relationship between genetically instrumented atopic dermatitis and broad depression, probable and International Classification of Disease, Ninth/Tenth Revision (ICD-9/10)-based major depressive disorder (MDD), as well as anxiety

		Weak IVs ($P < 5 \times 10^{-4}$)				Established AD loci ($P < 5 \times 10^{-9}$)[13]			
Outcome	Method	OR	95% CI	P-value	q-value	OR	95% CI	P-value	q-value
Broad depression	IVW	0·995	0·99–1·00	0·068	0·356	1·014	0·980–1·048	0·431	0·676
	Weighted median	0·994	0·987–1·001	0·105	0·356	1·018	0·990–1·047	0·206	0·676
	Robust-adjusted profile score	0·993	0·988–0·999	0·012	0·421	1·018	0·988–1·048	0·244	0·599
	IVW radial	0·995	0·991–1·00	0·071	0·246	1·014	0·980–1·048	0·430	0·610
	MR PRESSO	0·996	0·991–1·00	0·070	0·356	1·019	0·991–1·048	0·199	0·599
Probable MDD	IVW	0·999	0·998–1·001	0·413	0·596	1·002	0·996–1·008	0·568	0·676
	Weighted median	0·999	0·997–1·001	0·516	0·596	1·001	0·992–1·010	0·780	0·676
	Robust-adjusted profile score	0·999	0·998–1·001	0·226	0·645	1·002	0·996–1·009	0·475	0·780
	IVW radial	0·999	0·998–1·001	0·413	0·596	1·002	0·996–1·008	0·568	0·676
	MR PRESSO	0·999	0·998–1·001	0·413	0·596	1·002	0·996–1·008	0·574	0·676
ICD-9/10-based MDD	IVW	1·000	0·999–1·000	0·345	0·596	1·001	0·998–1·004	0·466	0·676
	Weighted median	1·000	0·999–1·001	0·580	0·596	1·001	0·997–1·005	0·759	0·676
	Robust-adjusted profile score	1·000	0·999–1·000	0·255	0·668	1·002	0·999–1·005	0·210	0·780
	IVW radial	1·000	0·999–1·000	0·346	0·596	1·001	0·998–1·004	0·466	0·599
	MR PRESSO	1·000	0·999–1·000	0·345	0·596	1·001	0·998–1·004	0·474	0·676
Anxiety	IVW	1·011	0·962–1·063	0·668	0·668	1·097	0·958–1·257	0·180	0·599
	Weighted median	1·030	0·954–1·113	0·447	0·668	1·040	0·861–1·255	0·685	0·599
	Robust-adjusted profile score	1·022	0·968–1·079	0·438	0·596	1·102	0·953–1·275	0·191	0·761
	IVW radial	1·011	0·963–1·062	0·662	0·596	1·097	0·976–1·234	0·121	0·599
	MR PRESSO	1·011	0·963–1·062	0·663	0·668	1·097	0·976–1·234	0·135	0·599

IVW, inverse-variance weighted; MR PRESSO, MR pleiotropy residual sum and outlier.

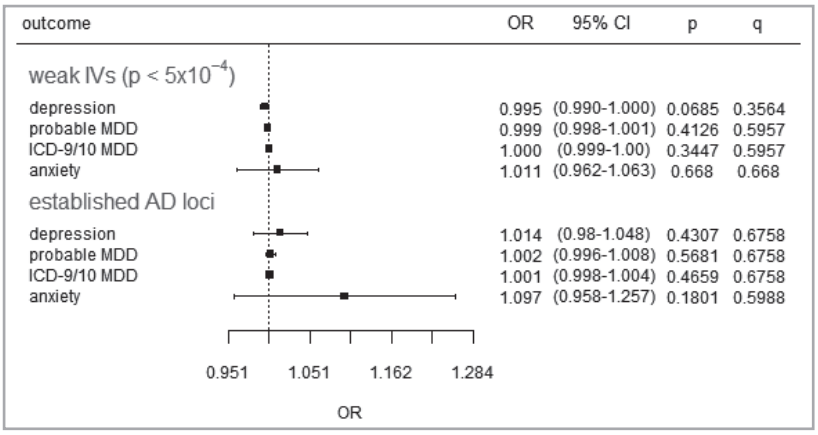

Figure 1 Mendelian randomization estimates for the relationship between genetically instrumented atopic dermatitis (AD) and broad depression, probable and International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10)-based major depressive disorder (MDD), as well as anxiety, using the inverse-variance (IV) weighted method. CI, confidence interval; OR, odds ratio.

Discussion

To the best of our knowledge, the current study represents the first MR analysis of genetically determined AD in relation to depressive disorders and anxiety. Using genetic instruments from the largest available AD GWAS summary statistics of 10 788 cases and 30 047 controls, as well as from the largest depression GWAS of 170 756 cases and 329 443 controls, we found no evidence for a role of AD in the risk of depressive disorders and anxiety. This finding does not support observational research, where AD has been associated with an increased incidence of depression and anxiety.[7] In a systematic review and meta-analysis including 18 studies on adults (91 324 patients with AD and 6 046 825 reference individuals) an association between AD and depression was shown (pooled OR 2·19, 95% CI 1·87–2·57).[8] In the same study, a meta-analysis on the relationship between AD and anxiety based on 13 studies (38 225 adults with AD and 4 523 540 reference individuals) also found a positve association (pooled OR 2·19, 95% CI 1·75–2·73). A further sytematic review and meta-analysis including observational studies confirmed the strong association between AD and higher depression scale scores.[29] Our analysis does not support a causal relationship between AD and depression. It is possible that the previously observed positive association between AD and depression or anxiety is coincidental or is confounded by an unknown factor and not directly caused by AD, for example symptoms associated with AD such as chronic itch or treatment burden/need. Furthermore, a causal link between AD and psychiatric diseases cannot be determined in observational studies because AD often occurs in combination with other diseases (e.g. asthma),[30,31] and thus it is possible that these comorbidities contribute to the positive association between AD and depression and anxiety. Finally, the associations between AD and psychiatric disorders reported from cross-sectional studies and clinical studies were largely confined to severe AD with high burden,[8,29] whereas the population of cases in the GWAS datsets used for this analysis probably reflects a wider spectrum of severity. Thus, although unlikely, we cannot completely rule out nonoverlapping sets of risk factors, extreme multiformity or even causal effects in severe AD strata.[32]

Two-sample MR enabled the use of the largest GWAS of depression, MDD and anxiety to date. To achieve sufficient statistical power to detect small effects of AD on risk depression, MDD and anxiety, we adopted a weak correlated instrument approach.[17] However, relaxing the significance threshold to increase the number of instruments could increase the likelihood of weak instrument bias or horizontal pleiotropy. The genetic instruments explained 18·7% of the phenotypic variability of the exposure variables. The minimum F statistic was 12·13, consistent with the absence of weak instrument bias. Moreover, analyses adopting a more stringent P-value for instrument selection and the application of pleiotropy-robust methods produced similar point estimates. The CAUSE analysis comparing the causal with the shared model corroborates the evidence of no association. The findings from our positive and negative control analyses provided additional reassurance against biasing pleiotropic pathways. A limitation is that MR based on genetic summary statistics limits the range of analyses that can be performed. However, based on the observed and consistent negative results from several complementary approaches with effect estimates close to one, it is unlikely that the finding is distorted by any form of bias.

In conclusion, our study provides no evidence that AD has a causal effect on depression, MDD or anxiety.

Data Availability Statement

All analyses were conducted using publicly available data. The summary statistics for the atopic dermatitis genome-wide association study (GWAS) are available at https://data.bris.ac.uk/data/dataset/28uchsdpmub118uex26ylacqm. The GWAS summary data for depression and major depressive disorder are available at https://datashare.is.ed.ac.uk/handle/10283/3203, and the GWAS summary data for anxiety are available at http://www.med.unc.edu/pgc/download. The analysis code in R is available on request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Power analyses.
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Table S7 Mendelian randomization estimates for the relationship between atopic dermatitis and positive control outcome asthma, as well as with negative control outcome type 2 diabetes.