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ORIGINAL ARTICLE

# Exploring the overlap between alopecia areata and major depressive disorder: Epidemiological and genetic perspectives

J. C. Foo[1] | S. Redler[2,3] | A. J. Forstner[2,4] | F. B. Basmanav[2] | L. Pethukova[5,6] | J. Guo[7] | F. Streit[1] | S. H. Witt[1] | L. Sirignano[1] | L. Zillich[1] | S. Awasthi[8] | S. Ripke[8] | A. M. Christiano[9] | F. Tesch[10] | J. Schmitt[10] | M. M. Nöthen[2] | R. C. Betz[2] | M. Rietschel[1] | J. Frank[1]

[1]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

[2]Institute of Human Genetics, Medical Faculty & University Hospital Bonn, University of Bonn, Bonn, Germany

[3]Institute of Human Genetics, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

[4]Institute of Neuroscience and Medicine (INM-1), Research Center Jülich, Jülich, Germany

[5]Department of Dermatology, Columbia University, New York City, New York, USA

[6]Department of Epidemiology, Columbia University, New York City, New York, USA

[7]Department of Biostatistics, Columbia University, New York City, New York, USA

[8]Laboratory for Statistical Genetics, Charité University Hospital Berlin, Berlin, Germany

[9]Department of Genetics and Development, Columbia University, New York City, New York, USA

[10]Center for Evidence-Based Healthcare, University Hospital Carl Gustav Carus and Carl Gustav Carus Faculty of Medicine, Technische Universität Dresden, Dresden, Germany

**Correspondence**
J. Frank, J5, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, 68159 Mannheim, Germany.
Email: josef.frank@zi-mannheim.de

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## Abstract

**Background:** Research suggests that Alopecia areata (AA) and Major Depressive Disorder (MDD) show substantial comorbidity. To date, no study has investigated the hypothesis that this is attributable to shared genetic aetiology.

**Objectives:** To investigate AA-MDD comorbidity on the epidemiological and molecular genetic levels.

**Methods:** First, epidemiological analyses were performed using data from a cohort of adult German health insurance beneficiaries ($n$ = 1.855 million) to determine the population-based prevalence of AA-MDD comorbidity. Second, analyses were performed to determine the prevalence of MDD in a clinical AA case–control sample with data on psychiatric phenotypes, stratifying for demographic factors to identify possible contributing factors to AA-MDD comorbidity. Third, the genetic overlap between AA and MDD was investigated using a polygenic risk score (PRS) approach and linkage disequilibrium score (LDSC) regression. For PRS, summary statistics from a large MDD GWAS meta-analysis (PGC-MD2) were used as the training sample, while a Central European AA cohort, including the above-mentioned AA patients, and an independent replication US-AA cohort were used as target samples. LDSC was performed using summary statistics of PGC-MD2 and the largest AA meta-analysis to date.

R. C. Betz, M. Rietschel and J. Frank contributed equally to this study.

**Results:** High levels of AA-MDD comorbidity were reported in the population-based (MDD in 24% of AA patients), and clinical samples (MDD in 44% of AA patients). MDD-PRS explained a modest proportion of variance in AA case–control status ($R^2$ = 1%). This signal was limited to the major histocompatibility complex (MHC) region on chromosome 6. LDSC regression (excluding MHC) revealed no significant genetic correlation between AA and MDD.
**Conclusions:** As in previous research, AA patients showed an increased prevalence of MDD. The present analyses suggest that genetic overlap may be confined to the MHC region, which is implicated in immune function. More detailed investigation is required to refine understanding of how the MHC is involved in the development of AA and MDD comorbidity.

## INTRODUCTION

Alopecia areata (AA) is a common non-scarring hair loss disease. It is characterized by reversible, recurrent or non-reversible patchy hair loss that can affect the entire scalp (alopecia totalis [AT]) or body (alopecia universalis [AU]).[1] It is a polygenic autoimmune disease and its onset has been associated with infections and psychological stress; triggering factors are uncertain and the efficacy of available therapies is limited.[2] While the course of the condition is medically benign, the loss of hair can be a main source of psychological stress, a well-known risk factor for developing Major Depressive Disorder (MDD).[3]

Major Depressive Disorder is a common mental health disorder with a complex genetic aetiology. The leading symptoms are a constant feeling of low mood and/or loss of interest in all otherwise pleasurable activities (https://www.who.int/news-room/fact-sheets/detail/depression); MDD episodes differ from usual mood fluctuations and short-lived emotional responses, and at worst can lead to suicide. MDD is also characterized by a wider range of symptoms including feelings of guilt, delusions, and disturbances of cognition, activity levels, sleep and appetite. Lifetime prevalence of MDD is ~20%,[4] with females being affected almost twice as often as males.[5] Main risk factors include traumatic events, chronic stress, being female and having a first-degree relative with an affective disorder.

Multiple studies have reported comorbidity between AA and MDD. This comorbidity was first observed in clinical AA collectives, with cross-study variation in lifetime MDD prevalence.[6–13] While findings in these clinical samples could have been biased, e.g., by a preponderance of individuals with psychological problems seeking help for AA, findings from population and register-based studies support such comorbidity.[6,8,14,15] The direction of causality, however, is an open question, as MDD itself has been reported to be a risk factor for the development of AA.[16,17] AA-MDD comorbidity may result from: (i) common aetiology, (ii) one disorder being a risk factor for the other, (iii) both disorders increasing the risk for the other, or (iv) ascertainment bias.

Clinical findings indicate that the immune system may play a crucial role in the comorbidity between AA and MDD.[1] And so do genetics studies: Genome wide association studies (GWAS) for AA show that most of the 14 susceptibility loci identified to date are implicated in immunological processes.[18,19] For MDD, the involvement of immunological processes is widely suggested,[20] and the extended Major Histocompatibility Complex (MHC) region, which is hosting many immune related genes, is one of the 101 independent genome-wide significant loci identified to date via large-scale GWAS meta-analyses.[21,22]

The aim of the present study was to investigate comorbidity of AA and MDD, identify influencing factors, and explore possible genetic basis underlying this comorbidity. First, routine healthcare data from a large population-based cohort of adult health insurance beneficiaries from the state of Saxony were analysed in order to generate population-based data on AA-MDD comorbidity in Germany. Second, analyses were performed to determine the prevalence of MDD in an AA case–control cohort that had undergone extensive characterization of psychiatric disorder related phenotypes in order to identify possible moderating or confounding factors for AA-MDD comorbidity and to determine whether one disorder precedes the other. Third, at the molecular genetic level, large-scale GWAS data were leveraged to determine a possible common genetic basis by calculating PRS for MDD and testing whether these could predict AA status. In the meta-analysed samples, genetic correlations between AA and MDD were calculated in order to identify a potential overlap.

## MATERIALS AND METHODS

### Samples

#### Routine healthcare sample for the epidemiological analyses

Epidemiological analyses were performed using data comprising adults who were beneficiaries of the health insurance scheme of the German health insurance AOK PLUS between 2005 and 2014 ($n$ = 1,855,230; 54% female; average age [±SD]: 46 [±26] years). These routine healthcare data were available due to a cooperation agreement between AOK PLUS and TU

Dresden. The use of these data in medical research was approved by the Saxon State Ministry for Social Affairs and Social Cohesion.

For the present analyses, quarterly data on the onset of MDD and AA were drawn. Individuals who had received a minimum of two outpatient diagnoses of MDD or AA in different quarters within any 4-quarter period were defined as AA or MDD cases. To restrict the analyses to newly-incident cases, individuals who fulfilled this criterion within the baseline period 2005–2006 were excluded. All diagnoses in the AOK Cohort were assigned based on International Classification of Diseases (ICD)-10 criteria (Alopecia Areata [AA]: L63, Major Depressive Disorder [MDD]: F32/F33).

### BoMa AA cohort (clinical AA sample and controls)

In the BoMa AA cohort investigating comorbidity between AA and MDD, Central European (CEU) AA patients underwent an assessment of MDD according to DSM criteria using telephone interviews and a comprehensive self-report questionnaire. AA cases ($n$ = 606) were recruited via outpatient clinics, dermatology practitioners, and AA self-support groups. Population-based controls ($n$ = 1204) for this sample were recruited from blood donation events hosted by the German Red Cross (DRK) in the state of Baden-Württemberg between 2009 and 2012. Data on MDD-related phenotypes were obtained from controls using detailed self-report questionnaires. Ethical approval for the study was obtained from the respective local internal review boards.

### AA GWAS sample

A detailed description of the cohort is provided elsewhere.[18] Briefly, the cohort combined two previously established GWAS case–control cohorts from: (i) Central Europe (CEU-AA; 1387 cases and 1986 controls); and (ii) the US (US-AA; 1054 cases, 3255 controls). Together, these comprised a total of >3000 patients and >7500 controls. CEU-AA cases were recruited via outpatient clinics, dermatology practitioners, and AA self-support groups; the AA patients in the BoMa AA cohort were a subsample of the CEU-AA cases. US-AA cases were recruited via the US National Alopecia Areata Registry (NAAR).[23] CEU-AA controls were drawn from three large population-based epidemiological cohorts,[24–26] which were established as universal GWAS controls within the German National Genome Research Network. US-AA controls were drawn from the New York Cancer Project[27] and the Cancer Genetic Markers of Susceptibility (CGEMS) breast and prostate cancer studies.[28–30]

The GWAS and downstream analyses for the CEU-AA and US-AA samples were reviewed and approved by the respective institutional review boards, and were performed in accordance with the principles of the Declaration of Helsinki.

### DNA preparation, genotyping, and quality control

A detailed description of all DNA extraction and genotyping methods is provided elsewhere.[18] Briefly, DNA was extracted from whole blood using standard methods, in accordance with the manufacturers' recommendations. For the CEU-AA cohort, genotyping was performed in two batches, using Illumina 660 or Illumina Omni Express for patients, and Illumina HumanHap550 or Illumina Omni Express BeadChips for controls. For the US-AA cohort, Illumina HumanHap610 and HumanHap 550v2 BeadChips were used for cases and controls respectively, as described elsewhere.[19] The CEU-AA and US-AA data were subjected to a stringent quality control (QC) procedure using PLINK 1.90,[18,31] (for details, see Appendix S1).

## Statistical analysis

### Epidemiological analysis in the routine healthcare sample

Poisson regression models with robust standard errors were calculated for both AA and MDD as binary response variables. For both disorders and across all models, sex was used as a covariate. Using available incidence data, Kaplan–Meier survival curves were calculated to evaluate survival time (age at onset) for AA and MD. As the proportional hazard assumption is violated in subjects aged >85 years, patients above this age cut-off were excluded.

### Analysis of MDD prevalence in AA and moderating factors in the BoMa AA cohort

Demographic analyses were performed to determine the prevalence of MDD in the AA patients and DRK controls, with stratification for sex and first-degree family history of psychiatric disorders. In addition, in subjects with comorbid AA and MDD, ages at onset were examined to determine which disorder had developed first (age at onset for the first major depressive episode in the case of MDD), and whether the difference was sex-dependent. An index variable was calculated (AaO MDD – AaO AA), and testing for differences from 0 was performed using $t$-tests.

In addition, analyses were performed to determine associations between AA severity and MDD prevalence. For this purpose, AA was stratified into: (i) patchy AA; and (ii) alopecia totalis (AT) and alopecia universalis (AU) combined.

## Genetic analyses

### Polygenic risk scores (PRS) for MDD in CEU-AA sample

In PRS profiling, risk variants and effect sizes are identified in a GWAS of a particular disease, performed in a so-called training sample. These are used to generate risk scores reflecting risk burden for this disease for each individual in an independent sample, that is, the so-called target sample.[32] In the present study, a large MDD sample from the Psychiatric Genomics Consortium (PGC-MD2 sample)[22] was used as the training sample and the target sample was the CEU-AA. As an overlap in German controls existed between the training and target samples, all German samples from the PGC-MD2 dataset were excluded to avoid biased test results. The final training sample comprised 56,686 MDD cases and 108,545 controls.

PRS were calculated using PRSice-2.[33] PRS analyses used a complete genome approach with clumping in order to retain only one representative variant per region of Linkage Disequilibrium (LD) using a threshold of pairwise $r^2 < 0.1$ within a maximum distance of 500 kb. Three approaches were used: (i) regular clumping, keeping the whole MHC region, (ii) removing all but the top-SNP contained in the target data set from the extended MHC region (Chr6: 25–35 Mb), and (iii) completely removing the extended MHC region. For all three approaches, PRSs were calculated for a range of *p*-value thresholds ($5 \times 10^{-8}$, $1 \times 10^{-6}$, $1 \times 10^{-4}$, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, 1.0).

Logistic regression analysis was performed to determine the contribution of MDD-PRS to AA status adjusting for population stratification (see Appendix S1). Case–control status was specified as the dependent variable. Explained variability was estimated using Nagelkerke pseudo-*R*.

### Replication of MDD-PRS in an independent sample (US-AA)

Using the above methods, PRS estimates were tested for association with AA status in the independent US-AA sample.[18]

### Linkage disequilibrium score regression

LDSC incorporates information on LD structure in order to generate estimates for heritability of a disorder and genetic correlations between disorders.[34] For details, please see Bulik-Sullivan et al.[34] and the SI. LDSC was applied to the AA-Meta[18] and PGC-MD2[22] meta-analyses summary statistics. The 1000 Genomes dataset served as a reference panel for LD structure (https://www.internationalgenome.org/data). The analyses involved a total of 1,057,819 variants.

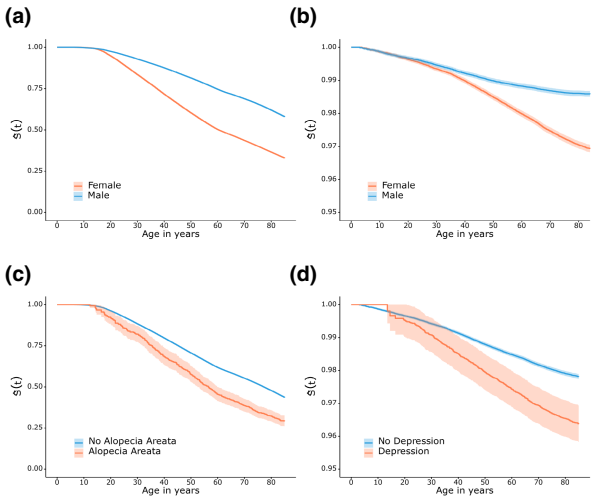


**FIGURE 1** Kaplan–Meier-Plots showing survival time until development of major depressive disorder (MDD) and alopecia areata (AA) in the routine healthcare sample. *x*-Axis shows age, *y*-axis depicts proportion of individuals still unaffected. (a) Time of survival until onset of MDD for males and females. (b) Time of survival until onset of AA for males and females. (c) Time of survival until onset of MDD for controls and AA patients. (d) Time of survival until onset of AA for controls and MDD patients.

## RESULTS

### Epidemiological analysis in the routine healthcare sample

In the routine healthcare sample of $n = 1.855$ million, a total of $n = 279{,}264$ (15%) individuals fulfilled ICD-10 criteria for MDD, and $n = 6388$ individuals (0.34%) for AA, respectively. $N = 1529$ (0.55%) had comorbid AA-MDD corresponding to 0.34% of all MDD patients and 24% of all AA patients. The relative risk ratios for MDD (i) having AA and (ii) being female were: 1.39 (95% CI: 1.33–1.45); and 2.23 (2.21–2.25), respectively. For AA, the relative risk ratios (i) having MDD and (ii) being female were: 1.57 (95% CI: 1.47–1.67) and 2.26 (95% CI: 2.13–2.39), respectively.

Figure 1a,b show Kaplan–Meier survival curves of MDD and AA, respectively, as stratified for sex, over the process variable (age). Figure 1c,d show Kaplan–Meier survival curves for MDD and AA, respectively, as stratified for comorbid disease status. The incidence of AA increased gradually from early childhood, while for MDD, an abrupt increase in incidence was observed in adolescence. (Figure 1c,d).

### MDD prevalence in AA and contributing factors in clinical sample

In the BoMa AA cohort, prevalence of MDD was higher in AA patients than in controls (44% versus 20%; Odds Ratio (OR) = 3.2, 95% confidence interval (CI) = [2.5–3.9]). Females

showed higher rates of MDD (34%) than males (18%). This was true for both AA cases (females 47% MDD, males 31% MDD; OR = 1.9, CI = [1.2–3.0]) and controls (females 24% MDD, males 15% MDD, OR = 1.7, CI = [1.3–2.3]; Figure 2).

Significantly higher rates of MDD were observed in individuals with a family history of psychiatric disorders (FH+: 58%) than in those without (FH−: 31%, $p = 1.5 \times 10^{-10}$). This was observed in both AA cases (FH+: 61% MDD, FH−: 37% MDD, $p = 1.1 \times 10^{-6}$) and controls (FH+: 48% MDD, FH−: 7.9% MDD, $p = 1.3 \times 10^{-6}$). Among AA patients, FH+ females had the highest rates of MDD ($FH+_{female}$: 60%, $FH+_{male}$: 50%, $FH-_{female}$: 34%, $FH-_{male}$: 20%; Figure 3).

In female but not male patients, hair loss severity was associated with MDD: a higher prevalence of MDD was observed among AT/AU patients compared to patients with patchy AA (Figure 4).

Ages at onset of AA and MDD were strongly correlated in both males ($r = 0.73$, $p < 0.001$) and females ($r = 0.55$, $p < 0.001$; Figure 5).

A comparison of the difference in age at onset between AA and MDD revealed that on average, the first MDD episode occurred prior to AA onset (absolute mean of differences: 2.46 years, $p = 0.013$). No sex difference was observed for this finding ($p = 0.96$).

## Polygenic risk scores

In the CEU-AA cohort, when all clumped SNPs from the MHC region were retained, the most informative threshold was the genome-wide significance level of $5 \times 10^{-8}$, which generated an $R^2$ of 1% (Figure 6a, $p = 4 \times 10^{-7}$). Removing all but the top SNP of this region led to a substantial reduction in $R^2$, and the association test showed only a trend towards significance ($p = 0.06$, Figure 6b). When PRS were calculated with the complete exclusion of the extended MHC region, no signal was observed at any significance threshold (Figure 6c).

## PRS replication

PRS results in the US-AA cohort were very similar. Again, the most informative threshold was $5 \times 10^{-8}$, with an explained proportion of variance in AA case–control status of $R^2 = 0.3\%$ (with the MHC included; $p = 0.004$; Figure 7a). When all but the top SNP of the MHC region (Figure 7b) and the entire MHC (Figure 7c) were removed, PRS were no longer informative of AA case–control status.

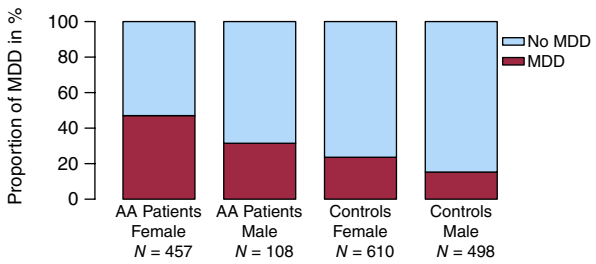


**FIGURE 2** Prevalence of major depressive disorder (MDD) in the BoMa AA cohort, as stratified according to alopecia areata (AA) case–control status and sex.

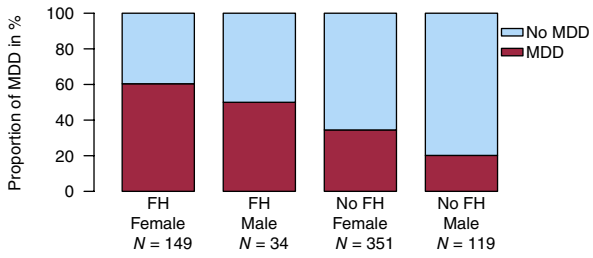


**FIGURE 3** Prevalence of major depressive disorder (MDD) in alopecia areata patients of the BoMa AA cohort, as stratified according to family history (FH) of psychiatric disorders in first-degree relatives and sex.

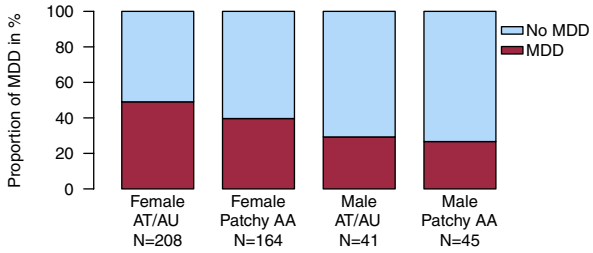


**FIGURE 4** Prevalence of major depressive disorder (MDD) in alopecia areata (AA) patients of the BoMa AA cohort, as stratified according to sex and AA severity (AT, Alopecia totalis; AU, alopecia universalis).

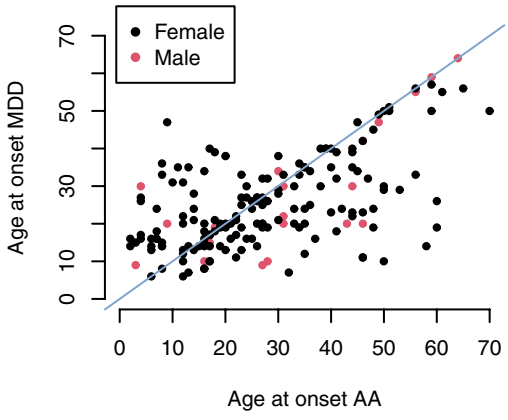


**FIGURE 5** Ages at onset for alopecia areata (AA) and major depressive disorder (MDD) in comorbid cases within the BoMa AA cohort. Solid diagonal line denotes the point at which the two ages at onset were equal.

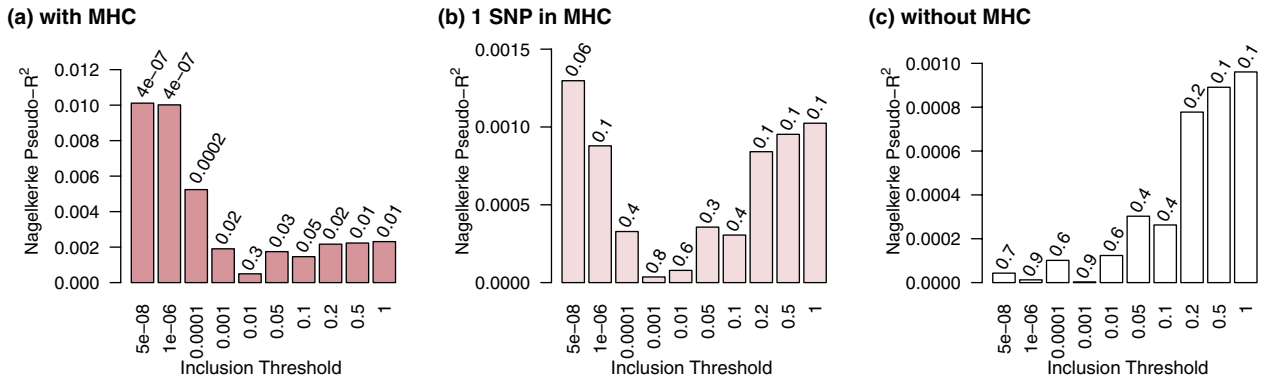


**FIGURE 6** Results of polygenic risk score (PRS) association tests in the CEU-AA sample. Values indicated above the bars denote the *p*-value for the association of PRS with alopecia areata case control status after adjustment for population stratification.

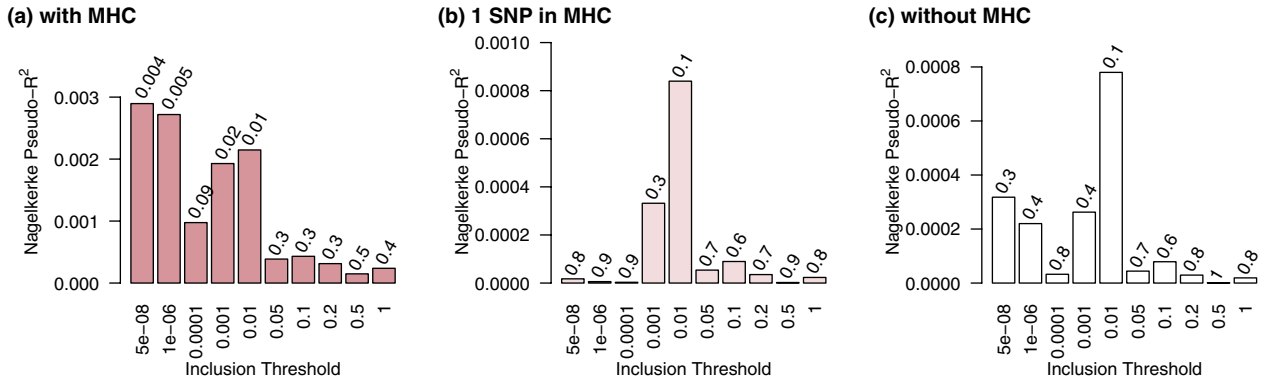


**FIGURE 7** Results of polygenic risk score (PRS) association tests in the US-AA sample. Values indicated above the bars denote the *p*-value for the association of PRS with alopecia areata case control status after adjustment for population stratification.

## LDSC regression

SNP-based heritability was 0.45 (SE = 0.08, $z = 5.6$) for AA and 0.08 for MD (SE = 0.005, $z = 16$) on the observed scale. No significant genetic correlation was observed between AA and MDD ($r_g = 0.01$, SE = 0.07, $z = 0.14$, $p = 0.89$).

## DISCUSSION

The present analyses generated evidence for a relationship between AA and MDD at the population level as well as in a clinical sample. The genetic analyses indicated a possible genetic overlap confined to the MHC region.

Epidemiological studies have shown an association between autoimmune diseases and mood disorders, although the issue of whether the potential relationship is uni- or bi-directional remains unclear. Depending on the disease, the relationship may be either or both,[17,35–38] with some more recent publications on AA and MDD having generated data in support of the latter.[17,38] The present study confirms prior findings also for Germany that individuals with AA or MDD are at increased risk of developing the other disease. With respect to the relationship of the two disorders, neither the population-based models nor the results from the BoMa AA cohort did generate an unequivocal indication of direction. However, the following observation may be of interest: In the BoMa AA cohort, in patients comorbid for AA and MDD, a strong correlation was observed between the ages at onset. The age at onset for MDD was on average earlier than that for AA, a finding that needs replication.

Our further findings in the BoMa AA cohort may be of potential clinical value, raising awareness of risk for MDD in AA patients, especially in female patients, and also in those who have a family history of psychiatric disorders.

The genetic analyses revealed that the MD2-PRS explained a small proportion of AA case–control status. This finding was replicated in an independent sample. The observation that in both samples this signal vanished when the MHC region was removed from the SNP set suggests that any possible genetic overlap between AA and MDD is confined to the MHC region on chromosome 6.

The MHC encodes many of the molecules that are involved in the immune response.[39] Alleles of HLA (human leukocyte antigen) genes within the MHC have shown strong associations with AA in several studies, with

HLA-DR representing the key etiological driver.[18,19,40,41] Significant correlations between MDD and variants in the MHC region have been found in recent GWAS.[21,22,42–44] However, recent work suggests that HLA variants associated with MDD are either rare or have only modest effect sizes.[45] Although the use of summary statistics and genome-level methods precludes a close examination of the implicated risk alleles, the present results point to the involvement of the MHC in both AA and MDD. Given the heterogeneous nature of MDD phenotypes, the observed genetic overlap at the MHC region may represent a distinct disease (sub)phenotype (or constellation of specific symptoms) where individuals who are enriched for autoimmune risk alleles develop both MDD and AA. This suggests that the comorbidity observed on the epidemiological level may be attributable to this enrichment in a subgroup of patients and in others to one disorder acting as a stressor or trigger for the onset of the other, rather than to the presence of a broad shared genetic aetiology.

One of the strengths of the present study was the use of a routine healthcare sample that enabled a selection/recall-bias free assessment and verification of the previously reported AA-MDD comorbidity in the literature.

Data from the routine healthcare sample were drawn from 2005–2014. While this is a considerable length of time, people who have developed MDD or AA outside of the study period are not captured. We observed in our clinical sample that while in many cases the onset of both disorders occurs within such a time frame, it can also occur farther apart. A full picture of correlation across the lifespan would be desirable, and may be possible in national registers.

Next, the routine healthcare sample was taken from a public health insurance institution which represents the vast majority of the population in Germany but may not generalize to all social backgrounds.

Another limitation of the present study was the size of the clinical/genetic analysis sample. While larger than those used in many studies to date, we are unable to exclude that a possible genetic overlap remained undetected. It should also be noted that the genetic results are derived from analysis of individuals of European ancestry, and it is of interest to test if these results can generalize to people of other ancestries.

Finally, this analysis accounted for sex as a contributing factor, but did not consider other covariates with potential effects, such as socio-economic status, childhood trauma, somatic disorders, etc. and future research should incorporate parameters such as these to better dissect underlying factors.

In conclusion, our study confirms that AA patients have a substantially increased prevalence of MDD compared to the general population, with MDD being especially prevalent in females and individuals with a family history of psychiatric disorders. This comorbidity appears not to be due to a broad genetic overlap; if at all, shared genetic predisposition seems to be confined to the MHC region.

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## CONFLICT OF INTEREST STATEMENT

JS reports institutional grants for investigator-initiated research from the German GBA, the BMG, BMBF, EU, Federal State of Saxony, Novartis, Sanofi, ALK, and Pfizer. He also participated in advisory board meetings as a paid consultant for Sanofi, Lilly, and ALK. AMC reports research grant support from Bristol Myers Squibb, Pfizer, and Sanofi Genzyme. She has received fees as consultant/scientific advisor from Aclaris Therapeutics, Almirall, Arcutis Biotherapeutics, Bioniz Therapeutics, Dermira, Intrinsic Medicine, Janssen Pharmaceuticals and Pfizer, is named as coinventor on several patents for methods of hair follicle neogenesis and the use of JAK inhibitors in hairloss disorders. Further she serves as secretary treasurer of the American Hair Research Society and previously served as president of the Society for Investigative Dermatology, serves on/chairs the scientific advisory boards for the Dystrophobic EB Research Association of America, and the National Alopecia Areata Foundation. She also is a shareholder of Aclaris Therapeutics and Intrinsic Medicine. The other authors have no conflicts of interest to declare.

## DATA AVAILABILITY STATEMENT

Summary statistics for MDD used in this study are available for download at https://pgc.unc.edu/for-researchers/download-results/. Individual clinical data, genotypes and health insurance data from AOK PLUS are not available due to German data protection and privacy regulations. Summary statistics may be available on reasonable request.

## ORCID

*J. C. Foo* https://orcid.org/0000-0003-1067-5725
*J. Guo* https://orcid.org/0000-0002-9774-9856
*R. C. Betz* https://orcid.org/0000-0001-5024-3623

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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