



The association between genetically determined ABO blood types and major depressive disorder

Linda Garvert^{a,*}, Bernhard T Baune^{b,c,d}, Klaus Berger^e, Dorret I Boomsma^f, Gerome Breen^{g,h}, Andreas Greinacherⁱ, Steven P Hamilton^j, Douglas F Levinson^k, Cathryn M Lewis^{h,l}, Susanne Lucae^m, Patrik K E Magnussonⁿ, Nicholas G Martin^o, Andrew M McIntosh^{p,q}, Ole Mors^{r,s}, Bertram Müller-Myhsok^{t,u,v}, Brenda W J H Penninx^w, Roy H Perlis^{x,y}, Giorgio Pistis^z, James B Potash^{aa}, Martin Preisig^z, Marcella Rietschel^{ab}, Jianxin Shi^{ac}, Jordan W Smoller^{y,ad,ae}, Henning Tiemeier^{af,ag,ah}, Rudolf Uher^{ai}, Uwe Völker^{aj,ak}, Henry Völzke^{ak,al}, Myrna M Weissman^{am,an}, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Hans J Grabe^{a,ao,#}, Sandra Van der Auwera^{a,ao,#}

^a Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany

^b Department of Psychiatry, University of Münster, Münster, Germany

^c Department of Psychiatry, Melbourne Medical School, University of Melbourne, Melbourne, Australia

^d Florey Institute for Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia

^e Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany

^f Department of Biological Psychiatry, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

^g NIHR Maudsley Biomedical Research Centre, King's College London, London, UK

^h Social, Genetic and Developmental Psychiatry Centre, King's College London, London, UK

ⁱ Institute for Immunology and Transfusion Medicine, University Medicine Greifswald, Greifswald, Germany

^j Department of Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, USA

^k Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA

^l Department of Medical and Molecular Genetics, King's College London, London, UK

^m Max Planck Institute of Psychiatry, Munich, Germany

ⁿ Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

^o Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

^p Division of Psychiatry, University of Edinburgh, Edinburgh, UK

^q Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

^r Psychosis Research Unit, Aarhus University Hospital, Aarhus, Denmark

^s iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark

^t Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

^u Institute for Translational Medicine, University of Liverpool, Liverpool, UK

^v Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

^w Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, The Netherlands

^x Department of Psychiatry, Harvard Medical School, Boston, MA, USA

^y Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

^z Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

^{aa} Department of Psychiatry, University of Iowa, Iowa City, IA, USA

^{ab} Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Mannheim, Germany

^{ac} Division of Cancer, Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

^{ad} Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, USA

^{ae} Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, USA

^{af} Department of Psychiatry, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

^{ag} Department of Epidemiology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

^{ah} Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, Rotterdam, The Netherlands

^{ai} Department of Psychiatry, Dalhousie University, Halifax, NS, Canada

^{aj} German Centre for Cardiovascular Research (DZHK), Partner Site Greifswald, Greifswald, Germany

^{ak} Department of Functional Genomics, University Medicine Greifswald, Greifswald, Germany

^{al} Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany

* **Corresponding author:** Linda Garvert, University Medicine Greifswald, Department of Psychiatry and Psychotherapy, Ellernholzstraße 1-2, 17489 Greifswald.
E-mail address: linda.garvert@med.uni-greifswald.de (L. Garvert).

^{am} Division of Translational Epidemiology, New York State Psychiatric Institute, New York, NY, USA

^{an} Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

^{ao} German Centre for Neurodegenerative Diseases (DZNE), Site Rostock/Greifswald, Greifswald, Germany

ARTICLE INFO

Keywords:

Blood group
Blood type
Depression
MDD
Association study
Psychiatric disorders
PGC

ABSTRACT

ABO blood types and their corresponding antigens have long been assumed to be related to different human diseases. So far, smaller studies on the relationship between mental disorders and blood types yielded contradicting results. In this study we analyzed the association between ABO blood types and lifetime major depressive disorder (MDD). We performed a pooled analysis with data from 26 cohorts that are part of the MDD working group of the Psychiatric Genomics Consortium (PGC). The dataset included 37,208 individuals of largely European ancestry of which 41.6% were diagnosed with lifetime MDD. ABO blood types were identified using three single nucleotide polymorphisms in the ABO gene: rs505922, rs8176746 and rs8176747. Regression analyses were performed to assess associations between the individual ABO blood types and MDD diagnosis as well as putative interaction effects with sex. The models were adjusted for sex, cohort and the first ten genetic principal components. The percentage of blood type A was slightly lower in cases than controls while blood type O was more prominent in cases. However, these differences were not statistically significant. Our analyses found no evidence of an association between ABO blood types and major depressive disorder.

1. Introduction

The ABO blood group system is the clinically most significant blood group system in transfusion and transplantation medicine. In addition to that, ABO blood types and their corresponding antigens have been shown to be associated with different human diseases (Ewald and Sumner, 2016; Groot et al., 2020). Studies indicate associations between ABO blood types and, for example, vascular disorders (higher risk for non-O blood groups), cancer (higher incidence for blood group A compared to O), metabolic diseases (lowest risk for type 2 diabetes mellitus in type O individuals) and cognitive impairment (increased risk in AB individuals) (Ewald and Sumner, 2016). Some smaller studies have also analyzed the relationship between ABO blood types and psychiatric disorders. A recent Croatian study on 156 psychiatric patients and 303 healthy blood donors indicates that psychiatric disorders occur almost three times more frequently in individuals with blood type AB compared to non-AB individuals. However, the authors found no statistically significant difference between the blood type distributions of individuals with mood disorders, psychotic disorders or addictions specifically (Pisk et al., 2019). An earlier U.S. study of the association between ABO blood types and depression severity, assessed with the Beck Depression Inventory (Beck and Steer, 1993), in a sample of 108 volunteers showed a significant difference between mean depression scores of individuals with blood types A, AB/B and O. Type O individuals exhibited a higher mean depression score ($M=10.7$, $SD=8.0$) than both the type A ($M=7.3$, $SD=5.8$) and B/AB ($M=5.8$, $SD=5.3$) groups (Singg and Lewis, 2001).

However, there are no recent studies analyzing the relationship between ABO blood types and depression on a larger dataset with sufficient power. To address this, we combined data from 26 cohorts of the Major Depressive Disorder (MDD) working group of the Psychiatric Genomics Consortium (PGC). The pooled dataset included 37,208 individuals of which 41.6% were diagnosed with lifetime MDD. ABO blood types were identified using the three single nucleotide polymorphisms (SNPs) rs505922, rs8176746 and rs8176747 in the ABO gene on chromosome 9. We performed regression analyses to assess associations between the individual ABO blood types and MDD diagnosis. Given the higher prevalence of depression among women (Salk et al., 2017), we also analyzed interaction effects of blood types and sex on lifetime MDD risk to examine putative sex-specific associations.

2. Methods

2.1. Dataset

For our analyses we combined data from 26 case-control studies that are part of the MDD working group of the PGC. For a detailed description of the cohort sizes, inclusion/exclusion criteria, diagnostic tests as well as genotyping and imputation procedures, see (Wray et al., 2018) as well as supplementary tables S1 and S2. In summary, the cohorts include individuals of mainly European ancestry as study participants were recruited in Europe, the USA and Australia. All cases were required to have a lifetime diagnosis of MDD based on international consensus criteria (DSM-IV, ICD-9 or ICD-10) (World Health Organization, 1978; American Psychiatric Association, 1994). This was ascertained using structured diagnostic instruments from direct interview by trained interviewers or clinician administered checklists. The majority of studies excluded individuals with bipolar disorder, non-affective psychosis or MDD related to substance use disorders. The resulting dataset included 37,208 individuals (45.2% male) of which 41.6% were diagnosed with lifetime MDD.

2.2. Determining ABO blood types

The ABO gene is located on chromosome 9q34.2 and codes glycosyltransferase, which transfers nucleotide donor sugars to the H antigen to form ABO blood group antigens (Alkebsi et al., 2019). The four ABO blood types A, B, AB and O can be distinguished with three SNPs located in this gene: rs8176719 (c.261delG), rs8176746 (c.796C>A) and rs8176747 (c.803G>C) (Yamamoto et al., 1990; Daniels, 2013). The single base deletion 261delG marks the O allele and variants rs8176746 and rs8176747 discriminate between alleles A and B. Since genetic data for the deletion variant rs8176719 was not available in our dataset we instead utilized SNP rs505922 which is in high linkage disequilibrium with rs8176719 ($D' = 0.99$, $r^2 = 0.87$ in Europeans (Machiela and Chacko, 2015)). The ABO blood types were derived from these genetic variants as described in Table 1.

2.3. Association analyses

To assess the association between the MDD diagnosis and the individual ABO blood types A, B, AB and O we performed four separate logistic regressions using the software tool R version 3.4.3. For each analysis we adjusted for sex, cohort and the first ten genetic principal components. As secondary analyses we also studied the interaction effect of ABO blood types and sex on lifetime MDD risk adjusting for

These authors contributed equally.

Table 1
Determination of ABO blood types based on three SNPs from the ABO gene.

rs505922	rs8176746	rs8176747	Genotype	Phenotype
C/T	T/G	G/C	BO	B
C/T	T/T	G/G	BO	B
C/T	G/G	C/C	AO	A
C/C	T/G	G/C	AB	AB
C/C	T/T	G/G	BB	B
C/C	G/G	C/C	AA	A
T/T	T/G	G/C	OO	O
T/T	NA	NA	OO	O
T/T	G/G	C/C	OO	O
NA	C/C	G/G	NA	NA
C/T	NA	NA	NA	NA
NA	T/G	G/C	NA	NA
C/C	NA	NA	NA	NA

NA: Allele not known / blood type cannot be determined

Table 2
Summary of minor allele frequencies in the individual PGC studies and selected populations of the 1000 Genomes Project. This table displays the minimal, mean and maximal minor allele frequencies (MAFs) of the individual studies as well as the MAFs in the combined dataset. For comparison, it also shows the MAFs in the combined European populations (EUR) of the 1000 Genomes Project (1000G, n=503) and in the dataset combining all populations (ALL) of the 1000 Genomes Project (n=2,504) (The 1000 Genomes Project Consortium, 2015; Alexander and Machiela, 2020).

	rs505922	rs8176746	rs8176747
Min.	27.74%	4.16%	4.16%
Mean	34.17%	7.56%	7.56%
Max.	39.72%	10.66%	10.66%
combined	34.49%	7.42%	7.42%
1000G: EUR	36.78%	8.45%	8.45%
1000G: ALL	35.40%	15.28%	15.28%

cohorts and the first ten genetic principal components.

3. Results

Table 2 displays the minimal, mean and maximal minor allele frequencies (MAFs) of rs505922, rs8176746 and rs8176747 across the 26 individual cohorts as well as the MAFs in the combined dataset. The

MAFs in the combined dataset (rs505922: 34.49%, rs8176746/rs8176747: 7.42%) agree with the MAFs observed in the European populations of the 1000 Genomes Project (rs505922: 36.78%, rs8176746/rs8176747: 8.45%) (The 1000 Genomes Project Consortium, 2015; Alexander and Machiela, 2020). However, the MAFs of rs8176746 and rs8176747 are significantly higher (15.28%) when all populations of the 1000 Genomes Project are combined. A detailed account of the MAFs in the individual datasets is listed in supplementary tables S3 and S4.

The distribution of blood types in each cohort is displayed in Fig. 1 A. In total, 42.49% of the 37,208 individuals had blood type A, 10.05% type B, 4.13% type AB and 43.34% had blood type O. This is in accordance with the expected distribution in a population of mainly European descent (Daniels, 2013). Fig. 1 B shows the difference in blood type distribution between MDD cases and controls. The percentage of blood type A was slightly lower in cases than controls (41.84% vs. 42.94%) while blood type O was more prominent in cases (43.87% vs. 42.96%). The percentage of blood types B and AB displayed only minimal differences between MDD cases and controls (10.10% vs. 10.01% and 4.19% vs 4.09%).

A χ^2 -Test of independence did not show a significant association between MDD diagnosis and ABO blood type distribution ($\chi^2(3)=4.59, p=0.205$).

Moreover, none of the four regression analyses assessing the association between the individual blood types and MDD reached statistical significance ($p<0.05$, Fig. 2). Fig. 2 displays the effect estimates, p-values and confidence intervals of the four regression models. The effects in the individual cohorts are shown in Fig.s S1-S4.

The secondary analyses examining the interaction effects of ABO blood types and sex on MDD risk also did not reach statistical significance. The effect estimates and p-values of the interaction effects as well as the effect estimates and confidence intervals of the sex stratified analyses are displayed in Fig. 3.

4. Discussion

Previous studies indicated an association between ABO blood types and psychiatric disorders (Singg and Lewis, 2001; Pisk et al., 2019), although the specific risk-conferring blood type has differed. The most recent study found a higher risk of psychiatric disorders (mood disorder, psychotic disorder, addiction and personality disorder) in

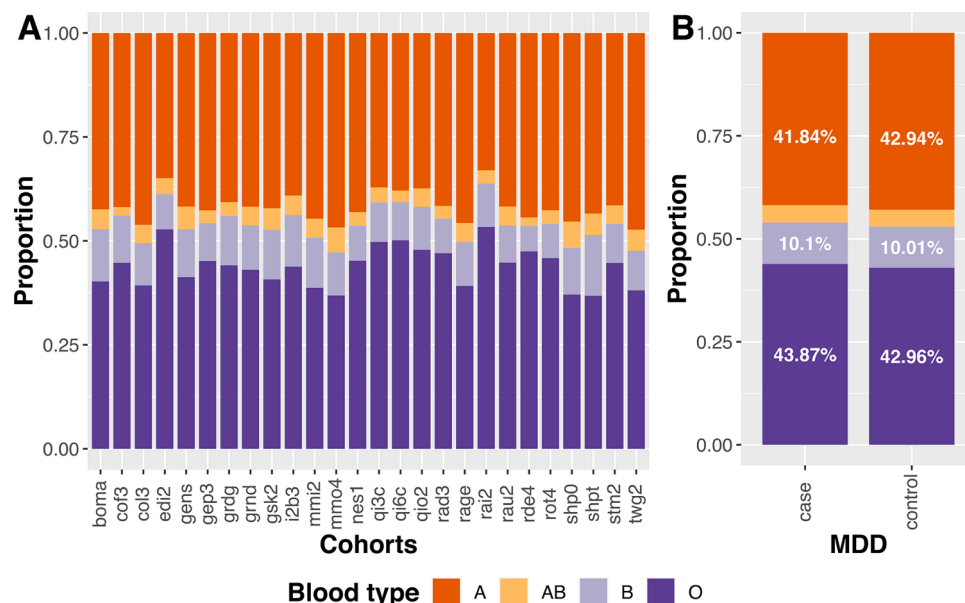


Fig. 1. Distribution of ABO blood types. A Distribution of blood types in each cohort. B Distribution of blood types in MDD cases and controls.

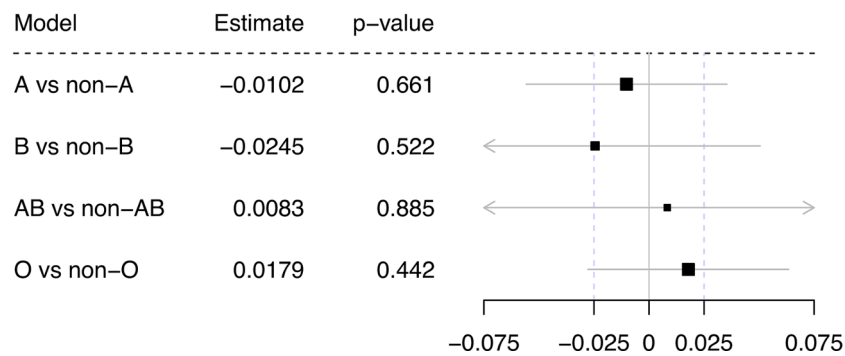


Fig. 2. Direct effects of ABO blood types on lifetime MDD risk. Forest plot displaying the estimates, p-values and confidence intervals of the four regression models adjusted for sex, cohort and the first ten genetic principal components. The boxes represent the estimates for the effects of the individual blood types on MDD risk. The horizontal lines represent the corresponding 95% confidence intervals.

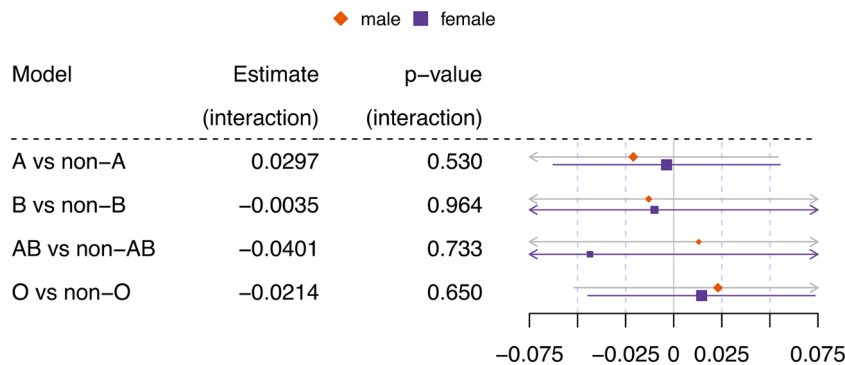


Fig. 3. Interaction effect of ABO blood types and sex on lifetime MDD risk. The columns display the effect estimates and the corresponding p-values for the interaction effect of blood types A, B, AB, O and sex on MDD risk. The boxes represent the individual estimates for the effect of the specific blood type on MDD risk in males and females, respectively. The horizontal lines represent the corresponding 95% confidence intervals.

AB-individuals (Pisk et al., 2019) whereas other studies indicate a higher risk for depressive symptoms in individuals with blood type O compared to non-O individuals (Singg and Lewis, 2001). One critical limitation of these studies is their low power as they included only up to ~500 individuals. With our sample size of 37,208 we had a power of 80% to detect a significant ($p < 0.05$) association with effect size 0.017 between blood type distribution and MDD diagnosis performing a χ^2 -test. However, we found no evidence to support such an association. This is in accordance with results from a recent study on the association between genetically determined ABO blood groups and different health and disease outcomes in the UK Biobank cohort that also did not find a significant association with a broader phenotype of depression classified by self-report and ICD 10 codes (supplement of (Groot et al., 2020)).

Since the probability of lifetime MDD increases with age, we performed secondary analyses on a subset of 24,917 individuals for which information on age at interview was available to examine whether adjustment for age affects the results. Again, no association was found in these analyses and additionally adjusting for age at interview did not affect the results on this dataset (Fig. S5-S7).

Overall, our analyses do not replicate significant findings of previous studies. However, we acknowledge several limitations of our study. Notably, the 26 cohorts included in our analysis were heterogeneous with respect to genotyping platforms (Table S2) and inclusion/exclusion criteria for cases and controls (Table S1). Moreover, some of the cohorts were ascertained from population-based studies while others focused on clinically-ascertained cases; to the extent that these differences reflect varying etiologic factors, they may have obscured an association between blood type and depression.

Furthermore, detailed data on individual depression symptoms or depression severity were not available for this study. Therefore, we are incapable of evaluating to what extent these factors are influenced by

blood types. However, considering the previously mentioned significant findings in smaller studies (Singg and Lewis, 2001) the association between ABO blood types and depression severity or symptoms presents an interesting research question for further analyses in suitable datasets.

Additionally, the individual cohorts combined in this study are largely of European ancestry. Further analyses on datasets with different ancestries are required to assess the generalizability of the results.

For future analyses, the inclusion of additional blood parameters such as rhesus (Rh) factor and secretor status could yield a more detailed understanding of the role of blood cell markers and depression.

Funding and disclosure

L.G. was supported by the German Research Foundation (DFG, grant no. 403694598). S.V. was supported by the German Federal Ministry of Education and Research (BMBF) within the framework of the e:Med research and funding concept (Integrement; grant no. 01ZX1614E). H.J.G. has received travel grants and speakers honoraria from Fresenius Medical Care and Janssen Cilag. He has received research funding from the German Research Foundation, the German Federal Ministry of Education and Research (BMBF), the DAMP Foundation, Fresenius Medical Care, the EU "Joint Programme Neurodegenerative Disorders" (JPNP: 01ED1615) and the European Social Fund (ESF). The PGC has received major funding from the US National Institute of Mental Health (5 U01MH109528-03).

All other authors state that they have nothing to disclose.

Names and affiliations of all members of the MDD working group of the PGC can be found in the supplement.

Author statement

Linda Garvert: Conceptualization, Methodology, Formal analysis, Writing – Original draft preparation **Hans J Grabe:** Conceptualization, Writing - Review & Editing, Supervision, Funding acquisition **Sandra Van der Auwera:** Conceptualization, Methodology, Writing - Review & Editing, Supervision, Funding acquisition **The remaining authors:** Resources, Data Curation, Writing – Review & Editing

Acknowledgments

The Study of Health in Pomerania (SHIP) is part of the Community Medicine Research net (CMR) (<http://www.medizin.uni-greifswald.de/icm>) of the University Medicine Greifswald, which is supported by the German Federal State of Mecklenburg- West Pomerania. MRI scans in SHIP and SHIP-TREND have been supported by a joint grant from Siemens Healthineers, Erlangen, Germany and the Federal State of Mecklenburg-West Pomerania.

We thank all participants who were part of the studies and enabled the work of the MDD working Group of the PGC.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2021.113837](https://doi.org/10.1016/j.psychres.2021.113837).

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