Received: 3 September 2019 | Revised: 23 September 2019 | Accepted: 25 September 2019

DOI: 10.1002/ddr.21609

RESEARCH ARTICLE

DDR WILEY

A pharmacogenetic risk score for the evaluation of major depression severity under treatment with antidepressants

Sofia H. Kanders[1] | Claudia Pisanu[1,2] | Marcus Bandstein[1] | Jörgen Jonsson[1] | Enrique Castelao[3] | Giorgio Pistis[3] | Mehdi Gholam-Rezaee[3] | Chin B. Eap[3,4] | Martin Preisig[3] | Helgi B. Schiöth[1,5] | Jessica Mwinyi[1]

[1]Department of Neuroscience, Uppsala University, Uppsala, Sweden

[2]Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy

[3]Department of Psychiatry, University of Lausanne, Lausanne, Switzerland

[4]Department of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Switzerland

[5]Institute for Translational Medicine and Biotechnology, Sechenov First Moscow State Medical University, Moscow, Russia

Correspondence
Sofia H. Kanders, Uppsala University, Department of Neuroscience, BMC, Box 593, 751 24 Uppsala, Sweden.
Email: sofia.kanders@neuro.uu.se

Funding information
Fondazione Umberto Veronesi; GlaxoSmithKline, Faculty of Biology and Medicine of Lausanne, Swiss National Science Foundation, Grant/Award Numbers: 3200B0-105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468, 33CS30-148401; Swedish Research Council, Grant/Award Number: 2013-2892

Abstract

The severity of symptoms as well as efficacy of antidepressants in major depressive disorder (MDD) is modified by single nucleotide polymorphisms (SNPs) in different genes, which may contribute in an additive or synergistic fashion. We aimed to investigate depression severity in participants with MDD under treatment with antidepressants in relation to the combinatory effect of selected genetic variants combined using a genetic risk score (GRS). The sample included 150 MDD patients on regular AD therapy from the population-based Swiss PsyCoLaus cohort. We investigated 44 SNPs previously associated with antidepressant response by ranking them with regard to their association to the Center for Epidemiologic Studies Short Depression Scale (CES-D) score using random forest. The three top scoring SNPs (rs12248560, rs878567, rs17710780) were subsequently combined into an unweighted GRS, which was included in linear and logistic regression models using the CES-D score, occurrence of a major depressive episode (MDE) during follow-up and regular antidepressant treatment during the 6 months preceding follow-up assessment as outcomes. The GRS was associated with MDE occurrence (p = .02) and ln CES-D score (p = .001). The *HTR1A* rs878567 variant was associated with ln CES-D after adjustment for demographic and clinical variables [p = .02, lower scores for minor allele (G) carriers]. Additionally, rs12248560 (*CYP2C19*) CC homozygotes showed a six-fold higher likelihood of regular AD therapy at follow-up compared to minor allele homozygotes [TT; ultrarapid metabolizers (p = .03)]. Our study suggests that the cumulative consideration of pharmacogenetic risk variants more reliably reflects the impact of the genetic background on depression severity than individual SNPs.

KEYWORDS
depression, genetic risk score, pharmacogenetics, random forest, treatment with antidepressants

1 | INTRODUCTION

Major Depressive Disorder (MDD) is a complex and common disease with a mean lifetime prevalence of 11% across surveys (Kessler et al., 2015). European prevalence ranges from 2.9% in Romania to 20.4% in France (Kessler et al., 2015). Treatment and disease course vary strongly across individuals. MDD is considered to be the result of both environmental (Kessler et al., 2015; Wang, 2005) and genetic

(Nivard et al., 2015) factors, with a heritability estimated at 40% (Nivard et al., 2015). The clinical and etiological heterogeneity complicates the prediction of therapy success and the optimal choice of the individual therapy approach, which is essentially needed for MDD.

The primary goals of maintenance therapy are to prevent future episodes of depression, thereby avoiding the development of chronicity, along with suicide prevention. The most common medications used include for example, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors (SNRIs) or monoamine oxidase inhibitors (MAOIs) (Bauer et al., 2015). Only one-third of patients achieve remission after an initial treatment (Rush et al., 2006) and genetic variation has been suggested to partly explain this variability in response (Ising et al., 2009).

Several genetic variants influence the metabolism and pharmacodynamics of antidepressant (AD) treatment. These variants include polymorphisms in Cytochrome P450 genes, such as *CYP2D6* and *CYP2C19*, which have been shown to be able to alter the plasma concentration of TCAs (Grasmader et al., 2004; Hicks et al., 2013) and SSRIs (Grasmader et al., 2004; Hicks et al., 2015) in patients with depression. Furthermore, polymorphisms in transporter genes [e.g., ATP binding cassette subfamily B member 1 (*ABCB1*)] and in serotonin receptor genes, such as 5-hydroxytryptamine receptor 1A (*HTR1A*), seem as well to affect AD response (O'Leary, O'Brien, O'Connor, & Cryan, 2014). Recently, Genome Wide Association Studies (GWAS) have detected numerous Single Nucleotide Polymorphisms (SNPs) that modify therapy response in MDD as measured by the Hamilton Depression Rating Scale (HAM-D) (Ising et al., 2009). However, the individual influence of each of the detected SNPs appears to be limited (Ising et al., 2009). In addition, no reliable predictor for antidepressant treatment outcome could be identified in a recent meta-analysis (GENDEP Investigators, MARS Investigators, & STAR*D Investigators, 2013). It is conceivable that the simultaneous consideration of several genetic factors may confer a better predictive ability regarding therapy outcome, than the individual SNPs per se.

Recent studies have attempted to move beyond the one-locus approach and instead investigate depression and AD therapy outcome in MDD by genetic risk score (GRS) analysis. A GRS based on 11 top hit SNPs associated with the mean number of depressive symptoms in GWAS was associated with depression severity, expressed as Center for Epidemiologic Studies Short Depression Scale (CES-D) score (Radloff, 1977) eight item version, in a study including 3,091 participants (Levine et al., 2014). Kautzky et al. predicted the AD treatment outcome for 225 subjects that received several different types of ADs including SSRIs, MAOI, SNRIs or TCAs using 12 SNPs located in 5 serotonin-related genes (Kautzky et al., 2015).

To our knowledge, no study has hitherto comprehensively evaluated to what extent the combinatory effect of SNPs, playing a role in pharmacokinetics and pharmacodynamics of ADs influences the long-term depression severity under treatment with antidepressants in MDD.

In the current study we investigated 69 SNPs previously associated with AD pharmacokinetics, pharmacodynamics of ADs or therapy outcome in MDD. We filtered SNPs based on quality control criteria as well as their relevance using random forest and evaluated the associations between a GRS constructed using top-hit SNPs with the CES-D score in participants with MDD and with a mean follow-up time of more than 5 years. Participants included in the study were from the community, fulfilling DSM-IV criteria for a current or a lifetime history of MDD at baseline with a regular AD treatment. In addition, we assessed the associations between the GRS and individual SNPs with the occurrence of a new major depressive episode (MDE) during the follow-up and regular AD treatment during 6 months prior to the follow-up evaluation.

2 | METHODS

2.1 | Subjects

We included clinical and SNP data from the CoLaus¦PsyCoLaus cohort (Firmann et al., 2008; Preisig et al., 2009), a prospective study designed to study mental disorders and cardiovascular risk factors (CVRF) in the community and to determine their associations. A total of 6,734 individuals aged between 35–75 years were randomly selected from the residents of the city of Lausanne, Switzerland between 2003 and 2006 according to the civil register. Sixty-seven percent of the 35 to 66 year-old participants of the physical baseline exam (n = 5,535) also accepted the psychiatric evaluation (Figure 1). Among them, 224 Caucasians had an ongoing regular AD treatment (69.6% treated in monotherapy with SSRI, 10.7% treated in monotherapy with SNRI, 7.6% treated in monotherapy with Tricyclics, 8.8% treated in monotherapy with other ADs, 4.0% treated with a combination of several types of ADs) and either a current or a lifetime history of MDD at the baseline evaluation. Out of them, 160 (71.4%) also accepted both the physical and the psychiatric follow-up evaluation (mean duration 5.5 ± 0.3 years, Table 1) and could be included in the present analyses.

2.2 | Assessment of clinical data

Diagnostic information on mental disorders was collected at baseline and follow-up investigation, using the French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Leboyer et al., 1995; Nurnberger Jr. et al., 1994; Preisig, Fenton, Matthey, Berney, & Ferrero, 1999). The DIGS was completed with anxiety disorder sections of the Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-L) (Endicott & Spitzer, 1978). Psychiatric diagnoses were assigned according to the DSM-IV. At the baseline evaluation, the participants were interviewed for presence of MDD at any time during their life until the interview ("lifetime MDD"). At the follow-up evaluation, participants were interviewed on presence of any MDE occurrence ("MDE occurrence", Yes/No), anxiety disorders (Yes/No) and substance dependence (Yes/No) during the time between baseline and the follow-up assessment (during follow-up). All interviews were conducted by master-level psychologists who

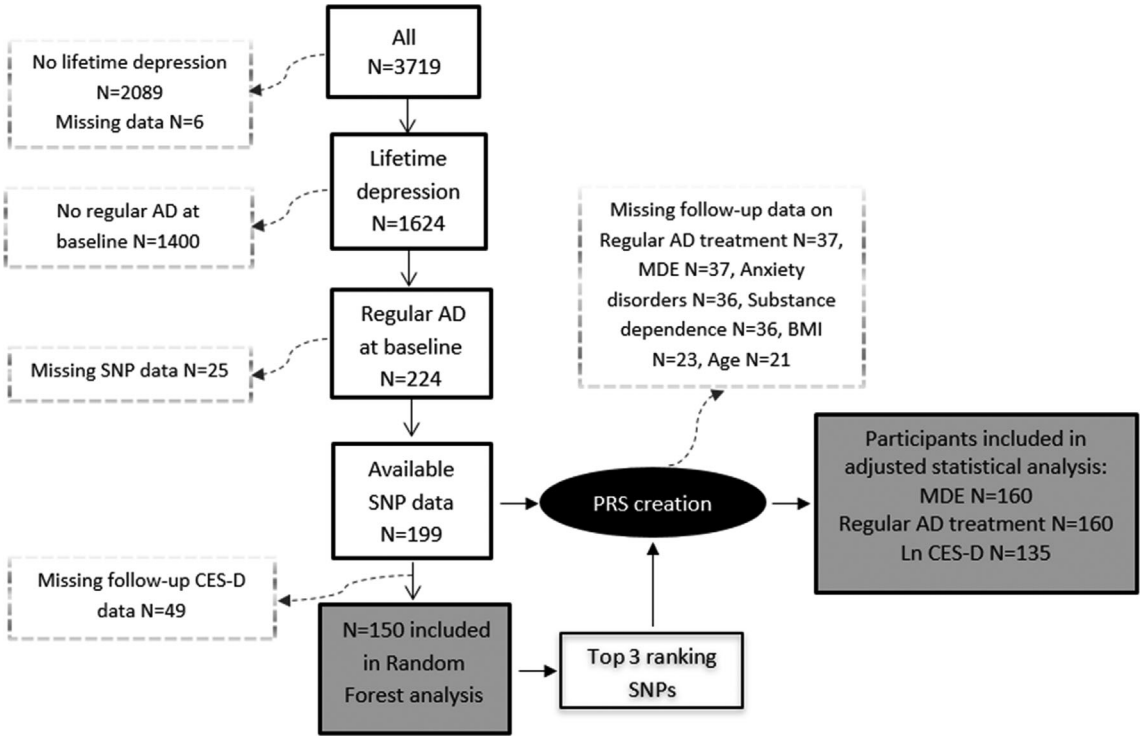

FIGURE 1 Selection process of the study sample and participants excluded due to missing data. Figure shows a description of the selection process of the study participants and missing data. Participants that at baseline had lifetime MDD and a regular AD treatment during the 6 months preceding the assessment were included in the present study. Participants with available SNP data and a record of CES-D score at the follow-up evaluation were included in the Random Forest analysis. The GRS was calculated in all participants with available SNP data. The adjusted statistical analyses were conducted on participants with available data for all included variables. AD, antidepressant; BMI, body mass index; CES-D, Center for Epidemiologic Studies Short Depression Scale; MDE, major depressive episode; GRS, genetic risk score; SNP, single nucleotide polymorphism

TABLE 1 Demographic and clinical characteristics of the sample at follow-up

	All	Regular AD treatment at follow-up	No regular AD treatment at follow-up	*p*
Total (N)	160	94	66	
Women (%)	71.9%	72.3%	71.2%	N.S
Age at follow-up (years)	56.5 ± 7.8	57.2 ± 7.8	55.4 ± 8.3	N.S
BMI at follow-up	26.8 ± 5.5	26.8 ± 5.9	26.9 ± 5.1	N.S
Not physically active at follow-up (%)	38.1%	40.4%	34.8%	N.S
High alcohol consumption at follow-up[a] (%)	11.9%	9.6%	15.2%	N.S
Any anxiety disorder during follow-up (%)	17.5%	18.1%	16.7%	N.S
Substance dependence during follow-up (%)	1.3%	1.1%	1.5%	N.S
MDE during follow-up (%)	26.3%	30.9%	19.7%	N.S
CES-D at follow-up[b]	18.5 ± 11.4	20.6 ± 10.6	15.3 ± 11.9	**0.007**
Ln CES-D at follow-up[b]	2.7 ± 0.8	2.9 ± 0.5	2.4 ± 1.0	**<0.001**

Note: Continuous variables are expressed as mean ± *SD*; *p*-values are calculated using *t*-test or chi square test. Significant results are reported in bold. Abbreviations: AD, antidepressant; BMI, body mass index; MDE, major depressive episode; N.S. not significant.

[a]≥14 drinks/week.

[b]*N* = 135 (81 regular treatment, 54 no regular treatment).

were trained over a one to two-month period and each interview was reviewed by an experienced senior psychologist.

Body height and weight were measured at the physical follow-up exam to determine the body mass index (BMI). Participants were considered physically active if they reported to practice at least 20 minutes twice a week at the physical follow-up exam. Alcohol consumption at follow-up was defined based on the number of standard drinks (a drink containing 14 g of pure alcohol) consumed by

participants in the 7 days preceding the interview (0: no alcohol consumption; 1–13: low consumption; ≥14: high consumption).

Depression severity was only assessed at the physical follow-up exam using the Centre for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977), translated to French. The CES-D scale was designed for use in the general population and is a 20-item instrument that measure depressive symptoms over the past week (Radloff, 1977).

At the physical baseline and follow-up evaluations, the participants reported their antidepressant treatment and if the treatment was either "occasional" or "regular" during the past 6 months. The baseline data were used for selection of the study population while the follow-up data were used for the statistical analyses.

2.3 | Genome wide SNP determination

In Colaus/PsyCoLaus, blood samples used for genotyping were collected at the physical baseline evaluation. Nuclear DNA was extracted from whole blood and the Affymetrix 500 K SNP chip technology was used for genome-wide genotyping. Samples with a proportion of genotypes <90% or exhibiting inconsistent genotypes in duplicate samples were excluded from the analyses. Moreover, SNPs were excluded using the following quality criteria: (1) SNPs that were monomorphic among all samples; (2) SNPs in Hardy–Weinberg disequilibrium ($p < 1{\cdot}0 \times 10^{-7}$) 3) SNPs with a genotype determination rate of less than 95% (Preisig et al., 2009). The population structure in CoLaus was extensively examined (Novembre et al., 2008). For imputation, only autosomal SNPs present in HapMap release 21 (build 35) were used; the dataset used for imputation included 5,435 CoLaus participants and 390,631 SNPs. Imputation was performed according to the method of Marchini et al. (2007) using IMPUTE version 0.2.0, and CEU haplotypes and fine scale recombination map from HapMap release 2.

2.4 | SNP selection and handling of SNP data

We performed searches on several online databases including PubMed ("The NCBI PubMed database, n.d."), SNPedia ("SNPedia, n. d."), PharmGKB pathways ("PharmGKB pathways, n.d."), National Human Genome Research Institute database ("National Human Genome Research Institute database, n.d.") and the literature describing susceptibility genes that are involved in uptake, metabolism and drug distribution of antidepressants. Search terms such as "depression," "antidepressant," "serotonin," and "polymorphisms" was used to generate a list of SNPs previously investigated with regards to their potential involvement in AD response among humans. SNPs with an estimated minor allele frequency (MAF) >5% in white populations according to the NCBI dbSNP online database ("The NCBI SNP database, n.d.") were considered in further analyses. We thus based our study on an initial selection of 69 SNPs located in or near 50 different genes (Supplementary Table 1). In the majority of cases, in our dataset these SNPs were imputed based on known linkage behavior to proxy SNPs (imputation quality; r^2hat ≥ 0.3). Imputed SNP data were rounded using MS © Excel (ver. 14.0.7166.5000) to "0" representing the major allele in homozygous form, "1" for heterozygotes and "2" for individuals homozygous for the minor allele. SNPs in linkage disequilibrium (LD) (D' > 0.8), as those occurring in *HTR1A*, *HTR2A*, and *CYP2D6* (Haploview V 4.2 [Barrett, Fry, Maller, & Daly, 2005]) were represented by one SNP each. For *CYP2D6*, we used rs5751222 as a proxy for rs1065852, a SNP that represents a decreased or non-functioning variant (Ji et al., 2014). After exclusion of SNPs with low MAF (<5%), SNPs not in Hardy–Weinberg equilibrium (HWE, $p < .05$) or in LD, 44 SNPs remained in the subsequent analyses.

2.5 | Random Forest analyses and development of a genetic risk score

The evaluation of which SNPs are significantly related to a certain trait is an important step in GRS development. Since only one of the 44 individual SNPs included in this study was associated with severity of depression (rs12248560, see Table 2) we used Random forest (RF) (Nguyen, Huang, Wu, Nguyen, & Li, 2015) as a SNP selection method. RF has the advantage of being able to rank variables with small effect sizes according to their importance (Rodin, Gogoshin, & Boerwinkle, 2011). The method has been successfully applied to evaluate the impact of BMI associated SNPs on weight loss after bariatric surgery (Bandstein et al., 2016) as well as the association between different genetic variants and migraine with or without aura (Pisanu et al., 2017).

RF analysis was applied using the Rattle package (Williams et al., 2016) in R. Logarithmically transformed CES-D overall score measured at the follow-up investigation [ln(CES-D + 1) as performed by (Noordam et al., 2015) due to non-normality] measuring the abundance of MDD associated symptoms was used as the outcome variable. We refer to the transformed variable as "ln CES-D" in the following. We included 44 SNPs determined in 150 individuals with available data on ln CES-D score in our RF model. Running conditions were set to 10,000 trees, evaluating six SNPs at each split. The top three SNPs inducing a mean squared error (MSE) ≥ 9 were selected to be included in the GRS. The random forest plot is shown in Figure 2. The three top scoring SNPs detected in random forest analysis were individually checked for association with ln CES-D values using one-way ANOVA. In case a significant association was detected, the risk allele was assigned based on data from the current study. Otherwise, the risk allele was chosen based on previous publications (Table 2). Subsequently, the GRS was constructed by summing the number of risk alleles in each individual giving a possible GRS range from zero (no risk allele) to six (six risk alleles in carriers homozygous for the major alleles of all three SNPs). SNPs included in the GRS were further investigated using UCSC Genome Browser (Kent et al., 2002) to find nearby genes and visualized using LDproxy on CEU population (Machiela & Chanock, 2015) to verify a possible SNP-gene association (Table 2).

TABLE 2 Description of the three SNPs included in the genetic risk score

SNP (chromosome) gene	MSE[a]	Genotype	*N*	Mean CES-D	Ln CES-D	Risk allele in this study[b]	Risk allele, reference publication	Reference publication
rs12248560 (10) CYP2C19	18.0%	C/C	102	18.7 ± 11.3	2.8 ± 0.7	C	T	Chang et al., 2014
		C/T	43	20.0 ± 11.7	2.8 ± 0.8			
		T/T	5	6.80 ± 7.2	1.8 ± 0.9			
		Total	150	18.6 ± 11.5	2.8 ± 0.8			
rs878567 (5) HTR1A	10.9%	A/A	40	20.5 ± 12.3	2.9 ± 0.8	A	A[c]	Kato et al., 2009
		A/G	70	19.0 ± 10.5	2.8 ± 0.7			
		G/G	40	16.2 ± 12.1	2.5 ± 0.9			
		Total	150	18.6 ± 11.5	2.8 ± 0.8			
rs17710780 (5) ARHGEF37	9.3%	T/T	114	19.3 ± 11.3	2.8 ± 0.7	T	T	GENDEP Investigators et al., 2013
		T/C	33	16.4 ± 12.3	2.5 ± 0.9			
		C/C	3	17.3 ± 3.2	2.9 ± 0.2			
		Total	150	18.6 ± 11.5	2.8 ± 0.8			

Abbreviations: ARHGEF37, Rho Guanine Nucleotide Exchange Factor 37; CES-D, The Center for Epidemiologic Studies Depression Scale; CYP2C19, Cytochrome P450 2C19; HTR1A, 5-Hydroxytryptamine Receptor 1A; MDD, Major Depressive Disorder; MSE, Mean Squared Error; N.S. not significant; SNP, Single Nucleotide Polymorphism.

[a]MSE induced by the respective SNP in Random Forest analyses.

[b]Observations from this study comparing mean CES-D and ln CES-D values in genotypes. Rs12248560 T/T; lower ln CES-D values (p = 0.012, ANOVA). C was considered risk allele. Rs878567 and rs17710780 N.S. The risk allele from the reference publications was used as risk allele in this study.

[c]Kato investigated the proxy rs6295 (C/G).

2.6 | Statistical analyses

The statistical analyses were performed using data from the follow-up evaluation. Mean differences in age, BMI and CES-D score were analyzed dependent of the regularity of AD treatment (Regular treatment/No regular treatment) using independent *t*-tests. Chi^2-tests were used to compare sex (men = 0, women = 1), physical activity (Yes/No), MDE occurrence (Yes/No), alcohol consumption (No/Low/High consumption), anxiety disorders (Yes/No) and substance dependence (Yes/No) in individuals treated or not treated regularly with ADs at follow-up.

Individual SNPs were investigated for their impact on CES-D using ANOVA and regular AD treatment (Yes/No) and MDE occurrence (Yes/No) using Chi^2 tests. The GRS was evaluated depending on sex, anxiety disorders (Yes/No), substance dependence (Yes/No) and regular AD treatment (Yes/No) using individual T-tests.

We used three outcome variables to assess the impact from individual SNPs and the GRS on therapy response in adjusted analyses. Our primary outcome was ln CES-D overall score (linear regression, N = 135) and our secondary outcomes were MDD occurrence (binary logistic regression, N = 160) and regular AD treatment (binary logistic regression, N = 160). While we considered ln CES-D and MDE occurrence as direct measurements of depression we used AD treatment as an indirect measurement of depression. In an initial model, we included the GRS and in three subsequent models, we included the individual SNPs in regression analyses, as shown in Table 2 for comparison. SNPs and our GRS were tested cross-sectional on follow-up data together with the covariates sex, age, BMI, prevalence of anxiety disorders and substance dependence. In the analyses on ln CES-D and MDE occurrence we also controlled for regular AD treatment. A p-value <.05 was considered to be statistically significant. Finally, the inclusion of identified genes in the druggable genome was checked using DGIdb (Cotto et al., 2018), while the functional effect of top scoring SNPs on gene expression in brain regions was checked using GTEx V.8 (GTEx Consortium, 2013).

Statistical analyses were performed using the SPSS software (V 21.0.0.0 © IBM Corporation) and RStudio (V 0.98.1028 © RStudio Inc. and Rattle version 3.5.0 © Togaware Pty Ltd.).

3 | RESULTS

3.1 | Clinical parameters and depression severity

Table 1 shows demographic and clinical characteristics of participants for the whole cohort at the follow-up investigation and after stratification according to AD treatment (regular/no regular treatment). The majority of included subjects were women. Within the total cohort of 160 participants, 94 (59%) were still being treated regularly with ADs at the follow-up investigation. The large majority of these (67%) were treated in monotherapy with SSRIs, while only minor fractions were treated with other AD drugs (10.6% treated in monotherapy with SNRIs, 7.4% treated in monotherapy with Tricyclics, 7.4% in monotherapy with other ADs). A proportion of 7.4% of the cohort was treated with AD belonging to several AD classes. Regularly treated participants showed higher CES-D scores compared to participants not regularly treated (Table 1).

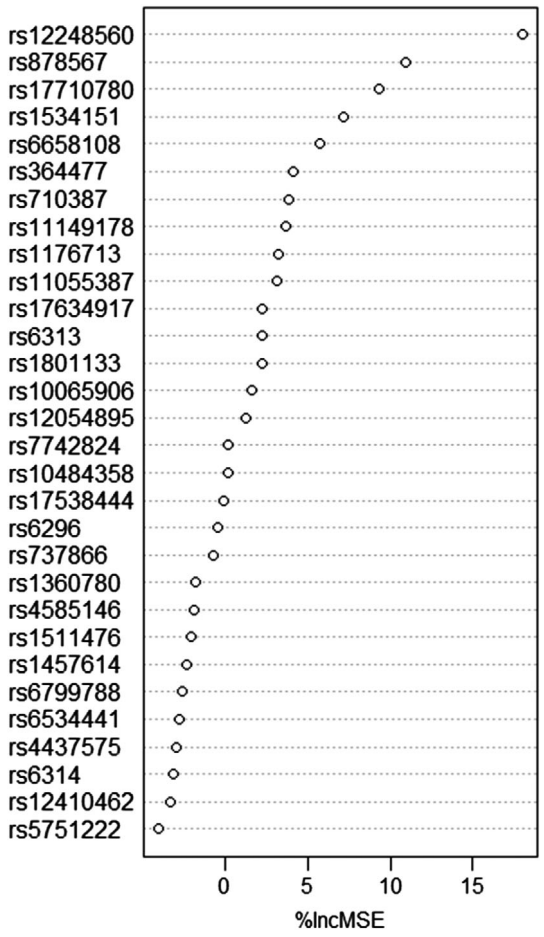

FIGURE 2 Random forest analysis variable importance. Figure shows the variable importance output from the Random Forest analysis. % Increase in mean squared error (%IncMSE) is computed from permuting the test data. The prediction error on test for each tree is compared with results from the permuted data results. The difference between the two are then averaged over all trees, and normalized by the *SD* of the differences. A variable (i.e., in this case a SNP) is considered more important for the dependent variable for higher values on %IncMSE whereas non important variables receive low values. SNP, single nucleotide polymorphism

3.2 | Association between individual SNPs, GRS and depression severity

We performed unadjusted analyses to evaluate the risk allele association of individual SNPs with the CES-D score. Only for rs12248560 (*CYP2C19*) ln CES-D values differed, which supported the use of a ranking method to find the highest impact SNPs. The RF analysis revealed three SNPs with a MSE≥9 for ln CES-D, that is, rs12248560 (*CYP2C19*), rs878567 (*HTR1A*) and rs17710780 (*ARHGEF37*) (Table 2). Subsequently, association analyses were performed for these top scoring SNPs individually and by including them in an unweighted GRS. This GRS reached a mean score of 4.3 in the cohort (range from 1 to 6, *SD* = 1.0). The GRS did not differ between subgroups of the cohort according to sex (women: 4.4 ± 1.0; men: 4.2 ± 1.1), the occurrence of anxiety disorders (No: 4.3 ± 1.1; Anxiety: 4.5 ± 0.9), the occurrence of substance dependence (No: 4.3 ± 1.1; substance dependence: 4.0 ± 0.0) or the presence of regular AD treatment (No: 4.4 ± 1.0; regular: 4.3 ± 1.1) in unadjusted analyses using Student's *t*-test (data not shown). Regarding individual SNPs, rs12248560-CC individuals showed higher ln CES-D scores than –CT and –TT carriers (p = .011, Bonferroni corrected post hoc analysis) and -C was treated as the risk allele. Conversely, rs17710780 and rs878567 were not significantly associated with ln CES-D. Therefore, in the construction of the GRS, the risk allele for these SNPs was selected based on previous publications (Table 2).

As shown in Table 3, the GRS and the genetic variant rs878567 (*HTR1A*) were associated with ln CES-D, with lower ln CES-D scores for individuals carrying the minor allele (G) after adjustment for sex, age, BMI, as well as anxiety disorders, substance dependence and regular AD treatment.

In the next step, we investigated the associations between the GRS or the individual SNPs and the occurrence of a MDE during the follow-up period. In contrast to the GRS, none of the SNPs were associated with occurrence of a MDE in unadjusted or adjusted analyses (Table 4).

In a third step we scrutinized to what extent the SNPs were important for regular AD treatment at follow-up. As shown in Table 5, rs12248560 (*CYP2C19*) was associated with ongoing regular AD treatment at follow-up in binary logistic regression analyses. Heterozygote (CT) individuals were 2.5 times more likely than wild type (CC) to be regularly treated with ADs at follow-up (Table 5). When we instead used the minor allele (TT) as the reference category, CC-carriers were 6.7 times (confidence interval: 1.3–35.4) more likely to be regularly treated with ADs at follow-up than TT-individuals.

In silico analyses using DGIdb showed that two of the three identified top scoring SNPs are located in genes which are part of the druggable genome (*CYP2C19* and *HTR1A*). Additionally, two of the three SNPs were found to be significant expression quantitative trait loci (eQTL) in different tissues including brain according to GTEx V. 8 (rs12248560, eQTL for *NOC3L* in cerebellum and nucleus accumbens; rs878567, eQTL for *RNF180* in cerebellum and putamen).

4 | DISCUSSION

Using data from a prospective cohort study, we measured the associations between three SNPs (both independently as well as combined in a GRS) and different depression parameters at follow-up in participants with lifetime MDD who were under AD treatment at baseline. Among the individual SNPs, only rs878567 (*HTR1A*) was associated with ln CES-D in adjusted analyses. None of the individual SNPs was associated with the occurrence of a MDE during follow-up. Conversely, the GRS was associated with both depression measurements, suggesting that the evaluation of the combined effect of multiple genetic variants playing a role in the pharmacokinetics and –dynamics of ADs reflects depression severity to a much better extent than the individual SNPs. These results underline the importance to evaluate the joint, multivariate influence of susceptibility factors in cases where

TABLE 3 Association between the GRS and three SNPs included in the GRS and Ln CES-D score

	Unstandardized coefficients		Standardized coefficients			
Variables[a]	*B*	*SE*	*β*	*t*	*p*	95% CI
GRS	0.19	0.06	0.26	3.31	**0.001**	0.08 to 0.31
Age at follow-up (y)	−0.01	0.01	−0.09	−1.07	0.29	−0.02 to 0.01
Sex	0.09	0.14	0.05	0.64	0.52	−0.19 to 0.37
BMI at follow-up	0.03	0.01	0.19	2.48	**0.01**	0.01 to 0.05
Substance dependence[b]	0.06	0.50	0.01	0.13	0.90	−0.93 to 1.06
Anxiety disorders[b]	0.37	0.16	0.18	2.28	**0.02**	0.05 to 0.69
AD regular use	0.55	0.12	0.35	4.45	**<0.001**	0.31 to 0.8
(constant)	1.18	0.57		2.09	0.04	0.06 to 2.3
rs12248560[c]	−0.20	0.11	−0.14	−1.77	0.08	−0.43 to 0.02
Age at follow-up (y)	0.00	0.01	−0.04	−0.51	0.61	−0.02 to 0.01
Sex	0.09	0.14	0.05	0.63	0.53	−0.19 to 0.38
BMI at follow-up	0.03	0.01	0.19	2.34	**0.02**	0.00 to 0.05
Substance dependence[b]	0.05	0.52	0.01	0.10	0.92	−0.97 to 1.08
Anxiety disorders[b]	0.40	0.17	0.20	2.42	**0.02**	0.07 to 0.73
AD regular use	0.54	0.13	0.34	4.19	**<0.001**	0.28 to 0.79
(constant)	1.87	0.55		3.42	0.00	0.79 to 2.96
rs878567[c]	−0.20	0.09	−0.19	−2.32	**0.02**	−0.38 to −0.03
Age at follow-up (y)	−0.01	0.01	−0.09	−1.12	0.26	−0.02 to 0.01
Sex	0.11	0.14	0.07	0.80	0.43	−0.17 to 0.4
BMI at follow-up	0.03	0.01	0.18	2.30	**0.02**	0.00 to 0.05
Substance dependence[b]	−0.03	0.51	−0.01	−0.06	0.95	−1.05 to 0.98
Anxiety disorders[b]	0.37	0.16	0.18	2.25	**0.03**	0.05 to 0.70
AD regular use	0.52	0.13	0.33	4.13	**<0.001**	0.27 to 0.77
(Constant)	2.31	0.58		3.97	0.00	1.16 to 3.46
rs17710780[c]	−0.21	0.13	−0.13	−1.63	0.11	−0.46 to 0.05
Age at follow-up (y)	−0.01	0.01	−0.05	−0.65	0.52	−0.02 to 0.01
Sex	0.09	0.14	0.05	0.63	0.53	−0.20 to 0.38
BMI at follow-up	0.03	0.01	0.21	2.60	**0.01**	0.01 to 0.05
Substance dependence[b]	0.07	0.52	0.01	0.13	0.89	−0.96 to 1.10
Anxiety disorders[b]	0.39	0.17	0.19	2.33	**0.02**	0.06 to 0.71
AD regular use	0.54	0.13	0.34	4.18	**<0.001**	0.28 to 0.79
(Constant)	1.84	0.55		3.35	0.00	0.75 to 2.93

Abbreviations: BMI, body mass index; CES-D, The Center for Epidemiologic Studies Depression Scale; CI, confidence interval.

[a]Linear regression analyses with outcome variable Ln CES-D at follow-up (N = 135) corrected for sex, age BMI, anxiety disorders, substance dependence, regular antidepressant treatment, and the GRS or isolated GRS related SNPs, respectively in four separate regressions. Significant results are shown in bold.

[b]Any occurrence during follow-up.

[c]WT = 0, heterozygotes = 1, homozygote minor allele = 2.

the individual effects of genetic risk parameters appear to be small, as for example, in the case of AD treatment.

Among the SNPs included in the GRS, *CYP2C19*17* (rs12248560 T allele) exhibited the most profound influence on ln CES-D. *CYP2C19* metabolizes the ADs citalopram and escitalopram and to a lesser extent fluoxetine and sertraline. The ultrarapid metabolizer allele *CYP2C19*17* has been repeatedly associated with changes in the pharmacokinetics of those ADs (Huezo-Diaz et al., 2012; Li-Wan-Po, Girard, Farndon, Cooley, & Lithgow, 2010; Ohlsson Rosenborg et al., 2008; Rudberg, Mohebi, Hermann, Refsum, & Molden, 2008; Tsai et al., 2010). While several studies have proven the impact of *CYP2C19*17* on the pharmacokinetics of CYP2C19 substrates such as ADs or omeprazole (Ohlsson Rosenborg et al., 2008), only one study has investigated the specific association between *CYP2C19*17* and the therapy outcome in MDD (Mrazek et al., 2011). Specifically, Mrazek et al. showed lower remission rates for medication tolerating

TABLE 4 Association between the PRS and the three SNPs included in the GRS and MDD status during follow-up according to binary logistic regression

Variable[a]	B	*SE*	Wald	*df*	*p*	OR (95% CI)
GRS	0.49	0.21	5.47	1.00	**0.02**	1.63 (1.08 to 2.46)
Age at follow-up (y)	−0.04	0.03	2.84	1.00	0.09	0.96 (0.91 to 1.01)
Sex (1)	0.13	0.47	0.08	1.00	0.78	1.14 (0.46 to 2.85)
BMI at follow-up	−0.05	0.04	1.67	1.00	0.20	0.95 (0.88 to 1.03)
Anxiety disorders (1)[b]	1.04	0.46	5.09	1.00	**0.02**	2.84 (1.15 to 7.02)
Substance dependence (1)[b]	1.14	1.46	0.61	1.00	0.44	3.12 (0.18 to 54.25)
AD regular use (1)	0.76	0.41	3.37	1.00	0.07	2.13 (0.95 to 4.79)
Constant	−0.24	1.90	0.02	1.00	0.90	0.78
rs12248560[c]			1.01	2.00	0.60	
rs12248560 (1)	−0.47	0.47	1.01	1.00	0.32	0.63 (0.25 to 1.56)
rs12248560 (2)	−20.12	13,679.55	0.00	1.00	1.00	
Age at follow-up (y)	−0.03	0.03	1.29	1.00	0.26	0.97 (0.93 to 1.02)
Sex (1)	0.13	0.46	0.08	1.00	0.78	1.14 (0.46 to 2.83)
BMI at follow-up	−0.05	0.04	1.87	1.00	0.17	0.95 (0.88 to 1.02)
Anxiety disorders (1)[b]	1.10	0.47	5.55	1.00	**0.02**	3.00 (1.02 to 7.49)
Substance dependence (1)[b]	1.05	1.46	0.52	1.00	0.47	2.85 (0.17 to 49.33)
AD regular use (1)	0.68	0.42	2.64	1.00	0.11	1.96 (0.87 to 4.43)
Constant	1.42	1.77	0.64	1.00	0.42	4.13
rs878567[c]			1.64	2.00	0.44	
rs878567 (1)	−0.54	0.48	1.29	1.00	0.26	0.58 (0.23 to 1.48)
rs878567 (2)	−0.62	0.54	1.32	1.00	0.25	0.54 (0.19 to 1.55)
Age at follow-up (y)	−0.04	0.03	2.49	1.00	0.12	0.96 (0.92 to 1.01)
Sex(1)	0.15	0.46	0.10	1.00	0.75	1.16 (0.47 to 2.85)
BMI at follow-up	−0.06	0.04	2.07	1.00	0.15	0.95 (0.88 to 1.02)
Anxiety disorders (1)[b]	1.07	0.46	5.43	1.00	**0.02**	2.91 (1.19 to 7.16)
Substance dependence (1)[b]	0.79	1.49	0.28	1.00	0.60	2.20 (0.12 to 41.06)
AD regular use (1)	0.69	0.40	2.94	1.00	0.09	2.00 (0.91 to 4.40)
Constant	2.37	1.88	1.59	1.00	0.21	10.69
rs17710780[c]			0.79	2.00	0.68	
rs17710780 (1)	−0.44	0.50	0.79	1.00	0.38	0.65 (0.24 to 1.7)
rs17710780 (2)	−20.41	22,826.90	0.00	1.00	1.00	
Age at follow-up (y)	−0.04	0.03	1.99	1.00	0.16	0.97 (0.92 to 1.01)
Sex (1)	0.10	0.46	0.05	1.00	0.83	1.11 (0.45 to 2.74)
BMI at follow-up	−0.05	0.04	1.75	1.00	0.19	0.95 (0.88 to 1.03)
Anxiety disorders (1)[b]	1.02	0.46	4.94	1.00	**0.03**	2.76 (1.13 to 6.77)
Substance dependence (1)[b]	1.06	1.46	0.53	1.00	0.47	2.89 (0.17 to 50.22)
AD regular use (1)	0.75	0.41	3.38	1.00	0.07	2.11 (0.95 to 4.67)
Constant	1.66	1.73	0.92	1.00	0.34	5.26

Abbreviations: AD, Antidepressant; BMI, Body Mass Index; CI, confidence interval; OR, odds ratio; GRS, genetic risk score; SNP, single nucleotide polymorphism. Significant results reported in bold.

[a]Binary logistic Regression, *N* = 160 on MDD according to DSM-IV during follow-up as the dependent variable. Variables entered: Sex, BMI, Age, anxiety disorders, substance dependence, regular AD treatment and the GRS or isolated GRS related SNPs, respectively in four separate regressions.

[b]At any time during follow-up.

[c]Wild type as reference, (1) reference versus heterozygote (2) reference versus homozygote minor allele.

TABLE 5 Associations between the GRS and three SNPs included in the GRS and regular AD treatment

Variable[a]	B	S.E.	Wald	p	OR (95% CI)
GRS ln CES-D	−0.10	0.16	0.39	0.53	0.91 (0.66 to 1.24)
Age at follow-up (y)	0.03	0.02	2.15	0.14	1.03 (0.99 to 1.07)
Sex (1)	0.10	0.37	0.08	0.78	1.11 (0.54 to 2.29)
BMI at follow-up	−0.01	0.03	0.09	0.77	0.99 (0.94 to 1.05)
Anxiety disorders (1)[b]	0.15	0.44	0.11	0.74	1.16 (0.49 to 2.73)
Substance dependence (1)[b]	−0.22	1.44	0.02	0.88	0.81 (0.05 to 13.53)
Constant	−0.84	1.55	0.30	0.59	0.43
rs12248560[c]			6.99	**0.03**	
rs12248560 (1)	0.90	0.41	4.77	**0.03**	2.47 (1.10 to 5.55)
rs12248560 (2)	−1.00	0.78	1.65	0.20	0.37 (0.08 to 1.70)
Age at follow-up (y)	0.04	0.02	3.07	0.08	1.04 (1.00 to 1.08)
Sex (1)	0.28	0.39	0.53	0.47	1.32 (0.62 to 2.83)
BMI at follow-up	−0.01	0.03	0.08	0.77	0.99 (0.93 to 1.05)
Anxiety disorders (1)[b]	0.21	0.45	0.23	0.63	1.24 (0.52 to 2.97)
Substance dependence (1)[b]	−0.46	1.48	0.10	0.75	0.63 (0.04 to 11.37)
Constant	−1.99	1.51	1.73	0.19	0.14
rs878567[c]			0.35	0.84	
rs878567(1)	0.22	0.41	0.27	0.60	1.24 (0.55 to 2.80)
rs878567(2)	0.05	0.46	0.01	0.92	1.05 (0.43 to 2.59)
Age at follow-up (y)	0.03	0.02	1.98	0.16	1.03 (0.99 to 1.08)
Sex (1)	0.09	0.37	0.06	0.81	1.09 (0.53 to 2.26)
BMI at follow-up	−0.01	0.03	0.08	0.78	0.99 (0.94 to 1.05)
Anxiety disorders (1)[b]	0.12	0.44	0.08	0.78	1.13 (0.48 to 2.67)
Substance dependence (1)[b]	−0.09	1.45	0.00	0.95	0.91 (0.05 to 15.62)
Constant	−1.35	1.56	0.75	0.39	0.26
rs17710780[c]			0.09	0.96	
rs17710780 (1)	−0.12	0.39	0.09	0.77	0.89 (0.41 to 1.92)
rs17710780 (2)	21.02	23,110.43	0.00	1.00	
Age at follow-up (y)	0.03	0.02	2.26	0.13	1.03 (0.99 to 1.08)
Sex (1)	0.14	0.38	0.15	0.70	1.15 (0.55 to 2.41)
BMI at follow-up	−0.01	0.03	0.04	0.83	0.99 (0.94 to 1.05)
Anxiety disorders (1)[b]	0.16	0.44	0.14	0.71	1.18 (0.50 to 2.77)
Substance dependence (1)[b]	−0.11	1.45	0.01	0.94	0.9 (0.05 to 15.23)
Constant	−1.43	1.46	0.96	0.33	0.24

Abbreviations: AD, antidepressant; BMI, body mass index; CI, confidence interval; OR, odds ratio; GRS, genetic risk score; SNP, single nucleotide polymorphism. Significant results reported in bold.

[a]Binary logistic regression, *N* = 160 on regular AD treatment at follow-up as the dependent variable. Variables entered: Sex, BMI, Age, anxiety disorders, substance dependence and the GRS or isolated GRS related SNPs, respectively in 4 separate regressions.

[b]At any time during follow-up.

[c]Wild type as reference, (1) reference versus heterozygote (2) reference versus homozygote minor allele.

*CYP2C19*17* carriers treated with citalopram compared to extensive and poor metabolizers (*CYP2C19*2*) as evaluated by a score below 5 points on the Quick Inventory of Depressive Symptomatology—Clinician Rating (QIDS-C) scale (Mrazek et al., 2011). In contrast with this study, we observed a lower depression severity in homozygous **17* carriers as shown by a lower CES-D score compared to heterozygous *17 and wild type carriers. Several hypotheses can be posed to explain these differences. While Mrazek et al. (2011) specifically studied citalopram, which is strongly metabolized by *CYP2C19* (Chang, Tybring, Dahl, & Lindh, 2014), we considered different AD treatments in the setup of our GRS. Furthermore, our observation is based on a unique evaluation of depression severity at the end of the follow-up period while Mrazek. et al., evaluated the rate of complete remission under citalopram treatment over time.

Interestingly, *CYP2C19*17* was also associated with regular AD treatment at follow-up in our investigation. Even though lower plasma concentrations were confirmed for example, escitalopram by (Rudberg et al., 2008), Uckun et al. (Uckun et al., 2015) suggested that *CYP2C19*17* polymorphism does not have an effect on citalopram metabolism. Sim et al. hypothesized that the ultrarapid variant could cause AD therapeutic failure due to lower plasma concentrations (Sim et al., 2010). Although this study reported lower depressive symptoms in poor metabolizers lacking CYP2C19 activity (*CYP2C19*2/*2*) compared to extensive metabolizers (*CYP2C19*1/*1*) in a sample of European adults characterized with the CES-D scale treated with different ADs, no effect was found for *CYP2C19*17* (Sim et al., 2010). In contrast with these results, a recent study found that patients undergoing treatment with escitalopram carrying the *CYP2C19*17* allele were more likely to switch to another antidepressant within one year of follow-up (Jukic, Haslemo, Molden, & Ingelman-Sundberg, 2018). Taken together, these findings suggest that the role of *CYP2C19* on depressive symptoms appears to be complex and might be different according to specific ADs, also in light of the fact that combinations of variants located in genes coding for different CYP enzymes, such as CYP2D6 (Penas-Lledo et al., 2015), might also be relevant to explain part of the variability in AD therapy outcome.

The second SNP included in the GRS, rs878567, which we used as a proxy for rs6295 (NIH, 2015), within the serotonin receptor gene *HTR1A*, showed an effect on ln CES-D only after adjustment for demographic and clinical covariates. Previous studies on rs6295 and AD response have been inconclusive. While Kato et al. observed a better response to ADs in homozygous rs6295 carriers (Kato et al., 2009), a meta-analysis from 2012 revealed no association between rs6295 and AD response (Zhao et al., 2012). The inconclusive results might be due to heterogeneities in the study design and/or follow-up time as well as due to an overall limited isolated influence of this variant on AD response.

The rs17710780 variant nearby the *ARHGEF37*, *PPARGC1B*, and *MIR378A* genes ("The NCBI Gene database") only exhibited an effect in the frame of the RF and GRS analyses, thus underlining the limited isolated effect of this variant. Variations in this chromosomal region have previously been associated with obesity (Andersen et al., 2005), plasma lipoprotein homeostasis (Liu & Lin, 2011), adipogenesis (Xu et al., 2014) and elevated cytokines (Jiang et al., 2014; Xu et al., 2014). This may be an indicator that lipid turnover and availability play a role for the severity of depression under AD treatment. Due to the large number of SNPs in high linkage with this SNP [LDproxy on CEU population (NIH, 2015)], the association for this specific SNP is highly speculative.

Our study has several limitations: (1) CES-D scores were not available from the baseline evaluation. Therefore, it was not possible to evaluate changes between the two time points. (2) We created a GRS in an unweighted manner based on cross-sectional data, as the inclusion of beta values obtained in GWAS analyses addressing the same question and applying a similar design was not available. (3) We could not stratify our analyses according to specific drug classes due to too small number of subjects in each subgroup. Future studies may benefit from a focus on a specific AD type in relation to CES-D score evaluation, in order to obtain drug group specific results. (4) No information was collected on the dosage of ADs at baseline, the duration of AD treatment during the follow-up and nonpharmacological treatment. Accordingly, we could not account for the effect of these treatments related variables in our analyses. (5) The results derived from our cohort recruited from the community may not be applicable to severe forms of MDD, which are rare in the general population but more frequent in treatment settings.

In summary, our data suggest that the combined effects of genetic variants important for pharmacokinetics and pharmacodynamics of ADs is a better predictor of the long-term depressive symptoms after treatment by ADs than isolated SNPs. However, this hypothesis needs confirmation from future independent studies.

ACKNOWLEDGMENTS

The authors want to thank Dr. Zoltán Kutalik and the inhabitants of Lausanne for their participation in the CoLaus|PsyCoLaus study and the enabling of this work.

CONFLICT OF INTEREST

S. H. K., M. B., C. P., J. J., E. C., G. P., M. G., and J. M. have nothing to disclose. C. B. E. received honoraria for conferences or teaching CME courses from Astra Zeneca, Forum für Medizinische Fortbildung, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Mepha, Otsuka, Servier, and Vifor-Pharma in the past 3 years, and for writing a review article for the journal "Dialogues in clinical neurosciences" (Servier). They received an unrestricted educational research grant from Takeda in the past 3 years.

AUTHOR CONTRIBUTIONS

S. H. K. and J. M. designed the study; M. P. and E. C. provided the data, S. H. K. analyzed the data; S. H. K., C. P., J. M., J. J., M. B., and H. B. S. interpreted the data, S. H. K., C. P., J. M., M. B., J. J., H. B. S., and M. P. drafted the manuscript. E. C., G. P., M. G. R. and C. B. E. revised the preliminary manuscript draft and gave critical comments and suggestions for improvement of content and analysis steps. All authors contributed to critical revisions and have approved the final manuscript.

ETHICS STATEMENT

The CoLaus|PsyCoLaus study was approved by the Institutional Ethics' Committee of the University of Lausanne. All participants signed a written informed consent after having received a detailed description of the goal and funding of the study. The regional Ethics' Committee in Uppsala (Dnr 2017/163) approved data handling in Sweden, of the previously collected data.

ORCID

Sofia H. Kanders https://orcid.org/0000-0002-5795-8100

REFERENCES

Andersen, G., Wegner, L., Yanagisawa, K., Rose, C. S., Lin, J., Glumer, C., … Pedersen, O. (2005). Evidence of an association between genetic variation of the coactivator PGC-1 beta and obesity. *Journal of Medical Genetics*, *42*(5), 402–407. https://doi.org/10.1136/jmg.2004.026278

Bandstein, M., Voisin, S., Nilsson, E. K., Schultes, B., Ernst, B., Thurnheer, M., … Schioth, H. B. (2016). A genetic risk score is associated with weight loss following roux-en Y gastric bypass surgery. *Obesity Surgery*, *26*, 2183–2189. https://doi.org/10.1007/s11695-016-2072-9

Barrett, J. C., Fry, B., Maller, J., & Daly, M. J. (2005). Haploview: Analysis and visualization of LD and haplotype maps. *Bioinformatics*, *21*(2), 263–265. https://doi.org/10.1093/bioinformatics/bth457

Bauer, M., Severus, E., Kohler, S., Whybrow, P. C., Angst, J., Moller, H. J., & Wfsbp Task Force on Treatment Guidelines for Unipolar Depressive, D. (2015). World Federation of Societies of biological psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. Part 2: Maintenance treatment of major depressive disorder-update 2015. *The World Journal of Biological Psychiatry*, *16*(2), 76–95. https://doi.org/10.3109/15622975.2014.1001786

Chang, M., Tybring, G., Dahl, M. L., & Lindh, J. D. (2014). Impact of cytochrome P450 2C19 polymorphisms on citalopram/escitalopram exposure: A systematic review and meta-analysis. *Clinical Pharmacokinetics*, *53*(9), 801–811. https://doi.org/10.1007/s40262-014-0162-1

Cotto, K. C., Wagner, A. H., Feng, Y., Kiwala, S., Coffman, A. C., Spies, G., … Griffith, M. (2018). DGIdb 3.0: A redesign and expansion of the drug–gene interaction database. *Nucleic Acids Research*, *46*(D1), D1068–D1073. https://doi.org/10.1093/nar/gkx1143

Endicott, J., & Spitzer, R. L. (1978). A diagnostic interview: The schedule for affective disorders and schizophrenia. *Archives of General Psychiatry*, *35*(7), 837–844.

Firmann, M., Mayor, V., Vidal, P. M., Bochud, M., Pecoud, A., Hayoz, D., … Vollenweider, P. (2008). The CoLaus study: A population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovascular Disorders*, *8*, 6. https://doi.org/10.1186/1471-2261-8-6

GENDEP Investigators, MARS Investigators, & STAR*D Investigators. (2013). Common genetic variation and antidepressant efficacy in major depressive disorder: A meta-analysis of three genome-wide pharmacogenetic studies. *The American Journal of Psychiatry*, *170*(2), 207–217. https://doi.org/10.1176/appi.ajp.2012.12020237

Grasmader, K., Verwohlt, P. L., Rietschel, M., Dragicevic, A., Muller, M., Hiemke, C., … Rao, M. L. (2004). Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. *European Journal of Clinical Pharmacology*, *60*(5), 329–336. https://doi.org/10.1007/s00228-004-0766-8

GTEx Consortium. (2013). The genotype-tissue expression (GTEx) project. *Nature Genetics*, *45*(6), 580–585. https://doi.org/10.1038/ng.2653

Hicks, J. K., Bishop, J. R., Sangkuhl, K., Muller, D. J., Ji, Y., Leckband, S. G., … Gaedigk, A. (2015). Clinical Pharmacogenetics Implementation consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clinical Pharmacology and Therapeutics*, *98*(2), 127–134. https://doi.org/10.1002/cpt.147

Hicks, J. K., Swen, J. J., Thorn, C. F., Sangkuhl, K., Kharasch, E. D., Ellingrod, V. L., … Clinical Pharmacogenetics Implementation, C. (2013). Clinical Pharmacogenetics Implementation consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clinical Pharmacology and Therapeutics*, *93*(5), 402–408. https://doi.org/10.1038/clpt.2013.2

Huezo-Diaz, P., Perroud, N., Spencer, E. P., Smith, R., Sim, S., Virding, S., … Aitchison, K. J. (2012). CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. *Journal of Psychopharmacology*, *26*(3), 398–407. https://doi.org/10.1177/0269881111414451

Ising, M., Lucae, S., Binder, E. B., Bettecken, T., Uhr, M., Ripke, S., … Muller-Myhsok, B. (2009). A genome-wide association study points to multiple loci predicting antidepressant treatment outcome in depression. *Pharmacopsychiatry*, *42*(5), 224–224.

Ji, Y., Schaid, D. J., Desta, Z., Kubo, M., Batzler, A. J., Snyder, K., … Weinshilboum, R. M. (2014). Citalopram and escitalopram plasma drug and metabolite concentrations: Genome-wide associations. *British Journal of Clinical Pharmacology*, *78*(2), 373–383. https://doi.org/10.1111/bcp.12348

Jiang, X. Y., Xue, M., Fu, Z. Y., Ji, C. B., Guo, X. R., Zhu, L., … Qu, H. M. (2014). Insight into the effects of adipose tissue inflammation factors on miR-378 expression and the underlying mechanism. *Cellular Physiology and Biochemistry*, *33*(6), 1778–1788. https://doi.org/10.1159/000362957

Jukic, M. M., Haslemo, T., Molden, E., & Ingelman-Sundberg, M. (2018). Impact of CYP2C19 genotype on Escitalopram exposure and therapeutic failure: A retrospective study based on 2,087 patients. *The American Journal of Psychiatry*, *175*(5), 463–470. https://doi.org/10.1176/appi.ajp.2017.17050550

Kato, M., Fukuda, T., Wakeno, M., Okugawa, G., Takekita, Y., Serretti, A., … Kinoshita, T. (2009). 5-HT1A gene polymorphisms contributed to antidepressant response in major depression. *Nihon Shinkei Seishin Yakurigaku Zasshi*, *29*(1), 23–31.

Kautzky, A., Baldinger, P., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., … Kasper, S. (2015). The combined effect of genetic polymorphisms and clinical parameters on treatment outcome in treatment-resistant depression. *European Neuropsychopharmacology*, *25*(4), 441–453. https://doi.org/10.1016/j.euroneuro.2015.01.001

Kent, W. J., Sugnet, C. W., Furey, T. S., Roskin, K. M., Pringle, T. H., … Haussler, D. (2002). The human genome browser at UCSC. *Genome Research*, *12*, 996–1006.

Kessler, R. C., Sampson, N. A., Berglund, P., Gruber, M. J., Al-Hamzawi, A., Andrade, L., … Wilcox, M. A. (2015). Anxious and non-anxious major depressive disorder in the World Health Organization world mental health surveys. *Epidemiology and Psychiatric Sciences*, *24*(3), 210–226. https://doi.org/10.1017/S2045796015000189

Leboyer, M., Barbe, B., Gorwood, P., Teherani, M., Allilaire, J. F., Preisig, M., … Ferrero, F. (1995). *Interview diagnostique pour les études génétiques*. Paris: INSERM.

Levine, M. E., Crimmins, E. M., Prescott, C. A., Phillips, D., Arpawong, T. E., & Lee, J. (2014). A polygenic risk score associated with measures of depressive symptoms among older adults. *Biodemography and Social Biology*, *60*(2), 199–211. https://doi.org/10.1080/19485565.2014.952705

Li-Wan-Po, A., Girard, T., Farndon, P., Cooley, C., & Lithgow, J. (2010). Pharmacogenetics of CYP2C19: Functional and clinical implications of a new variant CYP2C19*17. *British Journal of Clinical Pharmacology*, *69*(3), 222–230. https://doi.org/10.1111/j.1365-2125.2009.03578.x

Liu, C., & Lin, J. D. (2011). PGC-1 coactivators in the control of energy metabolism. *Acta Biochim Biophys Sin (Shanghai)*, *43*(4), 248–257. https://doi.org/10.1093/abbs/gmr007

Machiela, M. J., & Chanock, S. J. (2015). LDlink a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics*, *31*(21), 3555–3557. https://doi.org/10.1093/bioinformatics/btv402

Marchini, J., Howie, B., Myers, S., McVean, G., & Donnelly, P. (2007). A new multipoint method for genome-wide association studies by imputation of genotypes. *Nature Genetics*, *39*(7), 906–913. https://doi.org/10.1038/ng2088

Mrazek, D. A., Biernacka, J. M., O'Kane, D. J., Black, J. L., Cunningham, J. M., Drews, M. S., … Weinshilboum, R. M. (2011).

CYP2C19 variation and citalopram response. *Pharmacogenetics and Genomics*, *21*(1), 1–9.

Nguyen, T. T., Huang, J., Wu, Q., Nguyen, T., & Li, M. (2015). Genome-wide association data classification and SNPs selection using two-stage quality-based random forests. *BMC Genomics*, *16*(Suppl 2), S5. https://doi.org/10.1186/1471-2164-16-S2-S5

Nivard, M. G., Dolan, C. V., Kendler, K. S., Kan, K. J., Willemsen, G., van Beijsterveldt, C. E., … Boomsma, D. I. (2015). Stability in symptoms of anxiety and depression as a function of genotype and environment: A longitudinal twin study from ages 3 to 63 years. *Psychological Medicine*, *45*(5), 1039–1049. https://doi.org/10.1017/S003329171400213X

Noordam, R., Direk, N., Sitlani, C. M., Aarts, N., Tiemeier, H., Hofman, A., … Visser, L. E. (2015). Identifying genetic loci associated with antidepressant drug response with drug-gene interaction models in a population-based study. *Journal of Psychiatric Research*, *62*, 31–37. https://doi.org/10.1016/j.jpsychires.2015.01.005

Novembre, J., Johnson, T., Bryc, K., Kutalik, Z., Boyko, A. R., Auton, A., … Bustamante, C. D. (2008). Genes mirror geography within Europe. *Nature*, *456*(7218), 98–101. https://doi.org/10.1038/nature07331

Nurnberger, J. I., Jr., Blehar, M. C., Kaufmann, C. A., York-Cooler, C., Simpson, S. G., Harkavy-Friedman, J., … Reich, T. (1994). Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Archives of General Psychiatry*, *51*(11), 849–859; discussion 863–844.

O'Leary, O. F., O'Brien, F. E., O'Connor, R. M., & Cryan, J. F. (2014). Drugs, genes and the blues: Pharmacogenetics of the antidepressant response from mouse to man. *Pharmacology, Biochemistry, and Behavior*, *123*, 55–76. https://doi.org/10.1016/j.pbb.2013.10.015

Ohlsson Rosenborg, S., Mwinyi, J., Andersson, M., Baldwin, R. M., Pedersen, R. S., Sim, S. C., … Eliasson, E. (2008). Kinetics of omeprazole and escitalopram in relation to the CYP2C19*17 allele in healthy subjects. *European Journal of Clinical Pharmacology*, *64*(12), 1175–1179. https://doi.org/10.1007/s00228-008-0529-z

Penas-Lledo, E., Guillaume, S., Naranjo, M. E., Delgado, A., Jaussent, I., Blasco-Fontecilla, H., … A, L. L. (2015). A combined high CYP2D6-CYP2C19 metabolic capacity is associated with the severity of suicide attempt as measured by objective circumstances. *The Pharmacogenomics Journal*, *15*(2), 172–176. https://doi.org/10.1038/tpj.2014.42

PharmGKB pathways, n.d. Retrieved from https://www.pharmgkb.org/view/pathways.do.

Pisanu, C., Preisig, M., Castelao, E., Glaus, J., Pistis, G., Squassina, A., … Schioth, H. B. (2017). A genetic risk score is differentially associated with migraine with and without aura. *Human Genetics*, *136*(8), 999–1008. https://doi.org/10.1007/s00439-017-1816-5

Preisig, M., Fenton, B. T., Matthey, M. L., Berney, A., & Ferrero, F. (1999). Diagnostic interview for genetic studies (DIGS): Inter-rater and test-retest reliability of the French version. *European Archives of Psychiatry and Clinical Neuroscience*, *249*(4), 174–179. https://doi.org/10.1007/s004060050084

Preisig, M., Waeber, G., Vollenweider, P., Bovet, P., Rothen, S., Vandeleur, C., … Muglia, P. (2009). The PsyCoLaus study: Methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. *BMC Psychiatry*, *9*, 9. https://doi.org/10.1186/1471-244X-9-9

Radloff, L. S. (1977). The CES-D scale: A self report depression scale for research in the general population. *Applied Psychological Measurements*, *1*, 385–401.

Rodin, A. S., Gogoshin, G., & Boerwinkle, E. (2011). Systems biology data analysis methodology in pharmacogenomics. *Pharmacogenomics*, *12*(9), 1349–1360. https://doi.org/10.2217/pgs.11.76

Rudberg, I., Mohebi, B., Hermann, M., Refsum, H., & Molden, E. (2008). Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. *Clinical Pharmacology and Therapeutics*, *83*(2), 322–327. https://doi.org/10.1038/sj.clpt.6100291

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., … Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *The American Journal of Psychiatry*, *163*(11), 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Sim, S. C., Nordin, L., Andersson, T. M. L., Virding, S., Olsson, M., & Pedersen, N. L. (2010). Association between CYP2C19 polymorphism and depressive symptoms. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *153B*(6), 1160–1166. https://doi.org/10.1002/ajmg.b.31081

SNPedia, n.d. Retrieved from http://www.snpedia.com/.

The NCBI Gene database, n.d. Retrieved from http://www.ncbi.nlm.nih.gov/gene/.

The NCBI PubMed database, n.d. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/.

The NCBI SNP database, n.d. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/.

Tsai, M. H., Lin, K. M., Hsiao, M. C., Shen, W. W., Lu, M. L., Tang, H. S., … Liu, Y. L. (2010). Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. *Pharmacogenomics*, *11*(4), 537–546. https://doi.org/10.2217/pgs.09.168

Uckun, Z., Baskak, B., Ozel-Kizil, E. T., Ozdemir, H., Devrimci Ozguven, H., & Suzen, H. S. (2015). The impact of CYP2C19 polymorphisms on citalopram metabolism in patients with major depressive disorder. *Journal of Clinical Pharmacy and Therapeutics*, *40*(6), 672–679. https://doi.org/10.1111/jcpt.12320

Wang, J. L. (2005). Work stress as a risk factor for major depressive episode(s). *Psychological Medicine*, *35*(6), 865–871. https://doi.org/10.1017/S0033291704003241

Williams, G. J. (2011). *Data Mining with Rattle and R: The Art of Excavating Data for Knowledge Discovery*, Use R!, Springer. ISBN 978-1-4419-9889-7

Xu, L. L., Shi, C. M., Xu, G. F., Chen, L., Zhu, L. L., Zhu, L., … Ji, C. B. (2014). TNF-alpha, IL-6, and leptin increase the expression of miR-378, an adipogenesis-related microRNA in human adipocytes. *Cell Biochemistry and Biophysics*, *70*(2), 771–776. https://doi.org/10.1007/s12013-014-9980-x

Zhao, X. F., Huang, Y. L., Li, J. Y., Ma, H., Jin, Q., Wang, Y., … Zhu, G. (2012). Association between the 5-HT1A receptor gene polymorphism (rs6295) and antidepressants: A meta-analysis. *International Clinical Psychopharmacology*, *27*(6), 314–320. https://doi.org/10.1097/YIC.0b013e32835818bf

SUPPORTING INFORMATION

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

How to cite this article: Kanders SH, Pisanu C, Bandstein M, et al. A pharmacogenetic risk score for the evaluation of major depression severity under treatment with antidepressants. *Drug Dev Res*. 2019;1–12. https://doi.org/10.1002/ddr.21609