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Sociodemographic variables as predictors of antidepressant treatment outcome in major depressive disorder

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This is a preliminary, unedited version of a manuscript that has been accepted for publication in the Brazilian Journal of Psychiatry. As a service to our readers, we are providing this early version of the manuscript. The manuscript will still undergo copyediting, typesetting, and review of the resulting proof before it is published in final form. The final version may present slight differences in relation to the present version.

Sociodemographic variables as predictors of antidepressant treatment outcome in major depressive disorder

Running title: Sociodemographic variables and antidepressants

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Abstract

Objective: The aim of this study was to evaluate the influence of sociodemographic variables on remission to an initial trial with citalopram.
Methods: A sample of 2,682 patients with major depressive disorder was selected from the first level STAR*D trial database. Several sociodemographic variables available at baseline, as well as clinical variables, were selected a priori (based on literature review) and used to construct models that could predict remission after initiation of citalopram in a 3-month follow-up period.
Results: The logistic regression model was selected as the best performing model with the highest accuracy. The sociodemographic variables were as relevant as the clinical variables when predicting the probability of remission to antidepressant treatment. In particular, sociodemographic variables linked to low socioeconomic status were the most significant in decreasing the likelihood

of remission. Being older than 25 years old, Black race, and Hispanic ethnicity also had a negative influence on the likelihood of remission to antidepressant. **Conclusion:** Certain sociodemographic characteristics, particularly those linked to low socioeconomic status, would substantially reduce the likelihood of remission to a first-line treatment for major depressive disorder. The pattern of findings would have potential clinical and therapeutic implications that warrant future research on this topic.

Keywords: depression; social determinants; unemployment; education

Introduction

The prevalence of major depression (MDD) has increased in recent decades, becoming the leading cause of disability among psychiatric disorders.[1,2] Consequently, the prescription of antidepressants, one of the key resources for its treatment, has also increased.[3,4] Despite the widespread use, some concern remains based on data showing that the benefits in the acute treatment of MDD are, on average, modest. Several meta-analyses of randomized controlled trials found that antidepressants are slightly more effective than placebo in MDD, with an effect size that does not translate into clinically meaningful benefit in several cases.[5-8] Likewise, observational studies show that a substantial proportion of patients do not achieve remission after a trial with a first-line antidepressant.[9-11]

In this context, much research effort was directed towards identifying reliable predictors of treatment outcome. Pioneering studies focused on clinical variables, identifying certain features that predict a negative treatment outcome: higher baseline severity of the depressive symptoms, suicidal ideation, melancholic features, higher number of previous episodes, and comorbid anxiety or personality disorders.[12-14] Although more recently a growing body of research has highlighted the role of neuroimaging, genetics, and other laboratory biomarkers as predictors of treatment outcome, the findings are somewhat preliminary and have not yet been translated into clinical practice.[15,16] Conversely, there are relatively few studies that have focused on the role of sociodemographic variables as predictors of treatment, which could be relevant for several reasons. First, they have been consistently related to the risk of depression in epidemiological studies.[1,17,18] Second, preliminary evidence suggest that lower levels of socioeconomic status and social support might be predictors of negative

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outcome to antidepressants treatment in MDD, while the influence of age, sex, and race/ethnicity appear controversial among studies.[12-14,19] In addition, although explored individually, there have been few researches looking at the pooled effect of sociodemographic variables on the outcomes to antidepressant treatment.[20,21] It is indeed conceivable that if certain sociodemographic variables had a negative effect on the treatment outcome, this could be cumulative. Finally, these variables could be collected with minimal time and cost, being easily transferable to clinical practice and generalizable to any level of care.

Therefore, the aim of this study was to address sociodemographic variables as predictors of remission after treatment initiation of a first-line antidepressant using multivariate modelling. For this purpose, we used data from the first level of the STAR*D trial (Sequenced Treatment Alternatives to Relieve Depression), an observational study conducted in a large representative sample of depressed patients treated with citalopram, for whom numerous baseline sociodemographic variables were available. We hypothesized that low socioeconomic status, poor social support, and ethnic/racial minority status would be associated with negative outcome to treatment.

Methods

Study population

STAR*D is a multisite, multilevel trial designed to assess the comparative effectiveness of different antidepressants for patients with non-psychotic MDD.[22] A total of 4,041 male and female outpatients (18-75 years) were enrolled from 18 primary care and 23 psychiatric care practice settings in the first level of treatment in the STAR*D trial and represent the population of this study. All patients enrolled in the first level of STAR*D received treatment with citalopram.

STAR*D contains information on baseline socio-demographic variables (e.g., age, sex, education, race, ethnicity, work and social productivity, insurance), clinical history and comorbidities (e.g., prior episodes, age at onset, anxiety conditions), depressive symptoms (QIDS-C and QIDS-SR), and side-effects. Frequency of follow up and depressive symptomatology assessment

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was left at the discretion of the physicians but scheduled at 2, 4, 6, and 8 weeks of follow-up.

Because melancholia might have a different pattern of outcome to antidepressant treatment than non-melancholic depressions,[23] we excluded patients with melancholic features based on the same criteria as a previous study that reanalyzed data from the STAR*D trial.[24]

Outcome

The main outcome of interest was symptomatic remission following initiation of treatment with citalopram 20 mg/day. Remission was defined as a Quick Inventory of Depressive Symptoms (Clinician version) (QIDS-C) below or equal to 5 after at least 2 weeks of antidepressant treatment.[22]

Sociodemographic variables

We used several individual-level sociodemographic predictors available at baseline for all included patients. These variables were: (i) age (< 35, 35-50, over 50), (ii) race (Black, white, Asian-American, American Indian and Hawaiian, more than one reported race/other), (iii) female sex, (iv) Hispanic ethnicity, (v) marital status (divorced, married, single, widow), (vi) employment status (unemployed, retired, employed), (vii) insurance status (Medicaid vs. private insurance), (viii) educational level (less than high school or none; high school or GED; college, masters or doctorate), (ix) housing status (owners with and without mortgage, rent, other). All these variables were chosen a priori (before data analysis) based on literature review and subject matter knowledge.

Clinical variables

To understand the relative importance of sociodemographic predictors in comparison with other clinical variables, we included traditional clinical predictors of treatment outcome. Unlike previous studies using the STAR*D trial database that used clinical variables in an unsupervised manner (e.g., individual items on depressive symptom scales),[20,21] we selected clinical variables known as predictors of treatment outcome based on previous literature. These predictors were: (i) baseline depression severity measured by the Inventory of Depressive Symptomatology – Clinician (IDSC-30) scale (below

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24: mild, 24–36: moderate, 37–46: severe, above 46: very severe), (ii) chronic depression (length of current episode of more than two years), (iii) number of previous depressive episodes; (iv) age at illness onset, (v) comorbid anxiety disorder (present vs. absent), (vi), suicide ideation (present vs. absent based on Suicide item in IDSC-30 more than none). Furthermore, setting (primary vs. specialized care) and baseline citalopram dosage were also included as possible predictors of treatment outcome.

Model development

We used available variables to construct models that would predict remission after initiation of citalopram in a 3-month follow-up period. A correlation plot to identify highly correlated variables was used to remove those from the models. The dataset was then split into a training set and a test set in a 9:1 ratio stratified on clinical setting (primary care vs. specialized care) to assure representativeness in each dataset. The training set was used to train 6 different models (including all socio-demographic and clinical variables), and the test set was used to assess models' prediction performance.

We trained 6 models: (i) Logistic regression; (ii) Penalized regression (–Lasso); (iii) Penalized regression (Elastic net); (iv) Penalized regression (Ridge); (v) K-nearest neighbors (KNN); and (vi) Random forest. For details on models, see Supplementary Table S1. The "optimal" model was chosen based on lower overall error rates (see Supplementary Table S1).

Missing data and losses-to-follow-up

We dealt with missing data as follows. First, we excluded patients that had missingness in any item required to ascertain melancholia status. Second, patients with missingness in key demographic variables (i.e., age, sex, race) were excluded from the analysis. Third, predictors with missingness less than or equal to 5% were imputed using their mean values (for continuous predictors) and the most frequent category (for categorical predictors). Predictors with missingness of more than 5% were not considered in the models (e.g., income). Finally, as in any longitudinal data, a proportion of patients dropped out from the study yielding missing data on the study outcome. If the patients that are lost to follow-up differ clinically from those who stay under follow-up, our predictions

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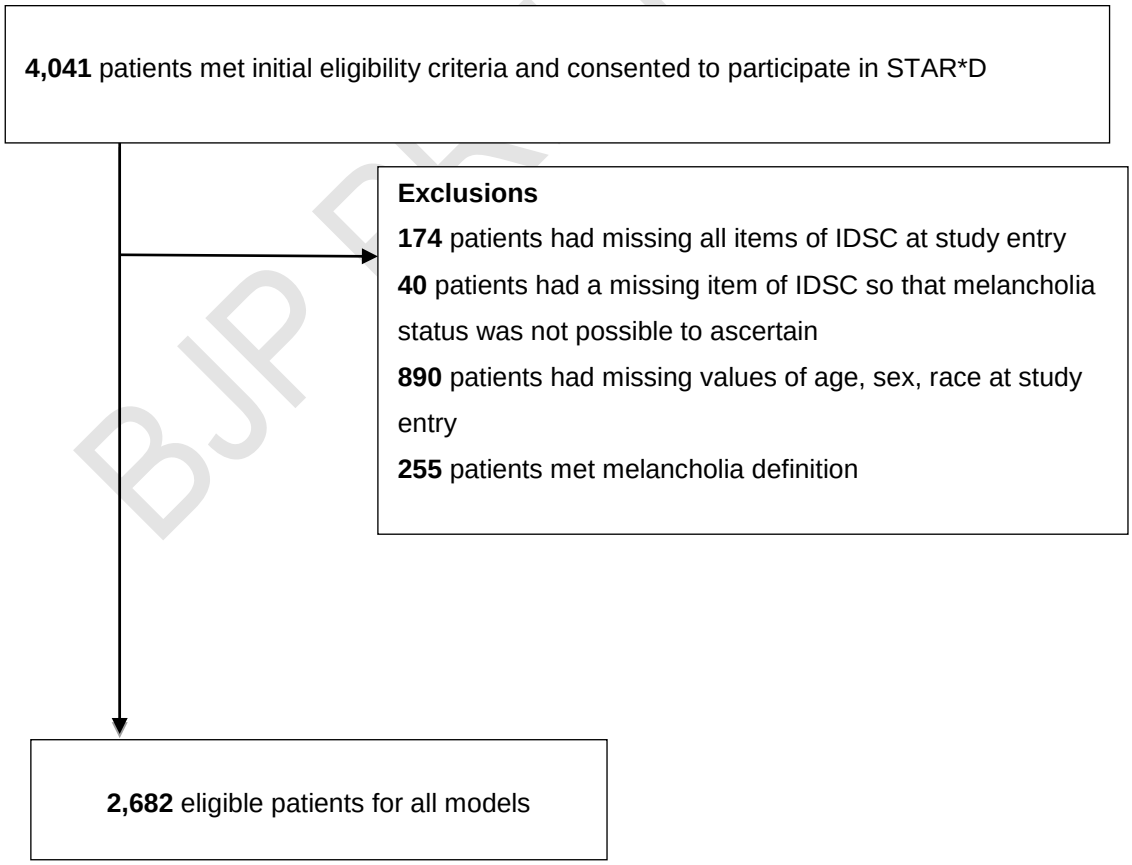
may be affected. To correct any potential distortions induced by losses to follow-up, we adjusted for longitudinal differences via inverse probability weighting, a causal inference technique for longitudinal data.

Results

Patient characteristics

Figure 1 shows the included patient sample. Table 1 shows the patients characteristics at baseline. The patients that showed remission within 3-months of follow-up were more likely to self-report white or American Indian and Hawaiian race, be married (cohabiting), be employed or retired, own a house, or have mild baseline severity; and less likely to self-report Hispanic ethnicity, have Medicaid, have High-school diploma or less than high-school education, have a chronic depressive episode (i.e., more than 2 years of symptoms), have a comorbid anxiety, and report suicide ideation.

Figure 1. Flowchart of included patients in analyses



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Table 1. Baseline characteristics of included patients. Numbers in parenthesis represent percentages unless otherwise specified

	Non-remission (N=1,541)	Remission (N=1,141)	Overall (N=2,682)
Socio-demographical predictors			
Age			
< 35	520 (33.7)	417 (36.5)	937 (34.9)
35 - 50	760 (49.3)	521 (45.7)	1281 (47.8)
>50	261 (16.9)	203 (17.8)	464 (17.3)
Race			
Black	167 (10.8)	79 (6.9)	246 (9.2)
White	1153 (74.8)	922 (80.8)	2075 (77.4)
Asian American	34 (2.2)	26 (2.3)	60 (2.2)
American Indian and Hawaiian	8 (0.5)	11 (1.0)	19 (0.7)
More than one / Other	172 (11.2)	102 (8.9)	274 (10.2)
Female sex	937 (60.8)	718 (62.9)	1655 (61.7)
Hispanic ethnicity	208 (13.5)	120 (10.5)	328 (12.2)
Marital status			
Divorced or separated	404 (26.2)	261 (22.9)	665 (24.8)
Married (cohabiting)	587 (38.1)	531 (46.5)	1118 (41.7)
Single (never married)	495 (32.1)	326 (28.6)	821 (30.6)
Widowed	55 (3.6)	23 (2.0)	78 (2.9)
Employment status			
Unemployed	671 (43.6)	334 (29.3)	1,005 (37.5)
Retired	80 (5.2)	81 (7.1)	161 (6.0)
Employed	790 (51.3)	726 (63.6)	1516 (56.5)
Medicaid	301 (19.5)	150 (13.1)	451 (16.8)
Educational degree			
None	207 (13.4)	102 (8.9)	309 (11.5)
High school or GED	1008 (65.4)	654 (57.3)	1662 (62.0)
College, master's, or doctoral degree	326 (21.2)	385 (33.7)	711 (26.5)
House ownership	716 (46.5)	630 (55.2)	1346 (50.2)
Clinical predictors			
Setting			
Primary care	596 (38.7)	453 (39.7)	1049 (39.1)
Specialized care	945 (61.3)	688 (60.3)	1633 (60.9)

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Baseline severity			
Mild	357 (23.2)	770 (67.5)	1127 (42.0)
Moderate	519 (33.7)	199 (17.4)	718 (26.8)
Severe	390 (25.3)	116 (10.2)	506 (18.9)
Very severe	275 (17.8)	56 (4.9)	331 (12.3)
Length of current episode of more than two years (Chronic depression)	418 (27.1)	259 (22.7)	677 (25.2)
Number of prior depressive episodes – mean (SD)	4.52 (10.1)	4.42 (9.18)	4.48 (9.68)
Comorbid anxiety disorder	206 (13.4)	105 (9.2)	311 (11.6)
Baseline citalopram dosage, mean (SD)	30.7 (15.0)	28.2 (12.3)	29.6 (13.9)
Suicide item in IDSC-30 More than "none"	639 (41.5)	204 (17.9)	843 (31.4)
Age of onset - Mean (SD)	25.0 (14.6)	25.9 (14.8)	25.4 (14.7)

Model development

Supplementary Figure S1 shows the correlation plot for all the included variables. Only a moderate correlation was found for age below 25 and single marital status (r=0.40). The highest missing rate corresponded with number of previous depressive episodes (5.2%).

In the training set (n=2,012 subjects), we fit all six models. Supplementary Table S1 shows the description of machine learning models.

Testing performance

Supplementary Table S2 shows the model performance (based on test error rate) in the testing dataset. The logistic regression had the better performance, followed by lasso and elastic net. Overall, KNN performed worst in the test set with large test errors. Based on this, we selected the logistic regression model as the best performing model with the highest accuracy.

Ranking of predictors of remission in the best performing models

The model coefficients in the logistic regression model, ranked by their relative magnitude are presented in Table 2. Briefly, (i) very severe, severe, and moderate severity at baseline, (ii) unemployment, (iii) presence of suicidal ideation, (iv) age older than 50, and (v) lower than high-school education, were the main predictors of treatment outcomes after initiating treatment with

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citalopram. Predictors and their ranking were unchanged after applying inverse probability weighting.

Table 2. Ranking of importance of predictors of treatment remission in the testing dataset (logistic regression)

Predictors*	ß coefficient#	OR (95% Confidence Interval)
Intercept	2.75	
Very severe	-1.99	0.14 (0.06, 0.30)
Severe	-1.38	0.25 (0.16, 0.39)
Moderate	-1.17	0.31 (0.18, 0.53)
Unemployed	-1.08	0.34 (0.13, 0.84)
Suicide ideation	-0.83	0.44 (0.27, 0.71)
Age greater than 50	-0.68	0.51 (0.24, 1.04)
Less than high school	-0.56	0.57 (0.37, 0.87)
Black	-0.54	0.58 (0.28, 1.16)
Specialty care setting	-0.46	0.63 (0.43, 0.93)
Age between 35-50	-0.46	0.63 (0.40, 1.00)
Anxiety disorder	-0.41	0.66 (0.34, 1.25)
Medicaid	-0.40	0.67 (0.38, 1.17)
Hispanic	-0.38	0.68 (0.37, 1.24)
Asian	-0.35	0.71 (0.20, 2.53)
Widow	-0.33	0.73 (0.21, 2.29)
High school education	-0.32	0.73 (0.35, 1.51)
American Indian	0.26	1.29 (0.20, 8.36)
Divorced	0.23	1.26 (0.78, 2.04)
Other race	-0.19	0.83 (0.43, 1.55)
Never married	-0.18	0.83 (0.52, 1.34)
Retired	0.10	0.90 (0.59, 1.36)
Female	-0.08	0.92 (0.62, 1.36)
Ownership	-0.06	0.94 (0.63, 1.42)
Chronic depression	-0.04	0.96 (0.61, 1.48)
Citalopram dosage	-0.02	0.98 (0.96 0.99)
Age of onset	0.01	1.01 (0.99, 1.02)
Number of prior episode	0.00	1.00 (0.99, 1.02)

*reference categories are: mild severity; college education or more; Age< 35; marital status; White race; employment

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[#]To construct the probabilities of remission, we sum the coefficients of a particular patient's characteristics (including the intercept) and the probability of remission is: exp(sum) / [1+exp(sum)]. See Table 3.

Using the logistic regression model, we predicted the probabilities of remission of six hypothetical patients. For the same level of clinical severity, the presence or absence of certain socio-demographic characteristics modified substantially the probabilities of remission. For example, in patients with very severe depression, the presence of certain disadvantageous socio-demographic predictors were associated with a nearly 40% lower chances of remission after initiating antidepressant treatment (Table 3). These probabilities are merely illustrative and do not reflect the degree of uncertainty around these predictions. Our intention was to use them for illustrative purposes and discuss the potential ramifications of the change in the direction of the point estimates (and not the magnitude).

Discussion

The main finding of this study was that certain sociodemographic variables might be as important as traditional clinical variables (e.g. depressive symptoms severity or suicidal ideation) in predicting remission to antidepressants among patients diagnosed with MDD. The results are consistent with prior studies showing associations between low socioeconomic status and probability of remission after initiating antidepressant treatment.[12-14,20,21] In our study, among sociodemographic variables, those linked to low socioeconomic status such as being unemployed or have low education attainment, were the most significant in decreasing the likelihood of remission. Black race, Hispanic ethnicity, and being older than 35 were also associated with a lower probability of remission; while sex and poorer social support (e.g. never married) seemed to have a minor influence. Black race and Hispanic ethnicity are likely proxies for systemic structural inequities, racism, and access to resources -not captured by other sociodemographic variables- rather than biological differences. Furthermore, when considered together, we found that possessing certain sociodemographic profiles can significantly modify the probabilities of achieving remission after initiating treatment with a first-line antidepressant.

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The pattern of results highlights the potential relevance of sociodemographic variables in predicting antidepressant treatment outcomes, warranting the need for future research in this topic. If the findings are corroborated in future studies, they could have several clinical and theoretical implications. From a clinical point of view, sociodemographic variables might contribute to clarifying the reports of modest treatment outcomes in MDD. The first level of the STAR*D trail recruited subjects spontaneously seeking medical care for MDD who were administered first-line antidepressant therapy. Although about a third of patients achieved remission with citalopram in that study,[9] heterogeneity of effects were observed when we stratified by certain sociodemographic variables such as employment status or educational attainment (Table 3). If this were the case, a poorer socioeconomic status (or to a lesser extent ethnic/racial minorities) might allow for early and easy identification of patients with a lower probability of remission to conventional antidepressant treatment. Strategies such as a closer clinical follow-up, increase in drug doses or the use of polypharmacotherapy, concomitant psychotherapy, or the use of support groups or job training programs might be studied as alternative or complementary approaches to usual treatment in these instances. At the population level, policymakers should note that worse socioeconomic conditions might not only contribute to a higher risk of MDD, as has been widely documented,[1,17,18,25] but also potentially to worse outcomes with standard treatments. Whether the implementation of social development programs aimed at improving education, working conditions, or eradicating poverty results in better outcomes for antidepressant treatment could also be the subject of empirical validation in future studies.

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Table 3. Representation of six hypothetical male patients and their predicted 3-month probability of remission based on severity of depressive episode and socio-demographic characteristics

Hypothetical male aged 55 with MDD and no comorbid anxiety and no suicidal ideation	**Predicted 3-month probability of remission (%)**
Very severe depression	
unemployed, Black, Hispanic, never married, less than high-school education.	6.5
employed, White, not Hispanic, married, college education	52.0
Moderate depression	
unemployed, Black, Hispanic, never married, less than high-school education.	13.7
employed, White, not Hispanic, married, college education	71.1
Mild depression	
unemployed, Black, Hispanic, never married, less than high-school education.	33.8
employed, White, not Hispanic, married, college education	88.8

From a theoretical perspective, sociodemographic variables may help refine inclusion and exclusion criteria in clinical trials to enhance statistical power. Furthermore, our findings also highlight the limitations of reporting only average treatment effects in the entire sample (e.g., remission, response), as this obscures variability linked to sociodemographic factors. The mechanisms connecting disadvantageous conditions (e.g., low socioeconomic status, ethnic/racial minorities) to poorer outcomes remain speculative but warrant further studies. Chronic stress and allostatic load are interesting targets for research, as they have been proposed as determinants of both MDD risk and a worse outcome to antidepressant treatment.[26-28] In fact, chronic psychosocial stress—and the resulting allostatic load—linked to disadvantageous living conditions is one of the most important advances in understanding the so-called social determinants of depression. Likewise, it has been proposed that

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neuroendocrine and metabolic dysregulation resulting from chronic stress and allostatic load could lead to a worse outcome to antidepressant treatment through different mechanisms such as inhibition of hippocampal neurogenesis, increased resistance to hormones in the hippocampus, or a reduction in monoamine biosynthesis.[28]

Some methodological limitations of this study should be taken into account when interpreting the findings. First, the goal of this study is to detect associations (i.e., a predictive study), and hence a causal relationship between predictors and treatment remission cannot be inferred. Second, we excluded melancholic/psychotic depressions, and hence the results cannot be extrapolated to these subtypes. However, non-melancholic/non-psychotic depressions are the most prevalent epidemiologically, so the sample of the present study is representative of the most frequently seen in clinical practice. Likewise, although antidepressants are referred to generically throughout the manuscript, our sample is derived from the first level of the STAR*D study in which only citalopram was used. Whether or not this pattern of results is reproduced with other antidepressants should be evaluated in future research. Furthermore, we were unable to include income as a predictor due to its high missingness, but some previous studies suggest that this could be another variable important to predict treatment outcome.[14,19] Similarly, evidence indicates that the shared social environment (e.g. states, provinces, or countries) also exerts significant effects on mental health. In particular, the association between income inequality and MDD may help explain differences in prevalence between different countries or between different states in the US.[29-31] Due to the characteristics of the sample, we were unable to explore the influence of the shared social environmental on outcome to antidepressants, which might be also the focus of future studies. Finally, STAR*D data is approximately 20 years old, which could limit the generalizability of the results.

In summary, sociodemographic variables, which are readily available in both clinical and research settings, have been relatively underexplored as treatment predictors. This study focused on the influence of sociodemographic variables as predictors of antidepressant treatment outcomes in MDD and found that they may be as important as clinical variables. These results suggest that

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sociodemographic variables are a relevant target for further research, with potential clinical and theoretical implications.

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Supplementary Material

Validation of the models

For evaluations in the test set, we used a confusion matrix of the classification results to evaluate the performance of proposed models. Overall error rates were calculated as the proportion of incorrectly classified samples to the total number of samples in the test set. False positive rates (FPR) were calculated as the proportion of individuals predicted as having remission among those that did not remit. False negative rates (FNR) were calculated as the proportion of individuals predicted as non-remitters among the remitters. The "optimal" model was chosen based on lower overall error rates.

Once the optimal model was identified, we explored the relative importance of each variable in predicting remission to citalopram treatment and ranked them based on their relative importance. We used the coefficients from the best model also to compute the predicted probabilities of remission for hypothetical patients to underscore clinical relevance of the results.

We trained 6 models: (i) Logistic regression; (ii) Penalized regression – Lasso, regularization parameter λ optimized using 10-fold cross-validation (CV) from a grid value of: {0.1, 0.2, …, 5.0}; (iii) Penalized regression – Elastic net, regularization parameters α and λ optimized using 10-fold CV from a grid value of α = {0.1, 0.2, …, 0.9}, λ = {0.1, 0.2, …, 5.0}; (iv) Penalized regression – Ridge, regularization parameter λ optimized using 10-fold CV from a grid value of {0.1, 0.2, …, 5.0}; (v) K-nearest neighbors (KNN), the number of neighbors k optimized using 10-fold CV from a grid value of {1, 3, 5, …, 15} (odd values only to avoid ties); (vi) Random forest, parameter m is set to the square root of number of predictors, i.e. m=sqrt(25)=5, optimized using 10-fold CV. All CV samples were run using accuracy as the evaluation summary metric.

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Supplementary Table S1. Descriptive statistics of machine learning models in training dataset

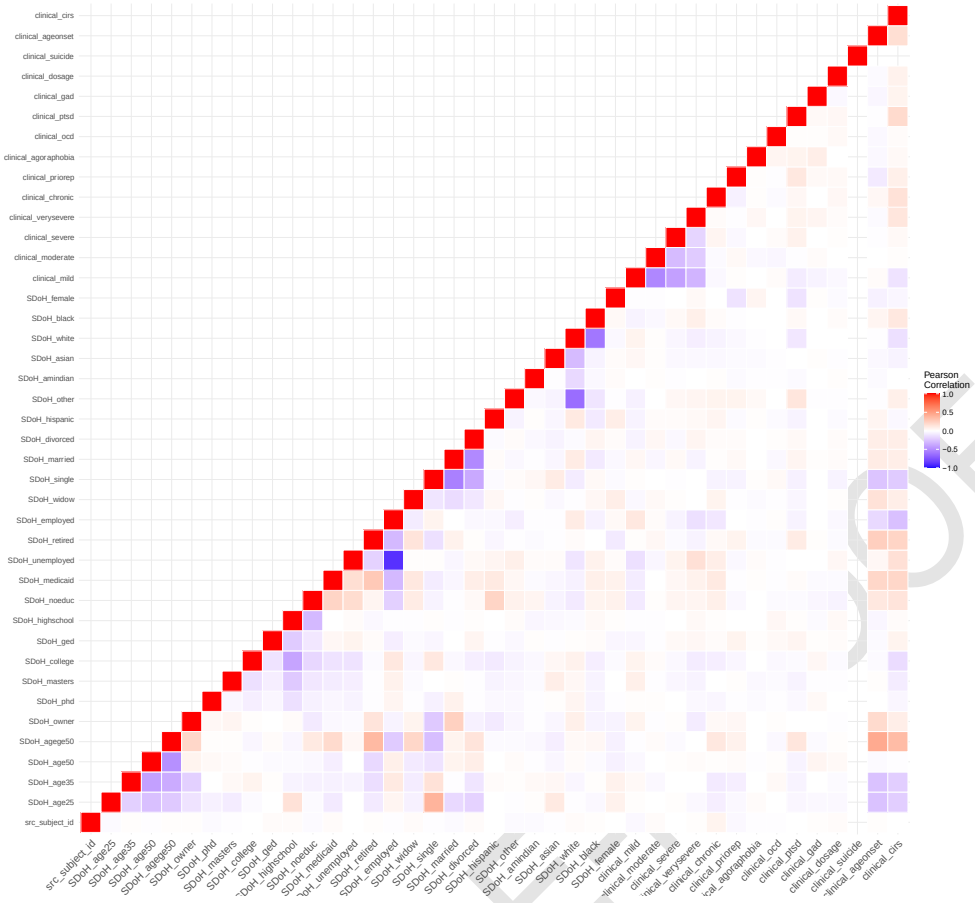
Model	Lambda	Alpha	Kappa	Accuracy
Lasso	0.1	1	0	0.7330920
Elastic net	0.1	0.1	0.46	0.7360746
Ridge	0.1	0	0.46	0.7355795
KNN			0.19	0.6088173
Random forest			0.40	0.709731

Supplementary Table S2. Model performance in testing dataset.

Models	Test error rate	Sensitivity	Specificity
Logistic regression	0.2656716	67.3	75.3
Lasso	0.2850746	65.4	76.1
Elastic net	0.2850746	65.6	76.0
Ridge	0.2895522	64.8	73.8
KNN	0.3791045	45.5	62.8
Random forest	0.3014925	65.3	73.3

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Supplementary Figure S1 Correlation plot



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