The influence of Polygenic Score on Depression among US Older Adults: Evidence from Wisconsin Longitudinal Study

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1 Introduction

Depression is a common mental disorder and the prevalence rates vary by age, peaking in older adulthood (above 7.5% among females aged 55-74 years, and above 5.5% among males) among global population[17]. Depression is influenced by many factors, including genetic factors, biochemical factors, serious illness, personal mental health history, social risks, stressful life events, and substance risk factors, etc.[2]. US is an aging society with increasing burden of depression, especially among the older adults. To better understand the combination of genetic and environmental influences on depression, this study is particularly interested in exploring how genetic factors modify the effect of the risk factors and vice versa. As John BS Haldane, who made one of the earliest attempts to study gene-environment interaction stated, "the interaction of nature and nurture is one of the central problems of genetics"[9].

There have been many studies examining the role of gene-environment interactions on depression. Most of them focus on a specific interaction between a polygenic score and one negative life event indicator which is hypothesized as the treatment effect in causal analysis, although the interaction would be multidimensional - a number of genetic and environmental factors may interact together to result in a phenotype. For instance, Mullins et al(2016)[14] examined child trauma as a strong risk factor for major depressive disorder among RADIANT UK samples using linear logistic regression models and found greater effect in individuals with lower polygenic risk score for the disorder. Domingue et al (2017)[5] using nonlinear mixed effects model found that adults in Health and Retirement Study (HRS) with higher wellbeing polygenic scores experienced fewer depressive symptoms during follow-up. Those who survived death of their spouses (n=1,647) experienced a sharp increase in depressive symptoms following the death and returned toward baseline over the following two years. Having a higher polygenic score buffered against increased depressive symptoms following a spouse's death. Another group (Musliner, 2015)[16] also using HRS data and logistic and negative binomial regression models found no evidence that stressful life events moderated the association between common variant polygenic risk and depressive symptoms. The effects found from the above-mentioned studies were small, and it is possible that the relationship between outcome and exposure in some subgroups are not stable. The heterogeneity of the subgroups are not well examined in previous studies on gene-environment interactions on depression.

Decision trees and random forests have been used mainly for predicting depression outcomes [1] [18] and feature reduction in prediction[21]. Since decision trees can perform automatic variable selection and can handle mixed discrete and continuous inputs, they could be used for survey data with a large number of variables per sample. Selecting the most important variables to be included in the models (feature reduction) predicting the phenotype might be the first step for a complex phenotype such as depression, which could be influenced by numerous factors while little mechanism is known to cause/shape the phenotype. Among various machine learning methods, decision trees are easy to interpret, relatively robust to outliers and can scale well to large data sets and handle missing inputs [15]. This study applies model-based recursive partitioning algorithm to explore gene-environment interactions on depression using older adults data from Wisconsin Longitudinal Study. Recursive partitioning algorithms for regression trees can examine the heterogeneity of associations among subgroups and allow the discovery of multidimensional interactions. The better understanding of the complexity of the genetic-environment interplay may help prevent depression in the future.

2 Methods

The most popular recursive partitioning algorithm is Classification and Regression Tress or CART models, also called decision trees. The tree-based algorithms are defined by recursively partitioning the input space and defining a local model in each resulting region of input space, which can be represented by a tree, with one leaf per region (subgroup) [15][3]. Unlike most non-parametric modelling such as CART, the model-based recursive partitioning approach (decision tree analysis) [24] can fit a parametric model and test for parameter instability over a set of partitioning variables. If there is some overall parameter instability, the algorithm will split the model with respect to the variable associated with the highest instability and repeat the procedure in each of the child nodes. In the other words, the model will search a number of covariates to see if there is heterogeneity in the relationship between outcome(depression) and exposure(e.g., socioeconomic status, widowhood, illness, etc.) and examine whether the associations vary among subgroups and if there is heterogeneity over sub-groups from any of these covariates. In summary, instead of only fitting one global parametric model for an entire data-set in classical regression analysis or only finding partitioning variables using non-parametric methods (e.g., CART), this model-based algorithm can assess and determine one (standard) global parametric model with all potential relevant covariates fitting the data or whether it is more appropriate to partition it with respect to further covariates. Instead of examining one specific interaction, this approach allows both statistical learning(search) and theoretical based models to discover more potential interactions or multidimensional interactions for a complex phenotype such as depression.

The tests used for assessing parameter instability belong to the class of generalized M-fluctuation tests([22][23]). For numerical partitioning variables Z_j, the sup LM statistic is used which is the maximum over all single split LM statistics. For categorical variables Z_j, a χ^2 statistics is employed which captures the fluctuation within each of the categories of the variable Z_j for testing. The overall instability is checked by examining whether the minimal p value $p_j* = min_{j=1,..,l}p_j$ falls below a pre-specified level α (by default $\alpha = 0.05$), and the p values can be Bonferroni adjusted for multiple testing. If there is significant instability, the variables Z_j associated with the minimal p-value is used for splitting the node. Currently the party package

in R only supports binary splits, which means every split will have two child nodes. To determine the split point, two child node models are fit at every concievable split point exhaustively and then the one associated with the minimal value of the objective function (by default deviance) is chosen[25][24].

The "mob" function in the party package in R is used to fit a parametric model and then scans over covariates to examine if associations differ by subgroups at each of those cut points. As genetic factor is known to play a role in predicting depression, the parametric regression only include polygenic scores for depression, obtained using Multi-Trait Analysis of GWAS [7]. The wave/year is also included as regressor in another tree model. Tree models are unstable due to the hierarchical nature of the tree-growing process, therefore predictions obtained through single tree models are very sensitive to small changes to inputs. Random forests are used to produce predictions based on multiple model-based tree models constructed on random samples achieved either through bootstrapping (random sampling with replacement)[8]. The "mobForest" R package is used to implements bagging and random forests technique for model-based recursive partitioning[8].

3 Data

This study uses the the Wisconsin Longitudinal Study (WLS) a one-third sample of all 1957 Wisconsin high school graduates who were born born between 1938 and 1940[10]. The graduate respondents first completed an in-person questionnaire (10317 graduates completed) at around age 18 (1957), which was followed with a 1964 mail survey (8922 graduates completed) of parents(of graduates at around age 25), 1975 telephone survey(at around age 36 with 9138 graduates completed), 1993 telephone and mail surveys(at around age 54 with 8493 graduates completed), 2003-4 telephone and mail surveys, as well as a spouse telephone survey(at around age 64 with 7732 graduates completed) and 2011 in-person and mail surveys (at around age 72 with 5968 graduates completed). This study focus on the most recent three waves (1993, 2004, and 2011) with consistent CES-D 20 questions (Appendix 6.1) about depression.

Outcome Variables

The WLS started collecting depression-related questions since Wave 4 - 1993 survey when most respondents were over age 50. In every wave (1993, 2004 & 2011) all participants were asked retrospective questions regarding any depression symptoms in the past week using standard 20 questions to produce a modified CES-D scale (0-120), and I re-scaled the outcome variable according to the standard CES-D scale (Center for Epidemiological Studies Depression scale) [6]) with a summary score (0-60) for psychological distress/depression (Appendix 6.1). According to the center for epidemiological studies, the CES-D scale score less than 16 does not have clinical significance [6].

Polygenic Scores (PGS) for Depression and Subjective Wellbeing

A polygenic score (PGS) for an individual is defined as a weighted sum of a person's genotypes at K SNPs. wj are the weights for SNPs.

$$\bar{y} = \sum_{j=1}^{k} x_{ij} wj \tag{1}$$

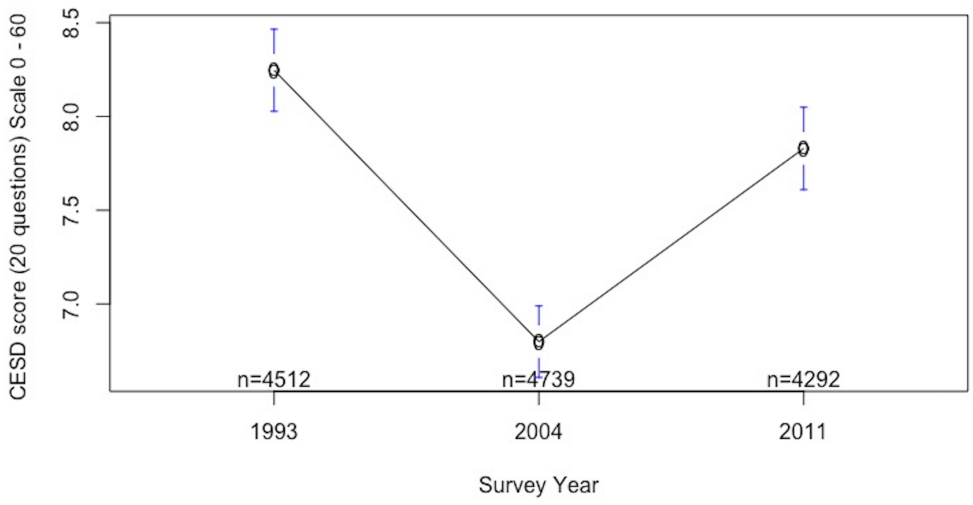

Figure 1: The mean of standard CES-D Scores (0-60) among graduate respondents in three waves

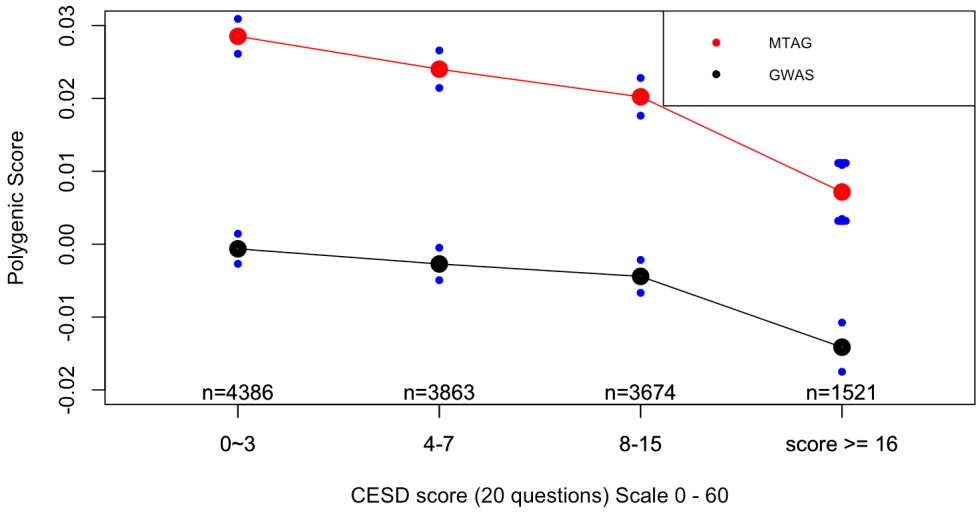

Figure 2: The mean of polygenic scores among respondents with different CES-D scores

The polygenic scores used in this study were created by Turley et al (2018)[7] using LDpred, a Bayesian method that includes all measured SNPs and weights each SNP by (an approximation) to its conditional effect, given other SNPs. In addition to GWAS-based polygenic scores of depressive symptoms and subjective wellbeing, MTAG (Multi-Trait Analysis of GWAS)-based polygenic scores were created by Turley et al (2018)[7] conducting joint analysis of summary statistics from GWASs of different traits, possibly from overlapping samples. The GWAS-based and MTAG-based polygenic scores are used respectively and compared. As Turley et al (2018) recommended, MTAG-based score should be used if the dependent variable and the polygenic scores correspond to the same phenotype (depression) in the regression. MTAG yield more informative bioinformatics analyses and increase variance explained by polygenic scores but it also could lead to spurious correlation since it could have a higher false positive rates at some cases. To address the concern about unaccounted-for population stratification, the top 10 principal components (PCs) of the covariance matrix of the individuals' genotypic data are included in the model.

Risk factors for Depression

WLS provides a number of variables documenting a graduates' important characteristics and life course transitions. The covariates that will be used in the model includes sex(***sex***), education(***edu***), wealth(***lnAssets***), current marital status (***mar***), military experience (***milty***), employment(***emply***), retirement status (***retire***), number of children (***nchd***), self-rated physical health(***selfhlth***), and major illness(es)(***illness***). The descriptive statistics of the covariates are in Table 1.

4 Results

The descriptive analysis of polygenic scores(PGS) among respondents with different levels of CES-D scores in Figure 2 shows a counter-intuitive weak correlation of lower polygenic scores for depression among those with higher CES-D score over 16. There is no significant differences of polygenic scores among graduate respondents with scores less than 16.

Decision tree analyses using GWAS-based PGS and MTAG-based PGS do not indicate significant differences. According to Turley et al (2018)'s recommendation[7], only results uisng MTAG-based PGS are presented. Three model-based tree models are presented to show the feature selection and interaction between PGS and partioning variables. The first model-based tree only fitted a global model of MTAG-based PGS across all nodes and selected partitioning variables shown in Figure 3 using the default settings in "mob" function. The model is estimated by OLS, the instability is assessed using a Bonferroni-corrected significance level of $\alpha = 0.05$ and the nodes are split with a required minimal segment size of 50 observations - $minsplit = 50$. The second tree fitted the same global model with different pruning parameters ($\alpha = 0.001, minsplit = 500$) in 4. The third tree model (Figure 5) used a different global regression model including wave/year by controlling the time differences in all child nodes. The pruning parameters are same as the second tree. Since the shape of the influence of the numerous environmental covariates on depression is unclear and not necessarily linear, the decision trees select the partitioning variables that may have more importance predicting depression among all inputting covariates. Also, a fitted linear

Table 1: Descriptive statistics of the important covariates in the models

Covariates	Wave 1993	Wave 2004	Wave 2011
Sex (baseline - Male) Female %	51.5%	52.4%	53.4%
Age - same age cohort	54	65	72
PGS_MTAG Mean(SD)	0.022 (0.081)	0.023 (0.081)	0.022 (0.081)
Education (baseline - High school)			
Associate's Degree %	2.5%	2.9%	2.9%
Bachelor's Degree %	17.5%	17.6%	17.5%
Master's Degree %	9.6%	9.8%	10.0%
Doctoral or Professional Degree %	3.0%	2.9%	3.3%
Employment (Yes - currently employed %)	90.4%	44.3%	27.8%
Retirement (baseline - Fully Retired)			
Partly retired %	3.8%	23.2%	22.2%
Still working %	88.9%	25.1%	8.3%
Assets $USD - Median (Mean)	155,000 (243,766)	378,900 (713,879)	367,750 (730,956)
Military experience (baseline - never joined army)			
Yes %	28.7%	28.2%	28.0%
Reported illness (baseline - No illness)			
One illness %	32.0%	31.1%	24.3%
Two illnesses %	15.3%	22.0%	24.4%
Three illnesses %	6.2%	12.6%	16.7%
Four and more than four illnesses %	4.2%	13.9%	21.8%
Self-reported health (baseline - Fair)			
Very good %	30.4%	22.3%	18.8%
Good %	60.2%	64.0%	65.5%
Poor %	0.7%	1.3%	1.5%
Very poor %	0.2%	0.3%	0.7%
Current Marital Status (baseline - married)			
Never married %	3.3%	3.1%	3.1%
Separate/Divorced %	10.4%	9.3%	10.1%
Widowed %	2.1%	7.5%	12.8%
Number of Children (baseline - No Child)			
One child %	6.0%	5.8%	5.5%
Two children %	28.0%	27.0%	26.3%
Three children %	27.1%	27.3%	26.3%
Four children %	17.6%	17.1%	17.8%
Five and more than five children %	14.8%	16.7%	18.7%
Depression CES-D scores Median/Mean(SD)	6/8.2 (7.5)	5/6.7(6.6)	6/7.8(7.3)
N	4120	4353	3902

regression is associated with every node, and the coefficients of global regressors are presented in Table 2.

From the visualization of the three trees, it can be seen that stricter pruning criteria makes a tree smaller from 45 nodes to 21 nodes and 17 nodes. Some important partitioning variables are shown in every tree including self-rated health, sex, illness, marital status and assets. Every node is representing a subgroup defined by the splits. For instance, the Node 21 in Figure 4 represents a subgroup with "Fair", "Poor" or "Very Poor" self-rated health and log-transformed asset less than 12.188. This subgroup has a very high intercept value (10.886), and PGS for depression has a significant negative association (-11.241***) with CES-D scores. The distribution of polygenic scores in each nodes is different and could be totally different in different nodes. For instance, Node 28 in the first tree shows a strong positive correlation (25.692*) between PGS and CES-D scores. The Node 28 represents a smaller subgroup of relatively rich ($lnAsset > 12.101$) graduate respondents who had "Good" self-rated health and smaller PC4, and were widowed or never married. Similarly, Node 19 shows a positive association (18.635***) with same "Good" health and lower-end asset splits but a different marital status (married or seperated/divorced) and different lnAssets upper bound (13.616). There are also nodes that do not show statistically significant association between PGS and depression. In general, there are more negative associations than positve association, and the negative association is especially significant among those more disadvantaged subgroups with worse self-rated health, more illnesses, unmarried and less assets with higher intercept values. The different associations of PGS and CES-D score indicate the interaction between gene and environments could be very complex and multidimensional. The influence of genetic factors may be stronger in a more advantaged environment, or the influence of environment factors could be different on people with different genetic "potentials".

As tree models are highly unstable, random forest technique is used to get a better sense of variable importance for variable selection. Figure 6 shows the variable importance from 100 different trees learned from the entire data-set and Figure 7 shows the performance of the trees. The result of random forest is consistent with the represented trees showing self-rated health and physical illness and assets have greater importance in predicting CES-D scores than other variables. The forest level $R^2 \approx 0.05$ is higher than mean or median of the tree levels with smaller MSE, which indicates forest level estimates perform better as expected.

5 Discussion

Based on previous studies[12][5][4], the subgroup with serious illness or those who experienced the death of the loved one may show the strongest associations. The decision analysis shows similar results by choosing self-rated health and physical illness as the main partitioning variables and indicate some importance of other variables such as marital status, and wealth, etc. The interaction between depression and PGS is not clear-cut, as the associations vary among different subgroups with both positive and negative associations. The complicated sub-group analyses may indicate that the real gene-environment interaction is very complex with multiple pathways and off-setting effects. The machine learning methods can be combined with other statistical methods to get more evidence of what influence depression. Table 3 in Appendix shows fixed effects models incorporating the interactions found in decision trees. Higher PGS for depression may surprisingly

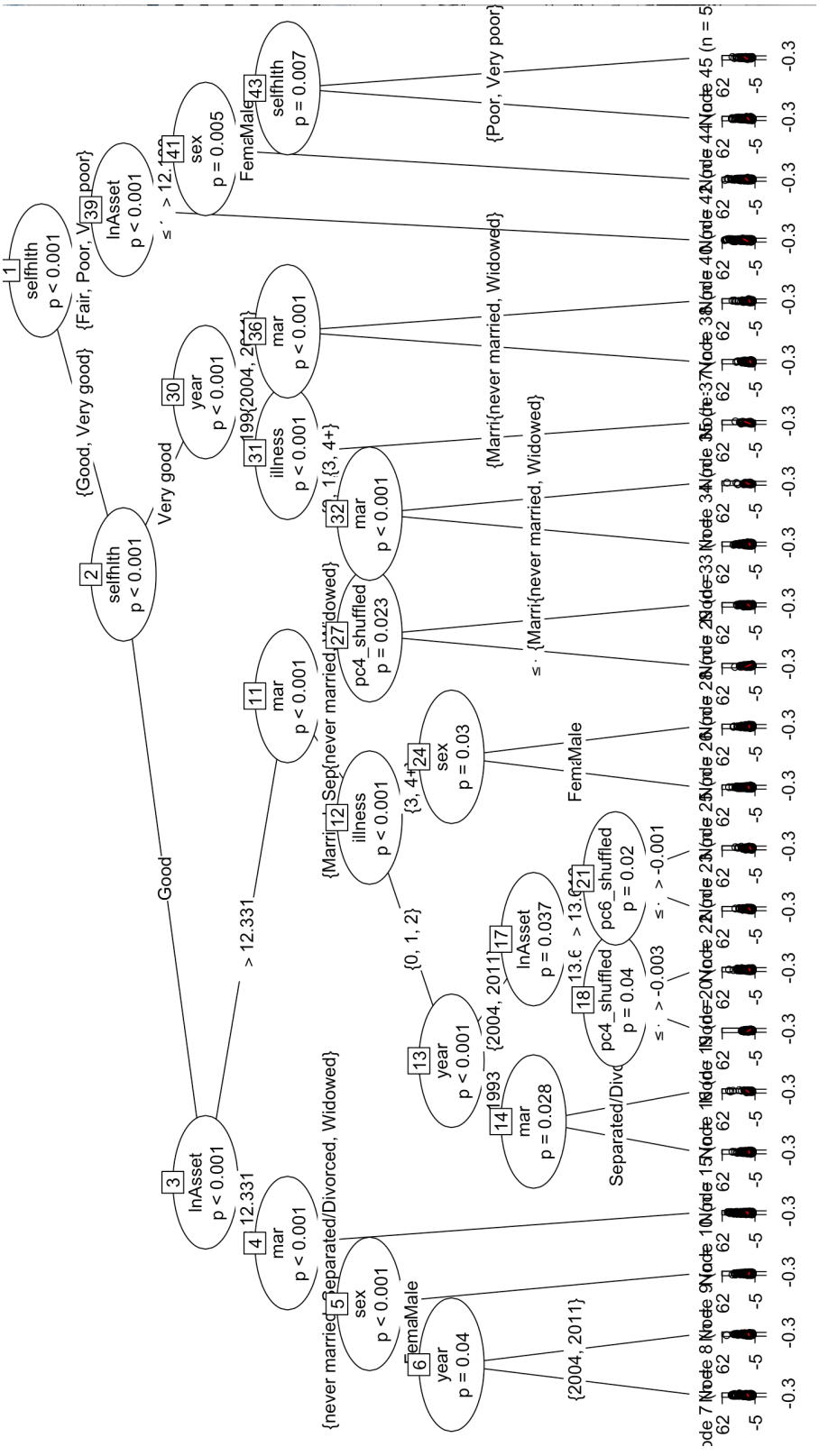

Figure 3: Model-based Recursive Partitioning Tree (MOB Tree)- 45 nodes

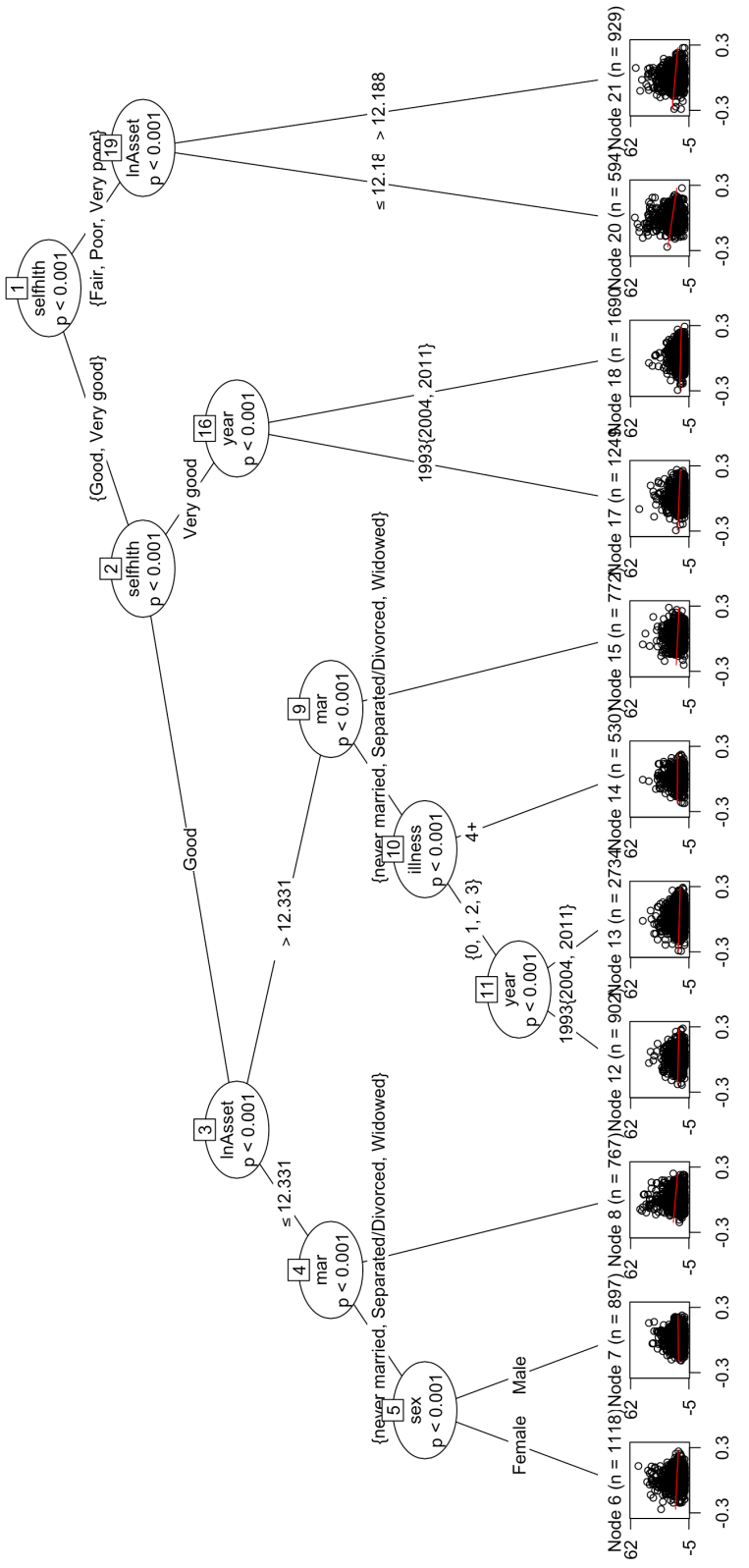

Figure 4: Pruned MOB Tree - 21 nodes - alpha = 0.001, minsplit = 500

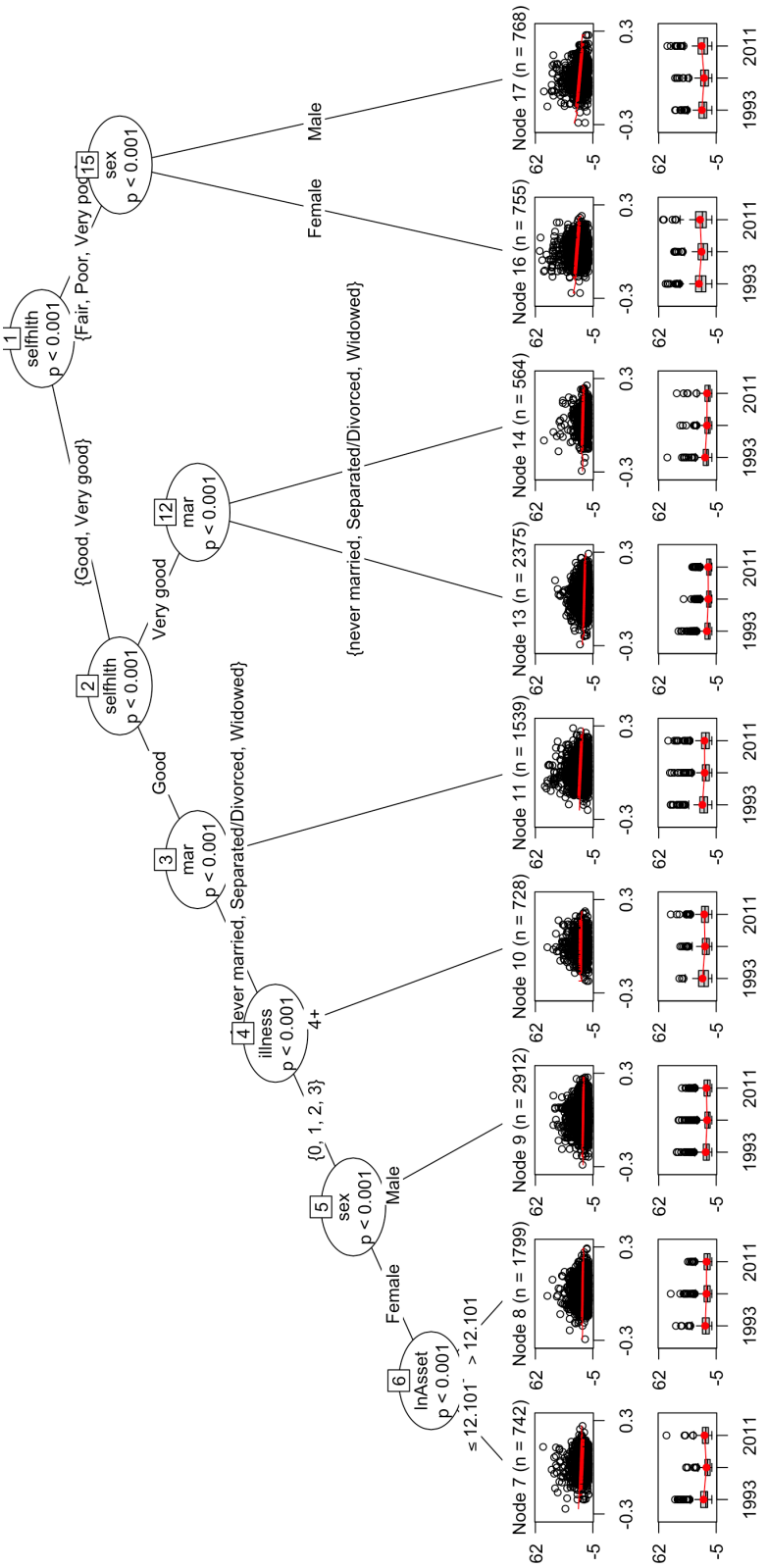

Figure 5: Pruned MOB Tree - 17 nodes - including waves as regressors

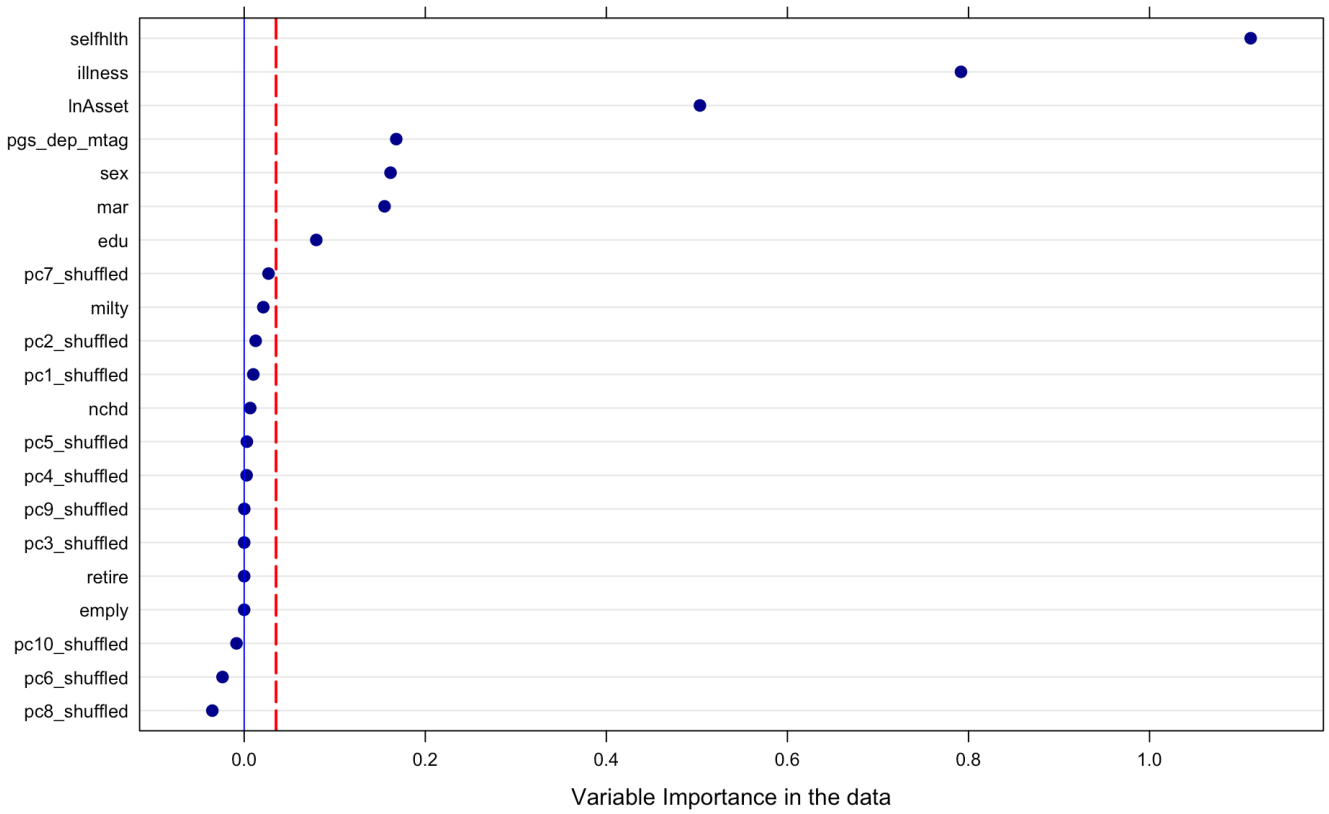

Figure 6: Variable Importance from random forest of MOB trees (n = 100)

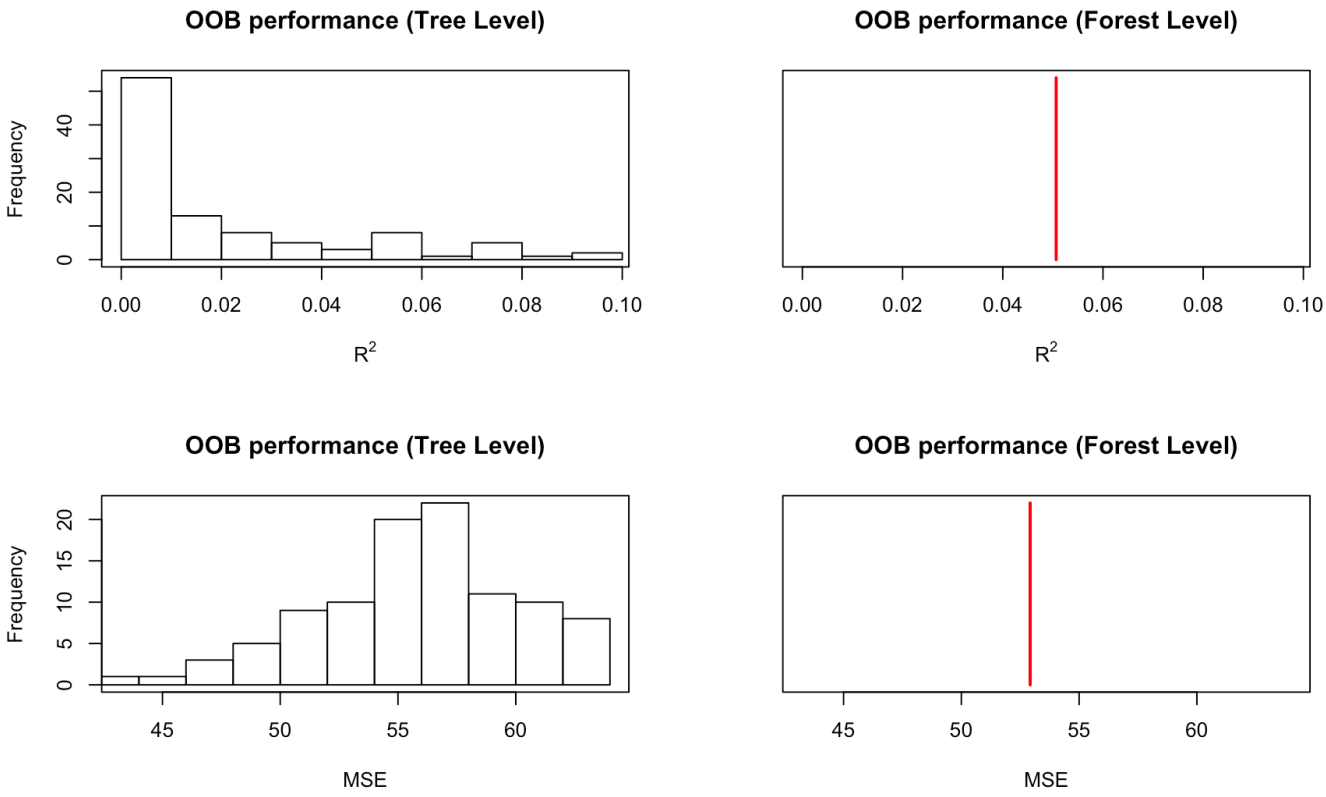

Figure 7: Out-of-bag(OOB) Performance of MOB forest (n = 100)

Table 2: Regressors' coefficients in Model-based Recursive Partitioning

First MOB Tree - 45 nodes			**Pruned MOB Tree - 21 nodes**			**Pruned Tree including wave as regressor - 17 nodes**		
Node	(Intercept)	PGS	Node	(Intercept)	PGS	Node	(Intercept)	PGS
7	9.662***	-7.682	6	8.872***	-5.844*	7	9.864***	-7.152*
8	7.928***	-4.214	7	7.254***	1.159	8	7.842***	-2.796
9	7.254***	1.159	8	10.632***	-11.164**	9	7.256***	-2.651*
10	10.632***	-11.164**	12	7.322***	-3.079	10	10.857***	-1.388
15	7.171***	-3.697	13	6.067***	-3.664**	11	11.173***	-8.474***
16	10.483***	-16.327	14	8.203***	-0.804	13	5.941***	-4.424***
19	6.880***	18.635**	15	8.087***	-6.051*	14	8.121***	-4.384
20	6.160***	-4.706**	17	6.332***	-5.824**	16	15.125***	-14.330**
22	6.376***	-7.709*	18	4.660***	-3.404*	17	11.661***	-16.467***
23	4.616***	-4.330	20	14.174***	-19.225***	***Same Tree as above***		
25	8.258***	-5.645	21	10.886***	-11.241***	Node	Y2004	Y2011
26	6.815***	-0.480				7	-3.443***	-1.257
28	8.399***	25.692***				8	-1.426***	-1.568***
29	8.578***	-11.494**				9	-1.637***	-0.781**
33	5.994***	-4.412*				10	-2.929**	-1.938*
34	10.858***	-22.463				11	-2.515***	-2.311***
35	10.990***	-31.153*				13	-1.667***	-1.393***
37	4.408***	-3.283*				14	-2.217***	-2.422***
38	6.413***	-4.553				16	-2.949**	-1.208
40	14.174***	-19.225				17	-2.425**	0.322
42	12.122***	-10.694						
44	9.366***	-10.522**						
45	14.241***	-18.690						

Note: *** <0.001 ** <0.01 * <0.05

have protective effects on people with adverse experiences (i.e. Very poor physical health and divorced/separated in the fixed effects models). Although this effect seems counter-intuitive since depression PGS should indicate higher probability of depression, genes' pleiotropic effects might be one of the reasons why PGS as a weighted measurement of various SNPs could be problematic for finding clear-cut interaction effects.

Measurement error is another major issue to be considered. Most variables in this analysis are prone to measurement errors - the construction of PGS, the self-reported depression symptoms, and covariates such assets and self-reported health status are all susceptible to biases such as social desirability bias, recall bias and information bias, etc. For instance, the lower mean of CES-D scores in 2004 wave than both 1993 and 2011 waves may indicate a systematic error in data collection. The longitudinal study of the rather homogeneous group (non-Hispanic whites with at least high school education born in late 1930s) may also make them "special", although large differences are still found among sub-groups. How to minimize the measurement errors and how to better randomize or isolate environment effects will remain challenges to better understand depression.

This study tries to use model-based recursive partitioning method to find more evidence of gene-environment interactions. Although better prediction is the main goal of the machine learning field, social science can still use machine learning methods to assist finding explanations and causes even if the variance explained (R^2) is usually very small (e.g., 0.05 in this study). The data-driven machine-learning methods are easy and cheap to implement and could assist classical social science research for variable selection and interaction exploration. Apart from the model-based method used in this study, many other tree-based algorithms are available using different splitting criteria and objective functions. Figure 8 and Figure 6.4 show two other examples using CART algorithm and conditional inference tree algorithm. In this analysis, time is used as a categorical variable for analysis, how to incorporate machine learning methods for longitudinal data is still a challenge with some progress [19] [13].

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6 Appendix

6.1 Depression measurement - CES-D score

Center for Epidemiologic Studies Depression Scale (CES-D)

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week. SCORING: zero for answers (Rarely or none of the time - less than 1 day), 1 for answers (Some or a little of the time 1-2 days), 2 for answers(Occasionally or a moderate amount of time 3-4 days), 3 for answers (Most or all of the time 5-7 days). The scoring of positive items(*) is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

During the Past week -

1. I was bothered by things that usually don't bother me.
2. I did not feel like eating; my appetite was poor.
3. I felt that I could not shake off the blues even with help from my family or friends.
4. I felt I was just as good as other people. (*)
5. I had trouble keeping my mind on what I was doing.
6. I felt depressed.
7. I felt that everything I did was an effort.
8. I felt hopeful about the future. (*)
9. I thought my life had been a failure.
10. I felt fearful.
11. My sleep was restless.
12. I was happy.(*)
13. I talked less than usual.
14. I felt lonely.
15. People were unfriendly.
16. I enjoyed life.(*)
17. I had crying spells.
18. I felt sad.
19. I felt that people dislike me.
20. I could not get "going."

6.2 Fixed effects Models

Table 3: Fixed Effects Models predicting CES-D scores

Covariates	Model 1	Model 2 selfhlth*PGS		Model 3 mar*PGS		Model 4 (lnAsset >13)*PGS	
Education (baseline - High school)	-0.997	-1.009		-0.951		-1.019	
Associate's Degree	(1.699)	(1.698)		(1.699)		(1.700)	
Bachelor's Degree	-0.481	-0.488		-0.450		-0.467	
	(1.609)	(1.608)		(1.609)		(1.609)	
Master's Degree	-0.104	-0.129		-0.047		-0.079	
	(1.893)	(1.892)		(1.892)		(1.893)	
Doctoral or Professional Degree	2.562	2.522		2.640		2.743	
	(3.190)	(3.188)		(3.189)		(3.191)	
Employment (Yes - currently employed)	-0.188	-0.178		-0.194		-0.192	
	(0.207)	(0.207)		(0.207)		(0.207)	
Retirement (baseline - Fully Retired)	-0.093	-0.104		0.506		0.487	
Partly retired	(0.206)	(0.205)		(0.241)		(0.242)	
Still working	0.503*	0.499*		0.506*		0.487*	
	(0.242)	(0.241)		(0.241)		(0.242)	
Log-transformed Assets $USD	- 0.179**	-0.179**		-0.183**			***PGS**
	(0.069)	(0.069)		(0.069)			
Log-transformed Assets $USD >13 (Yes)						-0.346*	2.638
						(0.168)	(1.780)
Reported illness (baseline - No illness)	-0.268	-0.271		-0.260		-0.267	
One illness	(0.162)	(0.162)		(0.162)		(0.162)	
Two illnesses	-0.222	-0.221		-0.221		-0.220	
	(0.195)	(0.195)		(0.195)		(0.195)	
Three illnesses	-0.079	-0.070		-0.082		-0.069	
	(0.239)	(0.239)		(0.239)		(0.239)	
Four and more than four illnesses	0.104	0.090	***PGS**	0.112		0.106	
	(0.267)	(0.267)		(0.267)		(0.267)	
Self-reported health (baseline - Fair)	-2.889***	-2.912***	1.158	-2.888***		-2.878***	
Very good	(0.275)	(0.282)	(3.293)	(0.275)		(0.275)	
Good	-2.108***	-2.120***	1.019	-2.109***		-2.105***	
	(0.221)	(0.224)	(2.731)	(0.221)		(0.221)	
Poor	4.048***	4.112***	-7.609	4.637***		4.067***	
	(0.639)	(0.640)	(8.411)	(1.050)		(0.639)	
Very poor	4.638***	4.222***	-46.861***	4.637***	***PGS**	4.605***	
	(1.050)	(1.059)	(14.067)	(1.050)		(1.050)	
Current Marital Status (baseline - married)	5.441*	5.446*		-5.150*	-59.589	5.407*	
Never married	(2.560)	(2.559)		(2.567)	(40.611)	(2.561)	
Separate/Divorced	0.335	0.315		0.563	-10.653*	0.381	
	(0.432)	(0.432)		(0.445)	(4.959)	(0.431)	
Widowed	2.541***	2.532***		2.508***	1.362	2.530***	
	(0.295)	(0.295)		(0.307)	(3.342)	(0.295)	
Number of Children (baseline - No Child)	-2.123	-2.118		-2.206		-2.118	
One child	(1.306)	(1.306)		(1.307)		(1.307)	
Two children	0.579	0.572		0.574		0.586	
	(1.139)	(1.139)		(1.140)		(1.140)	
Three children	-0.407	-0.413		-0.354		-0.407	
	(1.122)	(1.121)		(1.122)		(1.122)	
Four children	-0.698	-0.707		-0.612		-0.677	
	(1.176)	(1.175)		(1.176)		(1.176)	
Five and more than five children	-1.254	-1.266		-1.189		-1.246	
	(1.152)	(1.151)		(1.152)		(1.152)	
N	12286 (n = 5083 - Unbalanced Panel)						
R-squared	0.043	0.045		0.044		0.0430	
F-statistics	13.516***	12.038***		12.2782***		12.913***	

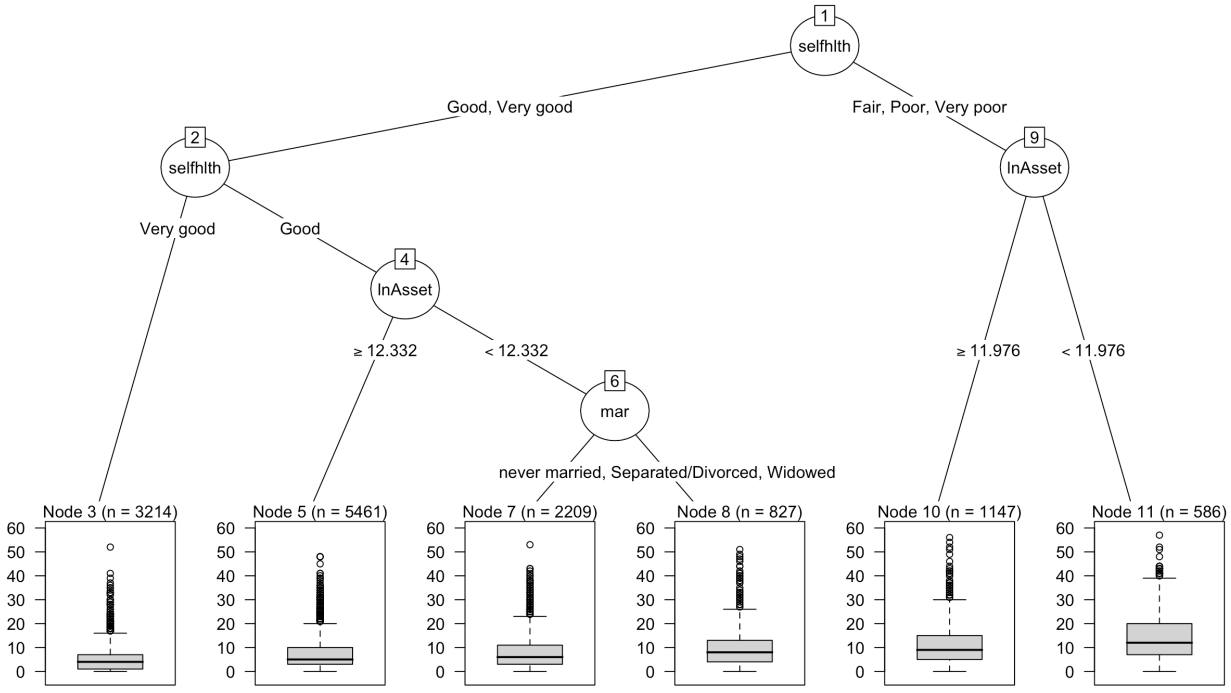

Figure 8: The CART Tree - complexity parameter = 0.003

6.3 CART Model

Complexity parameter = 0.003 Any split that does not decrease the overall lack of fit by a factor of 0.003 will likely be pruned off by cross-validation. With anova splitting, this means that the overall R-squared must increase by 0.03 at each step. The main role of this parameter is to save computing time by pruning off splits that are obviously not worthwhile.

6.4 Conditional Inference Tree Model - maxdepth = 4

The tree depth is limited to 4. Recursive partitioning by conditional inference means unified tests for independence are constructed by means of the conditional distribution of linear statistics in the permutation test framework developed by Strasser and Weber (1999) [20]. The determination of the best binary split in one selected covariate and the handling of missing values is performed based on standardized linear statistics within the same framework as well[11].

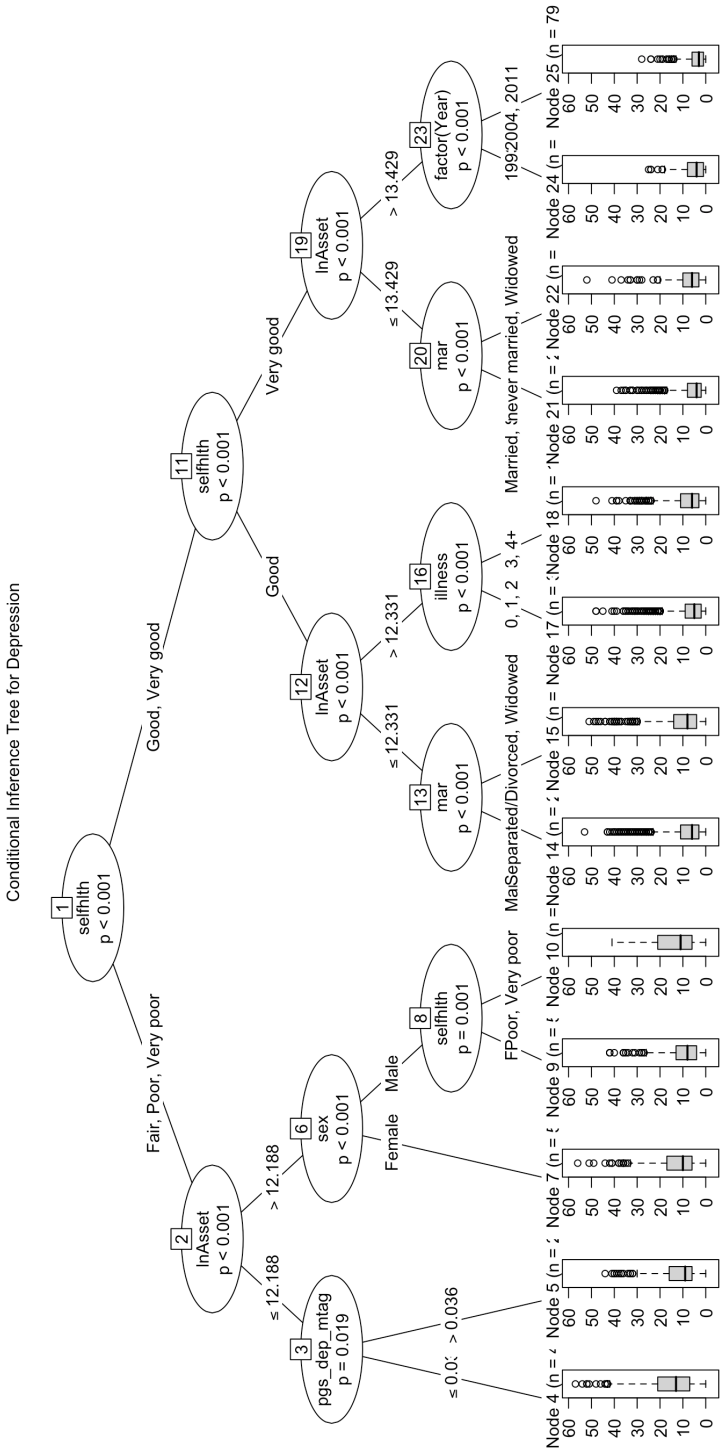

Figure 9: The Conditional Inference Tree - maxdepth = 4