A transfer to utility study using the R package TTU

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Abstract

Background: Background text.

Objectives: We aimed to: Add study objectives here.

Methods: Add abstract here.

Results: Add results here.

Conclusions: Add conclusion here

Data: Add details on dataset.

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1 Introduction

This article is an automatically generated scientific summary of a study that the authors implemented using the R package TTU [1].

This study aimed to identify the best TTU regression models to predict AQol-6D utility and evaluate the predictive ability of six candidate measures of psychological distress, depression and anxiety.

2 Methods

2.1 Sample and setting

2.2 Measures

Data was collected on utility weights, six candidate predictors of utility weights including Psychological distress, Depression and Anxiety as well as descriptive population information.

2.2.1 Utility weights

Utility weights were assessed using the AQol-6D multi-attribute utility instrument.

2.2.2 Candidate predictors

Data from six measures of Psychological distress (one measure), Depression (two measures) and Anxiety (three measures) were used as candidate predictors to construct TTU models.

The candidate predictors were the Behavioural Activation for Depression Scale (measured on a scale of 0-150), Generalised Anxiety Disorder Scale (measured on a scale of 0-21), Kessler Psychological Distress Scale (6 Dimension) (measured on a scale of 0-24), Overall Anxiety Severity and Impairment Scale (measured on a scale of 0-20), Patient Health Questionnaire (measured on a scale of 0-27) and Screen for Child Anxiety Related Disorders (measured on a scale of 0-82)

2.2.3 Population characteristics

Population characteristic data were age, relationship status, education and employment status, primary diagnosis and clinical stage

2.3 Statistical analysis

We applied a generalised form of the transfer to utility analysis algorithm developed by Hamilton, Gao and colleagues [2]. Basic descriptive statistics were used to characterise the cohort in terms of baseline population variables. Pearson's Product Moment Correlations (r) were used to determine the relationships between candidate predictors and the AQol-6D utility score.

2.3.1 TTU regression models

We compared predictive performance of a range of models predicting AQol-6D utility scores using the candidate predictor that had the highest Pearson correlation coefficient with utility scores. The models compared include OLS regression with no transformation, complementary log log transformation, logit transformation, log log transformation and log transformation and GLM using gaussian distribution and log link, beta distribution and complementary log log link and beta distribution and logit link. Ten-fold cross-validation was used to compare model fitting using training datasets and predictive ability using testing datasets using three indicators including R^2, root mean square error (RMSE) and mean absolute error (MAE) [3,4].

To evaluate whether candidate predictors could independently predict utility scores, we established multivariate prediction models using baseline data with the candidate predictor and a range of other risk factors including .

2.3.2 Candidate predictor comparison

We compared the usefulness of the candidate predictors by using a random forest model including all six candidate predictors and by evaluating the independent predictive ability of different candidate predictors using 10-fold cross-validation.

2.3.3 Longitudinal transfer to utility models

We next established longitudinal models using generalised linear mixed- effect models (GLMM) and Linear mixed effect model (LMM) that included both the baseline and follow-up data. Model fitting was evaluated using Bayesian R^2 [5].

2.3.4 Software

We undertook all our analyses using ***R*** 4.0.5 [6] using the TTU package [1].

3 Results

3.1 Cohort characteristics

Participants characteristics at baseline and follow-up are displayed in Table 1. This study included 1068 out of the 1068 participants with complete AQol-6D data. This cohort predominantly comprised individuals with anxiety/depression (76.7%) at early (prior to first episode of a serious mental disorder) clinical stages (91.7%). Participant ages ranged between 12-25 with a mean age of 17.56 (SD = 3.09).

There were 643 participants (60.2%) who completed AQol-6D questions at the follow-up survey three months after baseline assessment.

Table 1: Participant characteristics

		Baseline		Follow-Up	
		(N =	1068)	(N =	643)
Age	Mean (SD)	17.56	(3.09)	17.77	(3.09)
	Median (Q1 Q3)	17.00	(15.00 20.00)	18.00	(16.00 20.00)
	Min - Max	12.00	25.00	12.00	25.00
	Missing	0.00		0.00	
Relationship Status	In a relationship	317.00	(29.68%)	190.00	(29.55%)
	Not in a relationship	751.00	(70.32%)	453.00	(70.45%)
	Missing	0.00		0.00	
Education and Employment Status	Not studying or working	159.00	(15.35%)	152.00	(24.40%)
	Studying and working	305.00	(29.44%)	146.00	(23.43%)
	Studying only	405.00	(39.09%)	167.00	(26.81%)
	Working only	167.00	(16.12%)	158.00	(25.36%)
	Missing	32.00		20.00	
Primary Diagnosis	Anxiety	264.00	(26.01%)	175.00	(29.02%)
	Depression	182.00	(17.93%)	140.00	(23.22%)
	Depression and Anxiety	332.00	(32.71%)	152.00	(25.21%)
	Other	237.00	(23.35%)	136.00	(22.55%)
	Missing	53.00		40.00	
Clinical Stage	0-1a	625.00	(60.27%)	249.00	(39.78%)
	1b	326.00	(31.44%)	216.00	(34.50%)
	2-4	86.00	(8.29%)	161.00	(25.72%)
	Missing	31.00		17.00	

Table 2: Candidate predictors distribution parameters and correlations with AQoL-6D utility

		Baseline		Follow-Up		
		(N =	1068)	(N =	643)	p
Behavioural Activation for Depression Scale (0-150)	Mean (SD)	78.43	(25.61)	89.62	(25.20)	0.00
	Missing	7.00		4.00		0.00
	Correlation with AQOL-6D	0.73		0.73		0.00, 0.00
Generalised Anxiety Disorder Scale (0-21)	Mean (SD)	10.23	(5.53)	8.13	(5.23)	0.00
	Missing	6.00		2.00		0.00
	Correlation with AQOL-6D	-0.67		-0.74		0.00, 0.00
Kessler Psychological Distress Scale (6 Dimension) (0-24)	Mean (SD)	12.08	(5.60)	10.10	(5.66)	0.00
	Missing	1.00		2.00		0.00
	Correlation with AQOL-6D	-0.67		-0.69		0.00, 0.00
Overall Anxiety Severity and Impairment Scale (0-20)	Mean (SD)	7.85	(4.61)	6.40	(4.16)	0.00
	Missing	7.00		0.00		0.00
	Correlation with AQOL-6D	-0.73		-0.74		0.00, 0.00
Patient Health Questionnaire (0-27)	Mean (SD)	12.65	(6.23)	9.74	(6.21)	0.00
	Missing	4.00		2.00		0.00
	Correlation with AQOL-6D	-0.78		-0.80		0.00, 0.00
Screen for Child Anxiety Related Disorders (0-82)	Mean (SD)	33.40	(17.90)	29.33	(17.10)	0.00
	Missing	8.00		0.00		0.00
	Correlation with AQOL-6D	-0.67		-0.67		0.00, 0.00

3.2 AQol-6D and candidate predictors

Distribution of AQol-6D total utility score and sub-domain scores are displayed in Figure 1, the mean utility score at baseline is 0.61 (SD = 0.19) and 0.69 (SD = 0.18) at follow-up. Distribution of candidate predictors, BADS, GAD-7, K6, OASIS, PHQ-9 and SCARED, are summarised in Table 2. PHQ-9 was found to have the highest correlation with utility score both at baseline and follow-up followed by BADS and OASIS; baseline and follow-up SCARED was found to have the lowest correlation coefficients with utility score although all correlation coefficients can be characterised as being strong.

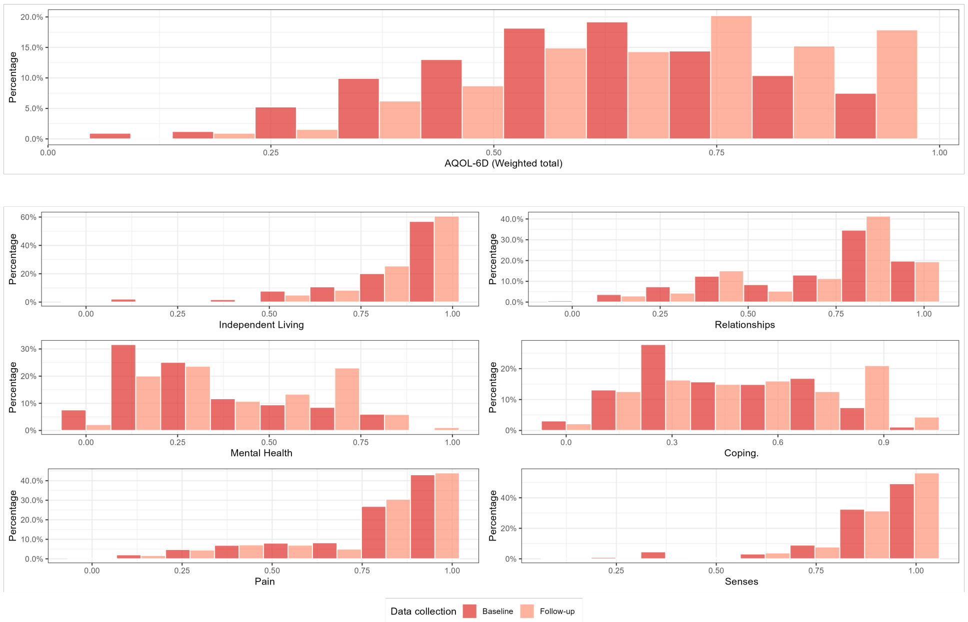

Figure 1: Distribution of AQol-6D domains

3.3 TTU regression model performance

The 10-fold cross-validated model fitting index from TTU models using PHQ9 are reported in Table A.1 in the Supplementary Material. The best OLS model was found to be either no transformation, log transformation or clog-log transformation. Both GLM with Gaussian distribution and log link and OLS with clog-log transformation were selected for further evaluation. Predictive ability of each candidate predictor using baseline data were also compared using 10-fold cross-validation.

As shown in Table A.2, PHQ9 had the highest predictive ability followed by OASIS, BADS, GAD7 and SCARED. K6 had the least predictive capability. This is consistent with the random forest model in which PHQ9 was found to be the most 'important' predictor (see Figure A.1). The confounding effect of other participant characteristics were also evaluated when using the candidate predictors in predicting utility score. Using the baseline data, SOFAS was found to independently predict utility scores in models for all six candidate predictors *($p<0.005$)*. No other confounding factor was identified for the either predictor prediction model; sex at birth was found to be a confounder for K6 model *($p<0.01$)*. A few other confounders, including primary diagnosis, clinical staging and age were identified as weakly associated with utility in TTU models using anxiety and depression measurements other than PHQ-9.

3.4 Longitudinal TTU regression models

Regression coefficients of the baseline score and score changes (from baseline to follow-up) estimated in individual GLMM and LLM models are summarised in Table 3. Bayesian R^2 from each model is reported. Modelled residual standard deviations (SDs) were also provided to support simulation studies which need to capture individual level variation. In both GLMM and LLM models, the prediction models using PHQ-9 had the highest R^2 (0.76 and 0.82) and lowest estimated residual SD. R^2 were above 0.8 for all LLM models and above 0.6 for all GLMM models. Variance of the random intercept was comparable with the residual variance.

Table 3: Estimated coefficients from longitudinal TTU models for candidate predictors

	GLMM with Gaussian distribution and log link					LMM with clog-log transformation				
Parameter	Estimate	SE	95CI	R2	Sigma	Estimate	SE	95CI	R2	Sigma
PHQ9 model				0.76	0.09				0.82	0.26
SD (Intercept)	0.11	0.01	0.10, 0.13			0.26	0.01	0.24, 0.28		
Intercept	-0.03	0.01	-0.05, -0.01			0.94	0.02	0.89, 0.98		
PHQ9 baseline	-3.81	0.09	-3.98, -3.65			-7.65	0.17	-7.98, -7.32		
PHQ9 change	-2.45	0.12	-2.68, -2.22			-4.74	0.21	-5.16, -4.32		
OASIS model				0.75	0.09				0.80	0.27
SD (Intercept)	0.14	0.01	0.13, 0.16			0.30	0.01	0.28, 0.33		
Intercept	-0.11	0.01	-0.13, -0.09			0.76	0.02	0.72, 0.81		
OASIS baseline	-5.01	0.14	-5.28, -4.75			-9.85	0.26	-10.35, -9.33		
OASIS change	-2.96	0.17	-3.30, -2.62			-5.72	0.30	-6.32, -5.13		
BADS model				0.75	0.09				0.81	0.27
SD (Intercept)	0.14	0.01	0.13, 0.16			0.30	0.01	0.28, 0.32		
Intercept	-1.19	0.02	-1.23, -1.15			-1.41	0.04	-1.49, -1.34		
BADS baseline	0.87	0.02	0.82, 0.92			1.77	0.05	1.68, 1.86		
BADS change	0.48	0.03	0.43, 0.53			0.98	0.05	0.89, 1.08		
SCARED model				0.73	0.10				0.78	0.28
SD (Intercept)	0.16	0.01	0.14, 0.17			0.34	0.01	0.31, 0.36		
Intercept	-0.10	0.01	-0.13, -0.08			0.78	0.03	0.73, 0.84		
SCARED baseline	-1.17	0.04	-1.24, -1.09			-2.34	0.07	-2.48, -2.20		
SCARED change	-0.59	0.04	-0.68, -0.51			-1.17	0.08	-1.32, -1.02		
K6 model				0.74	0.10				0.79	0.28
SD (Intercept)	0.16	0.01	0.15, 0.18			0.34	0.01	0.32, 0.36		
Intercept	-0.05	0.01	-0.08, -0.03			0.89	0.03	0.83, 0.95		
K6 baseline	-3.68	0.12	-3.91, -3.46			-7.45	0.23	-7.90, -6.99		
K6 change	-1.94	0.12	-2.19, -1.70			-3.85	0.22	-4.30, -3.42		
GAD7 model				0.74	0.10				0.80	0.27
SD (Intercept)	0.16	0.01	0.14, 0.17			0.34	0.01	0.32, 0.36		
Intercept	-0.11	0.01	-0.13, -0.09			0.76	0.03	0.71, 0.81		
GAD7 baseline	-3.82	0.11	-4.05, -3.60			-7.58	0.23	-8.03, -7.13		
GAD7 change	-2.32	0.14	-2.60, -2.05			-4.49	0.24	-4.96, -4.03		

The mean ratio between two coefficients ($\beta_{change}/\beta_{baseline}$) is 0.52 for K6, between 0.55 and 0.63 for depression measurements and between 0.5 and 0.6 for anxiety measurements.

Distribution of observed and predicted utility scores and their association from GLMM (Gaussian distribution and log link) and LLM (complementary log log transformation) using PHQ9 are plotted in Figure 2.

We also evaluated models with SOFAS at baseline and SOFAS change from baseline added to psychological distress, depression and anxiety predictors (see Tables A.3 and A.4).

Detailed summaries of all models are available in the online data repository (see "Availability of data and materials").

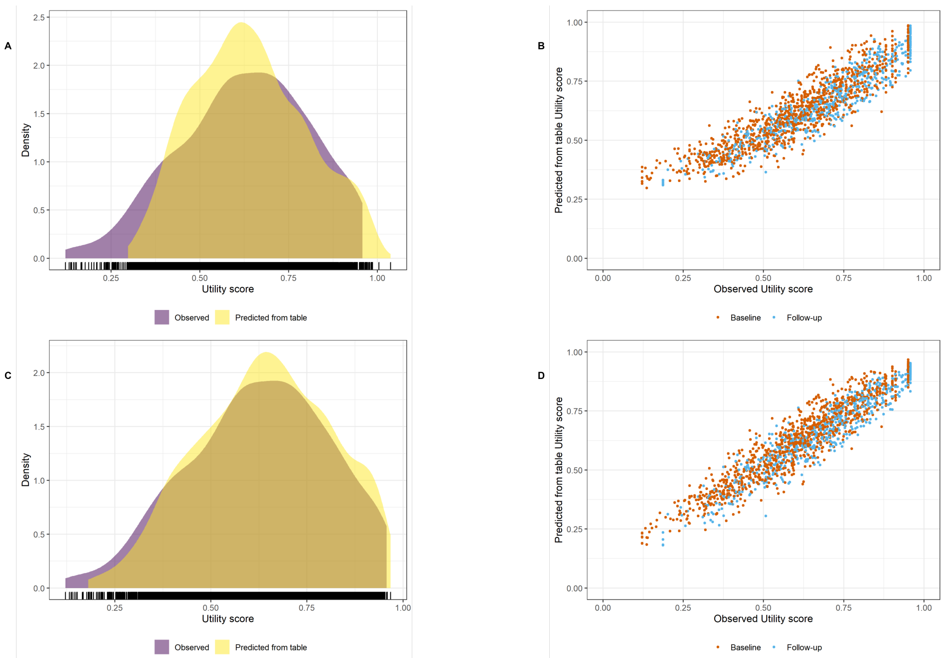

Figure 2: Comparison of observed and predicted AQol-6D utility score from longitudinal TTU model using PHQ9 (A) Density plots of observed and predicted utility scores (GLMM (Gaussian distribution and log link)) (B) Scatter plots of observed and predicted utility scores by timepoint (GLMM (Gaussian distribution and log link)) (C) Density plots of observed and predicted utility scores (LLM (complementary log log transformation)) (D) Scatter plots of observed and predicted utility scores by timepoint (LLM (complementary log log transformation))

4 Discussion

Add discussion text here.

5 Conclusions

Conclusion text goes here.

Availability of data and materials

None available

Ethics approval

Add ethics text here.

Funding

Add funding details.

Conflict of Interest

None declared.

References

1. Gao C, Hamilton M. TTU: Transfer to utility mapping algorithm toolkit. 2021.

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A Supplementary Material

A.1 Additional tables

Table A.1: 10-fold cross-validated model fitting index for different OLS or GLM models for using PHQ9 total scores as predictor with the baseline data

	Training model fit (averaged over 10 folds)			Testing model fit (averaged over 10 folds)		
Model	R2	RMSE	MAE	R2	RMSE	MAE
OLS						
No transformation	0.60	0.12	0.09	0.60	0.12	0.09
Complementary Log Log transformation	0.60	0.12	0.09	0.60	0.12	0.10
Logit transformation	0.59	0.12	0.10	0.59	0.12	0.10
Log Log transformation	0.57	0.12	0.10	0.57	0.12	0.10
Log transformation	0.57	0.12	0.10	0.57	0.12	0.10
GLM						
Gaussian distribution and log link	0.59	0.12	0.10	0.59	0.12	0.10
Beta distribution and complementary log log link	0.60	0.12	0.09	0.60	0.12	0.10
Beta distribution and logit link	0.60	0.12	0.10	0.60	0.12	0.10

* RMSE: Root Mean Squared Error; MAE: Mean Absolute Error

Table A.2: 10-fold cross-validated model fitting index for different candidate predictors estimated using GLM with Gaussian distribution and log link with the baseline data

	Training model fit (averaged over 10 folds)			Testing model fit (averaged over 10 folds)		
Model	R2	RMSE	MAE	R2	RMSE	MAE
PHQ9	0.59	0.12	0.10	0.59	0.12	0.10
OASIS	0.52	0.13	0.10	0.52	0.13	0.10
BADS	0.51	0.13	0.10	0.51	0.13	0.10
GAD7	0.45	0.14	0.11	0.45	0.14	0.11
SCARED	0.45	0.14	0.11	0.45	0.14	0.11
K6	0.44	0.14	0.11	0.44	0.14	0.11

* RMSE: Root Mean Squared Error; MAE: Mean Absolute Error

Table A.3: Estimated coefficients from longitudinal TTU models based on candidate predictors and SOFAS score using LLM (with cloglog transformation)

Parameter*	Estimate	SE	95CI	R2	Sigma
PHQ9 SOFAS model				0.84	0.24
SD (Intercept)	0.24	0.01	0.22, 0.26		
Intercept	-0.16	0.08	-0.32, 0.00		
PHQ9 baseline	-6.72	0.17	-7.05, -6.39		
PHQ9 change	-4.19	0.19	-4.58, -3.82		
SOFAS baseline	1.48	0.11	1.27, 1.70		
SOFAS change	1.05	0.10	0.86, 1.24		
OASIS SOFAS model				0.82	0.26
SD (Intercept)	0.28	0.01	0.25, 0.30		
Intercept	-0.51	0.09	-0.69, -0.33		
OASIS baseline	-8.42	0.26	-8.92, -7.93		
OASIS change	-5.02	0.28	-5.57, -4.46		
SOFAS baseline	1.76	0.12	1.52, 2.00		
SOFAS change	1.21	0.10	1.00, 1.42		
BADS SOFAS model				0.82	0.25
SD (Intercept)	0.27	0.01	0.25, 0.29		
Intercept	-2.35	0.07	-2.49, -2.20		
BADS baseline	1.51	0.05	1.42, 1.60		
BADS change	0.86	0.05	0.77, 0.95		
SOFAS baseline	1.72	0.12	1.49, 1.96		
SOFAS change	1.08	0.10	0.88, 1.28		
SCARED SOFAS model				0.80	0.27
SD (Intercept)	0.30	0.01	0.28, 0.32		
Intercept	-0.72	0.10	-0.90, -0.53		
SCARED baseline	-1.95	0.07	-2.09, -1.82		
SCARED change	-1.03	0.07	-1.17, -0.89		
SOFAS baseline	2.07	0.13	1.82, 2.33		
SOFAS change	1.30	0.11	1.09, 1.52		
K6 SOFAS model				0.81	0.26
SD (Intercept)	0.30	0.01	0.28, 0.32		
Intercept	-0.61	0.10	-0.80, -0.41		
K6 baseline	-6.24	0.22	-6.66, -5.81		
K6 change	-3.39	0.21	-3.81, -2.97		
SOFAS baseline	2.05	0.13	1.79, 2.31		
SOFAS change	1.24	0.10	1.03, 1.44		
GAD7 SOFAS model				0.82	0.26
SD (Intercept)	0.31	0.01	0.29, 0.33		
Intercept	-0.62	0.10	-0.81, -0.42		
GAD7 baseline	-6.33	0.23	-6.78, -5.88		
GAD7 change	-3.92	0.23	-4.37, -3.48		
SOFAS baseline	1.90	0.13	1.64, 2.16		
SOFAS change	1.17	0.10	0.98, 1.38		

* Calculated as original scores divided by 100

Table A.4: Estimated coefficients from longitudinal TTU models based on individual candidate predictors and SOFAS score using GLM (Gaussian distribution with log link)

Parameter*	Estimate	SE	95CI	R2	Sigma
PHQ9 SOFAS model				0.78	0.09
SD (Intercept)	0.10	0.01	0.09, 0.12		
Intercept	-0.58	0.04	-0.66, -0.49		
PHQ9 baseline	-3.36	0.09	-3.52, -3.19		
PHQ9 change	-2.19	0.11	-2.41, -1.98		
SOFAS baseline	0.74	0.06	0.63, 0.86		
SOFAS change	0.51	0.05	0.41, 0.61		
OASIS SOFAS model				0.77	0.09
SD (Intercept)	0.12	0.01	0.11, 0.14		
Intercept	-0.74	0.05	-0.83, -0.65		
OASIS baseline	-4.30	0.14	-4.57, -4.03		
OASIS change	-2.63	0.16	-2.95, -2.32		
SOFAS baseline	0.88	0.06	0.75, 1.00		
SOFAS change	0.59	0.05	0.48, 0.70		
BADS SOFAS model				0.76	0.09
SD (Intercept)	0.12	0.01	0.11, 0.14		
Intercept	-1.67	0.04	-1.75, -1.60		
BADS baseline	0.74	0.02	0.70, 0.79		
BADS change	0.42	0.03	0.37, 0.47		
SOFAS baseline	0.89	0.06	0.77, 1.01		
SOFAS change	0.54	0.06	0.43, 0.65		
SCARED SOFAS model				0.75	0.09
SD (Intercept)	0.14	0.01	0.12, 0.15		
Intercept	-0.86	0.05	-0.96, -0.77		
SCARED baseline	-0.98	0.04	-1.05, -0.91		
SCARED change	-0.53	0.04	-0.61, -0.46		
SOFAS baseline	1.05	0.07	0.92, 1.18		
SOFAS change	0.64	0.06	0.53, 0.76		
K6 SOFAS model				0.76	0.09
SD (Intercept)	0.14	0.01	0.12, 0.15		
Intercept	-0.81	0.05	-0.90, -0.71		
K6 baseline	-3.08	0.11	-3.30, -2.87		
K6 change	-1.71	0.12	-1.94, -1.48		
SOFAS baseline	1.03	0.06	0.90, 1.16		
SOFAS change	0.60	0.06	0.48, 0.71		
GAD7 SOFAS model				0.76	0.09
SD (Intercept)	0.14	0.01	0.12, 0.15		
Intercept	-0.80	0.05	-0.90, -0.70		
GAD7 baseline	-3.21	0.12	-3.43, -2.98		
GAD7 change	-2.03	0.13	-2.28, -1.78		
SOFAS baseline	0.94	0.07	0.81, 1.07		
SOFAS change	0.57	0.06	0.46, 0.68		

* Calculated as original scores divided by 100

Table A.5: R Packages used in data analysis and reporting

Package	Version	Citation
arsenal	3.6.3	Ethan Heinzen, Jason Sinnwell, Elizabeth Atkinson, Tina Gunderson and Gregory Dougherty (2021). arsenal: An Arsenal of 'R' Functions for Large-Scale Statistical Summaries. R package version 3.6.3. https://CRAN.R-project.org/package=arsenal
assertthat	0.2.1	Hadley Wickham (2019). assertthat: Easy Pre and Post Assertions. R package version 0.2.1. https://CRAN.R-project.org/package=assertthat
BCEA	2.3-1.1	Baio et al (2017). Bayesian Cost Effectiveness Analysis with the R package BCEA. Springer, New York, NY. doi: 10.1007/978-3-319-55718-2, URL: http://www.springer.com/us/book/9783319557168/.
betareg	3.1-4	Cribari-Neto F, Zeileis A (2010). "Beta Regression in R." _Journal ofStatistical Software_, *34*(2), 1-24. doi: 10.18637/jss.v034.i02 (URL:https://doi.org/10.18637/jss.v034.i02).
boot	1.3-28	Angelo Canty and Brian Ripley (2021). boot: Bootstrap R (S-Plus) Functions. R package version 1.3-28.
Boruta	7.0.0	Miron B. Kursa, Witold R. Rudnicki (2010). Feature Selection with the Boruta Package. Journal of Statistical Software, 36(11), 1-13. URL http://www.jstatsoft.org/v36/i11/.
brms	2.15.0	Paul-Christian Bürkner (2017). brms: An R Package for Bayesian Multilevel Models Using Stan. Journal of Statistical Software, 80(1), 1-28. doi:10.18637/jss.v080.i01
caret	6.0-88	Max Kuhn (2021). caret: Classification and Regression Training. R package version 6.0-88. https://CRAN.R-project.org/package=caret
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A.2 Additional figures

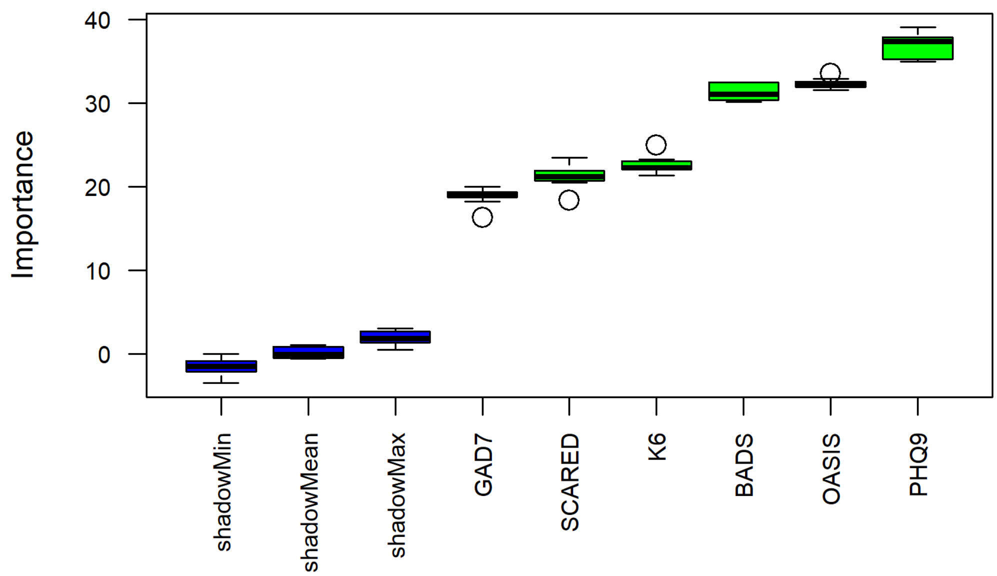

Figure A.1: Variable importance estimated using random forest