Modified Browne Data - Motivation for Modifications

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In this document, we justify the choices to add additional effects of covariates on the outcomes in the original Browne data. We only consider CESD at 6 months as outcome. These additional effects are artificially added to illustrate some ideas that cannot be illustrated with the original data because these (interaction) effects are not present there. We consider 2 artificial data sets.

1. We add a treatment-interaction effect for past major depressive disorder (MDD) (past\_MDD) and baseline CESD (cesd) for their effect on CESD at 6 months (cesd2). So, these two baseline covariates are artificially turned into treatment effect modifiers.
2. In addition to the changes in the first point, we add a quadratic effect main effect for age. So, the outcome regression model that we have used before will be misspecified. We consider two strengths for this quadratic effect.
3. In addition to the changes in the first point, we add a quadratic main effect for baseline CESD. This scenario differs from the second in that baseline CESD is an important effect modifier. We again consider two strengths.

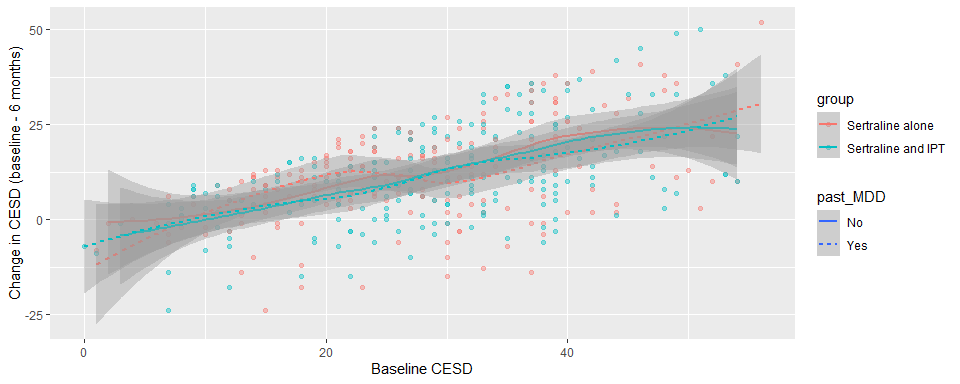
We first give some results and plots for the original data where we do an available case analysis to deal with the missing data. This provides a reference to compare the “updated” data sets with. The goal is to change the original data in such a way that the modified data are still plausible.

# 1 Original data

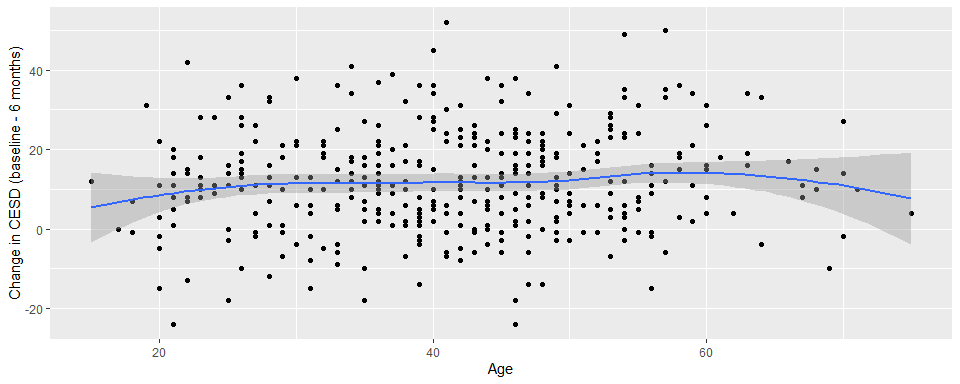
The outcome regression model for change in CESD is fitted with and without all interaction terms with treatment. These estimated models are summarized next. The values between brackets are the estimated standard errors.

|  | No Interactions | Treatment-Interactions |
| --- | --- | --- |
| (Intercept) | 13.571 (4.956)\*\* | 15.959 (7.452)\* |
| groupSertraline and IPT | -0.763 (1.026) | -3.810 (10.036) |
| sexFemale | -1.453 (1.100) | -1.645 (1.630) |
| age | 0.109 (0.051)\* | 0.054 (0.078) |
| past\_MDDYes | -0.254 (1.018) | -0.190 (1.515) |
| numchild | 0.037 (0.431) | 0.213 (0.666) |
| phealth | -2.643 (0.553)\*\*\* | -3.177 (0.843)\*\*\* |
| madrs | 0.072 (0.088) | 0.199 (0.130) |
| sas | -5.951 (1.651)\*\*\* | -5.448 (2.413)\* |
| famfun | -2.474 (0.877)\*\* | -3.216 (1.242)\*\* |
| cesd | 0.716 (0.070)\*\*\* | 0.665 (0.104)\*\*\* |
| vas | -0.048 (0.034) | -0.045 (0.050) |
| groupSertraline and IPT × sexFemale |  | 0.510 (2.246) |
| groupSertraline and IPT × age |  | 0.115 (0.105) |
| groupSertraline and IPT × past\_MDDYes |  | -0.065 (2.076) |
| groupSertraline and IPT × numchild |  | -0.379 (0.885) |
| groupSertraline and IPT × phealth |  | 0.930 (1.124) |
| groupSertraline and IPT × madrs |  | -0.279 (0.179) |
| groupSertraline and IPT × sas |  | -1.128 (3.338) |
| groupSertraline and IPT × famfun |  | 1.601 (1.786) |
| groupSertraline and IPT × cesd |  | 0.087 (0.141) |
| groupSertraline and IPT × vas |  | -0.015 (0.069) |
| R2 | 0.392 | 0.401 |
| R2 Adj. | 0.375 | 0.368 |
| +, p < 0.1; \*, p < 0.05; \*\*, p < 0.01; \*\*\*, p < 0.001. | | |

We next plot the change score against baseline CESD, stratified by treatment and past MDD. Smooth fits are added to facilitate the interpretation. The gray shaded regions are 95% confidence intervals around the smooth curves.



We next plot the change score against age. As before, a smooth curve is added together with a 95% confidence interval.



# 2 Update 1

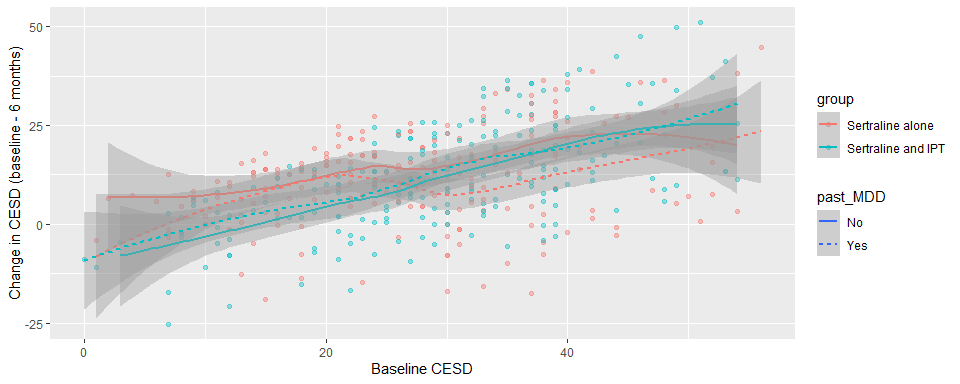
The first update involves the introduction of additional treatment effect heterogeneity. The modification of the outcome variable is as follows,

where a tilde indicates the updated value and group corresponds to “Sertraline and IPT”. Patients will thus benefit more “Sertraline and IPT” (as compared to “Sertraline alone”) if they have a more severe depression at baseline (larger CESD and past MDD).

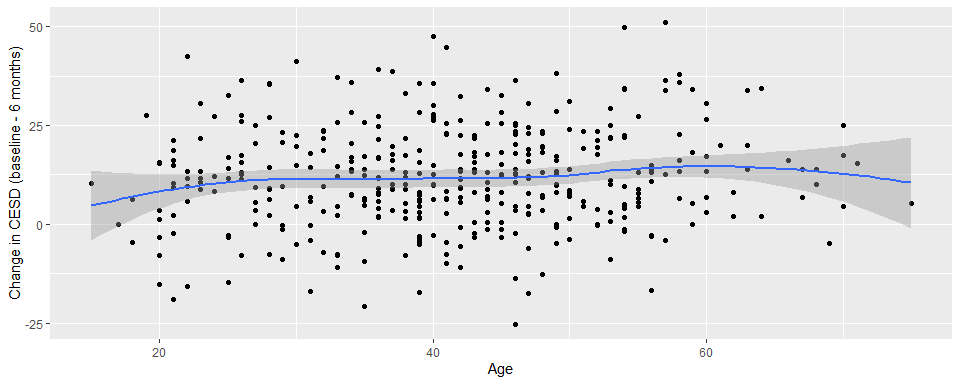
We next repeat the same regression models and plots as before. There now is a signficant interaction effect for past MDD and baseline CESD. Note also that there is a slight change in R-squared.

|  | No Interactions | Treatment-Interactions |
| --- | --- | --- |
| (Intercept) | 15.211 (5.121)\*\* | 23.959 (7.452)\*\* |
| groupSertraline and IPT | -1.206 (1.060) | -15.810 (10.036) |
| sexFemale | -1.621 (1.137) | -1.645 (1.630) |
| age | 0.120 (0.053)\* | 0.054 (0.078) |
| past\_MDDYes | -1.378 (1.052) | -4.190 (1.515)\*\* |
| numchild | 0.028 (0.446) | 0.213 (0.666) |
| phealth | -2.554 (0.572)\*\*\* | -3.177 (0.843)\*\*\* |
| madrs | 0.078 (0.091) | 0.199 (0.130) |
| sas | -6.254 (1.706)\*\*\* | -5.448 (2.413)\* |
| famfun | -2.253 (0.906)\* | -3.216 (1.242)\*\* |
| cesd | 0.668 (0.072)\*\*\* | 0.465 (0.104)\*\*\* |
| vas | -0.047 (0.035) | -0.045 (0.050) |
| groupSertraline and IPT × sexFemale |  | 0.510 (2.246) |
| groupSertraline and IPT × age |  | 0.115 (0.105) |
| groupSertraline and IPT × past\_MDDYes |  | 5.935 (2.076)\*\* |
| groupSertraline and IPT × numchild |  | -0.379 (0.885) |
| groupSertraline and IPT × phealth |  | 0.930 (1.124) |
| groupSertraline and IPT × madrs |  | -0.279 (0.179) |
| groupSertraline and IPT × sas |  | -1.128 (3.338) |
| groupSertraline and IPT × famfun |  | 1.601 (1.786) |
| groupSertraline and IPT × cesd |  | 0.387 (0.141)\*\* |
| groupSertraline and IPT × vas |  | -0.015 (0.069) |
| R2 | 0.347 | 0.398 |
| R2 Adj. | 0.329 | 0.365 |
| +, p < 0.1; \*, p < 0.05; \*\*, p < 0.01; \*\*\*, p < 0.001. | | |

The following plot is the same as for the original data, but the plot now suggests some degree of treatment effect heterogeneity.



The next plot is very similar to the corresponding plot for the original data. This is expected as we did not change the effect of age.



# 3 Update 2

The second update involves the introduction of a quadratic main effect of age that leads to our outcome model being misspecified. The modification of the outcome variable is as follows for a moderate and strong quadratic effect, respectively,

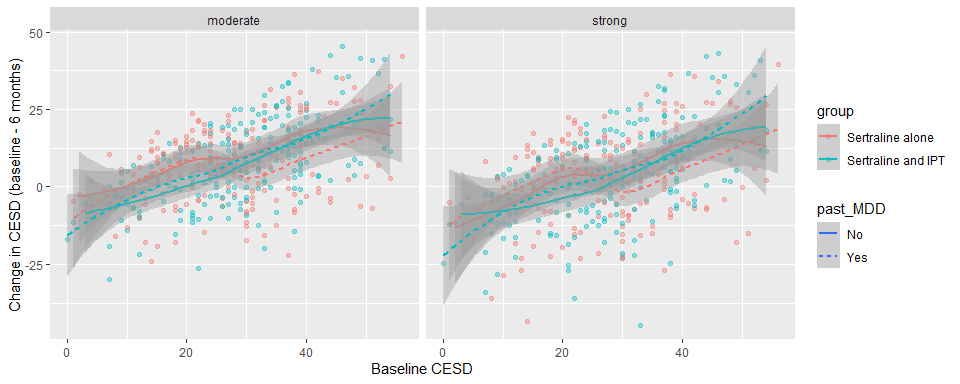
and

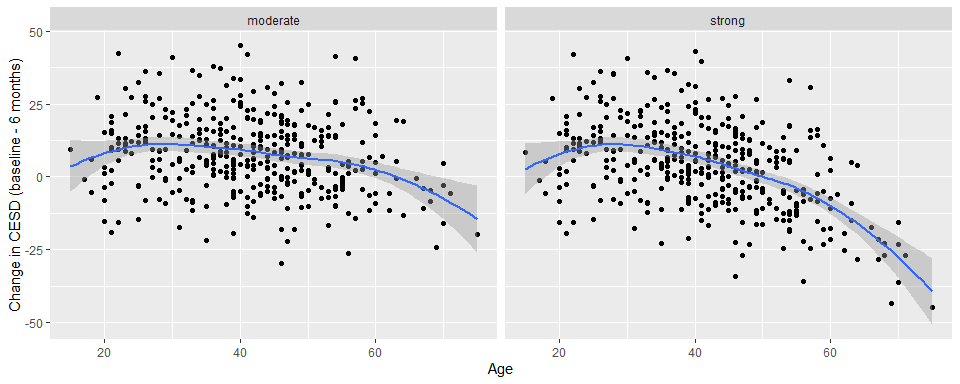
where a tilde indicates the updated value and is the value from the **first** update.

This is a quadratic main effect of age. Patients will thus do worse on average if they are further away from 25 years old. Since most patients are older than 25, this basically means that younger patients will do better.

We next repeat the same regression models and plots as before. Beside treatment effect heterogeneity, there is now evidence for a quadratic main effect of age (as shown in the last plot).

|  | moderate | strong |
| --- | --- | --- |
| (Intercept) | 20.451 (9.258)\* | 14.201 (9.258) |
| groupSertraline and IPT | -16.193 (10.075) | -16.193 (10.075) |
| sexFemale | -1.674 (1.633) | -1.674 (1.633) |
| age | 0.420 (0.279) | 0.920 (0.279)\*\* |
| past\_MDDYes | -4.106 (1.526)\*\* | -4.106 (1.526)\*\* |
| numchild | 0.232 (0.668) | 0.232 (0.668) |
| phealth | -3.184 (0.844)\*\*\* | -3.184 (0.844)\*\*\* |
| madrs | 0.199 (0.130) | 0.199 (0.130) |
| sas | -5.443 (2.416)\* | -5.443 (2.416)\* |
| famfun | -3.225 (1.243)\*\* | -3.225 (1.243)\*\* |
| cesd | 0.465 (0.104)\*\*\* | 0.465 (0.104)\*\*\* |
| vas | -0.047 (0.050) | -0.047 (0.050) |
| I(age^2) | -0.008 (0.003)\*\* | -0.018 (0.003)\*\*\* |
| groupSertraline and IPT × sexFemale | 0.502 (2.249) | 0.502 (2.249) |
| groupSertraline and IPT × age | 0.120 (0.106) | 0.120 (0.106) |
| groupSertraline and IPT × past\_MDDYes | 5.906 (2.079)\*\* | 5.906 (2.079)\*\* |
| groupSertraline and IPT × numchild | -0.384 (0.886) | -0.384 (0.886) |
| groupSertraline and IPT × phealth | 0.912 (1.126) | 0.912 (1.126) |
| groupSertraline and IPT × madrs | -0.282 (0.179) | -0.282 (0.179) |
| groupSertraline and IPT × sas | -1.008 (3.350) | -1.008 (3.350) |
| groupSertraline and IPT × famfun | 1.610 (1.788) | 1.610 (1.788) |
| groupSertraline and IPT × cesd | 0.387 (0.141)\*\* | 0.387 (0.141)\*\* |
| groupSertraline and IPT × vas | -0.013 (0.069) | -0.013 (0.069) |
| R2 | 0.426 | 0.544 |
| R2 Adj. | 0.393 | 0.518 |
| +, p < 0.1; \*, p < 0.05; \*\*, p < 0.01; \*\*\*, p < 0.001. | | |





# 4 Update 2

The third update involves the introduction of a quadratic main effect for baseline CESD that leads to our outcome model being misspecified. The modification of the outcome variable is as follows for a moderate and strong quadratic effect, respectively,

and

where a tilde indicates the updated value and is the value from the **first** update.

This is a quadratic main effect of baseline CESD. Patients will thus do worse on average if they are further away from the baseline CESD of 30. This is not very realistic, but whether this effect is plausible in this particular setting is of little interest.

We next repeat the same regression models and plots as before. Beside treatment effect heterogeneity, there is now evidence for a quadratic main effect of cesd (as shown in the last plot). Because we also want to compare the differential effect of misspecification of the main effect of effect modifiers versus no effect modifiers, we also try to get the correspond R-squared values to match.

|  | (1) | (2) |
| --- | --- | --- |
| (Intercept) | 13.497 (7.902)+ | -4.503 (7.902) |
| groupSertraline and IPT | -15.592 (10.052) | -15.592 (10.052) |
| sexFemale | -1.643 (1.632) | -1.643 (1.632) |
| age | 0.054 (0.078) | 0.054 (0.078) |
| past\_MDDYes | -4.185 (1.516)\*\* | -4.185 (1.516)\*\* |
| numchild | 0.230 (0.668) | 0.230 (0.668) |
| phealth | -3.178 (0.844)\*\*\* | -3.178 (0.844)\*\*\* |
| madrs | 0.204 (0.131) | 0.204 (0.131) |
| sas | -5.398 (2.417)\* | -5.398 (2.417)\* |
| famfun | -3.250 (1.245)\*\* | -3.250 (1.245)\*\* |
| cesd | 1.166 (0.208)\*\*\* | 2.366 (0.208)\*\*\* |
| vas | -0.043 (0.050) | -0.043 (0.050) |
| I(cesd^2) | -0.012 (0.003)\*\*\* | -0.032 (0.003)\*\*\* |
| groupSertraline and IPT × sexFemale | 0.433 (2.253) | 0.433 (2.253) |
| groupSertraline and IPT × age | 0.112 (0.105) | 0.112 (0.105) |
| groupSertraline and IPT × past\_MDDYes | 5.920 (2.078)\*\* | 5.920 (2.078)\*\* |
| groupSertraline and IPT × numchild | -0.365 (0.886) | -0.365 (0.886) |
| groupSertraline and IPT × phealth | 0.939 (1.125) | 0.939 (1.125) |
| groupSertraline and IPT × madrs | -0.285 (0.179) | -0.285 (0.179) |
| groupSertraline and IPT × sas | -1.252 (3.349) | -1.252 (3.349) |
| groupSertraline and IPT × famfun | 1.624 (1.788) | 1.624 (1.788) |
| groupSertraline and IPT × cesd | 0.394 (0.142)\*\* | 0.394 (0.142)\*\* |
| groupSertraline and IPT × vas | -0.011 (0.069) | -0.011 (0.069) |
| R2 | 0.430 | 0.529 |
| R2 Adj. | 0.397 | 0.502 |
| +, p < 0.1; \*, p < 0.05; \*\*, p < 0.01; \*\*\*, p < 0.001. | | |

