

Supplemental Results: Impact of baseline outcome values on slopes of outcome variables over time

Sensitivity analysis was performed to investigate whether baseline outcome values significantly alter associations of the treatments with changes in outcomes over time (trajectory slopes). If this is true, then we might see steeper trajectories in treatment groups due to higher baseline values, not because of the treatment. If this is not true, then steeper trajectories in treatment groups would not be due to higher initial values.

We took 2 approaches to investigating the impact of baseline values on associations of the treatments with the trajectory slopes. The first, based on the 2012 version of Regression Modeling Strategies by Frank Harrell, was to run mixed models using times greater than baseline for the outcomes, and including baseline value as a predictor. This was done overall (also including treatment as a predictor) and stratified within groups. Here, we were interested in the baseline x treatment x time (all data) or baseline x time (for treatment strata) interaction terms. The second, was to do a 2-stage approach where we estimated slopes over time for each patient (thereby reducing to 1 value per patient), and then used those slopes as outcomes in regression models.

The results of the first approach are summarized in Table 1.

Table 1. Mixed model results.

Stratum	Outcome	Regression Coefficient (std. error)	P-value
CEE	WMH	0.088 (0.023)	0.0002
17 β -estradiol	WMH	0.083 (0.018)	<0.0001
Placebo*	WMH	0.044 (0.019)	0.02
All*	WMH	CEE: 0.034 (0.031)	0.28
	WMH	17β-estradiol: 0.039 (0.029)	0.18

* Random intercepts only, not estimable with both random intercepts and slopes.

Within each group, we saw a significant association between baseline value and slope over time. The higher the baseline value, the greater the predicted increase over time. This appears to be a general phenomenon, present in each of the groups (including placebo). However, we did not see any significant p-values in the whole data analyses comparing the mHT groups to placebo. This is consistent with the baseline values not affecting the treatment differences over time.

The results of the second approach are summarized in Table 2.

Table 2. Linear regression model results.

Stratum	Outcome	Regression Coefficient (std. error)	P-value
CEE	WMH	-0.074 (0.017)	0.0002
17 β -estradiol	WMH	0.079 (0.023)	0.002
Placebo	WMH	0.034 (0.020)	0.10
All	WMH	CEE: 0.040 (0.036)	0.27
	WMH	17β-estradiol: 0.046 (0.035)	0.20

Again, results are similar to Table 1. We did not see any significant p-values in the whole data analyses comparing the mHT groups to placebo. We thus have no evidence that baseline values impacted the treatment differences over time.