SUPPLEMENTAL DATA

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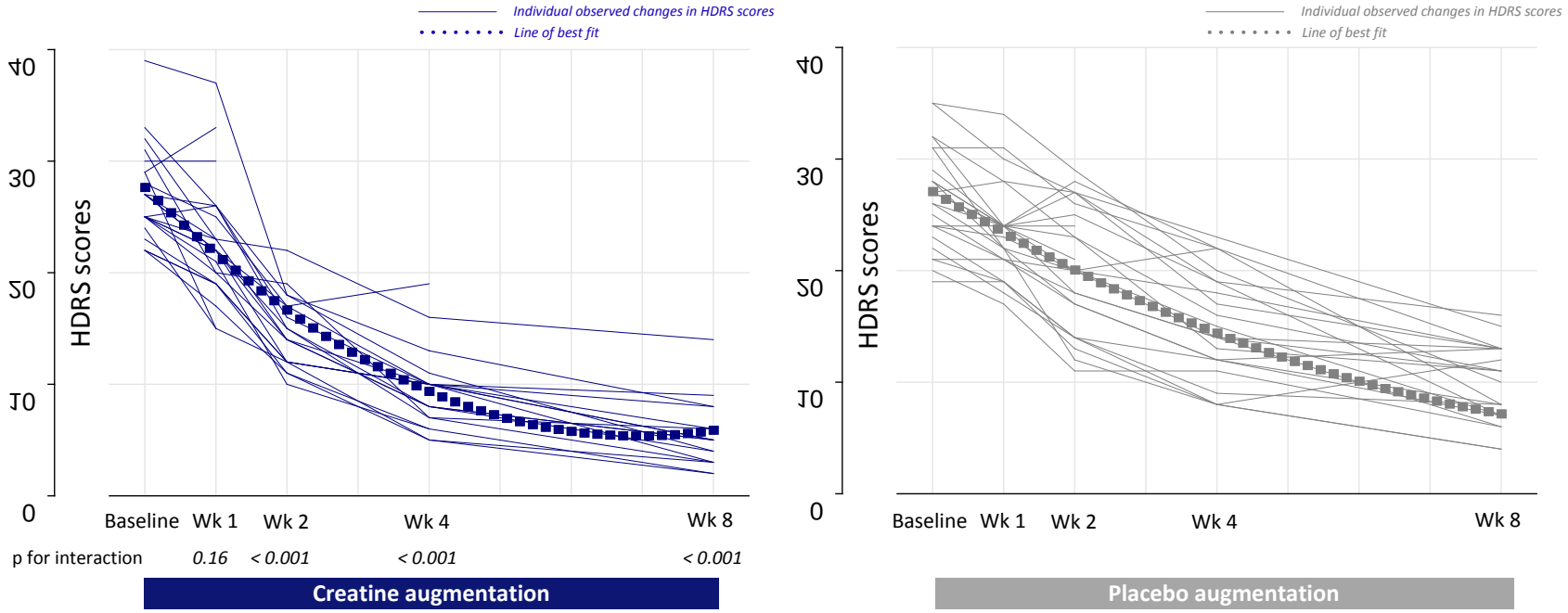
Appendix SA1. Reliability for measurements

All structured interviews including the Structured Clinical Interview for the DSM-IV, the 17-item Hamilton Depression Rating Scale (HDRS), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Clinical Global Impression Scale-severity-of-illness subscale were conducted by an experienced board-certified psychiatrist (T.S.K). High inter-rater reliability for the measurement was ensured between the rater (T.S.K) and another experienced board-certified psychiatrist (J.H.) indicating mean intraclass correlation coefficients during the study period for the total scores of the HDRS and the MADRS were 0.952 (standard deviation [SD], 0.027) and 0.939 (SD, 0.018), respectively. Quality control procedures for clinical assessments were conducted approximately every 6 months during the entire study period.

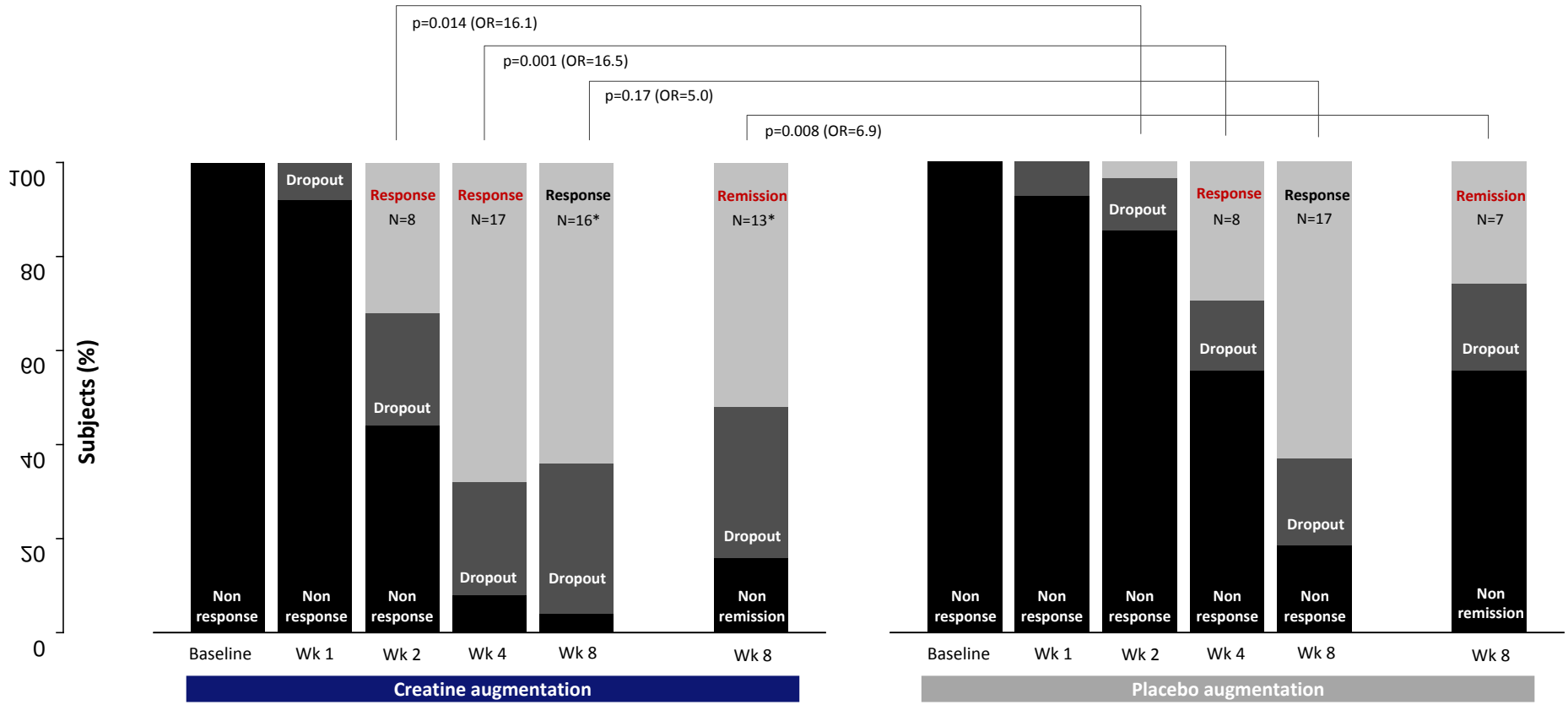
Figure SF1. Individual-level trajectories of changes in HDRS scores and their lines of best fit during treatment period



Changes in the HDRS scores during an 8-week of study period were analyzed by using the mixed-effects model repeated measures analysis for an intention-to-treat sample. Main effects for treatment groups and visits as well as their interaction terms were included into the model. Age and HDRS scores were also included as covariates into the model. Blue and gray dotted lines in the figures correspond to the lines of best fit of these mixed-effects models for the creatine and the placebo groups, respectively. P values for treatment groups by each week interaction terms were depicted in the figures..

Abbreviations: HDRS=Hamilton Depression Rating Scale, Wk=week.

Figure SF2. Proportions of responders and remitters after creatine monohydrate or placebo augmentation of SSRI by HDRS scores



P values and odds ratios were calculated using the logistic regression modeling for the effects of treatment groups with outcome measures of the treatment response or non-response at each visit as well as the remission or non-remission at week 8.

*One patient, who was assigned to the creatine group and responded/remitted at week 4, discontinued the trial at week 8.

Abbreviations: SSRI=selective serotonin reuptake inhibitor; HDRS=Hamilton Depression Rating Scale; OR=odds ratio; Wk=week.

Table ST1. Laboratory profiles of subjects with major depressive disorder randomly assigned to creatine monohydrate or placebo augmentation of SSRI

Laboratory profiles	Week	Creatine monohydrate augmentation		Placebo augmentation		p value [a]
		N	mean (SD)	N	mean (SD)	
Serum creatinine, mg/dL	Baseline	25	0.69 (0.08)	27	0.68 (0.10)	0.51
	Week 2	18[b]	0.81 (0.11)	24	0.66 (0.12)	<0.001
	Week 8	17	0.79 (0.15)	21[c]	0.67 (0.11)	0.01
Serum BUN, mg/dL	Baseline	25	12.5 (2.9)	27	12.8 (4.3)	0.79
	Week 8	17	13.5 (2.7)	21[c]	12.9 (2.9)	0.51
AST, units/L [d]	Baseline	25	21.4 (6.8)	27	21.0 (7.5)	0.83
	Week 8	17	23.6 (10.9)	21[c]	21.6 (5.8)	0.45
ALT, units/L [d]	Baseline	25	19.9 (7.6)	27	21.0 (15.5)	0.75
	Week 8	17	23.5 (13.5)	21[c]	20.0 (8.5)	0.35
BMI, kg/m^2	Baseline	25	24.2 (2.7)	27	23.1 (3.1)	0.18
	Week 8	17	24.2 (2.9)	22	22.8 (3.2)	0.18

[a] P values are calculated by the *t* statistics.
[b] One patient of the creatine group did not examine serum creatinine levels at week 2.
[c] One patient of the placebo group refused the laboratory tests at week 8.
[d] Two patients in the creatine group (one patient, AST 47 units/L and ALT 47 units/L; the other patient, AST 49 units/L and ALT 57 units/L) and one in the placebo group (ALT 42 units/L) showed mild increase in the levels of liver transaminases beyond the upper normal limit at week 8.
Abbreviations: SSRI=selective serotonin reuptake inhibitor; SD=standard deviation; BUN=blood urea nitrogen; AST=aspartate aminotransferase; ALT=alanine aminotransferase; BMI=body mass index.