

# Major Depressive Disorder in Children and Adolescents is Associated with Reduced Hair Cortisol and Anandamide (AEA): Cross-sectional and Longitudinal Evidence from a Large Randomized Clinical Trial

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## Supplementary

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## Hair Cortisol and AEA are Associated with Depression in Youth

**Table S1**

Bivariate Pearson Correlation Matrix for Baseline Biomarkers ( $n = 237$ )

	Cortisol	Cortisone	AEA	1AG-2AG	OEA	PEA	SEA
Cortisol	–						
Cortisone	<b>.42***</b>	–					
AEA	.09	-.12	–				
1AG-2AG	.10	-.05	<b>.29***</b>	–			
OEA	.04	-.11	.13	<b>.29***</b>	–		
PEA	-.05	-.07	-.01	.14	<b>.65***</b>	–	
SEA	-.02	-.17	<b>.46***</b>	<b>.28***</b>	<b>.53***</b>	<b>.62***</b>	–

Note.  $p$ -values were adjusted for multiple testing using the Holm-method.

\*\*\*  $p < .001$

**Table S2**

Effect of Depressive Status on Other Endocannabinoid Concentrations at Baseline Measurement ( $n = 237$ )

	1) No CV		2) + age, sex, bmi		3) + baseline AD	
Outcome	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
1AG-2AG	-1.3	[-9.0; 6.3]	-2.4	[-10.2; 5.5]	-2.2	[-11.5; 6.9]
OEA	417.1	[-143.5; 967.0]	384.1	[-203.3; 984.8]	407.4	[-276.9; 1087.6]
PEA	1221.1	[580.2; 1835.0]	1164.1	[522.2; 1805.9]	1360.3	[616.8; 2095.3]
SEA	-4.1	[-149.6; 144.5]	-10.0	[-160.0; 138.3]	77.1	[-95.6; 246.0]

Note. CV = covariates; AD = antidepressant medication; CI = credible interval.

**Table S3**

Effect of Cortisol on Other Endocannabinoid Concentrations Across Measurements ( $n = 237$ )

	1) No CV		2) + age, sex, BMI		3) + baseline AD	
Outcome	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
1AG-2AG	0.91	[-0.13; 2.01]	-	-	0.88	[-0.27; 2.11]
OEA	-44.22	[-115.00; 25.62]	-	-	-54.90	[-132.01; 18.37]
PEA	-57.58	[-156.98; 38.60]	-	-	-69.57	[-177.45; 34.99]
SEA	-5.89	[-28.05; 15.79]	-	-	-7.69	[-32.00; 15.97]

Note. CV = covariates; AD = antidepressant medication; CI = credible interval.

**Table S4**

Effect of Cortisone on Other Endocannabinoid Concentrations Across Measurements ( $n = 237$ )

	1) No CV		2) + age, sex, BMI		3) + baseline AD	
Outcome	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
1AG-2AG	0.60	[0.19; 1.06]	-	-	0.55	[0.09; 1.04]
OEA	-27.74	[-58.11; 2.49]	-	-	-32.36	[-66.22; 1.27]
PEA	-13.49	[-63.34; 35.00]	-	-	-17.71	[-71.47; 34.51]
SEA	-7.25	[-16.39; 1.53]	-	-	-8.50	[-18.38; 1.01]

Note. CV = covariates; AD = antidepressant medication; CI = credible interval.

**Table S5**

Effect of AEA Level on Other Endocannabinoid Concentrations Across Measurements ( $n = 237$ )

Outcome	1) No CV		2) + age, sex, BMI		3) + baseline AD	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
1AG-2AG	2.69	[0.70; 4.83]	-	-	2.53	[0.46; 4.80]
OEA	-51.57	[-210.26; 91.42]	-	-	-38.71	[-200.08; 106.51]
PEA	-70.77	[-332.85; 127.50]	-	-	-70.24	[-353.10; 132.33]
SEA	-72.52	[-345.26; 128.15]	-	-	-66.14	[-340.22; 131.16]

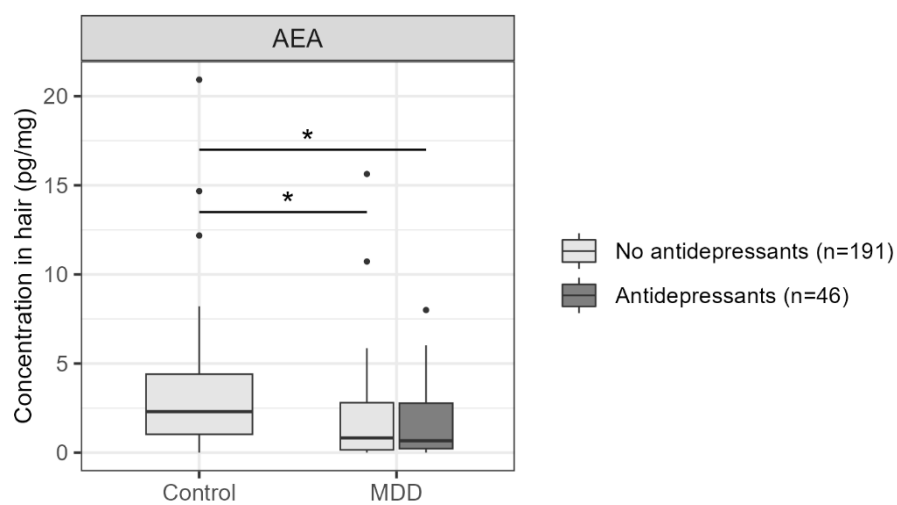
*Note.* CV = covariates; AD = antidepressant medication; CI = credible interval.

### Text S1

As detailed in Figure S1, analysis of AEA concentrations among the three groups (control, MDD with antidepressants, and MDD without antidepressants) revealed lower AEA concentrations in both MDD groups, regardless of antidepressant use. However, no difference was found between MDD children with and without antidepressants.

### Figure S1

Tukey-Posthoc Analysis of AEA Concentrations Stratified by Depressive Status and Antidepressant Medication Use at Baseline



## Text S2

We conducted two-way ANOVA to analyze the association of sex, depressive status, and their potential interaction on cortisol and AEA levels. The cortisol model showed only a main effect of depressive status on cortisol levels [ $F(1,230) = 9.97, p = .002, \eta^2 = .04$ ], but no sex effect [ $F(1,230) = 0.77, p = .381, \eta^2 = <.01$ ] and no interaction effect [ $F(1,230) = 0.57, p = .449, \eta^2 = .04$ ].

The AEA model showed significant main effects for both depressive status [ $F(1,230) = 14.62, p < .001, \eta^2 = .06$ ] and sex [ $F(1,230) = 5.29, p = .022, \eta^2 = .02$ ], as well as a significant interaction effect of depressive status and sex [ $F(1,230) = 7.52, p = .001, \eta^2 = .03$ ]. Tukey-post-hoc tests showed that male children in the control group had significantly higher AEA levels compared to all other groups (Figure S2).

**Figure S2**

Tukey-Posthoc Analysis of Cortisol and AEA Concentrations Stratified by Depressive Status and Sex at Baseline

