Supplementary Material

Citicoline: A Cholinergic Precursor with a Pivotal Role in Dementia and Alzheimer's Disease

Mini-Mental State Examination (MMSE)

Supplementary Table 1A. Summary statistics of MMSE with changes from baseline at each visit.

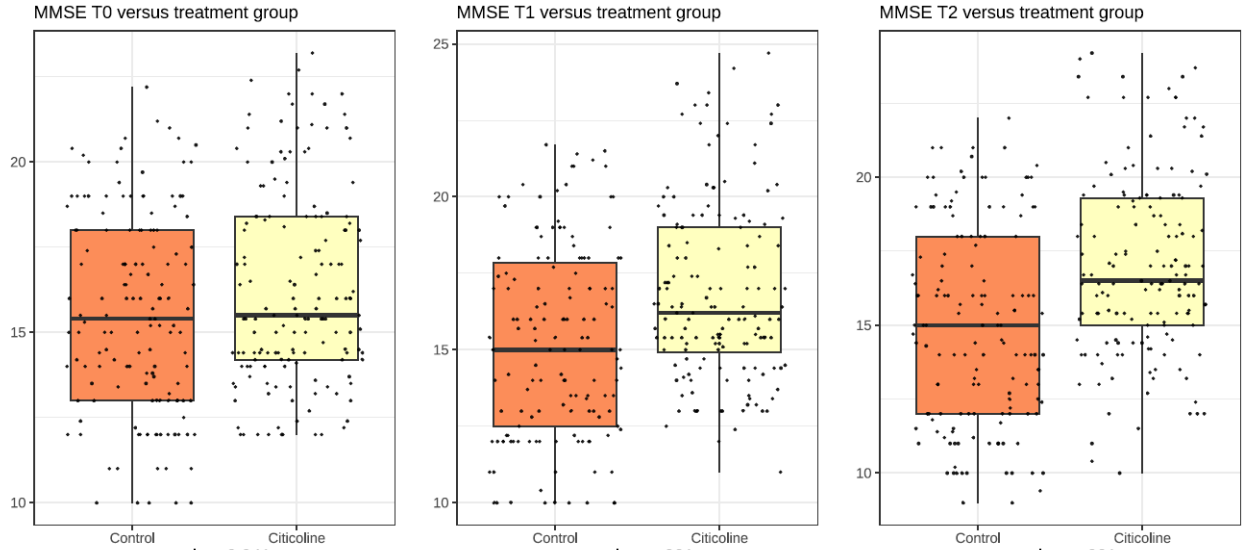
	Control, mean (SD)		Citicoline, mean (SD)		Total, mean (SD)	
	Obs. value	**Change**	**Obs. value**	**Change**	**Obs. value**	**Change**
Baseline	15.58 (2.95)		16.28 (2.89)		15.94 (2.93)	
6 months	15.24 (3.15)	-0.35 (0.96)	16.86 (2.93)	0.58 (0.99)	16.07 (3.14)	0.13 (1.08)
12 months	14.96 (3.36)	-0.63 (1.49)	17.03 (3.09)	0.75 (1.25)	16.02 (3.38)	0.08 (1.53)

As we can see from the Table, the treatment and the interaction between time and treatment have a significant effect in explaining the MMSE variable. Supplementary Table 1B will highlight the pairs that have led the interaction term to be significant at a level of 5%.

Supplementary Table 1B. Wilcoxon-Rank sum tests to pairwise comparisons between group levels with corrections for multiple testing (Bonferroni's correction).

	T0: Control	**T0: Citicoline**	**T1: Control**	**T1: Citicoline**	**T2: Control**
T0: Citicoline	1				
T1: Control	1	0.077			
T1: Citicoline	0.015	0.945	<0.001		
T2: Control	1	0.009	1	<0.001	
T2: Citicoline	0.003	0.282	<0.001	1	<0.001

Supplementary Figure 1. Two-way ANOVA with repeated measures over time (MMSE versus time and treatment). At each time point (indicated in the plot with T0, baseline, T1, 6 months and T2, 12 months), we found a significant difference in the average between the two groups of treatment (t-test with a 5% significance level).

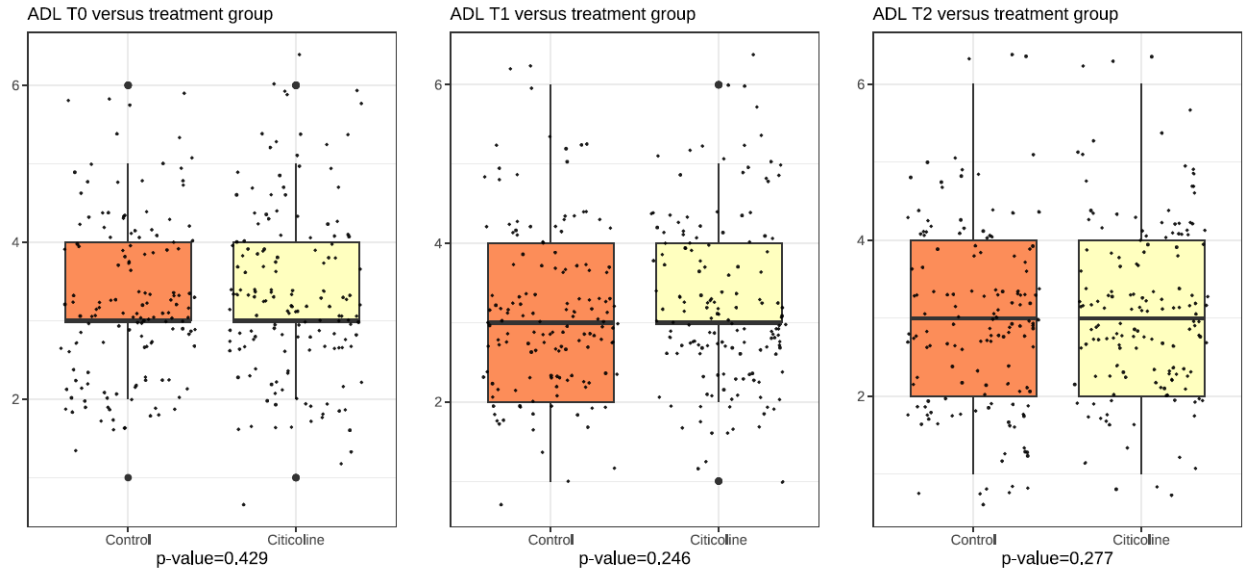


Activities of Daily Life (ADL)

Table 2. Summary statistics of ADL with changes from baseline at each visit.

	Control, mean (SD)		Citicoline, mean (SD)		Total, mean (SD)	
	Obs. value	**Change**	**Obs. value**	**Change**	**Obs. value**	**Change**
Baseline	3.24 (1.03)		3.34 (1.08)		3.29 (1.06)	
6 months	3.11 (1.01)	-0.13 (0.34)	3.25 (1.02)	-0.09 (0.51)	3.18 (1.02)	-0.11 (0.43)
12 months	2.97 (1.12)	-0.27 (0.6)	3.11 (1.08)	-0.23 (0.78)	3.04 (1.1)	-0.25 (0.69)

Figure 2. Two-way ANOVA with repeated measures over time (ADL versus time and treatment). At each time point (indicated in the plot with T0, baseline, T1, 6 months and T2, 12 months) we found a significant difference in mean between the two groups of treatment (t-test with a 5% significance level).

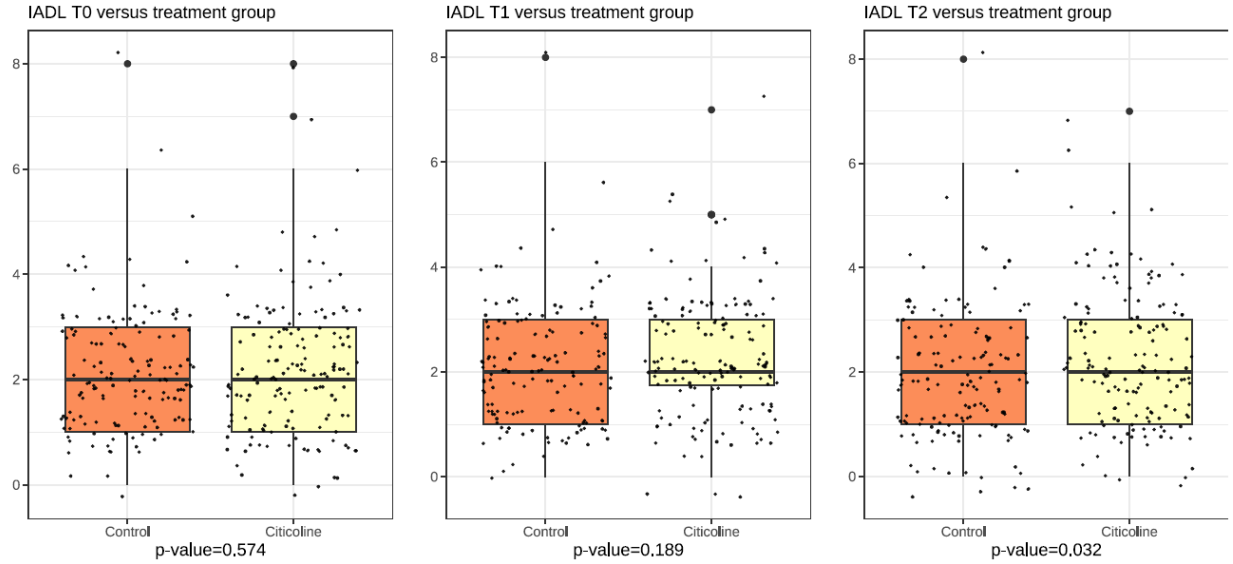


Instrumental Activities of Daily Life (IADL)

Table 3. Summary statistics of IADL with changes from baseline at each visit.

	Control, mean (SD)		Citicoline, mean (SD)		Total, mean (SD)	
	Obs. value	**Change**	**Obs. value**	**Change**	**Obs. value**	**Change**
Baseline	2.13 (1.12)		2.21 (1.25)		2.17 (1.19)	
6 months	2.08 (1.14)	-0.06 (0.23)	2.25 (1.11)	0.04 (0.61)	2.17 (1.13)	-0.01 (0.47)
12 months	1.94 (1.24)	-0.19 (0.43)	2.26 (1.26)	0.05 (1)	2.11 (1.26)	-0.07 (0.78)

Figure 3. Two-way ANOVA with repeated measures over time (IADL versus time and treatment). At each time point (indicated in the plot with T0, baseline, T1, 6 months and T2, 12 months), we found a significant difference in mean between the two groups of treatment (t-test with a 5% significance level).

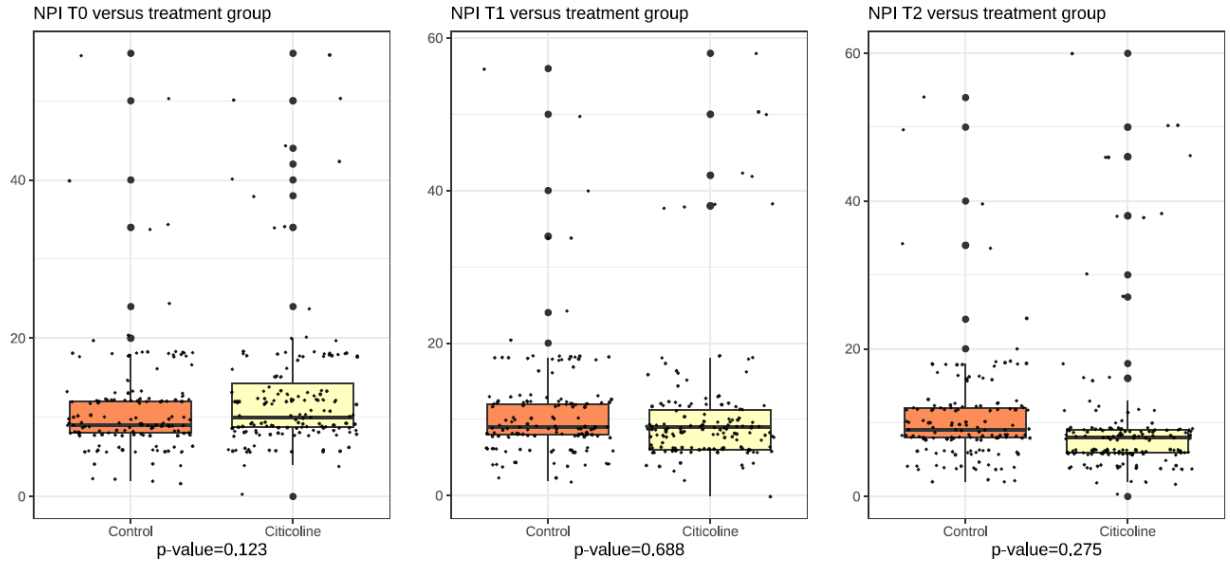


Neuropsychiatric Inventory Scale (NPI)

Table 4. Summary statistics of NPI with changes from baseline at each visit.

	Control, mean (SD)		Citicoline, mean (SD)		Total, mean (SD)	
	Obs. value	**Change**	**Obs. value**	**Change**	**Obs. value**	**Change**
Baseline	11.56 (7.51)		13.03 (8.76)		13.03 (8.76)	
6 months	11.25 (7.58)	-0.31 (1.18)	10.86 (9.06)	-2.17 (2.49)	11.04 (8.37)	-1.27 (2.18)
12 months	10.91 (7.55)	-0.65 (1.63)	9.79 (9.89)	-3.24 (4.18)	10.33 (8.85)	-1.99 (3.46)

Figure 4. At each time point (indicated in the plot with T0, baseline, T1, 6 months and T2, 12 months), there was a non-significant difference in mean between the two groups of treatment (t-test with a 5% significance level).



Geriatric Depression Scale (GDS)

Table 5. Summary statistics of GDS with changes from baseline at each visit.

	Control, mean (SD)		Citicoline, mean (SD)		Total, mean (SD)	
	Obs. value	**Change**	**Obs. value**	**Change**	**Obs. value**	**Change**
Baseline	2.76 (1.34)		2.55 (1.33)		2.65 (1.34)	
6 months	2.71 (1.33)	-0.04 (0.43)	2.12 (1.33)	-0.42 (0.92)	2.41 (1.36)	-0.24 (0.75)
12 months	2.6 (1.36)	-0.15 (0.76)	1.84 (1.45)	-0.71 (0.99)	2.21 (1.46)	-0.44 (0.93)

As we can see from Supplementary Table 5, treatment, time, and the interaction between treatment and time have a significant effect in explaining the GDS variable.

Figure 5. Two-way ANOVA with repeated measures over time (GDS versus time and treatment). At each time point (indicated in the plot with T0, baseline, T1, 6 months and T2, 12 months), we found a significant difference in mean between the two groups of treatment (t-test with a 5% significance level).