Effects of Carnosine on Cognitive Outcomes in Prediabetes and Well-Controlled Type 2 Diabetes: Results from a Randomised Placebo-Controlled Clinical Trial

Table S1. Sample characteristics at baseline

Stroop		
Total # of runs stroop off	5.688 ± 0.873	5.533 ± 0.64
Total # of runs stroop on	5.813 ± 1.424	5.667 ± 0.816
Delayed match to sample (DMS)		
DMS Mean choices to correct	1.13 ± 0.08	1.15 ± 0.14
DMS Correct latency	1226.99 ± 534.42	1009.97 ± 598.18
DMS Correct latency (0s delay)	1225.72 ± 890.07	1236.78 ± 1026.88
DMS Correct latency (12 s delay)	857.11 ± 835.86	1203.15 ± 620.46
DMS Correct latency (4 s delay)	1352.25 ± 803.33	1169.76 ± 781.03
DMS Correct latency (all delays)	1361.34 ± 617.77	1123.98 ± 623.24
DMS Correct latency (simultaneous)	747.20 ± 541.31	812.20 ± 394.15
DMS Median correct latency	3473.00 (1095.63)	2924.00 (999.50)
DMS Median correct latency (0 s delay)	2926.25 (1047.00)	2706.25 (1268.13)
DMS Median correct latency (12 s delay)	3535.75 (1155.75)	3348.00 (1319.50)
DMS Median correct latency (4 s delay)	4264.50 (1845.00)	3093.00 (2013.00)
DMS Median correct latency (all delays)	3740.50 (1254.63)	2896.00 (1096.00)
DMS Median correct latency (simultaneous)	3011.00 (1325.25)	2885.00 (1099.50)
DMS Mean correct latency	3586.84 ± 833.47	3606.9 ± 1542.73
DMS Mean correct latency (0 s delay)	3417.07 ± 1021.86	3441.5 ± 1446.84
DMS Mean correct latency (12 s delay)	3905.54 ± 1461.52	3844.02 ± 1894.79
DMS Mean correct latency (4 s delay)	4138.2 ± 1245.67	3881.77 ± 1939.08
DMS Mean correct latency (all delays)	3825.89 ± 949.7	3784.71 ± 1704.98
DMS Mean correct latency (simultaneous)	2987.015 ± 754.12	3142.698 ± 1339.82
DMS Percent correct (0 s delay)	100 (20)	100 (20)
DMS Percent correct (12 s delay)	80 (40)	80 (20)
DMS Percent correct (4 s delay)	90 (20)	80 (40)
DMS Percent correct (all delays)	87.00 (13.00)	87.00 (13.00)
DMS Percent correct (simultaneous)	100 (0)	100 (0)
DMS Total correct (0 s delay)	5.00 (1.00)	5.00 (1.00)
DMS Total correct (12 s delay)	4.00 (2.00)	4.00 (1.00)
DMS Total correct (4 s delay)	4.50 (1.00)	4.00 (2.00)
DMS Total correct (all delays)	13.00 (2.00)	13.00 (2.00)
DMS Total Errors	2.00 (2.00)	2.00 (2.00)
DMS Total Errors (All Delays)	2.00 (2.00)	2.00 (2.00)
DMS Error (incorrect colour)	0 (1.00)	1.00 (1.00)
DMS Error (all delays, incorrect colour)	0 (1.00)	1.00 (1.00)
DMS Error (Distractor)	0 (0)	0 (0)
DMS Error (all delays, distractor)	0 (0)	0 (0)
DMS Error (incorrect pattern)	2.00 (1.00)	2.00 (2.00)
DMS Error (all delays, incorrect pattern)	2.00 (1.00)	1.00 (2.00)
Motor Screening Task (MOT)		
MOT Median latency	109.77 (137.55)	138.55 (139.38)
Paired Associates Learning (PAL)		
PAL Total attempts 2 patterns	1.00 (0)	1.00 (0)
PAL Total attempts 4 patterns	2.00 (1.00)	1.00 (0)

PAL Total attempts 6 patterns	3.00 (1.50)	2.00 (2.00)
PAL Total attempts 8 patterns	4.00 (2.00)	3.50 (2.00)
PAL Total errors 2 patterns	0 (0)	0 (0)
PAL Total errors 4 patterns	1.00 (2.00)	0 (0)
PAL Total errors 6 patterns	4.00 (4.00)	2.50 (5.50)
PAL Total errors 8 patterns	6.00 (7.50)	8.50 (13.00)
PAL Total errors 2 shapes adjusted	0 (0)	0 (0)
PAL Total errors 4 shapes adjusted	1.00 (2.00)	0 (0)
PAL Total errors 6 shapes adjusted	4.00 (4.00)	2.50 (5.50)
PAL Total errors 8 shapes adjusted	7.00 (10)	11.00 (12.50)
Reaction Time Index (RTI)		
RTI Five-choice error score (inaccurate)	0 (0)	0 (0)
RTI Five choice error score (no response)	0 (0)	0 (0)
RTI Five choice error score (premature)	0 (0)	0 (0)
RTI Median five choice movement time	292.00 (130.50)	244.50 (59.00)
RTI Median five choice reaction time	415.50 (59.00)	396.00 (70.50)
RTI Mean five choice movement time	292.091 ± 82.544	255.142 ± 86.815
RTI Mean five choice reaction time	411.603 ± 46.920	411.581 ± 44.116
RTI Five-choice movement time: Standard Deviation	40.310 ± 17.223	37.491 ± 14.087
RTI Five-choice reaction time	47.04 (22.90)	46.05 (23.00)
RTI Simple error score (inaccurate)	0 (1.00)	0 (1.00)
RTI Simple error score (no response)	0 (0)	0 (0)
RTI Simple error score (premature)	0 (1.00)	0 (1.00)
RTI Median simple reaction time	349.00 (58.00)	333.00 (67.00)
RTI Mean simple movement time	232.699 ± 75.089	207.118 ± 79.628
RTI Mean simple reaction time	353.960 ± 38.800	350.280 ± 42.604
RTI Median simple movement time	34.32 (20.42)	25.05 (9.97)
Pattern Recognition Memory		
PRM average correct latency - Delayed	2144.31 (649.71)	1955.80 (689.36)
PRM average correct latency - Immediate	1708.91 (496.19)	1665.50 (493.60)
Rapid visual processing (RVP)		
RVP Median response latency	457.25 (98.75)	460 (68.00)
RVP Mean response latency	550.6 ± 113.53	531.99 ± 71.51
RVP Probability of false alarm	0.01 (0.02)	0 (0.01)
RVP Probability of hit	0.57 (0.19)	0.67 (0.24)
Spatial working memory (SWM)		
SWM Double errors	0 (1.00)	0 (1.00)
SWM Problem Reached	5.00 (0)	5.00 (0)
SWM Total errors	10.50 (19.75)	12.00 (10)
SWM Between errors 4 boxes	0 (2.00)	0 (0)
SWM Between errors 6 boxes	0.50 (6.25)	5.00 (6.00)
SWM Between errors 8 boxes	9.50 (13.25)	8.00 (10)
SWM Double errors 4 boxes	0 (0)	0 (0)
SWM Double errors 6 boxes	0 (0)	0 (0)
SWM Double errors 8 boxes	0 (0.25)	0 (0)
SWM Strategy (6- 8 boxes)	3.00 (3.00)	4.00 (1.00)
SWM Total errors 4 boxes	0 (2.00)	0 (0)
SWM Total errors 6 boxes	0.50 (6.25)	5.00 (6.00)
SWM Total errors 8 boxes	10 (14.00)	8.00 (10)

SWM Within errors	0 (1.00)	0 (1.00)
SWM Within errors 4 boxes	0 (0)	0 (0)
SWM Within errors 6 boxes	0 (0)	0 (0)
SWM Within errors 8 boxes	0 (1.00)	0 (1.00)

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Table S2: Digit Symbol Tests subgroup analysis

Table S2.1 Prediabetes: Digit Symbol test variables between carnosine supplementation and placebo.

Stroop test variables	Placebo			Carnosine			*P**	*P2 (Pooled)*	*P(adj)*
	Baseline	**Follow-Up**	**Δ**	**Baseline**	**Follow-Up**	**Δ**			
Score	70.54±11.48	75.33±12.94	3.92±11.18	63.78±20.04	74.78±11.58	11±14.05	0.21	0.18	0.64

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
*p-value for differences between groups estimated by independent samples t-test for change (Δ).
P2(Pooled): Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

Table S2.2 Diabetes: Digit Symbol test variables between carnosine supplementation and placebo.

Stroop test variables	Placebo			Carnosine			*P**		
	Baseline	**Follow-Up**	**Δ**	**Baseline**	**Follow-Up**	**Δ**		*P2 (Pooled)*	*P(adj)*
Score	73.17±9.02	76.33±4.55	3.17±5.49	67.00±16.57	77.10±16.34	10.1±12.53	0.23	0.19	0.64

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
*p-value for differences between groups estimated by independent samples t-test for change (Δ).
P2(Pooled): Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.
value

Table S2.3 Prediabetes: Multivariate regression analysis for the differences in change of Digit Symbol test variables between carnosine and placebo supplementation adjusted for covariates.

Digit Symbol test variables	Models	Change (Δ)						
		β	95% CI	SE	R^2	*P*	*P2 (Pooled)*	*P(adj)*
Score	Model 1	3.23	-6.24, 12.70	0.13	0.45	0.48	0.43	0.49
	Model 2	3.58	-5.93, 13.10	0.14	0.48	0.44	0.42	0.49
	Model 3	5.16	-5.15, 15.49	0.21	0.51	0.30	0.41	0.49

Model 1: Adjusted for baseline value
Model 2: Adjusted for baseline value, diabetic status
Model 3: Adjusted for baseline value, diabetic status, level of education and age.
* p-values are estimated by Analysis of Covariance (ANCOVA).
$P2_{(Pooled)}$: Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

Table S2.4 Diabetes: Multivariate regression analysis for the differences in change of Digit Symbol test variables between carnosine and placebo supplementation adjusted for covariates.

Digit Symbol test variables	Models	Change (Δ)						
		β	95% CI	SE	R^2	*P*	*P2 (Pooled)*	*P(adj)*
Score	Model 1	4.86	-6.29, 16.01	5.16	0.29	0.36	0.34	0.49

	Model 2	3.68	-8.18, 15.53	5.44	0.33	0.51	0.47	0.49
	Model 3	3.7	-8.77,16.18	5.67	0.33	0.53	0.49	0.49

Model 1: Adjusted for baseline value
Model 2: Adjusted for baseline value, diabetic status
Model 3: Adjusted for baseline value, diabetic status, level of education and age.
* p-values are estimated by Analysis of Covariance (ANCOVA).
$P2_{(Pooled)}$: Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

Table S3:Suplementary Stroop Tests

Table S3.1: STROOP test variables between carnosine supplementation and placebo.

Stroop test variables	Placebo			Carnosine			*P**	
	Baseline	Follow-Up	Δ	Baseline	Follow-Up	Δ		$P_{(adj)}$
Off Time (s)	66.81 ± 7.90	64.22 ± 10.44	-2.45 ± 12.87	70.14 ± 13.62	72.24 ±10.01	0.56 ± 7.84	0.05	0.75
Total number of runs (Stroop Off)	5.69 ± 0.87	5.53 ±1.36	-0.067 ± 1.33	5.53 ± 0.64	5.54 ± 0.66	-0.77 ± 0.95	0.99	0.99
Total number of runs (Stroop On)	5.81 ± 1.42	5.87 ± 0.99	0 ± 1.41	5.67 ± 0.82	6 ± 1.08	0.31 ± 1.11	0.74	0.83

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
* p-value for differences between groups estimated by independent samples t-test for change **(Δ).**
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.
value

Table S3.2: Multivariate regression analysis for the differences in change of STROOP test variables between carnosine and placebo supplementation adjusted for covariates.

STROOP test variables	Models	Change (Δ)						
		β	95% CI	SE	R^2	*P**	*P2 (Pooled)*	P(adj)
Total number of runs (Stroop Off)	Model 1	-0.02	-0.90, 0.85	0.43	0.19	0.96	1.00	1.00
	Model 2	-0.05	-0.95, 0.85	0.43	0.20	0.91	0.95	0.99
	Model 3	-0.17	-1.12, 0.77	0.46	0.23	0.71	0.94	1.00
	Model 4	-0.07	-1.06, 0.92	0.48	0.25	0.88	0.86	0.97
Total number of runs (Stroop On)	Model 1	0.22	-0.58, 1.02	0.39	0.44	0.58	0.71	0.96
	Model 2	0.20	-0.62, 1.02	0.40	0.44	0.62	0.75	0.97
	Model 3	-0.07	-0.87, 0.73	0.39	0.55	0.86	0.85	0.98
	Model 4	--0.22	-1.04, 0.60	0.39	0.58	0.58	0.95	0.99

Model 1: Adjusted for baseline value
Model 2: Adjusted for baseline value, diabetic status
Model 3: Adjusted for baseline value, diabetic status and level of education
Model 4: Adjusted for baseline value, diabetic status, level of education and age.
* p-values are estimated by Analysis of Covariance (ANCOVA).
$P2_{(Pooled)}$: Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

(β) Unstandardized beta-coefficient
(CI) confidence interval
(SE) standard error, and
(R^2) R-square value

Table S3.3: Subgroup analysis

Table S3.3.1 Prediabetes: STROOP test variables between carnosine supplementation and placebo.

Stroop test variables	Placebo			Carnosine			*P**	P(adj)
	Baseline	Follow-Up	Δ	Baseline	Follow-Up	Δ		
Off Time (s)	67.74 ± 9.66	62.23 ± 12.66	-5.4 ± 16.95	73.03 ± 13.18	75.05±11.30	-2.27 ± 2.65	0.67	0.90
On Time(s)	74.723 ± 9.36	82.59 ± 24.92	7.86 ± 23.42	88.052 ±18.92	98.25 ± 25.97	10.19 ± 27.36	0.85	0.91
Off Time + On Time(s)	142.46 ± 18.26	180.56 ± 130.24	38.10 ± 130.64	161.078 ± 31.56	214.22 ±101.19	53.14 ± 111.41	0.80	0.90
On time – Off time(s)	6.99 ± 5.30	12.96 ± 19.31	5.52 ± 19.57	15.03 ± 8.22	12.77 ± 4.00	-2.00 ± 6.560	0.39	0.73
Successful times x attempts (Off)	377.512 ± 86.49	329.47 ± 122.49	-34.88 ± 150.34	414.24 ± 113.48	437.55 ± 84.07	-14.52 ± 92.29	0.78	0.90
Successful times x attempts (On)	455.93 ± 125.24	423.49 ± 85.94	-44.26 ± 112.73	470.05±98.02	505.21±128.93	37.87 ± 88.31	0.16	0.64
Total number of runs (Stroop Off)	5.56 ± .88	5.13 ± 1.46	-0.25 ± 1.67	5.13 ± 1.46	5.83 ± 0.75	-2.7756e-17 ± 1.095	0.76	0.90
Total number of runs (Stroop On)	6.11 ± 1.62	5.63 ± .74	-0.63 ±1.506	5.50 ± 0.76	6.17 ±1.47	0.67 ± 0.816	0.08	0.48

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
* p-value for differences between groups estimated by independent samples t-test for change **(Δ).**
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.
value

S3.3.2 Diabetes: Multivariate regression analysis for the differences in change of STROOP test variables between carnosine and placebo supplementation adjusted for covariates.

Stroop test variables	Placebo			Carnosine			*P**	*P(adj)*
	Baseline	Follow-Up	Δ	Baseline	Follow-Up	Δ		
Off Time (s)	66.3 ± 5.56	66.0 ± 8.05	-0.303 ± 4.6	66.83 ± 14.36	69.83 ± 8.91	2.99 ± 10.10	0.49	0.87
On Time(s)	78.68 ± 8.13	82.18 ± 11.28	3.50 ± 7.74	78.05 ± 11.46	80.67 ± 12.52	2.63 ± 7.08	0.73	0.90
Off Time + On Time(s)	144.95 ± 12.100	148.15 ± 19.104	3.20 ± 11.39	144.88 ± 24.97	150.50 ± 21.13	5.62 ± 15.10	0.82	0.90
On time – Off time(s)	12.40 ± 6.91	16.20 ± 4.38	3.80 ± 5.65	11.214 ± 7.19	10.84 ± 5.06	-0.37 ± 8.73	0.28	0.64
Successful times x attempts (Off)	396.52 ± 57.97	405.57 ± 84.60	9.05 ± 64.46	361.59 ± 74.51	366.96 ± 36.83	5.36 ± 62.49	0.91	0.92
Successful times x attempts (On)	432.47 ± 102.85	505.44 ± 116.46	9.05 ± 64.46	452.44 ± 63.59	473.18 ± 93.17	5.36 ± 62.49	0.29	0.64
Total number of runs (Stroop Off)	6.00 ± 0.89	6.17 ± 1.17	0.17 ± 0.98	5.43 ± 0.54	5.29 ± 0.49	-0.14 ± 0.90	0.56	0.90
Total number of runs (Stroop On)	5.50 ± 1.23	6.17 ± 1.33	0.67 ± 1.03	5.86 ± 0.90	5.86 ± 0.69	0 ± 1.29	0.30	0.64

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
*p-value for differences between groups estimated by independent samples t-test for change **(Δ).**
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.
value

Table S3.3.3 Prediabetes: Multivariate regression analysis for the differences in change of STROOP test variables between carnosine and placebo supplementation adjusted for covariates.

STROOP test variables	Models	Change (Δ)						
		β	95% CI	SE	R^2	*P*	*P2 (Pooled)*	*P(adj)*
Off Time	Model 1	8.94	-1.30, 0.09	7.09	0.26	0.23	0.07	0.41
	Model 2	8.83	-8.45, 26.11	7.75	0.26	0.28	0.07	0.41
	Model 3	7.72	-12.28, 27.72	8.84	0.27	0.41	0.26	0.41

Model 1: Adjusted for baseline value

Model 2: Adjusted for baseline value, diabetic status
Model 3: Adjusted for baseline value, diabetic status, level of education and age.
* p-values are estimated by Analysis of Covariance (ANCOVA).
P2(Pooled): Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

(β) Unstandardized beta-coefficient
(CI) confidence interval
(SE) standard error, and
(R^2) R-square value

S3.3.4 Diabetes: Multivariate regression analysis for the differences in change of STROOP test variables between carnosine and placebo supplementation adjusted for covariates.

STROOP test variables	Models	Change (Δ)						
		β	95% CI	SE	R^2	*P*	*P2 (Pooled)*	*P(adj)*
Off Time	Model 1	2.50	-5.32, 10.33	3.56	0.37	0.50	0.48	0.5
	Model 2	3.12	-5.25, 11.48	3.75	0.40	0.43	0.41	0.5
	Model 3	3.18	-5.46, 11.82	3.82	0.44	0.43	0.41	0.5

Model 1: Adjusted for baseline value
Model 2: Adjusted for baseline value, diabetic status
Model 3: Adjusted for baseline value, diabetic status, level of education and age.
* p-values are estimated by Analysis of Covariance (ANCOVA).
P2(Pooled): Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

(β) Unstandardized beta-coefficient
(CI) confidence interval
(SE) standard error, and
(R^2) R-square value

Table S4: Trail Making Test subgroup analysis

Table S4.1 Prediabetes: Trail Making Test variables between carnosine supplementation and placebo.

Trail Making Test variables	Placebo			Carnosine			*P**	P(adj)
	Baseline	Follow-Up	Δ	Baseline	Follow-Up	Δ		
Trail making test A (seconds)	17.5±5.24	18.54±4.47	1.04±5.59	16.01±5.30	16.16±4.17	0.14±4.34	0.69	0.90
Trail making test B (seconds)	59.24±37.28	71.29±40.44	11.08±23.99	65.96±45.13	50.33±9.81	-15.62±46.28	0.09	0.48
B:A (seconds)	3.56±1.92	4.02±2.37	0.36±1.65	4.01±1.94	3.27 ±0.94	-0.74±2	0.18	0.64

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
* p-value for differences between groups estimated by independent samples t-test for change **(Δ).**
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.
value

Table S4.2 Diabetes: Trail Making Test test variables between carnosine supplementation and placebo.

Trail Making Test variables	Placebo			Carnosine			*P**	P(adj)
	Baseline	Follow-Up	Δ	Baseline	Follow-Up	Δ		
Trail making test A (seconds)	14.6±3.66	16.08±4.79	1.48±2.97	17.36±4.73	15.26±5.51	-2.10±6.68	0.24	0.64
Trail making test B (seconds)	54.32±14.02	46.33±16.68	-7.98±17	60.91±36.50	43.98±11.44	-16.93±41.15	0.62	0.90
B:A (seconds)	3.78±0.70	3±1.09	-0.78±1.25	3.56±1.98	3.01±0.66	-0.55±1.84	0.77	0.90

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
* p-value for differences between groups estimated by independent samples t-test for change **(Δ).**
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.
value

S4.3 <u>Prediabetes:</u> Multivariate regression analysis for the differences in change of STROOP test variables between carnosine and placebo supplementation adjusted for covariates.

Trail Making Test variables	Models	Change (Δ)						
		β	95% CI	SE	R^2	*P**	*P2 (Pooled)*	P(adj)
Trail making test A (seconds)	Model 1	-1.85	-5.41, 1.72	1.71	0.43	0.29	0.24	0.31
	Model 2	-1.83	-5.45, 1.80	1.74	0.44	0.31	0.19	0.31
	Model 3	-3.2	-6.34, -0.07	1.5	0.64	0.05	0.02	0.16
Trail making test B (seconds)	Model 1	-22.96	-47.93, 2	11.93	0.49	0.07	0.06	0.16
	Model 2	-23.28	-48.54, 1.98	12.02	0.51	0.07	0.06	0.16
	Model 3	-24.69	-51.05, 1.68	12.5	0.52	0.07	0.06	0.16
B:A (seconds)	Model 1	-.954	-2.469, 0.56	0.72	0.26	0.20	0.24	0.31
	Model 2	-.964	-2.51, 0.59	0.74	0.27	0.21	0.25	0.31
	Model 3	-.905	-2.54, 0.73	0.78	0.28	0.26	0.3	0.31

Model 1: Adjusted for baseline value
Model 2: Adjusted for baseline value, diabetic status
Model 3: Adjusted for baseline value, diabetic status, level of education and age.
* p-values are estimated by Analysis of Covariance (ANCOVA).
P2(Pooled): Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

S4.4 <u>Diabetes:</u> Multivariate regression analysis for the differences in change of STROOP test variables between carnosine and placebo supplementation adjusted for covariates.

STROOP test variables	Models	Change (Δ)						
		β	95% CI	SE	R^2	*P**	*P2 (Pooled)*	P(adj)

Trail making test A (seconds)	Model 1	-1.86	-7.78, 4.07	2.76	0.3	0.51	0.5	0.92
	Model 2	-1.28	-7.49, 4.94	2.88	0.34	0.67	0.66	0.92
	Model 3	-1.41	-7.91, 5.10	2.99	0.35	0.65	0.64	0.92
Trail making test B (seconds)	Model 1	-2.04	-17.15, 13.08	7.05	0.86	0.78	0.77	0.92
	Model 2	-0.89	-16.88, 15.1	7.4	0.86	0.91	0.9	0.92
	Model 3	-1	-16.75, 14.74	7.23	0.88	0.89	0.89	0.92
B:A (seconds)	Model 1	0.04	-0.86, 0.95	0.42	0.77	0.92	0.92	0.92
	Model 2	0.08	-0.9, 1.07	0.45	0.77	0.86	0.85	0.92
	Model 3	0.06	-0.93, 1.05	0.45	0.79	0.89	0.89	0.92

Model 1: Adjusted for baseline value
Model 2: Adjusted for baseline value, diabetic status
Model 3: Adjusted for baseline value, diabetic status, level of education and age.
* p-values are estimated by Analysis of Covariance (ANCOVA).
$P2_{(Pooled)}$: Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

Table S5.1: Supplementary CANTAB tests results for differences between carnosine supplementation and placebo.

CANTAB test variables	**Placebo (n=19)**			**Carnosine (n=20)**			P^*	
	Baseline	**Follow-Up**	**Δ**	**Baseline**	**Follow-Up**	**Δ**		$P_{(adj)}$
DMS Percent Correct (0 Second Delay)	92.00±10.05	84±17	-8.00±24.62	89.52±22.47	90±15	0.48±28.98	0.35	0.70
DMS Percent Correct (4 Second Delay)	87.00±14.90	90±15	4.00±16.67	80.95±18.41	85±18	3.81±27.29	0.98	1.00
DMS Percent Correct (12 Second Delay)	75.00±21.40	87±17	12.00±26.28	81.90±15.37	81±15	-0.95±23.22	0.10	0.46
PALTA 4 (Paired Associates Learning Total Attempts 4 Patterns)	1.58±0.61	1.24±0.70	-0.32±.89	1.25±0.72	1.45±0.83	0.21±0.71	0.05	0.59
PALTEA 8 (PAL Total errors 8 shapes adjusted)	10.05±8.38	8.66±8.41	-1.37±6.12	12.8±9.11	8.85±6.86	-3.79±9.29	0.35	0.67
SWMBE4 (SWM Between Errors 4 Boxes)	0.80±0.95	0.71±1.38	-0.05±1.36	0.57±1.25	0.33±0.73	-0.24±1.18	0.64	0.84

SWMBE6 (Spatial Working Memory - between errors 6 boxes)	3.30±3.90	3.50±3.22	0.20±3.81	3.81±3.17	2.00±2.68	-1.81±3.27	0.08	0.53
SWMBE8 (Spatial Working Memory - between errors 8 boxes)	7.70±6.43	8.10±6.89	0.40±7.37	7.95±5.31	7.10±5.97	-0.86±6.94	0.58	0.83

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
* p-value for differences between groups estimated by independent samples t-test for change **(Δ).**
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.
value

Table S5.2: Subgroup analysis

Table S5.2.1 Prediabetes: CANTAB test variables between carnosine supplementation and placebo.

CANTAB test variables	Placebo			Carnosine			*P**	P(adj)
	Baseline	Follow-Up	Δ	Baseline	Follow-Up	Δ		
PALFAMS (Paired Associates Learning First attempt memory score)	12.53 ± 3.04	14.87 ± 3.04	2.33 ± 2.41	12.56 ± 4.19	10.22 ± 4.06	-3.00 ± 3.70	0.001	0.03
PALMETS (Paired Associates Learning Mean Errors to Success)	2.13 ± 1.46	1.13 ± 0.74	-1.00 ± 1.46	1.44 ± 1.88	2.78 ± 1.39	1.38 ± 1.60	0.002	0.03
PALTA (Paired Associates Learning Total Attempts)	8.47 ± 1.85	6.93 ± 1.87	-1.53 ± 1.36	8.00 ± 2.12	8.67 ± 1.58	0.63 ± 2.50	0.013	0.14
PRMPCD (Pattern Recognition Memory Percent Correct Delayed)	95.24 ± 7.10	93.33 ± 7.84	-2.38 ± 8.29	85.83 ± 14.19	81.67 ± 14.06	-4.16 ± 19.35	0.76	0.90

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
* p-value for differences between groups estimated by independent samples t-test for change **(Δ).**

P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.
value

Table S5.2.2 <u>Prediabetes:</u> Multivariate regression analysis for the differences in change of CANTAB test variables between carnosine and placebo supplementation adjusted for covariates.

CANTAB tests	Models	Change (Δ)						
		β	95% CI	SE	R^2	*P*	*P2 (pooled)*	*P(adj)*
PALFAMS (Paired Associates Learning First attempt memory score)	Model 1	-5.30	-7.68 , -2.92	1.14	0.58	<0.001	<0.001	0.58
	Model 2	-5.31	-7.76 , -2.856	1.17	0.58	<0.001	<0.001	0.49
	Model 3	-5.25	-7.846 , -2.650	1.24	0.58	<0.001	<0.001	0.48
PALMETS (Paired Associates Learning Mean Errors to Success)	Model 1	1.92	1.037, 2.803	0.42	0.77	<0.001	<0.001	0.18
	Model 2	1.92	1.033, 2.811	0.43	0.78	<0.001	<0.001	0.18
	Model 3	1.90	0.952, 2.855	0.45	0.78	<0.001	<0.001	0.18
PALTA (Paired Associates Learning Total Attempts)	Model 1	1.92	0.494, 3.35	0.68	0.49	0.011	0.006	0.48
	Model 2	1.98	0.706, 3.25	0.61	0.62	0.004	0.003	0.36
	Model 3	1.94	0.574, 3.298	0.65	0.62	0.008	0.005	0.36
PRMPCD (Pattern Recognition Memory Percent Correct Delayed)	Model 1	-9.67	-20.05, 0.72	4.99	0.41	0.07	0.032	0.49
	Model 2	-9.97	-19.98, 0.03	4.80	0.48	0.05	0.023	0.40
	Model 3	-9.87	-20.19, 0.45	4.93	0.48	0.06	0.029	0.40
SWMS (Spatial Working Memory Strategey)	Model 1	-0.06	-1.82, 2.14	.794	-0.09	0.94	0.94	1.0
	Model 2	-0.05	-1.74, 1.63	.810	-0.13	0.95	0.95	1.0
	Model 3	-0.02	-1.86, 1.53	.814	-0.13	0.84	0.84	1.0
	Model 1	-2.22	-9.31, 4.86	3.42	0.12	0.52	0.52	0.84
	Model 2	-2.03	-8.38. 4.33	3.06	0.29	0.51	0.51	0.84

SWMBE (Spatial Working Memory – Between Errors)	Model 3	-2.25	-8.8, 4.31	3.14	0.27	0.48	0.48	0.83
SWMBE6 (Spatial Working Memory Between Errors – 6 trials)	Model 1	-0.58	-2.98, 1.8	1.15	0.26	0.62	0.61	0.99
	Model 2	-0.52	-2.64,1.6	1.02	0.42	0.62	0.61	0.99
	Model 3	-0.63	-2.79, 1.54	1.04	0.41	0.55	0.55	0.84

Model 1: Adjusted for baseline value
Model 2: Adjusted for baseline value, diabetic status
Model 3: Adjusted for baseline value, diabetic status, level of education and age.
* p-values are estimated by Analysis of Covariance (ANCOVA).
$P2_{(Pooled)}$: Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

(β) Unstandardized beta-coefficient
(CI) confidence interval
(SE) standard error, and
(R^2) R-square value

Table S5.2.3 Diabetes: CANTAB test variables between carnosine supplementation and placebo.

CANTAB test variables	**Placebo (n=)**			**Carnosine ()**			***P****	***P(adj)***
	Baseline	**Follow-Up**	**Δ**	**Baseline**	**Follow-Up**	**Δ**		
PALFAMS (Paired Associates Learning First attempt memory score)	11.00 ± 2.83	13.00 ± 5.22	1.25 ± 5.91	12.82 ± 4.14	14.36 ± 2.84	1.55 ± 4.74	0.92	0.92
PALMETS (Paired Associates Learning Mean Errors to Success)	1.75 ± 1.50	1.50 ± 1.52	-1.00 ± 1.83	1.55 ± 1.29	2.00 ± 1.26	0.45 ± 1.04	0.07	0.14

PALTA (Paired Associates Learning Total Attempts)	7.75 ± 1.50	6.67 ± 1.63	-1.50 ± 2.08	7.36 ± 1.75	6.82 ± 1.25	-0.55 ± 1.69	0.38	0.51
PRMPCD (Pattern Recognition Memory Percent Correct Delayed)	93.75 ± 7.98	93.33 ± 14.91	8.33 ± 8.34	88.33 ± 9.78	87.12 ± 13.62	-2.50 ± 15.74	0.29	0.46

(Δ): follow-up - baseline values.
All data are represented as Mean ± Standard Deviation.
*p-value for differences between groups estimated by independent samples t-test for change **(Δ).**
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.
value

Table S5.2.4 <u>Diabetes:</u> Multivariate regression analysis for the differences in change of CANTAB test variables between carnosine and placebo supplementation adjusted for covariates.

CANTAB tests	**Models**	**Change (Δ)**						
		β	95% CI	SE	R^2	*P*	*P2 (pooled)*	*P (adj)*
PALFAMS (Paired Associates Learning First attempt memory score)	Model 1	1.78	-3.52, 7.09	2.43	0.40	0.48	0.59	0.9
	Model 2	1.79	-4.01, 7.59	2.63	0.40	0.51	0.62	1.00
	Model 3	1.72	-4.47, 7.90	2.78	0.40	0.55	0.48	0.80
PALMETS (Paired Associates Learning Mean Errors to Success)	Model 1	1.34	-0.03, 2.71	0.63	0.49	0.05	0.31	0.61
	Model 2	1.50	0.07, 2.93	0.65	0.53	0.04	0.24	0.6
	Model 3	1.55	0.20, 2.89	0.60	0.63	0.03	0.27	0.6
	Model 1	0.66	-1.00, 2.32	0.76	0.54	0.40	0.67	0.97
	Model 2	0.98	-0.62, 2.58	0.73	0.64	0.21	0.38	0.78

PALTA (Paired Associates Learning Total Attempts)	Model 3	1.09	0.08, 2.10	0.45	0.87	0.04	0.41	0.79
PRMPCD (Pattern Recognition Memory Percent Correct Delayed)	Model 1	-13.66	-32.74, 5.43	8.56	0.38	0.14	0.46	0.79
	Model 2	-15.91	-35.58, 3.77	8.70	0.45	0.10	0.24	0.6
	Model 3	-15.35	-36.55, 5.85	9.19	0.46	0.13	0.19	0.58
SWMS (Spatial Working Memory Strategey)	Model 1	-0.98	-4.49, 2.54	1.63	0.38	0.56	0.55	0.84
	Model 2	-1.17	-4.93, 2.59	1.73	0.34	0.51	0.5	0.83
	Model 3	-0.79	-4.4, 2.65	1.57	0.46	0.62	0.44	0.77
SWMBE (Spatial Working Memory – Between Errors)	Model 1	-5.72	-14.92, 3.48	4.26	0.31	0.20	0.18	0.58
	Model 2	-6.14	-15.96, 3.68	4.51	0.26	0.20	0.17	0.58
	Model 3	-5.29	-14.95, 4.37	4.39	0.31	0.25	0.15	0.57
SWMBE6 (Spatial Working Memory Between Errors – 6 trials)	Model 1	-2.65	-5.46. 0.15	1.30	0.61	0.06	0.02	0.36
	Model 2	-2.46	-5.43, 0.51	1.36	0.01	0.1	0.04	0.48
	Model 3	-2.40	-5.51, 0.75	1.43	0.003	0.12	0.05	0.49

Model 1: Adjusted for baseline value
Model 2: Adjusted for baseline value, diabetic status
Model 3: Adjusted for baseline value, diabetic status, level of education and age.
* p-values are estimated by Analysis of Covariance (ANCOVA).
$P2_{(Pooled)}$: Pooled p-values estimated by ANCOVA after 5 imputations using predictive mean matching to replace missing data.
P(adj): Adjusted p-value for false discovery rate using Benjamini-Hochberg correction method.

(β) Unstandardized beta-coefficient
(CI) confidence interval
(SE) standard error, and
(R^2) R-square valu