Supplemental Table S1. Characteristics and cognitive performance of the participating patients with type 2 diabetes

Number of patients	37
Demographics	
Age (years)	66.7±8.7
Gender, men (%)	34 (92)
Formal education (years)	11.4±4.4
Diabetes characteristics	
Duration of type 2 diabetes (years)	8.3 (3.4 – 11.1)
HbA1c (%) (mmol/mol)	6.9 (6.6 – 7.3) (52 (49 - 56)
Fasting plasma glucose (mmol/L) (mg/dL)	7.4±1.1 (133.9±20.4)
Medication	
SU or glinide	15 (41)
Statins	25 (68)
Antihypertensive therapy	29 (78)
Anti-inflammatory drugs*	26 (70)

Cardiovascular risk factors

Systolic blood pressure (mmHg)	135±16
Diastolic blood pressure (mmHg)	79±7
Total cholesterol (mmol/L) (mg/dL)	4.3±0.9 (167.0±35.5)
LDL-cholesterol (mmol/L) (mg/dL)	2.3±0.8 (90.5±31.7)
HDL-cholesterol (mmol/L) (mg/dL)	1.2±0.3 (46.5±11.2)
Triglycerides (mmol/L) (mg/dL)	1.4 (1.0 – 2.1) (120.9 (91.0 – 183.1)
BMI (kg/m^2)	30.2±3.6
Waist circumference (cm)	109±10
Smoking:	
Never smoked	8 (22)
Ex-smoker	24 (65)
Current smoker	5 (13)
Urine-albumine-to-creatinine ratio:	
< 30 mg/g (normal)	29 (78)
30-300 mg/g (elevated)	5 (14)
>= 300 mg/g (high)	3 (8)

Macrovascular disease

Myocardial infarction, coronary artery disease or previous PCI or CABG	10 (27)
Cerebrovascular disease	8 (22)
Peripheral arterial occlusive disease	3 (8)

Cognitive performance

MMSE	29 (27 – 30)
RTI median five choice reaction time (ms)	346 (313 – 397)
AST median reaction latency (ms)	840 (772 – 1037)
PAL total errors adjusted (errors)	20 (11 – 33)
SWM between errors (4-8 boxes) (errors)	19±10
RVP A' (range 0.00 – 1.00)	0.88±0.05

Data are presented as mean±standard deviation or n (%) or median (interquartile range)

CV, cardiovascular risk; SU, sulfonylurea; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CES-D, Center for Epidemiological Studies Depression Scale; MMSE, mini-mental state examination; RTI, reaction time; AST, attention-switching task; PAL, paired associates learning; SWM, spatial working memory; RVP, rapid visual information processing

* Use of non-steroidal anti-inflammatory drugs or immuno-modulating drugs (i.e. corticosteroids)

Supplemental Table S2. Association between biomarkers of oxidation and endothelial function and cognition, additional adjustments for other covariates

	Standardized (β) and unstandardized (B) regression coefficients (95% confidence interval of B)	p-value	Standardized (β) and unstandardized (B) regression coefficients (95% confidence interval of B)	p-value	Standardized (β) and unstandardized (B) regression coefficients (95% confidence interval of B)	p-value
Analyses adjusted for age, gender and years of formal education (basic model as in table 1)*						
	Psychomotor speed†‡		*Mental flexibility†‡*		*Attention*	
Oxidation						
8-iso PGF₂ₐ†			β -0.47	**0.005**	β -0.34	**0.03**
			B -4.52		B -3.31	
			(-7.60 to -1.45)		(-6.36 to -0.26)	
Endothelial function						
ADMA	β -0.39	**0.02**			β -0.34	**0.046**
	B -8.01				B -7.08	

	Psychomotor speed	Mental flexibility	Attention
	(-14.67 to -1.35)		(-14.03 to -0.13)

Adjusted for basic model plus HbA1c

	Psychomotor speed†‡	Mental flexibility†‡	Attention
Oxidation			
8-iso PGF$_{2\alpha}$†		β -0.48 **0.003**	β -0.34 **0.038**
		B -4.70	B -3.32
		(-7.73 to -1.68)	(-6.43 to -0.20)
Endothelial function			
ADMA	β -0.40 **0.018**		β -0.34 0.05
	B -8.22		B -7.08
	(-14.92 to -1.52)		(-14.17 to 0.006)

Adjusted for basic model plus vascular risk factors§

	Psychomotor speed†‡	Mental flexibility†‡	Attention
Oxidation			

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	Psychomotor speed†‡		Mental flexibility†‡		Attention	
8-iso PGF$_{2\alpha}$†			β -0.44	**0.010**	β -0.38	**0.025**
			B -4.32		B -3.68	
			(-7.53 to -1.10)		(-6.86 to -0.50)	
Endothelial function						
ADMA	β -0.43	**0.012**			β -0.35	0.052
	B -8.77				B -7.12	
	(-15.48 to -2.06)				(-14.29 to 0.06)	

Adjusted for basic model plus macrovascular disease‖

	Psychomotor speed†‡		Mental flexibility†‡		Attention	
Oxidation						
8-iso PGF$_{2\alpha}$†			β -0.46	**0.007**	β -0.35	**0.037**
			B -4.43		B -3.33	
			(-7.54 to -1.32)		(-6.45 to -0.22)	
Endothelial function						
ADMA	β -0.39	**0.022**			β -0.34	0.05

| | B -8.01 | | B -7.08 | |
| | (-14.78 to -1.24) | | (-14.16 to -0.006) | |

Adjusted for basic model plus use of anti-inflammatory drugs{

	Psychomotor speed†‡	Mental flexibility†‡		Attention	
Oxidation					
8-iso PGF$_{2\alpha}$†		β -0.52	**0.002**	β -0.34	**0.041**
		B -5.01		B -3.30	
		(-8.00 to -2.02)		(-6.46 to -0.14)	
Endothelial function					
ADMA	β -0.43	**0.015**		β -0.36	0.052
	B -8.93			B -7.44	
	(-15.98 to -1.88)			(-14.96 to 0.07)	

Adjusted for basic model plus 8-iso PGF$_{2\alpha}$

	Psychomotor speed†‡	Mental flexibility†‡		Attention	

Endothelial function

	Psychomotor speed†‡	Mental flexibility†‡	Attention
ADMA	β -0.35 **0.033** B -7.29 (-13.96 to -0.62)		β -0.30 0.07 B -6.12 (-12.84 to 0.60)
Adjusted for basic model plus ADMA			
Oxidation			
8-iso PGF$_{2\alpha}$†		β -0.45 **0.008** B -4.41 (-7.57 to -1.25)	β -0.30 0.055 B -2.91 (-5.89 to 0.06)

8-iso PGF$_{2\alpha}$, 8-iso prostaglandin F$_{2\alpha}$; ADMA, asymmetric dimethyl arginine

* β, B and p-values are based on models adjusted for age, gender and years of formal education

† Variable was log-transformed prior to regression analyses because of non-normal distribution.

‡ Z-scores were negated (i.e. multiplied by -1), so that in all analyses higher values for cognitive scores reflect better performance

§ Vascular risk factor count, with one point for each risk factor, according to the modified NCEP-ATPIII criteria: adiposity (defined as waist circumference >102 cm (male), >88 cm (female), hypertension (defined as use of anti-hypertensive treatment or arterial pressure ≥ 130/85 mmHg), triglycerides > 1.70 μmol/ L, and HDL cholesterol < 1.03 μmol/L (male), < 1.29 μmol/ L (female) (9). Smoking ever (one point) was also included.

|| Presence of macrovascular disease defined as myocardial infarction, coronary artery disease or previous percutaneous coronary intervention, cerebrovascular disease or peripheral arterial occlusive disease

{ Use of non-steroidal anti-inflammatory drugs or immuno-modulating drugs (i.e. corticosteroids)