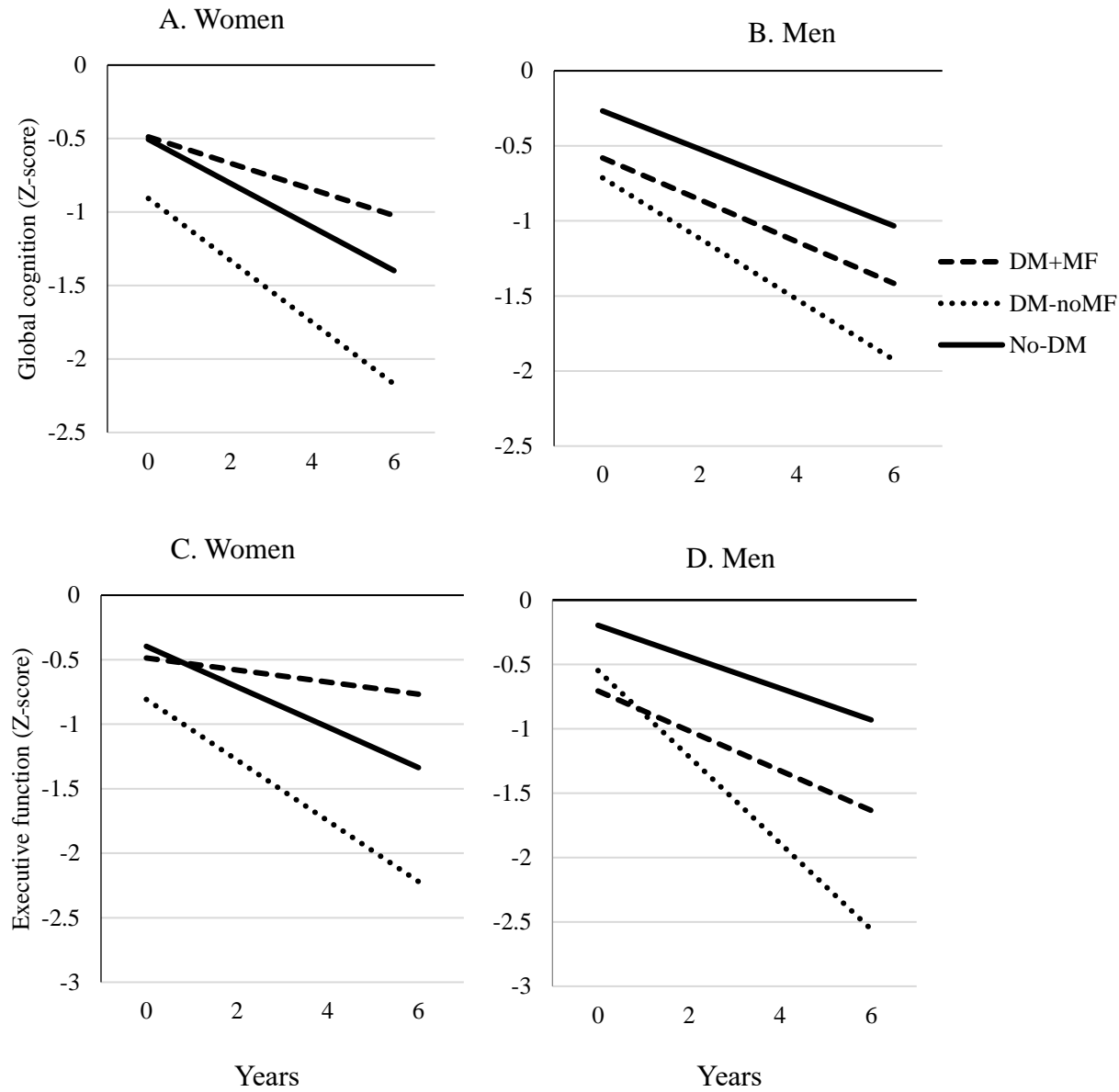


Supplementary Figure 1: Sex-stratified global cognition and executive function trajectories over 6 years for participants without diabetes, compared to those with diabetes receiving metformin or no metformin treatment.



Supplementary Table 1: Metformin use in the elderly with diabetes: relationships at baseline. The Sydney Memory and Ageing Study.

Measure	Group difference	Model 1 ^a			Model 2 ^b		
		B	95% CI	p	B	95%CI	p
Global cognition	Baseline score of DM+MF	-0.84	(-1.13, -0.54)	<0.001	-0.56	(-0.94, -0.19)	0.003
	DM-noMF vs. DM+MF	-0.43	(-0.85, 0.01)	0.052	-0.35	(-0.85, 0.15)	0.17
	no-DM vs. DM+MF	0.08	(-0.22, 0.38)	0.61	0.07	(-0.26, 0.41)	0.67
Memory	Baseline score of DM+MF	-0.79	(-1.05, -0.53)	<0.001	-0.80	(-1.14, -0.45)	<0.0001
	DM-noMF vs. DM+MF	-0.39	(-0.77, -0.01)	0.047	-0.29	(-0.76, 0.17)	0.22
	no-DM vs. DM+MF	-0.07	(-0.33, 0.20)	0.63	0.04	(-0.27, 0.35)	0.82
Attention / speed	Baseline score of DM+MF	-0.44	(-0.72, -0.17)	0.002	-0.16	(-0.54, 0.22)	0.40
	DM-noMF vs. DM+MF	-0.42	(-0.83, -0.01)	0.046	-0.45	(-0.96, 0.06)	0.08
	no-DM vs. DM+MF	0.003	(-0.29, 0.29)	0.99	0.001	(-0.34, 0.34)	0.99
Executive function	Baseline score of DM+MF	-0.67	(-0.98, -0.39)	<0.001	-0.58	(-0.98, -0.19)	0.004
	DM-noMF vs. DM+MF	-0.19	(-0.63, 0.27)	0.44	-0.20	(-0.74, 0.34)	0.47
	no-DM vs. DM+MF	0.16	(-0.15, 0.47)	0.31	0.20	(-0.16, 0.55)	0.28
Language	Baseline score of DM+MF	-0.80	(-1.14, -0.45)	<0.001	-0.45	(-0.88, -0.02)	0.04
	DM-noMF vs. DM+MF	-0.41	(-0.91, 0.09)	0.11	-0.36	(-0.93, 0.22)	0.22
	no-DM vs. DM+MF	0.08	(-0.28, 0.43)	0.67	-0.09	(-0.47, 0.30)	0.66
Visuospatial	Baseline score of DM+MF	-0.28	(-0.53, -0.04)	0.02	-0.15	(-0.48, 0.18)	0.38
	DM-noMF vs. DM+MF	-0.13	(-0.48, 0.23)	0.49	-0.06	(-0.51, 0.39)	0.80

no-DM vs. DM+MF	0.11	(-0.14, 0.36)	0.38	0.14	(-0.15, 0.44)	0.35
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Data shown are beta coefficients (B), 95% confidence intervals, and p-values. B reflects the mean difference in cognitive test performance at baseline between the groups, adjusting for model covariates. Differences are in standardized units of the cognitive test. Specifically, the coefficient is the mean baseline cognitive test performance of the first group minus the mean baseline cognitive test performance of the second group (i.e., DM+MF), where negative values indicate the first group had poorer average baseline performance than second group.

^a Adjusted for sex and mean-centred values of age and years of education.

^b Adjusted for sex and mean-centred values of age and years of education non-English speaking background (NESB), BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking and APOEε4 genotype carriage.

Abbreviations: DM+MF: Participants with diabetes using metformin; DM-noMF: participants with diabetes but no metformin; noDM: participants without diabetes.

Supplementary Table 2. Sex-specific analyses of metformin use in the elderly with diabetes and change in cognition over 6 years. The Sydney Memory and Ageing Study.

Measure	Group difference	Sub-analysis ^{c,d}	Model 1 ^a			Model 2 ^b		
			B	CI	p	B	CI	p
Global cognition	Rate of change in DM-noMF vs. DM+MF	Female	-0.22	(-0.45, 0.01)	0.05	-0.24	(-0.48, -0.01)	0.044
		Male	-0.02	(-0.32, 0.27)	0.87	-0.13	(-0.47, 0.21)	0.47
		Sex Difference	0.20	(-0.17, 0.57)	0.29	0.12	(-0.30, 0.53)	0.58
	Rate of change in no-DM vs. DM+MF	Female	-0.11	(-0.25, 0.03)	0.12	-0.12	(-0.26, 0.02)	0.10
		Male	0.08	(-0.13, 0.30)	0.45	0.02	(-0.21, 0.26)	0.85
		Sex Difference	0.19	(-0.06, 0.44)	0.14	0.14	(-0.13, 0.42)	0.31
Memory	Rate of change in DM-noMF vs. DM+MF	Female	-0.10	(-0.29, 0.09)	0.28	-0.13	(-0.33, 0.08)	0.23
		Male	0.04	(-0.21, 0.29)	0.73	0.02	(-0.27, 0.31)	0.89
		Sex Difference	0.15	(-0.17, 0.46)	0.36	0.15	(-0.21, 0.50)	0.43
	Rate of change in no-DM vs. DM+MF	Female	-0.04	(-0.16, 0.07)	0.45	-0.07	(-0.19, 0.05)	0.27
		Male	0.12	(-0.07, 0.30)	0.21	0.03	(-0.17, 0.23)	0.77
		Sex Difference	0.16	(-0.05, 0.38)	0.14	0.10	(-0.14, 0.34)	0.40
Attention and processing speed	Rate of change in DM-noMF vs. DM+MF	Female	-0.07	(-0.31, 0.17)	0.54	-0.08	(-0.32, 0.17)	0.54
		Male	-0.07	(-0.39, 0.25)	0.66	-0.08	(-0.44, 0.28)	0.65
		Sex Difference	0.01	(-0.40, 0.40)	0.99	-0.01	(-0.44, 0.43)	0.97
	Rate of change in no-DM vs. DM+MF	Female	0.01	(-0.14, 0.16)	0.91	-0.01	(-0.16, 0.15)	0.94
		Male	-0.01	(-0.23, 0.23)	0.98	-0.02	(-0.27, 0.23)	0.88
		Sex Difference	-0.01	(-0.28, 0.26)	0.94	-0.01	(-0.31, 0.28)	0.93
Executive function	Rate of change in DM-noMF vs. DM+MF	Female	-0.27	(-0.57, 0.02)	0.07	-0.38	(-0.70, -0.05)	0.023
		Male	-0.13	(-0.52, 0.27)	0.54	-0.36	(-0.89, 0.14)	0.13
		Sex Difference	0.15	(-0.35, 0.64)	0.56	0.02	(-0.58, 0.61)	0.96
	Rate of change in no-DM vs. DM+MF	Female	-0.19	(-0.38, -0.01)	0.05	-0.22	(-0.43, -0.01)	0.038
		Male	0.09	(-0.20, 0.37)	0.55	0.06	(-0.26, 0.39)	0.70

		Sex Difference	0.28	(-0.06, 0.62)	0.11	0.28	(-0.10, 0.67)	0.15
Language	Rate of change in DM-noMF vs. DM+MF	Female	-0.12	(-0.32, 0.08)	0.25	-0.09	(-0.30, 0.12)	0.41
		Male	0.04	(-0.22, 0.30)	0.76	0.04	(-0.27, 0.34)	0.83
		Sex Difference	0.16	(-0.17, 0.49)	0.35	0.12	(-0.25, 0.50)	0.51
	Rate of change in no-DM vs. DM+MF	Female	0.02	(-0.11, 0.14)	0.80	0.02	(-0.11, 0.15)	0.73
		Male	0.09	(-0.10, 0.28)	0.37	0.11	(-0.10, 0.32)	0.31
		Sex Difference	0.07	(-0.15, 0.30)	0.54	0.08	(-0.16, 0.33)	0.50
Visuospatial	Rate of change in DM-noMF vs. DM+MF	Female	0.03	(-0.13, 0.20)	0.70	-0.02	(-0.19, 0.16)	0.86
		Male	-0.03	(-0.24, 0.19)	0.81	-0.10	(-0.35, 0.16)	0.47
		Sex Difference	-0.06	(-0.33, 0.21)	0.68	-0.08	(-0.39, 0.23)	0.62
	Rate of change in no-DM vs. DM+MF	Female	-0.06	(-0.16, 0.05)	0.29	-0.09	(-0.20, 0.02)	0.12
		Male	-0.02	(-0.17, 0.14)	0.85	-0.07	(-0.25, 0.10)	0.41
		Sex Difference	0.04	(-0.14, 0.23)	0.67	0.02	(-0.19, 0.22)	0.88

Data shown are beta coefficients (B), confidence intervals and p-values.

^a Adjusted for sex and mean-centred values of age and years of education.

^b Adjusted for sex and mean-centred values of age and years of education non-English speaking background, BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking and APOE ϵ 4 genotype carriage.

^c For rows labelled *female* and *male*, B reflects the difference between metformin groups in their average change in cognitive test performance per year, in standardized units, adjusting for model covariates, within females and males respectively. Specifically, it is the annual rate of change in cognitive test performance for the first group minus the annual rate of change in cognitive test performance for the second group (e.g. DM+MF).

Negative values indicate that the first group had a slower rate of decline in cognitive test performance, per year (in standardized units) compared to the second group.

^dFor the rows labelled *sex difference*, B reflects the difference between sexes in the annual rate of change difference between the metformin groups listed (e.g., no-DM vs. DM+MF). Specifically the difference between the B coefficient in the rows labelled *female* versus *male*.

Supplementary Table 3. Baseline descriptive data for participants with and without MRI data, compared within group.

	No diabetes					Diabetes mellitus					Diabetes mellitus				
	Declined MR		Accepted MR			Declined MR		Accepted MR			Declined MR		Accepted MR		
	Mean (SD) or N (%)	N	Mean (SD) or N (%)	N	P ^a	Mean (SD) or (%)	N	Mean (SD) or (%)	N	P ^a	Mean (SD) or (%)	N	Mean (SD) or (%)	N	P ^a
Sex (F) N, (%)	258 (60)	433	261 (56)	467	0.26	13 (38)	34	12 (55)	22	0.23	10 (29)	34	12 (36)	33	0.55
Age (years)	79.3 (4.99)	433	78.4 (4.6)	467	0.003	80.2 (4.8)	34	79.6 (4.6)	22	0.65	78.6 (4.3)	34	78.0 (4.9)	33	0.60
Education (years)	11.3 (3.3)	433	11.9 (3.6)	467	0.025	10.9 (2.8)	34	11.4 (3.5)	22	0.60	12.2 (3.6)	34	12.2 (4.3)	33	0.96
Physical measures															
Weight (kg)	72.0 (15.5)	416	71.3 (13.8)	461	0.46	78.0 (15.1)	32	74.2 (16.7)	21	0.40	84.3 (19.3)	32	81.6 (17.3)	33	0.56
BMI (kg/m ²)	27.0 (4.7)	420	26.6 (3.9)	460	0.14	29.0 (4.7)	32	27.2 (4.5)	21	0.19	30.6 (5.6)	32	29.6 (5.7)	33	0.47
Systolic BP (mmHg)	145 (22)	428	144 (20)	454	0.88	153 (24)	32	151 (18)	20	0.67	146 (19)	34	137 (20)	33	0.07
Diastolic BP (mmHg)	83 (11)	416	84 (10)	445	0.83	82 (11)	30	83 (10)	20	0.84	81 (10)	33	79 (10)	33	0.42
Prevalence of vascular diseases and dementia risk factors															
Heart disease N, (%)	172 (40)	429	118 (25)	466	0	12 (35)	34	9 (41)	22	0.672	19 (58)	33	15 (46)	33	0.33
Stroke N, (%)	24 (6)	430	10 (2)	462	0.01	3 (9)	33	2 (10)	21	0.96	2 (6)	33	0 (0)	33	0.99
TIA N, (%)	27 (6.4)	423	25 (5.4)	459	0.56	7 (21)	34	4 (20)	20	0.96	3 (9)	34	2 (6)	32	0.70
Hypertension N, (%)	269 (62)	432	258 (55)	466	0.04	27 (80)	34	13 (62)	21	0.16	27 (82)	33	24 (73)	33	0.38
Ever-smoked N, (%)	238 (55)	432	235 (51)	466	0.16	24 (71)	34	13 (59)	22	0.38	22 (65)	34	21 (64)	33	0.93

ApoEε4 N, (%)	74 (24)	312	95 (24)	399	0.98	3 (17)	18	6 (32)	19	0.30	5 (23)	22	5 (18)	28	0.67
Laboratory measures															
Total cholesterol (mmol/L)	4.7 (1.0)	316	4.9 (1.0)	408	0.01	4.3 (0.8)	18	4.3 (0.8)	19	0.99	3.9 (0.7)	22	4.0 (1.0)	29	0.46
HDL cholesterol (mmol/L)	1.5 (0.4)	315	1.5 (0.4)	407	0.26	1.3 (0.5)	18	1.1 (0.4)	19	0.25	1.1 (0.3)	22	1.3 (0.3)	29	0.17
LDL cholesterol (mmol/L)	2.8 (0.9)	315	2.9 (0.9)	407	0.03	2.5 (0.6)	17	2.5 (0.8)	19	0.99	2.0 (0.6)	21	2.2 (0.9)	28	0.50
Triglycerides (mmol/L)	1.0 (0.5)	316	1.0 (0.5)	408	0.79	1.24 (0.8)	18	1.4 (0.6)	19	0.64	1.5 (0.8)	22	1.3 (0.9)	29	0.44
C-reactive protein (mg/L)	3.1 (5.6)	315	2.8 (4.6)	409	0.45	3.3 (3.0)	17	3.0 (2.5)	19	0.71	2.3 (2.0)	22	1.6 (1.8)	29	0.24
Insulin (uU/mL)	15 (6)	307	15 (6)	395	0.30	20 (12)	15	19 (8)	19	0.94	24 (22)	22	19 (10)	28	0.30
Vitamin B12 (pmol/L)	210 (237)	308	214 (341)	386	0.86	200 (78)	16	176 (110)	18	0.46	137 (60)	21	168 (78)	28	0.14
Uric acid (mmol/L)	0.3 (0.1)	253	0.3 (0.1)	300	0.33	0.3 (0.1)	13	0.3 (0.1)	17	0.48	0.3 (0.1)	16	0.3 (0.1)	19	0.40
Cognitive domain measures (Z-scores)															
Global cognition	-0.76 (1.38)	433	-0.6 (1.38)	465	0.082	-1.65 (1.31)	34	-0.82 (0.99)	22	0.014	-0.65 (1.14)	34	-0.64 (1.27)	33	0.96
Memory	-0.51 (1.18)	429	-0.47(1.24)	463	0.627	-1.11(1.11)	33	-0.69 (1.17)	21	0.18	-0.57 (1.06)	34	-0.44 (1.14)	33	0.63
Attention and processing speed	-0.45 (1.24)	429	-0.32 (1.23)	459	0.123	-1.16 (1.17)	33	-0.53 (0.82)	22	0.03	-0.49 (1.05)	33	-0.17 (0.97)	33	0.21
Language	-0.75 (1.48)	431	-0.65 (1.54)	464	0.286	-1.62 (1.83)	34	-0.83 (1.31)	22	0.08	-0.70 (1.62)	34	-0.72 (1.3)	33	0.95
Executive function	-0.47 (1.26)	398	-0.41 (1.3)	434	0.484	-1.17 (0.97)	27	-0.54 (1.0)	20	0.035	-0.39 (1.0)	31	-0.46 (1.52)	30	0.85

Visuospatial function	-0.4 (1.12)	433	-0.26 (1.08)	466	0.057	-0.68 (1.05)	34	-0.33 (0.85)	22	0.195	-0.21 (0.93)	34	-0.37 (1.03)	33	0.51
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^a P-values from post-hoc Scheffe comparisons for continuous variables, and logistic regression for categorical variables.

Abbreviations: ApoE4 apolipoprotein E4; BMI: body mass index; BP: blood pressure; BRVT: Benton Visual Retention Test; DM+MF: participants with diabetes receiving metformin; DM-NoMF: participants with diabetes not receiving metformin; HDL: high-density lipoprotein; hs-CRP: highly sensitive C-reactive protein; LDL: low-density lipoprotein; MR: magnetic resonance imaging; noDM: Participants without diabetes; RAVLT: Rey Auditory Verbal Learning Test; TIA: transient ischaemic attack.

Supplementary Table 4. Brain volume changes over 2 years in participants with diabetes receiving metformin, compared to diabetes without metformin and no diabetes.

			Model 1 ^a			Model 2 ^b		
Outcome	Brain region	Comparison group	B	CI	p	B	CI	p
Change over time	Total brain volume	Diabetes- no metformin	0.173	(-0.12, 0.46)	0.24	0.09	(-0.22, 0.40)	0.57
		No diabetes	0.182	(-0.01, 0.37)	0.053	0.17	(-0.02, 0.36)	0.07
	Grey matter	Diabetes- no metformin	0.125	(-0.26, 0.51)	0.52	0.03	(-0.39, 0.45)	0.90
		No diabetes	0.112	(-0.13, 0.36)	0.37	0.09	(-0.16, 0.34)	0.48
	White matter	Diabetes- no metformin	0.165	(-0.17, 0.50)	0.34	0.11	(-0.26, 0.47)	0.56
		No diabetes	0.186	(-0.03, 0.40)	0.09	0.19	(-0.03, 0.41)	0.09
	Cerebrospinal fluid	Diabetes- no metformin	-0.103	(-0.56, 0.36)	0.66	0.02	(-0.46, 0.50)	0.93
		No diabetes	-0.368	(-0.66, -0.07)	0.015	-0.25	(-0.54, 0.04)	0.09
	Hippocampus	Diabetes- no metformin	-0.385	(-0.85, 0.08)	0.10	-0.48	(-0.99, 0.02)	0.06
		No diabetes	0.076	(-0.22, 0.37)	0.62	-0.01	(-0.31, 0.30)	0.99
	Parahippocampus	Diabetes- no metformin	-0.18	(-0.60, 0.25)	0.41	-0.22	(-0.69, 0.24)	0.35
		No diabetes	0.12	(-0.16, 0.39)	0.41	0.06	(-0.22, 0.34)	0.66
	Precuneus	Diabetes- no metformin	0.18	(-0.17, 0.53)	0.32	0.09	(-0.29, 0.47)	0.64
		No diabetes	0.09	(-0.13, 0.32)	0.42	0.06	(-0.17, 0.29)	0.59

Data shown are beta coefficients (B), 95% confidence intervals, and p-values for baseline brain volume and change over time among participants with diabetes receiving metformin, compared to those with diabetes not receiving metformin and those without diabetes. Beta coefficients reflect

the difference between groups in their average change in brain volume per year, in mm^3 , adjusting for the covariates specified for that model. Negative B values indicate a faster rate of decline in brain volume per year in for the labelled group (i.e., Diabetes no-metformin or No diabetes), compared to participants with diabetes receiving metformin

^a Adjusted for sex and mean-centred values of age and years of education.

^b Adjusted for sex and mean-centred values of age, body mass index, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking, years of education, non-English speaking background, intracranial volume and APOE ϵ 4 genotype carriage.