

# Supplementary Material

## The Mediating Roles of Neurobiomarkers in the Relationship Between Education and Late-Life Cognition

Supplementary Table 1. Relationships between education with memory mediated by biomarkers.

N=537	Model 1 (Adjusted for age, sex/gender, race, <i>APOE</i> ε4)			Model 2 (M1 plus health risk factors)		
	Est	95% CI	p	Est	95% CI	p
<b>Hippocampal volumes</b>						
Total Effect (exposure-outcome)	0.08	(0.06, 0.11)	<0.0001	0.07	(0.05, 0.10)	<0.0001
Exposure - Mediator	0.05	(0.01, 0.08)	0.0037	0.04	(0.01, 0.07)	0.0217
Mediator - Outcome	0.38	(0.32, 0.44)	<0.0001	0.35	(0.29, 0.41)	<0.0001
Natural Direct Effect	0.07	(0.05, 0.09)	<0.0001	0.06	(0.04, 0.08)	<0.0001
Natural Indirect Effect	0.02	(0.01, 0.03)	0.0047	0.01	(0.001, 0.02)	0.0247
% mediated	19.47	(7.39, 31.56)	0.0016	15.72	(3.23, 28.22)	0.0137
<b>Total cortical grey matter</b>						
Total Effect (exposure-outcome)	0.08	(0.06, 0.11)	<0.0001	0.07	(0.05, 0.10)	<0.0001
Exposure - Mediator	0.04	(0.005, 0.07)	0.0241	0.03	(-0.002, 0.06)	0.0645
Mediator - Outcome	0.21	(0.14, 0.28)	<0.0001	0.18	(0.11, 0.24)	<0.0001
Natural Direct Effect	0.08	(0.05, 0.10)	<0.0001	0.07	(0.05, 0.09)	<0.0001
Natural Indirect Effect	0.01	(0.0004, 0.01)	0.0354	0.005	(-0.0006, 0.01)	0.0829
% mediated	7.97	(0.71, 15.23)	0.0313	6.28	(-0.70, 13.27)	0.0779
<b>Tau PET (meta-temporal)</b>						
Total Effect (exposure-outcome)	0.08	(0.06, 0.11)	<0.0001	0.07	(0.05, 0.10)	<0.0001
Exposure - Mediator	-0.03	(-0.07, 0.00)	0.0468	-0.03	(-0.06, 0.00)	0.0845
Mediator - Outcome	-0.38	(-0.43, -0.33)	<0.0001	-0.37	(-0.42, -0.31)	<0.0001
Natural Direct Effect	0.07	(0.05, 0.09)	<0.0001	0.06	(0.04, 0.08)	<0.0001
Natural Indirect Effect	0.01	(0.00005, 0.02)	0.0490	0.01	(-0.002, 0.02)	0.0869
% mediated	14.87	(1.71, 28.03)	0.0268	14.25	(-0.30, 28.80)	0.0549
<b>White matter hyperintensities</b>						
Total Effect (exposure-outcome)	0.08	(0.06, 0.11)	<0.0001	0.07	(0.05, 0.10)	<0.0001
Exposure - Mediator	-0.05	(-0.08, -0.02)	0.0030	-0.04	(-0.08, -0.01)	0.0049
Mediator - Outcome	-0.19	(-0.26, -0.13)	<0.0001	-0.18	(-0.24, -0.11)	<0.0001
Natural Direct Effect	0.08	(0.05, 0.10)	<0.0001	0.07	(0.04, 0.09)	<0.0001
Natural Indirect Effect	0.01	(0.002, 0.01)	0.0106	0.01	(0.001, 0.01)	0.0151
% mediated	9.15	(2.13, 16.18)	0.0107	9.23	(1.73, 16.72)	0.0159

M1, model 1; *APOE* ε4, apolipoprotein ε4; CI, confidence interval; PET, positron emission tomography

**Supplementary Table 2.** Relationships between education with executive functioning mediated by biomarkers.

N=537	<b>Model 1 (Adjusted for age, sex/gender, race, <i>APOE</i> ε4)</b>			<b>Model 2 (M1 plus health risk factors)</b>		
	<b>Est</b>	<b>95% CI</b>	<b>p</b>	<b>Est</b>	<b>95% CI</b>	<b>p</b>
<b>Hippocampal volumes</b>						
<b>Total Effect (exposure-outcome)</b>	0.10	(0.07, 0.14)	<0.0001	0.09	(0.06, 0.12)	<0.0001
<b>Exposure - Mediator</b>	0.05	(0.01, 0.08)	0.0037	0.04	(0.01, 0.07)	0.02
<b>Mediator - Outcome</b>	0.44	(0.35, 0.52)	<0.0001	0.39	(0.30, 0.48)	<0.0001
<b>Natural Direct Effect</b>	0.08	(0.05, 0.12)	<0.0001	0.08	(0.05, 0.11)	<0.0001
<b>Natural Indirect Effect</b>	0.02	(0.01, 0.03)	0.0055	0.01	(0.001, 0.02)	0.0268
% mediated	17.99	(6.12, 29.85)	0.0030	14.49	(2.34, 26.64)	0.0194
<b>Total cortical grey matter</b>						
<b>Total Effect (exposure-outcome)</b>	0.10	(0.07, 0.14)	<0.0001	0.09	(0.06, 0.12)	<0.0001
<b>Exposure - Mediator</b>	0.04	(0.005, 0.07)	0.02	0.03	(-0.002, 0.06)	0.06
<b>Mediator - Outcome</b>	0.42	(0.34, 0.51)	<0.0001	0.38	(0.30, 0.47)	<0.0001
<b>Natural Direct Effect</b>	0.09	(0.06, 0.12)	<0.0001	0.08	(0.05, 0.11)	<0.0001
<b>Natural Indirect Effect</b>	0.01	(0.001, 0.03)	0.0284	0.01	(-0.0009, 0.02)	0.0707
% mediated	13.63	(2.26, 25.00)	0.0187	11.88	(-0.24, 24.00)	0.0546
<b>Tau PET (meta-temporal)</b>						
<b>Total Effect (exposure-outcome)</b>	0.10	(0.07, 0.14)	<0.0001	0.09	(0.06, 0.12)	<0.0001
<b>Exposure - Mediator</b>	-0.03	(-0.07, -0.001)	0.05	-0.03	(-0.06, 0.004)	0.08
<b>Mediator - Outcome</b>	-0.49	(-0.57, -0.42)	<0.0001	-0.47	(-0.55, -0.40)	<0.0001
<b>Natural Direct Effect</b>	0.09	(0.06, 0.12)	<0.0001	0.08	(0.05, 0.10)	<0.0001
<b>Natural Indirect Effect</b>	0.02	(0.00004, 0.03)	0.0494	0.01	(-0.002, 0.03)	0.0873
% mediated	15.78	(1.76, 29.80)	0.0274	15.43	(-0.36, 31.21)	0.0554
<b>White matter hyperintensities</b>						
<b>Total Effect (exposure-outcome)</b>	0.10	(0.07, 0.14)	<0.0001	0.09	(0.06, 0.12)	<0.0001
<b>Exposure - Mediator</b>	-0.05	(-0.08, -0.02)	0.003	-0.04	(-0.08, -0.01)	0.0049
<b>Mediator - Outcome</b>	-0.23	(-0.32, -0.14)	<0.0001	-0.21	(-0.30, -0.12)	<0.0001
<b>Natural Direct Effect</b>	0.09	(0.06, 0.13)	<0.0001	0.08	(0.05, 0.11)	<0.0001
<b>Natural Indirect Effect</b>	0.01	(0.002, 0.02)	0.0146	0.01	(0.001, 0.01)	0.0203
% mediated	8.81	(1.61, 16.02)	0.0165	9.07	(1.18, 16.95)	0.0242

M1, model 1; *APOE* ε4, apolipoprotein ε4; CI, confidence interval; PET, positron emission tomography

**Supplementary Table 3.** Relationships between education with language mediated by biomarkers.

N=537	Model 1 (Adjusted for age, sex/gender, race, <i>APOE</i> ε4)			Model 2 (M1 plus health risk factors)		
	Est	95% CI	p	Est	95% CI	p
<b>Hippocampal volumes</b>						
Total Effect (exposure-outcome)	0.11	(0.08, 0.14)	<0.0001	0.10	(0.07, 0.13)	<0.0001
Exposure - Mediator	0.05	(0.01, 0.08)	0.0037	0.04	(0.01, 0.07)	0.02
Mediator - Outcome	0.39	(0.31, 0.46)	<0.0001	0.35	(0.27, 0.43)	<0.0001
Natural Direct Effect	0.09	(0.07, 0.12)	<0.0001	0.09	(0.06, 0.11)	<0.0001
Natural Indirect Effect	0.02	(0.005, 0.03)	0.0055	0.01	(0.001, 0.02)	0.0266
% mediated	14.57	(5.00, 24.14)	0.0028	11.44	(1.91, 20.97)	0.0187
<b>Total cortical grey matter</b>						
Total Effect (exposure-outcome)	0.11	(0.08, 0.14)	<0.0001	0.10	(0.07, 0.13)	<0.0001
Exposure - Mediator	0.04	(0.005, 0.07)	0.02	0.03	(-0.002, 0.06)	0.06
Mediator - Outcome	0.33	(0.25, 0.41)	<0.0001	0.30	(0.22, 0.37)	<0.0001
Natural Direct Effect	0.10	(0.07, 0.13)	<0.0001	0.09	(0.06, 0.12)	<0.0001
Natural Indirect Effect	0.01	(0.001, 0.02)	0.0300	0.01	(-0.0008, 0.02)	0.0731
% mediated	9.65	(1.37, 17.93)	0.0224	8.00	(-0.38, 16.38)	0.0612
<b>Tau PET (meta-temporal)</b>						
Total Effect (exposure-outcome)	0.11	(0.08, 0.14)	<0.0001	0.10	(0.07, 0.13)	<0.0001
Exposure - Mediator	-0.03	(-0.07, -0.001)	0.05	-0.03	(-0.06, 0.004)	0.08
Mediator - Outcome	-0.36	(-0.43, -0.29)	<0.0001	-0.3450	(-0.41, -0.28)	<0.0001
Natural Direct Effect	0.10	(0.07, 0.12)	<0.0001	0.09	(0.06, 0.12)	<0.0001
Natural Indirect Effect	0.01	(-0.00005, 0.02)	0.05	0.01	(-0.002, 0.02)	0.0892
% mediated	10.58	(0.71, 20.45)	0.04	9.83	(-0.74, 20.39)	0.0682
<b>White matter hyperintensities</b>						
Total Effect (exposure-outcome)	0.11	(0.08, 0.14)	<0.0001	0.10	(0.07, 0.13)	<0.0001
Exposure - Mediator	-0.05	(-0.08, -0.02)	0.003	-0.04	(-0.08, -0.01)	0.0049
Mediator - Outcome	-0.19	(-0.27, -0.11)	<0.0001	-0.1743	(-0.25, -0.10)	<0.0001
Natural Direct Effect	0.10	(0.07, 0.13)	<0.0001	0.09	(0.07, 0.12)	<0.0001
Natural Indirect Effect	0.01	(0.001, 0.01)	0.02	0.01	(0.0008, 0.01)	0.0248
% mediated	6.53	(1.09, 11.98)	0.02	6.43	(0.75, 12.10)	0.0264

M1, model 1; *APOE* ε4, apolipoprotein ε4; CI, confidence interval; PET, positron emission tomography

**Supplementary Table 4.** Relationships between education with memory mediated by biomarkers in dementia-free sample.

N=482	Model 1 (Adjusted for age, sex, race, <i>APOE</i> ε4)				Model 2 (M1 plus health risk factors)			
	Est	95% CI		p	Est	95% CI		p
<b>Hippocampal volumes</b>								
<b>Total Effect (exposure-outcome)</b>	0.07	0.05	0.09	<0.0001	0.06	0.04	0.08	<0.0001
<b>Natural Direct Effect</b>	0.06	0.04	0.08	<0.0001	0.06	0.04	0.08	<0.0001
<b>Natural Indirect Effect</b>	0.01	-0.0004	0.01	0.07	0.003	-0.001	0.01	0.16
% mediated	7.52	-0.38	15.42	0.06	5.56	-1.96	13.09	0.15
<b>Total cortical grey matter</b>								
<b>Total Effect (exposure-outcome)</b>	0.07	0.05	0.09	<0.0001	0.06	0.04	0.08	<0.0001
<b>Natural Direct Effect</b>	0.07	0.05	0.09	<0.0001	0.06	0.04	0.08	<0.0001
<b>Natural Indirect Effect</b>	0.00	-0.001	0.003	0.31	0.0005	-0.0009	0.002	0.46
% mediated	1.51	-1.39	4.42	0.31	0.84	-1.41	3.09	0.46
<b>Tau PET (meta-temporal)</b>								
<b>Total Effect (exposure-outcome)</b>	0.07	0.05	0.09	<0.0001	0.06	0.04	0.08	<0.0001
<b>Natural Direct Effect</b>	0.07	0.05	0.09	<0.0001	0.06	0.04	0.08	<0.0001
<b>Natural Indirect Effect</b>	0.00	-0.01	0.01	0.92	0.0002	-0.01	0.01	0.95
% mediated	0.54	-10.01	11.09	0.92	0.38	-11.31	12.07	0.95
<b>White matter hyperintensities</b>								
<b>Total Effect (exposure-outcome)</b>	0.07	0.05	0.09	<0.0001	0.06	0.04	0.08	<0.0001
<b>Natural Direct Effect</b>	0.06	0.04	0.08	<0.0001	0.06	0.04	0.08	<0.0001
<b>Natural Indirect Effect</b>	0.01	0.001	0.01	0.02	0.01	0.0008	0.01	0.02
% mediated	8.88	1.56	16.19	0.02	8.77	1.13	16.41	0.02

M1, model 1; *APOE* ε4, apolipoprotein ε4; CI, confidence interval; PET, positron emission tomography

**Supplementary Table 5.** Relationships between education with executive functioning mediated by biomarkers in dementia-free sample.

N=482	Model 1 (Adjusted for age, sex, race, <i>APOE</i> ε4)				Model 2 (M1 plus health risk factors)			
	Est	95% CI		p	Est	95% CI		p
<b>Hippocampal volumes</b>								
<b>Total Effect (exposure-outcome)</b>	0.08	0.05	0.11	<0.0001	0.07	0.04	0.10	<0.0001
<b>Natural Direct Effect</b>	0.07	0.04	0.10	<0.0001	0.06	0.04	0.09	<0.0001
<b>Natural Indirect Effect</b>	0.01	-0.0006	0.01	0.08	0.004	-0.002	0.01	0.17
% mediated	7.40	-0.74	15.54	0.07	5.35	-2.24	12.93	0.17
<b>Total cortical grey matter</b>								
<b>Total Effect (exposure-outcome)</b>	0.08	0.05	0.11	<0.0001	0.07	0.04	0.10	<0.0001
<b>Natural Direct Effect</b>	0.07	0.05	0.10	<0.0001	0.07	0.04	0.09	<0.0001
<b>Natural Indirect Effect</b>	0.004	-0.002	0.01	0.19	0.003	-0.003	0.01	0.31
% mediated	5.36	-2.51	13.23	0.18	4.17	-3.70	12.04	0.30
<b>Tau PET (meta-temporal)</b>								
<b>Total Effect (exposure-outcome)</b>	0.08	0.05	0.11	<0.0001	0.07	0.04	0.10	<0.0001
<b>Natural Direct Effect</b>	0.08	0.05	0.11	<0.0001	0.07	0.04	0.10	<0.0001
<b>Natural Indirect Effect</b>	0.0004	-0.01	0.01	0.92	0.0002	-0.01	0.01	0.95
% mediated	0.49	-9.11	10.10	0.92	0.35	-10.55	11.26	0.95
<b>White matter hyperintensities</b>								
<b>Total Effect (exposure-outcome)</b>	0.08	0.05	0.11	<0.0001	0.07	0.04	0.10	<0.0001
<b>Natural Direct Effect</b>	0.07	0.04	0.10	<0.0001	0.06	0.03	0.09	<0.0001
<b>Natural Indirect Effect</b>	0.01	0.0009	0.01	0.02	0.01	0.0005	0.01	0.03
% mediated	8.87	0.89	16.86	0.03	9.12	0.40	17.84	0.04

M1, model 1; *APOE* ε4, apolipoprotein ε4; CI, confidence interval; PET, positron emission tomography

**Supplementary Table 6.** Relationships between education with language mediated by biomarkers in dementia-free sample.

N=482	<b>Model 1 (Adjusted for age, sex, race, <i>APOE</i> ε4)</b>				<b>Model 2 (M1 plus health risk factors)</b>			
	<b>Est</b>	<b>95% CI</b>		<b>p</b>	<b>Est</b>	<b>95% CI</b>		<b>p</b>
<b>Hippocampal volumes</b>								
<b>Total Effect (exposure-outcome)</b>	0.09	0.07	0.12	<0.0001	0.09	0.06	0.11	<0.0001
<b>Natural Direct Effect</b>	0.09	0.06	0.11	<0.0001	0.08	0.06	0.11	<0.0001
<b>Natural Indirect Effect</b>	0.005	-0.0006	0.01	0.08	0.003	-0.001	0.01	0.17
% mediated	5.30	-0.58	11.18	0.08	3.80	-1.58	9.19	0.17
<b>Total cortical grey matter</b>								
<b>Total Effect (exposure-outcome)</b>	0.09	0.07	0.12	<0.0001	0.09	0.06	0.11	<0.0001
<b>Natural Direct Effect</b>	0.09	0.06	0.12	<0.0001	0.08	0.06	0.11	<0.0001
<b>Natural Indirect Effect</b>	0.003	-0.002	0.01	0.20	0.002	-0.002	0.01	0.31
% mediated	3.69	-1.81	9.19	0.19	2.79	-2.52	8.11	0.30
<b>Tau PET (meta-temporal)</b>								
<b>Total Effect (exposure-outcome)</b>	0.09	0.07	0.12	<0.0001	0.09	0.06	0.11	<0.0001
<b>Natural Direct Effect</b>	0.09	0.07	0.12	<0.0001	0.09	0.06	0.11	<0.0001
<b>Natural Indirect Effect</b>	0.0003	-0.01	0.01	0.92	0.0002	-0.01	0.01	0.95
% mediated	0.33	-6.06	6.72	0.92	0.22	-6.69	7.14	0.95
<b>White matter hyperintensities</b>								
<b>Total Effect (exposure-outcome)</b>	0.09	0.07	0.12	<0.0001	0.09	0.06	0.11	<0.0001
<b>Natural Direct Effect</b>	0.09	0.06	0.11	<0.0001	0.08	0.05	0.11	<0.0001
<b>Natural Indirect Effect</b>	0.01	0.0005	0.01	0.03	0.01	0.0002	0.01	0.04
% mediated	6.07	0.44	11.71	0.03	5.92	0.12	11.71	0.05

M1, model 1; *APOE* ε4, apolipoprotein ε4; CI, confidence interval; PET, positron emission tomography