

Data Supplement for Holleran et al., The Relationship Between White Matter Microstructure and General Cognitive Ability in Patients With Schizophrenia and Healthy Participants in the ENIGMA Consortium. Am J Psychiatry (doi: 10.1176/appi.ajp.2019.19030225)

SUPPLEMENTARY MATERIAL

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Study cohort	Scanner	Field Strength	Acquisitions	Voxel Size and Slice thickness (mm)	Gradient directions and b-value (mm/s²)	b=0 scans
ASRB 1	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
ASRB 2	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
ASRB 3	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
ASRB 4	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
ASRB 5	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
EDIN	Siemens	3T	1	2.2x2.5x2.5	56 at	6
Dublin	Philips Achieva	3T	1	2x2x2.3	15 at b=800	1
Galway	Siemens	1.5T	1	2.5x2.5x2.5	64 at	7
HUBIN	GE	3T	1	0.94 x 0.94	60 at	10
MPRC	Siemens Alegra	3T	1	1.7x1.7x4.0	12 at	8
TOP	GE	3T	1	2x2x2.5	30 at	1
MCIC 1	Siemens Sonata	1.5T	1	2x2x2	12 at	1
MCIC 2	Siemens Trio	3T	1	2x2x2	6 at b=1000	1
MCIC 3	Siemens Trio	3T	1	2x2x2	12 at	1
MCIC 4	Siemens Sonata	1.5T	1	2x2x2	60 at b=700	1
COBRE	Siemens TIM Trio	3T	2	2x2x2	30 at b=800	5
Madrid	Philips Intera	1.5T	1	1.75x1.75x2	15 at b=800	1
Madrid	Philips Intera	1.5T	2	2x2x2	32 at b=800	1
Madrid	Philips Intera	1.5T	1	2x2x2	64 at	1
Oxford	Siemens Sonata	1.5T	3	2.5x2.5x2.5	60 at	5

TABLE S1. DTI acquisition protocols for contributing ENIGMA-Schizophrenia working group site. **ASRB**=Australian Schizophrenia Research Bank, **EDIN**=Edinburgh, **HUBIN**=Human Brain Informatics, **MPRC**=Maryland Psychiatric Research Center, **MCIC**=MIND Clinical Imaging Consortium, **COBRE**=Center for Biomedical Research Excellence.

Abbreviation	White Matter Tract
Avg-FA	Average FA
GCC	Genu of Corpus Callosum
BCC	Body of Corpus Callosum
SCC	Splenium of Corpus Callosum
FX	Fornix
ALIC	Anterior Limb of the Internal Capsule*
IC	Internal Capsule
CC	Corpus Callosum
ACR	Arcuate Fasciculus*
SCR	Superior Corona Radiata
PCR	Posterior Corona Radiata
CR	Corona Radiata
PTR	Posterior Thalamic Radiation
SS	Sagittal stratum
EC	External capsule
CGC	Cingulum (cingulate gyrus)*
SLF	Superior Longitudinal Fasciculus*
SFO	Superior Fronto-Occipital Fasciculus
FX-ST	Fornix/Stria Terminalis
IFO	Inferior Fronto Occipital Fasciculus*
UNC	Uncinate Fasciculus*

TABLE S2. The 19 white matter tracts which were reported in Kelly et al to have significantly reduced FA in patients with schizophrenia compared to controls. The ENIGMA-DTI protocol outputs average FA for each bilateral white matter tract. The present analysis combined FA from both hemispheres for the tracts listed above to avoid any potential issues of left/right flipping. gFA was computed using a principal component analysis of the tracts listed above. * identifies tracts used to generate LA-gFA.

ENIGMA Site	PCA total % Variance Explained	
	<i>gFA</i>	<i>LA-gFA</i>
ASRB-1	58	49
ASRB-2	55	51
ASRB-3	57	52
ASRB-4	56	51
ASRB-5	50	44
EDIN	61	57
Dublin	52	46
Galway	63	64
HUBIN	48	50
MPRC	67	67
TOP	44	43
MCIC	52	42
COBRE	58	57
Madrid	55	54
Oxford	70	67
Median	56	51
Range	44-70	42-67

TABLE S3. Total percent variance explained for the first unrotated component representing global fractional anisotropy (gFA) and the first unrotated component representing six long association tracts fractional anisotropy (LA-gFA).

		sample size		Mean Age		Mean IQ	
				st. dev		st. dev	
		HC	SZ	HC	SZ	HC	SZ
ASRB1	Male	16	89	40	39	118	100
	Female	17	32	14.1	10.9	11	17
ASRB2	Male	41	54	41	38	115	105
	Female	38	31	13.8	10.4	11	13
ASRB3	Male	9	12	44	42	113	112
	Female	9	5	13.6	8.7	12	12
ASRB4	Male	15	28	37	39	120	101
	Female	14	11	13.7	10.4	8	17
ASRB5	Male	18	42	40	40	118	105
	Female	20	22	13.9	10.4	13	14
Edin	Male	19	17	37	35	116	105
	Female	17	11	15.2	10.1	11	16
Dublin	males	27	22	35	44	118	91
	females	33	6	12.1	11.1	16	14
Galway	males	20		34		92	
	females	5		11.1		21	
HUBIN	male	20	22	54	52	104	88
	female	12	5	8.96	7.5	18	18
MPRC	male	26	21	39	37	99	91
	female	46	10	14.3	12.5	18	15
TOP	male	137	18	32	29	113	97
	female	99	11	7.6	8.4	11	15
MCIC	males	72	69	31	33	115	98
	females	41	26	10.9	11.4	14	19
COBRE	males	62	72	39	39	111	99
	females	22	22	11.9	13.8	13	17
Madrid	male	53	31	13	17	111	80
	female	31	10	4.3	3.3	15	25
Oxford	males	24	18	13	14	109	91
	females	19	18	1.2	1.4	13	15
		957	760	36	36	113	97
				10.1	9.1	6	8

Table S4. Demographic data collected from 11 collaborating ENIGMA-Schizophrenia DTI working group. The final sample size consisted of 1049 healthy participants and 798 patients with schizophrenia. *indicates sites with data from adolescent participants. **ASRB**=Australian Schizophrenia Research Bank, **EDIN**=Edinburgh, **HUBIN**=Human Brain Informatics, **MPRC**=Maryland Psychiatric Research Center, **MCIC**=MIND Clinical Imaging Consortium, **COBRE**= Center for Biomedical Research Excellence.

Site	n	Hedge's g	CI Lower	CI Upper	p	Z
HC	ASRB-1	33	0.14	-0.58	0.86	0.71
	ASRB-2	79	0.32	-0.13	0.78	0.16
	ASRB-3	18	0.12	-0.89	1.13	0.82
	ASRB-4	29	0.28	-0.49	1.06	0.47
	ASRB-5	38	0.28	-0.39	0.95	0.41
	EDIN	36	0.21	-0.48	0.89	0.56
	Dublin	60	0.00	-0.52	0.52	1.00
	HUBIN	32	0.09	-0.64	0.82	0.81
	MCPR	72	0.39	-0.09	0.87	0.11
	TOP	236	0.38	0.12	0.64	0.00
SZ	MCIC	113	0.48	0.10	0.87	0.01
	COBRE	84	0.40	-0.05	0.84	0.08
	Madrid	84	0.32	-0.12	0.76	0.15
	Oxford	43	0.18	-0.45	0.80	0.58
	<i>HC mean</i>	957	0.32	0.18	0.45	<0.001
	ASRB-1	121	0.23	-0.14	0.59	0.22
	ASRB-2	85	0.04	-0.40	0.47	0.87
	ASRB-3	17	0.31	-0.75	1.37	0.57
	ASRB-4	39	0.20	-0.46	0.85	0.56
	ASRB-5	64	0.34	-0.17	0.84	0.20
	EDIN	28	1.57	0.55	2.58	0.00
	Dublin	28	0.30	-0.50	1.09	0.46
	Galway	25	0.36	-0.49	1.21	0.40
	HUBIN	27	0.17	-0.63	0.98	0.67
	MCPR	31	0.11	-0.64	0.85	0.78
	TOP	29	0.28	-0.50	1.05	0.48
	MCIC	95	0.11	-0.30	0.52	0.60
	COBRE	94	0.13	-0.29	0.54	0.55
	Madrid	41	0.11	-0.53	0.74	0.74
	Oxford	36	0.06	-0.62	0.75	0.86
Overall	<i>SZ mean</i>	760	0.20	0.05	0.35	<0.01
		1717	0.27	0.17	0.36	2.66

TABLE S5. gFA meta-analysis results using a random effects model. gFA accounted for a significant amount of variance in IQ in the full sample (average Hedges' g ES=0.27), healthy participant (ES=0.32) and patient (ES=0.20) groups. HC=healthy control, SZ=patients with schizophrenia, CI=95% confidence intervals.

Site	n	Hedge's g	CI Lower	CI Upper	p	z
HC	ASRB-1	33	0.04	-0.66	0.74	0.91
	ASRB-2	79	0.46	0.01	0.92	0.05
	ASRB-3	18	0.18	-0.79	1.15	0.71
	ASRB-4	29	0.06	-0.69	0.81	0.87
	ASRB-5	38	0.19	-0.47	0.84	0.57
	EDIN	36	0.06	-0.61	0.73	0.86
	Dublin	60	0.21	-0.31	0.72	0.43
	HUBIN	32	0.94	0.15	1.73	0.02
	MCPR	72	0.18	-0.29	0.65	0.46
	TOP	236	0.37	0.11	0.63	0.00
	MCIC	113	0.48	0.10	0.87	0.01
	COBRE	84	0.35	-0.08	0.79	0.11
	Madrid	84	0.13	-0.31	0.56	0.57
	Oxford	43	0.22	-0.39	0.83	0.49
HC mean		957	0.31	0.18	0.44	<0.0001
SZ	ASRB-1	121	0.38	0.02	0.75	0.04
	ASRB-2	85	0.01	-0.42	0.44	0.97
	ASRB-3	17	0.23	-0.77	1.24	0.65
	ASRB-4	39	0.18	-0.47	0.82	0.59
	ASRB-5	64	0.09	-0.41	0.58	0.73
	EDIN	28	1.58	0.60	2.56	0.00
	Dublin	28	0.21	-0.56	0.97	0.60
	Galway	25	0.12	-0.69	0.93	0.77
	HUBIN	27	0.19	-0.59	0.96	0.64
	MCPR	31	0.54	-0.21	1.29	0.16
	TOP	29	0.00	-0.75	0.75	1.00
	MCIC	95	0.34	-0.07	0.75	0.10
	COBRE	94	0.06	-0.34	0.47	0.76
	Madrid	41	0.35	-0.28	0.98	0.28
	Oxford	36	0.11	-0.56	0.78	0.75
SZ mean		760	0.23	0.09	0.38	<0.0001
Overall		1717	0.28	0.18	0.37	<0.0001
						5.56

TABLE S6. LAgFA meta-analysis results using a random effects model. LA-gFA accounted for a significant amount of variance in IQ in the full sample (average Hedges' g ES=0.28), healthy participant (ES=0.31) and patient (ES=0.23) groups. HC=healthy control, SZ=patients with schizophrenia, CI=95% confidence intervals.

ENIGMA Site	gFA - LA-gFA cc
ASRB-1	0.95
ASRB-2	0.96
ASRB-3	0.96
ASRB-4	0.95
ASRB-5	0.93
EDIN	0.95
Dublin	0.93
Galway	0.96
HUBIN	0.95
MPRC	0.96
TOP	0.92
MCIC	0.91
COBRE	0.97
Madrid	0.96
Oxford	0.98
Median	0.95
Range	0.91-0.98

TABLE S7. Pearson's correlation coefficient for gFA and LA-gFA components. cc=correlation coefficient.

Omitted Site	Mean	CI Lower	CI Upper	p	z
HC	ASRB	0.30	0.17	0.42	<0.001
	Cobre	0.28	0.16	0.39	<0.001
	Dublin	0.34	0.22	0.45	<0.001
	EDIN	0.29	0.18	0.40	<0.001
	Galway	0.29	0.18	0.40	<0.001
	HUBIN	0.30	0.19	0.41	<0.001
	Madrid	0.29	0.17	0.40	<0.001
	MCIC	0.27	0.15	0.38	<0.001
	MCPR	0.28	0.17	0.40	<0.001
	Oxford	0.29	0.18	0.40	<0.001
	Top	0.26	0.14	0.39	<0.001
HC mean		0.29	0.25	0.32	<0.001
SZ	ASRB	0.21	0.04	0.37	<0.01
	Cobre	0.21	0.08	0.35	<0.01
	Dublin	0.20	0.06	0.33	<0.01
	EDIN	0.18	0.05	0.30	<0.01
	Galway	0.20	0.07	0.33	<0.01
	HUBIN	0.20	0.07	0.33	<0.01
	Madrid	0.21	0.08	0.34	<0.01
	MCIC	0.22	0.08	0.35	<0.01
	MCPR	0.21	0.08	0.34	<0.01
	Oxford	0.21	0.08	0.34	<0.01
	Top	0.20	0.07	0.33	<0.01
SZ mean		0.20	0.16	0.24	<0.001
Overall		0.25	0.23	0.28	<0.001
					18.78

TABLE S8. Leave-one-out meta-analysis for gFA. For each meta-analysis iteration a single site was omitted to determine if significant findings were driven by a single site. The leave-one-out analysis indicates that for each site omitted the results remain significant with the mean Hedges' g ES=0.25 for the full sample, ES=0.20 for patients, and ES=0.29 for healthy participants, $p<0.001$. HC=healthy control, SZ=patients with schizophrenia, CI=95% confidence intervals.

Omitted Site	Mean	CI Lower	CI Upper	p	z
HC	ASRB	0.32	0.20	0.44	<0.001
	Cobre	0.31	0.19	0.42	<0.001
	Dublin	0.33	0.21	0.44	<0.001
	EDIN	0.32	0.21	0.43	<0.001
	Galway	0.31	0.20	0.42	<0.001
	HUBIN	0.29	0.17	0.40	<0.001
	Madrid	0.33	0.21	0.44	<0.001
	MCIC	0.29	0.17	0.40	<0.001
	MCPR	0.32	0.21	0.43	<0.001
	Oxford	0.31	0.20	0.42	<0.001
	TOP	0.29	0.17	0.41	<0.001
HC mean		0.31	0.27	0.34	<0.001
SZ	ASRB	0.26	0.09	0.43	<0.001
	Cobre	0.25	0.12	0.39	<0.001
	Dublin	0.23	0.10	0.36	<0.001
	EDIN	0.20	0.07	0.33	<0.001
	Galway	0.23	0.10	0.36	<0.001
	HUBIN	0.23	0.10	0.36	<0.001
	Madrid	0.22	0.09	0.35	<0.001
	MCIC	0.21	0.08	0.35	<0.001
	MCPR	0.22	0.09	0.35	<0.001
	Oxford	0.24	0.11	0.37	<0.001
	TOP	0.24	0.11	0.37	<0.001
SZ mean		0.23	0.19	0.27	<0.001
Overall		0.27	0.25	0.30	<0.001
					20.64

TABLE S9. Leave-one-out meta-analysis for LAgFA. For each meta-analysis iteration a single site was omitted to determine if significant findings were driven by a single site. The leave-one-out analysis indicates that for each site omitted the results remain significant with the mean Hedges' g ES=0.27 for the full sample, ES=0.23 for patients, and ES=0.31 for healthy participants, $p<0.001$. HC=healthy control, SZ=patients with schizophrenia, CI=95% confidence intervals.

	Site	Hedge's g	CI Lower	CI Upper	p	z
Female	ASRB-1	0.52	-0.08	1.12	0.09	1.71
	ASRB-2	0.21	-0.28	0.69	0.40	0.84
	ASRB-3	0.27	-0.93	1.46	0.66	0.44
	ASRB-4	0.00	-0.84	0.84	1.00	0.00
	ASRB-5	0.45	-0.19	1.10	0.17	1.37
	EDIN	0.26	-0.60	1.12	0.55	0.59
	Dublin	0.06	-0.59	0.72	0.85	0.19
	HUBIN	1.00	-2.52	4.52	0.58	0.56
	MCPR	0.32	-0.74	1.39	0.55	0.59
	TOP	0.17	-0.37	0.71	0.55	0.60
	MCIC	0.73	0.33	1.13	<0.001	3.54
	COBRE	0.95	0.41	1.50	<0.001	3.43
	Madrid	0.21	-0.41	0.82	0.51	0.66
	Oxford	0.12	-0.51	0.76	0.70	0.38
	Oxford	0.22	-0.45	0.90	0.52	0.65
	mean	0.39	0.22	0.55	<0.001	4.57
Male	ASRB-1	0.32	-0.08	0.71	0.11	1.58
	ASRB-2	0.29	-0.12	0.70	0.17	1.38
	ASRB-3	0.12	-0.80	1.05	0.80	0.26
	ASRB-4	0.09	-0.53	0.71	0.78	0.28
	ASRB-5	0.30	-0.23	0.82	0.27	1.10
	EDIN	0.93	0.15	1.71	0.02	2.32
	Dublin	0.11	-0.47	0.69	0.71	0.37
	Galway	0.14	-0.82	1.09	0.78	0.28
	HUBIN	0.53	-0.12	1.18	0.11	1.60
	MCPR	1.03	0.36	1.70	0.00	3.01
	TOP	0.28	-0.04	0.60	0.09	1.69
	MCIC	0.53	0.18	0.87	<0.01	3.00
	COBRE	0.40	0.05	0.74	0.03	2.22
	Madrid	0.20	-0.24	0.64	0.37	0.89
	Oxford	0.23	-0.40	0.87	0.47	0.72
	mean	0.35	0.23	0.48	<0.001	5.57
Overall		0.37	0.27	0.47	<0.001	7.20

TABLE S10. Meta-analysis results for gFA and IQ in males & females. There was no significant difference in the observed Hedges' g effect size for males (ES=0.35, CI=0.23-0.48) and females (ES=0.39, CI=0.22-0.55), $\chi^2(1)=0.09$ $p=0.77$. CI=95% confidence intervals.

Site	Hedge's g	CI Lower	CI Upper	p	z
Female	ASRB-1	0.46	-0.14	1.05	0.13
	ASRB-2	0.27	-0.22	0.75	0.28
	ASRB-3	0.10	-1.08	1.29	0.86
	ASRB-4	0.00	-0.84	0.84	1.00
	ASRB-5	0.26	-0.38	0.89	0.43
	EDIN	0.25	-0.62	1.11	0.58
	Dublin	0.09	-0.57	0.74	0.79
	HUBIN	0.82	-2.47	4.11	0.63
	MCPR	0.37	-0.70	1.44	0.50
	TOP	0.09	-0.45	0.63	0.75
	MCIC	0.76	0.36	1.17	<0.0001
	COBRE	0.90	0.36	1.44	<0.01
	Madrid	0.18	-0.44	0.79	0.58
	Oxford	0.28	-0.36	0.92	0.39
	Oxford	0.11	-0.57	0.78	0.75
mean		0.37	0.20	0.53	<0.001
4.37					
Male	ASRB-1	0.46	0.06	0.85	0.02
	ASRB-2	0.36	-0.05	0.78	0.09
	ASRB-3	0.12	-0.80	1.05	0.80
	ASRB-4	0.00	-0.62	0.62	1.00
	ASRB-5	0.26	-0.26	0.78	0.33
	EDIN	0.83	0.06	1.60	0.03
	Dublin	0.15	-0.43	0.73	0.61
	Galway	0.06	-0.89	1.01	0.90
	HUBIN	0.55	-0.11	1.20	0.10
	MCPR	0.99	0.33	1.66	<0.01
	TOP	0.21	-0.11	0.53	0.20
	MCIC	0.54	0.19	0.88	<0.01
	COBRE	0.33	-0.02	0.68	0.06
	Madrid	0.00	-0.44	0.44	1.00
	Oxford	0.23	-0.41	0.86	0.48
mean		0.33	0.21	0.46	<0.001
5.23					
Overall	0.35	0.25	0.45	<0.001	6.81

TABLE S11. Meta-analysis results for LAgFA and IQ in males & females. There was no significant difference in the observed Hedges' g effect size for males (ES=0.33, CI=0.21-0.46) and females (ES=0.37, CI=0.20-0.53), $\chi^2(1)=0.11$ $p=0.74$. CI=95% confidence intervals.

DTI parameter	Sample	n	Hedge's G	CI lower	CI upper	p
MD	HC	397	0.25	0.05	0.46	0.01
	Sz	467	0.19	0.00	0.38	0.05
	All	864	0.22	0.08	0.36	<0.01
RD	HC	397	0.37	0.02	0.72	0.04
	Sz	467	0.31	0.07	0.55	0.01
	All	864	0.33	0.13	0.52	<0.01
AD	HC	397	0.32	0.11	0.52	<0.01
	Sz	467	0.07	-0.12	0.25	0.47
	All	864	0.24	0.11	0.37	0.01
LA-gMD	HC	397	0.19	-0.01	0.34	0.07
	Sz	467	0.09	-0.09	0.28	0.33
	All	864	0.14	0.00	0.27	0.05
LA-gRD	HC	397	0.27	-0.08	0.62	0.13
	Sz	467	0.42	0.04	0.80	0.03
	All	864	0.34	0.08	0.60	0.01
LA-gAD	HC	397	0.28	0.08	0.48	0.01
	Sz	467	0.14	-0.05	0.32	0.15
	All	864	0.20	0.06	0.34	<0.01

TABLE S12. Meta-analysis results for secondary diffusion MRI parameters. MD=mean diffusivity, RD=radial diffusivity, AD=axial diffusivity, LA=long association tract analysis. The largest effect sizes were observed for measures relating to radial diffusivity (RD & LA-gRD).

	ASRB	EDIN	Dublin	HUBIN	MPRC	Galway
gFA	0.057	0.369	0.037	0.251	0.273	0.193
gMD	-0.053	-0.106	-0.221	-0.344	-0.01	-0.173
gRD	-0.105	-0.245	-0.153	-0.347	-0.423	-0.197
gAD	0.049	0.195	-0.296	-0.153	-0.101	-0.049
LA-gFA	0.139	0.344	0.079	0.253	0.229	0.064
LA-gMD	-0.12	-0.158	-0.135	-0.28	-0.021	-0.077
LA-gRD	-0.063	-0.265	-0.131	-0.324	-0.385	-0.064
LA-gAD	0.088	0.164	-0.114	-0.115	-0.094	-0.033

TABLE S13. Per-Site Regression Standardized Beta Coefficients for secondary diffusion MRI parameters. The standardized Beta's reported here support our findings that higher FA is associated with higher cognitive functions, which is primarily driven by increased radial diffusivity.

FIGURE S1. Sex dependent meta-analysis results for (A) gFA and (B) LAgFA. There was no significant difference in the observed Hedges' g effect size for gFA between males (ES=0.35, CI=0.23-0.48) and females (ES=0.39, CI=0.22-0.55), $\chi^2(1)=0.09 p=0.77$. Similarly for LAgFA there was no significant difference in the observed Hedges' g effect size for males (ES=0.33, CI=0.21-0.46) and females (ES=0.37, CI=0.20-0.53), $\chi^2(1)=0.11 p=0.74$.

FIGURE S1A.

gFA Females and Males

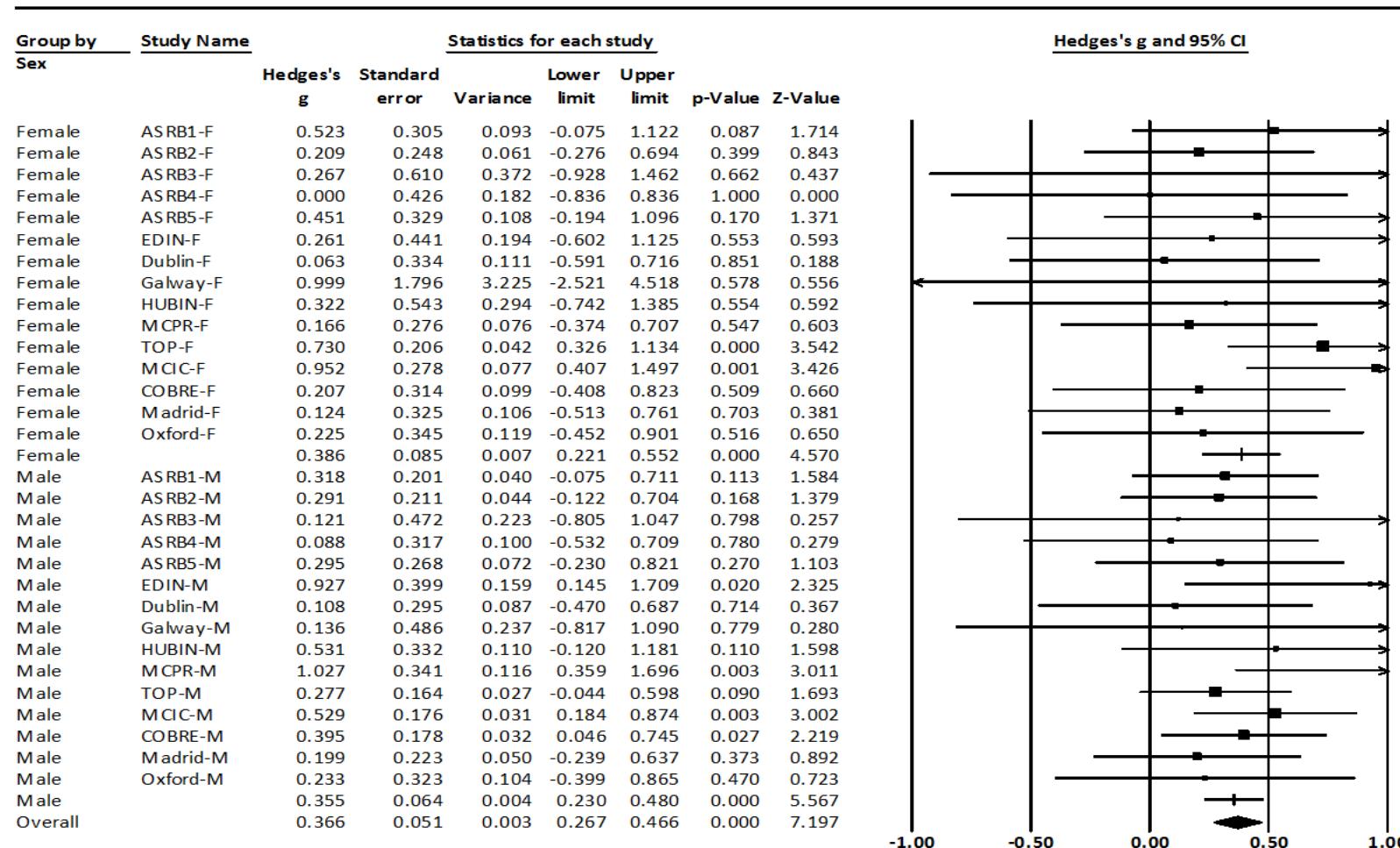


FIGURE S1B.

LAgFA Females and Males

