Supplementary Online Content

de Haan L, Sutterland AL, Schotborgh JV, Schirmbeck F, de Haan L. Association of *Toxoplasma gondii* seropositivity with cognitive function in healthy people: a systematic review and meta-analysis. *JAMA Psychiatry*. Published online July 14, 2021. doi:10.1001/jamapsychiatry.2021.1590

This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods 1. Search Strategy

PubMed and MEDLINE (search date: June 7, 2019)
Search (toxoplasmosis OR toxoplasmic OR toxoplasma OR Neurotoxoplasmosis OR t gondii OR toxopl*) AND (cognition OR cognitive OR neuropsychological OR neuropsychology OR psychomotor performances OR motor performance*[tw] OR reaction time OR TMT OR CPT)

PsycINFO and EMBASE (search date: June 7, 2019)
(toxoplasmosis or toxoplasma gondii or toxoplasma).ab,sh,ti.
(toxoplasmosis or toxoplasmic or Neurotoxoplasmosis or t gondii or toxopl*).ab,ti.
1 or 2 [t gondii sensitief]
(cognitive defect or cognition disorder or cognition or cognition disorder or neuropsychology or mental disorder or psychomotor performance? or psychophysiology or arousal or reaction time).ab,sh,ti.
(cognitive or motor performance* or neuropsychological).ab,ti.
3 and 6

Web of Science (search date: June 7, 2019)
TS=(toxoplasmosis) OR TS=(toxoplasma gondii) OR TS=(toxoplasma)
TS=(cognition) OR TS=(cognitive) OR TS=(neuropsychology) OR TS=(reaction time) OR TS=(motor performance) OR TS=(neuropsychological) OR TS=(tmt) OR TS=(cpt) OR TS=(psychomotor performances)
#1 AND #2

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eMethods 2. Aggregation of Results

When aggregating outcome measures of cognitive tests into cognitive domains, we aimed to create categories as homogenous as possible (following the Strauss and Lezak compendium of neuropsychological assessments and the MATRICS Consensus Cognitive Battery initiative)[1–3], while at the same time avoiding too many categories with small numbers, which could not be pooled for meta-analysis. We maintained a minimum of four studies required per meta-analysis.

eTable 1 shows which cognitive tests and corresponding measures within that test were categorized into a domain. The order of presentation in each table is also the order of preference when multiple tests from the same study were categorized in the same domain.

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eTable 1. Aggregation of Tests in Cognitive Domains

A

	Test measure
Processing speed	
Trail Making Test part A (TMT A)	seconds
Simple Reaction Time Test (SRTT)	seconds
GO reaction time test	seconds

B

	Test measure
Working memory	
Digit span forward	total number correct
Digit span backward	total number correct
Digit span scaled	total number correct

C

	Test measure
Short term verbal memory	
Verbal Learning and Memory Test (VLMT)	sum score trials 1-5
Verbal Learning and Memory Test (VLMT)	verbal learning score
(Rey-) Auditory Verbal Learning Test (AVLT)	total short recall score
California Verbal Learning Test (CVLT)	short term memory score
Verbal Learning Test (VLT)	sum score

D

	Test measure
Executive functioning	
Trail Making Test part B (TMT B)	seconds
Verbal Fluency Test (VFT)	total number of words
TMT B, VFT and clock drawing scaled	sum score

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eTable 2. Insufficient Reported Outcome Measures

The following table shows an overview of outcome measures that were reported in insufficient studies to be pooled in a meta-analysis.

Domain	Test	N studies
Attention	Continuous performance task II (CPT II Conners')	1
	d2	1
Visual memory	Wechsler memory scale (WMS) - family pictures	1
Visuospatial memory	Brief visuospatial memory	1
	Rey-osterrieth complex figure (ROCF)	1
Executive functioning - visuospatial	Mental rotation task - mirrored figures	1
Associate learning	WMS Associate learning	1
Intelligence	MWT-B	1
Motor ability	Grooved pegboard test	1
Verbal memory/ learning	Selective reminding test (SRT)	1
	Wide range achievement test revised (WRAT-R)	1
	Serial digit learning (SDL)	1
Overall cognition	Global deficit score (GDS)	1
	Cognitive failures questionnaire (CFQ)	1

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eTable 3. Newcastle-Ottawa Scale Quality Assessment: Male and Female Participants Combined

	Selection				**Comparability**	**Exposure**			**Total score**
Study, year	Case definition (N/1)	Representativeness (N/1)	Selection controls (N/1)	Definition controls (N/1)	Comparability (N/2)	Ascertainment (N/1)	Same method (N/1)	Non-response rate (N/1)	**(N/9)**
Berrett 2017[4]	1	1	1	1	0	1	1	0	6
Cobia 2017[5]	1	0	1	1	0	1	1	1	6
El-Hadidy 2013[6]	1	0	1	1	0	1	1	1	6
Ene 2016[7]	1	0	0	1	0	1	1	1	5
Gajewski 2014[8]	1	0	1	1	0	1	1	1	6
Guenter 2012[9]	1	0	1	1	0	1	1	1	6
Hamdani 2017[10]	1	0	1	1	0	1	1	0	5
Mendy 2015[11] *children*	1	1	1	1	1	1	1	0	7
Nimgaonkar 2016[12]	1	1	1	1	2	1	1	1	9
Novotna 2008[13] *1*	1	0	1	1	0	1	1	1	6
Novotna 2008[13] *2*	1	0	1	1	0	1	1	1	6
Novotna 2008[13] 3	1	0	1	1	2	1	1	0	7
Stock 2014[14]	1	0	1	1	2	1	1	1	8
Sugden 2016[15]	1	1	1	1	1	1	1	0	7
Torniainen-Holm 2019[16]	1	1	1	1	0	1	1	0	6

Legend:
Underlined and in italic: See eTable 4: male and female separated
N/...: number out of …

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eTable 4. Newcastle-Ottawa Scale Quality Assessment: Male and Female Participants Separated

	Selection				**Comparability**	**Exposure**			**Total score**
Study, year	Case definition (N/1)	Representativeness (N/1)	Selection controls (N/1)	Definition controls (N/1)	Comparability (N/2)	Ascertainment (N/1)	Same method (N/1)	Non-response rate (N/1)	**(N/9)**
Gajewski 2014[8]	1	0	1	1	1	1	1	1	7
Guenter 2012[9]	1	0	1	1	1	1	1	1	7
Mendy 2015[11] *children*	1	1	1	1	2	1	1	0	8
Nimgaonkar 2016[12]	1	1	1	1	2	1	1	1	9
Novotna 2008[13] *1*	1	0	1	1	1	1	1	1	7
Novotna 2008[13] *2*	1	0	1	1	1	1	1	1	7
Torniainen-Holm 2019[16]	1	1	1	1	1	1	1	0	7

Legend:
Italic: Changed relative to eTable 3
N/…: number out of …

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eTable 5. Results From Meta-analyses and Subgroup Analysis

A

Cognitive domain	N studies	N participants	SMD	Lower	Upper	P-value	I^2
Processing speed							
Processing speed	11	9495	0.122	0.054	0.190	<.001	13.356
*Processing speed: SRTT	5	9105	0.119	0.038	0.199	.004	35.523
*Processing speed: TMT A	4	303	0.003	-0.241	0.247	.98	0
*Processing speed: healthy controls (instead of population representative)	9	1258	0.068	-0.050	0.186	.26	0
*Processing speed: male	5	3247	0.182	0.093	0.272	<.001	0
*Processing speed: female	5	3701	0.141	0.064	0.217	<.001	0
*Processing speed: without the study of Ene (low quality) Fig. S1	10	9444	0.126	0,067	0.185	<.001	6.502

B

Cognitive domain	N studies	N participants	SMD	Lower	Upper	P-value	I^2
Working memory							
Working memory	6	2951	0.162	0.061	0.262	.002	0

C

Cognitive domain	N studies	N participants	SMD	Lower	Upper	P-value	I^2
Short term verbal memory							
Short term verbal memory	5	7352	0.179	0.087	0.270	<.001	21.561

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D

Cognitive domain	N studies	N participants	SMD	Lower	Upper	P-value	I^2
Executive functioning							
Executive functioning	8	8413	0.146	0.012	0.279	.03	63.475
Executive functioning: TMT B[a]	5	1130	0.039	-0.126	0.205	.64	14.303
Executive functioning: healthy controls (instead of population representative) [a]	6	1376	0.119	0.028	0.209	.01	4.277
Executive functioning: male[a]	4	3281	0.208	0.071	0.345	.03	23.198
Executive functioning: female[a]	4	4135	0.241	0.054	0.427	.01	63.245
Executive functioning: without the study of Ene (low quality) (fig. S2)[a]	7	8362	0.146	0.004	0.287	.04	68.668
Executive functioning: without the study of Nimgaonkar (fig. S3 [a]	7	7431	0.105	0.032	0.177	.005	6.059

Abbreviations: SMD = standardized mean difference; lower = lower limit of confidence interval; upper = upper limit of confidence interval; SRTT = simple reaction time test; TMT A = trail making test A; TMT B = trail making test B.

[a] subgroup or sensitivity analyses

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eTable 6. Results From Meta-regression Analyses

Covariate	N studies	Q	P-value	R^2
Processing speed				
Mean age	10	2.50	.11	85%
Study quality	11	3.22	.07	100%
Seropositivity cut off	10	3.06	.08	100%
Working memory				
Mean age	6	0.52	0.47	0%
Study quality	6	0.04	0.84	0%
Seropositivity cut off	5	1.35	0.25	0%
Short term verbal memory				
Mean age	5	0.40	0.53	0%
Study quality	5	0.72	0.40	0%
Executive functioning				
Mean age	8	6.17[a]	.01	81%
Study quality	8	3.27	.07	42%
Seropositivity cut off	6	1.78	.18	37%

[a] significant effect

We did not run a meta-regression analysis of seropositivity cut off values in the short term memory domain because the studies that provided results measuring short term verbal memory either used a cut off value of 50 IU/ml, or cut off values were unknown.

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eTable 7. Meta-regression Analysis Dichotomized by Mean Age

Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
<40	4	0,035	0,067	0,005	-0,096	0,167	0,524	0,600	4,263	3	0,234	29,622	0,014	0,040	0,002	0,120
>40	4	0,176	0,028	0,001	0,121	0,231	6,273	0,000	11,147	3	0,011	73,087	0,019	0,028	0,001	0,136
Total within									15,410	6	0,017					
Total between									3,755	1	0,053					
Overall	8	0,155	0,026	0,001	0,104	0,206	5,989	0,000	19,165	7	0,008	63,475	0,016	0,018	0,000	0,126
Mixed effects analysis																
<40	4	0,040	0,105	0,011	-0,166	0,246	0,380	0,704								
>40	4	0,215	0,093	0,009	0,032	0,398	2,306	0,021								
Total between									1,551	1	0,213					
Overall	8	0,138	0,070	0,005	0,001	0,275	1,978	0,048								

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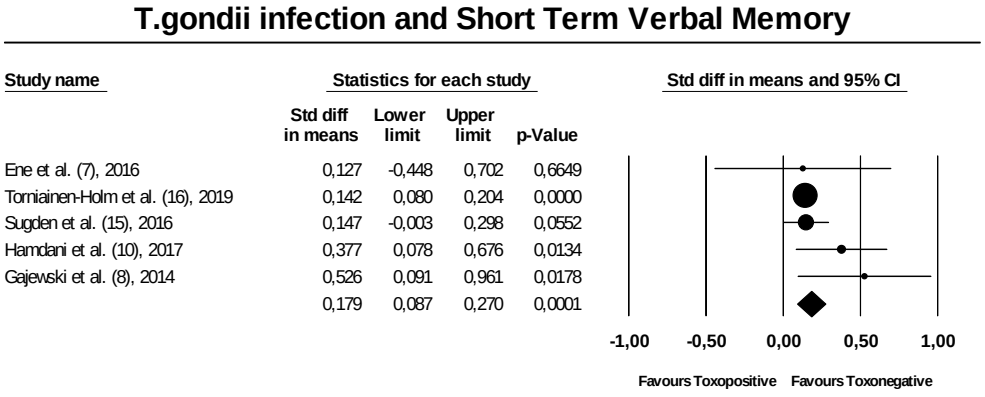
eFigure 1. Forest Plot for Short-term Verbal Memory



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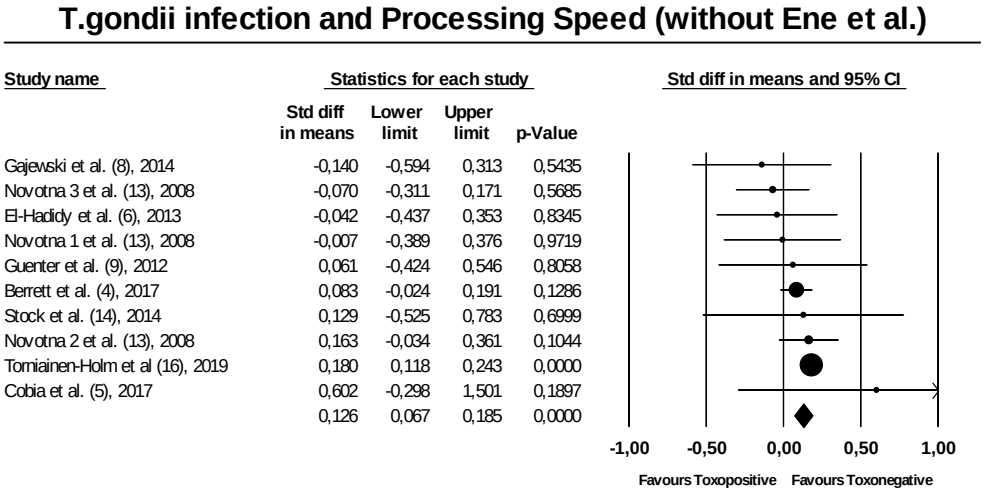
eFigure 2. Forest Plot for Processing Speed Without Ene et al[7] Study (Low Quality)



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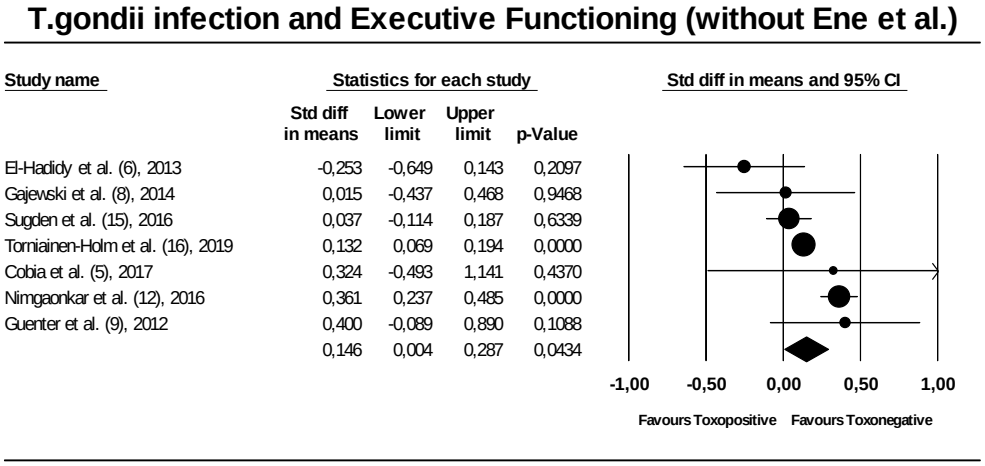
eFigure 3. Forest Plot for Executive Functioning Without Ene et al[7] Study (Low Quality)



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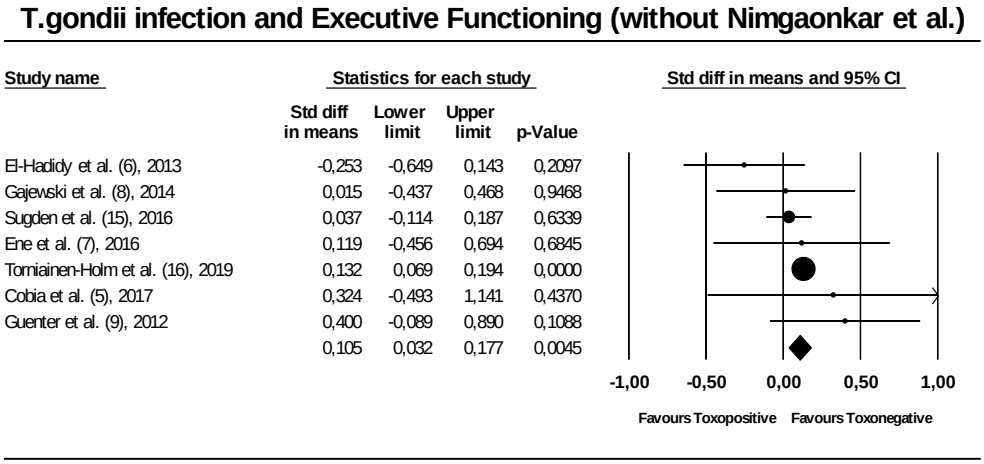
eFigure 4. Forest Plot for Executive Functioning Without Nimgaonkar et al[12] Study



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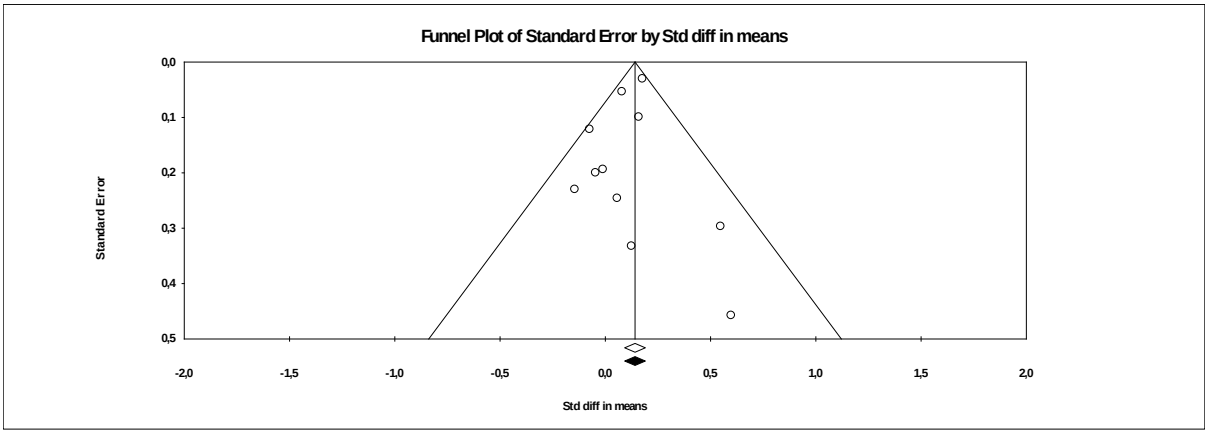
eFigure 5. Funnel Plot for Processing Speed



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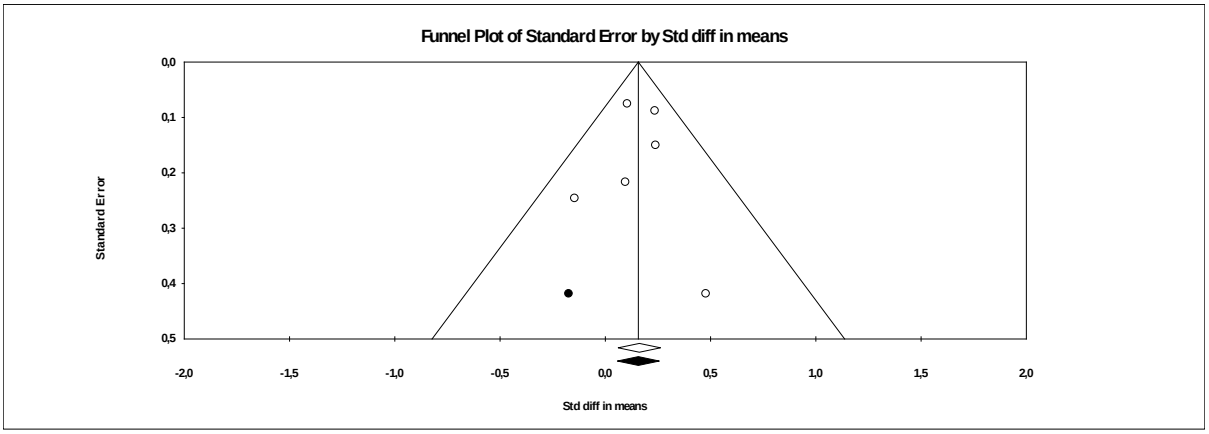
eFigure 6. Funnel Plot for Working Memory



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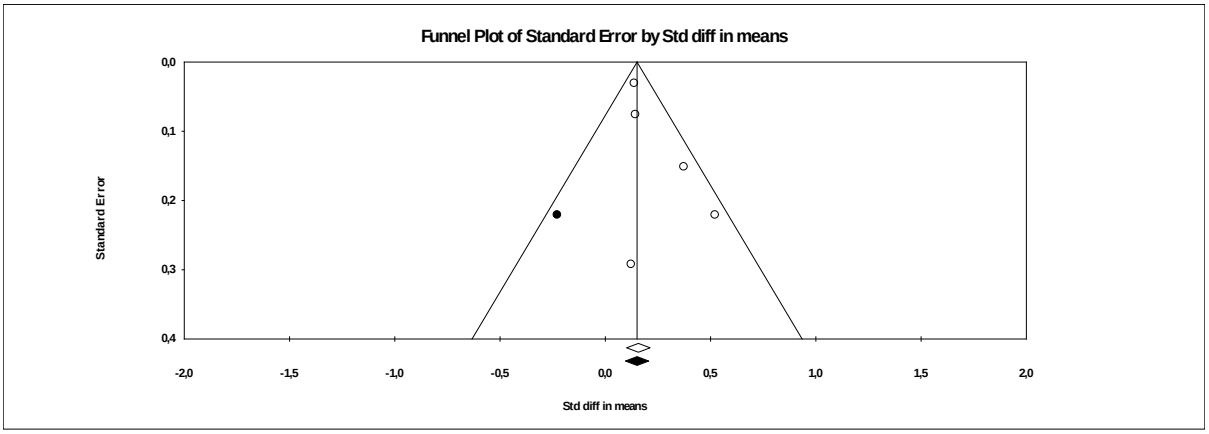
eFigure 7. Funnel Plot for Short-term Verbal Memory



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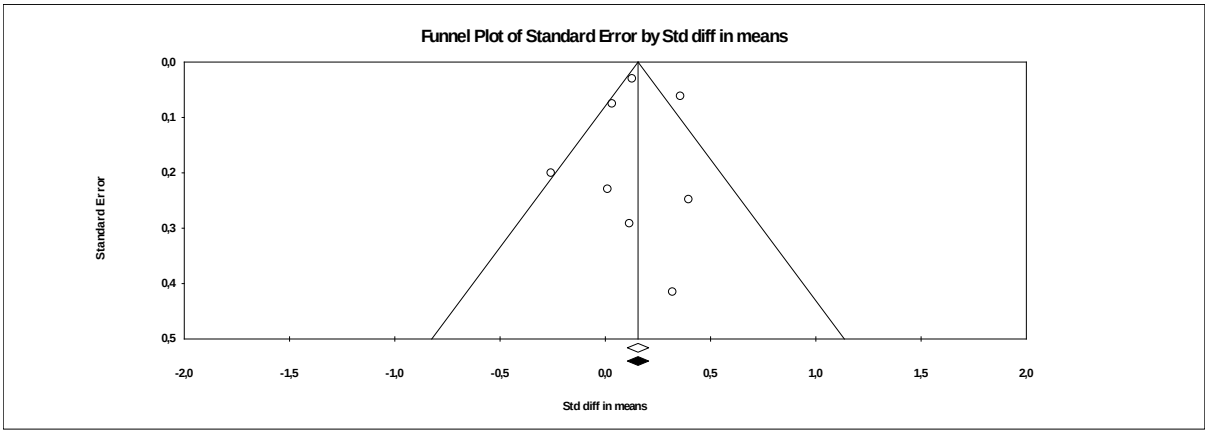
eFigure 8. Funnel Plot for Executive Functioning



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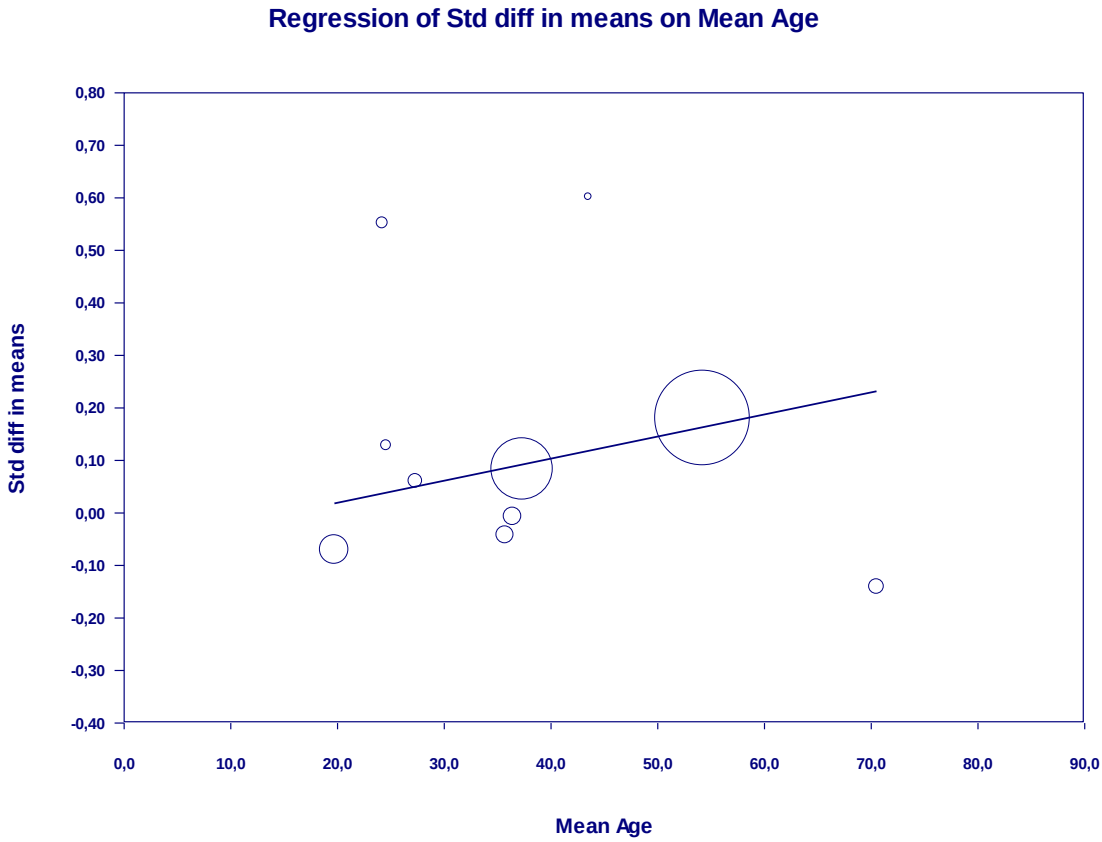
eFigure 9. Meta-regression Analysis of Processing Speed: Mean Age



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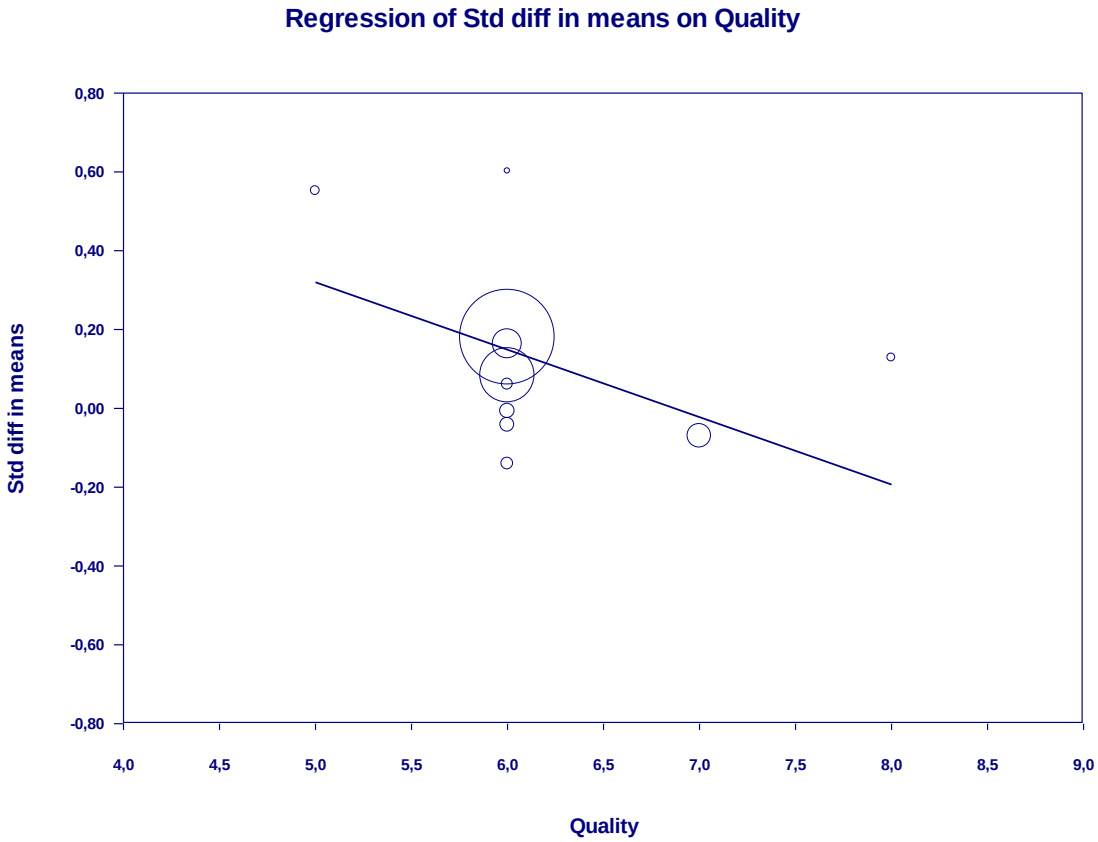
eFigure 10. Meta-regression Analysis of Processing Speed: Study Quality



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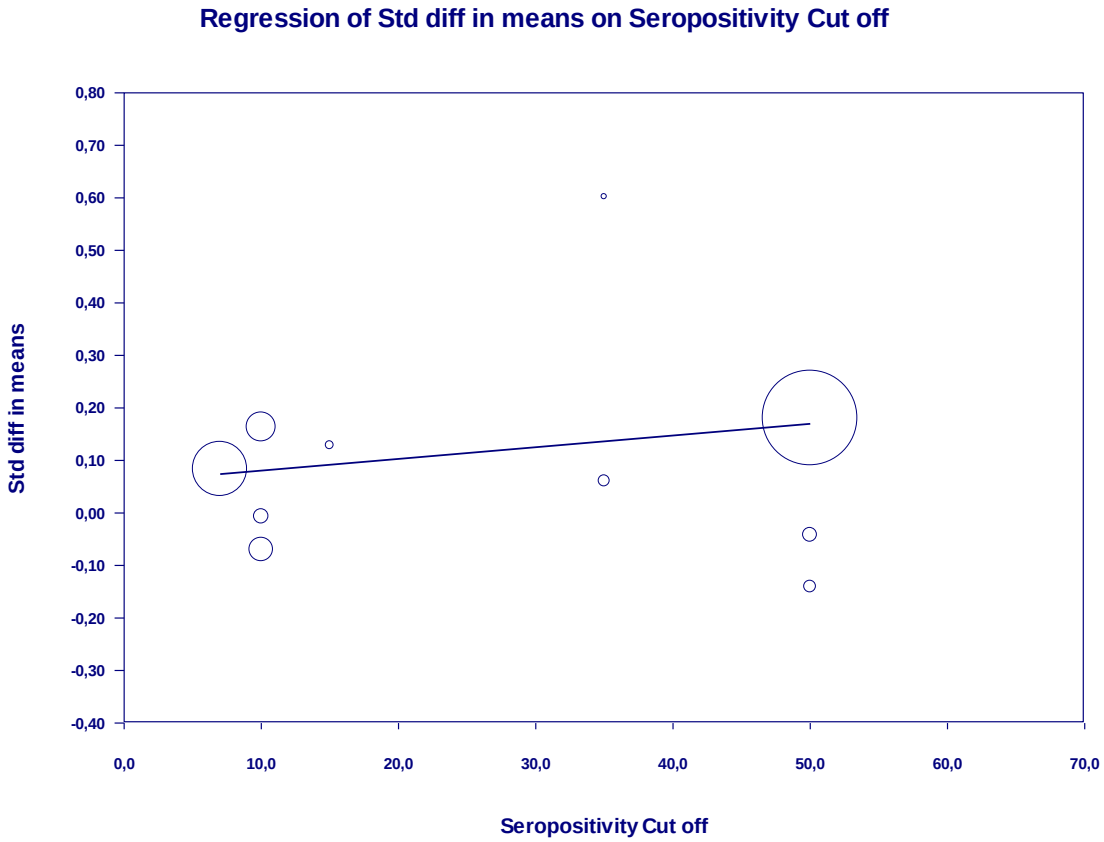
eFigure 11. Meta-regression Analysis of Processing Speed: Seropositivity Cutoff



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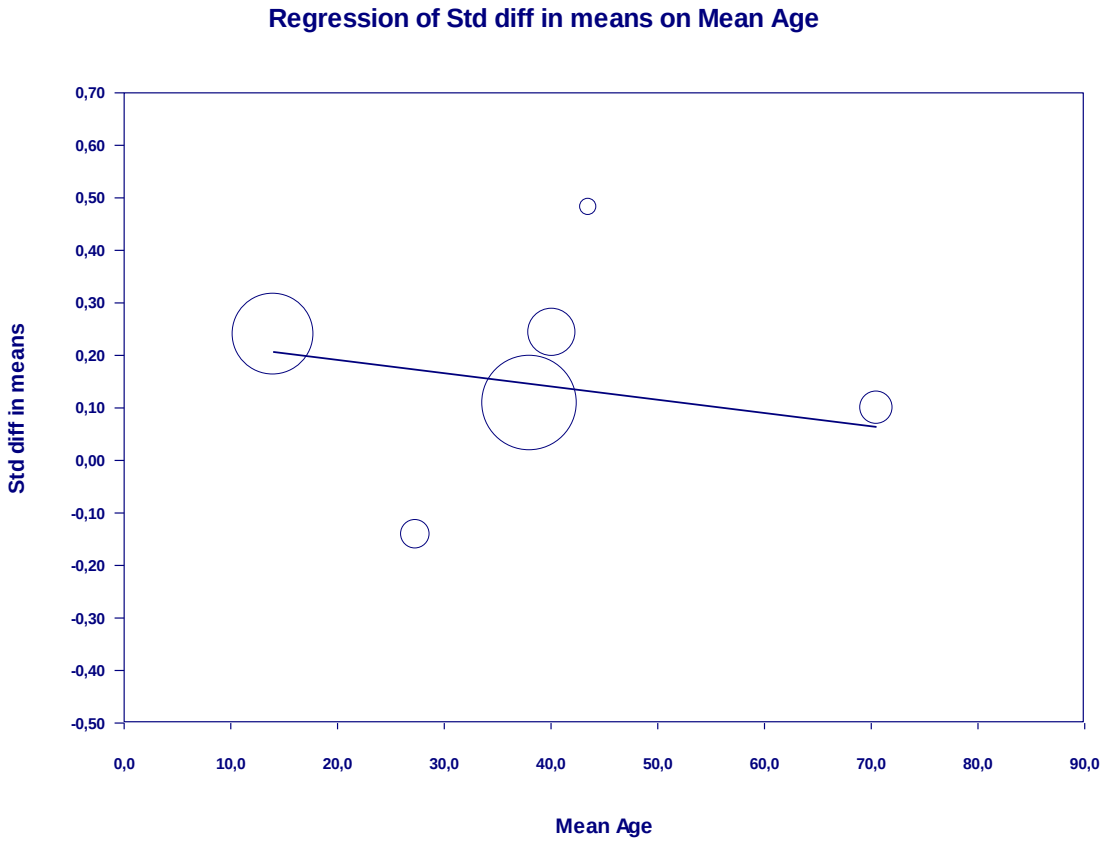
eFigure 12. Meta-regression Analysis of Working Memory: Mean Age



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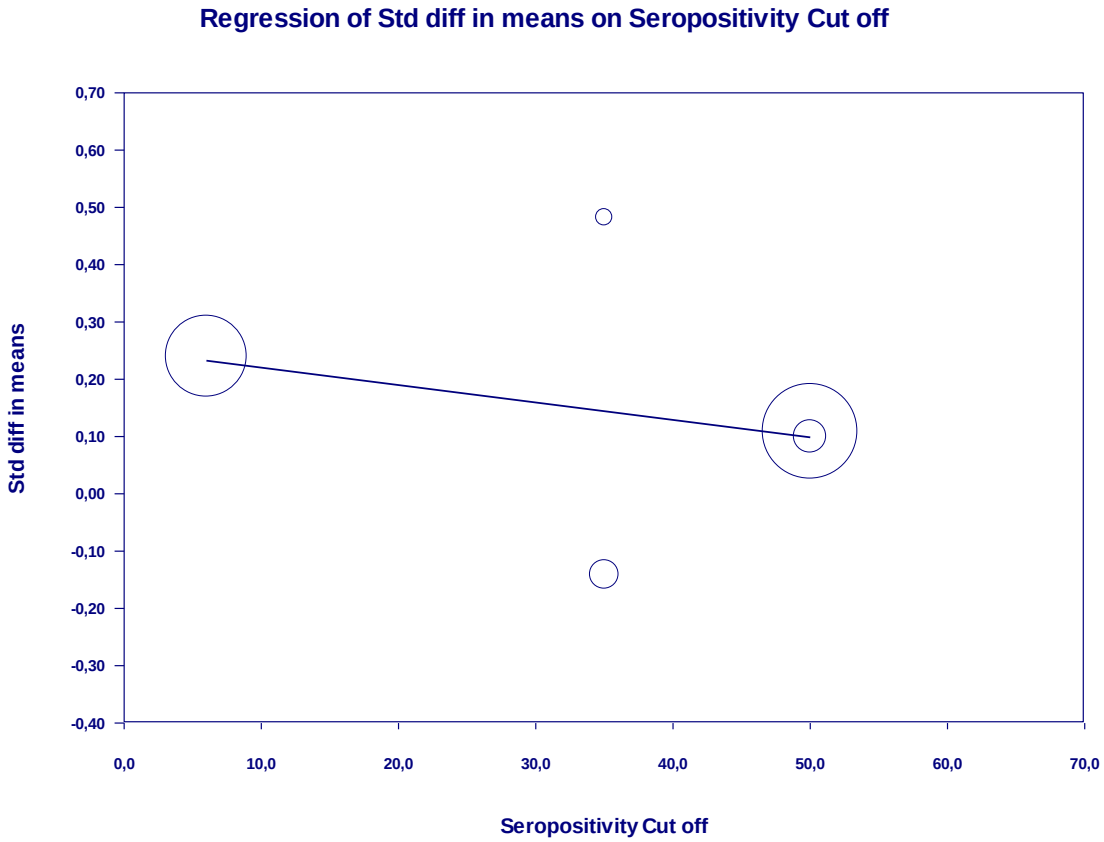
eFigure 13. Meta-regression Analysis of Working Memory: Seropositivity Cutoff



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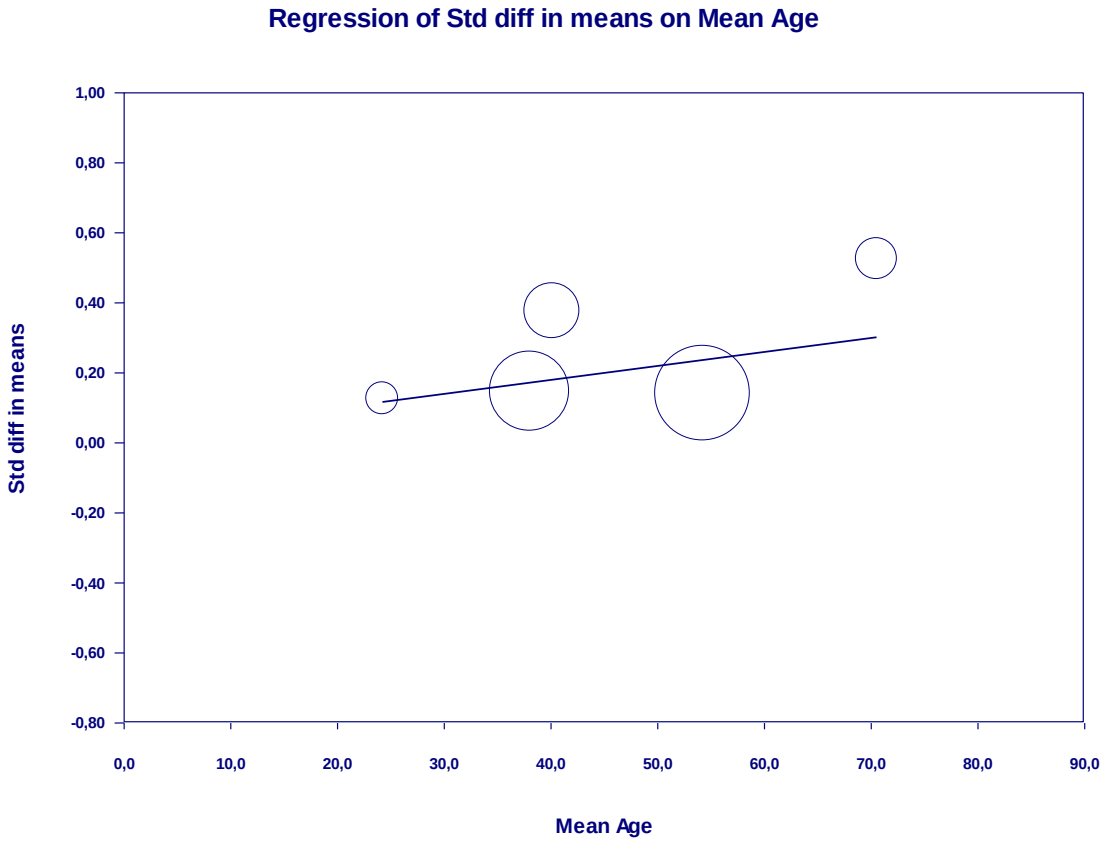
eFigure 14. Meta-regression Analysis of Short-term Verbal Memory: Mean Age



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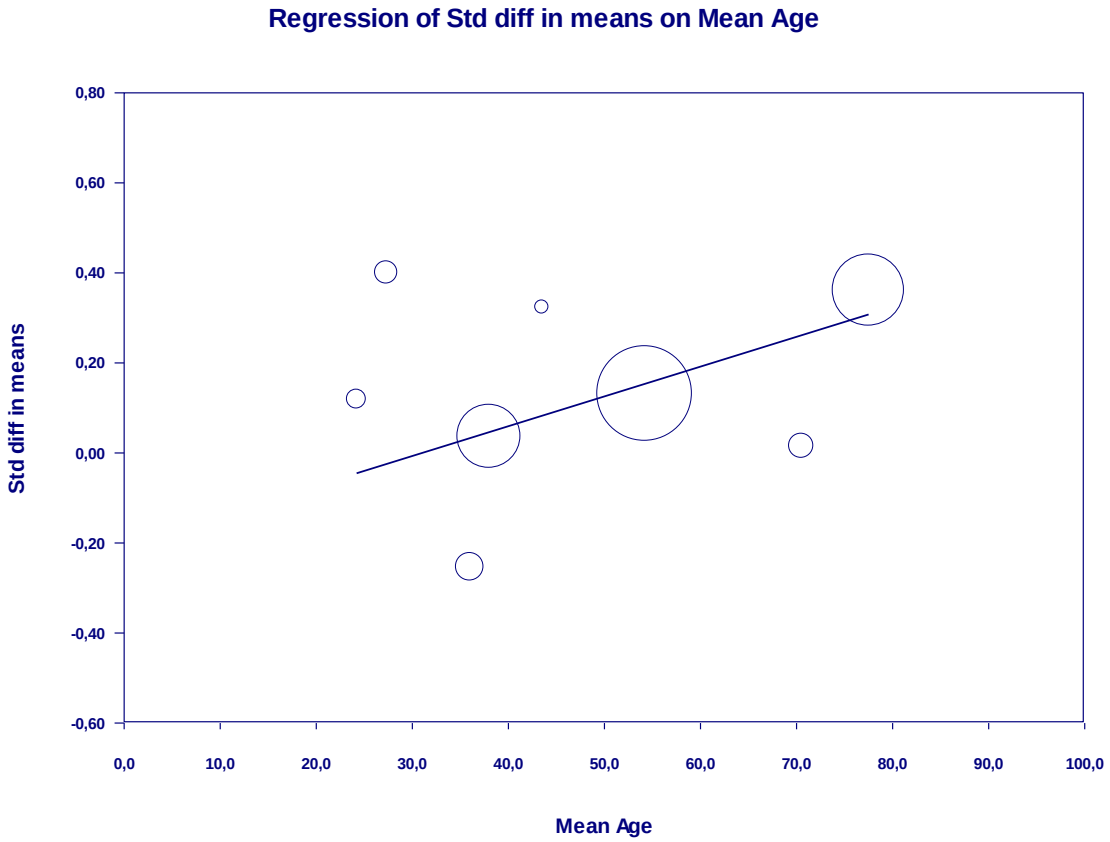
eFigure 15. Meta-regression Analysis of Executive Functioning: Mean Age



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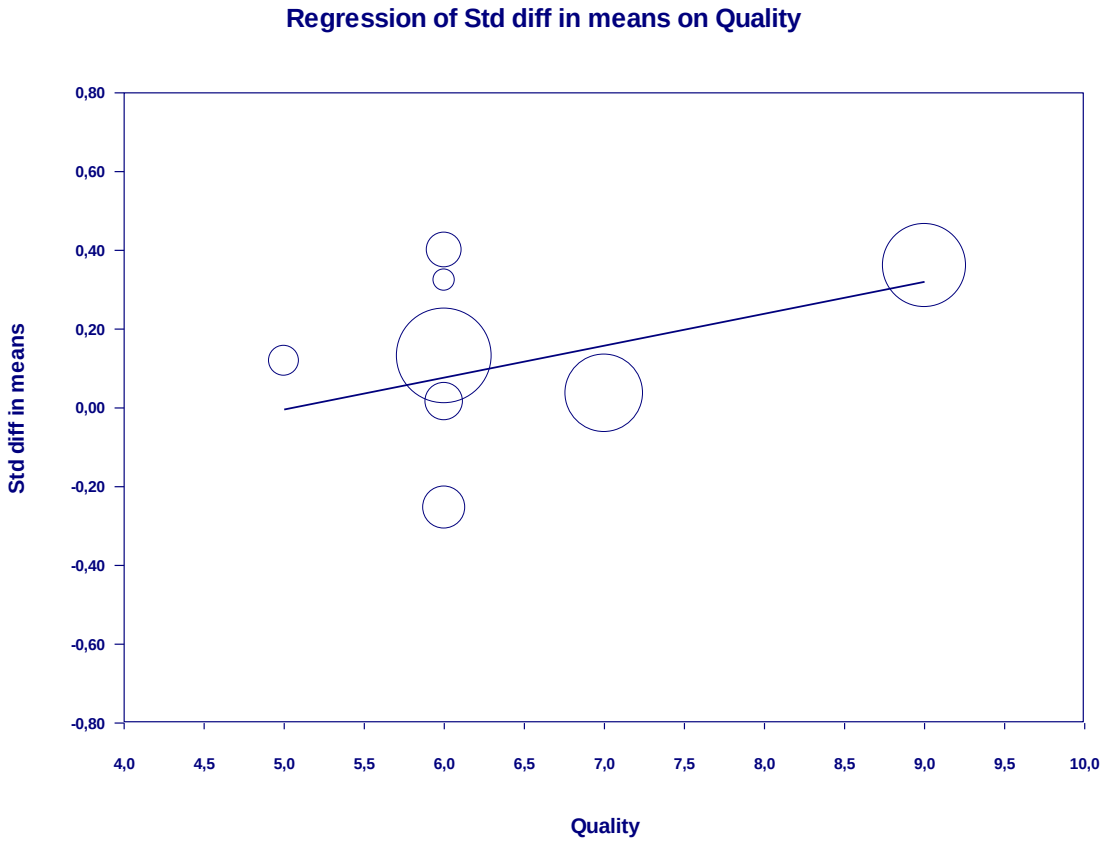
eFigure 16. Meta-regression Analysis of Executive Functioning: Study Quality



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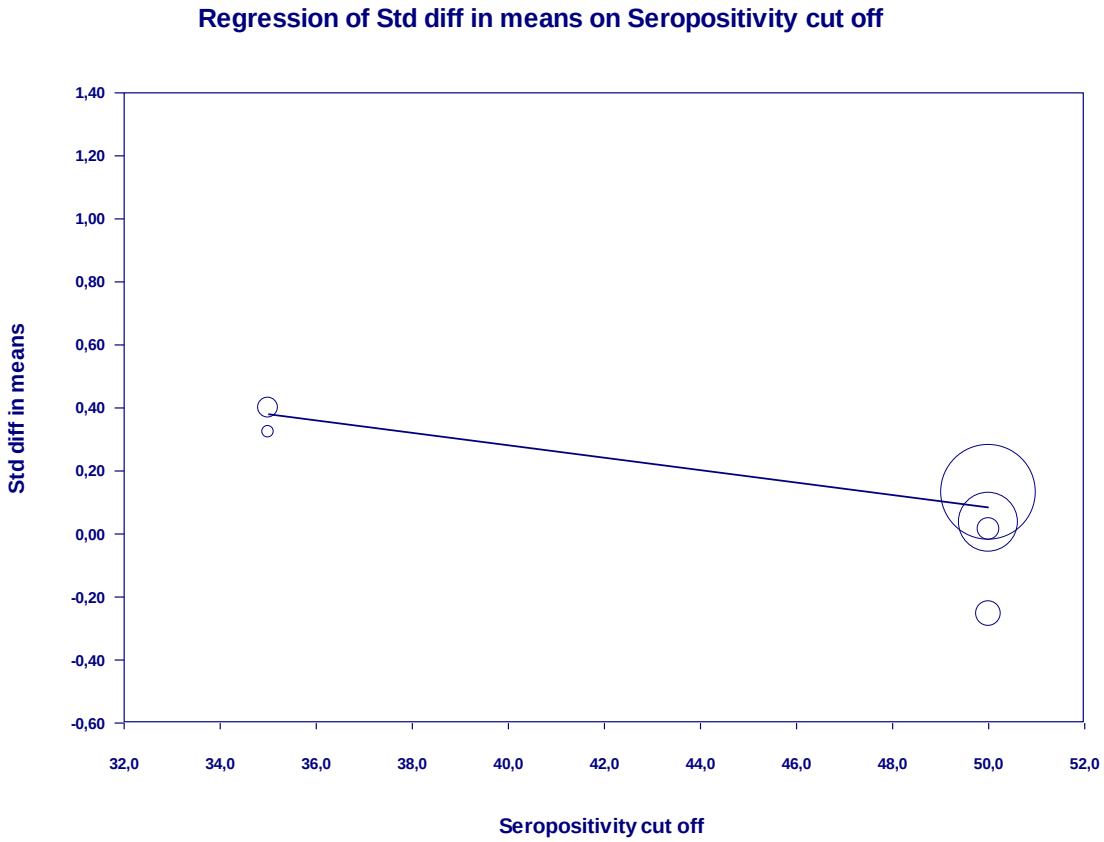
eFigure 17. Meta-regression Analysis of Executive Functioning: Seropositivity Cutoff



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