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Supplementary Material

Article Title: Long-Term Changes in Cognition Among Patients With Schizophrenia Spectrum Disorders and Different Durations of Illness: A Meta-Analysis

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Table 1. Search history

PsycInfo

#	Query / limiters
1	(Schizophrenia or Disorganized or Paranoid or Acute Schizophreniform disorder or Psychosis Schizoaffective disorder or Schizophrenia spectrum disorder Psychotic disorder).af.
2	(Delusion or Thought disturbances or Paranoia or Hallucinations or Visual or Auditory).af.
3	(Course or Prognosis or Disease or Evaluation or Rehabilitation or Remission or Recovery or Changes or Improvement or Deterioration or Development or Enhancement or Decrease or Decay or Depravation).af.
4	(Functioning or Social or Vocational or Work or Education or Relationships or Functional or Society or Symptom or Symptoms or Positive or Negative or Disorganized or Disorganization or Depression or Mood or Psychotic or Quality of life or QOL or Subjective or Well-being or Self-esteeem or Stigma or Personal or Recovery or Personal recovery or Cognition or Intelligence or IQ or Memory or Working or Long-term or Executive or Language or Motor or Perception or Processing speed or Recognition or Visuospatial).af.
5	1 and 2
6	3 and 4 and 5
7	limit 6 to (english language and abstracts and (2100 general psychology or 2224 clinical psychological testing or 2225 neuropsychological assessment or 2820 cognitive & perceptual development or 2840 psychosocial & personality development or 3000 social psychology or 3040 social perception & cognition or 3210 psychological disorders or 3213 schizophrenia & psychotic states or 3300 health & mental health treatment & prevention or 3310 psychotherapy & psychotherapeutic counseling or 3380 rehabilitation or 3384 occupational & vocational rehabilitation) and adulthood <18+ years> and ("300 adulthood <age 18 yrs and older>" or 320 young adulthood <age 18 to 29 yrs> or 340 thirties <age 30 to 39 yrs> or 360 middle age <age 40 to 64 yrs> or "380 aged <age 65 yrs and older>") and ("0100 journal" or "0110 peer-reviewed journal") and journal article and human")
Results	**5267**

Pubmed

Search number	Query	Results
1	(((((((schizophrenia[MeSH Terms]) OR (disorganized schizophrenia[MeSH Terms])) OR (catatonic schizophrenia[MeSH Terms])) OR (disorders, schizophreniform[MeSH Terms])) OR (disorders, schizophrenic[MeSH Terms])) OR (disorders, schizoaffective[MeSH Terms])) OR (psychosis[MeSH Terms])) OR (disorder, psychotic[MeSH Terms])	152,257
2	((((delusion[MeSH Terms]) OR (thought disturbance[MeSH Terms])) OR (behavior, paranoid[MeSH Terms])) OR (auditory hallucination[MeSH Terms])) OR (visual hallucinations[MeSH Terms])	12,750
3	((((((((((((((course, short term[MeSH Terms]) OR (course[MeSH Terms])) OR (prognosis[MeSH Terms])) OR (evaluation[MeSH Terms])) OR (care, self rehabilitation[MeSH Terms])) OR (rehabilitation[MeSH Terms])) OR (remission[MeSH Terms])) OR (recovery[MeSH Terms])) OR (changes[MeSH Terms])) OR (improvement[MeSH Terms])) OR (deterioration[MeSH Terms])) OR (development[MeSH Terms])) OR (enhancement[MeSH Terms])) OR (decrease[MeSH Terms])) OR (decay[MeSH Terms])) OR (depravation[MeSH Terms])	550,904
4	((((((((((((((((((((((((((((((((((((functioning[MeSH Terms]) OR (social[MeSH Terms])) OR (vocational[MeSH Terms])) OR (work[MeSH Terms])) OR (education[MeSH Terms])) OR (relationship[MeSH Terms])) OR (functional[MeSH Terms])) OR (society[MeSH Terms])) OR (friends society[MeSH Terms])) OR (symptoms[MeSH Terms])) OR (affective symptoms[MeSH Terms])) OR (positive symptoms[MeSH Terms])) OR (negative symptoms[MeSH Terms])) OR (disorganization[MeSH Terms])) OR (depression[MeSH Terms])) OR (disorder, mood[MeSH Terms])) OR (psychotic[MeSH Terms])) OR (quality of life[MeSH Terms])) OR (qol[MeSH Terms])) OR	1,655,594

	(subjective[MeSH Terms])) OR (wellbeing[MeSH Terms])) OR (self-esteem[MeSH Terms])) OR (social stigma[MeSH Terms])) OR (internalized stigma[MeSH Terms])) OR (self-stigma[MeSH Terms])) OR (personal recovery[MeSH Terms])) OR (cognition[MeSH Terms])) OR (intelligence[MeSH Terms])) OR (IQ[MeSH Terms])) OR (memory[MeSH Terms])) OR (working memory[MeSH Terms])) OR (long-term memory[MeSH Terms])) OR (executive functions[MeSH Terms])) OR (language[MeSH Terms])) OR (activity, motor[MeSH Terms])) OR (perception[MeSH Terms])) OR (processing speed[MeSH Terms])) OR (recognition[MeSH Terms])) OR (visuospatial[MeSH Terms])	
5	#1 AND #2 AND #3 AND #4	2862

CINAHL

#	Query	Limiters/Expanders	Results
S1	TI schizophrenia OR TI disorganized OR TI paranoid OR TI acute OR TI schizophreniform disorder OR TI schizoaffective disorder OR TI psychosis OR TI psychotic disorder OR TI schizophrenia spectrum OR TI delusion OR TI hallucination OR TI thought disturbance	Limiters - Abstract Available; English Language; Peer Reviewed; Research Article; Human; Journal Subset: Peer Reviewed; Publication Type: Journal Article; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years	49,264
S2	TI course OR TI prognosis OR TI evaluation OR TI rehabilitation OR TI remission OR TI recovery OR TI changes OR TI improvement OR TI enhancement OR TI development OR TI decrease OR TI deterioration	Limiters - Abstract Available; English Language; Peer Reviewed; Research Article; Journal Subset: Peer Reviewed; Publication Type: Journal Article; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years	13,042
S3	TI quality of life OR TI qol OR TI subjective OR TI well-being OR TI self-esteem OR TI self-efficacy OR TI empowerment OR TI stigma OR TI self-stigma OR TI personal recovery OR TI recovery	Limiters - Abstract Available; English Language; Peer Reviewed; Research Article; Journal Subset: Peer Reviewed; Publication Type: Journal Article; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years	2,236
S4	S1 OR S2 OR S3		11,490
S8	S1 AND S2 AND S4		1568

Pubmed

Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Schizophrenia] OR Schizophrenia Spectrum and Other Psychotic Disorders] OR [Psychotic Disorders] OR [Delusions] OR [Hallucinations] explode all trees	9795
#2	MeSH descriptor: [Disease Progression] OR [Mental Health Recovery] explode all trees OR (course of illness) OR (prognosis of illness) OR (changes in illness):ti,ab,kw	18104
#3	MeSH descriptor: [Mental Processes] explode all trees	124937
#4	#1 AND #2 AND #3	1357

Supplementary Table 2. Differences of demographic and functional characteristics at baseline between the baseline duration of illness subgroups

Continuous variables										
	Duration of illness (DOI) subgroups						Analysis of subgroup differences			
	1. DOI <5 years		2. DOI 5-10 years		3. DOI >10 years		ANOVA			
Baseline demographic, clinical and functional characteristics	M (SD)	K studies	M (SD)	K studies	M (SD)	K studies	F	Df	p	Specific subgroup differences
Age at baseline	34.1 (13.3)	28	33.0 (13.0)	7	42.7 (14.0)	14	0.49	2	0.62	None
Age at onset	24.5 (3.1)	25	26.1 (2.1)	6	25.0 (4.2)	12	0.54	2	0.59	None
Baseline level of motor skills and construction[H]	27.6 (20.2)	10	53.0 (39.9)	3	62.6 (26.1)	7	4.16	2	0.03	1 < 3
Baseline level of attention and vigilance[H]	66.8 (19.5)	6	53.9 (21.1)	4	20.6 (29.0)	3	4.34	3	0.04	1 > 3
Baseline level of verbal memory[H]	66.3 (26.5)	13	59.6 (20.9)	6	49.7 (22.5)	8	1.16	2	0.33	None
Baseline level of visual memory[H]	67.3 (29.9)	10	65.7 (24.3)	6	50.3 (29.3)	5	0.65	2	0.54	None
Baseline level of executive functioning[H]	52.6 (29.3)	16	58.2 (37.3)	5	48.7 (37.7)	10	0.14	2	0.89	None
Baseline level of processing speed[H]	50.8 (25.4)	6	26.3 (19.3)	5	42.8 (27.2)	8	1.37	2	0.28	None
Baseline level of language skills[H]	41.8 (43.1)	7	42.7 (3.0)	3	47.7 (29.6)	3	0.03	2	0.97	None
Baseline level of overall cognition[H]	36.9 (26.3)	14	69.9 (27.5)	3	48.2 (32.8)	7	1.75	2	0.20	None
Baseline severity of negative symptoms[L]	44.3 (27.7)	16	23.2 (19.1)	5	28.8 (25.9)	6	1.62	2	0.22	None
Baseline severity of overall symptoms[L]	37.0 (24.8)	12	26.1 (32.6)	6	36.1 (23.1)	6	0.37	2	0.70	None
Baseline severity of positive symptoms[L]	45.3 (22.9)	17	20.9 (11.3)	5	38.2 (25.3)	7	2.35	2	0.12	1 > 2
Duration of Untreated Psychosis (DUP) in months	13.2 (11.7)	5	13.3 (2.2)	3	NA	NA	0.26	2	0.78	None
Ethnicity: % caucasian / white / born in country of residence	66.5 (24.6)	10	NA	NA	69.2 (18.9)	4	0.15	2	0.86	None
Gender: % female	34.1 (14.4)	27	38.3 (11.2)	7	31.5 (15.1)	15	0.57	2	0.57	None
General functioning at baseline[H]	35.2 (13.1)	6	75.2 (21.8)	3	45.7 (4.3)	2	2.90	2	0.11	None
Hospitalization: Percentage (%) of participants who are hospitalized at baseline	64.0 (46.5)	7	34.9 (49.3)	2	100.0 (0.0)	2	1.11	2	0.38	None
IQ score at baseline[H]	97.6 (6.7)	8	NA	NA	93.4 (11.7)	7	0.75	2	0.40	None
Percentage (%) of schizoaffective disorder	15.3 (9.0)	12	6.4 (6.9)	2	10.7 (7.9)	6	0.62	2	0.61	None

Categorical variables										
	Duration of illness (DOI) subgroups						Analysis of subgroup differences			
	1. DOI <5 years		2. DOI 5-10 years		3. DOI >10 years		Chi-squared			
Baseline demographic, clinical and functional characteristics	n (%)	K studies	n (%)	K studies	n (%)	K studies	χ^2	Df	p	Specific subgroup differences
All participants diagnosed with schizophrenia	14 (53.8%)	26	5 (71.4%)	7	7 (53.8%)	13	0.75	2	0.69	None
Antipsychotic use by all participants	9 (52.8%)	17	4 (66.7%)	6	4 (40.0%)	10	1.10	2	0.58	None
Duration of illness subgroup overlap: The range of the duration of illness of the study sample overlaps with other duration of illness subgroups	9 (45.0%)	20	1 (20.0%)	5	5 (45.5%)	11	1.12	2	0.57	None
High level of education	9 (50.0%)	18	2 (33.3%)	6	7 (58.3%)	12	1.00	2	0.61	None
Publication less than 10 years ago	10 (35.7%)	28	1 (14.3%)	7	4 (26.7%)	15	1.34	2	0.51	None
Study design: clinical trial	3 (10.7%)	28	0 (0.0%)	7	3 (20.0%)	15	1.91	2	0.39	None
Treatment focused on outcomes	1 (16.7%)	6	0 (0.0%)	2	1 (16.7%)	7	0.39	2	0.82	None

^{H} = a higher score indicates better functioning and lower severity; ^{L} = a lower score indicates better functioning and lower severity

* NA = Not Applicable: baseline data available for less than 2 studies

Supplementary Table 3. Meta-analysis of subdomains of cognition.

Sensation and perception						
(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		9	506 - 499	*d* = 0.10 [N] (-0.13 to 0.33)	+ = 0/ - = 1	**I^2 = 79%** (67-87%)
Subgroups						
Baseline subgroup	*Follow-up cohort*					
Duration of illness < 5 years	< 2 years	3	299 - 299	*d* = **0.19** [N] (0.06 to 0.33)[2]	+ = 0/ - = 0	I^2 = 0% (0-52%)
	≥ 2 - < 5 years	3	196 - 196	*d* = **0.40** [S] (0.21 to 0.59)[3]	+ = 0/ - = 0	I^2 = 16% (0-48%)
	≥ 8 years	2	58 - 58	*d* = -0.48 [S] (-1.33 to 0.37)	+ = 0/ - = 1	**I^2 = 86%** (NA)
	Subgroup differences between follow-up cohorts			χ^2 = 5.81; *df* = 2; *p* = 0.05		
Duration of illness 5-10 years	< 2 years	1	39 - 39	*d* = 0.70 [M] (0.24 to 1.16)[1]	+ = 0/ - = 0	Not Applicable
	≥ 8 years	1	12 - 12	*d* = 0.07 [N] (-0.87 to 0.73)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 2.67; *df* = 1; *p* = 0.10		
Duration of illness >10 years	≥ 2 - < 5 years	1	50 - 43	*d* = -0.56 [M] (-0.97 to -0.15)[1]	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			*Not Applicable*		
Duration of illness unclear	**There are no studies available for this subgroup**					
Motor skills and construction						
(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K (%) large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		20	1782 - 1736	*d* = 0.05 [N] (-0.07 to 0.16)	+ = 0/ - = 0	**I^2 = 73%** (59-83%)
Subgroups						
Baseline subgroup	*Follow-up cohort*					
Duration of illness < 5 years	< 2 years	6	698 - 577	*d* = **0.12** [N] (0.02 to 0.23)[3]	+ = 0/ - = 0	I^2 = 0% (0-73%)
	≥ 2 - < 5 years	2	660 - 660	*d* = **0.30** [S] (0.20 to 0.40)	+ = 0/ - = 0	I^2 = 0% (NA)
	≥ 8 years	4	283 - 283	*d* = 0.11 [N] (-0.29 to 0.52)	+ = 0/ - = 0	I^2 = 47% (0-76%)
	Subgroup differences between follow-up cohorts			χ^2 = 5.99; *df* = 2; *p* = 0.05		
Duration of illness 5-10 years	< 2 years	2	86 - 86	*d* = 0.24 [S] (-0.65 to 1.13)	+ = 0/ - = 0	**I^2 = 88%** (NA)
	≥ 2 - < 5 years	1	11 - 10	*d* = -0.07 [N] (-0.92 to 0.78)	+ = 0/ - = 0	Not Applicable

	≥ 5 - < 8 years	1	58 - 58	*d* = 0.24 [S] (-0.13 to 0.61)	+ = 0/ - = 0	Not Applicable
	≥ 8 years	1	12 - 12	*d* = -0.45 [N] (-1.26 to 0.36)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 2.54; *df* = 3; *p* = 0.47		
Duration of illness >10 years	< 2 years	2	193 - 193	*d* = -0.11 [N] (-0.25 to 0.03)[1]	+ = 0/ - = 0	I^2 = 0% (NA)
	≥ 2 - < 5 years	1	50 - 43	*d* = -0.37 [S] (-0.78 to 0.04)	+ = 0/ - = 0	Not Applicable
	≥ 5 - < 8 years	3	331 - 331	*d* = -0.21 [S] (-0.63 to 0.21)	+ = 0/ - = 0	**I^2 = 82%** (34-95%)
	Subgroup differences between follow-up cohorts			χ^2 = 1.53; *df* = 2; *p* = 0.47		
Duration of illness unclear	< 2 years	1	38 - 38	*d* = -0.24 [S] (-0.56 to 0.08)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			*Not Applicable*		

Attention and vigilance

(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K (%) large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		16	2240 - 1873	*d* = -0.02 [N] (-0.07 to 0.02)	+ = 2/ - = 0	**I^2 = 84%** (78-88%)
Subgroups						
Baseline subgroup	*Follow-up cohort*					
Duration of illness < 5 years	< 2 years	5	440 - 420	*d* = 0.22 [S] (-0.02 to 0.46)[2]	+ = 0/ - = 0	**I^2 = 78%** (50-91%)
	≥ 2 - < 5 years	4	757 - 754	*d* = -0.12 [N] (-0.41 to 0.18)	+ = 0/ - = 0	**I^2 = 88%** (70-95%)
	≥ 8 years	1	149 - 149	*d* = -0.16 [N] (-0.39 to 0.07)[2]	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 19.21; *df* = 2; *p* < 0.01		
Duration of illness 5-10 years	< 2 years	3	154 - 121	*d* = 0.02 [N] (-0.60 to 0.55)[1]	+ = 1/ - = 0	**I^2 = 88%** (60-97%)
	≥ 2 - < 5 years	1	12 - 12	*d* = 0.06 [N] (-0.74 to 0.86)	+ = 0/ - = 0	Not Applicable
	≥ 8 years	1	12 - 12	*d* = **1.01** [L] (0.15 to 1.87)[1]	+ = 1/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 8.45; *df* = 2; *p* < 0.05		
Duration of illness >10 years	≥ 2 - < 5 years	2	957 - 654	*d* = 0.07 [N] (-0.40 to 0.54)	+ = 0/ - = 0	**I^2 = 75%** (NA)
	Subgroup differences between follow-up cohorts			*Not Applicable*		
	< 2 years	2	113 - 105	*d* = 0.19 [N] (-0.38 to 0.77)	+ = 0/ - = 0	**I^2 = 85%** (NA)

Duration of illness unclear	**Subgroup differences between follow-up cohorts**		*Not Applicable*		
Verbal memory					
(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K (%) large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		31	3402 - 2898	*d* = **0.21** [S] (0.13 to 0.28)	+ = 1/ - = 0	**I^2 = 77%** (72-81%)
Subgroups						
Baseline subgroup	*Follow-up cohort*					
Duration of illness < 5 years	< 2 years	8	728 - 690	*d* = **0.25** [S] (0.18 to 0.31)[2]	+ = 0/ - = 0	I^2 = 5% (0-70%)
	≥ 2 - < 5 years	4	778 - 778	*d* = **0.27** [S] (0.16 to 0.38)[3]	+ = 0/ - = 0	**I^2 = 65%** (7-87%)
	≥ 8 years	4	465 - 380	*d* = -0.06 [N] (-0.41 to 0.29)	+ = 0/ - = 0	**I^2 = 76%** (35-91%)
	Subgroup differences between follow-up cohorts			χ^2 = 3.24; *df* = 2; *p* = 0.20		
Duration of illness 5-10 years	< 2 years	6	333 - 265	*d* = **0.49** [S] (0.28 to 0.69)[13]	+ = 1/ - = 0	I^2 = 55% (17-76%)
	≥ 2 - < 5 years	1	50 - 50	*d* = **0.27** [S] (0.07 to 0.47)[3]	+ = 0/ - = 0	Not Applicable
	≥ 5 - < 8 years	1	58 - 58	*d* = 0.11 [N] (-0.15 to 0.37)	+ = 0/ - = 0	Not Applicable
	≥ 8 years	1	12 - 12	*d* = <u>0.36</u> [S] (-0.45 to 1.17)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 5.20; *df* = 3; *p* = 0.16		
Duration of illness >10 years	< 2 years	4	295 - 273	*d* = 0.05 [N] (-0.24 to 0.35)[2]	+ = 0/ - = 0	**I^2 = 83%** (53-94%)
	≥ 2 - < 5 years	4	1043 - 737	*d* = -0.01 [N] (-0.13 to 0.12)[12]	+ = 0/ - = 0	I^2 = 31% (0-62%)
	≥ 5 - < 8 years	3	334 - 334	*d* = 0.01 [N] (-0.11 to 0.13)	+ = 0/ - = 0	I^2 = 0% (0-93%)
	Subgroup differences between follow-up cohorts			χ^2 = 0.14; *df* = 2; *p* = 0.93		
Duration of illness unclear	< 2 years	2	113 - 105	*d* = <u>0.61</u> [M] (0.28 to 0.94)	+ = 0/ - = 0	**I^2 = 75%** (NA)
	≥ 2 - < 5 years	1	14 - 14	*d* = -0.09 [N] (-0.83 to 0.65)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 2.84; *df* = 1; *p* = 0.09		
Visual memory					
(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K (%) large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		24	2909 - 2393	*d* = **0.17** [N] (0.07 to 0.26)	+ = 2/ - = 0	**I^2 = 80%** (74-84%)

Subgroups						
Baseline subgroup	*Follow-up cohort*					
Duration of illness < 5 years	< 2 years	7	708 - 603	*d* = **0.22** [S] (0.07 to 0.38)[3]	+ = 0/ - = 0	**I^2 = 64%** (35-80%)
	≥ 2 - < 5 years	4	721 - 721	*d* = **0.31** [S] (0.18 to 0.43)	+ = 0/ - = 0	I^2 = 21% (0-90%)
	≥ 8 years	4	476 - 377	*d* = 0.10 [N] (-0.24 to 0.44)	+ = 0/ - = 0	**I^2 = 85%** (60-94%)
	Subgroup differences between follow-up cohorts			χ^2 = 1.60; *df* = 2; *p* = 0.45		
Duration of illness 5-10 years	< 2 years	5	276 - 190	*d* = 0.30 [S] (-0.14 to 0.75)	+ = 2/ - = 0	**I^2 = 86%** (70-94%)
	≥ 2 - < 5 years	1	50 - 50	*d* = 0.04 [N] (-0.24 to 0.32)	+ = 0/ - = 0	Not Applicable
	≥ 5 - < 8 years	1	58 - 58	*d* = 0.23 [S] (-0.03 to 0.49)	+ = 0/ - = 0	Not Applicable
	≥ 8 years	1	12 - 12	*d* = -0.27 [S] (-0.84 to 0.30)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 3.44; *df* = 3; *p* = 0.33		
Duration of illness >10 years	< 2 years	3	129 - 129	*d* = 0.00 [N] (-0.12 to 0.13)[1]	+ = 0/ - = 0	I^2 = 0% (0-95%)
	≥ 2 - < 5 years	2	999 - 696	*d* = 0.20 [S] (-0.29 to 0.69)	+ = 0/ - = 0	**I^2 = 95%** (NA)
	≥ 5 - < 8 years	1	78 - 78	*d* = **0.53** [M] (0.08 to 0.98)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 5.28; *df* = 2; *p* = 0.07		
Duration of illness unclear	< 2 years	2	113 - 105	*d* = 0.10 [N] (-0.14 to 0.35)	+ = 0/ - = 0	I^2 = 41% (NA)
	Subgroup differences between follow-up cohorts			*Not Applicable*		
Executive functioning						
(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K (%) large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		36	3568 - 3058	*d* = **0.19** [N] (0.12 to 0.26)	+ = 2/ - = 1	**I^2 = 75%** (70-80%)
Subgroups						
Baseline subgroup	*Follow-up cohort*					
Duration of illness < 5 years	< 2 years	9	692 - 653	*d* = **0.23** [S] (0.09 to 0.38)	+ = 1/ - = 0	**I^2 = 77%** (61-87%)
	≥ 2 - < 5 years	6	863 - 863	*d* = **0.29** [S] (0.06 to 0.53)	+ = 1/ - = 0	**I^2 = 73%** (45-87%)
	≥ 8 years	4	481 - 371	*d* = 0.08 [S] (-0.15 to 0.30)	+ = 0/ - = 0	I^2 = 56% (0-82%)
	Subgroup differences between follow-up cohorts			χ^2 = 1.86; *df* = 2; *p* = 0.39		
Duration of illness 5-10 years	< 2 years	6	334 - 283	*d* = **0.45** [S] (0.28 to 0.62)	+ = 0/ - = 0	I^2 = 56% (18-76%)
	≥ 2 - < 5 years	3	77 - 77	*d* = 0.25 [S] (-0.11 to 0.61)	+ = 0/ - = 0	**I^2 = 61%** (0-89%)
	≥ 5 - < 8 years	1	58 - 58	*d* = 0.10 [N] (-0.11 to 0.31)	+ = 0/ - = 0	Not Applicable

	≥ 8 years	1	12 - 12	*d* = -0.01 [N] (-0.41 to 0.39)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 8.79; *df* = 3; *p* < 0.05		
Duration of illness >10 years	< 2 years	4	147 - 136	*d* = 0.14 [N] (-0.01 to 0.28)	+ = 0/ - = 0	I^2 = 0% (0-99%)
	≥ 2 - < 5 years	6	1175 - 862	*d* = 0.04 [N] (-0.18 to 0.27)	+ = 0/ - = 1	**I^2 = 86%** (72-93%)
	≥ 5 - < 8 years	2	116 - 116	*d* = 0.07 [N] (-0.22 to 0.35)	+ = 0/ - = 0	I^2 = 0% (NA)
	Subgroup differences between follow-up cohorts			χ^2 = 0.55; *df* = 2; *p* = 0.76		
Duration of illness unclear	< 2 years	2	167 - 159	*d* = 0.02 [N] (-0.08 to 0.12)	+ = 0/ - = 0	I^2 = 0% (NA)
	≥ 2 - < 5 years	1	14 - 14	*d* = -0.27 [S] (-1.01 to 0.47)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 0.58; *df* = 1; *p* = 0.45		

Processing speed

(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K (%) large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		21	2940 - 2445	*d* = **0.32** [S] (0.22 to 0.41)	+ = 1/ - = 0	**I^2 = 76%** (%)
Subgroups						
Baseline subgroup	*Follow-up cohort*					
Duration of illness < 5 years	< 2 years	4	459 - 439	*d* = 0.20 [S] (0.01 to 0.39)	+ = 0/ - = 0	**I^2 = 64%** (5-86%)
	≥ 2 - < 5 years	2	660 - 660	*d* = **0.45** [S] (0.34 to 0.56)[3]	+ = 0/ - = 0	I^2 = 0% (NA)
	≥ 8 years	3	420 - 325	*d* = 0.27 [S] (-0.35 to 0.89)	+ = 0/ - = 0	**I^2 = 89%** (61-97%)
	Subgroup differences between follow-up cohorts			χ^2 = 4.92; *df* = 2; *p* = 0.09		
Duration of illness 5-10 years	< 2 years	3	294 - 226	*d* = 0.43 [S] (0.01 to 0.85)	+ = 1/ - = 0	**I^2 = 87%** (67-95%)
	≥ 2 - < 5 years	2	65 - 65	*d* = **0.40** [S] (0.12 to 0.69)	+ = 0/ - = 0	I^2 = 0% (NA)
	≥ 8 years	1	12 - 12	*d* = -0.07 [S] (-0.87 to 0.73)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 1.28; *df* = 2; *p* = 0.53		
Duration of illness >10 years	< 2 years	1	78 - 78	*d* = 0.29 [S] (-0.02 to 0.60)	+ = 0/ - = 0	Not Applicable
	≥ 2 - < 5 years	4	1065 - 759	*d* = 0.18 [N] (-0.02 to 0.38)[1]	+ = 0/ - = 0	**I^2 = 66%** (10-87%)
	≥ 5 - < 8 years	2	138 - 138	*d* = 0.21 [S] (-0.03 to 0.45)	+ = 0/ - = 0	I^2 = 5% (NA)
	Subgroup differences between follow-up cohorts			χ^2 = 0.31; *df* = 2; *p* = 0.86		
	< 2 years	2	113 - 105	*d* = 0.40 [S] (0.27 to 0.54)	+ = 0/ - = 0	I^2 = 0% (NA)
	≥ 2 - < 5 years	1	84 - 84	*d* = 0.58 [M] (0.27 to 0.89)	+ = 0/ - = 0	Not Applicable

Duration of illness unclear	**Subgroup differences between follow-up cohorts**			χ^2 = 1.06; *df* = 1; *p* = 0.30		
Language skills						
(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K (%) large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		15	1438 - 1311	*d* = **0.13** [N] (0.05 to 0.22)	+ = 0/ - = 0	**I^2 = 63%** (51-72%)
Subgroups						
Baseline subgroup	*Follow-up cohort*					
Duration of illness < 5 years	< 2 years	5	501 - 481	*d* = **0.16** [N] (0.01 to 0.30)	+ = 0/ - = 0	I^2 = 50% (2-75%)
	≥ 2 - < 5 years	1	93 - 93	*d* = 0.21 [S] (0.10 to 0.32)	+ = 0/ - = 0	Not Applicable
	≥ 8 years	1	246 - 140	*d* = 0.16 [N] (-0.04 to 0.36)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 0.39; *df* = 2; *p* = 0.82		
Duration of illness 5-10 years	< 2 years	3	114 - 114	*d* = 0.14 [N] (-0.06 to 0.34)	+ = 0/ - = 0	I^2 = 0% (0-44%)
	≥ 2 - < 5 years	2	26 - 25	*d* = 0.39 [S] (-0.12 to 0.89)	+ = 0/ - = 0	I^2 = 16% (NA)
	≥ 5 - < 8 years	1	58 - 58	*d* = -0.11 [N] (-0.47 to 0.25)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 2.64; *df* = 2; *p* = 0.27		
Duration of illness >10 years	< 2 years	2	246 - 246	*d* = 0.05 [N] (-0.23 to 0.33)	+ = 0/ - = 0	**I^2 = 80%** (NA)
	≥ 2 - < 5 years	2	395 - 395	*d* = 0.40 [S] (0.22 to 0.57)	+ = 0/ - = 0	I^2 = 0% (NA)
	≥ 5 - < 8 years	4	409 - 409	*d* = 0.01 [N] (-0.19 to 0.22)	+ = 0/ - = 0	**I^2 = 65%** (6-87%)
	Subgroup differences between follow-up cohorts			χ^2 = 9.14; *df* = 2; *p* < 0.05		
Duration of illness unclear	**There are no studies available for this subgroup**					
Social cognition						
(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K (%) large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		6	1135 - 824	*d* = 0.11 [N] (-0.07 to 0.28)	+ = 0/ - = 0	**I^2 = 59%** (22-78%)
Subgroups						
Baseline subgroup	*Follow-up cohort*					
	< 2 years	2	89 - 89	*d* = **0.23** [S] (0.06 to 0.41)	+ = 0/ - = 0	I^2 = 26% (NA)

Duration of illness < 5 years	≥ 2 - < 5 years	1	25 - 25	*d* = -0.67 [S] (-1.24 to -0.10)[3]	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 8.83; *df* = 1; *p* < 0.01		
Duration of illness 5-10 years	**There are no studies available for this subgroup**					
Duration of illness >10 years	< 2 years	1	25 - 25	*d* = -0.02 [N] (-0.30 to 0.26)	+ = 0/ - = 0	Not Applicable
	≥ 2 - < 5 years	1	921 - 618	*d* = 0.25 [S] (-0.11 to 0.61)[1]	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 1.32; *df* = 1; *p* = 0.25		
Duration of illness unclear	< 2 years	1	75 - 67	*d* = 0.12 [N] (-0.11 to 0.35)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			*Not Applicable*		

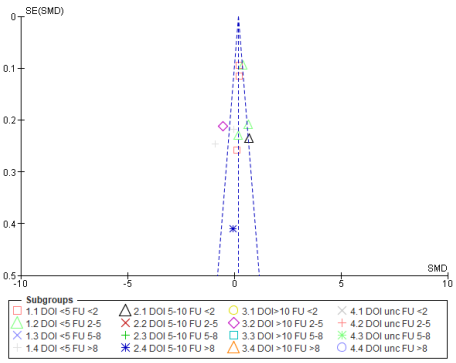
Overall cognition

(Sub)analysis		K (studies)	N (baseline-FU)	Effect size (95% CI)* and magnitude of effect**	K (%) large effect** [+/-]***	Heterogeneity (I^2 (95%CI))*
All studies and outcomes		30	3607 - 3123	*d* = **0.13** [N] (0.05 to 0.22)	+ = 1/ - = 0	**I^2 = 78%** (73-82%)
Subgroups						
Baseline subgroup	*Follow-up cohort*					
Duration of illness < 5 years	< 2 years	6	347 - 330	*d* = **0.35** [S] (0.17 to 0.52)	+ = 0/ - = 0	**I^2 = 40%** (2-63%)
	≥ 2 - < 5 years	5	1681 - 1249	*d* = 0.11 [N] (-0.10 to 0.32)	+ = 0/ - = 0	**I^2 = 81%** (57-92%)
	≥ 5 - < 8 years	1	1022 - 602	*d* = **0.35** [S] (0.25 to 0.45)	+ = 0/ - = 0	Not Applicable
	≥ 8 years	3	200 - 200	*d* = 0.07 [N] (-0.48 to 0.62)[3]	+ = 0/ - = 0	**I^2 = 85%** (45-96%)
	Subgroup differences between follow-up cohorts			χ^2 = 4.88; *df* = 3; *p* = 0.18		
Duration of illness 5-10 years	< 2 years	1	47 - 47	*d* = -0.03 [N] (-0.43 to 0.37)	+ = 0/ - = 0	Not Applicable
	≥ 2 - < 5 years	2	58 - 57	*d* = -0.02 [N] (-0.38 to 0.34)	+ = 0/ - = 0	I^2 = 0% (NA)
	≥ 5 - < 8 years	1	58 - 58	*d* = 0.26 [S] (0.00 to 0.52)	+ = 0/ - = 0	Not Applicable
	≥ 8 years	1	12 - 12	*d* = -0.01 [N] (-0.47 to 0.45)[3]	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			χ^2 = 2.49; *df* = 3; *p* = 0.48		
Duration of illness >10 years	< 2 years	6	859 - 775	*d* = 0.08 [N] (-0.11 to 0.28)	+ = 0/ - = 0	**I^2 = 77%** (53-89%)
	≥ 2 - < 5 years	4	504 - 504	*d* = -0.08 [N] (-0.29 to 0.12)	+ = 0/ - = 0	I^2 = 31% (0-62%)
	≥ 5 - < 8 years	4	409 - 409	*d* = 0.19 [N] (-0.25 to 0.64)	+ = 1/ - = 0	**I^2 = 89%** (73-96%)
	≥ 8 years	1	44 - 44	*d* = -0.66 [M] (-0.96 to -0.36)[12]	+ = 0/ - = 0	Not Applicable

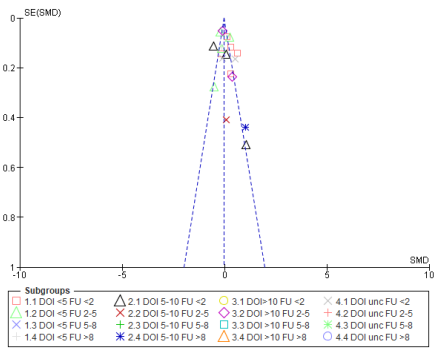
	Subgroup differences between follow-up cohorts			$\chi^2 = 17.95$; $df = 3$; $p < 0.01$		
Duration of illness unclear	< 2 years	2	182 - 168	d = <u>0.28</u> [S] (0.07 to 0.48)	+ = 0/ - = 0	I^2 = 12% (NA)
	≥ 2 - < 5 years	3	208 - 184	d = **0.21** [S] (0.04 to 0.39)	+ = 0/ - = 0	I^2 = 0% (0-63%)
	≥ 8 years	1	80 - 48	d = <u>0.42</u> [S] (0.24 to 0.60)	+ = 0/ - = 0	Not Applicable
	Subgroup differences between follow-up cohorts			$\chi^2 = 2.68$; $df = 2$; $p = 0.26$		

Supplementary figure 1. Overview of funnel plots

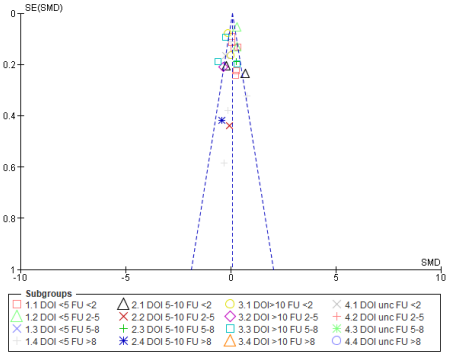
Sensation and perception



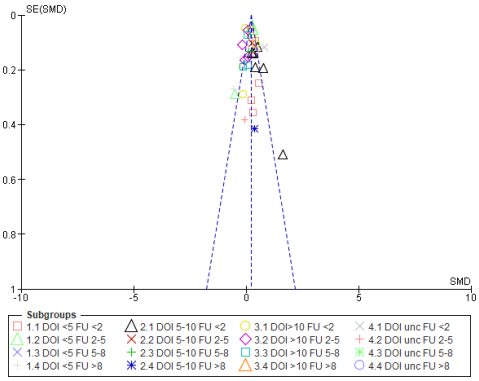
Motor skills and construction



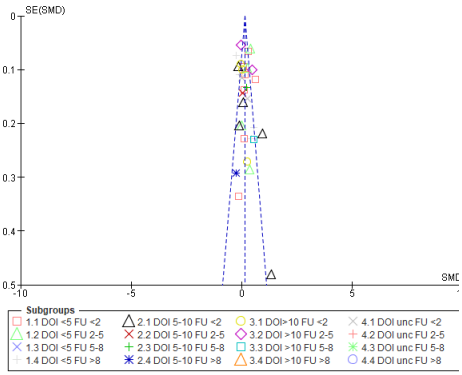
Attention and vigilance



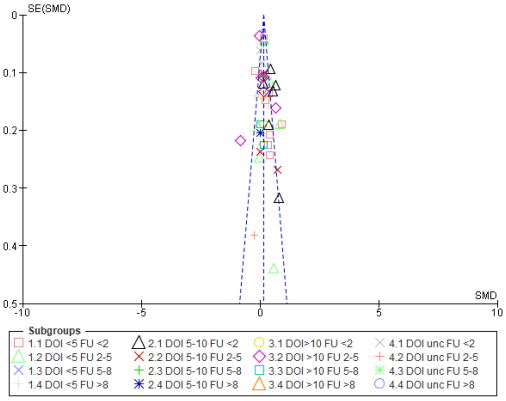
Verbal memory



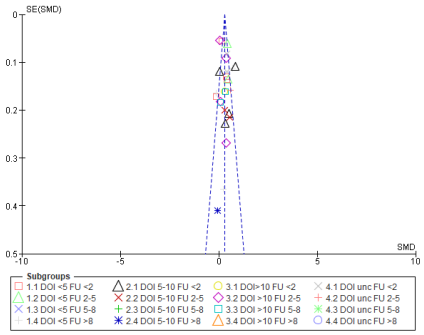
Visual memory



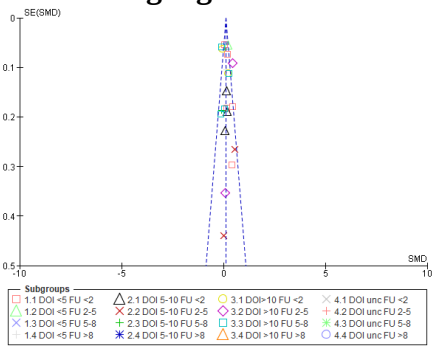
Executive functioning



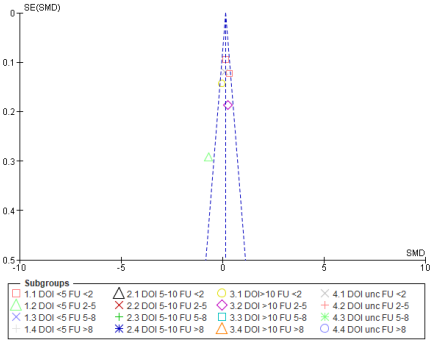
Processing speed



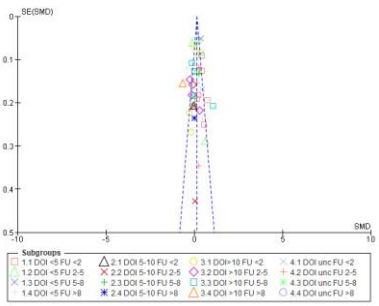
Language skills



Social cognition



Overall cognition



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