Long-Term Changes in Cognition Among Patients With Schizophrenia Spectrum Disorders and Different Durations of Illness:

A Meta-Analysis

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Abstract

Objective: In this meta-analysis, we evaluated changes in cognition for patients with schizophrenia spectrum disorders (SSD) with different durations of illness (DOIs).

Data Sources: Records were identified through searches in PubMed, PsycINFO, CINAHL, and Cochrane until December 2021. We used terms related to SSDs, chronicity, course, and recovery.

Study Selection and Data Extraction: We included 57 longitudinal studies, with a follow-up length of at least 1 year, investigating changes in 10 domains of cognition of patients who are all diagnosed with SSD. Changes in cognition were analyzed through effect sizes of change between baseline and follow-up assessments within each study. These changes were evaluated in different subgroups of studies including patients with a DOI <5 years, 5–10 years, or >10 years. We also investigated the influence of 19 potential moderators on these changes in cognition.

Results: We found marginal improvements in overall cognition ($d = 0.13$), small improvements in verbal memory ($d = 0.21$), processing speed ($d = 0.32$), marginal improvements in visual memory ($d = 0.17$), executive functioning ($d = 0.19$), and language skills ($d = 0.13$), and no significant improvements in the other cognitive domains. The largest improvements were achieved for patients with a DOI <10 years. Changes are more favorable for patients with a younger age, no schizophrenia diagnosis, female gender, higher education level, and low negative symptom severity.

Conclusions: We observed only modest cognitive improvement in SSD almost exclusively in patients with early psychosis. Future research should focus on optimizing interventions targeting cognition in specific subgroups and the interrelationships with other life domains.

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Schizophrenia spectrum disorders (SSD) are characterized by distortions in thinking and perception, cognitive impairments, motor abnormalities, avolition and apathy, difficulties in communication, and restricted affective expression.[1] SSD affect people on multiple life domains. Deficits in cognitive functioning are a key feature of SSD.[2–4] Cognitive functioning influences improvement in other recovery domains, such as social functioning, personal recovery, and symptoms.[5–9] As cognition is a crucial part of recovery for people with SSD, and it affects other recovery domains, it is of clinical importance to know in which phase of SSD cognition can improve. Therefore, an overview of actual changes in cognition in distinct phases of SSD is a clinically relevant topic to investigate.

A variety of studies examined changes in cognitive functioning over time in SSD. These changes vary across different domains of cognition.[10–14] In general, small or no improvement of cognition was found, and people with SSD generally have lower cognitive capacity compared to healthy age-matched controls.[12,13,15] Previous research also indicated a cognitive decline in people with SSD,[16] which is larger for aging patients with schizophrenia compared to healthy controls.[17] Furthermore, a variety of factors, such as a younger age, higher quality and quantity of social relationships, a higher education level, a higher level of social

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Clinical Points

- Cognitive functioning is crucial for recovery of people with schizophrenia spectrum disorders (SSD). Therefore, it is important to investigate longitudinal changes in cognition in SSD.
- We found only modest improvement of cognition, specifically in people with early psychosis.
- It is important to address improvement of cognitive functioning early in the course of SSD.

functioning, a low severity of negative symptoms or substance abuse, and a short duration of illness (DOI), positively influenced improvement in cognition over time.[9,11,13,18,19]

Previous literature about changes in cognition is mostly focused on patients with early psychosis. This is related to a paradigm shift to potentially prevent chronic stages of SSD[3,15] by focusing on the first years after the onset of psychosis. In this meta-analysis, we have built on this knowledge by compiling all longitudinal studies investigating changes in cognition over time, also concerning later phases of the disorder, and investigating these changes within different subgroups based on the DOI (the duration after first diagnosis of SSD) of the patient population and follow-up length of the study. Furthermore, we also investigated possible moderating effects that may influence both total changes in cognition over time and changes in cognition within each DOI subgroup, as patient characteristics, levels of functioning on different domains, and needs might differ between patients with a short and a long DOI.[20,21] Our aim is to gain insights in whether changes in cognitive functioning are observed in patients with different DOIs, if these changes are achieved after a short or long time-period, and which factors contribute to these changes in cognition. Previous meta-analyses already investigated longitudinal changes in cognition for people with SSD[14,15,22,23] or factors that influence changes in cognition,[18,19,24] but a meta-analysis about longitudinal changes in cognition throughout the course of SSD is missing. We aimed to answer the following questions: (1) To what extent does cognition change over the course of SSD? (2) Which moderators at baseline are associated with changes in cognition over time?

METHODS

The meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[25] Our protocol was preregistered in PROSPERO (CRD42022377107).

Data Sources

We identified records through searches in PubMed, PsycINFO, CINAHL, and Cochrane until December 2021. We used terms related to SSD, chronicity, course, and recovery (see Supplementary Table 1). Additional records were traced through references of included studies and systematic reviews.

Eligibility Criteria

Four assessors (L.d.W., K.K., R.M., and A.J.) independently selected the studies. Disagreements regarding inclusion were resolved by consensus. The included studies meet the following criteria:

1. **Patient population:** Studies including adults (mean age ≥18 years) who are all diagnosed with SSD[26] were included. Studies including patients not diagnosed with SSD were excluded.
2. **Study design:** Longitudinal cohort study or randomized controlled trial, with a follow-up length of at least 1 year, was included. Other study designs were excluded.
3. **Outcomes:** Studies reporting standardized or uncorrected quantitative and objective assessments of cognition for at least 2 time points were included. Qualitative studies and studies which outcomes could not be calculated into effect sizes were excluded.
4. **Publication:** Only studies published in English in peer-reviewed journals were included.

Outcome Domains

After study selection, we categorized outcomes of cognition into separate outcome domains. First, we added overall cognition as an outcome, including composite scores of cognitive assessment instruments (eg MATICS Consensus Cognitive Battery[27] or Brief Assessment of *Cognition in Schizophrenia*[28]) and intelligence tests (eg Wechsler Adult Intelligence Scale[29] or Wide Range Achievement Test-Revised[30]). Furthermore, we chose to categorize our study outcomes in subdomains of cognition following the study of Harvey[31] and the MATRICS domains.[27] The categorization of study outcomes in each domain was executed by 2 authors (L.d.W. and M.T.) and checked by all coauthors. This led to the following outcome domains: sensation and perception, motor skills and construction, attention and vigilance, verbal memory, visual memory, executive functioning, processing speed, language skills, and social cognition. An overview of the categorization and definitions of outcome domains can be requested from the corresponding author.

Assessment of DOI Subgroups

Included studies investigated patients with different DOIs at baseline and assessed outcomes over different follow-up periods. Therefore, in this meta-analysis, we

categorized study outcomes in subgroups based on the baseline DOI and follow-up length of our included studies following the categorization process as described in previous publications.[20,21,32] Based on the availability of study data, we categorized outcomes into 4 subgroups based on the baseline DOI: (1) DOI <5 years; (2) DOI 5–10 years; (3) DOI >10 years; (4) DOI unknown. Within each baseline DOI subgroup, we categorized studies into separate subgroups based on their follow-up length: (1) follow-up <2 years; (2) follow-up between 2 and 5 years; (3) follow-up between 5 and 8 years; and (4) follow-up >8 years.

This categorization process shows that the DOI at the follow-up assessment could overlap between the different subgroups. Nevertheless, we still expect substantial differences in changes of outcomes between subgroups and consider these subgroups as the most optimal classification for current study.

Selection and Assessment of Moderators of Outcome

We selected potential moderators at baseline through a three-step approach. First, we established 55 moderators that significantly influenced study outcomes in at least one of our included studies or in comparable reviews.[6,15,18,22,24,33,34] Second, we extracted baseline data of these moderators from our included studies. If baseline data were available in at least 10 studies, generally indicated as the minimal number for representative outcomes,[35] we included this moderator in our analysis (see Statistical Analysis). Third, we added additional moderators that were considered crucial for the interpretation of our findings due to our study design: age at onset, baseline level of cognition, DOI subgroup overlap (ie, if the DOIs of all patients in the study match with the baseline DOI subgroup of the study: yes or no), publication year, the prevalence of schizoaffective disorders, study design (clinical trial or cohort study), and whether treatment was applied that targeted improvement of cognition. Based on this selection process, we selected 19 potential moderators at baseline: age at baseline; age at onset; antipsychotic use; baseline level of cognition; duration of untreated psychosis; DOI subgroup overlap; education level; ethnicity; gender; general functioning; IQ; negative symptoms; overall symptoms; positive symptoms; publication year; schizoaffective disorder diagnosis; schizophrenia diagnosis; study design (clinical trial or cohort study); and delivery of treatment targeting the outcome. For moderators that were evaluated by different assessment instruments (ie, assessment of symptoms, functioning, and baseline level of cognition), we calculated percentile scores based on normative data to ensure that each assessment was assessed in the same scale range. Due to the strict selection criteria, not all potential moderators could be analyzed in each outcome domain. For the outcome domains of sensation and perception ($k = 9$) and social cognition ($k = 6$), the number of included studies was too low to include in this analysis.

Quality Assessment

Quality assessment was conducted using the Quality in Prognostic Studies (QUIPS) tool.[36] The first author (L.d.W.) assessed all studies, and a second assessor (A.J.) independently conducted quality assessment of 10% of the studies. The level of agreement was substantial ($\kappa = 0.72$). Disagreements were resolved by consensus. We investigated the influence of study quality on outcomes through an analysis of subgroup differences.[35]

Statistical Analysis

Meta-analytic procedure. Meta-analyses were conducted using RevMan 5.3.[37] We calculated effect sizes of change (Cohen *d*) in study outcomes by comparing outcomes at baseline and follow-up. For clinical trials, we analyzed both treatment and control groups together. Magnitude of effect was considered marginal when $d < 0.2$, small when $d \geq 0.2$ and <0.5, medium when $d \geq 0.5$ and <0.8, and large when $d \geq 0.8$.[38] We used random-effects models, weighted by the method of inverse variance.[39] Statistical heterogeneity was assessed by calculating the I^2 statistic (including 95% CI).[39] We controlled for multiple testing effects in all analyses through a Benjamini–Hochberg correction, with the false discovery rate set on 0.3.[40]

Subgroup analyses and calculation of moderators. All study outcomes were categorized into one of the baseline DOI subgroups and subgroups based on the follow-up length. In case 1 study reported multiple outcomes within the same subgroup, we clustered all effect sizes of change within that study into 1 composite effect size of change through the method of inverse variance.[39] The influence of moderating effects was analyzed through a metaregression analysis using R.[40] For significant moderators, we further analyzed moderating effects within each baseline DOI subgroups between studies with high levels or presence vs studies with low levels or absence of any significant moderator, using an analysis of subgroup differences.[35]

Handling outliers and publication bias. Outliers are defined as effect sizes of individual study outcomes which CI exceeded the upper or lower bound of the CI of the overall effect size. We controlled for the influence of outliers by comparing subgroups of all study outcomes with subgroups in which outliers are excluded through an analysis of subgroup differences.[35] Potential publication bias was detected by visual inspection of funnel plots.

RESULTS

Study Selection

We identified 10,477 records through database search and reference tracking. We excluded 9,573 records after

title and abstract screening. From the remaining 904 records, we excluded 826 records after full-text screening. Most records were excluded because they did not report on cognition, the articles were no longitudinal studies, or the patient population was not exclusively patients with SSD (see Figure 1). The remaining 78 articles reported results of 57 studies.

Study Characteristics

The 57 studies examined changes in cognition from 6,225 patients with SSD, their mean age was 35.5 years (SD = 8.7 years; range = 21–68.7 years), and 33.7% were female (see Table 1). Twenty-nine studies (50.9%) exclusively included people with schizophrenia. Twenty-three studies (n = 3,214) specifically reported different SSD diagnoses. In these studies, 2.0% of the participants were diagnosed with brief psychotic disorders, 0.4% with delusional disorders, 2.0% with other psychotic disorders, 7.6% with psychotic disorders not otherwise specified, 11.1% with schizoaffective disorders, 9.6% with schizophreniform disorders, and 67.1% with schizophrenia. The 5 remaining studies indicated that all participants were diagnosed with SSD, without further specifications. Seven studies (12.3%) were clinical trials, and 50 studies (81.3%) were cohort studies. Sixteen studies implemented treatment programs; in 3 of those studies (all clinical trials), treatment programs specifically targeted improvement in cognition. In 19 studies (33.3%), all patients used antipsychotics. In 28 studies (49.1%), the baseline DOI was shorter than 5 years; in 7 studies (12.3%), baseline DOI was 5–10 years; in 15 studies (26.3%), baseline DOI was more than 10 years; and in 7 studies (12.3%), baseline DOI was unclear. Finally, in 23 studies (40.3%), the dropout rate was low (ie <20%); in 16 studies (28.0%), the dropout rate was moderate (ie ≥20%–≤40%); and in 17 studies (29.8%), the dropout rate was high (ie >40%). In 1 study, the dropout rate was not reported.

We observed a lower level of motor skills and construction, a higher level of attention and vigilance, and a higher severity of positive symptoms at baseline in studies with a shorter baseline DOI than in studies with a longer baseline DOI (see Supplementary Table 2).

Results of Meta-Analysis of Study Outcomes With Different DOIs

We presented a general overview of the outcomes and differences between DOI subgroups in Figure 2. Detailed information of overall cognition is reported in Table 2 and for all other outcome domains in Supplementary Table 3. In the text below, d stands for the effect size of change, I^2 for heterogeneity, and k for number of studies.

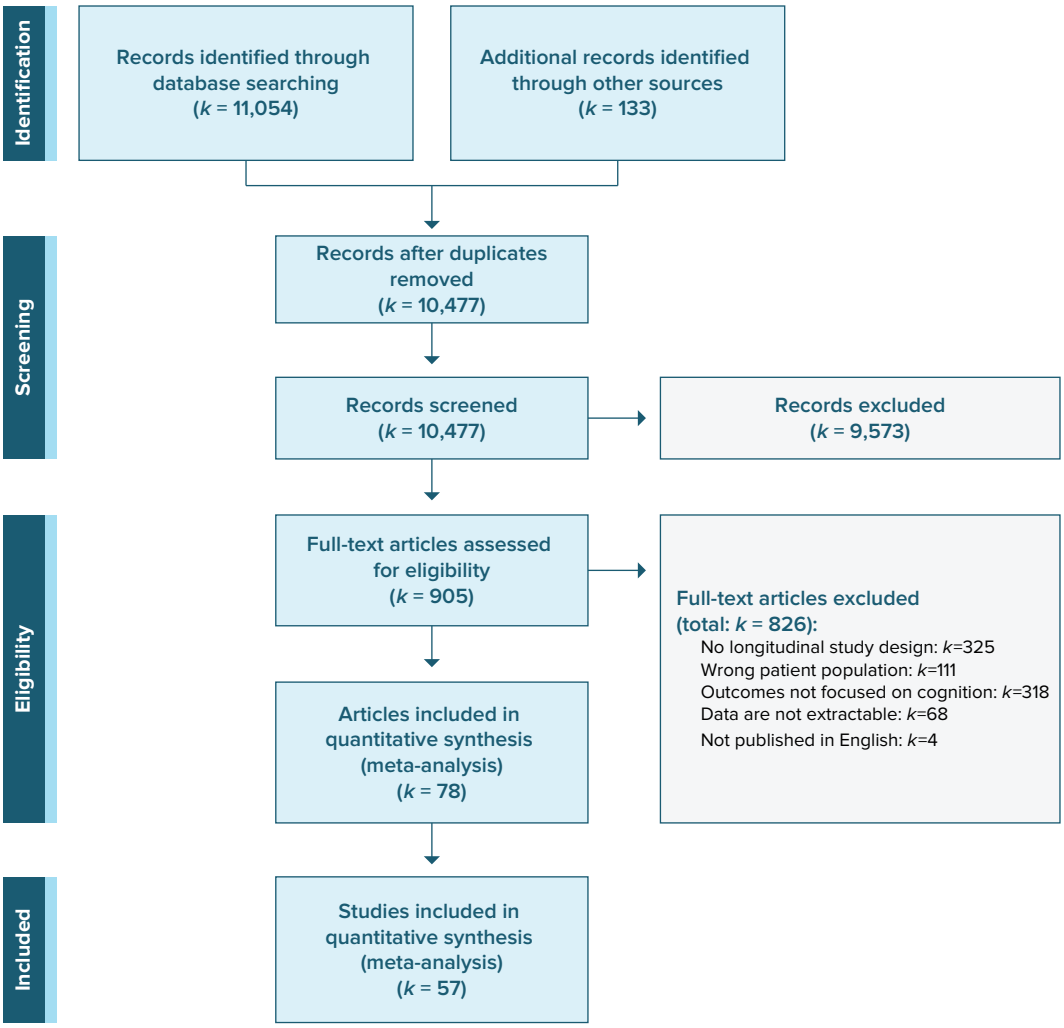
Overall changes in cognition. Overall, we found marginal improvement of overall cognition (d = 0.13 [0.05 to 0.22]; I^2 = 78%; k = 30). For all other cognitive outcome domains, we found small improvements of verbal memory (d = 0.21 [0.13 to 0.28]; I^2 = 77%; k = 31) and processing speed (d = 0.32 [0.22 to 0.41]; I^2 = 76%; k = 21) over time. Furthermore, we found marginal improvements of visual memory (d = 0.17 [0.07 to 0.26]; I^2 = 80%; k = 24), executive functioning (d = 0.19 [0.12 to 0.26]; I^2 = 75%; k = 36), and language skills (d = 0.13 [0.05 to 0.22]; I^2 = 63%; k = 15). Finally, we found no significant changes in sensation and perception (d = 0.10 [−0.13 to 0.33]; I^2 = 79%; k = 9), motor skills and construction (d = 0.05 [−0.07 to 0.16]; I^2 = 73%; k = 20), attention and vigilance (d = −0.02 [−0.07 to 0.02]; I^2 = 84%; k = 16), and social cognition (d = 0.11 [−0.07 to 0.28]; I^2 = 59%; k = 6).

Outcomes for subgroups with a baseline DOI of less than 5 years. For overall cognition, we found a small improvement after less than 2 years and 5–8 years of follow-up. For all other cognitive outcome domains, we found for both sensation and perception and motor skills and construction marginal improvements after a follow-up length of less than 2 years, a small improvement after 2–5 years of follow-up, and no significant improvement after more than 8 years of follow-up. For verbal memory, visual memory, and executive functioning, we found small improvements after less than 2 years and 2–5 years follow-up, but no significant improvement after more than 8 years follow-up. For language skills and social cognition, we only found a small improvement after a follow-up length of less than 2 years, and for processing speed, after a follow-up length between 2 and 5 years. Finally, we found no significant improvement of attention and vigilance in this subgroup. For social cognition (χ^2 = 8.83; df = 1; P < .01) and attention and vigilance (χ^2 = 19.21; df = 2; P < .01), we found larger improvements after a shorter follow-up length.

Outcomes for subgroups with a baseline DOI of 5–10 years. We found no significant improvement in overall cognition over time in this subgroup. For verbal memory, we found a small improvement of outcomes after less than 2 years and 2–5 years follow-up. For executive functioning, we found a small improvement of outcomes after a follow-up length of less than 2 years. For processing speed, we found a small improvement after 2–5 years of follow-up. For attention and vigilance, we found a large improvement after a follow-up length of more than 8 years, though this was only based on 1 study. For all other outcome domains, we found no significant improvement over time in this subgroup. For executive functioning, we found a larger improvement after a shorter follow-up length (χ^2 = 8.79; df = 3; P < .05), and for attention and vigilance, we found a larger improvement after a longer follow-up length (χ^2 = 8.45; df = 2; P < .05).

Outcomes for subgroups with a baseline DOI of more than 10 years. In the subgroup of studies investigating patients with a baseline DOI of more than 10 years, we found no significant improvements in any outcome domain, except for visual memory, where we found a

Figure 1.
PRISMA Flowchart of Selection of Studies (k)



Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

medium improvement over time after 5–8 years of follow-up. However, this outcome was only based on 1 study. We found no consistent differences between outcomes with a short or long follow-up length in any of the outcome domains.

Differences between subgroups based on their DOI. Analysis of subgroup differences indicated a larger improvement of overall cognition in the subgroup with a baseline DOI of less than 5 years compared with the subgroup with a baseline DOI of more than 10 years. We found similar results in the subdomains sensation and perception, motor skills and construction, verbal memory, visual memory, and processing speed. We found a larger improvement of attention and vigilance but a smaller improvement of sensation and perception and verbal memory in the subgroup with a baseline DOI of less than 5 years compared with the subgroup with a baseline DOI between 5 and 10 years. Finally, we found a larger improvement of overall cognition and verbal memory in the subgroup with a baseline DOI between 5 and 10 years compared with the subgroup with a baseline DOI of more than 10 years.

Outliers and Publication Bias

We found no outliers for motor skills and construction, language skills, and social cognition. Furthermore, we found 1 negative outlier for sensation and perception and 1 positive outlier for processing speed and attention and vigilance. For verbal memory, we found 3 negative outliers and 2 positive outliers, for visual memory, we found 1 negative outlier and 2 positive outliers, and for both executive functioning and overall cognition, we found 3 positive and 3 negative outliers. We found no indications of a significant influence in any direction due to outliers in any of the outcome domains.

Table 1.

Descriptive Statistics of Included Studies

Study name[a]	N (baseline FU)	Age (SD)	% female	Primary diagnosis	Comorbidity	Treatment	Baseline DOI (y)	FU duration (y)	Attrition rate	Outcome categories reported
Albus 2002[S1,S2]	58–58	29.7 (9.1)	49.3%	Schizophrenia (100%)	NR	Butyrophenones (100%)	6.2 y	2 y; 5 y	30.0%	Executive functioning; language skills; motor skills and construction; overall cognition; processing speed; verbal memory; visual memory
Balanzá -Martínez 2005[S3,S4]	47–47	33.4 (8.2)	21.3%	Schizophrenia (100%)	NR	Antipsychotics (100%); antidepressants (12.8%); benzodiazepines (31.9%); psychosocial rehabilitation (19.2%)	8.7 y	1 y; 3 y	9.6%	Attention and vigilance; executive functioning; language skills; motor skills and construction; overall cognition; processing speed; verbal memory; visual memory
Barnett 2007[S5]	26–26	41.9 (12.0)	29.3%	Schizophrenia (77.6%); schizoaffective disorder (15.5%); delusional disorder (6.9%)	NR	First-generation antipsychotics (29.3%); second-generation antipsychotics (70.7%)	16.5 y	0.2 y; 0.5 y; 1	35.6%	Executive functioning; motor skills and construction; visual memory
Bonner-Jackson 2010[S6]	84–84	22.9 (3.9)	44.2%	Schizophrenia (57.1%); other types of psychotic disorder (42.9%)	NR	NR	NR	2	7.8%	Overall cognition; processing speed
Bosnjak Kuharic 2021[S7]	129–129	24.0 (13.0)	36.4%	First episode psychotic disorder (100%)	NR	First-generation antipsychotics (34.9%); second-generation antipsychotics (93.8%); antidepressants (11.6%); anxiolytics (51.2%); mood stabilizers (23.3%)	1.0 y	1.5	18.9%	Executive functioning; language skills; motor skills and construction; overall cognition; processing speed; verbal memory; visual memory
Bowie 2008[S8–S14]	317–317	67.7 (11.5)	37.5%	Schizophrenia (100%)	NR	Antipsychotics (99.7%)	41.2 y	1 y; 1.2 y; 2.1 y; 4 y; 6 y	31.2%	Language skills; motor skills and construction; overall cognition; verbal memory
Breier 2018[S15]	60–60	23.6 (4.9)	21.7%	Schizophrenia (68.3%); schizophreniform disorder (13.3%); schizoaffective disorder (8.3%); psychotic disorder NOS (10.1%)	NR	Antipsychotics (100%)	1.4 y	1 y	46.7%	Overall cognition
Buonocore 2018[S16]	60–60	34.9 (9.7)	45.3%	Schizophrenia (100%)	NR	Computer-assisted CRT (100%); SRT (100%); risperidone (23.0%); haloperidol (15.0%); clozapine (39.0%); olanzapine (7.0%); aripiprazole (8.0%); paliperidone (2.0%); fluphenazine (3.0%); chlorpromazine (3.0%)	10.8 y	5 y	6.3%	Executive functioning; language skills; motor skills and construction; overall cognition; processing speed; verbal memory
Chang 2014[S17–S21]	93–93	31.5 (9.5)	57.1%	Schizophrenia (79.6%); schizophreniform disorder (14.0%); schizoaffective disorder (5.4%)	NR	First-generation antipsychotics (100%)	1.3 y	1 y; 2 y; 3 y	32.6%	Executive functioning; language skills; verbal memory; visual memory
Chanpattana 2010[S22]	253–253	34.1 (8.0)	53.8%	Schizophrenia (100%)	NR	Electroconvulsive therapy (100%); flupenthixol (100%)	13.3 y	1.6 y	0.0%	Overall cognition

(continued)

Table 1 (continued).

Study name[a]	N (baseline FU)	Age (SD)	% female	Primary diagnosis	Comorbidity	Treatment	Baseline DOI (y)	FU duration (y)	Attrition rate	Outcome categories reported
Chen 2000[S23]	50–43	48.9 (8.9)	30.2%	Schizophrenia (100%)	NR	NR	23.5 y	3 y	14.0%	Executive functioning; motor skills and construction; sensation and perception
Dal Santo 2020[S24]	17–17	45.4 (8.1)	0.0%	Schizophrenia (100%)	NR	Clozapine (100%)	NR	2.9 y	0.0%	Overall cognition
Dempster 2017[S25]	16–16	24.1 (7.2)	23.1%	First episode nonaffective psychosis (100%)	NR	Antipsychotics (23.1%)	2.0 y	1 y	0.0%	Executive functioning; verbal memory
Ekerholm 2012[S26]	36–36	41.1 (7.9)	13.9%	Schizophrenia (100%)	NR	Antipsychotics (95.8%)	17.6 7	4.6 y	49.3%	Attention and vigilance; executive functioning; processing speed; verbal memory
Fett 2020[S27,S28]	246–140	28.5 (8.5)	34.6%	Schizophrenia spectrum disorder (100%)	NR	NR	<0.5 y	2 y; 15 y; 19 y; 20 y	47.4%	Attention and vigilance; executive functioning; language skills; processing speed; verbal memory; visual memory
Galderisi 2020[S29]	921–618	40.2 (10.7)	30.4%	Schizophrenia (100%)	Substance abuse (5.0%); Alcohol abuse (4.9%)	Antipsychotics (76.8%); integrated treatment (26.8%)	16.2 y	4 y	32.9%	Attention and vigilance; executive functioning; processing speed; social cognition; verbal memory; visual memory
Granholm 2020[S30]	107–101	56.0 (7.5)	17.5%	Schizophrenia (80.7%); schizoaffective disorder (19.3%)	NR	Cognitive-behavioral social skills training (CBSST; 45.6%); mobile assisted CBSST (MA-CBSST; 29.8%)	NR	0.3 y; 0.5 y; 1 y	40.4%	Overall cognition
Harvey 2010[S31]	61–61	57.0 (9.0)	27.0%	Schizophrenia (100%)	NR	Second-generation antipsychotics (100%)	33.3 y	3.8 y	45.0%	Overall cognition
Heaton 2001[S32]	142–142	47.6 (15.7)	30.3%	Schizophrenia (100%)	NR	Atypical antipsychotics (17.6%)	18.8 y	1.6 y	47.2%	Overall cognition
Heeramun-Aubeeluck 2015[S33]	38–38	25.9 (7.3)	51.5%	Schizophrenia (100%)	NR	Aripiprazole (33.7%); olanzapine (32.7%); risperidone (32.7%)	NR	0.5 y; 1 y	62.4%	Attention and vigilance; motor skills and construction; processing speed; verbal memory; visual memory
Ho 2018[S34]	34–34	27.0 (6.6)	61.8%	Schizophrenia (100%)	no	Antipsychotics (100%)	1.3 y	1.7 y	17.1%	Social cognition
Hoff 2005[S35]	21–21	37.9 (5.7)	28.6%	Schizophrenia (74.3%); schizoaffective disorder (5.7%)	NR	Antipsychotics (92.9%)	1.5 y	10 y	58.0%	Executive functioning; motor skills and construction; overall cognition; processing speed; sensation and perception; verbal memory; visual memory
Horan 2012[S36]	55–55	22.3 (4.3)	23.6%	Schizophrenia (56.8%); schizoaffective disorder (12.4%); schizophreniform disorder (30.9%)	NR	Risperidone (100%)	0.7 y	1 y	32.1%	Social cognition
Hui 2012[S37]	37–37	32.1 (10.4)	48.7%	Schizophrenia spectrum disorder (100%)	NR	Antipsychotics (48.7%)	0.0 y	1 y; 2 y; 3 y	NR	Sensation and perception

(continued)

Table 1 (continued).

Study name[a]	N (baseline FU)	Age (SD)	% female	Primary diagnosis	Comorbidity	Treatment	Baseline DOI (y)	FU duration (y)	Attrition rate	Outcome categories reported
Keefe 2004[S38,S39]	167–167	23.9 (4.6)	16.2%	Schizophrenia (64.7%); schizoaffective disorder (8.4%); schizophreniform disorder (27.0%)	NR	Olanzapine (53.3%); haloperidol (46.7%)	1.2 y	0.5 y; 1 y	31.6%	Attention and vigilance; executive functioning; language skills; motor skills and construction; overall cognition; processing speed; sensation and perception; verbal memory; visual memory
Klingberg 2008[S40]	151–100	33.6 (10.3)	51.7%	Schizophrenia (88.7%); schizoaffective disorder (11.3%)	NR	Antipsychotics (94.7%); anticholinergics (31.1%); benzodiazepines (47.7%); antidepressants (19.9%); mood stabilizers (9.3%)	8.1 y	0.8 y; 1.3 y; 1.5 y	50.9%	Attention and vigilance; executive functioning; processing speed; verbal memory; visual memory
Kukla 2018[S41]	75–67	50.2 (10.3)	6.7%	Schizophrenia (70.7%); schizoaffective disorder (29.3%)	NR	Cognitive behavioral therapy (66.7%); cognitive remediation (33.3%)	NR	0.5 y; 1 y	10.7%	Attention and vigilance; executive functioning; overall cognition; processing speed; social cognition; verbal memory; visual memory
Kurtz 2005[S42]	12–12	29.9 (5.9)	NR	Schizophrenia (100%)	NR	Typical antipsychotics (67.0%); clozapine (33.0%)	8.0 y	10 y	75.5%	Attention and vigilance; executive functioning; motor skills and construction; overall cognition; processing speed; sensation and perception; verbal memory; visual memory
Leeson 2009[S43]	54–54	25.5 (8.0)	18.5%	Schizophrenia (96.3%); schizoaffective disorder (3.7%)	NR	First-generation antipsychotics (50.0%); second-generation antipsychotics (35.2%)	<0.3 y	1 y; 4 y	7.0%	Executive functioning; overall cognition; visual memory
Lindgren 2020[S44]	52–32	26.7 (5.7)	40.4%	Schizophrenia (50.0%); schizophreniform disorder (21.1%); psychotic disorder NOS (23.1%); brief psychotic disorder (5.8%)	NR	Antipsychotics (94.2%); antidepressants (26.9%)	0.0 y	1 y	38.5%	Attention and vigilance; executive functioning; language skills; motor skills and construction; processing speed; verbal memory; visual memory
Lysaker 1994[S45]	92–92	43.3 (9.2)	6.5%	Schizophrenia or schizoaffective disorder (100%)	NR	NR	NR	0.4 y; 1 y	22.0%	Executive functioning
McGurk 2003[S46]	30–27	39.7 (6.9)	23.3%	Schizophrenia (53.3%); schizoaffective disorder (46.7%)	NR	Supported employment (100%); antipsychotics (100%); clozapine (23.3%); risperidone (26.7%); olanzapine (13.3%)	15.7 y	2 y	10.0%	Executive functioning; processing speed; verbal memory
Meagher 2004[S47]	82–82	68.7 (10.1)	41.9%	Schizophrenia (100%)	NR	Antipsychotics (100%)	44.7 y	2.9 y	36.4%	Executive functioning; overall cognition
Okin 1995[S48]	53–53	37.6 (14.2)	41.5%	Schizophrenia (100%)	NR	Community residential treatment (100%)	11.5 y	7.5 y	0.0%	Language skills; motor skills and construction; overall cognition

(continued)

Table 1 (continued).

Study name[a]	N (baseline FU)	Age (SD)	% female	Primary diagnosis	Comorbidity	Treatment	Baseline DOI (y)	FU duration (y)	Attrition rate	Outcome categories reported
Olbrich 2001[S49]	36–36	28.1 (7.1)	43.9%	Schizophrenia (100%)	NR	Neuroleptics (100%)	2.1 y	0.5 y; 1 y; 1.5 y	3.0%	Attention and vigilance
Oribe 2015[S50]	18–18	21.7 (4.6)	27.8%	Schizophrenia (100%)	NR	Atypical antipsychotics (72.2%); mood stabilizers (5.6%); antidepressants (33.3%); Anxiolytics (16.7%)	1.2 y	1 y	0.0%	Visual memory
Rodríguéz-Sánchez 2008[S51–S54]	549–549	30.1 (9.6)	43.4%	Schizophrenia (50.6%); schizophreniform disorder (28.1%); brief psychotic disorder (11.1%); psychotic disorder NOS (8.4%); schizoaffective disorder (1.5%); delusional disorder (0.4%)	Cannabis use (43.0%)	Antipsychotics (100%); anticholinergics (6.5%); hypnotics (15.5%); benzodiazepines (52.9%)	1.8 y	0.1 y; 1 y; 3 y; 10 y	27.5%	Attention and vigilance; executive functioning; motor skills and construction; overall cognition; processing speed; verbal memory; visual memory
Rund 1989[S55]	14–14	24.3 (3.8)	14.3%	Schizophrenia (100%)	NR	Neuroleptics (71.4%)	NR	4 y	30.0%	Executive functioning; verbal memory
Rund 2007[S56]	111–111	28.2 (9.0)	42.3%	Schizophrenia (52.3%); schizophreniform disorder (4.5%); schizoaffective disorder (10.8%); delusional disorder (5.4%); psychosis NOS (27.0%)	Affective disorder (18.9%)	TIPS treatment program: antipsychotic medication, individual psychosocial treatment, and psychoeducational family work; psychotherapy (100%)	0.2 y	0.3 y; 1 y	38.9%	Attention and vigilance; executive functioning; motor skills and construction; processing speed; sensation and perception; Verbal memory
Ryu 2006[S57–S59]	78–78	54.6 (7.2)	34.6%	Schizophrenia (100%)	NR	Optimal Treatment Project (OTP; 100%); antipsychotics (100%)	31.5 y	1 y; 2 y; 3 y; 4 y; 5 y; 6 y; 12 y; 15 y	28.2%	Executive functioning; language skills; overall cognition; processing speed; verbal memory; visual memory
Scottish Schizophrenia Research Group 1988[S60]	111–111	30.6 (NR)	53.1%	Schizophrenia (100%)	NR	Pimozide (50.0%); flupenthixol (50.0%)	0.2 y	1 y; 2 y; 5 y	16.3%	Executive functioning; motor skills and construction; overall cognition; verbal memory
Seidman 1991[S61]	12–12	28.7 (6.5)	16.7%	Schizophrenia (100%)	NR	Neuroleptics (91.7%)	8.8 y	3 y	0.0%	Attention and vigilance; executive functioning; language skills; motor skills and construction; overall cognition
Shrivastava 2011[S62]	61–61	28.8 (7.5)	26.7%	Schizophrenia (100%)	NR	Pharmacologic treatment (100%)	0.0 y	10 y	49.5%	Motor skills and construction
Smith 2002[S63]	46–45	37.0 (9.0)	41.3%	Schizophrenia (60.9%); schizoaffective disorder (39.1%)	NR	Standard ambulatory treatment (medication management, case management, psychotherapy; 100%); vocational rehabilitation (100%); antipsychotics (100%)	19.0 y	0.3 y; 0.5 y; 0.8 y; 1 y	37.5%	Executive functioning; verbal memory
Stip 2005[S64]	57–57	34.0 (12.0)	29.8%	Schizophrenia (77.2%); schizoaffective disorder (22.8%)	NR	NR	6.4 y	0.7 y; 1.3 y; 1.6 y	0.0%	Executive functioning; processing speed; verbal memory

(continued)

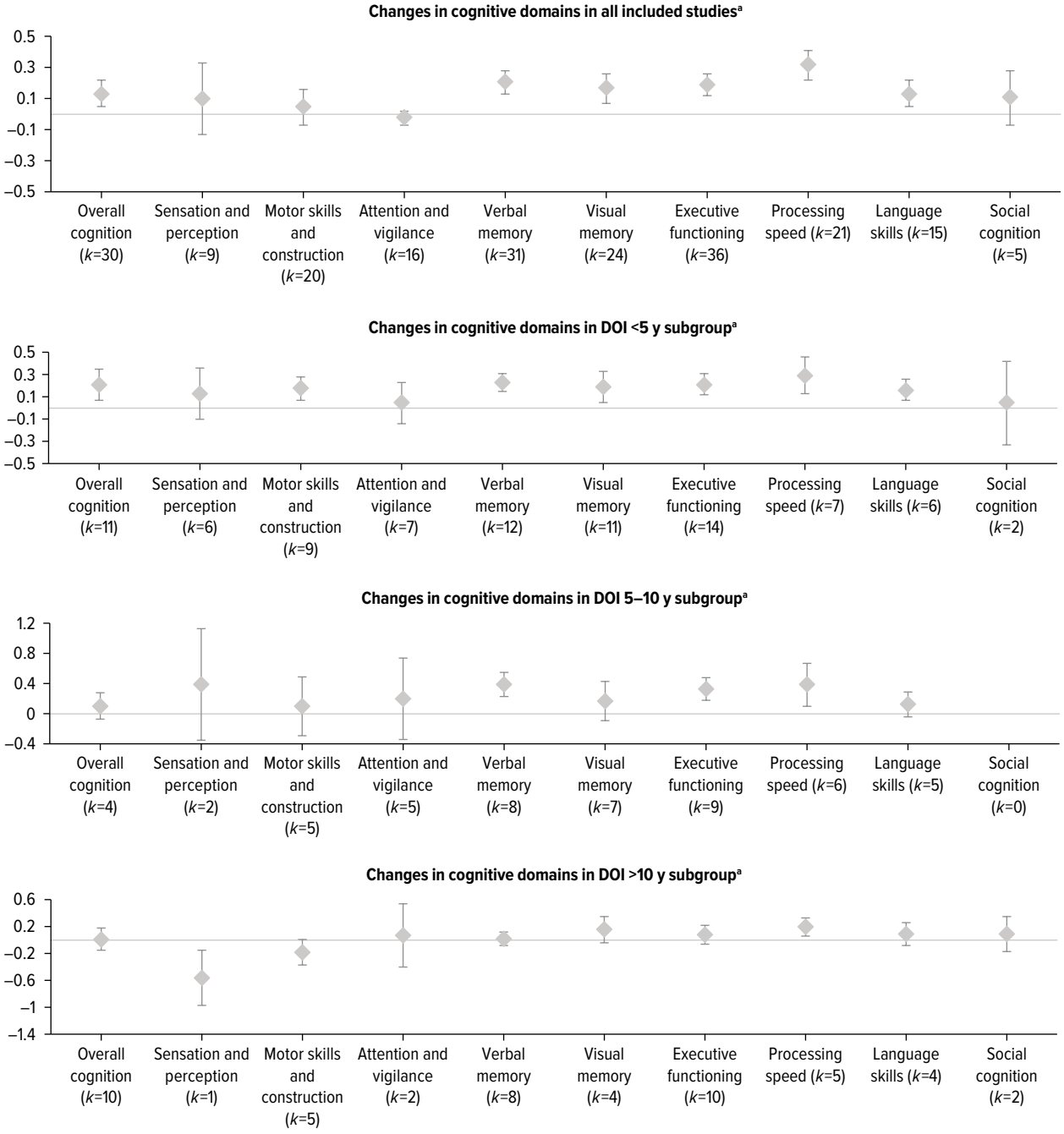
Table 1 (continued).

Study name[a]	N (baseline FU)	Age (SD)	% female	Primary diagnosis	Comorbidity	Treatment	Baseline DOI (y)	FU duration (y)	Attrition rate	Outcome categories reported
Stirling 2003[S65]	49–49	26.3 (NR)	42.9%	Schizophrenia (81.6%); schizoaffective disorder (12.2%); schizophreniform disorder (6.1%)	NR	Neuroleptics (98.0%)	0.0 y	10.6 y	21.0%	Executive functioning; motor skills and construction; overall cognition; sensation and perception; verbal memory; visual memory
Sweeney 1991[S66]	39–39	28.6 (8.6)	38.5%	Schizophrenia (74.4%); schizophreniform disorder (10.3%); schizoaffective disorder (15.4%)	NR	Antipsychotics (100%)	6.6 y	0.3 y; 1 y; 1.3 y; 1.5 y	0.0%	Executive functioning; language skills; motor skills and construction; processing speed; sensation and perception; verbal memory; visual memory
Torgalsbøen 2015[S67]	25–25	21.0 (2.6)	39.3%	Schizophrenia (75.0%); schizoaffective disorder (21.4%); psychotic disorder NOS (3.6%)	Substance abuse (3.6%)	Psychotherapy (71.4%); group therapy (7.1%); psychoeducation (64.3%)	<0.4 y	2 y	10.7%	Attention and vigilance; executive functioning; overall cognition; social cognition; verbal memory; visual memory
Tyson 2005[S68]	28–28	34.0 (10.0)	35.7%	Schizophrenia (100%)	NR	Antipsychotics (100%)	8 y	0.8 y; 1.5 y	0.0%	Executive functioning; language skills; verbal memory; visual memory
Van Haren 2019[S69]	1022–622	27.7 (7.8)	23.5%	Schizophrenia (71.6%); Schizoaffective disorder (15.1%); psychosis NOS (13.3%)	NR	NR	4.3 y	3 y; 6 y	42.3%	Overall cognition
Van Winkel 2006[S70,S71]	80–48	23.2 (4.0)	30.0%	Schizophrenia (100%)	NR	NR	NR	10.7 y	47.0%	Overall cognition
Veerman 2016[S72]	25–25	42.0 (10.4)	24.0%	Schizophrenia (100%)	Alcohol use (20.0%); nicotine use (56.0%); cocaine use (12.0%)	Clozapine (100%); psychotherapy (8.0%)	19.6 y	1 y	19.4%	Executive functioning; social cognition; verbal memory; visual memory
Veijola 2014[S73]	28–28	34.0 (0.6)	42.4%	Schizophrenia (100%)	NR	Antipsychotics (100%)	11.1 y	9 y	45.9%	Overall cognition
Waddington 1996[S74]	41–41	54.1 (12.5)	46.3%	Schizophrenia (100%)	NR	Anticholinergics (51.0%)	27.9 y	10 y	59.4%	Overall cognition
Wittorf 2004[S75]	11–11	31.9 (10.9)	66.7%	Schizophrenia (93.3%); schizoaffective disorder (6.7%)	NR	Antipsychotics (100%)	6.1 y	1.1 y	60.5%	Attention and vigilance; executive functioning; verbal memory; visual memory
Xu 2014[S76,S77]	60–60	25.3 (10.4)	45.0%	Schizophrenia (51.7%); schizophreniform disorder (20.0%); psychosis NOS (21.7%); schizoaffective disorder (6.7%)	NR	Antipsychotics (95.0%); anticholinergics (18.3%)	0.0 y	1 y; 3 y	23.1%	Executive functioning; language skills; overall cognition
Zhuo 2018[S78]	48–48	21.5 (1.7)	52.1%	Schizophrenia (100%)	NR	NR	0.0 y	3 y	0.0%	Sensation and perception

[a]Supplementary references appear with an "S" preceding them and can be found at Psychiatrist.com.
Abbreviations: CRT = cognitive rehabilitation therapy,DOI = duration of illness, FU = follow-up, NOS = not otherwise specified, NR = not reported, SRT = standard rehabilitation therapy, TIPS = Early Treatment and Identification of Psychosis, y = years.

Figure 2.

Effect Sizes of Improvement and/or Deterioration of the 12 Outcome Categories of Cognition Within 3 Baseline DOI Subgroups[a]



[a]Abbreviations: DOI = duration of illness, *k* = number of studies reporting on each outcome domain.

We found no skewed funnel plots in any of our outcome domains (see Supplementary Figure 1), which indicates there are no indications of publication bias in the outcomes of this meta-analysis.

Analysis of Potential Moderators of Change in Outcomes at Baseline

A summary of the analysis of subgroup differences is presented in Figure 3. We present the significant

Table 2.

Meta-Analysis of Overall Cognition Outcomes[a]

(Sub)analysis		K (studies)	N (baseline FU)	Effect size (95% CI)[b] and magnitude of effect[c]	K (%) large effect [+/−][d]	Heterogeneity (I^2 [95% CI])[b]
All studies and outcomes		30	3607–3123	d = **0.13** [N] (0.05–0.22)	+=1/−=0	I^2 = **78%** (73%–82%)
Baseline subgroup	**Follow-up cohort**					
Duration of illness <5 y	<2 y	6	347–330	d = **0.35** [S] (0.17–0.52)	+=0/−=0	I^2 = **40%** (2%–63%)
	≥2–<5 y	5	1681–1249	d = 0.11 [N] (−0.10 to 0.32)	+=0/−=0	I^2 = **81%** (57%–92%)
	≥5–<8 y	1	1022–602	d = **0.35** [S] (0.25–0.45)	+=0/−=0	Not applicable
	≥8 y	3	200–200	d = 0.07 [N] (−0.48–0.62)[3]	+=0/−=0	I^2 = **85%** (45%–96%)
	Subgroup differences between follow-up cohorts				χ^2 = 4.88; df = 3; P = .18	
Duration of illness 5–10 y	<2 y	1	47–47	d = −0.03 [N] (−0.43 to 0.37)	+=0/−=0	Not applicable
	≥2–<5 y	2	58–57	d = −0.02 [N] (−0.38 to 0.34)	+=0/−=0	I^2 = 0% (NA)
	≥5–<8 y	1	58–58	d = 0.26 [S] (0.00–0.52)	+=0/−=0	Not applicable
	≥8 y	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 = .48	
Duration of illness >10 y	<2 y	6	859–775	d = 0.08 [N] (−0.11–0.28)	+=0/−=0	I^2 = **77%** (53%–89%)
	≥2–<5 y	4	504–504	d = −0.08 [N] (−0.29 to 0.12)	+=0/−=0	I^2 = 31% (0%–62%)
	≥5–<8 y	4	409–409	d = 0.19 [N] (−0.25–0.64)	+=1/−=0	I^2 = **89%** (73%–96%)
	≥8 y	1	44–44	d = −0.66 [M] (−0.96 to −0.36)[1,2]	+=0/−=0	Not applicable
	Subgroup differences between follow-up cohorts				χ^2 = 17.95; df = 3; P < .01	
Duration of illness unclear	<2 y	2	182–168	d = 0.28 [S] (0.07–0.48)	+=0/−=0	I^2 = 12% (NA)
	≥2–<5 y	3	208–184	d = **0.21** [S] (0.04–0.39)	+=0/−=0	I^2 = 0% (0%–63%)
	≥8 y	1	80–48	d = 0.42 [S] (0.24–0.60)	+=0/−=0	Not applicable
	Subgroup differences between follow-up cohorts				χ^2 = 2.68; df = 2; P = .26	

[a]Detailed information about other outcome domains of cognition can be requested from the corresponding author.
[b]Outcomes in bold are significant (P < .05) after a Benjamini–Hochberg correction; outcomes underlined are no longer significant after a Benjamini–Hochberg correction for multiple testing.
[c]N = no effect (d >−0.20 to <0.20); S = small effect (d ≤−0.20 and >−0.50 to ≥0.20 and <0.50); M = medium effect (d ≤−0.50 and >−0.80 to ≥0.50 and <0.80); L = large effect (d <−0.80 to >0.80).
[d]+ = Improvement of outcome at follow-up; − = deterioration of outcome at follow-up.
[1]Significant subgroup differences with the duration of illness <5 years subgroup outcome within the same follow-up cohort. [2]Significant subgroup differences with the duration of illness 5–10 years subgroup outcome within the same follow-up cohort. [3]Significant subgroup differences with the duration of illness >10 years subgroup outcome within the same follow-up cohort.
Abbreviations: FU = follow-up, L = large effect, M = medium effect, N = no effect, S = small effect.

moderators from our outcome domains below. More detailed statistics can be requested from the corresponding author.

Metaregression analysis showed that a younger age at baseline (B = −0.01; P < .05) and a high education level (B = 0.29; P < .05) were associated with more favorable changes in overall cognition. The moderating effects of education level were specifically indicated in the subgroup with a baseline DOI of <5 years (χ^2 = 14.65; df = 1; P < .01).

Furthermore, a lower baseline severity of negative symptoms was associated with more favorable changes in motor skills and construction (B = −0.01; P < .05). We specifically found this moderating effect in the subgroup with a baseline DOI of 5–10 years (χ^2 = 4.56; df = 1; P < .05). We also found that studies including treatment targeting cognition negatively influenced changes in motor skills and construction. However, these results are based on only 1 study in which treatment was focused on outcomes, and this study was represented in the subgroup with a baseline DOI of >10 years in which generally less favorable outcomes are achieved.

We also found that studies including more females showed better overall improvement of executive functioning (B = 0.01; P < .05) and verbal memory (B = 0.01; P < .05). For verbal memory, this was specifically indicated in the subgroup with a baseline DOI of <5 years (χ^2 = 5.09; df = 1; P < .05).

Finally, studies in which all participants were diagnosed with schizophrenia showed worse overall improvement of motor skills and construction (B = 0.37; P < .05), visual memory (B = 0.41; P < .05), and executive functioning (B = 0.25; P < .05). For motor skills and construction (χ^2 = 7.00; df = 1; P < .01) and executive functioning (χ^2 = 19.97; df = 1; P < .01), this was specifically indicated in the subgroup with a baseline DOI of 5–10 years.

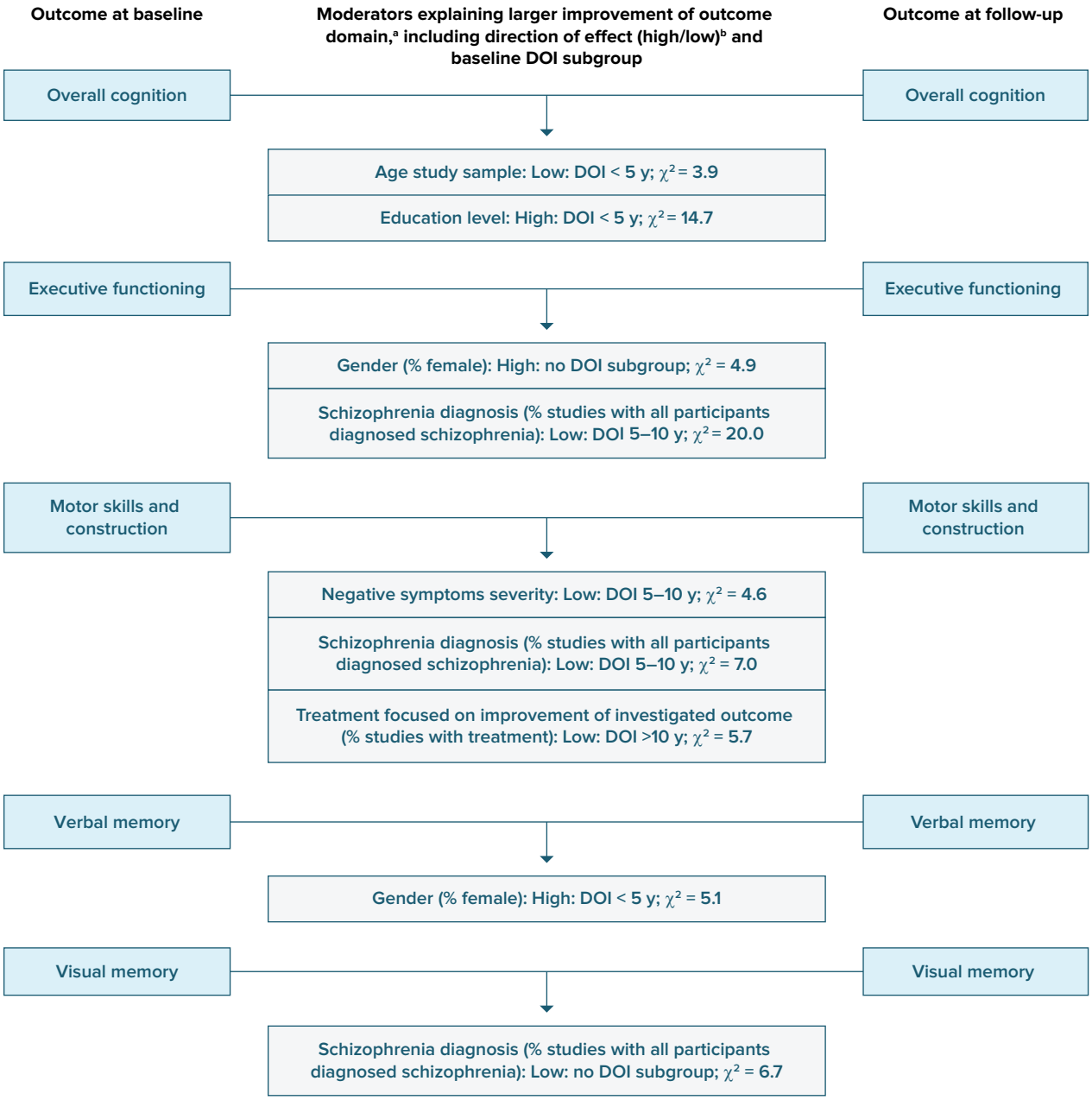
Quality Assessment

In general study, the quality was relatively good. However, a relatively larger number of studies reported high risk of bias for the QUIPS items study attrition and study confounding.

Analysis of subgroup differences indicated that a higher quality of study participation positively

Figure 3.

Overview of Significant Moderators at Baseline for Different Outcome Domains of Cognition[a]



[a]All moderators are statistically significant with a *P* value <.05.
[b]Abbreviations: High = high level, proportion, or presence of moderator at baseline is associated with more improvement in the outcome domain. Low = low level, proportion, or absence of moderator at baseline is associated with more improvement in the outcome domain. For example, studies with a high percentage of females at baseline are associated with more improvement in executive functioning.

influenced changes in motor skills and construction, verbal memory, language skills, and overall cognition but negatively influenced changes in attention and vigilance. A lower quality of study attrition positively influenced changes in attention and vigilance. Furthermore, a higher quality of prognostic factor measurement positively influenced changes in motor skills and construction, attention and vigilance, and overall cognition. Finally, a higher quality of outcome measurement positively influenced changes in attention and vigilance. In conclusion, we did not find a consistent line of specific QUIPS domains influencing study outcomes. Results of the quality assessment could be requested from the corresponding author.

DISCUSSION

In this meta-analysis, we examined changes in cognition over time in patients with SSD. We found marginal improvements in overall cognition. For the cognitive subdomains, we found small improvements in verbal memory and processing speed, marginal improvements in visual memory, executive functioning, and language skill, and no significant improvements in sensation and perception, motor skills and construction, attention and vigilance, or social cognition. In all cognitive domains, except for attention and vigilance, improvement was larger for patients with a shorter DOI after a short follow-up, compared to patients with a DOI >10 years. We found no significant improvement in any cognitive domain in the subgroup with a DOI >10 years. Changes in cognition are consistently smaller in patients diagnosed with schizophrenia compared to other diagnoses of SSDs and in males compared to females. On specific domains of cognition, we found moderating effects for age, education level, and negative symptoms.

Reflection on the Influence of DOI on Changes in Cognition

Overall, the findings are in line with results of previous studies: modest cognitive improvement is only observed in people with early psychosis.[10–14,23] Furthermore, we only found improvements in cognition after a short follow-up. This is also in line with previous research, which found stable patterns of cognition with no significant improvement over time after a long follow-up.[10,11,13] These short-term effects might partially be explained by a practice effect due to repeated assessments after a relatively short time, especially when parallel versions are not used. Previous research for people with mild cognitive impairment[41] and schizophrenia[42] already indicated these practice effects. Another explanation of more favorable changes in cognition after a short follow-up might be contributed by a novelty effect. This novelty effect suggests that the novelty of cognitive tasks, after baseline or first follow-up, requires extra cognitive processing and more brain activation at first, resulting in better performances after a short follow-up, especially for participants on a declining neurocognitive trajectory.[43] This is often followed by reduced demands of cognitive functioning once a task becomes familiar.[44] Given those modest improvements in cognition and the substantially lower level of cognitive functioning compared to healthy age-matched controls,[12,13,15,17] we presume that these modest changes result in a sustained lower level of cognitive functioning at follow-up compared to healthy controls. However, as we did not include healthy controls in our analysis, we cannot test this hypothesis in our meta-analysis. We found small improvements of verbal memory and processing speed, which is in line with previous meta-analyses.[14,23] However, we found less favorable indications of improvement in visual memory and executive functioning compared to previous meta-analyses,[14,23] presumably because we included different studies with a wider selection of assessment instruments, compared to previous meta-analyses.

We found no significant improvement of cognition for patients with a DOI >10 years. However, in contrast to previous studies,[16,17,45] we also did not find indications of cognitive decline in this group. This might be explained by the fact that those landmark papers in the field of cognition[17,45] were mostly focused on patients with an older age (ie, patients aged above 50 years), whereas in our analysis we also focused on younger patients with a longer DOI. Taken together, included studies did not indicate cognitive impairment. However, older age negatively influenced changes in overall cognition in our meta-analysis. This suggests that cognitive decline in patients with a long DOI predominantly occurs in older age patients. Furthermore, our findings are in line with previous research that indicated cognitive deterioration throughout the development of psychotic disorders, but stabilization after the first episode of psychosis.[16,46] We found stronger indications of cognitive improvement in patients with a shorter DOI. These differences between DOI subgroups could not be explained by differences in cognitive impairment at baseline. This strengthens our finding that, regardless of cognitive impairment, the highest potential of cognitive improvement could be achieved earlier in the course of illness, especially in patients with a DOI <5 years.

The Influence of Moderators of Changes in Cognition

We found several moderating effects on changes in cognition. First, we found significantly less favorable changes in verbal memory, visual memory, and executive functioning in studies that included more males. Previous studies did not find moderating effects of gender.[46] However, previous studies did indicate better verbal memory performances in females.[46–48] Nevertheless, our findings might suggest that tailoring interventions targeting cognitive improvement on gender differences might be necessary to achieve optimal results.[49] For example, we could investigate potential gender-specific adaptations in cognitive tasks to practical learning situations that are more relatable for men or women to facilitate them better in developing strategies to compensate for their cognitive deficits.

Furthermore, we found less favorable changes in motor skills and construction, visual memory, executive functioning, and processing speed for patients who were diagnosed with schizophrenia compared to other diagnoses of SSD. Possibly, schizophrenia

patients are more affected by the consequences from neurodevelopmental disruptions compared to patients with other psychotic disorders.[3,50] Our finding that more severe negative symptoms are associated with less favorable cognitive improvement, combined with previous findings indicating a more chronic pattern of negative symptoms throughout the course of illness for patients with schizophrenia,[21] might also partially explain these moderating effects.

We also found that people with an older age and lower education level show less favorable changes in overall cognition. This may be explained by an overrepresentation of subgroups with an older age in the subgroup with a baseline DOI >10 years. Previous research indicated that cognitive aging may be accelerated for people with SSDs.[51] This might suggest that age and DOI together reinforce less favorable changes in cognition. Furthermore, the association between higher education levels and cognitive improvements is in line with previous research.[11,52] A possible explanation is that patients with a higher education level are more exposed to cognitive activities and therefore better equipped against cognitive decline.[53] This explanation is in line with the cognitive reserve theory, which states that longer education and more involvement in cognitive activities in early life might be a protective factor for the development of functional and cognitive limitations in later life.[54,55]

Finally, we found that a lower severity of negative symptoms is associated with better improvement of motor skills and construction. This is in line with previous studies that indicated that certain aspects of negative symptoms, especially diminished emotional expressions, are overlapping and interrelated with motor skills and construction.[56,57] Therefore, a focus on improvement of negative symptoms might also contribute to improvements in motor skills and construction.

Limitations

Several limitations should be considered. First, we evaluated changes in cognition on a study level. Therefore, we could not entirely grasp the clinical diversity of our target group and their unique individual process of cognitive changes within each study. Second, the findings concerning the domains sensation and perception and social cognition are based on a limited number of studies, making these outcomes less reliable.[35] Furthermore, we included studies conducted in different contexts and using a wide variety of assessment instruments with both uncorrected and standardized scores. This inevitably leads to heterogeneity.[58] We attempted to explore this clinical heterogeneity through our analyses of moderating effects in this meta-analysis and through an analysis of baseline differences of those moderators between DOI subgroups. Although several of these analyses were based on a limited number of studies, we propose that the combination of these analyses gave reliable insights into subgroup differences which were taken into account in the interpretation of our findings. Another limitation is that DOI in our subgroups was based on the mean DOI of the study sample. Therefore, it is possible that a part of the sample in a given study has a shorter or longer DOI than the upper or lower limit of the DOI subgroup. We controlled for this overlap in DOI and did not find indications that this significantly influenced our study outcomes. Another limitation is that we only focused on objective assessments of cognition and no subjective ratings of cognitive functioning. These subjective ratings could give some valuable additional insights into changes of cognition and are therefore an important topic for future research. Finally, our inclusion criteria are relatively strict by only including longitudinal studies exclusively investigating patients with SSDs with extractable data of cognition on multiple time points and a follow-up length of at least 1 year. As a consequence, long-term outcomes might be based on a selective sample of possibly higher functioning patients who were still able to participate during a long follow-up. Especially, we included a small number of clinical trials targeting cognitive improvement as these generally selected a broader target group, also including patients with no primary diagnosis of SSD, or investigated changes over a shorter follow-up period of less than 1 year. However, we decided to use these strict inclusion criteria to diminish heterogeneity. Additionally, the longer follow-up of our included studies might give a selective, more positive, indication of our outcomes as only patients with a higher level of functioning might be able to complete the cognitive tasks at follow-up as well. This effect of a selective sample might have been applicable for the outcomes of attention and vigilance, as a lower study quality on study attrition positively influenced changes in this outcome domain, and attention and vigilance was the only outcome domain with more favorable outcomes after a long follow-up. However, for all other cognitive outcome domains, we did not find any indications for a selective group that remained at follow-up.

Conclusions

Based on the findings of our meta-analysis, we can conclude that people with SSD show modest cognitive improvements in some cognitive domains up until 10 years after their first diagnosis of SSD. This gives a slightly more optimistic view than the conclusion of some previous studies that improvement of cognition is not possible for people with psychosis.[16,45,59] Nevertheless, there is still a long way to go in the recovery of cognition for patients with SSD. Future research could focus on the development of treatment specifically focused on cognitive improvement as early as possible and the interrelationships of cognitive changes with other life

domains. Especially, improvement of negative symptoms might lead to more substantial improvements of cognition over time.

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Data Availability Statement: The majority of relevant data and materials are presented in the tables and supplementary materials, as well as partially available in the review protocol that is submitted in PROSPERO (CRD42022377107). All other data are not available online. Further questions and requests about availability of the data could be sent to the corresponding author.

Supplementary Material: Available at Psychiatrist.com.

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The Journal of Clinical Psychiatry

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*		

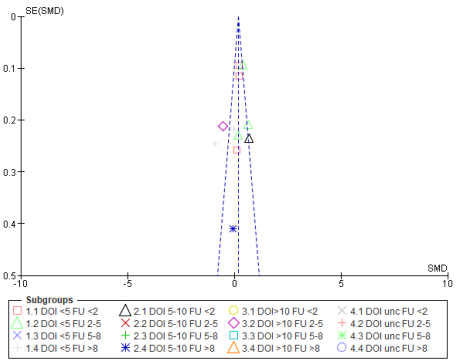
Overall cognition

(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

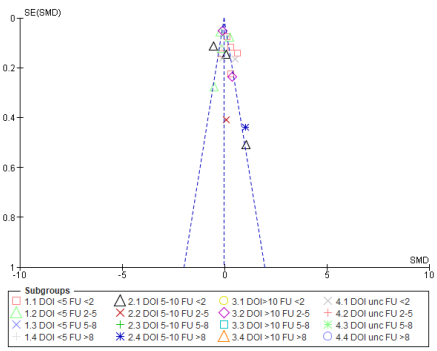
	Subgroup differences between follow-up cohorts			$\chi^2 = 17.95$; $df = 3$; $p < 0.01$		
Duration of illness unclear	< 2 years	2	182 - 168	d = <u>0.28</u> [S] (0.07 to 0.48)	+ = 0/ - = 0	I^2 = 12% (NA)
	≥ 2 - < 5 years	3	208 - 184	d = **0.21** [S] (0.04 to 0.39)	+ = 0/ - = 0	I^2 = 0% (0-63%)
	≥ 8 years	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

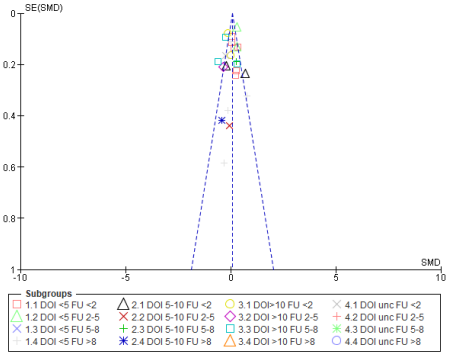
Sensation and perception



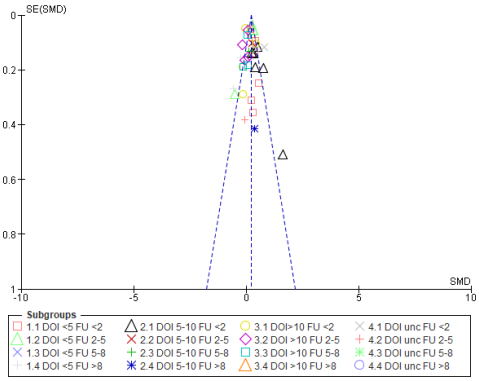
Motor skills and construction



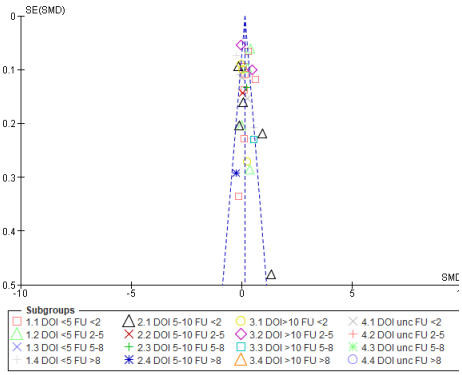
Attention and vigilance



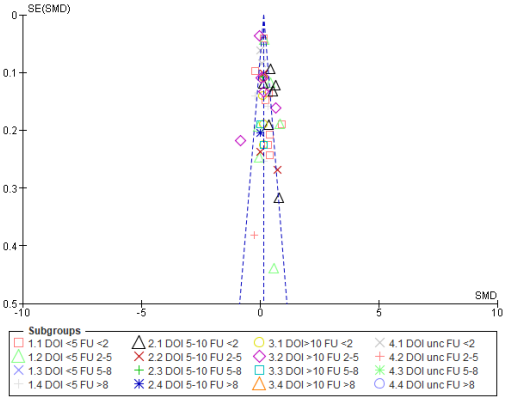
Verbal memory



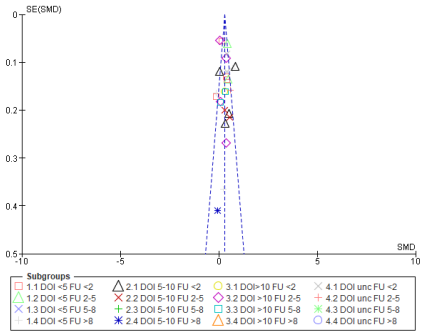
Visual memory



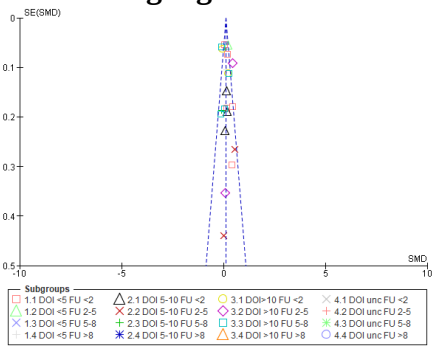
Executive functioning



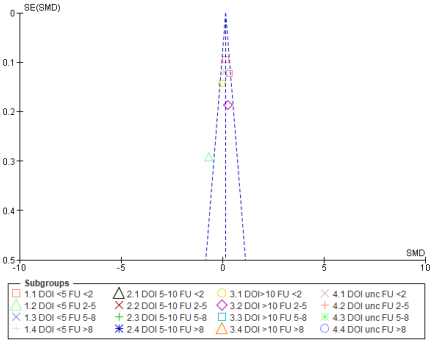
Processing speed



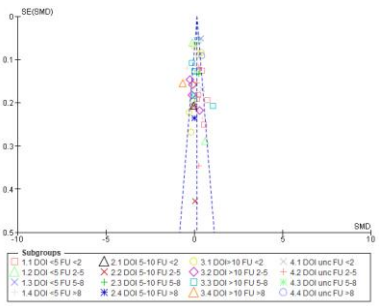
Language skills



Social cognition



Overall cognition



Supplementary references

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