Schizophrenia Research: Cognition 41 (2025) 100371

Contents lists available at ScienceDirect

Schizophrenia Research: Cognition

journal homepage: www.elsevier.com/locate/scog

# Cognitive changes in schizophrenia before and after illness onset: A meta-analysis examining consistency in measurement tools as a moderator☆

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ARTICLE INFO

*Keywords:*
Meta-analysis
IQ
Schizophrenia
Psychosis
Cognitive impairment
Neuropsychological assessments

ABSTRACT

*Background:* Cognitive impairment, a core feature of schizophrenia, is often evident before the onset of illness. The current study aimed to quantify IQ decline following the onset of illness by conducting a meta-analysis of longitudinal studies that evaluated cognitive functioning both before and after the first psychotic episode. Consistency in measurement tools – i.e. whether the same measurement tool was used at both assessments – was considered a potential moderating variable.

*Method:* Eleven studies were included in the meta-analysis - seven using the same measurement tool at both time-points and four using different tools. In addition, meta-regression explored whether the magnitude of IQ decline was associated with age at baseline.

*Results:* The meta-analysis effect size was −0.343 (95 % CI: −0.503 to −0.184), equivalent to a decrease of 5 IQ points. Use of the same (SMD −0.321, 95 % CI: −0.501 to −0.142) vs different (SMD −0.427, 95 % CI: −0.777 to −0.077) measurement tools was not a moderator of IQ change ($p = 0.279$). The meta-regression results were not significant ($p = 0.544$).

*Conclusion:* The current meta-analysis indicates a slight cognitive decline from the premorbid stage to post-onset. The use of different measurement tools yielded a slightly larger effect size and greater heterogeneity, suggesting that employing the same assessment tool could lead to more accurate results. Future longitudinal studies should focus on determining the timeline of cognitive decline.

## 1. Introduction

Although not a DSM requirement, cognitive impairment is a core feature of schizophrenia (Reichenberg and Harvey, 2007; Keefe, 2014), dating back to the writings of Emil Kraepelin and Eugen Bleuler (Kraepelin, 1919; Bleuler, 1950). Cognitive impairments are known to predict functional disability more strongly than psychotic symptoms and can have a significant impact on an individual's quality of life (Goldberg et al., 2010).

Multiple longitudinal studies have investigated cognitive decline in individuals with schizophrenia across different life stages, including late childhood (Agnew-Blais et al., 2015; Gochman et al., 2005; Reichenberg et al., 2010), adolescence (Davidson et al., 1999; MacCabe et al., 2013; Mollon and Reichenberg, 2018), adulthood (Fioravanti et al., 2005; Jones, 1997; Seidman et al., 2006), and old age (Kremen et al., 2010; Harvey et al., 1999). In most of these studies, cognitive decline has been evident at every life stage.

Lower IQ in childhood is linked to a higher risk of developing

☆ This article is part of a Special issue entitled: 'Ten Year Anniversary' published in Schizophrenia Research: Cognition.

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https://doi.org/10.1016/j.scog.2025.100371
Received 18 February 2025; Received in revised form 24 April 2025; Accepted 25 May 2025

schizophrenia spectrum disorders (Koenen et al., 2009; Zammit et al., 2004). A meta-analysis by Woodberry and colleges' found that adults who develop schizophrenia typically have an average childhood IQ deficit of 8 points (0.5 SD) (Woodberry et al., 2008). Moreover, multiple studies indicate that individuals tested during the premorbid period leading to their first psychotic episode exhibit lower IQ scores compared to healthy controls (Davidson et al., 1999; Mollon and Reichenberg, 2018; Woodberry et al., 2008; Dickson et al., 2012; Schulz et al., 2014). A meta-analysis by Mesholam-Gately and colleges' (Mesholam-Gately et al., 2009) indicated that IQ impairments are larger after the first episode compared to the premorbid period, with an IQ deficit of 14–15 points (1 SD). These findings have been supported by other studies that demonstrate an even more significant decline (Reichenberg and Harvey, 2007; Meier et al., 2014).

Despite well-established theories regarding cognitive decline in patients with schizophrenia, it is essential to conduct assessments over different time points to accurately measure cognitive changes. Several meta-analyses have examined cognitive impairments in patients with schizophrenia but only with one-time point - either premorbid (Woodberry et al., 2008; Fusar-Poli et al., 2012) or post-onset (Bora and Murray, 2014a; Rajji et al., 2014). To date, there has been no meta-analysis that analyzed cognitive changes from before to after the onset of psychosis.

Many previous studies have faced methodological challenges that can impact their outcomes. For example, some longitudinal studies included neuropsychological assessments after the onset of schizophrenia but attempted to estimate premorbid cognitive function (Barder et al., 2015; MacCabe et al., 2012; Ohi et al., 2019; Sørensen et al., 2010). Additionally, some studies focused on the premorbid stage to identify individuals who might later develop schizophrenia (Amminger et al., 2000; Fuller et al., 2002; Urfer-Parnas et al., 2010), but again relied on one-time point. Furthermore, while some studies compared cognitive performance at multiple points, these comparisons were made only after the onset of illness (Hoff et al., 1999; Leeson et al., 2009; van Winkel et al., 2006; Zanelli et al., 2019) and they lacked premorbid data.

It is important to note that while longitudinal studies are ideal for measuring change across time, these may be challenging when involving patients with schizophrenia. One major issue is maintaining contact with participants, as high dropout rates and a tendency to disengage are common in this population (Eichler et al., 2008; Jobe and Harrow, 2005). Additionally, ethical concerns regarding informed consent arise, especially when patients are experiencing psychotic episodes (Kovnick et al., 2003). This makes it challenging to ensure their continued participation in longitudinal studies.

Another methodological issue is that some longitudinal studies that evaluated participants at two different time-points used different measurement tools. For instance, they might have used school records during the premorbid stage (T1) and an IQ test (WAIS) in the post-onset stage (T2) (Albee et al., 1963; Bilder et al., 2006; Sheitman et al., 2000). The use of inconsistent measurement tools can significantly undermine the accuracy and reliability of the results. Differences in neuropsychological assessments—such as item difficulty or test duration—between the first and second assessments can lead to significant score discrepancies (Harvey et al., 2005). Pietrzak and colleges' emphasize the necessity of consistently using the same measurement tool to minimize biases and yield more reliable results (Pietrzak et al., 2009).

The primary goal of this meta-analysis is to compare longitudinal studies that used the same cognitive measurement tool with those that employed different tools. Our focus is on two time points: the first occurring prior to the onset of psychosis, and the second after the onset of illness. We aim to determine whether the magnitude of change in IQ scores is related to the use of the same versus different measurement tools. This analysis will improve our understanding and help guide the selection of appropriate methodologies for studying cognitive change in schizophrenia. Specifically, we aim to identify which approach – using the same or different measurement tools – yields more accurate results.

## 2. Methods

### 2.1. Literature search

A comprehensive literature search was carried out to evaluate changes in IQ scores obtained before and after onset of schizophrenia. The following keywords and their combinations were searched in the MEDLINE (PubMed) database: ([Schizophrenia OR Psychosis OR First Episode] AND [Longitudinal] AND [Premorbid] AND [Post-onset] AND [IQ OR Intelligence quotient OR Intelligence tests OR Intelligence OR Cognitive OR Neuropsychological OR Intellectual] AND [IQ Decline OR IQ Deficits]. The screening process involved reviewing titles, abstracts, and references to ensure that inclusion criteria were met. Based on the search keywords, we identified 4795 studies. The PRISMA 2020 flow diagram for study selection through databases, registries, and other methods (Page et al., 2020) is presented in Fig. 1.

### 2.2. Study selection

#### 2.2.1. Inclusion criteria

(1) Longitudinal studies related to cognitive decline in schizophrenia, which tested at least one time-point before and one after illness onset, (2) published in English until 2022, and (3) data were available to calculate standardized means difference (SMD) in full scale IQ or equivalent tests.

#### 2.2.2. Exclusion criteria

(1) Study groups included less than ten participants. (2) Studies that examined schizophrenia among children. (3) In cases where multiple studies examined the same cohort, the most recent publication was selected. (4) The premorbid IQ results were obtained using estimate tests rather than actual measurements.

By examining the studies that were found in the literature search and reviewing the reference lists of relevant studies, we identified 11 studies that met our criteria (see Table 1) – seven studies examined cognition in patients with schizophrenia before and after the first psychotic episode using the same measurement tool, and four used different measurement tools at different time points.

### 2.3. Data synthesis

We reviewed all 11 studies and extracted data from each time point, including number of and age of participants, and the mean and standard deviation of the full scale IQ [FSIQ] score or equivalent test. Next, the difference between the two means (T1 and T2), and standard error of the difference were calculated.

Differences in IQ between the two time points, before (T1) and after (T2) the first psychotic episode, were expressed as SMD, which is appropriate when different studies assess the same variable but measure it in different ways (Egger et al., 2001). Meta-analysis combined the SMDs of cognitive decline across studies. Heterogeneity between study samples was assessed using Cochrane's heterogeneity statistic Q; random effect methods were used to allow for heterogeneity between studies (Egger et al., 2001). The $I^2$ statistic was calculated to quantify the proportion of variability between studies attributable to heterogeneity, i.e. the proportion that is explained by differences between the included studies rather than by sampling error (Higgins et al., 2003).

In Caspi's study (Caspi et al., 2003), four subtests were examined. We chose to include the RPM-R test. Similarly, in Albee's study (Albee et al., 1963), three different tests were examined. We used the Stanford-Binet test. In both studies we selected validated tests that have a strong correlation with overall IQ (Albee et al., 1963; Baizanis et al., 2016) and included the highest number of participants.

In order to test the difference in mean effect size between subgroups we chose to use a moderator variable indicating whether or not the same measurement tool was used at both time points. This was tested with the

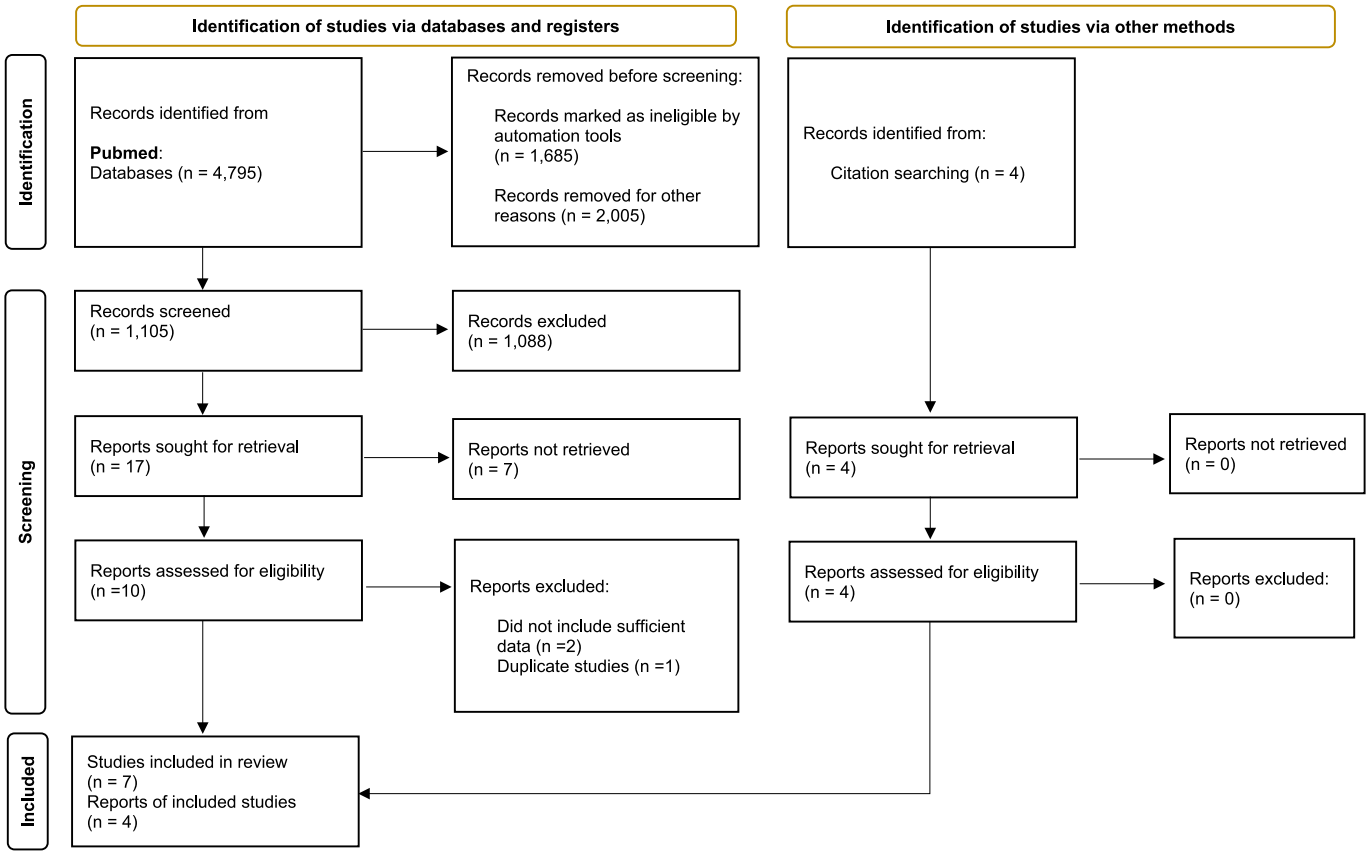


**Fig. 1.** Flow diagram for studies identification (Prisma, 2020).

**Table 1**
Longitudinal studies assessing change in IQ schizophrenia patients from the premorbid phase to after onset.

| | Author | T1 | | T2 | | Cognitive test | Same test | | Average follow up years | IQ change |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Age M(SD) | N | Age M(SD) | | Yes | No | | |
| 1 | Rappaport & Webb (1950) (Rappaport and Webb, 1950) | 10 | During junior/senior high school years | 10 | 22.4 | High school assessments | √ | | – | Decline |
| 2 | Lubin et al., 1962 (Lubin et al., 1962) | 159 | – | 159 | 26 | ACB[a] (Army classification Battery) | √ | | – | Decline |
| 3 | Schwartzman & Douglas (1962) (Schwartzman and Douglas, 1962) | 50 | 22.7 (SD = 4.8) | 50 | 32.5 (SD = 4.3) | Revised Examination "M"[b] | √ | | 10 | Decline |
| 4 | Russell et al. (1997) (Russell et al., 1997) | 34 | 13.2 (SD = 3.2) | 34 | 32.9 (SD = 10.4) | WISC/WAIS-R | √ | | 19.4 | Decline |
| 5 | Seidman et al. (2006) (Seidman et al., 2006) | 31 | 7 | 27 | 36.2 (SD = 2.5) | WISC/WAIS-R | √ | | 29 | Decline |
| 6 | Kremen et al. (2010) (Kremen et al., 2010) | 10 | 6.6 (SD = 2.06) | 10 | 39 (SD = 1.8) | PPVT[c] | √ | | 32 | Decline |
| 7 | Meier et al. (2014) (Meier et al., 2014) | 31 | Mean of measurements at ages 7,9,11,13 | 31 | 38 | WISC/WAIS-IV | √ | | 28 | Decline |
| 8 | Albee et al., (1963) (Albee et al., 1963) | 98 | – | 98 | – | School records/WAIS-R | | √ | – | No Decline |
| 9 | Sheitman et al., (2000) (Sheitman et al., 2000) | 27 | 14.22 (SD = 2.21) | 27 | 40.26 (SD = 7.7) | School records/WAIS-R | | √ | 26.04 | Decline |
| 10 | Caspi et al. (2003) (Caspi et al., 2003) | 44 | 16–17 | 44 | 22.54 (SD = 3.5) | Israeli draft board[d] | | √ | 5–6 | Decline |
| 11 | Bilder et al., (2006) (Bilder et al., 2006) | 39 | Age at time of taking college entrance exams | 39 | 23.2 (SD = 5.8) | School records/WAIS-R | | √ | – | Decline |

[a] Including five subtests (Reading and Vocabulary, Arithmetic Reasoning Test, Pattern Analysis Test. Mechanical Aptitude Test, Army Clerical Speed).
[b] Entered test to the Canadian army.
[c] Peabody Picture Vocabulary Test.
[d] Including one subtest Raven's Progressive Matrices-R (RPM-R).

Q statistical method developed by Hedges and Olkin (Hedges and Olkin, 2014). In this method Q is divided in two as $Q_{between}$ ($Q_b$) and $Q_{within}$ ($Q_w$) and analyses are performed on these two different Qs.

Meta regression was used to assess whether the magnitude of IQ decline was associated with age at baseline, available in seven of the 11 studies examined. Data were analyzed using Comprehensive Meta-

Analysis Version 2.0 (Biostat Inc., Englewood, NJ, USA) and SPSS 28.

## 3. Results

The meta-analysis of all 11 studies revealed a significant decline (SMD −0.343, 95 % CI −0.503 to −0.184, z = −4.213, $p < 0.001$), equivalent to a mean decline of 5 IQ points between the premorbid and post-onset assessments.

When stratifying the studies according to use of the same measurement tool, a significant decline was observed in both group: studies that used the same measurement tool in both assessments (SMD −0.321, 95 % CI −0.501 to −0.142, z = −3.508, $p < 0.001$) and studies that did not (SMD −0.427, 95 % CI −0.777 to −0.077, z = −2.393, p < 0.001). Fig. 2 displays the results of the meta-analysis in a forest plot. No significant heterogeneity was detected in studies using the same measurement tool (Q = 11.143, df = 6, $p = 0.084$; $I^2 = 46.152$ %), whereas studies using different measurement tools exhibited significant heterogeneity (Q = 15.691, df = 3, p < 0.001; $I^2 = 80.881$ %).

Although studies using different measurement tools showed a slightly larger effect size and greater heterogeneity, no significant difference was observed between studies using the same and different measurement tools ($Q_b = 0.279$, $p = 0.597$). This indicates that use of the same measurement tool is not a moderator of these findings (Table 2).

We examined the studies included in the meta-analysis for possible outliers by performing a forest plot inspection. According to this method, a study is defined as an outlier if the confidence intervals of the effect size do not overlap with those of the pooled estimate (Viechtbauer and Cheung, 2010). Rappaport and Webb's study met these criteria (Rappaport and Webb, 1950). Hence, we performed a sensitivity analysis excluding this study. This did not change the findings regarding the pooled effect size of cognitive decline (SMD −0.317, 95 % CI −0.424 to −0.209, z = −5.757, $p < 0.001$).

Seven studies were included in the meta regression examining the association between age at baseline and cognitive decline (Seidman et al., 2006; Kremen et al., 2010; Meier et al., 2014; Sheitman et al., 2000; Caspi et al., 2003; Russell et al., 1997; Schwartzman and Douglas, 1962). The meta regression was not statistically significant ($p = 0.544$), suggesting that the magnitude of cognitive decline is not associated with age at first assessment. Fig. 3 presents the meta-regression Bubble Plot.

## 4. Discussion

We meta-analyzed 11 studies in which premorbid and post-onset cognitive functioning were measured by neuropsychological assessments. The use of different neuropsychological assessments at various time points can make it challenging to determine whether changes in scores are due to actual changes in cognitive function or due to measurement error. Hence, we examined whether the use of the same or different measurement tools is a moderator in these analyses.

Previous studies reported that the IQ of patients with schizophrenia ranges between 0.5 and 1 standard deviations below the population mean (Reichenberg and Harvey, 2007; Heinrichs and Zakzanis, 1998; Stirling et al., 2003). The current study shows a mean decrease of −0.343 effect size in IQ between premorbid and post-onset assessments, which is lower than previous findings. Given the magnitude of this finding, it is plausible, as Woodberry and colleges' suggested, that most of the decline occurs during the premorbid stage (Woodberry et al., 2008).

Our findings align with research on individuals at ultra-high risk (UHR) for psychosis (Carrión et al., 2015; Cheng et al., 2022). A meta-analysis by Bore and Murry (Bora and Murray, 2014b) found no evidence of cognitive decline in patients with UHR and first-episode psychosis (FEP), suggesting that cognitive deficits exist prior to the prodromal phases of psychosis.

It is also possible that differences between our results and previous findings can be partially explained by differences between studies included in the meta-analysis. These may be affected by changes in diagnostic criteria for schizophrenia. Studies from the 1950s and 1960s used the DSM-I, while later studies relied on the DSM-III or DSM-IV, released >30 years later (Rappaport and Webb, 1950; Schwartzman and Douglas, 1962; Lubin et al., 1962). The shift from DSM-I to DSM-III was significant, as DSM-III defined schizophrenia based on specific observable symptoms rather than broad categories and psychoanalytic concepts (Gonçalves et al., 2018).

Another possible reason for the differences in results may be related to the clinical characteristics of study participants. There are populations that may be more impaired at the time of the first measurement. For example, in Albee's Study (Albee et al., 1963), the initial cognitive assessments were conducted using a test designed for children in special education classes. Similarly, Russell's (Russell et al., 1997) study involved children first assessed at a child psychiatry clinic. In contrast, the studies conducted by Lubin (Lubin et al., 1962), Douglas &

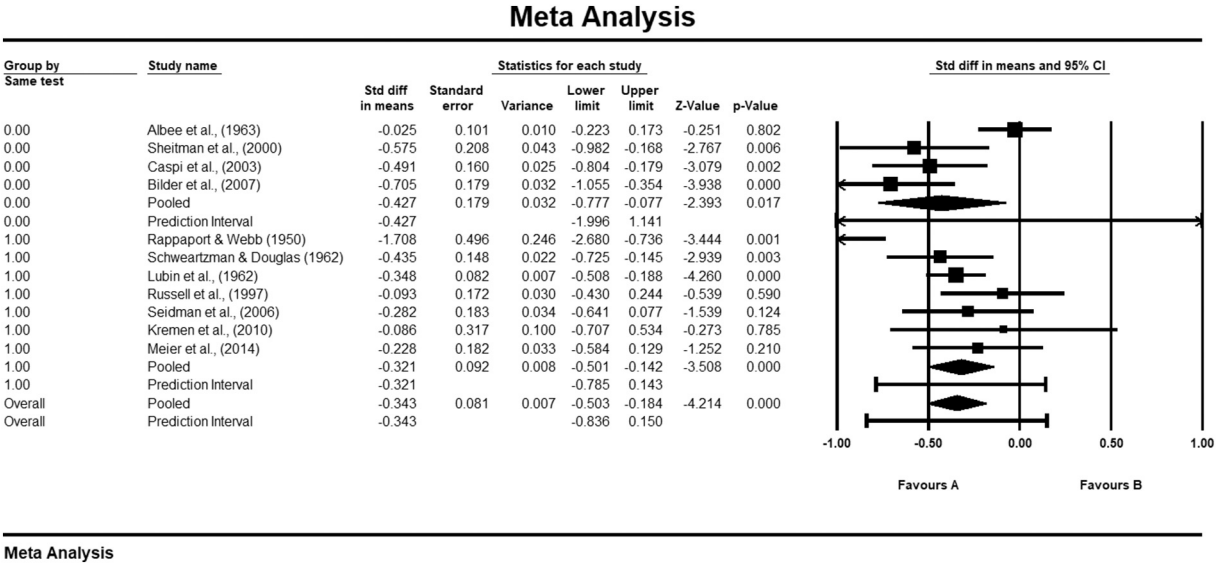


**Fig. 2.** Forest plot of cognitive decline.

**Table 2**
Meta-analysis between groups.

| | Studies | N | Effect Size | 95 % CI | | Q | $Q_b$ |
|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | |
| | | | | | | | 0.279 |
| Same measurement tool | 7 | 325 | −0.321 | −0.777 | −0.077 | 11.143 | |
| Different measurement tool | 4 | 208 | −0.427 | −0.501 | −0.142 | 15.691 | |

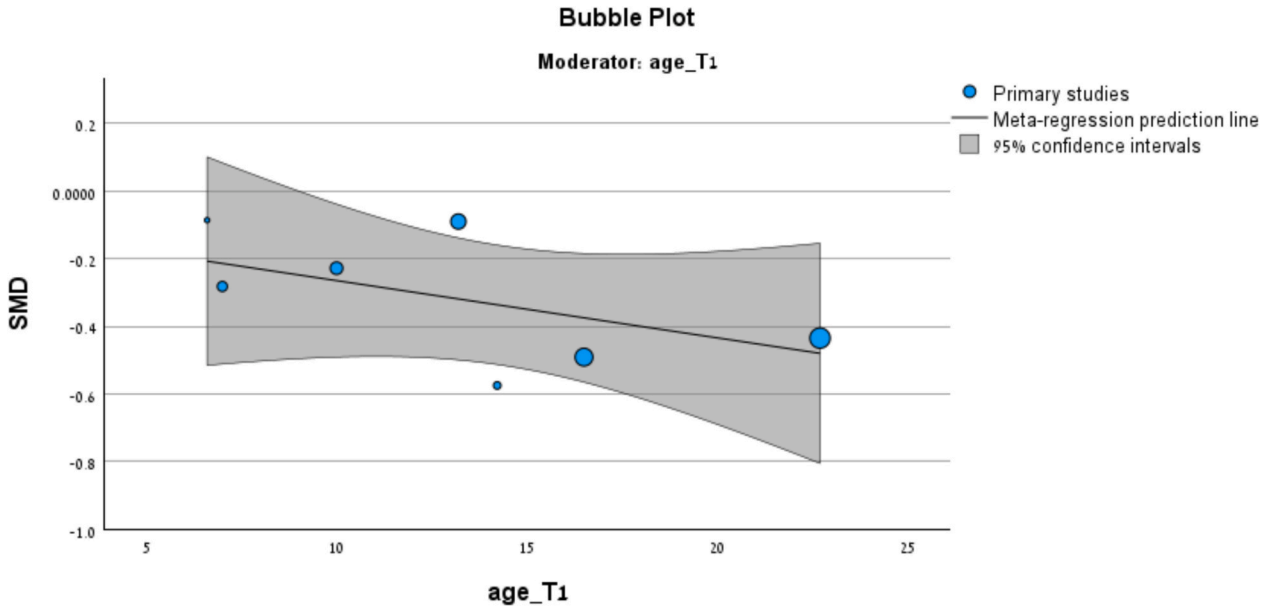


**Fig. 3.** Meta-regression of age at first assessment predicting cognitive decline.

Schwartzman (Schwartzman and Douglas, 1962), and Caspi (Caspi et al., 2003) included individuals who had been drafted into military service, and were not considered to be at-risk at the time of the first assessment. Participants in Sheitman's study (Sun et al., 2024) were patients with treatment-resistant schizophrenia (Sheitman et al., 2000), also known to be characterized by poorer cognitive functioning.

Although the use of the same measurement tool was not a significant moderator in these analyses, the effect size was larger in the group that did not use the same measurement tools, as was heterogeneity. This suggests that employing the same tool may result in a more conservative but more accurate outcome. Neurocognitive tests often assess multiple domains of functioning (Keefe and Eesley, 2012), such as attention, memory, and executive function. Using the same tool ensures comparisons reflect accurate cognitive changes rather than difference in measurement. A study by Floyd (Floyd et al., 2008) provides evidence that different test batteries produce different IQ scores.

Another possible explanation for these findings is related to practice effects, which refer to the tendency of individuals to improve on cognitive tests simply due to repeated exposure to the testing instruments, paradigms, and items, rather than experiencing genuine cognitive enhancement (Goldberg et al., 2010; Goldberg et al., 2015). In a study by Goldberg and colleagues' (Goldberg et al., 2007), the observed cognitive improvements were consistent in magnitude with the practice effects seen in healthy controls. This suggests that some of the cognitive improvements noted in schizophrenia may be influenced by practice effects, which involve exposure, familiarity, and procedural learning. The time intervals between measurements in Goldberg and colleagues' (Goldberg et al., 2007) study were only a few weeks. In contrast, the time differences in the current meta-analysis spanned from several years to decades. Therefore, it is less likely that practice effects affected the results.

Our findings indicate that cognitive decline is not associated with age at first assessment. This data indirectly supports existing studies that suggest that cognitive decline typically occurs before or during the early stages of the disorder and remains relatively stable over the follow-up years (Reichenberg et al., 2010; Meier et al., 2014; Bora and Murray, 2014a; Hoff et al., 2005; Rund, 1998). However, in some studies, age at baseline varied across participants. This variability should be taken into account when interpreting the meta-regression results, as the predictors are study-level aggregates. Additionally, these findings must be interpreted with caution, as the recommended number for meta-regression is at least ten studies (Borenstein et al., 2021; Thompson and Higgins, 2002).

## 5. Limitations

There are several limitations in the current study: First, there is a small number of studies that examined cognitive impairment among schizophrenia patients before and after the psychotic outbreak in each subgroup. Second, most of the studies had only two time-points and a large gap in time between the two measurements, making it impossible to identify specific periods of decline. Thirdly, it is known from the literature that other variables are associated with cognitive decline among schizophrenia patients, such as taking antipsychotic medication (Davidson et al., 2009; Faber et al., 2012; Omachi and Sumiyoshi, 2018), substance abuse (Cheng et al., 2018; Mata et al., 2008), number of hospitalizations (Harvey et al., 1999; Harvey et al., 2013), education (Dickson et al., 2020; Ullman et al., 2017), and more. These variables can affect cognitive functioning, and were not examined in this study. Fourth, we were only able to examine total IQ scores and not specific cognitive domains due to insufficient data. Finally, although the effect sizes of cognitive change were converted to standardized mean

differences (SMD) for purposes of the meta-analysis, the neuropsychological tests still vary in accuracy and stability over time. Currently, there is no widely used cognitive screening tool for schizophrenia, making it hard to compare study results (Gold et al., 1999).

## 6. Recommendations for future studies

Longitudinal studies must be well designed to obtain more accurate results and gain a better understanding of cognitive decline in schizophrenia. Future studies should include several assessments before and after illness onset. In addition, the same neuropsychological assessment should be used at each time point, while accounting for practice effects and addressing them through strategies that can reduce the impact of retest with the same version, as proposed by Goldberg and colleagues' (Goldberg et al., 2015). Also, rigorous study designs should examine and control for other variables such as: antipsychotic medication, substance abuse, number of hospitalizations, education, etc. Such studies could provide a more accurate understanding of the timing of cognitive decline in schizophrenia.

## CRediT authorship contribution statement

**Noaz Cohen:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Mark Weiser:** Writing – review & editing, Conceptualization. **Abraham Reichenberg:** Writing – review & editing. **John M. Davis:** Writing – review & editing, Formal analysis. **Michael Davidson:** Writing – review & editing. **Nomi Werbeloff:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

All other authors have no conflict of interests to declare.

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