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Neurocognitive Deficits in Individuals at Ultra-High-Risk for Psychosis: An Overview of Systematic Reviews

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Abstract

Objective: Identifying individuals at ultra-high risk for psychosis (UHRP) is crucial for early intervention and prevention strategies. Neurocognitive deficits have been increasingly recognized as potential predictors of psychosis onset. This overview aims to consolidate current evidence and elucidate the role of neurocognitive predictors in identifying UHRP individuals.
Method: we systematically searched three scientific databases, i.e., PubMed, Scopus, and Google Scholar using predefined keywords related to predictive neurocognitive markers and ultra-high risk psychosis. By following the PRISMA procedure, we included all relevant systematic-reviews and meta-analyses in our data-synthesis.
Results: Neurocognitive deficits, including impairments in working memory, attentional control, verbal learning, and executive functions, have been consistently identified as predictors of psychosis conversion in individuals at UHRP. Structural and functional neuroimaging studies have further revealed aberrant brain connectivity, reduced gray matter volume, and altered neural activation patterns in key brain regions to be involved in psychosis. Moreover, the combination of neurocognitive and clinical risk factors has been shown to enhance the accuracy of predicting psychosis onset and inform personalized intervention strategies.
Conclusion: Neurocognitive deficits serve as valuable predictors of the risk of psychosis in individuals with UHRP, offering insights into the underlying neurobiological mechanisms and potential targets for early intervention. Future research should focus on refining predictive models, elucidating the neurodevelopmental trajectories, and evaluating the efficacy of targeted interventions in mitigating the psychosis risk.

Key words: *Early Detection; Neurocognitive; Predictors; Psychosis; Ultra-High Risk*

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Psychotic disorders are among the most severe and impairing mental health conditions, leading to profound effects not only on the individuals who suffer from them but also on families and communities at large (1). These disorders, which include schizophrenia and the schizoaffective disorder, are often characterized by a range of debilitating symptoms, such as hallucinations, delusions, and disorganized thinking, that typically manifest in late adolescence or early adulthood (2, 3). This period of onset is particularly concerning as it coincides with critical developmental milestones in emotional, social, and cognitive maturation. Recent epidemiological studies indicate that the prevalence of psychotic disorders is steadily rising, highlighting an urgent need for effective early intervention strategies to mitigate the risk of transition to full-blown psychosis (4, 5).

Prior to the emergence of overt psychotic symptoms, individuals often pass through a prodromal phase, characterized by subtle, yet significant, shifts in psychological and cognitive functioning (6). This at-risk state is frequently referred to as the ultra-high risk for psychosis (UHRP), which encompasses a variety of clinical presentations including unusual thoughts, social withdrawal, and heightened anxiety (7). Identifying individuals within this UHRP phase is crucial, as early recognition and targeted interventions can dramatically improve long-term outcomes, with the potential to delay or even prevent the onset of psychosis altogether (8).

In recent years, the scientific community has increasingly devoted attention to the identification of neurocognitive markers that could reliably predict the transition from a UHRP state to a psychotic disorder (9). Neurocognitive deficits refer to impairments in essential cognitive processes, including memory, attention, and executive functioning, which are pivotal for daily functioning and overall quality of life. While these deficits have been rigorously documented in individuals diagnosed with established psychosis (10), their manifestation in those at UHRP remains the focus of ongoing research. This distinction is critical, as understanding the neurocognitive profile of individuals with UHRP may provide insights into the underlying mechanisms of psychosis and lead to improved intervention strategies (11).

A plethora of studies have explored various neurocognitive domains in relation to psychosis risk, revealing a complex interplay of factors that may exacerbate cognitive impairment. Notably, deficits in verbal memory, processing speed, attention, working memory, and executive function have emerged as prominent areas of concern among UHRP populations (12). Although these cognitive abilities are known to be compromised in individuals with established psychosis, they are also present as markers of risk in individuals at UHRP, albeit often to a lesser degree. The challenge that remains is to delineate which specific cognitive deficits serve as the most reliable predictors of a subsequent transition to a full-blown psychotic episode, and how these deficits can be effectively integrated into existing predictive frameworks for clinical use (13).

Furthermore, neurocognitive deficits in individuals with UHRP are frequently accompanied by subtle neurobiological alterations, as evidenced by neuroimaging studies. Neuroanatomical and functional imaging research has identified structural and functional changes within critical brain regions, such as the prefrontal cortex and hippocampus, both of which are integral to cognitive processes including memory and executive functioning (14). These neurobiological markers underscore the hypothesis that cognitive impairments in UHRP populations may not merely reflect the initial stages of emerging psychosis, but rather indicate deeper-seated brain abnormalities that predispose individuals to the eventual development of psychotic disorders (15).

Despite growing interest and research in this domain, the predictive validity of neurocognitive deficits remains contentious. Some investigations strongly advocate for the presence of specific cognitive impairments, particularly in verbal memory and executive function, as harbingers of psychosis; however, inconsistencies in findings across studies complicate this narrative. Factors such as variations in study design, heterogeneity in sample characteristics, and differences in the cognitive assessment tools employed may contribute to these discrepancies. Thus, there is an urgent demand for more robust methodologies and the comprehensive incorporation of neurocognitive assessments into predictive models to enhance our understanding of the risk of psychosis. This article aims to provide a comprehensive overview of systematic reviews and meta-analyses that have examined neurocognitive dysfunctions associated with psychosis in UHRP populations. By synthesizing findings across a broad spectrum of literature, this overview aspires to elucidate the most compelling neurocognitive markers, emphasizing their potential applicability in clinical settings. Ultimately, this endeavor seeks to advance the field's understanding of how neurocognitive assessments can inform early intervention strategies, paving the way for improved outcomes for at-risk individuals.

Materials and Methods

In the present study we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) to identify rigorous evidences regarding neurocognitive predictors of transition to psychosis in cases at UHRP. We conducted a comprehensive search on PubMed, Scopus, and Google Scholar using a predefined search strategy to identify peer-reviewed articles relevant to our objective. After eliminating duplicates, we screened the remaining references by reviewing their titles and abstracts. Then, we assessed the full text of articles for eligibility.

Eligibility Criteria

We included papers in our review if they: 1) were published in peer-reviewed journals, 2) were systematic reviews or meta-analyzes, and 3) focused on studies examining neurocognitive deficits in individuals at a clinically high risk for psychosis. Papers such as conference proceedings, narrative reviews, and reports on interventional studies were excluded.

Data Extraction

The reviewers extracted the following information: 1) the first author and the year of publication; 2) the number of studies and participants included, along with the review type; and 3) the key findings.

Quality Assessment

We used the *"A Measurement Tool to Assess Systematic Reviews (AMSTAR 2)"* checklist to thoroughly evaluate the quality of the evidence gathered from the studies analysed. The AMSTAR 2 is an updated and refined tool designed to evaluate the methodological quality of systematic reviews, especially those that encompass both randomized and non-randomized studies of healthcare interventions (16). Unlike its predecessor, which focused primarily on randomized controlled trials, AMSTAR 2 is broader in scope and includes 16 items spread across several key domains, such as protocol registration, literature search strategy, study selection and data extraction, risk of bias assessment, heterogeneity and publication bias, data synthesis, and interpretation of results. Among these, seven items are deemed "critical domains," where deficiencies can significantly compromise the credibility of a review. These critical areas include the registration of a review protocol, clarity in study selection criteria, a comprehensive literature search, proper risk of bias assessment, justification for study exclusions, appropriate meta-analytical methods, and a thorough discussion of the potential impact of bias on the review's conclusions. Unlike the original AMSTAR, which provided an overall score, AMSTAR 2 does not generate a cumulative score, but instead, guides users in identifying critical flaws, leading to a classification of the review's quality as high, moderate, low, or critically low.

Results

We identified a total of 282 references through searches in three different databases. After eliminating duplicates, 220 unique references remained. In the subsequent stage, we screened these 220 references by reviewing their titles and abstracts, which led to the identification of 89 studies that appeared relevant. Since the full text of 4 references was unavailable, we proceeded with a thorough review of the remaining 85 papers, applying our predefined inclusion and exclusion criteria. As a result of this detailed assessment, 17 systematic reviews and meta-analyzes were deemed eligible for inclusion in the final data synthesis (Figure 1). Our findings can be categorized into two groups: a) neurocognitive differences between individuals at UHRP and other clinical groups or healthy controls, and b) neurocognitive differences between individuals with UHRP who transition to psychosis and those who do not.

Neurocognitive Differences between Individuals with UHRP and other Clinical Groups or Healthy Controls

In total, 16 out of the 17 eligible studies identified neurocognitive differences between individuals with UHRP and other clinical groups or healthy controls. The studies included in these 16 articles examined a range of cognitive functions, including global cognition, executive functioning, attention, memory, learning ability, and social cognition (10, 17-30).

Healthy Control Group

Our findings indicate notable differences in cognitive functioning between UHRP individuals and the healthy population. Ekin *et al*. conducted a meta-analysis of 17 studies, encompassing a total sample of 860 participants in the first-episode psychosis (FEP), UHRP, and familial high risk for psychosis (FHRP) groups, along with 817 healthy controls. The analysis revealed that both clinical and familial high-risk groups exhibited small but statistically significant increases in antisaccade errors, with effect sizes of g = 0.26 (95% CI: 0.02–0.52) and g = 0.34 (95% CI: 0.13–0.55), respectively (17). Pedruzo *et al*. conducted a systematic review comparing 151 individuals at clinical high risk for psychosis (CHRP) [mean age: 16.48 years, SD: 2.41; 32.45% female] with 64 healthy controls (HC) [mean age: 16.79 years, SD: 2.38; 42.18% female]. Their findings indicated that CHRP individuals performed worse than HCs in verbal learning, sustained attention, and executive functioning (19). Similarly, Millman *et al.*, in a meta-analysis of 21 studies involving 1,556 CHRP individuals and 973 HC participants, reported significant cognitive impairments in CHRP individuals compared to the HCs (e.g., global cognition: g = −0.48, 95% CI: -0.60 to -0.34). However, when compared to clinical controls (CC), CHRP individuals showed only minimal cognitive impairments (e.g., global cognition: g = −0.13, 95% CI: -0.20 to -0.06) (31). In another meta-analysis, Hedges *et al*. (10) observed that HCs showed greater performance improvements over time compared to CHRP individuals in tasks measuring letter fluency (g = −0.32, P = 0.029) and digit span (g = −0.30, P = 0.011). Another area of interest has been the within-group variability in neurocognitive functioning. Atalan *et al*., in a meta-analysis of 78 studies, found that the CHRP group exhibited significantly greater variability than the HC group across multiple domains (variability ratios (VR)), ranked by effect size: verbal learning (VR = 1.29, 95% CI: 1.15–1.45), visual learning (VR = 1.20, 95% CI: 1.07–1.34), executive functioning (VR = 1.31, 95% CI: 1.18–1.45), visual memory (VR = 1.41, 95% CI: 1.02–1.94), processing speed (VR = 1.26, 95% CI: 1.07–1.48), premorbid IQ (VR = 1.27, 95% CI: 1.09–1.49), and reasoning and problem-solving (VR = 1.17, 95% CI: 1.03–1.34) (20).

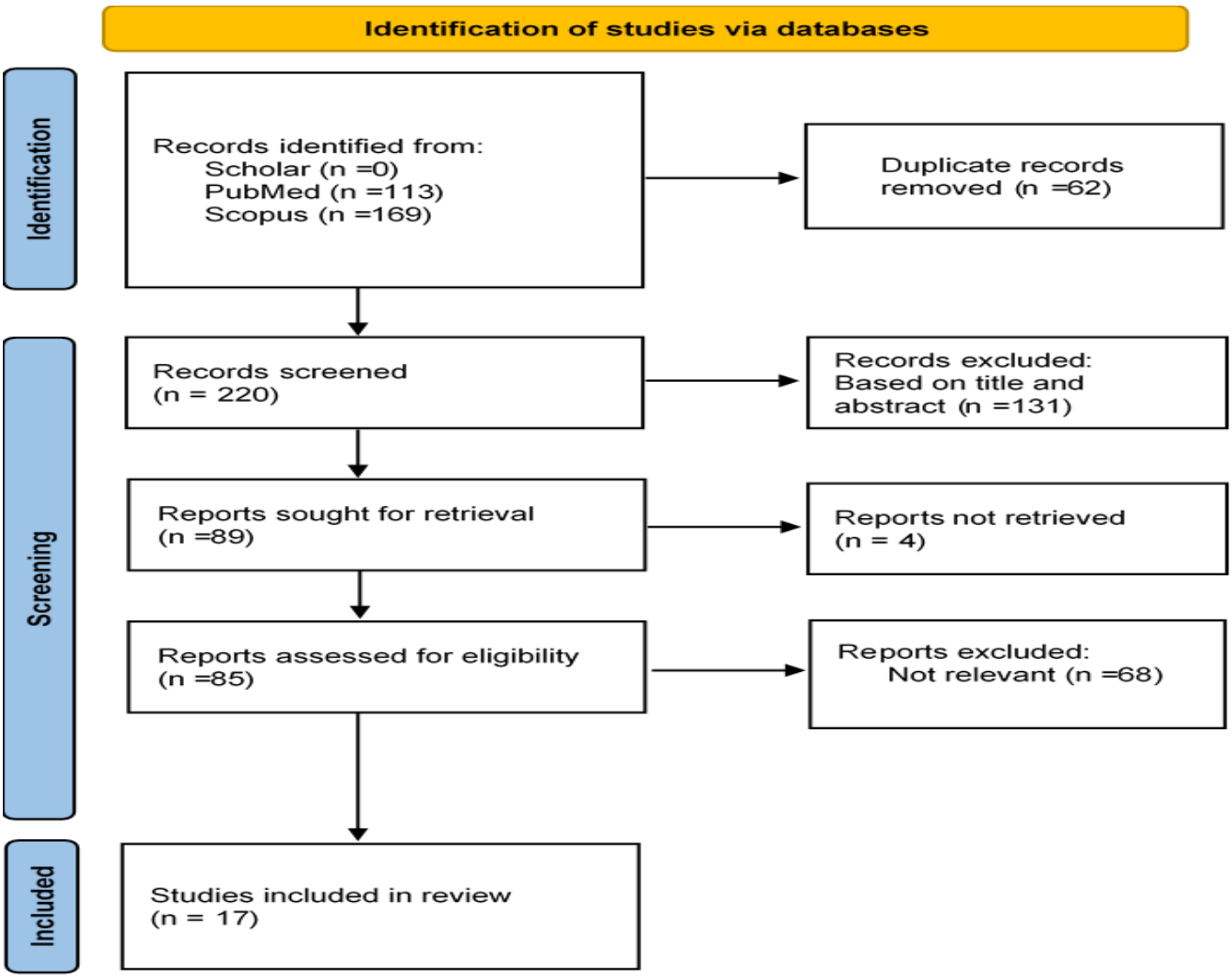

Figure 1. PRISMA Flowchart for Identification of Included Studies on Neurocognitive Deficits in Individuals at Ultra-High-Risk for Psychosis

In an earlier published meta-analysis on the same set of included studies, Catalan *et al*. (21) reported that CHRP individuals exhibited medium to large cognitive deficits compared to HCs. These deficits were observed across several tasks, including the Digit Symbol Coding Test (g = −0.74, 95% CI: -1.19 to -0.29), Stroop Color-Word Reading Task (g = −1.17, 95% CI: -1.86 to -0.48), Brief Assessment of Cognition Scale Symbol Coding (g = −0.67, 95% CI: -0.95 to -0.39), Hinting Task (g = −0.53, 95% CI: -0.77 to -0.28), Hopkins Verbal Learning Test-Revised (g = −0.86, 95% CI: -1.43 to -0.28), California Verbal Learning Test (g = −0.50, 95% CI: -0.64 to -0.36), Rey Auditory Verbal Learning Test (g = −0.50, 95% CI: -0.78 to -0.21), University of Pennsylvania Smell Identification Test (g = −0.55, 95% CI: -0.97 to -0.12), and National Adult Reading Test (g = −0.52, 95% CI: -1.01 to -0.03). A meta-analysis of six case-control studies revealed that CHRP individuals had significantly impaired overall cognition compared to HCs, with a large effect size (SMD = −1.00, 95% CI: -1.38 to -0.63, P < 0.00001, I2 = 2%). Specific impairments included large deficits in attention/vigilance (SMD = −0.83S) and processing speed (SMD = −1.21), and moderate deficits in working memory (SMD = −0.76), visual learning (SMD = −0.68), reasoning and problem-solving (SMD = −0.71), and verbal learning (SMD = −0.67)(22). Like Catalan *et al*. (21), Hauser *et al*. (23) conducted a meta-analysis focusing on neuropsychological test performance and found that CHRP individuals performed significantly worse than HCs in seven out of nine cognitive domains. Effect sizes ranged from g = −0.17 (95% CI: -0.30 to -0.04) for attention/vigilance to g = −0.43 (95% CI: -0.68 to -0.18) for social cognition, with the largest deficits observed in verbal learning and processing speed (g = −0.42, 95% CI: -0.64 to -0.20). The California Verbal Learning Test (g = −0.65, 95% CI: -0.84 to -0.46) and Digit Symbol Test (g = −0.63, 95% CI: -0.86 to -0.40) were particularly effective in distinguishing between the CHRP and the HC groups. Reasoning/problem-solving and working memory showed no significant differences in cross-sectional analyses, but were distinct in longitudinal studies.

Regarding social cognition, Van Donkersgoed *et al*. (24) conducted a meta-analysis demonstrating that UHRP individuals exhibit moderate deficits in social cognition, particularly in affect recognition and discrimination, both in facial and vocal expressions, as well as in verbal Theory of Mind (ToM). Another meta-analysis reported an overall medium effect size for social cognition (g = −0.477), with the largest deficits observed in attributional bias (AB; g = −0.708), medium deficits in emotional perception (EP; g = −0.446) and ToM (g = −0.425), and smaller deficits in social perception (SP; g = −0.383) (25). Additionally, Bora *et al*. (26) meta-analysed 44 studies on youths at UHRP and FHRP. Compared to controls, high-risk individuals showed impairments across all social cognition domains, with effect sizes ranging from d = 0.34 to d = 0.71 for UHRP and d = 0.24 to d = 0.81 for FHRP. The low heterogeneity in effect sizes across studies (I^2 = 0%−18%) adds robustness to these findings. Notably, the combination of genetic risk and attenuated symptoms in both risk paradigms was associated with greater cognitive impairments. In an earlier meta-analysis including 21 original studies, Bora *et al*. (27) found that ToM was notably diminished in individuals at UHRP when compared to HCs (d = 0.45), with very low heterogeneity in the effect sizes (I^2 = 0.03) and a fail-safe N of 42. Impairments were significant in both verbal (d = 0.49) and visual (d = 0.40) aspects of ToM. However, effect sizes for the mental state decoding test (Eyes Task) could not be calculated because of the limited number of studies (n = 3), and two of these studies reported no impairment (d = 0.06 and d = 0.09) in UHRP individuals. The analysis indicated that relatives of individuals with psychosis exhibited poorer performance compared to healthy controls, with a standardized effect size of d = 0.37. Deficits were slightly more pronounced in studies that included non-schizophrenic psychoses, yielding an effect size of d = 0.41 (95% CI: 0.22–0.60, Z = 4.1, P < 0.001). Significant impairments were found in both verbal (d = 0.24) and visual (d = 0.36) ToM tasks among relatives. Task-specific analyses revealed difficulties with the Hinting Task, while performance on the Eyes Task did not show similar deficits. The heterogeneity of the effect sizes was low (I^2 = 0% − 0.09%), and the fail-safe N was 146. Additionally, meta-regression analyses indicated that variations in educational background may play a role in the observed differences in ToM between relatives of individuals with psychosis and HCs (B = 0.41, SE = 0.13, Z = 3.1, P = 0.002). Valli *et al*. conducted a review of 32 studies focused on memory and learning in populations at UHRP. They found notable deficits in areas such as verbal learning and memory, executive functioning and working memory, attention, and processing speed. Cognitive abilities in individuals at high risk, whether due to clinical factors or genetic predisposition, frequently fell between those of HCs and patients experiencing FEP (28). Neurofunctional research has revealed changes in brain activity within circuits associated with memory and learning processes. These results align with the conclusions of two previous review studies (29, 30).

Clinical Control Group

Individuals with schizophrenia were the primary clinical group compared to those at UHRP. A recent meta-analysis of 114 studies (18) utilizing the Chinese version of the MATRICS Consensus Cognitive Battery (MCCB) assessed cognitive functioning across 392 CHRP individuals, 4,922 individuals with first-episode schizophrenia (FES), 1,549 with chronic schizophrenia (CS), and 2,925 with schizophrenia of unspecified duration. The findings revealed that both the FES and CS groups exhibited significantly greater cognitive impairments than the CHRP group in six of seven cognitive domains, including visual learning, working memory, processing speed, reasoning, verbal learning and problem-solving, and social cognition. Moreover, within the schizophrenia spectrum, the CS group demonstrated more pronounced deficits than the FES group, particularly in reasoning and problem-solving.

In another study, Catalan *et al*. (20) conducted a meta-analysis to explore within-group variability in neurocognitive functioning among young CHRP individuals and comparison groups, including those with FEP. The analysis of pooled variability ratios (VR) revealed that the FEP group demonstrated greater variability in executive functioning (VR = 1.28, 95% CI: 1.08–1.51) compared to the CHRP group. Similarly, coefficient of variation ratio (CVR) analyses indicated higher variability in verbal learning for the FEP group (CVR = 1.23, 95% CI: 1.09–1.39). When comparing variability measures between CHRP and FEP groups, the FEP group showed greater variability in specific tasks, such as Wisconsin Card Sorting Test (WCST) Perseverative Errors (VR = 1.03, 95% CI: 1.04–1.14), and CVR analyses highlighted higher variability in California Verbal Learning Test (CVLT; CVR = 1.24, 95% CI: 1.07–1.44) and WCST Categories (CVR = 1.81, 95% CI: 1.18–2.79). In a prior meta-analysis of the same set of studies, Catalan *et al*. (21) reported that individuals at CHRP exhibited less severe cognitive impairments than those with FEP. Similar findings have been reported by Hauser *et al*. (23). The analysis revealed that CHRP individuals demonstrated significantly better performance than those with FEP in five out of six cognitive domains. Effect sizes ranged from d = 0.29 (95% CI: 0.03–0.56) for processing speed to d = 0.39 (95% CI: 0.17–0.62) for attention/vigilance and verbal learning, and d = 0.40 (95% CI: 0.18–0.64) for working memory. However, there was no significant difference between the two groups in the domain of reasoning and problem-solving.

Neurocognitive Functioning in Individuals at UHRP Associated with Transition to Psychosis and non-Transition to Psychosis

Predicting whether an individual with UHRP will transition to psychosis or not, is an important issue. Our findings indicate that greater cognitive impairments are linked to a higher likelihood of transitioning to psychosis (see Table 1). For example, Millman *et al*. (31) reported that the cognitive impairments observed among CHRP individuals were largely attributable to those who transitioned to psychosis (CHR-T), while those who did not transition (CHR-NT) exhibited performance comparable to CCs. For instance, in global cognition, CHR-T individuals showed moderate deficits (g = −0.42, 95% CI: -0.64 to -0.19), whereas CHR-NT individuals exhibited minimal impairments (g = −0.09, 95% CI: -0.18 to 0.00). Similar patterns were observed in processing speed (g = −0.59, 95% CI: -0.82 to -0.37 for CHR-T; g = −0.12, 95% CI: -0.25 to 0.07 for CHR-NT) and working memory (g = −0.42, 95% CI: -0.62 to -0.22 for CHR-T; g = −0.03, 95% CI: -0.14 to 0.08 for CHR-NT). Hedges *et al*. (10) further highlighted differences in longitudinal performance, where CHR-T and CHR-NT individuals differed significantly on tasks such as the Trail Making Test A (TMT-A; g = 0.24, P = 0.014) and Symbol Coding (g = −0.51, P = 0.011). CHR-NT individuals improved over time on both tasks, whereas CHR-T individuals showed lesser improvements on TMT-A and a decline in Symbol Coding performance. Additionally, a meta-analysis of 78 studies found that transition to psychosis from a CHRP state was associated with medium to large cognitive deficits, particularly in the California Verbal Learning Test (CVLT; g = −0.58, 95% CI: -1.12 to -0.05) (21). Hauser *et al*. (23) compared CHR-T and CHR-NT performance across 60 neuropsychological tests comprising nine domains. CHR-T individuals performed significantly worse in six of eight domains, with effect sizes ranging from moderate (g = −0.24, 95% CI: -0.44 to -0.03 for attention/vigilance) to large (g = −0.49, 95% CI: -0.76 to -0.22 for verbal learning; g = −0.54, 95% CI: -0.80 to -0.27 for visual learning). No significant differences were observed in reasoning/problem solving and working memory. Among individual tests, the Rey-Osterrieth Complex Figure Test, Verbal Fluency Test/Controlled Oral Word Association Test, and CVLT most effectively differentiated CHR-T from CHR-NT, with effect sizes of g = −0.49 (95% CI: -0.82 to -0.16), g = −0.45 (95% CI: -0.86 to -0.03), and g = −0.40 (95% CI: -0.80 to -0.00), respectively. Similar results have been corroborated in other review studies (24, 26, 28, 29, 32).

Table 1. Overview of the Results from the Systematic Review and Meta-Analysis on Neurocognitive Deficits in Individuals at Ultra-High-Risk for Psychosis

Author, Year	Number of Studies / Participants	Main Findings	Review's Quality
Ekin, 2024 (17)	A meta-analysis encompassing 17 studies involved a total of 860 participants with UHRP, FEP and FHRP, alongside 817 HC subjects.	Both the clinical group and the familial high-risk group showed small but statistically significant increases in antisaccade (AS) errors, with effect sizes of g = 0.26 (95% CI: 0.02–0.52) and g = 0.34 (95% CI: 0.13–0.55), respectively.	High
Cai, 2024 (18)	A meta-analysis of 114 studies using the Chinese MCCB to assess cognition included a total sample of 7,394 HC, 392 CHRP, 4,922 FES, 1,549 CS, and 2,925 with schizophrenia of unspecified duration.	The meta-analysis revealed significantly greater cognitive impairments in FES and CS compared to CHRP across six of seven domains: reasoning and problem-solving, verbal learning, speed of processing, visual learning, working memory, and social cognition. Additionally, CS showed more pronounced deficits than FES in reasoning and problem-solving.	High
Pedruzo, 2023 (19)	A systematic review encompassing three studies included a total of 151 CHRP patients and 64 HC individuals.	Individuals with CHRP exhibited poorer performance in the domains of verbal learning, sustained attention, and executive functioning compared to HCs. Among children and adolescents, neurocognitive deficits may already be present prior to the onset of psychosis and tend to remain consistent during the transition to psychosis.	Low

Millman, 2022 (31)	A meta-analysis of 21 studies included a total sample of 1,556 CHR-P, 1,398 CC, and 973 HC cases. Cognitive data stratified by transition status were reported in seven studies, encompassing 110 CHR-T and 553 CHR-NT participants.	Individuals at CHR-P demonstrated significant cognitive impairments compared to HCs (e.g., global cognition: g = −0.48 [95% CI: -0.60, -0.34]), while showing only minimal impairments compared to CCs (global cognition: g = −0.13 [95% CI: -0.20, -0.06]). Notably, the additional cognitive deficits observed in CHR-P were largely attributed to the CHR-T subgroup, as youth at CHR-P without transition (CHR-NT) exhibited cognitive performance that was generally comparable to CCs (global cognition: CHR-T: g = −0.42 [95% CI: -0.64, -0.19]; CHR-NT: g = −0.09 [95% CI: -0.18, 0.00]; processing speed: CHR-T: g = −0.59 [95% CI: -0.82, -0.37]; CHR-NT: g = −0.12 [95% CI: -0.25, 0.07]; working memory: CHR-T: g = −0.42 [95% CI: -0.62, -0.22]; CHR-NT: g = −0.03 [95% CI: -0.14, 0.08]).	High
Hedges, 2022 (10)	Meta-analysis of 13 studies.	Meta-analyses revealed that HC individuals demonstrated significantly greater longitudinal improvements than CHR individuals in tasks such as letter fluency (g = −0.32, P = 0.029) and digit span (g = −0.30, P = 0.011). Additionally, differences were observed in the longitudinal performance of CHR-T and CHR-NT groups on the Trail Making Test A (TMT-A (g = 0.24, P = 0.014) and symbol coding (g = −0.51, P = 0.011). While CHR-NT participants showed improvement on both tasks over time, CHR-T participants exhibited smaller gains in TMT-A and a decline in symbol coding performance.	High
Catalan, 2022 (20)	A meta-analysis of 78 studies included a total sample of 5,162 CHRP individuals, 2,865 HC participants, and 486 FEP individuals.	In the CVR analyses, the CHRP group demonstrated increased variability across the previously identified neurocognitive domains, with additional variability emerging in attention/vigilance (CVR: 1.24, 95% CI 1.07–1.44), working memory (CVR: 1.18, 95% CI 1.03–1.35), social cognition (CVR: 1.12, 95% CI 1.01–1.24), and visuospatial ability (CVR: 1.15, 95% CI 1.03–1.28). The CHRP group transitioning to psychosis exhibited higher variability in executive functioning (VR: 1.31, 95% CI 1.18–1.45) compared to those who did not transition to psychosis and to the FEP group. Overall, individuals at clinical high risk for psychosis displayed greater variability in neurocognitive performance relative to healthy controls.	High

Catalan, 2021 (21)	A meta-analysis of 78 independent studies was conducted, involving 5162 individuals at CHRP, 2865 HCs, and 486 individuals with FEP.	Individuals classified into the CHRP group demonstrated moderate to significant deficits in various cognitive tasks when compared to HCs. These tasks included the Stroop color-word reading test (g = −1.17; 95% CI, −1.86 to −0.48), the Hopkins Verbal Learning Test–Revised (g = −0.86; 95% CI, −1.43 to −0.28), the digit symbol coding assessment (g = −0.74; 95% CI, −1.19 to −0.29), the Brief Assessment of Cognition Scale Symbol Coding (g = −0.67; 95% CI, −0.95 to −0.39), the University of Pennsylvania Smell Identification Test (g = −0.55; 95% CI, −0.97 to −0.12), the Hinting Task (g = −0.53; 95% CI, −0.77 to −0.28), the Rey Auditory Verbal Learning Test (g = −0.50; 95% CI, −0.78 to −0.21), the California Verbal Learning Test (g = −0.50; 95% CI, −0.64 to −0.36), and the National Adult Reading Test (g = −0.52; 95% CI, −1.01 to −0.03). Nonetheless, their cognitive impairments were not as pronounced as those observed in individuals experiencing a First Episode of Psychosis (FEP). Additionally, a longitudinal progression to psychosis from a CHR-P state revealed medium to large deficits in the California Verbal Learning Test (CVLT) (g = −0.58; 95% CI, −1.12 to −0.05). Meta-regression analyses indicated significant influences by age and educational background on the processing speed.	High
Zheng, 2018 (22)	A meta-analysis was performed on six case-control studies involving a total of 396 participants to evaluate neurocognitive functions in CHRP subjects (n = 197) compared to HCs (n = 199), utilizing the MCCB.	Individuals at CHRP demonstrated considerable cognitive impairments compared to HCs, with large effect sizes noted in overall cognition (n = 128, SMD = -1.00, 95% CI: -1.38 to -0.63, P < 0.00001; I^2 = 2%), as well as in processing speed (SMD = -1.21) and attention/vigilance (SMD = -0.83). Additionally, moderate effect sizes were observed in working memory (SMD = -0.76), reasoning and problem-solving (SMD = -0.71), along with visual learning (SMD = -0.68) and verbal learning (SMD = -0.67). However, no significant differences were identified in the social cognition domain, where CHRP subjects had a small effect size (SMD = -0.33, 95% CI: -0.76 to 0.10, P = 0.14; I^2 = 70%). Overall, apart from social cognition, CHRP individuals exhibited poorer performance than healthy controls across all cognitive domains assessed by the MCCB, with the most pronounced deficits found in processing speed, attention/vigilance, and working memory.	Moderate

Hauser, 2017 (23)	A meta-analysis was conducted involving 60 neuropsychological assessments across 9 different domains, derived from 32 studies with 21 distinct samples. This analysis included 1,684 patients in the CHR, 986 HCs, and 405 FEP cases.	Individuals with CHR showed significantly poorer performance than HCs in seven out of nine assessed domains, with Hedges g effect sizes ranging from -0.17 [-0.30, -0.04] in attention/vigilance to -0.42 [-0.64, -0.20] for verbal learning and speed of processing, and -0.43 [-0.68, -0.18] in social cognition. The only areas where no significant difference was observed were reasoning/problem solving and working memory, which were highlighted in longitudinal studies. The California Verbal Learning Test (-0.65 [-0.84, -0.46]) and the Digit Symbol Test (-0.63 [-0.86, -0.40]) were the most effective in distinguishing between these groups. In comparison to FEP subjects, those with CHR performed better in 5 out of 6 domains, with effect sizes ranging from 0.29 [0.03, 0.56] in speed of processing to 0.39 [0.17, 0.62] for attention/vigilance and verbal learning, although no difference was noted in reasoning/problem solving. Among CHR participants, those with CHR-P performed worse than those without CHR-NP in 6 out of 8 domains, with effect sizes ranging from -0.24 [-0.44, -0.03] in attention/vigilance to -0.54 [-0.80, -0.27] in visual learning, while both groups showed similar outcomes in reasoning/problem solving and working memory. Three specific tests —the Rey-Osterrieth Complex Figure Test, Verbal Fluency Test/Controlled Oral Word Association Test, and California Verbal Learning Test— were the most effective at differentiating between CHR-P and CHR-NP, with effect sizes of -0.49 [-0.82, -0.16], -0.45 [-0.86, -0.03], and -0.40 [-0.80, -0.00], respectively.	High
Van Donkersgoed, 2015 (24)	The analysis encompassed a total of seventeen studies.	The overall effect size was determined to be medium (d = 0.52, 95% CI = 0.38–0.65), with no evidence of moderation by age, gender, or sample size. Subgroup analyses indicated that individuals in the UHRP phase demonstrate significant moderate impairments in affect recognition and discrimination across both facial expressions and vocal tones, as well as in verbal ToM. Because of the limited number of studies, effect sizes were not computed for attributional bias or social perception/knowledge. Most studies did not find a link between deficits in social cognition and the transition to psychosis, indicating that social cognition might not serve as a reliable indicator of psychosis risk. Nevertheless, some research suggests that verbal ToM and the ability to recognize certain emotions in facial expressions could have predictive significance for the transition to psychosis. Additional investigation in these areas is warranted.	High
Lee, 2015 (25)	A meta-analysis of 20 studies, with 1229 individuals at CHR and 825 HCs who met the inclusion criteria.	The overall effect size for social cognition was moderate (g = -0.477). The most substantial effect was observed for AB (g = -0.708), followed by medium effect sizes for EP (g = -0.446) and ToM (g = -0.425). Small effect sizes were found for SP (g = -0.383).	High

Bora, 2014 (26)	A meta-analysis of 44 studies comparing FHR or UHR individuals (n = 2113) with HCs (n = 1748) in youth populations, with a mean age of 15-29 years.	In comparison to the control group, individuals identified as high risk demonstrated deficits in all assessed domains, with effect sizes ranging from d = 0.34 to 0.71 for the UHRP group and d = 0.24 to 0.81 for the FHRP group. The variation in effect sizes across different studies was minimal, which enhances the reliability of the results obtained from this meta-analysis (I^2 = 0-0.18%). Both risk categories showed that a combination of genetic predisposition and milder symptoms was associated with greater cognitive impairments. Specifically, in the UHRP group, a delayed onset of psychosis correlated with more significant cognitive deficits across all domains (d = 0.31-0.49), with the exception of sustained attention. Nevertheless, cognitive impairment on its own proved to have limited ability to predict outcomes for those at high risk.	High
De Herdt, 2013 (32)	A meta-analysis of nine studies, including 583 CHR individuals (CHR-C = 195, CHR-NC = 388), met all inclusion criteria.	CHR-P individuals performed significantly worse than CHR-NP individuals on two MATRICS domains: working memory (ES = −0.29, 95% CI = −0.53 to −0.05) and visual learning (ES = −0.40, 95% CI = −0.68 to −0.13). No significant differences were found between CHR-P and CHR-NP in the remaining four domains (processing speed, attention/vigilance, verbal learning, reasoning/problem solving). According to findings, it may be concluded that working memory and visual learning can differentiate between CHR-P and CHR-NP. Including these tasks in psychosis prediction models could enhance their predictive accuracy.	High
Bora, 2013 (27)	This meta-analysis, comprising 21 studies, compared ToM performance of 3005 individuals with FEP, UHR individuals, and unaffected relatives, with 1351 HCs.	Unaffected relatives performed significantly worse than HCs (d = 0.37), with this deficit becoming slightly more pronounced when studies involving non-schizophrenic psychoses were included (d = 0.41, 95% CI = 0.22–0.60, Z = 4.1, P < 0.001). Significant impairments were observed in both verbal ToM (d = 0.24) and visual ToM (d = 0.36). Task-specific analyses revealed that the Hinting task, but not the Eyes test, was impaired in relatives. The heterogeneity for effect sizes was minimal (I^2 = 0–0.09), and the fail-safe N was 146 studies. Meta-regression analyses suggested that differences in educational duration might contribute to the ToM differences between controls and relatives (B = 0.41, SE = 0.13, Z = 3.1, P = 0.002). For UHR subjects, ToM was significantly impaired compared to HCs (d = 0.45), with no heterogeneity observed in the effect sizes (I^2 = 0.03). Both verbal ToM (d = 0.49) and visual ToM (d = 0.40) showed significant deficits. Due to limited studies, we could not calculate an effect size for the Eyes task, which was used in only three studies, two of which did not show impairment in UHR patients (d = 0.06 and 0.09).	High

Valli, 2012 (28)	A comprehensive review was conducted on thirty-two studies focusing on memory and learning in individuals deemed to be at clinical and genetic high risk for psychosis.	Cross-sectional research has shown that individuals at clinical or genetic high risk for psychosis experience cognitive impairments related to verbal learning and memory, executive function/working memory, attention, and processing speed. Generally, their cognitive abilities fall between those of HC participants and individuals experiencing their first episode of psychosis. Neurofunctional studies also indicate altered brain activity within the neural networks associated with memory and learning. Nonetheless, findings are less consistent when it comes to differentiating cognitive variations or tracking their development over time in those who eventually develop psychosis compared to those who remain non-psychotic. Despite these discrepancies, research that incorporates cognitive factors into regression models or predictive algorithms suggests that certain cognitive areas, particularly verbal memory, can enhance the accuracy of predictions regarding the onset of psychosis, surpassing predictions based solely on psychopathological assessments. This implies that combining neurocognitive evaluations with predictive capabilities could improve the processes of stepwise risk assessment.	Moderate
Fusar-Poli, 2012 (29)	A total of 19 studies met the inclusion criteria, including 1188 HR subjects and 1029 controls.	When compared to control subjects, individuals with HR showed deficits in various cognitive areas, impacting general intelligence, executive function, verbal and visual memory, verbal fluency, attention, working memory, and social cognition. While there was also an observed decline in processing speed, this difference did not achieve statistical significance. A delayed onset of psychosis was associated with more severe impairments, especially in verbal fluency and memory tasks. The examined studies revealed fairly uniform results, with no indications of publication bias. Additionally, a sensitivity analysis reinforced the reliability of the main findings.	Moderate
Thompson, 2011 (30)	We identified seven studies that investigate social cognition within the UHR population, one of which is a conference abstract or paper currently under review. Among these studies, two explored various aspects of social cognition.	Among the two studies that assessed theory of mind, significant deficits were noted in UHRP patients. Similarly, out of four studies that focused on emotion recognition, two revealed noteworthy impairments in UHRP individuals. Both studies that evaluated social perception or knowledge also identified significant differences. Furthermore, the only study that explored attributional bias also reported disparities between UHR patients and HC subjects.	Low

HR: High risk, UHR: Ultra high risk, UHRP: Ultra high risk for psychosis, AB: attributional bias, CC: clinical comparators, CHR: Clinical high risk, CHR-NT: clinical high risk without transition, CHRP: clinical high risk for psychosis, CHR-T: clinical high risk with transition, CHR-P: CHR subjects who later convert to psychosis, CHR-NP: CHR subjects who do not later convert to psychosis, MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia, CS: chronic schizophrenia, CVR: coefficient of variation ratio, EP: emotion processing, FES: first-episode schizophrenia, FHR: Familial high-risk, FHRP: familial high-risk for psychosis, HC: healthy controls, MCCB: MATRICS Consensus Cognitive Battery, SP: social perception, ToM: theory of mind, VR: Metanalytic variability ratio

Discussion

This umbrella review provides valuable insights into the neurocognitive differences observed in UHRP individuals relative to HCs and clinical populations, as well as the cognitive predictors of transition to psychosis. Significant cognitive impairments in UHRP individuals relative to both HCs and other clinical groups were evident across the studies. These deficits spanned the domains of general cognition, executive function, attention, memory, and learning and social cognition. Consistent with prior research, UHRP individuals demonstrated a cognitive profile that was

typically intermediate between HCs and individuals with FEP (33-35). Thus, studies by Pedruzo *et al*. (19) and Millman *et al*. (31) found a deficit in verbal learning and sustained attention and executive performance when age- and sex-matched patients with UHRP were compared against normal controls. These cognitive anomalies thereby extend the notion that UHRP states may have an increased psychosis propensity, even in the presence of only partial clinical signs of the disease.

Neurofunctional studies further reinforced these cognitive findings, revealing altered brain activity within neural circuits related to memory and learning processes in ultra-high-risk populations (36-39). Such neural disruptions may underlie the cognitive deficits observed and offer insights into the neurobiological mechanisms that could predispose individuals at UHR to psychosis. However, overall, the cognitive performance of UHRP individuals was not as impaired as those with FEP, supporting the hypothesis that UHRP individuals may be in a prodromal phase of psychosis (40). This finding underlines the importance of early intervention to mitigate the risk of psychosis progression.

Social cognition emerged as a prominent area of impairment in UHRP individuals. Studies consistently showed deficits in various aspects of social cognition, including emotion recognition, ToM, and social perception (21, 41). Specifically, significant impairments were found among UHRP individuals in tasks assessing emotion recognition, attributional bias, and verbal ToM. Deficits in social cognition within UHRP populations may, therefore, underpin difficulties in social interactions, enhancing vulnerability to the development of psychotic symptoms, which, in turn, is often associated with social withdrawal and interpersonal problems (42, 43).

The results presented by Bora *et al*. (26) and Van Donkersgoed *et al*. (24) support the suggestion that deficits in social cognition represent an important feature of the UHRP state. These impairments might represent early signs of the onset of psychosis, as tasks like emotion recognition and ToM are showing medium to large effect sizes in UHRP individuals compared to HCs. Further studies on the relationship between social cognition and the risk of psychosis are necessary; because such deficits may not only signal the risk for psychosis, but also represent targets for early interventions designed to enhance social functioning.

A major aim of this review was to elucidate neurocognitive predictors of transition to psychosis in UHRP individuals. Our results suggest that the greater the cognitive impairment -particularly in verbal learning, processing speed, and working memory- the higher the risk for transitioning to psychosis. For example, studies by Millman *et al*. (31) and Hauser *et al*. (23) detected that transitioners to psychosis (CHR-T) had significantly more severe cognitive impairments when compared to non-transitioners (CHR-NT). More precisely, CHR-T showed moderate-to-large deficits in global cognition, processing speed, and verbal learning; whereas CHR-NT presented only mild impairments and thus were closer to CCs.

These findings indicate that cognitive deficits, especially in the domains of memory and speed of processing, may be useful biomarkers for predicting the onset of psychosis. Longitudinal studies in this review showed that UHRP individuals who transition to psychosis have a greater decline in cognition over time, further supporting the predictive value of cognitive assessments. The identification of these cognitive markers could help refine risk assessment strategies and enable more targeted interventions for those at greatest risk of psychosis onset.

Limitation

This study on neurocognitive deficits in UHRP individuals is subject to several limitations that must be considered. First, the variability in study designs across the literature —ranging from cross-sectional to longitudinal— poses challenges in drawing consistent conclusions about the predictive value of specific cognitive impairments. Additionally, the heterogeneity of UHRP populations, characterized by diversity in demographic factors and clinical presentations, complicates the interpretation of cognitive data. The assessment tools used to evaluate neurocognition also vary, leading to potential inconsistencies in findings and affecting the reliability of comparisons. Furthermore, many UHR individuals may have comorbid conditions that can confound cognitive assessments, making it difficult to distinguish cognitive deficits specific to the UHRP state. Moreover, the focus on short-term outcomes limits our understanding of how these cognitive impairments might evolve over time and of how they correlate with the eventual onset of psychosis. The generalizability of findings is another concern, as differences in geographical and cultural contexts may affect applicability across diverse clinical settings. Lastly, the lack of unified diagnostic criteria for UHRP individuals complicates population stratification and hinders the establishment of clear neurocognitive profiles associated with this at-risk state. To improve the validity and applicability of neurocognitive markers for predicting psychosis, it will be crucial for future research to tackle these limitations.

Conclusion

This umbrella review highlights that individuals at UHRP demonstrate major cognitive impairments, particularly in the domains of attention, memory, executive functioning, and social cognition. These deficits represent a differential point between UHRP people and HCs; but, overall, are milder compared with FEP. Importantly, greater cognitive impairments in UHRP individuals are linked to an elevated likelihood of transition to psychosis, providing a possible target for

early intervention strategies. Therefore, future research is needed to further elucidate the neurocognitive mechanisms specifically driving the vulnerability to psychosis. Longitudinal studies conducted with larger samples and finer cognitive assessments hold promise for an improved determination of which persons might be at greater risk of onsets and allow for targeting appropriate interventions. Furthermore, the study of the effects of cognitive remediation therapies may form very promising avenues in UHRP for preventing or at least deferring transition to psychosis. Neurocognitive deficits in UHRP populations have been a critical area of research, both in regard to early diagnosis of and targeted interventions for individuals at risk for psychosis. By identifying those cognitive markers that predict transition to psychosis, the clinical outcomes can be improved to a greater extent and may also prevent the onset of a full-blown psychotic disorder.

Conflict of Interest

None.

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