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"Short" Versus "Long" Duration of Untreated Psychosis in People with First-Episode Psychosis: A Systematic Review and Meta-Analysis of Baseline Status and Follow-Up Outcomes

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***Background and Hypothesis*: Duration of untreated psychosis (DUP) has been linked to worse mental health outcomes in psychotic disorders. We meta-analytically studied the relationship between "long" vs. "short" DUP and mental health outcomes.**

***Study Design*: This PRISMA/MOOSE-compliant meta-analysis searched for nonoverlapping individual studies from database inception until November 01, 2023, reporting data from author-defined "short"/"long" DUP (according to author's definition) in patients with first-episode psychosis (FEP). We compared differences between "short"/"long" DUP groups at baseline and/or follow-up in continuous and binary outcomes. We conducted random-effects meta-analyses, stratified analyses, heterogeneity analyses, meta-regression analyses, and quality assessment (PROSPERO: CRD42023479321).**

***Study Results*: From 16,055 citations, 34 studies were included (n = 6,425, age = 27.5 ± 7.1 years, males = 60.4%, white = 70.2%, DUP: mean = 60.8 ± 43.8 weeks, median = 52.5, interquartile range = 31.3, 68.0 weeks, follow-up = 19.2 ± 35.0 months). The definition of "short"/"long" varies significantly between the studies. Compared to "short" DUP (mean = 10.2 ± 11.2 weeks), "long" DUP (mean = 58.8 ± 76.4 weeks) was associated with higher baseline Positive and Negative Syndrome Scale (PANSS) negative (k = 14, ES = 0.45, 95%CI = 0.16, 0.74) and Scale for the Assessment of Negative Symptoms (k = 7, ES = 0.29, 95%CI = 0.11, 0.47) scores, lower**

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remission (k = 7, OR = 0.40, 95%CI = 0.24, 0.67) and more suicide attempts (k = 4, OR = 2.01, 95%CI = 1.36, 2.96). At follow-up, compared to "short" DUP, "long" DUP was associated with lower Global Assessment of Functioning (k = 4, ES = −0.63, 95%CI = −0.83, −0.43) and higher PANSS negative subscale scores (k = 5, ES = 0.66, 95%CI = 0.05, 1.27).

***Conclusions*: In FEP, longer DUP is related to greater baseline negative symptoms, less remission, and more suicide attempts, as well as greater postbaseline negative symptom severity and functional disability. To what degree longer DUP contributes to poorer outcomes or whether DUP only correlates with these outcomes requires further study. A greater consensus on the definition of long DUP is needed to make comparisons between studies more feasible.**

Key words: prognosis; early psychosis; treatment; schizophrenia; diagnosis; onset.

Introduction

Psychotic disorders are associated with high personal[1] and familial burden[2] and negative outcomes, such as hospitalizations,[3] poor social functioning,[4,5] poor cognitive performance[6] and low employment.[7] However, some studies with long follow-up highlighted the existence of a subgroup of patients with more stable evolution over time and even with preserved function after the onset of the psychosis.[8–11] Detecting the modifiable factors involved in this "long" -term prognosis is important.

A longer duration of untreated psychosis (DUP) has been related previously to worse prognosis after a first-episode of psychosis (FEP), in terms of remission rate and global functioning,[12–14] cognitive functioning,[15] brain functional connectivity[16] and suicidal behavior.[17]

Nevertheless, there is no clear consensus on how to define DUP exactly. While some authors define DUP as the time from the onset of psychotic symptoms to first hospitalization,[18] others define it as the time from the first onset of psychotic symptoms or from the first psychotic disorder diagnosis to the first specific/effective/antipsychotic treatment.[19] This variability in the definition of DUP highlights the complexity of assessing its impact and the need for a standardized approach. Defining "short" and "long" DUP is particularly challenging, with "long" DUP cut-offs ranging from 4.1[20] weeks to 2 years.[21]

Despite the difficulties in reaching a consensus definition of a "long" DUP, the implications of a prolonged DUP are particularly significant in early psychosis, as this period represents a critical window for intervention.[22] Early detection and prompt initiation of treatment have been associated with improved outcomes in psychosis.[23] Therefore, understanding the effects of a "long" DUP, especially in the early stages of psychosis, is essential for informing clinical practice and developing effective interventions. By elucidating the relationship between DUP duration, socio-demographic factors, and clinical outcomes, this review aimed to contribute to the ongoing efforts of optimizing the management of psychosis and improving patient prognosis. Our meta-analysis takes a novel approach by systematically examining the variability in how "long" and "short" DUP are defined across different studies. Previous research[18] has largely overlooked this variability, despite its potential impact on the consistency and comparability of findings. By addressing this gap, our study aims to advance the understanding of DUP's role in clinical outcomes and contribute to the development of more standardized definitions in the field.

The aim of this review therefore was to (1) describe the different authors´ definitions of "short" and "long" DUP; (2) describe socio-demographic and clinical variables in individuals with FEP with a "short" and "long" DUP at baseline; and (3) analyze the differential clinical and functional outcomes in individuals with FEP and a "short" vs. "long" DUP at follow-up.

Methods

We conducted a systematic review and meta-analysis (PROSPERO CRD42023479321) that followed the guidelines of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA, Supplementary Table 1)[24] and the "Meta-analyses of Observational Studies in Epidemiology" (Moose) checklist (Supplementary Table 2).[25]

Search Strategy and Selection Criteria

A systematic search strategy was used to identify relevant articles, and a two-step literature search was implemented by two independent researchers (GSP, CA). As a first step, PubMed, PsycINFO, SciElo Citation Index, and KCI Korean Journal databases were searched in English from inception until 1st November 2023. Relevant articles were also manually reviewed for additionally relevant references. The following search terms were applied: ("schizophrenia" OR "schizoaffective" OR "schizophreniform" OR "psychosis" OR "psychotic") AND ("first episode" OR "early episode" OR "early phase" OR "first break" OR "duration untreated psychosis)." Articles identified through these steps were then screened at title and abstract level. After excluding those that did not meet our inclusion criteria, the full texts of the remaining articles were assessed for eligibility.

Inclusion criteria were (1) individual studies (sample overlap <50% (according to the recruitment site, dates and authors); (2) published in English; (3) conducted in FEP schizophrenia-spectrum disorders according to DSM or ICD criteria (schizophrenia, schizophreniform disorder, and schizoaffective disorder); (4) reporting at least two groups of subjects where DUP was dichotomized in "short" vs "long," and (5) reporting data from any

clinical standardized scale. Exclusion criteria were the following: (1) reviews, clinical cases, abstracts, conference proceedings, and study protocols; (2) studies not reporting DUP; (3) studies with mean age patients under 18 years; and (4) overlapping studies (50% sample overlap).

Operationalization of the Duration of Untreated Psychosis

DUP is commonly defined as the time from when psychotic symptoms first appear to when treatment begins.[18] The starting point for measuring DUP can vary, with some research defining it from the emergence of first positive psychotic symptoms[26] or any psychiatric symptoms,[27] or the beginning of behavioral changes[21] or first psychotic disorder diagnosis to the initiation of antipsychotic medication,[28] or initial contact with a mental health professional,[20] or hospitalization,[29] or the onset of effective treatment, or even when treatment adherence with an antipsychotic is established.[30] Evidence has shown that depending on the way DUP is operationalized, the predictive power can vary, therefore making this a critical issue for prognosis.[31] Various tools, like the Circumstances of Onset and Relapse Schedule (CORS),[32] the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS),[33] and the Nottingham Onset Schedule (NOS)[34] scales, were used to determine DUP in the included articles of this review (eMethods 1).

Equally challenging is the dichotomization of the "short" vs. "long" DUP concept, with definitions of the cut-off varying widely from one month[35] to more than a year.[36] Therefore, all definitions provided by the different authors were included (**Table 1**). When three or more groups of DUP definitions were characterized (i.e., "short," medium, and "long" DUP), the groups were consolidated into two groups. This dichotomization was performed to facilitate a clearer comparative analysis, allowing for assessing outcomes between individuals with "short" er versus "long" er DUP (**Table 1**). Two articles defined the DUP in more than two groups.[35,37] The first work[35] divided the DUP into three groups (1 month ("short" DUP), between 1 and 7 months (medium DUP), and >7 months ("long" DUP)), we characterized "short" vs. "long" as follows: <7 months. In the second work[37] the division was into four groups (DUPQ1: 0 months; DUPQ2: >0-0.6 months; DUPQ3: >0.6-4.0 months; DUPQ4: >4.0-54.0 months), we considered DUPQ1 and DUPQ2 as "short" DUP, consolidating the first two quartiles (<0.6 months) to facilitate our comparative analysis.

Outcome Measures and Data Extraction

Reported outcomes were meta-analyzed when three of more studies reported raw data (mean and SD) in both groups ("short" and "long" DUP) of a standardized scale or number of events in the case of binary outcomes. Other outcomes reported in less studies comparing patients with "short" and "long" DUP were also extracted but summarized only narratively in a systematic review section. Three researchers (JG, LM, MP) independently extracted data from all included studies. The variables were: first author and year of publication, country, FEP diagnosis (structured vs. clinical), sample size, definition of DUP, definition of "short" and "long" DUP, age, % males, % nonaffective psychosis, % white, % single, % married, % living alone, study design (cross-sectional vs longitudinal), quality of the study (total Newcastle-Ottawa Scale score). The databases were then cross-checked, and discrepancies were resolved through consensus under the supervision of a senior researcher (AC). Any definition provided by the authors was accepted to define "short" vs "long" DUP (definitions available in **Table 1**).

Statistical Analyses

Since high heterogeneity was expected, random-effects meta-analyses were conducted. Heterogeneity was assessed using *Q* statistics. The proportion of the total variability in the effect size estimates was evaluated with the I^2 index. Publication bias was assessed by visual inspection of the funnel plots and by conducting Egger´s test.[38]

We conducted meta-regression analyses to estimate the association between "short" vs. "long" DUP and outcomes whenever seven or more studies were available as done before[39] to estimate the association between the respective outcome and the (1) % of the sample with affective psychosis, (2) mean age, (3) sex (% males), (4) sample size, (5) year of publication, (6) % white race, (7) % single, (8) DUP mean and median in weeks for the overall study, and (9) quality of the study (total Newcastle-Ottawa Scale score).

For continuous outcomes, we estimated the Hedges' g (effect size, EF), with negative values reflecting better outcomes in FEP with "short" DUP and positive values reflecting worse prognosis (except for the case of Global Functioning Scale (GAF), where higher scores reflect better punctuation). The Hedges' g is obtained through the difference between the means of the "long" DUP versus the "short" DUP group divided by the standard deviation and weighted for sample size. For binary outcomes, the meta-analysis was performed using a random-effects model. For each study, we calculated the risk ratio (RR) and 95% confidence interval (CI) to compare the dichotomous outcomes between patients with "short" and "long" DUP. The random-effects model was chosen to accommodate potential heterogeneity among study findings, which was assessed using the I^2 statistic. Studies were weighted inversely to their variance to balance the influence of small and large studies on the overall effect size.

Study-defined cut-off points for "long" and "short" DUP were kept for each study as, as stated above, there

Table 1. Main Characteristics of Included Studies

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Albert, 2017[16]	Denmark	CS	296	The period from first occurrence of a psychotic symptom with an intensity equivalent to a score of ≥3 on one of two of the global domains (global hallucination and global delusion) on the SAPS	≤3 months	79 (26.7%) 217 (73.3%)	25.1 ± 4.1	50.0	SANS	CS	7	In treatment-naive schizophrenia patients, a longer DUP was linked to decreased gray matter volume in temporal and occipitotemporal regions, emphasizing the importance of early intervention to prevent brain structural changes and improve long-term outcomes
Barnes, 2008[17]	UK	LT (fu: 1 year)	98	The time from onset of psychotic symptoms to first treatment with AP medication	≤20 weeks	52 (53.1%) 46 (46.9%)			SANS, SAPS	CS	7	A longer DUP was associated with more severe positive and negative symptoms, poorer social function, and a complex relationship with social function, where DUP had a direct impact independent of positive symptoms and potentially mediated by negative symptoms, but it did not significantly affect cognitive functioning after one year of treatment in first-episode schizophrenia
Black, 2001[18]	Canada	LT (fu: 6 months)	19	The period from the onset of positive psychotic symptoms until the beginning of treatment with AP medication. IRAOS scale[19]	<57 weeks	9 (47.4%) 10 (52.6%)	23.4 ± 6.0	78.9	GAF, PANS-G, PANSS-N, PANSS-P, PANSS-T	CS, LT	5	A longer DUP in patients with FEP was linked to poorer clinical outcomes, including more severe positive symptoms and lower global functioning after six months of treatment, with significantly higher positive symptom ratings and lower Global Assessment of Functioning (GAF) scores

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Briend, 2020[20]	USA	CS	54	Duration between the first positive psychotic symptoms to the time of initial first AP treatment	<12 months	37 (68.5%) 17 (31.5%)	23.9 ± 6.2	64.8	BPRS	CS	8	In antipsychotic-naive FEP patients, a longer DUP was linked to significantly higher hippocampal glutamate (Glx) levels and reduced hippocampal volume, particularly in the CA1, subiculum, and presubiculum subfields, suggesting that prolonged untreated psychosis may cause structural brain deficits and altered glutamatergic neurotransmission, underscoring the importance of early intervention to improve outcomes and prevent brain damage
Browne, 2000[21]	Ireland	CS	53	No definition	<12 months	30 (56.6%) 23 (43.4%)	27.1 ± 9.2	68.0	PANSS-G, PANSS-N, PANSS-P, PANSS-T, QLS	CS	7	Quality of life in first-episode schizophrenia was primarily influenced by negative symptoms, social functioning, and the duration of untreated psychosis, highlighting the need for early intervention and targeted treatment strategies
Chang, 2012[22]	China	LT (fu: 3 years)	700	Time interval between onset of positive symptoms and first contact to psychiatric service	<3 months	346 (49.43%) 354 (50.57%)	20.45 ± 3.40	51.43	Systematic review	LT	8	Prolonged duration of DUP in FEP is associated with worse outcomes in positive symptoms, recovery, and sustained employment, emphasizing the importance of early intervention across different cultural contexts

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Chang, 2013[23]	China	LT (fu: 3 years)	84	The time interval between the onset of positive psychotic symptoms and treatment initiation. IRAOS scale	<180 days	41 (48.8%) 43 (51.2%)	31.5 ± 9.5	43.0	PANSS-P	CS, LT	8	Prolonged DUP in first-episode schizophrenia was linked to worse memory function and more severe negative symptoms over three years, emphasizing the need for early intervention
Chiang, 2005[24]	China	CS	35	No definition	<122 days	17 (48.6%) 18 (51.4%)	22.2	40.0	PANSS-G, PANSS-N, PANSS-T	CS	9	A longer DUP in FEP patients was associated with more severe clinical symptoms, highlighting the importance of early intervention through engagement with primary care physicians and social workers in Hong Kong
Compton, 2006[25]	United States	CS	59	Estimated by subtracting the number of weeks since the patient was first prescribed an antipsychotic medication' from the number of weeks from the first onset of prominent psychotic symptoms (delusions, hallucinations, disorganized speech, grossly disorganized behavior, or negative symptoms)	≤ 4 weeks	31 (52.54%) 28 (47.46%)	24.99 ± 27.5	59.0	Systematic review	CS	6	Patients with nonaffective psychotic disorders experienced significantly longer DUP compared to those with affective psychoses, with nonaffective psychosis being the strongest independent predictor of a prolonged DUP
Dama, 2019[26]	Canada	LT (fu: 3 years)	207	The Circumstance of Onset and Relapse Schedule,[13] a semi-structured interview supported by collateral information from family and educational/health records	≤12 weeks	101 (46.5%) 106 (53.5%)	22.4 ± 4.4	68.0	SANS, SAPS, remission[a]	CS	9	A short duration of DUP significantly improved negative symptom remission in patients receiving extended early intervention services (EEIS) for psychosis, supporting the recommendation of reducing DUP to enhance long-term outcomes

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Galińska, 2009[27]	Poland	CS	30	Duration from the onset of psychosis to the beginning of adequate AP treatment	<10 weeks	15 (50.0%) 15 (50.0%)	22.5 ± 3.6	66.7	Calgary Depression Scale, CGI, GAF, PANSS-G, PANSS-N, PANSS-P, PANSS-T	CS	6	A relatively short DUP did not significantly influence brain metabolism in first-episode schizophrenia, as measured by proton magnetic resonance spectroscopy (1H-MRS), indicating no significant differences in metabolite levels between patients and controls.
Gonzalez-Valderrama, 2017[28]	Chile	LT (fu: 10 weeks)	55	Using the Symptom Onset Schizophrenia Inventory	3 months	17 (30.9%) 38 (69.1%)	20.2 ± 2.1	11.0	PANSS-N, remission[b]	CS	6	A shorter DUP in FEP patients was associated with significantly higher rates of negative symptom remission, emphasizing the importance of early intervention in reducing the risk of persistent negative symptoms.
Guo, 2013[29]	China	CS	57	Evaluated using the Nottingham Onset Schedule	≤26 weeks	27 (47.4%) 30 (52.6%)	25.4 ± 6.5	56.1	PANSS-N, PANSS-P, PANSS-T	CS	8	In treatment-naive patients with schizophrenia, a longer DUP was associated with significant decreases in gray matter volume in temporal and occipitotemporal brain regions, indicating that untreated psychosis may contribute to brain structural abnormalities and lead to poorer long-term outcomes

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Izquierdo, 2020[30]	Spain	LT (fu: 3 years)	441	The time from the first continuous psychotic symptoms (present most of the time) to the initiation of adequate AP treatment, was recorded in months. Symptom Onset in Schizophrenia inventory	<7 months[g]	160 (58.6%) 143 (41.4%)	29.8 ± 1.4	58.0	SAPS, SANS	CS	8	Longer DUP was associated with higher disability, particularly in areas like social withdrawal, household activities, and general interest, which acted as bridge areas linking other functioning domains, highlighting the importance of targeting these areas in treatment for patients with a prolonged DUP
Kaymak, 2011[31]	Turkey	CS	162	The time between the first psychotic symptoms and the beginning of AP treatment	<6 months	57 (35.2%) 105 (64.8%)	35.6 ± 11.3	64.0	CGI, GAF, PANSS-G, PANSS-N, PANSS-P, PANSS-T	CS	7	Longer DUP was associated with more severe negative symptoms, poorer global functioning, and worse executive function performance in schizophrenia patients, particularly those with a longer duration of illness, emphasizing the need for early intervention to improve clinical and cognitive outcomes
Kim, 2017[32]	South Korea	CS	34	No definition	⩽ 4 months	18 (52.9%) 16 (47.1%)	23.2 ± 4.7	64.7	CGI	CS	6	In young patients with early psychosis, a shorter DUP was associated with more significant improvements in subjective well-being, attitude toward treatment, and depression following group cognitive-behavioral therapy (CBT), highlighting the importance of early intervention to maximize the therapeutic benefits of psychosocial treatments

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Larsen, 1998[33]	Norway	CS	34	The time interval between onset of psychotic symptoms and hospitalization for psychosis or initiation of adequate treatment	<54 weeks	17 (50.0%) 17 (50.0%)	27.4 ± 8.6	71.0	GAF, PANSS-G, PANNS-N, PANSS-P	CS	6	In first-episode schizophrenia, a long duration of DUP was associated with greater deterioration in premorbid functioning, weaker social networks, and more severe social withdrawal, highlighting the importance of early detection and the challenges posed by social isolation in accessing treatment
Malik, 2010[34]	Pakistan	CS	60	The duration of untreated emergent psychosis (from the appearance of first psychotic symptom to the start of treatment) to treatment	<80 weeks	28 (46.67%) 32 (53.33%)	25 ± 5.0	68.0	Systematic review	CS	6	In FEP patients in Pakistan, a longer DUP was associated with poorer performance in recognizing facial expressions of emotion, particularly anger, surprise, and sadness, highlighting the importance of early intervention to improve social functioning and emotion recognition
Malla, 2002[35]	Canada	LT (fu: 1 year)	86	From the time of onset of first psychotic symptoms contiguous with the presenting episode to the time of having received antipsychotic therapy for a period of 2 months unless significant response to medication was achieved earlier	<22 weeks	43 (50.0%) 43 (50.0%)	24.2 ± 7.8	80.0	Calgary Depression Scale, SAPS, SANS, remission[c]	CS	9	A longer DUP was associated with more severe positive and negative symptoms, poorer global functioning, and greater social withdrawal, highlighting the critical importance of early intervention in improving outcomes for FEP patients

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Malla, 2011[36]	Canada	CS	80	The period between the time of onset of psychotic symptoms, at syndromal threshold based on the SCID-IV, to adequate treatment with antipsychotics (30 days of continuous treatment or less if positive symptoms remitted)	≤18 weeks	40 (50.0%) 40 (50.0%)	23.3 ± 3.6	72.5	Calgary Depression Scale, GAF, PANSS-N, PANSS-P	CS	9	A longer DUP in FEP patients was associated with significant reductions in gray matter volume, particularly in the orbital-frontal regions, suggesting that prolonged untreated psychosis may contribute to structural brain abnormalities
Myaba, 2021[37]	Malawi	CS	140	No definition	<6 months	37 (26.4%) 103 (73.6%)		60.0	GAF, SAPS, SANS	CS	6	Longer DUP was associated with employment status, a diagnosis of schizophrenia, more severe negative symptoms, and public self-consciousness in Malawi
Nkire, 2022[38]	Ireland	LT (fu: 7 years)	62	The period between emergence of first noticeable psychotic symptoms and receipt of AP treatment	<0.6 months[h]	46 (74.2%) 15 (25.8%)	34.1 ± 18.2	56.0	PANSS-G, PANSS-N, PANSS-P, QLS	CS, LT	6	Longer DUP and duration of untreated illness (DUI) were associated with greater psychopathology, particularly negative symptoms, and lower quality of life, functionality, and service engagement over a 7-year period, with the strongest effects observed in the longest quartile of DUP-DUI values, highlighting the enduring impact of delayed treatment in FEP

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Oliveira, 2010[39]	Brazil	CS	200	The period between the onset of the first psychotic symptom and the first contact with a mental health service due to psychosis. The psychotic symptoms included in this definition were any delusion, hallucination or thought disorder	<4.1weeks	98 (49.0%) 102 (51.0%)	32.3 ± 11.3	48.0	PANSS-G, PANSS-N, PANSS-P, PANSS-T	CS	8	In Brazil, individuals with FEP who lived with relatives had a significantly shorter DUP compared to those with other living arrangements, highlighting the protective role of family involvement in early treatment seeking
Qin, 2014[40]	China	LT (fu: 2 years)	43	The time interval between the first occurrence of obvious abnormal behaviors (based on information provided by a coresident family informant) and the beginning of systematic treatment with AP medications	≤ 24 weeks	22 (51.2%) 21 (48.8%)	36.7 ± 10.8	34.8	BPRS	CS, LT	8	Longer DUP was associated with poorer long-term social functioning, higher rates of hospitalization at the time of diagnosis, and increased likelihood of re-hospitalization during the first two years of treatment in first-episode schizophrenia patients, underscoring the importance of early intervention
Ran, 2018[41]	China	LT (fu: 14 years)	146	The first occurrence of positive symptoms, with the end marked by the date of admission at the index hospitalization or taking AP medication	≤6m	38 (26.0%) 108 (74.0%)	28.90 ± 22.17	43.1	GAF, PANSS-G, PANSS-N, PANSS-P, PANSS-T, remission[d]	LT	5	A longer duration of DUP in individuals with schizophrenia in rural China was associated with more severe negative and general mental symptoms, a longer duration of illness, and a higher likelihood of living alone over a 14-year follow-up period

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Ricci, 2021[42]	Italy	LT (fu: 6 months)	62	The time elapsed from the onset of key symptoms (hallucinations, delusions, or bizarre behavior) to the beginning of treatment (pharmacotherapy/psychotherapy) prescribed by a psychiatrist. Early Recognition Inventory Retrospective Assessment of Symptoms checklist used	<1 year	31 (50.0%) 31 (50.0%)	22.9 ± 3.9	52.0	GAF, PANSS-G, PANSS-N, PANSS-P, PANSS-T	CS, LT	6	Longer DUP was associated with more severe positive and negative symptoms, poorer overall functioning, and higher dissociative experiences in young Italian patients with FEP, and cannabis use did not significantly alter the duration of DUP but was linked to greater dissociative symptoms
Sullivan, 2019[43]	UK	LT (fu:12 months)	2134	The NOS[15] was used in both cohorts, although a shortened	<6 months	1209 (70.20%) 636 (29.80%)	23.23 ± 4.83	58.29%	Systematic review	CS	8	Longer DUP was associated with worse outcomes in positive psychotic symptoms, recovery, and global functioning at 12 months, but the association with negative psychotic symptoms was less clear, indicating the complex nature of these relationships and the need for further research
Schimmelman, 2008[44]	Australia	LT (fu: 18 months)	636	As age at entry into EPPIC subtracted by age when first sustained positive psychotic symptoms (duration of >1 week) started	<3 months	350 (55.0%) 286 (45.0%)	21.3 ± 3.6	67.0	CGI, GAF, remission[e]	CS, LT	7	A longer DUP in FEP was associated with worse premorbid functioning, a higher rate of schizophrenia-spectrum disorders, lower rates of remission of positive symptoms, and poorer global functioning at 18-month follow-up

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Shrivastava, 2010[47]	India	LT (fu: 10 years)	101	Elicit the time of first-distressing symptoms either positive or negative symptom to decide the onset of illness	<12 months	54 (53.5%) 47 (46.5%)	28.8 ± 8.2	73.3	GAF, PANSS-G, PANSS-N, PANSS-P, PANSS-T, QLS	CS	7	Longer DUP in first-episode schizophrenia was not significantly associated with clinical or social outcomes over a 10-year follow-up, suggesting that DUP alone may not determine long-term outcomes due to the complex nature of schizophrenia and other influencing factors
Takizawa, 2021[48]	Japan	LT (fu: 6 months)	276	As the time since the onset of the first psychotic symptom to the time of the interview	<3 months	160 (58%) 30 (42%)	32.7 ± 10.2	63	Remission[f]	LT	5	A shorter DUP was associated with a higher chance of remission among FEP patients with schizophrenia in Taiwan
Thirthalli, 2011[49]	India	LT (fu: 1 year)	93	The time since the onset of the first psychotic symptom to the time of the interview. The interview for retrospective assessment of onset of schizophrenia (IRAOS)[14]	<16-72 weeks	62 (66.66%) 31 (33.33%)	30.5 ± 8.8	45	Systematic review	CS	6	In never-treated schizophrenia patients in India, a longer DUP was associated with poorer symptomatic and functional outcomes after a one year follow-up, highlighting the need for reducing treatment delays to improve patient outcomes in low- and middle-income countries
Thomas, 2009[50]	UK	CS	74	From the manifestation of the first psychotic symptom to the initiation of adequate antipsychotic drug treatment	<12 weeks	46 (62.16%) 28 (37.84%)		68.92%	Systematic review	CS	7	A longer DUP was significantly associated with being male, having an insidious onset of illness, comorbid substance misuse, unemployment, and less family involvement, emphasizing the influence of early clinical course and social factors on treatment delays in FEP

Table 1. Continued

Author, year	Country	Design	Sample size	Operationalization DUP	DUP dichotomized	N (%) short vs long	**Mean age ± SD**	% males	Outcomes	**Data available (CS, LT)**	NOS score (total 9)	Key findings
Üçok, 2004[51]	Turkey	LT (fu: duration of admission)	79	From the time of onset of first positive symptoms to the first hospitalization	≤6 months	41 (51.9%) 31 (48.1%)	21.2 ± 4.9	53.0	BPRS, SAPS, SANS	CS, LT	7	A longer DUP in first-episode schizophrenia was associated with a poorer response to acute treatment, particularly in reducing positive symptom severity
Ussorio, 2015[52]	Italy	LT (fu: 4 months)	56	No definition	≤12 months	21 (37.5%) 14 (62.5%)	22.2 ± 4.6	73.0	BPRS, PANSS-G, PANSS-N, PANSS-P, PANSS-T	CS, LT	7	The study explored the effects of metacognitive training (MCT) for young individuals in the early stages of psychosis and found that both short and long duration of DUP groups showed significant improvements in symptoms, cognitive functions, and social functioning after the intervention. However, the differences in DUP did not significantly influence the outcomes, suggesting that MCT can be effective regardless of the length of untreated psychosis
Wang, 2005[53]	Japan	LT (fu: 2 months)	18	The period from the onset of the first nonspecific psychotic symptoms, as reported by patients, family, or family doctors, to the time that AP medication was initiated	<2 years	10 (55.6%) 8 (44.4%)	29.8 ± 7.5	61.0	BPRS	CS, LT	6	In first-episode schizophrenia patients, a longer duration of DUP was associated with reduced recovery of P300 amplitude, particularly in the left temporo-parietal area, after treatment with neuroleptic medication, suggesting that prolonged untreated psychosis may contribute to more severe impairments in temporal brain structures

Table 1. Continued

Abbreviations: AP, antipsychotic; BPRS, brief psychiatric rating scale; CS, cross-sectional; CGI, clinical global impressions scale; fu, follow-up; FEP, first-episode of psychosis; GAF, global assessment of functioning; IRAOS, interview for the retrospective assessment of the onset and course of schizophrenia and other psychoses; LT, longitudinal; NOS, newcastle-ottawa scale; PANS-G, positive and negative syndrome scale general psychopathology scale; PANSS-N, positive and negative syndrome negative scale; PANSS-P, positive and negative syndrome positive scale; PANSS-T, positive and negative syndrome total scale; QLS, quality of life scale; SANS, scale for assessment of negative symptoms; SAPS, scale for assessment of positive symptoms; SCID, semi-structured diagnostic interview.

[a]Remission: assessed using the SAPS and the SANS. Length of remission was defined as the cumulative time that patients remained in remission during the 3 years of EEIS or regular care.

[b]Remission: according to the Andreasen criteria.

[c]Remission: all SAPS global items being rated 0 or 1.

[d]No definition.

[e]Remission: at discharge was defined according to Kane et al.[45]. Kane JM, Leucht S, Carpenter D, Docherty JP, Expert Consensus Panel for Optimizing Pharmacologic Treatment of Psychotic D. The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. *J Clin Psychiatry*. 2003;64:5–19. as absence of positive symptoms for at least 12 weeks, medication non-adherence as failure to take medication for 1 week or longer in accordance with Robinson et al.[46]. Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophr Res*. 2002;57:209–219.

[f]Remission: criteria proposed by the Remission in Schizophrenia Working Group (RSWG).

[g]1 month (short DUP), the second by those who have a DUP between 1 and 7 months (medium DUP), and the third one by those whose treatment has been delayed more than 7 months (long DUP).

[h]DUPQ1: 0 months; DUPQ2: >0-0.6 months; DUPQ3: >0.6-4.0 months; DUPQ4: >4.0-54.0 months; DUIQ1: 0-1.1 months; DUIQ2: >1.1-4.4 months; DUIQ3: >4.4-11.9 months; DUIQ4: >11.9-336.0 months.

was no consensus among them. Sensitivity analyses were performed by the cut-off of "short" DUP (<6 moths). Also, we employed a cumulative analysis[40] approach for this meta-analysis using the overall mean duration of DUP for each individual study. This iterative process involved conducting the analysis initially with only the first study and then progressively including each additional study. This method was executed using the "cumulative" option applied. The cumulative analysis was structured based on the overall time of DUP, allowing for the observation of changes in the estimated effect size as more studies were included.

In addition to the primary analyses, we conducted descriptive comparisons of demographic characteristics between individuals with long and short DUP. These comparisons included variables such as mean age, years of education, percentage of males, race (specifically white race), and marital status (specifically single).

All analyses were two-sided with alpha = 0.05. All meta-analyses were conducted in STATA v18[41] using the random-effects methods.

Risk of Bias Quality Assessment

Study quality was assessed in all included studies using the Newcastle-Ottawa Scale for cohort studies.[42] A score of 0-9 was reported based on the representativeness, selection of cohorts, ascertainment of exposure, outcome of interest, comparability of cohorts, assessment of outcomes, and duration and adequacy of follow-up (eMethods 2).

Results

Sample Characteristics

Of 16,055 citations identified and screened for eligibility, 377 full-text articles were assessed. Finally, 34 studies (with 33 independent samples) were included in the systematic review and meta-analysis (Supplementary Figure 1), 17 with cross-sectional design and 17 with longitudinal design (mean follow-up (standard deviation [SD]) = 19.17 (35.04) months, range: 2 to 60 weeks). The studies included 6,425 individuals with FEP (range = 18-2,134) with a mean age of 27.53 ± 7.15 years old, 60.45% males, and 11.22 ± 1.97 years of education. Altogether, 70.19% were white and 78.32% were single. The main characteristics of included studies and the different definitions of "long" vs "short" DUP are detailed in **Table 1**. The mean DUP for the included studies was 60.75 ± 43.83 weeks, and the median DUP was 52.5, interquartile range: 31.3, 68.0 weeks, for "short" DUP 10.25 ± 11.25 weeks and for "long" DUP 54.84 ± 76.39 weeks. It is important to note that not all studies provided these specific breakdowns, which is why the overall mean DUP can appear higher than the mean for "long" DUP, as the overall mean includes a broader range of data from all studies.

There were no differences between individuals with FEP with a "long" vs "short" DUP in terms of mean age (27.85 ± 7.33 vs. 25.92 ± 4.39), years of education (11.66 ± 2.33 vs. 11.86 ± 1.35), % of males (54.19% vs. 58.76%), white race (69.99% vs 70.39%) or marital status (single 71.31% vs. 68.00%).

Operationalization Duration Of Untreated Psychosis

There were different definitions for the delimitation of DUP and for the cut-off of "short" vs. "long" DUP. The exact definitions of the different included studies are detailed in **Table 1**.

Baseline Analyses

Data were available to analyze the differences between "long" DUP and "short" DUP at baseline in the following outcomes: Brief Psychiatric Rating Scale[43] (BPRS) (k = 5, N = 251), Calgary Depression Scale for Schizophrenia[44] (k = 3, N = 196), Clinical Global Impressions Severity Scale[51] (CGI-S) (k = 3, N = 226), GAF[52] scale (k = 9, N = 1,264), Positive and Negative Syndrome Scale (PANSS) total (k = 10, N = 775), positive[53] (k = 13, N = 1,089), negative (k = 14, N = 1,005), and general psychopathology (k = 11, N = 813), Quality of Life Scale[45] (QLS) (k = 3, N = 130), Scale for the Assessment of Positive Symptoms (SAPS)[46] (k = 6, N = 906), Scale for the Assessment of Negative Symptoms[47] (SANS) (k = 7, N = 1,219).

At baseline, "long" DUP was associated with significantly higher PANSS negative scale scores (ES = 0.45, 95%CI 0.16 to 0.74) and SANS scale scores (ES = 0.29, 95%CI 0.11 to 0.47), (**Figures 1** and **2**), without significant differences in the other outcomes (Supplementary Figures 2-10).

Regarding binary outcomes, patients with "long" DUP had lower remission rates (k = 7, N = 1,494, odds ratio (OR) = 0.40, 95%CI 0.24 to 0.68) and more suicide attempts (k = 4, N = 1,242, OR = 2.01, 95%CI 1.36 to 2.96) (Supplementary Figures 11-12).

When dichotomizing the included studies into two groups according to DUP duration (<6 months vs.≥ 6 months), the difference for the PANSS negative symptom score remained significant just for the studies defining "short" DUP as <6 months (ES = 0.46, 95%CI 0.06 to 0.86) (Supplementary Figure 13). For remission and suicide attempts, no differences were found concerning the main analyses. In the case of the SANS scale, just one study presented a DUP

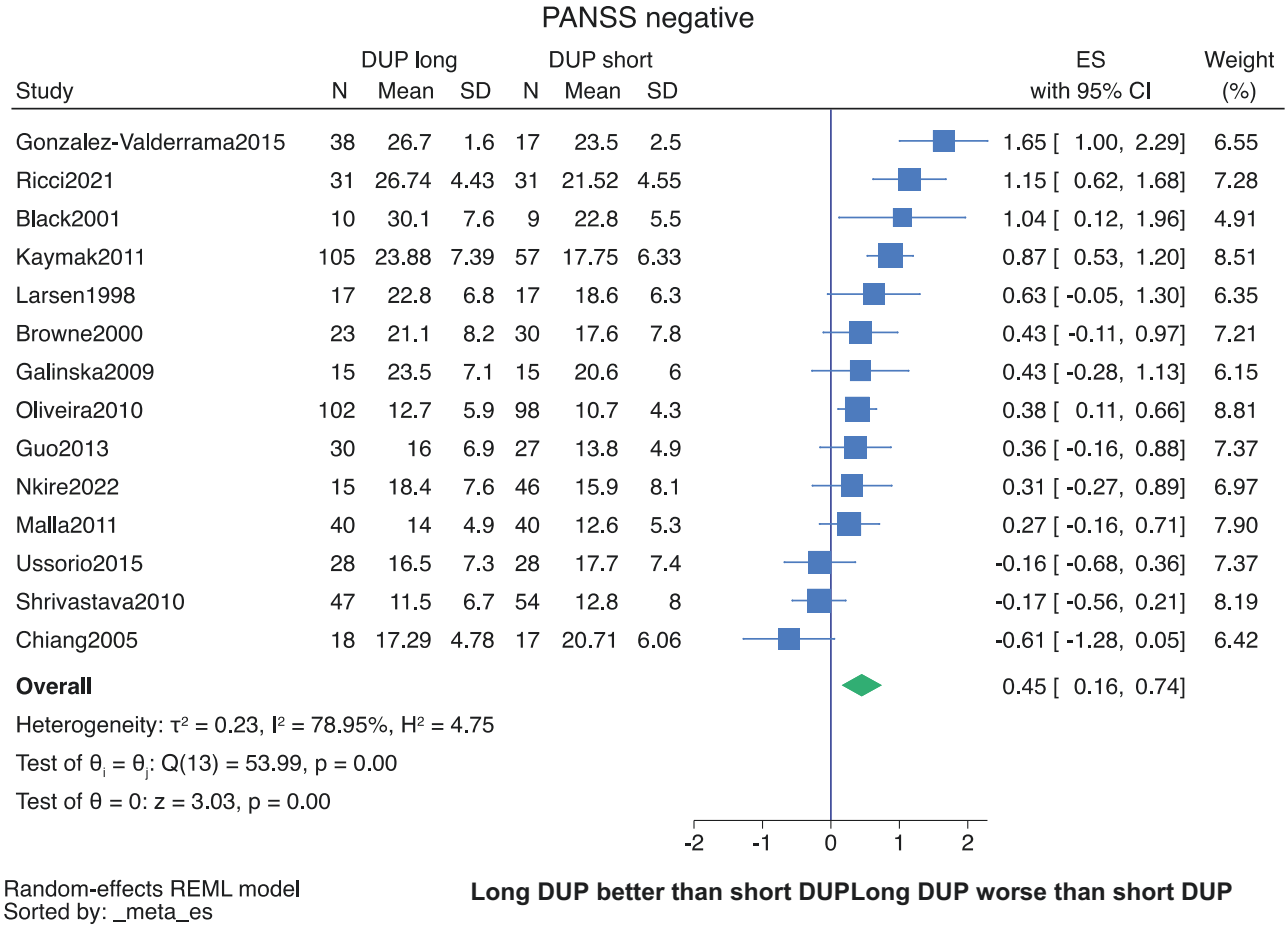

Figure 1. Forest Plot Outcomes "Long" vs "Short" DUP at Baseline. Positive and Negative Syndrome Scale (PANSS) Negative Subscale

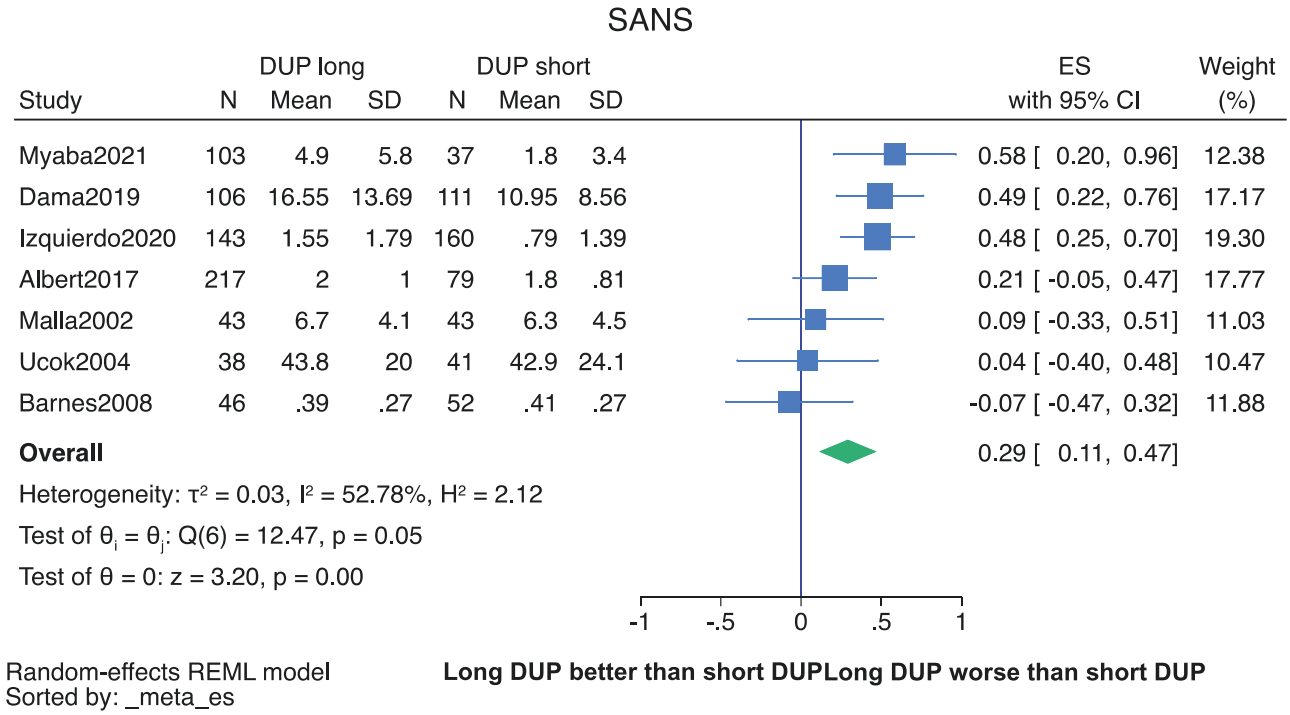

Figure 2. Forest Plot Outcomes "Long" vs "Short" DUP at Baseline. Scale for the Assessment of Negative Symptoms (SANS)

≥6 months, so we did not perform this analysis. There was no cumulative effect for a longer DUP duration beyond 6 months (Supplementary Figure 14).

Heterogeneity and Publication Bias Assessment. Heterogeneity at baseline ranged from 0.00% to 81.10%, depending on the analyzed outcome, i.e., PANSS negative subscale: $I^2 = 78.95\%$, $Q = 53.99$, $P < .001$, τ^2=0.23; and SANS: $I^2 = 52.78\%$, $Q = 12.47$, $P = .05$, $\tau^2 = 0.03$. Publication bias was not identified for any of the studied outcomes through visual inspection of funnel plots or in the results of Egger's test (Supplementary Figure 15).

Metaregression Analyses. There were only data to perform meta-regression analyses of the PANSS negative subscale score, without any significant effects of the variables studied (% of affective psychosis, age, sex, sample size, year of publication, race, marital status, mean DUP) (Supplementary Table 3), except for the NOS quality study, where a higher quality of the study was related to fewer differences between "short" and "long" DUP.

Follow-Up Analyses

We analyzed cross-sectionally the available data from the following scales at follow-up: BPRS ($k = 4$, $N = 190$), GAF ($k = 4$, $N = 863$), PANSS total ($k = 4$, $N = 283$), positive ($k = 6$, $N = 397$), negative ($k = 5$, $N = 344$), and general ($k = 5$, $N = 344$) scale scores (Supplementary Figures 16 to 19). Significant differences emerged with lower GAF scale (ES = −0.63, 95%CI −0.83 to −0.43) and higher PANSS negative subscale scores (ES = 0.66, 95%CI 0.05 to 1.27) (**Figures 3** and **4**), each disfavoring the longer DUP group, and without significant differences in the other outcomes.

Heterogeneity and Publication Bias Assessment. Heterogeneity at follow-up ranged from 21.51% to 97.95%, depending on the analyzed outcome, i.e., PANSS negative subscale: $I^2 = 83.60\%$, $Q = 24.03$, $P < .001$, $\tau^2 = 0.39$; GAF scale: $I^2 = 21.51\%$, $Q = 4.45$, $P = .11$, $\tau^2 = 0.22$. Publication bias was not identified for any of the studied outcomes through visual inspection of funnel plots or in the results of Egger's test (Supplementary Figure 20).

Systematic Review

Several studies offered results in patients with a "short" DUP vs. "long" DUP that could not be meta-analyzed. A comprehensive summary of these findings is presented in Supplementary Table 3.

Regarding the neurocognitive performance, Kaymak[48] et al. described significantly worse performance in the Frontal Assessment Battery (FAB) and Wisconsin Card Sorting Test (WCST) scores in the "long" DUP group, suggesting variations in cognitive flexibility and executive functioning between groups. Furthermore, Chang et al.[49] indicated that patients with a "long" DUP showed higher negative symptoms and less improvement in verbal memory over the 3-year follow-up period. Malik[50]

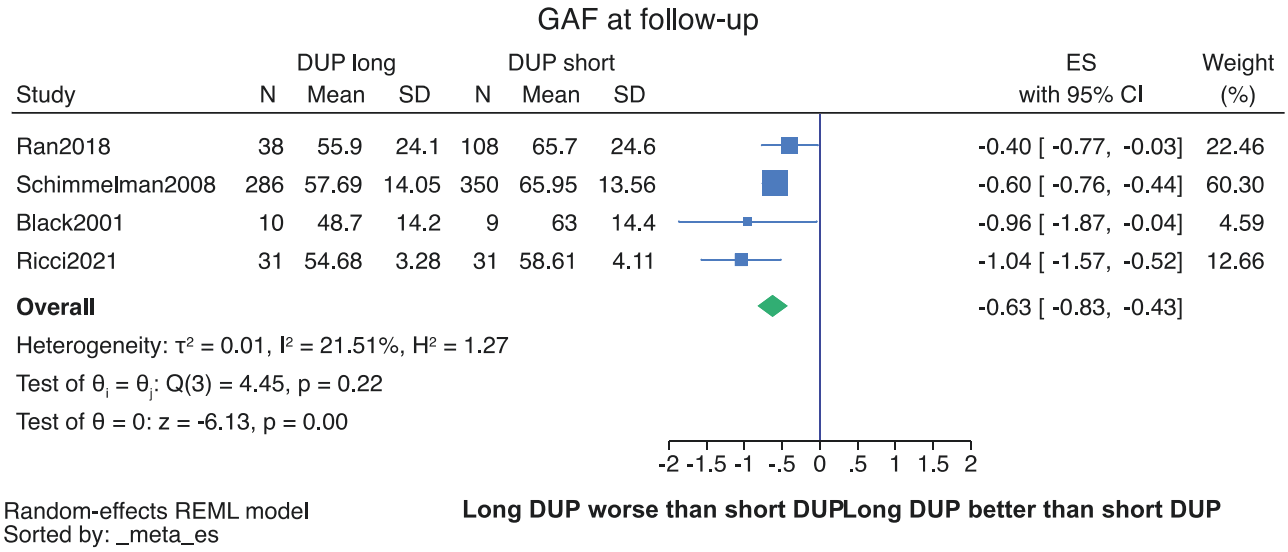

Figure 3. Forest Plot Outcomes "Long" vs "Short" DUP at Follow-Up. Global Assessment of Functioning (GAF) Scale

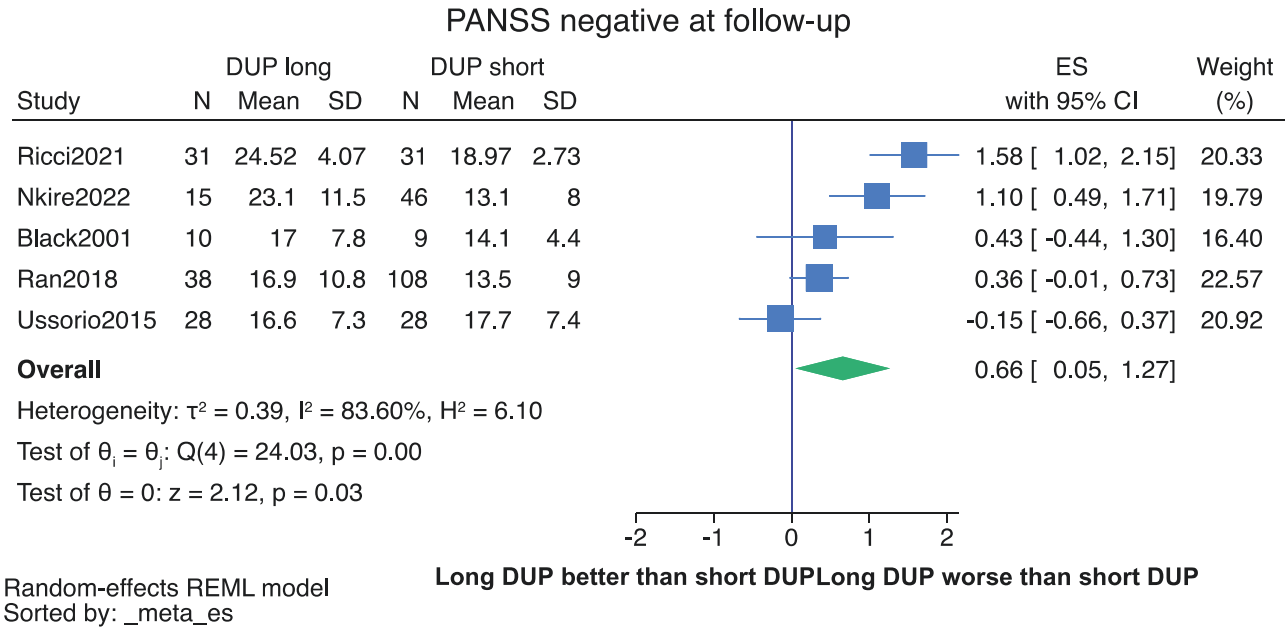

Figure 4. Forest Plot Outcomes "Long" vs "Short" DUP at Follow-Up. Positive and Negative Syndrome Scale (PANSS) Negative Subscale

et al. found that patients with prolonged DUP showed poorer performance in recognition of facial expressions of emotion than those with short durations of untreated psychosis. Other studies did not show significant differences between the "short" and "long" groups in cognitive and memory functions, including logical memory, visual memory, social cognition, and working memory assessments.[28,54]

Regarding the pharmacological treatments, while some authors[49] did not find differences in treatment dosages used in both groups, others described the use of higher antipsychotic doses in the "long" DUP group,[55] and a marked difference in the Drug Attitude Inventory scores indicating varying perceptions towards medication, with worse perception in the "long" DUP group. In contrast, other authors found[28] that antipsychotic doses were higher on average in the "short" DUP group, but medication adherence scores were the same across the two DUP groups.

In general, schizophrenia-spectrum diagnoses were more common in the "long" DUP group[35,50,56,57] while affective psychosis diagnoses were more common in the "short" DUP group.[20,58] Generally, an acute onset of psychosis (compared to an insidious one) was more related to a "short" DUP.[56,59]

Most of the included studies reported worse[20,60] social functioning in groups with a "long" DUP compared to a "short" DUP, although Barnes et al.[61] showed no significant differences between the two DUP groups across the Social Functioning Scale (SFS) total score. Data regarding disability showed that "long" DUP was associated with more severe negative symptoms and poorer functioning.[35] However, other authors[27] described rates of social impairment, work impairment, extrapyramidal symptoms (EPS), independent living challenges, aggression, and suicidality to be similar between the two DUP groups.

In terms of insight, patients with "short" DUP were less likely to be uncertain or deny having a mental illness.[20,58] Finally, Myaba[62] et al. described that individuals with higher public self-consciousness were likelier to have a "long" DUP.

Discussion

In this meta-analysis comparing outcomes between "long" and "short" DUP in individuals with FEP, "long" DUP was associated at baseline with greater negative psychotic symptoms, lower symptom remission, and a higher number of suicide attempts. At follow-up, "long" DUP was associated with greater negative psychotic symptoms and lower functioning. No significant differences between the "short" and "long" DUP groups emerged regarding age, sex, or education years.

In addition to these meta-analyzed results, other findings from individual studies suggested worse cognitive performance and the use of higher antipsychotic doses in patients with "long" DUP. These non-meta-analyzed findings should be interpreted with caution, as they are based on a small number of studies with significant heterogeneity in the cut-offs between "short" and "long" groups.

The onset of FEP is a critical period in severe mental health disorders, such as schizophrenia and bipolar disorder with psychotic features.[63] A key modifiable factor influencing outcomes is the DUP.[13,64] The pooled mean DUP across 283 studies was recently described as 42.6 weeks, with a median of 14 weeks.[65] In our study, the mean DUP was 60.75 ± 43.83 weeks and the median was 26.64, both considerably longer. This difference may be attributed to variations in study selection criteria, population characteristics, and the methodologies used to measure and report DUP.

Our decision to focus on dichotomizing DUP into "long" versus "short" categories aligns with the methodology used in the studies included in our meta-analysis. By adhering to this approach, we were able to aggregate and compare findings across different studies, thereby enhancing the robustness of our conclusions regarding the impact of DUP on clinical outcomes.

Different reviews have demonstrated that longer DUP is associated with a poorer prognosis in people with psychosis,[13,66,67] and there is also evidence of a treatment moderation effect by DUP,[68] with longer DUP being associated with a worse response to treatment. "Long" DUP is often associated with a variety of negative outcomes,[69] especially in the evolution of psychotic symptoms.[70] Clinically, patients with longer DUP show less favorable responses to antipsychotic medications,[71] more persistent symptoms,[72] worse functioning,[61] might experience more profound social withdrawal, diminished occupational functioning, and overall poorer quality of life.[15] Nevertheless, despite these results, there have been concerns regarding the relationship between the DUP and the prognosis of psychosis because DUP may constitute a confounded factor[66,73] related more to premorbid characteristics of the psychotic episode than to the outcome per se. In our review, no differences in the reported and meta-analyzable socio-demographic characteristics between "short" and "long" DUP were identified. This lack of observed differences may suggest that socio-demographic factors alone do not significantly influence the length of DUP or its impact on outcomes, indicating that other variables, such as clinical and treatment-related factors, might play a more crucial role.

Concordantly, it has also been argued that a prolonged DUP could be related to clinical, social, or demographic factors that delay the identification of the disease, thus contributing to a worse prognosis. There may be a group of patients with an inherently worse prognosis, which would delay the timely detection and treatment of the disease. This type of disease would present with more negative symptoms, fewer positive symptoms, and disruption of social behavior. Supporting this hypothesis, some studies have indicated that factors associated with longer DUP include male sex, unemployment, being single, lack of family support, stigma, and behaviors related to social isolation[56,74–76] (**Figure 5**).

Some researchers have suggested that premorbid adjustment may be an important variable related to DUP[77,78] and it has been considered a moderator of the association between DUP and symptomatology.[79–81] While no significant differences between the "short" and "long" DUP groups emerged regarding age, sex, or education years, longer DUP was associated with significantly worse negative symptom severity at baseline and follow-up, along with lower GAF scores. The more severe negative psychotic symptoms could have delayed treatment seeking, being a correlate of longer DUP rather than a contributor to worse outcomes. Furthermore, a lead time bias has been proposed, where patients with longer DUP had deterioration before the study baseline, while the "shorter" DUP group would accrue poor outcomes during longer follow-up.[82]

In this review, patients with a "short" DUP demonstrated better cognitive flexibility, executive function, and verbal memory, as well as improved recognition of emotions in facial expressions.[48–50] The extent to which

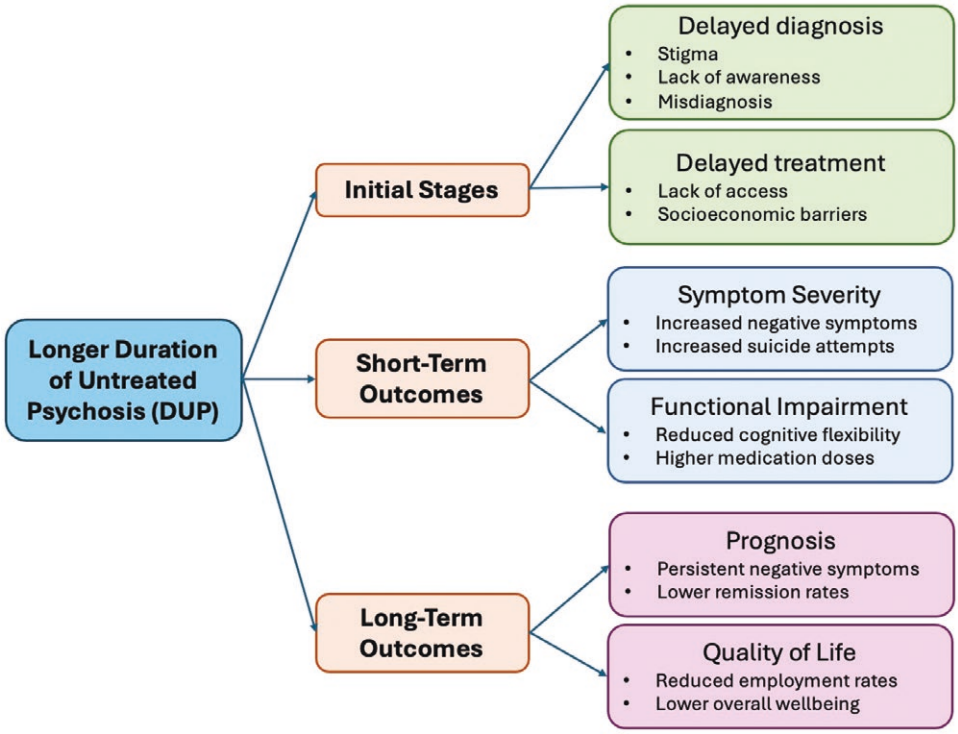

Figure 5. DUP Role in Determining Outcome

this could be a biomarker of a more severe disorder and/or a secondary effect of higher antipsychotic doses or otherwise the direct effect of the delayed antipsychotic treatment remains unclear. Regarding pharmacological treatment, the findings were mixed: some studies reported higher antipsychotic doses in patients with a longer DUP,[55] while others found no significant differences in dosages or medication adherence between groups.[49] Diagnoses of schizophrenia-spectrum disorders were more common in the "long" DUP group, with acute onset psychosis being more associated with a "short" DUP.[56] Overall, better social functioning was reported in the "short" DUP group,[60] although some studies found no significant differences.[83] Traditionally, an acute psychotic illness onset has been related to a shorter DUP due to its relationship with the higher prevalence of positive symptoms[84] while a more insidious onset has been associated with greater negative psychotic symptomatology and a longer DUP.[15]

Due to the association with worse outcomes, it is not surprising that the group with a longer DUP had lower remission rates at baseline, as a longer DUP is usually associated with more negative psychotic symptoms.[85] Other studies, similar to ours, have found higher suicide attempt rates and longer DUP.[17,86] A potential reason for this link might be that DUP serves as a surrogate for another variable connected to both DUP and suicidal behaviors. Clarke et al.[86] proposed that patients with longer DUP could have more severe forms of schizophrenia or comorbidities linked to suicidal tendencies. The overlap between negative symptoms and unmeasured depression[87–90] driving suicidality at baseline in people with long DUP requires further study.

Given these complexities, future research should further aim to characterize patients with a "long" vs "short" DUP to clarify potential confounding effects. Moreover, studies with sufficiently "long" follow-up periods are needed in epidemiologically generalizable samples. These should include patients with naturally longer DUP and subsamples with shortened DUP who received intense outreach and earlier intervention, allowing for a comparison of outcomes between these groups.

On the other hand, there is no established definition of "short" vs. "long" DUP. Some authors established the cut-off at 6 months,[6,91,92] while others at one year,[13,93] or split the groups according to the median of the samples.[28,29,48,94,95] This variability is reflected in our work with significant differences in the duration of "short" and "long" DUP and may have impacted our results. This heterogeneity of definitions complicates the interpretation of results from different studies reporting on outcomes associated with a longer vs shorter DUP. Based on the data, a six-month cut-off could be proposed to define "long" DUP, as this may mark the critical point where delays in initiating treatment become particularly impactful. This result may suggest that from six months onward, the effect of the prolonged DUP could be potentially harmful and irreversible, but more and more fine-grained data are needed to substantiate this finding. The

findings of this meta-analysis underscore the importance of consistent definitions of "long" and "short" DUP across studies. Our work reveals how variations in these definitions can lead to differing conclusions about the impact of DUP on clinical outcomes. This insight highlights the need for future research to adopt standardized definitions to ensure that findings are more comparable and reliable. Moreover, our study serves as a foundation for further research aimed at establishing clear guidelines for defining DUP durations in clinical research.

The association between DUP and negative psychotic symptoms has been previously described,[67] but this is the first meta-analysis showing a relationship between "long" DUP and the negative dimension of psychosis in FEP at both baseline and follow-up, without an association with other symptomatic dimensions. The few studies with follow-up data and variability in length (10 weeks to 14 years) limit these results. These findings highlight the importance of detecting negative psychotic symptoms early.[96] One primary barrier is the lack of public awareness about early signs of psychosis, leading to delays in help-seeking.[97] Moreover, stigma and the insidious onset of symptoms or overlap with comorbidities, including substance use, can make it difficult for patients and families to recognize the need for professional intervention.[64,98]

In meta-regression analyses, solely study quality reduced the effect of longer DUP on adverse outcomes, suggesting a potential bias in lower-quality studies, which may exaggerate negative effects of longer DUP. It is important to define studies with methodological rigor. This includes having multiple definitions of "short" and "long" DUP, both using mean and median DUP values that differ substantially due to outliers, a large sample size, and appropriate outcome measurements. This approach and international agreement on the definition of the beginning and end of DUP and "long" vs "short" DUP could lead to a more nuanced understanding of how early intervention impacts "long" -term outcomes in psychosis.

This study has several limitations. First, heterogeneous definitions of DUP and of "long" and "short" DUP complicate direct comparison between studies. The categorization of DUP into "long" and "short" is an arbitrary division of what is essentially a continuous variable, and this represents one of the primary limitations of our study. This limitation is derived from the original studies included in our meta-analysis, where the inclusion criteria were designed to capture studies that specifically utilized this dichotomous classification. However, such cut-offs can vary significantly between studies, potentially leading to different conclusions. To address this concern, we have revised our analysis to emphasize this limitation more clearly. Additionally, we propose a more standardized definition of "long" DUP (≥6 months) to provide some consistency in future studies. Based on the data, the relevant cut-off for the "long" DUP was six months, marking the point at which the delay in initiating treatment may become critical. Furthermore, it is important to note that not all studies provided the necessary data to analyze DUP as a continuous variable. For instance, some studies, e.g., Black et.,[99] did not report the standard deviation of the entire sample, which could have influenced the selection of included studies and contributed to variability in the results. Second, the small number of included studies limits generalizability of the results and the ability to perform subgroup and meta-regression analyses. Third, we could only meta-analyze endpoint scores and not change scores of the outcomes over time due to the lack of data, making it unclear if patients with worse scores keep these scores at follow-up or if a subgroup deteriorates over time. Fourth, we were unable to consider treatments and treatment effects in these analyses. Fifth, patients with FEP represent a highly heterogeneous group, including varying types, and expressions of psychotic disorders, making it difficult to generalize findings. Our work excluded the studies focused solely on affective psychosis, which might limit the generalizability of our findings to this subgroup. Although our meta-regression analysis accounted for the presence of affective psychosis within mixed samples, the specific outcomes related to affective psychosis may differ. Finally, another limitation of our study is the potential confounding effect of contextual differences across the included studies, particularly in terms of variability in early psychosis services and mental health systems across different countries. These differences may influence the duration of untreated psychosis (DUP) and subsequent outcomes, thereby affecting the generalizability of our findings. Another potential limitation of our findings relates to the issue of lead time bias, which occurs when earlier detection and initiation of treatment might appear to improve outcomes simply because the intervention begins sooner rather than due to a genuine therapeutic effect. This bias is particularly relevant in studies examining DUP, as longer untreated durations might reflect delays in diagnosis rather than differences in disease severity. To address this, our meta-analysis took a novel approach by including multiple definitions of "short" and "long" DUP across studies, which allowed us to assess whether the associations between DUP and clinical outcomes were consistent despite this variability. Additionally, we conducted sensitivity analyses using different cut-off points (e.g., <6 months) to examine whether alternative definitions would lead to similar conclusions. These approaches helped to mitigate the impact of lead time bias by demonstrating that, irrespective of the specific cut-off used, longer DUP was consistently associated with poorer clinical outcomes. Our findings underscore the importance of developing standardized definitions of DUP to ensure comparability across studies and minimize potential biases in future research. Future studies should address these limitations and fill these gaps to the greatest extent feasible.

In conclusion, DUP appears to be a relevant determinant of outcomes in people with FEP, especially regarding negative psychotic symptoms, early suicide attempts, and impaired functioning. The contrast between the impacts of "long" versus "short" DUP underscores the importance of educational campaigns, early detection, and timely intervention. Understanding the nature and effects of DUP, and effectively reducing it remains a critical research area to improve clinical and functional outcomes for patients.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Conflicts of Interest

Ana Catalan has received honoraria from Jassen Cilag, ROVI, Otsuka, and Lundbeck outside the current work; Gonzalo Salazar de Pablo has received honoraria from Janssen Cilag and Menarini outside the current work; Claudia Aymerich has received honoraria from Neuraxpharm and Janssen outside the current work; Nathalia Garrido has received honoraria from Lundbeck and Takeda outside the current work. CU Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Alkermes, Allergan, Angelini, Aristo, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Eli Lilly, Eumentis Therapeutics, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, MedLink, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neuraxpharm, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Saladax, Sanofi, Seqirus, Servier, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Terran, Tolmar, Vertex, Viatris and Xenon Pharmaceuticals. He provided expert testimony for Janssen, Lundbeck and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, IntraCellular Therapies, Relmada, Reviva, Rovi. He has received grant support from Boehringer-Ingelheim, Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Medlink, Mindpax, Quantic, Terran.

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