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Characteristics and clinical correlates of risk symptoms in individuals at clinical high-risk for psychosis: A systematic review and meta-analysis

Saskia M. Cooper [a], Paolo Fusar-Poli [b,c,d,e], Peter J. Uhlhaas [a,f,*]

[a] Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, United Kingdom
[b] Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
[c] OASIS service, South London and Maudsley NHS Foundation Trust, London, United Kingdom
[d] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[e] National Institute for Health Research Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, London, United Kingdom
[f] Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany

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ABSTRACT

Emerging evidence suggests that the duration of risk symptoms (DUR) may have an impact on clinical outcomes in clinical high-risk for psychosis (CHR—P) participants. To explore this hypothesis, we performed a meta-analysis on studies that examined DUR in CHR-P individuals in relation to their clinical outcomes. This review was conducted in accordance with the PRISMA guidelines and the protocol was registered with PROSPERO on 16th April 2021 (ID no. CRD42021249443). Literature searches were conducted using PsycINFO and Web of Science in March and November 2021, for studies reporting on DUR in CHR-P populations, in relation to transition to psychosis or symptomatic, functional, or cognitive outcomes. The primary outcome was transition to psychosis, while the secondary outcomes were remission from CHR-P status and functioning at baseline. Thirteen independent studies relating to 2506 CHR-P individuals were included in the meta-analysis. The mean age was 19.88 years (SD = 1.61) and 1194 individuals (47.65 %) were females. The mean length of DUR was 23.61 months (SD = 13.18). There was no meta-analytic effect of DUR on transition to psychosis at 12-month follow-up (OR = 1.000, 95%CI = 0.999–1.000, k = 8, p = .98), while DUR was related to remission (Hedge's g = 0.236, 95%CI = 0.014–0.458, k = 4, p = .037). DUR was not related to baseline GAF scores (beta = −0.004, 95%CI = −0.025–0.017, k = 3, p = .71). The current findings suggest that DUR is not associated with transition to psychosis at 12 months, but may impact remission. However, the database was small and further research in this area is required.

1. Introduction

Schizophrenia is a severe psychotic disorder that is associated with sustained and disabling functional and cognitive impairments (Green, 2016). Clinical outcomes have only marginally improved over recent decades and as a result, clinical and research efforts have shifted towards earlier illness stages with the goal of impacting on clinical trajectories (Fusar-Poli et al., 2017).

Evidence has accumulated that the onset of psychosis is usually preceded, in the majority of cases, by a clinical high-risk for psychosis (CHR—P) state (Schultze-Lutter et al., 2015; Shah et al., 2017), which is characterised by subtle signs and symptoms coupled with functional and neurocognitive impairments (Catalan et al., 2021; Fusar-Poli et al., 2015; Haining et al., 2021). As a result, CHR-P criteria have been formulated to enable the detection of individuals with an elevated risk of developing a psychotic disorder (Fusar-Poli et al., 2015). CHR-P individuals have an enhanced risk of developing psychosis, which cumulates to 20 % at 2 years and 35 % at 10 years (Salazar de Pablo et al., 2021b), but those who do not transition typically retain mental health difficulties (Salazar de Pablo et al., 2022).

Recently, several studies have examined the potential relationship between the duration of risk symptoms (DUR) and clinical outcomes in CHR-P participants (Carrión et al., 2016; Fujioka et al., 2020; Zhang et al., 2018). Research into DUR has been motivated by the observation that a longer duration of untreated psychosis (DUP) in first episode psychosis (FEP) patients has been linked to worse clinical outcomes, in

* Corresponding author at: Department of Child and Adolescent Psychiatry, Augustenburger Platz 1, Charité Universitätsmedizin, Berlin 13353, Germany.
E-mail address: peter.uhlhaas@charite.de (P.J. Uhlhaas).

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terms of severity of positive and negative symptoms, lower general functioning, and lower remission rates (Howes et al., 2021; Marshall et al., 2005; Penttilä et al., 2014).

While DUP concerns the time elapsed between the onset of full-blown psychotic symptoms and the initiation of treatment (Norman and Malla, 2001), DUR in CHR—Ps has been conceptualised as the interval between the first manifestation of attenuated positive or negative symptoms and the onset of FEP, or a time-point where treatment was initiated (Zhang et al., 2018). It is currently unclear, however, whether DUR has a relationship to transition to psychosis, remission, or functional and cognitive outcomes in CHR-P participants (Allott et al., 2017; Boonstra et al., 2012).

To address these questions, we systematically reviewed and meta-analysed the results of studies that examined the DUR in CHR-P populations in relation to clinical outcomes, such as transition to psychosis and remission from CHR-P status, as well as functional outcomes and cognition. Based on findings in FEP populations, we predicted that a longer DUR would be associated with poorer outcomes in CHR-P samples.

2. Method

This review was conducted in accordance with the PRISMA guidelines (Page et al., 2021) and the protocol was registered with PROSPERO on 16th April 2021 (ID no. CRD42021249443.)

2.1. Search strategy and selection criteria

A literature search was conducted using PsycINFO and Web of Science from inception to March 2021, using the following search terms: (duration OR period OR time OR length) AND (prodrom* OR attenuated OR subsyndromal OR subthreshold) AND (clinical high risk OR ultra high risk) AND (psycho*). This was followed by an additional literature search in November 2021. Inclusion of studies was based on the following criteria: Randomised controlled trials, cross-sectional, prospective, and retrospective studies reporting on the DUR in CHR-P populations, as well as data on transition to psychosis, and/or symptomatic outcomes and/or functional and/or cognitive outcomes. Studies were excluded if they reported data from patients diagnosed with schizophrenia, schizoaffective disorder, delusional disorder, schizotypal personality disorder, schizophreniform disorder, brief psychotic disorder or psychosis associated with substance use or medical conditions. Additionally, unpublished studies, qualitative studies, study protocols, reviews, and meta-analyses were excluded.

2.2. Quality assessment

The Joanna Briggs Institute Critical Appraisal Checklists (Joanna Briggs Institute, 2020a, 2020b, 2020c, 2020d) were used to assess the quality of individual studies. Each study was scored on items relating to representativeness of the sample, confounding factors, outcomes, follow-up times and study attrition.

2.3. Statistical analysis

A series of random-effects meta-analyses were conducted to pool overall effect sizes for the primary outcome (transition to psychosis), and the secondary outcomes (remission from CHR-P status and global functioning). A meta-analytic approach was only performed where there were more than three studies reporting on the same variable.

For transition to psychosis, effect size measures were synthesised using odds ratios (OR). Hazard ratios were converted to odds and (log) odds ratios in three samples (Fusar-Poli et al., 2020; Nelson et al., 2013; Zhang et al., 2018) and the DUR at the level of the dichotomous outcome was transformed into (log) odds ratios in two samples (Chung et al., 2017; Pantelis et al., 2003) using predetermined formulae (Borenstein et al., 2009). Remission from CHR-P status was analysed using Hedge's g. For functional outcomes, Pearson's and Spearman's correlations and regression betas were converted into a single comparable effect size (LogBetaXY; the regression coefficient between the log DUR and the log outcome) using Souverein et al.'s (2012) formulae. Where relevant data were missing, the corresponding authors were contacted.

Overall effects for symptomatic outcomes were analysed using ORs for transition to psychosis, Hedge's g for remission from CHR-P status, and LogBetaXY for GAF score at baseline. An OR above 1 indicates a relationship between a longer DUR and an increased risk of transition to psychosis. A positive value for Hedge's g indicates that DUR is longer in those who do not remit from CHR-P status, compared to those who do. A negative beta value indicates a relationship between longer DUR and lower GAF score at baseline. Heterogeneity was assessed using the I^2 statistic and the χ^2 test. Where sample sizes permitted, sub-group analyses were conducted to compare outcomes in studies that included only positive symptoms in their definition of DUR, to those combining both positive and negative symptoms. Data were analysed using Comprehensive Meta-Analysis (v3).

3. Results

3.1. Study characteristics

The literature searches returned 499 results in PsycINFO and 1553 in Web of Science, totalling 2052 searches overall (Fig. 1). After the removal of duplicates, non-English papers, and studies such as reviews and meta-analyses, 1296 titles and abstracts were screened. At this stage, 1093 papers were excluded based on the fact that they did not measure psychosis or DUR, or that they included other clinical populations (such as schizophrenia and FEP patients). This left 203 full texts that were assessed for eligibility, and a further 190 studies were excluded. Thirteen papers were included in the final meta-analysis.

Table 1 presents the main characteristics of the primary studies included in the meta-analyses. The total number of participants was 2506, their mean age was 19.88 years (SD = 1.61), 47.65 % were female, and the mean length of follow-up was 3.05 years (SD = 2.10). All studies recruited CHR-P samples from clinical services, apart from one cohort that utilised a community sample (Staines et al., 2021). The mean length of DUR when combining positive and negative symptoms was 17.47 months (SD = 6.07), which was shorter than when measuring positive symptoms alone (M = 29.90 months, SD = 9.68) and negative symptoms alone (53.24 months); (Fig. 2).

DUR definitions differed across studies. Only one study (Staines et al., 2021) defined DUR as the duration of APS, while others included the onset of APS and negative symptoms, but used different endpoints such as first contact with a service (n = 5) or commencement of professional help, such as receiving a diagnosis or taking part in a specialised treatment program (n = 4). N = 5 studies did not provide information regarding the exact onset and offset parameters for the definition of DUR. Eight studies measured DUR using the SIPS, compared to 4 that used the CAARMS and 2 using the BPRS. Seven studies combined both positive and negative symptoms when measuring DUR, whereas 6 considered only positive symptoms and 1 included only negative symptoms.

Criteria for transition to psychosis varied across studies (*see* Table 1). Remission from CHR-P status included both symptomatic and functional remission, defined by different reductions in APS items across studies, and different scores on the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al., 1992) or the Global Assessment of Functioning scale (GAF; Caldecott-Hazard and Hall, 1995); (Table 1). In line with previous DUP research (Howes et al., 2021; Marshall et al., 2005), these outcomes were analysed using the definitions provided in the primary studies.

If studies reported on identical samples for the same outcome measure, the study utilising the shorter follow-up period was excluded. If

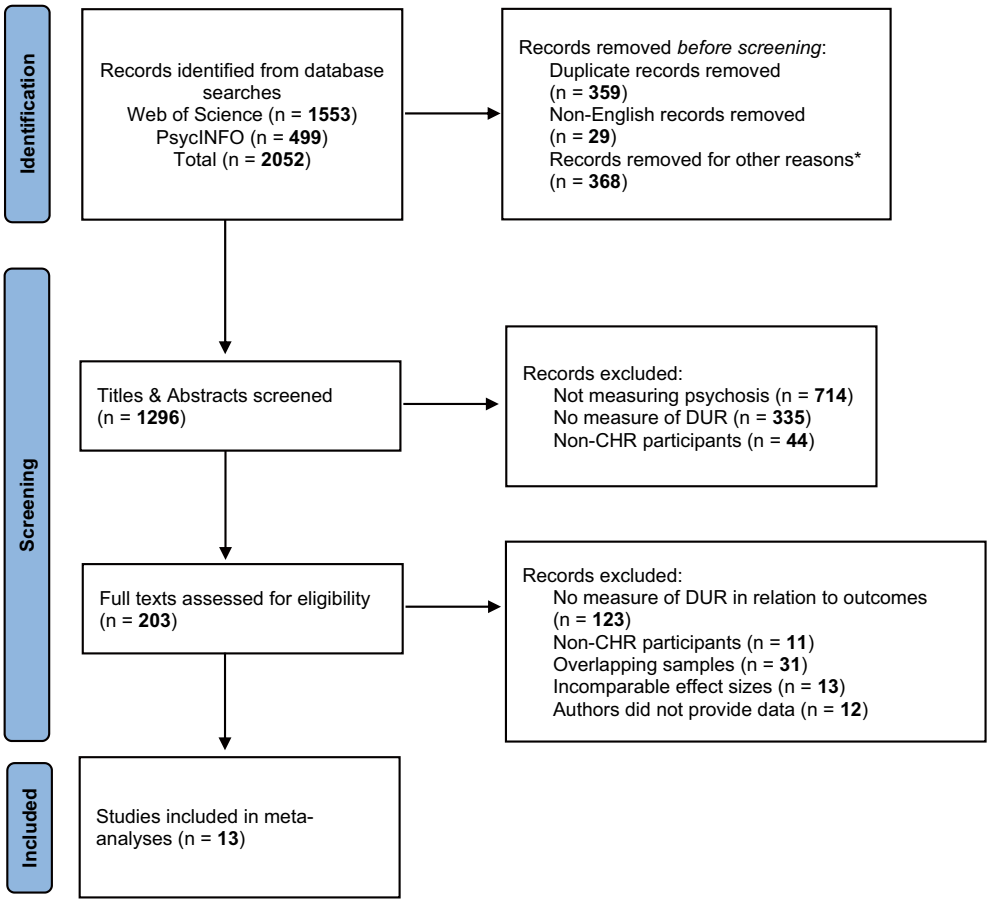

Fig. 1. * Book chapters, comments, reviews, summaries of theories/models, case reports, audits, meta-analyses, qualitative studies, unpublished studies. PRISMA Flowchart: Flow diagram detailing the search and selection of reports included in the review.

reporting on overlapping samples for the same outcome measure, the study with the smaller sample was removed from the analysis. Authors provided raw data for $n = 3$ studies.

3.2. Transition to psychosis

The pooled estimate indicated no overall effect of DUR on transition to psychosis at 12-month follow-up (OR = 1.000, 95%CI = 0.999–1.000, $k = 8$, $p = .98$). There was no significant heterogeneity for this outcome ($I^2 = 31.15$, $p = .18$). In addition, there were no differences between studies that combined positive and negative symptoms (OR = 0.991, 95%CI = 0.926–1.060, $k = 4$, $p = .79$) and those that measured positive symptoms only (OR = 1.000, 95%CI = 0.998–1.002, $k = 3$, $p = .96$).

3.3. Remission

There was a significant overall effect of remission status on DUR (Hedge's g = 0.236, 95%CI = 0.014–0.458, $k = 4$, $p = .037$), indicating that a longer DUR was associated with a decrease in likelihood of remission. No heterogeneity was detected for this outcome ($I^2 = 11.52$, $p = .34$).

3.4. Functioning at baseline

DUR revealed no overall effect on GAF at baseline (beta = −0.004, 95%CI = −0.025–0.017, $k = 3$, $p = .71$). There was no statistical evidence of heterogeneity detected ($I^2 = 0.00$, $p = .55$).

Using raw data available from 2 studies, both a significant ($r = -0.191$, $p < .001$; Zhang et al., 2018) and non-significant negative correlation ($r = -0.214$, $p = .069$; Chon et al., 2015) were found between DUR and highest GAF score in the year following baseline assessment. In these two samples, the relationship between DUR and GAF decrease in the past year, measured as the difference between baseline GAF score and the highest GAF score recorded in the year following baseline assessment, was also calculated. Significant negative correlations were found ($r = -0.236$, $p = .044$ and $r = -0.133$, $p = .009$); (Chon et al., 2015 and Zhang et al., 2018, respectively), indicating that a longer DUR was associated with a smaller GAF decrease.

3.5. Cognitive deficits

Only two studies reported on the relationship between DUR and cognition at baseline. Chon et al. (2015) found that DUR was not significantly correlated with cognitive deficits, while Staines et al. (2021) found that DUR predicted impaired verbal fluency ($B = -0.003$, $p = .022$). However, this effect did not survive corrections for multiple comparisons.

4. Discussion

There is meta-analytic evidence that DUP impacts clinical outcomes in FEP populations (Howes et al., 2021; Marshall et al., 2005). However,

Table 1
Study characteristics.

Study	N		Mean age, years (SD)	Mean DUR, months (SD)	Symptoms measured for DUR	Definitions	Results
	Baseline	Follow-up					
Carrión et al. (2016)	76	76	16.0 (2.2)	APS = 40.2 (40.3) Neg. = 53.2 (48.9)	Positive and negative separately	DUR = Duration of attenuated positive (APS) and negative symptoms (measured using SIPS). Conversion to psychosis = presence of psychotic level positive symptom (SOPS score of 6 with minimum duration of 1 week).	[From raw data]: No significant correlation between duration of APS and GAF score at baseline or follow-up. [From raw data]: No significant correlation between duration of negative symptoms and GAF score at baseline and follow-up. Neither the duration of APS nor duration of negative symptoms significantly predicted conversion to psychosis.
Chon et al. (2015)	73	57	20.8 (3.5)	18.4 (16.2)	Positive	DUR = Period from fulfilment of the operational criteria of UHR focused on prodromal positive symptoms until participation in a specialised UHR program (measured using SIPS).	[From raw data]: No correlation between DUR and baseline GAF score. [From raw data]: Negative correlation between DUR and GAF drop in past year. Cognitive performance was not significantly correlated with the DUR.
Chung et al. (2017)	267	267	19.6 (4.2)	Converters = 39.6 (37.2) Non-converters = 30.0 (36.0)	Combination of positive and negative	DUR = Duration of prodromal symptoms (measured using SIPS).	DUR longer in the converter group than the non-converters.
Fujioka et al. (2020)	24	24	20.4 (3.7)	Remitters = 10.3 (14.4) Non-remitters = 10.1 (16.5)	Combination of positive and negative	DUR = Period between first appearance of the first prodromal symptom and first hospital visit (measured using SIPS). Remission from UHR status = score of ≥61 on GAF and ≤2 on all SOPS pos. Subscales at last follow-up time- point.	DUR in UHR-remitters longer than in non-remitters.
Fusar-Poli et al. (2020)	600	600	22.6 (4.9)	22.2 (36.3)	Positive	DUR = Duration of untreated attenuated psychotic symptoms (measured using CAARMS).	DUR did not predict psychosis onset.
Lee et al. (2014a) Overlap with Chon et al. (2015)	73	73	19.7 (3.2)	Remitters = 29.6 (19.9) Non-remitters = 27.6 (25.6)	Combination of positive and negative	DUR = Duration of untreated prodromal psychosis (measured using SIPS). Remission from CHR-P status = score of >60 on GAF and ≤2 on all positive SOPS symptoms.	DUR in CHR-remitters longer than non-remitters.
Lemos-Giráldez et al. (2009)	61	42	21.7 (3.8)	22.5 (27.4)	Combination of positive and negative	DUR = estimated on the basis of time between onset of symptoms and entry into the service (measured using SIPS).	DUR predicted transition to psychosis.
Nelson et al. (2013)	414	311	18.9 (3.4)	14.7 (7.2)	Positive	DUR = Duration of symptoms before first contact with clinic (measured using BPRS before 1999 and CAARMS after 1999). Transition to psychosis = At least 1 fully positive psychotic symptom several times a week for >1 week.	DUR significantly predicted transition to psychosis.
Pantelis et al. (2003)	75	21	20.6 (3.7)	Converters = 20.1 (18.7) Non-converters = 10.5 (16.4)	Combination of positive and negative	DUR = Duration of symptoms (measured using BPRS). Development of psychosis = at least one of: hallucinations (≥3 on BPRS), delusions (≥4 on UTC or suspiciousness on BRPS, or ≥3 on CASH, or formal thought disorder (≥4 on conceptual disorganisation on BPRS)). Frequency ≥ several times a week. Duration of mental state change ≥1 week.	DUR in people who developed psychosis longer than in people who did not.
Polari et al. (2021)	202	202	19.1 (4.6)	29.3 (35.3)	Positive	DUR = Defined as in Nelson et al. (2013). Remission = no longer presenting with APS	DUR longer in non-remitters than in remitters.

(*continued on next page*)

Table 1 (*continued*)

Study	N		Mean age, years (SD)	Mean DUR, months (SD)	Symptoms measured for DUR	Definitions	Results
	Baseline	Follow-up					
						along with SOFAS score ≥ 70 or increase of at least 5 SOFAS points.	
Staines et al. (2021)	134	–	20	39 (54)	Positive	DUR = Duration of APS obtained from CAARMS & SPI-A assessments. CAARMS: frequency score of 3–5 and intensity rating of ≥3 on UTC or non-bizarre ideas, or perceptual abnormalities scale or ≥4 on disorganised speech scale.	DUR did not significantly predict GAF score at baseline. DUR did not significantly predict cognitive outcomes (BACS) apart from verbal fluency.
Zhang et al. (2018)	391	334	20.4 (6.1)	4.8 (3.8)	Combination of positive and negative	DUR = The period between the onset of the first attenuated positive symptom (at least moderate level, corresponding to 3 points or higher on SOPS), based on information from the SIPS interview, and the commencement of professional help at mental health services. Conversion to psychosis = score ≥ 6 on at least one of: UTC, suspiciousness, grandiosity, perceptual abnormalities, disorganised communication with either sufficient frequency and duration (at least 1 h/d, avg. frequency of 4d/wk for 1 month), or at level that was disorganising or dangerous.	[From raw data]: No correlation between DUR and GAF score at baseline. [From raw data]: Significant negative correlation between DUR and highest GAF score in past year. [From raw data]: Significant negative correlation between DUR and GAF drop. [From raw data]: DUR did not predict conversion to psychosis.
Zhang et al. (2021) Overlap with Zhang et al. (2018)	105	105	18.6 (5.1)	5.6 (3.6)	Combination of positive and negative	DUR = same as above. Remission = current GAF score of >70 and symptom scores of <3 for all positive symptoms.	DUR longer in remitters than non-remitters.

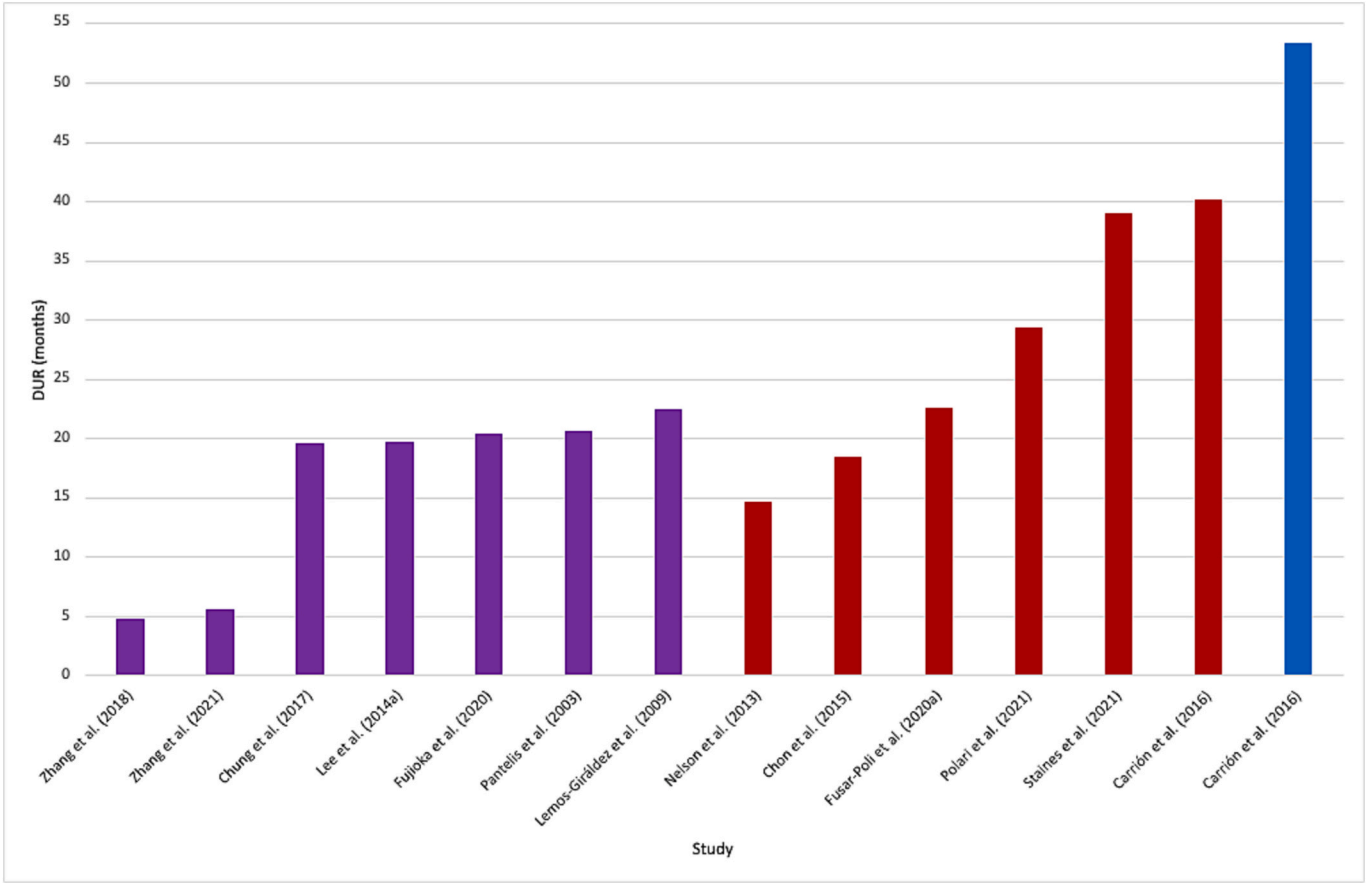

Fig. 2. DUR across studies. Purple = combination of positive & negative symptoms; red = positive symptoms; blue = negative symptoms. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

it is unclear whether a similar relationship holds for DUR and clinical and functional outcomes in CHR—Ps. Accordingly, we investigated whether DUR was related to transition to psychosis and remission, as well as functional trajectories in CHR-P participants. We found meta-analytic evidence for an overall effect of DUR on remission from CHR-P status. However, DUR was not related to risk of transition to psychosis at 12 months, nor global functioning at baseline. With a mean duration of M = 23.61 months, the DUR in the present study is consistent with the estimated mean DUR in FEP populations (Crumlish et al., 2009; Moller and Husby, 2000).

4.1. Transition to psychosis

In the present analysis, longer DUR was not associated with an elevated risk for transition to psychosis at 12 months. The absence of a relationship here is potentially important, as interventions implemented during the prodromal phase are centred around the notion that reducing DUR will, in turn, reduce the risk of transitioning to psychosis (Carrión et al., 2016; McGlashan, 1998). However, only 25 % of CHR—Ps go on to develop an FEP within 3 years (Salazar de Pablo et al., 2021b). Accordingly, the identification of predictors for those CHR—Ps who will develop an FEP is an important objective for current research (Addington et al., 2020). Previous studies reported that the severity of APS is a better predictor of transition to psychosis in CHR-Ps, compared to global functioning and severity of basic, disorganised or negative symptoms (Cornblatt et al., 2015; Oliver et al., 2020). Accordingly, this suggests that the severity of APS, but not their duration, may be more important for assessing risk of transition in CHR-Ps.

4.2. Remission from CHR-P status

We found preliminary evidence that a shorter DUR predicted remission from CHR-P status at follow-up, although the effect was small (Hedge's g = 0.236). This result is consistent with previous meta-analyses that reported a relationship between a longer DUP and reduced likelihood of remission in FEP populations (Marshall et al., 2005; Penttilä et al., 2014). However, further studies in CHR-Ps are required to elucidate whether longer DUR is related to remission from CHR-P status, given that persistent APS are associated with poorer clinical outcomes and sustained cognitive deficits (Lee et al., 2014b; Rutigliano et al., 2016).

4.3. Functioning and cognition

Functional deficits are a prominent feature of the CHR-P state, with individuals experiencing difficulties in interpersonal relationships and impairments in academic performance and/or occupational functioning (Addington et al., 2008; Fusar-Poli et al., 2013). Both poor baseline functioning and a change in functioning have also been identified as significant predictors of transition to psychosis in CHR-Ps (Cannon et al., 2008; Fusar-Poli et al., 2015; Oliver et al., 2020). In the current analysis, there was no evidence of an effect of DUR on GAF score at baseline. This is notable as functional impairments often develop early during the course of the illness and can precede the onset of psychosis by several years (Malla and Payne, 2005). However, the current finding suggests that DUR has no impact on functioning at baseline, which is also consistent with a recent meta-analysis in FEP populations (Howes et al., 2021).

A recent meta-analysis by Salazar de Pablo et al. (2021a) highlighted the importance of not only assessing baseline functioning in CHR-Ps, but also the change in level of functioning. Although there were not sufficient data to meta-analyse this outcome in the present study, two of the primary studies did report a relationship between a shorter DUR and an increased GAF drop (Chon et al., 2015; Zhang et al., 2018), which is also consistent with a previous study investigating the duration of BS and change in GAF scores (Fusar-Poli et al., 2009).

In addition to functioning, cognitive deficits are also an important feature of CHR-Ps (Bora et al., 2014). The only two studies to examine the link between DUR and cognitive deficits did not find any significant associations, which is also consistent a meta-analysis that reported a lack of relationship between DUP and cognitive impairment in FEP patients (Bora et al., 2018).

4.4. Limitations and methodological issues

The current review revealed considerable differences in the definition of DUR. Some studies combined both positive and negative symptoms when measuring DUR, whereas others included only positive symptoms. Given that negative symptoms can precede the onset of psychosis and may affect clinical outcome trajectories differently than positive symptoms (Häfner, 2000; Iyer et al., 2008), it would therefore be useful to evaluate DUR for positive and negative symptoms separately. As only one study measured the duration of negative symptoms (Carrión et al., 2016), we were unable to explore the differences in duration of APS and negative symptoms, or whether negative symptoms precede positive symptoms, as has been previously described in ScZ patients (Remington et al., 2011).

Secondly, the endpoint for DUR is inconsistently defined. Norman and Malla (2001) highlighted similar discrepancies in the definition of DUP in FEP patients, arguing that the length of symptoms is critical, regardless of whether or not they are being treated. As such, perhaps the time of symptom resolution may be a more appropriate endpoint for DUR in CHR-P individuals.

Research into the duration of APS and negative symptoms remains somewhat sparse in the context of clinical outcomes in CHR-P participants. Ten studies with potential relevance could not be included in the current series of meta-analyses as they reported on DUR and outcomes separately, but did not report an effect size on the relationship between them.

Finally, due to the variation in the statistical methods used and the effect sizes reported, outcomes could not be meta-analysed using the effect size measure most commonly reported in the primary studies. While some studies had artificially dichotomised the DUR into 'short' and 'long' time frames, others dichotomised outcomes (i.e. remission, transition to psychosis) when measuring DUR continuously. Alongside a general lack of consensus on what defines 'short' and 'long' DUR, there is also no strong a-priori justification for specifying a particular timepoint, with cut-offs ranging from 3 to 12 months in the primary studies included in this review. Such dichotomisation can potentially lead to a reduction in statistical power and obscure the true relationship between DUR and continuous outcomes.

4.5. Recommendations for future research

The lack of consistency in the definition of DUR highlights the need for a standardised assessment approach. This should include clear onset and offset criteria that distinguish between APS and negative symptoms. Since the use of self-reports and retrospective interviews introduces the potential for recall bias, patient reports could also be complemented by using information from family members and health professionals, as demonstrated in studies by Drake et al. (2018) and Sarpal et al. (2017).

5. Conclusions

This systematic review and meta-analysis suggests that there is currently only modest evidence for a relationship between DUR and clinical and functional outcomes in CHR-P individuals. Specifically, our results indicate that DUR reduces the likelihood of remission from CHR-P status, although does not impact the likelihood of transition to psychosis or baseline functioning and cognitive deficits. These preliminary findings contrast with the evidence from data on the relationship between DUP and clinical outcomes in FEP populations (Howes et al.,

2021). However, further research using a standardised assessment approach is required to determine whether DUR may be a clinically relevant target for understanding clinical trajectories and outcomes in CHR-P populations.

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CRediT authorship contribution statement

Author PU designed the study and SC wrote the protocol. The literature review and data extraction were conducted by SC and supervised by PU. SC undertook the statistical analysis and wrote the first and subsequent drafts of the manuscript. PU and PFP contributed to the interpretation of the results and reviewed and edited all drafts of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

PU has received research support from Lilly and Lundbeck outside the submitted work.

PFP has received grant fees from Lundbeck and honoraria from Lundbeck, Menarini and Angelini, outside the submitted work.

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