



Research paper

Longitudinal outcome of attenuated positive symptoms, negative symptoms, functioning and remission in people at clinical high risk for psychosis: a meta-analysis

Gonzalo Salazar de Pablo, MD^{a,b,c}, Filippo Besana, MD^{d,#}, Vincenzo Arienti, MD^{d,#}, Ana Catalan, MD, PhD^{e,f}, Julio Vaquerizo-Serrano, MD^{b,c,f}, Anna Cabras, MD^g, Joana Pereira, MD^h, Livia Soardo, MD^d, Francesco Coronelli, MD^d, Simi Kaur, MSc^f, Josette da Silva, MSc^f, Dominic Oliver, PhD^a, Natalia Petros, PhD^f, Carmen Moreno, MD, PhD^b, Ana Gonzalez-Pinto, MD, PhDⁱ, Covadonga M Díaz-Caneja, MD, PhD^b, Jae Il Shin, MD, PhD^j, Pierluigi Politi, MD, PhD^d, Marco Solmi, MD, PhD^{a,k}, Renato Borgatti, MD, PhD^{d,l}, Martina Maria Mensi, MD, PhD^{d,l}, Celso Arango, MD, PhD^b, Christoph U Correll, MD^{m,n,o,p}, Philip McGuire, MD, PhD, FRCPsych, FMedSci^{f,q,r}, Paolo Fusar-Poli, MD, PhD^{a,d,q,r,*}

^a Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

^b Institute of Psychiatry and Mental Health, Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), CIBERSAM, Madrid, Spain

^c Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

^d Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

^e Mental Health Department - Biocruces Bizkaia Health Research Institute, Basurto University Hospital, Faculty of Medicine and Dentistry, UPV/EHU, Vizcaya, Spain

^f Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

^g Department of Neurology and Psychiatry, University of Rome La Sapienza, Rome, Italy

^h Lisbon Psychiatric Hospital Centre, Lisbon, Portugal

ⁱ Hospital Universitario Araba, Servicio de Psiquiatría, UPV/EHU, Bioaraba, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain

^j Department of Paediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea

^k Neurosciences Department, University of Padova, Italy

^l IRCCS Mondino Foundation, Child and Adolescent Neuropsychiatric Unit, Italy

^m Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, New York, USA

ⁿ Department of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA

^o Center for Psychiatric Neuroscience, The Feinstein Institutes for Medical Research, Manhasset, New York, USA

^p Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany

^q OASIS Service, South London and Maudsley National Health Service Foundation Trust, UK

^r National Institute for Health Research, Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, London, UK

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ABSTRACT

Background: Little is known about clinical outcomes other than transition to psychosis in people at Clinical High-Risk for psychosis (CHR-P). Our aim was to comprehensively meta-analytically evaluate for the first time a wide range of clinical and functional outcomes beyond transition to psychosis in CHR-P individuals.

Methods: PubMed and Web of Science were searched until November 2020 in this PRISMA compliant meta-analysis (PROSPERO:CRD42020206271). Individual longitudinal studies conducted in individuals at CHR-P providing data on at least one of our outcomes of interest were included. We carried out random-effects pairwise meta-analyses, meta-regressions, and assessed publication bias and study quality. Analyses were two-tailed with $\alpha=0.05$.

* Corresponding author: Paolo Fusar-Poli, MD, PhD, Department of Psychosis Studies, 5th Floor, Institute of Psychiatry, Psychology & Neuroscience, PO63, 16 De Crespigny Park, SE5 8AF London, UK.

E-mail address: paolo.fusar-poli@kcl.ac.uk (P. Fusar-Poli).

These authors have contributed equally.

Findings: 75 prospective studies were included (n=5,288, age=20.0 years, females=44.5%). Attenuated positive symptoms improved at 12 (Hedges' $g=0.753$, 95%CI=0.495–1.012) and 24 (Hedges' $g=0.836$, 95%CI=0.463–1.209), but not ≥ 36 months (Hedges' $g=0.315$, 95%CI=–0.176–0.806). Negative symptoms improved at 12 (Hedges' $g=0.496$, 95%CI=0.315–0.678), but not 24 (Hedges' $g=0.499$, 95%CI=–0.137–1.134) or ≥ 36 months (Hedges' $g=0.033$, 95%CI=–0.439–0.505). Depressive symptoms improved at 12 (Hedges' $g=0.611$, 95%CI=0.441–0.782) and 24 (Hedges' $g=0.583$, 95%CI=0.364–0.803), but not ≥ 36 months (Hedges' $g=0.512$, 95%CI=–0.337–1.361). Functioning improved at 12 (Hedges' $g=0.711$, 95%CI=0.488–0.934), 24 (Hedges' $g=0.930$, 95%CI=0.553–1.306) and ≥ 36 months (Hedges' $g=0.392$, 95%CI=0.117–0.667). Remission from CHR-P status occurred in 33.4% (95%CI=22.6–44.1%) at 12 months, 41.4% (95%CI=32.3–50.5%) at 24 months and 42.4% (95%CI=23.4–61.3%) at ≥ 36 months. Heterogeneity across the included studies was significant and ranged from $I^2=53.6\%$ to $I^2=96.9\%$. The quality of the included studies (mean \pm SD) was 4.6 ± 1.1 (range=2–8).

Interpretation: CHR-P individuals improve on symptomatic and functional outcomes over time, but these improvements are not maintained in the longer term, and less than half fully remit. Prolonged duration of care may be needed for this patient population to optimize outcomes.

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Research in context

Evidence before this study

To date, studies of the clinical outcomes of individuals at clinical high-risk for psychosis (CHR-P) have mainly focused on transition to psychosis, while the magnitude and consistency of other outcomes have not been comprehensively evaluated. To overcome this limitation, we searched with a wide combinations of search terms PubMed and Web of Science databases until November 2020, looking for individual studies that evaluated longitudinally attenuated positive symptoms, negative symptoms, depressive symptoms, level of functioning and overall remission. Meta-analytic random-effects models, meta-regression analyses, publication bias assessment and quality assessment using a modified version of the Newcastle-Ottawa Scale (NOS) for cohort studies were carried out.

Added value of this study

This first meta-analysis comprehensively evaluating the magnitude and consistency of clinical outcomes other than transition to psychosis in CHR-P individuals identified 75 studies and showed that most clinical outcomes improve within the first two years, but such improvement is not maintained in the longer term. Functional improvements are maintained, yet at a smaller magnitude after three years. Less than half of the subjects fully remit from CHR-P status.

Implications of all the available evidence

The present work advances clinical knowledge about the longitudinal outcomes in CHR-P individuals, which will inform the clinical management of this group.

Understanding the exact prognosis and longitudinal trajectories of this patient group is pivotal for informing their clinical care [13]. To date, transition to psychosis has been the primary outcome of interest in this field [14–16]. However, the CHR-P group is clinically heterogeneous [17] and display several other outcomes beyond transition to psychosis. These outcomes include varying levels of attenuated positive [18] and negative [19] symptoms, depressive symptoms [20], impairments in functioning [21] and quality of life [22], and overall remission [23]. Many recent studies have examined these outcomes (in addition to transition to psychosis), but the findings have been mixed. Some meta-analyses have addressed the magnitude and consistency of these other outcomes in CHR-P individuals. Still, these meta-analyses have been either limited to randomised controlled trials (e.g. positive [24] and negative [25] symptoms, depression [26]), provided only baseline results (e.g. functioning [9]), or are more than five years old (e.g. remission [23]). To the best of our knowledge, there is no recent comprehensive meta-analysis addressing the magnitude and consistency of clinical outcomes other than transition to psychosis in CHR-P cohorts.

The current meta-analysis seeks to fill this knowledge gap by evaluating comprehensively for the first time longitudinal outcomes beyond transition to psychosis in CHR-P individuals at different follow-up periods while testing for potential outcome moderators.

2. Methods

The protocol for this systematic review and meta-analysis was registered on PROSPERO (CRD42020206271). This study was conducted following the "Preferred Reporting Items for Systematic reviews and Meta-Analyses" (PRISMA [27]) checklist.

2.1. Search strategy and selection criteria

A multi-step literature search was performed by three independent researchers (GSdP, VA, JP) in PubMed and Web of Science database (Clarivate Analytics), incorporating the Web of Science Core Collection, BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index, as well as Cochrane Central Register of Reviews and Ovid/PsycINFO databases, from inception until November 1st, 2020. Different combinations of search terms related to CHR-P individuals, their outcomes and progression were applied (eMethods 1). The references for previously published articles were reviewed using MEDLINE, and additional relevant titles were included. Same authors screened the articles as abstracts. After excluding those that did not meet our inclusion criteria, the full texts of the remaining articles were assessed for eligibility and decisions were made regarding their final inclusion in the review.

1. Introduction

At present, indicated prevention in individuals at clinical high-risk for psychosis (CHR-P) [1] is one of the most promising primary preventive approaches in psychiatry [2,3]. The CHR-P paradigm is grounded in three concatenated components: detection, prognosis and intervention [4]. CHR-P individuals are adolescents and young adults, and typically accumulate risk factors for psychotic disorders [5–7], present with subtle clinical symptoms [8] and suffer from functional impairment [9]. Because of these problems (as well as comorbid psychiatric conditions), they often seek help at mental health clinics [10,11], where specialised psychometric instruments are used to formulate a group-level prognosis [12].

2.2. Condition and individuals being studied

Studies included were: a) individual longitudinal studies; b) conducted in individuals that fulfilled criteria for CHR-P according to psychometric instruments, which are established in the literature (eMethods 2); c) providing data on at least one of our outcomes of interest (see below); d) published in English. Studies excluded were: a) clinical cases, conference proceedings, study protocols, grey literature or reviews; b) studies with a cross-sectional design; c) studies conducted in samples not fulfilling CHR-P criteria— with or without formal assessment with CHR-P instruments—, such as those at genetic risk for psychosis (e.g., twins, first or second-degree relatives) or schizotypal personality disorder without fulfilling CHR-P instruments' functional decline criteria; d) data from samples including either non-transitioning or transitioning CHR-P individuals only; e) studies in a language other than English; f) overlapping samples for a given outcome. No additional exclusion criterion was applied for CHR-P individuals transitioning to psychosis, as long as they did not report transitioning CHR-P samples only. For clinical trials, only data from the placebo/needs-based intervention arm was included, while data from the experimental intervention arms were excluded. When two or more studies from the same cohort were found, we contacted corresponding authors to clarify whether there was an overlap in the respective samples. The largest and most recently published sample was retained for each of the outcomes. Disagreements in selection criteria were resolved through discussion and consensus.

2.3. Outcome Measures and Data Extraction

At least two independent researchers (JV-S, AC, JP, LS, FC, SK, JDS) extracted data from all the included studies into an excel file. When the agreement in the data extraction of the different variables was <95% between researchers, a third independent researcher (GSdP, FP, VA) cross-checked the data to ensure accuracy of the extraction. After that step, data extraction disagreements were resolved through discussion and consensus between both extractors and with the study leads. From each study, a predetermined set of variables was included (eMethods 3): first author and year of publication, country, design, CHR-P sample size, CHR-P subgroups [i.e. Attenuated Psychosis Symptoms (APS); Brief Intermittent Psychotic Symptoms (BIPS)/ Brief Limited Intermittent Psychotic Symptoms (BLIPS); Genetic Risk and Deterioration syndrome (GRD); Basic symptoms (BS)], age, sex, CHR-P assessment tool (eMethods 2), follow-up period and outcome. Outcomes measured were: (a) change in severity of attenuated positive symptoms; (b) change in severity of negative symptoms; (c) change in severity of depressive symptoms; (d) change in level of functioning; (e) remission. All outcomes were operationalised as indicated in eTable 1. For outcomes (a)-(d), raw data, including mean value and standard deviation (SD), were extracted at baseline and then at 12/24/≥36 months of follow-up. For outcome (e), we extracted the raw counts of CHR-P individuals in remission (i.e., not fulfilling CHR-P criteria anymore) at 12/24/≥36 months follow-up.

2.4. Risk of bias (quality) assessment

The quality of the included studies was evaluated using a modified version of the Newcastle-Ottawa Scale (NOS) for cohort studies, which has been frequently employed in systematic reviews and meta-analysis in the field [9,15] [28,29] (see eTable 2).

2.5. Data analysis

Outcomes were meta-analysed using Meta and Metaprop packages of Stata statistical software version 16 (StataCorp) [30] and Comprehensive Meta-Analysis software, version 3 (Biostat, Inc) [31], whenever at least two studies per outcome and time point were

available. The primary effect size for outcomes (a)-(d) was Hedges' g^{33} , indicating the magnitude and direction of change from baseline to each follow-up time point (12/24/≥36 months) for each outcome. Positive values of Hedges' g indexed improvements in the outcome of interest from baseline to follow-up. Hedges' $g=0.2$ was interpreted as a small effect size, Hedges' $g=0.5$ as a medium effect size and Hedges' $g=0.8$ as a large effect size [32,33]. The primary effect size for outcome (e) was the meta-analytical proportion of the categorical event remission at each time point (12/24/≥36 months follow-up). Because the studies were expected to be heterogeneous, meta-analytic random-effects models were used. Heterogeneity among study point estimates was assessed with the Q statistic. The I^2 index evaluated the magnitude of heterogeneity with $I^2>50\%$ and $p<0.10$ [34] indicating significant heterogeneity. For outcomes (a)-(d), publication bias was evaluated by visually inspecting funnel plots and performing Egger's test [35]. When small effect bias was detected, "trim and fill" sensitivity analyses were employed [36]. Publication bias is not typically assessed for proportions—outcome (e)—, as there are generally no "negative" or "undesirable" results or study characteristics that may have biased publications [37].

Meta-regression analyses were performed when ≥7 studies per outcome were available. We investigated the influence of the following factors: continent (Europe vs North America vs Asia vs other), psychometric instrument (Comprehensive Assessment of At-Risk Mental States [38] -CAARMS- vs Structured Interview for Psychosis-risk Syndromes -SIPS [39,40]- vs other), quality of the included studies (NOS total score), mean age, sex (% female), year of publication, follow-up duration, duration of untreated psychotic symptoms, proportion of APS, proportion of BIPS/BLIPS, proportion of GRD, proportion of BS, functional level, frequency of baseline ICD or DSM-defined comorbidity and exposure to baseline interventions (antipsychotics, antidepressants, other psychotropics, psychotherapy) (eMethods 3). Analyses were two-tailed with $\alpha=0.05$. In meta-regression analyses, we used $\alpha=0.01$ to correct for multiple testing.

Role of the funding: There was no funding source for this study. All authors had access to the study data and the corresponding author and lead author had final responsibility for the decision to submit for publication.

3. Results

3.1. Database

The literature search yielded 70,441 citations after removing duplicates; 1,632 were assessed for eligibility at full text. After excluding 1,557 studies, a final set of 75 studies were included in at least one of the meta-analyses per timepoint (in descending order of frequency): 32 studies evaluated functioning, 29 negative psychotic symptoms, 26 attenuated positive symptoms, 19 remission and 17 studies depressive symptoms (Figure 1; eTable 3). Sixty-one (81.3%) studies were longitudinal cohorts, 12 (16.0%) were randomised clinical trials and two (2.7%) were non-randomised clinical trials. Twenty-seven (36.0%) studies were conducted in Europe, 20 (26.7%) in North America, 14 (18.7%) in Asia, four (5.3%) in Australia, and 10 (13.3%) in more than one country. The mean duration of the follow-up in the included studies was 25.3 months (median=18 months; IQR=12-34 months; range 6.7-192 months). The overall database comprised 5,288 non-overlapping CHR-P individuals (mean age=20.0 years, 44.5% females) (eTable 3). 22.6% were on antipsychotics, 25.2% on antidepressants and 9.3% on anxiolytics at baseline.

3.2. Psychopathological outcomes

Attenuated positive symptoms in CHR-P individuals had improved at 12 ($k=16$, $n=663$, Hedges' $g=0.753$, 95%CI=0.495–1.012) and 24 months follow-up ($k=7$, $n=273$, Hedges' $g=0.836$, 95%CI=0.463–1.209), but not at

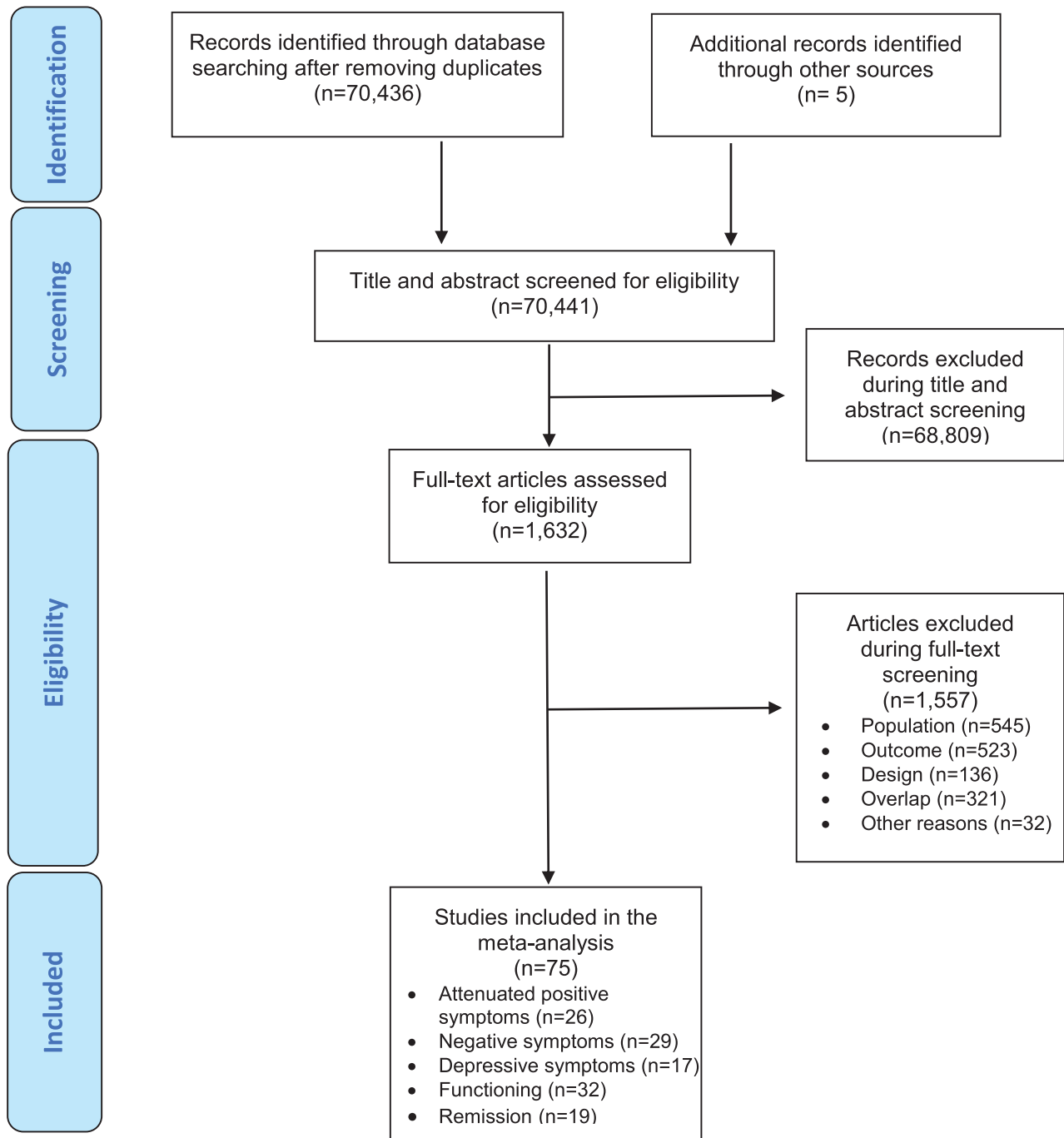


Figure 1. Study selection and inclusion.

≥ 36 months ($k=6$, $n=848$ Hedges' $g=0.315$ 95%CI= $-0.176-0.806$). Negative symptoms had improved in CHR-P individuals at 12 ($k=20$, $n=930$, Hedges' $g=0.496$, 95%CI= $0.315-0.678$), but not at 24 ($k=7$, $n=214$, Hedges' $g=0.499$, 95%CI= $-0.137-1.134$) or ≥ 36 months follow-up ($k=5$, $n=840$, Hedges' $g=0.033$, 95%CI= $-0.439-0.505$). Depressive symptoms had improved at 12 ($k=12$, $n=1,111$, Hedges' $g=0.611$, 95%CI= $0.441-0.782$) and 24 months follow-up ($k=6$, $n=347$, Hedges' $g=0.583$, 95%CI= $0.364-0.803$), but not at ≥ 36 months ($k=3$, $n=404$, Hedges' $g=0.512$ 95%CI= $-0.337-1.361$) (Table 1, Figure 2).

3.3. Functioning

Functioning in CHR-P individuals was improved at 12 ($k=20$, $n=1,005$, Hedges' $g=0.711$, 95%CI= $0.488-0.934$), 24 ($k=11$, $n=778$,

Hedges' $g=0.930$, 95%CI= $0.553-1.306$) and ≥ 36 months follow-up ($k=7$, $n=980$, Hedges' $g=0.392$, 95%CI= $0.117-0.667$) (Table 1, Figure 1).

3.4. Remission from CHR-P status

Remission was observed in 33.4% of subjects (95%CI= $22.6-44.1\%$) after 12 ($k=9$, $n=572$), 41.4% (95%CI= $32.3-50.5\%$) after 24 ($k=6$, $n=1,317$) and 42.4% (95%CI= $23.4-61.3\%$) after ≥ 36 months follow-up ($k=3$, $n=199$) (Table 1, Figure 3 and 4).

3.5. Heterogeneity and Publication bias

Heterogeneity across the included studies was statistically significant for all the outcomes ($p<0.05$), ranging from $I^2=53.6\%$ (depressive

Table 1

Meta-analytic outcomes other psychosis in CHR-P individuals: psychopathology, functioning and remission

Outcome, follow-up period	No. of Studies ^a	Sample size	Hedges' g		z Score	p-values	Test for Heterogeneity			Funnel plot asymmetry	Egger's test p	Trim and fill bias	
			Mean	95% CI			Q	I ²	p-values				
Change in attenuated positive symptoms from baseline to follow-up													
12 months follow-up	16	663	0.753	0.495	1.012	5.709	<0.001	121.798	87.685	<0.001	Yes	0.002*	No change
24 months follow-up	7	273	0.836	0.463	1.209	4.089	<0.001	38.643	84.473	<0.001	No	0.828	D.n.a
≥36 months follow-up	6	848	0.315	-0.176	0.806	1.256	0.209	159.749	96.870	<0.001	No	0.671	D.n.a
Change in negative symptoms from baseline to follow-up													
12 months follow-up	20	930	0.496	0.315	0.678	5.360	<0.001	118.240	83.931	<0.001	Yes	0.085	D.n.a
24 months follow-up	7	214	0.499	-0.137	1.134	1.537	0.124	96.214	93.764	<0.001	No	0.187	D.n.a
≥36 months follow-up	5	840	0.033	-0.439	0.505	0.138	0.890	124.240	96.780	<0.001	No	0.835	D.n.a
Changes in depressive symptoms from baseline to follow-up													
12 months follow-up	12	1,111	0.611	0.441	0.782	7.018	<0.001	79.473	53.588	<0.001	No	0.213	D.n.a
24 months follow-up	6	347	0.583	0.364	0.803	5.201	<0.001	14.535	65.601	0.013	No	0.491	D.n.a
≥36 months follow-up	3	404	0.512	-0.337	1.361	1.182	0.237	65.376	96.941	<0.001	Yes	0.497	D.n.a
Changes in functioning from baseline to follow-up													
12 months follow-up	20	1005	0.711	0.488	0.934	6.239	<0.001	171.658	88.931	<0.001	Yes	0.059	D.n.a
24 months follow-up	11	778	0.930	0.553	1.306	4.838	<0.001	166.286	93.986	<0.001	No	0.257	D.n.a
≥36 months follow-up	7	980	0.392	0.117	0.667	2.793	0.005	81.221	92.613	<0.001	Yes	0.134	D.n.a
Outcome, follow-up period	No. of Studies ^a	Sample size	Proportion		z Score	P	Test for Heterogeneity			Funnel plot asymmetry	Egger's test p	Trim and fill bias	
			%	95% CI			Q	I ²	P				
Remission													
12 months follow-up	9	572	0.334	0.226	0.441	D.n.a	D.n.a	54.091	85.210	<0.001	D.n.a	D.n.a	D.n.a
24 months follow-up	6	1,317	0.414	0.323	0.505	D.n.a	D.n.a	34.039	85.311	<0.001	D.n.a	D.n.a	D.n.a
≥36 months follow-up	3	199	0.424	0.234	0.613	D.n.a	D.n.a	15.378	86.994	<0.001	D.n.a	D.n.a	D.n.a

D.n.a: does not apply

^a Overlapping samples can contribute with different outcomes data at different follow-up periods.

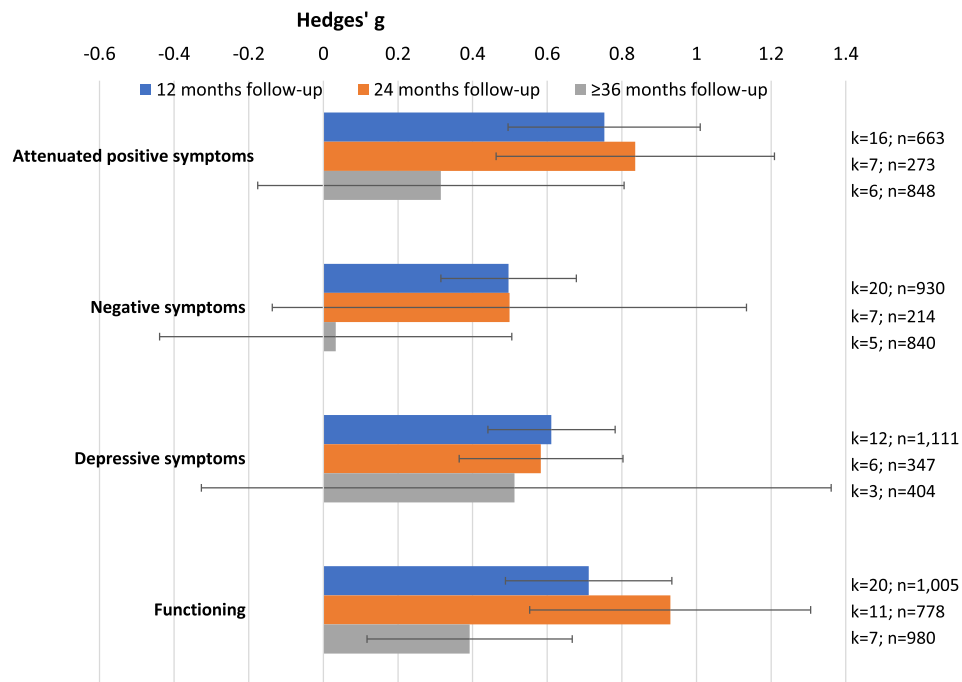


Figure 2. Meta-analytic outcomes other than psychosis in CHR-P individuals: change in psychopathology and functioning. Error bars indicate 95% CI. Blue colour indicates 12 months follow-up; orange colour indicates 24 months follow-up; grey colour indicates ≥ 36 months follow-up.

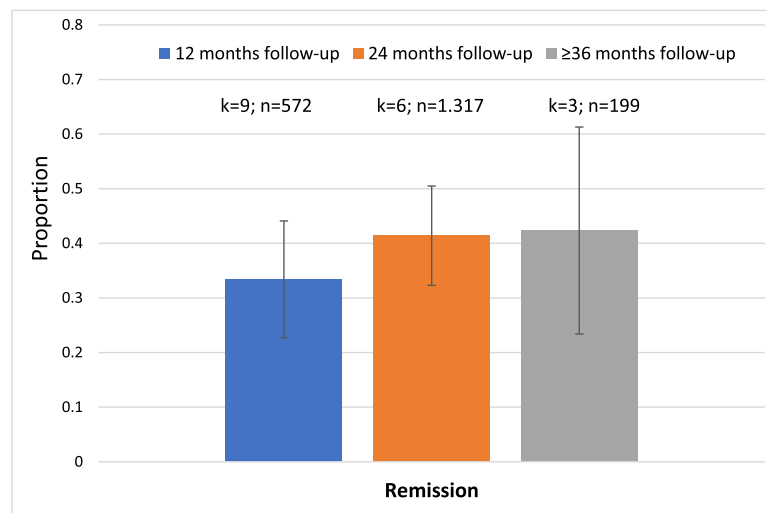


Figure 3. Meta-analytic outcomes other than psychosis in CHR-P individuals: remission at follow-up. Error bars indicate 95% CI. Blue colour indicates 12 months follow-up; orange colour indicates 24 months follow-up; grey colour indicates ≥ 36 months follow-up.

symptoms at 12 months follow-up) to $I^2=96.9\%$ (depressive symptoms at ≥ 36 months follow-up). Egger's test was significant for attenuated positive symptoms at 12 months follow-up ($p=0.002$). However, results remained the same when the trim and fill method was applied (Table 1).

3.6. Quality Assessment and Meta-regression analyses

The quality of the included studies (mean \pm SD) was 4.6 ± 1.1 (range=2-8). A higher baseline exposure to antipsychotics ($\beta=0.032$, $p<0.001$) was associated with greater improvement in attenuated positive symptoms at the last available follow-up for each sample. A lower functional level ($\beta=-0.080$, $p<0.001$) was associated with greater improvement in negative symptoms at the last available follow-up for each sample. The meta-regression analyses did not reveal any other significant association (all $p>0.05$) (eTable 4).

4. Discussion

To our knowledge, this is the first meta-analysis of CHR-P individuals to comprehensively evaluate longitudinal outcomes other than transition to psychosis, including attenuated positive symptoms, negative symptoms, depressive symptoms, functioning and remission. The main finding is that while attenuated positive symptoms, negative symptoms, depressive symptoms and functioning improved during the first two years of follow-up, these improvements were not maintained at/beyond three years. Furthermore, less than half of the subjects achieved remission.

This meta-analysis is based on a large dataset encompassing 75 studies and 5,288 CHR-P individuals. The mean age of 20 years and minimally higher frequency of males (55.5%) in the CHR-P individuals of the meta-analysed cohorts is consistent with the typical sociodemographic profile of this group [11]. The large number of studies

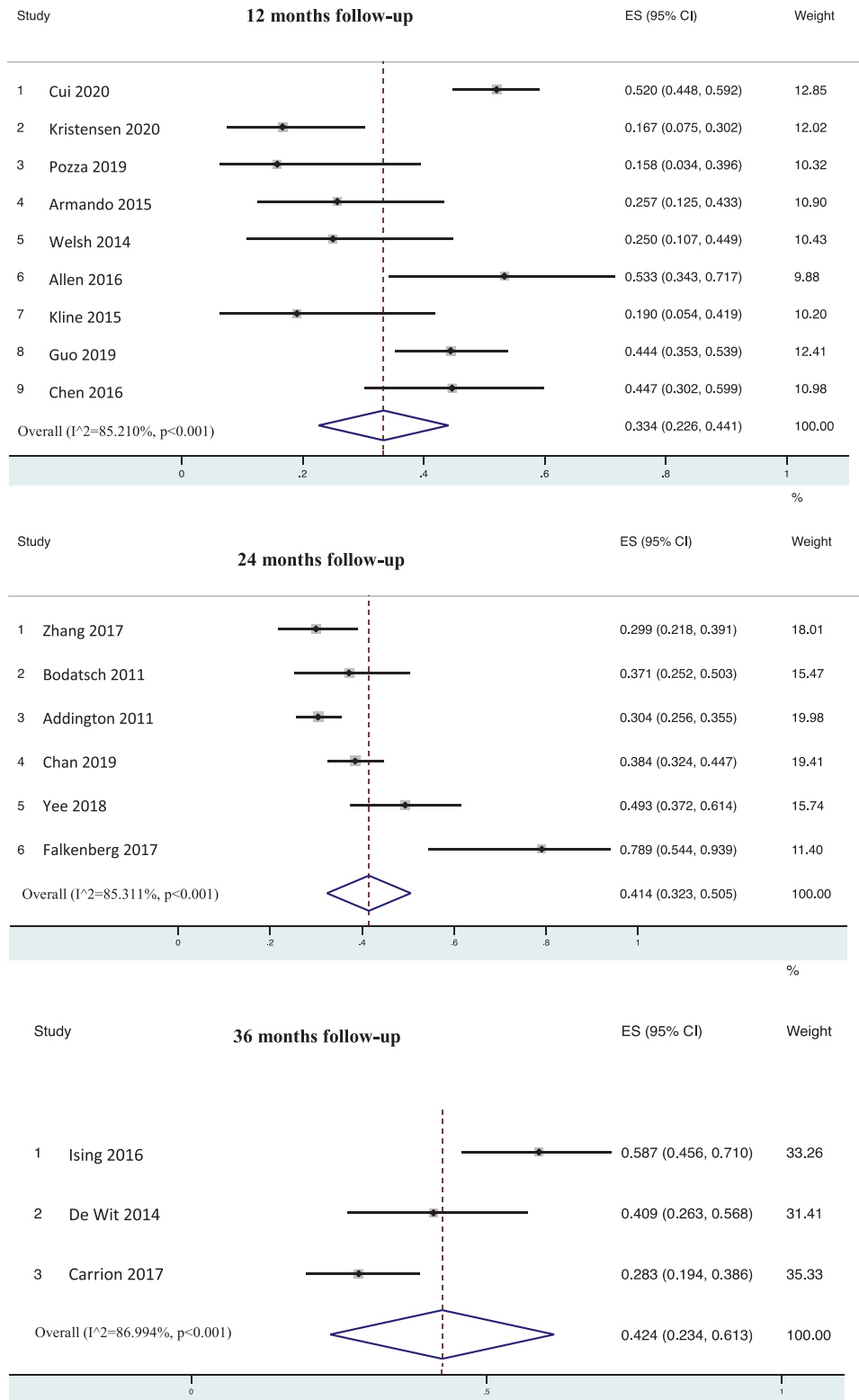


Figure 4. Forest plot remission at follow-up in CHR-P individuals. Error bars indicate 95% CI. Lines indicate individual study results; diamonds indicate overall meta-analytical results. Follow up was considered at 12, 24 and 36 months.

identified indicates that, as well as transition to psychosis, other outcomes are increasingly being evaluated in prospective studies of CHR-P subjects.

The first key finding is that psychopathology and functioning consistently improved within the first 1-2 years in individuals at CHR-P. These improvements appear to be most marked for attenuated

positive symptoms (medium to large Hedges' $g=0.8$ at 1-2 years), followed by depressive symptoms (medium to large Hedges' $g=0.6$ at 1-2 years) and then negative symptoms (medium Hedges' $g=0.5$ at 1 year only). This is similar to the pattern of symptom improvement in first episode psychosis, where positive symptoms improve more than depressive or negative symptoms [41,42]. This pattern is paralleled

by similar functional improvements, with medium to large effects (Hedges' $g=0.7-0.9$) in the first two years. Beyond the defining attenuated positive symptoms, CHR-P individuals frequently present with high levels of baseline negative symptoms— particularly social isolation¹⁹—, which are often the first presenting symptoms [43]. Similarly, functional impairments in CHR-P individuals can be frequent and severe, arguably similar to functional impairments in other psychiatric disorders [9]. These findings provide some indirect support for the clinical staging model of psychotic disorders, which postulates more marked improvements during the earlier stages [2].

Interpretation of these findings is complex. A first hypothesis is that the observed improvements could be secondary to the effects of specific preventive interventions implemented in CHR-P services (70.7% of the studies involved CHR-P clinical services). However, at present, there is no robust evidence to favour any specific preventive intervention over the others for improving the severity of attenuated positive symptoms [24], negative symptoms [25], depressive symptoms [26] or functioning [44,45] in CHR-P individuals [4,16,46]. Furthermore, not all the studies included in the current meta-analysis implemented recommended preventive interventions. An alternative hypothesis may also be that these improvements represent the natural history of the condition, independent of clinical input. However, as noted below, the improvement trajectory is typically discontinued in the long-term. A third hypothesis may be that these symptomatic and functional improvements could also be related to the care that is often provided by CHR-P clinical services, which can include clinical monitoring, crisis management, support, case management, psychosocial assistance, psychoeducation and medications [47–49]. However, as antipsychotic medications typically used in CHR-P clinics do not reach the minimum effective dosage for treating psychotic symptoms [50], their impact on outcomes is questionable.

Furthermore, the possibility of a negative effect of systematically truncated care for CHR-P individuals is supported by our second core finding that the observed improvements were not maintained in the long-term (i.e. at ≥ 3 years). Improvements in attenuated positive and depressive symptoms were not maintained after 3-year follow-up, and in negative symptoms not even beyond the first year. Similarly, the magnitude of functional improvement was reduced at 3 years (from large to small effect size, Hedges' $g=0.4$). It is thus possible that some of the initial improvements are diminished following discharge from clinical CHR-P services. A similar effect has previously been observed for transition to psychosis, the risk of which persists after the cessation of clinical care from CHR-P services [50]. Notably, the baseline severity of attenuated positive, negative/depressive symptoms and functioning are the strongest meta-analytic predictors of outcome in CHR-P samples (attenuated positive symptoms $SMD=0.35$, global functioning $SMD=-0.29$, negative symptoms $SMD=0.39$) [7]. For example, depression has been associated with a reduced likelihood of remission [51] (although not with an increased risk of transition to psychosis [51,52]). Not surprisingly, the lack of sustained symptomatic and functional improvement at 3 years aligns with our additional analysis showing that only 42.4% of CHR-P individuals were in remission at this timepoint. Nevertheless, this estimate is higher than in our previous meta-analysis (1–3 year follow-up: remission of 35.4% [23]). Overall, these findings caution against the argument of “false positives” frequently leveraged to criticise the CHR-P paradigm, particularly in those with help-seeking behaviour, indicating that this group is at risk of displaying several persisting poor mental health outcomes beyond transition to psychosis [53], which are not currently well addressed. In particular, the suboptimal proportion of those remitting from CHR-P status [54] calls for urgent clinical research on this outcome. The development of a clear and widely established definition of favourable outcomes, including remission or recovery, is essential. Furthermore, research on the likely even larger subgroup of people with poor functional outcome may be even more important than whether or not individuals

retained or lost their CHR-P status. Establishing clinical outcomes across multiple domains has the advantages of maximising the numerator of preventable targets against the denominator of efforts and costs [75].

There was high heterogeneity across the observed outcomes. This finding is partially due to the fact that, in contrast to transition to psychosis, there are no standardised criteria to define non-psychotic outcomes in CHR-P groups. Future global collaborative initiatives could take the opportunity to operationalise good outcomes [55,56], such as clinically significant symptomatic and/or functional improvements, remission (or recovery [57]), which is hardly ever reported in the current CHR-P literature) and promotion of good mental health [58]. Our meta-regression analyses showed a positive association between baseline antipsychotic exposure and the magnitude of improvement of attenuated positive symptoms. This is in line with evidence that the therapeutic effects of antipsychotic medications are much greater on positive symptoms than on negative symptoms [57,59]. However, two recent meta-analyses of randomised controlled trials conducted in CHR-P individuals found that antipsychotics were not superior to other interventions for improving APS [24,60]. It is also likely that antipsychotics are initially prescribed to those CHR-P individuals who have higher levels of APS [11,61] and are perceived as being at higher risk of developing psychosis, and therefore have more chances to display relative improvements over follow-up time. Although in the past antipsychotics have been compared to placebo in CHR-P individuals [47], they are currently not recommended by clinical guidelines for CHR-P individuals due to the lack of preventive evidence and low benefit to risk ratio [4].

The main clinical implication of this study is to provide evidence for extending clinical CHR-P care in the long-term, beyond 2 years. This conclusion is supported by evidence that other negative outcomes keep increasing in the long-term (after 2 years), including the risk of psychosis onset, informal and compulsory hospital admissions and cumulative exposure to psychotropic medications [50]. Extending the duration of care might be able to address many of these risks and poor outcomes. Although there is currently no evidence that any specific intervention is more effective than others, our findings suggest that prolonged intervention could be recommended. Such extended care would ideally take place in a stepped care/individualized fashion, providing longer care to those who are in greater need and also varying the content and intensity of specialized or of need-based intervention elements to target individualized goals, as has been suggested for first episode/early psychosis services [62]. These efforts should be refined by precision medicine approaches, which could personalise the efficacy of long-term provision of care, accounting for the individual variability in clinical outcomes [63]. While a plethora of prediction models have been developed and validated on the transition to psychosis and psychosis onset in CHR-P [64–72], only a few have evaluated non-psychotic outcomes [73,74]. Future prognostic and interventional research should address this gap.

This study has several limitations. First, the evidence for some of the evaluated outcomes at some follow-up periods was limited, for instance, for depressive symptoms and remission after ≥ 36 months follow-up (only three cohorts provided this data). However, the database was large and sufficiently powered to test our a priori defined outcomes at most time points. Second, other outcomes that could have been relevant were not assessed, including quality of life, categorically defined functional outcomes or other psychiatric disorders. Third, there was high heterogeneity across studies and samples, which we tried to address in the meta-regression analyses. Fourth, we included a wide range of CHR-P individuals, some of which transitioned to psychosis, who are expected to present worse outcomes throughout the follow-up. Future studies should evaluate these outcomes in both individuals who transition and who do not transition to psychosis. Finally, limited data precluded certain meta-regression analyses. For example, we could not conduct meta-regression

analyses for the duration of untreated APS, proportion of individuals with BS, exposure to antidepressants, exposure to other psychotropics, exposure to psychotherapy, or type of comorbidity.

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Data sharing statement

The studies included in this review were publicly available. Data are available upon reasonable request to the lead or corresponding author.

Contributors

GSdP had full access to the data and take responsibility for its accuracy and reporting. GSdP, FP, VA, JV-S, AC, JP, LS, FC, SK and JDS did the literature search, data selection, and data extraction. All the authors critically revised the manuscript for important intellectual content. Senior academic PF-P provided expert supervision during all stages of elaboration of the study.

Declaration of Competing Interest

Dr Salazar de Pablo has received honoraria from Janssen Cilag and grants from Alicia Koplowitz Foundation. Dr Vaquerizo-serrano has received grants from Alicia Koplowitz Foundation. Dr Moreno has been a consultant to or has received honoraria from Janssen Cilag, Angelini, Servier, Nuvelution, Otsuka, Lundbeck, Pfizer and Esteve outside the submitted work. Prof Gonzalez-Pinto has received grants from the Spanish Ministry of Science and the European Framework and has been a consultant to or has received honoraria from Janssen-Cilag, Angelini, and Roche, support for attending meetings from Janssen, participations in a data advisory board for Janssen, Takeda and Angelini and is president of the Spanish society of Biological Psychiatry and of the Spanish Foundation of Psychiatry and mental health. Dr Díaz-Caneja has received honoraria from AbbVie, Sanofi, Exeltis and Lundbeck. Dr Solmi has been a consultant to or has received honoraria from Angelini and Lundbeck. Prof Arango has received grants or contracts from Bristol-Myers Squibb, Narsad, Sumitomo Dainipon Pharma and Stanley Foundation. He has been a consultant to or has received honoraria or grants from Acadia, Angelini, AstraZeneca, Bristol-Myers Squibb, Gedeon Richter, Janssen Cilag, Lundbeck, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Stanley Foundation, Takeda and Alicia Koplowitz Foundation. Prof Correll has been receiving grants from Janssen, royalties from UpToDate, consulting fees from Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva, payment or honoraria for lectures from Angelini, Gedeon Richter, Janssen/J&J, Lundbeck, Mitsubishi Tanabe Pharma, Mylan, Sumitomo Dainippon, Otsuka, Recordati, Sunovion (no speakers bureau), payment for expert testimony from Janssen and Otsuka, participation on a data safety monitoring Board for Lundbeck, Rovi, Supernus, and Teva, leadership or fiduciary role in other boards for ASCP, receipt of equipment from Takeda and is a shareholder of LB Pharma.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.eclinm.2021.100909](https://doi.org/10.1016/j.eclinm.2021.100909).

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