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Overoptimistic literature and methodological biases favouring cognitive behavioural therapy for the prevention of psychosis

Indicated prevention in young people at Clinical High Risk for Psychosis (CHR-P) originated in Australia more than twenty years ago[1] and subsequently impacted national and international clinical guidelines[2] and diagnostic manuals[3]. While the most recent umbrella reviews (reviews of meta-analyses) demonstrated substantial achievements in detection and prognostic assessment of young CHR-P individuals[4], the most updated network meta-analysis found no robust evidence to favour Cognitive Behavioural Therapy (CBT) compared to the control condition (i.e., needs-based interventions)[5]. An independent pairwise meta-analysis by the Cochrane group corroborated these findings, concluding "there was no convincing unbiased, high-quality evidence" that any type of intervention is more effective than needs-based interventions[6] (two other pairwise meta-analyses were published[7,8] but either used older data[7] than the network and Cochrane meta-analyses or were discussed elsewhere, with significant concerns in regard to study inclusion[8,9]). Overall, these studies cautioned that uncertainty of evidence is high for CBT in preventing psychosis among CHR-P individuals[5,6,10].

In contrast to these cautionary evidence-based findings, a recent pairwise meta-analysis included ten CBT trials and identified robust evidence that "cognitive behavioural therapy is effective in reducing both psychosis transition rates and attenuated psychotic symptoms" over more than two years follow-up[11]. However, this meta-analysis appears to have major methodological problems as well as explicit errors.

First, the authors of this meta-analysis stated that an update was necessary because of the "low-quality of evidence"[11] of published trials included in the latest network/Cochrane meta-analyses[5,6], and state robust trials would require at least 300 CHR-P individuals[11]. No high-quality, large-scale, randomised controlled trials of CBT have been published since the network/Cochrane meta-analyses[5,6]—rather, only three new CBT trials have emerged, one from Italy and two from China[11]. The latter two did not acknowledge registering the trial protocol and admitted utilising "low-intensity CBT"[11] (fewer than the minimum 16 sessions recommended by the NICE QS80[12]) as well as specific contents of their CBT protocol "were not clear"[11]. Accordingly, these two trials were rated as at high risk of bias within the meta-analysis[11]. Furthermore, although these studies enrolled first-degree relatives of schizophrenia patients, they did not clarify whether all trial participants presented with functional impairment, which is necessary to meet the Genetic Risk and Deterioration subgroup of the CHR-P criteria

beyond familial risk[1,4]. The other (small) Italian CBT trial (n=58) by Pozza et al. 2020[13] has several weaknesses relating to the measurement of outcomes, incorrect interpretation of Kaplan–Meier outputs, selective reporting, and failure to adhere to CONSORT guidance (e.g., failure to register the trial)[14]. As a result, we suggested claims made by this study that CBT can prevent psychosis, should be tempered[14]. The authors of the meta-analysis acknowledged that all ten trials included were at high risk of bias or at unclear risk[11]. It is difficult to understand how strong conclusions relating to the effectiveness of CBT for prevention of psychosis could be reached with no trials free of this degree of bias.

Second, but of principal concern, is the presence of numerous data extraction errors, which may have increased the likelihood of the meta-analytic results being significant in favour of CBT. For example, the short-term (within 6-month) meta-analytic forest plot and analysis[11] omit the trial by Morrison et al. 2004 (two transitions in the CBT and three in the control group at 6-month follow-up)[15], which was included in previous meta-analyses[16], as well as the 6-month data from Pozza et al[13]. Other examples include the medium-term (6-12 months) meta-analytic forest plot, which reports one transition in the CBT group for Pozza et al.[11], while the Kaplan-Meier curve in Pozza et al. shows that there are at least three transitions in the CBT group at 12-months[13]. Furthermore, the number of transitions in the CBT arm of McGorry 2013 included at 12-months (four) diverge from the number (seven) indicated by the authors of this trial in previous meta-analyses[17]. The long-term (12-24 months) meta-analytic forest plot omits the follow-up data provided by Pozza et al. at 61 weeks/14-months; these data are rather used in the ultra-long term (more than 24 months) forest plot[11]. The transitions extracted from Bechdolf et al. 2012 in the 6-12 and 12-24 months analyses do not reflect the primary outcome of the meta-analysis (i.e. a transition from a CHR-P state to frank psychosis[11]) but rather the progression from an "early initial prodromal phase" of risk (in which symptoms, disability and biological deficits are less severe than CHR-P) to any later stage, including subthreshold psychosis (i.e. the CHR-P state itself); the data used therefore diverge from those employed by previous meta-analyses[17].

Third, while the authors stated that their literature search was planned to include unpublished literature[11], they failed to include the large CBT trial, PREVENT (n=216, as did the other pairwise meta-analysis[8,9]), which published baseline data a decade ago[18]. While the final manuscript is yet to be published, preliminary findings showing no statistical significance for CBT in preventing psychosis were presented at a major international conference in 2016[19] and included in previous meta-analyses[5]. Publication biases were not formally investigated with funnel plots because of the small number of studies, and no other sensitivity analyses for

publication biases (e.g. trim and fill, fail-safe N) were attempted[11]. Consequently, this meta-analysis could not exclude that its findings may be affected by publication biases[11].

Fourth, a previous umbrella review demonstrated no evidence that CBT impacts other clinical outcomes such as acceptability of treatments, severity of attenuated positive/negative psychotic symptoms, depression, symptom-related distress, social functioning, general functioning, and quality of life[10]. The authors of the meta-analysis confirmed all these findings but report a "robust" effect that CBT improves attenuated psychotic symptoms[11]. This statement conflicts with the small effect size approaching the non-significance level (Standardised Mean Difference = −0.24, 95% CI: −0.43, −0.06), which is unlikely to make any appreciable difference to patients in practice[11].

Given these major methodological biases and explicit errors listed above, the analyses, results and conclusions of this meta-analysis[11] should be corrected, and the record amended. While we caution against presenting meta-analyses without full and transparent reporting, to demonstrate the potential impact of these errors we have repeated the medium term (6-12 months) meta-analysis after removing the biased studies (one Chinese study and Pozza et al.[13]), adding PREVENT and amending the transitions: the updated risk ratio for CBT vs control interventions to prevent transition to psychosis at 12 months is 0.635 (95% CI: 0.391-1.029, p=0.065, random effect models), which shows no significant meta-analytic evidence that CBT can robustly prevent transition to psychosis. Furthermore, to avoid multiple testing every time a new CBT trial is being published, meta-analyses that regularly update the evidence given an a priori sample size would be required in this field[10].

Overall, we conclude that the lack of robust meta-analytic evidence to favour CBT to prevent psychosis, as appraised by the most recent network meta-analysis[5] and the Cochrane meta-analysis[6], still stands. Transparent appraisal of limitations of knowledge is a prerequisite for any reliable scientific advancements. The lack of robust meta-analytic evidence to favour CBT aligns with its "black box" mechanism of action[20] and uncharted side effects[21], particularly in vulnerable minorities[22]. Collegial and global initiatives combining individual participant data meta-analyses, experimental therapeutics, strategies to control risk enrichment, innovative youth mental health services, adaptive trial designs, stratification and precision medicine approaches will hopefully deliver effective interventions to prevent psychosis in these individuals[10].

Paolo Fusar-Poli[1,2], Joaquim Radua[1,3,4], Cathy Davies[1], Sameer Jauhar[1]

1 Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; OASIS Service, South London and Maudsley NHS Foundation Trust, London, UK; 2 Department of Brain and Behavioral Science, University of Pavia, Pavia, Italy; 3 Imaging Mood- and Anxiety-Related Disorders (IMARD) group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); Mental Health Research Networking Center (CIBERSAM); Barcelona, Spain; 4 Centre for Psychiatric Research and Education, Department of Clinical Neuroscience, Karolinska Institutet.

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