Figure 1: Study selection

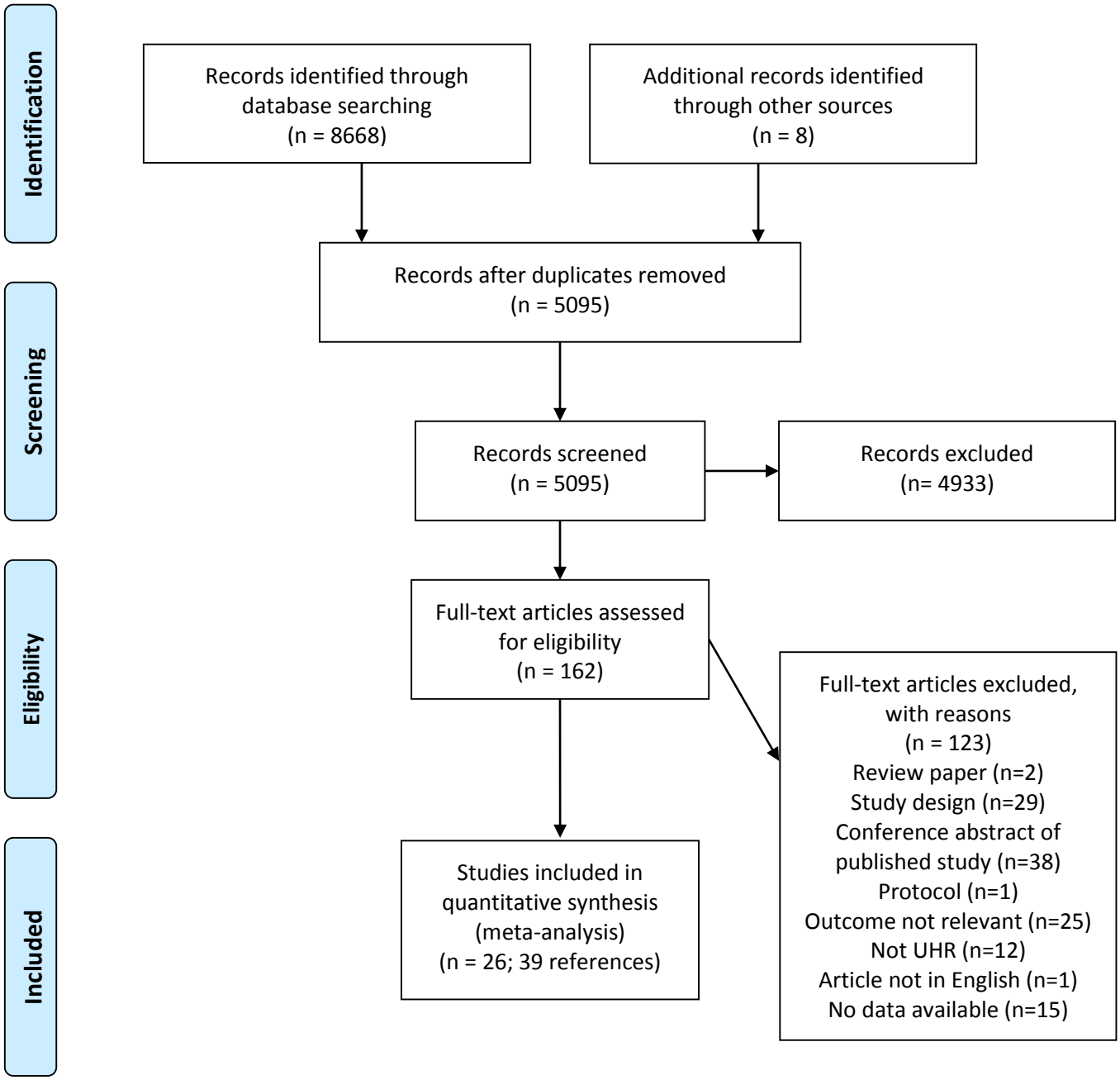
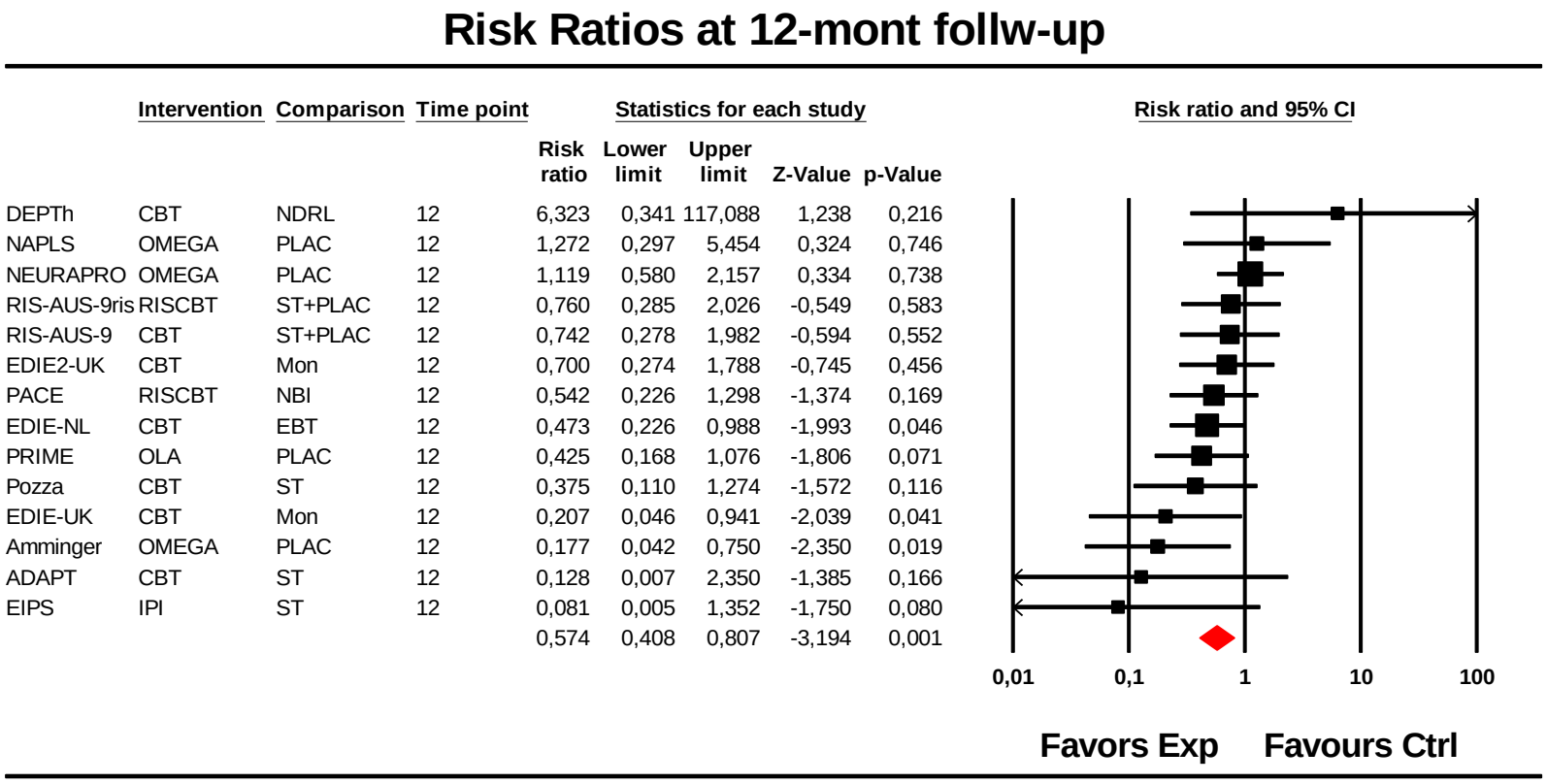
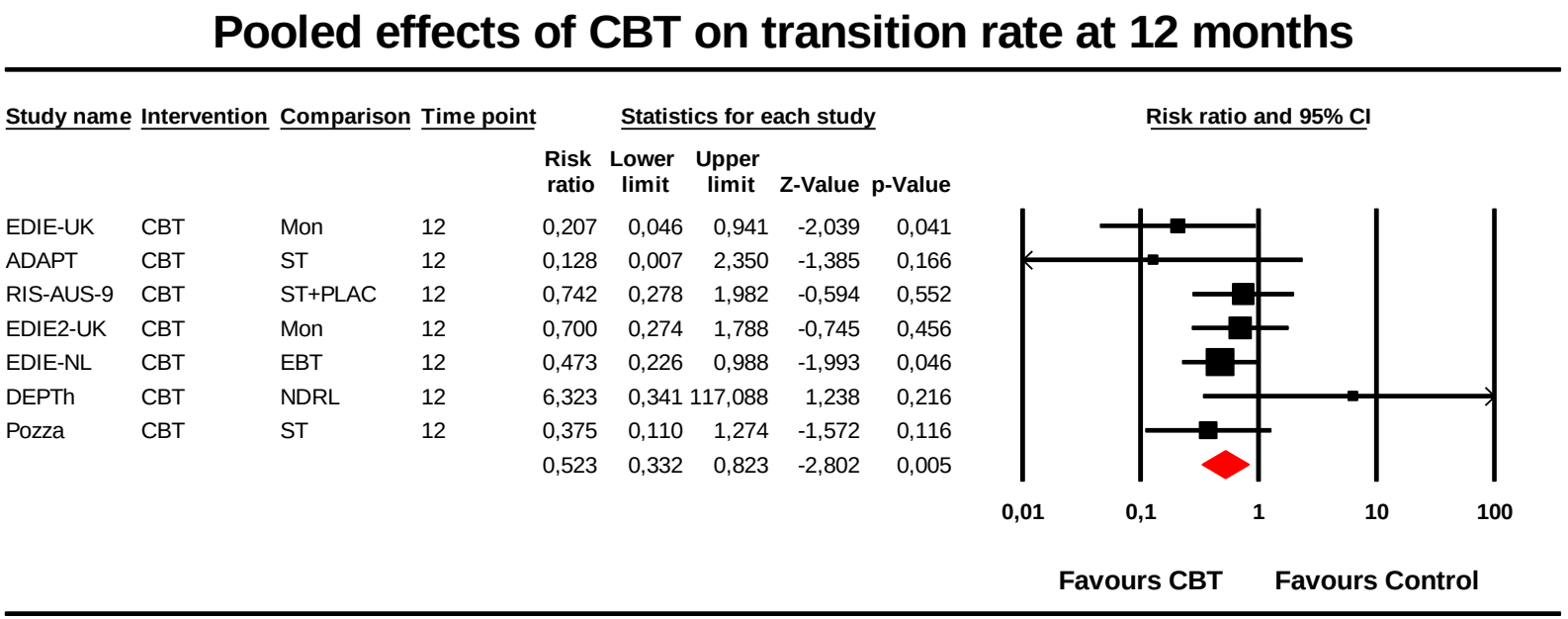


Figure 2: Risk ratios of individual contrasts in the prevention of transition to psychosis at 12-months follow-up



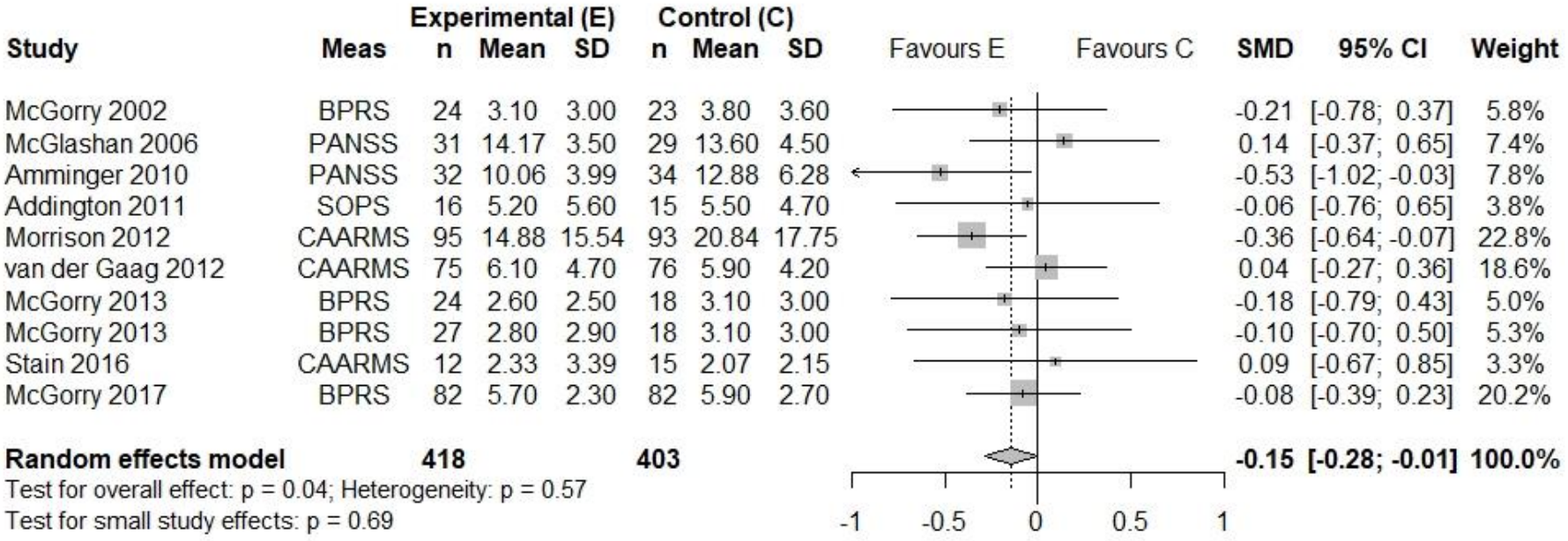
CBT=Cognitive Behavioral Therapy; OMEGA=Omega-3 fatty acids; RISCBT=Risperidone plus Cognitive Behavioral therapy; OLA=Olanzapine; IPI=Integrated psychological Intervention; NDRL=Non-directive reflective listening; PLAC=Placebo; Mon=monitoring; ST=Supportive therapy; EBT=Evidence based therapy; NBI=Needs-based intervention

Figure 3: The pooled risk ratio of CBT versus any control on risk of transition to psychosis at 12 months follow-up



CBT=Cognitive behavioral therapy; Mon=Monitoring; ST=Supportive therapy; PLAC=Placebo; EBT=Evidence-based therapy for help-seeking disorder; NDRL=Non-directive Reflective Listening

Figure 4: The pooled standardized mean difference of all experimental interventions versus any control on attenuated positive psychotic symptoms at 12-months



BPRS = Brief Psychiatric Rating Scale; CAARMS = Comprehensive Assessment of At-Risk Mental States; PANSS = Positive and Negative Syndrome Scale; SOPS = Scale of Prodromal Symptoms.

Table 1: Characteristics of included studies

Study (first author, year)	Acronym	Country	Transition instrument	Intervention duration (months)	Assessment time points (months)	Experimental condition				Control condition			
						Intervention	n	Age, Mean (SD)	Sex, % Male	Control	n	Age, Mean (SD)	Sex, % Male
Addington (2011b)	ADAPT	Canada	SOPS	6	6, 12, 18	CBT	27	20.8 (4.5)	67%	ST	24	21.1 (3.7)	75%
Amminger (2010; 2015)	Amminger	Austria	PANSS	3	3, 6, 12, 84	Omega-3	41	16.8 (2.4)	41%	Placebo	40	16.0 (1.7)	39%
Appiah-Kusi (2020)	Appiah-Kusi	UK	NA	1wk	1wk	CBD	16	22.3 (5.1)	63%	Placebo	17	25.1 (5.4)	41%
Bechdolf (2012; 2007)	EIPS	Germany	PANSS	12	12, 24	IPI	63	25.2 (5.4)	62%	ST	65	26.8 (6.2)	65%
Cadenhead (2020; 2017)	NAPLS	US	SOPS	6	12, 24	Omega-3	65	19.0 (4.7)	59%	Placebo	62	18.4 (4.7)	53%
Choi (2017)	Choi	US	NA	2	2, 4	Processing speed training	30	18.2 (3.8)	52%	Common tablet games	32	18.5 (3.7)	50%
Friedman-Yakoobian (in press)	CLUES	US	NR	6	6, 9	Social- and neurocognitive remediation	20	19.2 (2.9)	55%	Enriched acceptance and commitment therapy	18	19.1 (3.0)	67%
Glenthøj (in press)	FOCUS	Denmark	NA	6	6, 12	Cognitive remediation + TAU	73	23.9 (4.7)	48%	TAU	73	23.9 (3.8)	40%
Kantrowitz (2015)	Kantrowitz	US	SOPS	4	4	D-serine	20	20 (4.9)	53%	Placebo	24	19 (3.5)	75%
Loewy (2016)	Loewy	US	NA	2	2	Auditory training	50	17.8 (3.1)	52%	Computer games	33	18.7 (4.6)	48%
McFarlane (2016; 2011)	EDIP	US	SOPS	24	24	FA-ACT	50	16.5 (3.1)	52%	ET	50	16.1 (2.8)	52%
McGlashan (2006; 2003)	PRIME	US, Canada	PPS	12	12, 24	Olanzapine + supportive psychosocial interventions	31	18.2 (5.5)	68%	Placebo + supportive psychosocial interventions	29	17.2 (4.0)	62%
McGorry (2002); Phillips (2007)	PACE	Australia	BPRS	6	6, 12, 36-48	CBT + risperidone	31	20 (4)	65%	NBI	28	20 (3)	50%
McGorry (2017); Nelson (2018b)	NEURAPRO	Multinational	BPRS	6	6, 12, 18-68	Omega-3 + CBCM	153	19.4 (4.8)	51%	Placebo + CBCM	151	18.9 (4.3)	40%
Miklowitz (2014)	Miklowitz	US, Canada	SOPS	6	6	Family-focused therapy	66	17.3 (4.2)	59%	Enhanced care	63	17.4 (3.9)	56%

Morrison (2007; 2004)	EDIE-UK	UK	PANSS	6	6,12, 36	CBT	37	20.6 (4.9)	60%	Monitoring	23	21.5 (5.2)	83%
Morrison (2012)	EDIE2-UK	UK	CAARMS	6	6, 12, 18, 24	CBT + monitoring	144	20.7 (4.2)	62%	Monitoring	144	20.8 (4.5)	63%
Piskulic (2015)	Piskulic	Canada	NA	3	3, 9	Brain fitness program	18	19.7 (5.7)	61%	Computer games	14	17.5 (3.5)	71%
Pozza (2020)	Pozza	Italy	CAARMS	7	7, 14	CBT	29	25.4 (6.1)	66%	ST	29	26.0 (6.0)	69%
Shi (2017)	Shi	China	SOPS	6	6	Systemic therapy	13	18.9 (1.0)	31%	ST	13	18.9 (1.3)	62%
Stain (2016)	DEPTh	Australia	CAARMS	6	6, 12	CBT + TAU	30	16.2 (2.7)	33%	NDRL + TAU	27	16.5 (3.2)	48%
Urben (2012); Holzer (2014)	Urben	Switzerland	NA	2	2, 6	Computer assisted cognitive remediation	7	15.9 (1.4)	29%	Computer games	5	15.8 (1.6)	60%
van der Gaag (2012); Ising (2016); Rietdijk (2010)	EDIE-NL	Netherlands	CAARMS	6	6, 12, 18, 48	CBT + TAU	98	22.9 (5.6)	50%	TAU	103	22.6 (5.5)	49%
Woods (2013)	Woods-GL	US	SOPS	3	3	Glycine	4	15.3 (0.5)	75%	Placebo	4	16.5 (2.4)	75%
Woods (2017; 2016)	Woods-DS	US	SOPS	6	6	Ziprasidone	23	21.9 (4.7)	57%	Placebo	27	22.6 (3.7)	70%
Yung (2011); McGorry (2013); Phillips (2009)	RIS-AUS-9	Australia	BPRS	12	6,12	CBT+ risperidone CBT+ placebo	43 44	17.6 (3.0) 18.0 (2.7)	35% 39%	ST+ placebo	28	18.8 (3.7)	46%

BPRS, Brief Psychiatric Rating Scale; CAARMS, Comprehensive Assessment of At-Risk Mental States; CBCM, cognitive behavioral case management; CBD, cannabidiol; CBT, cognitive behavioral therapy; ET, enhanced assertive community treatment; FA-ACT, Family-aided Assertive Community treatment; IPI, integrated psychological intervention; NA, not applicable; NBI, needs-based intervention; NDRL, non-directive reflective listening; NR, not reported; PANSS, Positive and Negative Syndrome Scale; PPS, Presence of Psychosis Scale; SOPS, Scale of Psychotic Symptoms; ST: supportive therapy; TAU, treatment as usual.

Table 2: Quality ratings of the studies using the Clinical Trials Assessment Measure (CTAM)

Study	Total (100)	Sample (10)	Allocation (16)	Assessment (32)	Control group (16)	Analysis (15)	Active control (11)
Amminger et al. (2010; 2015)	81	7	16	16	16	15	11
Addington et al. (2011b)	76	2	13	29	16	5	11
Appiah-Kusi et al. (2020)	53	2	10	16	10	9	6
Bechdolf et al. (2007; 2012)	53	7	13	6	6	15	11
(Cadenhead et al., 2017)	63	7	10	16	16	11	3
Choi et al. (2017)	77	7	10	29	10	15	6
Friedman-Yakoobian et al. (in press)	53	0	10	16	10	11	6
Glenthøj et al. (in press)	84	7	16	29	6	15	11
Kantrowitz et al. (2015)	71	2	16	29	16	5	3
Loewy et al. (2016)	57	7	10	16	10	11	3
McFarlane et al. (2011)	60	7	10	16	16	5	6
McGlashan et al. (2006)	63	7	10	13	16	11	6
McGorry et al. (2002); Phillips et al. (2007)	80	7	10	26	16	15	6
McGorry et al. (2017); Nelson et al. (2018b)	89	7	16	29	16	15	6
Miklowitz et al. (2014)	91	7	13	29	16	15	11
Morrison et al. (2004; 2007)	67	2	16	26	16	15	6
Morrison et al. (2012)	87	7	16	32	6	15	11
Piskulic et al. (2015)	59	2	10	26	10	8	3
Pozza and Dèttore (2020)	97	7	16	32	16	15	11
Shi et al. (2017)	45	2	10	16	6	5	6
Stain et al. (2016)	94	7	16	29	16	15	11
Urben et al. (2012); Holzer et al. (2014)	63	7	16	16	10	11	3
van der Gaag et al. (2012); Ising et al. (2016)	87	7	16	32	6	15	11
Woods et al. (2013)	49	2	10	16	6	9	6
Woods et al. (2017)	26	2	10	0	6	5	3
Yung et al. (2011); McGorry et al. (2013)	81	7	16	16	16	15	11

Maximum total score is 100. Total scores below 65 indicate poorer methodological quality.

Table 3: (Pooled) Risk Ratios of interventions targeted to prevent the transition to psychosis at different measurement time points

Intervention	[k] RR (95%CI) Q(df), p I^2 (95%CI)	[k] RR (95%CI) Q(df), p I^2 (95%CI)	[k] RR (95%CI) Q(df), p I^2 (95%CI)	[k] RR (95%CI) Q(df), p I^2 (95%CI)
	End of treatment	6 months	12 months	18 plus months
Olanzapine	[1] 0.43 (0.17-1.08)		[1] 0.43 (0.17-1.08)	
Ziprasidone	[1] 0.59 (0.06-6.01)	[1] 0.59 (0.06-6.06)		
D-Serine	[1] 0.60 (0.06-6.14)			
Glycine	[1] 0.33 (0.02-6.37)			
Omega-3 Fatty Acids	[3] 0.79 (0.23-2.69) Q(2)=4.68, p=0.10 I^2=57 (0-86)	[2] 0.39 (0.03-5.02) **Q(1)=5.53, p=0.02** **I^2=82 (n.a.)**	[3] 0.69 (0.23-2.11) Q(2)=5.49, p=0.06 I^2=64 (0-88)	[2] 0.51 (0.10-2.55) Q91)=3.35, p=0.07 I^2=70
ALL PHARMACOLOGICAL	[7] 0.67 (0.37-1.22) Q(6)=6.93, p=0.33 I^2=13 (0-64)	[3] 0.47 (0.09-2.43) Q(2)=5.59, p=0.06 I^2=64 (0-88)	[4] 0.62 (0.27-1.40) Q(3)=7.18, p=0.07 I^2=58 (0-84)	[2] 0.51 (0.10-2.55) Q91)=3.35, p=0.07 I^2=70
Risperidone + Cognitive Behavioral Therapy	[2] 0.48 (0.18-1.31) Q(1)=1.73 p=0.19 I^2=42 (n.a.)	**[2] 0.35 (0.13-0.95)** Q(1)=0.59, p=0.44 I^2=0 (n.a)	[2] 0.63 (0.33-1.21) Q(1)=0.26, p=0.61 I^2=0 (n.a.)	[1] 0.75 (0.39-1.47)
Cognitive Behavioral Therapy	**[7] 0.55 (0.31-0.99)** Q(6)=7.09, p=0.31 I^2=15 (0-65)	[7] 0.57 (0.29-1.13) Q(6)=7.75, p=0.26 I^2=23 (0-67)	**[7] 0.52 (0.33-0.82)** Q(6)=6.36, p=0.38 I^2=6 (0-61)	**[6] 0.60 (0.42-0.84)** Q(5)=2.09, p=0.84 I^2=0 (0-61)
Systemic Therapy	[1] 0.33 (0.02-7.50)	[1] 0.33 (0.02-7.50)		
Family intervention	[1] 0.17 (0.02-1.41)	[1] 0.17 (0.02-1,41)		
Family-aided Assertive Community treatment	[1] 0.71 (0.24-2.10)			[1] 0.71 (0.24-2.10)
Cognitive Behavioral Therapy + skills training + cognitive remediation + multifamily psychoeducation	[1] 0.08 (0.01-1.35)		[1] 0.08 (0.01-1.35)	[1] 0.16 (0.02-1.17)
ALL PSYCHOLOGICAL	**[11] 0.52 (0.33-0.82)** Q(10)=10.33, p=0.41 I^2=3 (0-53)	**[9] 0.51 (0.28-0.92)** Q(8)=8.97, p=0.35 I^2=11 (0-59)	**[8] 0.50 (0.31-0.80)** Q(7)=8.01, p0.33 I^2=13 (0-62)	**[8] 0.58 (0.42-0.80)** Q(7)=3.89, 0=0.79 I^2=0 (0-59)

k=number of studies; RR=Risk Ratio; 95%CI=95 percent confidence interval; Q=Chi2 for heterogeneity with p significance level;
I^2=Heterogeneity (0 to 100); Q can only by calculated if k>1; The 95%CI of I^2 can only be calculated at k>2. Bold means statistical significance.

Preventive interventions for individuals at ultra high risk for psychosis: An updated and extended meta-analysis

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Abstract

Intervention at the earliest illness stage, in ultra or clinical high-risk individuals, or indicated prevention, currently represents the most promising strategy to ameliorate, delay or prevent psychosis. We review the current state of evidence and conduct a broad-spectrum meta-analysis of various outcomes: transition to psychosis, attenuated positive and negative psychotic symptoms, mania, depression, anxiety, general psychopathology, symptom-related distress, functioning, quality of life, and treatment acceptability. 26 randomized controlled trials were included. Meta-analytically pooled interventions reduced transition rate (risk ratio [RR]=0.57, 95%CI 0.41–0.81) and attenuated positive psychotic symptoms at 12-months (standardized mean difference=-0.15, 95%CI=-0.28–-0.01). When stratified by intervention type (pharmacological, psychological), only the pooled effect of psychological interventions on transition rate was significant. Cognitive behavioral therapy (CBT) was associated with a reduction in incidence at 12-months (RR=0.52, 95%CI=0.33–0.82) and 18-48-months (RR=0.60, 95%CI=0.42–0.84), but not 6-months. Findings at 12-months and 18-48-months were robust in sensitivity and subgroup analyses. All other outcomes were non-significant. To date, effects of trialed treatments are specific to transition and, a lesser extent, attenuated positive symptoms, highlighting the future need to target other symptom domains and functional outcomes. Sound evidence supports CBT in reducing transition and the value of intervening at this illness stage.

Study registration: Research Registry ID: reviewregistry907

Key words: ultra-high risk, psychosis, prevention, cognitive behavior therapy, omega-3 fatty acid, family intervention

1. Introduction

1.1 The UHR paradigm: Risk for psychosis and need for care for emerging mental illness

The development of the ultra-high risk (UHR) criteria, as part of a new early intervention approach to psychosis in the early 1990s, to detect individuals at high and imminent risk of developing first episode psychosis (FEP) (Yung et al., 1996) was a major advance in the potential for indicated prevention of psychosis. In fact, indicated prevention in psychosis is really a form of early intervention, given that these patients are already highly symptomatic, help-seeking and functionally impaired. True primary prevention (universal and selective) is, of course, not yet achievable. Since the first studies of this early stage of illness were conducted over two decades ago, rates of transition to psychosis in UHR samples have declined from an initial level of 40% (Yung et al., 2003), and it is currently estimated that 22% of UHR cases develop a psychotic disorder over the medium term (Fusar-Poli et al., 2020b). This decline has not been adequately explained (Hartmann et al., 2016; Nelson et al., 2016; Yung et al., 2007) but it could represent true incidence reduction due to the positive impact of improved clinical interventions (Nelson et al., 2020b). However, even those individuals who do not develop sustained psychosis remain at risk of a range of other adverse outcomes, including persistent attenuated positive psychotic symptoms (in 28-71% of cases), persistent negative psychotic symptoms (6-19%), persistent or incident non-psychotic disorders, notably anxiety and depression (70%), and impaired psychosocial functioning (~50%) (Beck et al., 2019; Devoe et al., 2020b; Lin et al., 2015; Yung, Nelson, McGorry, Wood, & Lin, 2019).

Although preventing the worsening of psychotic symptoms and transition to sustained psychosis is a core target of treatment, the heterogenous clinical trajectories and risk factors for psychosis (Fusar-Poli et al., 2020b; Polari et al., 2018) have led to the increasing

recognition that treatment targets during the UHR stage should be broadened to address the range of clinical and functional needs (McGorry, Hartmann, Spooner, & Nelson, 2018; van der Gaag, van den Berg, & Ising, 2019; Yung, Nelson, Thompson, & Wood, 2010). The persistence of attenuated psychotic symptoms has been associated with a significantly worse clinical profile (compared to remitted cases) characterized by lower levels of functioning and more severe negative, anxiety and depressive symptoms (Cropley et al., 2016), while persistent negative symptoms have been associated with poor long-term social functioning and quality of life (Yung et al., 2019). In addition to consistent evidence indicating that UHR status is a marker of poor prognosis transdiagnostically (Addington et al., 2011a; Hazan et al., 2020; Lin et al., 2015), recent evidence suggests that co-morbid depression reduces the probability of remitting from UHR status (Kline et al., 2018). Even when remission is achieved, functional levels often remain significantly impaired (de Wit et al., 2014), in line with evidence that functional impairment is not solely dependent on positive symptoms and psychosis onset (Carrión et al., 2013). Impairments in functioning often remain stable (Cornblatt et al., 2012), with nearly a quarter of UHR patients experiencing consistent levels of severe impairment (in addition to severe symptom severity) over a 2-year period (Allswede et al., 2019).

1.2 Twenty years of intervention research in UHR: A success story?

It was recognized very early on that UHR patients, while being in the early stages of a mental illness, were distressed, impaired and manifesting a clear-cut “need for care”, despite not meeting traditional thresholds for a psychotic diagnosis (Fusar-Poli et al., 2015). This recognition justified sustained efforts to improve the outcomes of UHR patients, and to examine the effectiveness of a range of preventive or proactive interventions in randomized controlled trials (RCTs). Initial meta-analyses confirmed that receiving *any* trial intervention

(e.g., cognitive behavioral therapy [CBT], omega-3 fatty acids, antipsychotic medication) reduced transition to psychosis by 54% at 12-months (van der Gaag et al., 2013). The effects of psychological and pharmacological treatments on functioning, positive and negative symptoms, depression, mania, symptom-related distress and quality of life were not as promising (Hutton & Taylor, 2014; Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013), although CBT was associated with a small effect on overall symptoms at 12-months (Hutton & Taylor, 2014). However, the lack of significant treatment effects on these outcomes may have been due in part to a lack of power, reflecting the limited number of trials available that examined non-transition outcomes. At present, only CBT has shown demonstrable effectiveness in UHR samples across several pairwise meta-analyses (Bosnjak Kuharic, Kekin, Hew, Rojnic Kuzman, & Puljak, 2019; Hutton & Taylor, 2014; Stafford et al., 2013; van der Gaag et al., 2013). In earlier meta-analyses, the pooled risk ratio (RR) for CBT varied from 0.47 (Stafford et al., 2013) to 0.54 (Hutton & Taylor, 2014), indicating that the risk of psychosis was reduced by 53% and 46%, respectively. The quality of evidence was moderate in Stafford et al. (2013), and Hutton and Taylor (2014) reported that all studies were at least concealed with random allocation. Recent pairwise meta-analytic evidence confirmed the efficacy of CBT on reducing transition (Devoe, Farris, Townes, & Addington, 2020a), with trend-level reductions in attenuated psychotic symptoms (Devoe, Farris, Townes, & Addington, 2019a). This research has shown that it is possible to “bend the curve” on incidence and early course of psychotic illness to a certain extent.

1.3 Efficacy and superiority

Network meta-analyses (NMAs) have indicated that no treatment is currently superior to other treatments during the UHR stage of illness (Davies et al., 2018a; Davies et al., 2018b;

Devoe et al., 2019a, 2020a). This fact had been already recognized by earlier authors (Preti & Cella, 2010; van der Gaag et al., 2013). The absence of superiority does not mean that all interventions have been proven effective or ineffective. If we inspect efficacy in pairwise meta-analyses, then the effectiveness of CBT is statistically significant. Other interventions may be effective too, but just lack sufficient evidence to reach statistical power at the moment. In depression for instance, several different interventions, such as CBT, interpersonal therapy and problem-solving therapy, have comparable benefits without one intervention being superior to the other interventions (Barth et al., 2013).

1.4 Technical aspects of meta-analysis and UHR outcomes

Compared to pairwise meta-analysis, NMA does have the advantage of making optimal use of all available evidence by combining multiple comparisons in one analysis and by using direct and indirect evidence (i.e., the relative effectiveness of intervention A versus B is deduced by triangulation with intervention C). NMAs consequently produce more precise estimates of the differences between treatments, have greater statistical power, and can present consolidated comparisons among alternative treatments (Mavridis, Giannatsi, Cipriani, & Salanti, 2015). Heterogeneity is an issue in pairwise and network meta-analyses and is caused, among other factors, by variation within the same treatment modality (e.g., treatment dose), gender ratios, baseline symptom severity, therapist experience, and blind ratings. Transitivity (the assumption that potential effect modifiers are similarly distributed across comparisons) is an additional prerequisite for NMAs but is often violated as an assumption as patients could never have been randomized across multiple studies: patients can only be randomized over conditions within one study. Study samples can differ considerably despite meeting the same intake criteria, reflecting local circumstances.

Multiple effect moderators may cause inconsistency between direct and indirect evidence. Although there is a statistical check on consistency, confidence intervals become very large if too many head-to-head comparisons are missing and have to be estimated indirectly. Meta-analysis attempts to gain statistical power to detect pooled effects, but NMAs may in fact lose power if too much evidence is estimated indirectly.

This is the likely scenario in two recent NMAs. The first found a trend-level effect for CBT on attenuated psychotic symptoms at 12-months in a pairwise meta-analysis and no significant effects in the NMA (Devoe et al., 2019a). The authors concluded that a lack of direct comparisons and a limited number of trials may have increased the chances of type 2 error. In another NMA, no effects on transition rates were found, but "many nodes were not well connected, with the corollary of limited ability to check for inconsistency, more imprecise estimates and wide 95% CIs…– suggesting that true effects may be substantially different from the estimates" (Davies et al., 2018a). This is an understatement. Of the 55 comparisons at 6-months, 54 were estimated indirectly and only one comparison was based on direct evidence. This indicates that the use of NMAs in the field of UHR for psychosis may well be premature. More direct comparisons between interventions are needed, so that findings can be interpreted with greater confidence. Another approach, based on clinical staging, is the use of sequential multiple assignment randomized trial (SMART) methodologies, where a stepwise intervention approach is offered, which mirrors the way clinicians work, guided by safety and choice considerations (Nelson et al., 2018c).

A further issue of recent meta-analyses is that the bar or target for improvement has been set too high. A living meta-analysis (i.e., a meta-analysis that is continually updated) on CBT

for preventing psychosis set the target at a minimum 50% transition reduction with a power of 0.90 (Fusar-Poli et al., 2019). The argument for such a high risk ratio is based on the fact that trials to date have not been powered to detect smaller effect sizes. CBT in fact produces a risk reduction rate of ~45% and a number needed to treat (NNT) of ~13 (van der Gaag et al., 2013), indicating that 13 patients would need to be treated to prevent transition in one additional patient. CBT therefore failed the arbitrary threshold set by the authors. The bar should be set at the level of an agreed clinically important benefit. In another recent pairwise meta-analysis of the range of UHR interventions trialed, the significant findings for CBT on transition to psychosis at 12-months (RR=0.47, 95% CI 0.29-0.76; NNT=13) were minimized (Bosnjak Kuharic et al., 2019). Setting such an inappropriately high bar in order to regard an intervention as being of value would not be accepted in other medical disciplines such as type 1 diabetes (Dayan, Korah, Tatovic, Bundy, & Herold, 2019) and cardiovascular disease (Chou et al., 2016; Saglietto et al., 2020). Atrial fibrillation catheter ablation has a 3.5 year hazard ratio (HR) of 0.64 (NNT=33) to prevent heart failure/hospitalization; a HR of 0.63 (NNT=59) to prevent stroke; and a HR of 0.62 (NNT=28) to prevent mortality (Saglietto et al., 2020). Cholesterol reduction by statin has a RR of 0.70 (NNT=72) to prevent composite cardiovascular outcomes; a RR of 0.64 (NNT=123) to prevent myocardial infarction; a RR of 0.71 (NNT=263) to prevent stroke; and a RR of 0.82 (NNT=500) to prevent cardiovascular mortality (Chou et al., 2016). Both treatments are well accepted and used globally.

1.5 The need for a fresh look

There is concern that the findings, and especially their interpretation, from recent network meta-analyses of non-superiority have created the perception that current interventions are not effective (McGorry, Mei, Hartmann, Yung, & Nelson, in press; McGorry & Nelson, 2020;

McGorry et al., 2020; Nelson et al., 2020a; Nelson, Amminger, & McGorry, 2018a; Nelson et al., 2020b). Although superiority over other therapeutic options has not been demonstrated via NMA, which is not unexpected, pairwise meta-analyses have shown clear benefits in favor of CBT. At a clinical level, differences in interpretation of the evidence pose challenges for frontline clinicians in ensuring that all patients are provided with evidence-based care. Since the publication of the recent meta-analyses, five new RCTs have been published, which includes a trial of integrated social- and neurocognitive remediation that reported medium sized effects on social functioning (Friedman-Yakoobian, Parrish, Eack, & Keshavan, in press), an area that has been resistant to treatment in previous trials (Devoe, Farris, Townes, & Addington, 2019b). For these reasons, we believe a new pairwise meta-analysis with a wider focus and more careful interpretation is needed.

The present meta-analysis addresses a further issue. Transition rates have declined over the years (Formica et al., in press), potentially due to increased attention to the early stages of psychosis onset, resulting in earlier detection and intervention (Nelson et al., 2020b). Consequently, intervention trials with lower transition rates lose statistical power. Our analysis has compared studies with low and high transition rates.

In the current work, we conducted pairwise meta-analyses with the updated database (searched until March 2020; most recent study published in September 2020) of all preventive interventions. We included reports with participants who fulfilled criteria of UHR or At Risk Mental State, who received any preventive treatment, compared against any control, in an RCT. Recognizing the need to broaden treatment outcomes for this population, the current work extended our previous 2013 meta-analysis of 10 studies with 1,150 participants focused

specifically on transition to psychosis (van der Gaag et al., 2013) to 26 studies with 2,351 participants focused on 12 outcomes, which included the primary outcome of transition to psychosis and secondary outcomes encompassing symptomatology, functioning, quality of life and treatment acceptability.

2. Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & The Prisma Group, 2009) and was registered with Research Registry (ID: reviewregistry907).

2.1 Search strategy

Seven electronic databases were searched from inception to March 13, 2020: Medline, PsycINFO, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, Web of Science (excluding Medline), and ProQuest Dissertations and Theses. The search was for peer-reviewed and unpublished RCTs comparing any intervention with another control condition in individuals at UHR for psychosis. The search strategy is available in the supplemental material (Appendix 1). The searches were restricted to English-language articles. We manually searched the reference lists of included studies and recent systematic reviews and meta-analyses (Bosnjak Kuharic et al., 2019; Davies et al., 2018a; Davies et al., 2018b; Devoe et al., 2019a, 2019b; Devoe, Peterson, & Addington, 2018). An additional grey literature search was performed on OpenGrey and clinical trial registries (ClinicalTrials.gov, EU Clinical Trials Register, WHO International Clinical Trials Registry Platform, ISRCTN Registry, and Australian New Zealand Clinical Trials Registry).

2.2 Screening and selection criteria

The titles and abstracts of identified studies were independently screened for eligibility by three authors (CM, MB, MK) in pairs of two. Relevant full-text articles were reviewed against the inclusion and exclusion criteria. Any disagreements were resolved by a fourth author (BN).

Studies were eligible for inclusion if they met the following criteria: (a) original empirical study written in English, (b) RCT, including crossover designs, of any intervention (pharmacological and non-pharmacological, including combination) that was compared against any control condition, and (c) participants were at clinical high risk for psychosis, as defined by meeting either UHR for psychosis or basic symptoms criteria (e.g. Comprehensive Assessment of At-Risk Mental States, CAARMS; Structured Interview for Psychosis Risk Symptoms, SIPS; Scale of Prodromal Symptoms, SOPS; Schizophrenia Proneness Instrument, Adult, SPI-A). We excluded quasi-randomized trials, single dose trials, conference abstracts reporting overlapping data, and trials that involved participants with a diagnosis of schizotypal disorder.

2.3 Outcomes

The primary outcome was transition to psychosis at 12-months. The number of all randomized subjects was used in risk ratios. We chose to handle dropouts as non-transitioned cases since dropouts in general have lower symptoms and better functioning at baseline (Ising et al., 2016). Secondary outcomes were attenuated positive and negative psychotic symptoms, mania, depression, anxiety, general psychopathology, symptom-related distress, global and social functioning, quality of life, and treatment acceptability (all-cause discontinuation) at 12-months. Secondary time points of interest were end-of-treatment, 6-

month follow-up, and 18+ month follow-up. Details on outcome definitions and measures are provided in Table S1.

2.4 Data extraction

Outcome data were independently extracted from the included trials by a single author for transition (MG) and non-transition variables (HPY). The following information was also recorded: first author, year of publication, country, outcomes reported and measurement tool, intervention type and duration, control condition, duration of follow-up, and sample characteristics for each treatment arm (sample size, age, gender).

For the EIPS study we used the transition to psychosis rates and not the rates of transition to subclinical symptoms (Bechdolf et al., 2012). The EDIE-UK study had three overlapping primary outcome measures: Positive and Negative Syndrome Scale (PANSS) criteria transition, antipsychotic medication, and DSM diagnosis (Morrison et al., 2004). It was agreed, following correspondence with the first author, that patients with missing transition data at follow-up who had commenced antipsychotic medication and had a DSM schizophrenia diagnosis at 6 and 12-months would be considered as transitioned cases. At the 36-month follow-up, 53% of the EDIE-UK sample had missing transition interviews, but medical records showed 7 DSM psychotic disorder diagnoses in both treatment conditions, made by a consultant psychiatrist blind to treatment status (Morrison et al., 2007). These were considered the most accurate data on transition rates and were used in the meta-analysis. For the Pozza and Dèttore (2020) study, we confirmed with the first author, given the recent uncertainty (Fusar-Poli et al., 2020a), that transitioned cases experienced frank psychotic symptoms for at least eight

consecutive days according to the CAARMS criteria (as opposed to a DSM brief psychotic disorder).

2.5 Study quality

Included studies were appraised using the Clinical Trials Assessment Measure (CTAM). CTAM ratings from our 2013 meta-analysis were retained (n=9) and new trials (n=17) were independently rated by authors in pairs of two (CM, MG, MB). Any disagreements were resolved by referring to the full-text article and reaching consensus.

The CTAM was designed to appraise the quality of psychosocial intervention trials. It examines methodological rigor in six areas of trial design: sample size and recruitment method, allocation to treatment, assessment of outcome, control group, description of treatments, and analysis (Tarrier & Wykes, 2004; Wykes, Steel, Everitt, & Tarrier, 2008). It has demonstrated good inter-rater agreement and excellent concurrent validity (Wykes et al., 2008). The CTAM has a maximum total score of 100, with scores below 65 indicating poorer trial quality (Wykes et al., 2008).

2.6 Data synthesis and analysis

We conducted a random-effects meta-analysis using Comprehensive Meta-Analysis version 2.2 (www.meta-analysis.com) and Stata version 16.1 (StataCorp, 2019) for transition outcomes, and the statistical software R (R Core Team, 2020) and the R package meta (Balduzzi, Rücker, & Schwarzer, 2019) for non-transition outcomes. The approach of DerSimonian and Laird was used (DerSimonian & Kacker, 2007; DerSimonian & Laird, 1986). All outcomes were continuous except for transition to psychosis and treatment acceptability.

For these two outcomes, the treatment effect was estimated by the risk ratio (RR). For continuous outcomes, the treatment effect was provided by either the mean difference (MD) when the measures concerned were identical or the standardized mean difference (SMD) when the measures were different, calculated using the formula of Hedges' *g* (Hedges, 1982). Heterogeneity was tested with a χ^2 distributed Q-test. We also report the I^2 statistic and its 95% confidence interval (Ioannidis, Patsopoulos, & Evangelou, 2007). The 95% confidence interval was calculated using the non-central χ^2-based approach proposed by Higgins and Thompson (2002). I^2 values of 0%, 25%, 50% or 75% indicated no, low, moderate and high heterogeneity, respectively (Higgins, Thompson, Deeks, & Altman, 2003). We conducted Egger's Regression intercept to quantify any publication bias captured by the funnel plot and to test whether it was statistically significant. The Egger's test is apt to type 2 error in small samples. Where missing publications were detected in the funnel plot, the effect was corrected using Duval and Tweedie's trim and fill.

The following sensitivity and subgroup analyses were performed: (1) exclusion of studies with inadequate methodology (CTAM score ≤65), (2) exclusion of unblinded studies, (3) exclusion of studies without an active control condition, (4) removal of one study at a time to detect a single source of heterogeneity, (5) effect of the two studies using the subtype of CBT intervention with education on odd experiences and homework assignment on experiencing the emotional and cognitive consequences of cognitive biases, and (6) comparison of studies with high (12.0-18.9%) versus low (5.3-5.9%) transition rates.

3. Results

3.1 Study selection

5,095 unique records were identified from the searches (Figure 1). Of the 162 full-text articles retrieved for further eligibility screening, 39 met criteria for inclusion, comprising 26 independent RCTs (23 published, the most recent in September 2020, and 3 unpublished). The PREVENT trial (Bechdolf et al., 2011) was excluded on advice from the study's corresponding author as it was in the process of publication. Two conference abstracts described the results from this trial, but did not contain meta-analyzable data.

-Figure 1-

3.2 Characteristics of the included studies

The 26 RCTs included a total of 2,351 participants (range: 8-304; 53% male), with a mean age of 19.8 years (SD 2.8) (Table 1). The interventions trialed were CBT (n=7), cognitive remediation (n=5), integrated social- and neurocognitive remediation (n=1), CBT + risperidone (n=2), omega-3 fatty acids (n=3), family interventions (n=3), integrated psychological intervention (n=1), olanzapine (n=1), ziprasidone (n=1), D-serine (n=1), cannabidiol (CBD, n=1), and glycine (n=1). One trial, a three-arm RCT involving two experimental treatments and one control treatment, provided two comparisons (McGorry et al., 2013; Yung et al., 2011). Another trial included a mixed sample of participants with psychosis or at high risk of psychosis (Holzer et al., 2014; Urben, Pihet, Jaugey, Halfon, & Holzer, 2012), with only outcomes for the latter group included in the meta-analysis.

-Table 1-

3.3 Study quality

CTAM total scores ranged from 26 to 97 (Table 2). Applying the recommended cut-off of 65, 12 studies (46%) were at risk of bias due to methodological limitations and 14 studies (54%) had adequate to good methodology with low risk of bias. Three of the low quality studies were from conference abstracts that did not report study characteristics in sufficient detail. Ten studies had small sample sizes (<27 participants per condition). Twelve studies did not describe the randomization process, including whether randomization was performed independent from the research staff. Ratings for assessment (e.g., independent and blinded assessors, standardized measurements) varied from 0 to 32, with ten studies scoring 29 or higher. Three studies were not blinded. Fifteen studies analyzed by intent-to-treat. Nine studies described the manualized interventions and conducted fidelity checks.

-Table 2-

3.4 Transition to psychosis

The pooled RR of all pharmacological and psychological interventions combined at 12-months was 0.57 (95% CI 0.41, 0.81, p=0.001), indicating that the risk of transitioning to psychosis was significantly reduced by 43%, favoring the experimental condition (Figure 2). The NNT was 16. The top three studies in Figure 2 showed RRs higher than 1.00, indicating that transition to psychosis occurred less frequently in the control group than in the experimental group. Reduced transition rates were reported in four pharmacological and seven psychological trials. All but two were statistically non-significant (Figure 2). Of the 19 studies providing transition to psychosis data, 12 had sound methodological quality (Table 2).

-Figure 2-

When the effects of individual interventions at the primary time point of 12-months were examined, only CBT was more effective than control interventions (RR 0.52, 95% CI 0.33, 0.82; I^2=6%) (Table 3, Figure 3). The NNT was 16. CBT was also associated with significantly reduced rates of transition at the end-of-treatment (RR 0.55, 95% CI 0.31, 0.99; I^2=15%) and at 18-48-months (RR 0.60, 95% CI 0.42, 0.84; I^2=0%). Findings at 6-months were not significant (Table 3). Although heterogeneity was low or absent, as indicated by the I^2 values, confidence intervals were broad (Table 3).

-Figure 3, Table 3-

Risperidone plus CBT was not associated with a significant reduction in incidence at 12-months and at medium-term follow-up, although it was associated with a significant effect at 6-months (RR 0.35, 95% CI 0.13, 0.95; I^2=0%) (Table 3). Omega-3 was not associated with significant effects at 12-months and at all other time points, with moderate to high heterogeneity (Table 3). The trial by Amminger et al. (2010; 2015), which found a significant and sustained effect in favor of omega-3 that was not replicated in the two larger multisite trials (NAPLS and NEURAPRO), was the source of the heterogeneity. The remaining eight interventions included in Table 3 were investigated in a single trial each.

All psychological studies pooled (e.g., CBT, systemic therapy, family interventions, integrated psychological intervention) were significantly effective with low heterogeneity at 12-months (RR 0.50, 95% CI 0.31, 0.80; I^2=13%). Findings at all remaining time points were also

statistically significant with low to no heterogeneity (Table 3). All pharmacological studies pooled (e.g., omega-3 fatty acids, antipsychotic medication, N-methyl-D-aspartate receptor modulators) did not have a significant effect on transition at 12-months and at the remaining time points (Table 3).

There was no indication of statistically significant publication bias in the CBT and omega-3 studies and in the pooled pharmacological and psychosocial studies ($p>0.05$), as measured by Egger's Regression intercept. For the CBT studies, although there was no publication bias in the funnel plots and in Egger's Regression analyses, Duvall and Tweedie is very sensitive and corrected for 1 missing study at the end-of-treatment, rendering results non-significant (corrected RR: 0.59 (0.33-1.05)). The 6-month outcome had no publication bias, but was statistically non-significant. Of the seven CBT trials providing end-of-treatment data, measurement occurred at 6-months in six trials and at 12-months in one trial (RIS-AUS-9). The 12-month (primary) outcome had no publication bias (with the same seven trials) and the 18-48 month follow-up (with six trials) also showed no publication bias. The medium to long-term outcomes are quite robust, although confidence intervals are still large.

For the omega-3 studies, no missing studies were detected. For the pharmacological studies, two studies were missing at end-of-treatment (corrected RR: 0.81 (0.42-1.54)). For the psychosocial studies, funnel plots showed 3 missing studies at end-of-treatment (corrected RR: 0.59 (0.37.0.97)); 1 missing at 6-months (corrected RR: 0.54 (0.30-0.96)); 1 missing at 12-months (corrected RR: 0.52 (0.31-0.86)); and 1 missing at 18-48 months (corrected RR: 0.60 (0.43-0.82)). The statistical results did not change.

Sensitivity and subgroup analyses were performed as planned for exploratory reasons on the seven CBT studies (Addington et al., 2011b; McGorry et al., 2013; Morrison et al., 2012; Morrison et al., 2004; Pozza & Dèttore, 2020; Stain et al., 2016; van der Gaag et al., 2012). The number of studies available for the other interventions was insufficient to perform a sensitivity or subgroup analysis.

(1) We were unable to contrast studies based on methodological rigor as all studies had a CTAM score of 65 or more, indicating good to adequate methodology and low risk of bias.

(2) Exclusion of Morrison et al. (2004), which reported occasional unblinding without correction, did not substantially change the results (RR=0.57 (0.36-0.89) z=-2.453, p=0.014). Another study reported occasional unblinding, but had the complete assessment replaced by a newly assigned blind rater (van der Gaag et al., 2012).

(3) Restricting the analysis to studies with an active control condition removed the EDIE-UK and EDIE2-UK studies (Morrison et al., 2012; Morrison et al., 2004), but results did not change (RR=0.54, (0.30-0.96) z=-2.085, p=0.037).

(4) In the leave-one-out analysis, removal of the DEPTh trial (Stain et al., 2016) shifted the results to statistically significant for CBT at 6-months (RR=0.51 (95%CI: 0.29-0.95) z=-2.259, p=0.024). This trial included a younger sample (mean age 16 years) and the study's inclusion criteria did not include diminished social functioning, which may have contributed to the low transition rate (5.3%) and high remission of UHR status (89%). The study also included a participant in the CBT condition who transitioned to psychosis at baseline.

(5) The effects of the two studies utilizing the enriched CBT protocol (Pozza & Dèttore, 2020; van der Gaag et al., 2012) indicated the benefit of education and homework assignments on experiencing the reasoning and emotional effects of cognitive biases. The enriched CBT protocol was effective at end-of-treatment (RR=0.34 (0.14-0.81) z=-2413, p=0.016; NNT=10.1)

and at 12-months (RR=0.44 (0.24-0.84) z=-2.518, p=0.012; NNT=8.5), with lower transition rates in the CBT condition than the other CBT studies.

(6) Comparing studies with high (12.0-18.9%) and low transition rates (5.3-5.9%) showed that the experimental condition in the former studies (EDIE-UK; RIS-AUS-9; EDIE-NL; Pozza: RR=0.47 (0.28-0.77) z=-2.98, p=0.003; NNT=8.5), perform better than the latter (EDIE2-UK; ADAPT; DEPTh: RR=0.78 (0.16-3.88) z=-.307, p=0.76; NNT=70) in reducing transition rates.

3.5 Attenuated positive and negative psychotic symptoms, mania, depression, anxiety and general psychopathology

For attenuated positive psychotic symptoms, a significant effect favoring the experimental condition was found at 12-months when all pharmacological and psychological interventions were pooled (SMD -0.15, 95% CI -0.28, -0.01, p=0.04) (Figure 4, Table S4a). There was no heterogeneity (I^2=0%) although the confidence interval was wide (0-56). The *Q* statistic indicated no statistically significant heterogeneity (p=0.57). Egger's test for small-study effects indicated no publication bias (p=0.69). Of the nine studies providing data at 12-months, eight had sound methodological quality. Findings remained significant when the low quality study (McGlashan et al. 2006) was removed from the analysis (SMD -0.17, 95% CI -0.31, -0.03, p=0.02; I^2 0%, 95% CI 0-55). Findings at the end-of-treatment and at 6 and 18-84-month follow-up were not significant (Tables S2a, S3a, S5a). Findings for pharmacological and psychological interventions pooled separately were not significant at all time points (see Tables S2b-c, S3b-c, S4b-c, S5b-c for results).

- Figure 4 -

For all other symptom outcomes (attenuated negative psychotic symptoms, mania, depression, anxiety, and general psychopathology), treatment effects were not significantly different between experimental and control treatments at 12-months and at all secondary time points (results are shown in Tables S2-S5).

3.6 Symptom-related distress, functioning and quality of life

For symptom-related distress, measured by the CAARMS, there was no statistically significant difference between experimental and control treatment conditions at 12-months when psychological interventions were pooled (MD -2.80, 95% CI -6.66, 1.07, p=0.16; I^2=0%, 95% CI 0-88; Table S4c). No pharmacological trial reported data on symptom-related distress. When all psychological and pharmacological interventions were pooled, there was no apparent difference between experimental and control treatment groups at 12-months with respect to global functioning, measured by the Global Assessment of Functioning, (MD 1.57, 95% CI -1.22, 4.36, p=0.27; I^2=28%, 95% CI 0-68); social functioning (SMD 0.06, 95% CI, -0.13, 0.25, p=0.54; I^2=0%, 95% CI 0-66); and quality of life (SMD -0.03, 95% CI -0.20, 0.14, p=0.75; I^2=0%, 95% CI 0-0) (Table S4a). Effects for all these outcomes were not significant at end-of-treatment (Table S2a), 6-months (Table S3a), and 18+ months (Table S5a). For functioning (social and global) and quality of life, effects remained non-significant at all time points when pharmacological and psychological interventions were pooled separately (Tables S2b-c, S3b-c, S4b-c, S5b-c).

3.9 Treatment acceptability

For all-cause treatment discontinuation, there was no significant difference between experimental and control conditions across all pharmacological and psychological

interventions combined at 12-months (RR 1.09, 95% CI 0.96, 1.25, p=0.19; I^2=0%, 95% CI 0-21) (Table 4a). Findings for the secondary time points were not significant at end-of-treatment (Table S2a), 6-months (Table S3a), and 18-84-months (Table S5a). Findings for pharmacological and psychological interventions pooled separately were not significant at all time points (see Tables S2b-c, S3b-c, S4b-c, S5b-c for results).

4. Discussion

4.1 Main findings

In this comprehensive meta-analysis, we examined the effectiveness of interventions across 12 key outcomes, based on 26 independent trials involving 2,351 UHR participants. Our main findings are that (1) receiving any type of trial intervention (pharmacological or psychological) significantly reduced the risk of transition to psychosis at 12-months by 43% compared to control conditions, (2) CBT has been trialed the most and there is robust evidence in support of its use in reducing rates of transition to psychosis at 12-months and up to 18-48-month follow-up, but not at 6-months (only one missing trial could render the end-of-treatment results non-significant), (3) all pooled pharmacological and psychological interventions had a small significant effect on attenuated positive psychotic symptoms at 12-months, however, this did not maintain significance when the two groups of interventions were pooled separately, potentially due to a lack of power, and (4) there was no apparent difference between experimental interventions and control conditions for the outcomes of attenuated negative psychotic symptoms, mania, depression, anxiety, general psychopathology, symptom-related distress, social and global functioning, quality of life, and treatment acceptability at all time points of interest.

These findings indicate that treatment effects of psychological treatments, particularly CBT, are largely specific to reducing rates of transition to psychosis. The significant finding for attenuated positive psychotic symptoms at 12-months supports the specificity for subclinical symptoms as a target of intervention. The non-significant findings for the other non-transition outcomes, should be interpreted within the context that these are secondary outcomes that were not specifically targeted. Inspection of the primary studies indicated that in most cases *both* the experimental and control conditions showed group-level improvements across specific symptomatic and functional outcomes, although this was variable and it is unclear to what extent this reflects natural improvement or the beneficial effects of non-specific psychosocial therapies. Consistent with the recognition that treatment targets for UHR individuals should be broadened and the notion that the UHR state represents a transdiagnostic at-risk mental state (Hartmann et al., 2019; McGorry et al., 2018), our findings highlight the need for future trials to investigate and develop effective interventions, particularly multimodal approaches, that target the range of clinical and functional needs (e.g., symptomology, distress, co-morbidities, social and vocational functioning, quality of life).

4.2 Transition to psychosis

We identified sound evidence for CBT in reducing rates of transition to psychosis at 12-months. Efficacy was found to be unchanged (RR=0.52) in 2013 and 2020 and the effect is statistically significant (z=-2.802, p=0.005). Confidence intervals are also now smaller, but still remain large (Table 3). The NNT for CBT was slightly lower in 2013 (13 compared to 16), but remains relatively potent. The risk reduction by CBT varied from 40% at medium-term follow-up (18-48 months) to 48% at 12-months to 45% at the end-of-treatment. Although attempts

were made to minimize publication bias through the searching of multiple clinical trial registries and contacting authors for unpublished data, we were unable to include all unpublished trials (e.g., the PREVENT trial), and a missing study rendered the end-of-treatment effect non-significant. At later time points (12-months and 18-48 months), findings for CBT were significant with no publication bias and were robust in sensitivity and subgroup analyses, which supports its efficacy. This may suggest that the effects of treatment on transition rates are not detected until after a delay and once the number of cases who transition to psychosis accumulates at follow-up. Removal of the DEPTh trial as an extreme outlier resulted in significant risk ratios at 6-months as well. The significant effects at 18-48-months may indicate that CBT induces a durable change that counters evolution of positive psychotic symptoms and that it does not only delay transition during therapy, but also long after the termination of the intervention and may have a truly preventive effect in a substantial number of UHR patients. Altogether the evidence justifies the deployment of CBT for UHR, it is also the fact that if negative trials are published in the future, the meta-analytic results may change to non-significant. More well conducted trials are needed.

Other psychological interventions, particularly integrated psychological intervention (Bechdolf et al., 2012), showed positive results but require replication. Family interventions were also promising but results are confounded by psychotropic medication prescribed prior to transition to frank psychosis (McFarlane; McFarlane, Cook, & Woodberry, 2011; Miklowitz et al., 2014). Family interventions may assist in supporting adolescents and should be further researched. The pooled psychosocial interventions were associated with significant effects with low to no heterogeneity, suggesting a potential common shared pathway from UHR to psychosis via psychological mechanisms.

Antipsychotic medication was associated with non-significant reduced transition rates and the effect of all pharmacological trials pooled was also non-significant. Trials of antipsychotic medications and glycine were underpowered (McGlashan et al., 2006; Woods et al., 2017; Woods et al., 2013) and the pooled pharmacological interventions were highly varied. Current guidelines recommend against prescribing antipsychotic medication during the UHR stage (NICE, 2014) due to the unfavorable risk-benefit ratio, although they may be indicated when CBT and other psychosocial interventions are not effective and symptoms are associated with risk of self-harm or aggression (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016; Nelson et al., 2018c).

Our findings for omega-3 fatty acids were also non-significant, with moderate to large heterogeneity due to two recent studies failing to replicate the findings of Amminger et al. (2010). There are important differences between these studies that may have contributed to the failed replication. The control condition in McGorry et al. (2017) consisted of placebo plus an intensive psychosocial treatment compared to placebo alone in Amminger et al. (2010). The latter also included a young sample, with the majority female. Future omega-3 trials may examine moderating effects of age and may specifically target participants with low levels of omega-3 fatty acids who are more likely to benefit from supplementation (Amminger et al., 2020).

4.3 Non-transition outcomes

There are three factors that may have contributed to the lack of difference between experimental and control conditions for the majority of non-transition outcomes. First, few

studies have investigated these outcomes, especially at follow-up, potentially reducing the power needed to detect an effect. For example, the significant improvement in positive psychotic symptoms identified at 12-months when all interventions were pooled was not maintained when pharmacological and psychological interventions were analyzed separately, although the effect sizes and confidence intervals were relatively comparable. The future creation of a core outcomes assessment set for UHR clinical trials would have the benefit of facilitating consistency in outcomes reported across trials (Woods, Mourgues-Codern, & Powers, in press), which in turn may clarify the effect of specific interventions on non-transition outcomes.

Second, given the substantial heterogeneity that exists within this clinical population, individual variation in treatment response is an important consideration, meaning that particular subgroups may have in fact benefitted from a specific intervention but at a group-level there is no demonstrable difference between experimental and control treatment arms. For example, confidence intervals for a number of outcomes were wide, suggesting variability. This could be explored in future individual participant data meta-analyses. At present, knowledge regarding factors that predict treatment response are lacking, limiting the ability to personalize interventions, which may be addressed though the development of adaptive interventions, where the type or dose of an intervention is tailored to a patient's clinical presentation and adapted over time depending on treatment response and potentially psychosocial variables and biomarkers (Nelson et al., 2018c). Biomarker guided-treatment is an increasingly promising avenue. Secondary analysis of the NEURAPRO trial revealed the effectiveness of omega-3 supplementation in individuals with low levels of omega-3 fatty acid at baseline (Amminger et al., 2020). There is also evidence that *N*-acetylcysteine

supplementation is associated with greater improvements in positive symptoms in the sub-group of FEP patients with high oxidation status at baseline (Conus et al., 2017), which is a potential area of future investigation in UHR patients (Yung, 2017).

Third, treatment at UHR services appears to have progressively improved over time to provide more effective treatments, which has likely also contributed to the decline in transition rates (Formica et al., in press; Nelson et al., 2020b; Nelson et al., 2016). This indicates that specific experimental treatments may not provide any significant added clinical benefits over high-quality standard care at a group level. This may have been the case in the largest trial conducted to date, which found that improvements in symptomatology and functioning occurred across both the experimental (omega-3 plus cognitive behavioral case management [CBCM]) and control groups (placebo plus CBCM) (McGorry et al., 2017). Future well-powered studies are needed to investigate the specificity of the effects of diverse and generic preventive interventions (e.g., supportive psychosocial therapies).

4.4 Enriched recruiting environments

The largest well-conducted trials did not have statistically significant effects, but also had the lowest transition rates, and the negative findings may be due to small statistical power (Fusar-Poli, 2017), effective psychosocial care being provided to both treatment groups (McGorry et al., 2017), or samples being insufficiently enriched for psychosis risk. Three of the four studies (EDIE2-UK, ADAPT, DEPTh) with low transition rates did not apply decline in social functioning as an inclusion criterion. To reduce the number of treated false positive cases, sampling strategies must be enriched with social decline (Yung et al., 2008) and help-seeking as patients have consistently large impairments in functioning similar to other coded disorders (Fusar-

Poli et al., 2015). Experiencing some psychotic experiences without other risk factors may be associated with a rather benign prognosis. Future sampling of UHR cohorts should combine low-level symptoms with a decline in social and vocational functioning, young age and help-seeking for diverse psychiatric problems.

4.5 CBT versus targeted CBT with education and homework assignments on experiencing consequences of cognitive biases

Behavioral experiments to test psychotic hypotheses of current situations is part of CBT for UHR to enable patients to reject delusional and paranoid ideas about other people's involvement in what is going on in their minds. This may be amplified with special attention to and education about odd experiences, as was suggested by the effects of two studies with these additions (Pozza & Dèttore, 2020; van der Gaag et al., 2012).

4.6 Future directions

Although CBT has a range of targets based on individual patient formulation (e.g., depression, anxiety, post-traumatic stress disorder, social functioning), CBT for the psychotic dimension of the UHR state is targeted towards a common psychological route from UHR to FEP, aiming to prevent the intensification of delusional ideation and inculcating adaptive ways of responding to anomalous perceptual and cognitive experiences. This is only one modality for intervention among many risk factors and comorbidities associated with the UHR phenotype. From the prevention of heart disease, we know that it is possible to lower the incidence of heart accidents by screening for and treating multiple risk factors (Koopman et al., 2016). For the UHR population, a similar focus should be placed on the detection and treatment of risk factors and comorbidities to improve general health, well-being, and social and vocational

functioning. Research indicates that the route from UHR to FEP is paved with interacting risk factors such as traumatic experiences, drug abuse (Belbasis et al., 2018), cognitive biases (Frydecka et al., 2020), worry, anxiety, insomnia and negative self-beliefs (Freeman, Taylor, Molodynski, & Waite, 2019) that may be effectively addressed with psychotherapy, which appears to improve resilience and the skills needed to cope with future problems. In psychotic disorders, recent studies have shown promising results in treating post-traumatic stress disorder (van den Berg et al., 2015), worry (Freeman et al., 2015a), sleep disorder (Freeman et al., 2015b), and other causal risk factors in the development and maintenance of psychosis.

Although CBT is recommended in several guidelines as a potent and effective intervention for help-seeking UHR patients, further studies are needed to examine promising pharmacological treatments and family interventions, as well as support in educational and vocational contexts. In general, these interventions have demonstrable effectiveness in early psychosis (e.g., individual placement and support; Killackey et al., 2019) and may also contribute to the health, well-being and functional recovery of UHR patients. New treatment approaches, such as mindfulness and compassion-based approaches, which target symptom-related distress, may be promising strategies to improve non-transition outcomes, including functioning and quality of life (Hickey, Nelson, & Meadows, 2017). Preliminary evidence from an uncontrolled pilot study found that an online mindfulness and strengths-based intervention was associated with improved social functioning and wellbeing in UHR individuals (Alvarez-Jimenez et al., 2018), now currently being trialed in a randomized controlled design. Mindfulness-based approaches may also represent a new approach to improve negative symptoms (Jansen, Gleeson, Bendall, Rice, & Alvarez-Jimenez, 2020).

A number of other promising interventions that may improve non-transition outcomes require further investigation. Physical exercise interventions are feasible, acceptable and potentially effective in improving positive, negative and depressive symptoms as well as functioning and cognition in individuals at risk for psychosis (Dean et al., 2017; Lederman et al., 2020). CBD, which was investigated in a single short-term trial included in this meta-analysis, has been shown to partially normalize aberrant brain function in regions associated with the pathophysiology of psychosis (Bhattacharyya et al., 2018). It has also been associated with beneficial effects on attenuated psychotic symptoms, anxiety and depression (Berger, Li, & Amminger, 2020), and on psychotic symptoms in patients with schizophrenia (Leweke et al., 2012; McGuire et al., 2017). Results of larger RCTs, which are currently underway (ISRCTN10334895), may clarify the effectiveness of CBD in UHR populations.

4.7 Strengths and limitations

The strength of this meta-analysis is that, for the primary outcome, the number of participants increased from 1150 (10 trials) in 2013 to 1886 (19 trials) in 2020 and that conclusions benefit from greater statistical power for obtaining more precise pooled estimates. The current meta-analysis also included more trials than the other recent meta-analyses. Furthermore, we conducted a pairwise meta-analysis that is based on direct head-on comparisons given that too little direct evidence is currently available to successfully conduct an NMA without excessive imprecision and a high risk of type 2 error. It appears premature to conduct NMAs of UHR treatment trials as many interventions have only been tested in one study without active comparisons, leading to an imbalance between direct and indirect evidence and the inability to adequately assess inconsistency and transitivity.

There are limitations of this meta-analysis that should be noted. The total number of participants for several outcomes was small, especially in some pharmacological trials and for some non-transition outcomes. Also, a high number of interventions were investigated in only a single trial each. While the approach utilized of pooling pharmacological and psychological interventions is advantageous to clarify if transition rates and adverse non-transition outcomes can be reduced at all, its limitation is that it involves grouping a diverse range of interventions. Only a few trials provided medium to long-term follow-up data and it still remains uncertain whether interventions have indeed prevented the onset of psychosis. Reflecting the lack of trials utilizing direct measures of treatment acceptability, we examined this outcome using a common proxy indicator, which may have potentially underestimated treatment effects as study withdrawal may occur despite an intervention being acceptable.

5. Conclusions

Results from this meta-analysis demonstrate the real and proven benefit of UHR interventions, specifically on the outcomes of transition to psychosis and, to a lesser extent, attenuated positive psychotic symptoms. CBT was associated with a relatively durable reduction in transition rates at 12-months and over the medium-term that was robust to sensitivity and subgroup analyses. CBT is not only effective but also cost-effective and potentially cost-saving (Ising et al., 2017; Ising et al., 2015; Jin, Tappenden, MacCabe, Robinson, & Byford, 2020). Although receiving any type of intervention had a small effect on attenuated positive psychotic symptoms, this was not maintained when stratified by intervention type (psychological and pharmacological), indicating that further research is needed to determine optimal treatment selection for this symptom domain. Similarly, further trials are needed to develop targeted interventions that improve the spectrum of

symptomatic and functional outcomes, particularly via multimodal, sequential and novel biomarker-guided treatment approaches.

The finding that psychosis incidence can be reduced by 45% at 12-months and by 40% at 18-48-months is a unique finding in the long history of stable incidence rates of psychotic disorders over the past century. Future well-designed trials and novel interventions may open the route to lower prevalence rates. Although the risk reduction identified here has wide confidence intervals, individuals experiencing this stage of psychosis warrant increased research attention and expert routine clinical care to prevent future long-term treatment trajectories.

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