REGULAR RESEARCH ARTICLE

Negative Prognostic Effect of Baseline Antipsychotic Exposure in Clinical High Risk for Psychosis (CHR-P): Is Pre-Test Risk Enrichment the Hidden Culprit?

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Abstract

Introduction: Sample enrichment is a key factor in contemporary early-detection strategies aimed at the identification of help-seekers at increased risk of imminent transition to psychosis. We undertook a meta-analytic investigation to ascertain the role of sample enrichment in the recently highlighted negative prognostic effect of baseline antipsychotic (AP) exposure in clinical high-risk (CHR-P) of psychosis individuals.
Methods: Systematic review and meta-analysis of all published studies on CHR-P were identified according to a validated diagnostic procedure. The outcome was the proportion of transition to psychosis, which was calculated according to the Freeman-Tukey double arcsine transformation.
Results: Thirty-three eligible studies were identified, including 16 samples with details on AP exposure at baseline and 17 samples with baseline AP exposure as exclusion criterion for enrollment. Those with baseline exposure to AP (n = 395) had higher transition rates (29.9%; 95% CI: 25.1%–34.8%) than those without baseline exposure to AP in the same study (n = 1289; 17.2%; 15.1%–19.4%) and those coming from samples that did not include people who were exposed to AP at baseline (n = 2073; 16.2%; 14.6%–17.8%; *P* < .05 in both the fixed-effects and the random-effects models). Heterogeneity within studies was substantial, with values above 75% in all comparisons.
Conclusions: Sample enrichment is not a plausible explanation for the higher risk of transition to psychosis of CHR-P individuals who were already exposed to AP at the enrollment in specialized early-detection programs. Baseline exposure to AP at CHR-P assessment is a major index of enhanced, imminent risk of psychosis.

Keywords: Antipsychotic, clinical high risk, prevention, prognosis, psychosis, treatment

Introduction

Research on clinical high-risk for psychosis (CHR-P) is central for the deployment of suitable clinical care pathways aiming at preventing (or mitigating) the biopsychosocial consequences of psychosis. In the last 30 years, the early-detection field has been engaged in a robust effort to conceptualize and develop prognostic models for trans-diagnostic staging and individualized

Significance Statement

Major guidelines do not indicate antipsychotic medication as first-line treatment for the prevention of psychosis in individuals at clinical high risk (CHR-P). Despite that, recent meta-analyses reveal that the use of such medications is relatively widespread in the field and seems to be associated with higher imminent risk of transition to psychosis. Therefore, we wished to test if such increased risk could reflect differences in pre-recruitment risk enrichment (aka pre-test risk enrichment) across the studies rather than medication exposure. We found, however, that despite heterogeneities in referral and sampling strategies, pre-test risk enrichment in CHR-P does not seem to play any specific role in the observed negative prognostic effect of baseline antipsychotic exposure. Given the intuitive implications for the treatment of psychosis and the prevention of its undesired long-term outcomes, the results urge further investigations on the clinical effects of antipsychotic medications in young help-seekers at high risk for psychosis.

risk stratification (see Sanfelici et al., 2020 for an overview). However, in such tumultuous growth, the accelerated search for scalable predictors has led to some undetected distortion, such as the neglect of obvious clinical confounders. This is the case of baseline exposure to antipsychotics (AP) in individuals enrolled within the CHR-P group (Raballo et al., 2019, 2020a,b, 2021; Raballo and Poletti, 2019).

There is indeed substantial meta-analytical evidence that almost 1 out of 5/4 individuals enrolled as CHR-P in specialist centers is already undergoing AP treatment at the moment of the first CHR-P evaluation (Raballo et al., 2019, 2020a,b). Needless to say, such exposure may alter the clinical presentation (e.g., modulating the frequency or severity of positive psychotic symptoms during the CHR assessment) as well as the natural course of transition to psychosis (see Raballo et al., 2019 for a synthetic overview). Even more crucially, there is meta-analytic evidence that baseline AP exposure in CHR-P individuals is associated with an even higher imminent risk of transition to psychosis (Raballo et al., 2020a,b).

The magnitude of this confounder and its implications for the field have been overlooked until recently (Raballo and Poletti, 2019). Among other things (e.g., reduced precision of current prognostic estimates and risk stratification), the widespread conflation of AP-naïve and AP-exposed help-seekers in the same CHR-P group might hamper the identification of the effectiveness of new pharmacological and non-pharmacological treatments, given that a treatment that is effective in AP-naïve CHR-P individuals may be less effective in AP-exposed help-seekers (who might already be in a first-episode psychosis even if psychometrically attenuated due to the AP treatment).

Most importantly, there is meta-analytic evidence that CHR-P individuals undergoing AP treatment at the time of enrollment have different longitudinal trajectories and risk of transition to psychosis compared with AP-naïve CHR-P patients (29% vs 16%: risk ratio of transition 1.47 in the fixed-effects model) (Raballo et al., 2020b). This suggests that (1) baseline AP treatment plausibly signals an increased clinical severity (although still formally within the psychometric criteria for CHR-P), which is associated with increased risk of longitudinal transition to psychosis; and/or (2) the AP-exposed CHR group at baseline presumably includes a fraction of "pharmacologically attenuated first-episode psychosis" that have a higher likelihood to convert into psychometric full-blown psychosis.

However, another explanatory hypothesis is also possible, that is, that the higher conversion rates in AP-exposed CHR-P might be an epiphenomenon of the enrichment strategies adopted in the different study settings (aka pretest risk enrichment). Concretely, it is possible that the different recruitment and sampling strategies in the studies could lead to different pretest prevalence of more severe cases across the CHR-P centers (Fusar-Poli et al., 2016, 2017).

The guiding question of the current meta-analytic investigation is therefore the following: is pre-test risk enrichment the key to the apparent negative prognostic effect of baseline antipsychotic exposure in CHR-P?

Aim

The current study was designed to test the possible hidden role of pretest risk enrichment on the (previously demonstrated) impact of baseline AP on CHR-P transition to psychosis risk. We wanted to verify if AP-naïve CHR-P participants present similar transition prevalence independently if they belong to CHR-P samples that exclude baseline AP exposure (i.e., pure AP-naïve CHR-P source samples) or from CHR-P samples that allow the inclusion of help-seekers under ongoing AP treatment at baseline (i.e., source samples encompassing both AP-naïve and AP-exposed CHR-P). Therefore, we meta-analytically contrasted the risk of transition in 3 sub-populations: CHR-P with baseline exposure to AP, CHR-P without baseline exposure to AP who were enrolled from the same source studies, and CHR-P enrolled in studies having AP exposure as explicit exclusion criterion.

Indeed, we expected that, should higher pretest risk enrichment be involved in the higher transition rates of baseline AP-exposed CHR-P, the overall transition rate of AP-naïve CHR-P drawn from these latter samples should be higher than one of those AP-naïve CHR-P from samples that never enrolled individuals undergoing AP treatment at baseline.

Methods

Study Selection

The systematic review and meta-analysis were planned and executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009). We searched PubMed/Medline and the Cochrane library from inception up to October 30, 2020, by using the following key terms: "Ultra high risk" OR "Clinical high risk" AND "psychosis" AND "transition" OR "conversion." This search retrieved 1842 articles, of which 98 were systematic review or meta-analysis, in PubMed/Medline and 196 trials in the Cochrane Central Register of Controlled Trials. Two authors (M.P., A.P.) evaluated the list of extracted articles and decided about inclusion or exclusion according to the following criteria:

- Written in English;
- Details information about samples with people diagnosed at CHR-P of psychosis based on a validated diagnostic procedure (i.e., using an interview and formal criteria to determine the CHR-P status of the participants);

–   Reports numeric data about the sample and the outcome at a predefined follow-up time, and has transition to psychosis as one of the outcomes;
–   Reports AP exposure as exclusion criterion, or in case of inclusion of participants on AP, reports raw data on AP baseline exposure in relation to the transition outcome.

Data Extraction

After exclusion of duplicates (including articles repeatedly reporting the results of the same trial or with overlapping samples) and articles that were unrelated to the main topic (i.e., studies on brain imaging or genetic markers), individual studies were included when they matched the inclusion criteria. Discrepancies were solved by discussion consulting a third experienced researcher (A.R.). The references of the retrieved articles and extracted reviews on the topic were scanned to identify potentially missed studies. At the end of this procedure, 33 independent studies were included in the systematic analysis and the subsequent meta-analysis (Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow chart).

The following variables were extracted from the included studies: authors and year of publication of the study, location of the study, criteria and instrument for diagnosis, criteria for transition to psychosis, sample size at baseline and follow-up, data on AP exposure (yes/no) based on the outcome (transition/no transition), duration of the follow-up, and number of

cases that transitioned psychosis at the end of follow-up by group. Three aggregated subgroups were then analyzed: CHR-P with baseline exposure to AP, CHR-P without baseline exposure to AP from the same source studies, and CHR-P enrolled from samples that excluded individuals who were exposed to AP at baseline. Quality assessment was rated according to the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Discrepancies in extraction of data were solved by discussion within the research team.

Statistical Analysis

All analyses were carried out with the "meta" package (Schwarzer et al., 2015) and the "metafor" package (Viechtbauer, 2010) running in R version 3.5.1 (R Core Team, 2018).

The outcome of the meta-analysis was the proportion of transition to psychosis. All proportions were estimated with the variance-stabilizing [Freeman and Tukey (1950)] double arcsine transformation, since there is evidence that it outperforms other proposed methods (e.g., logit transformation) of estimating prevalence (Barendregt et al., 2013), especially when the proportion of cases is expected to be small. Between-study variance and variance of the effect size parameters across the population were estimated with the tau-squared statistics using Empirical Bayes estimator (Veroniki et al., 2016); its 95% CI was calculated by using the Q-Profile method
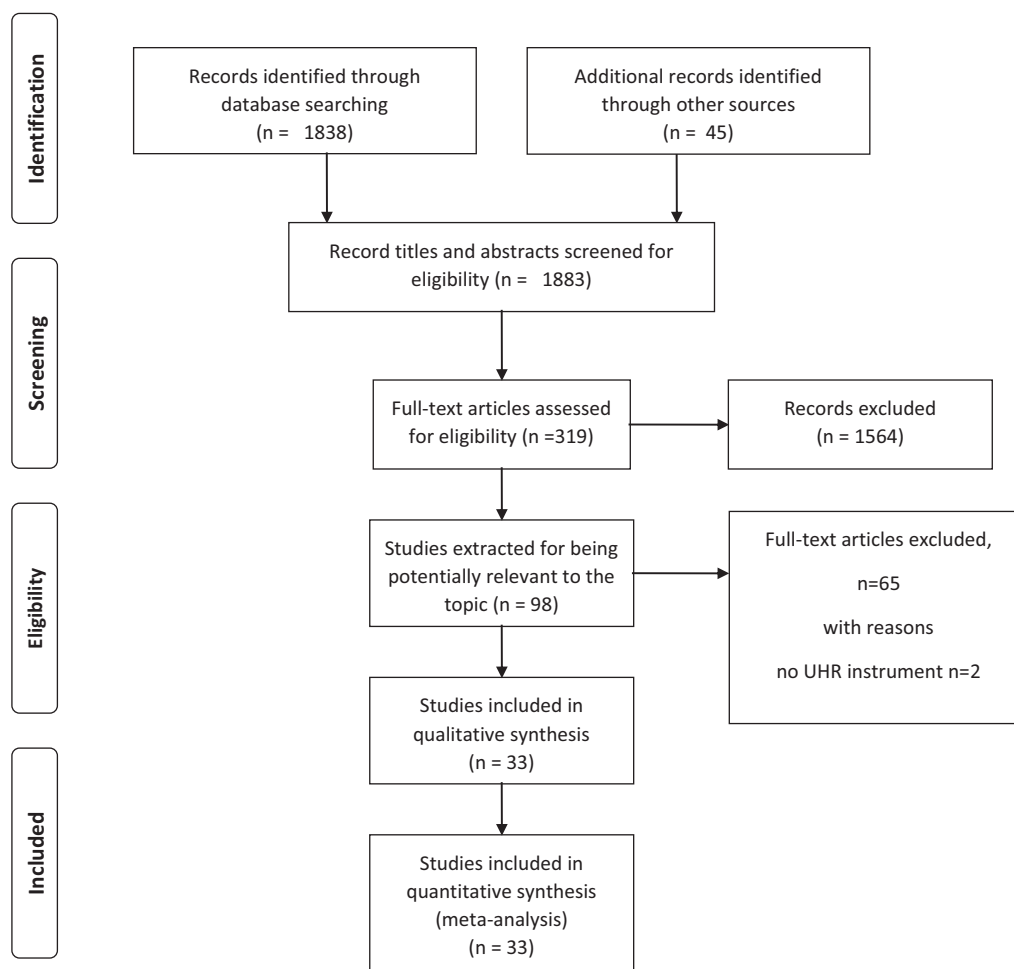

Figure 1. PRISMA 2009 flow diagram.

(Viechtbauer, 2010) with Knapp and Hartung (2003) correction. Continuity correction of 0.5 was applied in studies with zero cell frequencies.

Both fixed- and random-effects summary estimates were reported along with a corresponding 95% confidence interval (CI) for each outcome in forest plots. Fixed-effects models estimate a common effect for the studies included in the meta-analysis (Viechtbauer, 2010). The random-effects models aim to provide inference about the average effect in the entire population from which the studies are expected to be drawn. Essentially, the random-effects model accounts for the heterogeneity of the studies, that is, the fact that the effects that are estimated from the studies come from a distribution of true effects, which depend on a source of variability that is not limited to sampling error (Borenstein et al., 2010). It should be borne in mind that, in the attempt to model some (but not all) heterogeneity in the studies, the random-effects model tends to inflate the role of small studies (Borenstein et al., 2010); in doing so, it loses power compared with the fixed-effects model (Jackson and Turner, 2017).

In all analyses, heterogeneity was assessed with Cochran's Q and I^2 statistics (Huedo-Medina et al., 2006). Cochran's Q test assesses the null hypothesis that the true effect size is the same in all studies (Borenstein, 2020). A low P value (i.e., $P < .10$) of the Q-statistic indicates that variation in the study-specific effect estimates is due to heterogeneity beyond that depending on sampling error. The I^2 statistic measures the extent to which the variance in observed effects reflects variance in true effects rather than sampling error (Borenstein, 2020). The higher the I^2, the greater the impact of the variance in true effects. According to an agreed rule of thumb, I^2 values 40% to 60% indicated moderate heterogeneity, and values above 75% were considered indicative of substantial heterogeneity (Higgins and Cochrane Collaboration, 2002).

Results

The literature search identified 33 eligible studies: 16 studies that allowed baseline AP exposure and specified the transition outcome based on AP exposure vs AP no exposure (reported in Table 1), and 17 studies that considered baseline AP exposure as exclusion criterion (reported in Table 2).

Studies that included CHR-P with AP exposure at baseline disproportionally used the Structured Interview for Prodromal Symptoms as a measure to define CHR-P status (13 out of 16 studies: 81.2%); conversely, in the studies that included only CHR-P participants who were never exposed to AP, the Comprehensive Assessment of At Risk Mental States was the most used tool to define the condition (9 out of 17 studies: 52.9%).

Most studies were from European countries (19 out of 33 studies: 57.6%), while others were from North American countries (USA and Canada: 7 out of 33 studies: 21.2%) and Asian countries (7 out of 33 studies: 21.2%). There were no studies from Central or South America or from Africa.

Those studies including CHR-P with AP exposure at baseline were almost equally distributed from the North American countries (USA and Canada: 6 out of 16 studies: 37.6%), Asian countries (5 out of 16 studies: 31.2%), and European countries (5 out of 16 studies: 31.2%), while the majority of studies including only drug-naive CHR-P patients were from European countries (14 out of 17 studies: 82.4%).

Compared by probability of transition to psychosis according to the criteria listed in each study, the 3 groups of AP-exposed, AP-not exposed, and AP-never exposed patients were found to differ both within and between studies (Figure 2, forest plot). The

3 groups differed from each other, with the AP-exposed samples having higher transition rates than the AP-not exposed samples and the AP-never exposed samples (Table 3). The AP-not exposed samples and the AP-never exposed samples did not differ from each other. The differences were statistically significant at the conservative threshold of $P < .05$ in both the fixed-effects and random-effects models (Table 3 for details).

Heterogeneity within studies was substantial, with values above 75% in all comparisons. However, there was no relevant asymmetry in the funnel plot of each group of samples, and the Egger test showed no relevant bias in publication (see supplementary Figs. 1–3).

Discussion

The results of the present meta-analysis indicate that sample enrichment is not a plausible explanation for the higher risk of transition to psychosis of CHR-P participants who were already exposed to AP at the enrollment in specialized early-detection programs. Rather, the results further corroborate the evidence that baseline exposure to AP (at the moment of CHR-P assessment) is a major index of enhanced, imminent risk of incurring a full-blown psychotic episode at follow-up (Raballo et al., 2020a,b).

While this is clearly an important aspect to consider for refining current risk stratification (and amending some of the shortcomings of current CHR-P definitions; see Preti et al., 2014 and van Os and Guloksuz, 2017), it would be essential to further deconstruct the nature of such phenomenon. Three main explanatory hypotheses can be advanced in this respect, each of which warranting further, targeted empirical exploration.

Hypothesis 1

Pro-Psychotic Effect of AP in CHR-P via Sensitization or Neurotoxicity—AP exert per se a psychotogenic action on the brain of CHR-P individuals. The reason can be a sensibilization effect on the dopaminergic neurons because of persistent block of the pre- and post-synaptic receptors, causing a hypersensitivity of the neurons to dopaminergic discharge (Chouinard et al., 2017; Nakata et al., 2017; Yin et al., 2017). A second mechanism may be a direct toxic effect on the neurons. There is some evidence that long-term AP treatment may associate with brain structure changes (Ho et al., 2011), especially a parietal lobe reduction and basal ganglia increase (Huhtaniska et al., 2017). Brain structural changes were reported in both CHR-P individuals (Katagiri et al., 2019) and first-episode psychosis patients (Akudjedu et al., 2020).

Hypothesis 2

Masking Effect of AP "Attenuating" the Clinical Presentation of the Psychotic Episode—Individuals exposed to AP may have already transitioned towards psychosis, yet the ongoing AP treatment at baseline might have prevented the psychometric identification of these "pharmacologically attenuated first-episode psychosis" cases (Raballo et al., 2020a). Strictly speaking, this group is no longer in a high-risk condition, but rather it has already reached the endpoint outcome (i.e., the first-episode psychosis) although unrecognized.

Hypothesis 3

Delaying Effect of AP "Postponing" Transition to Psychosis— The subgroup of CHR-P who had been prescribed AP before

Table 1. Studies Included in the Meta-Analysis and Reporting Raw Baseline Data on AP Exposure in Relation to Transition to Psychosis

Study first author	Year	Site	Baseline CHR sample	Follow-up	Follow-up sample	Raw transitions	UHR instrument	Baseline AP exposure	Mean age (SD)	Gender (F)	Conv. on AP baseline	Conv. no AP baseline	Nonconv. on AP baseline	Nonconv. no AP baseline
			n	mo	n	n		%	y	%	n	n	n	n
van Tricht	2010	Netherlands	61	36	61	18	SIPS	26.2	19.6 (2.7)	31.1	7	11	9	34
Liu	2011	Taiwan	59	36	59	21	SIPS	79.6	21.5 (4)	44.1	20	1	27	11
Ziermans	2011	Netherlands	72	12	58	9	SIPS	24.1	15.3 (1)	38.9	1	8	13	36
Schlosser	2012	USA	125	12	84	27	SIPS	22.4	16.9 (3.5)	38	13	14	15	42
Katsura	2014	Japan	106	30	82	14	CAARMS	37.3	20 (4.3)	62.3	3	11	31	37
DeVylder	2014	USA	100	30	100	26	SIPS	14	20.1 (3.8)	24	4	22	10	64
Perez	2014	USA	38	24	31	15	SIPS	28.9	17.4 (3.5)	39.5	5	10	3	13
Schultze-Lutter	2014	Germany	194	24	194	74	SIPS	13.8	24.9 (6)	37	14	67	14	99
Bedi	2015	USA	34	30	34	5	SIPS	20.8	21.4 (3.5)	67.6	1	4	6	23
Katagiri	2015	Japan	41	12	41	7	SIPS	17.1	23.1 (6.7)	75.6	7	0	0	34
Labad	2015	Spain	39	12	39	10	PANSS	17.9	22.3 (4.6)	30.8	4	6	3	26
Brucato	2017	USA	200	24	200	60	SIPS	5.5	20 (3.85)	27	9	51	22	118
Collin	2020	China	158	13	158	23	SIPS	15.2	18.77 (4.9)	49.4	6	17	18	117
Bang	2019	Korea	77	24	77	16	SIPS	31.2	19.9 (3.4)	40.3	4	12	20	41
Yoviene-Sykes	2020	USA	764	12	431	33	SIPS	20.4	19.1 (4.4)	41.8	21	12	67	331
Zarogianni	2019	Switzerland	37	48	35	16	BSIP	20	25.2 (6.33)	40	6	10	1	18

Abbreviations: AP, antipsychotic; BSIP, Basel Screening Instrument for Psychosis; CAARMS, Comprehensive Assessment of At Risk Mental States; Conv., converters to psychosis at follow-up; CHR, Clinical High Risk; Nonconv., nonconverters to psychosis at follow-up; PANSS, Positive and Negative Syndrome Scale; SIPS, Structured Interview for Prodromal Syndromes.

enrollment in the program of care consists of individuals with severe ongoing symptoms and a rapidly deteriorating clinical picture (i.e., sufficiently alarming as to motivate the treating staff to initiate AP prescription before the emergence of full-blown positive symptoms). This subgroup might have an accelerated evolution towards psychosis, and the ongoing AP administration at enrollment temporarily delays the transition to psychosis so that they fulfill baseline CHR-P criteria yet develop a full psychotic state soon afterwards. Therefore, (1) this group is a hyper-CHR-P subpopulation (i.e., a subgroup with the highest imminent risk of transition within CHR-P), and (2) AP prescription is to be considered a red warning flag for enhanced transition to psychosis.

In favor of hypothesis 3, there are 2 randomized controlled trials that tested the preventive action of low-dose AP against placebo in CHR-P help-seekers (McGorry et al., 2002; McGlashan et al., 2006). Both studies found low-dose AP was able to reduce transition to psychosis in the short term (6 months) compared with placebo, but the protective effects fade at 12 months (McGlashan et al., 2006; McGorry et al., 2013). However, hypothesis 2 cannot be entirely ruled out by these findings. Indeed, distinguishing "pharmacologically attenuated first-episode psychosis" (hypothesis 2) cases from hyper-CHR-P patients with rapid progression towards psychosis (hypothesis 3) is clearly a clinical priority and an important step forward in the field. In this respect, time-dependent trajectories may be a key feature to operate such distinction, since CHR-P patients with rapid evolution towards psychosis are likely to be recognized relatively early as transitioned cases, whereas "pharmacologically attenuated first-episode psychosis" cases are presumably more likely to persist into an "attenuated symptom condition" until additional factors (social stress, substance use, and/or discontinuation of the AP treatment) intervene.

As for hypothesis 1, the best test of the hypothesis is knowing in detail the longitudinal clinical history of the participants in the study. If participants were maintained under AP during the study, they might have benefitted from the attenuation of their first-episode psychosis status until relapse into full-blown psychosis. Conversely, when the AP prescription has been suspended as per current guidelines (NICE, 2014; European Psychiatric Association: Schmidt et al., 2015), they might have been exposed to the sensibilization effect of the AP on the dopaminergic receptors and led by this sensibilization to an enhanced risk of transition to psychosis.

There was a high variability within the studies included in this meta-analysis. The main source of variability across the studies was in all likelihood the different procedures of enrollment of the participants. Differences in the procedures of enrollment indeed led to samples that allowed the inclusion of participants who had already received or were currently prescribed AP treatment, whereas other samples excluded them from enrollment. Nonetheless, sample enrichment did not seem a sufficiently powerful mechanism to explain the substantial divergence in transition prevalence between AP-exposed and AP-naïve CHR-P individuals. Bias in publication was not present in the analyzed groups. However, as can be seen in the provided forest plot, there were differences in transition to psychosis prevalence within groups not attributable to past exposition to AP that might depend on the characteristics of the sample (age, gender proportion, comorbidity, and so on). We were not able to explore the role of these characteristics because they were not systematically reported in the source studies, that is, the details about associated characteristics by subgroup (AP exposed and not exposed in the same sample) were too few to allow a meta-regression.

Table 2. Studies Included in the Meta-Analysis and Considering Baseline AP Exposure as Exclusion Criterion

Study first author	Year	Site	Baseline CHR sample (n)	Follow-up (mo)	Follow-up sample (n)	Raw transitions (n)	UHR instrument	Mean age (SD) (y)	Gender (F) (%)
Kéri	2009	Hungary	67	12	67	31	CAARMS	21.2 (3.6)	46.3
Lemos-Giráldez	2009	Spain	61	36	45	14	SIPS	21.7 (3.83)	34.4
Amminger	2010	Austria	40	12	40	11	PANSS	16 (1.7)	67.5
Ruhrmann	2010	EU	245	18	183	37	SIPS	23.0	44.1
Addington	2012	Canada/USA	172	24	146	26	SIPS	19.76 (4.5)	42.7
Koutsouleris	2012	Germany	48	48	35	15	PANSS	24.7 (5.8)	33.3
Simon	2012	Switzerland	73	24	42	10	SIPS	20.4 (5.2)	39.7
Lee	2013	Singapore	173	6	173	6	CAARMS	21.3 (3.5)	32.4
Hui	2013	UK	60	12	60	6	CAARMS	20.2 (2.9)	48.3
Fusar-Poli	2013	UK	290	24	278	44	CAARMS	22.9 (4.61)	43.9
Welsh	2014	UK	30	24	28	2	CAARMS	15.8 (1.4)	53.3
Armando	2015	Italy	35	12	35	7	SIPS	13.8 (2.1)	48.57
Spada	2016	Italy	22	6	22	4	CAARMS	16.1 (1)	45.5
Francesconi	2017	Italy	67	24	58	21	CAARMS	24.5 (3.4)	42.2
Poletti	2018	Italy	51	24	21	4	CAARMS	15.4 (1.56)	58.8
Zhang	2020	China	273	36	219	55	SIPS	20.5 (6.21)	51.6
			244	36	216	52	SIPS	15.8 (1.26)	54.1
Howes	2020	UK	51	15	36	10	CAARMS	23 (4)	43

Abbreviations: AP, antipsychotic; CAARMS, Comprehensive Assessment of At Risk Mental States; Conv., converters to psychosis at follow-up; CHR, Clinical High Risk; Nonconv, nonconverters to psychosis at follow-up; PANSS, Positive and Negative Syndrome Scale; SIPS, Structured Interview for Prodromal Syndromes.
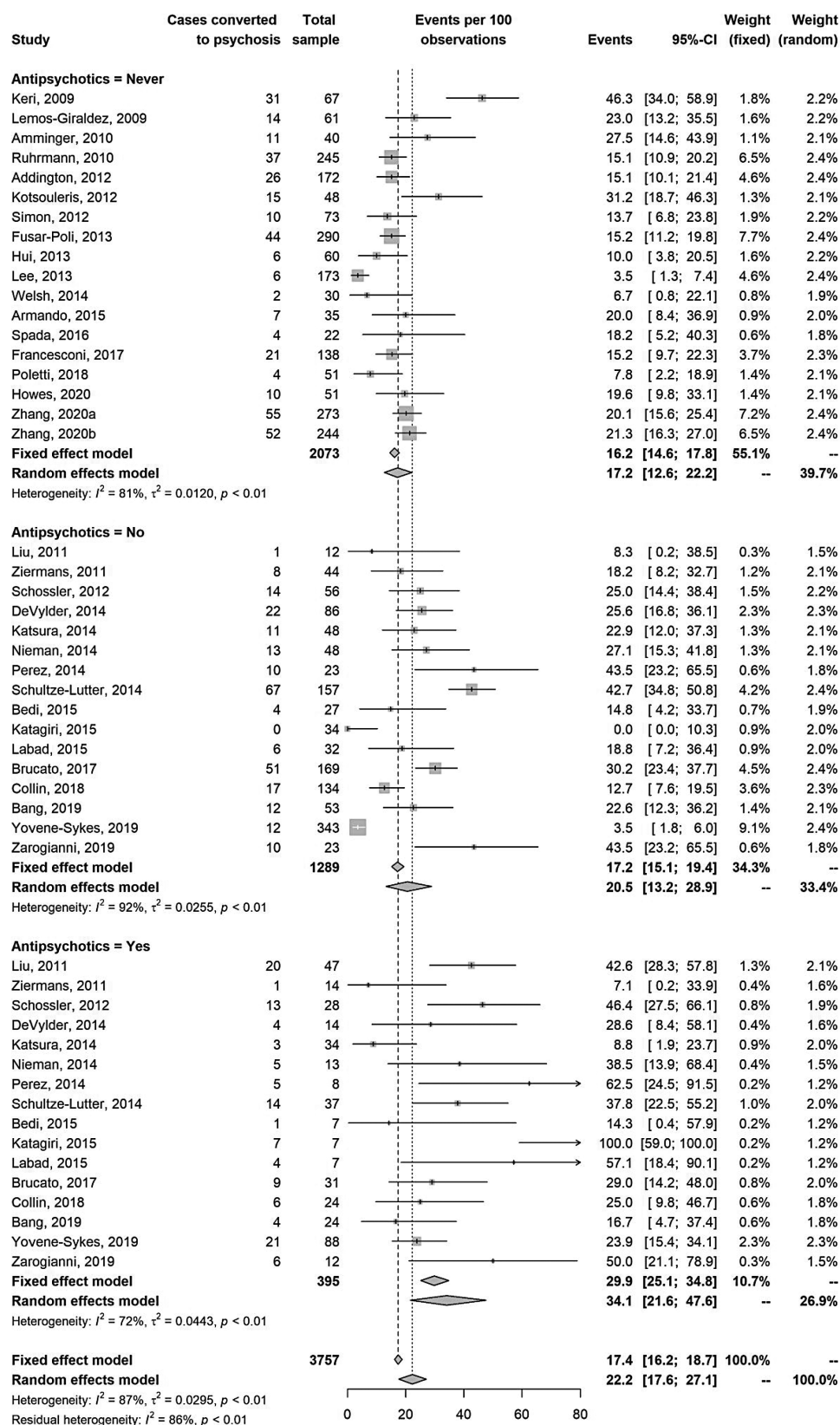
Study	Cases converted to psychosis	Total sample	Events per 100 observations	Events	95%-CI	Weight (fixed)	Weight (random)
Antipsychotics = Never							
Keri, 2009	31	67		46.3	[34.0; 58.9]	1.8%	2.2%
Lemos-Giraldez, 2009	14	61		23.0	[13.2; 35.5]	1.6%	2.2%
Amminger, 2010	11	40		27.5	[14.6; 43.9]	1.1%	2.1%
Ruhrmann, 2010	37	245		15.1	[10.9; 20.2]	6.5%	2.4%
Addington, 2012	26	172		15.1	[10.1; 21.4]	4.6%	2.4%
Kotsouleris, 2012	15	48		31.2	[18.7; 46.3]	1.3%	2.1%
Simon, 2012	10	73		13.7	[6.8; 23.8]	1.9%	2.2%
Fusar-Poli, 2013	44	290		15.2	[11.2; 19.8]	7.7%	2.4%
Hui, 2013	6	60		10.0	[3.8; 20.5]	1.6%	2.2%
Lee, 2013	6	173		3.5	[1.3; 7.4]	4.6%	2.4%
Welsh, 2014	2	30		6.7	[0.8; 22.1]	0.8%	1.9%
Armando, 2015	7	35		20.0	[8.4; 36.9]	0.9%	2.0%
Spada, 2016	4	22		18.2	[5.2; 40.3]	0.6%	1.8%
Francesconi, 2017	21	138		15.2	[9.7; 22.3]	3.7%	2.3%
Poletti, 2018	4	51		7.8	[2.2; 18.9]	1.4%	2.1%
Howes, 2020	10	51		19.6	[9.8; 33.1]	1.4%	2.1%
Zhang, 2020a	55	273		20.1	[15.6; 25.4]	7.2%	2.4%
Zhang, 2020b	52	244		21.3	[16.3; 27.0]	6.5%	2.4%
Fixed effect model		2073		16.2	[14.6; 17.8]	55.1%	--
Random effects model				17.2	[12.6; 22.2]	--	39.7%
Heterogeneity: $I^2 = 81\%$, $\tau^2 = 0.0120$, $p < 0.01$							
Antipsychotics = No							
Liu, 2011	1	12		8.3	[0.2; 38.5]	0.3%	1.5%
Ziermans, 2011	8	44		18.2	[8.2; 32.7]	1.2%	2.1%
Schossler, 2012	14	56		25.0	[14.4; 38.4]	1.5%	2.2%
DeVylder, 2014	22	86		25.6	[16.8; 36.1]	2.3%	2.3%
Katsura, 2014	11	48		22.9	[12.0; 37.3]	1.3%	2.1%
Nieman, 2014	13	48		27.1	[15.3; 41.8]	1.3%	2.1%
Perez, 2014	10	23		43.5	[23.2; 65.5]	0.6%	1.8%
Schultze-Lutter, 2014	67	157		42.7	[34.8; 50.8]	4.2%	2.4%
Bedi, 2015	4	27		14.8	[4.2; 33.7]	0.7%	1.9%
Katagiri, 2015	0	34		0.0	[0.0; 10.3]	0.9%	2.0%
Labad, 2015	6	32		18.8	[7.2; 36.4]	0.9%	2.0%
Brucato, 2017	51	169		30.2	[23.4; 37.7]	4.5%	2.4%
Collin, 2018	17	134		12.7	[7.6; 19.5]	3.6%	2.3%
Bang, 2019	12	53		22.6	[12.3; 36.2]	1.4%	2.1%
Yovene-Sykes, 2019	12	343		3.5	[1.8; 6.0]	9.1%	2.4%
Zarogianni, 2019	10	23		43.5	[23.2; 65.5]	0.6%	1.8%
Fixed effect model		1289		17.2	[15.1; 19.4]	34.3%	--
Random effects model				20.5	[13.2; 28.9]	--	33.4%
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.0255$, $p < 0.01$							
Antipsychotics = Yes							
Liu, 2011	20	47		42.6	[28.3; 57.8]	1.3%	2.1%
Ziermans, 2011	1	14		7.1	[0.2; 33.9]	0.4%	1.6%
Schossler, 2012	13	28		46.4	[27.5; 66.1]	0.8%	1.9%
DeVylder, 2014	4	14		28.6	[8.4; 58.1]	0.4%	1.6%
Katsura, 2014	3	34		8.8	[1.9; 23.7]	0.9%	2.0%
Nieman, 2014	5	13		38.5	[13.9; 68.4]	0.4%	1.5%
Perez, 2014	5	8		62.5	[24.5; 91.5]	0.2%	1.2%
Schultze-Lutter, 2014	14	37		37.8	[22.5; 55.2]	1.0%	2.0%
Bedi, 2015	1	7		14.3	[0.4; 57.9]	0.2%	1.2%
Katagiri, 2015	7	7		100.0	[59.0; 100.0]	0.2%	1.2%
Labad, 2015	4	7		57.1	[18.4; 90.1]	0.2%	1.2%
Brucato, 2017	9	31		29.0	[14.2; 48.0]	0.8%	2.0%
Collin, 2018	6	24		25.0	[9.8; 46.7]	0.6%	1.8%
Bang, 2019	4	24		16.7	[4.7; 37.4]	0.6%	1.8%
Yovene-Sykes, 2019	21	88		23.9	[15.4; 34.1]	2.3%	2.3%
Zarogianni, 2019	6	12		50.0	[21.1; 78.9]	0.3%	1.5%
Fixed effect model		395		29.9	[25.1; 34.8]	10.7%	--
Random effects model				34.1	[21.6; 47.6]	--	26.9%
Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.0443$, $p < 0.01$							
Fixed effect model		3757		17.4	[16.2; 18.7]	100.0%	--
Random effects model				22.2	[17.6; 27.1]	--	100.0%
Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.0295$, $p < 0.01$							
Residual heterogeneity: $I^2 = 86\%$, $p < 0.01$							

(x-axis: 0 20 40 60 80)

Figure 2. Forest plot.

Additional limitations should be considered. First, included studies are not primarily aimed to address the issue of pretest risk enrichment and rarely mentioned the steps of specific recruitment strategy. Therefore, we opted for a clinically rational epidemiologic proxy, that is, we considered studies with baseline AP-exposed CHR-P as putatively indicative of a

Table 3. Main Results of the Meta-analysis of Studies on Transition to Psychosis in Sample of CHR-P Subjects With or Without Baseline Exposure to Antipsychotics

		k	n	Effect size	95% CI		Between Q	P	Q	P	tau²	I²	95% CI	
Main analysis	Exposed to AP	16	395	29.9%	25.1%	34.8%								
	Not exposed to AP	16	1289	17.2%	15.1%	19.4%								
	Never exposed to AP	18	2073	16.2%	14.6%	17.8%								
	FE model						39.7	<0.0001						
	Exposed to AP	16	395	34.1%	21.6%	47.6%								
	Not exposed to AP	16	1289	20.5%	13.2%	28.9%								
	Never exposed to AP	18	2073	17.2%	12.6%	22.2%								
	RE model						8.8	0.0123	373.7	<.001	0.029	85.9%	82.2%	88.9%
Sensitivity analysis	Exposed to AP	16	395	29.9%	25.1%	34.8%								
	Not exposed to AP	16	1289	17.2%	15.1%	19.4%								
	FE model						29.0	<0.0001						
	Exposed to AP	16	395	34.1%	21.6%	47.6%								
	Not exposed to AP	16	1289	20.5%	13.2%	28.9%								
	RE model						4.2	0.0396	271.9	<.001	0.0382	88.6%	85.0%	91.3%
	Exposed to AP	16	395	29.9%	25.1%	34.8%								
	Never exposed to AP	18	2073	16.2%	14.6%	17.8%								
	FE model						39.3	<0.0001						
	Exposed to AP	16	395	34.1%	21.6%	47.6%								
	Never exposed to AP	18	2073	17.2%	12.6%	22.2%								
	RE model						8.8	0.0031	183.3	<.001	0.0327	82.0%	75.6%	86.7%
	Not exposed to AP	16	1289	17.2%	15.1%	19.4%								
	Never exposed to AP	18	2073	16.2%	14.6%	17.8%								
	FE model						0.9	0.3369						
	Not exposed to AP	16	1289	20.5%	13.2%	28.9%								
	Never exposed to AP	18	2073	17.2%	12.6%	22.2%								
	RE model						0.7	0.3929	281.8	<.001	0.0179	88.6%	85.1%	91.3%

Abbreviations: AP, antipsychotics; FE, fixed-effects model; k, number of studies; RE, random-effects model.

higher severity of the referred group (i.e., a mental state severe enough to justify AP prescription instead of psychosocial interventions only or non-AP medications such as antidepressant, anxiolytics, and mood-stabilizers). Similarly, we wished to analyze the impact of other non-AP drugs as well, since they might contribute to the baseline clinical presentation (e.g., non-AP medications can have an influence on reducing anxiety and mood oscillations as well as sleep disturbances), but only a few studies reported analyzable information (e.g., on the type and dose of medications).

Nonetheless, the results indicate that the pretest risk enrichment due to the heterogeneity of sampling strategies in CHR-P research is unlikely to justify the apparent negative prognostic effect of baseline antipsychotic exposure on the risk of transition to psychosis. This further highlights the importance of deconstructing this phenomenon (Raballo et al., 2021), which has paramount implications for the treatment of psychosis and the prevention or mitigation of its undesired long-term outcomes.

Conclusions

This meta-analysis further investigates the prognostic impact of baseline AP prescription in CHR-P help-seekers and tests whether pre-test risk enrichment could be implicated in the increased meta-analytic risk of transition that characterizes those CHR-P with ongoing AP at inclusion. The results indicate that transition prevalence in AP-naïve CHR-P is similar independently of whether they were enrolled in studies with rigorous exclusion criteria on AP exposure or more lenient ones (i.e., allowing the enrollment of CHR-P individuals under AP therapy). Therefore, pre-test risk enrichment is not implicated in the observed negative prognostic effect of baseline antipsychotic exposure in CHR-P. The results invite a further dissection of such phenomenon, possibly discriminating "pharmacologically attenuated first-episode psychosis" from those CHR-P in which AP prescription likely indexes a subgroup with the highest imminent risk of transition because of rapidly escalating severity.

The investigation of the potential negative prognostic effect of AP in young help-seekers is not merely an academic topic. Indeed, there is increasing awareness that AP are often prescribed in youth for conditions that did not receive approved indication, especially in youth from underserved communities (Olfson et al., 2015; Mackie et al., 2021). Moreover, little information exists so far about the long-term effects of antipsychotics on a still-developing brain (Harrison et al., 2012), and evidence on safety outcomes in children and adolescents is often indirect or based on just 1 study (Krause et al., 2018). Even if in some early-intervention services for CHR-P, AP are often used to treat comorbid disorders rather than emerging psychosis (Fusar-Poli et al., 2020; Kotlicka-Antczak et al., 2020), a proper investigation of their impact on the risk of transition to psychosis is mandatory before endorsing more specific indications on their use (Zhang et al., 2020) or disallowing tout court their prescription as per recommendation 1.2.3.2 of the current NICE guidelines.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

Acknowledgments

Statement of Interest

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