Predicting Psychosis

Meta-analysis of Transition Outcomes in Individuals at High Clinical Risk

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Context: A substantial proportion of people at clinical high risk of psychosis will develop a psychotic disorder over time. However, the risk of transition to psychosis varies between centers, and some recent work suggests that the risk of transition may be declining.

Objective: To quantitatively examine the literature to date reporting the transition risk to psychosis in subjects at clinical high risk.

Data Sources: The electronic databases were searched until January 2011. All studies reporting transition risks in patients at clinical high risk were retrieved.

Study Selection: Twenty-seven studies met the inclusion criteria, comprising a total of 2502 patients.

Data Extraction: Transition risks, as well as demographic, clinical, and methodologic variables, were extracted from each publication or obtained directly from its authors.

Data Synthesis: There was a consistent transition risk, independent of the psychometric instruments used, of 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years. Significant moderators accounting for heterogeneity across studies and influencing the transition risks were the age of participants, publication year, treatments received, and diagnostic criteria used. There was no publication bias, and a sensitivity analysis confirmed the robustness of the core findings.

Conclusions: The state of clinical high risk is associated with a very high risk of developing psychosis within the first 3 years of clinical presentation, and the risk progressively increases across this period. The transition risk varies with the age of the patient, the nature of the treatment provided, and the way the syndrome and transition to psychosis are defined.

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Early treatment will prevent the necessity of placing some patients in a lunatic asylum.
Maudsley, 1909[1]

ALTHOUGH PRODROMAL symptoms of psychosis have long been recognized,[2] the clinical management of psychotic disorders conventionally begins at the first episode of frank psychosis, and, until recently, the period immediately preceding the first episode received relatively little attention. For the past 15 years, there has been increasing academic and clinical interest in people presenting with potentially prodromal symptoms.[3] This clinical syndrome has been termed an *at risk mental state*,[4] and operationalized criteria—the *ultra high risk* (UHR)[5] or *clinical high risk* (HR)[6] criteria—have been developed to identify the syndrome.[4] The criteria apply to young help-seeking patients and require 1 of 3 presentations: "attenuated" psychotic symptoms, full-blown psychotic symptoms that are brief and self-limiting, or a significant decrease in functioning in the context of a genetic risk for schizophrenia.[7] Additional prodromal criteria emerging from the basic symptoms (BS) literature[8] include subjective disturbances of cognitive processing and the perception of the self and the world.[9] Belonging to one of these prodromal groups, which we hereafter term the *clinical high risk* syndrome, is associated with impairments in neuropsychologic performance[10] and alterations in the structure[11-13] (for meta-analyses, see Fusar-Poli et al[14,15]), function[16-18] (for meta-analyses, see Smieskova et al[19] and Fusar-Poli et al[20]), connectivity,[21] and neurochemistry[22-24] of the brain.

Interest in this field has grown to the extent that several clinical trials[25] of preventative intervention have been con-

ducted in this population, and there is an ongoing debate[26] about including an HR syndrome diagnostic category in the *DSM-5*.[26-29] A key concept to emerge from work in this area is that although people presenting with prodromal features have a greatly increased risk of developing a psychotic disorder within a relatively short period,[30] only a few will do so. Furthermore, the risk of transition to psychosis in samples of HR patients has varied between studies with inconsistent findings. In addition, the risks reported in some recent studies have been lower than those in earlier studies, leading to suggestions that the risk of transition may be declining.[31] This apparent inconsistency in the risks across centers, and even within centers over time, raises questions about the predictive validity of the HR state and about the appropriateness of preventative intervention in this group: the lower the transition risk, the less ethical and practicable preventative treatment appears.[3] It is thus important to clarify the risk of transition to psychosis across HR samples and to examine the consistency of the risk estimates in the literature. There are a number of plausible reasons why transition risks may vary between studies. Although some reviews addressing these points are available in the current literature,[32,33] at present there are no standardized means of assessing and defining the HR state nor of defining the transition to psychosis.[34] Although there are similarities between the different instruments used for these purposes,[35,36] the extent to which they produce comparable results has yet to be formally evaluated.

The first aim of the present study was to estimate the mean risk of transition to psychosis in HR patients by performing a meta-analysis of data from all studies in the existing literature. We specifically estimated how the risk of transition varied with the duration of clinical follow-up after presentation. Finally, we tested the potentially confounding effect of between-center variations in the assessment instruments and diagnostic criteria used, the demographic features of the samples, and the types of treatment they received.

METHODS

SELECTION PROCEDURES

A systematic search strategy was used to identify relevant studies. Two independent researchers conducted a 2-step literature search. First, a PubMed and EMBASE search was performed to identify putative studies reporting transition risks in patients at HR for psychosis. The search was conducted between December 1, 2010, and January 1, 2011, with no time span specified for date of publication. The following search terms were used: *psychosis risk*, *ultra high risk*, *UHR*, *prodromal psychosis*, *psychosis transition*, *basic symptoms*, and *psychosis onset*. Second, the reference lists of the articles included in the review were manually checked for any studies not identified by the computerized literature search. There was no language restriction, although all the included papers were in English.

SELECTION CRITERIA

Studies were included if they met the following criteria: (1) were reported in an original paper in a peer-reviewed journal, (2) had involved patients at HR for psychosis defined according to established international criteria, and (3) had reported the transition risk to psychosis in the sample investigated. When the inclusion criteria for the HR group were not clearly defined, the study was excluded. Studies of patients at genetic risk (twins or first- or second-degree relatives) for psychosis[37,38] or schizotypal personality disorder[39] were not included. When there were 2 or more studies from the same center, we contacted the authors to determine whether there was overlap in the respective samples; overlapping samples were excluded. Disagreements in selection criteria were resolved through discussion and consensus. To achieve a high standard of reporting, we adopted the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[40] (**Figure 1**).

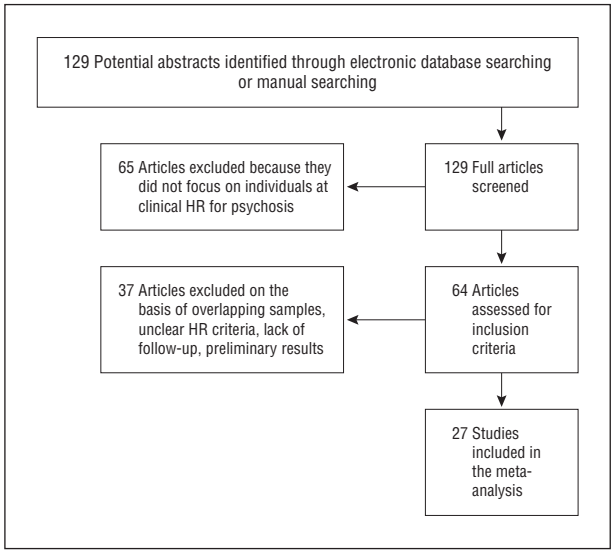


Figure 1. Search strategy used for the inclusion of the studies considered in the present meta-analysis. HR indicates the clinical high risk state for psychosis.

RECORDED VARIABLES

The variables for each article included in the meta-analysis were inclusion criteria for the HR state, psychometric instruments used to assess the psychosis risk, year of publication, sex, mean age of participants, duration of follow-up, transition risk at different time points, criteria used to define transition to psychosis, exposure to antipsychotics, and treatment provided.

QUALITY ASSESSMENT

Although quality assessments can be reliably conducted in meta-analyses of experimental studies, their use in observational research is controversial, with no clear consensus on rating methods or their appropriate use in the analysis.[41] In the present meta-analysis, we used a simple objective rating system (based on the meta-analysis of Paulson and Bazemore[42]) that coded studies on a scale of 0 to 10. Because evidence on the validity of quality ratings in observational research is lacking, we adopted the Meta-analysis of Observational Studies in Epidemiology[43] approach of broadly including studies and using sensitivity analysis to determine incremental effects of lower-quality studies.

STATISTICAL ANALYSIS

Data were entered into an electronic database and analyzed with a quantitative meta-analytical approach using Comprehensive

Meta-Analysis Software, version 2 (Biostat, Inc).[44] This software allows the meta-analysis of risks in a single group using the number of events and the total sample[45] and uses the same computational algorithms used by the Cochrane collaborators to weigh studies by the inverse variance method.[44] The primary outcome was the risk of transition to psychosis in HR patients across the overall database. In a secondary step, we conducted additional meta-analyses to address transition risks at different follow-up times (6, 12, 18, 24, 36, and >36 months). Furthermore, to provide a better temporal resolution, studies reporting survival curves were included in a subanalysis of Kaplan-Meier estimates of transition risks over time. Kaplan-Meier curves were digitally measured from publications using the GNU imaging manipulation program, version 2.6.1.[46] For each day beyond the 24 months after presentation, the combined transition risk was calculated by summing the number of transitions from each publication and dividing by the total number of patients at baseline. One large study in this analysis[47] had originally published a transition curve ending at 18 months. Because a 2-order polynomial curve fitted the data accurately (R^2=0.99), we projected the survival curve to 24 months, allowing this sample to be included in the combined Kaplan-Meier curve.

To determine whether categorical factors modified the transition risks in HR patients (inclusion criteria for the HR state [UHR or basic symptoms {BS}], subgroup of UHR criteria [Comprehensive Assessment of At-Risk Mental States {CAARMS} or Structured Interview for Prodromal Syndromes {SIPS}], treatment with antipsychotics or psychotherapy, criteria used to define psychosis onset [standard, CAARMS, or SIPS]), subgroup analyses were performed.[42] The influence of continuous moderator variables (age, year of publication, and proportion of females) was tested using meta-regression analyses. The slope of meta-regression (β-coefficient: direct [+] or inverse [-]) of the regression line indicates the strength of a relationship between moderator and outcome. To limit the risk of false-positive (type I) errors arising from multiple comparisons, we adjusted $P<.05$ by dividing α by the number of meta-regressions.

Heterogeneity among study point estimates was assessed with the Q statistic,[42] with magnitude of heterogeneity being evaluated with the I^2 index.[48] Because the studies in this meta-analysis were characterized by heterogeneity, random-effects models were used. In general, random-effects models are more conservative than fixed-effects models and appear to better address heterogeneity between studies and study populations, allowing for greater flexibility in parsing effect-size variability. Moreover, they are less influenced by extreme variations in sample size.[49] Studies with negative results are less likely to be published than studies with statistically significant results. The possibility of a publication bias in the present study was examined by visually inspecting funnel plots and applying the regression intercept of Egger et al.[50] In this way, we assessed whether there was a tendency for selective publication of studies based on the nature and direction of their results. In addition, we used the fail-safe procedure of Orwin,[51] which is based on effect sizes that would be considered practically insignificant, rather than the traditional null-effect reference. This generated a number of unpublished studies with effects at the estimated population base risk for psychosis transition (1%)[52] that would be needed to move estimates to a nonsignificant difference from base risks. To assess the robustness of the results, we performed sensitivity analyses by sequentially removing each study and rerunning the analysis. We also conducted a separate analysis excluding studies with quality ratings in the lowest third to determine whether potential methodologic weaknesses influenced meta-analytic estimates.

RESULTS

RETRIEVED STUDIES

Twenty-seven studies published between 1996 and 2011 met the inclusion criteria (Figure 1). The overall database comprised 2502 HR patients (mean [SD] age, 19.9 [3.6] years; 58.3% males) (**Table**). In summary, there were 2 main forms of diagnostic criteria used to define HR features in help-seeking patients, the UHR and the BS, and most centers worldwide have adopted one of these. The UHR state was independently assessed with the CAARMS,[36] the Basel Screening Instrument for Psychosis,[72] and the SIPS.[35] Psychosis transition was defined according to "standard" criteria (from the 2 major psychiatric diagnostic guidelines, *DSM* and *International Classification of Diseases* [*ICD*]) or criteria from the main UHR clinical schedules.[73] A detailed discussion of the inclusion and transition criteria used with studies is provided as an eAppendix and eTable (http://www.archgenpsychiatry.com).

TRANSITION RISKS IN SUBJECTS AT HR FOR PSYCHOSIS

Across the overall database, the mean transition risk to a full psychotic episode from an HR state was 29.2% (95% CI, 27.3%-31.1%), with a mean follow-up of 31 months. Additional meta-analyses were performed on subsets of studies to assess the transition risks at different times after clinical presentation. The transition risks at 6, 12, 18, 24, 36, and more than 36 months were 17.7%, 21.7%, 26.9%, 29.1%, 31.5%, and 35.8%, respectively ($P<.001$ for all) (**Figure 2**). To provide a better temporal resolution, the subset of studies (n=6) that reported Kaplan-Meier estimates of transition risks of psychosis are summarized in **Figure 3**.

EFFECT OF MODERATORS

Age

Across all studies, there was a significant effect for the age of HR patients on transition risks. Meta-regression analysis revealed a modest but significant increase of transition risk with increasing age of patients at HR for psychosis (β=0.07; 95% CI, 0.05-0.09; Q=27.94; $P<.001$ for both) (**Figure 4**).

Sex

Across all studies, the effect of the sex of HR patients on the meta-analytical estimates was nonsignificant (β=0.002; 95% CI, –0.08 to 0.12; $P=.88$).

Criteria Used to Define the HR

The mean transition risk from HR state to established psychosis in studies using the BS approach was 48.5% (95% CI, 41.9%-55.9%); however, there was a large variance in the risks across studies (I^2=96.95; $P<.001$). In studies using

Table. Studies of Patients at Clinical HR for Psychosis Included in the Meta-analysis

Source	Research Center	Type of Risk	Assessment Instrument	HR Patients			RW
				No.	Female Sex, %	Age, Mean (SD), y	
Yung et al, 1996[4]	Melbourne, PACE	APS, BLIPS, GRD	BPRS[a]	33	26.0	19.0	1.06
Yung et al, 1998[53]	Melbourne, PACE	APS, BLIPS, GRD	BPRS[a]	20	. . .	. . .	1.21
Klosterkötter et al, 2001[9]	Multicenter, CER	BS	BSABS	110	46.4	28.8 (9.8)	5.08
Miller et al, 2003[35]	New Haven, PRIME	APS, BLIPS, GRD	SOPS/SIPS	14	. . .	17.9 (5.8)	0.75
Yung et al, 2004[5]	Melbourne, PACE	APS, BLIPS, GRD	BPRS[a]	104	51.0	19.4 (3.5)	5.47
Mason et al, 2004[54]	Newcastle, PAS	APS, BLIPS, GRD	BPRS[a]	74	47.3	17.3 (2.8)	4.07
Lencz et al, 2006[55]	New York, RAP	APS	SOPS/SIPS	38	42.0	16.5 (2.2)	1.95
Schultze-Lutter et al, 2007[56]	Cologne, FETZ	BS	SPIA	146	30.8	24.4 (5.2)	7.09
Phillips et al, 2007[57]	Melbourne, PACE	APS, BLIPS, GRD	BPRS[a]	59	42.3	20.0	3.04
Morrison et al, 2007[58]	Manchester, EDIE	APS, BLIPS, GRD	PANSS[a]	60	30.0	22.0 (4.5)	2.11
Cornblatt et al, 2007[6]	New York, RAP	APS	SOPS/SIPS	48	39.6	15.8 (2.2)	1.98
Yung et al, 2008[7]	Melbourne, PACE	APS, BLIPS, GRD	CAARMS	119	. . .	18.3	3.51
Riecher-Rössler et al, 2009[59]	Basel, FEPSY	APS, BLIPS, GRD	BSIP	64	40.0	26.5 (8.6)	3.18
Koutsouleris et al, 2009[11]	Munich, FETZ	BS, APS, BLIPS	SPIA, SIPS	46	37.0	25.1 (5.9)	2.51
Woods et al, 2009[60b]	Multicenter, NAPLS	APS, BLIPS, GRD	SIPS	377	37.9	18.2	17.14
Keri et al, 2009[61]	Hungary	APS, BLIPS, GRD	CAARMS	67	46.3	21.0	3.80
Lemos-Giráldez et al, 2009[62]	Cantabria	APS, BLIPS, GRD	SIPS	61	34.4	21.7	2.37
Ruhrmann et al, 2010[47]	Multicenter, EPOS	BS, APS, BLIPS, GRD	BSABS, SIPS	245	44.1	23.0 (5.2)	8.36
Nelson and Young, 2010[63]	Melbourne, PACE	APS, BLIPS, GRD	CAARMS	168	60.7	18.3 (2.7)	3.01
Bechdolf et al, 2010[64]	Melbourne, PACE	APS, BLIPS, GRD	CAARMS	92	65.2	18.0 (3.0)	3.44
Demjaha et al, 2010[65]	London, OASIS	APS, BLIPS, GRD	CAARMS	122	42.6	23.4 (4.9)	3.38
Simon and Umbricht, 2010[66]	Bruderholz, Switzerland	APS, BLIPS, GRD	SIPS	72	40.3	20.3 (4.9)	1.89
Sabb et al, 2010[67]	Los Angeles	APS, BLIPS, GRD	SIPS	43	30.0	17.4 (3.5)	2.15
Velthorst et al, 2010[68]	Amsterdam	APS, BLIPS, GRD	SIPS	77	33.8	19.2 (3.8)	3.26
Mittal et al, 2010[69]	Multicenter, Los Angeles	APS, BLIPS, GRD	SIPS	90	32.2	15.6 (3.0)	3.87
Amminger et al, 2010[70]	Vienna	APS, BLIPS, GRD	CAARMS	81	66.7	16.4 (2.0)	2.40
Ziermans et al, 2011[71]	Utrecht, DUPS	BS, APS, BLIPS, GRD	BSABS, SOPS/SIPS	72	30.5	15.3 (1.9)	2.05

Abbreviations: APS, Attenuated Psychotic Symptoms; BLIPS, Brief Limited Intermittent Psychotic Symptoms; BPRS, Brief Psychiatric Rating Scale; BS, Basic Symptoms; BSABS, Bonn Scale for the Assessment of Basic Symptoms; BSIP, Basel Screening Instrument for Psychosis; CAARMS, Comprehensive Assessment of At-Risk Mental States; CER, Cologne Early Recognition; DUPS, Dutch Prediction of Psychosis Study; EDIE, Early Detection and Intervention Evaluation; EPOS, European Prediction of Psychosis Study; FEPSY, Früherkennung von Psychosen; FETZ, Early Recognition and Intervention Centre for mental crises; GRD, Genetic Risk and Deterioration Syndrome; HR, clinical high risk; NAPLS, North American Prodrome Longitudinal Study; OASIS, Outreach and Support in South London; PACE, Personal Assessment and Crisis Evaluation; PANSS, Positive and Negative Syndrome Scale; PAS, Psychological Assistance Service; PRIME, Prevention Through Risk Identification, Management, and Education; RAP, Recognition and Prevention; RW, Relative Weight of the individual studies in the overall meta-analysis on the basis of its sample size; SIPS, Structured Interview for Prodromal Syndromes; SOPS, Scale of Prodromal Symptoms; SPIA, Schizophrenia Proneness Instrument, Adult Version.

[a] Used the PACE (At-Risk Mental State) criteria before the CAARMS was developed and used BPRS or PANSS to assess APS, BLIPS, or GRD. Additional details on the inclusion HR criteria, psychometric instruments, and criteria used for psychosis transition are provided as an eAppendix and eTable (http://www.archgenpsychiatry.com).

[b] Revised analysis of Cannon et al, 2008.[30]

the UHR approach, the transition risk was 27.7% (95% CI, 25.6%-29.9%), whereas in studies combining both approaches, it was 22.5% (95% CI, 18.4%-27.3%). There was considerable variability across the 3 instruments ($Q=46.56_2$; $P<.001$) (**Figure 5**). In a separate analysis, we compared the transition risk in UHR studies that used the SIPS and the CAARMS criteria. The transition risks were similar (CAARMS, 27.4% [95% CI, 24.6%-30.4%], and SIPS, 28.1% [25.1%-31.3%]) and were not statistically different (CAARMS vs SIPS, Q=0.12; $P=.73$).

Criteria Used to Define Transition to Psychosis

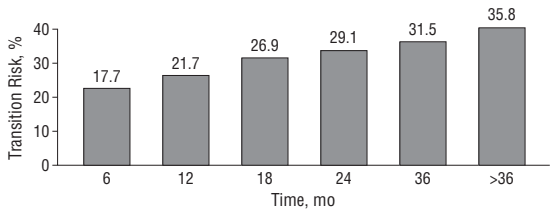
The definition of psychosis transition was consistent when psychometric criteria were used (standard vs CAARMS vs SIPS). Thus, transition risks were 27.3% (95% CI, 25.0%-29.7%) in studies that defined transition in accordance with the CAARMS criteria and 27.5% (24.3%-30.9%) in studies that used the SIPS transition criteria (CAARMS vs SIPS, Q=0.008; $P=.93$). Conversely, when transition was defined in accordance with the standard classification (*ICD-10*, *DSM-III*, or *DSM-IV*), there was a large variance in the risks across studies (mean transition risk, 51.1%; 95% CI, 43.4%-58.7%; $I^2=97.23$).

YEAR OF PUBLICATION

Meta-regression of the year of publication (1996-2011) revealed a modest but significant effect toward reduced transition risks for the most recently published studies ($\beta=-0.15$; 95% CI, −0.17 to −0.11; Q=85.18; $P<.001$ for both).

TREATMENT

The transition risks in patients receiving some specific form of psychologic treatment (such as cognitive behavioral therapy) was 24.9% (95% CI, 23.2%-28.0%) com-



No. of Studies	Follow-up, mo	Transition Risks, 95% CI
9	6	17.7 (12.3-24.9)
13	12	21.7 (16.6-27.8)
4	18	26.9 (19.5-35.9)
12	24	29.1 (23.2-35.7)
6	36	31.5 (23.8-35.0)
4	>36	35.8 (29.6-42.5)

P<.001 for all.

Figure 2. Meta-analyses of transition risks from clinical high risk to full psychosis at different time points of follow up.

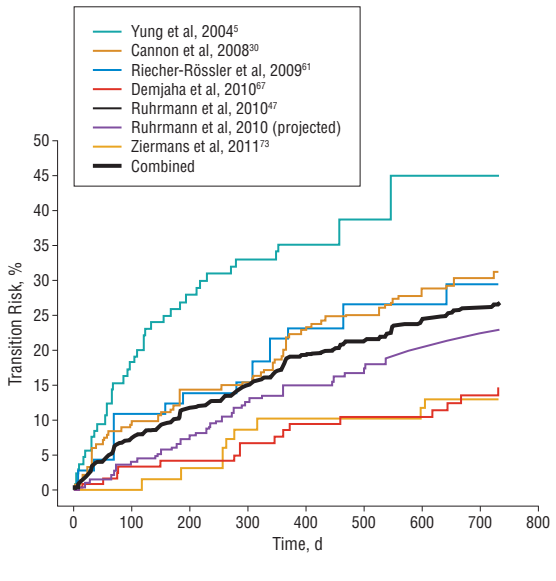


Figure 3. Kaplan-Meier estimates of transition risks (6 studies) in the clinical high risk (HR) state for psychosis. The proportion of HR subjects who developed a frank psychotic episode is depicted on the *y* axis. Follow-up time is depicted on the *x* axis.

pared with 32.8% (29.5%-36.2%) in studies in which patients received nonspecific psychiatric care (case management), termed *care as usual* (psychologic treatment vs care as usual, Q=11.69; *P*=.001). The transition risk in studies in which HR patients had been offered antipsychotics was 22.9% (95% CI, 20.5%-25.5%), whereas the risk in studies in which patients were not exposed to antipsychotics was 36.5% (32.1%-41.3%) (exposed vs nonexposed, Q=28.32; *P*<.001).

TESTS FOR PUBLICATION BIAS

Visual inspection of funnel plots revealed no obvious evidence of publication bias, and quantitative evaluation of publication bias, as measured by the Egger intercept, was nonsignificant (*P*=.70). The Orwin fail-safe procedure estimated that 171 unpublished studies would be needed

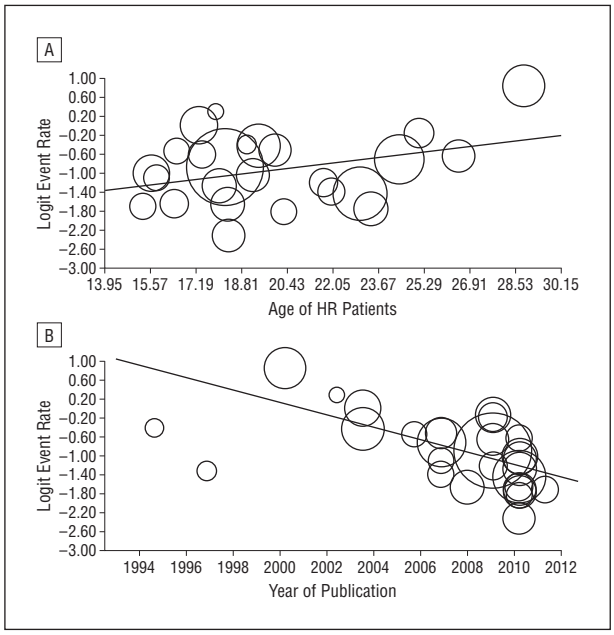


Figure 4. Meta-regression on the effects of age of subjects at clinical high risk (HR) and publication year on transition risks to psychosis. Circle size reflects the weight a study obtained in the meta-regression. Excluding the outlier on the right (panel A) and the 2 outliers on the left (panel B) did not reverse statistical significance (age: β=0.07, 95% CI, 0.05 to 0.09, *P*<.001; Q=27.94, *P*<.001; publication year: β=−0.15, 95% CI, −0.17 to −0.11, *P*<.001; Q=85.18, *P*<.001).

to make the overall meta-analytic estimate of transition risk nonsignificantly different from the base risk.[52]

SENSITIVITY ANALYSES

No study affected the meta-analytic estimate by more than 5%. Because of their large sample sizes, the multicenter studies (North American Prodrome Longitudinal Study,[60] 377 HR patients included; and European Prediction of Psychosis Study,[47] 245 HR patients included) were given the highest relative weights on the overall meta-analytical estimates (Table). Removing studies with quality ratings in the lowest 30% decreased the meta-analytic estimate of transition risk by only 7%. The pattern of differences across the subanalyses remained essentially unchanged in direction and magnitude.

TESTS FOR HETEROGENEITY

According to the criteria set by Higgins and Thompson,[74] the heterogeneity in published risks of transition to psychosis was statistically significant and large in magnitude (Q=204.48; *P*<.001; I^2=83.11). Because the overall interstudy variance in effect sizes was substantial, it encouraged consideration of possible explanatory factors.

COMMENT

To our knowledge, this is the first comprehensive meta-analysis of transition risks to psychosis in patients at HR for psychosis. It provides an update of the HR literature since the 2006 systematic review by Olsen and Rosenbaum.[32] This review concluded by noting the need for fur-

ther research in larger multicenter samples. This research has occurred in the intervening years, with publication of 2 multicenter studies[30,47] with sample sizes of more than 200. We found strong evidence for consistent validity of HR criteria across all available psychometric instruments. The transition risk was lowest after 6 months of follow-up and progressively increased as the follow-up period was extended. Significant moderators of the transition risk were the age of the HR patients, the treatments they received, and the year of publication. The use of detailed psychometric criteria to define the transition to psychosis reduced heterogeneity across studies.

In a total sample of approximately 2500 HR patients, we found that the currently used psychopathologic criteria confer, on average, a 29% risk of developing psychosis in the 31 months following first clinical presentation. Because the meta-analysis was well powered, robust, and not undermined by significant publication bias, this finding has strong statistical significance. It indicates that the diagnosis of HR is reliable across different centers worldwide, despite differences in the way patients were ascertained and even though the criteria used were not identical. A key finding from the present study was that the risk of developing psychosis in HR patients appears to increase as the follow-up time increases, at least within the first 3 years of presentation. Thus, the risk was approximately 18% at 6 months, 22% at 1 year, 29% at 2 years, and 36% after 3 years. Although these values must be interpreted with caution because they were derived by pooling data from different samples rather than by using data from a single prospective sample, they are consistent with recent evidence that some HR patients develop psychosis after the first 24 months following presentation, when the risk of transition is thought to be maximal.[30]

Our analysis of the potentially confounding effect of publication year revealed a small but significant decrease in the reported transition risks over time. This is in line with the recent suggestion that transition risks to psychosis in HR samples may be decreasing.[31] One possible explanation is that more recent studies are recruiting individuals who would have made a transition to a psychotic disorder had it not been for the effect of clinical engagement.[75] We found some support for this hypothesis in the fact that transition risks were significantly lower in samples receiving active interventions (antipsychotic medication or psychologic therapy) compared with those that were not. Moreover, most clinical trials of these interventions in HR patients have reported reductions in transition risk,[76,77] although the samples studied have been small, and it is still unclear whether the effects persist in the long term. In addition, nonspecific clinical care in these patients may have an effect on the transition risks, making it harder to detect the effects of specific treatments. Another potential factor in decreasing transition risks is that clinical services are detecting HR individuals and providing them with care at an earlier stage than in the past.[59] As a given center for HR individuals becomes more established and as referrers and the local community become more familiar with the HR state, it is likely that individuals with HR features may be detected and referred earlier. If these individuals are presenting at an earlier stage of the prodrome,

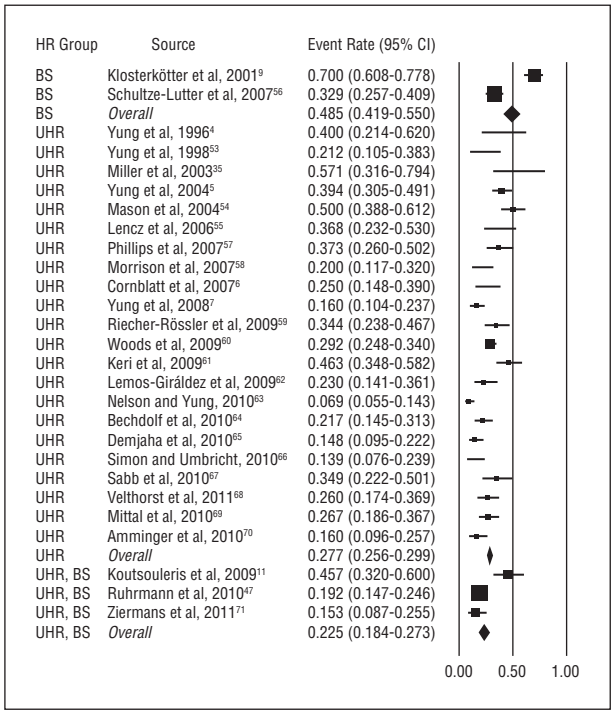


Figure 5. Effect on inclusion criteria (BS, UHR, and UHR plus BS) of the transition risks. Studies are stratified by inclusion criteria with point estimates and 95% CI. Test for between-groups variability, $Q=46.56_2$; $P<.001$. BS indicates basic symptoms; and UHR, ultra high risk.

there may be a relatively longer period before transition to psychosis.[31] This is consistent with our finding of a trend toward an increase in transition risks with increasing duration of follow-up, from 18% at 6 months to 36% after 3 years. In addition, we identified a significant effect of the age of HR patients at presentation on transition risks, with older individuals having higher transition risks than the younger ones. This effect was modest in its magnitude but statistically significant. Again, once a clinical service for those at HR is well established, it may receive a greater proportion of younger referrals, whose risk of transition may be relatively lower. The age of the sampled population also may change through a strategic alteration in the organization of the service.[31]

The field of psychopathologic assessment instruments for evaluating HR is currently dominated by 2 main approaches: the UHR and the BS.[33] The former focuses on attenuated positive symptoms, whereas the latter is based on a detailed phenomenologic way of describing self-perceived disturbances.[78] In our sample, the risks for the BS approach tended to be higher, but they were derived from a relatively small number of studies with large heterogeneity. Some centers have sought to capitalize on the complementary nature of the 2 approaches by combining them in the hope that patients who did not meet the UHR criteria might be identified by the BS criteria and vice versa. However, although initial studies reported a higher transition risk using the UHR-plus-BS approach,[11] later studies reported lower risks.[47,71] In our meta-analysis, the transition risks for studies in which the BS and UHR inclusion criteria were combined was 23%, which was lower than in studies using either set of criteria alone. Because BS may be present in an earlier

stage of the HR than attenuated psychotic symptoms assessed with the UHR approach, a longer follow-up time may be needed to clarify the actual predictive value of the UHR-plus-BS approach.

We further addressed putative differences in the sensitivity of different instruments used to define the UHR groups by comparing transition risks in the CAARMS-based[36] and SIPS-based[35] studies. The overall transition risks at 2 years were almost the same (27.4% and 28.1%). In a recent study,[79] the predictive validity of SIPS inclusion criteria was retested in a CAARMS sample. The authors confirmed that 3 of 5 variables that had been found to be associated with transition in the SIPS cohort (high unusual thought content scores, low functioning, and having genetic risk with functional decline) were also associated with transition in the CAARMS sample.[79] Although the UHR criteria (SIPS or CAARMS) as a whole have been found to reliably identify young people at risk of psychosis, some UHR patients may be at higher short-term risk than others.[80] Some authors suggest that the BS characterize the early HR phase whereas attenuated positive symptoms characterize the late HR phase.[73,80] The final significant moderators of transition risks were the criteria used to define transition to psychosis. The criteria for transition detailed in the CAARMS and SIPS approaches appeared to be more useful for HR patients than the standard criteria for psychotic disorders described in the *DSM* and *ICD* because the latter yielded heterogeneous results with substantial variance across centers. Overall, we were able to explain most of the observed heterogeneity with the previously mentioned moderator factors: year of publication (explaining 42% of the observed heterogeneity), diagnostic criteria (23%), age (13%), antipsychotic medication (12%), and psychologic interventions (5%). However, it is still possible that other confounders, such as the cognitive status of the HR patients,[81] substance abuse,[82] or antidepressant administration[83] may have played a role in explaining some of the observed heterogeneity.

These findings can inform the ongoing debate about the inclusion of an HR syndrome in the next edition of the *DSM* (*DSM-5*). The current proposal is to include a category of "attenuated psychosis syndrome" in the *DSM-5*, which is based on the HR attenuated psychotic symptoms subgroup (www.dsm5.org/ProposedRevisions). This new category was previously called the *psychosis risk syndrome*. The name has been changed in an attempt to highlight current symptoms as the focus for treatment rather than the risk that the symptoms pose for future psychotic disorder.[84] This "attenuated psychosis syndrome" category also requires the symptoms to be sufficiently distressing and disabling to the person and/or a parent or guardian to lead them to seek help.[84]

At present, there is no diagnostic category in the *DSM* or *ICD* for the HR syndrome. In conventional clinical practice, patients who present with features of the HR syndrome usually are not enrolled in psychiatric services. However, this group experiences psychotic and other symptoms and problems[85,86] that are distressing enough for them to seek help, and the present meta-analysis shows that they have a HR of developing psychosis in a relatively short time. Defining an HR as a new diagnostic category may encourage clinicians to identify and manage these patients. Although our results suggest that most HR patients will not develop a psychotic disorder (at least within 3 years after presentation), the purpose of clinical management at this state is not solely to prevent the later onset of frank illness. Treatment also can ameliorate the presenting symptoms and problems, which are often more of a concern to the patient than their long-term risk of transition.[85] This is consistent with the newly proposed diagnostic label of attenuated psychosis syndrome rather than risk syndrome. Moreover, when HR patients are engaged at this stage and then later develop psychosis, the delay before the psychosis is treated can be markedly reduced and the first episode may be less traumatic.

On the other hand, there are counterarguments against the inclusion of HR in the *DSM-5*. Despite its new name, the rationale for inclusion of the attenuated psychosis syndrome in the *DSM-5* remains that the symptoms confer risk for full-blown disorder. Thus, there is still concern about the decreasing transition rate and the high number of false-positives who are not actually at risk of psychotic disorder.[87] Furthermore, there is still the danger that risk will be seen as disorder.[29,88] That is, there will be incorrect conceptions that people meeting the criteria are on the schizophrenia spectrum and that a lifelong underlying "process" has started,[87] even though some of them will remit from their presenting symptoms.[66] These unintended consequences include stigma, discrimination, and unnecessary treatment,[87,89] including antipsychotics (which may have significant effects on the brain[90]), despite the lack of recommendation for these medications in clinical guidelines for treatment of HR individuals.[91] Diagnostic creep may occur, resulting in lowering of the HR threshold and subsequent reduction in transition risk.[87] Also, more research is needed to discover factors in addition to the HR criteria that increase the risk of transition. Ironically, the codification of HR may actually reduce research in the area[89] because it may give a false degree of comfort with the current definition.

Finally, the predictive accuracy of HR criteria depends on the prevalence of the HR state in the population sampled and, therefore, on the population from which the sample is drawn.[79] As in most studies involving existing clinical populations, systematic sampling of HR cohorts is not achievable. To date, transition estimates have been made in samples of help-seeking patients who were engaged by specialized early-intervention services. These individuals often are referred to these services because they are regarded as potentially at risk for psychosis and, therefore, they would be expected to have a higher risk of psychosis than those in the general population. It is not known whether there are individuals in the community who would meet HR criteria but who do not seek clinical help. If this group were large and were included in the estimates of risks, the predictive value of the HR state might be considerably lower,[92] closer to community prevalence estimates of psychotic-like experiences (8%) and of subclinical psychotic symptoms (4%).[93] However, the transition rate to psychosis in patients with HR symptoms who are referred to clinical services but who do not engage with them is comparable with that in HR

patients who are engaged with these services.[94] The inclusion of a criterion for the proposed attenuated psychosis syndrome requiring the seeking of treatment and distress or disability may prevent otherwise well individuals who experience subthreshold psychotic symptoms from being labeled and treated unnecessarily. Concerns remain, however, that the inclusion of this new syndrome may pathologize such people and lead them to seek treatment or lead others to seek treatment on their behalf.

In addition to the findings themselves, a number of suggestions for future research in this field have arisen from the present meta-analysis. Ideally, all studies in HR patients would adopt the same criteria for the HR state and for the transition to psychosis. Using a combination of criteria that focus on complementary aspects of the clinical features, such as the CAARMS and SIPS, which focus on attenuated positive symptoms, and the BS criteria, which concentrate on cognitive features, is an example of this approach, and many centers now use both sets of criteria, accepting patients who meet either of them. Modification of the existing inclusion criteria to include negative symptoms[95] and mood disturbances—which are common features in HR patients and appear to be associated with later transition, but which are not part of the existing inclusion criteria—may also be helpful. Clearly combining HR criteria and expanding them to include mood and negative symptoms may increase the heterogeneity of samples. As Olsen and Rosenbaum[32] noted, analysis by HR subgroup would be useful, especially if the HR concept further expands. Although our analysis indicated that most HR patients who developed psychosis did so within 2 years of presentation, our transition risk increased up to 3 years. Moreover, with increasing awareness of the HR state and of clinical services for this group, it is likely that HR patients may present to services at an earlier stage than previously. Thus, it seems sensible to aim for at least 3 years of clinical follow-up of HR patients from the time of first presentation to avoid the mislabeling of nontransition. It is also important to repeat the assessment of the UHR criteria during follow-up to confirm whether patients are still at UHR for psychosis: a substantial proportion of HR patients may improve to the extent that they no longer meet HR criteria. Finally, with the increasing availability of specialized clinical services for HR patients, this population has increasing access to clinical interventions. It is, therefore, critical that the nature of the clinical treatment that patients receive be carefully documented and the potential of nonspecific clinical input to influence the clinical outcome be recognized.

The literature to date, despite comprising studies that varied in the method of patient ascertainment and the criteria used to define the HR and the transition to psychosis, suggests that the HR is valid and consistently associated with an increased risk of transition to psychosis. Nevertheless, the transition risk of a given sample is influenced by the age of the patients, the nature of any clinical intervention, and the particular criteria for the HR and transition that are used. Furthermore, the transition risk also depends on the duration of the follow-up period, with higher risks in studies with longer follow-up. The standardization of diagnostic criteria across centers should facilitate further progress in this field and inform the ongoing debate on the introduction of a new diagnostic category that is recognized as defining the HR state.

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