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REVIEW ARTICLE

Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results

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Background. The base rate of transition from subthreshold psychotic experiences (the exposure) to clinical psychotic disorder (the outcome) in unselected, representative and non-help-seeking population-based samples is unknown.

Method. A systematic review and meta-analysis was conducted of representative, longitudinal population-based cohorts with baseline assessment of subthreshold psychotic experiences and follow-up assessment of psychotic and non-psychotic clinical outcomes.

Results. Six cohorts were identified with a 3–24-year follow-up of baseline subthreshold self-reported psychotic experiences. The yearly risk of conversion to a clinical psychotic outcome in exposed individuals (0.56%) was 3.5 times higher than for individuals without psychotic experiences (0.16%) and there was meta-analytic evidence of dose–response with severity/persistence of psychotic experiences. Individual studies also suggest a role for motivational impairment and social dysfunction. The evidence for conversion to non-psychotic outcome was weaker, although findings were similar in direction.

Conclusions. Subthreshold self-reported psychotic experiences in epidemiological non-help-seeking samples index psychometric risk for psychotic disorder, with strong modifier effects of severity/persistence. These data can serve as the population reference for selected and variable samples of help-seeking individuals at ultra-high risk, for whom much higher transition rates have been indicated.

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Introduction

Psychotic experiences are common in the general population (van Os *et al*. 2009). A systematic review of 285 rates of prevalence or incidence of psychotic experiences showed that half of the considerable heterogeneity in rates of subclinical psychotic experiences across studies is due to study cohort and design factors (Linscott & van Os, 2010). In particular, rates were found to be higher in studies using smaller sample sizes, convenience sampling and self-report assessment.

A major and hitherto unresolved issue is that the base risk of conversion to clinical disorder, given earlier expression of subclinical psychotic experiences in unselected, representative and non-help-seeking general population samples, remains unknown. Assessment of the risk is important because it can serve as the population reference against which reported risk of conversion from 'ultra-high' risk status to psychotic disorder in variable and highly selected samples can be compared. To address this issue, we reviewed the literature on the risk of developing

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psychotic disorder given earlier expression of subclinical psychotic experiences in non-service-using representative population samples. To this end, the method of systematic review and meta-analysis was used, as these generally provide a transparent and quantitative approach to identify, summarize and critically appraise relevant studies, enabling an integrated presentation of results. Furthermore, systematic review and meta-analysis can address meta-hypotheses over and above primary studies by quantitative exploration of the patterns of results from single investigations. Specific aims of the meta-analysis were: (i) to examine the risk of conversion to psychotic disorder given the presence of subclinical psychotic experiences in representative general population samples, (ii) to examine the risk of conversion to non-psychotic disorder given the presence of subclinical psychotic experiences in representative general population samples, and (iii) to examine which factors moderate risk of conversion. To achieve these goals, the methodology for systematic review as described in Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup *et al*. 2000) was applied. For some studies, additional analyses were conducted in the original data so that non-psychotic outcomes that had not been included in the original publications could also be reported.

Method

To reduce methodological variation of studies to be entered in the meta-analysis, *a priori* criteria for inclusion were formulated. Thus, data of published studies were added to the meta-analysis database if they (i) were published in a peer-reviewed journal after 1950; (ii) were written using the English, Spanish, French, German or Dutch language; (iii) represented a population-based or comparably representative follow-up study of individuals with and without a defined measure of subclinical psychotic experiences at baseline (the 'exposure'); and (iv) provided cumulative incidence rates (or data allowing computation of these) of defined psychotic disorder outcomes (the 'outcome').

A computerized search strategy was developed to sensitively query the MEDLINE, PsycINFO and EMBASE databases to identify potentially relevant articles in English, Spanish, German, French or Dutch, published from 1951 to April 2010. A sensitive search string was compiled, based on three elements. The first was defined as: (((psychosis OR psychotic) AND (subthreshold OR subclinical OR non-clinical)) OR psychosis-like OR psychotic-like OR schizotypy OR 'psychotic experience*' OR 'psychotic symptom*' OR 'psychosis proneness' OR hallucinat* OR delusion* OR hallucination-like OR delusion-like OR delusional-like); this was combined ('AND') with a second search element of (follow-up OR transition OR conversion OR longitudinal OR incidence OR predict* OR 'cohort study') while excluding ('NOT'), in the third search element (mice OR mouse OR rat OR dementia OR Parkinson's OR Lewy body OR cancer OR aids). This yielded over 3000 citations. Two investigators independently screened citations and selected publications for further consideration on the basis of consensus, using three consecutive filters. The first selection filter was at the level of citations, applying the broad criterion of relevance for the topic of the meta-analysis. The second selection filter was applied at the level of abstracts, excluding studies that did not meet a single inclusion criterion as defined above. The final filter was based on inspection of full-text articles. In the case of multiple reports involving a single study population, the publication with the largest sample size and/or the longest follow-up was selected. The great majority of studies identified in the initial search were rejected because (i) reports were on patients with established psychotic disorder or other disorders, or on non-representative, non-epidemiological samples of help-seeking individuals meeting ultra-high risk criteria, (ii) samples included cross-sectional data only or (iii) follow-up measures did not include a defined clinical outcome. Five studies (Chapman *et al*. 1994; Poulton *et al*. 2000; Hanssen *et al*. 2005; Welham *et al*. 2009; Dominguez *et al*. 2011) thus remained that after full inspection were deemed suitable for inclusion. Reference lists of these articles were screened to encounter additional articles (yielding no additional citations). In addition, a process of forward and backward citation tracking was executed using the Web of Science database (yielding no additional citations). Finally, researchers with expertise in the field were contacted to identify additional publications and/or data potentially relevant for the meta-analysis. This resulted in the following additional data. First, original individual participant data from two cohort studies, the Netherlands Mental Health Survey and Incidence Study (NEMESIS; Bijl *et al*. 1998*a*,*b*) and the Early Developmental Stages of Psychopathology (EDSP) study (Wittchen *et al*. 1998; Lieb *et al*. 2000), were subjected to additional analyses to add information on non-psychotic outcomes, not published before, to the meta-analysis database. Second, one additional study (Werbeloff *et al*. 2012) was identified that was suitable for inclusion in the meta-analysis.

In the next step, two investigators independently extracted quantitative and qualitative data from the six selected publications. *A priori* qualitative data included factors impacting on internal validity, such

as methodological and design features, in addition to the potential for confounding and also bias due to differential attrition or possible differential assessment of exposure and/or outcome. None of the six identified studies were excluded on the basis of these considerations. Quantitative data included cumulative conversion rates as a function of baseline exposure status (i.e. with and without subclinical psychotic experiences). Data pertaining to studies using continuous exposure measures were extracted and analysed according to the original continuous exposure format, and additionally analysed as a dichotomous exposure to facilitate comparison of results across studies. Dichotomization was carried out by contrasting, in the case of three-level exposure variables (e.g. no symptoms, weak symptom, strong symptom), the highest category *versus* the lowest two. In the case of four-level exposures, the highest category was similarly compared to the lowest three. If data could not be extracted in a format suitable for meta-analysis, the authors were contacted for reanalysis of the original data in the required format.

Table 1*a* was compiled to provide a descriptive summary of selected studies, showing, for both psychotic and non-psychotic outcomes, the principal study characteristics including populations, observation periods, exposure and outcome definitions, main results and sample and study design features. Tables 1*b* and 1*c* show the quantitative data extracted from each study for psychotic and non-psychotic outcomes respectively.

Approach to meta-analysis

Data from the selected studies were combined to estimate pooled rates with their corresponding 95% confidence intervals (CIs) under a random effects model, assuming that true effects were randomly distributed around the mean effect size. The random effect model presumes that variation in samples and design factors will occasion different true effect sizes across studies and represented a valid *a priori* choice, given that methods and populations across studies did not correspond to a degree that they could be regarded as estimating the same underlying effect. The between-study variance in the random effects model reflects heterogeneity across studies, the magnitude of which was evaluated using a χ^2 test for heterogeneity, testing whether individual studies varied more than could be explained by chance alone. In the phase of reading and comparing the articles, various hypotheses for heterogeneity were identified.

Additional analyses undertaken in original datasets

For the specific purpose of the meta-analysis, exposure and outcome data as reported in the NEMESIS by Hanssen *et al*. (2005) and in the EDSP study by Dominguez *et al*. (2011) were subjected to additional analyses. Both the NEMESIS and the EDSP study followed general population cohorts, interviewing the entire cohort with the Composite International Diagnostic Interview (CIDI) on three occasions (NEMESIS: T0, T1 and T2; EDSP: T0, T2 and T3) over time (Bijl *et al*. 1998*a*, *b*; Wittchen *et al*. 1998; Lieb *et al*. 2000). In the NEMESIS, fresh analyses were conducted to provide additional risk estimates for prevalent exposure [defined as lifetime report of subclinical psychotic experiences at T0, as described in van Os *et al*. (2000)], in addition to the incident exposure reported in the original paper (Hanssen *et al*. 2005). In both the NEMESIS and the EDSP data sets, additional analyses were conducted with the following non-psychotic outcomes: T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of bipolar disorder, excluding individuals with a similar diagnosis at T0/T1 (NEMESIS) or T0/T2 (EDSP) (Regeer *et al*. 2006, 2009; Tijssen *et al*. 2010*a*, *b*); T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of depressive disorder, excluding individuals with a similar diagnosis at T0/T1 (NEMESIS) or T0/T2 (EDSP) and individuals with a T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of bipolar disorder (Regeer *et al*. 2006, 2009; Tijssen *et al*. 2010*a*, *b*); and T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of anxiety disorder, excluding individuals with a similar diagnosis at T0/T1 (NEMESIS) or T0/T2 (EDSP) and also individuals with a T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of depressive disorder or bipolar disorder (Bijl *et al*. 1998*a*, *b*; Zimmermann *et al*. 2003). All extra analyses were conducted in strict accordance with the methodology described in the original studies and are therefore not reported again in detail here (details available upon request).

Statistical analysis

All analyses were performed using Stata 11 (StataCorp, 2009). A data file including data pertaining to both psychotic and non-psychotic outcomes was constructed. One study reported five different psychotic outcomes (Chapman *et al*. 1994); these were combined into a single psychotic outcome.

First, dichotomized exposures were analysed. For these analyses, each record in the data included sample size, number of subjects with a particular outcome, years of study follow-up and information on modifiers. Using the first three variables, rates per 100 000 person-years were calculated. For each study, at least two records were filled (exposed, non-exposed). More records were used when rates were stratified by possible outcome modifiers (psychotic/non-psychotic disorder, hospital admission yes/no,

Table 1*a*. *Qualitative description of longitudinal studies in representative samples studying predictive value of self-reported subclinical psychotic experiences* (*exposure*) *for transition to clinical psychotic and non-psychotic disorders* (*outcome*)

Study ID	Study type and goals	Sample size (*n*)	Mean age at baseline and follow-up (years)	Baseline psychotic predictor (exposure)	Follow-up clinical psychotic outcome	Follow-up clinical non-psychotic outcome	Assessment type/ instruments: baseline exposure follow-up outcome
Chapman *et al.* 1994	10-year follow-up of undergraduate students with low and high scores on four schizotypy scales	Of 7800 students, 534 subjects were selected for 10-year follow-up; *n* = 508 (95%; 355 exposed, 153 non-exposed) had outcome assessment	20–30	Scoring ⩾1.96 S.D. on any of the four scales (exposed, *n* = 375) and <0.5 S.D. above the mean on each scale (159, non-exposed)	DSM-III-R diagnosis: (1) Schizophrenia (2) Psychosis NOS (3) Delusional disorder (4) Psychotic bipolar disorder (5) Psychotic depression	DSM-III-R diagnosis: (1) Mania/bipolar disorder (2) Depression (3) Hypomania	*Baseline*: Self-reported psychosis proneness scales: (*a*) Physical anhedonia (*b*) Perceptual aberration (*c*) Magical ideation (*d*) Impulsive non-conformity *Follow-up*: Clinical interview face to face using the SADS-L and PDE
Poulton *et al.* 2000	Birth cohort assessed at age 11 years for presence of delusions and hallucinations and at age 26 years for presence of psychiatric disorder	Baseline *n* = 1019 Follow-up *n* = 972 (95%) Risk set: *n* = 761	11–26	Self-reported psychotic DISC-C symptom: (1) No symptom (2) Weak symptom (score 1 = likely) (3) Strong symptom (score 2 = definitely)	DSM-IV Schizophreniform disorder	DSM-IV diagnosis: (1) Mania (2) Depression (3) Anxiety disorder	*Baseline*: Self-reported using DISC-C (administered by child psychiatrist) *Follow-up*: Clinical interview by health worker using DIS
Hanssen *et al.* 2005	Three-year longitudinal general population cohort study (NEMESIS) assessing psychotic symptoms and psychiatric disorders at three time points (baseline, year 1 and year 3)	T0[a]: 7076 T1: 5618 (79%) T2: 4848 (68%) Risk set for analysis: 4042	41–43	(1) T1 Incident CIDI self-reported CIDI psychotic symptom, plus: (*a*) single *versus* multiple (*b*) with *versus* without depression (2) T0 Lifetime CIDI self-reported psychotic symptom, plus: (*a*) single *versus* multiple (*c*) with *versus* without depression	T2 diagnosis of clinical psychotic disorder based on BPRS severity of psychosis and CAN need for care	(see below)	*Baseline*: CIDI at all three measurement points by trained interviewers plus clinical reinterview of individuals scoring positive *Follow-up*: CIDIs by trained interviewers and telephone clinical reinterview by clinician for persons scoring positive on CIDI psychosis items; BPRS and need for care scored by clinician

Welham *et al.* 2009	Birth cohort (1981–1983) assessed after 5 and 14 years for psychotic symptoms and after 21 years for SP-NAP	Birth: $n=7223$; age 14 years: $n=5172$ (72%); age 21 years: $n=3801$ (53%). Risk set: 3573	14–21	Self-reported YSR item age 14: 'I hear sounds or voices that other people think aren't there' – rarely/never *versus* sometimes/often	Caseness: CIDI DSM-IV non-affective psychotic disorder or past medical diagnosis of schizophrenia	–	*Baseline*: YSR hallucination item *Follow-up*: CIDI + self-reported past diagnosis of schizophrenia
Dominguez *et al.* 2011	Ten-year longitudinal general population cohort study, assessing mental health four times over a period of 10 years. Clinical outcomes were assessed over a 5-year period (from T2 to T3)	Analyses restricted to youngest group aged 14–17 at baseline [T0: $n=1395$, T1: $n=1228$, T2: $n=1169$, T3: $n=1022$ (73%)]. Risk set for analysis: $n=845$	14–24	Degree of persistence over the 5 years from T0 to T2 of self-reported SCL-90-R psychotic/paranoid symptoms in the highest 10% of scores: once, twice or three times	T3 Diagnosis of clinical psychotic disorder based on (i) help-seeking, (ii) service use and (iii) impairment	(see below)	*Baseline*: Self-report questionnaires (SCL-90-R) at T0, T1 and T2 *Follow-up*: DIA-X/M-CIDI administered as clinical interview by clinical psychologists
Werbeloff *et al.* 2012	Twenty-four-year follow-up through national case register of general population cohort assessed for presence of psychotic symptoms at baseline	4914 community subjects (subjects with psychotic disorder were screened and excluded) Risk set for analysis: 4726	29–52	Self-reported psychotic experiences: 0 = no symptom 1 = weak symptom (rarely/sometimes) 2 = strong symptom (often/very often)	ICD-10 register: Non-affective psychotic disorder	ICD-10 register diagnosis: Non-psychotic disorder	*Baseline*: Clinical interview (mental health worker) using the PERI (Hebrew version); a subsample was interviewed by a psychiatrist using the SADS *Follow-up*: National case-register clinical hospital diagnosis
Current report	Additional data analysis of (*a*) Hanssen *et al.* (2005) NEMESIS	NEMESIS: see Hanssen *et al.* (2005)	NEMESIS: see Hanssen *et al.* (2005)	NEMESIS: see Hanssen *et al.* (2005)	–	DSM-III-R/IV: NEMESIS: T2 (1) Bipolar disorder (2) Depression (3) Anxiety disorder	NEMESIS: see Hanssen *et al.* (2005)
	(*b*) Dominguez *et al.* (2011) EDSP study	(*b*) EDSP: risk set differs from Dominguez *et al.* (2011) as not restricted to youngest cohort; risk sets were $n=1876$, $n=1608$ and $n=1221$ for bipolar disorder, depression and anxiety respectively	(*b*) EDSP: see Dominguez *et al.* (2011)	(*b*) EDSP: differs from Dominguez *et al.* (2011): exposure was presence of any T2 CIDI psychotic symptom	–	EDSP: T3 (1) Bipolar disorder (2) Depression (3) Anxiety disorder	EDSP: see Dominguez *et al.* (2011)

NEMESIS, The Netherlands Mental Health Survey and Incidence Study; EDSP, Early Developmental Stages of Psychopathology; SP-NAP, screen-positive non-affective psychotic disorder; NOS, not otherwise specified; S.D., standard deviation; PDE, Personality Disorder Examination; SADS-L, Schedule for Affective Disorders and Schizophrenia – Lifetime version (Endicott & Spitzer, 1978); DISC, Diagnostic Interview Schedule for Children (Costello *et al.* 1982; NIHM DIS for Children: Child Version); DIS, Diagnostic Interview Schedule for DSM-IV (Robins *et al.* 1995); CIDI, Composite International Diagnostic Interview (WHO, 1992); YSR, Youth Self Report questionnaire (Achenbach, 1991); SCL-90-R, Self-Report Symptom Checklist-90-R (Derogatis & Cleary, 1977); DIA-X/M-CIDI: updated version of the World Health Organization's CIDI version (Wittchen & Pfister, 1997; DIA-X versions of the WHO CIDI); PERI, Psychiatric Epidemiology and Research Interview (Shrout *et al.* 1986; Hebrew version: Roberts & Vernon, 1981); BPRS, Brief Psychiatric Rating Scale (Overall & Gorham, 1962); CAN, Camberwell Assessment of Need (Slade *et al.* 1996).

[a] T0 baseline, T1 first follow-up, T2 second follow-up, T3 third follow-up.

Table 1b. *Longitudinal studies in representative samples studying predictive value of self-reported subclinical psychotic experiences (exposure) for transition to psychotic disorders (outcome): qualitative data*

Study	Type outcome	Type exposure	Exposed *n*	Risk[a] exposed *n* (%)	Non-exposed *n*	Risk non-exposed *n* (%)	Reported relative risk (95% CI)[e]
Chapman *et al*. 1994	Schizophrenia	High schizotypy	355	4 (1.1)	153	1 (0.3)	
	Psychosis NOS		355	3 (0.9)	153	0 (0)	
	Delusional disorder		355	1 (0.3)	153	0 (0)	
	Psychotic BPD		355	3 (0.9)	153	0 (0)	
	Psychotic MDD		355	1 (0.3)	153	1 (0.3)	
Poulton *et al*. 2000[b]	SCF	No symptoms	–	–	654	13 (2)	1[c]
		Weak symptoms	95	9 (9.5)	–	–	5.1 (1.7–18.3)
		Strong symptoms	12	3 (25)	–	–	16.4 (3.9–67.8)
Hanssen *et al*. 2005	Clinical psychotic disorder	T1 no incident PE			3964	5 (0.1)	1[c]
		T1 incident PE	79	6 (7.6)			65.1 (19.4–218.1)
		T1 incident single PE	60	2 (3.3)			27.3 (5.2–143.6)
		T1 incident multiple PE	19	4 (21.1)			211.2 (51.6–864.1)
		T1 incident PE with depression	34	5 (14.7)			136.5 (37.4–497.1)
		T1 incident PE without depression	45	1 (2.2)			18.0 (2.1–157.2)
		T1 incident multiple PE with depression	10	4 (40.0)			527.9 (113.2–2460.9)
		T0 no prevalent PE			4045	7 (0.2)	1[c]
		T0 prevalent PE	746	26 (3.5)			20.8 (9.0–48.1)
		T0 prevalent single PE	447	2 (0.5)			2.6 (0.5–12.5)
		T0 prevalent multiple PE	299	24 (8.0)			50.3 (21.5–117.9)
		T0 prevalent PE with depression	463	22 (4.8)			28.8 (12.2–67.8)
		T0 prevalent PE without depression	283	4 (1.4)			8.3 (2.4–28.4)
		T0 prevalent multiple with depression PE	213	21 (9.9)			63.1 (26.5–150.2)
Welham *et al*. 2009	SP-NAP	Self-reported auditory hallucinations	451	18 (4.0)	3112	38 (1.2)	

Dominguez *et al.* 2011	Psychotic disorder	Level 0	–	–	666	23 (3.7)	1.0[e]
		Level 1	132	6 (5.3)	–	–	1.5 (0.6–3.7)
		Level 2	33	4 (16.0)	–	–	5.0 (1.6–15.9)
		Level 3	14	3 (27.3)	–	–	9.9 (2.5–39.8)
Werbeloff *et al.* 2012[d]	Hospitalization for non-affective psychosis	No symptoms	–	–	1306	2 (0.1)	1[c]
		Weak symptoms	2614	13 (0.5)	–	–	3.6 (0.8–16.7)
		Strong symptoms	652	8 (1.3)	–	–	9.5 (1.9–47.2)

NOS, not otherwise specified; BPD, bipolar disorder; MDD, major depressive disorder; SP-NAP, screen-positive non-affective psychotic disorder; SCF, schizophreniform disorder; PE, psychotic experience; CI, confidence interval.

[a] Transition rate in the group with PEs.

[b] The odds ratios (ORs) remained almost unchanged after controlling for sex, social class origins and age 11 IQ scores.

[c] Reference category.

[d] Weighted results.

[e] Mostly adjusted ORs from published studies, some ORs for the Netherlands Mental Health Survey and Incidence Study (NEMESIS) and the Early Developmental Stages of Psychopathology (EDSP) study were calculated on the basis of new analyses for the current paper.

incident/prevalent exposure). Bar charts were generated to present the rates per study for psychotic and also for non-psychotic outcomes (Saha *et al*. 2008; Linscott & van Os, 2010).

A meta-analysis stratified by exposure and by type of outcome (psychotic/non-psychotic) generated forest plots (Stata METAN command). Subsequently, the rates were analysed using meta-regression analysis (Stata METAREG command). As rates are not normally distributed, and the number of studies was small and heterogeneity was expected, meta-regression was repeated using 1000 permutations (Stata METAREG command with option PERMUTE). In addition, meta-regression analyses were repeated for more homogeneous subsets of studies (as described below).

Second, to study dose–response effects, exposures were analysed as three-level variables including three categories of graded severity/frequency where available; if there were four categories, the two lowest categories were combined to create a similar three-level exposure variable. For this analysis, rates were also presented in a figure and meta-regression analysis was performed.

The study by Chapman *et al*. (1994) was carried out in a sample of students and not in the general population. In addition, there was one study that can be considered an outlier with respect to outcome assessment (hospital admission) (Werbeloff *et al*. 2012). Therefore, a planned sensitivity analysis was carried out excluding these studies, focusing on the four studies that used comparable CIDI-based methodology (Poulton *et al*. 2000; Hanssen *et al*. 2005; Welham *et al*. 2009; Dominguez *et al*. 2010).

Results

Search results

The search yielded seven articles with data that were pertinent to the meta-analysis as specified in the criteria above. One study (Kwapil *et al*. 1997) was excluded as it concerned a subgroup of persons included in the study by Chapman *et al*. (1994), already included in the meta-analysis.

The characteristics of the six studies included in the meta-analysis are listed in Table 1*a*. Most studies had general population sampling frames (two birth cohorts: (Poulton *et al*. 2000; Welham *et al*. 2009); three representative general population cohorts (Hanssen *et al*. 2005; Dominguez *et al*. 2011; Werbeloff *et al*. 2012) and one study presented a representative sample of undergraduate students (Chapman *et al*. 1994); follow-up varied from 3 to 24 years. All studies reported on variably defined self-reported psychotic experiences in the general population and the rate of

Table 1c. *Longitudinal studies in representative samples studying predictive value of self-reported subclinical psychotic experiences (exposure) for transition to non-psychotic disorders (outcome): quantitative data*

Study	Type outcome	Type exposure	Exposed, *n*	Risk exposed[a], *n* (%)	Non-exposed, *n*	Risk non-exposed, *n* (%)	Reported relative risk[b], (95% CI)
Chapman *et al*. 1994	Major depression	High schizotypy	355	103 (29)	153	31 (20.3)	–
	Mania		355	7 (2.0)	153	0 (0)	–
	Hypomania		355	15 (4.2)	153	2 (1.3)	–
Poulton *et al*. 2000	Major depression	No symptoms ($n=654$)	–	–	654	99 (15.2)	–
		Weak symptoms ($n=95$)	95	19 (20.0)	–	–	
		Strong symptoms ($n=12$)	12	1 (8.3)	–	–	
	Mania	No symptoms ($n=654$)	–	–	654	13 (2.0)	–
		Weak symptoms ($n=95$)	95	1 (1.1)	–	–	
		Strong symptoms ($n=12$)	12	0 (0.0)	–	–	
	Anxiety disorder	No symptoms ($n=654$)	–	–	654	144 (22.0)	–
		Weak symptoms ($n=95$)	95	32 (33.7)	–	–	
		Strong symptoms ($n=12$)	12	4 (33.3)	–	–	
Werbeloff *et al*. 2012[c]	Hospitalization for non-psychotic disorder	No symptoms ($n=64$)			1308	4 (0.3)	1[d]
		Weak symptoms ($n=95$)	2616	16 (0.6)	–	–	1.6 (0.5–4.7)
		Strong symptoms ($n=12$)	650	7 (1.0)	–	–	2.1 (0.6–7.5)
	–						
NEMESIS current analysis	Major depression	$\geqslant$1 psychotic symptom lifetime	491	33 (6.7)	3374	110 (3.3)	2.1 (1.4–3.2)
	Mania	$\geqslant$1 psychotic symptom lifetime	695	6 (0.9)	3972	6 (0.2)	5.8 (1.9–17.9)
	Anxiety disorder	$\geqslant$1 psychotic symptom lifetime	417	14 (3.4)	3169	58 (1.8)	1.9 (1.03–3.4)
EDSP current analysis	Major depression	$\geqslant$1 psychotic symptom lifetime	304	28 (9.2)	1304	79 (6.0)	1.6 (1.01–2.5)
	Mania	$\geqslant$1 psychotic symptom lifetime	383	4 (1.0)	1493	0 (0)	[e]
	Anxiety disorder	$\geqslant$1 psychotic symptom lifetime	219	22 (10.1)	1002	76 (7.6)	1.4 (0.8–2.2)

NEMESIS, Netherlands Mental Health Survey and Incidence Study; EDSP, Early Developmental Stages of Psychopathology; CI, confidence interval.

[a] Transition rate in the group with psychotic experiences.

[b] Mostly adjusted odds ratios (ORs) from published studies, some ORs for the NEMESIS and the EDSP study were calculated on the basis of new analyses for the current paper.

[c] Weighted results.

[d] Reference category.

[e] OR infinite as no transition in non-exposed.

transition to variably defined psychotic and non-psychotic clinical outcomes. One study used high level of schizotypy as predictor (Chapman *et al*. 1994); all other studies used CIDI or related measures of subthreshold psychotic experiences. Non-psychotic outcomes were depression, mania, anxiety disorder and admission to hospital for non-psychotic disorder. Some studies described various exposure subgroups, including classification on the basis of number of symptoms (no symptom, single symptom, multiple symptoms); frequency/certainty of psychotic symptoms (no symptom, 'weak' symptom and 'strong' symptom); psychopathological context (no symptom, symptom without depression, symptom with depression); and degree of persistence over 5 years (present at none, one, two or three assessments over 5 years). Some studies also described rates as a function of combinations of subgroups (e.g. multiple symptoms with and without co-morbid depression; Hanssen *et al*. 2005). All six studies reported on psychotic clinical outcomes, and five studies additionally reported on other, non-psychotic, clinical outcomes. For one study (Hanssen *et al*. 2005), measures of both incident (psychotic experiences with first onset in the previous year) and prevalent (lifetime presence of psychotic experiences) exposure were available. One study (Werbeloff *et al*. 2012) reported service-based clinical outcome, defined as admission to hospital. All study populations were from developed nations including The Netherlands, Germany, Israel, Australia, New Zealand and the USA.

Description of the possible modifiers as causes of heterogeneity of the studies

Four studies (Poulton *et al*. 2000; Hanssen *et al*. 2005; Welham *et al*. 2009; Dominguez *et al*. 2011) used similar methodology for exposure and outcome assessment based on the CIDI (Robins *et al*. 1988) whereas other studies (Chapman *et al*. 1994; Werbeloff *et al*. 2012) used different instruments. Similarly, all studies reported exposure assessment based on prevalence estimates whereas one study also reported assessment of incident exposure (Hanssen *et al*. 2005). Another important factor was that one study provided outcomes based on hospital admission (Werbeloff *et al*. 2012), whereas all other studies were independent of health-care use.

Results for dichotomous exposure meta-analysis

Original study results

Findings from individual studies are summarized in Tables 1*b* (psychotic outcomes) and 1*c* (non-psychotic outcomes).

All studies showed that subclinical psychotic experiences strongly predicted clinical psychotic outcomes. The 3- to 24-year risk for the exposed was in the range 5–25%, substantially higher than the corresponding risk in the non-exposed (ranging from 0.1% to 3.7%), with 3- to 24-year odds ratios (ORs) in excess of 10 for the strongest level of exposure (Table 1*b*). The ORs for non-psychotic outcomes were weaker, mostly of the order of 2 (Table 1*c*).

Meta-analysis

To facilitate comparison, rates for all studies were uniformly transformed to express incidence of psychotic and non-psychotic outcomes per 100 000 person-years (Fig. 1*a*, 1*b*). This confirmed the pattern of results in Tables 1*b* and 1*c*, in that the incidence of psychotic clinical outcome in the exposed was much higher than in the non-exposed, and that the difference in incidence between exposed and non-exposed was much greater for psychotic than for non-psychotic clinical outcome. In addition, the results showed that the absolute risk for clinical outcome in the only study based on hospital admission (Werbeloff *et al*. 2012) was only a fraction of the risk in studies that did not depend on service use.

Meta-analysis results for psychotic (Fig. 2*a*) and non-psychotic (Fig. 2*b*) clinical outcomes [for the Hanssen *et al*. (2005) study, based on NEMESIS data, results with prevalence exposure were included] show that the combined yearly incidence rate of psychotic clinical outcome, given the presence of a prevalent subclinical psychotic experience, was 159 per 100 000 person-years (0.2% per year) in the non-exposed and 558 per 100 000 person-years (0.6% per year) in the exposed. For the non-psychotic outcomes, yearly transition incidence rates for exposed and non-exposed were 2.6% and 1.8% respectively. For non-psychotic outcomes, CIs were wide and for both psychotic and non-psychotic outcomes, CIs overlap (Fig. 2*a*, *b*), indicating that the difference in yearly incidence rate between exposed and non-exposed was non-significant for both psychotic and non-psychotic clinical outcome. Heterogeneity was large (psychotic outcomes non-exposed: $\chi^2 = 81.6$, df = 5, $p < 0.001$; psychotic outcomes exposed: $\chi^2 = 54.1$, df = 5, $p < 0.001$; non-psychotic outcomes non-exposed: $\chi^2 = 666.9$, df = 4, $p < 0.001$; non-psychotic outcomes exposed: $\chi^2 = 235.4$, df = 4, $p < 0.001$).

Planned sensitivity analysis

Excluding the student-based and hospital-based studies (Chapman *et al*. 1994; Werbeloff *et al*. 2012), focusing on the four studies that used similar CIDI-based methodology for exposure and outcome

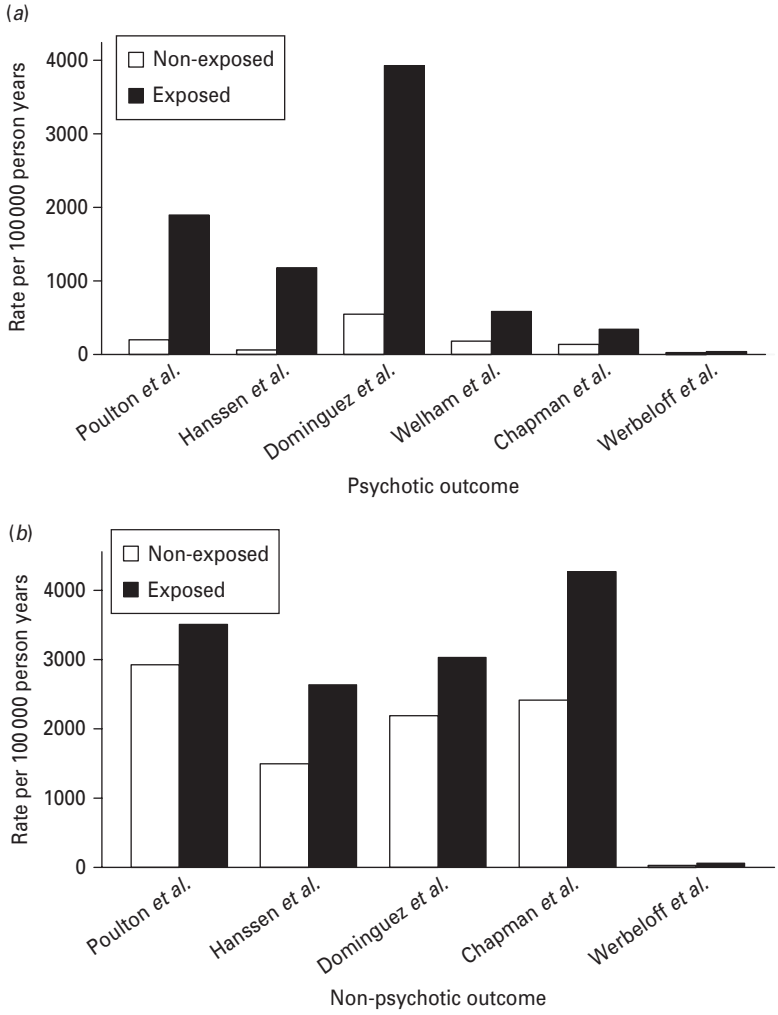

Fig. 1. Rate per 100 000 person-years of (*a*) psychotic and (*b*) non-psychotic outcomes in exposed and unexposed subjects (prevalent exposure only).

assessment (Poulton *et al*. 2000; Hanssen *et al*. 2005; Welham *et al*. 2009; Dominguez *et al*. 2010) revealed transition rates of psychotic outcomes in exposed and non-exposed of 1.0% (95% CI 0.38–1.6) and 0.2% (95% CI 0.09–0.37) respectively, with non-overlapping CIs. For psychotic outcomes, these rates were 2.8% (95% CI 2.3–3.4) and 2.2% (95% CI 1.3–3.1) respectively.

Meta-regression, including the four studies that used similar CIDI-based methodology for exposure and outcome assessment (Poulton *et al*. 2000; Hanssen *et al*. 2005; Welham *et al*. 2009; Dominguez *et al*. 2010), suggested that the effect of subclinical self-reported psychotic experiences on psychotic clinical outcome was significant (difference in incidence between exposed and non-exposed 648 per 100 000 person-years, $p=0.043$), whereas the effect for non-psychotic clinical outcome was not statistically significant (difference in incidence 694 per 100 000 years, $p=0.31$). Meta-regression using permutations showed similar or more conservative p values (non-psychotic outcomes exposure $p=0.52$; psychotic outcomes exposure $p=0.11$; t values were all in the same direction).

Results of the dose–response meta-analysis

Original study results

Where examined, studies reported clear dose–response relationships for variably defined levels of exposure severity (certainty of symptom, frequency of symptom, number of symptoms, persistence over time, co-morbid depression) in relation to risk of transition to psychotic clinical outcome (Tables 1*a* and 1*b*). Only weak evidence for dose–response was present for non-psychotic clinical outcome (Tables 1*a* and 1*c*).

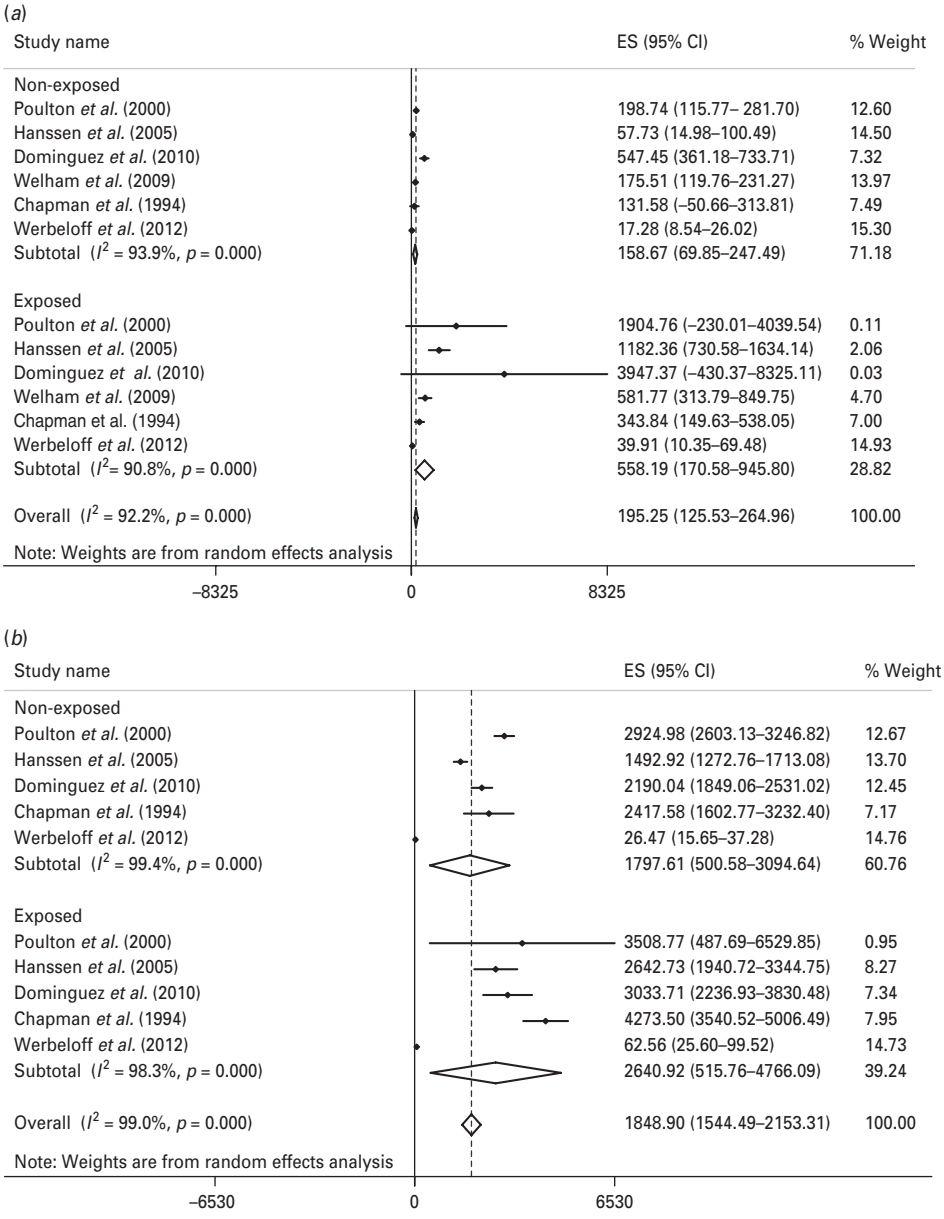

Fig. 2. Forest plot of rates per 100 000 person-years of (*a*) psychotic and (*b*) non-psychotic outcomes in each study of the exposed and non-exposed subjects, prevalent exposure only.

Meta-analysis

Transformation of all studies to the same person-year denominator showed comparable dose–response effects for psychotic clinical outcome, and also for the study reporting hospital-based outcomes (Werbeloff *et al*. 2012) and incident exposure assessment (Hanssen *et al*. 2005). Thus, the bars in Fig. 3 show that rates increase when exposure severity increases. Meta-regression including the three CIDI-based studies with linear multiple categories of exposure (Poulton *et al*. 2000; Hanssen *et al*. 2005; Dominguez *et al*. 2010) showed a statistically significant linear increase in yearly incidence of psychotic outcomes per unit increase in exposure severity ($\beta = 962$, $p = 0.02$). Permutation analysis of this result was also significant ($p = 0.03$).

Discussion

Subjects with a history of subclinical psychotic experiences displayed higher yearly rates of psychotic clinical outcome, as evidenced particularly by significant meta-analytic dose–response effects. The analyses suggest a degree of specificity, indicating increased

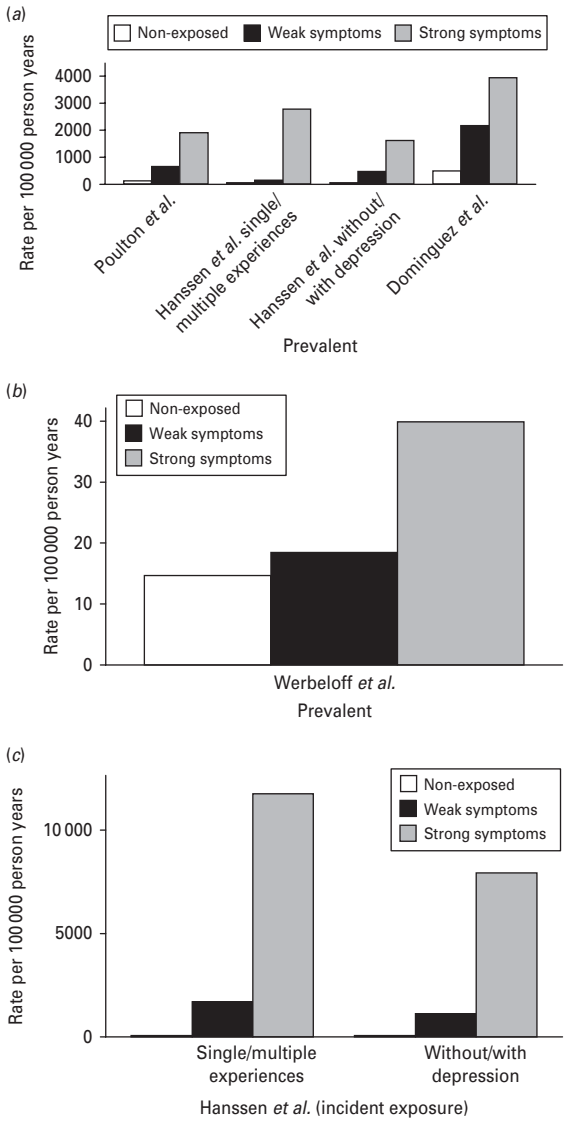

Fig. 3. Rate per 100 000 person-years of psychotic outcomes in three categories of exposure: (*a*) outcome is diagnosis, prevalent exposure (*b*) outcome is hospital admission, prevalent exposure and (*c*) incident exposure (outcome is need for care).

transition for psychotic but not for non-psychotic outcomes, which was evident particularly in the sensitivity analysis of similar CIDI-based studies. However, this may reflect low statistical power as there were suggestive, albeit attenuated, differences between exposed and non-exposed in the transition to non-psychotic outcomes too (2.6% *versus* 1.8% respectively). In addition, individuals with transition to psychotic outcomes may have presented with unmeasured affective outcomes earlier in the trajectory. There was meta-analytic evidence for dose–response associated with number, certainty, frequency, persistence and level of affective co-morbidity of psychotic experiences. Furthermore, subsequent analyses in some of the individual studies presented here have also shown the importance of motivational impairment (Dominguez *et al*. 2010) and social dysfunction (Werbeloff *et al*. 2012). Follow-up of these findings of individual studies is needed in future meta-analytic work when new studies are available.

In combination, these studies provide strong evidence for the validity of the notion that even self-reported subclinical psychotic experiences represent psychometric risk for later psychotic clinical outcome. Although it could be argued that CIDI measures of clinical outcome yield high rates of false positives, the predictive value of subclinical psychotic experiences was also apparent in predicting the 'hard' outcome of hospital admission. Additional validity is suggested by the presence of dose–response.

All studies in the meta-analysis assessed self-reports of psychotic experiences, precluding a comparison of transition rates as a function of mode of assessment. Self-reports of psychotic experiences generate false-positive ratings. Depending on how data are analysed, the rate of false-positive self-reported psychotic experiences when verified by clinical interview may vary from 7% (van Os *et al*. 2001) to 61% (Kelleher *et al*. 2009). In the study by van Os *et al*. (2001), lay interviewer CIDI ratings of adult participants were compared with clinicians' ratings after telephone interviews. In the study by Kelleher *et al*. (2009), clinicians' ratings were compared to self-report questionnaires filled out by adolescent participants. There is evidence, however, that 'false positive' in this context does not indicate absence of risk. Thus, Bak *et al*. (2003) found that 'false positive' psychotic experiences (i.e. the presence of CIDI self-reports of psychotic experiences that were not confirmed by clinical interview) nevertheless were strongly associated with future psychotic disorder, albeit at a lower level than self-reported psychotic experiences confirmed by clinical interview. These findings echo those by Poulton *et al*. (2000), who showed that both 'definite' and ' likely' psychotic symptoms predicted later clinical outcomes, and suggest that self-reported psychotic experiences do not come as either 'true' or 'false' positive. Instead, they may index risk as a continuum reflecting the level of certainty (Poulton *et al*. 2000) as to what degree the experience of aberrant attribution of salience (Kapur, 2003) that an individual reports can be regarded as 'psychotic'. A recent study that specifically compared self-report with interview-based assessment of psychotic experiences in a large general population sample ($n = 6646$) suggested that self-reported psychotic experiences not confirmed by clinical interview may indeed represent the softest expression of an extended phenotype of aberrant

attribution of salience that is phenotypically continuous with clinical psychosis, but discontinuous in need for care (van Nierop *et al*. 2011).

Methodological issues

A comparison with the high-risk literature is not possible, as studies in this area follow selected samples of help-seeking subjects with psychotic experiences that are not population based, are assessed with different instruments, and use a range of sample enrichment strategies to boost the risk of transition. Nevertheless, the base rate of transition as analysed in this study may serve as a standard against which risk-enriched ultra-high-risk studies are conducted.

Many of the studies have not followed their samples through the age of peak risk for development of psychotic disorders. In addition, in calculating yearly incidence rates, the assumption was that the rate of transition would be spread evenly over the follow-up periods. This may not be valid, as there is some evidence that transition rates may be higher in the first 5–10 years (Werbeloff *et al*. 2012). Therefore, yearly incidence rates in two studies with longer follow-ups (Poulton *et al*. 2000; Welham *et al*. 2009) may vary and be somewhat higher in the earlier phases of the follow-up. Similarly, rates may vary according to age and sex, factors that could not be taken into account. Nevertheless, most studies were carried out in young people.

Because the present analysis included only six studies and the analyses focused on rates rather than ORs, funnel plots are difficult to interpret. Publication bias cannot be ruled out, as the small number of studies precluded formally testing this.

Permutation methods within meta-regression have been developed and implemented in Stata (StataCorp, 2009). Permutation is necessary because meta-regression gives increased rates of false positives when the number of studies is small and when heterogeneity is present (Higgins & Thompson, 2004). In addition, in the present study the outcomes, which are rates, are not normally distributed, another reason to conduct permutations. As expected, p values were more conservative after permutations, but because results were similar, original coefficients and p values were presented.

The number of studies included in the meta-analysis was small and statistical power low, resulting in inconclusive findings in the more conservative permutation analysis. Nevertheless, meta-analytic evidence of dose–response remained statistically significant even in the permutation analysis.

Conclusions

Subthreshold self-reported psychotic experiences in epidemiological non-help-seeking samples index psychometric risk for psychotic disorder, with strong modifier effects of severity/persistence. The yearly transition rates are low and can serve as the population reference for selected and variable samples of help-seeking individuals at ultra-high risk, for whom much higher transition rates have been indicated.

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Declaration of Interest

None.

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