

A population-based cohort study examining the incidence and impact of psychotic experiences from childhood to adulthood, and prediction of psychotic disorder

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Abstract

Objective: To investigate the incidence, course and outcome of psychotic experiences from childhood through early adulthood in the general population, and prediction of psychotic disorder.

Methods: A population-based cohort study using the semi-structured Psychosis-like Symptoms interview of psychotic experiences at ages 12, 18, and 24 (N=7900 with any data). Incidence rates were estimated using flexible parametric modelling, and positive predictive values (PPV), sensitivity, specificity, and area under the curve estimated for prediction.

Results: The incidence rate of psychotic experiences increased between ages 13-24 years, peaking during late adolescence. Of 3866 interviewed at age 24, 313 (8.1%, 95%CI 7.2%, 9.0%) had a definite psychotic experience since age 12. 109 individuals (2.8%) met criteria for a psychotic disorder up to age 24, of whom 70% had sought professional help.

Prediction of current psychotic disorder at age 24 (N=47, 1.2%) by both self-report and interviewer-rated measures of psychotic experiences at age 18 (PPVs 2.9% and 10.0% respectively) was improved by incorporating information on frequency and distress (PPVs 13.3% and 20.0% respectively), although sensitivities were low. The PPV of an at-risk mental state at age 18 predicting incident disorder ages 18-24 was 21.1% (95%CI 6.1%-45.6%; sensitivity 14.3%, 95%CI 4.0%-32.7%).

Conclusions: Our study shows a peak in incidence of psychotic experience during late adolescence, and an unmet need for care in young people with psychotic disorders. Because of the low sensitivity, targeting individuals in non-help-seeking samples based only on more severe symptom cut-off thresholds will likely have little impact on population-levels of first-episode psychosis.

Background

Psychotic disorders have a lifetime prevalence of approximately 3% (1) and have a substantial impact on individuals, their families, and society. While psychotic disorders are defined, in part, by the presence of psychotic experiences, psychotic experiences commonly occur outside the context of a full psychotic disorder (2). Studies using semi-structured interviews, which are similar to the cross-examination style of clinical practice, report 6-month prevalence estimates of approximately 5% in late childhood or adolescence (3-5), although estimates from fully-structured interviews and questionnaires are generally higher (2).

In the general population, the vast majority of people with psychotic experiences do not present to clinical services, let alone with a psychotic disorder (6-9). Whilst psychotic experiences are usually transient (7, 10-15), they are nevertheless often distressing and associated with impaired social and occupational function, both concurrently, and longitudinally (4, 16, 17), and with suicidality (18-22); thus psychotic experiences may index a common, and under-recognised, public health burden (8, 23). Given the global burden of disease of psychotic disorders such as schizophrenia, and promise of benefit of early intervention to improve clinical outcomes, there is an imperative to understand the developmental trajectories from onset of psychotic experiences to clinical disorder, and to improve identification of individuals at greatest risk of requiring intervention.

A number of studies suggest that psychotic experiences are more common in children and young adolescents compared to adults (2, 24, 25), but few longitudinal studies have assessed psychotic phenomena at multiple time-points using semi-structured interviews, and none has assessed such experiences sequentially from childhood through adolescence and early adulthood.

The aims of this study were to i) describe the change in incidence of psychotic experiences in the general population from ages 12 through 24 years, ii) describe the prevalence of at-risk mental states for psychosis and psychotic disorder at age 24 years and quantify the likely burden of unmet clinical need of young adults in the general population, and iii) examine the predictive ability of both self-reported and interviewer-rated measures of psychotic experiences during childhood and adolescence for identifying psychotic disorder by age 24 years.

Methods

Sample:

Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 (N enrolled = 14,541; N live births alive at 1 year = 13,988) were invited to take part in the Avon Longitudinal Study of Parents and Children (ALSPAC) (26) (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>). To estimate incidence rates, we examined data from 7919 individuals who were assessed at either age 12, 18, or 24 years. The focus of the rest of the study were the 3866 young adults (9958 invited; response rate 39%) who participated at age 24 (mean 24.04 years, SD=0.85). All participants provided written consent. Ethical approval was obtained from the ALSPAC Law and Ethics Committee and the local research ethics committees.

Measures:

Psychotic Experiences

The semi-structured Psychosis-Like Symptom Interview (PLIKSi) (8, 27) includes 12 core questions eliciting key psychotic experiences: hallucinations (visual and auditory), delusions (spied on, persecution, thoughts read, reference, control, grandiosity, and other) and experiences of thought interference (broadcasting, insertion, and withdrawal). Questions about each experience started with a structured stem question asking if the participant had *ever* had that experience since the age of 12. Participants endorsing 'yes' or 'maybe' responses (henceforth referred to as 'self-reported experiences') were then cross-questioned to establish whether the experience was psychotic (henceforth referred to as 'interview-rated experiences'). Coding of psychotic experiences followed glossary definitions and rating rules for the SCAN (28). Interviewers rated psychotic experiences as not present, suspected, or definitely present. Unclear responses after probing were "rated down", and items only rated as definite when an example that clearly met SCAN rating rules was provided (further details in Supplement S1).

We have previously published studies of the age-12 PLIKSi (27) that assesses current (past 6-months) self-reported and interviewer-rated psychotic experiences, and of the age-18 PLIKSi (4) that assesses ever (since age 12) self-reported and interviewer-rated psychotic experiences, and current (past 6-months) interviewer-rated psychotic experiences. At age 18 information on current (past 6-months) self-reported experiences was *only* available for auditory hallucinations and delusions of being spied on. In this study we report data from the age-24 PLIKSi, and compare this to data from the previous

interviews. Reliability of the age-24 PLIKSi was good (inter-rater reliability: ICC 0.81, 95% CI 0.68, 0.89; test-retest reliability: 0.9, 95%CI 0.83, 0.95), and comparable to the PLIKSi at ages 12 (27) and 18 (4) years.

At-risk mental state for psychosis

Individuals with a current at-risk mental state for psychosis were identified by relating the PLIKS interview data to the Structured Interview for Prodromal Symptoms (SIPS)(29, 30) definitions of prodromal symptoms at age 18 (4), and to both SIPS and Comprehensive Assessment of At-Risk Mental State (CAARMS)(31) criteria at age 24 (see Supplement S4 for criteria).

Psychotic disorder

We classified individuals as having a psychotic disorder if i) they were rated as having a definite psychotic experience not attributable to the effects of sleep or fever, ii) this had recurred regularly (at least once per month) averaged over the previous 6 months, and iii) they reported this as either very distressing, or having a very negative impact on their social or occupational functioning, or having led them to seek help from a professional source. Psychotic disorder was assessed at age 18 (4) (current), and age 24 (current and lifetime (since age 12)).

Sociodemographic characteristics: Data on sex, parental social class, maternal marital status, financial difficulty, housing type and parental education were collected from birth records and parental questionnaires (Supplement S2).

Statistical Methods:

We used data from the PLIKSi conducted at ages 12, 18 and 24 years to identify the first reported psychotic experiences and age at which this first occurred. To estimate the change in incidence with age, we used the Royston-Parmar flexible parametric modelling approach allowing for interval-censored data and employing splines for modelling the log-cumulative hazard as a function of time (32, 33), excluding 928 participants with an event rated at the age 12 visit as there was no information on age of onset at that assessment. As a sensitivity analysis we also estimated incidence rates including these 928 individuals, making the assumptions that i) age of risk for psychotic

experiences starts at age 6, and ii) a constant hazard from ages 6 to 12 (see Supplement Figure SF2). For estimating sex-specific incidence rates, probability weights were used based on modelling age at drop-out. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95%CI) for psychotic disorder occurring at age 24 years in relation to psychotic experiences reported at 12 and 18 years. These, and positive predictive values (PPV), sensitivity and specificity estimates, and the area under the curve (AUC) for receiver operator characteristics graphs were estimated using Stata, version 15(34).

Individuals were more likely to be missing at age 24 years if they were male or came from more socio-economically disadvantaged backgrounds, or if they had more severe psychotic experiences at the age 18 (Supplementary Table ST1). To address potential attrition bias we undertook multiple imputation of missing data (imputed up to N=7919; see sample description) using flexible additive imputation models as implemented in the 'aregImpute' function (35) in the R statistical package, with estimates averaged over 100 imputed data sets using Rubin's rules (36). We included auxiliary variables that could inform psychotic experience or missingness status to make the missingness-at-random assumption more plausible. Analyses using imputed data (Supplementary Table ST6) showed that estimates were very similar to those presented below from complete-case data.

Results

Frequency of psychotic experiences at age 24

Of 3866 individuals interviewed at age 24 years, 490 (12.7%, 95% CI 11.6%, 13.8%) were rated as having ever experienced a suspected ($n=177$, 4.6%) or definite ($n=313$, 8.1%) psychotic experiences since age 12 (see Figure 1 and Supplementary Table ST2 for individual items). Of those with a definite psychotic experience, 268 (6.9% of the sample) had experienced a hallucination, and 91 (2.4%) a delusion, with 46 individuals (1.2%) having experienced both.

Of those who were rated as having a psychotic experience, 43.7% described their experience as quite or very distressing. A higher proportion of those with a definite psychotic experience rated the experience as quite or very distressing (54.0%) compared to those with a suspected psychotic experience (25.4%; $p \leq 0.001$). Similarly, those with a definite psychotic experience were more likely than those with a suspected psychotic experience to describe any impaired social (27.5% vs 10.9% $p \leq 0.001$) or occupational (27.1% vs 7.2%; $p \leq 0.001$) functioning, and to report help-seeking from a professional source (29.4% vs 6.2%; $p \leq 0.001$).

The prevalence of current (past 6-months) definite psychotic experiences at age 24 was 3.5% (95% CI 3.0%, 4.2%). This was similar to the prevalence of current definite psychotic experiences at age 18 (3.2%) but substantially less than the prevalence at age 12 (5.6%).

The risk of ever having a definite psychotic experience between ages 12 to 24 years estimated using *only* data from the interview at age 24 (8.1%) increased when supplementing this information with data from the interview at age 18 (9.6%), and substantially so when further including information from the age 12 interview (13.4%). This was due, at least in part, to measurement error from inconsistent responses across time-points (Supplementary Table ST3).

Incidence rates

The incidence rate of the repeatedly-assessed 12 psychotic experiences items increased overall from early adolescence to early adulthood, with a peak around ages 17 to 19 (Figure 3 and Supplementary Tables ST4-ST5). This pattern was similar when restricting the analyses to only definite psychotic experiences, or to psychotic experiences recurring at least monthly over a 6-month period, or to individuals with completely observed data. There was no evidence of a difference in incidence rates between males and females (Supplementary Figure SF1). The overall incidence rate in our study was

approximately 1.0 per 100 person-years for suspected or definite psychotic experiences, and 0.6 per 100 person-years for definite psychotic experiences.

In a sensitivity analysis including experiences rated at the age-12 interview where age of onset was unmeasured, the pattern of rates for definite psychotic experiences remained very similar, whereas that for suspected experiences was higher in childhood (Supplement Figure S2).

At-risk mental states for psychosis and psychotic disorder

In total, 36 individuals (0.9% of sample; 95%CI 0.7%, 1.3%) met either SIPS or CAARMS criteria for a current at-risk mental state at age 24. There were 47 individuals (1.2%; 95%CI 0.9%, 1.6%) who met our criteria for a current psychotic disorder at this age.

From the age 24 assessment, 109 individuals (2.8%) met criteria for ever having had a psychotic disorder since the age of 12. Of these, 38 (34.9%) had been prescribed medication for their symptoms, whilst 69.7% (95%CI 60.2%, 78.2%) had sought professional help for their symptoms.

Continuity of psychotic experiences

There were 2804 individuals who participated in the interviews at ages 18 and 24 years (Figure 2). Of 84 individuals with definite psychotic experiences present at age 18, 16 (19.1%) had current definite psychotic experiences at age 24 (i.e. had recurrent definite psychotic experiences over a period of approximately 6 years), whilst 68 (80.9%) no longer had current definite psychotic experiences at age 24 (i.e. had transient psychotic experiences over this period).

Prediction

We examined the utility of both the self-reported stem questions and the interviewer-rated measures of psychotic experiences at ages 12 and 18, to predict the presence of current psychotic disorder at age 24.

As can be seen in Tables 1-2, the PPV of experiences at ages 12 and 18 years increased the more stringently defined the experiences were, with the poorest predictor being self-reported psychotic experiences that were not endorsed by the interviewer as being psychotic. Approximately 60% of those who met criteria for a psychotic disorder at age 24 had endorsed a 'yes' or 'maybe' response to the stem questions at age 12. However, only 4.8% of those rated by the interviewer as having

definite, non-attributed psychotic experiences at this age met criteria for a psychotic disorder 12 years later.

The PPV for predicting psychotic disorder at age 24 was greater for interviewer ratings from the age 18 assessment compared to the age 12 assessment, with 10.0% of those rated as having non-attributed definite psychotic experiences at age 18 meeting criteria for a current psychotic disorder at age 24.

Whilst simple 'yes or maybe' responses to the stem (self-reported) items at age 18 performed more poorly than interviewer-ratings for predicting psychotic disorder, their PPV was improved by addition of information on frequency and distress (Table 1). Approximately 6% of people who self-reported frequent or distressing experiences of hearing voices or believing they were being spied on met criteria for a psychotic disorder at age 24, rising to 13% for those reporting experiences that were both frequent and distressing. The corresponding estimates for interview-rated definite auditory hallucinations or delusions of being spied on were 13% and 20% respectively.

As a result of the trade-off between sensitivity and specificity, evidence of a difference in discriminative ability between interview ratings and self-report measures at age 18 for predicting psychotic disorder at age 24 (all psychotic experiences items: AUC 0.79 vs 0.75; $p < 0.001$; auditory hallucinations and delusions of being spied on *only*: AUC 0.70 vs 0.68; $p = 0.038$) was lost once information on frequency and distress was included (auditory hallucinations and delusions of being spied on: AUC 0.70 vs 0.70; $p = 0.868$) (Table 1).

Of 19 individuals who met ARMS criteria at age 18 years, 4 (21.1%, 95%CI 6.1%, 45.6%) developed an incident psychotic disorder between ages 18 and 24, and the sensitivity was 14.3% (95%CI 4.0%, 32.7).

Discussion

In this study we have conducted semi-structured interviews, for the third time over a 12-year period, to assess the presence of psychotic experiences occurring from late childhood through early adulthood in a population-based birth cohort sample. Whilst the presence of current definite psychotic experiences has remained relatively stable since late adolescence, the incidence rate of such experiences increased slightly from ages 13 to 24, with a substantial peak during late adolescence, occurring a few years earlier than the sharp rise in incidence of schizophrenia in early adulthood (37).

The estimate of cumulative risk of psychotic experiences up to age 24 using data from multiple assessments indicates a higher occurrence of psychotic experiences than our estimate obtained when using only the age 24 years measure, and demonstrates the importance of a repeated-measures design. Reasons for this measurement error include forgetfulness, changing interpretation of questions with maturity, changing valuation of social norms, and a learning bias to avoid longer assessments. Indeed, under-estimates in single time-point recall of a measure compared to multiple time-point assessments is common (38-40). Such measurement error, and error in recalling age of onset of experiences, might have affected the patterns of incidence observed, although our use of repeat measures with relatively short time intervals between them, will have helped minimise this.

The transitory nature of most psychotic experiences recorded in general population samples has been well-documented (7, 10-15), and our findings here are consistent with this. Nevertheless, it is germane that almost a third of individuals rated as having had a definite psychotic experience had sought professional help for these, or reported impaired function because of their occurrence, indicating that as well as indexing a heightened risk of developing a psychotic disorder in the future (8, 9, 20, 41), these experiences in themselves are often of current clinical relevance (42, 43).

Furthermore, 30% of those meeting our criteria for a psychotic disorder had not sought professional help for their experiences, indicating a significant and important unmet public health need in adolescents and young adults in the general population.

The use of individual-level interventions to reduce the individual and population health burden of psychotic illnesses requires identification of individuals at high risk. Our study demonstrates that approximately 60% of those meeting criteria for a psychotic disorder at age 24 had a self-reported psychotic experience at age 12, indicating that onset of odd or unusual experiences, even if not meeting interviewer-rated criteria for being psychotic, are present from childhood in the majority of

people who develop a psychotic disorder by their mid-twenties. Whilst the positive predictive value of such self-rated experiences was poor, it was improved by the addition of information on frequency and distress, although sensitivity reduced. The predictive ability of these measures may well be improved by utilising additional information on functional decline, cognitive ability, and other biomarkers of early transitioning to psychosis (44, 45).

Structured interviews and questionnaires over-estimate psychopathology compared to semi-structured approaches, especially in general population samples (46, 47), and indeed in our study, interviewer ratings of psychotic experiences performed better than self-report measures of psychotic experiences at predicting psychotic disorder. However, this distinction was less clear after including measures of frequency and distress. Further studies, particularly ones that can utilise linkage to clinical health records, are required to examine whether self-report measures supplemented with information on frequency and distress are more efficient than semi-structured interviews for prediction of psychotic disorder in general population samples.

Approximately 1% of our general population sample met criteria for an at-risk mental state for psychosis at age 24, as defined using CAARMS or SIPS criteria, compared with 0.6% at age 18 (8). Our finding, that approximately 21% of those with an at-risk mental state at age 18 transitioned to a new-onset psychotic disorder by age 24 is compatible with the estimates of transition in clinical services (48, 49), and substantially greater than the transition risk of 0.9% in those not meeting at-risk criteria at age 18. Nevertheless, this means almost 80% of those meeting at-risk criteria did not transition over this 6-year period.

It is not known to what extent cases of first-episode psychosis can be prevented by identifying a larger pool of people with an at-risk mental state in the general population. In our population-based study, not sampled on help-seeking behaviour, approximately 85% of people with new-onset psychotic disorder between ages 18 and 24 did not meet criteria for an at-risk mental state at age 18.

These findings appear consistent with the observation within a clinical service in the UK, where only 4% of people with a first-episode psychosis in a service in South London came through the at-risk mental state route (50). Sensitivity was similarly very low for the cut-off thresholds of frequent and/or distressing experiences for both self-reported and interviewer-rated measures at age 18. Further studies examining the trajectory of symptoms and referral pathways of people with first-episode psychosis into services are required. However, our findings suggest that targeting individuals in the general population based only on severity characteristics of psychotic or psychotic-

like experiences, or on at-risk mental state criteria, whilst beneficial at an individual-patient level, might have little impact on rates of first-episode psychosis at a population level (49).

Our study has a number of strengths including use of a large and well-characterised birth-cohort, semi-structured interviews to assess psychotic experiences, and measures repeated at three time-points from childhood through early adulthood to allow us to estimate patterns of incidence over this age period. However, there are also some important limitations. First, whilst our sample is probably the largest cohort study available worldwide with this level of detailed information (with over 7000 individuals interviewed on at least one of the three assessments), it is nevertheless relatively small for examining uncommon outcomes such as psychotic disorder. Our results therefore are often imprecisely estimated.

Second, there has been substantial attrition over time, as is common with long follow-ups. However, our estimates using multiple imputation were very similar to those from observed data, suggesting they are unlikely to be substantially affected by selection bias, though this remains possible.

Third, whilst the incidence rate for psychotic experiences from age 13 onwards increased overall through adolescence and early adulthood, most psychotic experiences that occurred in this cohort (928 out of 1547; 60%) were rated at the age 12 interview. As age of first onset was not measured at this interview our primary analysis did not model incidence rates prior to age 13. However, under specific assumptions, as shown in the Supplement, we can see that the incidence of suspected experiences may be higher before age 13, whereas the incidence of definite experiences is consistent with our primary analysis, rising from mid-childhood onwards and peaking around late adolescence or early adulthood.

Finally, there may be some misclassification of at-risk mental states as the PLIKSi is not wholly comparable to the SIPS or CAARMS, whilst it is also possible that our definition of psychotic disorder is too broad and includes individuals who would not be classed as having a disorder in a clinical setting. However, our requirement that psychotic experiences are recurring and causing either severe distress, very impaired function, or help-seeking from a professional suggests that these individuals have a need for clinical care. Furthermore, applying more stringent criteria so that experiences need to be recurring on a weekly rather than monthly basis, which might be more akin to the frequency level that would be seen in clinical practice, only changes our estimate of psychotic disorder at age 24 from 1.2% to 1.0%.

Therefore, whilst our findings need to be interpreted within the context of the limitations described above, our study shows a peak in incidence of psychotic experiences during late adolescence, and highlights an important unmet need for care in the general population of young people with a psychotic disorder. Furthermore, we demonstrate potential utility of both self-report and semi-structured assessments of psychotic experiences for prediction of psychotic disorders in the general population, but because of the low sensitivity, targeting individuals based only on more severe symptom characteristics will likely have little impact on population-levels of first-episode psychosis.

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Conflict of Interests

None of the authors have any conflicts of interest to disclose in relation to this work

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