Psychological Medicine

cambridge.org/psm

Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis

Colm Healy[1], Ross Brannigan[1,2], Niamh Dooley[1], Helen Coughlan[1], Mary Clarke[1,2], Ian Kelleher[1] and Mary Cannon[1,3]

[1]Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin 2, Ireland; [2]Department of Psychology, Royal College of Surgeons in Ireland, Dublin 2, Ireland and [3]Department of Psychiatry, Beaumont Hospital, Dublin 9, Ireland

Review Article

Cite this article: Healy C, Brannigan R, Dooley N, Coughlan H, Clarke M, Kelleher I, Cannon M (2019). Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis. *Psychological Medicine* **49**, 1589–1599. https://doi.org/10.1017/S0033291719000485

Received: 7 August 2018
Revised: 7 February 2019
Accepted: 20 February 2019
First published online: 15 May 2019

Author for correspondence:
Colm Healy, E-mail: colmhealy@rcsi.com

Abstract

Background. Psychotic experiences (PEs) are common in childhood and adolescence and their association with mental disorders is well-established. We aim to conduct a quantitative synthesis the literature on the relationship between childhood and adolescent PEs and (i) any mental disorder; and (ii) specific categories of mental disorder, while stratifying by study design.

Method. Three electronic databases (PUBMED, PsycINFO and EMBASE) were searched from inception to August 2017 for all the published literature on childhood and adolescent PEs and mental disorder (outcome) in non-help-seeking community samples. Study quality was assessed using a recognised quality assessment tool for observational studies. Two authors conducted independent data extraction. Pooled odds ratios were calculated for mental disorders using random-effects models. Additional analyses were conducted investigating different categories of mental disorder while stratifying by study design.

Results. Fourteen studies from 13 community samples ($n = 29\,517$) were identified with 9.8% of participants reporting PEs. PEs were associated with a three-fold increased risk of any mental disorder [odds ratio (OR) 3.08, confidence interval (CI) 2.26–4.21, $k = 12$]. PEs were associated with four-fold increase risk of psychotic disorder (OR 3.96, CI 2.03–7.73, population-attributable-fraction: 23.2%, $k = 5$). In addition, PEs were associated with an increased risk of affective disorders, anxiety disorders, behavioural disorders and substance-use disorders. Few longitudinal studies have investigated childhood and adolescent PEs and subsequent non-psychotic disorders which limited a meaningful synthesis and interpretation of these results.

Conclusion. This meta-analysis confirms that PEs are prevalent in childhood and adolescent community samples and are associated with a variety of mental disorders beyond psychotic disorders. Further longitudinal research is necessary to fully determine the longitudinal relationship between PEs and non-psychotic disorders.

Introduction

Research over the past two decades has highlighted that psychotic experiences (PEs) are far more prevalent in the population than psychotic disorders (Linscott and van Os, 2013). While approximately 5% of adults report PE phenomena (Linscott and van Os, 2013; McGrath *et al.*, 2015; Maijer *et al.*, 2018), the prevalence is higher in children and adolescents, with estimates ranging between 8% and 17% (Kelleher *et al.*, 2012*a*; Maijer *et al.*, 2018).

Initial research on the clinical significance of PEs focused on their association with future risk of psychotic disorders (Poulton *et al.*, 2000; Dominguez *et al.*, 2011; Zammit *et al.*, 2013). Subsequent research found that individuals with PEs were also at risk of a range of non-psychotic disorders such as affective, anxiety and behavioural disorders (Kelleher *et al.*, 2012*b*; Calkins *et al.*, 2014; Jeppesen *et al.*, 2015; McGrath *et al.*, 2016*b*), with findings identifying an association between PEs and both concurrent (Calkins *et al.*, 2014) and later mental disorders (Dhossche *et al.*, 2002). An existing meta-analysis confirmed the association between PEs and both psychotic and non-psychotic disorders (Kaymaz *et al.*, 2012). However, that analysis was primarily focused on adult samples and did not specifically examine the association among children and adolescents. Given that the prevalence of PEs in childhood is notably higher than adulthood (Kelleher *et al.*, 2012*a*) and most individuals with lifetime PEs have their first onset by early adulthood (McGrath *et al.*, 2016*a*), clarifying if childhood and adolescent PEs are also associated with an increased risk of mental disorders (both psychotic and non-psychotic disorders) is therefore an important goal. With childhood and adolescent PEs being considered as an early pluripotent marker for subsequent psychiatric vulnerability (McGorry *et al.*, 2018), it is also important to clarify any differences between cross-sectional and longitudinal relationships between PEs and mental disorders.

CAMBRIDGE UNIVERSITY PRESS

Specifically, the aims of this systematic review and meta-analysis are (i) to assess the association between childhood and adolescent PEs and mental disorder (any mental disorder, any non-psychotic disorder and sub-categories of mental disorder) in non-help seeking individuals from the general population (2) to assess the effect of study design (cross-sectional or longitudinal design) on the relationship between childhood and adolescent PEs and mental disorders.

Method

Search strategy

A systematic review was conducted investigating all of the published literature (from inception to August 2017) pertaining to childhood and adolescent PEs (⩽18 years) and mental disorder in non-help-seeking community samples. Searches were carried out in August 2017 by CH using three electronic databases PUBMED, EMBASE and PsycINFO. A search strategy was devised with the assistance of a librarian. The search terms used were General population OR normal population OR normal healthy population OR healthy individuals OR community sample OR child and adolescent AND mental disorder OR psychiatric disorder OR psychopathology OR mental illness OR DSM* OR ICD* AND psychotic experience OR psychotic symptoms OR psychotic-like experiences OR psychotic-like symptoms OR auditory hallucinations OR hallucinat* OR delusion*. Additionally, the reference lists of all selected papers were searched for potential study inclusion.

Inclusion criteria

Only studies published in a peer reviewed journal and written in English were included in the review.

Sample

Only non-help-seeking samples of children and/or adolescents were used in this investigation. We included samples if the majority of participants were aged 18 years or younger at the first enquiry of PEs.

Exposure

For the purpose of this investigation, childhood and adolescent PEs were considered as exposure. Data on PEs reported by both questionnaire and interview format were included. Within the literature, PEs are reported either dichotomously (i.e. as the presence or absence of any PE phenomena) or by sub-types (e.g. auditory hallucinations or paranoia). All studies that reported PEs dichotomously were included in this investigation. Where PEs were not reported in this way, and only data on sub-types of PEs were reported, only studies that reported on auditory hallucinations or hallucinations were included. The decision to include these two categories of PE as valid outcomes for this investigation was based on evidence that endorsement of auditory hallucinations on questionnaires has demonstrated predictive validity for the presence of PEs when subsequently assessed by clinical interview (Kelleher *et al.*, 2009; Laurens *et al.*, 2012; and Granö *et al.*, 2016). Where different 'strengths' or 'levels' of PEs were reported (e.g. 'weak' and 'strong' PEs or 'definite' and 'possible' PEs) only the strong or definite category was used to estimate the relationship with mental disorders (weak and possible PEs were combined with controls to improve community sample representation). If a study examined multiple reporting of PEs (e.g. participants were grouped into whether they had reported PEs never, once, twice or three times), these groups were combined (any PEs ever). Information on the criteria used for PEs in each selected study is given in Table 1.

Outcome

For inclusion in this investigation, participants must have met criteria for a mental disorder in accordance with Diagnostic and Statistical Manual (DSM) or International Classification of Disease (ICD) standards (any edition). Diagnosed mental disorders were grouped into any mental disorder, any non-psychotic disorder and five specific categories of disorder: psychotic disorder, affective disorder (mania or depression), anxiety disorder (generalised anxiety, panic, obsessive-compulsive and phobias), behavioural disorder (conduct, oppositional defiant or attention-deficit/hyperactivity disorder) and substance use disorder (any).

Exclusion criteria

Sample

Help-seeking, high-risk samples were excluded from the investigation. This was done to increase the representativeness of the pooled estimate relative to the general population. Inclusion of help-seeking samples is likely to bias the pooled estimates. Additionally, case-control studies were excluded from the investigation. While pooled point estimates based on case-control studies are likely to be similar to cohort studies, the confidence intervals (CIs) for these estimates are narrower than for cohort studies as the number of individuals within the exposure group are inflated relative to the general population. For this reason, case-control studies were excluded.

Non-diagnostic assessment of psychopathology and temporality

Any study that did not use ICD or DSM diagnostic criteria to determine rates of mental disorder was excluded from the review and meta-analysis. Additionally, as PEs were considered our exposure of interest and mental disorder our outcome, for cross-sectional studies PEs and mental disorder had to be assessed contemporaneously and for longitudinal studies PEs had to precede the assessment of mental disorder. If the temporal relationship between PEs and mental disorder explicitly stated that mental disorder preceded PEs, the study was excluded.

Study selection and data extraction

Literature search was conducted by CH in August 2017 with studies reviewed by CH and RB. An assessment of study quality was conducted using the National Heart, Lung, and Blood Institute quality assessment tool for observational cohort and cross-sectional studies (see online Supplement A, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). The data extraction was conducted by two reviewers (CH and ND), with an initial reviewer consistency of 87.5%. Data extraction discrepancies between the two reviewers were resolved via joint discussion with a third reviewer (RB). We report the location of where the data was extracted from in each study in online Supplement B.

Metrics

Unadjusted odds ratios (ORs) were used when available. When ORs were not present but were calculable based on the information presented in the study (number of individuals were available), ORs were calculated. If the unadjusted ORs were not calculable or were

https://doi.org/10.1017/S0033291719000485 Published online by Cambridge University Press

Table 1. Descriptive summary of the studies included

Author	Title	Population (*N*)	PE assessment type, PE criteria used, age range and prevalence (%)	Mental disorder assessment instrument, diagnostic criteria, diagnosis available and age at outcome (longitudinal only)	Analysed outcomes	Metrics and adjustment
Cross-sectional						
Clemmensen *et al*. (2016)	Psychotic experiences and hyper-theory-of-mind in preadolescence – a birth cohort study	Copenhagen Child Cohort ($n = 1614$)	K-SADS; PE group; age range: 11–12; (10.5%)	DAWBA DSM-IV Any mental disorder	Any mental disorder	Unadjusted odds ratio and 95% confidence interval used
Kelleher *et al*., (2012*b*)	Clinicopathological significance of psychotic experiences on non-psychotic young people: evidence from four population based studies	Adolescent Brain Development ($n = 212$) Challenging times ($n = 211$)	K-SADS; PE group; ABD: age range: 11–13; 22.6%; CT: age range: 13–16; 7%	K-SADS DSM-IV Any mental disorder; affective disorder; behavioural disorders anxiety disorders	Any mental disorder; Any non-psychotic mental disorder; affective disorder; behavioural disorders anxiety disorders	Unadjusted odds ratio and 95% confidence interval used
Jeppesen *et al*. (2015)	Psychotic experiences co-occur with sleep problems, negative affect and mental disorders in preadolescence	Copenhagen Child Cohort ($n = 1632$)	K-SADS; PE group; age range: 11–12; (10.5%)	DAWBA DSM-IV Anxiety; obsessive-compulsive disorder; depression; oppositional deficient disorder; conduct disorder; attention deficit hyper-activity disorder	Any non-psychotic mental disorder; affective disorder; anxiety disorder; behavioural disorder	Unadjusted odds ratio and 95% confidence interval used
Scott *et al*. (2009)	The prevalence and correlates of hallucinations in Australian adolescents: results from a national survey	Australian National Survey of Mental Health and Well-Being ($n = 1261$)	YSR; Hallucinations (auditory or visual); Age range: 13–18; (8.4%)	DIS-C DSM-IV Depressive disorder; conduct disorder; attention deficit hyper-activity disorder	Any mental disorder; any non-psychotic mental disorder; affective disorder; behavioural disorder	Unadjusted odds ratio and 95% confidence interval used
Calkins *et al*. (2014)	The psychosis spectrum in a young U.S. community sample: findings from the Philadelphia Neuro-developmental Cohort	Philadelphia Neurodevelopmental Cohort ($n = 4665$)	GOASSESS, K-SADS; PE group; Age range: 11–21; (19.7%)	GOASSESS/K-SADS DSM-IV Depression; mania; generalised anxiety; separation anxiety; specific phobia; social phobia; panic; agoraphobia; obsessive compulsive; post-traumatic stress; attention deficit; oppositional defiant; conduct; eating disorder	Any mental disorder; any non-psychotic mental disorder; affective disorder; anxiety disorder; behavioural disorder	Unadjusted odds ratio and 95% confidence interval used
Adriaanse *et al*. (2015)	School-based screening for psychiatric disorders in Moroccan-Dutch youth	Dutch-Moroccan Cohort ($n = 152$)	K-SADS; PE group; Age range: 9–16; continuous PE score reported ($\bar{x} = 3.4$; SD = ± 3.4)	K-SADS DSM-IV Any mental disorder	Any mental disorder; any non-psychotic mental disorder	Unadjusted odds ratio and 95% confidence interval used
Longitudinal						
Poulton *et al*. (2000)	Children's self-reported psychotic symptoms and adult schizophreniform disorder	Dunedin ($n = 761$)	DISC-C; PE group (strong only); Age: 11; (1.8%)	DIS DSM-IV Schizophreniform disorder; mania disorder; depressive disorder; anxiety disorder Age: 26 $\bar{x}$ Follow-up: 15 years	Any mental disorder; any non-psychotic mental disorder; psychotic disorder; affective disorder; anxiety disorder	Unadjusted odds ratio and 95% confidence interval used

(*Continued*)

Table 1. (*Continued.*)

Author	Title	Population (*N*)	PE assessment type, PE criteria used, age range and prevalence (%)	Mental disorder assessment instrument, diagnostic criteria, diagnosis available and age at outcome (longitudinal only)	Analysed outcomes	Metrics and adjustment
Dhossche *et al.* (2002)	Diagnostic outcome of self-reported hallucinations in a community sample of adolescents	Erasmas (*n* = 779)	YSR; Hallucinations (auditory); Age range: 11–18; (5%)	CIDI DSM-IV Any mental disorder; depressive disorder; substance-use disorder; specific phobia; PTSD; social phobia Age range: 19–26 $\bar{x}$ Follow-up: 9 years	Any mental disorder; any non-psychotic mental disorder; substance-use disorder; affective disorder; anxiety disorder	Unadjusted odds ratio and 95% confidence interval used
Fisher *et al.* (2013)	Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study	Dunedin (*n* = 776)	DISC-C; PE group (strong only); Age: 11; (1.6%)	DIS DSM-III-R and DSM-IV Schizophrenia; persistent anxiety; persistent depression; PTSD; persistent substance dependence Age: 38 $\bar{x}$ Follow-up: 27 years	Substance-use disorder	Unadjusted odds ratio and 95% confidence interval used
Dominguez *et al.* (2011)	Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study	Early Developmental Stages of Psychopathology (*n* = 845)	SCL-90; PE group; Age range: 14–17; (21.18%)	DIA-X/M-CIDI DSM-IV and ICD-10 Psychotic impairment $\bar{x}$ Follow-up: 4.9 years from T2 to T3	Any mental disorder; psychotic disorders	Unadjusted odds ratio and 95% confidence interval used
McGrath *et al.* (2010)	Association between Cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults	Mater-University Study of Pregnancy (*n* = 3801)	YSR Hallucinations (auditory or visual) Age: 14 (15.8%)	CIDI ICD-10 Non-affective psychosis Age range: 18–23 $\bar{x}$ Follow-up: 7 years	Any mental disorder; psychotic disorder	Unadjusted odds ratio and 95% confidence interval used
Bechtold *et al.* (2016)	Concurrent and sustained cumulative effects of adolescent marijuana use on subclinical psychotic symptoms	Pittsburgh (*n* = 908)	YSR; PE group (any sub-clinical); Age range: 13–18; (24.1%)	DIS DSM-IV Psychotic disorder Age range: 26–36 $\bar{x}$ Follow-up: ∼13 years	Any mental disorder; psychotic disorder	Unadjusted odds ratio and 95% confidence interval used
Zammit *et al.* (2013)	Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study	Avon Longitudinal Study of Parents and Children (*n* = 4724)	PLSI; PE group (definite); Age: 12 (4.9)	SCAN DSM-IV and ICD-10 Psychotic disorder Age: 18 $\bar{x}$ Follow-up: 6 years	Any mental disorder; psychotic disorder	Unadjusted odds ratio and 95% confidence interval used
Cederlöf *et al.* (2017)	A longitudinal study of adolescent psychotic experiences and later development of substance use disorder and suicidal behaviour	Child and Adolescent Twin Study in Sweden (*n* = 9242)	Seven individual PE items; auditory hallucinations; Age: 15 and 18 (5.6%)	National Patient Registry ICD-10 Substance use disorder; $\bar{x}$ Follow-up: 2.7 years	Any mental disorder; any non-psychotic mental disorder; substance disorder	Hazard ratio presented. Authors contacted and unadjusted odds ratio used

PE, psychotic experiences; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; DAWBA, Development and Well-Being Assessment; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; YSR, Youth Self-Report Questionnaire; DISC-C, Diagnostic Interview Schedule for Children; DIS, Diagnostic Interview Schedule; CIDI, Composite International Diagnostic Interview; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, revised third edition; SCL-90, Symptom Checklist-90; DIA-X/M-CIDI computerised version of the Munich-Composite International Diagnostic Interview; ICD-10, International Classification of Disease tenth edition; PLSI, Psychosis-Like Symptom Interview; and SCAN, Schedules for Clinical Assessment in Neuropsychiatry.

not available within the text, adjusted ORs were used and the confounders are documented in Table 1. If the study presented alternative metrics (hazard ratio or risk ratio) relevant authors were contacted to request information for calculating ORs.

Disorder grouping and sub-categories

Mental disorders were grouped into two overall categories: (i) any mental disorder and (ii) any non-psychotic disorder. We also investigated five sub-categories of mental disorder: affective, anxiety, psychotic, behavioural and substance-use disorder. Affective disorders included both depressive disorders and mania. Anxiety disorders included generalised anxiety, separation anxiety, specific phobia, social phobia, panic, agoraphobia, obsessive compulsive disorder and post-traumatic stress disorder (PTSD). As the majority of studies reviewed use DSM-IV diagnostic criteria, PTSD was included under anxiety disorder classifications. Psychotic disorders included schizophrenia, schizophreniform disorder, non-affective psychosis and psychotic disorders not otherwise specified. Behavioural disorders included oppositional defiant, conduct and attention deficit/hyperactivity disorders.

When not explicitly reported in the text the 'any mental disorder' category and the 'any non-psychotic mental disorder' ORs were calculated by pooling the ORs of the disorders presented in the study. This was calculated by averaging the log odds for each disorder (i.e. logodds disorder X + the logodds disorder Y/No. of disorders) and averaging the standard error for each disorder (i.e. standard error of disorder X + standard error of disorder Y/No. of disorders). We used these metrics to calculate the OR and 95% CI for the 'any mental disorder' category for that study. We also used this approach if sub-categories of a disorder group were reported (i.e. reported on different types of anxiety disorders such as generalised anxiety disorder and panic disorder). This method reduced the likelihood of artificially narrowing the CIs.

Data analysis

All data analyses were conducted using Stata Version 15 (StataCorp, 2017).

Effects model

We used random effects models as we expected heterogeneity in the distribution of the ORs. Heterogeneity was statically measured using the I^2 metric. Heterogeneity was expected for many reasons including differences in: the temporal relationship between PEs and mental disorders (concurrent or subsequent), the methodology used to investigate PEs (questionnaire *v.* interview), the age of the participants, the manner of selection into each study and differences in diagnostic criteria. Model selection based on the heterogeneity estimates has been deemed inappropriate as the assumptions of the fixed and random models differ (Borenstein *et al.*, 2010).

Analysis 1

Firstly, we investigated the association between childhood and adolescent PEs and both any mental disorder and any non-psychotic disorder. Random effects pooled ORs are reported with estimates of heterogeneity across studies. Funnel plots (see online Supplements C and D) and the Egger's regression test for publication asymmetry (Egger *et al.*, 1997) were examined and trim and fill (Duval and Tweedie, 2000) adjustments were applied. Secondly, we stratified the results by study design to examine the effects design had on the relationship between PEs and mental disorder (any and any non-psychotic) separately. Finally, post-hoc meta-regressions were conducted on several variables that could explain the between-study variance in the relationship between PEs and any mental disorder (this was not conducted for any non-psychotic disorder as too few studies were available). The independent variables in these univariate regressions were PE assessment type (interview or questionnaire), study design (cross-sectional or longitudinal), population size and follow-up time (longitudinal studies only). Bubble plots and non-descriptive results of this analysis are presented in online Supplement E.

Analysis 2

In the second analysis we investigated the association between childhood and adolescent PEs with each sub-category of mental disorder: psychotic disorders, affective disorders, anxiety disorders, behavioural disorders and substance-use disorders. Similar to analysis 1, we report the random effects pooled ORs and heterogeneity based on I^2. Again, we stratify by study design to investigate the relationship between PEs and the sub-categories of each mental disorder in separate cross-sectional and longitudinal analyses. Finally, for longitudinal studies we report the population attributable fraction (PAF) where this was calculable (psychotic disorders only).

Results

Study selection

Based on the search terms, we extracted 3092 studies from the three databases. In total, 2877 remained after removing duplicates. The titles and abstracts of all 2877 were reviewed for relevance, which resulted in the identification of 186 for full text screening. Of those, 117 were excluded because the studies did not use a child or adolescent community sample. Based on the inclusion and exclusion criteria, 14 of the remaining 69 studies met criteria for inclusion in the review, 13 of which also met inclusion criteria for meta-analysis. The specific reasons for exclusion are given in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram (Fig. 1).

Search yield

The search yielded 14 studies from 13 ($n = 29\,517$) different community samples (Poulton *et al.*, 2000; Dhossche *et al.*, 2002; Scott *et al.*, 2009; McGrath *et al.*, 2010; Dominguez *et al.*, 2011; Kelleher *et al.*, 2012*b*; Fisher *et al.*, 2013; Zammit *et al.*, 2013; Calkins *et al.*, 2014; Adriaanse *et al.*, 2015; Jeppesen *et al.*, 2015; Bechtold *et al.*, 2016; Clemmensen *et al.*, 2016; Cederlof *et al.*, 2017). This included six cross-sectional studies from six different community samples and eight longitudinal reports from seven different community samples (average follow-up time of 10.5 years, range: 0.12–27 years). The characteristics of each study are presented in Table 1. Two community samples were represented in more than one investigation (the Copenhagen and the Dunedin cohorts). The two studies presenting data from the Copenhagen cohort examined different outcomes (see Table 1). We found an overlap between the outcomes in the two Dunedin cohort studies selected for review: Poulton *et al.* (2000) investigated the longitudinal relationship between PEs and any disorder, non-psychotic disorder, psychotic disorder, affective disorder and anxiety disorder while Fisher *et al.* (2013) investigated the longitudinal relationship between PEs and substance use disorder.

https://doi.org/10.1017/S0033291719000485 Published online by Cambridge University Press

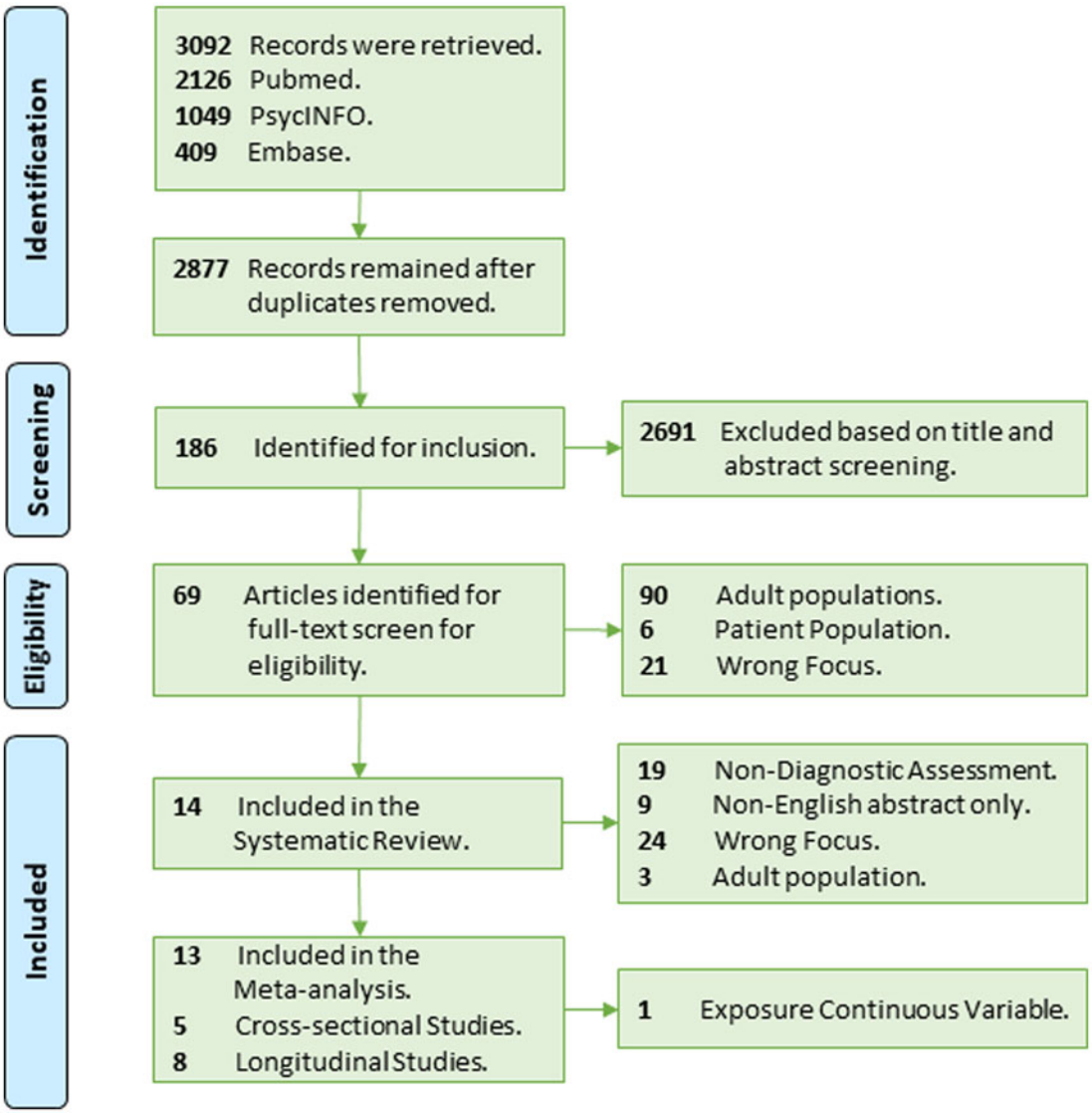

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram for study inclusion.

Prevalence of psychotic experiences

Data from 12 community samples ($n = 29\,365$) were used to calculate the prevalence of PEs (prevalence estimates could not be calculated from Adriaanse *et al.*, 2015). The point prevalence (defined as the prevalence at time point 1 in all longitudinal studies) of children and adolescents reporting PEs was 9.83% ($n = 2886$). The prevalence in cross-sectional studies was 16.11% ($k = 5$; $n = 1315$) and the prevalence reported in longitudinal studies was 7.41% ($k = 7$; $n = 1571$).

There was a minor discrepancy in the prevalence of PEs between the methods of reporting. In questionnaire-based studies the pooled prevalence of PEs was 11.83% ($n = 912$; $k = 5$). In interview-based studies the pooled prevalence was 9.12% ($n = 1974$; $k = 8$).

Multiple reports of PEs

Two longitudinal studies reported PEs at multiple time points prior to the assessment of mental disorder (Dominguez *et al.*, 2011; Bechtold *et al.*, 2016). As so few studies ($k = 2$) reported on PEs at multiple time points, statistical analyses were not carried out to investigate the relationship between persistent PEs and mental disorders. Both of these studies investigated the relationship between PEs and subsequent psychotic disorder and both indicated a greater risk in those who repeatedly reported PEs.

Meta-analysis

Analysis 1: PEs and any mental disorder and any non-psychotic disorder

Twelve of the 13 samples were used to investigate the relationship between child and adolescent PEs and mental disorder. Adriaanse *et al.* (2015) were not included in this analysis because PEs were measured as continuous variable in their study. We found that PEs were associated with a three-fold increased odds of any mental disorder (OR 3.08, CI 2.26–4.21, $k = 12$, see Fig. 2). When the investigation was narrowed to any non-psychotic disorder, those who report PEs had a 2.8-fold increase in the odds of meeting criteria for a mental disorder than their peers (OR 2.82, CI 1.86–4.28, $k = 8$, see Fig. 3).

https://doi.org/10.1017/S0033291719000485 Published online by Cambridge University Press

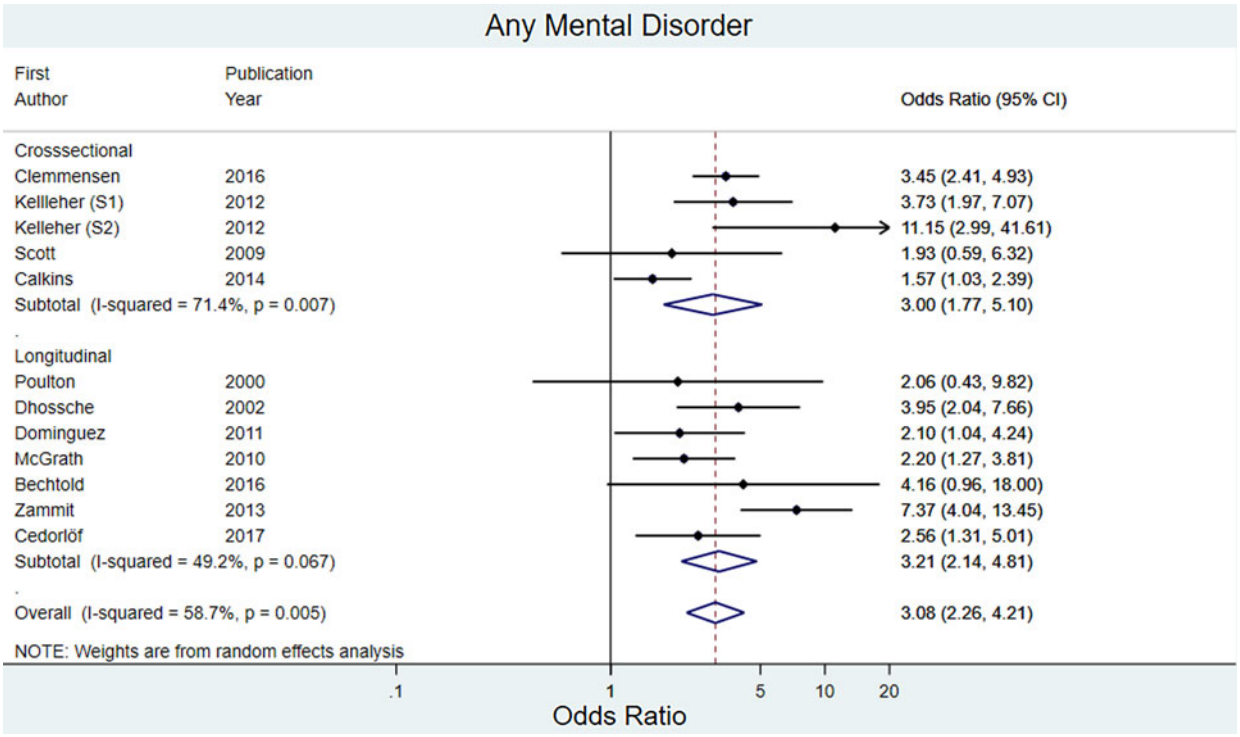

Fig. 2. Forest plot of the relationship between child and adolescent PEs and any mental disorder.

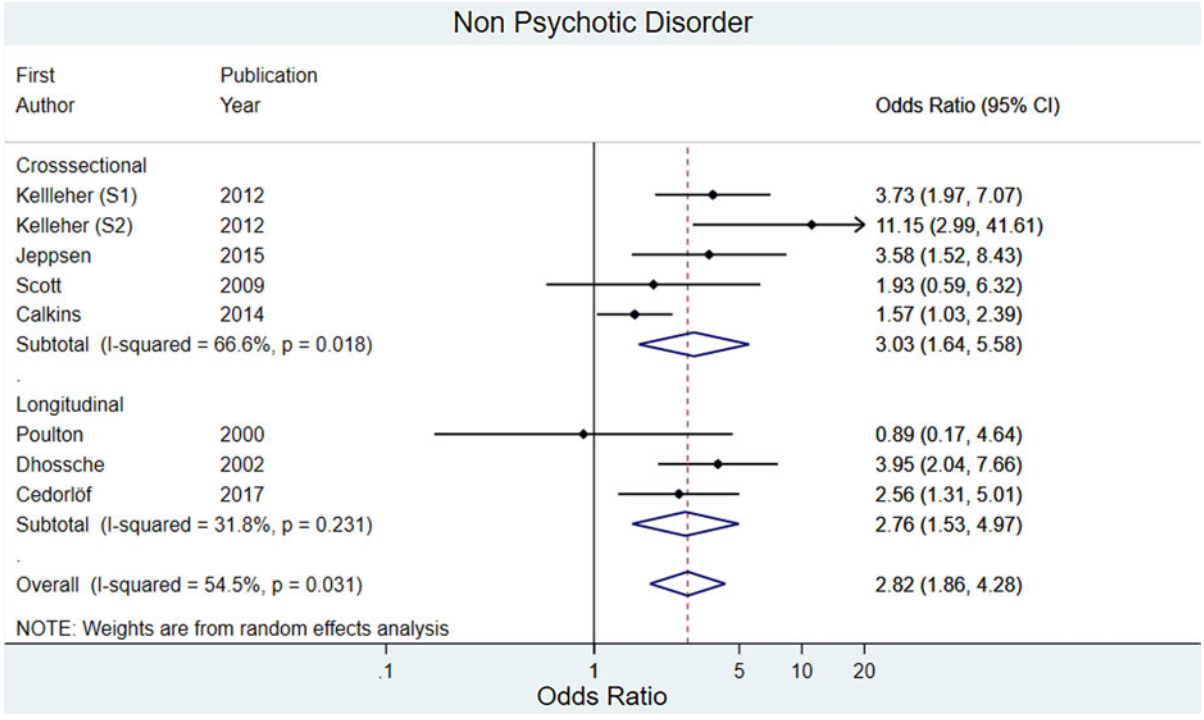

Fig. 3. Forest plot of the relationship between child and adolescent PEs and any non-psychotic disorder.

Visual assessment of the funnel plots and Egger's regression test did not suggest an asymmetry in the published literature for any mental disorder or any non-psychotic disorder (any mental disorder: $t = 0.66$, $p = 0.526$, see online Supplement C; and any non-psychotic disorder: $t = 0.98$, $p = 0.364$, see online Supplement D). Statistical adjustment for one potentially missing study using a trim and fill method somewhat adjusted the OR for any non-psychotic disorder in those with PEs (adjusted OR 2.51, CI 1.60–3.92, $p < 0.001$). Significant between-study heterogeneity was evident for the relationship between PEs and both any mental disorder ($I^2 = 58.7$, $p = 0.005$) and any non-psychotic disorder ($I^2 = 54.5$, $p = 0.031$).

https://doi.org/10.1017/S0033291719000485 Published online by Cambridge University Press

Study design stratification

When investigated separately, we found a three-fold increase in odds of any mental disorder in children and adolescents who reported PEs among both cross-sectional ($k = 5$) and longitudinal studies ($k = 7$) (see Fig. 2). Between-study heterogeneity was evident across cross-sectional studies ($I^2 = 71.4$, $p = 0.007$) and was somewhat suggested across longitudinal studies ($I^2 = 49.2$, $p = 0.067$). When limited to non-psychotic disorders, both cross-sectional ($k = 5$) and longitudinal ($k = 3$) studies indicated increased odds of any non-psychotic disorder in children and adolescents reporting PEs (see Fig. 3). However, the number of studies available was limited in both design methods and there was significant heterogeneity across the cross-sectional studies ($I^2 = 66.6$, $p = 0.018$).

Meta-regression analysis

Given the significant between-study heterogeneity, we investigated whether a number of variables were likely to influence the relationship between PEs and any mental disorder. These included PE assessment type, study design type, the total population of the study and follow-up time in longitudinal studies. None of these variables had a significant effect on the relationship between PEs and any mental disorder (see online Supplement E).

Analysis 2. PEs and sub-categories of mental disorders

There was a significant association between PEs and all sub-categories of mental disorder (see Table 2 and online Supplements F and G). These results were particularly prominent for psychotic disorders (OR 3.96, CI 2.03–7.73), affective disorders (OR 3.83, CI 2.26–6.49, for depressive disorders only see online Supplement H) and substance use disorders (OR 3.41, CI 2.03–5.74). For example, analysis of data from the five longitudinal studies investigated the relationship between PEs and psychotic disorders found an approximate four-fold increased risk of psychotic disorders in those with PEs. The PAF was calculable from these five studies and indicated that childhood and adolescent PEs accounted for 23.2% of psychotic disorders. Heterogeneity was evident in the analysis investigating psychotic disorders and affective disorders.

Study design stratification

In studies using a cross-sectional study design, children and adolescents reporting PEs had an increased risk of affective and behavioural disorders. There was significant heterogeneity in the investigation of affective disorders. In those using longitudinal study designs, childhood and adolescent PEs were associated with over a three-fold increased risk of substance use and psychotic disorders (Table 2). However very few studies ($k = 2$) investigated the longitudinal relationship between child and adolescent PEs and subsequent affective disorders or anxiety disorders. No study included in this investigation had examined the longitudinal relationship between PEs and subsequent behavioural disorders.

Discussion

This is, to the best of our knowledge, the first systematic review of studies looking at risk of mental disorders in non-help-seeking children and adolescents who report PEs. Childhood and adolescent PEs were associated with increased odds of psychotic and affective, anxiety, behavioural and substance use disorders.

Table 2. The pooled ORs and the heterogeneity assessments of the relationship between childhood and adolescent PEs and each category of mental disorder (overall association and stratified by study design type)

	Overall			Longitudinal study design			Cross-sectional study design		
Mental disorder categories	No. of samples	I^2	Pooled OR (95% CI)	No. of samples	I^2	Pooled OR (95% CI)	No. of samples	I^2	Pooled OR (95% CI)
Psychotic	5	**70.1**	**3.96 (2.03–7.73)**	5	**70.1**	**3.96 (2.03–7.73)**	N/A	N/A	N/A
Affective	7	**59.1**	**3.83 (2.26–6.49)**	2	68.7	1.71 (0.23–12.52)	5	**62.7**	**4.35 (2.44–7.77)**
Anxiety	6	0.0	**1.45 (1.09–1.94)**	2	0.0	1.80 (0.71–4.55)	4	17.9	1.45 (0.98–2.14)
Behavioural	5	50.3	**2.09 (1.24–3.53)**	0	–	–	5	50.0	**2.09 (1.24–3.53)**
Substance use	3	11.0	**3.41 (2.03–5.74)**	3	11.0	**3.41 (2.03–5.74)**	0	–	–

I^2, percentage of heterogeneity; CI, confidence interval; N/A, non-applicable; –, no study available.
Bold values denote a probability of $p < 0.05$.

https://doi.org/10.1017/S0033291719000485 Published online by Cambridge University Press

The prevalence of PEs in included studies was 9.3%, which is in keeping with meta-analytic estimates (Kelleher *et al.*, 2012*a*; Maijer *et al.*, 2018). It also is in keeping with the observation that PEs are more prevalent in early life than in adulthood (Linscott and van Os, 2013). Childhood and adolescent PEs were associated with a three-fold increased odds of having any mental disorder or any non-psychotic disorder in both cross-sectional and longitudinal studies. Roughly a quarter of psychotic disorders were attributable to PEs in childhood or adolescence.

These results align with the suggestion that childhood PEs are an early stage pluripotent psychiatric marker (McGorry *et al.*, 2018) and may therefore be considered as an early trans-diagnostic marker for vulnerability to subsequent mental disorder. This theory is empirically supported by follow-up research using a sub-sample of the Philadelphia cohort, which found that those with persistent PEs had increased rates of psychotic, affective and behavioural disorders while those with transient PEs had an increased rate of subsequent depressive disorders (Calkins *et al.*, 2017). All three of their PE groups also had higher treatment history prevalence than controls at follow-up. Similarly, Fisher *et al.* (2013) found that, by age 38, 93.3% of those who reported PEs in childhood had met criteria for a mental disorder at some stage of their life. These results suggest that PEs may be a useful marker for identifying those at risk of subsequent mental disorder. Our own research has highlighted that childhood PEs are not just a marker for subsequent risk but including PEs in assessments actually improves the prediction of subsequent psychopathology over and above the effects of a history of mental disorder, childhood functioning and traumatic experiences (Healy *et al.*, 2018). While the meta-analysis results from this investigation support the theory that those who report childhood and adolescent PEs have an increased risk of subsequent mental disorders (any and any non-psychotic disorder), there were very few longitudinal studies investigating the relationships between PEs and specific categories of non-psychotic disorders (Poulton *et al.*, 2000; Dhossche *et al.*, 2002; Fisher *et al.*, 2013; Cederlof *et al.*, 2017). More research, specifically targeting the relationship between childhood PEs and subsequent non-psychotic disorder is therefore warranted.

In addition to the longitudinal outcomes, results from cross-sectional study design provided converging evidence suggesting that those who report childhood and adolescent PEs are more likely to have a co-occurring non-psychotic disorder. The synthesis of the cross-sectional literature provides evidence that childhood and adolescent PEs are a potential feature of non-psychotic disorders. Research over the last two decades has challenged the homotypic nature of these phenomena, as those who report PEs have increased rates of a variety of different disorders (Calkins *et al.*, 2014). However, similar to longitudinal research, the number of studies investigating the relationship between these phenomena and mental disorders is still relatively limited and subsequent research is necessary to fully examine the prevalence of each sub-category of mental disorder and PEs.

Heterogeneity

Most analyses revealed heterogeneity in the effects reported across studies. This was expected, given the variability between the studies in design characteristic such as PEs assessment type and follow-up time. These characteristics may affect the relationship between PEs and mental disorder. To investigate this, we ran four univariate meta-regressions (online Supplement E). None of the variables we investigated had an effect on the relationship between PEs and any mental disorder. It is possible that other study or sample characteristics could have influenced this relationship. Such characteristics might include participant demographic characteristics or cross-study cultural differences, differences in diagnostic instrument or the interactive effects of a number of features. Additionally, the number of studies available precluded an investigation of how study characteristics affect the relationship between PEs and specific mental disorders.

Strengths and limitations

Strengths of the current study include investigation of both longitudinal and cross-sectional studies. A limitation is that some of the cross-sectional studies asked about lifetime (not current or recent) PEs. Interestingly, however, previous research has shown that, even when asked about lifetime experiences, most young people who report PEs have experienced these symptoms within the last year (Kelleher *et al.*, 2012*a*). The studies examined were restricted to published reports within peer-reviewed journals adding to the credibility of the findings; however, this also leaves open the possibility of publication bias. However, visual assessment of funnel plots and statistical assessment using Egger's regression test for the main analysis suggests that there is minimal asymmetry in the overall investigation. It was noted that there are a number of studies that examine the relationship between PEs and psychopathology using non-diagnostic questionnaires, such as the *Strengths and Difficulties Questionnaire* (Goodman, 2001). While this investigation was restricted to the relationship between childhood and adolescent PEs and clinically defined mental disorder, we acknowledge that there is body of literature using these methods (Laurens *et al.*, 2008; Bartels-Velthuis *et al.*, 2010; Dolphin *et al.*, 2015; Bartels-Velthuis *et al.*, 2016). The majority of these studies have indicated an increased risk of internalising and externalising behavioural problems in those who report PEs. This, coupled with the results of the current study, suggests converging evidence across assessment tools in the relationship between childhood and adolescent PEs and psychopathology. However this remains to be confirmed. Only two of the studies in this investigation had examined PEs at multiple time points (Dominguez *et al.*, 2011; Bechtold *et al.*, 2016). This limited our ability to meaningfully assess the relationship between persistent PEs and mental disorder. It has been reported, using non-diagnostic questionnaires, that children with persistent PEs have an elevated risk of internalising and externalising problems relative to transient PEs and healthy participants (Downs *et al.*, 2013). Future research should investigate the relationship between persistent PEs and common mental disorder using diagnostic clinical assessments.

Conclusion

Children who report PEs are at increased risk of psychotic, affective, anxiety, behavioural and substance use disorders. Further research is necessary to understand why some young people with PEs go on to develop psychotic disorders while other young people with PEs go on to develop, for example, affective disorders (or, indeed, some young people with PEs do not develop any mental disorder at all).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719000485

https://doi.org/10.1017/S0033291719000485 Published online by Cambridge University Press

Author ORCIDs. Colm Healy, 0000-0001-7974-1861

Acknowledgements. This research was funded by a European Research Council Consolidator Award to M Cannon (Grant Code 724809 iHEAR) and a Health Research Board Award (HRA-PHR-2015-1323).

Conflict of interest. None.

References

Adriaanse M, Van Domburgh L, Zwirs B, Doreleijers T and Veling W (2015) School-based screening for psychiatric disorders in Moroccan-Dutch youth. *Child and Adolescent Psychiatry and Mental Health* **9**, 13. https://doi.org/10.1186/s13034-015-0045-8

Bartels-Velthuis AA, Jenner JA, Van De Willige G, Van Os J and Wiersma D (2010) Prevalence and correlates of auditory vocal hallucinations in middle childhood. *British Journal of Psychiatry* **196**, 41–46.

Bartels-Velthuis AA, Wigman JT, Jenner JA, Bruggeman R and Van Os J (2016) Course of auditory vocal hallucinations in childhood: 11-year follow-up study. *Acta Psychiatrica Scandinavica* **134**, 6–15.

Bechtold J, Hipwell A, Lewis DA, Loeber R and Pardini D (2016) Concurrent and sustained cumulative effects of adolescent marijuana Use on subclinical psychotic symptoms. *American Journal of Psychiatry* **173**, 781–789.

Borenstein M, Hedges LV, Higgins JP and Rothstein HR (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods* **1**, 97–111.

Calkins ME, Moore TM, Merikangas KR, Burstein M, Satterthwaite TD, Bilker WB, Ruparel K, Chiavacci R, Wolf DH, Mentch F, Qiu HJ, Connolly JJ, Sleiman PA, Hakonarson H, Gur RC and Gur RE (2014) The psychosis spectrum in a young US community sample: findings from the Philadelphia Neurodevelopmental Cohort. *World Psychiatry* **13**, 296–305.

Calkins ME, Moore TM, Satterthwaite TD, Wolf DH, Turetsky BI, Roalf DR, Merikangas KR, Ruparel K, Kohler CG, Gur RC and Gur RE (2017) Persistence of psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort: a prospective two-year follow-up. *World Psychiatry* **16**, 62–76.

Cederlöf M, Kuja-Halkola R, Larsson H, Sjolander A, Ostberg P, Lundstrom S, Kelleher I and Lichtenstein P (2017) A longitudinal study of adolescent psychotic experiences and later development of substance use disorder and suicidal behavior. *Schizophrenia Research* **181**, 13–16.

Clemmensen L, Van Os J, Drukker M, Munkholm A, Rimvall MK, Vaever M, Rask CU, Bartels-Velthuis AA, Skovgaard AM and Jeppesen P (2016) Psychotic experiences and hyper-theory of mind in pre-adolescence – a birth cohort. *Psychological Medicine* **46**, 87–101.

Dhossche D, Ferdinand R, Van Der Ende J, Hofstra MB and Verhulst F (2002) Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. *Psychological Medicine* **32**, 619–627.

Dolphin L, Dooley B and Fitzgerald A (2015) Prevalence and correlates of psychotic like experiences in a nationally representative community sample of adolescents in Ireland. *Schizophrenia Research* **169**, 241–247.

Dominguez MDG, Wichers M, Lieb R, Wittchen HU and Van Os J (2011) Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophrenia Bulletin* **37**, 84–93.

Downs JM, Cullen AE, Barragan M and Laurens KR (2013) Persisting psychotic-like experiences are associated with both externalising and internalising psychopathology in a longitudinal general population child cohort. *Schizophrenia Research* **144**, 99–104.

Duval S and Tweedie R (2000) Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455–463.

Egger M, Smith GD, Schneider M and Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634.

Fisher HL, Caspi A, Poulton R, Meier MH, Houts R, Harrington H, Arseneault L and Moffitt TE (2013) Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. *Psychological Medicine* **43**, 2077–2086.

Goodman R (2001) Psychometric properties of the strengths and difficulties questionnaire. *American Academy of Child and Adolescent Psychiatry* **40**, 1337–1345.

Granö N, Kallionpää S, Karjalainen M, Roine M, Ranta K and Heinimaa M (2016) Discrepancy between self-reported and interviewed psychosis risk symptoms: auditory distortions are the most reliably reported symptom by self-report. *Early Intervention in Psychiatry* **10**, 129–136.

Healy C, Gordon AA, Coughlan H, Clarke M, Kelleher I and Cannon M (2018) Do childhood psychotic experiences improve the prediction of adolescent psychopathology? A longitudinal population-based study. *Early Intervention in Psychiatry* (in press). doi: 10.1111/eip.12762.

Jeppesen P, Clemmensen L, Munkholm A, Rimvall MK, Rask CU, Jorgensen T, Larsen JT, Petersen L, Van Os J and Skovgaard AM (2015) Psychotic experiences co-occur with sleep problems, negative affect and mental disorders in preadolescence. *Journal of Child Psychology and Psychiatry* **56**, 558–565.

Kaymaz N, Drukker M, Lieb R, Wittchen HU, Werbeloff N, Weiser M, Lataster T and Van Os J (2012) 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. *Psychological Medicine* **42**, 2239–2253.

Kelleher I, Connor D, Clarke MC, Devlin N, Harley M and Cannon M (2012*a*) Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. *Psychological Medicine* **42**, 1857–1863.

Kelleher I, Harley M, Murtagh A and Cannon M (2009) Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophrenia Bulletin* **37** 362–369.

Kelleher I, Keeley H, Corcoran P, Lynch F, Fitzpatrick C, Devlin N, Molloy C, Roddy S, Clarke MC, Harley M, Arseneault L, Wasserman C, Carli V, Sarchiapone M, Hoven C, Wasserman D and Cannon M (2012*b*) Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *British Journal of Psychiatry* **201**, 26–32.

Laurens KR, Hobbs MJ, Sunderland M, Green MJ and Mould GL (2012) Psychotic-like experiences in a community sample of 8000 children aged 9 to 11 years: an item response theory analysis. *Psychological Medicine* **42**, 1495–1506.

Laurens KR, West SA, Murray RM and Hodgins S (2008) Psychotic-like experiences and other antecedents of schizophrenia in children aged 9–12 years: a comparison of ethnic and migrant groups in the United Kingdom. *Psychological Medicine* **38**, 1103–1111.

Linscott RJ and van Os J (2013) An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine* **43**, 1133–1149.

Maijer K, Begemann MJH, Palmen SJMC, Leucht S and Sommer IEC (2018) Auditory hallucinations across the lifespan: a systematic review and meta-analysis. *Psychological Medicine* **48**, 879–888.

Mcgorry PD, Hartmann JA, Spooner R and Nelson B (2018) Beyond the 'at risk mental state' concept: transitioning to transdiagnostic psychiatry. *World Psychiatry* **17**, 133–142.

Mcgrath J, Welham J, Scott J, Varghese D, Degenhardt L, Hayatbakhsh MR, Alati R, Williams GM, Bor W and Najman JM (2010) Association between Cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. *Archives of General Psychiatry* **67**, 440–447.

Mcgrath JJ, Saha S, Al-Hamzawi A, Alonso J, Bromet EJ, Bruffaerts R, Caldas-De-Almeida JM, Chiu WT, De Jonge P, Fayyad J, Florescu S, Gureje O, Haro JM, Hu CY, Kovess-Masfety V, Lepine JP, Lim CCW, Mora MEM, Navarro-Mateu F, Ochoa S, Sampson N, Scott K, Viana MC and Kessler RC (2015) Psychotic experiences in the general population: A cross-national analysis based on 31,261 respondents from 18 countries. *JAMA Psychiatry* **72**, 697–705.

Mcgrath JJ, Saha S, Al-Hamzawi A, Alonso J, Andrade L, Borges G, Bromet EJ, Oakley Browne M, Bruffaerts R, Caldas-De-Almeida JM

https://doi.org/10.1017/S0033291719000485 Published online by Cambridge University Press

and Fayyad J (2016*a*) Age of onset and lifetime projected risk of psychotic experiences: cross-national data from the World Mental Health Survey. *Schizophrenia Bulletin* **42**, 933–941.

Mcgrath J, Saha S, Al-Hamzawi A, Andrade L, Benjet C, Bromet EJ, Browne MO, De Almeida JMC, Chiu WT, Demyttenaere K, Fayyad J, Florescu S, De Girolamo G, Gureje O, Haro JM, Ten Have M, Hu CY, Kovess-Masfety V, Lim CCW, Navarro-Mateu F, Sampson N, Posada-Villa J, Kendler KS and Kessler RC (2016*b*) The bidirectional associations between psychotic experiences and DSM-IV mental disorders. *American Journal of Psychiatry* **173**, 997–1006.

Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R and Harrington H (2000) Children's self-reported psychotic symptoms and adult schizophreniform disorder - A 15-year longitudinal study. *Archives of General Psychiatry* **57**, 1053–1058.

Scott J, Martin G, Bor W, Sawyer M, Clark J and Mcgrath J (2009) The prevalence and correlates of hallucinations in Australian adolescents: results from a national survey. *Schizophrenia Research* **107**, 179–185.

StataCorp (2017) *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC.

Zammit S, Kounali D, Cannon M, David AS, Gunnell D, Heron J, Jones PB, Lewis S, Sullivan S, Wolke D and Lewis G (2013) Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *American Journal of Psychiatry* **170**, 742–750.

https://doi.org/10.1017/S0033291719000485 Published online by Cambridge University Press