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

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Abstract

Background: Psychotic experiences (PEs) are common in childhood and adolescence and their association with mental disorders is well-established. We aimed to quantitatively 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: 14 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 (OR:3.08,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 8-17% (Kelleher et al., 2012a, 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, Zammit et al., 2013, Dominguez et al., 2011). 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., 2012b, McGrath et al., 2016, Calkins et al., 2014, Jeppesen et al., 2015), 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., 2012a) and most individuals with lifetime PEs have their first onset by early adulthood (McGrath et al., 2016), 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.

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 PsychINFO. 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 the 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, 2012; Laurens et al, 2012; and Grauö et al, 2011). 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 (for example 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 can be found on 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 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 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 Supplement B.

Metrics. Unadjusted odds ratios were used when available. When odd ratios were not present but were calculable based on the information presented in the study (number of individuals were available) odds ratios were calculated. If the unadjusted odds ratios were not calculable or were not available within the text, adjusted odds ratios were used and the confounders documented in Table 1. If the study presented alternative metrics (Hazard Ratio or Risk ratio) relevant authors were contacted to request the information to calculate an odds ratios.

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 disorders 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' odds ratios were calculated by pooling the odds ratios 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 odds ratio and 95% confidence interval 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 confidence intervals.

Data Analysis

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

Effects Model. Random effects analyses were used as heterogeneity in the distribution of the odd ratios was expected. This 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 versus 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 have 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 odds ratios are reported with estimates of heterogeneity across studies. Funnel plots (see Supplement C and D) and the Egger regression test for publication asymmetry (Egger et al, 1997) were examined and trim and fill (Duval & 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 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 odds ratios 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 3 092 studies from the three databases. 2 877 remained after removing duplicates. The titles and abstracts of all 2 877 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 the meta-analysis. The specific reasons for exclusion are given in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram (Figure 1).

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Flow Diagram for Study inclusion

Insert Figure 1

Search Yield

The search yielded 14 studies from 13 (n=29 517) different community samples (Clemmensen et al., 2016, Jeppesen et al., 2015, Scott et al., 2009, Calkins et al., 2014, Kelleher et al., 2012b, Adriaanse et al., 2015, Poulton et al., 2000, Dhossche et al., 2002, Fisher et al., 2013, Dominguez et al., 2011, Bechtold et al., 2016, Zammit et al., 2013, Cederlof et al., 2017, McGrath et al., 2010). This included 6 cross-sectional studies from 6 different community samples and 8 longitudinal reports from 7 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 Cophenhagen and the Dunedin cohorts). The two studies presenting data from the Cophenhagen 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.

Table 1. Descriptive Summary of Studies Included in the Investigation

Insert Table 1

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=2 886). The prevalence in cross-sectional studies was 16.11% (k=5; n=1 315) and the prevalence reported in longitudinal studies was 7.41% (k=7; n=1 571).

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=1 974; 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) was not included in this analysis because PEs were measured as continuous variable in the study. We found that PEs were associated with a 3-fold increased odds of any mental disorder (OR:3.08, CI: 2.26-4.21, k=12, see Figure 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 Figure 3). 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 Supplement C; and any non-psychotic disorder: t=0.98, p=0.364, see Supplement D). Statistical adjustment for one potentially missing study using a trim and fill method somewhat adjusted the odd ratio 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).

Figure 2. Forest Plot of the Relationship between Child and Adolescent PEs and any Mental Disorder

Insert Figure 2

Study Design Stratification. When investigated separately, we found a 3-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 Figure 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 Figure 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).

Figure 3. Forest Plot of the Relationship between Child and Adolescent PEs and any Non-psychotic Disorder

Insert Figure 3

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 Supplement E).

Table 2. Pooled Odds Ratios and Heterogeneity Assessments of the Relationship between Childhood and Adolescent PEs and each Category of Mental Disorder (overall association and stratified by study design type)

Insert Table 2

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 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 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 4-fold increased risk of psychotic disorders in those with PEs. The population attributable fraction (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 3-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 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.

The prevalence of PEs in included studies was 9.3%, which is in keeping with meta-analytic estimates (Kelleher et al., 2012a, 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 3-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 rates 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; Fisher et al., 2013; Dhossche et al., 2002; and 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-occuring 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 (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 past year (Kelleher et al., 2012). 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 Eggers regression test for the main analysis suggests that there minimal asymmetry in the overall investigation. It was noted that there are a number of the 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 (Bartels-Velthuis et al., 2016, Dolphin et al., 2015, Bartels-Velthuis et al., 2010, Laurens et al., 2008). 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).

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Conflict of Interest: None**.**

References

ADRIAANSE, M., VAN DOMBURGH, L., ZWIRS, B., DORELEIJERS, T. & VELING, W. 2015. School-based screening for psychiatric disorders in Moroccan-Dutch youth. *Child and Adolescent Psychiatry and Mental Health,* 9.

BARTELS-VELTHUIS, A. A., JENNER, J. A., VAN DE WILLIGE, G., VAN OS, J. & WIERSMA, D. 2010. Prevalence and correlates of auditory vocal hallucinations in middle childhood. *British Journal of Psychiatry,* 196**,** 41-46.

BARTELS-VELTHUIS, A. A., WIGMAN, J. T., JENNER, J. A., BRUGGEMAN, R. & VAN OS, J. 2016. Course of auditory vocal hallucinations in childhood: 11-year follow-up study. *Acta Psychiatr Scand,* 134**,** 6-15.

BECHTOLD, J., HIPWELL, A., LEWIS, D. A., LOEBER, R. & PARDINI, D. 2016. Concurrent and Sustained Cumulative Effects of Adolescent Marijuana Use on Subclinical Psychotic Symptoms. *American Journal of Psychiatry,* 173**,** 781-789.

CALKINS, M. E., MOORE, T. M., MERIKANGAS, K. R., BURSTEIN, M., SATTERTHWAITE, T. D., BILKER, W. B., RUPAREL, K., CHIAVACCI, R., WOLF, D. H., MENTCH, F., QIU, H. J., CONNOLLY, J. J., SLEIMAN, P. A., HAKONARSON, H., GUR, R. C. & GUR, R. E. 2014. The psychosis spectrum in a young US community sample: findings from the Philadelphia Neurodevelopmental Cohort. *World Psychiatry,* 13**,** 296-305.

CALKINS, M.E., MOORE, T.M., SATTERTHWAITE, T.D., WOLF, D.H., TURETSKY, B.I., ROALF, D.R., MERIKANGAS, K.R., RUPAREL, K., KOHLER, C.G., GUR, R.C. AND GUR, R.E., 2017. Persistence of psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort: a prospective two-year follow-up. *World Psychiatry,* 16(1), 62-76.

CEDERLOF, M., KUJA-HALKOLA, R., LARSSON, H., SJOLANDER, A., OSTBERG, P., LUNDSTROM, S., KELLEHER, I. & 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, M. K., VAEVER, M., RASK, C. U., BARTELS-VELTHUIS, A. A., SKOVGAARD, A. M. & JEPPESEN, P. 2016. Psychotic Experiences and Hyper-Theory of Mind in Preadolescence - a birth cohort. *Psychological Medicine,* 46**,** 87-101.

COLLABORATION, T. C. 2008. Review Manager (RevMan). Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration.

DHOSSCHE, D., FERDINAND, R., VAN DER ENDE, J., HOFSTRA, M. B. & VERHULST, F. 2002. Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. *Psychological Medicine,* 32**,** 619-627.

DOLPHIN, L., DOOLEY, B. & 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, M. D. G., WICHERS, M., LIEB, R., WITTCHEN, H. U. & 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, J. M., CULLEN, A. E., BARRAGAN, M. & LAURENS, K. R. 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. & TWEEDIE, R. 2000. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics,* 56 (2), pp.455-463.

FISHER, H. L., CASPI, A., POULTON, R., MEIER, M. H., HOUTS, R., HARRINGTON, H., ARSENEAULT, L. & MOFFITT, T. E. 2013. Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. *Psychological Medicine,* 43**,** 2077-86.

GOODMAN, R. 2001. Psychometric properties of the strenghts and difficulties questionaire. *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(2), pp.129-136.

HEALY, C., GORDON, A.A., 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, M. K., RASK, C. U., JORGENSEN, T., LARSEN, J. T., PETERSEN, L., VAN OS, J. & SKOVGAARD, A. M. 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, H. U., WERBELOFF, N., WEISER, M., LATASTER, T. & 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, M. C., DEVLIN, N., HARLEY, M. & CANNON, M. 2012a. Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. *Psychological Medicine* 42**,** 1857-63.

KELLEHER, I., KEELEY, H., CORCORAN, P., LYNCH, F., FITZPATRICK, C., DEVLIN, N., MOLLOY, C., RODDY, S., CLARKE, M. C., HARLEY, M., ARSENEAULT, L., WASSERMAN, C., CARLI, V., SARCHIAPONE, M., HOVEN, C., WASSERMAN, D. & CANNON, M. 2012b. Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *British Journal of Psychiatry,* 201**,** 26-32.

LAURENS, K. R., WEST, S. A., MURRAY, R. M. & 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, R. J. & 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, M. J. H., PALMEN, S. J. M. C., LEUCHT, S. & SOMMER, I. E. C. 2018 Auditory hallucinations across the lifespan: a systematic review and meta-analysis. *Psychological medicine,* 48**,** 879-888.

MCGORRY, P. D., HARTMANN, J. A., SPOONER, R. & NELSON, B. 2018. Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. *World Psychiatry,* 17**,** 133-142.

MCGRATH, J., SAHA, S., AL-HAMZAWI, A., ANDRADE, L., BENJET, C., BROMET, E. J., BROWNE, M. O., DE ALMEIDA, J. M. C., CHIU, W. T., DEMYTTENAERE, K., FAYYAD, J., FLORESCU, S., DE GIROLAMO, G., GUREJE, O., HARO, J. M., TEN HAVE, M., HU, C. Y., KOVESS-MASFETY, V., LIM, C. C. W., NAVARRO-MATEU, F., SAMPSON, N., POSADA-VILLA, J., KENDLER, K. S. & KESSLER, R. C. 2016. The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *American Journal of Psychiatry,* 173**,** 997-1006.

MCGRATH, J., WELHAM, J., SCOTT, J., VARGHESE, D., DEGENHARDT, L., HAYATBAKHSH, M. R., ALATI, R., WILLIAMS, G. M., BOR, W. & NAJMAN, J. M. 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, J. J., SAHA, S., AL-HAMZAWI, A., ALONSO, J., ANDRADE, L., BORGES, G., BROMET, E.J., OAKLEY BROWNE, M., BRUFFAERTS, R., CALDAS-DE-ALMEIDA, J.M. & FAYYAD, J. 2016. Age of onset and lifetime projected risk of psychotic

experiences: cross-national data from the World Mental Health Survey. *Schizophrenia bulletin*, 42(4), pp.933-941.

MCGRATH, J. J., SAHA, S., AL-HAMZAWI, A., ALONSO, J., BROMET, E. J., BRUFFAERTS, R., CALDAS-DE-ALMEIDA, J. M., CHIU, W. T., DE JONGE, P., FAYYAD, J., FLORESCU, S., GUREJE, O., HARO, J. M., HU, C. Y., KOVESS-MASFETY, V., LEPINE, J. P., LIM, C. C. W., MORA, M. E. M., NAVARRO-MATEU, F., OCHOA, S., SAMPSON, N., SCOTT, K., VIANA, M. C. & KESSLER, R. C. 2015. Psychotic Experiences in the General Population A Cross-National Analysis Based on 31 261 Respondents From 18 Countries. *Jama Psychiatry,* 72**,** 697-705.

PETERS, E., WARD, T., JACKSON, M., MORGAN, C., CHARALAMBIDES, M., MCGUIRE, P., WOODRUFF, P., JACOBSEN, P., CHADWICK, P. & GARETY, P. A. 2016. Clinical, socio-demographic and psychological characteristics in individuals with persistent psychotic experiences with and without a "need for care". *World Psychiatry,* 15**,** 41-52.

POULTON, R., CASPI, A., MOFFITT, T. E., CANNON, M., MURRAY, R. & 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(2-3), pp.179-185.

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

UNTERRASSNER, L., WYSS, T. A., WOTRUBA, D., HAKER, H. & ROSSLER, W. 2017. The Intricate Relationship between Psychotic-Like Experiences and Associated Subclinical Symptoms in Healthy Individuals. *Frontiers in Psychology*, 8.

VARGHESE, D., SCOTT, J., WELHAM, J., BOR, W., NAJMAN, J., O'CALLAGHAN, M., WILLIAMS, G. & MCGRATH, J. 2011. Psychotic-Like Experiences in Major Depression and Anxiety Disorders: A Population-Based Survey in Young Adults. *Schizophrenia Bulletin,* 37**,** 389-393.

ZAMMIT, S., KOUNALI, D., CANNON, M., DAVID, A. S., GUNNELL, D., HERON, J., JONES, P. B., LEWIS, S., SULLIVAN, S., WOLKE, D. & 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. *Am J Psychiatry,* 170**,** 742-50.

Table 1. Descriptive summary of the studies include.

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., 2012b	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; Agorphobia; 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 Schizohphreniaform Disorder; Mania Disorder; Depressive Disorder; Anxiety Disorder. Age: 26 x̄ 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
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 x̄ 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 x̄ 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 x̄ Follow up: 4.9 Years from T2-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 x̄ 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 x̄ 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 18in Relation to Psychotic Experiences at Age 12 in a Longitudinal	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 x̄ Follow up: 6 Years	Any Mental Disorder; Psychotic Disorder	Unadjusted odds ratio and 95% confidence interval used

	Population-Based Cohort Study					
Cedorlöf 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; x̄ 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

Note: 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; DIS-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 computerized 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.

Table 2. The pooled odds ratios 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).

Mental Disorder Categories	Overall			Longitudinal Study Design			Cross-Sectional Study Design		
	No of Samples	I^2	Pooled Odds Ratio (95% CI)	No of Samples	I^2	Pooled Odds Ratio (95% CI)	No of Samples	I^2	Pooled Odds Ratio (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	-	-

Note: I^2: Percentage of heterogeneity; CI: Confidence interval; N/A: Non-applicable; -=No study available; Emboldened values denote a probability of $p < .05$.

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Flow Diagram for Study inclusion

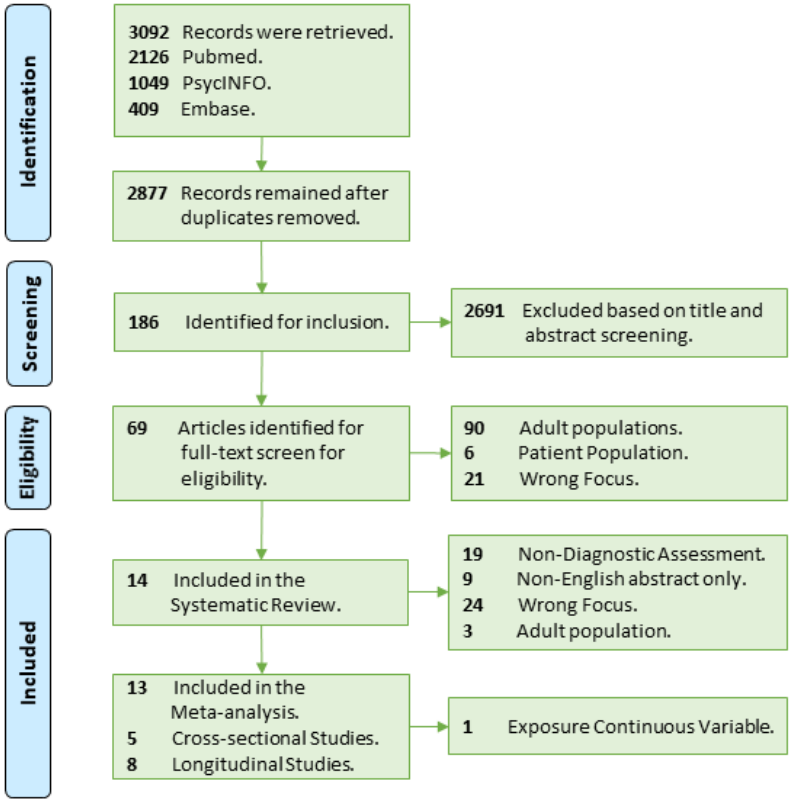

Figure 2. Forest Plot of the Relationship between Child and Adolescent PEs and any Mental Disorder

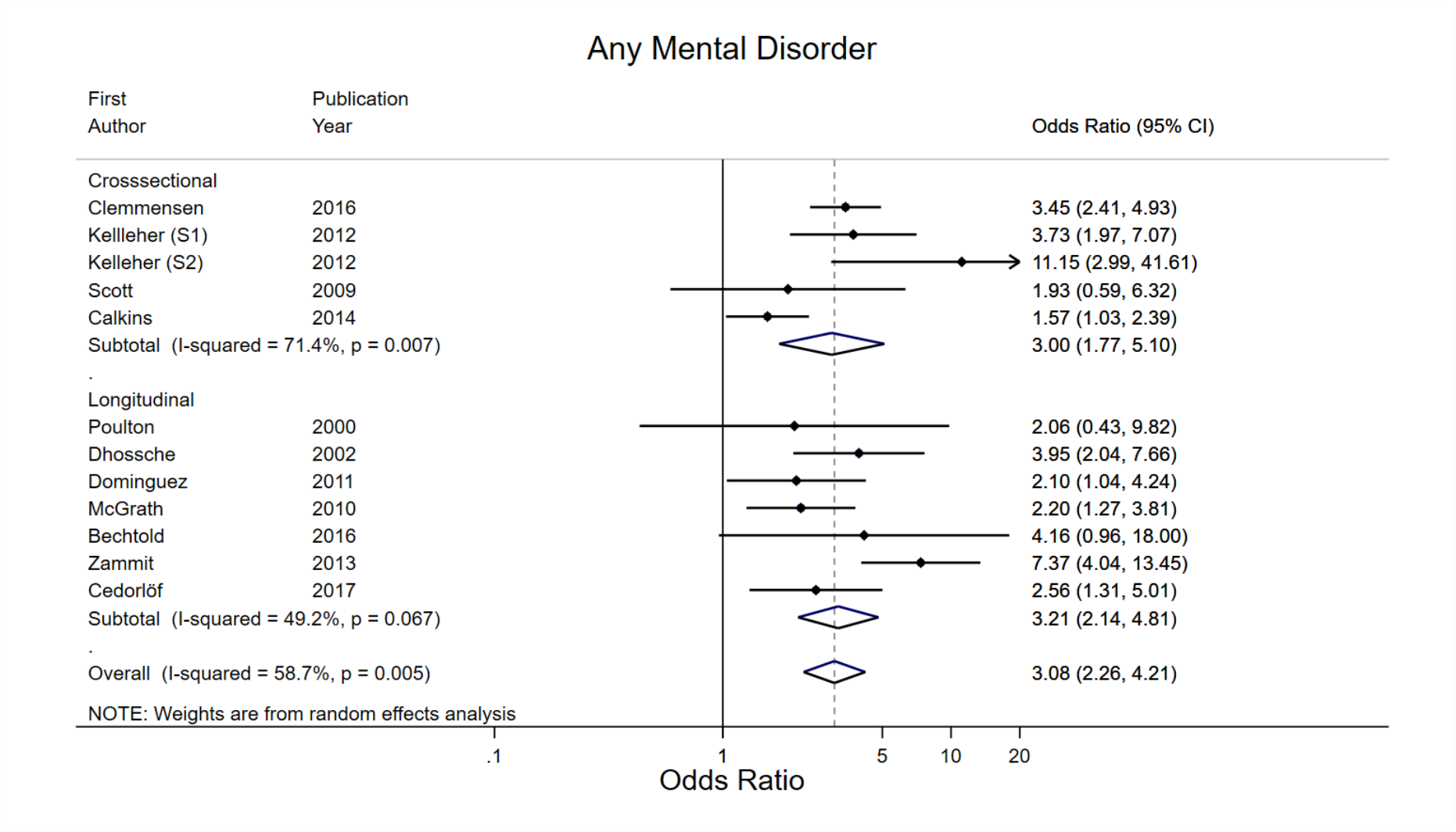

Figure 3. Forest Plot of the Relationship between Child and Adolescent PEs and any Non-psychotic Disorder