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Psychotic experiences and incident suicidal ideation and behaviour: disentangling the longitudinal associations from connected psychopathology.

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ABSTRACT

This study examines the longitudinal associations between psychotic experiences (PE) and incident suicidal ideation and behaviour in the general population, and to what degree the association may be confounded by non-psychotic psychopathology. Data from three prospective, general population cohorts were combined into one dataset (n=15837) and analysed using logistic regression, controlling for continuous measures of depression, anxiety and mania symptoms. Analyses were conducted in the entire sample, and in subsamples stratified by presence or absence of mental disorders. The presence of PE at baseline increased the risk of incident suicidal ideation and behaviour. However, adjustment for dimensional measures of psychopathology reduced effect sizes, although PE remained significantly associated with suicide attempts. Further examination of the associations revealed that PE were only associated with suicide attempts in individuals with at least one mental disorder. Similarly, in individuals without mental disorders, the risk of suicidal ideation increased as PE co-occurred with more symptom domains. The results of this study confirm that individuals with PE are at increased risk of suicidal ideation and behaviour. However, these associations are not specific, but reflect the increased risk of suicidal ideation in individuals with subthreshold multidimensional psychopathology and suicide attempts in individuals with co-occurring mental disorders.

1. Introduction

The presence of low grade psychotic experiences (PE) in the general population has been associated with an increased risk of suicidal ideation and behaviour (Honings et al., 2015). It remains unclear, however, how to isolate this specific association from the association between non-psychotic psychopathology and suicidal ideation and behaviour, since non-psychotic psychopathology is strongly connected to both PE (DeVylder et al., 2014; Guloksuz et al., 2015; Jeppesen et al., 2015; Kelleher et al., 2012b; Van Os et al., 2000), and suicidal behaviour (Cavanagh et al., 2003; ten Have et al., 2009; Ten Have et al., 2013).

Suicidality comprises various phenomena on a continuum ranging from suicidal ideation, suicide plans and suicide attempts to completed suicide (Nock, 2010; Svetlicic and De Leo, 2012). Since suicide and suicide attempts are highly prevalent, identification of causal risk factors is urgently required, as knowledge in this area may assist in reducing the number of suicidal acts (Hawton and van Heeringen, 2009; Nock et al., 2008; World Health Organization, 2014). Even though the mechanisms underlying suicidal behaviour remain poorly understood, research has shown that it is likely determined by a complex interplay of biological, psychological, environmental and cultural factors (O'Connor et al., 2011; World Health Organization, 2014). Mental disorders are an important risk factor for suicidal behaviour (Bostwick and Pankratz, 2000; Nordentoft et al., 2011; Palmer et al., 2005): of the individuals who committed suicide, 91% had a mental disorder, most commonly a depressive disorder, substance abuse or schizophrenia (Cavanagh et al., 2003; ten Have et al., 2009; Ten Have et al., 2013). Recently, PE have been identified as a risk factor for suicidal ideation and behaviour in general population individuals (Honings et al., 2015). A similar association has been reported for individuals at risk for psychosis (Taylor et al., 2015).

PE refer to delusional or hallucinatory experiences below the threshold of a diagnosable psychotic disorder, often in absence of significant psychological distress (Kelleher et al., 2012a; Linscott and van Os, 2013). General population surveys have shown that PE are highly prevalent in the general population, with a meta-analytical prevalence of 7.2% (Kelleher et al., 2012a; Linscott and van Os, 2013). PE were identified as a risk factor for several mental health outcomes including both psychotic (Kaymaz et al., 2012; Linscott and van Os, 2013) and non-psychotic psychopathology (Kelleher et al., 2012b) and are associated with increased treatment use and need for care in general population samples (Murphy et al., 2012). Moreover, PE serve as an indicator of illness severity and poor outcome in persons with non-psychotic psychopathology (Guloksuz et al., 2015; Kelleher et al., 2012b; Perlis et al., 2011; Wigman et al., 2012; Wigman et al., 2014).

A recent meta-analysis reported that general population individuals with PE had an increased risk of both suicidal thoughts (i.e. suicidal ideation or suicidal plans) and suicidal behaviour (i.e. suicidal attempts or completed suicide) compared with individuals without PE. Pooled odds ratios (OR) were 2.47 (95% CI 1.71 – 3.59; suicidal thoughts) and 3.03 (95% CI 2.08 – 4.41; suicidal behaviour), respectively (Honings et al., 2015). However, the association between PE and suicidal ideation and behaviour is confounded, since adjustment for non-psychotic psychopathology in longitudinal studies resulted in a 74% excess risk reduction (Honings et al., 2015).

At least half of all individuals with PE have a diagnosable mental disorder (DeVylder et al., 2014; Jeppesen et al., 2015; Kelleher et al., 2012b; Van Os et al., 2000). Moreover, individuals with PE without a mental disorder are at increased risk to develop one (Kaymaz et al., 2012; Kelleher et al., 2012b; Linscott and van Os, 2013). Therefore, it remains unclear whether there is a specific association between PE and suicidal behaviour or whether the association reflects the increased risk of suicidal behaviour in more severe states of mental distress associated with multidimensional psychopathology (Guloksuz et al., 2015; van Nierop et al., 2015b). In a previous study, PE were only associated with suicide attempts in individuals with associated psychological distress, while in the absence of psychological distress there was no association (Martin et al., 2015). Similarly, PE were particularly predictive of suicidal behaviour in the context of a mental disorder (DeVylder et al., 2015b; Kelleher et al., 2013). Recent cross-sectional studies similarly provided evidence that the link between PE and suicidal behaviour is not specific, and can be explained by psychosocial factors and shared common causes that contribute to cumulative stress (DeVylder et al., 2015a; Jahn et al., 2016).

Previous studies had some methodological limitations. First, the association between PE and suicidal ideation and behaviour has been investigated mostly in cross-sectional studies (Capra et al., 2015; DeVylder et al., 2015b; Jang et al., 2014; Kelleher et al., 2012c; Nishida et al., 2010; Saha et al., 2011; Temmingh et al., 2011), disabling causal inferences. Second, several studies included psychiatric diagnoses in the regression models to control for confounding (Calkins et al., 2014; DeVylder et al., 2015b; Fisher et al., 2013; Koyanagi et al., 2015; Lewis-Fernandez et al., 2009; Olsson et al., 2002; Saha et al., 2011; Sharifi et al., 2015). However, it is conceptually impossible to examine a confounder in the association between PE and suicidal behaviour when that confounder, for example depression, is fundamentally associated with the outcome (Miller and Chapman, 2001). Moreover, the addition of a dichotomous confounder to a regression model (i.e. presence or absence of a diagnosable disorder) leaves room for residual confounding, while the use of a continuous, dimensional estimate of psychopathology can prevent that.

The present study aims to examine the longitudinal associations between PE and suicidal ideation and behaviour in a dataset combining three different prospective, general population cohorts. In addition, it was attempted to disentangle the associations between PE and suicidal ideation and behaviour from the associations between co-occurring nonpsychotic psychopathology and suicidality, both at the level of mental disorders and at the level of dimensional psychopathology. Furthermore, methodological limitations associated with earlier analyses were addressed by using three prospective cohort studies, stratified by presence or absence of various mental disorders.

The hypothesis was that the associations between PE and suicidal ideation and behaviour reflect the increased risk of these outcomes in participants with more severe mental distress in the context of mental disorders or multidimensional psychopathology falling under the threshold of a mental disorder. If this is the case, the associations between PE and suicidal ideation and behaviour would only exist in participants with a mental disorder or with high levels of psychopathology. Thus, PE in the absence of either a mental disorder or high levels of sub-disorder psychopathology were hypothesized to not display an associations with suicidal ideation and behaviour.

2. Methods

2.1 Samples and design

This study uses data from three different prospective-longitudinal community studies: the Early Developmental Stages of Psychopathology study (EDSP) and the first and second Netherlands Mental Health Survey and Incidence Studies (NEMESIS and NEMESIS-2).

The EDSP is a prospective study in the German general population. A random sample of all residents was drawn from the population registers to mirror the distribution of 14 to 24-year-olds in Munich. Detailed information about the study characteristics including the instruments and procedures used can be found elsewhere (Lieb et al., 2000; Wittchen et al., 1998). The study consisted of a baseline survey (T0, $n=3021$) and three follow-up assessments (T1, T2, T3). Because PE was first enquired at T2, only waves T2 and T3 were used. At T2, the average age of participants was 21.7 years ($SD=3.4$). The mean follow-up time between T2 and T3 was 4.8 years ($SD=0.7$). Response rates were 84% at T2 ($n=2548$) and 73% at T3 ($n=2210$).

NEMESIS, and its successor NEMESIS-2 are longitudinal cohort studies of the prevalence, incidence, course and consequences of mental disorders in the Dutch general population. Both studies applied multistage, random sampling procedures of municipalities and households. Detailed information about the study characteristics was published elsewhere (Bijl et al., 1998; de Graaf et al., 2010). NEMESIS included 7076 participants aged 18-64 years (average age at baseline 41.2 years, $SD=12.2$) and consisted of two follow-up surveys, respectively one (T1) and three (T2) years after the baseline measurement (T0). At T2, a total of 4796 persons participated (response rate 68%). NEMESIS-2 included 6646 participants aged 18-65 years (average age at baseline 44.2 years, $SD=12.5$). Three years after baseline (T0), 5303 persons participated in the follow-up assessment (T1,

response rate 80%). For the present analysis, waves T0, T1 and T2 from NEMESIS and waves T0 and T1 from NEMESIS-2 were used, both covering a time period of three years.

A flowchart visualizing the inclusion, exclusion and attrition of participants is shown in Figure 1.

2.2 Diagnostic instruments

In all three studies, participants were interviewed using various versions of the Composite International Diagnostic Interview (CIDI) (World Health Organization, 1990). This is a comprehensive and standardized diagnostic interview assessing symptoms, syndromes and diagnoses of mental disorders according to the diagnostic criteria of a version of the Diagnostic and Statistical Manual of Mental disorders (DSM). The instrument is designed to be used by trained lay interviewers, who read questions in a standardized way and record participants' answers. Therefore, the CIDI is essentially a self-report instrument (Eaton et al., 2000). Both the validity (Haro et al., 2006; Reed et al., 1998) and the test-retest reliability have been established, showing that the CIDI provides valid diagnoses for almost all non-psychotic disorders with good to excellent kappa coefficients for most diagnostic sections (Wittchen, 1994).

In the EDSP, a computerized version of the Munich-Composite International Diagnostic Interview (M-CIDI) (Wittchen and Pfister, 1997) was used. This instrument is based on the CIDI version 1.2 (World Health Organization, 1990) and assesses symptoms and diagnoses according to the third revised edition of the Diagnostic and Statistical Manual of Mental disorders (DSM-III-R). Interviews were conducted by trained psychologists. In NEMESIS, interviews were performed using the CIDI version 1.1 by trained lay interviewers (Smeets and Dingemans, 1993). Like the M-CIDI, this version of the CIDI generated DSM-III-R diagnoses. Participants of the NEMESIS-2 were interviewed at home by trained interviewers using the CIDI version 3.0 (Alonso et al., 2004; de Graaf et al., 2008). This version of the CIDI generated DSM-IV diagnoses and contained a screening section with key questions for most mental disorders (de Graaf et al., 2010). Only participants answering positively on a key question were administered the complete disorder section.

For reasons of consistency across studies, only baseline lifetime diagnoses of any anxiety disorder, major depressive episode, dysthymia, any substance use disorder and bipolar disorder were used in the analyses.

2.3 Assessment of psychotic experiences

In the EDSP, PE were first assessed at T2 using the G section of the M-CIDI. This section included 14 items on delusions and 5 items on hallucinations corresponding to classic psychotic symptoms like persecution, various hallucinations and thought interference. The interviews were conducted by trained psychologists who were allowed to probe with follow-up clinical questions. For the present analysis, T2 was used as baseline. In NEMESIS, the G section of the CIDI version 1.1 was used to assess PE. This section consists of 13 items on delusions and 4 items on hallucinations, corresponding with the EDSP items. In NEMESIS-2, a psychosis add-on instrument based on the G section of the previous CIDI versions was included. This add-on instrument consists of 20 psychotic symptoms corresponding to the symptoms assessed in the NEMESIS and EDSP. Detailed descriptions of the specific PE items can be found in previous work using EDSP (van Rossum et al., 2011), NEMESIS (Smeets et al., 2013) and NEMESIS-2 (van Nierop et al., 2012).

In both the NEMESIS and NEMESIS-2, an experienced clinician did a follow-up telephone interview when participants reported a psychotic symptom to assess whether this symptom was a true PE using questions from the Structured Clinical Interview for DSM-III-R or DSM-IV, respectively. In NEMESIS, the proportion of participants eligible for a telephone interview that was actually re-interviewed was 47%. The CIDI rating was corrected to match clinical follow-up interview where possible. Re-interview resulted in a change in 6.9% of the ratings (van Os et al., 2001). In NEMESIS-2, 74% of all eligible participants was re-assessed. From the NEMESIS-2 data, only clinically validated PE were used in the analyses.

For the present analysis, PE were dichotomised. Thus, presence of PE was defined as at least one CIDI psychotic symptom, consistent with previous work in EDSP, NEMESIS and NEMESIS-2 (Cougnard et al., 2007; Gevonden et al., 2014; Van Os et al., 2000; van Os et al., 2001). At baseline, lifetime prevalence of PE was assessed.

2.4 Assessment of suicidal ideation and behaviour

The outcome measures in the present study were incident suicidal ideation (hereafter suicidal ideation) and incident suicide attempts (hereafter suicide attempts). In EDSP and NEMESIS, suicidal ideation and suicide attempts were assessed using the following questions from the CIDI depression section: a) Have you had a period of two weeks or more during which you wanted to be dead? b) Have you been so down that you thought of committing suicide? c) Have you attempted suicide? In NEMESIS-2, the suicidality questions in the depression section were slightly different: a) Have you thought of committing suicide? b) Have you made plans to end your life? c) Have you attempted suicide? In NEMESIS-2, these questions were only asked to participants

who answered positively to the stem questions of the depression section. Therefore, to prevent false negatives in participants with suicidal ideation or suicide attempts outside the context of depression, three additional items from the suicidality section of the CIDI version 3.0 were used. In this section, all participants are asked about the following three events: a) Have you seriously thought about committing suicide? b) Have you made a plan for committing suicide? c) Have you attempted suicide? In all three studies, questions referred to any incident of suicidal ideation or suicide attempt since the baseline assessment.

For the present analysis, incident suicidal ideation was defined as a positive answer to question (a) or (b) at one of the follow-up measurements; incident suicide attempt was defined as a positive answer to question (c) at follow-up. Individuals with either suicidal ideation or suicide attempts at baseline were excluded from the analyses.

2.5 Symptom domains

In each prospective cohort, a continuous symptom scale was constructed for depression, anxiety and mania symptoms at baseline by summing the subject's binary scores of the individual items of the respective CIDI sections, thus generating a continuous scale for each symptom domain (van Nierop et al., 2015a; van Nierop et al., 2015b). The section on depression included 27 symptoms in EDSP, 19 symptoms in NEMESIS and 24 symptoms in NEMESIS-2. Items on suicidal ideation and suicide attempts were excluded from the continuous scale for depression symptoms. The section on mania included 11 symptoms in both EDSP and NEMESIS and 17 symptoms in NEMESIS-2. Finally, the section on anxiety included 40 symptoms in EDSP, 54 symptoms in NEMESIS and 43 items in NEMESIS-2. Since the number of depressive, anxiety and mania symptoms varied among the CIDI-versions that were used in the different studies, the symptom scales were standardized in each cohort by dividing the sum scores by their standard deviations before merging the three databases. In addition, quadratic terms were generated for the various symptom scales, since the association between symptom domains and suicidal ideation and behaviour may be nonlinear (Schiepek et al., 2011).

2.6 Statistical analyses

Statistical analyses were performed in Stata version 13.0 (StataCorp., 2013). The three prospective datasets were first prepared by identifying and renaming variables and by generating identification variables. Then, databases were merged using the append command in Stata. As the research question focussed on association rather than incidence or prevalence, sampling weights were not applied. In order to adjust for clustering of data within

studies, all regression models included two dummies for the study (study-ID) (Snijders and Bosker, 2011). Only participants with complete data were analysed. Participants with psychotic disorder at baseline were excluded from all analyses. The outcome variables were incident suicidal ideation and incident suicide attempt.

First, the association between baseline PE and suicidal ideation or suicide attempts at follow-up was tested in a logistic regression model including baseline PE, study-ID, age and sex as the independent variables and suicidal ideation or suicide attempts as the dependent variable. To sensitively correct for the influence of depression, anxiety and mania symptoms, adjusted regression models included the continuous measures of these symptom domains as covariates. To assess whether the association between the various symptom domains and suicidal ideation and suicide attempts was linear, both the linear and the quadratic term of the continuous symptom variables were added to the regression model. If the quadratic term did not reach significance, only the linear term was used. If the quadratic term reached statistical significance, both the quadratic term and the linear term were used. In the final model, demographic variables and all three symptom scales were added simultaneously.

Second, all analyses were repeated in the following subgroups: (1) individuals without a diagnosis of any mental disorder (i.e. any anxiety disorder, major depressive episode, dysthymia, any substance use disorder, bipolar disorder or psychotic disorder) at baseline; (2) individuals with any baseline mental disorder (as defined for first group).

Third, to further assess the influence of baseline non-psychotic mental disorders on the association between PE and suicidal ideation and behaviour, and to examine dose-response relationships between the co-occurrence of mental disorders and PE, an additional logistic regression was performed with a categorical variable as main independent variable including the following categories: (1) No PE and no baseline mental disorder, (2) PE but no baseline mental disorder, (3) PE and one baseline mental disorder, (4) PE and two or more baseline mental disorders.

Finally, to assess whether co-occurrence of various symptom domains next to PE increased the risk of suicidal ideation and behaviour in a dose-response fashion in participants without baseline mental disorders, a logistic regression model was used with a categorical predictor variable containing the following categories (van Nierop et al., 2015a; van Nierop et al., 2015b): (1) No PE and no anxiety, depression or mania symptoms, (2) PE but no anxiety, depression or mania symptoms, (3) PE and one symptom dimension (anxiety, depression or mania) present, (4) PE and two symptom dimensions present, (5) PE and three symptom dimensions present.

3. Results

3.1 Baseline characteristics

Of the included participants, 13.0% (n=2065) reported lifetime PE at baseline. The group with PE was significantly younger and the proportion of males was lower than in the group without PE (Table 1). The lifetime prevalence of all baseline mental disorders, suicidal ideation and suicide attempts was significantly higher in participants with PE compared to participants without PE. Furthermore, the mean number of baseline depression, anxiety or mania symptoms was significantly higher in the PE group.

3.2 Associations between psychotic experiences and suicidal ideation and suicide attempts

3.2.1 General population

The OR of the association between PE and suicidal ideation was 2.07 (95% CI 1.50 – 2.87; Table 2). Including continuous measures of depression, mania or anxiety symptoms in the model reduced the association considerably. Adding all three symptom scales simultaneously resulted in a 70% reduction of the excess risk associated with PE (OR=1.32; 95% CI 0.93 – 1.87). The OR of the association between PE and suicide attempts was 3.95 (95% CI 1.85 – 8.43; Table 2). Adjustment for baseline depression, mania and anxiety symptoms slightly decreased the OR, but the association remained statistically significant (OR=3.44, 95% CI 1.54 – 7.69).

3.2.2 Subgroup without baseline mental disorders

In the subsample without a lifetime history of any mental disorder, the OR of the association between PE and suicidal ideation was 1.87 (95% CI 1.10 – 3.17; Table 2). Adjusting the analysis for depression, anxiety and mania symptoms resulted in a statistically non-significant association (OR=1.20, 95% CI 0.68 – 2.10). There was no association between PE and suicide attempts in this subsample.

3.2.3 Subgroup with any baseline mental disorders

In the subsample with any baseline mental disorder, the OR of the association between PE and suicidal ideation was 1.79 (95% CI 1.18 – 2.71; Table 2). Including continuous measures of non-psychotic symptomatology decreased ORs, resulting in a non-significant OR of 1.37 (95% CI 0.89 – 2.13). The OR of the association between PE and suicide attempts was 8.90 (95% CI 2.91 – 27.21; Table 2). Adjustment for baseline depression, mania and anxiety symptoms slightly increased the OR (OR=9.16, 95% CI 2.84 – 29.52).

3.3 Dose-response relationships with connected psychopathology

3.3.1 General population

Participants with PE at baseline but without a lifetime comorbid mental disorder were at increased risk of suicidal ideation, compared to participants without PE and comorbid mental disorders (OR=1.95, 95% CI 1.15 – 3.29; Table 3). The risk of suicidal ideation increased in a dose-response fashion as the number of comorbid mental disorders at baseline increased, resulting in an OR of 2.73 (95% CI 1.54 – 4.84) for participants with PE and one mental disorder and an OR of 5.50 (95% CI 3.20 – 9.45) for individuals with PE and two or more comorbid mental disorders. In the absence of a co-occurring mental disorder there was no association between PE and suicide attempts. However, PE were associated with suicide attempts when co-occurring with at least one mental disorder.

3.3.2 Subgroup without baseline mental disorders

The risk of suicidal ideation increased in participants with PE but without baseline mental disorders as the number of endorsed non-psychotic symptom domains increased (Table 4), ranging from 0.89 (95% CI 0.12–6.81) for participants with PE and no other symptom domain to 13.98 (5.18 – 37.71) for participants with PE and three other symptom domains. In the subgroup without baseline mental disorder there were only two cases of incident suicide attempts, thus making it impossible to validly examine dose-response associations in this group.

4. Discussion

4.1 Main findings

The present study is the first to analyse the longitudinal association between PE and suicidal ideation and behaviour merging multiple prospective, general population cohorts. In the complete sample, individuals with baseline PE were at increased risk of suicidal ideation and suicide attempts at follow-up. After adjustment for baseline anxiety, depression and mania symptoms, PE were no longer associated with suicidal ideation. However, PE remained significantly associated with suicide attempts. Further examination of these associations in subgroups of individuals with and without baseline mental disorders revealed that PE were only associated with suicide attempts in the subgroup with any baseline mental disorder. In the subgroup without baseline mental disorder, the risk of suicidal ideation increased as the number of co-occurring symptom domains increased.

4.2 Interpretation

A recent meta-analysis concluded that general population individuals with PE are at increased risk of suicidal ideation and behaviour, but that this association is confounded by the presence of co-occurring non-psychotic psychopathology (Honings et al., 2015). The reported association between PE and suicidal ideation and behaviour was hypothesized to reflect the increased risk of these outcomes in distressed participants with comorbid mental disorders or high levels of psychopathology. The present study supports this hypothesis.

After adjustment for depression, anxiety and mania symptoms, PE were no longer associated with suicidal ideation, both in the complete sample and in subgroups with and without baseline mental disorders, indicating that the association is confounded by non-psychotic psychopathology. Similarly, in the group without baseline mental disorders, the risk of suicidal ideation increased as the number of co-endorsed symptom domains increased. Previous research showed that the earliest expressions of psychopathology are nonspecific and contain a mixture of psychotic, affective, and anxiety symptoms that dynamically affect each other and gradually differentiate into more specific syndromes over time, thus resulting in a 'general distress syndrome' (McGorry and van Os, 2013; van Os, 2013; Wigman et al., 2013). Therefore, the finding that the co-occurrence of PE with other symptom domains is associated with an increased risk of suicidal ideation, likely reflects the increased risk of suicidal ideation in participants who do not yet meet criteria for a diagnosis, but possibly display early expressions of psychopathology.

In the complete sample, individuals with PE were at increased risk of suicide attempts, even after adjustment for depression, anxiety and mania symptoms. However, examination of this association in subgroups stratified by presence or absence of baseline mental disorder revealed that PE were only associated with suicide attempts in presence of at least one mental disorder. This finding supports the hypothesis of the present study that the association between PE and suicide attempts reflects the increased risk of suicide attempts in participants with more severe mental distress in the context of mental disorders. Previous cross-sectional (DeVylder et al., 2015b) and longitudinal (Kelleher et al., 2013) studies reported similar results. In the subgroup without baseline mental disorders, there was no association between PE and suicide attempts.

The present study shows that PE are a risk factor for suicide attempts in individuals with mental disorders. However, the mechanism behind this association remains unclear. Previous work identified shared common causes for PE and suicide attempts, including psychological and social factors (DeVylder et al., 2015a), increased emotional reactivity to stress (Lataster et al., 2009), emotion oriented coping styles (Lin et al., 2011) and exposure to traumatic life events (Iga et al., 2007). However, more research on underlying mechanisms is

required. The results of the present study show that PE serve as an indicator of illness severity and poor outcome in persons with non-psychotic psychopathology, in line with previous research (Guloksuz et al., 2015; Kelleher et al., 2012b; Perlis et al., 2011; Wigman et al., 2012; Wigman et al., 2014). Therefore, assessment of PE in individuals with non-psychotic psychopathology should be incorporated both in clinical practice and in future research, as previously suggested (Kelleher et al., 2013), in order to identify individuals at risk of suicidal behaviour. In addition, future research should examine the role of PE in the transition of suicidal ideation to suicide attempts, since evidence shows that most risk factors for suicidal ideation do not distinguish between ideators and attempters (Klonsky and May, 2014; May and Klonsky, 2016).

4.3 Strengths and limitations

Strength of the present study is the large sample size including both adults and adolescents. Moreover, a three year follow-up is longer than follow-up periods in most previous studies (Kelleher et al., 2013; Martin et al., 2015; Sullivan et al., 2015), thus increasing the likelihood of suicidal ideation or suicide attempts to occur, and enhancing statistical power. The present study is also the first longitudinal study that included dimensional symptom scales in the statistical analyses and used general population samples stratified by the presence or absence of mental disorders in an attempt to disentangle longitudinal associations between PE and suicidal ideation and suicide attempts from connected psychopathology, while minimizing residual confounding.

The results of the present study should be interpreted in the light of some methodological limitations. First, the outcome of incident suicide attempt was rare. Even though three general population cohorts were merged into one database, the statistical power was low in some analyses, resulting in wide 95% confidence intervals.

Second, the individual studies that were merged into one dataset for this analysis differed with regard to study design and assessment of PE. NEMESIS and NEMESIS-2 had three year follow-up periods, while the EDSP study had a five year follow-up. In order to obtain sufficient power, the data sets were merged and analysed as if the follow-up periods were identical based on the assumption that the three-year risk of suicidal ideation and suicide attempts is not substantially different from the five-year risk of suicidal behaviour (Nock et al., 2012). Moreover, the present study included both self-reported PE (EDSP data, albeit elicited by interviewers who were allowed to probe with clinical follow-up questions), clinically validated PE (NEMESIS-2 data) and partially clinically validated PE (NEMESIS). To examine whether these methodological differences between the individual studies influenced the results, sensitivity analyses were conducted in the individual datasets (results not shown). Although analyses had low statistical power and 95% confidence intervals were wide, ORs in EDSP

and NEMESIS data, separately, were similar. However, ORs in NEMESIS-2 were larger than in EDSP and NEMESIS. A possible explanation for this difference is that in NEMESIS-2 only clinically validated PE were used. Previous work showed that individuals with clinically validated PE have more non-psychotic psychopathology and seek help for their PE more often, compared with individuals with self-reported PE (van Nierop et al., 2012). This might explain why clinically validated PE are associated more strongly with suicidal ideation and suicide attempts than self-reported PE or partially clinically validated PE. Nevertheless, evidence suggests that self-reported PE are also predictive of several poor mental health outcomes and measure the same underlying construct as clinically validated PE (Bak et al., 2003; Kaymaz et al., 2012; Poulton et al., 2000; van Nierop et al., 2012). Therefore, both assessments of PE can be validly combined into one variable. Moreover, all regression models included two dummies for the studies to adjust for clustering of data within studies.

Third, the mental disorders that were diagnosed in the three individual studies were not fully congruent. To reach conformity among the studies, it was necessary to restrict the included mental disorders to the ones that were measured across all three studies. Inclusion of more mental disorders might have resulted in stronger evidence that PE are mostly predictive of suicide attempts in participants with co-occurring mental disorders.

Fourth, the three year follow-up period can be considered a limitation as well, since suicidality may fluctuate over a longer follow-up period (Gabennesch, 1988; Noble, 1996). Moreover, from a suicide prevention perspective, a shorter follow-up period could be useful, since it provides information on impending acts. However, previous longitudinal work assessed the association between PE and suicide attempts at three and twelve months after baseline and found similar results as the present study (Kelleher et al., 2013).

Fifth, follow-up data was missing for a substantial proportion of the participants (25%). Attrition occurred more often in individuals with PE (OR=1.23, 95% CI 1.11 – 1.37). However, further examination of attrition in the individual datasets showed that PE were only associated with attrition in NEMESIS. Previous work showed that attrition in NEMESIS was higher in respondents with one or more mental disorders (de Graaf et al., 2000). Therefore, the association between PE and attrition found in the present study, reflects the increased risk of attrition in individuals with mental disorders in NEMESIS; in individuals without mental disorders PE were not associated with attrition. Since individuals with PE and mental disorders are also at risk of suicidal ideation and behaviour, the reported associations might have been stronger in absence of attrition.

Finally, the CIDI version used in NEMESIS-2 included a screening section with key questions for most mental disorders. Therefore, not all participants answered all questions about depression, anxiety or mania symptoms. This may have caused an underestimation of the symptom scores in this study.

In conclusion, the present study showed that PE in the general population are associated with an increased risk of suicidal ideation and behaviour. However, these associations are not specific but reflect the increased risk of suicidal ideation in individuals with subthreshold multidimensional psychopathology and suicide attempts in individuals with co-occurring mental disorders.

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Declaration of interest:

None

References

- Alonso, J., Angermeyer, M.C., Bernert, S., Bruffaerts, R., Brugha, T.S., Bryson, H., de Girolamo, G., Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J.M., Katz, S.J., Kessler, R.C., Kovess, V., Lepine, J.P., Ormel, J., Polidori, G., Russo, L.J., Vilagut, G., Almansa, J., Arbabzadeh-Bouchez, S., Autonell, J., Bernal, M., Buist-Bouwman, M.A., Codony, M., Domingo-Salvany, A., Ferrer, M., Joo, S.S., Martinez-Alonso, M., Matschinger, H., Mazzi, F., Morgan, Z., Morosini, P., Palacin, C., Romera, B., Taub, N., Vollebergh, W.A., ESEMeD/MhedeA Investigators, E.S.o.t.E.o.M.D.P., 2004. Sampling and methods of the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl*(420), 8-20.
- Bijl, R.V., van Zessen, G., Ravelli, A., de Rijk, C., Langendoen, Y., 1998. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. *Soc Psychiatry Psychiatr Epidemiol* 33 (12), 581-586.
- Bostwick, J.M., Pankratz, V.S., 2000. Affective disorders and suicide risk: a reexamination. *Am J Psychiatry* 157 (12), 1925-1932.
- 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., Connolly, J.J., Sleiman, P.A., Hakonarson, H., Gur, R.C., Gur, R.E., 2014. The psychosis spectrum in a young U.S. community sample: Findings from the Philadelphia Neurodevelopmental Cohort. *World Psychiatry* 13 (3), 296-305.
- Capra, C., Kavanagh, D.J., Hides, L., Scott, J.G., 2015. Subtypes of psychotic-like experiences are differentially associated with suicidal ideation, plans and attempts in young adults. *Psychiatry Res* 228 (3), 894-898.
- Cavanagh, J.T., Carson, A.J., Sharpe, M., Lawrie, S.M., 2003. Psychological autopsy studies of suicide: a systematic review. *Psychological Medicine* 33 (3), 395-405.
- Cougnard, A., Marcelis, M., Myin-Germeys, I., De Graaf, R., Vollebergh, W., Krabbendam, L., Lieb, R., Wittchen, H.U., Henquet, C., Spauwen, J., Van Os, J., 2007. Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychol Med* 37 (4), 513-527.
- de Graaf, R., Bijl, R.V., Smit, F., Ravelli, A., Vollebergh, W.A., 2000. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Am J Epidemiol* 152 (11), 1039-1047.
- de Graaf, R., Ormel, J., ten Have, M., Burger, H., Buist - Bouwman, M., 2008. Mental disorders and service use in the Netherlands: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD), The WHO World Mental Health Surveys: Global Perspectives on the Epidemiology of Mental Disorders. Cambridge University Press, New York.
- de Graaf, R., Ten Have, M., van Dorsselaer, S., 2010. The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. *Int J Methods Psychiatr Res* 19 (3), 125-141.
- DeVylder, J.E., Burnette, D., Yang, L.H., 2014. Co-occurrence of psychotic experiences and common mental health conditions across four racially and ethnically diverse population samples. *Psychological Medicine* 44 (16), 3503-3513.

- DeVylder, J.E., Jahn, D.R., Doherty, T., Wilson, C.S., Wilcox, H.C., Schiffman, J., Hilimire, M.R., 2015a. Social and psychological contributions to the co-occurrence of sub-threshold psychotic experiences and suicidal behavior. *Soc Psychiatry Psychiatr Epidemiol* 50 (12), 1819-1830.
- DeVylder, J.E., Lukens, E.P., Link, B.G., Lieberman, J.A., 2015b. Suicidal ideation and suicide attempts among adults with psychotic experiences: data from the collaborative psychiatric epidemiology surveys. *JAMA Psychiatry* 72 (3), 219-225.
- Eaton, W.W., Neufeld, K., Chen, L.S., Cai, G., 2000. A comparison of self-report and clinical diagnostic interviews for depression: diagnostic interview schedule and schedules for clinical assessment in neuropsychiatry in the Baltimore epidemiologic catchment area follow-up. *Arch Gen Psychiatry* 57 (3), 217-222.
- 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 (10), 2077-2086.
- Gevonden, M.J., Selten, J.P., Myin-Germeys, I., de Graaf, R., ten Have, M., van Dorsselaer, S., van Os, J., Veling, W., 2014. Sexual minority status and psychotic symptoms: findings from the Netherlands Mental Health Survey and Incidence Studies (NEMESIS). *Psychol Med* 44 (2), 421-433.
- Guloksuz, S., van Nierop, M., Lieb, R., van Winkel, R., Wittchen, H.U., van Os, J., 2015. Evidence that the presence of psychosis in non-psychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology. *Psychological Medicine*, 1-13.
- Haro, J.M., Arbabzadeh-Bouchez, S., Brugha, T.S., de Girolamo, G., Guyer, M.E., Jin, R., Lepine, J.P., Mazzi, F., Reneses, B., Vilagut, G., Sampson, N.A., Kessler, R.C., 2006. Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health surveys. *Int J Methods Psychiatr Res* 15 (4), 167-180.
- Hawton, K., van Heeringen, K., 2009. Suicide. *Lancet* 373 (9672), 1372-1381.
- Honings, S., Drukker, M., Groen, R., van Os, J., 2015. Psychotic experiences and risk of self-injurious behaviour in the general population: a systematic review and meta-analysis. *Psychol Med*, 1-15.
- Iga, J., Ueno, S., Yamauchi, K., Numata, S., Tayoshi-Shibuya, S., Kinouchi, S., Nakataki, M., Song, H., Hokoishi, K., Tanabe, H., Sano, A., Ohmori, T., 2007. The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with psychotic feature and suicidal behavior in Japanese major depressive patients. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 144B (8), 1003-1006.
- Jahn, D.R., DeVylder, J.E., Hilimire, M.R., 2016. Explanatory risk factors in the relations between schizotypy and indicators of suicide risk. *Psychiatry Res* 238, 68-73.
- Jang, J.H., Lee, Y.J., Cho, S.J., Cho, I.H., Shin, N.Y., Kim, S.J., 2014. Psychotic-like experiences and their relationship to suicidal ideation in adolescents. *Psychiatry Research* 215 (3), 641-645.
- 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. *J Child Psychol Psychiatry* 56 (5), 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. *Psychol Med* 42 (11), 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 (9), 1857-1863.
- 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. *The British Journal of Psychiatry* 201 (1), 26-32.
- Kelleher, I., Lynch, F., Harley, M., Molloy, C., Roddy, S., Fitzpatrick, C., Cannon, M., 2012c. Psychotic symptoms in adolescence index risk for suicidal behavior: Findings from 2 population-based case-control clinical interview studies. *Archives of General Psychiatry* 69 (12), 1277-1283.
- Kelleher, I., Corcoran, P., Keeley, H., Wigman, J.T., Devlin, N., Ramsay, H., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., Cannon, M., 2013. Psychotic symptoms and population risk for suicide attempt: a prospective cohort study. *JAMA Psychiatry* 70 (9), 940-948.
- Klonsky, E.D., May, A.M., 2014. Differentiating suicide attempters from suicide ideators: a critical frontier for suicidology research. *Suicide Life Threat Behav* 44 (1), 1-5.
- Koyanagi, A., Stickley, A., Haro, J.M., 2015. Subclinical psychosis and suicidal behavior in England: Findings from the 2007 Adult Psychiatric Morbidity Survey. *Schizophrenia Research*.
- Lataster, T., Wichers, M., Jacobs, N., Mengelers, R., Derom, C., Thiery, E., Van Os, J., Myin-Germeys, I., 2009. Does reactivity to stress cosegregate with subclinical psychosis? A general population twin study. *Acta Psychiatrica Scandinavica* 119 (1), 45-53.
- Lewis-Fernandez, R., Horvitz-Lennon, M., Blanco, C., Guarnaccia, P.J., Cao, Z., Alegria, M., 2009. Significance of endorsement of psychotic symptoms by US latinos. *Journal of Nervous and Mental Disease* 197 (5), 337-347.
- Lieb, R., Isensee, B., von Sydow, K., Wittchen, H.U., 2000. The Early Developmental Stages of Psychopathology Study (EDSP): a methodological update. *Eur Addict Res* 6 (4), 170-182.
- Lin, A., Wigman, J.T., Nelson, B., Vollebergh, W.A., van Os, J., Baksheev, G., Ryan, J., Raaijmakers, Q.A., Thompson, A., Yung, A.R., 2011. The relationship between coping and subclinical psychotic experiences in adolescents from the general population--a longitudinal study. *Psychological Medicine* 41 (12), 2535-2546.
- 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 (6), 1133-1149.
- Martin, G., Thomas, H., Andrews, T., Hasking, P., Scott, J.G., 2015. Psychotic experiences and psychological distress predict contemporaneous and future non-suicidal self-injury and suicide attempts in a sample of Australian school-based adolescents. *Psychological Medicine* 45 (2), 429-437.

- May, A.M., Klonsky, E.D., 2016. What Distinguishes Suicide Attempters From Suicide Ideators? A Meta-Analysis of Potential Factors. *Clinical Psychology: Science and Practice* 23 (1), 5-20.
- McGorry, P., van Os, J., 2013. Redeeming diagnosis in psychiatry: timing versus specificity. *Lancet* 381 (9863), 343-345.
- Miller, G.A., Chapman, J.P., 2001. Misunderstanding analysis of covariance. *The Journal of Abnormal Psychology* 110 (1), 40-48.
- Murphy, J., Shevlin, M., Houston, J., Adamson, G., 2012. A population based analysis of subclinical psychosis and help-seeking behavior. *Schizophr Bull* 38 (2), 360-367.
- Nishida, A., Sasaki, T., Nishimura, Y., Tanii, H., Hara, N., Inoue, K., Yamada, T., Takami, T., Shimodera, S., Itokawa, M., Asukai, N., Okazaki, Y., 2010. Psychotic-like experiences are associated with suicidal feelings and deliberate self-harm behaviors in adolescents aged 12-15 years. *Acta Psychiatrica Scandinavica* 121 (4), 301-307.
- Nock, M.K., Borges, G., Bromet, E.J., Cha, C.B., Kessler, R.C., Lee, S., 2008. Suicide and suicidal behavior. *Epidemiol Rev* 30, 133-154.
- Nock, M.K., 2010. Self-injury. *Annual Review of Clinical Psychology* 6, 339-363.
- Nordentoft, M., Mortensen, P.B., Pedersen, C.B., 2011. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry* 68 (10), 1058-1064.
- O'Connor, R.C., Platt, S., Gordon, J., 2011. Achievements and Challenges in Suicidology: Conclusions and Future Directions, *International Handbook of Suicide Prevention*. John Wiley & Sons, Ltd, pp. 625-642.
- Olfson, M., Lewis-Fernandez, R., Weissman, M.M., Feder, A., Gameroff, M.J., Pilowsky, D., Fuentes, M., 2002. Psychotic symptoms in an urban general medicine practice. *American Journal of Psychiatry* 159 (8), 1412-1419.
- Palmer, B.A., Pankratz, V.S., Bostwick, J.M., 2005. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry* 62 (3), 247-253.
- Perlis, R.H., Uher, R., Ostacher, M., Goldberg, J.F., Trivedi, M.H., Rush, A.J., Fava, M., 2011. Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. *Archives of General Psychiatry* 68 (4), 351-360.
- Reed, V., Gander, F., Pfister, H., Steiger, A., Sonntag, H., Trenkwalder, C., Sonntag, A., Hundt, W., Wittchen, H.-U., 1998. To what degree does the Composite International Diagnostic Interview (CIDI) correctly identify DSM-IV disorders? Testing validity issues in a clinical sample. *International Journal of Methods in Psychiatric Research* 7 (3), 142-155.
- Saha, S., Scott, J.G., Johnston, A.K., Slade, T.N., Varghese, D., Carter, G.L., McGrath, J.J., 2011. The association between delusional-like experiences and suicidal thoughts and behaviour. *Schizophrenia Research* 132 (2-3), 197-202.
- Schiepek, G., Fartacek, C., Sturm, J., Kralovec, K., Fartacek, R., Ploderl, M., 2011. Nonlinear dynamics: theoretical perspectives and application to suicidology. *Suicide Life Threat Behav* 41 (6), 661-675.
- Sharifi, V., Eaton, W.W., Wu, L.T., Roth, K.B., Burchett, B.M., Mojtabai, R., 2015. Psychotic experiences and risk of death in the general population: 24-27 year follow-up of the Epidemiologic Catchment Area study. *The British Journal of Psychiatry* 207 (1), 30-36.

- Smeets, F., Lataster, T., van Winkel, R., de Graaf, R., Ten Have, M., van Os, J., 2013. Testing the hypothesis that psychotic illness begins when subthreshold hallucinations combine with delusional ideation. *Acta Psychiatr Scand* 127 (1), 34-47.
- Smeets, R.M.W., Dingemans, P.M.A.J., 1993. Composite International Diagnostic Interview (CIDI) Versie 1.1. World Health Organisation, Amerstam/Geneva.
- Snijders, T.A.B., Bosker, R.J., 2011. Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling. SAGE Publications.
- StataCorp., 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.
- Sveticic, J., De Leo, D., 2012. The hypothesis of a continuum in suicidality: a discussion on its validity and practical implications. *Mental illness* 4 (2), e15.
- Taylor, P.J., Hutton, P., Wood, L., 2015. Are people at risk of psychosis also at risk of suicide and self-harm? A systematic review and meta-analysis. *Psychological Medicine* 45 (5), 911-926.
- Temmingh, H., Stein, D.J., Seedat, S., Williams, D.R., 2011. The prevalence and correlates of hallucinations in a general population sample: Findings from the South African Stress and Health Study. *African Journal of Psychiatry (South Africa)* 14 (3), 211-217.
- ten Have, M., de Graaf, R., van Dorsselaer, S., Verdurmen, J., van 't Land, H., Vollebergh, W., Beekman, A., 2009. Incidence and course of suicidal ideation and suicide attempts in the general population. *Can J Psychiatry* 54 (12), 824-833.
- Ten Have, M., van Dorsselaer, S., de Graaf, R., 2013. Prevalence and risk factors for first onset of suicidal behaviors in the Netherlands Mental Health Survey and Incidence Study-2. *J Affect Disord* 147 (1-3), 205-211.
- van Nierop, M., van Os, J., Gunther, N., Myin-Germeys, I., de Graaf, R., ten Have, M., van Dorsselaer, S., Bak, M., van Winkel, R., 2012. Phenotypically continuous with clinical psychosis, discontinuous in need for care: evidence for an extended psychosis phenotype. *Schizophrenia Bulletin* 38 (2), 231-238.
- van Nierop, M., Bak, M., de Graaf, R., Ten Have, M., van Dorsselaer, S., Genetic, R., Outcome of Psychosis, I., van Winkel, R., Genetic, R., Outcome of Psychosis, G.I., 2015a. The functional and clinical relevance of childhood trauma-related admixture of affective, anxious and psychosis symptoms. *Acta Psychiatr Scand*.
- van Nierop, M., Viechtbauer, W., Gunther, N., van Zelst, C., de Graaf, R., Ten Have, M., van Dorsselaer, S., Bak, M., Genetic Risk and Outcome of Psychosis Investigators, van Winkel, R., 2015b. Childhood trauma is associated with a specific admixture of affective, anxiety, and psychosis symptoms cutting across traditional diagnostic boundaries. *Psychol Med* 45 (6), 1277-1288.
- Van Os, J., Hanssen, M., Bijl, R., Ravelli, A., 2000. Straus (1969) revisited: A psychosis continuum in the general population? *Schizophrenia Research* 45 (1-2), 11-20.
- van Os, J., Hanssen, M., Bijl, R.V., Vollebergh, W., 2001. Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. *Arch Gen Psychiatry* 58 (7), 663-668.
- van Os, J., 2013. The dynamics of subthreshold psychopathology: implications for diagnosis and treatment. *Am J Psychiatry* 170 (7), 695-698.

- van Rossum, I., Dominguez, M.D., Lieb, R., Wittchen, H.U., van Os, J., 2011. Affective dysregulation and reality distortion: a 10-year prospective study of their association and clinical relevance. *Schizophr Bull* 37 (3), 561-571.
- Wigman, J.T., van Nierop, M., Vollebergh, W.A., Lieb, R., Beesdo-Baum, K., Wittchen, H.U., van Os, J., 2012. Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity--implications for diagnosis and ultra-high risk research. *Schizophrenia Bulletin* 38 (2), 247-257.
- Wigman, J.T., van Os, J., Thiery, E., Derom, C., Collip, D., Jacobs, N., Wichers, M., 2013. Psychiatric diagnosis revisited: towards a system of staging and profiling combining nomothetic and idiographic parameters of momentary mental states. *PLoS One* 8 (3), e59559.
- Wigman, J.T., van Os, J., Abidi, L., Huibers, M.J., Roelofs, J., Arntz, A., Kelleher, I., Peeters, F.P., 2014. Subclinical psychotic experiences and bipolar spectrum features in depression: association with outcome of psychotherapy. *Psychological Medicine* 44 (2), 325-336.
- Wittchen, H.U., 1994. Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res* 28 (1), 57-84.
- Wittchen, H.U., Pfister, H., 1997. DIA-X-Interviews: Manual für Screening-Verfahren und Interview; Interviewheft. Swets & Zeitlinger, Frankfurt.
- Wittchen, H.U., Perkonig, A., Lachner, G., Nelson, C.B., 1998. Early developmental stages of psychopathology study (EDSP): objectives and design. *Eur Addict Res* 4 (1-2), 18-27.
- World Health Organization, 1990. Composite International Diagnostic Interview (CIDI). . World Health Organization, Division of Mental Health, Geneva.
- World Health Organization, 2014. Preventing suicide: A global imperative.

Table 1: Baseline characteristics.

		Complete dataset	Individuals with PE	Individuals without PE	t	χ^2	df	p*
Demographics:	N	15837	2065	13772	-	-	-	
	Number of males (%)	7388 (46.7)	905 (43.8)	6483 (47.1)	-	7.61	1	0.006
	Age (SD)	39.4 (13.8)	35.1 (13.6)	40.0 (13.73)	15.08	-	15835	<0.001
Baseline suicidality:	Suicidal ideation, n (%)	2670 (16.9)	750 (36.3)	1920 (13.9)	-	641.57	1	<0.001

Psychotic experiences and incident suicidal ideation and behaviour

	Suicide attempts, n (%)	1344 (8.5)	387 (18.7)	957 (7.0)	-	321.47	1	<0.001
Baseline	Major depressive episode, n	2921	663 (32.1)	2258	-	294.67	1	<0.001
mental	(%)	(18.4)		(16.4)				
disorders:								
	Dysthymia, n (%)	664 (4.2)	222 (10.6)	442 (3.2)	-	254.23	1	<0.001
	Any anxiety disorder, n (%)	3471 (21.9)	809 (39.2)	2662 (19.3)	-	413.36	1	<0.001
	Bipolar disorder, n (%)	280 (1.8)	136 (6.6)	144 (1.1)	-	317.38	1	<0.001
	Any substance use disorder, n (%)	2735 (17.3)	541 (26.2)	2194 (15.9)	-	132.51	1	<0.001
	Lifetime prevalence of any of the above diagnoses, n (%)	6771 (42.8)	1339 (64.8)	5432 (39.4)	-	473.37	1	<0.001
Baseline	Mean number of anxiety	0.64	1.0 (1.3)	0.6 (0.9)	-	-	15830	<0.001
symptom	symptoms, n (SD)	(1.0)			19.69			
dimensions:								
	Mean number of depression	0.70	1.4 (1.2)	0.6 (0.9)	-	-	15835	<0.001
	symptoms, n (SD)	(1.0)			33.29			
	Mean number of mania	0.43	1.2 (1.5)	0.3 (0.8)	-	-	15834	<0.001
	symptoms, n (SD)	(1.0)			40.80			

*p-value resulting from t-test or chi-square test for difference between participants with vs. without PE.

Table 2: Results from logistic regressions on the associations between baseline psychotic experiences and suicidal ideation and suicide attempts, while controlling for continuous measures of baseline psychopathology, in both the complete dataset and in subgroups of participants with and without baseline mental disorders (anxiety disorder, major depressive episode, dysthymia, any substance use disorder or bipolar disorder).

Exposure variable:	Covariates	Complete dataset (n=10254)		Subgroup without lifetime mental disorder at baseline (n=6357)		Subgroup with lifetime mental disorder at baseline (n=3897)	
		Suicidal ideation	Suicide attempts	Suicidal ideation	Suicide attempts	Suicidal ideation	Suicide attempts
Baseline PE	Demographics (age, sex)	2.07 (1.50 – 2.87)**	3.95 (1.85 – 8.43)**	1.87 (1.10 – 3.17)*	1.17 (0.26 – 5.23)	1.79 (1.18 – 2.71)**	8.90 (2.91 – 27.21)**
	Demographics + baseline depression symptoms	1.54 (1.10 – 2.16)**	3.49 (1.60 – 7.62)**	1.50 (0.87 – 2.59)	1.18 (0.26 – 5.37)	1.51 (0.98 – 2.31)	8.23 (2.64 – 25.62)**
	Demographics + baseline anxiety symptoms	1.75 (1.26 – 2.44)**	3.40 (1.57 – 7.37)**	1.71 (1.00 – 2.91)	1.12 (0.25 – 5.05)	1.62 (1.07 – 2.48)*	7.79 (2.51 – 24.17)**
	Demographics + baseline mania symptoms	1.52 (1.08 – 2.14)*	3.75 (1.69 – 8.32)**	1.39 (0.80 – 2.40)	1.04 (0.23 – 4.77)	1.49 (0.97 – 2.30)	9.89 (3.09 – 31.71)**
	Demographics + baseline depression, anxiety and mania symptoms	1.32 (0.93 – 1.87)	3.44 (1.54 – 7.69)**	1.20 (0.68 – 2.10)	1.04 (0.23 – 4.83)	1.37 (0.89 – 2.13)	9.16 (2.84 – 29.52)**
* p<0.05							
** p<0.01							

Table 3: Results from logistic regression in the complete dataset on the associations between psychotic experiences and suicidal ideation and suicide attempts in presence and absence of one or more mental disorders.

Baseline (complete sample, n=6656)	Suicidal ideation, OR (95% CI)	Suicide attempt, OR (95% CI)
No PE + no mental disorder	1.00 (reference)	1.00 (reference)
PE present + no mental disorder	1.95 (1.15 – 3.29)*	1.29 (0.29 – 5.76)
PE present + 1 mental disorder	2.73 (1.54 – 4.84)**	6.72 (2.50 – 18.07)**
PE present + at least 2 mental disorders	5.50 (3.20 – 9.45)**	5.20 (1.46 – 18.50)*
* p<0.05		
** p<0.01		

Table 4: Results from logistic regression on the associations between psychotic experiences and suicidal ideation and suicide attempts in presence or absence of one or more symptom domains, in a subgroup of patients without mental disorders at baseline.

Baseline (subgroup without mental disorders, n=2918)	Suicidal ideation, OR (95% CI)	Suicide attempt, OR (95% CI)
No PE + 0 symptom domains	1.00 (reference)	1.00 (reference)
PE present + 0 symptom domains	0.89 (0.12 – 6.81)	N.A.
PE present + 1 symptom domains	2.12 (0.59 – 7.64)	N.A.
PE present + 2 symptom domains	5.36 (2.08 – 13.82)**	1.58 (0.18 – 13.74)
PE present + 3 symptom domains	13.98 (5.18 – 37.71)**	3.57 (0.40 – 31.48)
* p<0.05		

** p<0.01

Figure 1: Flowchart of inclusion, exclusion and attrition of participants"

Highlights

- Psychotic experiences are associated with incident suicidal ideation and suicide attempts.
- The association is not specific, but reflects the increased risk of suicidal ideation in individuals with subthreshold multidimensional psychopathology and suicide attempts in individuals with co-occurring mental disorders.